Phosphinates as new electrophilic reagents for cross-coupling reactions

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7.2.1 General Experimental Methods 182

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Abbreviations

The following abbreviations are used in this report:

Ac	Acetyl
acac	Acetylacetonate
9-BBN	9-Borabicyclo[3.3.1]nonane
aq.	Aqueous
BINAP	2,2'-bis(Diphenylphosphino)-1,1'-binapthyl
bipy	Bipyridyl
Boc	*tert*-Butyloxycarbonyl
b.p.	Boiling point
CBz	Carbobenzyloxy
COSY	Correlation spectroscopy
Cyp	Cyclopentane
d	Doublet
dba	Dibenzylideneacetone
Diglyme	Diethylene glycol dimethyl ether
DMAP	4-N,N-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
Dppb	1,4-bis(Diphenylphosphino)butane
Dppe	1,2-bis(Diphenylphosphino)ethane
Dppp	1,3-bis(Diphenylphosphino)propane
DoE	Design of Experiments
e.e.	Enantiomeric excess

eq.	Equivalents
Eq.	Equation
GC	Gas Chromatography
GCMS	Gas Chromatography - Mass Spectrometry
PCA	Principal Component Analysis
h	Hours
HPLC	High Performance Liquid Chromatography
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Correlation
HRMS	High Resolution Mass Spectroscopy
IMES	1,3-Dimesitylimidazol-2-ylidene
IR	Infared
J	Coupling constant
LAH	Lithium Aluminium Hydride
LDA	Lithium Diisopropylamide
LCMS	Liquid Chromatography – Mass Spectrometry
LHMDS	Lithium Hexamethyldisilazide
M	Molar
m	Multiplet
Me	Methyl
min	Minutes
mmHg	Millimetres of mercury
mmol	Millimole
mol	Mole
m.p.	Melting Point
mw	Microwave
MS	Mass Spectrometry

NBS	N-Bromosuccinimide
NEt_3	Triethylamine
Nf	Nonaflate
NOE	Nuclear Overhauser Effect
NMP	N-Methylpyrrolidinone
NMR	Nuclear Magnetic Resonance
pent	Pentet
py	Pyridine
pyphos	(2-Diphenylphosphinoethyl)pyridine
q	Quartet
R_f	Retention factor
r.t.	Room Temperature
s	Singlet
Sia_2BH	Disiamylborane
SM	Starting Material
t	Triplet
Tf	Triflate
TFA	Trifluoroacetic Acid
TLC	Thin Layer Chromatography
TMEDA	N,N,N',N'-Tetramethylethylenediamine
Tol	Toluene
Ts	Tosyl

Abstract

Phosphinates as New Electrophilic Reagents for Cross-Coupling Reactions

Tom M. Woods

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Activated esters, e.g. triflates, sulfonates, nonaflates and phosphates are excellent electrophiles for a variety of cross-coupling reactions. However, other phosphorus-based esters have received little attention in these protocols. This thesis discusses the synthesis and cross-coupling chemistry of vinyl phosphinates, a new class of electrophilic species. A simple model vinyl phosphinate, N-(*tert*-butyloxycarbonyl)-4,5,6,7-tetrahydro-1*H*-azepin-2-yl-diphenylphosphinate, was prepared in excellent yield from commercially available caprolactam. A screening study identified Suzuki cross-coupling conditions under which this phosphinate smoothly coupled with a variety of electron-rich, electron-poor and sterically-hindered boronic acids. The scope and limitations of this chemistry were investigated and a variety of electron-withdrawing nitrogen protecting groups, e.g. Boc, CO_2Ph, CO_2Bn and Ts could be used without problem. However, electron-donating protecting groups, e.g. Me and Bn proved unsuccessful. Additionally, where seven and eight-membered ring lactam phosphinates coupled efficiently, five and six-membered ring derivatives proved largely unsuccessful. Relative reactivity studies were carried out with N-phenyloxycarbonyl-2-(diphenylphosphinoyloxy)-3,4-dihydro-6-bromoquinolone and indicated that the reactivity of vinyl phosphinates lies between that of aryl chlorides and aryl bromides in the Suzuki reaction. Attempts to improve the efficiency of the cross-coupling of this substrate using DoE and PCA modelling was attempted, but was largely unsuccessful. Studies towards the total synthesis of Lennoxamine *via* a cross-coupling reaction

between a benzazepine-derived vinyl phosphinate and 2,3-dimethoxy-N-(2'-phenylpropan-2-yl)-6-(tributylstannyl)benzamide were commenced. Synthesis of the stannane was achieved in high yield *via* a directed metallation strategy. Unfortunately, preliminary attempts to cross-couple this stannane with N-(benzyloxycarbonyl)-4,5,6,7-tetrahydro-1H-azepin-2-yl diphenylphosphinate in a model reaction were unsuccessful. Synthesis of the desired benzazepine phosphinate fragment proved more difficult and although progress has been made, this work remains unfinished. Additionally, treatment of N-([4'-methylphenyl]sulfonyl)-2-oxo-azepane with LDA/TMEDA in the presence of diphenylphosphoryl chloride afforded the sultam 1,2,3,4-tetrahydro-7-methylazepino[1,2-b][1,2]benzothiazole-10,10-dioxide in moderate yield. A range of aryl sulfonamides could be used affording the corresponding sultams in moderate yields.

Declaration

The work contained in this thesis was carried out in the department of chemistry, University of Durham, or GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts. between October 2004 and December 2007. All the work is my own unless otherwise stated. It has not previously been submitted for a degree at this or any other university.

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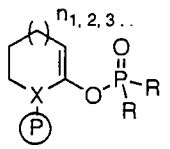
1 Introduction

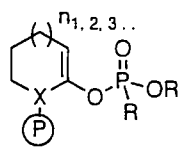
1.1 General Introduction

Late-transition-metal-catalysed cross-coupling chemistry represents one the most common and powerful methods for the formation of new a carbon-carbon bond in synthetic organic chemistry and this broad area has been the subject of extensive research over the past 40 years or so.[1] The development of cross-coupling chemistry has added a considerable weapon to the armoury of the synthetic chemist and the utility of this chemistry is evident throughout the literature.

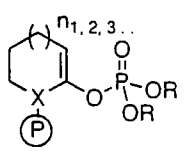
This thesis is concerned with the development of phosphorous-based substrates as the electrophilic partners for use in cross-coupling reactions. In particular, it will focus on the development of vinyl phosphinates of type **A** (Figure 1) and their application in cross-coupling strategies. Phosphinates and phosphonates of types **A** and **B**, respectively, have been the subject of surprisingly little research despite the recent re-emergence of the analogous phosphate group **C** as an effective and useful alternative to the more commonly employed triflates and sulfonates in a variety of cross-coupling reactions (Figure 1).



A
Phosphinate



B
Phosphonate



C
Phosphate

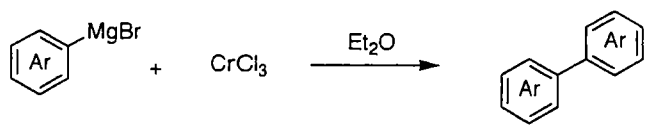
X = C, N, O R = Alkyl, aryl

Figure 1

The remainder of this chapter serves to highlight the important factors surrounding modern cross-coupling chemistry including its development over the past century, the general mechanism, the transition metal and ligand employed and a more detailed discussion of the known electrophilic species. The results of the research undertaken will be discussed in chapters two, three, four and five. Conclusions and suggestions for future work will be given in chapter six whilst chapter seven details the experimental methods and data.

1.2 Development of cross-coupling chemistry

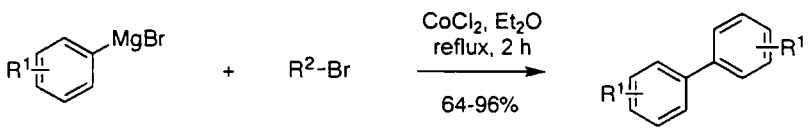
In 1914 whilst attempting to prepare organometallic derivatives of chromium, Bennet and Turner unexpectedly discovered that biaryl compounds could be formed in quantitative yields by treatment of aromatic Grignard reagents with stoichiometric amounts of chromium (III) chloride (Scheme 1).[2] This discovery was the first of many in the field of transition-metal-mediated reactions that would eventually lead to the development of modern cross-coupling chemistry. Following Bennet and Turner's groundbreaking discovery, several alternative metal halides were also shown to be capable of mediating similar transformations with various different Grignard reagents.[3] However, in comparison to modern cross-coupling chemistry these early dimerisation examples were neither catalytic nor could they be classed as true cross-coupling reactions.



Ar = Phenyl, napthyl, benzyl, tolyl

Scheme 1

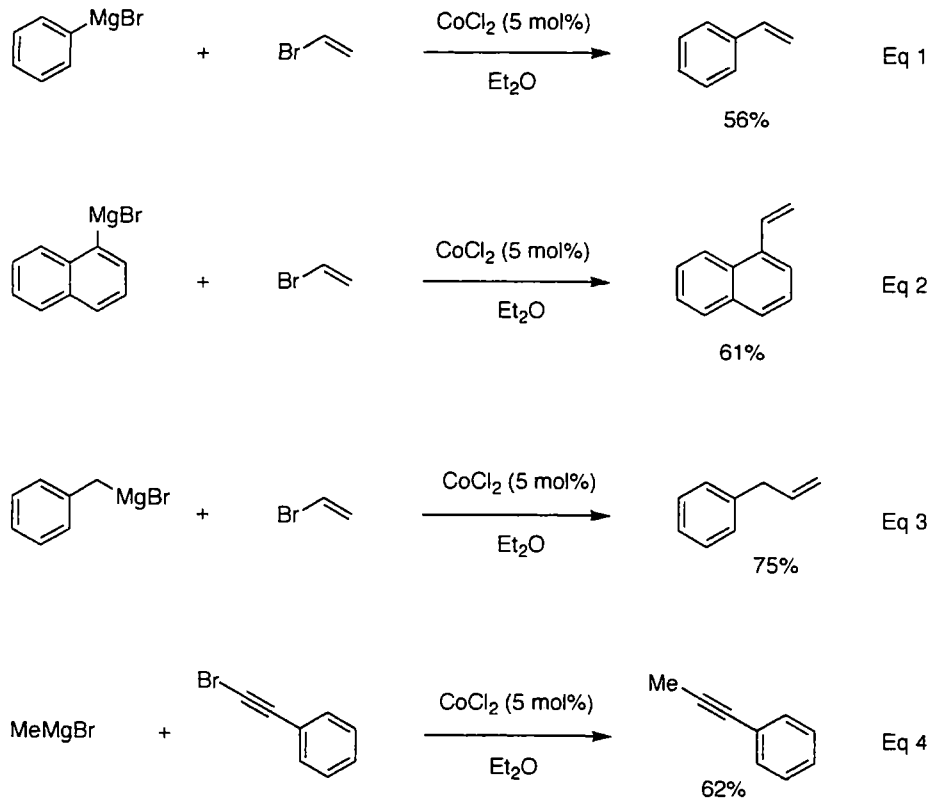
The first catalytic version of the above reaction was described by Kharasch and Fields in 1941.[4] In this they prepared a range of biaryls from substituted Grignard reagents in good yields using catalytic (1-10 mol %) amounts of group VIII metal halides, e.g. $CoCl_2$ (Scheme 2). The key to the success of this process was the addition of a stoichiometric amount of either bromoethane or bromobenzene. Importantly, there was no incorporation of the organic moiety of the bromide into the product from the reaction and, from this observation, it was postulated that the bromide was acting as an oxidising agent. After being reduced by the Grignard reagent, the metal halide is re-oxidised to its original oxidation state by the halide, thus allowing the metal halide to function as a catalyst. This was a significant discovery as it demonstrated that these types of transition metal complexes were capable of undergoing redox pathways.



R^1 = *o*-Methyl, *p*-Methyl, *o*-Ethyl or *p*-Anisyl. R^2 = Phenyl or ethyl

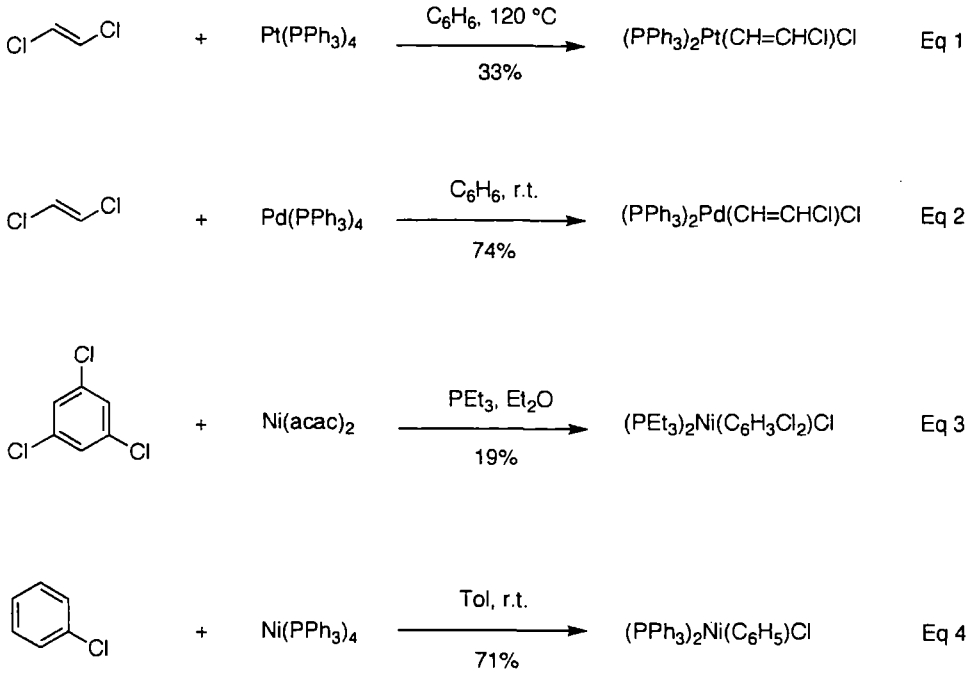
Scheme 2

Subsequently, during extensive studies on the effects of metallic halides on the reactions of Grignard reagents with organo halides, Kharasch reported the first examples of catalytic cross-coupling reactions (Scheme 3).[5] For example, vinyl bromide was successfully coupled with phenylmagnesium bromide (Eq. 1), naphthylmagnesium bromide (Eq. 2) and benzylmagnesium bromide (Eq. 3) furnishing cross-coupled products in useful yields. Similarly, an alkynyl bromide was successfully cross-coupled with methylmagnesium bromide in high yield (Eq. 4). However, these early protocols suffered from a lack of generality and the formation of substantial quantities of by-products, including polymeric hydrocarbons and homo-coupling products.



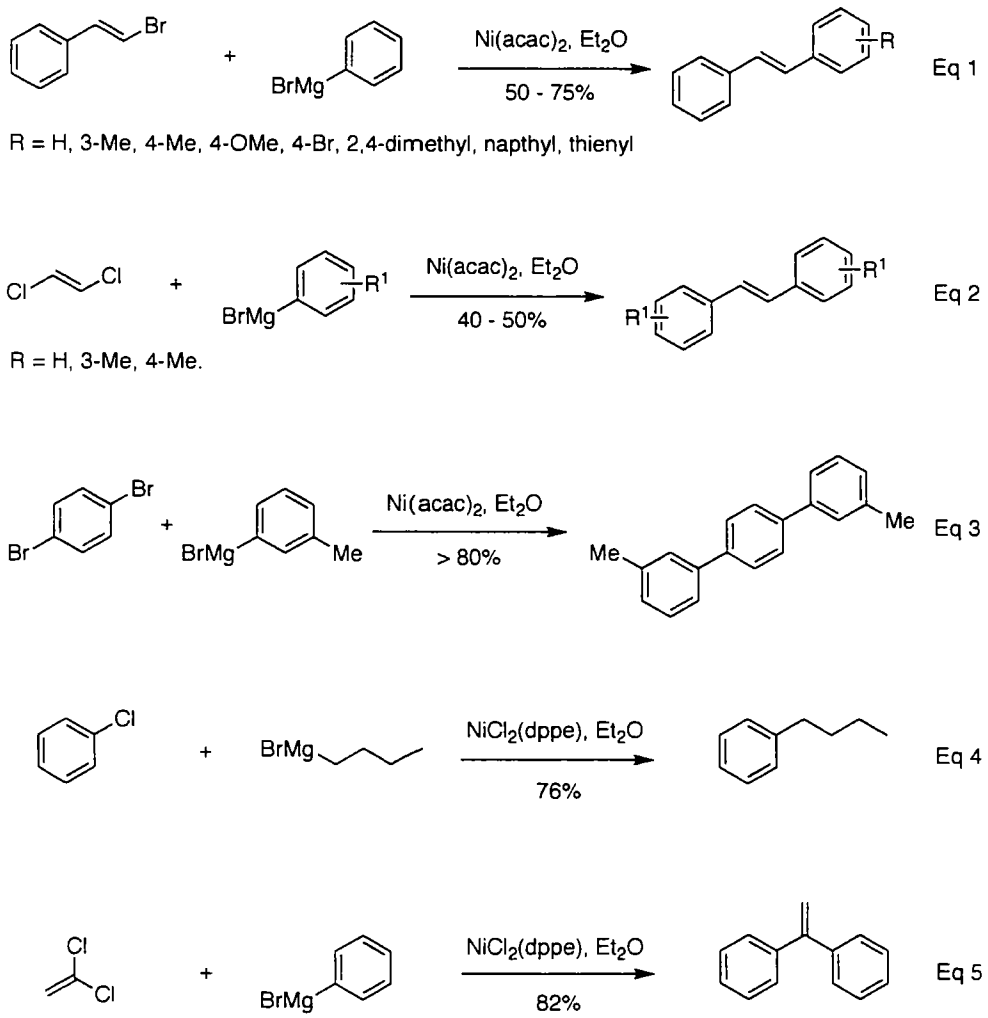
Scheme 3

Kharasch's exhaustive investigations paved the way for research groups to more fully explore the chemistry of the various other group VIII metals. Importantly, it was shown that platinum (Eq. 1),[6] palladium (Eq. 2)[7] and nickel (Eq. 3 and 4)[8] were all capable of undergoing oxidative addition reactions with vinyl and aryl halides furnishing stable organometallic species (Scheme 4).



Scheme 4

These early investigations were important stepping-stones on the path to modern cross-coupling chemistry. The genesis of this can be said to be the seminal reports by Corriu[9] and Kumada[10] who, in 1972, independently discovered what is now known as the Kumada-Corriu reaction. Corriu and co-workers reported the nickel-catalysed cross-couplings of a vinyl bromide (Eq. 1), a vinyl chloride (Eq. 2) and an aryl bromide (Eq. 3) with various substituted Grignard reagents affording stillbenes and terphenyls, respectively (Scheme 5). Similarly, Kumada and co-workers found that in the presence of catalytic amounts of $NiCl_2$(dppe), a range of aryl (Eq. 4) and vinyl chlorides (Eq. 5) could be selectively coupled with aryl and alkyl Grignard reagents furnishing coupled products in excellent yields (Scheme 5).



Scheme 5

With these results Corriu and Kumada had developed the first generally applicable, selective and efficient method for forming a new carbon-carbon bond between two unlike organic moieties. Their discovery sparked the development of a plethora of similar reactions and resulted in the evolution of what is now one of the most important and widely used methodologies in organic chemistry.

1.3 Modern Cross-Coupling Chemistry

The majority of cross-coupling reactions involve the formation of a new C-C bond between two sp or sp^2 hybridised carbon atoms. These usually take the form of

an electrophilic aryl or vinyl iodide, bromide or triflate and a nucleophilic organometallic reagent (although this may also be a terminal alkyne or an alkene). In addition, other electrophilic species have been reported and are discussed in more detail in section 1.3.4. Before focusing on the electrophilic species, a very brief introduction to the other important features of this chemistry is given. These are the general mechanism, the catalyst and ligand and the nucleophilic component.

1.3.1 General mechanism

Despite the huge range of reagents and conditions that can be utilised in cross-coupling reactions, the fundamental mechanism by which each reaction progresses is basically the same and involves four key steps as outlined in Figure 2. Integral to the reaction mechanism is the presence of a transition-metal'catalyst. Before any reaction can take place the catalyst must be present in its active form, an electron-rich, nucleophilic species. The first step of the mechanism involves the addition of the electrophilic partner, R-X, to the electron-rich catalyst **A**. The result is the formation of a stable, *trans*-σ-alkylmetal^{2+} complex, **B**, where the metal centre has been oxidised and one of the two organic groups, which are coupled to give the product, is now attached to the catalyst. Consequently, this step is commonly known as the oxidative addition step. The second step of the mechanism involves the transfer of an organic group (R^2) from the organometallic reagent, R^2-M, to the metal catalyst **B** in exchange for the leaving group (X) and results in a *trans*-σ-diorganometal^{2+} complex, **C**. This step, known as transmetallation, often requires the addition of an additive, e.g. a base, in the Suzuki or Hiyama reaction, and/or increased temperature to ensure its success. With both the organic groups now bound to the catalyst, the final two steps are rapid. The first of these is *trans-cis* isomerisation affording complex **D** where the two organic groups are correctly aligned to allow the final step, reductive elimination, which affords

the desired coupled product, R-R^2, with the new C-C bond. This regenerates the active catalyst species **A**, which is then free to begin the catalytic cycle again (Figure 2).

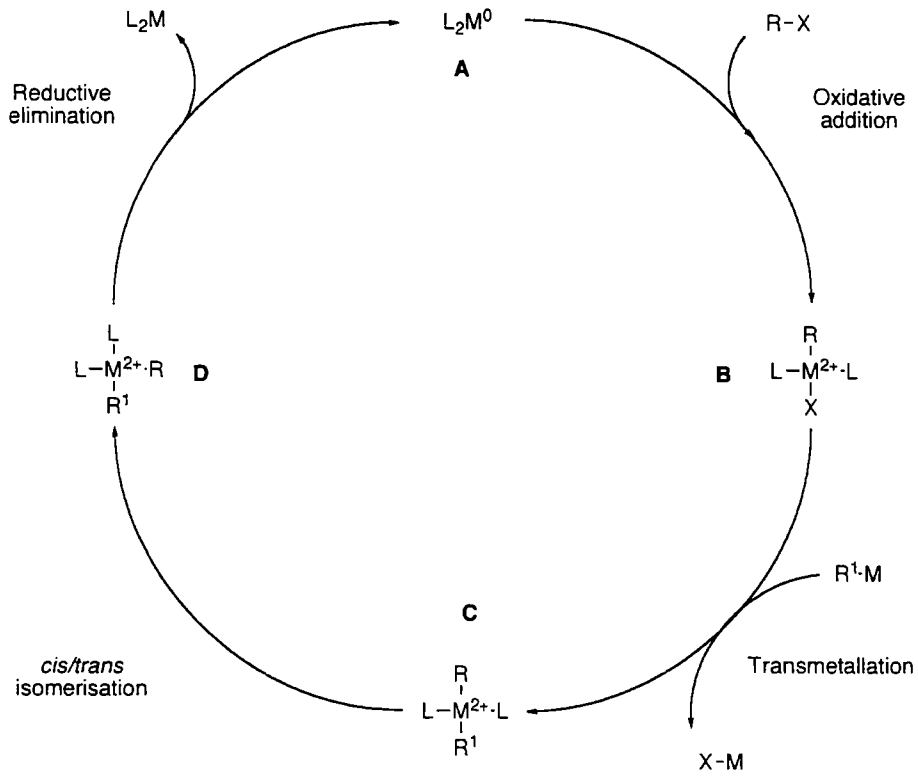


Figure 2: Generally accepted mechanism for cross-coupling reactions

1.3.2 Catalyst and ligand

The active transition-metal catalysts are a combination of metal centre and co-ordinating ligands.[11] The transition metal in question is most commonly palladium, but both nickel and iron are also utilised, whilst the most commonly used ligands are phosphines [12] and N-heterocyclic carbenes. [13] When carrying out cross-coupling reactions, slight changes in reaction conditions or the substrates can lead to a catalyst that is highly active in one protocol but being less or even completely inactive in a similar protocol. This lack of a universal catalyst system was and still is one of the major issues surrounding cross-coupling chemistry, the result being that there are a

daunting number of metal and ligand combinations which have been developed for cross-coupling reactions. Recently however, the development of catalytic systems capable of coupling less reactive electrophilic partners has gone someway to solving the universal catalyst problem. These highly active catalyst species are not only useful for coupling unreactive electrophiles but also find use for coupling more trivial partners as well. These systems rely on the use of specialised ligands such as the electron-rich and bulky trialkyl phosphines developed by Fu[14] and Buchwald,[15] e.g. tri-*tert*-butyl phosphine **E**, tricyclohexyl phosphine **F** and di-*tert*-butylbiphenyl phosphine **G**, as well as the use of N-heterocyclic carbenes,[13] e.g. IMES **H** (Figure 3). However, a detailed discussion of the chemistry of the catalyst and ligands remains outside the scope of this review.

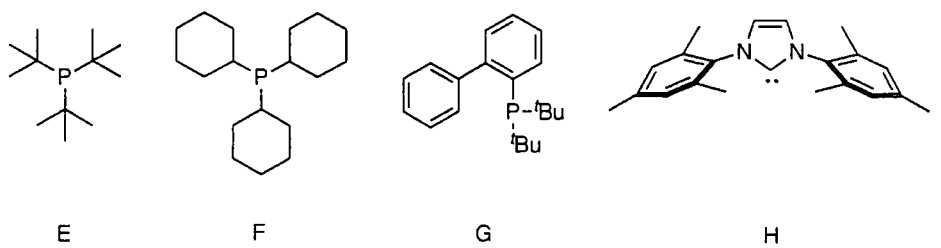


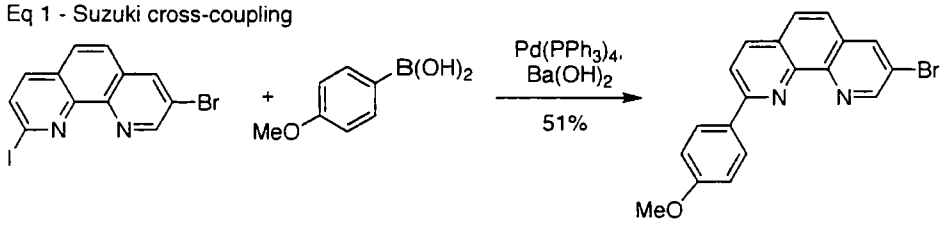
Figure 3

1.3.3 The Nucleophilic Component (Scheme 6)

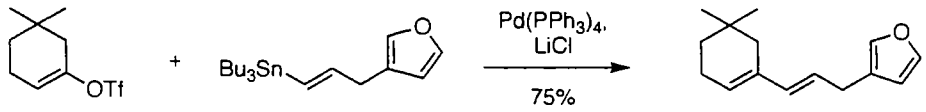
The second integral component of cross-coupling chemistry is the organometallic partner or nucleophilic component and since the development of the Corriu-Kumada reaction, which employs Grignard reagents, there has been enormous development in this field also. The two most widely employed substrates are the boronic acids (Eq. 1, Scheme 6) and organostannanes (Eq. 2) developed by Miyaura and Suzuki[16] and Stille,[17] respectively. In addition to these huge contributions there are numerous others which are no less important, e.g. the Corriu-Kumada reaction

(Scheme 5), the Negishi coupling of alanes, organozinc (Eq. 3) and zirconium reagents,[18] Hiyama coupling of organosilicon reagents (Eq. 4),[19] the Sonogashira coupling of terminal alkynes (Eq. 5)[20] and the Heck coupling of simple alkenes (Eq. 6).[21] Whilst a detailed discussion of the chemistry of the nucleophilic components would exceed the space available, examples of most of the common nucleophiles will arise during the discussion that follows.

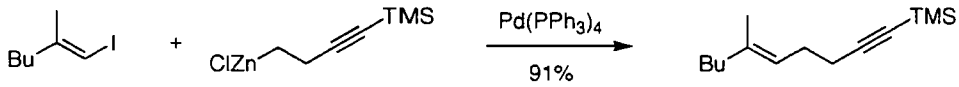
Eq 1 - Suzuki cross-coupling



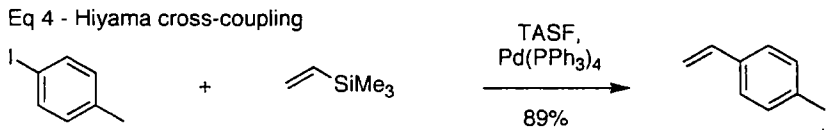
Eq 2 - Stille cross-coupling



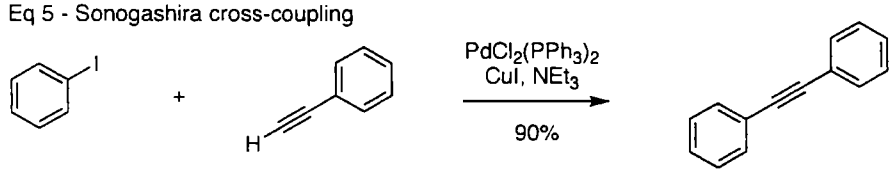
Eq 3 - Negishi cross-coupling



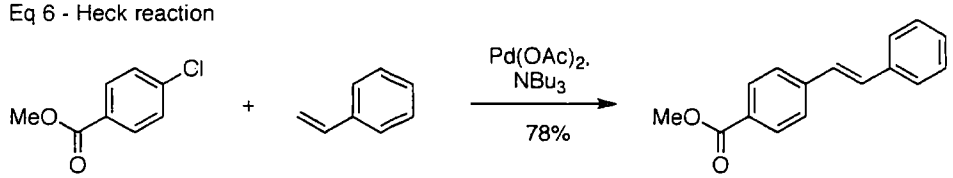
Eq 4 - Hiyama cross-coupling



Eq 5 - Sonogashira cross-coupling



Eq 6 - Heck reaction



Scheme 6

The third and final fundamental component of a cross-coupling reaction is the electrophile and this component is discussed in detail in the next section.

1.3.4 Electrophiles in cross-coupling chemistry

1.3.4.1 Introduction

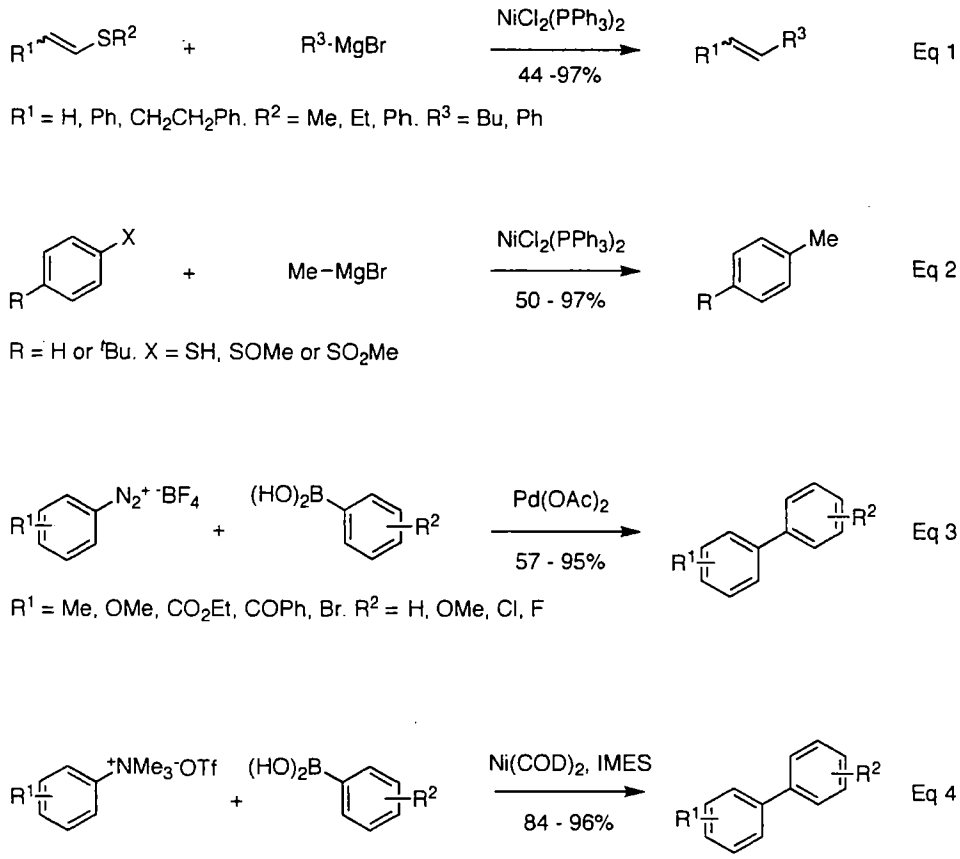
This section will review the role and development of electrophilic reagents in transition-metal-catalysed cross-coupling chemistry. A large number of electrophiles have been employed in cross-coupling reactions. These involve groups based on the halogens, oxygen, nitrogen, sulfur and selenium. Given the diversity of this chemistry a detailed review of all these groups would exceed the space available. Consequently, this review will focus largely on electrophilic species based on the halogens and activated esters. However, the following section highlights some of the less commonly utilised electrophiles that are based on the other leaving groups mentioned above.

1.3.4.2 Sulfur, nitrogen and activated carboxylic acids

Cross-coupling reactions employing sulfur-based electrophiles were first reported in 1979 by the groups of Wenkert[22] and Takei.[23] Takei and co-workers found that vinyl sulfides were efficiently coupled to Grignard reagents under nickel catalysis in moderate to good yields and with good stereoselectivity (Eq. 1, Scheme 7). Wenkert and co-workers discovered that in addition to alkenyl sulfides, aromatic sulfones, sulfoxides, sulfides and even thiols could be activated towards cross-coupling (Eq. 2, Scheme 7). In addition to these early examples, several other sulfur moieties have been reported as electrophilic partners in cross-coupling strategies including sulfoxamines,[24] sulfonium salts,[25] thiolesters,[26] sulfonyl chlorides[27, 28] and cyclic thioamides.[29]

Cross-coupling reactions employing nitrogen-based electrophiles were also developed at an early stage. In 1977, Kikukawa and co-workers reported the palladium-

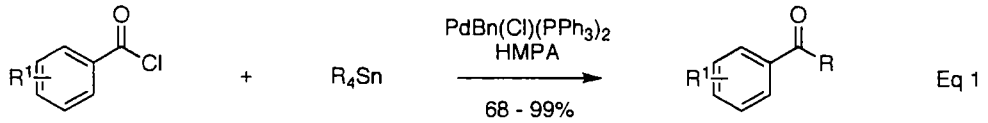
catalysed coupling of aryldiazonium salts with alkenes,[30] and subsequently carbon monoxide [31] and organotin compounds. [32] More recently, Genet and co-workers demonstrated that the same compounds could be coupled under Suzuki reaction conditions (Eq. 3, Scheme 7).[33] Aryl trialkylammonium salts have also been shown to be efficient partners for cross-coupling strategies, first by Wenkert and co-workers in 1988[34] and later by MacMillan and Blakey who reported the Suzuki cross-coupling of trimethylammonium triflates (Eq. 4, Scheme 7).[35] Further examples of diazonium salts have been reported by Beller[36] and Sengupta,[37] whilst Buszek recently reported the Suzuki cross-coupling of vinyl pyridinium and vinyl trialkylammonium salts.[38]



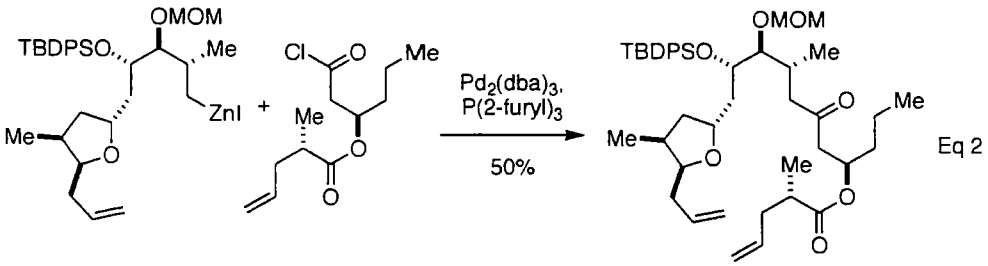
Scheme 7

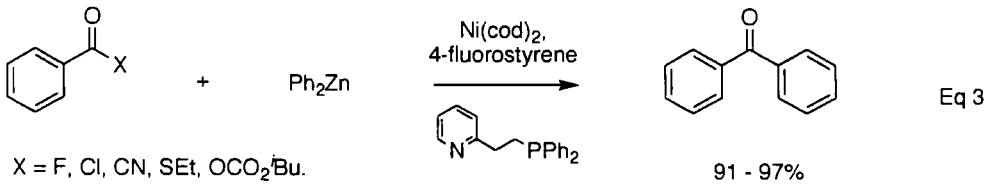
Acyl chlorides are also suitable electrophilic partners for cross-coupling reactions and they provide a mild and efficient method for accessing unsymmetrical

ketones. Oxidative addition of acyl chlorides to transition metals is facile due to the longer and weaker C-X bond when compared to aryl and vinyl chlorides.[39] The first cross-coupling reaction of an acyl chloride was reported in 1978 by Stille *et al.*[40] who described the palladium-catalysed coupling of a range of acyl chlorides with different tetraorganotin reagents (Eq. 1, Scheme 8). In addition to the Stille reaction, acyl chlorides have also found use in various other cross-coupling strategies including Suzuki[16] and Negishi couplings.[41] Moreover, cross-couplings of acyl chlorides have also been utilised in total synthesis projects, e.g. a key intermediate in the total synthesis of amphidinolide T1 was constructed by the cross-coupling of an acyl chloride (Eq. 2, Scheme 8).[42] In addition to acyl chlorides, Rovis and Zhang have demonstrated that other carboxylic acid derivatives can also be utilised. For example, acyl fluorides, anhydrides, cyanides and thioesters were coupled with diphenyl zinc in excellent yields (91–97%) using a Ni/pyphos complex (Eq. 3, Scheme 8).[43]



R = Me, *n*-Bu, Bn. R^1 = H, 4-MeO, -CN, $-NO_2$, -Cl, -Br, -CHO, 2-NO_2, $-CO_2Me$





X = F, Cl, CN, SEt, $OCO_2{}^tBu$.

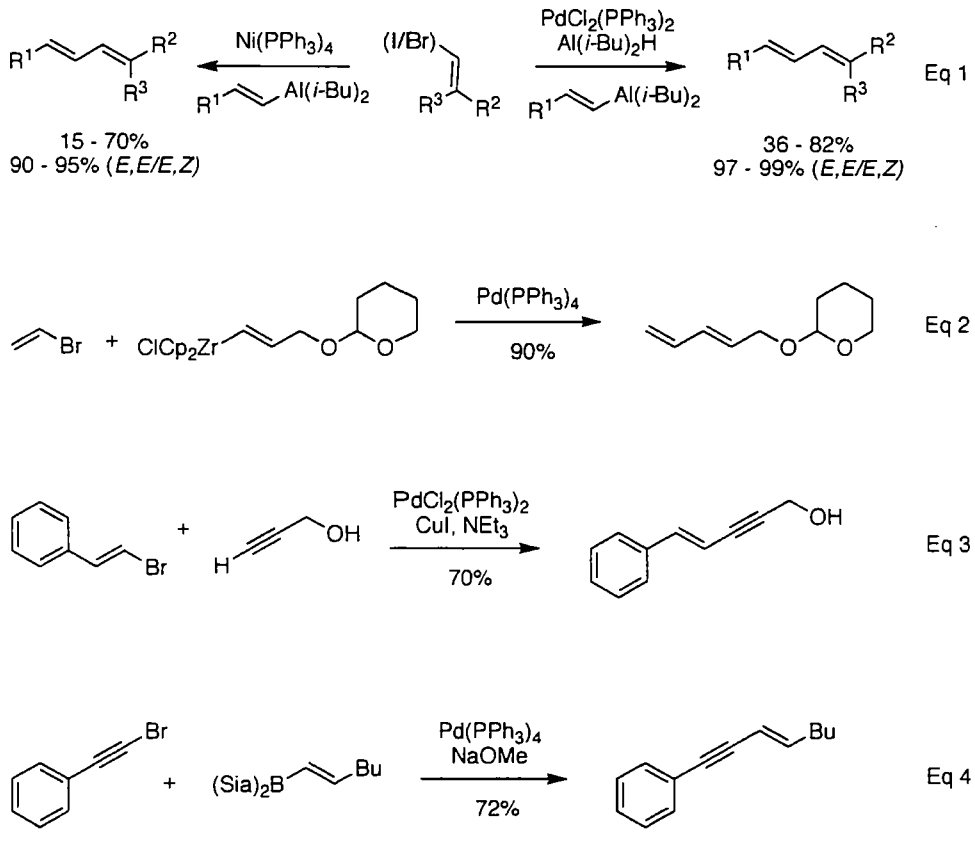
Scheme 8

1.3.4.3 Halides

1.3.4.3.1 sp^2-Hybridised bromides and iodides

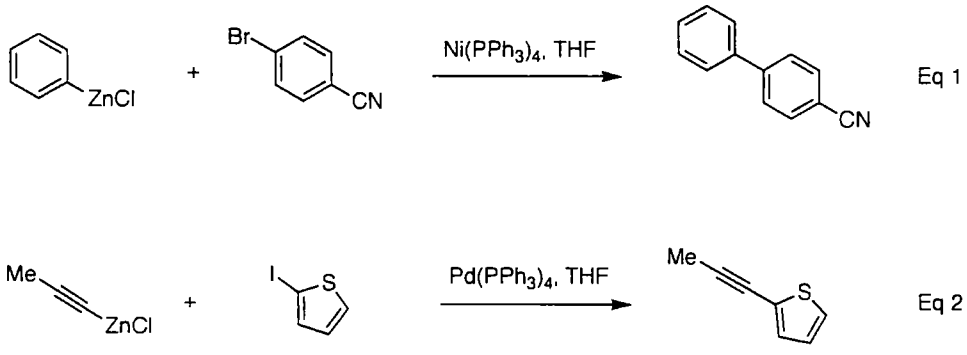
As a consequence of their high affinity towards oxidative addition to transition metal catalysts, the use of aryl and vinyl bromides and iodides in cross-coupling strategies has been commonplace since the earliest coupling strategies were developed. Moreover, they are the most widely employed of all the electrophiles and examples of their use can be found throughout the literature. The majority of the early developments in cross-coupling chemistry utilised these electrophiles, e.g. in 1976, Negishi and Baba described the first general methodology for the stereoselective synthesis of dienes. A range of alkenylalanes were coupled with both vinyl iodides and bromides affording dienes in a highly stereoselective fashion using both Ni and Pd

catalysis (Eq. 1, Scheme 9).[44] The functional group tolerance of the previous protocol was subsequently improved by the use of vinyl zirconates in place of alanes, again vinyl bromides and iodides were utilised including vinyl bromide (Eq. 2, Scheme 9).[45] Vinyl bromides were also among the first reported electrophiles to undergo Sonogashira cross-coupling reactions with alkynes affording enynes (Eq. 3, Scheme 9).[20] In addition to vinyl bromides and iodides, alkynyl bromides and iodides are also useful electrophiles in cross-coupling strategies. This was demonstrated by Suzuki *et al.* in 1979, who reported the coupling of both vinyl and alkynyl bromides and iodides with vinylboranes under Pd catalysis.[46] For example, the reaction of phenyl alkynyl bromide and a vinylborane proceeded without complication affording the desired enyne in high yield (Eq. 4, Scheme 9).



Scheme 9

Aryl bromides and iodides are no less ubiquitous than their vinyl counterparts in cross-coupling chemistry and several early cross-coupling protocols were developed using these substrates. Negishi reported the first cross-couplings of organozinc reagents, another important nucleophilic component, using aryl bromides and iodides, e.g. *p*-cyanobromobenzene was coupled with phenylzinc chloride in excellent yield under nickel catalysis (Eq. 1, Scheme 10).[47] Subsequently, Negishi demonstrated that aryl bromides and iodides could be efficiently coupled with alkynylzinc reagents affording alkynyl-aryl products, e.g. the coupling of 2-iodothiophene with an alkynylzinc reagent furnished the desired product in 82% yield (Eq. 2, Scheme 10). Further examples of aryl bromides and iodides in cross-coupling strategies have already been discussed, e.g. in the Kumada-Corriu reaction (Eq. 3, Scheme 5) and in the Hiyama and Sonogashira reactions (Eq. 4 and 5, respectively, Scheme 6).

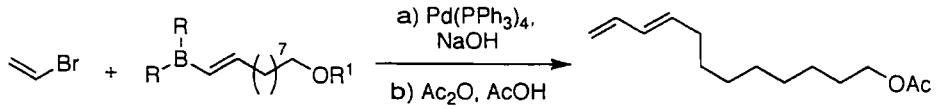


Scheme 10

The ease with which both sp^2-bromides and iodides undergo oxidative addition and subsequent cross-coupling reactions means they are very often the electrophile of choice for applications in total synthesis. One of the very first applications of a cross-coupling reaction in a total synthesis project was reported by Rossi and co-workers in 1981.[48] In this, vinyl bromide and a vinylborane were coupled together in a highly stereoselective manner. Subsequent removal of the THP group and acetylation furnished the desired insect sex pheromone in good overall yield (54%, Eq. 1, Scheme

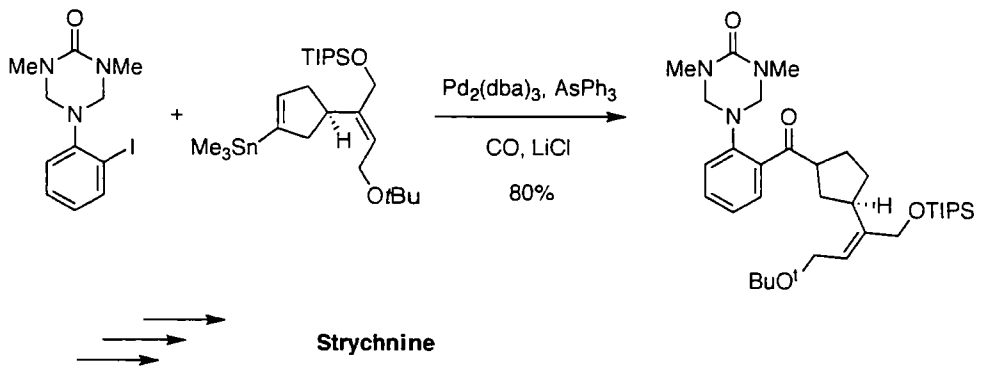
11). In 1993, Overman *et al.* published the first enantioselective synthesis of strychnine,[49] a naturally occurring alkaloid with a complex polycyclic structure. The synthesis was made possible, in part, by a carbonylative Stille cross-coupling of an aryl iodide furnishing the required ketone, further elaboration led to strychnine (Eq. 2, Scheme 11).

Eq 1 - Suzuki cross-coupling of a vinyl bromide in total synthesis of insect sex pheromones



54%

Eq 2 - Carbonylative Stille cross-coupling of an aryl iodide in the total synthesis of strychine

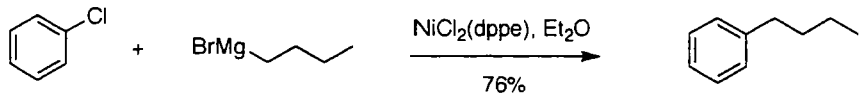


Scheme 11

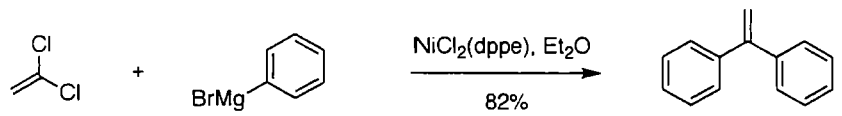
1.3.4.3.2 sp^2-Hybridised chlorides

The lower cost and increased availability of chlorides when compared to bromides and iodides make the chlorides the more appealing of the halide partners for use in cross-coupling chemistry. However, in contrast to iodides and bromides, chlorides display a considerable lack of reactivity towards oxidative addition. The difference in reactivity of these species is in the order Ar-I > Ar-Br >> Ar-Cl and can be attributed to the strength of the C-X bond which increases in the order I < Br < Cl < F,[50] to the extent that the coupling of aryl/vinyl fluorides is presently unknown. It is known

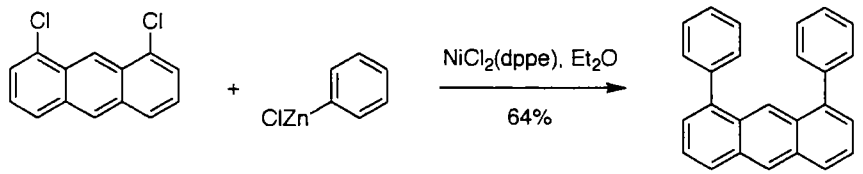
that reactivity towards oxidative addition of group VIII metal complexes bearing similar or identical ligands decreases in the order nickel > palladium > platinum.[50, 51, 52] Whilst for the more reactive electrophiles (Br, I) this difference is not noticeable (both Pd and Ni catalysts can be employed without problem), in reactions using sp^2-hybridised chlorides the difference in reactivity becomes apparent. This is evident from the time period (fourteen years) between the first nickel-catalysed[9,10] and the first palladium-catalysed[53] cross-coupling reactions involving sp^2-chlorides. The first examples of the Kumada-Corriu reaction reported in 1972 that werre discussed earlier (Scheme 5) and are shown again (Eq. 1 and 2, Scheme 12) involved the nickel-catalysed cross-coupling of both aryl and vinyl chlorides with Grignard reagents.[9, 10] In addition to Grignard reagents, early examples of cross-coupling reactions of sp^2-chlorides with organozinc reagents were also reported. For example, in 1980 House *et al.* reported the Ni-catalysed cross-coupling of a *bis*-(arylchloride) with phenylzinc chloride furnishing the desired cross-coupled product in 64% yield (Eq. 3, Scheme 12).[54] Despite these early examples of Ni-catalysed Kumada-Corriu and Negishi reactions, it was several years before these methodologies received further development. Moreover, Ni-catalysed cross-coupling reactions of sp^2-chlorides with various other nucleophilic reagents were also slow to emerge. This is largely a result of the popularity of Pd as a catalyst in the intervening years. For example, Ni-mediated Suzuki couplings of sp^2-chlorides were not reported until the mid 1990s and were developed largely because of the lack of success with the analogous Pd protocols. This was illustrated by Miyaura who, in 1996, demonstrated that electron-deficient aryl chlorides efficiently coupled with phenylboronic acid under both Ni and Pd catalysis (Eq. 4, Scheme 12) whereas, under the same conditions electron-rich chlorides gave almost no conversion with Pd catalysis, but high yields with Ni (Eq. 5, Scheme 12).[55]



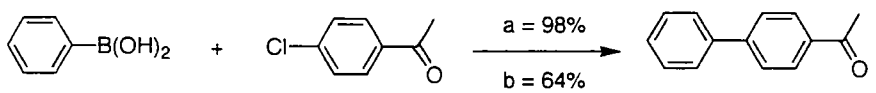
Eq 1



Eq 2

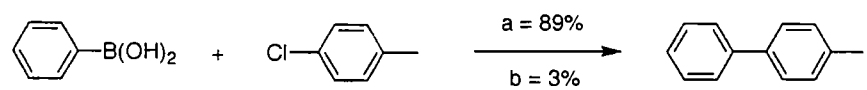


Eq 3



Eq 4

a) $NiCl_2(dppf)$, K_3PO_4, dioxane, 80 °C, 16 h.
b) $Pd(PPh_3)_4$, DME/H_2O, 80 °C, 16 h.



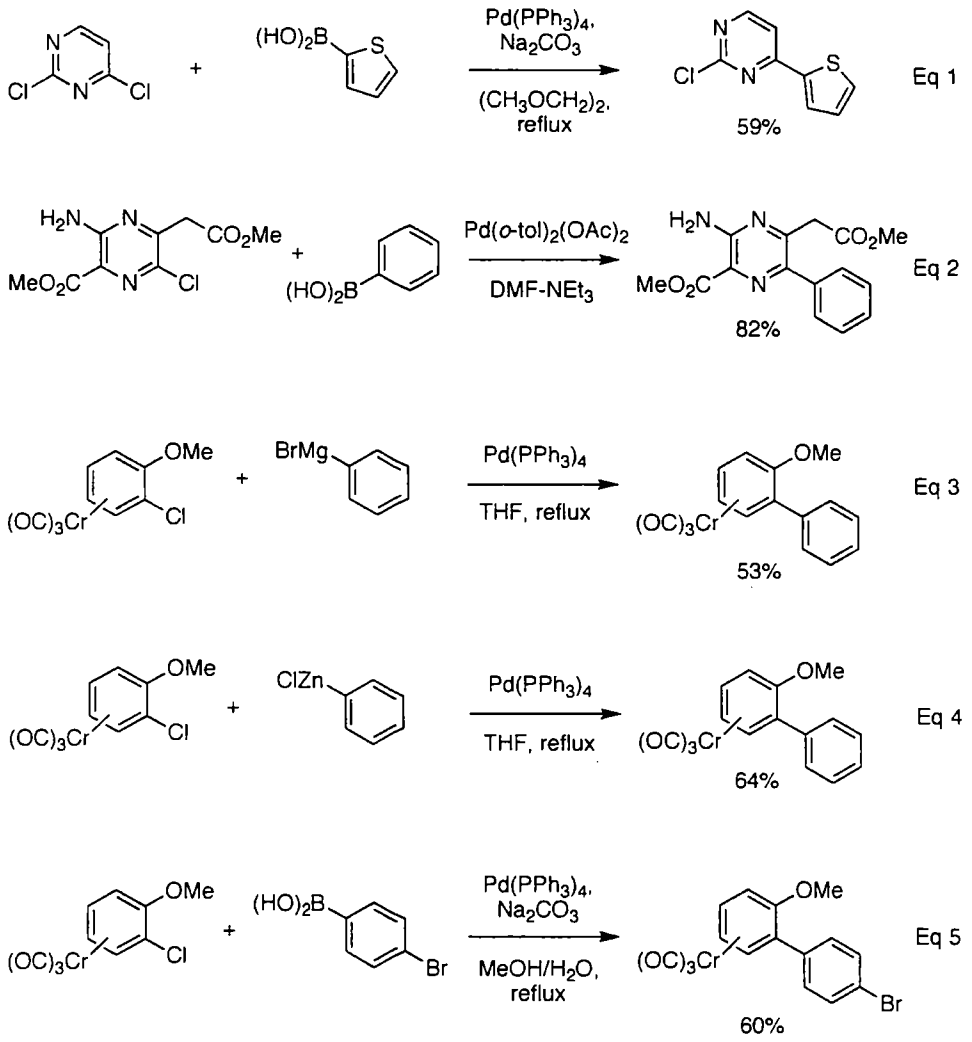
Eq 5

a) $NiCl_2(dppf)$, K_3PO_4, dioxane, 80 °C, 16 h.
b) $Pd(PPh_3)_4$, DME/H_2O, 80 °C, 16 h.

Scheme 12

In 1986, ten years before Miyaura's example, Gronowitz and co-workers described the first palladium-catalysed cross-coupling of an sp^2-hybridised chloride.[53] In this $Pd(PPh_3)_4$ was used to couple 2,4-dichloropyrimidine with thiopheneboronic acid affording the desired product in good yield (59%, Eq. 1, Scheme 13). Two years later, in 1988, Thompson *et al.* described the cross-coupling of a similar heteroaromatic chloride;[56] again a Suzuki protocol was used and the desired product was isolated in high yield (82%, Eq. 2, Scheme 13). Other organometallic reagents have also been employed, e.g. in 1994 Uemura and co-workers reported Pd-catalysed cross-coupling reactions of chromium-complexed aryl chlorides with Grignard reagents,[57] organozinc

compounds and boronic acids in good yields (Eq. 3, 4 and 5, respectively, Scheme 13). As with Miyaura's example described above (Eq. 4, Scheme 12), these early examples were not generally useful as they were limited to the use of highly electron deficient aryl chlorides only.

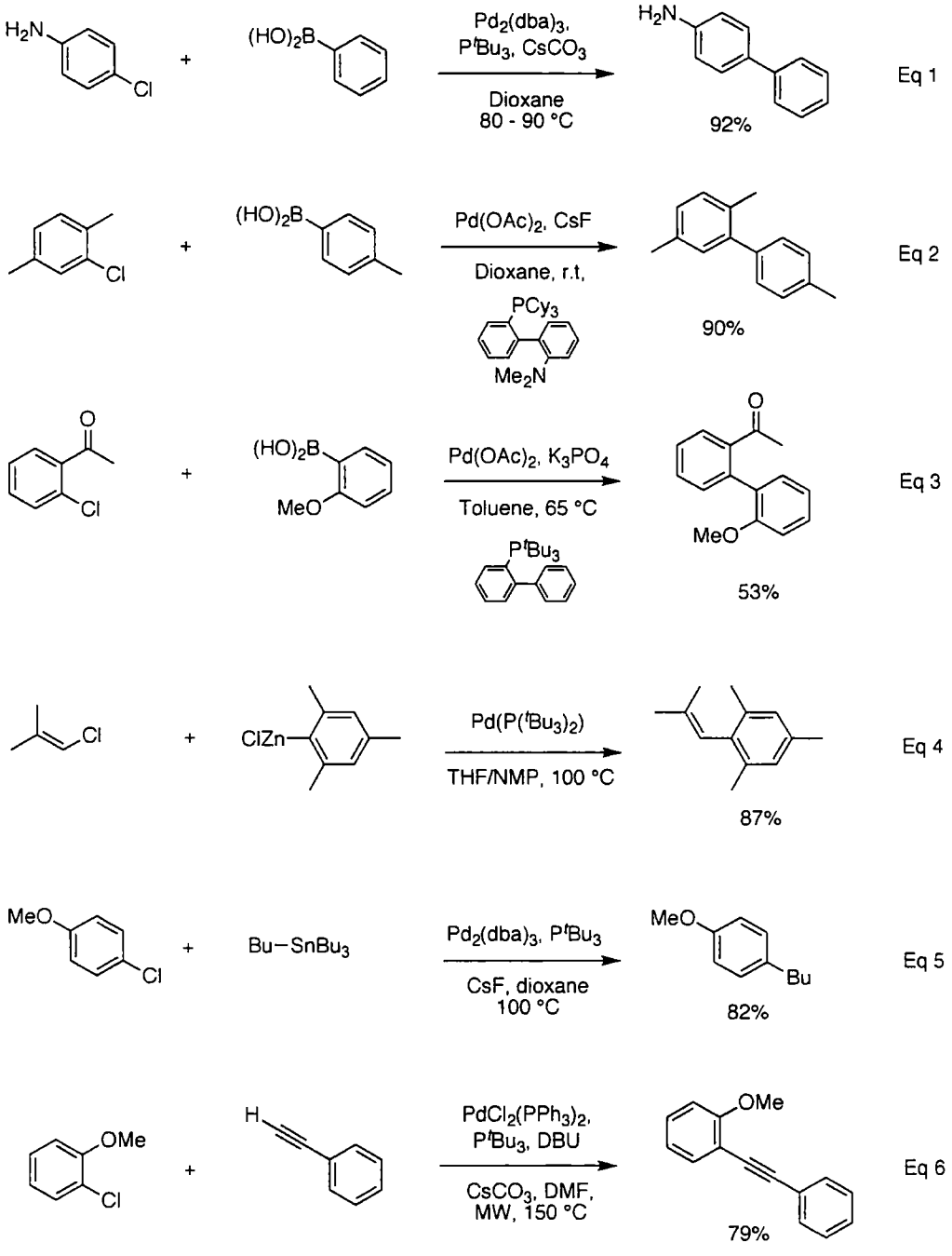


Scheme 13

It was not until the late 1990s that the problems surrounding palladium-catalysed cross-coupling reactions of sp^2-chlorides, specifically the lack of reactivity and therefore generality were solved. The solution to the problem lay in the development of new, highly-active catalyst systems. It had been shown by Huser *et*

al.[58] and Grushin *et al.*[59] that oxidative addition of palladium complexes to aromatic chlorides was far easier if the phosphine ligand employed was an electron-rich trialkyl phosphine rather than a triaryl phosphine. The electron-rich phosphine ligands increase the nucleophilicity of the metal centre thereby making it more reactive as shown by Figdore *et al.*[51] Additionally, bulky phosphine ligands can be advantageous as they create large cone angles leading to more reactive coordinatively unsaturated, monoligated metal centres.[12] By exploiting these observations Buchwald[15] and Fu[14] independently developed the first generally applicable palladium-catalysed cross-coupling strategies for sp^2-chloride substrates. Hence, in 1998, Fu and co-workers reported the Suzuki cross-coupling reactions of a range of electron-rich and electron-poor aryl chlorides employing either a Pd/P^{t}Bu$_3$ or Pd/PCy$_3$ complex. An excellent example is the coupling of 4-chloroaniline with phenylboronic acid in the presence of a Pd/^{t}Bu$_3$P complex that furnished the desired biaryl in 92% yield (Eq. 1, Scheme 14). In the same year, Buchwald and co-workers developed a shelf-stable electron-rich aminophosphine ligand that in combination with Pd(OAc)$_2$, was capable of cross-coupling a range of aryl chlorides and bromides with boronic acids in high yields. Remarkably, many of these transformations were carried out at room temperature. For example, the sterically-hindered and electron-rich 2,5-dimethylchlorobenzene reacted with tolylboronic acid affording the coupled product in excellent yield (90%) after 20 h at room temperature (Eq. 2, Scheme 14). The following year Buchwald and co-workers reported a similar, but improved phosphine ligand, 2-(di-*tert*-butylphosphine)biphenyl, capable of affecting mild and efficient Suzuki cross-coupling reactions of electron-rich and sterically-hindered chlorides (Eq. 3, Scheme 14).[60] Fu and co-workers further demonstrated the scope and generality of the Pd/P^{t}Bu$_3$ catalyst, using it to successfully couple a range of vinyl and aryl chlorides employing Negishi[61] and Stille[62] protocols (Eq. 4 and 5, respectively, Scheme 14). Utilising the same ligand, Liu and co-workers

recently reported a general, Cu-free, Pd-catalysed Sonogashira cross-coupling protocol for aryl chlorides.[63] For example, electron-deficient *m*-chloroanisole was coupled with phenylacetylene in good yield (Eq. 6, Scheme 14).

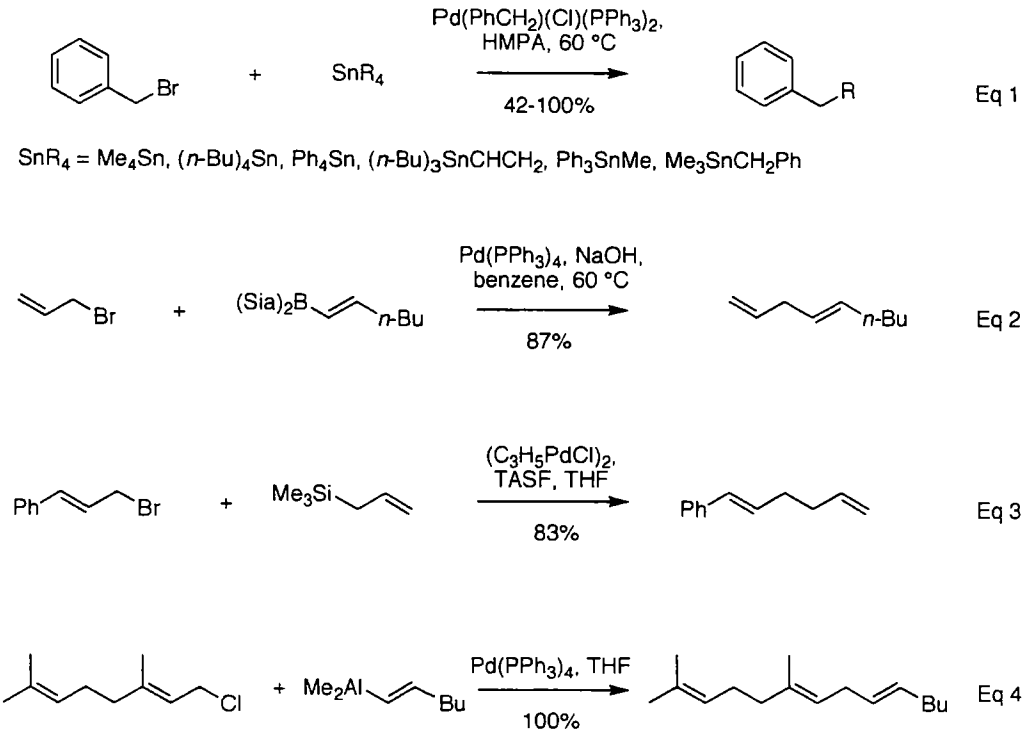


Scheme 14

1.3.4.3.3 sp^3-Hybridised Halides (Alkyl Electrophiles)

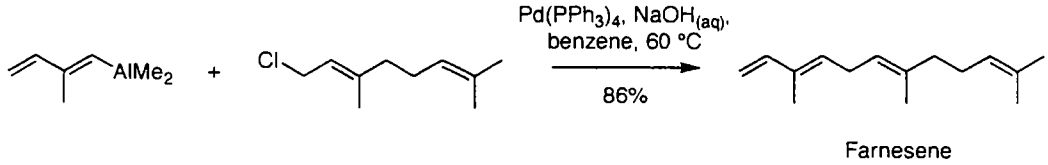
The use of alkyl electrophiles in cross-coupling reactions is severely limited for two principal reasons; a) the low reactivity of alkyl halides compared to aryl and vinyl halides and b) facile β-hydride elimination from the catalyst following oxidative addition of these electrophiles. However, allyl and benzyl halides are exceptions as they are both reactive and not susceptible to β-hydride elimination. Consequently, they have been extensively used in cross-coupling chemistry. In fact, it was shown by Milstein and Stille that allylic and benzylic halides were more reactive than their analogous vinyl and aryl counterparts towards oxidative addition, with the order of reactivity having been shown to be $PhCH_2Br$ > $PhCH_2Cl$ > Ar-Br.[64] This observation is possibly due to enhancement of the rate of oxidative addition through stabilisation of the transition state *via* a π-allyl type interaction. However, the generally high regioselectivity of these cross-coupling reactions conflicts with a π-allyl nucleophilic substitution mechanism. The coupling of allyl and benzyl groups with sp^2-hybridised organometallic reagents gives access to 1,4-unsaturated compounds. The stereochemistry of the olefin is, as always, retained, whilst the configuration at the benzylic position is inverted as oxidative addition occurs in a similar fashion to an S_N2 mechanism and subsequent reductive elimination with retention of stereochemistry.[65] Transition-metal-catalysed cross-coupling of benzyl bromide was first illustrated by Milstein and Stille in 1979 during their development of the Stille cross-coupling reaction.[64] They demonstrated that treatment of benzyl bromide with a range of organostannanes in the presence of a palladium catalyst afforded coupled products in high yields (Eq. 1, Scheme 15). During these investigations both benzyl chloride and bromobenzene were found to be unreactive. The following year Suzuki and co-workers described the application of allyl and benzyl bromides in the synthesis of 1,4-dienes and allylbenzenes, respectively.[66] A range of (*E*)-alkenyldisiamylboranes, obtained *via* the hydroboration of alkynes, were coupled

with a variety of allyl and benzyl bromides. For example, palladium-catalysed coupling of allyl bromide afforded an 87% yield of the desired 1,4-diene product (Eq. 2, Scheme 15). Further examples of cross-coupling reactions of allylic and benzylic halide electrophiles were reported by Hiyama[67] and Negishi[68] (Eq. 3 and 4, respectively, Scheme 15).



Scheme 15

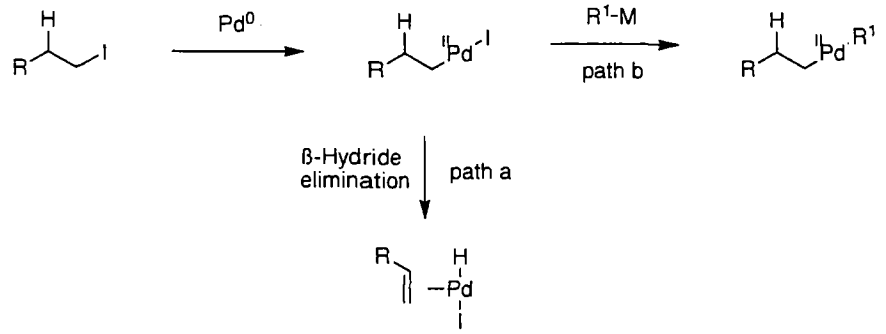
The exclusive regio- and stereo-selectivity of these reactions was exploited by Negishi and co-workers in a straightforward synthesis of the natural product α-Farnesene.[69] A vinylalanane was accessed *via* hydroalumination of the requisite alkyne and subsequently coupled with an allylic chloride under palladium catalysis affording the desired natural product in high yield (86%, Scheme 16).



Farnesene

Scheme 16

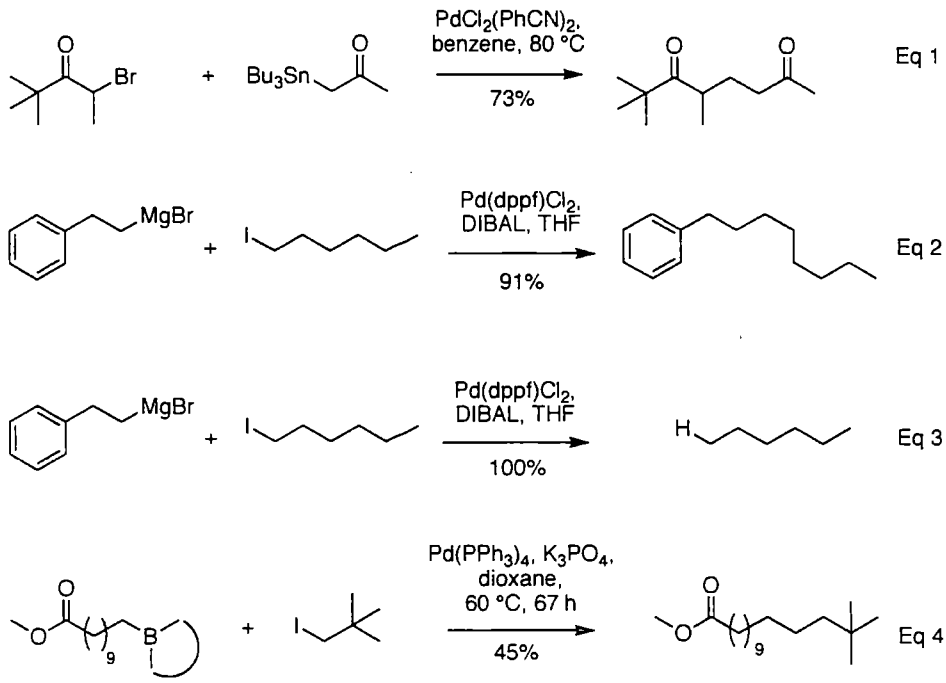
It was long considered that sp^3-alkyl halides and pseudohalides bearing β-hydrogen atoms were not suitable substrates for cross-coupling reactions. The two main reasons for this are a) their lack of reactivity towards and consequently, slow rate of oxidative addition to transition-metal catalysts[50, 51] and b) facile β-hydrogen elimination from the catalyst following oxidative addition. Thus, following oxidative addition of an alkyl halide to the active catalyst species (Pd has been used to illustrate, Scheme 17), the resulting σ-alkylpalladium complex undergoes undesired β-hydride elimination (path a) which is kinetically much more favourable than the desired transmetallation process (path b) with which it competes (Scheme 17). Moreover, alkyl substrates lacking β-hydrogen atoms, e.g. tertiary centres, have also found limited use because of the general lack of reactivity of these substrates towards oxidative addition. Consequently, the use of alkyl electrophiles in cross-coupling reactions remains limited and, although some groups are now making progress in this area, the choice of the electrophile is usually limited to those discussed previously. It is worth noting however, that in contrast to the electrophile, the use of organometallic reagents possessing β-hydrogens is better tolerated as the rate of the desired *cis/trans* isomerisation/reductive elimination is much faster than that of β-hydride elimination.



Scheme 17

However, in 1984 Migita and co-workers reported that treating a mixture of an α-halo ketone and a tributyltin enolate with catalytic quantities of $PdCl_2(PhCN)_2$ in refluxing benzene afforded cross-coupled products in moderate to good yields.[70] Both primary and secondary bromides could be employed, but not tertiary, e.g. employing α-bromomethylpinacolone led to 73% yield of coupled product (Eq. 1, Scheme 18). In 1986, Castle and Widdowson described the Pd-catalysed cross-couplings of various alkyl iodides with Grignard reagents, e.g. iodohexane and phenethylmagnesium bromide afforded the desired product in 91% yield (Eq. 1, Scheme 18).[71] However, these results were contested in a subsequent paper by Yuan and Scott who observed only reduction and elimination products using the same substrates and conditions (Eq. 2, Scheme 18).[72] In 1992, Suzuki and co-workers demonstrated that various 9-BBN derivatives could be successfully coupled with a range of alkyl iodides in moderate yields.[73] For example, the coupling of neopentyl iodide, a particularly unreactive and hindered substrate, with a 9-BBN derivative afforded the desired product in 45% yield (Eq. 4, Scheme 18). No examples of alkyl bromides or chlorides were included and the reaction was found to be particularly sensitive to the identity of the organometallic reagent. The only organometallics that afforded any desired products were 9-BBN derivatives. Zn, Mg, Al, Sn, Zr, Hg and even alternative boronates proved unsuccessful.

In addition to the iodide shown in Eq. 4, which lacks a β-hydrogen, several examples in which β-hydrogens were present were also reported.

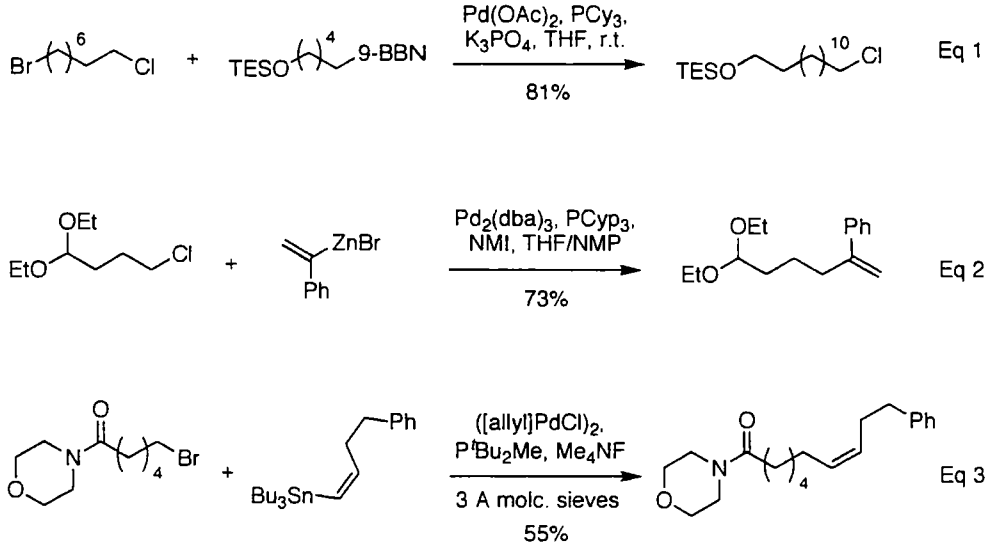


Scheme 18

These early developments demonstrated that, contrary to earlier opinion, couplings of unactivated, β-hydrogen-containing alkyl halides was possible and provided the inspiration for the development of milder and more general protocols.

The lack of reactivity that affects sp^2-hybridised chlorides (discussed in the previous section) also affects alkyl halide electrophiles. Fu and co-workers circumvented this problem for sp^2-chlorides by employing bulky, electron-rich phosphine ligands, e.g. P^tBu_3, to give highly-active catalyst systems (Scheme 14). Subsequently, the same researchers postulated that this precedent might also be used for the coupling of unactivated alkyl halide electrophiles and, in 2001 reported $Pd(OAc)_2/PCy_3$ as an effective catalyst system for Suzuki cross-coupling reactions of a range of primary alkyl bromides with alkyl and vinylboranes.[74] This was the first

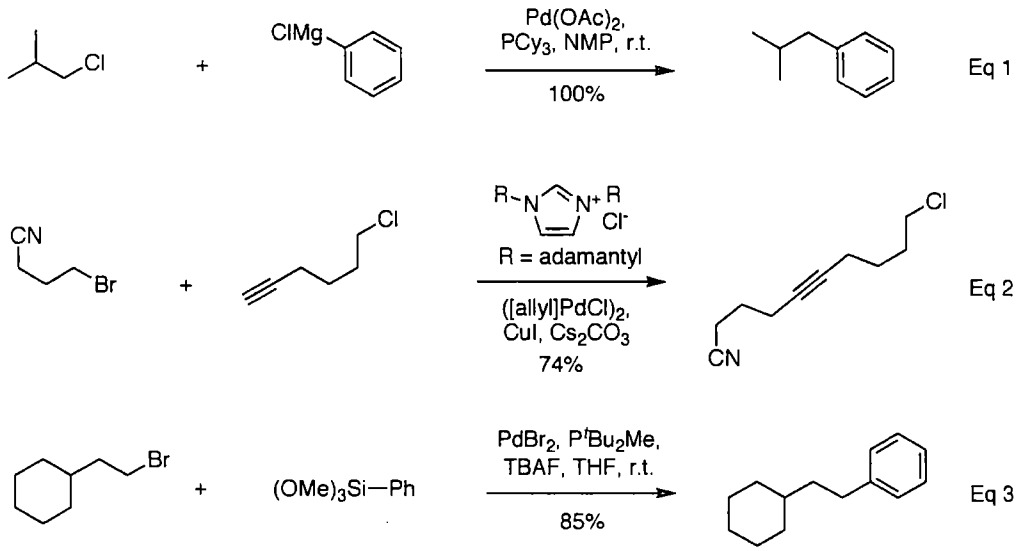
example of a cross-coupling reaction of an unactivated alkyl bromide, all previous examples having been iodides. The reactions were carried out under mild conditions (room temperature) and were highly tolerant of other functionalities in either partner. Unsurprisingly, bromides were shown to react in preference to chlorides (Eq. 1, Scheme 20). Several more mild and general cross-coupling protocols employing both Ni and Pd and capable of coupling unactivated primary alkyl halides were subsequently developed. The groups of Fu (alkyl chlorides)[75] and Arentsen[76] described further examples of Suzuki protocols. Several examples of Negishi cross-couplings of primary alkyl halides have been developed, much of this work was carried out by Knochel and co-workers using Ni-based catalysts with additives such as styrene.[77] A more general protocol was reported in 2003 by Fu and co-workers [78] who described a $Pd_2(dba)_3/PCyp_3$ combination as a useful catalyst for coupling primary alkyl iodides, bromides, chlorides (Eq. 2, Scheme 20) and tosylates with sp^2 and sp^3-organozinc reagents in moderate to good yields (48 – 97%). Following the early reports concerning Stille reactions, a more general protocol was described in 2003 by Fu and co-workers.[79] In this, a Pd/PCy_3 catalyst was employed. However, the addition of an additive, Me_4NI, and molecular sieves were crucial to the success of the reaction. A range of functionality was tolerated including esters, amides (Eq. 3, Scheme 20), ethers and nitriles. However, only vinylstannanes were shown to be effective nucleophilic partners, somewhat limiting the usefulness of the reaction.



Scheme 19

In addition to nucleophilic components based on B, Zn and Sn, those based on Mg, Si and alkynes (Cu) have also been shown to couple with primary, unactivated alkyl halides. Numerous groups have reported examples of Kumada-Corriu reactions of primary alkyl halides with Grignard reagents including Kambe,[80] Luh[81] and Beller.[82] The latter demonstrated that alkyl chlorides, e.g. 1-chloro-2-methylpropane (Eq. 1, Scheme 20), and aryl Grignard reagents furnished generally excellent yields of the desired coupled products under Pd catalysis (43 – 99%). The sole report concerning a Sonogashira cross-coupling reaction of an unactivated alkyl halide with a β sp^3-H was reported by Fu and co-workers.[83] A range of alkyl bromides and alkynes were shown to be suitable substrates, e.g. 4-bromobutanenitrile and 6-chlorohex-1-yne afforded the coupled product in 74% yield (Eq. 2, Scheme 20). Interestingly, considering the examples just discussed and those that follow, phosphine ligands were found to be ineffective for this reaction and success was only realised upon employing an N-heterocyclic carbene ligand. Finally, a mild (room temperature) protocol for coupling bromides and iodides with arylsilanes in Hiyama-type couplings was also developed by Fu and co-workers.[84] The active catalyst was a Pd/P^{t}Bu$_2$Me system and a fluoride

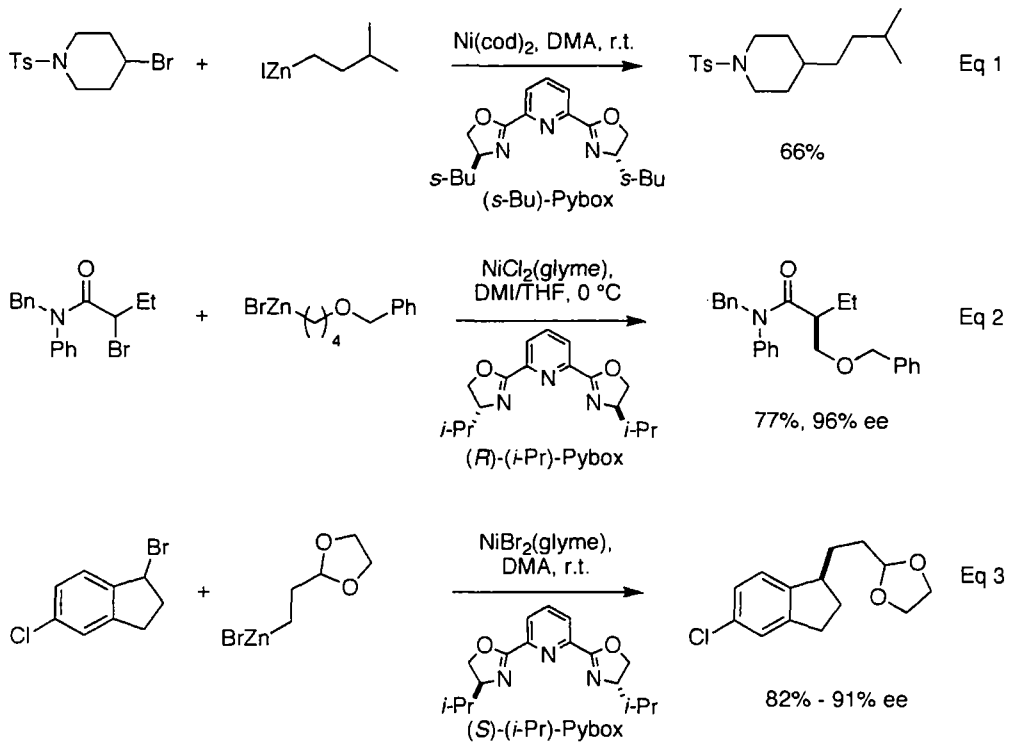
source was needed to activate the silyl reagent, e.g. under these conditions, (2-bromoethyl)cyclohexane and phenyltrimethoxysilane afforded the coupled product in 85% yield (Eq. 3, Scheme 20).



Scheme 20

In addition to the primary halides, noteworthy progress has been made concerning cross-couplings of unactivated secondary halides, a more difficult prospect simply by virtue of their being more hindered and therefore less reactive. In 2003 Fu *et al.* reported a generally useful Negishi cross-coupling protocol for unactivated secondary alkyl bromides and iodides.[85] Interestingly, neither phosphines nor N-heterocyclic carbenes proved useful as ligands for this reaction and success was achieved through an (*s*-Bu)-pybox/Ni(cod)$_2$ system. Good functional group tolerance was observed and a range of secondary bromides and iodides were coupled with various organozinc reagents in high yields; e.g. N-tosyl-4-bromopiperidine and *iso*-pentylzinc iodide furnished the desired product in 66% yield (Eq. 1, Scheme 21). The reaction proved very sensitive to slight changes in the conditions. For example, replacement of Ni(cod)$_2$ with alternative Ni salts resulted in lower efficiency whilst the

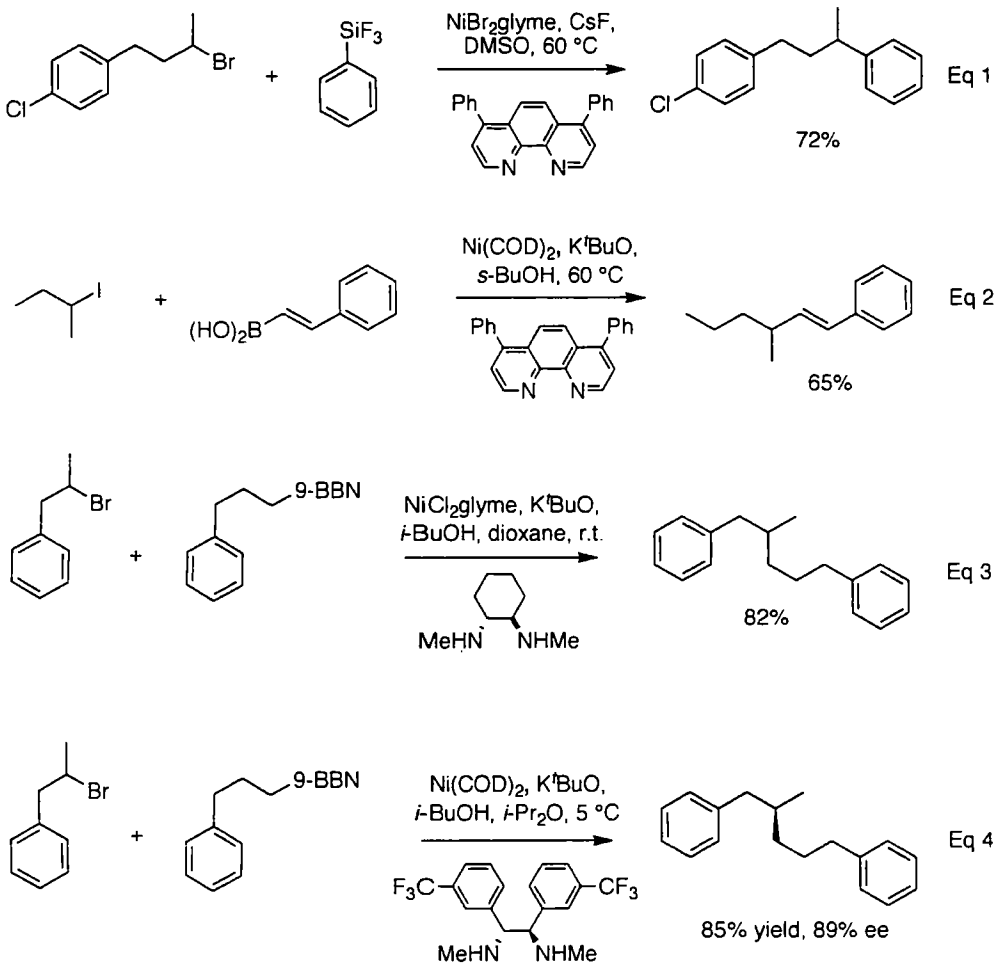
use of Pd salts resulted in no products whatsoever. The efficient cross-coupling of secondary alkyl halides was an important development in this area of chemistry, not only due to the inherent difficulties of this process, but also as it opened the door to the possibility of carrying out enantioselective coupling reactions. The first example of such a reaction was reported in 2005 by Fu and co-workers.[86] In this it was shown that a $NiCl_2$.glyme/(*R*)-(*i*-Pr)-pybox combination effected the cross-coupling of a range of α-bromoamides with alkylzinc halides in high yields and enantiomeric excesses (51 – 90% yield, 87 – 96% ee). Although only four α-bromoamides were used, a reasonable degree of functionality was tolerated in the nucleophilic component including an imide, acetal, nitrile and a benzyl ether (Eq. 2, Scheme 21). As with the previous reaction, slight changes in the reagents, in particular the Ni source and ligand, were not tolerated, e.g. coupling of an α-bromoamide using the conditions employed in Eq. 1 gave only 5% yield and 19% e.e.. At about the same time Fu *et al.* reported an enantioselective Negishi cross-coupling of benzylic halides.[87] This time the active catalyst was a $NiBr_2$.diglyme/(*S*)-(*i*-Pr)-pybox combination, both bromides and chlorides were shown to react and the best results were obtained with 1-haloindanes (91 – 99% e.e.). Acyclic halides resulted in poorer enantioselectivities (75% e.e.) and the reaction was shown to be selective for alkyl halides, which reacted preferentially to aryl chlorides (Eq. 3, Scheme 21).



Scheme 21

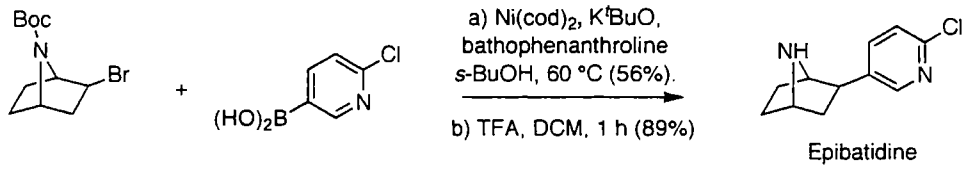
In addition to Negishi protocols, secondary alkyl halides have also been utilised in Hiyama and Suzuki-Miyaura cross-coupling protocols. The only example concerning Hiyama cross-couplings of secondary alkyl halides was reported by Fu and co-workers.[88] In this a range of bromides and iodides were successfully coupled with various trifluoroarylsilanes using a combination of $NiBr_2$.glyme and bathophenanthroline as the catalyst, e.g. phenyltrifluorosilane and a secondary bromide afforded 72% yield of the desired product (Eq. 1, Scheme 22). However, it was found that only arylsilanes were effective partners for the reaction, somewhat limiting its usefulness. The first Suzuki cross-couplings of secondary alkyl halides were also reported by Fu and co-workers.[89] A number of cyclic and acyclic bromides and iodides were coupled with unsaturated boronic acids in high yields (63 – 75%), e.g. 2-iodobutane afforded the desired product in 65% yield (Eq. 2, Scheme 22). Unfortunately, only unsaturated boronic acids were found to be useful, as attempts to

couple alkylboranes proved unsuccessful. However, in 2007, Fu and co-workers expanded the scope of the Suzuki reaction to include couplings of alkylboranes.[90] The active catalyst was again based on Ni. However, the systems described above for the Hiyama (Eq. 1) and Suzuki (Eq. 2) reactions proved inefficient. Following a reagent screen, it was found that certain diamine ligands in combination with $NiCl_2$.glyme effected the desired cross-coupling reaction. The most efficient ligand proved to be N,N'-dimethyl-1,2-cyclohexanediamine with which a range of alkyl 9-BBN derivatives were coupled with secondary bromides and iodides in high yields (64 – 94%), e.g. 2-bromo-3-phenylpropane afforded the coupled product in 82% yield (Eq. 3, Scheme 22). The enantioselective Negishi cross-coupling reactions detailed above (Eq. 2 and 3, Scheme 21) both relied on activated secondary halides. Recently Fu and co-workers reported the first examples of enantioselective cross-coupling reactions of unactivated secondary alkyl halides.[91] Although not mentioned in the original report, the Suzuki reaction between 2-bromo-3-phenylpropane and a 9-BBN derivative just discussed (Eq. 3) occurred with moderate enantioselectivity (53% e.e.). Consequently, an optimisation study led to the development of reaction conditions capable of carrying out high yielding (64 – 86%) and highly selective (70 – 94% e.e.) Suzuki couplings of secondary alkyl bromides. For example, 2-bromo-3-phenylpropane now furnished the desired product in 85% yield and 89% e.e. (Eq. 4, Scheme 22). However, the electrophilic species is limited to alkyl bromides bearing an aryl group in the β-position and a simple alkyl chain on the opposite side; positioning of the aryl group one carbon further down the chain results in almost complete loss of enantioselectivity.



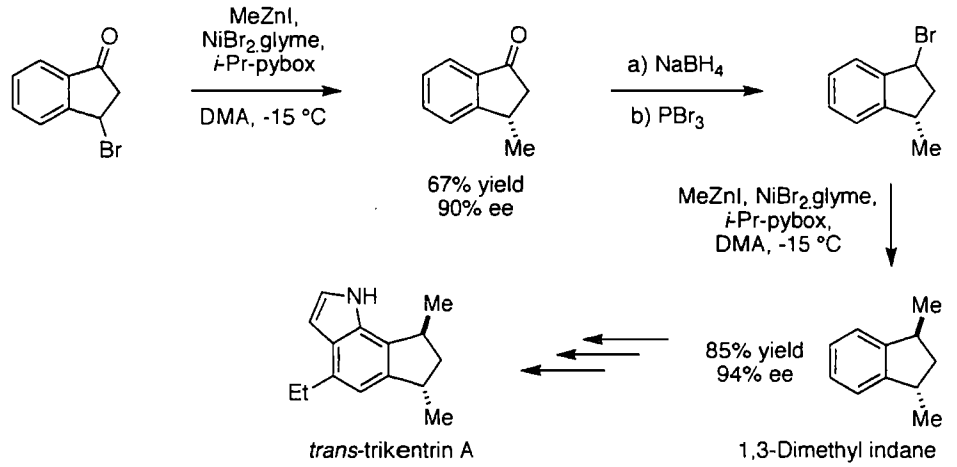
Scheme 22

The cross-coupling of unactivated alkyl halides is now well enough developed to be utilised in total synthesis projects. For example, after attempting several other approaches without success, Armstrong and co-workers finally synthesised (+,-)-epibatidine by employing a Suzuki reaction of a secondary alkyl bromide as the key step. [92] The cross-coupling reaction proceeded in moderate yield (56%) using conditions developed by Fu *et al.*,[89] subsequent Boc deprotection afforded the final compound (Scheme 23).



Scheme 23

More interestingly, Fu and co-workers utilised two asymmetric Negishi cross-coupling reactions in the preparation of 1,3-dimethyl indane,[87] an intermediate in Macleod's synthesis of *trans*-trikentrin A (Scheme 24).



Scheme 24

Cross-coupling reactions of unactivated, primary, β sp^3-H containing alkyl halides can now be achieved with all the commonly used nucleophilic species. Moreover, most of these reactions have been shown to be functional group tolerant and occur under mild conditions making them generally useful. Although not currently widely employed in synthetic strategies, these reactions should find more use in the coming years. Couplings of unactivated secondary alkyl halides are less well developed but should similarly find more use in organic synthesis in the future. The development of enantioselective protocols is a particularly interesting area.

1.3.4.4 Oxygen-based electrophiles

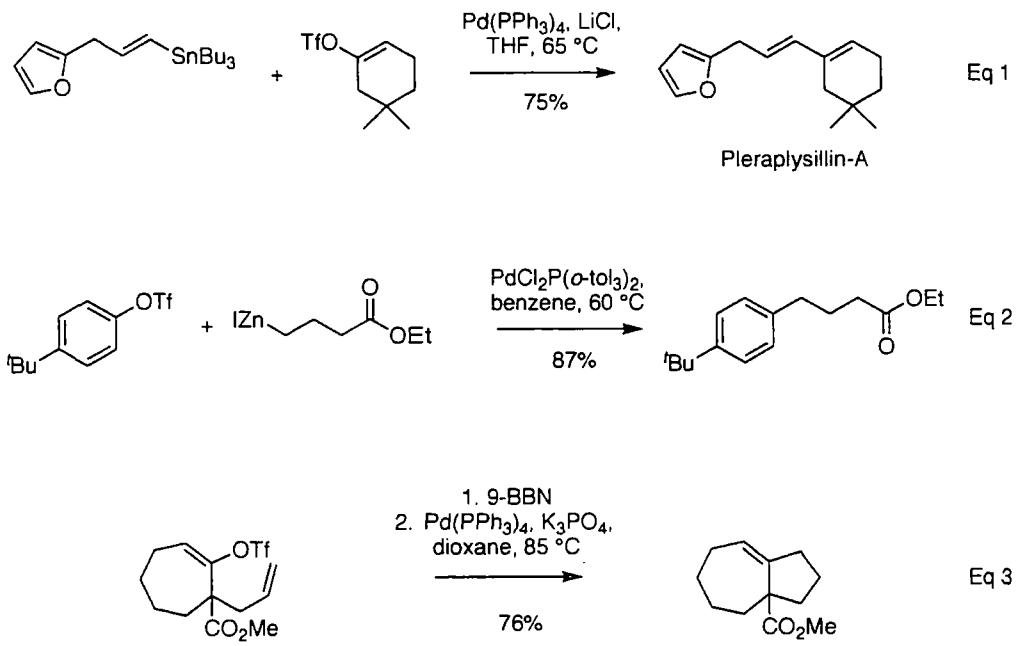
1.3.4.4.1 Introduction

The capacity of the halides to function as leaving groups is the fundamental property that enables them to successfully participate in cross-coupling reactions. Several other functional groups are also known to be good leaving groups in organic chemistry and as such, have also been successfully employed in cross-coupling strategies. These include those based on sulphur and nitrogen, which were discussed earlier (Scheme 7) and those based on oxygen, which are discussed in this section. Carbonyl compounds (*via* their enolates), alcohols and phenols can all be activated as good leaving groups by conversion in to their activated esters. This method of activation has been exploited for use in cross-coupling chemistry, most commonly for the activation of phenols and carbonyl compounds affording vinyl and aryl electrophilic species, but also for the activation of primary alcohols. The majority of oxygen substrates in cross-coupling protocols are activated as sulfonyl esters using a variety of different sulfonyl groups including triflates, nonaflates, fluorosulfonates as well as the less reactive alkyl and aryl sulfonates. The development of oxygen-based electrophiles considerably expanded the scope of cross-coupling chemistry and the sulfonates, particularly triflates, are practical and useful alternatives to halides in these strategies.

1.3.4.4.2 Activation with sulfur

Of the sulfonates described above the most useful and by far the most commonly employed is the triflate group. It was Stille who first recognised the possibility, based on leaving group properties, that sp^2-hybridised sulfonates might be useful electrophilic partners in cross-coupling reactions. Thus, in 1984, Stille *et al.* reported the first example of a cross-coupling reaction employing a vinyl triflate as the

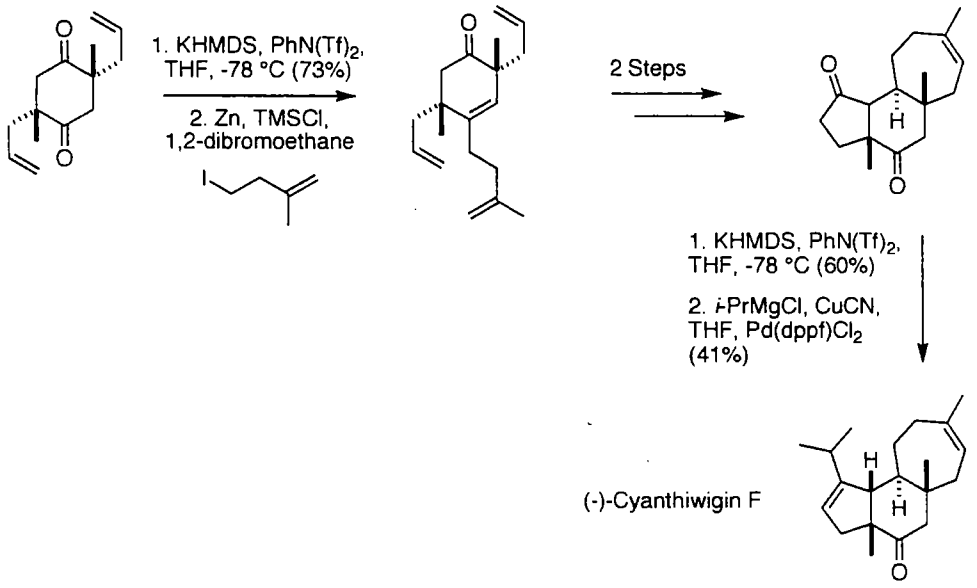
electrophilic partner.[93] In this a variety of vinyl triflates, prepared from the corresponding carbonyl compounds, were coupled with alkyl, alkenyl and alkynyl organotin reagents in high yields. This methodology was subsequently applied to the synthesis of Pleraplysillin-A (Eq. 1, Scheme 25). Following Stille's pioneering development, protocols for coupling triflates with other organometallic reagents were also developed. In 1986 Tamaru reported palladium-catalysed cross-couplings of both vinyl and aryl triflates with organozinc compounds, e.g. 4-*tert*-butylphenyltrifluoromethane sulfonate furnished the coupled product in 87% yield (Eq. 2, Scheme 25).[94] In 1993, Suzuki *et al.* demonstrated that a variety of vinyl and aryl triflates, derived from phenols and ketones, respectively, could be successfully coupled with organoboron derivatives.[95] For example, an alkyl 9-BBN derivative was coupled in an intramolecular fashion with a vinyl triflate (Eq. 3, Scheme 25).



Scheme 25

Since these early examples, cross-coupling protocols utilising vinyl and aryl triflates have been fully developed and it is now a useful substrate across the whole

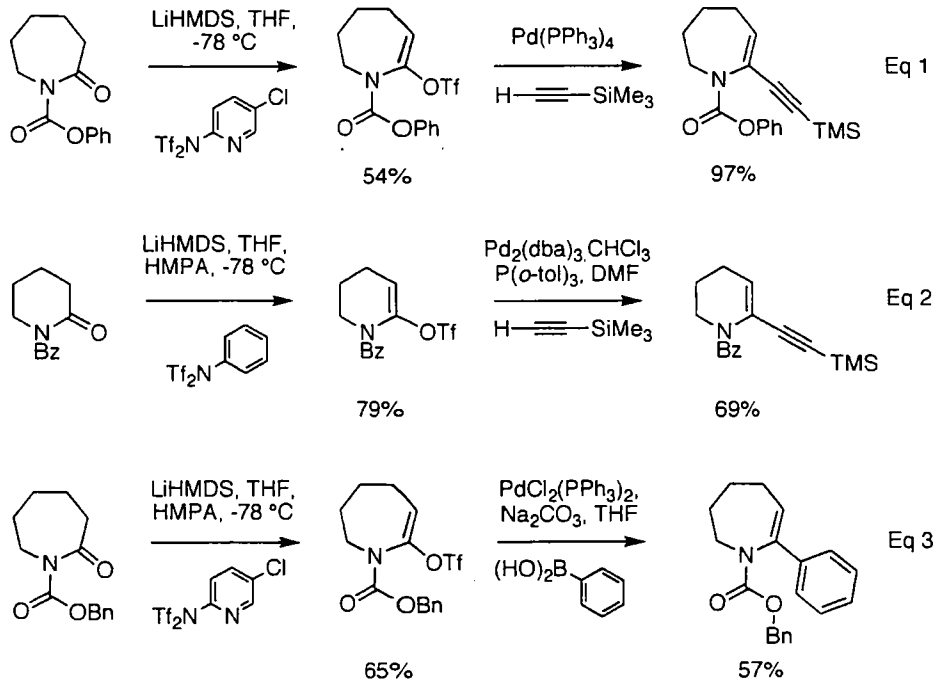
range of cross-coupling strategies. Moreover, when activating carbonyls or phenols for use in cross-coupling strategies it is very often the choice of substrate. The utility of the triflate group can be seen from its widespread use in total synthesis projects, e.g. Stoltz and Enquist utilised two cross-coupling reactions of vinyl triflates in their recent synthesis of (-)-cyanthiwigin F (Scheme 26).[96]



Scheme 26

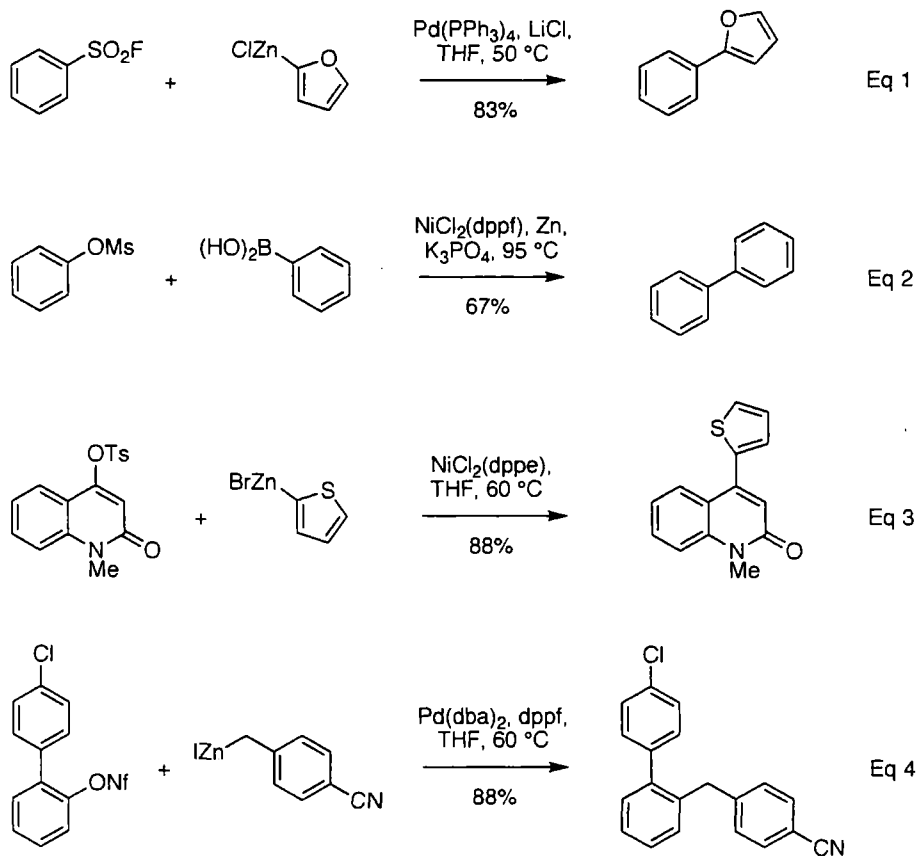
The activation of the carbonyl functionality of lactams as the analogous triflate group and subsequent cross-coupling of this species has also been demonstrated and provides a simple and attractive means for the preparation of N-heterocycles. Several reports concerning the activation and cross-coupling of lactams in this manner have been reported. Foti and Comins reported the earliest of these examples in 1995.[97] In this, triflates derived from both six and seven-membered ring lactams were synthesised in moderate to good yields (54 - 90%) by treatment of the starting lactam with LiHMDS followed by N-(5-chloro-2-pyridyl)triflimide. The use of these triflates was then explored in various cross-coupling protocols including Stille and Sonogashira reactions, e.g. the Pd-catalysed Sonogashira reaction of a caprolactam-derived triflate with

trimethylacetylene furnished the coupled product in 97% yield (Eq. 1, Scheme 27). The same year, during efforts towards the total synthesis of dynemicin A, Isobe and Okita also reported Sonogashira reactions of lactam-derived triflates.[98] For example, an N-benzyl protected valerolactam-derived triflate was coupled with trimethylsilylacetylene in good yield (69%, Eq. 2, Scheme 27). It was noted that attempts to cross-couple triflates derived from the five- and seven-membered ring lactams under the same conditions were unsuccessful due to the instability of the triflates in these cases. Occhiato and co-workers demonstrated that Suzuki cross-coupling reactions of lactam-derived triflates are also possible.[99] Here, six- and seven-membered ring vinyl triflates were prepared and coupled with a variety of organoboron derivatives. It was found that, in contrast to the six-membered ring triflates, which gave high yields and were found to be stable at room temperature, the seven-membered ring triflate was prone to decomposing during purification and storage. Following chromatography the seven-membered ring N-Cbz protected triflate was isolated in 65% yield together with substantial quantities of the starting lactam (25%). The seven-membered ring triflate also performed less well in coupling reactions than the six, the best result being 57% yield when coupled with phenylboronic acid (Eq. 3, Scheme 27); decomposition of the triflate back to the lactam was again the major problem.



Scheme 27

Despite its versatility and widespread use in organic chemistry, the triflate group often suffers from a lack of stability, as illustrated in the examples above (Scheme 27). Moreover, the preparation of triflates requires the use of either triflic anhydride or the *bis*-triflimides. Of these two options, the former is corrosive, produces triflic acid as a by-product and often gives poor yields whilst the latter reagents suffer from being relatively expensive. As a result much effort has been focused on developing alternatives to the triflate group for activating oxygen functionalities towards cross-coupling protocols. The majority of these alternatives have explored different sulfonate groups including fluorosulfonates first developed by Roth and Fuller (Eq. 1, Scheme 28),[100] alkyl sulfonates, first reported in 1995 by Perec and co-workers (Eq. 2, Scheme 28); various arylsulfonates were also explored,[101] arylsulfonates, in particular the tosylate group were also reported by Wu *et al.* (Eq. 3, Scheme 28)[102] and finally nonaflates, first reported by Knochel in 1998 (Eq. 4, Scheme 28).[103]



Scheme 28

Although each of the examples described above has its merits when compared to triflates, whether it is similar reactivity (fluorosulfonates and nonaflates) or higher stability and ease of preparation (alkyl/arylsulfonates), none has proven as useful as the triflate group as a general substrate for transition-metal-catalysed cross-coupling protocols and they remain rarely utilised.

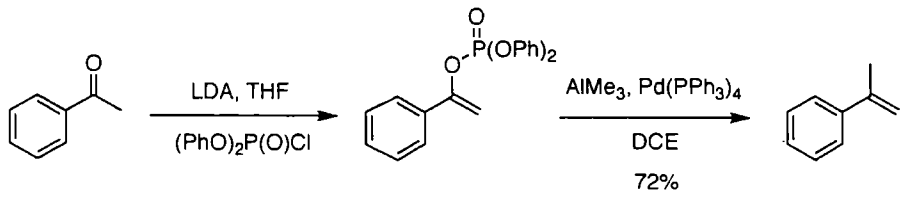
1.3.4.4.3 Activation with phosphorus

In addition to sulfur-based esters, activation of oxygen as a good leaving group can also be achieved with phosphorous derivatives, in particular phosphoryl esters. Consequently, electrophilic species based on this type of activation are now well known in cross-coupling chemistry and are discussed in this section.

1.3.4.4.3.1 Phosphates

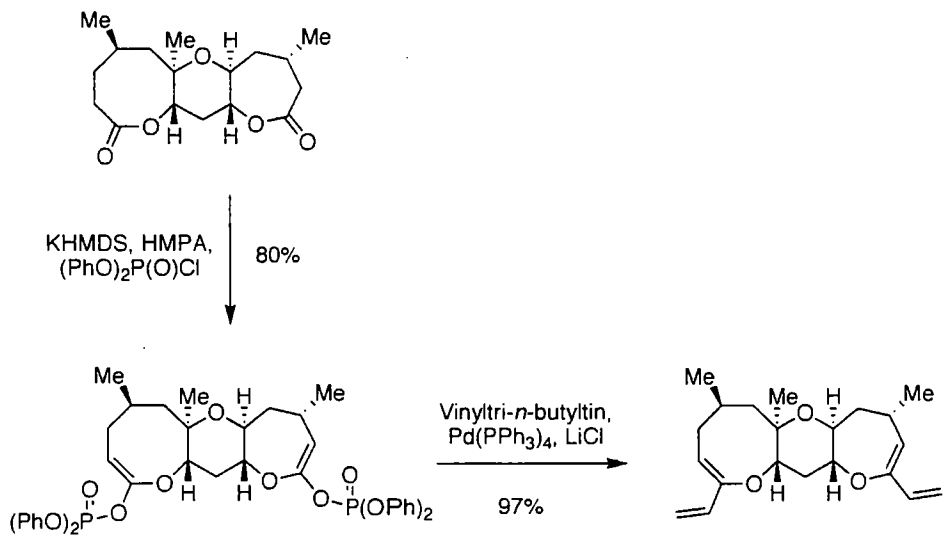
The phosphate group is by far the most widely employed electrophilic phosphorus species in cross-coupling chemistry. Both vinyl and benzyl phosphates (mainly vinyl) are useful substrates and have been shown to couple with numerous organometallic reagents. However, aryl phosphates are not suitable substrates as the C-O bonds of these species have been shown to be un-reactive towards oxidative addition. Consequently, cross-coupling reactions of these substrates are still unknown. However, this lack of reactivity provides a useful selectivity and allows the use of diphenylvinyl phosphates in cross-coupling protocols, where the vinyl group reacts selectively. Diphenyl chlorophosphate is both cheap and commercially available, allowing a simple, efficient and cost effective route to the desired substrates. The use of diethyl chlorophosphate, also commercially available, is less attractive due to its high toxicity.

The earliest example of a cross-coupling reaction employing a vinyl phosphate was reported by Oshima and co-workers in 1980.[104] In this, three vinyl phosphates were coupled with various organoaluminium reagents in moderate to good yields (57 – 94%). For example, diphenyl-1-phenylvinylphosphate, prepared from acetophenone, afforded 2-phenylpropene in 72% yield when reacted with trimethylaluminium in the presence of a $Pd(PPh_3)_4$ catalyst (Scheme 29). Surprisingly, it was 16 years before the next report concerning the cross-coupling of a vinyl phosphate appeared in the literature, suggesting that the phosphate group was largely overlooked in favour of the triflate group in the intervening years.



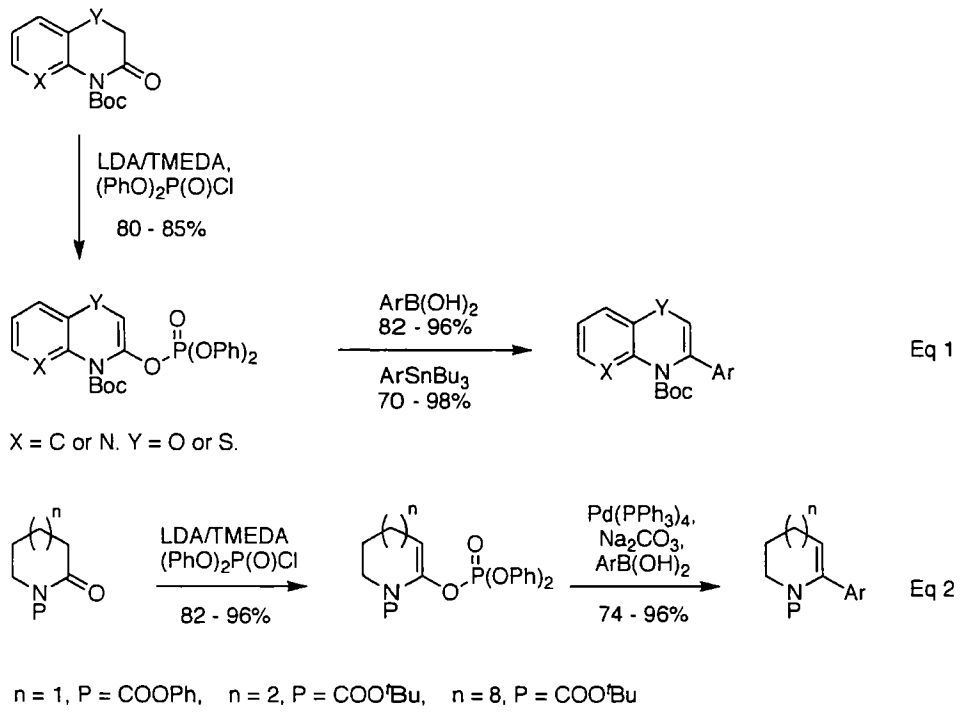
Scheme 29

It was in 1996 when Nicolaou and co-workers next demonstrated the usefulness of vinyl phosphates as substrates for cross-coupling reactions.[105] They described the synthesis (from lactones) and subsequent palladium-catalysed Stille cross-couplings of a range of cyclic ketene acetal phosphates. The coupling reactions proceeded in generally excellent yields (58 – 97%). For example, treatment of a *bis*-(lactone) (Scheme 30) with KHMDS followed by phosphoryl chloride afforded the desired *bis*-phosphate in high yield. Subsequent Stille cross-coupling of the *bis*-phosphate furnished the desired coupled product in excellent yield (97%). The use of the phosphate group in this example was crucial as attempts to form the analogous *bis*-triflate were unsuccessful, highlighting the improved stability of the phosphate group in comparison to the triflate.



Scheme 30

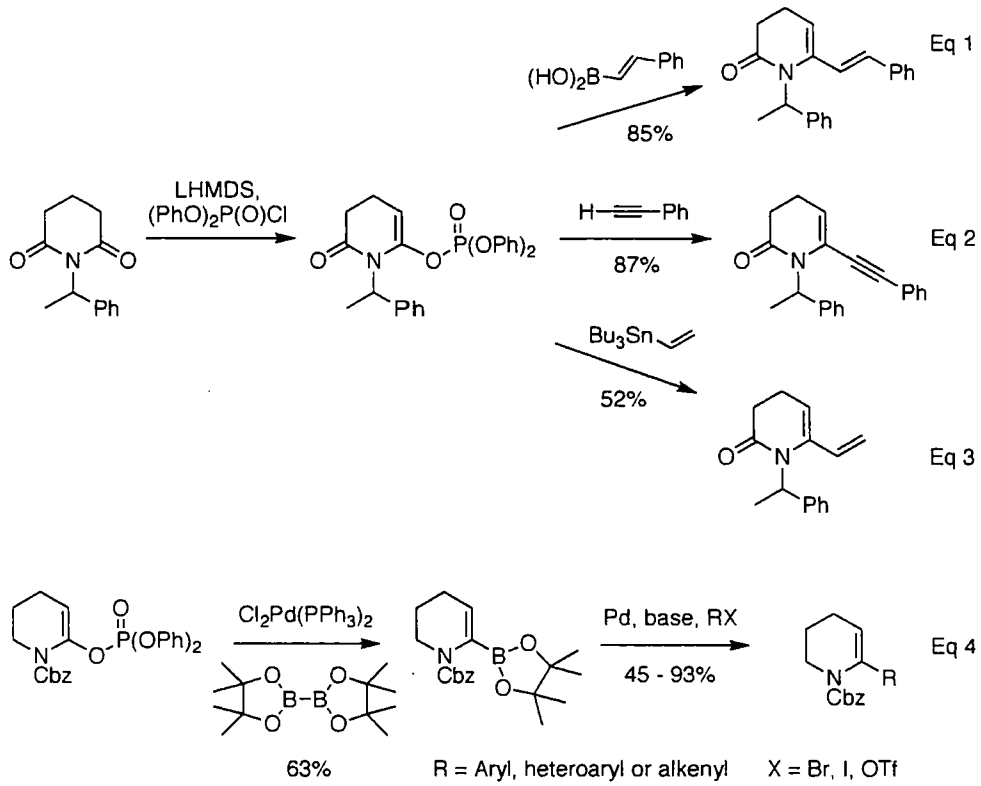
In 1999 the first in a series of reports by Coudert *et al.* [106] concerning the cross-coupling of lactam-derived vinyl phosphates described the Pd-catalysed Suzuki cross-coupling of various N-Boc-protected heterocycles. Phosphate formation was achieved in high yield by metallation of the appropriate lactam with LDA/TMEDA followed by phosphoryl chloride quench. Subsequent Pd-catalysed Suzuki cross-coupling afforded the desired substituted heterocycles in excellent yields (Eq. 1, Scheme 31). The following year the scope of this chemistry was expanded to include the Stille cross-coupling reaction and the same phosphates were coupled with several stannanes, again in high yield (Eq. 1, Scheme 31). The use of the phosphate functionality was crucial in this chemistry as the analogous triflate group was found to be unstable above -50 °C and could not be isolated. In 2001, Coudert and co-workers prepared vinyl phosphates from 6-, 7- and 13-membered ring lactams using the same method as that described above. Boc protection was found to be unsuitable for the 6-membered ring lactam and phosphate formation was only successful using a phenyl carbamate. Subsequent Suzuki cross-couplings proceeded in excellent yields with all substrates (Eq. 2, Scheme 31).



Scheme 31

Cross-coupling reactions of lactam-derived vinyl phosphates were also utilised to good effect by Occhiato and co-workers as a means to access Diels-Alder substrates.[107] The desired phosphate was prepared quantitatively from the protected imide by treatment with LHMDS followed by phosphoryl chloride. It was noted that attempts to purify the phosphate by chromatography led to its partial degradation on the column and recovery of the starting material. Moreover, even when stored at 4 °C some degradation was observed. However, the phosphate could be used without purification in the subsequent cross-coupling reactions within a few days of preparation. Despite the minor instability, the phosphate functionality again proved superior to the corresponding triflate moiety, which was found to be unsuitable as it could not be isolated efficiently from the imide. The phosphate proved to be an efficient substrate for palladium-catalysed Suzuki (Eq. 1), Sonogashira (Eq. 2) and Stille cross-coupling reactions (Eq. 3, Scheme 32) affording the coupled products in good yields. In 2005, Occhiato *et al.* utilised a lactam-derived vinyl phosphate to prepare the analogous

vinylboronate *via* a Pd-catalysed coupling with *bis*-pinacolato diboron. The boronate was then coupled with various electrophilic species in Pd-catalysed Suzuki reactions (Eq. 4, Scheme 32).[108]

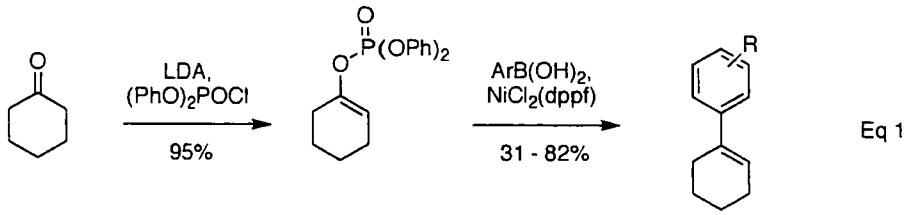


Scheme 32

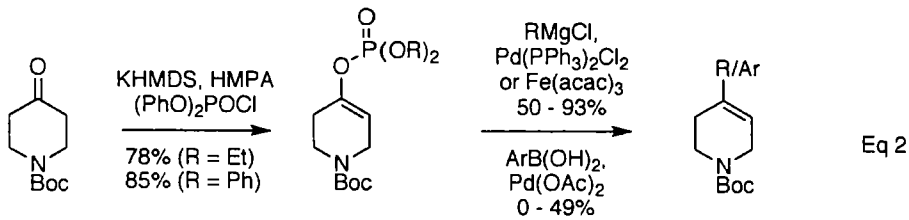
The examples described above by Nicolaou (Scheme 30), Coudert (Scheme 31) and Occhiato (Scheme 32) all utilise either lactams or lactones in which the phosphate moiety is activated by the presence of an α-heteroatom. Moreover, in each example a phosphate group was employed because the analogous triflate group was found to be unsuitable due to stability issues. Thus, phosphates can be seen as the substrate of choice when activating lactams or lactones towards cross-coupling reactions. The presence of the α-heteroatom in these cases aids the difficult oxidative addition step by making the reacting centre more electrophilic. Activated vinyl phosphates have also been coupled successfully in Negishi[109] and Kumada-Corriu[110]

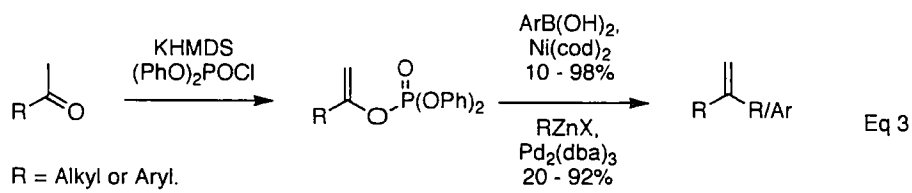
reactions as well as the Suzuki, Stille and Sonogashira strategies described above. Examples where the electrophilic centre is not activated by an α-heteroatom are less common but not unknown. The first such example being being that of Oshima discussed earlier (Scheme 29).[104] A more recent example was reported by Yang and co-workers who prepared 1-cyclohexylvinyl diphenylphosphate in high yield by treatment of cyclohexanone with LDA and phosphoryl chloride (Eq. 1, Scheme 33).[111] Initially, several palladium catalysts were explored for the coupling of this substrate, but only trace amounts of products were obtained, highlighting the lower reactivity of this phosphate in comparison to those derived from lactams and lactones. Consequently, the authors investigated the use of a nickel catalyst to effect the desired reaction and treatment of the phosphate with $NiCl_2$(dppf) complex, boronic acid and K_3PO_4 in toluene furnished the desired coupled products in moderate to good yields (31 – 82%, Eq. 1, Scheme 33). The protocol proved to be reasonably general and allowed the coupling of electron-rich, electron-poor and hindered boronic acids. In 2005 Bergtrup and co-workers reported Kumada and Suzuki cross-coupling reactions of unactivated diphenyl and diethylvinyl phosphates as a means of accessing 4-substiuted dihydropyridines (Eq. 2, Scheme 33).[112] However, only the diphenyl phosphate proved reactive in the Suzuki reaction, the diethyl derivative afforded only trace amounts of product, indicating the higher reactivity of the diphenyl derivative towards oxidative addition. In 2006 Skrydstrup and co-workers described a method for the synthesis of 1,1-diaryl alkenes *via* a nickel-catalysed Suzuki cross-coupling of unactivated aromatic alkenyl phosphates.[113] Subsequently, the scope and limitations of this chemistry were expanded to include alkyl- and aryl-substituted phosphates, which were coupled in Negishi and Suzuki cross-coupling protocols.[114] Standard conditions were developed, which provide straightforward access to a diverse range of 1,1-disubstituted alkenes in generally high yields (Eq. 3, Scheme 33). The number of examples is too large to be

included, but the formation of the hindered, *tert*-butylalkene from an arylzinc reagent and *tert*-butylvinyl phosphate illustrates the utility of this chemistry (Eq. 4, Scheme 33).

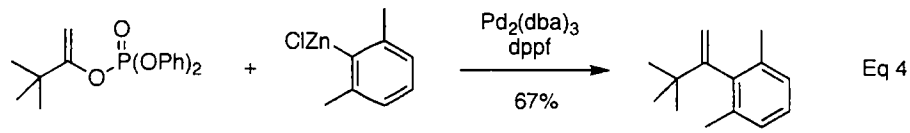


R = H, 2-OMe, 4-OMe, 2-F, 4-F, 4-CF_3, 3-$COCH_3$, 1-Napthyl, 2-Napthyl, 3-NH_2,



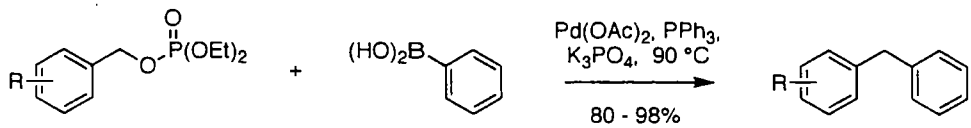


R = Alkyl or Aryl.



Scheme 33

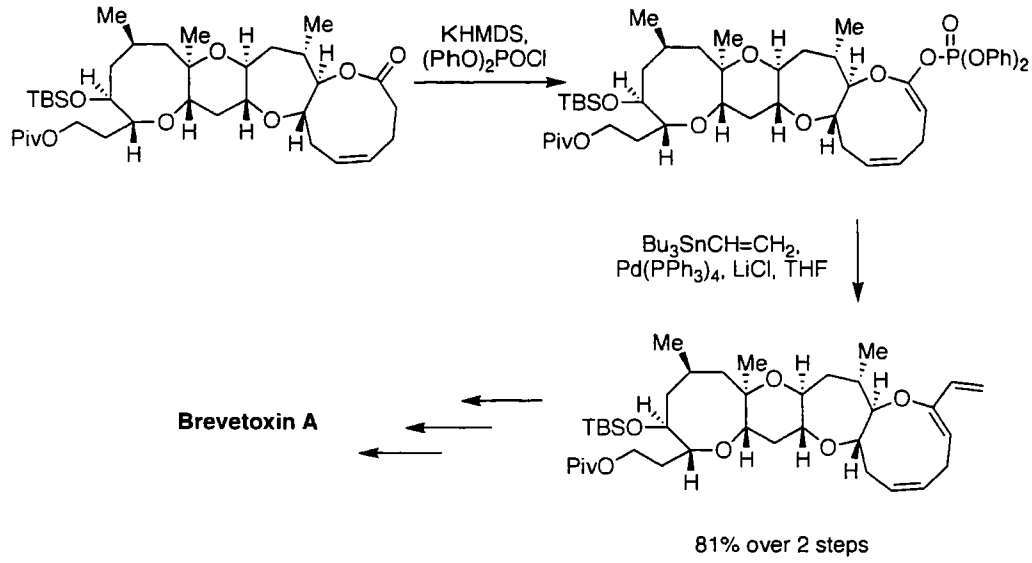
In addition to vinyl phosphates, benzylic phosphates are also suitable substrates for cross-coupling strategies. For example, McLaughlin described the Suzuki coupling of a range of benzylic phosphates with phenylboronic acid, furnishing diarylmethanes in excellent yields (Scheme 34).[115]



R = 2-Me, 4-Me, 4-Cl, Napthyl, 4-NO_2, 4-OMe,

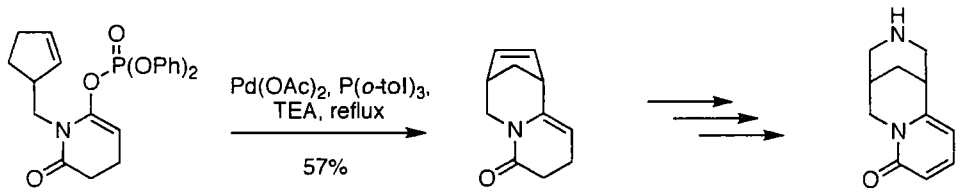
Scheme 34

In comparison to the triflate group, the phosphate group is still rarely used as the electrophilic species in cross-coupling chemistry and has seen only limited development over the past decade or so. However, the advantages of the phosphate group over triflates and tosylates, particularly in activating lactams or lactones, has resulted in numerous examples of its use in total synthesis projects. The majority of these are focused on the construction of fused polycyclic ether compounds, e.g. brevetoxin A,[116] ciguatoxin[117] and azaspiracid,[118] all of which contain highly complex structures. Nicolaou's synthesis of brevetoxin A relied on a Stille cross-coupling reaction of a vinyl phosphate.[116] Thus, the key phosphate intermediate was prepared from the lactone precursor and subsequently cross-coupled with vinyltributyltin to give the new diene in 81% yield over the two steps, further steps provided the natural product (Scheme 35).



Scheme 35

In addition to lactones, lactam-derived vinyl phosphates have also been found to be useful substrates in total synthesis. For example, in his synthesis of the natural product cytisine,[119] Coe utilised a lactam-derived vinyl phosphate in an intramolecular Heck cyclisation reaction (Scheme 36). The phosphate was prepared in quantitative yield from the corresponding imide *via* its lithium enolate and phosphoryl chloride; the analogous triflate proved unsuitable, as it could not be prepared efficiently (< 10% yield).



Scheme 36

The increased stability and generally high reactivity of vinyl phosphates across a range of cross-coupling protocols, coupled with the fact that they can be prepared in excellent yields from low cost and non-corrosive reagents, makes them particularly

attractive alternatives to the triflate group for cross-coupling strategies, especially for industry.

1.4 Background to the current research (phosphonates and phosphinates)

The phosphonate and phosphinate functionalities closely resemble the phosphate group (Figure 4). However, these groups remain largely unexplored in cross-coupling chemistry. Whilst retaining the vinyl-O-P bond, these substrates differ from the phosphate group through the oxidation level at phosphorus, which is reduced *via* the replacement of one or two P-O bonds with a P-C bond. Since replacing P-O bonds with P-C bonds lowers the leaving group ability, these groups are predicted to be more stable and thus more tolerant of reactive functionality. Considering the lack of stability of many triflate species and even some phosphate species, phosphonates and phosphinates represent attractive alternatives to these electrophiles for the use in cross-coupling reactions. Additionally, and similarly to the phosphate group, the reagents required for the synthesis of these substrates are extremely cheap and non-corrosive, further increasing their appeal in organic synthesis. However, lowering the leaving group ability has the adverse effect of lowering the reactivity of the C-O bond towards oxidative addition and thus cross-coupling reactions in comparison to phosphates. A program of research was initiated in the Steel research group with the aim of developing and exploring vinyl phosphonates and phosphinates in cross-coupling strategies.

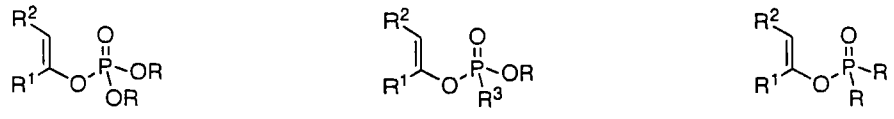
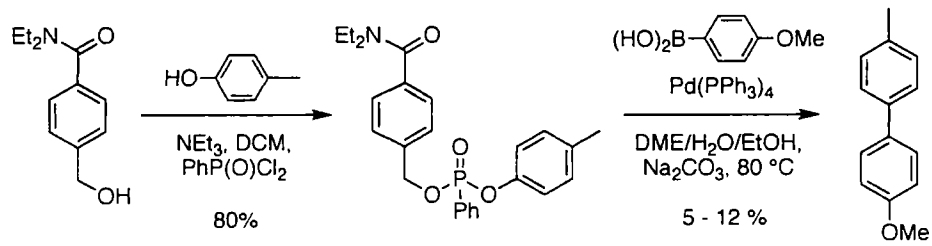


Figure 4

1.4.1 Phosphonates

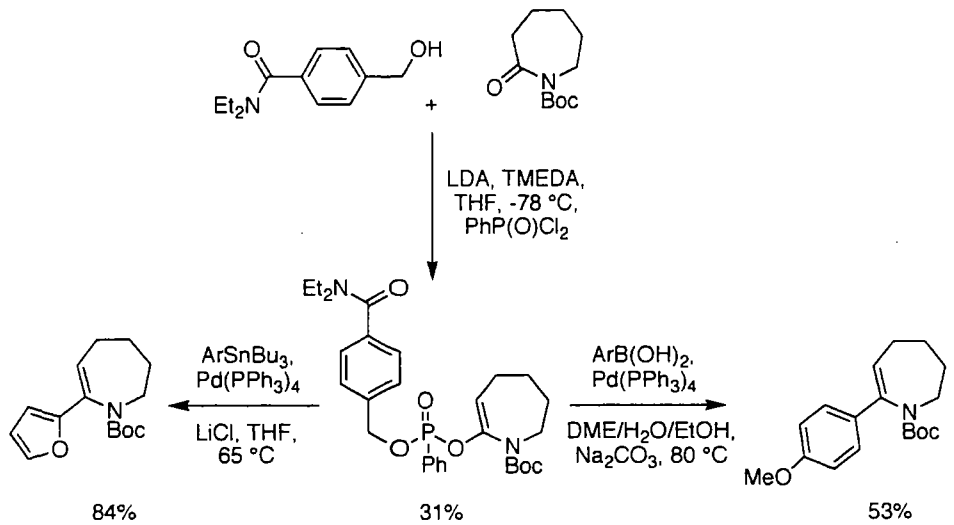
In 2004, Steel and co-workers reported the first examples of palladium-catalysed cross-coupling reactions of vinyl phosphonates.[120] In this, they describe the synthesis and subsequent cross-couplings of two homogeneous N-Boc caprolactam-derived vinyl phosphonates as well as a resin bound vinyl phosphonate.

Initially, a phosphonate containing an aryl unit and a benzylic unit was prepared in high yield by the reaction of N,N-diethyl(4-hydroxymethyl)benzamide and *p*-methylphenol with NEt_3 (Scheme 37). Treatment of the phosphonate under palladium-catalysed Suzuki reaction conditions afforded only trace amounts of the product due to cross-coupling of the aryl unit, indicating that in a similar fashion to phosphates, the P-O-C bond of aryl phosphonates is not susceptible to oxidative addition to transition metal catalysts. However, it is possible that the failure of the aryl moiety to react is due to a competing and perhaps kinetically favourable reaction of the catalyst with the benzylic phosphate species.[64]



Scheme 37

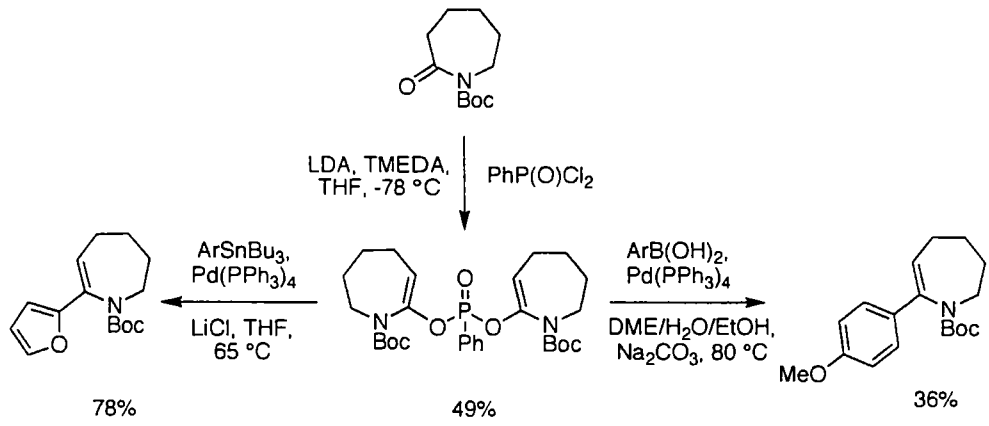
It was then postulated, based on precedent from phosphate electrophiles, that lactam-derived vinyl phosphonates might be sufficiently reactive to undergo cross-coupling reactions. Consequently, a phosphonate containing a vinyl unit and a benzylic unit was prepared by treatment of N-Boc caprolactam with LDA and TMEDA followed by $PhP(O)Cl_2$ and N,N-diethyl(4-hydroxymethyl)benzamide. Unfortunately, formation of the phosphonate could not be achieved efficiently and the best yield observed was 31%. However, subsequent treatment of the phosphonate under *both* Suzuki and Stille reaction conditions afforded the desired coupled products in moderate and high yields, respectively, (Scheme 38).120 It is possible that the moderate yield observed in the Suzuki reaction is a consequence of competing oxidative addition at the benzylic phosphonate linkage, although the high yield for the desired product in the Stille reaction suggests the vinyl moiety is more reactive than the benzyl group.



Scheme 38

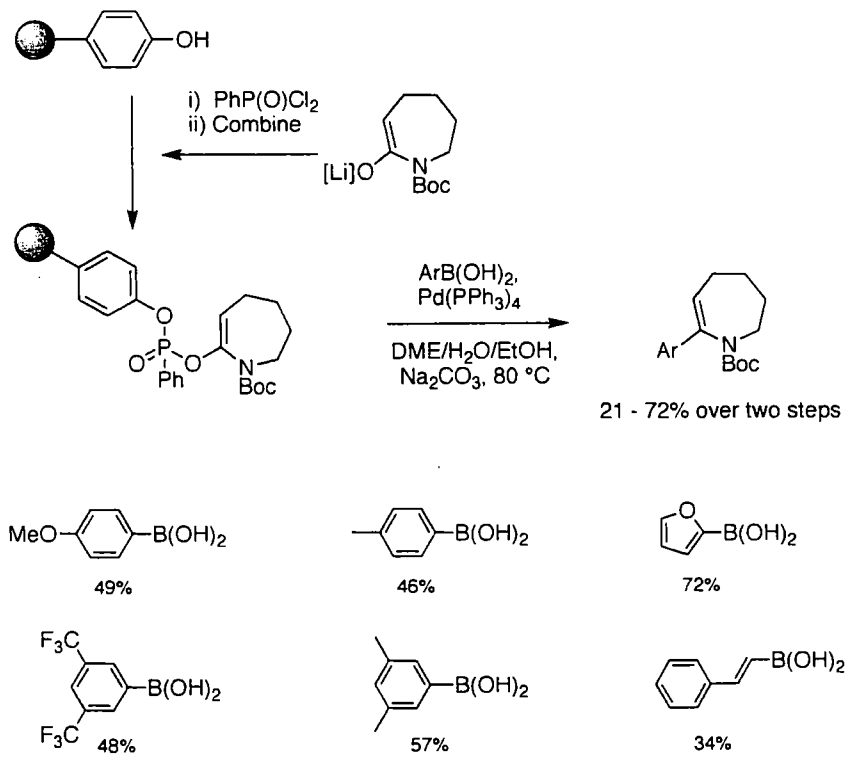
Having shown that lactam-derived vinyl phosphonates were suitable partners for cross-coupling reactions, the synthesis and cross-coupling of a *bis*-(phosphonate) was explored. Preparation of the desired phosphonate was achieved by the reaction of two equivalents of N-Boc-protected caprolactam with $PhP(O)Cl_2$ and was isolated in

moderate yield. Subsequent cross-coupling with both *p*-methoxyphenylboronic acid and tributylfurylstannane afforded the desired coupled products in 36% and 78% yields, respectively (Scheme 39).[120]



Scheme 39

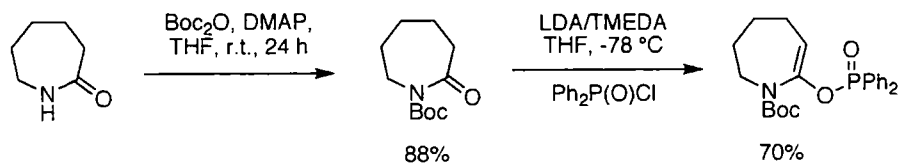
Having explored homogeneous solution phase cross-couplings of phosphonates, it was then shown that the methodology could be extended to a heterogeneous solid phase system. A solid supported vinyl phosphonate moiety was shown to act as a simple diversity linker for solid phase organic synthesis. The immobilised phosphonate was prepared from phenol-on-polystyrene resin and N-Boc-protected caprolactam. Cleavage from the resin was achieved under Suzuki cross-coupling conditions with range of boronic acids affording the desired coupled products in variable yields (selected examples are given, Scheme 40).120 It is worth noting that the yields are calculated over two steps from the loading of the initial polystyrene resin.



Scheme 40

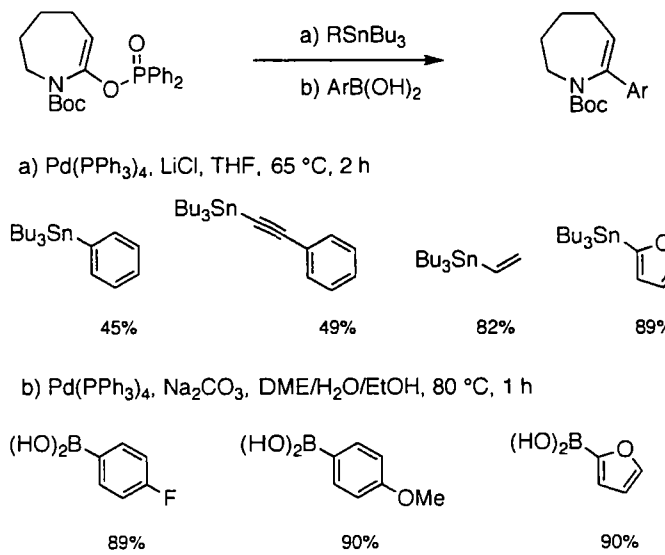
1.4.2 Phosphinates

In addition to lactam-derived vinyl phosphonates, previous (unpublished) work in the Steel research group by Guo and Jones had shown that the analogous lactam-derived vinyl phosphinates are also suitable electrophiles for cross-coupling protocols.[121] The required phosphinate was readily prepared in two steps in excellent yield from commercially available caprolactam (Scheme 41).



Scheme 41

Having successfully synthesised the phosphinate, some preliminary cross-coupling studies were undertaken. Utilising the conditions described above for the coupling of phosphonates, the caprolactam phosphinate was coupled in Suzuki and Stille cross-coupling protocols with extremely promising results for both Stille (45 – 89%) and Suzuki (89 – 90%, Scheme 42) reactions. The Suzuki cross-coupling yields are of particular interest, occurring much more efficiently than the analogous reaction with the phosphonates, an observation that is in contrast with the expected reactivity of these substrates. The yields obtained in the Stille coupling are similar. However, the limited number of examples given does not allow for good comparisons to be made.



Scheme 42

1.4.3 Aims of the current research

The previous work within the group had shown that both phosphinates and phosphonates are readily prepared from cheap, non-corrosive phosphorus reagents and display promising reactivity in palladium-catalysed cross-coupling protocols. However, with the exception of the Suzuki reaction of immobilised phosphonates

(Scheme 40), this work remained only as a preliminary investigation into these systems and a number of questions still deserved investigation.

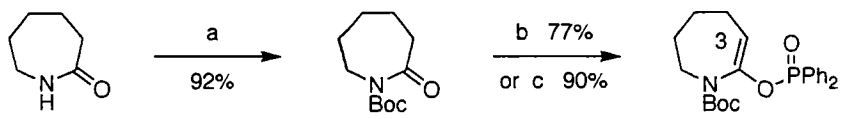
- Despite the promising initial results from the Suzuki and Stille cross-coupling reactions of phosphinates and homogeneous phosphonates, only a single set of conditions had been attempted in each case. Identification of the optimal reaction conditions for both the Stille and Suzuki protocols would be undertaken.
- The scope and limitations of these processes needed to be fully explored. Areas needing further investigation included:
  1. The range of boronic acids or stannanes that can be employed.
  2. The lactam ring size and identity of the protecting group.
- The relative reactivity of both the phosphinates and phosphonates in comparison to the more commonly employed halides and triflates would be investigated. This would be achieved through the use of substrates containing two electrophilic sites, either a phosphinate or phosphonate and a halide or triflate.
- Given sufficient differences in reactivity the aim was to extend the chemistry to immobilised phosphonates containing a halide or triflate, such a substrate would allow for a combinatorial chemistry approach to be adopted.
- The application of this methodology to the synthesis of a natural product would be explored.

The next chapter of this report will detail the work undertaken and the progress that has been made addressing the aims and limitations just described.

2 Lactam-derived phosphinates

2.1 N-Boc caprolactam phosphinate

As a simple system to explore phosphinate-based electrophiles in cross-coupling chemistry it was decided to build on previous work in the group and utilise simple N-Boc caprolactam enolates as test substrates. Although reaction with Boc_2O in DCM was unsuccessful, simple treatment of commercially available caprolactam **1** with DMAP and Boc anhydride in THF smoothly furnished **2** in an excellent yield (92%). Evidence for the formation of **2** was given by the appearance of a strong signal in the ^1H NMR spectrum due to the *tert*-butyl group at 1.50 ppm (9H, s). Subsequent treatment of a cold THF solution of **2** with LDA and TMEDA followed by trapping of the resultant anion with diphenylphosphonic chloride afforded the desired phosphinate **3** in 77% yield. Formation of the phosphinate was characterised by a single peak in the ^{31}P NMR spectrum at 29.7 ppm and a distinctive signal in the ^1H NMR spectrum at 5.36 ppm (1H, dt, J_P = 3 Hz, J_H = 7 Hz) due to the new *C*-3 vinylic proton. Subsequently replacing LDA/TMEDA by NaHMDS proved to be cleaner and more efficient providing phosphinate **3** in a much improved 90% yield (Scheme 43).



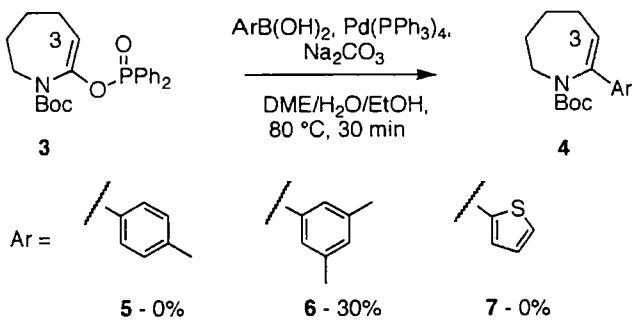
1 **2** **3**

a) DMAP, Boc anhydride, THF, r.t., 3 h. b) i) LDA, TMEDA, THF, -78 °C, ii) $Ph_2P(O)Cl$. c) NaHMDS, THF, -78 °C, ii) $Ph_2P(O)Cl$.

Scheme 43

With the phosphinate now readily available, attention turned to its use in cross-coupling reactions. Reflecting its widespread use, and low toxicity of the reagents

involved, it was decided to commence these studies using the Suzuki-Miyaura reaction. Following the protocol successfully applied in the cross-coupling of enol phosphonates and phosphinates described earlier (1.5 eq. $ArB(OH)_2$, 2 Eq. Na_2CO_3, 0.05 eq. $Pd(PPh_3)_4$, DME-EtOH-H_2O, 80 °C, 1 h, Scheme 40 and Scheme 42), the reaction of phosphinate **3** with three boronic acids (**5**, **6** and **7**) was attempted. However, despite numerous attempts and in contrast to the preliminary results reported above (Scheme 42) the obtained yields of the Suzuki cross-couplings were poor. Cross-coupling with 3,5-dimethylphenylboronic acid afforded the desired product, but only in low yield (30%). The coupled product was characterised by a shift in the resonance and change in the splitting pattern for the C-3 vinylic proton to 5.85 ppm (1H, t, J = 7 Hz) and supported by HRMS, which showed a molecular ion at MNa^+ of *m/z* = 324.1934 consistent with a molecular formula of $C_{19}H_{27}NO_2Na$. Moreover, coupled product **4** was isolated as a mixture of rotamers (4:1 ratio) as characterised by two sets of signals in the ^1H NMR spectrum, e.g. a second peak due to the C-3 vinylic proton can be observed at 6.11 ppm (t, J = 7 Hz). Disappointingly, reactions with boronic acids **5** and **7** failed to afford any of the desired coupled products (Scheme 44).

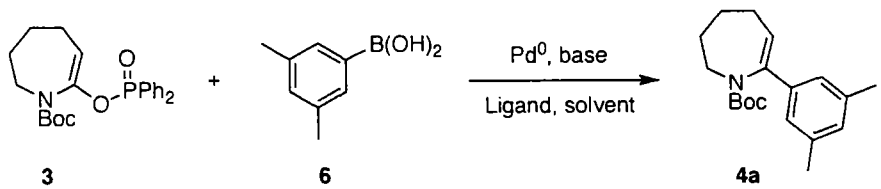


Scheme 44

Consequently, a simple screening strategy was initiated to identify conditions to effect the coupling of phosphinate **3** with a range of boronic acids in good yields. Since the number and range of variables are extensive, rendering a complete and systematic

screen impractical, selected combinations were drawn from a total of four palladium salts, seven ligands ten bases and eight solvents.‡ Using the Suzuki reaction between phosphinate **3** and 3,5-dimethylphenylboronic acid **6** as the test transformation, an array of reactions were carried out in parallel using a Radley Technologies Greenhouse Parallel Synthesiser™. The reactions were carried out on a 0.1 mmol scale and analysed *via* GC using dodecane as an internal standard to enable conversion levels and chemical yields to be calculated for each run.

Table 1: Optimisation of Suzuki cross-coupling protocol between phosphinate 3 and 3,5-dimethylphenylboronic acid.



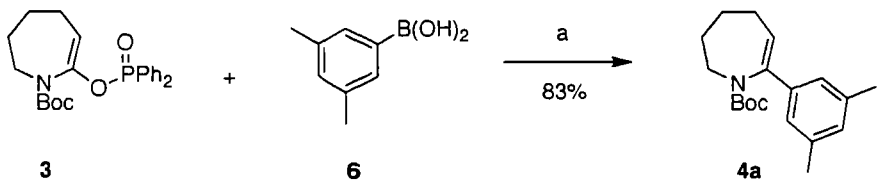
3 **6** **4a**

Entry	Catalyst	Ligand	Base	Solvent	GC yield **4a**
A2	$Pd(PPh_3)_4$		K_3PO_4	DMF	23%
A4	$Pd(PPh_3)_4$		$NaHCO_3$	DME / H_2O	98%
A5	$Pd(PPh_3)_4$		$Ba(OH)_2$	DME / H_2O	72%
C5	$Pd(OAc)_2$	$^tBu_2P(BiPh)$	K_3PO_4	EtOH / H_2O	44%
D1	$Pd_2(dba)_3$		KOAc	Toluene/EtOH	31%
D4	$PdCl_2$(Binap)		$NaHCO_3$	DME / H_2O	46%
D6	$PdCl_2$(Binap)		CsF	THF / H_2O	63%

Reaction conditions: $ArB(OH)_2$ (1.0 eq), phosphinate 3 (1 eq), dodecane (1 eq), Pd source (0.05 eq), phosphine (0.05 eq), base (3 eq), solvent (1 ml total), 80 °C, 18 h.

‡ A full listing of all combinations explored can be found in the experimental

This simple screen revealed that, regardless of the choice of solvent, the use of an amine base (NEt_3) resulted in poor yields of the desired product (≤ 11%) indicating that an inorganic/aqueous base is essential to the success of the reaction. Of the seven conditions that fulfilled this requirement and gave yields that merit discussion (Table 1), six employed a protic solvent (EtOH or H_2O) and the five highest yielding entries all employed water as a co-solvent in tandem with an organic solvent with which it is miscible. It is suspected that such an aqueous/organic solvent combination provides greater solubility of all the reagents in the reaction leading to better results. Using the most promising conditions identified from the array (Table 1, A4) the Suzuki cross-coupling of phosphinate **3** was then carried out on a preparative (0.4 mmol) scale. The reaction was followed by TLC analysis and no starting material remained after 1 h and following a standard work-up the coupled product **4a** was isolated in an excellent yield (83%, Scheme 45, Table 2, entry 1).



3 **6** **4a**

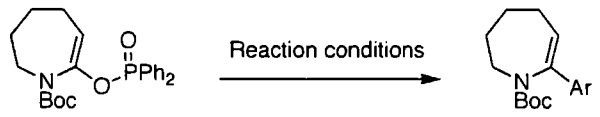
a) $ArB(OH)_2$ (1.1 eq), **3** (1 eq), $NaHCO_3$ (3 eq), $Pd(PPh_3)_4$ (0.05 eq), DME/H_2O (7:3), 80 °C, 1 h

Scheme 45

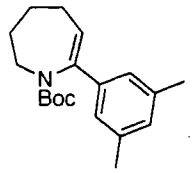
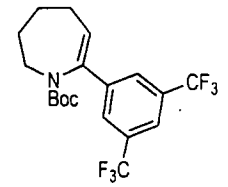
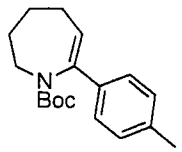
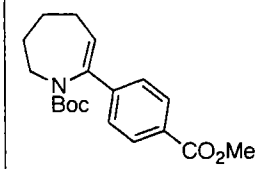
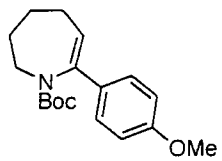
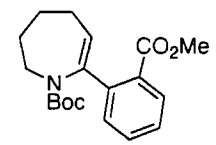
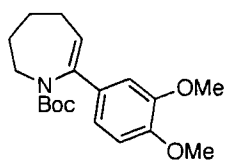
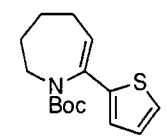
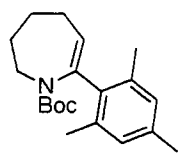
Importantly these optimised conditions proved to be relatively general across a range of boronic acids affording cross-coupled products **4a-i** in generally excellent yields apart from **4h** (32 - 99%, Table 2, entries 1-9). Of particular note is the coupling of the highly-hindered 2,4,6-trimethylphenylboronic acid giving coupled product **4e** in a 65% yield (Table 2, entry 5) as well as electron-poor boronic acids, yielding coupled products **4f** and **4g** in 87% and 72%, respectively (Table 2, entries 6 and 7). Unsurprisingly however, employing a boronic acid that is both electron-poor and

sterically-hindered resulted in a marked drop in yield giving **4h** in a 32% yield (Table 2, entry 8). This product also contained small amounts (approx 8% by ^{1}H NMR) of an impurity, which despite several attempts, could not be removed by chromatography. The impurity is thought to arise from homocoupling of the boronic acid and three of the four aromatic signals expected from this impurity can clearly be seen in the ^{1}H NMR spectrum at 7.20 ppm (1H, d), 7.55 ppm (1H, t) and 8.0 ppm (1H, d). The presence of the impurity is supported by LCMS analysis of the material, which revealed two peaks; R_t = 5.36 min, *m/z* (ES^+) 271.1 (MH^+ impurity), 293.0 (MNa^+ impurity) and R_t = 6.62 min, *m/z* (ES^+) 332.2 (MH^+ product), 354.1 (MNa^+ product). Presence of the desired product is supported by the appearance of the characteristic olefinic signal in the ^{1}H NMR spectrum at 5.56 ppm (1H, t, J = 6 Hz). Significantly, in contrast to the preliminary studies, thiopheneboronic acid was now successfully employed in the Suzuki reaction furnishing **4i** in 68% yield (Table 2, entry 9). All of the coupled products have been fully characterised, in particular all contain the distinctive triplet peak between 5-6 ppm in the ^{1}H NMR spectrum that corresponds to the olefinic proton at position 3 in the lactam ring.

Table 2: Suzuki cross-coupling reactions of phosphinate 3.



3 4

Entry	Product	4	Yield	Entry	Product	4	Yield
1		4a	83 %	6		4f	87%
2		4b	81 %	7		4g	72%
3		4c	99 %	8		4h	32%
4		4d	75 %	9		4i	68%[a]
5		4e	65%[a]	-	-	-	-

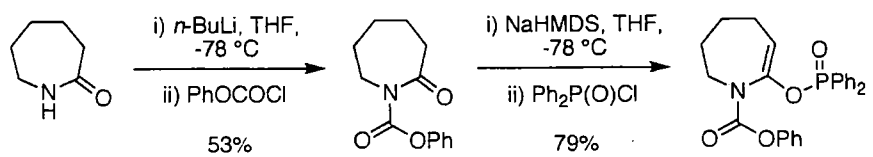
Reaction conditions: 1.1 eq. $ArB(OH)_2$, 0.05 eq. $Pd(PPh_3)_4$, 3 eq. $NaHCO_3$, DME/H_2O (7:3), 85 °C, 0.5-1 h. [a] Quoted yield based on recovered starting material.

2.2 Alternative protecting groups

Having established the viability of the N-Boc caprolactam phosphinate **3** as the electrophilic component in the Suzuki cross-coupling reaction, the scope and limitations of the process were investigated by varying the protecting group. Four common nitrogen protecting groups with varying electronic properties were chosen (PhOCO, Ts, Me and Bn) and the results are discussed below.

2.2.1 N-CO_2Ph caprolactam phosphinate

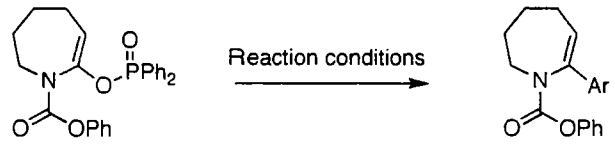
Owing to their similarity, it was expected that changing the protecting group from a Boc group to a phenyl carbamate would have little effect on the outcome of the Suzuki reaction. N-Protection was achieved by treatment of **1** with *n*-BuLi followed by PhOCOCl affording protected lactam **8** in a moderate yield (53%). Subsequent treatment of a cold THF solution of **8** with NaHMDS and trapping of the resultant anion with diphenylphosphonic chloride afforded the desired phosphinate **9** in a 79% yield (Scheme 46). The formation of phosphinate **9** was characterised by a single peak in the ^{31}P NMR spectrum (29.4 ppm, 283 MHz) and purity was confirmed by microanalysis; Found; C, 69.29; H, 5.57; N, 3.12%; Calc. for $C_{25}H_{24}NO_4P$; C, 69.28; H, 5.58; N, 3.23%. As with N-Boc derivative **3** (Scheme 43), phosphinate formation also proved to be more efficient using NaHMDS (79%) rather than LDA/TMEDA (72%).



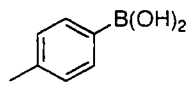
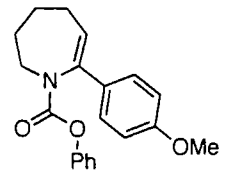
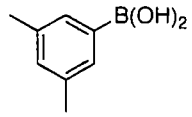
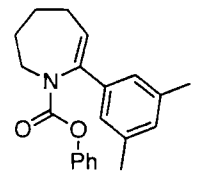
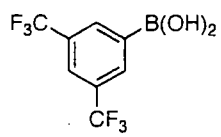
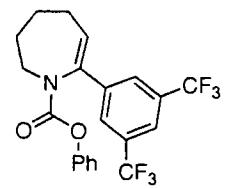
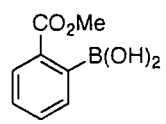
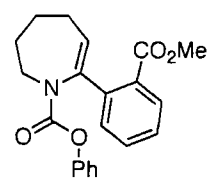
Scheme 46

With phosphinate **9** in hand investigation of the Suzuki cross-coupling reaction was undertaken. Employing the standard conditions identified from the screen for N-Boc phosphinate **3**, phosphinate **9** was coupled with four boronic acids. As expected, slightly reducing the steric crowding of the protecting group (*tert*-butyl to phenyl) had little effect on the outcome of the reaction and the desired products **10a**, **10b** and **10c** were isolated in excellent yield, 83%, 82% and 69%, respectively, Table 3, entries 1-3). Again, electron-rich and electron-poor boronic acids both perform well, the exception being the sterically demanding and deactivated 2-carboxymethylphenylboronic acid, which afforded coupled product **10d** in only moderate yield (37%, Table 3, entry 4). This result is in accordance with the same reaction for the N-Boc derivative **3**, which gave a 32% yield of coupled product **4h** (Table 2, entry 8).

Table 3: Suzuki cross-coupling reaction of phosphinate 9



9 10

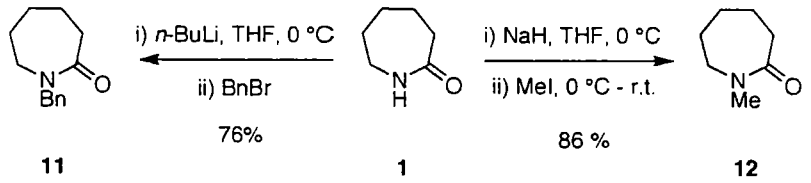
Entry	Boronic acid	Product	10	Yield
1			**10a**	**83%**
2			**10b**	**75%**
3			**10c**	**69%**
4			**10d**	**37%**

Reaction conditions: 1.1 eq. $ArB(OH)_2$, 0.05 eq. $Pd(PPh_3)_4$, 3 Eq. $NaHCO_3$, DME/H_2O (7:3), 85 °C, 0.5-1 h.

2.2.2 Methyl and benzyl protected caprolactam phosphinates

Having successfully explored the electron-withdrawing carbamate protecting group, attention turned to the use of electron-donating alkyl protecting groups and both

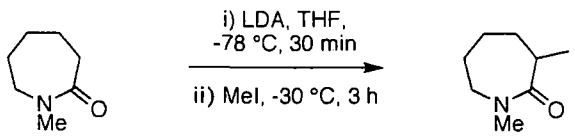
the N-methyl and N-benzyl derivatives were explored. Metallation of caprolactam **1** with *n*-BuLi and trapping of the anion with BnBr afforded N-benzyl caprolactam **11** in high yield (76%). Similarly, treatment of **1** with NaH followed by MeI afforded the N-methyl derivative **12**, also in high yield (86%, Scheme 47).



11 **1** **12**

Scheme 47

With **11** and **12** in hand, phosphinate formation using enolate chemistry was now explored. The precedent for this was found in the report by Ghosez *et al.*[122] who reported the synthesis of 1,3-dimethylcaprolactam **13** by treatment of **12** with LDA followed by MeI (Scheme 48). It was expected, that replacing the MeI with the more oxophilic $Ph_2P(O)Cl$ would lead to an O-alkylation and formation of the desired phosphinate product and not one arising from a C-alkylation.

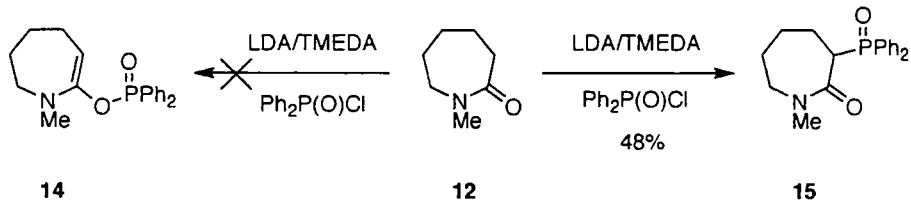


12 68% **13**

Scheme 48

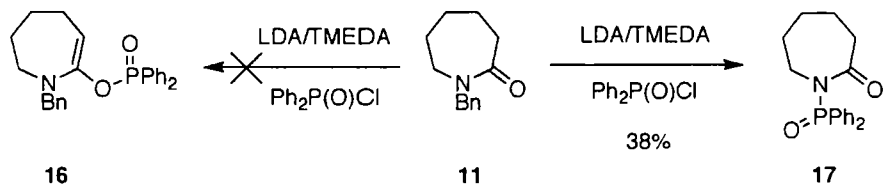
Thus, a cold THF solution of **12** was treated with LDA and the lithium enolate trapped with diphenylphosphoryl chloride. Surprisingly, the major product from the reaction was found to be the C-phosphorylated compound **15** (48%) with none of the desired phosphinate **14** formed (Scheme 49). The lack of the distinctive peak in ^1H NMR spectrum between 5-6 ppm due to the expected newly formed vinyl proton at C-3 indicated the absence of the phosphinate species. Formation of **15** was evident from a

single peak in the ^{31}P NMR spectrum at 35.0 ppm and supported by HRMS analysis which gave a molecular ion at *m/z* = 328.1461, which is consistent with a molecular formula $C_{19}H_{23}NO_2P$ (MH^+). The structure was proven using a combination of COSY, NOE, HSQC and HMBC NMR experiments. Further attempts to form the phosphinate using NaHMDS and KHMDS instead of LDA were also unsuccessful, in both cases only starting material was recovered.



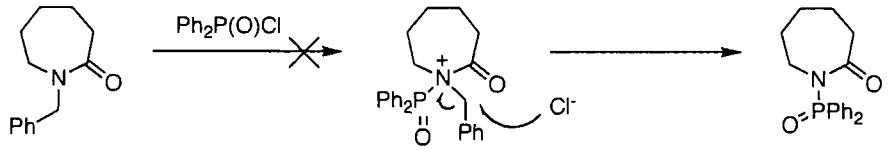
Scheme 49

Unfortunately, treatment of N-benzyl protected caprolactam **11** with LDA/TMEDA and trapping of the enolate anion with diphenylphosphoryl chloride also failed to furnish any of the desired phosphinate **16**. Purification by flash chromatography afforded recovered starting material (37%) and a new phosphorus-containing compound (38%), which was shown to be the N-phosphorylated caprolactam **17** (Scheme 50). Formation of **17** was characterised by a single peak in the ^{31}P NMR spectrum at 32.8 ppm and a molecular ion in the LRMS with *m/z* = 314.2 (MH^+). Further evidence was obtained from the IR and ^1H NMR spectra, which lacked an N-H stretching frequency and the benzylic CH_2 signal seen in the starting material at 4.59 ppm (2H, s, PhCH_2), respectively.



Scheme 50

It was proposed that formation of **17** proceeds *via* formation of quaternary intermediate **18**, which is formed by attack at phosphorous by nitrogen. Quaternary intermediate **18** can then be debenzylated by attack at the benzylic CH_2 with the previously liberated Cl^- ion. However, this mechanistic pathway was discounted when treatment of a THF solution of **11** (at either -78 °C or r.t.) with a THF solution of $Ph_2P(O)Cl$ failed to furnish any of the N-phosphorylated product **17** (Scheme 51). It is therefore possible to conclude that the LDA plays some role in the mechanism. However, no further mechanistic investigations were carried out.



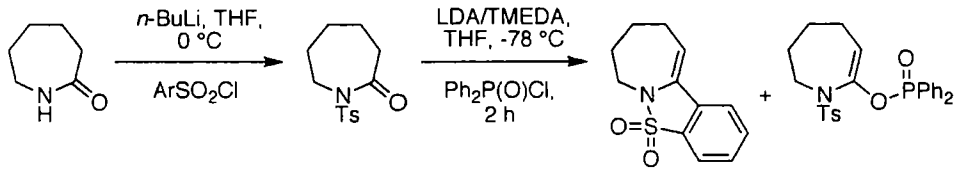
11 **18** **17**

Scheme 51

2.2.3 N-Ts caprolactam phosphinate

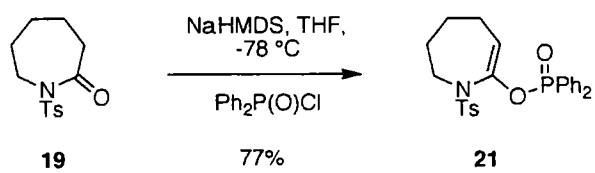
The final protecting group that was investigated was the tosyl group. Preparation of N-tosylcaprolactam **19** was achieved in moderate yield (46%) by treatment of **1** with *n*-BuLi followed by tosyl chloride. Subsequent treatment of **19** with LDA and TMEDA in THF and trapping the resultant anion with $Ph_2P(O)Cl$ was expected to furnish phosphinate **21**. However, chromatography afforded a new product (44%) that did not contain phosphorus accompanied by smaller amounts of the desired phosphinate **21** (15%) and recovered starting material (Scheme 52). Analysis of the ^1H NMR spectrum for the unknown product indicated only three aromatic protons (7.29, d; 7.41 s; 7.64 d) together with a new olefinic signal at 5.78 ppm (t, J = 7 Hz). Moreover, this last signal showed correlations in its NOESY and HMBC spectra with the aromatic proton signal at 7.41 ppm and a quaternary carbon signal at 132.4 ppm, respectively.

Combined with a molecular ion in the HRMS at *m/z* = 250.0896 which is consistent with the molecular formula $C_{13}H_{16}NO_2S$ (MH^+), this suggested the unusual fused sultam **20**. Formation of the sultam can be explained when the powerful directing metallating properties of the sulfonamide group are taken into account.[123] Further investigation of this chemistry is discussed later (Chapter 5).



Scheme 52

The presence of both phosphinate **21** and sultam **20** in the above reaction indicates competing reaction pathways. Therefore, it was expected that by suppressing the *ortho*-lithiation reaction it would be possible to form phosphinate **21** exclusively. It was postulated that changing the counter ion from Li to Na would have the desired effect as Na is only known to undergo *ortho*-metallation reactions under speacialised conditions.[124] Hence, a cold (-78 °C) THF solution of **19** was treated with NaHMDS and the anion trapped with $Ph_2P(O)Cl$. Changing the base had the desired effect and chromatography furnished the desired phosphinate **21** in high yield (73%, Scheme 53).

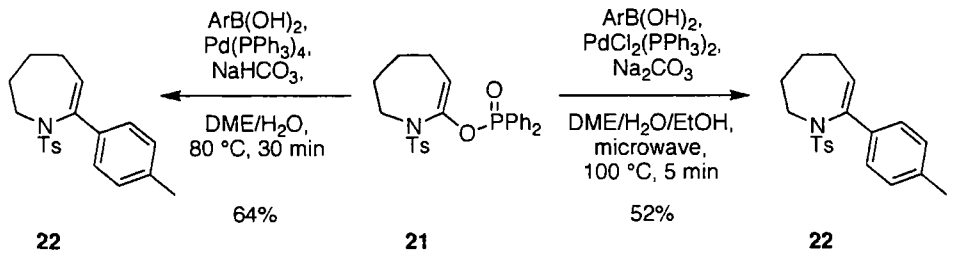


Scheme 53

All that remained was to test phosphinate **21** in the Suzuki cross-coupling reaction. Hence, employing the optimal conditions identified earlier, Suzuki cross-

coupling of phosphinate **21** and *p*-tolylboronic acid afforded the desired coupled product in a 64% yield (Scheme 54).

Microwave-assisted reactions, first reported in 1986 by Giguere[125] and Geyde[126] often benefit from drastically shortened reaction times due to much more efficient heating of the reaction mixture.[127] An additional advantage of carrying out cross-coupling reactions in a microwave is that the reaction mixture need not be degassed beforehand, as the oxygen present in the solvent is expelled during the initial stages of the reaction, saving additional time. Hence, Suzuki cross-coupling of phosphinate **21** with *p*-tolylboronic acid using a standard set of Suzuki microwave conditions[128] was attempted. The reaction was worked up after 5 min and the desired product isolated in 52% yield (Scheme 54). It is worth noting that the overall process takes just 15 min and the yield is comparable to the yield from the thermal reaction. Neither the microwave nor the thermal reaction went to completion and some starting material was recovered in each case.



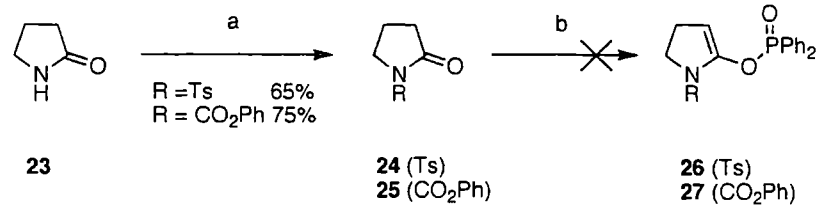
Scheme 54

2.3 Varying the lactam ring size

Having fully explored the nature of the protecting group, attention then turned to investigating the effect of the lactam ring size upon the process. Five-, six- and eight-membered rings were all investigated with varying results.

2.3.1 Five-membered lactam ring (pyrrolidinone)

Before phosphinate formation could be attempted, a suitable protecting group was required. Previous work had shown the Boc group to be unstable in combination with a six-membered ring lactam phosphinate due to the high ring strain present. It was therefore not considered for use with the five-membered ring phosphinate. Instead, the tosyl and phenyl carbamate protecting groups were explored in combination with pyrrolidinone **23**. Hence, treatment of a cold THF solution of **23** with *n*-BuLi followed by either tosyl chloride or phenylchloroformate was undertaken and afforded the desired products **24** and **25** in good yields (65% and 75%, respectively, Scheme 55). The N-Ts derivative **24** was characterised by two new aromatic signals in the ^{1}H NMR spectrum at 7.33 ppm (2H, d, J = 8 Hz) and 7.91 ppm (2H, d, J = 8 Hz) due to the tosyl ring protons. Evidence for the formation of **25** was given by the appearance of three signals in the ^{1}H NMR spectrum due to the new aromatic ring at 7.16 ppm (2H, d, J = 8 Hz), 7.23 ppm (1H, t, J = 8 Hz), and 7.37ppm (2H, t, J = 8 Hz). In addition, neither compound revealed an N-H stretching frequency in their IR spectra. Whilst attempts to generate the five-membered ring enol phosphinates **26** and **27** appeared successful by LCMS analysis of the crude material, all attempts to purify these substrates proved unsuccessful leading only to recovered lactams **24** and **25** (Scheme 55). Similar results were obtained on using the phosphinates directly in cross-coupling experiments. These results suggest that enol-phosphinates-derived from five-membered ring lactams are not useful substrates for cross-coupling protocols, the strained nature of the unsaturated ring making them very prone to degradation.



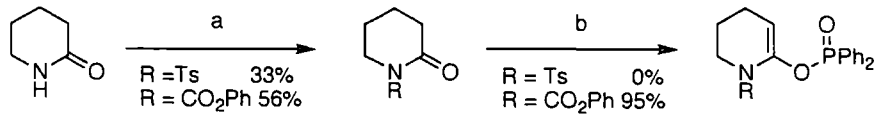
23 **24** (Ts) **25** (CO_2Ph) **26** (Ts) **27** (CO_2Ph)

a) i) *n*-BuLi, THF. ii) TsCl or $PhCO_2Cl$. b) i) NaHMDS, THF, -78 °C. ii) $Ph_2P(O)Cl$, THF

Scheme 55

2.3.2 Six-membered ring (valerolactam)

As mentioned above, the Boc protecting group is unsuitable for six-membered ring lactams. Therefore, it was hoped that altering the protecting group might enhance the stability of the phosphinate moiety and in turn the efficiency of the subsequent cross-coupling reactions. As with the five-membered ring lactam, both the tosyl and phenyl carbamate-protecting groups were explored. Thus, valerolactam **28** was readily protected by treatment with *n*-BuLi followed by addition of the appropriate electrophile affording **29** and **30** in moderate yields (33% and 56%, respectively, Scheme 56). Synthesis of phosphinates **31** and **32** was attempted by metallation with NaHMDS and quenching with $Ph_2P(O)Cl$. Analysis of the crude material for each reaction by LCMS revealed almost complete conversion in to the desired phosphinates. Phosphinate **31**, R_t = 3.33 min *m/z* = 454.1 (MH^+) and phosphinate **32**, R_t = 1.60 min, *m/z* = 420.3 (MH^+). Disappointingly, the N-Ts phosphinate **31** could not be isolated efficiently and flash chromatography resulted in degradation and furnished only protected lactam **29**, presumably due to acid-promoted hydrolysis on the silica gel. However, phosphinate **32** proved stable to flash chromatography and was isolated in excellent yield (95%, Scheme 56). Formation of **32** was characterised by a distinctive olefinic signal in the ^1H NMR spectrum at 5.23 ppm (1H, dt, J^P = 2 Hz, J^H = 6 H) and a single resonance in the ^{31}P NMR spectrum at 31.1 ppm.

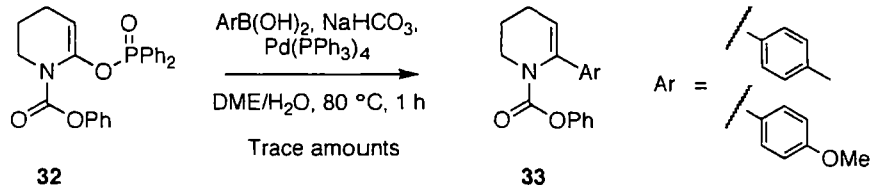


28 **29** (Ts) **30** (CO_2Ph) **31** (Ts) **32** (CO_2Ph)

a) i) *n*-BuLi, THF. ii) TsCl or $PhCO_2Cl$. b) i) NaHMDS, THF, -78 °C. ii) $Ph_2P(O)Cl$, THF

Scheme 56

Disappointingly, several attempts to couple **32** with both *p*-methoxyphenyl and *p*-tolylboronic acids were unsuccessful with only trace amounts (< 10%) of enamine **33** being observed in each case (Scheme 57).

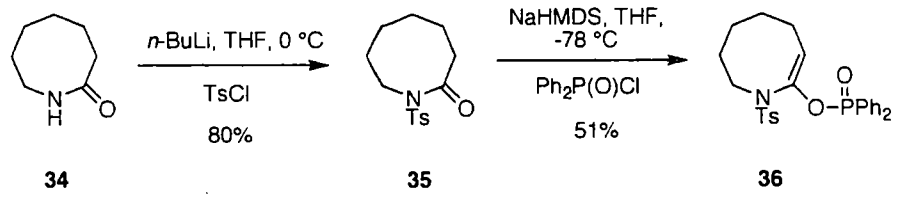


32 **33**

Scheme 57

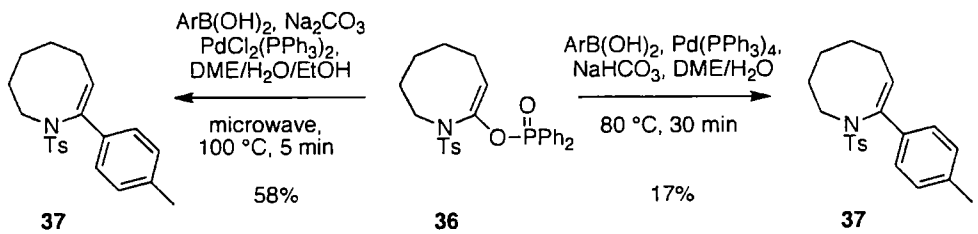
2.3.3 Eight-membered ring lactam

In contrast to the five- and six-membered ring lactams, it was postulated that ring strain in the eight-membered ring lactam should be significantly reduced making phosphinate formation uncomplicated. Protection of lactam **34** proceeded smoothly affording **35** in high yield (80%). Subsequent metallation of **35** with NaHMDS followed by enolate trapping with $Ph_2P(O)Cl$ furnished, as expected, the desired phosphinate **36** in 51% yield (Scheme 58). Formation of **36** was indicated by the distinctive signal due to the newly formed C-3 vinylic proton in the ^1H NMR spectrum at 5.54 ppm (1H, dt, J^P = 2 Hz, J^H = 8 Hz) and a molecular ion in the HRMS of *m/z* = 482.1554, which is consistent with the molecular formula $C_{26}H_{29}N_1O_4S_1P_1$ (MH^+).



Scheme 58

Suzuki cross-coupling of phosphinate **36** with *p*-tolylboronic acid employing the optimal conditions identified earlier afforded both the desired coupled product (58%, Scheme 59) and recovered starting material (33%). Formation of **37** was characterised by a new signal in the ^{1}H NMR spectrum at 6.39 ppm (1H, t, J = 8 Hz) due to the vinylic proton at C-3. Suzuki cross-coupling of phosphinate **36** employing microwave heating was less efficient than the thermal protocol and furnished only 17% of cross-coupled product **37** (Scheme 59). Notably, this substrate performed better in the thermal Suzuki reaction than the analogous N-Ts-protected seven-membered ring phosphinate **21** (Scheme 54).



Scheme 59

2.4 Summary

Vinyl phosphinates derived from seven- and eight-membered ring lactams with an electron-withdrawing nitrogen protecting group are readily prepared (51 – 95%) and undergo Suzuki cross-coupling reactions in good to excellent yields (58 – 99%). The use of a sterically hindered and electron-deficient boronic acid resulted in a drop in

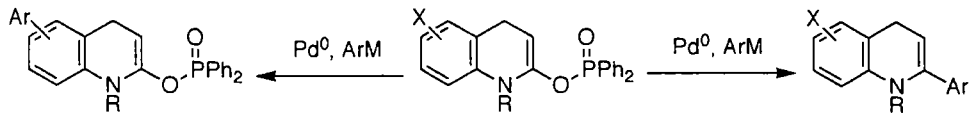
yield (32 and 37%). When using electron-donating nitrogen protecting groups (Me and Bn) the phosphinate fails to form. Phosphinate formation is also possible employing five-membered rings. However, due to the increased ring strain present in these substrates they were found to be highly unstable and could not be isolated efficiently. The N-CO_2Ph-protected six-membered ring phosphinate was isolated in excellent yield (95%). However, despite several attempts it could not be coupled efficiently in the Suzuki cross-coupling reaction. The use of NaHMDS is preferential to the use of LDA/TMEDA as the metallating reagent in the phosphinate-forming step as it gives a more efficient reaction and eliminates competing reactions such as *ortho*-lithiation or lithium-halogen exchange. Preliminary studies have shown that the Suzuki reaction can also be carried out in a microwave reactor.

3 Relative reactivity studies

3.1 Introduction

It has been shown that palladium-catalysed Suzuki cross-coupling reactions of simple lactams can be made possible by activation of the carbonyl group as either a vinyl phosphinate or phosphonate. Whilst investigating these species in cross-coupling protocols, it was considered important to determine their reactivity in comparison to the more commonly employed electrophilic species, namely the halides and triflates. It was expected that both the phosphinate and phosphonate moieties would be more reactive than chlorides but less so than both bromides and triflates.

Phosphinates-derived from 2-quinolinones substituted with either a halogen or triflate on the aromatic ring, e.g. compound **38**, contain two possible sites at which a cross-coupling reaction can occur, furnishing either compound **39** or **40**. Such a system represents an attractive means of carrying out relative reactivity studies between vinyl phosphinates and aryl halides and triflates (Scheme 60).



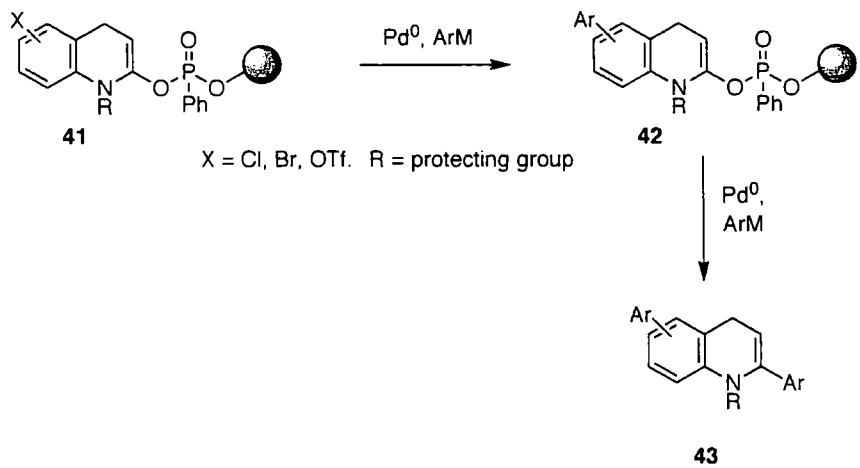
39 **38** **40**

X = Cl, Br, OTf. R = protecting group

Scheme 60

A similar substrate can be imagined for investigating the relative reactivity of vinyl phosphonates **41** (Scheme 61). Moreover, previous work in the group has shown that phosphonates can be immobilised on a phenol on polystyrene resin giving access to simple diversity linkers (Scheme 40). By carrying out reactivity studies on resin **41** it

is hoped that selective coupling at one electrophilic species in preference to the other will be realised. This then has implications in solid phase organic synthesis, where a combinatorial approach to the synthesis of substituted quinoline-type heterocycles *via* sequential cross-coupling reactions and a diversity cleavage step can be adopted (Scheme 61). This type of six-six-fused heterocyclic structure is commonly found in natural and biologically active compounds and methods for the construction of these motifs remain important.



Scheme 61

Before investigating vinyl phosphonates, it was decided to explore phosphinate chemistry first. With this in mind the synthesis and subsequent cross-coupling chemistry of the methyl-, chloro- and bromo-substituted quinolinone-derived phosphinates **44**, **45** and **46** were investigated (Figure 5).

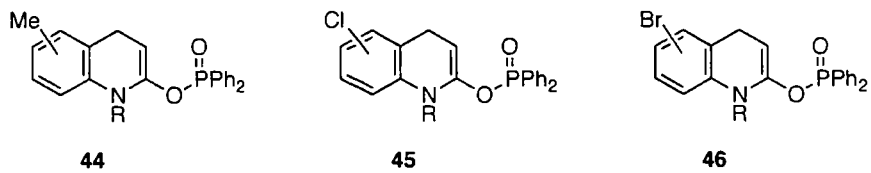
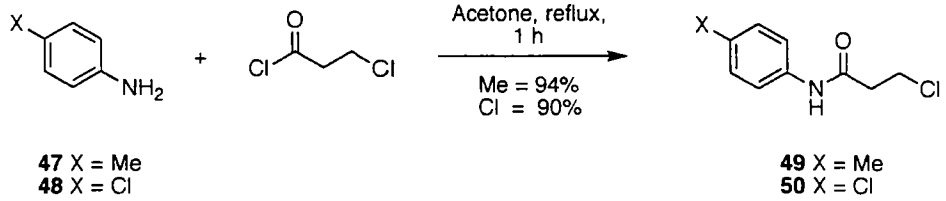


Figure 5

3.2 Quinolinones

A search of the literature revealed that the synthesis of the methyl- and chloro-substituted quinolinones such as **44** and **45** could be achieved from commercially available toluidene or *p*-chloroaniline, **47** and **48**, respectively. These starting materials would lead to the methyl or chloro substituent taking the 6-position in the subsequent quinolinone substrates. Thus, according to the method of Guarna *et al.*[129] slow addition of 3-chloropropionyl chloride to a refluxing acetone solution of the appropriate aniline afforded amides **49** and **50** in excellent yields (94% and 90%, respectively, Scheme 62). The pure amides were precipitated from the cooled reaction mixture upon addition of 5 M aq. HCl and characterised by the correct mass and isomer ratio in their LRMS. Compound **49**, *m/z* = 220.1/222.1 [3:1 ratio] (MNa^+ Cl^{35}:Cl^{37}) and compound **50**, *m/z* = 217.9/219.9 [3:1 ratio] (MH^+ Cl^{35}:Cl^{37}).



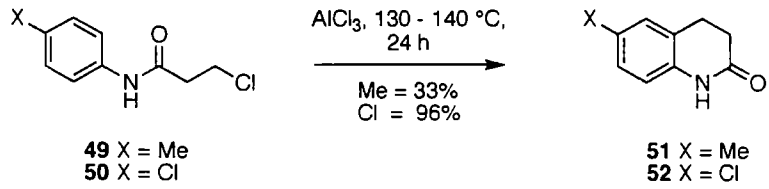
47 X = Me
48 X = Cl

49 X = Me
50 X = Cl

Scheme 62

With amides **49** and **50** in hand, Friedel-Crafts cyclisation was carried out by treating a melt of the desired amide with $AlCl_3$ and heating for 24 h. Following the method of Guarna,[129] amide **49** was treated with 1.1 Eq. of $AlCl_3$. Under these conditions the methyl derivative **49** afforded the desired product **51** in a disappointing yield (33%) as well as a significant quantity of recovered starting material. Attempts to improve the efficiency of the transformation by varying the equivalents of $AlCl_3$, the reaction time and the temperature were largely unsuccessful with either limited or no formation of the desired quinolinone observed. Friedel-Crafts cyclisation of the chloro-

derivative **52** required 2 equivalents of $AlCl_3$ and proceeded smoothly under thermal conditions affording quinolinone **52** in quantitative yield (96%) without the need for further purification (Scheme 63).

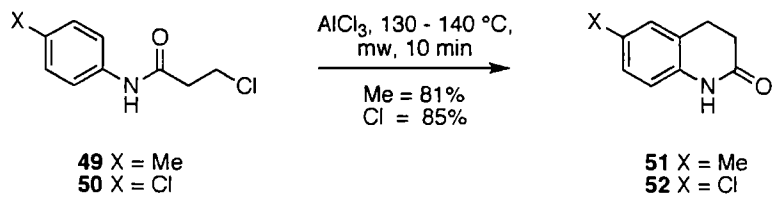


49 X = Me
50 X = Cl

51 X = Me
52 X = Cl

Scheme 63

As a consequence of the long reaction times needed to carry out these transformations the possibility of using a microwave reactor was explored. Employing the same conditions as in the thermal reactions (chloro – 2 eq. $AlCl_3$, 140 °C, methyl – 1.1eq. $AlCl_3$, 130 °C) it was possible to dramatically reduce the reaction times for the formation of both the methyl and chloro quinolinones from between 24 - 96 h to less than 10 min. In contrast to the thermal protocol, formation of the methyl quinolinone was now achieved in high yield (81%), as was the chloro derivative (85%, Scheme 64). Moreover, the reactions were extremely clean often requiring no purification and formation of methyl derivative **51** proceeded without any isomerisation. An upfield shift in the ^1H NMR spectrum due to the C4-H_2 signal from 3.85 ppm to 2.92 ppm (2H, t, J = 7 Hz, 4-H_2) and 3.89 ppm to 2.94 ppm (2H, t, J = 7 Hz, 4-H_2) for **51** and **52**, respectively gave evidence that cyclisation had been successful and was confirmed when the data matched that in the literature.[129]

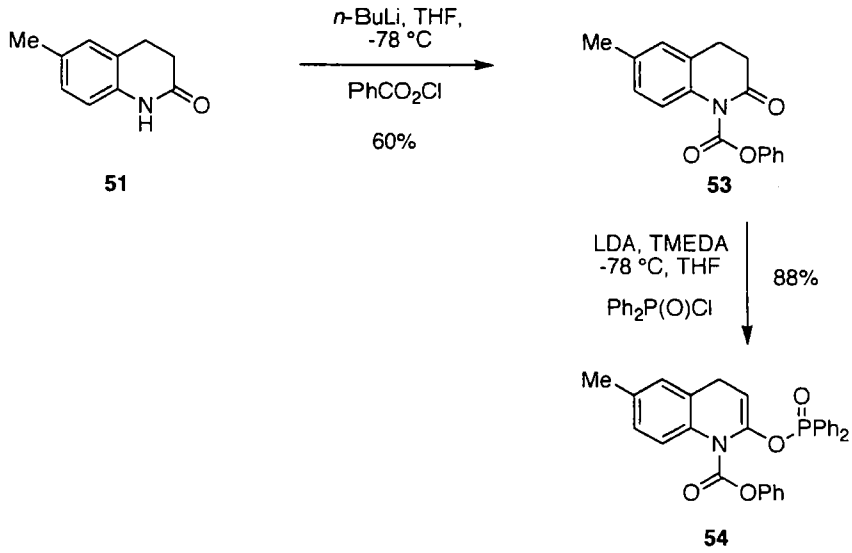


49 X = Me
50 X = Cl

51 X = Me
52 X = Cl

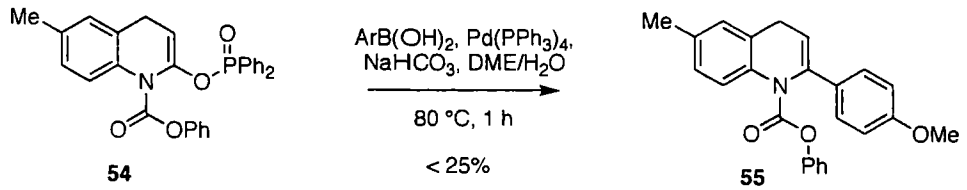
Scheme 64

With quinolinones **51** and **52** in hand, phosphinate formation and subsequent cross-coupling chemistry was explored. Before investigating the chloro-derivative, a model study was carried out using the 6-methyl derivative **52**. Prior to phosphinate formation a suitable protecting group was required. Based on previous experience it was decided to employ a phenylcarbamate-protecting group as this had proved the most stable during the valerolactam studies undertaken earlier (Scheme 56). Thus, using the same method as was used for valerolactam **30**, compound **51** was treated dropwise with *n*-BuLi then quenched with phenyl chloroformate. Chromatography furnished the protected quinolinone **53** in good yield (60%, Scheme 65). Formation of **53** was characterised by the appearance of two carbonyl-stretching frequencies in the IR spectrum at 1783 cm^{-1} and 1699 cm^{-1}. The correct molecular mass and purity were confirmed by a single peak in the GCMS, R_t = 23.4 min, with *m/z* = 281.1 (M^+), 188.1 (M^+ - PhO), 160.1 (M^+ - CO_2Ph). Subsequent formation of the phosphinate by treatment of **53** with LDA/TMEDA followed by $Ph_2P(O)Cl$ afforded phosphinate **54** in an 88% yield (Scheme 65). The appearance of the distinctive signal due to the newly formed olefinic proton in the ^1H NMR spectrum at 5.60 ppm (1H, dt, $^4J_{HP}$ = 3 Hz, J_{HH} = 7 Hz) and a single peak in the ^{31}P NMR spectrum at 31.5 ppm gave evidence for **54**. However, the product was found to be slightly impure and although attempts to further purify the material *via* column chromatography afforded clean material, it also resulted in a greatly reduced yield (46%). The identity and purity was confirmed at this stage by a single peak in the GCMS, R_t = 23.49 min, *m/z* = 281.1 (M^+ - $C_{12}H_9OP$).



Scheme 65

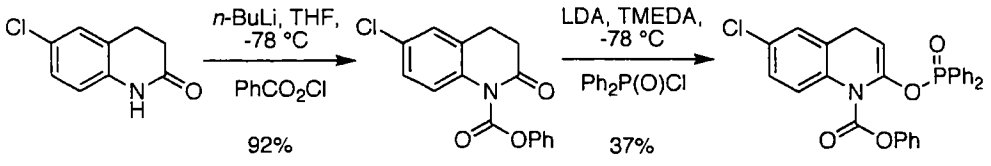
With phosphinate **54** in hand the Suzuki cross-coupling reaction was then investigated. Following the protocol successfully applied in the cross-coupling of caprolactam enol-phosphinates ($ArB(OH)_2$, $NaHCO_3$, $Pd(PPh_3)_4$, DME/H_2O, 80 °C, 1 h) the reaction of **54** with *p*-methoxyphenylboronic acid was attempted. Attempts to purify the material by flash chromatography failed to afford a clean sample of the desired product and a reliable yield could not be obtained (< 25%). However, following chromatography, evidence for the formation of the coupled product was given in the ^1H NMR spectrum by a new olefinic signal at 5.91 ppm (1H, t) due to the C-3 proton. The reaction also afforded a small amount of recovered starting material (17%); the rest of the isolated material was the unprotected quinolinone **51**. The latter observation suggests the phosphinate/protecting group combination is unstable to the Suzuki cross-coupling conditions (Scheme 66). This observation was disappointing as the simple N-CO_2Ph-protected valerolactam phosphinate **32** proved extremely stable. However, being fused to a flat aromatic ring, it is expected that the strain present in phosphinate **54** will be greater than that in the corresponding valerolactam phosphinate therefore making it less stable.



54 55

Scheme 66

The model study with methyl quinolinone **54** indicated that phosphinate formation and subsequent Suzuki cross-coupling were both viable experiments with these substrates and on this basis it was decided to attempt the synthesis of the chloro phosphinate derivative. In a similar fashion to the 6-methyl derivative, 6-chloro quinolinone **52** was protected as the phenyl carbamate affording **56** in excellent yield (92%). Trapping of the lithium enolate of **56** with phosphoryl chloride furnished the desired phosphinate **57** in 37% yield (Scheme 67). Formation of **57** was characterised by a single resonance in the ^{31}P NMR spectrum at 31.9 ppm and the characteristic signal in the ^{1}H NMR spectrum due to the new olefinic proton at C-3, 5.59 ppm (1H, dt, $^{4}J_{HP}$ = 2 Hz, J_{HH} = 5 Hz, 3-*H*). Although isolable by flash column chromatography, phosphinate **57** is not stable to storage in the solid state and significant decomposition back to the starting material **56** was observed over a period of days. Decomposition of the material during flash chromatography was also suspected and 2D TLC confirmed this suspicion.

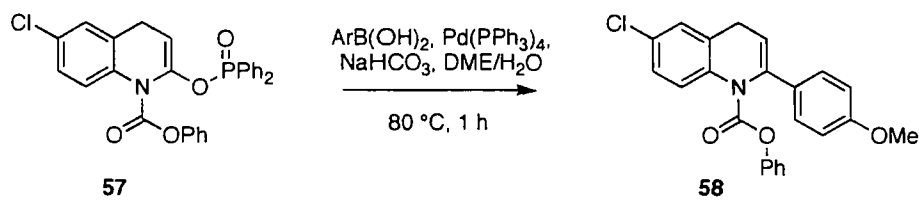


52 56 57

Scheme 67

With phosphinate **57** in hand, the reactivity of the two electrophilic centres could be investigated. It is well known that aryl chlorides show limited reactivity in cross-

coupling protocols unless specialised conditions are employed (Scheme 14). Moreover, in the model study with methyl quinolinone phosphinate **53**, the phosphinate moiety was found to be reactive towards standard Suzuki reaction conditions (Scheme 66). In light of these two observations, it was postulated that subjecting **57** to the same Suzuki conditions would result in selective coupling at the phosphinate in preference to the aryl chloride. Hence, a solution of **57**, *p*-methoxyphenylboronic acid, $NaHCO_3$ and $Pd(PPh_3)_4$ in DME/H_2O was heated at reflux for 1 h (Scheme 68). Purification of the crude material by flash chromatography proved problematic and the amount of material obtained from the column was minimal. Moreover, both ^1H NMR spectroscopy and GCMS showed the chromatographed material to be impure. However, evidence for coupling at the phosphinate moiety was given by the appearance of a new olefinic signal at 5.9 ppm (1H, t) in the ^1H NMR spectrum of the crude material. Moreover, a molecular ion of *m/z* = 391 and 393 [3:1 ratio] in the GCMS of the crude material also indicated coupling had occurred at the phosphinate moiety. There was no evidence for cross-coupling having occurred at the aryl chloride moiety. From these observations it appears that, as expected, the phosphinate functionality is more reactive than the chloride. However, the instability of the phosphinate moiety in these compounds was proving particularly problematic. It was hoped that these problems could be overcome whilst investigating the bromide derivative.



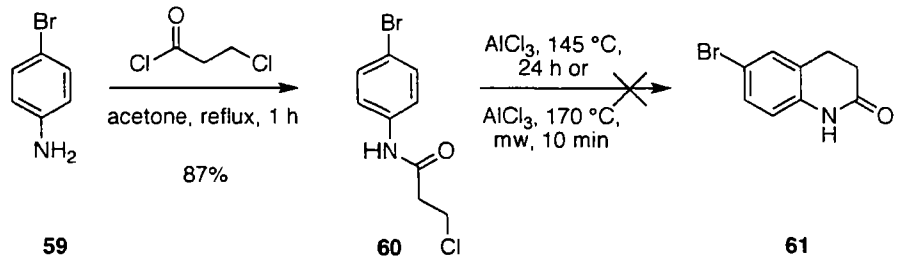
57 **58**

Scheme 68

Aryl bromides exhibit far higher reactivity in cross-coupling reactions than the corresponding aryl chlorides and in general do not require specialised conditions in

these protocols. Having shown the phosphinate moiety to be more reactive than simple aryl chlorides, their reactivity in comparison to simple aryl bromides was subsequently explored.

Although the 6-bromo quinolinone, **61**, was not reported in Guarna's original paper,[129] it was expected that it could be synthesised in a similar fashion to the methyl and chloro derivatives discussed above. Hence, N-acylation of *p*-bromoaniline **59** was achieved by treatment of a refluxing acetone solution of **59** with 3-chloropropionyl chloride. Compound **60** was characterised by the presence of an amide carbonyl signal in the ^{13}C NMR spectrum at 169.9 ppm and a carbonyl stretching frequency in the IR spectrum at 1697 cm^{-1}. Unfortunately, all attempts at the $AlCl_3$-mediated Friedel-Crafts cyclisation of amide **60** were unsuccessful, leading to a complex mixture of products and none of the desired quinolinone **61** (Scheme 69).

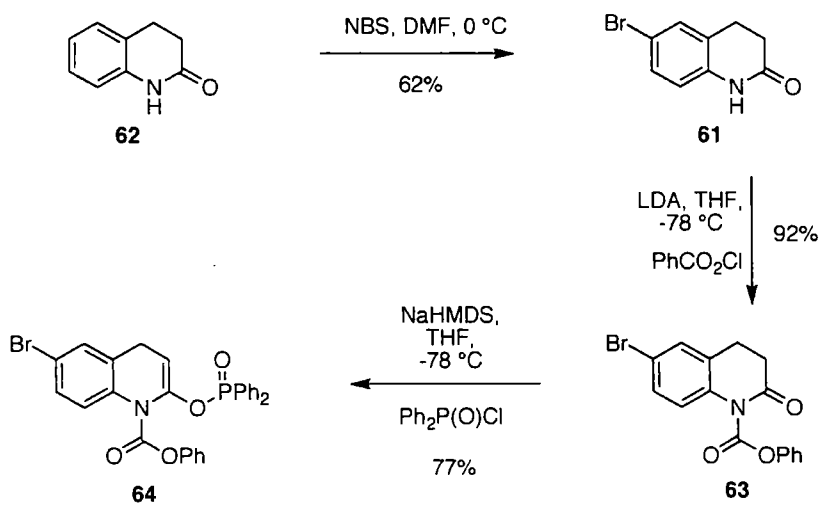


59 **60** **61**

Scheme 69

An alternative approach can be imagined from commercially available unsubstituted quinolinone **62** as reported in a later paper by Guarna *et al.*[130] Thus, dropwise treatment of a cold, DMF solution of **62** with a solution of NBS in DMF afforded the desired brominated quinolinone, **61**, in good yield (62%). This compound was subsequently sourced commercially. **61** was characterised by a single peak in the LCMS, R_t = 2.65 min, *m/z* = 267.0/269.0 [1:1 ratio] ($MMeCN^+$ Br^{79}:Br^{81}) and the appearance of only three aromatic protons in the ^1H NMR spectrum at 6.76 ppm (1H, d, J = 10 Hz) and 7.24-7.28 ppm (2H, m). All the data matched that of the commercially

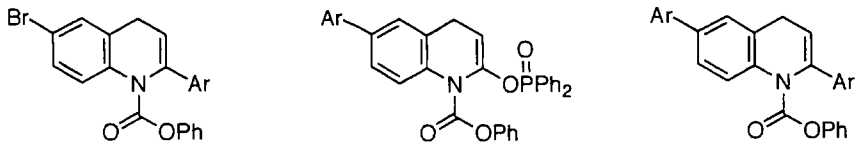
obtained sample. Protection of **61** was attempted by metallation with *n*-BuLi followed by slow addition of $PhCO_2Cl$ but resulted only in reduction of the aryl bromide. A brief investigation of alternative bases ended when metallation with LDA in THF followed by treatment with $PhCO_2Cl$ afforded **63** in excellent yield (92%). The desired phosphinate, **64**, was isolated in 77% yield following treatment of **63** with NaHMDS followed by $Ph_2P(O)Cl$ (Scheme 70). Formation of **64** was confirmed by the appearance of the distinctive peak at 5.60 ppm (1H, dt, J_{HH} = 5 Hz, $^4J_{PH}$ = 2 Hz) in the ^1H NMR spectrum corresponding to the olefinic proton at C-3. Unsurprisingly, storage of phosphinate **64** was problematic, the highly strained nature of the substrate causing gradual decomposition to the starting lactam **63**. Reliable investigations using **64** require it to be made and used immediately. However, decomposition of the phosphinate is also observed during purification and the presence of some starting material was unavoidable. With phosphinate **64** in hand the reactivity of the two electrophilic sites in this compound were investigated in the Suzuki cross-coupling reaction.



Scheme 70

It was hoped that subjecting phosphinate **64** to a Suzuki cross-coupling protocol would lead to one of three possible products, **65**, **66** or **67** (Figure 6). Compounds **65**

and **66** would occur due to selective coupling at the phosphinate or bromide, respectively, and **67** as a result of competing, non-selective cross-coupling in which both centres react simultaneously. The aim of this work was to develop selective coupling strategies for the two electrophilic centres. Therefore it was hoped that competing cross-coupling would not be observed.



65 **66** **67**

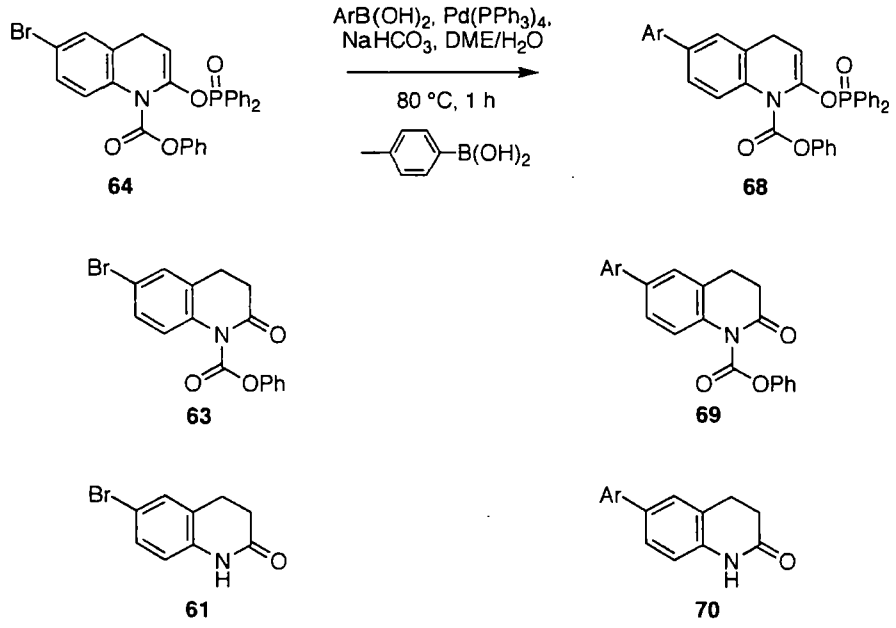
Figure 6

Suzuki cross-coupling of phosphinate **64** was undertaken using the same conditions as were used for the coupling of the methyl- and chloro-derivatives discussed above. Analysis of the crude material by a combination of thin layer chromatography, ^{1}H NMR spectroscopy and LCMS revealed the presence of several compounds including recovered starting material **64**, bromides **63** and **61** and biaryls **68**, **69** and **70** (Scheme 71). These findings indicated that;

- Unsurprisingly, the phosphinate functionality was unstable to the reaction conditions as was the carbamate protecting group and both were prone to hydrolysis during the reaction.
- Cross-coupling occurred with complete selectivity for the aryl bromide over the phosphinate.
- Despite this selectivity, the coupling of the bromide was not particularly efficient and substantial amounts of bromide remained unreacted.

In conclusion, poor conversion of the bromide and facile decomposition of the phosphinate and protecting group under the reaction conditions was leading to a complex mixture of reaction products. However, a useful selectivity for the bromide

over the phosphinate was observed and it was expected that optimisation of the reaction could circumvent the limitations. Efforts towards the optimisation of this reaction are discussed in the following section.



Scheme 71

3.2.1 Experimental design and principal component analysis

This section will discuss attempts to optimise the above process using statistical design of experimental methods (DoE) in combination with PCA (principal component analysis) models of reagents and solvents. Almost all of the work discussed in this section was carried out with the help and guidance of GSK employees who are experts in this field. Consequently, the general principals of these methods will be discussed to familiarise the reader with the basic ideas behind the approach. However, owing to the depth of the subject and its background in statistics, a detailed discussion is beyond the scope of this review and the reader is referred to the book 'Design and optimisation in organic synthesis' by Rolf and Johan Carlson.[131]

3.2.1.1 Experimental design

Experimental design is a method that uses statistically designed experiments and multivariate methods to optimise processes in synthetic chemistry. Over the past twenty years or so the method has become a valuable tool in many manufacturing processes including those employed by most pharmaceutical companies' process departments. However, it is still largely overlooked by the synthetic organic academic community.

A chemical reaction is a complex process involving many different factors, e.g. the cross-coupling reaction that is to be optimised has at least nine factors. These include the reaction time, temperature and concentration, the method of stirring (mechanical or magnetic or none), identity of the solvent, base, catalyst and ligand and the catalyst loading. Rarely is the outcome of a chemical reaction governed by a single factor alone but, by several factors acting at once and often by interactions between these different factors. There are two possible methods for optimising chemical reactions; the 'one factor at a time approach' or the 'factorial approach' and each will be discussed in turn.

3.2.1.2 Factorial design approach vs one factor at a time approach

In order to look at the two approaches in more detail, a simple example will be used. Imagine that the reduction of cyclohexanone to cyclohexanol using $NaBH_4$ in a THF solution at -78 °C is to be optimised (Figure 7) and the response to be measured is the yield of cyclohexanol. The identity of the reagents is already known, the temperature is to remain constant and the stirring is magnetic, there are therefore three possible factors to be investigated.

1. The equivalents of $NaBH_4$ to be used.

2. The concentration of the reaction mixture.

3. The time that the reaction is allowed to run for.

The value given to each factor can theoretically range from zero to infinity. Therefore, upper and lower limits need to be assigned to each factor that provide sensible ranges, e.g. the equivalents of $NaBH_4$ to be used might take a lower limit of 1 eq. and an upper limit of 2 eq. Similarly, sensible limits can be chosen for the concentration (0.1 M – 1 M) and the reaction time (0.5 h – 2.5 h). Doing this generates an experimental domain or space for the reaction in which the boundaries are defined by the values of the upper and lower limits given to each factor. Using a three factor design, the experimental domain can be easily visualised using a set of axis (x, y and z) along which the factors are placed. In this way the experimental domain becomes the area inside the box (Figure 7). It is important to note that any given point within the experimental domain has three precise co-ordinates, which correspond to a set of experimental conditions for the given reaction. Moreover, each set of reaction conditions potentially has a different response, i.e. yield of cyclohexanol. Importantly, somewhere within the experimental domain will be an area where the response is greater than the rest of the domain, i.e. the optimal reaction conditions, this is the area of interest.

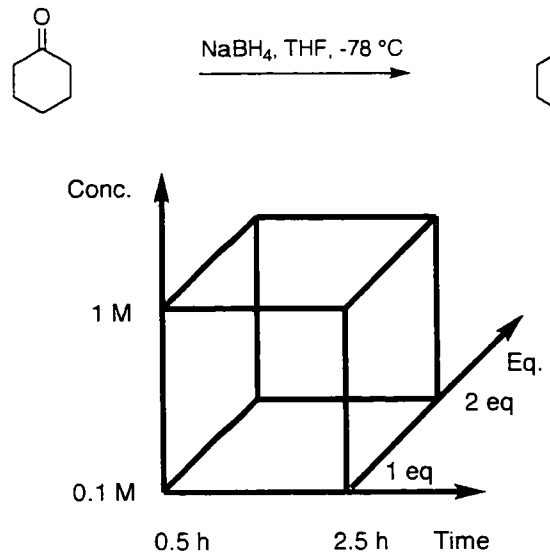


Figure 7 - Representation of the experimental domain for a three factor reaction (reduction of cyclohexanone), the experimental domain is the area inside the box.

3.2.1.2.1 One factor at a time

The most common method of reaction optimisation remains the 'one factor at a time' approach, where a single factor is varied whilst the others are kept constant until the highest response is found. This factor is then maintained at the supposed optimal value and the next factor is explored in an identical manner. This is illustrated for the reduction of cyclohexanone using experimental domain diagrams shown in Figure 8. In diagram **A** the time and equivalents are held at a constant level whilst the concentration is varied, in diagram **B** the concentration and equivalents are held constant and time varied. In this example a total of eight experiments would have been carried out to generate the results. This approach is suitable only if the factors are acting independently of one another, which is rarely the case. Optimising a reaction in this manner interrogates only a very small area of the experimental domain. As a result, this method is particularly inefficient and will usually fail to identify the optimal conditions for the reaction.

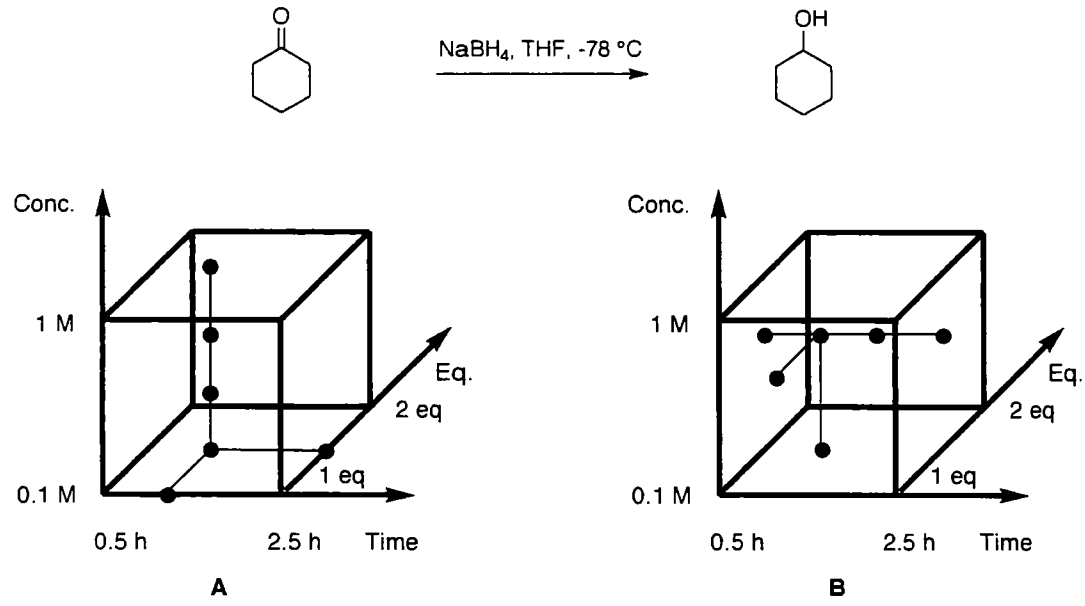


Figure 8: A 'one factor' at a time approach to optimisation of a three factor reaction (X, Y and Z). The experimental domain is the area inside the box.

3.2.1.2.2 DoE Approach

Conversely, a DoE approach allows the experimenter to investigate all three factors simultaneously. As with the 'one factor' method, the reduction of cyclohexanone will be used to help explain the basics of a factorial design. Again, sensible values are assigned to each factor resulting in the formation of an experimental domain. In this example a two-level factorial design will be used. This is the simplest and most commonly used factorial design and simply means that each factor is investigated at two discrete values, which take the upper and lower limits chosen by the experimenter. For example, the concentration will be investigated at 0.1 M and 1 M, the time at 0.5 h and 2.5 h and the equivalents at 1 Eq. and 2 Eq. Experimentally, each value for each factor is investigated in combination with every other value for every other factor. This arrangement arranges the reactions to be carried out, or reaction conditions to be used, at the corners of the experimental domain, this is illustrated in Figure 9. In the example being used where there are a total of three factors this requires a total of eight

experiments. In addition to these eight experiments, multiple centre points must also be carried out to estimate the level of experimental error in the subsequent data, four is usually sufficient. Therefore, a total of 12 reactions must be run to generate the required data. A designed approach like this, where the experiments are arranged in a logical fashion, means that the data can also be analysed in a logical fashion using computer software. The software is able to correlate variations in the outcomes of the experiments back to variations in the reaction conditions. In this way, the software generates a mathematical model of the process. The accuracy of the model is checked by predicting the outcome of the reactions that were run in the initial screening experiment. If sufficiently accurate the model then predicts the outcome (yield of cyclohexanol) of all the other possible combinations of factors (reaction conditions) within the experimental domain that were not run in the original design, thereby mapping the entire experimental domain. The predictions that give the best outcomes can then be tested experimentally. The model also reveals which factors have the most pronounced effects on the outcome of the reaction and, how varying these factors alter the outcome. It also reveals which factor interactions are important and how they influence the outcome. Although all the factors may be necessary for the reaction to proceed, some will undoubtedly have a more important role to play in the outcome than others and this understanding can aid further optimisation should it be required.

Although a degree of careful planning is required when considering a DoE approach, this method of optimisation requires very few experiments to be carried out in order to investigate a large reaction space making it particularly efficient method for optimisation. With careful planning and consideration prior to the experimentation, the optimal conditions, or more accurately the range of conditions that give the required outcome for the reaction can be quickly identified and then tested through experimentation.

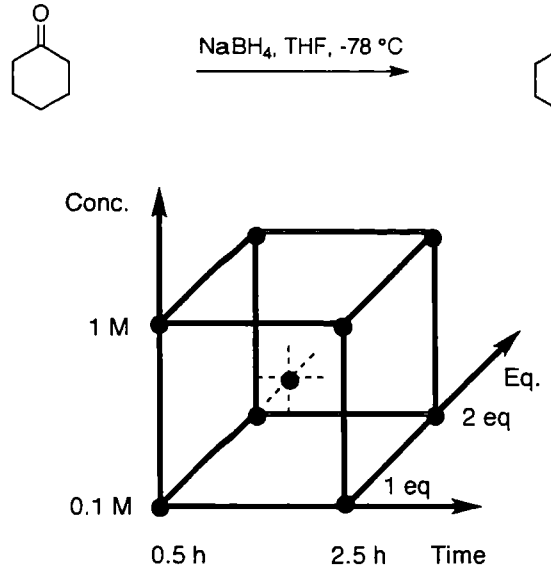


Figure 9: A complete factorial design including centre point

3.2.1.2.3 Complete factorial designs and fractional factorial designs

In the factorial design discussed above all the possible combinations of factor settings were investigated requiring a total of 8 experiments. This type of design is classified as a 'complete factorial design' and is possible because the number of factors being investigated is small, just three. A complete factorial design can be carried out using any number of factors but, as the number of factors increases so does the number of experiments required. For example, a two-level five factor design requires 32 experiments (2^5) whereas a two-level ten factor design needs 1024 experiments (2^{10}). So, where a complete design for five factors is feasible on a practical level, a complete design for ten factors is not. In order to optimise processes that have a large number of factors a 'fractional-factorial design' can be used. A fractional-factorial design approach looks at only a fraction of all the possible combinations of factor settings, this reduces the number of reactions to be run to a manageable level. To illustrate this, a fractional, two-level three-factor design is illustrated in Figure 10. In this, only four experiments are required as well as the necessary centre points

(indicated by the black dots). Using a complete design strategy is often wasteful of time and resources as sufficient data is almost always obtainable from a fractional-factorial design. However, by running a fractional design and hence, fewer experiments, it becomes more difficult to identify the effect and importance of the factors and factor interactions upon the process in question. The bigger the fraction of the design the more ambiguous the factor effects become. It is worth noting that the single factor effects usually remain reasonably accurate and it is the effects of interactions between factors that become obscured. Analysing a fractional factorial design is carried out in an identical manner to a complete design.

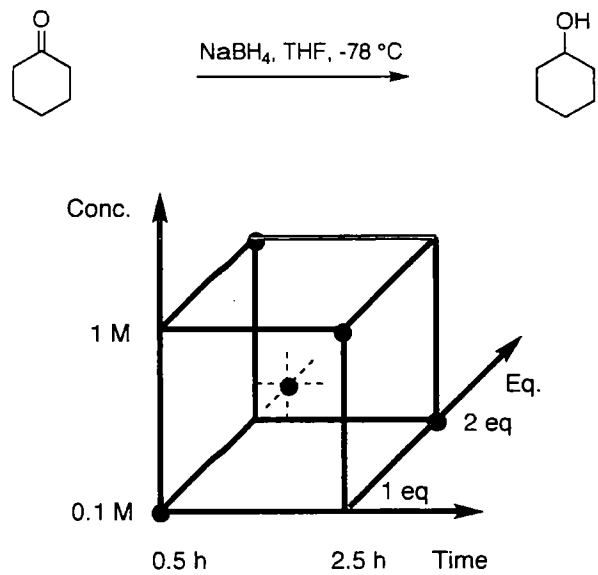


Figure 10: A representation of a two-level, three-factor fractional-factorial design for the reduction of cyclohexanone.

3.2.1.2.4 Factors and principal component analysis

The first and most important decision to be made when planning an optimisation is whether to a) optimise the current procedure or b) screen for alternative reagents. In the example used above (the reduction of cyclohexanone), optimisation of the current procedure is being carried out. As mentioned earlier the factors under

investigation are the equivalents of $NaBH_4$, the reaction concentration (solvent volumes) and reaction time. Theoretically, these factors can take any value between zero and infinity, these factors are classified as numerical factors because they can take an unlimited range of values. However, some factors are not numerical factors, e.g. they can be either X or Y, that is, they can take only one of two/three/four etc possible values/settings and nothing inbetween. These factors are classified as categorical factors, e.g. the method of stirring could be either mechanical or magnetic or, either stirring or no-stirring whilst the method of addition could be either as a solid or as a solution. If, in the beginning, it is decided to screen for alternative reagents then categorical factors become more important, i.e. the question being posed is which solvent or which base gives the best outcome for the reaction, is it solvent A, B or C? These are effectively categorical factors. However, the problem that arises in this situation is that there are now multiple options available, e.g. the choice of solvent could be EtOAc, Et_2O, MeOH, EtOH, toluene, DME, hexanes, IPA, DMSO, H_2O etc and the problem is the same for bases or Lewis acids etc. Obviously, it is not possible to screen all the different possibilities together. However, this problem can be circumvented using principal component analysis (PCA) and PCA models, which enable alternative reagents to be screened using a DoE approach.

3.2.1.2.5 Principal component analysis (PCA)

PCA is a statistical method of analysing a data set for a group of items, in this case different chemical properties for chemical reagents and solvents. The result of PCA is such that the items in question are arranged in multidimensional space (2D or 3D) in a manner that describes their overall character relevant to each other based on their chemical properties. Their position within this space is described by a set of principal components (vectors) and the software used to generate the models allows the user to visualise the reagents/solvents in this multidimensional space. Applying this

method to a range of reagents or solvents by analysing properties such as melting point, boiling point, density, pKa, etc, clusters reagents/solvents with similar properties close together within the space. Reagents/solvents which are close together within this space can be expected to have similar chemical behaviour. A PCA model for a range of solvents is illustrated in Figure 11, two vectors are used to describe the positions of the solvents. Each dot in the model represents a different solvent. In this, H_2O and hexane are found at opposite corners of the model demonstrating their contrasting properties whereas pentane and hexane are found very close together. This model is only an example used to illustrate the principal of PCA modelling and is not an actual model. Unfortunately, the models used during the optimisation to be discussed were GSK confidential and cannot be shown in this report.

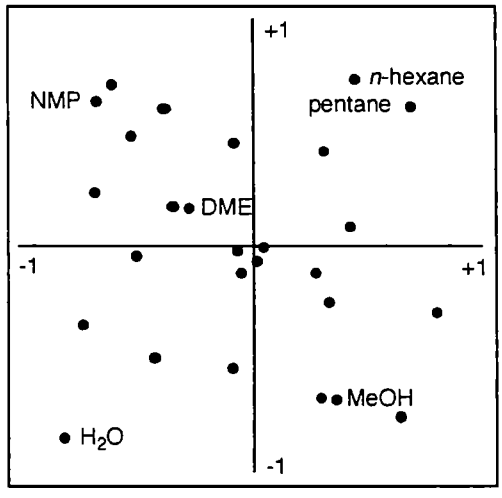


Figure 11: An example of a solvent PCA model

How is the information generated from a PCA model incorporated into an experimental design? The first point to note is that each vector from a PCA model becomes a factor when generating the experimental design, e.g. there are two vectors and therefore two factors in the example of a solvent PCA model used above. Remember that in a two level factorial design each factor is investigated at an upper

and lower value. Therefore, each principle component in the PCA model must be assigned with an upper and lower value, these are given +1 and -1. Also remember that a DoE approach investigates combinations of factor settings (in either a fractional or complete design). Because each vector is inputted into the design as a factor, once the design is generated it will contain combinations of the two factors that relate to the two vectors. Since, each vector had a lower limit of -1 and upper limit of +1 these combinations of factors result in one of four possible sets of coordinates (+1,+1), (+1,-1), (-1,+1) or (-1,-1). When applied to the PCA model each set of coordinates describes a different quadrant of the PCA model, as illustrated in Figure 12 (**A**). A solvent is then selected from each quadrant of the PCA model to represent the coordinates that describe it (Figure 12, **B**) and whenever its coordinates appear in the experimental design it is simply incorporated into the design. A centre point must also be incorporated into the design.

This process can be carried out for any set of reagents for which a PCA model has been generated. Using PCA models allow the user to quickly select a chemically diverse range of reagents and solvents to be used in the optimisation process. When deciding which solvent or reagent to pick from each quadrant several issues need to be considered including cost, availability, ease of handling and suitability to the process in question.

The principal of analysis is the same as for the factorial design discussed above. However, the model that is generated from the results using a PCA screen predicts which reagent/s or solvent/s will give the best outcome for the reaction in question. These combinations of reagents and solvents can then be tested experimentally.

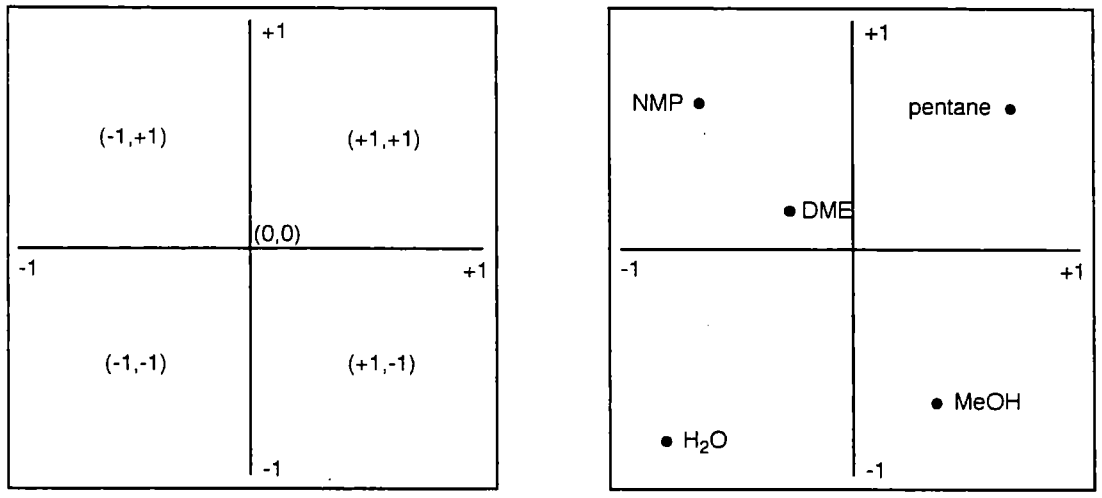
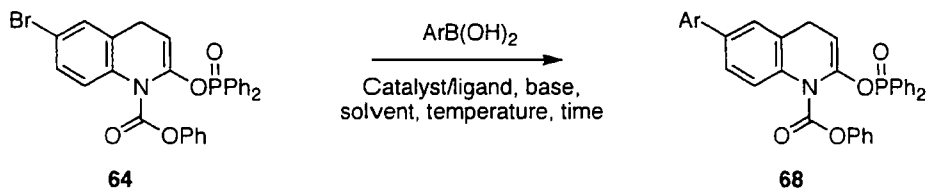


Figure 12: Diagrams illustrating the use of co-ordinates to select solvents from PCA models

3.2.1.3 Optimisation of the Suzuki cross-couping of phosphinate 64

The Suzuki cross-coupling of phosphinate **64** using the original reaction conditions ($ArB(OH)_2$, $NaHCO_3$, $Pd(PPh_3)_4$, DME/H_2O, 80 °C, 1 h) was found to give a complex mixture of products as a result of hydrolysis of the phosphinate moiety and the protecting group (Scheme 71). In order to successfully optimise this reaction it was decided that a new set of reaction conditions would be beneficial (Scheme 72). Hence, it was decided to optimise the reaction using a combination of the methods discussed in the previous sections (DoE and PCA).

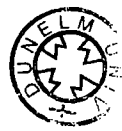


Scheme 72

Having made the decision to utilise DoE and PCA to optimise the process, significant planning was needed and the following considerations were taken into account.

- What were the objectives of the optimisation?
- What responses will be measured?
- Which factors needed investigating and over what range should they be explored?
- What kind of equipment is available, how can it best be utilised and what limitations does it place on the optimisation process?
- How many reactions is it practical to attempt and how many are needed to get good data?
- What scale will the reactions be run on?
- How will the reactions be analysed?

The objectives were to identify a set of conditions that furnished a high yield (> 70%) of the desired product **68** whilst minimising or eradicating the formation of impurities (**61**, **63**, **69** and **70**, Scheme 71). The responses to be measured were therefore the yields of the desired product **64** and the known impurities. The reactions were analysed using HPLC employing biphenyl as an internal standard enabling chemical yields to be calculated for each experiment. The factors considered as having the largest bearing on the reaction were the identity of the solvent, base, phosphine ligand and palladium source as well as the reaction temperature. Due to the large number of possible variables it was decided to keep the reaction time and concentration constant. PCA models were used to select which solvents, bases and phosphine ligands would be screened in the array. As mentioned earlier the PCA models that were used were generated by GSK and are therefore confidential and cannot be shown in this report. The solvent model required three principal components to describe the solvents (3D



model) whilst both the bases and ligands required two components (2D models). Incorporation of these variables into the experimental design required seven factors (one for each vector). The PCA models allowed a chemically diverse range of 9 solvents, 5 bases and 5 phosphine ligands to be identified. In addition, two palladium sources [$Pd(dba)_2$, $Pd(OAc)_2$] and two temperatures (55 and 75 °C) were chosen taking the total number of factors to nine. It was decided to employ a fractional factorial design as a complete factorial design with nine factors would require 512 reactions (2^9 reactions) to be carried out. The reactions were carried out using a Radley Technologies Greenhouse reactor which allows a total of 24 reactions to be carried out simultaneously but cannot heat reactions independently of one another. Therefore, two separate arrays were required, one for each temperature meaning that a total of 48 reactions were possible. Carrying out more than 48 reactions was deemed impractical and the design was generated with this in mind. The equipment available and the practical considerations meant a maximum of 48 reactions could be run and therefore a ¼ fractional design was chosen where the total reactions would be $2^{(9-4)} = 32$ reactions. By including 4 centre points and an organic base (NEt_3) to complement the aqueous bases from the PCA model, the total number of reactions was made up to 48. Using all the above information an experimental design was generated using design expert 6 software. Having generated the experimental design, the identity of the different solvents, phosphine ligands and bases were worked out according to the factor combinations (co-ordinates) generated in the design. The arrays were implemented in the lab over the course of two days.[**]

The results obtained from the two screening arrays were particularly disappointing, the best result giving only a 33% yield of the desired product 64 by HPLC analysis (Entry A6, Table 7). The majority of experiments gave less than 10% of

[**] The full designs including the HPLC yields for each experiment can be seen in the experimental

the desired product with hydrolysis by-products dominating. Although disappointing, the results were used to generate a partial least squares (PLS) model using a commercially available computer program called SIMCA. Basically, the model relates the properties of the solvent, base and phosphine ligand, identity of the palladium salt and the reaction temperature to the distribution of products for each reaction. It then discards any factors that show a negligible effect on the outcome of the reactions and a final model for the reaction is generated. The final model predicts the outcome of the cross-coupling reaction of phosphinate 64 with all the other combinations of solvents, bases and ligands from the PCA models that were not attempted in the original screening array (amounting to millions of possible reactions). The conditions predicted to give the best outcomes can then be tested experimentally.

Despite the disappointing results obtained from the screening experiments the model found some trends amongst the data. It suggested that the source of palladium was unimportant, the best ligand was identified as P(*o*-tol)$_3$ and lower temperatures gave a noticeable improvement. Importantly, it suggested that the factors showing the most significant effect on the outcome of the reaction were the nature of the base and the solvent. The use of an amine base (NEt_3) furnished very little, if any, coupled products. However, it did appear to inhibit decomposition of the starting material (entries D1-6, Table 7 and Table 8). In contrast, the use of inorganic bases resulted in varying amounts of the desired product, starting material and hydrolysis products thereof (Entries A1-C6, Table 7 and Table 8). Inorganic bases possessing lower pKa's gave superior results than those with higher ones. Solvent lipophilicity was also identified as playing an important role in product distribution for the reaction, with more lipophilic (less water soluble) solvents leading to superior results.

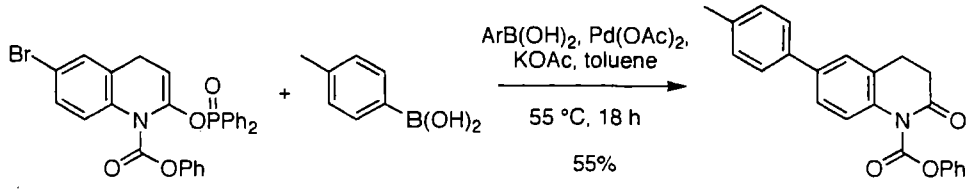
At this stage a further 12 reactions were attempted, 11 sets of reaction conditions, predicted by the model to give high yield of the desired product, were taken

(Entries 1-11, Table 4) as well as the set of conditions which gave the best result from the original screening array (Entry 12, Table 4). These reactions were carried out in parallel using the Greenhouse equipment described earlier. Disappointingly, none of the 11 sets of conditions predicted by the model gave HPLC yields in the region of the predicted yields and only one experiment gave a yield in excess of 10% (Entry 4, Table 4). The majority of the reactions contained sizeable quantities of unwanted by-products **63** and/or **69** as well as varying amounts of starting material. Moreover, the conditions that were repeated from the previous array failed to reproduce the same result giving only 12% yield (Entry 12, Table 4) in contrast to the previous result of 33% for the same conditions (Entry A6, Table 8). This reproducibility issue coupled with the failure of the experimental yields to correspond to the predicted yields was a major setback and disappointment.

Entry	Solvent (3 mL)	Base (3 eq)	Phosphine (0.1 eq)	Catalyst (0.05 eq)	Temp °C	Predicted yield (%)	HPLC Yield (%)
1	*cis*-Decaline	KOAc	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	83	3
2	Toluene	KH_2PO_4	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	76	1
3	Toluene	$BaCO_3$	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	55	1
4	Mesitylene	KOAc	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	47	19
5	Heptane	KOAc	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	46	5
6	Chlorobenzene	KOAc	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	27	6
7	Cyclohexane	KOAc	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	30	0
8	Toluene	K_3PO_4	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	54	3
9	Toluene	KOAc	$PHPh_2$	Pd(OAc)$_2$	55	40	5
10	Toluene	$NaHCO_3$	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	36	1
11	*p*-Xylene	KOAc	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	35	4
12	Toluene	KOAc	P(*o*-tol)$_3$	Pd(OAc)$_2$	55	N/A	12

Table 4: Reaction conditions predicted too give good outcomes for the Suzuki reaction of 64.

It was decided to take the most promising conditions identified from the screening array (KOAc, P(*o*-tol)$_3$, Pd(OAc)$_2$, toluene, 55 °C) and attempt the Suzuki cross-coupling on a preparative scale. Thus, phosphinate **64** was treated under these conditions. Unfortunately analysis of the crude reaction mixture indicated that no desired product was present. The only product isolated by flash chromatography was compound **69** in a moderate yield (55%, Scheme 73).

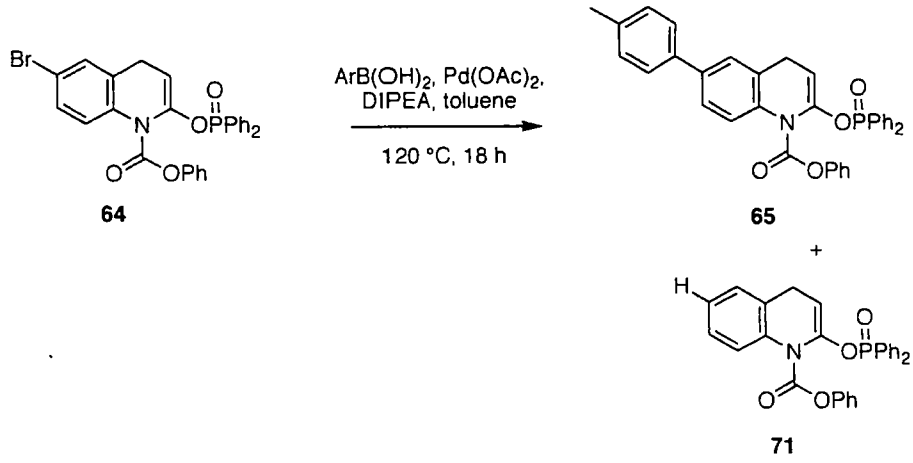


64 5 69

Scheme 73

It was apparent from the results of the screening arrays that phosphinate 64 was reasonably stable to hydrolysis at temperatures up to 75 °C regardless of the choice of solvent when NEt_3 was employed as the base. This observation suggests that the principal cause of hydrolysis of the phosphinate functionality, and in some cases the protecting group, is the presence of an aqueous base and can thus be avoided by employing an amine base. However, the highest yield observed when employing NEt_3 as a base was poor (14%, Entry D3, Table 8) with the remainder of the material being unreacted starting material. This suggests that either a) the oxidative addition of the bromide to the catalyst is slow (unlikely) and only a small amount of starting material has time to react or that b) the catalyst stays active for only a short period of time during the reaction. The rate-limiting step in the Suzuki reaction is often transmetallation from the boronic acid to the catalyst. For this to be successful the boronic acid must first be quaternised by the base present in the reaction, thus activating it towards transmetallation. It was postulated that employing NEt_3 severely slows down the transmetallation step of the catalytic cycle as it is less efficient at quaternising the boronic acid than an inorganic base. If transmetallation occurs only slowly and the catalytic cycle is broken then the next most likely outcome is that the stabilising ligands will dissociate from the catalyst and the metal precipitates from the reaction mixture. It was hoped that increasing the temperature of the reaction would overcome the barrier to quaternising the boronic acid, thereby increasing the rate of transmetallation and allowing the catalyst to continue in the catalytic cycle. Employing

DIPEA (b.p. = 129 °C) as the base and toluene as the solvent the temperature of the reaction could be increased to 120 °C. Hence, a mixture of phosphinate 64, DIPEA, boronic acid, P(*o*-tol)$_3$ and Pd(OAc)$_2$ was heated at reflux overnight (Scheme 74). Appearance of a fine black precipitate in the reaction mixture after less than 1 h suggested decomposition of the active catalyst. All attempts to repeat the reaction also resulted in decomposition of the active catalyst in under 2 h. Analysis of the crude material revealed three peaks in the ^{31}P NMR spectrum (δ = 33, 34 and 35) as well as three olefinic signals in the ^{1}H NMR spectrum. The olefinic proton signals appeared between 5 and 6 ppm and each was split into a double triplet characteristic of the phosphinate functionality. LCMS analysis confirmed the presence of starting material 64 R_t = 19.5 min, *m/z* = 546/548 (MH^+ Br^{79}:Br^{81}), desired product 65 R_t = 21.0 min, *m/z* = 558.3 (MH^+) and a previously unseen compound 71 resulting from reduction of the aryl bromide, R_t = 18.3 min, *m/z* = 468.3 and *m/z* = 957.5 ($2MNa^+$). However, all attempts to purify the crude material by flash chromatography were unsuccessful and the three compounds could not be separated. Formation of reduced compound 71 provided further evidence for a rate limiting transmetallation step. However, these results confirm the observations from the previous study that the aryl bromide is more reactive than the phosphinate functionality as no evidence for coupling at the phosphinate was observed in these reactions.

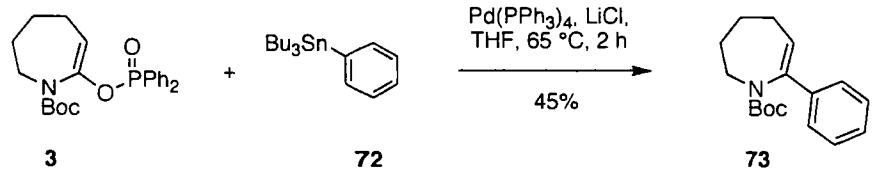


Scheme 74

At this stage, after significant time and effort had been expended and despite the progress that had been made, it was apparent that a Suzuki cross-coupling protocol for **64** in which the aryl bromide couples efficiently and the phosphinate moiety remains intact was not going to be realised. The biggest issue remains the stability of the phosphinate moiety under aqueous conditions; moving away from aqueous conditions goes some way to solving this problem. However, it introduces a new problem in that the transmetallation step becomes more difficult due to inefficient quaternisation of the boronic acid. The lack of stability of the phosphinate functionality in these substrates can be attributed to the strained nature of the six-six fused aryl-vinyl ring system, which is prone to decomposition under aqueous reaction conditions. Two possible solutions to the problems being encountered were envisaged a) explore an alternative cross-coupling protocol or b) design an alternative phosphinate substrate with greater stability.

The Stille cross-coupling reaction can be carried out under nonaqueous conditions and does not require the addition of a base to activate the stannane towards transmetallation. Moreover, previous work within the Steel research group by Guo (Scheme 42) had shown that simple caprolactam phosphinates can be coupled in Stille

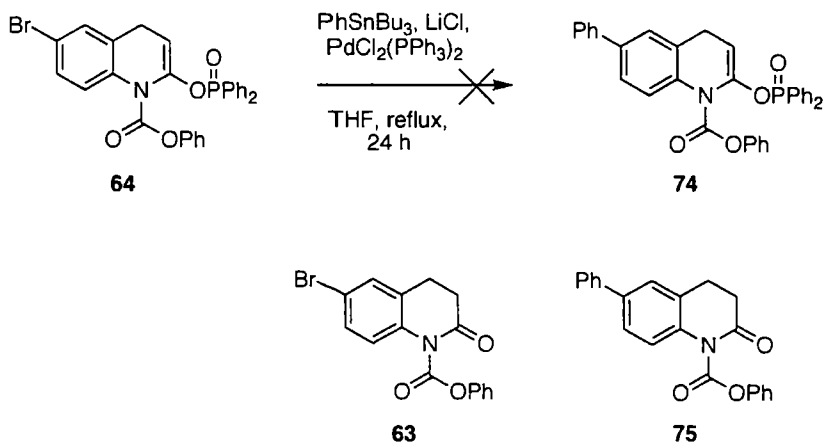
cross-coupling protocols, e.g. phosphinate **3** and phenyl tributyl stannane **72** afforded the desired coupled product **73** in moderate yield (45%, Scheme 75). With these observations in mind, it was hoped that employing a Stille cross-coupling reaction could circumvent the problems encountered in the Suzuki reaction discussed above.



3 **72** **73**

Scheme 75

Hence, a solution of quinolinone-derived phosphinate **64**, LiCl and phenyltributyl stannane in dry THF was degassed *via* three freeze/pump/thaw cycles. $PdCl_2(PPh_3)_2$ was added and the reaction mixture heated at reflux for 24 h. Unfortunately, neither starting material **64** nor the desired coupled product **74** were evident in the reaction mixture and analysis of the crude material revealed the presence of compounds **63** and **75** (Scheme 76). These results indicate that under these Stille reaction conditions not only is decomposition of the phosphinate still a major problem, but also the aryl bromide does not couple efficiently. Repeating the reaction confirmed these results.



64 **74**

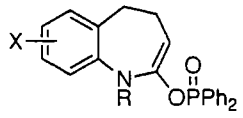
63 **75**

Scheme 76

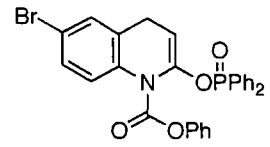
Having shown the reactivity of vinyl phosphinates to be between that of aryl chlorides and bromides and, that aryl bromides can be reacted with complete selectively in the presence of vinyl phosphinates, the next aim of this work was to carry out some bi-directional syntheses. In order for this to be successful two conditions must be met, a) the coupling of the aryl bromide must occur in high yield and conversion and b) the phosphinate moiety must remain intact during the cross-coupling of the aryl bromide and also in any subsequent purification. It was apparent that these two conditions could not be met when using the quinolinone-based phosphinate **64**. Therefore, this approach was abandoned in favour of the second solution to the problem.

3.3 Benzazepine phosphinates

It was proposed that the highly strained nature of the aryl-vinyl fused ring system was responsible for the instability inherent to phosphinate **64**. Similar stability issues were encountered when exploring the synthesis and cross-coupling of simple pyrrolidinone and valerolactam phosphinates. However, no stability issues were observed when exploring phosphinates of larger rings, i.e. seven and eight membered rings. Therefore, it was proposed that changing from a six-six fused quinolinone system, e.g. **64**, to a six-seven fused benzazepine system, e.g. **76**, would provide the desired increase in stability (Figure 13). Hence, an efficient synthesis of substituted benzazepine phosphinates and their use in cross-coupling reactions was explored.



76

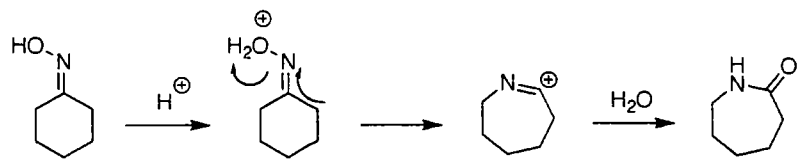


64

X = Br or OTf, R = protecting group

Figure 13

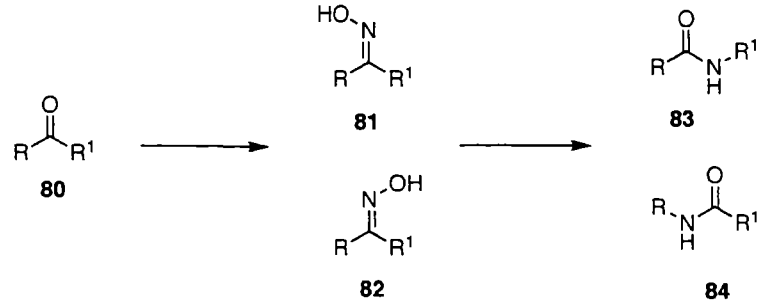
It was envisaged that the core benzazepine structure could be accessed *via* the Beckmann rearrangement. The Beckmann rearrangement[132] is the acid-catalysed rearrangement of an oxime to an amide. Possibly the most famous example is the rearrangement of the ketoxime of cyclohexanone **77** to caprolactam **1**, a process used in the manufacture of nylon. Initial protonation of the oxime is followed by an alkyl group migration furnishing cationic intermediate **79**, this reactive intermediate is then attacked by H_2O affording the amide product, in this case caprolactam **1** (Scheme 77).



77 **78** **79** **1**

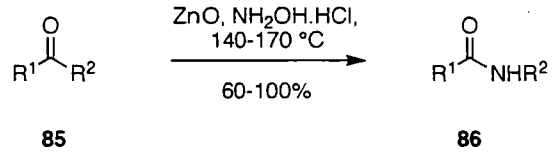
Scheme 77

In the example above, oxime **77** is symmetrical and therefore, only one amide product is possible as migration of either alkyl group furnishes the same product. If an unsymmetrical ketone is used, e.g. **80**, there are two possible oximes that can arise, **81** or **82**. There are now two different groups that can migrate in each oxime and which one does so is exclusively controlled by the stereochemistry of the oxime double bond. As with alkenes, oximes exist as either the *cis* or the *trans* isomer and it is almost without exception the group *trans* to the leaving group that migrates (Scheme 78).



Scheme 78

Oximes are easily accessible from the corresponding carbonyl compounds and it was envisaged that Beckman rearrangement of oximes derived from substituted tetralones would lead directly to substituted benzazepines. A search of the literature revealed a number of protocols to effect the Beckmann rearrangement. Sharghi and Hosseini[133] reported a ZnO-mediated, solvent-free, one-step Beckmann rearrangement of a range of aldehydes and ketones, **85** furnishing the corresponding amides **86** in high yields (Scheme 79).

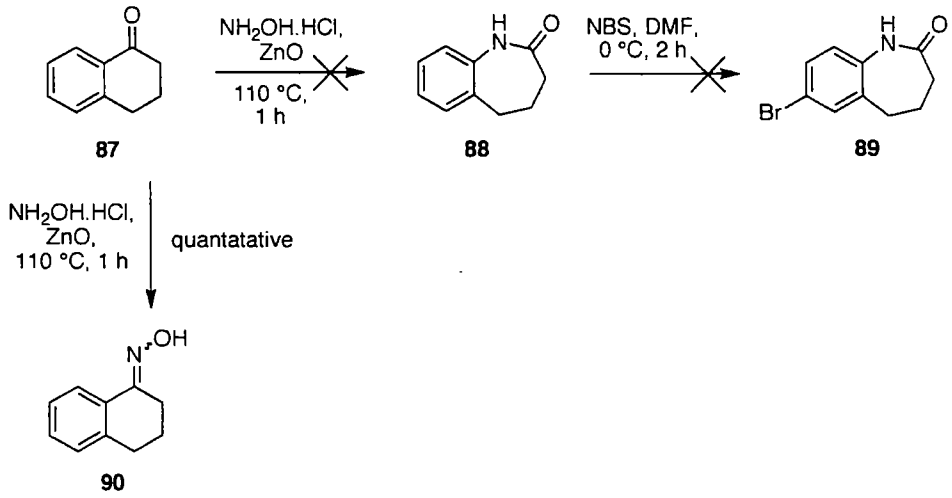


R^1 = alkyl, aryl, cycloalkyl. R^2 = H, alkyl, aryl, cycloalkyl

Scheme 79

Following this method α-tetralone **87**, $NH_2OH.HCl$ and ZnO were heated at 140 °C for 1 h. TLC analysis indicated complete conversion of starting material to a new compound and flash chromatography afforded what was initially thought to be lactam **88** in quantitative yield. Evidence for the formation of lactam **88** was given by the correct mass in the LRMS, *m/z* (ES^+) 162.1 (MH^+). It was expected that bromination of the lactam would proceed without complication. However, treatment of a DMF solution of **88** with a solution of NBS proved unsuccessful and resulted in complete recovery of

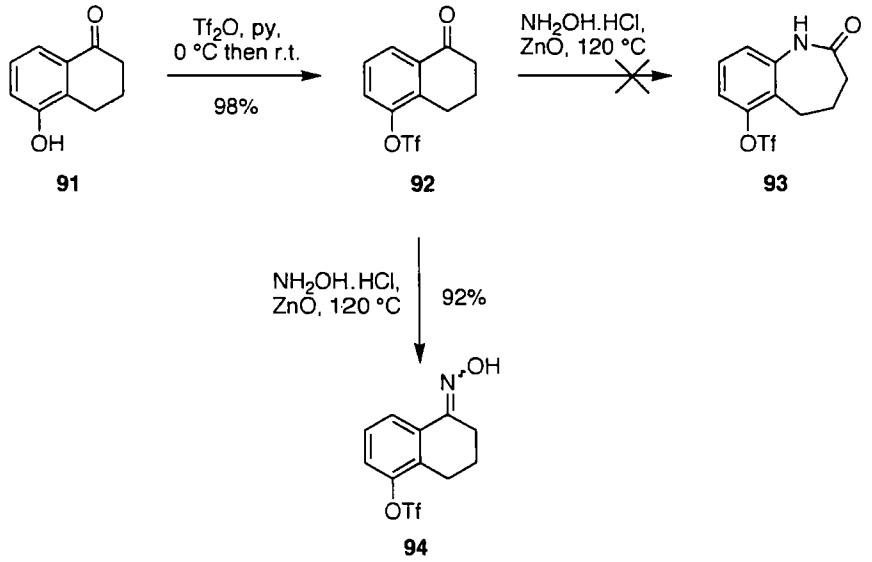
starting material (Scheme 80). This was surprising considering that the fused 6-membered ring lactam **62** was successfully brominated in identical fashion affording **61** in good yield (62%, Scheme 70). It was subsequently realised that the Beckmann rearrangement had been unsuccessful, furnishing not the desired lactam, **88**, but the intermediate oxime **90**. This was confirmed on further inspection of the data, in particular the ^{13}C NMR spectrum of oxime **90** which, having no signals to higher frequency than 155.0 ppm lacked an obvious carbonyl signal.



Scheme 80

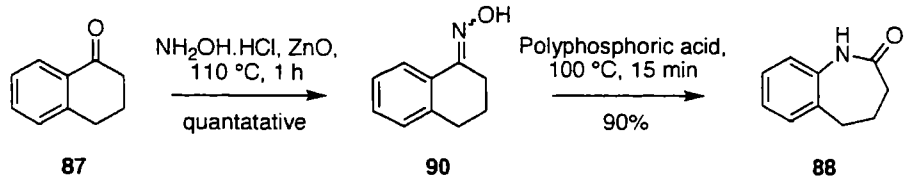
Before recognising the error in assignment and under the impression that benzazepine **88** could not be brominated, the synthesis of the triflate-substituted benzazepine **93** was attempted. Hence, slow addition of triflic anhydride to a solution of alcohol **91** in pyridine afforded the desired triflate, **92**, in 98% yield. This compound was characterised by a single peak in the ^{19}F NMR spectrum at -75.9 ppm. The Beckmann rearrangement was attempted in an identical fashion to the previous example and a mixture of **92**, ZnO and $NH_2OH.HCl$ was heated at 140 °C for 1 h. TLC analysis indicated a clean reaction and flash chromatography afforded what was initially thought to be the desired lactam **93** in 92% yield (Scheme 81). However, careful inspection of

the data suggested that the Beckmann rearrangement had not occurred and the product obtained was the oxime **94**. Evidence for the oxime was given in the IR spectrum, which lacked a carbonyl stretching band something that was supported by the lack of an obvious carbonyl signal (nothing to higher frequency than 154.4 ppm) in the ^{13}C NMR spectrum.



Scheme 81

Having unintentionally synthesised oximes **90** and **94** in excellent yields, it was expected that the Beckmann rearrangement would be trivial. Following the method of Moody,[134] acid-mediated Beckmann rearrangement of oxime **90** was achieved by treatment with an excess of polyphosphoric acid at 110 °C for 10 min (Scheme 82). Benzazepine **88** was obtained in 90% yield without the need for purification and was characterised by the appearance of a carbonyl stretching band in the IR spectrum at 1652 cm^{-1} and supported by LRMS *m/z* = 162.1 (MH^+) and a signal in the ^{13}C NMR spectrum due to the amide carbonyl at 176.1 ppm.



87 90 88

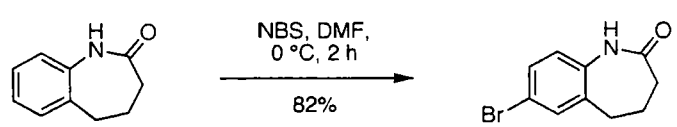
Scheme 82

The Beckmann rearrangement of oxime **90** furnished a single benzazepine isomer resulting from migration of the aryl group in preference to the alkyl group. This indicates that only one isomer of oxime **90** can be present in the starting material. This observation can be explained by a much greater steric interaction between the OH group of the *cis* oxime, **90a**, and the proton on C-8 than in the *trans* oxime, **90b**, and the proton on C-2, as illustrated in Figure 14.

90a **90b**

Figure 14

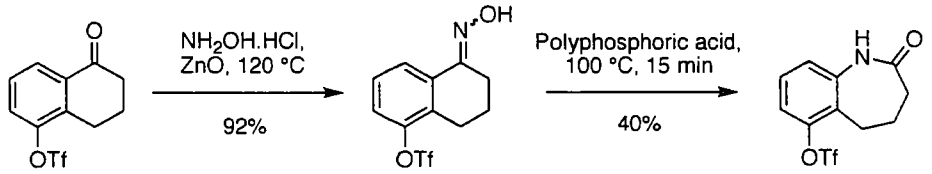
With benzazepine **88** in hand, bromination proceeded smoothly affording aryl bromide **89** in excellent yield (82%, Scheme 83). The brominated lactam was characterised by a single peak in the GCMS, R_t = 20.74 min, *m/z* = 239/241 [1:1 ratio] and only three aromatic signals in the ^{1}H NMR spectrum, 6.87 ppm (1H, d, J = 8 Hz, 9-*H*), 7.33 ppm (1H, dd, J = 8 Hz, $^4J_{HH}$ = 3 Hz, 8-*H*) and 7.35 ppm (1H, d, $^4J_{HH}$ = 3 Hz, 6-*H*).



88 89

Scheme 83

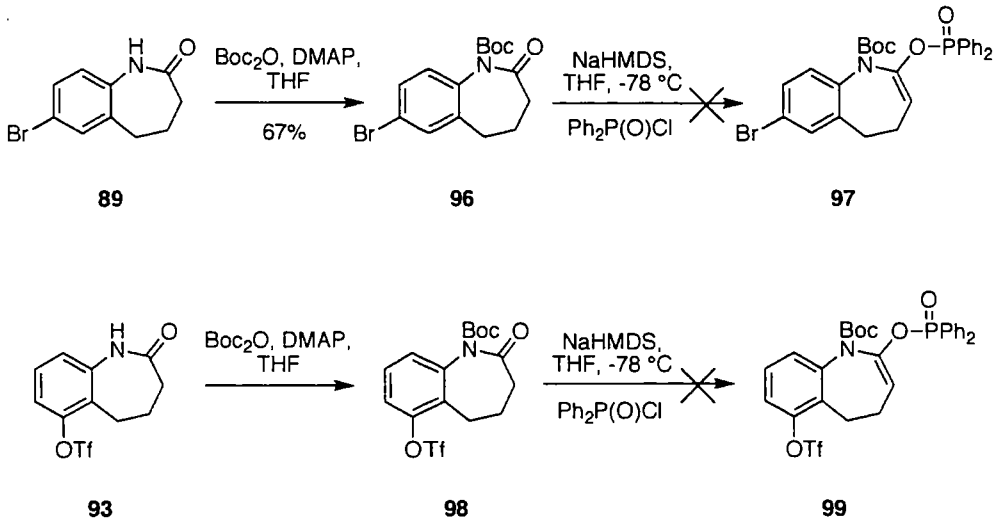
Having successfully synthesised the desired bromide-substituted benzazepine **89**, synthesis of triflate benzazepine **93** was attempted. The Beckmann rearrangement of triflate **94** by treatment with polyphosphoric acid proceeded without complication and the desired triflate substituted benzazepine **93** was isolated in 40% yield (Scheme 84). Benzazepine **93** was characterised by the presence of an amide-carbonyl stretching band in the IR spectrum at 1682 cm^{-1}. Further evidence was given by a signal in the ^{13}C NMR spectrum at 175.5 ppm due to the new carbonyl amide bond. Additionally, a single peak in the ^{19}F NMR spectrum at -73.9 ppm confirmed presence of the triflate functionality.



92 **94** **93**

Scheme 84

Having successfully synthesised both the 6-trifluoromethanesulfonyl- and the 7-bromo-substituted benzazepines **93** and **89**, respectively, preparation of the corresponding phosphinates was attempted. Bromo-benzazepine **89** was protected by treatment with Boc anhydride and DMAP in THF affording **96** in good yield (67%). Unfortunately, treatment of a THF solution of **96** with NaHMDS and trapping of the resultant enolate with phosphoryl chloride failed to afford any of the desired phosphinate **97** (Scheme 85). Conversion of the triflate-substituted benzazepine **95** into the protected phosphinate **99** was attempted in an identical fashion leading to similar results. Boc-protection proceeded smoothly affording **98** in 63% yield and, although trace amounts of phosphinate **99** were present in the crude material as indicated by LCMS analysis, R_t = 7.4 min, *m/z* = 610.1 [MH^+] and 1236.1 [$2MH_2O^+$] none of this product was isolated following chromatography (Scheme 85).

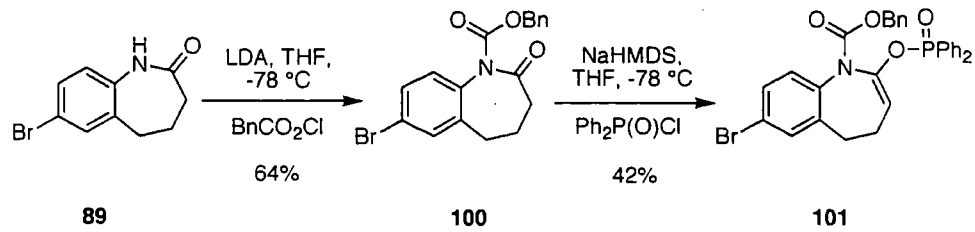


89 **96** **97**

93 **98** **99**

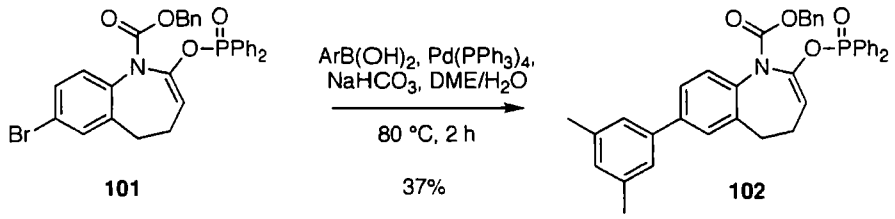
Scheme 85

Consequently, an alternative protecting group was explored and treatment of 7-bromo benzazepine **89** with LDA followed by benzylchloroformate afforded the desired product **100** in 64% yield. Formation of **100** was characterised by a new signal in the ^{1}H NMR spectrum at 5.25 ppm (2H, s) due to the benzylic CH_2 protons and the corresponding signal in the ^{13}C NMR spectrum at 69.2 ppm. In contrast to the Boc derivative, treatment of the N-CO_2Bn derivative with NaHMDS followed by $Ph_2P(O)Cl$ afforded the desired phosphinate **101** in 42% yield as well as recovered starting material (36%, Scheme 86). Formation of **101** was confirmed by a single peak in the LCMS, R_t = 6.9 min, with a molecular ion of *m/z* = 574.1/576.1 [1:1 ratio] (MH^+ Br^{79}:Br^{81}), the presence of the phosphinate was confirmed by a single peak in the ^{31}P NMR spectrum at 30.3 ppm. Importantly, and in stark contrast to quinolinone-derived phosphinate **64**, the benzazepine phosphinate, **101**, showed no signs of instability during purification or handling. 2D TLC analysis indicated that the starting material recovered from the reaction was a result of poor conversion and not decomposition of the product during purification.



Scheme 86

The use of phosphinate **101** in the Suzuki cross-coupling reaction was then investigated. In order to explore the stability of the phosphinate functionality towards aqueous cross-coupling conditions the original conditions from the screen were employed (Scheme 45). A solution of **101**, 3,5-dimethylphenylboronic acid and $NaHCO_3$ in a DME/H_2O mixture was degassed. The catalyst was added and the reaction heated at reflux for 2 h, after which time no starting material remained by TLC analysis. Purification of the crude material by flash chromatography afforded a single compound that was shown to arise from selective cross-coupling at the aryl bromide functionality **102** (Scheme 87). The presence of the phosphinate functionality in **102** was confirmed by a signal in the ^{31}P NMR spectrum at 29.2 ppm. Further evidence for **102** was given in the HRMS that contained a molecular ion at *m/z* = 600.2309, which is consistent with the molecular formula $C_{38}H_{35}O_4NP$ (MH^+). No other products were isolated from the reaction and, importantly, no evidence of decomposition of the phosphinate moiety during the reaction was found. Moreover, like the starting material, the product from the reaction did not show any signs of instability during purification or handling. These observations indicate that, as postulated, increasing the size of the lactam ring provides the desired increase in stability. However, the moderate yield from the reaction and the fate of the remainder of the material from the reaction, which remains unnaccounted for, are issues that need addressing. Unfortunately, time restrictions prevented any further progress being made in this area of the project.



101 **102**

Scheme 87

3.4 Summary

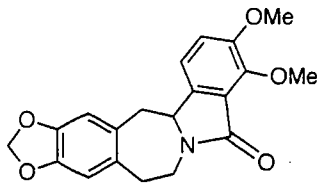
Quinolinone-derived phosphinates, substituted on the aromatic ring with a methyl, chloride or bromide were prepared in good yields from simple starting materials. Relative reactivity studies carried out with these substrates indicated that aryl chlorides are less reactive and aryl bromides more reactive than vinyl phosphinates in the Suzuki cross-coupling reaction. The instability of the phosphinate moiety in these substrates, due to the strained nature of the aryl-vinyl fused ring, complicated the cross-coupling studies. However, cross-coupling of the bromide substrate provided complete selectivity for the aryl bromide over the phosphinate. Optimisation of the Suzuki cross-coupling reaction of the bromide substrate using DoE and PCA models was undertaken, but was largely unsuccessful. However, these studies did indicate that the stability of the phosphinate moiety is greatly improved when employing nonaqueous cross-coupling reaction conditions, particularly when using amine bases in the Suzuki reaction. However, poor reactivity of the aryl bromide functionality was problematic in these protocols. Synthesis of a bromo-substituted benzazepine vinyl phosphinate was also carried out. This phosphinate was found to be more stable than the quinolinone derivative. Suzuki cross-coupling of this substrate under standard aqueous reaction conditions afforded the coupled product due to selective coupling of the aryl bromide moiety supporting the observed relative reactivities in the quinolinone studies.

4 Lennoxamine

4.1 Introduction

Having successfully established the vinyl phosphinate moiety as a viable electrophilic partner in cross-coupling reactions, in particular the Suzuki reaction, it was decided to explore this chemistry in a total synthesis project.

Previous work had revealed that phosphinates-derived from seven-membered ring lactams performed better than those from smaller sized rings. On this basis it was decided to pursue a target that comprises the desired nitrogen-containing seven-membered ring and which could be constructed in a novel manner employing the phosphinate-based cross-coupling methodology as a key step. A search of the literature led to the identification of the naturally occurring alkaloid Lennoxamine **103**, which fulfils the above criteria (Figure 15).

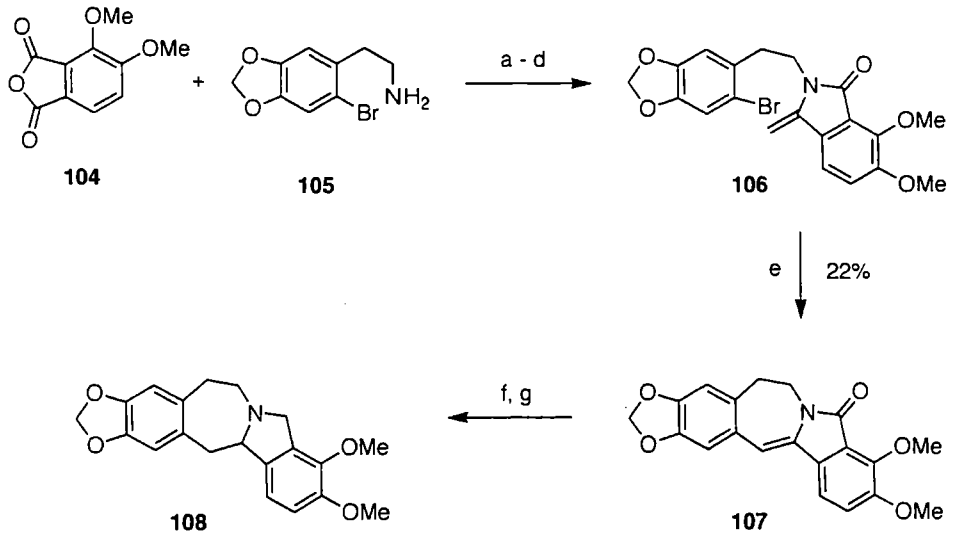


103

Figure 15

Lennoxamine, an isoindolobenzazepine alkaloid was first isolated in 1984 from the *Berberis Darwinii* Hook (Berberidaceae) plant that is found in the southern regions of Chile.[135] Although no biological activity has been reported for this compound its interesting structural features, a fused five and seven-membered ring lactam each fused to a functionalised aromatic ring, have resulted in various synthetic approaches over the past 20 years. Thirteen years before the isolation and structural elucidation of

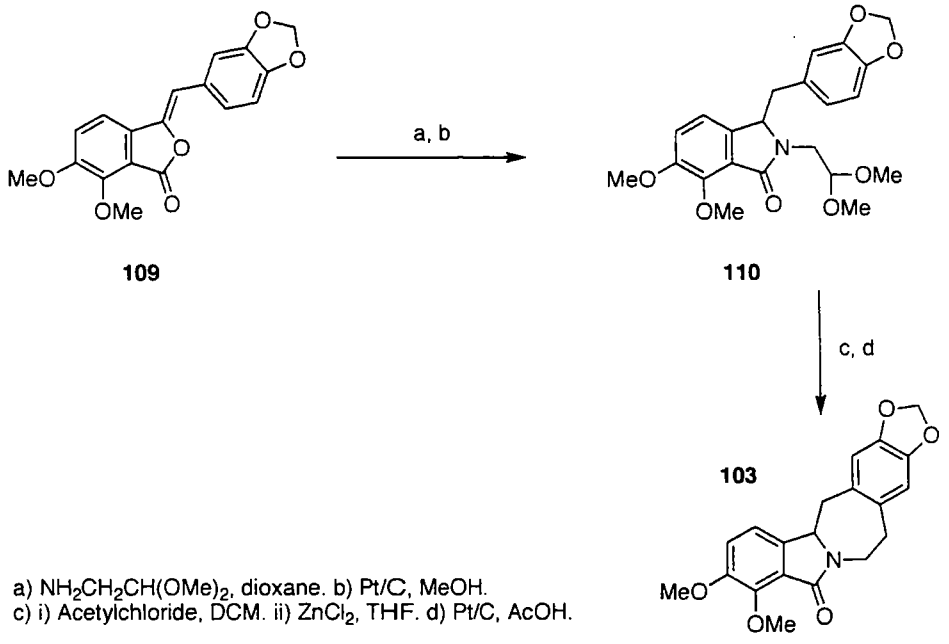
Lennoxamine, Bernhard and Snieckus described a synthetic route to precursors of a known group of alkaloids, the Rhoeadines.[136] However, what they did not realise at the time was that they had also described the earliest synthetic route to Lennoxamine. The key transformation was the low yielding (22%) photocyclisation of bromide **106**, itself synthesised in four unexceptional, but high yielding steps from **104** and **105**. The unsaturated intermediate **107** was subsequently reduced, first with LAH to remove the carbonyl, then with $NaBH_4$ removing the double bond to furnish **108** (Scheme 88).



a) C_6H_6, reflux . b) Ac_2O. c) MeMgI, Et_2O. d) Ac_2O, Pyridine, reflux. e) *hv*, NEt_3, C_6H_6. f) LAH. g) $NaBH_4$.

Scheme 88

Isolation of the natural product in 1984[135] was followed shortly afterwards (1986) by the first unambiguous total synthesis.[137] This first total synthesis, described by Napolitano and co-workers, relied on an electrophilic substitution reaction to close the seven-membered ring. This was realised upon treatment of the dimethoxyacetal **110** with acetyl chloride in DCM followed, without purification, by $ZnCl_2$ in THF, finally removal of the alkene by catalytic hydrogenation afforded Lennoxamine **103** (Scheme 89).

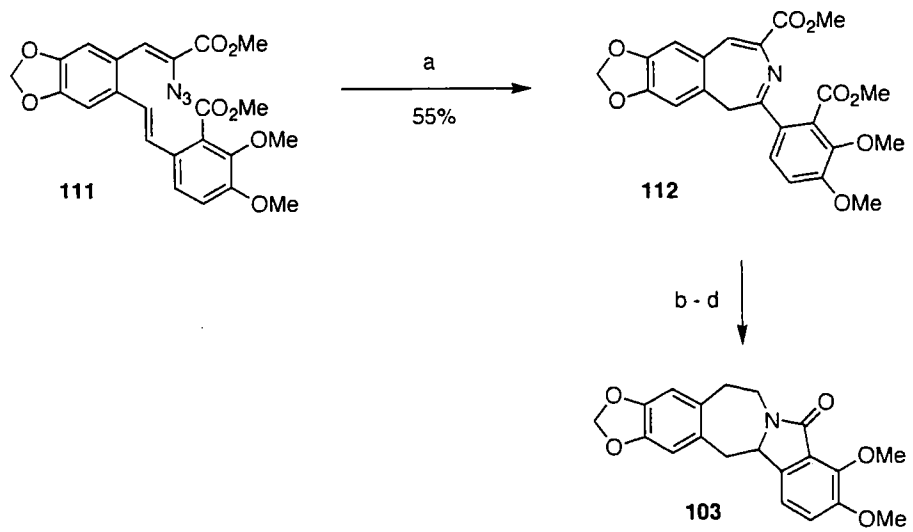


Scheme 89

Since this first report there has been many other syntheses of Lennoxamine reported and, as in the example above (Scheme 89), the majority are based on two common building blocks, an isoindolone and benzodioxole. These two fragments are then brought together forming the desired seven-membered ring.[138] The following pages will discuss four further published synthetic approaches to Lennoxamine including the only stereoselective synthesis known to date. Then the results generated within our laboratories will be discussed including model studies.

In 1987 Moody and co-workers reported a slightly different approach in which they first form the benzazepine unit before closing the five-membered ring.[139] The key step in their synthesis was the formation of the benzazepine unit **112** from azide **111** which proceeded in moderate yield (55%) simply by heating the unstable azide in xylene. Reduction of both double bonds with $NaBH_3CN$ and concomitant cyclisation of the free NH on to an aromatic ester was followed by a DIBAL reduction of the

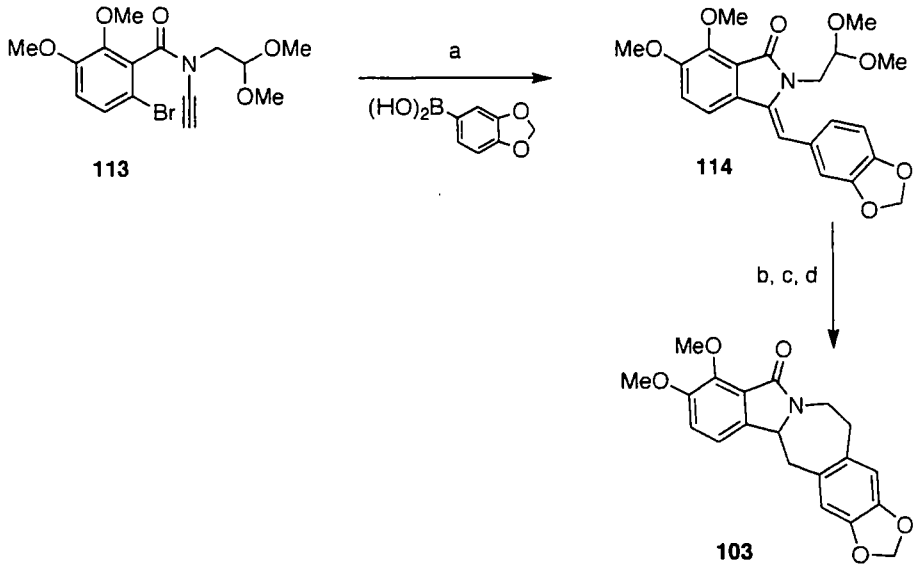
remaining ester and a decarbonylation reaction affording Lennoxamine **103** (Scheme 90).



a) Xylene, reflux. b) $NaBH_4CN$, AcOH. c) DIBAL, toluene, -70 °C. d) $RhCl(CO)(PPh_3)_2$, dppe, xylene, reflux.

Scheme 90

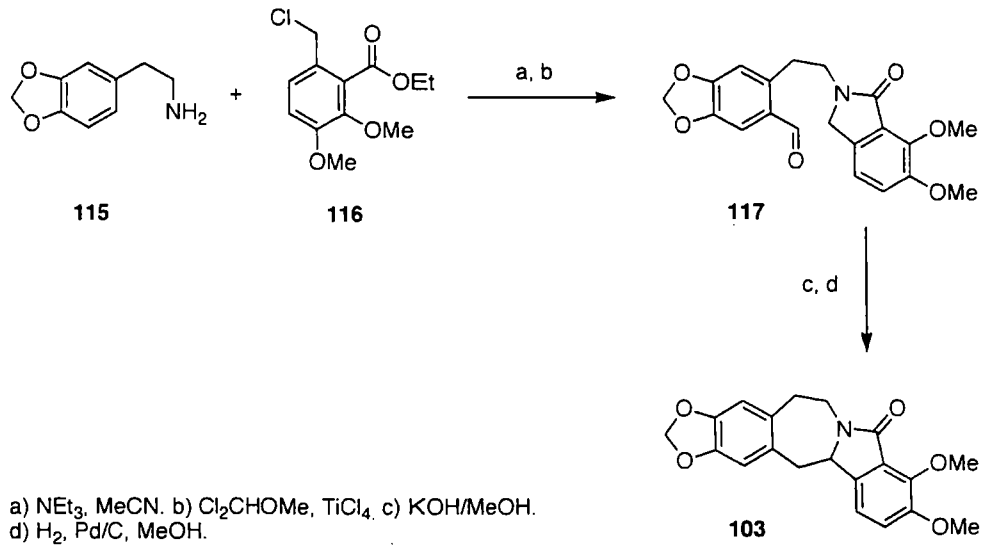
An elegant approach utilising a domino reaction was described in 2006 by Cossy and co-workers.[140] Lennoxamine was accessed in eight steps from ynamide **113** *via* a palladium-catalysed domino Heck-Suzuki-Miyaura reaction as the key step. The ynamide **113** was prepared from 2,3-dimethoxybenzoic acid in four steps and the alkene product **114** of the domino reaction was easily manipulated to furnish Lennoxamine **103** (Scheme 91).



a) $Pd(OAc)_2$, PPh_3, NaOH, THF, reflux. b) H_2, Pd/C, MeOH. c) H_2SO_4, AcOH. d) H_2, Pd/C, AcOH.

Scheme 91

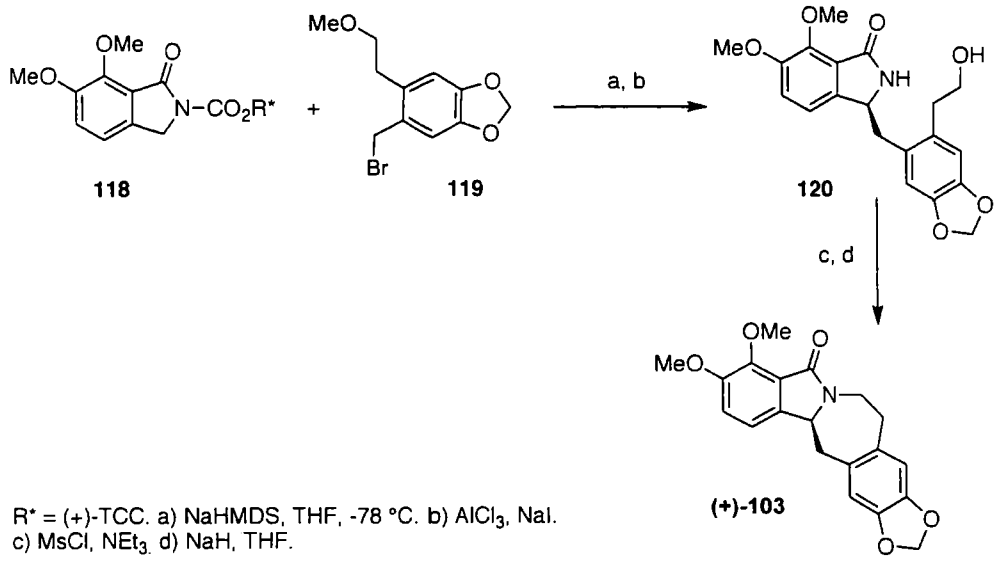
Ruchirawat and Sahakitpichan described the synthesis of Lennoxamine and related isoindolobenzazepines in only four steps from primary amine **115** and substituted benzyl chloride **116**.[141] Formation of the key isoindole intermediate **117** was achieved through a domino alkylation/acylation sequence followed by a formylation reaction to insert the aldehyde functionality. Subsequent treatment with KOH/MeOH followed by hydrogenation of the resultant double bond afforded the natural product **103** in good overall yield (50%, Scheme 92).



a) NEt_3, MeCN. b) Cl_2CHOMe, $TiCl_4$. c) KOH/MeOH.
d) H_2, Pd/C, MeOH.

Scheme 92

Despite containing a chiral centre, it was not until 2005, more than 20 years after its discovery, that the first and only asymmetric synthesis of Lennoxamine was reported.[142] In this, Comins and co-workers carried out a chiral-auxillary-mediated asymmetric alkylation of an isoindolone. Following attachment of the chiral auxiliary, (+)-*trans*-2-(α-cumyl)hexanol or (+)-TCC, isoindolone **118** was deprotonated with NaHMDS and alkylated with bromide **119**. Selective demethylation and removal of the chiral auxiliary was achieved in a single step furnishing intermediate **120**, which was mesylated and then cyclised affording (+)-Lennoxamine **103** which was shown to be enantiopure by chiral HPLC analysis (Scheme 93).



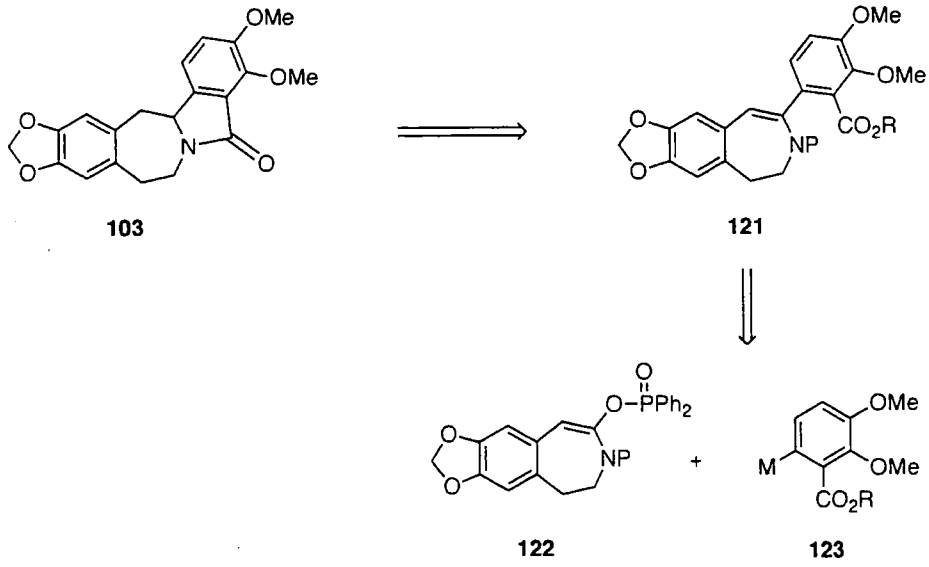
R* = (+)-TCC. a) NaHMDS, THF, -78 °C. b) $AlCl_3$, NaI.
c) MsCl, NEt_3. d) NaH, THF.

Scheme 93

4.2 Retrosynthetic plan

A retrosynthetic analysis of Lennoxamine showing the final key steps in the proposed synthesis, including the crucial cross-coupling reaction of vinyl phosphinate **122**, is shown in Scheme 94. Initial disconnection of the lactam bond followed by a FGI leads to unsaturated benzazepine **121**. Disconnection of the C-C bond in **121** reveals two fragments, organometallic reagent **123** and the desired phosphinate **122**. The synthesis of these two fragments is discussed later in this chapter.

The proposed approach bears resemblances to the approach of Moody *et al.* (Scheme 90) in that the benzazepine ring will be formed first followed by formation of the lactam ring by a cyclisation. This approach also installs the alkene functionality in the correct position to allow an asymmetric hydrogenation to provide a route to enantiopure Lennoxamine and derivatives.

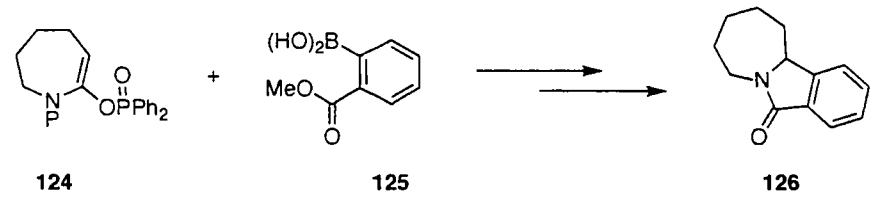


Scheme 94

4.3 Model studies

As indicated in the retrosynthetic analysis, the final steps in the synthesis relied on two important transformations a) the cross-coupling reaction and b) the final cyclisation of the benzazepine nitrogen onto the carbonyl functionality of the aromatic ring. If either of these transformations could not be performed then the approach would fail. Therefore, before embarking on the total synthesis, it was decided the viability of the chemistry should be explored by carrying out some model studies.

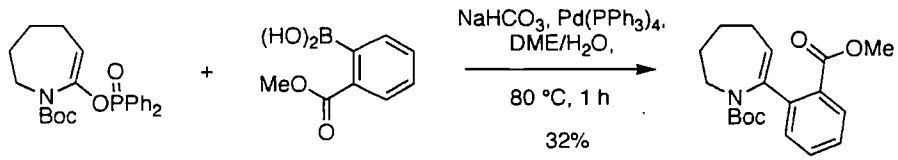
It was decided that an initial evaluation of these steps should be carried out using a simple caprolactam-derived phosphinate, e.g. **124**. Following Suzuki cross-coupling with commercially available 2-(methoxycarbonyl)phenylboronic acid **125**, it was hoped that reduction and subsequent cyclisation would lead to the seven-five-six-fused ring system **126** (Figure 16).



124 125 126

Figure 16

As reported earlier (Table 2), Suzuki cross-coupling of the N-Boc-protected phosphinate **3** with boronic acid **125** afforded coupled product **4h** in a moderate yield (32%, Scheme 95). Formation of **4h** was characterised by the appearance of a new olefinic signal in the ^{1}H NMR spectrum at 5.56 ppm (1H, t, J = 6 Hz). This product contained a small amount (approx 8% by ^{1}H NMR analysis) of the homo-coupled boronic acid as an impurity, which could not be removed.

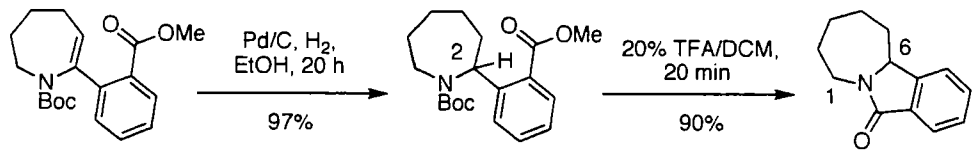


3 125 4h

Scheme 95

With enamine **4h** in hand, reduction of the double bond proved trivial under standard hydrogenation conditions (Pd/C, EtOH, H_2, 20 h). Removal of the impurity carried through from the previous step was now possible by flash chromatography and protected amine **127** was isolated in an excellent yield (97%, Scheme 96). Formation of **127** was characterised by a new signal in the ^{1}H NMR spectrum at 5.61 ppm (1H, dd, J = 12 Hz, J = 5 Hz) due to the newly introduced proton at C-2 and supported by a shift to lower frequency of the signal for this carbon from 143.5 ppm to 58.9 ppm. Subsequent removal of the Boc group was achieved by treatment of **127** with a 20% solution of TFA/DCM and resulted, as had been hoped, in a spontaneous cyclisation of the free secondary amine on to the ester carbonyl group furnishing amide **126** in high

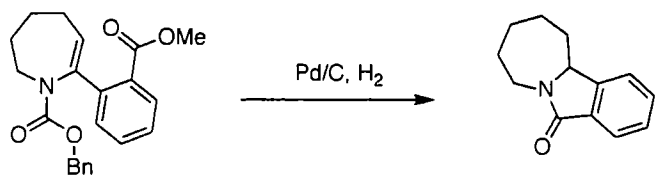
yield (90%, Scheme 96). Formation of **126** was characterised by the lack of a methoxy signal in the ^{1}H NMR spectrum. Moreover, the carbonyl carbon (δ = 168.9) now showed HMBC correlations to the proton signals at 3.44 ppm (1H, m, 1-H*H*), 3.96 ppm (1H, m, 1-*H*H) and 4.60 ppm (1H, m, 7-*H*). Confirmation of the correct molecular formula was obtained by HRMS analysis that showed a molecular ion at MH^+ of *m/z* 202.1226 consistent with the proposed formula.



4h **127** **126**

Scheme 96

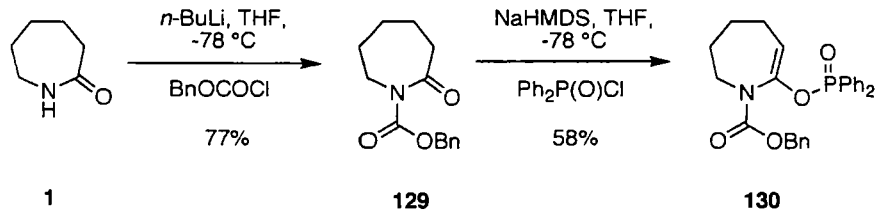
Although the sequence of reactions described above confirmed the viability of the end game strategy, the yield of the Suzuki cross-coupling reaction was insufficient for a total synthesis project. Consequently, attempts were made to improve it, starting with the identity of the protecting group. Suspecting that steric factors were contributing to the problem, a less bulky protecting group was investigated. It was decided to test the use of the benzyl carbamate group as, in addition to being less sterically demanding, if successfully coupled, a tandem reduction/deprotection/cyclisation reaction of the coupled product **128** would lead directly to the desired fused amide **126** (Scheme 97).



128 **126**

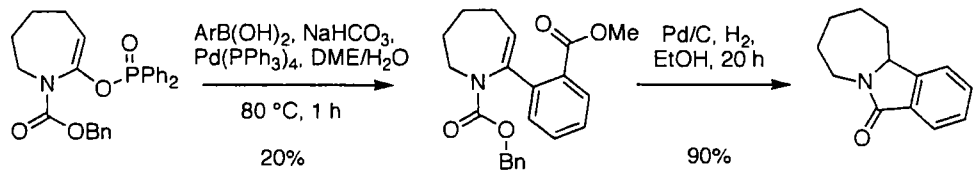
Scheme 97

Hence, preparation of the N-CO_2Bn caprolactam phosphinate **130** and its cross-coupling with boronic acid **125** was explored. N-Protection was achieved by treatment of caprolactam **1** with *n*-BuLi followed by $BnCO_2Cl$, affording protected lactam **129** in a good yield (77%). Phosphinate formation was carried out by treatment with NaHMDS and diphenylphosphonic chloride, affording the desired phosphinate **130** in a 58% yield (Scheme 98). Formation of phosphinate **130** was characterised by a single peak in the ^{31}P NMR (29.0 ppm) and purity confirmed by microanalysis.



Scheme 98

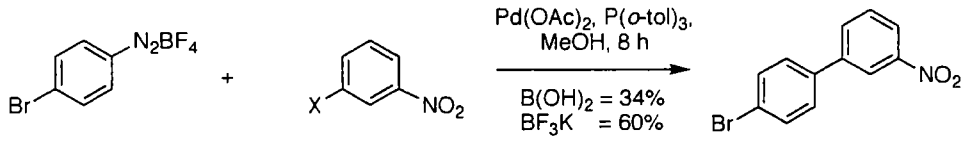
Unfortunately, benzyl carbamate protection proved to be less efficient than Boc protection and Suzuki coupling of phosphinate **130** with 2-(methoxycarbonyl)phenylboronic acid resulted in a poor yield of the desired coupled product **128** (20%). However, as planned, hydrogenation of **128** (Pd/C, EtOH, H_2, 20 h) afforded the desired fused amide **126** in excellent yield in a single operation (90%, Scheme 99). Having successfully employed caprolactam-derived phosphinates in the Suzuki cross-coupling reaction previously, it was suspected that the poor yields obtained here were a result of the low reactivity of the boronic acid. Therefore, it was hoped that altering the organometallic reagent would provide an increased yield.



130 **128** **126**

Scheme 99

Aryl trifluoroborate salts represent a useful alternative to boronic acids for use in Suzuki cross-coupling protocols. Genet and co-workers reported the first example of a cross-coupling reaction utilising a trifluoroborate salt in 1997.[143] A range of aryl trifluorborate salts were coupled under palladium-catalysis with various aryldiazonium salts, e.g. diazonium salt **131** and trifluoroborate salt **133** afforded biaryl **134** in 60% yield (Scheme 100). The corresponding boronic acid, **132**, only gave 34% yield in the same reaction demonstrating the superior reactivity of the trifluoroborate salt.

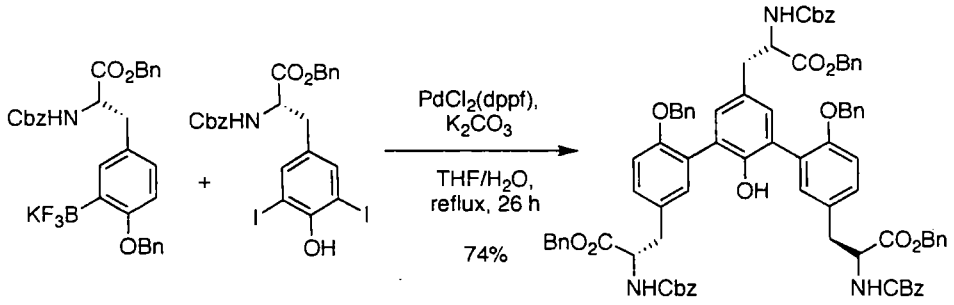


131 **132** - X = $B(OH)_2$
133 - X = BF_3K **134**

Scheme 100

Recently, trifluoroborate salts have been shown to be useful substrates in all manner of Suzuki strategies from aryl-aryl through to alkenyl-alkyl bond formation. Several different electrophiles have been utilised in these strategies including aryl chlorides. The greater functional group stability of aryl trifluoroborate salts means they can be considered as protected boronic acids.[144] Most importantly, aryl trifluoroborate salts have been shown to be effective substrates when boronic acids and boronate esters have failed, particularly when attempting to couple electron-deficient or sterically-hindered organoboron compounds. For example, Skaff and co-workers

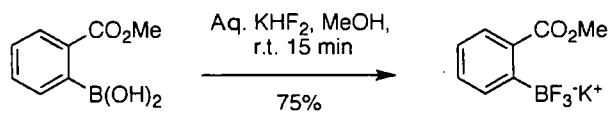
synthesised protected trityrosine **135** *via* a double Suzuki coupling of diiodide **136** with aryl trifluoroborate salt **137** in high yield (74%, Scheme 101) where the analogous pinocol boronate ester afforded none of the desired product.[145]



135 **136** **137**

Scheme 101

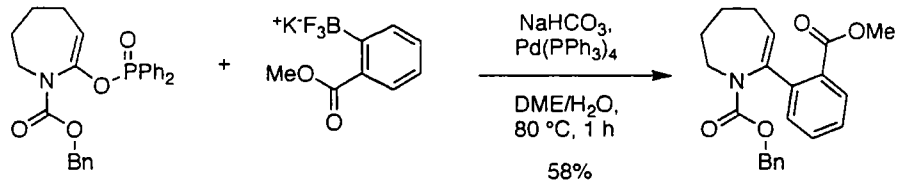
Following this precedent, it was decided to investigate the synthesis and Suzuki coupling of potassium 2-(methoxycarbonyl)phenyl trifluoroborate salt **139** with phosphinate **130**. Thus, following the method first described by Vedejis *et al.*,[146] treatment of a methanolic solution of **138** with a saturated aqueous solution of KHF_2 followed by recrystallisation from MeCN afforded the desired trifluoroborate salt **139** in a 75% yield (Scheme 102). Formation of **139** was characterised by a single peak in both the ^{19}F and the ^{11}B NMR spectra (-137.4 ppm and 2.5 ppm, respectively) and a molecular mass (*m/z*, ES^-) of 203.0 ($M\text{-}K^-$).



138 **139**

Scheme 102

Pleasingly, Suzuki cross-coupling of phosphinate **130** with potassium trifluoroborate salt **139** in place of the boronic acid resulted in a three-fold increase in the isolated yield of the desired coupled product **131** (58%, Scheme 103).

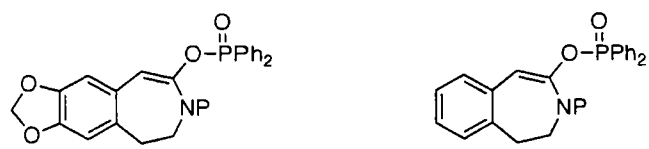


130 **139** **131**

Scheme 103

The caprolactam model study had demonstrated that a) the desired Suzuki reaction could be effected in good yield (58%) through the use of a trifluoroborate salt and b) the final cyclisation to form the fused five-membered lactam ring was feasible and could be achieved in a single step from the N-protected cross-coupled product.

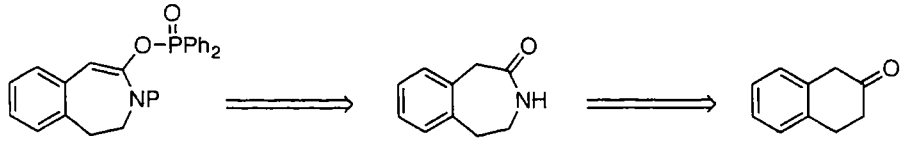
It was now important to establish whether the synthesis of the required benzazepine-derived phosphinate **122** (Figure 17) was possible and, if so, whether it could be successfully employed in a Suzuki cross-coupling protocol. It was decided to explore the viability of this chemistry using another model system and the synthesis of unfunctionalised benzazepine phosphinate **140** was explored (Figure 17).



122 **140**

Figure 17

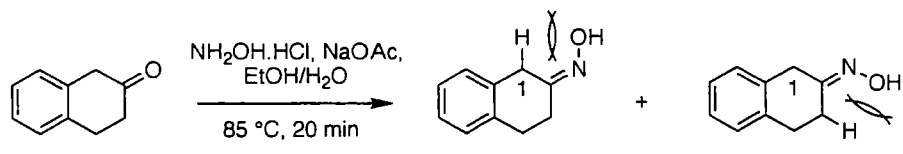
In a similar fashion to the synthesis of benzazepine phosphinate **101** (Scheme 86) that was used as a substrate in the relative reactivity studies discussed earlier, access to phosphinate **140** was envisaged to arise from simple benzazepine, **141**, which in turn could be generated *via* a Beckmann rearrangement of the oxime of commercially available β-tetralone **142** (Scheme 104).



140 **141** **142**

Scheme 104

Following this strategy, a solution of β-tetralone **142** in EtOH was treated with $NH_2OH.HCl$ and NaOAc in H_2O and the reaction heated at 85 °C until there was complete conversion of starting material as indicated by TLC analysis. Purification by flash chromatography afforded an inseparable mixture (1:1 ratio) of the *cis*- and *trans*-isomers of the oxime **143** and **144**, respectively, in 85% yield (Scheme 105). Formation of two isomers was evident from the ^1H NMR spectrum of the purified material which contained two C1-H_2 signals, one for each isomer, 3.46 ppm (2H, s) and 3.76 ppm (2H, s) and the isomeric ratio was easily determined from the integrals of these two signals. Equal quantities of each can be expected as neither isomer experiences increased steric hindrance relative to the other (Scheme 105). This is in contrast to the oxime formed from α-tetralone **87**, which gave exclusively the *trans*-oxime isomer **90b** (Scheme 82).

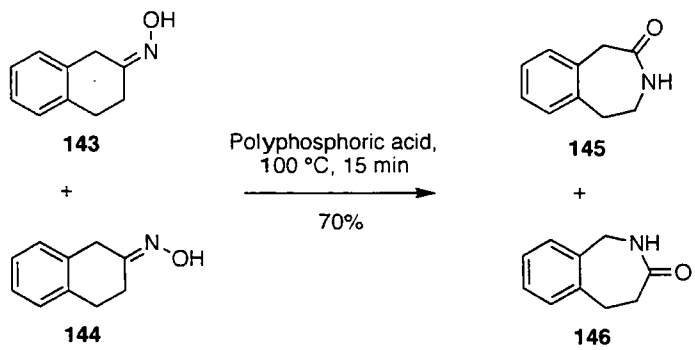


142 **143** **144**

Scheme 105

Since they had proved inseparable, the *cis*- and *trans*-oxime isomers were carried through to the next step as a mixture. Hence, a mixture of **143** and **144** and polyphosphoric acid was heated at 100 °C for 15 min. Following work-up the crude material was isolated as a brown solid (60-80% mass balance). Formation of the

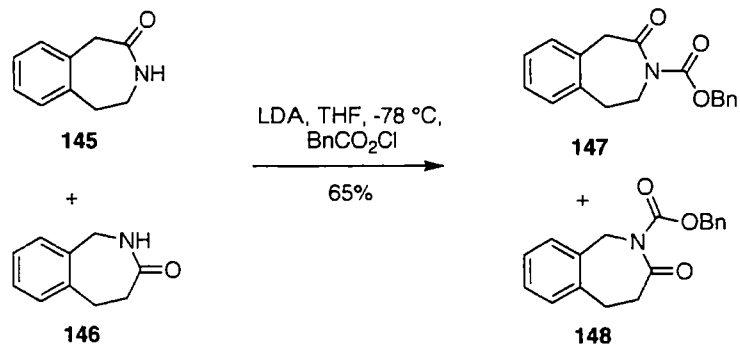
benzazepine unit was confirmed by the appearance of a strong band in the IR spectrum of the crude material at 1660 cm^{-1} due to the new carbonyl functionality (Scheme 106). The reaction was clean and, as expected, two benzazepine isomers were present and evident in the ^1H NMR spectrum, which clearly showed the C1-H_2 signal for each isomer at 3.83 ppm (2H, s, 1-H_2, **145**) and 4.34 ppm (2H, d, J = 6 Hz, 1-H_2 **146**). The integrals of these signals revealed a 1:1 ratio of the two isomers. Since only one of the benzazepines, **145**, had the correct arrangement of carbonyl and nitrogen required for this study, it was hoped that the two isomers could be separated at this stage. However, all attempts to purify the crude material by chromatography were unsuccessful. No material was recovered from the column during these attempts and it is believed that the lactams are hydrolysed on silica furnishing the primary amine/carboxylic acid product that cannot be recovered from the solid phase. Basifying the silica and the eluent prior to purification also proved unsuccessful and consequently, it was decided to take the material through to the next stage without purification.



Scheme 106

With benzazepine **146** now readily available, albeit as a crude mixture with the undesired structural isomer **145**, protection of the nitrogen with a benzyl carbamate group was attempted. Thus, a cold solution of **145** and **146** was treated with LDA and the resultant anion trapped with benzyl chloroformate. The benzazepines **147** and **148**

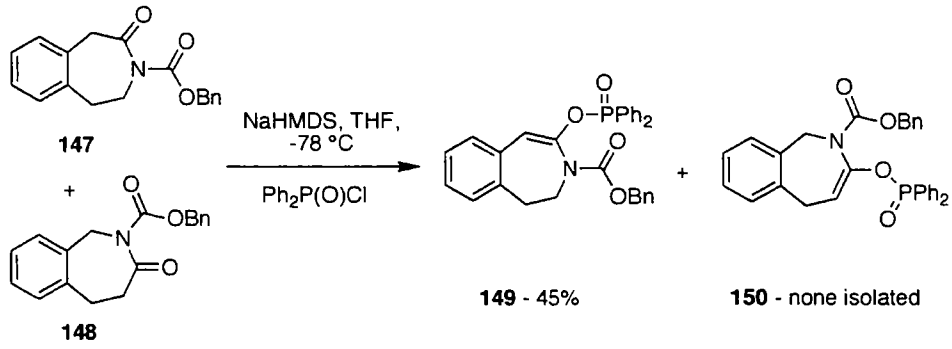
were formed in good yield (65%, Scheme 107), but could not be separated by chromatography. Moreover, subsequent attempts to separate the isomers resulted in loss of valuable material suggesting that both **147** and **148** are unstable on silica. The formation of **147** and **148** was confirmed by the ^{1}H NMR spectrum of the purified material, which displayed a total of eight CH_2 signals, including two new signals due to the two benzylic CH_2 groups at 5.25 ppm (2H, s, C*H*$_2$) and 5.29 ppm (2H, s, C*H*$_2$). Further evidence for these structures was demonstrated by the appearance of ions with the correct molecular mass in the LRMS, *m/z* (ES^+) 296.2 (MH^+), 359.2 ($MNaMeCN^+$), 613.4 ($2MNa^+$).



Scheme 107

With protected benzazepines **147** and **148** in hand, phosphinate formation was attempted. Thus, a cold THF solution of **147** and **148** was treated with NaHMDS and the resultant enolate trapped with $Ph_2P(O)Cl$. TLC analysis indicated complete consumption of starting materials. Evidence for the formation of both phosphinates could be seen in the ^{1}H NMR spectrum of the crude material, which contained two new olefinic signals (δ = 5.41 [dt] and δ = 6.22 [d]). Interestingly, the integrals of these peaks suggested a 4:1 ratio in favour of the desired phosphinate **149**, markedly different from the 1:1 ratio of the benzazepine starting materials. Pleasingly, flash chromatography afforded the desired phosphinate **149** in an excellent yield (45% from a 1:1 mixture of starting benzazepines **147** and **148**, Scheme 108). Compound **149** was

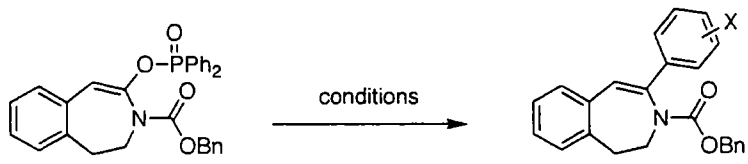
characterised by a single peak in the ^{31}P NMR spectrum at 31.4 ppm and a distinctive signal in the ^{1}H NMR spectrum due to the new olefinic proton at 6.26 ppm (1H, d, $^{4}J^{HP}$ = 2 Hz) which is split by a four-bond phosphorus to hydrogen coupling. Despite the evidence for the formation of the undesired isomer, **150**, in the ^{1}H NMR analysis described above, it proved unstable to chromatography and could not be isolated efficiently.



Scheme 108

Having managed to separate the benzazepine isomers at this stage, a pure sample of phosphinate **149** was available for exploring the Suzuki cross-coupling reaction. Since trifluoroborate salt **139** had been used to good effect during the caprolactam model study carried out previously (Scheme 103), it was hoped that treatment of phosphinate **149** under identical conditions would lead to the desired coupled product **151**. Unfortunately, subjecting **149** to these conditions (Entry 1, Table 5) afforded none of the desired product. LCMS and ^{1}H NMR analysis of the crude material indicated the presence of a small amount of starting material coupled with larger quantities of benzazepine **147**. This result suggests a sluggish oxidative addition step resulting in competitive hydrolysis of the phosphinate in the aqueous reaction conditions becoming favourable. The failure of benzazepine phosphinate **149** to furnish any desired product was slightly surprising given the previous success of the caprolactam-derived phosphinate **130** under the same reaction conditions (Scheme

103). The two substrates differ only by the presence of an aromatic ring, which therefore must be responsible for the poor outcome in the case of benzazepine phosphinate **149**. It is possible that conjugation of the vinyl phosphinate species with the aromatic ring has a stabilising effect, thus making the phosphinate less susceptible to oxidative addition and leaving hydrolysis as the preferred outcome. On this basis it was postulated that a more active catalyst/ligand system might increase the rate of the oxidative addition sufficiently to favour cross-coupling. Aryl and vinyl chlorides as well as alkyl electrophiles were deemed to be too unreactive towards oxidative addition to be useful substrates for cross-coupling chemistry. However, since the late 1990s several highly reactive catalyst/ligand systems have been developed that are capable of oxidatively adding into these relatively unreactive bonds (Scheme 14). Fu and co-workers described various sets of conditions for the coupling of aryl chlorides, vinyl chlorides and alkyl halides with different organometallic reagents. The success of these methods relied on the use of various bulky trialkylphosphine ligands, e.g. $^{t}Bu_3P$ in combination with Pd salts. It was hoped that employing a strategy similar to this would circumvent the problems encountered. Therefore, coupling of phosphinate **149** with trifluoroborate salt **130** was attempted using a $PdCl_2(PPh_3)_2/^{t}Bu_3P$ combination. Unfortunately, in a similar fashion to the previous attempt, the only product evident from the reaction was the result of hydrolysis. As discussed earlier, the Suzuki cross-coupling of *p*-methoxyphenylboronic acid with a caprolactam phosphinate proceeded in quantitative yield (Table 2). In order to prove that the problem in the current system was due to the oxidative addition step and not to some alternative factor, coupling of **149** with *p*-methoxyphenylboronic acid was attempted. Unfortunately, under these conditions benzazepine phosphinate **149** yielded only trace amounts of the cross-coupled product **151** (Entry 3, Table 5) as evidenced in the LCMS (R_t = 7.48 min) *m/z* (ES^+) 352.1 (MH^+). Again the major product was benzazepine **147** (96%) as a result of hydrolysis of the phosphinate moiety.



149 **151**

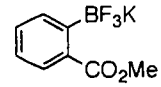
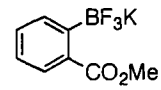
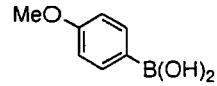
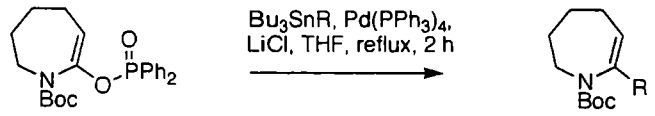
Entry	Pd source	PR_3	ArM	Base	Solvent	Yield **151**
1	$Pd(PPh_3)_4$	-		$NaHCO_3$	DME/H_2O	None
2	$PdCl_2(PPh_3)_2$	P^tBu_3		$NaHCO_3$	IPA	None
3	$Pd(PPh_3)_4$	-		$NaHCO_3$	DME/H_2O	Trace

Table 5

Since the aqueous reaction conditions employed in the Suzuki cross-couplings appeared to be a major problem with this particular phosphinate, a possible solution to this problem would be the use of nonaqueous Suzuki conditions. However, the presence of H_2O in Suzuki coupling protocols, particularly when using trifluoroborate salts[144] can be critical to the success of the reaction. Bearing all the above in mind, it was decided to explore alternative organometallic substrates, which couple under nonaqueous conditions. Previous work within our group by Guo, had shown that the simple caprolactam phosphinate **3** could be successfully coupled under standard Stille reaction conditions, ($Pd(PPh_3)_4$, LiCl, THF, reflux) with a range of stannanes in moderate to excellent yields (45-89%, Scheme 109).

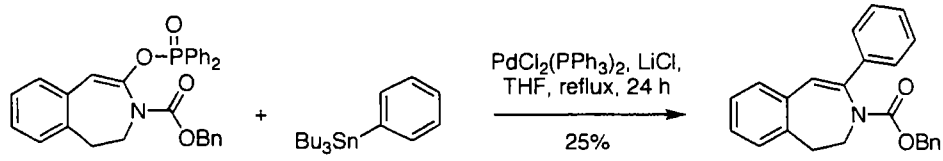


3 **152**

R = Phenyl (45%), phenylethynyl (49%), furyl (89%), vinyl (82%).

Scheme 109

Consequently it was decided to change the approach and investigate benzazepine phosphinate **149** in the Stille cross-coupling reaction, which importantly, is carried out under nonaqueous conditions. Hence, a solution of **149**, phenyltributyltin **153**, LiCl and $PdCl_2(PPh_3)_2$ in dry THF was degassed *via* three freeze/pump/thaw cycles, then stirred under reflux for 24 h (Scheme 110). Pleasingly, the desired product, **154**, was isolated in a 25% yield and characterised by a new olefinic signal at 6.44 ppm (1H, s) in the ^1H NMR spectrum. In addition, confirmation of the correct molecular formula, $C_{24}H_{22}NO_2$, was given by HRMS, which gave a molecular ion at MH^+ 356.1647. TLC analysis of the reaction prior to purification indicated that no starting material remained and only one product had formed. In the light of the TLC analysis and the fact that no byproducts were isolated during purification, the low yield is slightly puzzling and suggests loss of the desired material during purification. At this stage, mainly due to time restrictions and having shown that formation of the benzazepine phosphinate **149** was possible, the product stable and that it could be coupled under Stille reaction conditions, it was decided to attempt the total synthesis. It was reasoned that optimisation of the key cross-coupling reaction could be attempted at a later stage if required.



149 153 154

Scheme 110

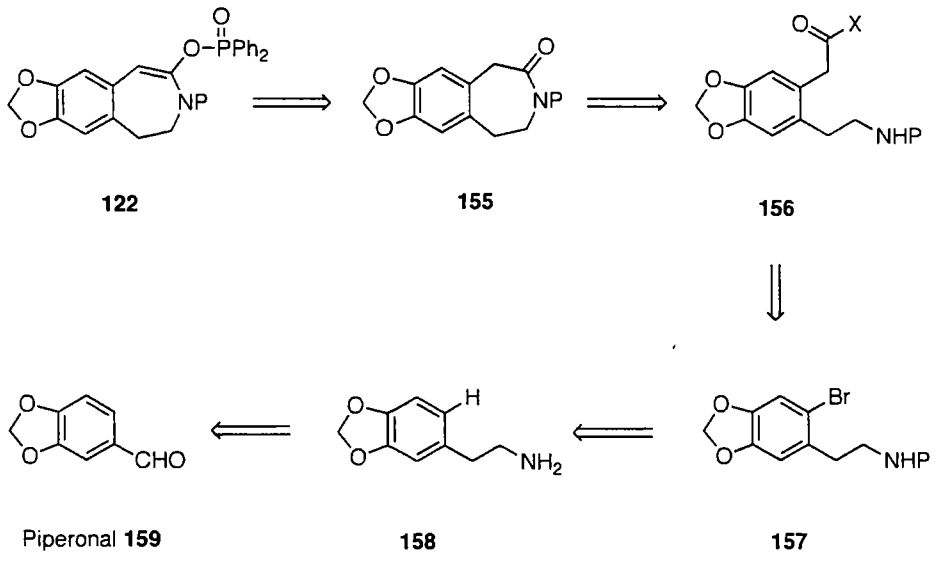
4.4 Final synthesis

At the beginning of the chapter a basic retrosynthetic plan outlined the final key steps in the proposed approach to the synthesis of Lennoxamine (Scheme 94). It revealed two key intermediates, phosphinate **122** and organometallic reagent **123**. Following the model studies described above the organometallic reagent can be identified as an organostannane. The synthesis of each of these substrates will be discussed in the following two sections starting with the phosphinate fragment.

4.4.1 Phosphinate fragment

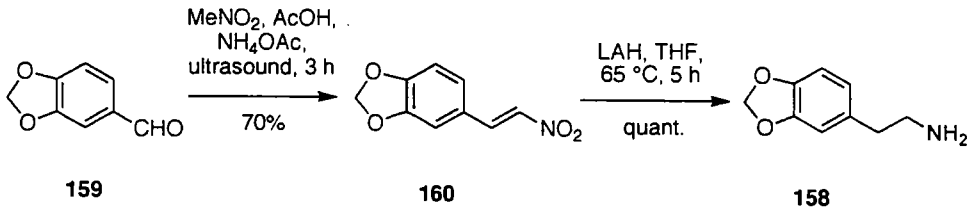
In the light of the reactivity studies carried out previously, the obvious strategy for the synthesis of the phosphinate fragment was to employ a Beckmann rearrangement of a tetralone. However, there were numerous drawbacks associated with this approach, chiefly the non-selective formation of two isomers resulting in the loss of at least 50% of the material. Moreover, poor conversions and problematic purification of benzazepine intermediates affected the sequence. An alternative strategy that would circumvent the issues described above was devised and is outlined in Scheme 111. It was hoped that the core benzazepine unit **155** could be formed from a protected amine, e.g. **156** *via* a simple cyclisation with a carbonyl functionality. Compound **156** would be accessed from cheap and commercially available piperonal **159** through intermediates such as **158** and **157** in a limited number of steps.

Formation of the final phosphinate **122** would be achieved using previously developed chemistry.



Scheme 111

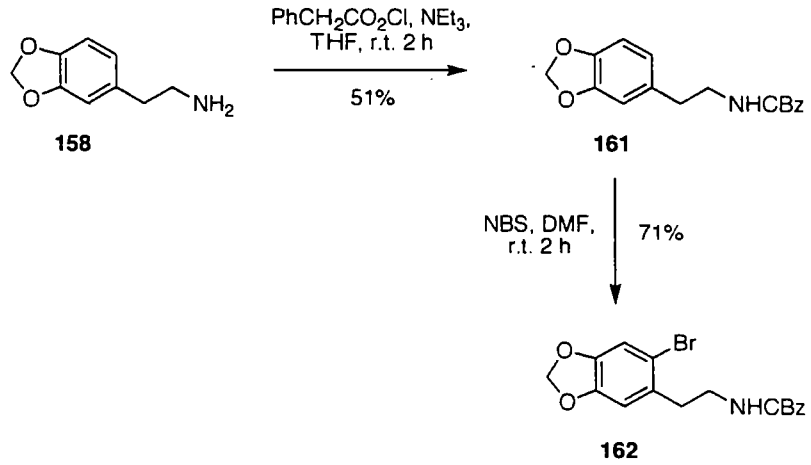
Preparation of primary amine **158** was carried out according to the method of Batra and co-workers.[147] Thus, commercially available piperonal **159**, nitromethane and ammonium acetate in acetic acid were subjected to ultrasound for three hours at room temperature. Recrystallisation from EtOH afforded nitroalkene **160** in a 70% yield, the data for which matched that reported in the literature, including the two olefinic signals in the ^{1}H NMR spectrum at 7.48 ppm (1H, d, J = 14 Hz) and 7.95 ppm (1H, d, J = 14 Hz). Subsequent reduction of the alkene and nitro functionalities by the dropwise addition of a THF solution of **160** to a suspension of $LiAlH_4$ (4 eq) afforded the desired amine **158**, which was sufficiently pure to be used directly in the next step (Scheme 112).



159 **160** **158**

Scheme 112

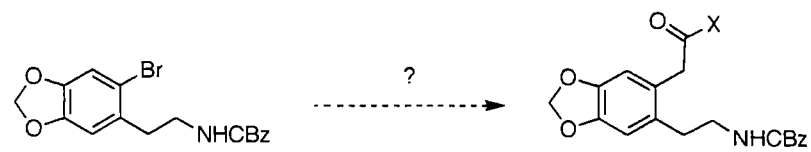
With **158** readily available, protection of the amine and bromination of the aromatic ring was explored. The CBz protecting group had been identified from the model studies as the protecting group of choice. Thus, **158** was treated with NEt_3 and benzyl chloroformate and purified by flash chromatography affording protected amine **161** in moderate yield (51%). Formation of **161** was characterised by the appearance of a carbonyl stretching frequency in the IR spectrum at 1680 cm^{-1} complementing the N-H stretching frequency at 3321 cm^{-1}. Confirmation of the correct molecular formula was obtained by HRMS analysis that showed a molecular ion at MH^+ of *m/z* 300.1232 consistent with the proposed formula, $C_{17}H_{18}NO_4$. Subsequently, bromination of **161** by treatment with NBS proceeded smoothly furnishing aryl bromide **162** in a good yield (71%, Scheme 113). Evidence for the formation of the aryl bromide was obtained from the ^1H NMR spectrum, which indicated a total of seven aromatic protons (δ = 7.26-7.41 [5H, m], δ = 6.70 [1H, s, 3-*H*] and δ = 6.99 [1H, s, 6-*H*]) and a typical bromine isotope pattern in the LRMS *m/z* = 378.1/380.1 [1:1 ratio] (MH^+ Br^{79}:Br^{81}).



158 **161** **162**

Scheme 113

With aryl bromide **162** in hand, the next goal of the synthesis was to convert the bromide in to a carbonyl compound, e.g. **163**, preferably at the ester oxidation state (Scheme 114). Initially, protocols that could carry out the desired transformation directly were explored and a search of the literature revealed two such procedures.



162 **163**

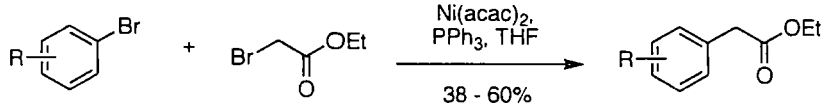
Scheme 114

In 2007 Durandetti and co-workers[148] described the Ni-catalysed cross-coupling reactions of a range of aryl bromides and iodides with various α-chloroesters, **164** and **165**, respectively, as a simple direct method for the synthesis of α-aryl esters. Electron-poor and electron-rich aromatics were coupled in good to excellent yields (51 - 99%, Scheme 115). Unfortunately, this methodology proved unsuccessful for the coupling of aryl bromide **162** and treatment of a DMF solution of **162**, catalytic $NiBr_2$(bipy) and stoichiometric amounts of manganese metal with ethyl chloro acetate resulted in complete recovery of starting material.

164 **165** **166**

Scheme 115

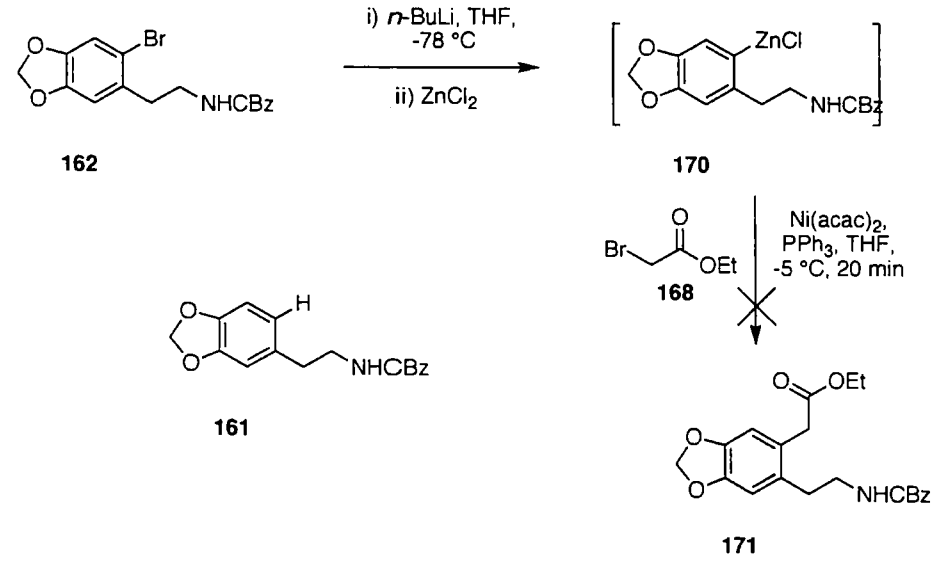
Consequently, attention turned to the method of Frejd and co-workers who described the Ni-catalysed synthesis of a range of α-aryl esters **169** from aryl bromides **167** and ethyl bromoacetate **168** (Scheme 116).[149]



167 **168** **169**

Scheme 116

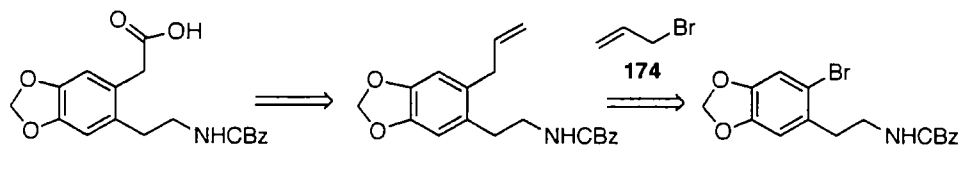
Following this protocol, aryl bromide **162** was treated with *n*-BuLi followed by $ZnCl_2$ and the expected arylzinc intermediate **170** was added to a solution of $Ni(acac)_2$, PPh_3 and ethyl bromoacetate **168** (Scheme 117). Unfortunately, LCMS analysis of the crude material suggested that none of the desired product had formed and gave evidence of recovered starting material **162** (R_t = 5.19 min, *m/z* = 378.1/380.1 [MH^+ Br^{79}:Br^{81}]) and the reduced aromatic **161** (R_t = 4.02min, *m/z* = 300.2 [MH^+]). The presence of starting material indicates that the initial lithium-halogen exchange reaction is not efficient. Moreover, the appearance of the reduced compound **161** suggests the organometallic species is being quenched before the coupling reaction can be carried out. Whether quenching of the organometallic occurs before or after the transmetallation step is not clear. However, several attempts at this reaction resulted in the same outcome each time.



162 **170** **168** **161** **171**

Scheme 117

Having failed to install the desired ester functionality directly, an alternative route was envisaged *via* a simple lithium-halogen exchange reaction of **162** and trapping of the resulting aryllithium species with allyl bromide **174**. It was hoped that ozonolysis of the alkene product **173** followed by oxidation of the aldehyde would furnish carboxylic acid **172**, which could be further functionalised to furnish the desired lactam (Scheme 118).

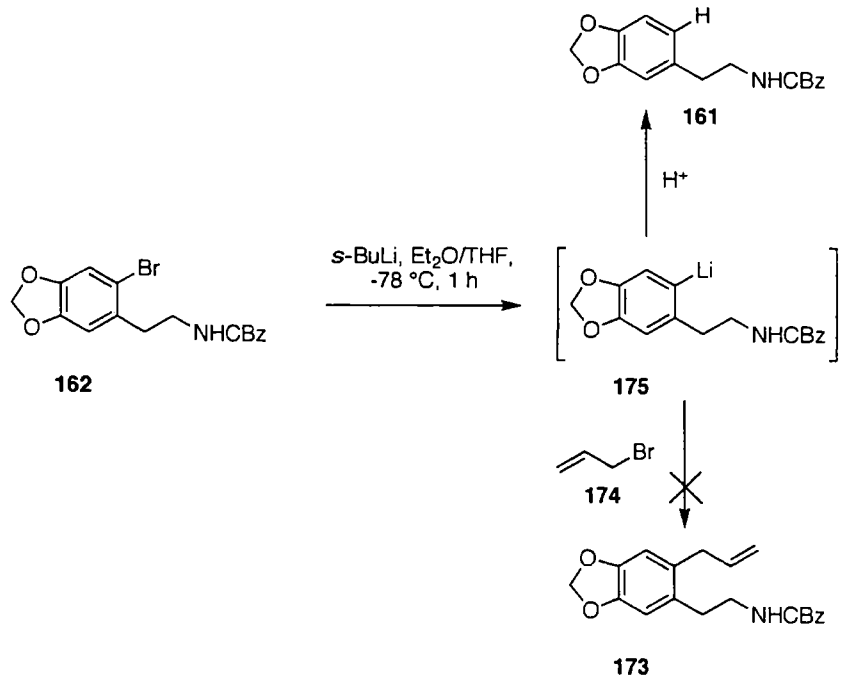


172 **173** **162**

Scheme 118

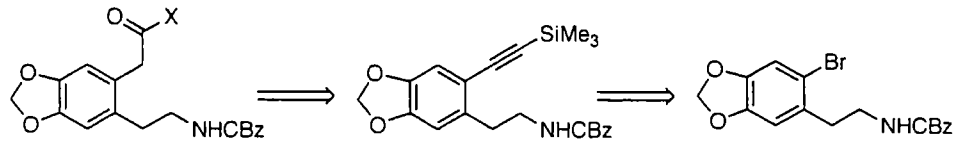
Unfortunately, treatment of **162** with *s*-BuLi followed by allyl bromide **174** proved unsuccessful and failed to afford any of the desired product **173** (Scheme 119). In a similar fashion to the arylzinc coupling reaction described above, the only products evident from LCMS analysis of the crude material were recovered starting material **172**

and the reduced aromatic **161**. Formation of **161** is evidence that the lithium-halogen exchange is taking place and leads to the conclusion that the reactive intermediate lithium species **175** is being quenched before the electrophilic allyl bromide **174** is added.



Scheme 119

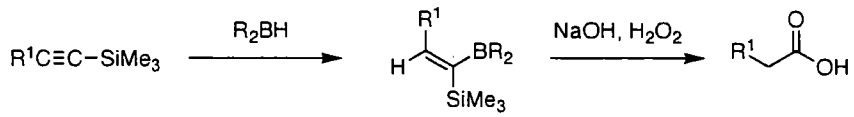
Having been thwarted by the lithiation approach, investigation of an alternative method to functionalise aryl bromide **162** was required. The obvious choice was to use the aryl bromide as the electrophilic partner in a cross-coupling strategy. It was hoped that a Sonogashira reaction would furnish acetylene **176**, which could then be transformed to the desired carbonyl functionality **163**, possibly through a hydroboration/oxidation type sequence (Scheme 120).



163 **176** **162**

Scheme 120

Pleasingly, a search of the literature revealed a one-pot procedure for carrying out the desired hydroboration/oxidation sequence. In 1977 Zweifel and Buckland described the hydroboration/oxidation of a range of alkynylsilanes **177** to afford their corresponding carboxylic acids **179** in greater than 80% yield (Scheme 121).[150]



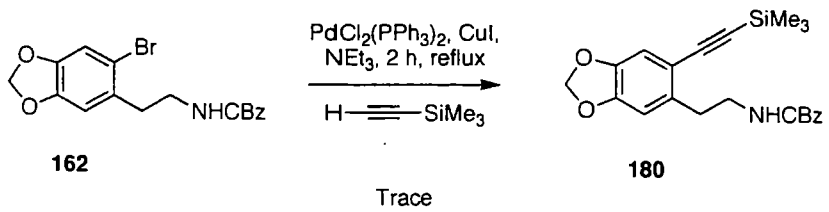
177 **178** **179**

R^1 = alkyl, aryl or alkene. R = cyclohexyl

Scheme 121

A possible limitation of this approach was thought to be the electron-rich and sterically hindered nature of aryl bromide **162**, which might make oxidative addition to the catalyst difficult. However, it was felt that the potential advantages of this approach justified the means. With this in mind the Sonogashira cross-coupling reaction between aryl bromide **162** and trimethylsilylacetylene was investigated. Thus, a solution of **162** in NEt_3 was degassed *via* freeze/pump/thaw and then CuI, Pd salt and TMSA added and the reaction stirred at reflux for 2 h. However, it is suspected that the reaction was stalled in less than 5 min due to decomposition of the active catalyst and formation of palladium black. Purification of the crude reaction mixture afforded recovered starting material (87%) and a trace amount of the desired coupled product **180** (< 8%), which was found to be impure (Scheme 122). Formation of the coupled product was indicated by the appearance of a signal in the ^1H NMR spectrum at 0.18 ppm (9H, s) due to the

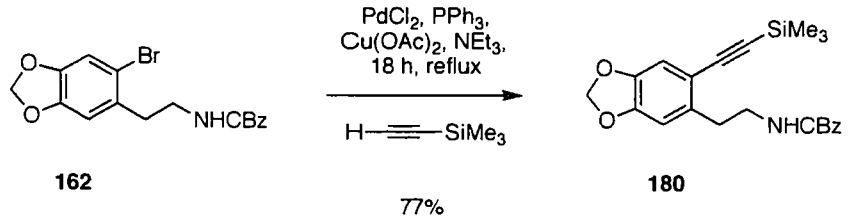
newly introduced TMS group and LRMS which showed a molecular ion at *m/z* = 396.2 (MH^+) and 813.3 ($2MNa^+$). Further attempts to improve the yield of **180** were similarly unsuccessful. It appeared that, as expected, oxidative addition of aryl bromide **162** to the catalyst was difficult. Consequently, without being able to enter the catalytic cycle the ligands dissociate from the metal and the active palladium-catalyst decomposes, resulting in the formation of inactive palladium black.



162 Trace **180**

Scheme 122

The formation of trace amounts of the acetylene product **180** in the Sonogashira reaction above was encouraging and suggested that, if a suitable catalyst system could be identified, then workable quantities of the desired product might be synthesised. It was postulated that using a large excess of PPh_3 (5 eq) compared to the Pd salt would halt decomposition of the catalyst by ensuring that every ligand that dissociates from the metal centre is replaced with another. Hence, a degassed solution of **162** (1 eq), $PdCl_2$ (0.05 eq), PPh_3 (0.25 eq), $Cu(OAc)_2$ (0.05 eq) and TMSA in NEt_3 were heated at reflux overnight. Pleasingly, no Pd black was observed and following purification the desired product **180** was isolated in an improved yield of 28%. Moreover, a large quantity of starting material was also recovered (63%) which gives a yield based on recovered starting material of 77% (Scheme 123). Unfortunately, no more time was available and the synthesis of the phosphinate had to be halted at this stage, the remainder of the synthesis is discussed in the future work section.



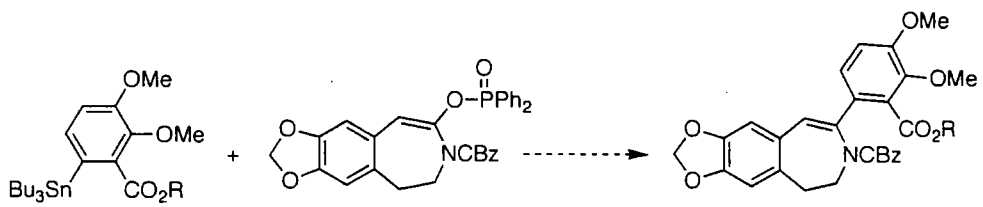
162 **180**

77%

Scheme 123

4.4.2 Organometallic fragment

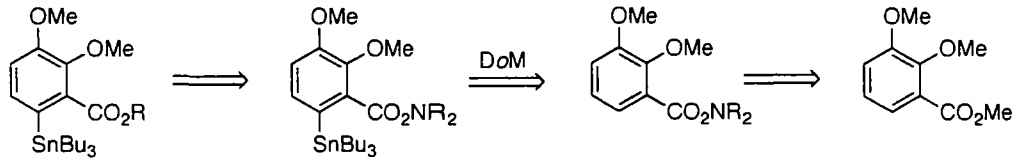
Following the benzazepine model study discussed earlier (Scheme 110), it was decided that a Stille cross-coupling protocol would be used to form the key carbon-carbon bond in the final synthesis (Scheme 124). Therefore, access to organostannane **181** was required and its synthesis is discussed in this section.



181 **182** **183**

Scheme 124

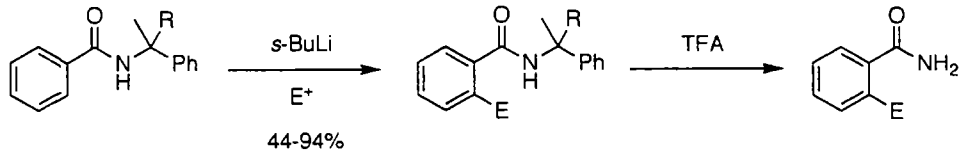
The synthetic strategy devised for organostannane **181** relied on a directed *ortho*-metallation (DoM)/electrophile quench reaction of an amide, e.g. **185**, to install the desired tin functionality. It was thought that the amide would be synthesised from commercially available methyl-2,3-dimethoxybenzoate **186** *via* its acid and the corresponding acyl chloride (Scheme 125).



181 **184** **185** **186**

Scheme 125

With this in mind, the first goal was to synthesise a suitable amide to carry out the directed metallation chemistry. Amides are among the most widely used and powerful of the DoM groups.[151] For example, in 1999 Snieckus and co-workers described the synthesis and directed metallation/electrophile quench of two N-cumylbenzamides **187** furnishing a variety of substituted products **188** in moderate to excellent yields (44-94%). Importantly, Snieckus was able to introduce the tributylstannane functionality albeit only in a moderate yield (44%) using tributylstannylchloride as the electrophile. Moreover, in contrast to other amide DoM groups, the N-cumylbenzamides are easily hydrolysed to primary amides **189** on treatment with TFA (Scheme 126).



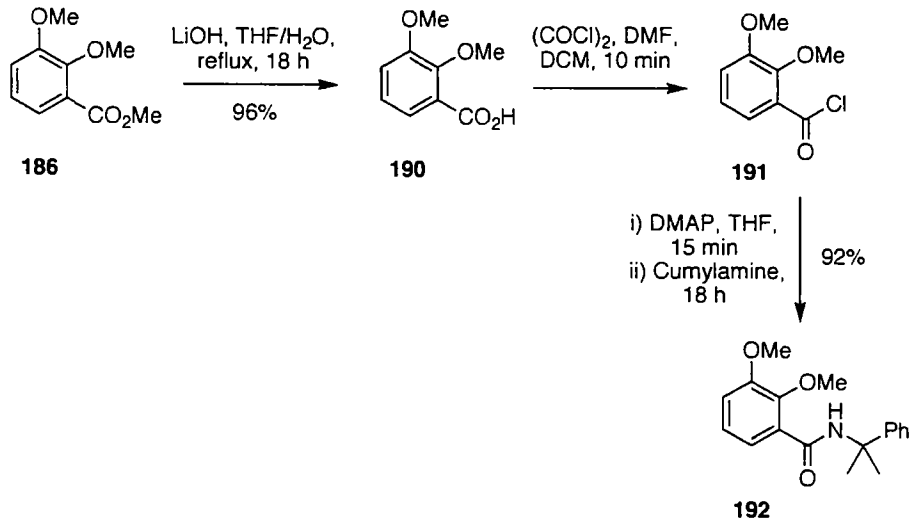
187 **188** **189**

R = Me or Ph. E^+ = MeI, PhCHO, PhNCO, DMF, SO_2Cl, TMSCl, $(MeS)_2$, $(PhS)_2$, $SnBu_3Cl$, I_2, $B(OMe)_3$

Scheme 126

Following this precedent, the desired amide **192** was generated from the commercially available methyl-2,3-dimethoxybenzoate **186**. Initial hydrolysis of **186** was achieved in excellent yield (96%) under standard conditions (LiOH, THF/H_2O). The carboxylic acid product **190** was characterised by a broad band between 2400-3200 cm^{-1} and a strong band at 1681 cm^{-1} in the IR spectrum due to the O-H and C=O

bond, respectively. Subsequent treatment of acid **190** with oxalyl chloride and catalytic DMF smoothly furnished the acid chloride intermediate **191**, the presence of which was confirmed by IR spectroscopy which revealed the lack of an O-H stretching frequency and a shift in the carbonyl stretching frequency to 1774 cm^{-1}. Treatment of a THF solution of this acid chloride with DMAP followed by cumylamine afforded the desired amide **192** in 92% yield (Scheme 127). The amide was characterised by a distinctive signal in the ^1H NMR spectrum at 1.80 ppm (6H, s) due to the two methyl groups in the amide side chain and supported by HRMS analysis which gave a molecular ion at MH^+ 300.1595 consistent with the correct molecular formula, $C_{18}H_{22}NO_3$.

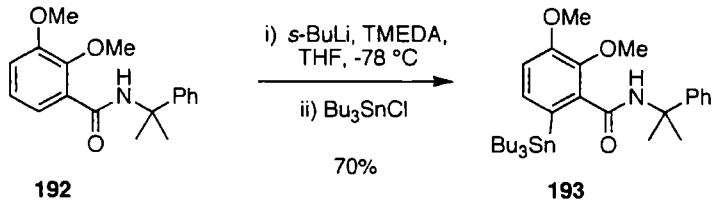


186 **190** **191** **192**

Scheme 127

With amide **192** now readily available, introduction of the tributyltin functionality was attempted. Following the method of Snieckus *et al.*, treatment of a THF solution of **192** with TMEDA and *s*-BuLi and quenching of the resulting organo-lithium species with Bu_3SnCl afforded the desired product **193** in a good yield (70%) when based on recovered starting material (Scheme 128). Formation of the organostannane was confirmed by the appearance of two distinctive aromatic signals in the ^1H NMR spectrum due to the two aromatic protons on the newly functionalised ring, $\delta = 7.02$

(1H, d, J = 8 Hz, 4-*H*) and δ = 7.32 (1H, d, J = 8 Hz, 5-*H*). This was supported by HRMS analysis, which gave a molecular ion at MH^+ 590.2658 consistent with the correct molecular formula, $C_{30}H_{48}NO_3Sn^{120}$.

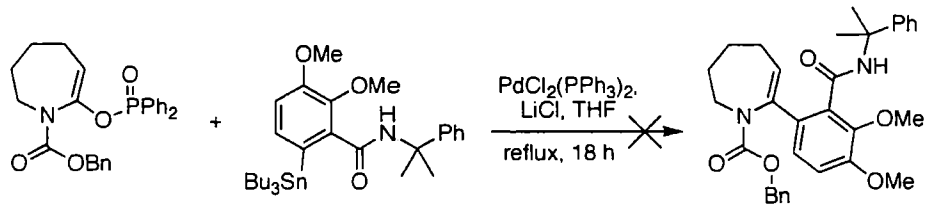


192 **193**

Scheme 128

Unfortunately, preparation of the final phosphinate fragment, **182**, needed for the synthesis of Lennoxamine had not been completed at this stage and the key Stille cross-coupling reaction (Scheme 124) could not be attempted in the timeframe of these studies.

However, the Stille coupling between readily available N-benzyl caprolactam phosphinate **130** and the newly synthesised organostannane **193** was possible. The outcome of this reaction would give an indication as to whether or not the important coupling with phosphinate **122** would be successful. Unfortunately, subjecting phosphinate **130** and organostannane **193** to standard Stille cross-coupling conditions (LiCl, $PdCl_2(PPh_3)_2$, THF) failed to furnish any of the desired coupled product **194** (Scheme 129). The probable reason for the failure is the sterically hindered environment of the stannane due to the large cumyl amide group. Unfortunately, time restrictions prevented further exploration of this step and therefore only a single attempt was made at this transformation. Further options and ideas are discussed in the future work section.



130 **193** **194**

Scheme 129

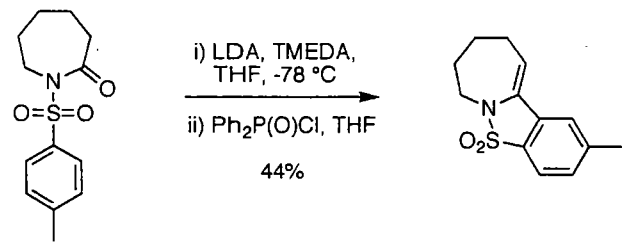
4.5 Summary

The caprolactam phosphinate model substrate indicated that the final step of the proposed synthesis, the cyclisation to form the five-membered lactam ring, was viable. Moreover, this transformation was achieved directly from the cross-coupled product **128** *via* a tandem reduction/deprotection/cyclisation reaction in excellent yield. Suzuki cross-coupling studies with the benzazepine model substrate **149** were unsuccessful resulting in hydrolysis of the phosphinate moiety. This was attributed to the increased stability of the vinyl phosphinate towards oxidation due to conjugation with the adjacent aromatic ring. However, under non-aqueous Stille cross-coupling conditions, benzazepine phosphinate **149** and phenyltributylstannane provided the desired coupled product in 25% yield. The desired organostannane, **193**, required for the final synthesis of Lennoxamine was prepared in three steps in high overall yield (60%). Although not complete, the synthesis of desired phosphinate fragment **182** is at an advanced stage and it is expected that final steps in the synthesis will prove trivial. Finally, initial attempts to cross-coupling stannane **193** with a simple caprolactam-derived phosphinate were unsuccessful and suggest that the sterically hindered nature of the stannane will further increase the difficulty of the key cross-coupling step. The final steps in the synthesis are outlined in the future work section.

5 Sultams

5.1 Introduction

Whilst investigating the synthesis and cross-coupling chemistry of caprolactam-derived phosphinates (Scheme 52) it was found that treating N-tosyl-protected lactam **19** with LDA and TMEDA followed by $Ph_2P(O)Cl$ afforded the fused sultam **20** as the major product (44%, Scheme 130).

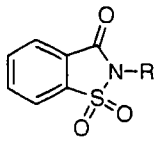


19 **20**

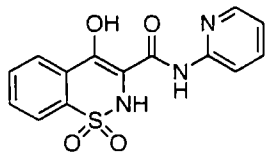
Scheme 130

These interesting compounds are well documented in the literature and are often found to posses interesting biological properties. For example, 3,5-diamino-1,2,6-thiadiazine-1,1-dioxide derivatives, **195**, possess anti-parasitic activity, [152] 1,2-benzisothiazolinone-1,1-dioxides, **196**, (saccharin derivatives) exhibit, among other properties, human leukocyte elastase inhibitory[153] and anti-fungal[154] activity and 1,2-benzisothiazine-1,1-dioxides such as the oxicams, e.g. piroxicam **197** are known for their anti-inflammatory properties[155] (Figure 18).

195



196

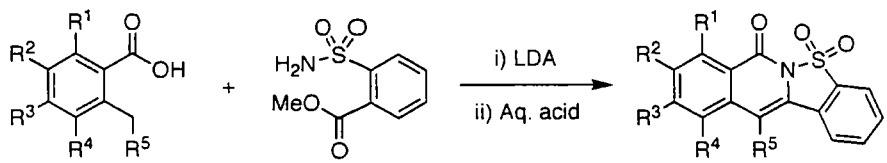


197

Figure 18

Reflecting these diverse roles there have been many methods described for the synthesis of sultams. These include, Diels-Alder cycloadditions, [156] radical cyclisations, [157] intramolecular Heck couplings, [158] ring-closing metathesis, [159] aziridination of iminoiodinanes [160] and N-chloramine sulfonamides, [161] ortho-lithiation (DMG) strategies [162] and lithiation of o-tolyl sulfonamides. [163-164]

Surprisingly, there have only been a limited number of methods describing the synthesis of fused amidosultams. [165] The most recent of these approaches was described by Dunn and co-workers who synthesised a range of fused sultams **200** in good yields (50-96%) from *ortho*-toluic acids **198** and methyl-2-(aminosulfonyl)benzoate **199** (Scheme 131).[164]



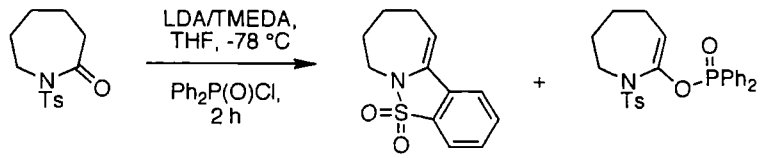
198 199 200

Scheme 131

5.2 N-Tosyl caprolactam

To summarise the original reaction, treatment of lactam **19** with LDA and TMEDA in THF and trapping the resultant anion with $Ph_2P(O)Cl$ was expected to furnish phosphinate **21**. However, chromatography afforded sultam **20** as the major

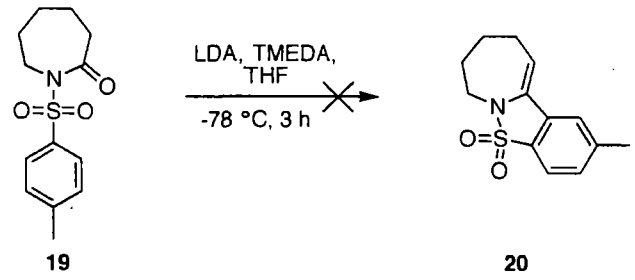
product (44%) accompanied by smaller amounts of the desired phosphinate **21** (15%, Scheme 132) indicating competing reaction pathways. Evidence for the formation of **21** was given in the ^{1}H NMR spectrum, which indicated only three aromatic protons were present, 7.29 ppm (1H, d, J = 8 Hz, 8-*H*), 7.41 ppm (1H, s, 6-*H*) and 7.64 ppm (1H, d, J = 8 Hz, 9-*H*) together with a new olefinic signal at 5.78 ppm (1H, t, J = 7 Hz, 5-*H*). Furthermore, this last signal showed NOESY and HMBC correlations with an aromatic proton signal at 7.41 ppm and a quaternary carbon signal at δ = 132.4, respectively. This was supported by a molecular ion in the HRMS at *m/z* = 250.0896 which is consistent with the molecular formula $C_{13}H_{16}NO_2S$ (MH^+).



19 **20** **21**

Scheme 132

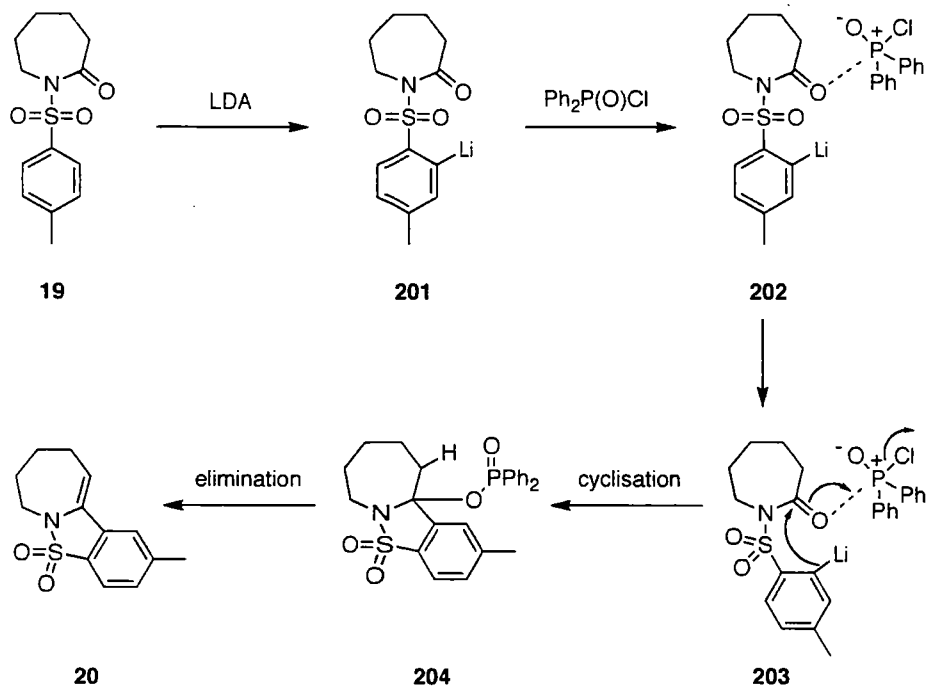
Taking into account the powerful directing metallation properties of the sulfonamide group[166] and the use of a lithium-derived base, it was inferred that formation of the sultam was occurring *via* an *ortho*-lithiation/cyclisation process. However, the role of the phosphorus reagent was less clear but its presence was found to be essential to the success of the reaction when, experiments undertaken in its absence and simply quenched with water afforded only recovered starting material **19** (Scheme 133).



19 **20**

Scheme 133

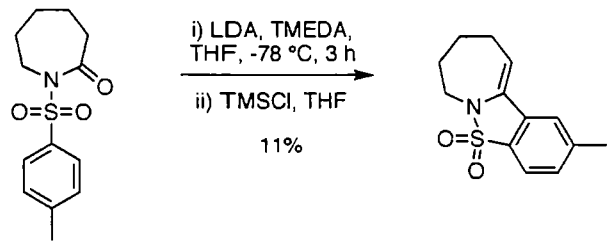
Consequently, a mechanism was postulated for the reaction beginning with an initial *ortho*-lithiation of aryl sulfonamide **19** affording aryllithium species **201**. This reactive species then attacks the lactam carbonyl group, which is activated by co-ordination to the oxyphilic phosphorus centre **202**. The resulting cyclic intermediate **204** is arranged to undergo an elimination reaction, in either an inter- or intra-molecular fashion, affording the observed sultam product **20** (Scheme 134).



19 **201** **202** **203** **204** **20**

Scheme 134

If the suggested mechanism is correct, it was surmised that replacing the electrophilic phosphorus reagent with a similar oxyphilic electrophile would also lead to the sultam product. Hence, the reaction was repeated in an identical fashion and the phosphoryl chloride was replaced with trimethylsilyl chloride (TMSCl). As predicted, the desired sultam was isolated but in a much reduced yield (10%) compared to the phosphoryl chloride (44%). The reaction was repeated and found to be consistent when the second attempt furnished the sultam **20** in a similarly poor yield (11%, Scheme 135).



19 **20**

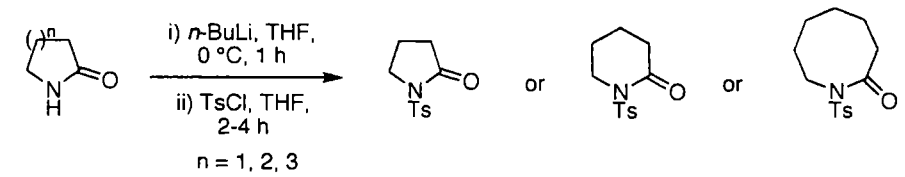
Scheme 135

Having undertaken these preliminary studies, the scope and limitations of the methodology were then examined by varying both the size of the lactam ring and identity of the aromatic sulfonyl group.

5.3 Five, six and eight membered ring lactams

In addition to the seven-membered ring, it was decided to explore the five, six and eight-membered ring lactams as well. Thus, commercially available pyrrolidinone **23** (n = 1), valerolactam **28** (n = 2) and 2-azacyclooctanone **34** (n = 4) were protected as their N-tosyl derivatives **24**, **29** and **35** in variable, but unoptimised yields (65%, 33%, 80%, respectively) by metallation of the parent lactam with *n*-BuLi and subsequent reaction with tosylchloride (Scheme 136). The lack of an N-H stretching

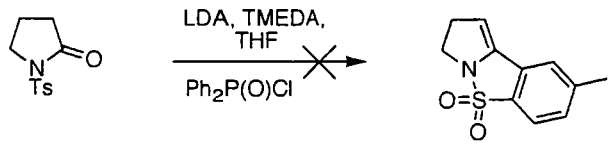
frequency in the IR spectra for the protected lactams gave evidence for the formation of the desired products. In addition, the LRMS for each compound gave a molecular ion at MH^+ with the correct molecular weight, *m/z* = 240.1 (**24**), 254.1 (**29**) and 282.1 (**35**).



23, 28 or 34 **24** - 65% **29** - 33% **35** - 80%

Scheme 136

Each of the protected lactams was subjected to the cyclisation conditions beginning with the five-membered derivative **24**. Unfortunately, treatment of a cold THF solution of **24** and TMEDA with LDA followed after 1 h with phosphoryl chloride furnished none of the desired product **205** (Scheme 137). The reaction yielded a reasonable quantity of recovered starting material (43%) whilst the remainder of the material was lost as indeterminate by-products.

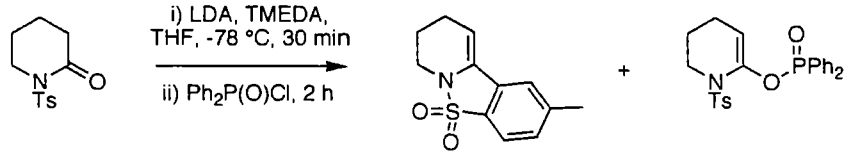


24 **205**

Scheme 137

Treatment of N-tosyl piperidinone **29** under identical conditions furnished equal quantities of phosphinate **31** (30%) and recovered starting material (32%) with only trace amounts of the desired sultam **206** evident (Scheme 138). Phosphinate **206** was found to be unstable, decomposing during storage and column chromatography and could not be isolated cleanly, this is in accord with observations made earlier (Scheme 56). The failure of both the five- and six-membered derivatives to undergo cyclisation to

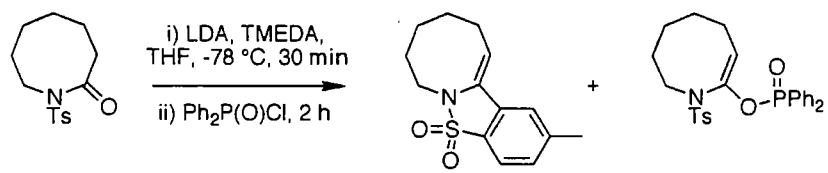
the desired sultams can be attributed to the increased ring strain present in the transition state disfavouring cyclisation and leading in the case of the six-membered ring to preferential formation of the phosphinate.



29 **206** - 0% **31** - 30%

Scheme 138

Moving from the six- to the eight-membered ring it was expected that formation of the sultam would now be successful, as the ring strain present in the transition state should be greatly reduced. As expected, treatment of **35** with LDA/TMEDA followed by phosphoryl chloride afforded the desired sultam **207** but, surprisingly only in poor yield (18%). In addition to sultam **207**, phosphinate **36** was also isolated in a slightly higher but still poor yield (24%, Scheme 139). Based on these investigations, it appears that the process is limited to seven-membered rings only with both larger and smaller rings proving much less efficient.



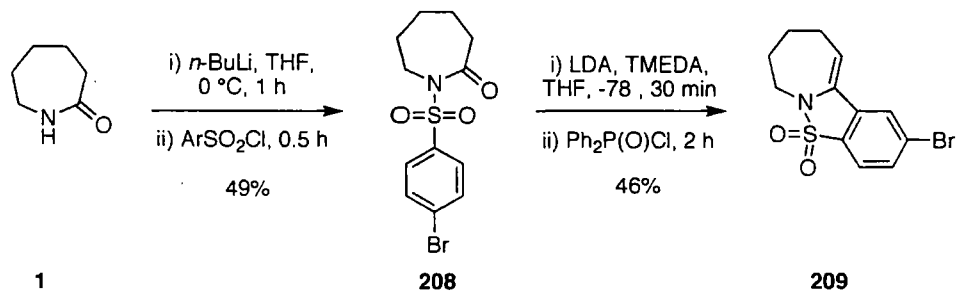
35 **207** - 18% **36** - 24%

Scheme 139

5.4 Alternative arylsulfonyl groups

Having explored the lactam ring size, attention then turned to the identity of the aromatic sulfonyl group. Four aryl sulfonyl chlorides were chosen to complement the

tosyl derivative already investigated. Those chosen included a napthyl derivative, an electron-deficient 4-bromophenyl and two non-symmetrical examples, one electron-rich and one electron-poor, 3-methoxyphenyl and 3-nitrophenyl, respectively. Since it had proven the optimal ring size for formation of the sultam, the seven-membered ring lactam (caprolactam) was used in combination with each of the above aryl sulfonyl groups. The tosyl group is a relatively electron-rich aromatic ring and should decrease the acidity of the *ortho*-proton making it less susceptible to deprotonation. However, by the same token it should also make the subsequent aryllithium species more reactive. On the same basis, an electron-deficient aromatic ring should have the equal and opposite effect to that just described. To determine the effect that the electronic character of the aromatic ring has on the cyclisation reaction, the 4-bromophenylsulfonyl-derivative was explored. Thus, preparation of bromolactam **208** was achieved by metallation of caprolactam **1** with *n*-BuLi and the anion quenched with 4-bromophenylsulfonyl chloride affording **208** in 49% yield. Formation of **208** was indicated by the lack of an N-H absorption band in the IR spectrum and supported by a molecular ion at MH^+ in the LRMS at *m/z* = 332.2/334.2 with the correct isomeric ratio (1:1 ratio, Br^{79}:Br^{81}). Cyclisation of **208** was carried out under the standard conditions furnishing sultam **209** in a moderate yield (46%). Interestingly, none of the corresponding phosphinate was isolated (Scheme 140).



1 **208** **209**

Scheme 140

In a similar fashion to the tosyl-derivative, formation of bromo-substituted sultam **209** was established using NMR and mass spectrometry techniques. However, ultimate confirmation of the structure was realised when bromo-derivative **209** provided crystals suitable for an X-ray structure determination (Figure 19). Acknowledgement goes to Dimitry Yufit of Durham University for obtaining the crystal structure.

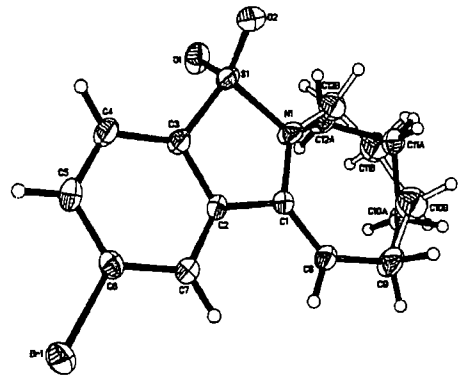
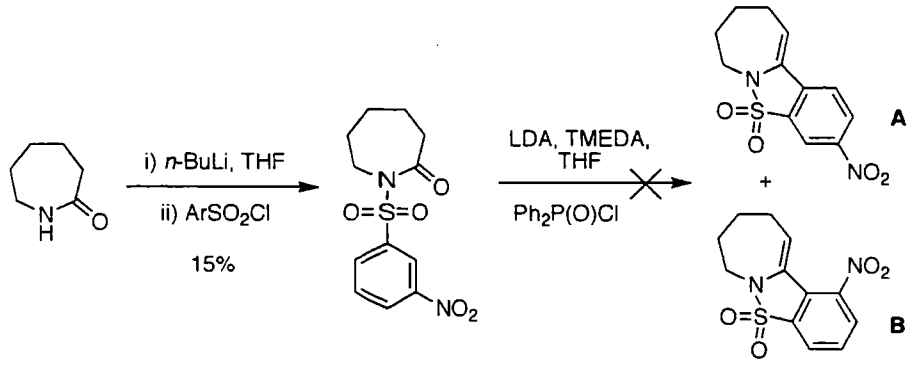


Figure 19: Molecular structure of sultam 209

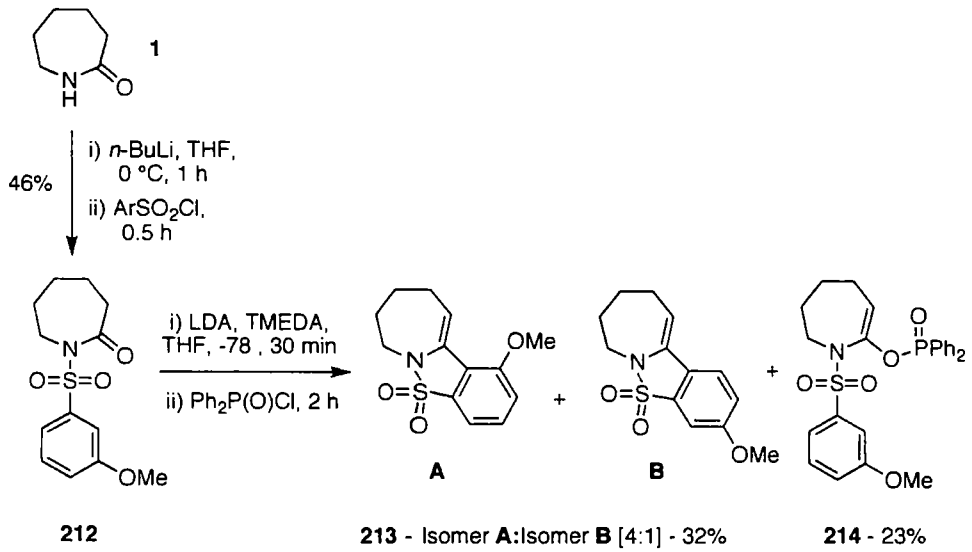
Employing a non-symmetrical aryl group, e.g. a phenyl group substituted at the 3 position, causes the two protons lying *ortho* to the sulfonyl group to become inequivalent. Treatment of such a compound with LDA should lead to two isomeric products. To explore this, both the 3-nitro and the 3-methoxyphenyl derivatives were investigated. Protection of caprolactam **1** with 3-nitrophenylsulfonylchloride proved problematic and **210** could not be isolated efficiently (15%) despite several attempts. However, sufficient material was acquired to attempt the cyclisation reaction. Unfortunately, when treated under standard cyclisation conditions **210** failed to furnish either the desired sultam isomers **211 A** or **B** or the corresponding phosphinate (Scheme 141).



1 **210** **211** isomers **A** and **B**

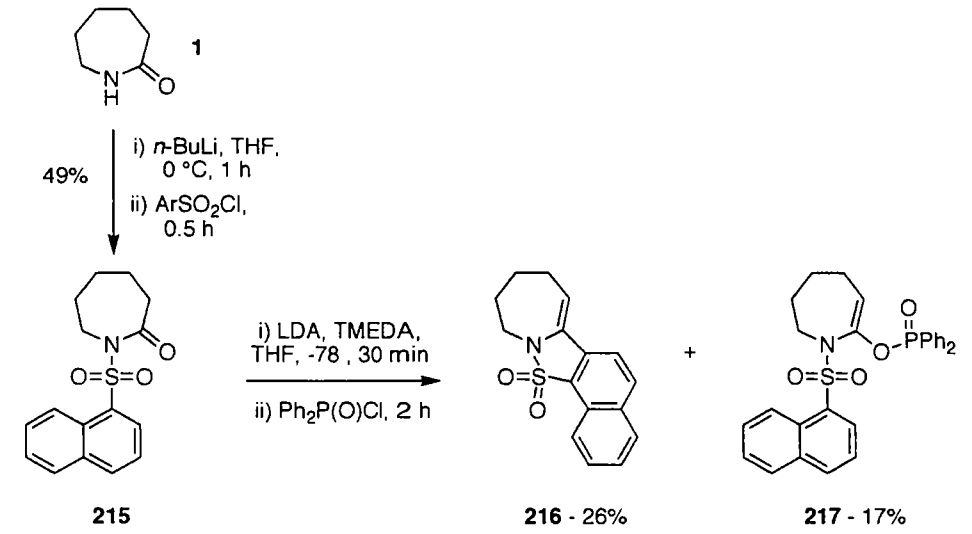
Scheme 141

Protection of caprolactam **1** with 3-methoxyphenylsulfonyl chloride proceeded smoothly and **212** was isolated in 46% yield and characterised by the appearance of a methoxy signal in the ^{1}H NMR spectrum at 3.86 ppm (3H, s, OCH_3) as well as four aromatic protons $\delta = 7.12$ (1H), 7.40 (1H) and 7.53 (2H). In contrast to the nitro-derivative, treatment of the methoxy-analogue, **212**, with LDA/TMEDA and quenching with $Ph_2P(O)Cl$ afforded the three compounds, both regioisomers of the expected sultam **213** in 32% overall yield as well as corresponding phosphinate **214** (23%, Scheme 142). It was not possible to separate the two regioisomers and therefore, their ratio was determined from the ^{1}H NMR spectrum and was found to be 4:1 in favour of isomer **A**. This was calculated from the integrals of the olefinic signal for each isomer which appear at 6.52 ppm (t, J = 6 Hz) and 5.65 ppm (t, J = 6 Hz) for the major (**A**) and minor isomer (**B**), respectively. The difference in the resonances for the two isomers is presumably due to the proximity of the methoxy group. Methoxy groups are also efficient D*o*M groups[166] and this helps explain the selectivity observed in the reaction. The proton at position 2 of the phenyl ring, *ortho* to both the methoxy and sulfonyl groups, is more highly activated than the proton at position 5 on the ring, which is activated only by the sulfonyl group.



Scheme 142

In addition to phenylsulfonyl groups, the use of a fused aromatic napthyl group was also explored. Protection proceeded smoothly furnishing the desired product, **215**, in 49% yield. Treatment of **215** under the standard cyclisation conditions afforded the desired sultam **216** in a 29% yield as well as the corresponding phosphinate **217** (17%, Scheme 143).



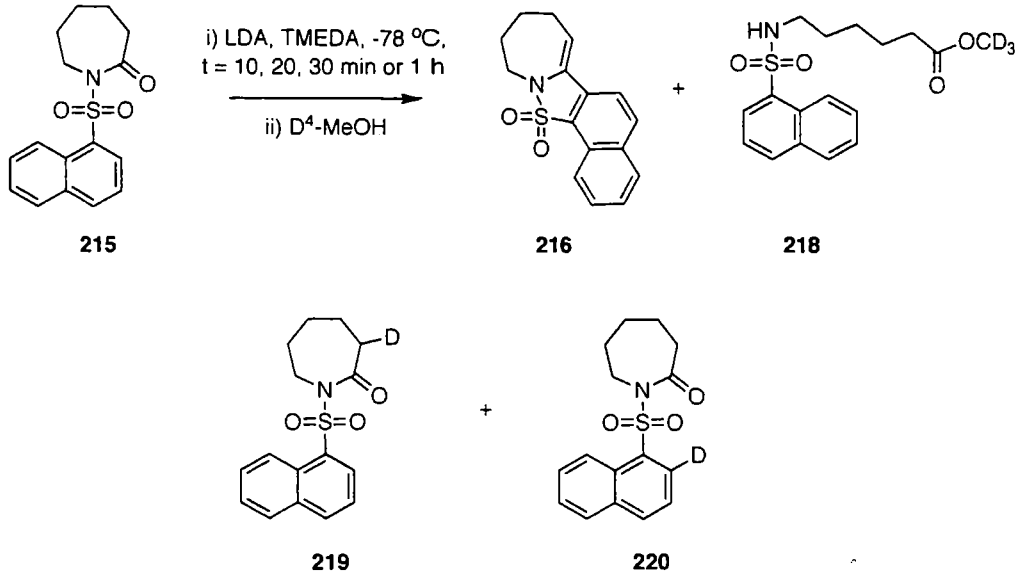
Scheme 143

5.5 Mechanistic investigations

It is proposed that the competing formation of the phosphinate during the cyclisation process can arise either by a direct metallation of the carbonyl functionality or through an *ortho*-lithiation of the aryl group, which can then act as a base giving rise to the enolate anion in either an intra- or inter-molecular fashion. In an effort to gain a better understanding of this mechanism it was decided to carry out a series of time and concentration dependant deuteration experiments.

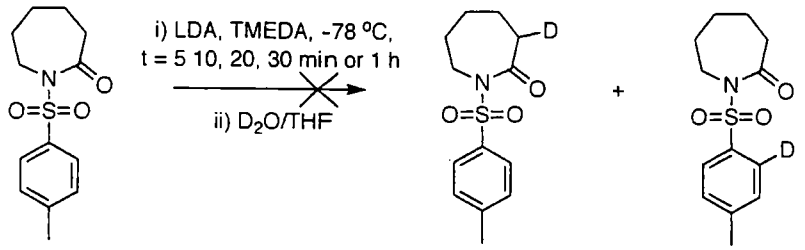
5.5.1 Time dependant deuteration experiments

Initial studies were undertaken using the napthylsulfonamide **215**. Four reactions were carried out which were quenched at intervals (10 min, 20 min, 30 min and 1 h) with D^4-MeOH (Scheme 144). It was expected that the products from the reactions would result from incorporation of deuterium either in the *ortho*-position of aromatic ring, **219**, or *alpha* to the carbonyl, **220**. The ratio of these two compounds would be determined by ^1H NMR analysis of the crude reaction mixtures. Following work up, TLC analysis confirmed the presence of two compounds, neither of which had the same R_f as the starting material. Chromatography and subsequent ^1H and ^2H NMR and MS analysis revealed the compounds to be ring opened derivative **218** and more surprisingly the sultam **216** (Scheme 144). It was subsequently shown that a simple MeOH quench furnished the same products.



Scheme 144

Previously it had shown that metallation of tosylsulfonamide **19** with LDA/TMEDA followed by a simple water quench resulted in quantitative recovery of the starting lactam (Scheme 133). On this basis, it was envisaged that metallation of **19** and quenching with D_2O rather than D^4-MeOH would lead to the expected deuteration products **221** and **222** (Scheme 145). Five reactions were carried out and quenched at intervals of 5 min, 10 min, 20 min, 30 min and 1h. TLC analysis of each reaction was encouraging, revealing the presence of starting material. However, ^1H and ^2H NMR analysis of the crude material for each reaction suggested that there was little or no deuterium incorporation into the substrate. At this stage due to more pressing issues this approach was abandoned.

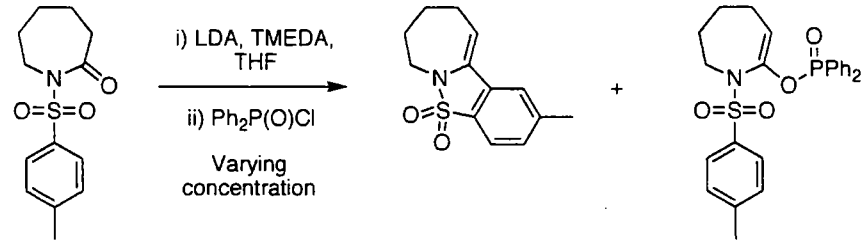


19 **221** **222**

Scheme 145

5.5.2 Reaction concentration studies

Having encountered problems with the deuteration experiments just discussed, whilst investigating the effect of concentration on the outcome of the reaction it was decided to quench the reactions with $Ph_2P(O)Cl$. This would allow the ratio of the sultam to the phosphinate to be calculated from the integrals of the C-3 proton signals of these two products in ^1H NMR spectrum of the crude material. Tosyl caprolactam **19** was used for the study and the reaction carried out at four concentrations. Thus, four solutions of lactam **19** (0.04 M, 0.08 M, 0.16 M and 0.32 M) were treated with LDA/TMEDA and subsequently quenched with $Ph_2P(O)Cl$, the outcome of each reaction can be seen in Table 6. Increasing the concentration leads to an increase in the formation of phosphinate. This trend is suggestive of an initial aryl metallation followed by an intermolecular proton abstraction to generate the enolate. At lower concentrations sultam formation dominates, however, if the reaction is too dilute no reaction is observed and only the starting lactam is recovered.

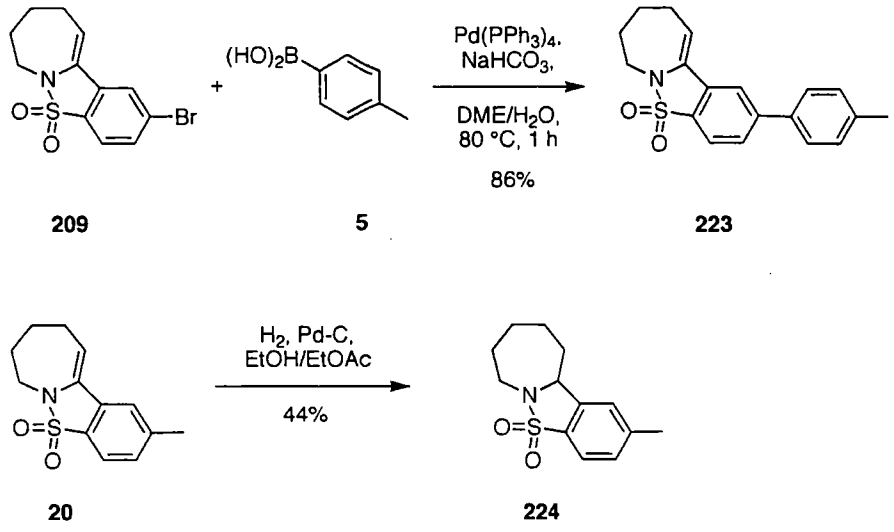


Entry	Sulfonamide	Concentration [a]	Ratio **20** : **21** [b]
1	**19**	0.04 M	Recovered SM
2	**19**	0.08 M	3:1
3	**19**	0.16 M	1:1
4	**19**	0.32 M	1:1.6

Table 6 [a] Of the initial solution before LDA addition. [b] Calculated from ^{1}H NMR spectrum of crude material

5.5.3 Further functionalisation

Further functionalisation of the sultam products was straightforward, e.g. treatment of bromide **209** under standard Suzuki cross-coupling reaction conditions furnished biaryl **223** in 86% yield (Scheme 146). Compound **223** was characterised by ^{1}H NMR spectroscopy, which contained the correct number of aromatic protons and was supported by HRMS that did not contain the characteristic bromine isotope pattern and found a molecular ion at *m/z* = 326.1208, consistent with the molecular formula $C_{19}H_{20}NO_2S$. Moreover, reduction of the enamine functionality of sultam **20** afforded tertiary amine **224** in 44% yield (Scheme 146). Evidence for the formation of **224** was given by HRMS which found a molecular ion at *m/z* = 252.1060, consistent with the molecular formula $C_{13}H_{17}NO_2S$. This was supported by NMR spectroscopy.



Scheme 146

5.5.4 Summary

Treatment of N-arylsulfonyl-protected caprolactams with LDA in the presence of diphenylphosphoryl chloride furnishes mixtures of phosphinates and cyclic sulfonamides *via* an *ortho*-lithiation/cyclisation/elimination sequence. Employing an unsymmetrical aryl groups leads to mixtures of isomeric products whilst the presence of a nitro group in the aromatic ring is not tolerated. The reaction is limited to the seven-membered ring caprolactam, as five-, six- and eight-membered ring lactams were either unsuccessful or much less efficient. Further functionalisation of the sultam products was trivial.

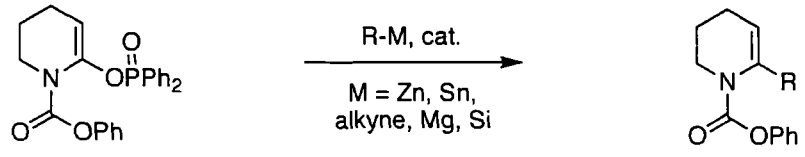
6 Conclusions and future work

6.1 Lactam phosphinates

Phosphinates can be considered as a useful new class of electrophile for use in cross-coupling chemistry. They provide a further option for chemists wishing to activate carbonyls towards cross-coupling reactions. They should prove particularly useful when the corresponding triflate cannot be prepared efficiently or is found to be unstable. Seven- and eight-membered ring lactam-derived phosphinates are particularly useful as they are readily prepared and are excellent electrophilic substrates for Suzuki-Miyaura cross-coupling reactions. The inherent stability (they are shelf- and air-stable indefinitely whereas the corresponding triflates are difficult if not impossible to isolate efficiently) and high reactivity of these species should make them the substrate of choice when activating lactams. However, successful formation of the phosphinate is limited at present to the use of lactams with an electron-withdrawing-nitrogen-protecting group only. Phosphinate formation is also possible employing five- and six-membered ring lactams. Unfortunately, due to the increased ring strain present in these substrates they were found to be generally unstable and therefore of little use in cross-coupling reactions under the conditions employed in these studies. However, the preparation and isolation of the six-membered ring N-CO_2Ph-protected vinyl phosphinate **32** was the exception and provides evidence that the required stability can be generated in these systems.

Before lactam-derived vinyl phosphinates can be considered as generally useful substrates, more fundamental studies need to be carried out. These include, developing conditions for coupling these substrates in the various other cross-coupling strategies including Negishi, Stille, Sonogashira, Kumada and Hiyama protocols. The

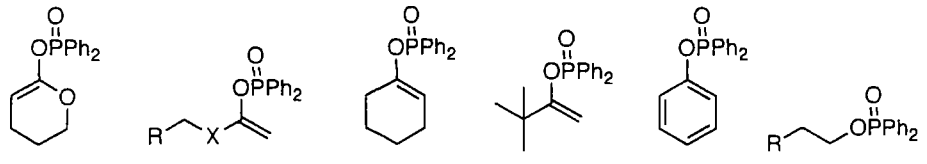
development of these reactions should be undertaken employing the stable six-membered ring lactam phosphinate **32** (Scheme 147). It is expected that conditions developed using this substrate will be transferable to vinyl phosphinates derived from larger sized rings whereas experience has shown that the reverse may not be true. Moreover, the inclusion of six-membered ring lactams to complement seven- and eight-membered rings will greatly improve this methodology.



32 **225**

Scheme 147

Additionally, the methodology would be further improved if the range of substrates that can be utilised were further reaching. Substrates that would merit investigation are alternative activated vinyl phosphinates such as those derived from lactones, e.g. **226** as well as acyclic examples derived from amides and esters, e.g. **227**. More interesting would be unactivated vinyl phosphinates such as those derived from cyclic and acyclic ketones, e.g. **228** and **229** and perhaps the most interesting would be aryl phosphinates, e.g. **230** or simple alcohols **231**, the latter requiring coupling of an sp3 centre (Figure 20).

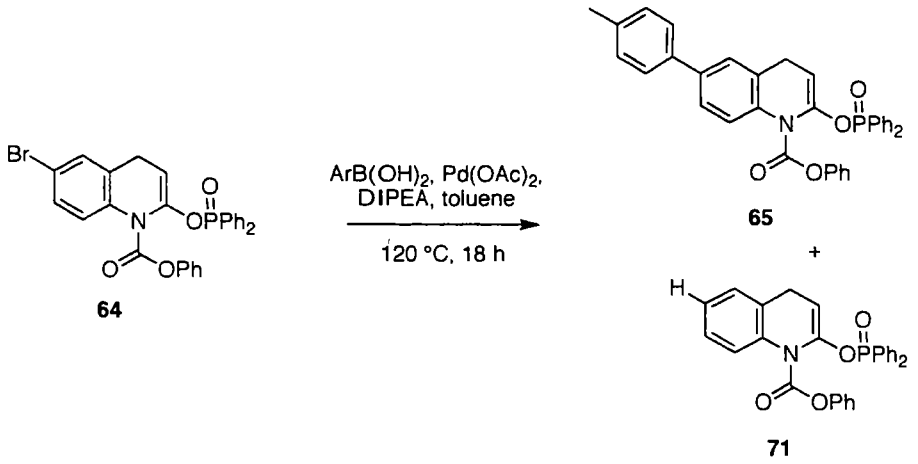


226 **227** X = O or NH **228** **229** **230** **231**

Figure 20

6.2 Reactivity studies

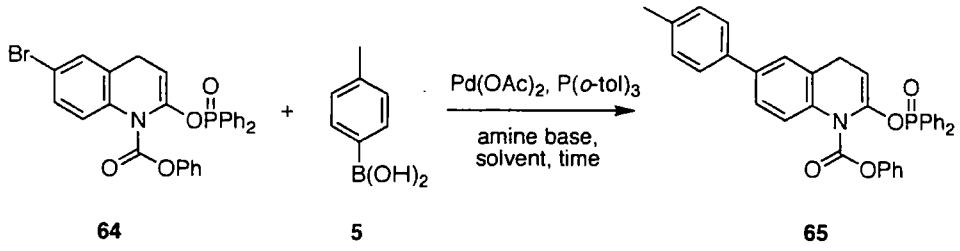
Vinyl phosphinates were shown to be more reactive than aryl chlorides and less reactive than aryl bromides in the Suzuki cross-coupling reaction. Given that aryl chlorides are now considered to be generally useful substrates, vinyl phosphinates should also find general applicability across the range of cross-coupling protocols. The difference in reactivity between aryl bromides and phosphinates is sufficient to afforded complete selectivity for the aryl bromide in cross-coupling reactions. This provides a synthetically valuable selectivity between that of oxygen-based electrophiles and aryl bromides and allows for the incorporation of both these species in the same molecule without competing reactions occurring. Unfortunately, the poor stability of quinolinone derived-phosphinates has so far prevented them from being useful substrates for cross-coupling protocols. In-depth optimisation studies of the Suzuki reaction of quinolinone-derived phosphinate **64** using DoE and PCA techniques had failed to give the desired outcome. However, some progress had been made in this area and Suzuki conditions under which the phosphinate was stable had been identified. This introduced a new problem that was suspected to arise as a result of inefficient transmetallation leading to decomposition of the active catalyst and poor conversion of the aryl bromide starting material (Scheme 148). It appeared that both sufficient reactivity of the bromide and stability of the phosphinate were unattainable under the same reaction conditions.



Scheme 148

A possible solution to this problem would be to screen alternative cross-coupling protocols, specifically those that are carried out under nonaqueous conditions. However, preliminary studies with standard Stille reaction conditions were unsuccessful and suggest this may not provide the answer. Although if successfully developed using the simple lactam phosphinate **32** discussed above an alternative protocol might prove successful. Alternatively, it is postulated that optimisation of the above Suzuki reaction (Scheme 148) using a combination of DoE and PCA techniques might prove fruitful. There are several factors that point towards a positive outcome. By utilising PCA models of amine bases and solvents it will be possible to screen a large variety of combinations of these two factors, both of which are known to be critical from the previous DoE study. The optimal catalyst/ligand combination was identified in the original screen and can therefore be kept the same thereby simplifying the process. Importantly, the loading of both the ligand and catalyst, which intuitively seem important in this reaction, can also be investigated. Moreover, the phosphinate moiety is stable under these conditions meaning that it is likely that no by-products due to its decomposition will be formed, further simplifying the process. Finally, of the three components observed in the reaction both the unreacted starting material **64** and the

reduced bromide **71** will be eliminated if formation of the cross-coupled product is optimised (Scheme 149).



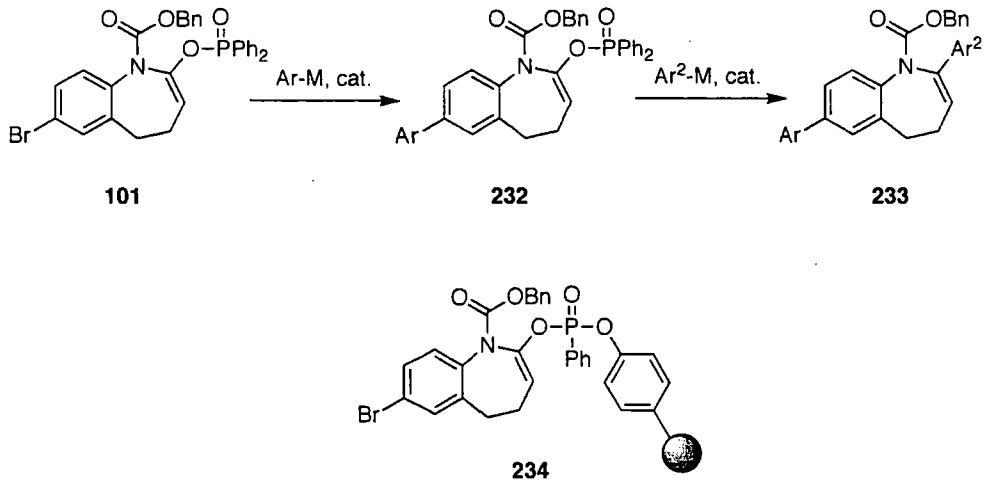
64 **5** **65**

Scheme 149

The initial approach to circumventing the problem outlined above was to increase the size of the lactam ring from a six-membered quinolinone to seven-membered benzazepine system. This approach was successful and provided a more stable phosphinate, **101**, which was storable and more importantly stable under standard aqueous Suzuki reaction conditions. Preliminary cross-coupling studies with **101** supported the previous results from the relative reactivity studies with the quinolinone substrate. However, complications due to hydrolysis of the phosphinate moiety were avoided. Unfortunately, time restraints and lack of material meant that only the initial cross-coupling of the aryl bromide was explored with this system. However, it is expected that this phosphinate will provide a suitable substrate to be utilised in a bi-directional synthesis strategy where the relative reactivities of the phosphinate and bromide can be exploited.

In order for this to be successful the synthesis of benzazepine-derived phosphinate **101** needs to be repeated and the yields for this process optimised. The initial cross-coupling reaction in which the aryl bromide moiety of **101** is selectively cross-coupled also requires repeating and optimising. The viability of the second cross-coupling reaction in which a phosphinate such as **232** is coupled needs exploring to demonstrate the idea of bi-directional synthesis. Providing a sufficient reactivity

difference is also observed between vinyl phosphonates and aryl bromides (this is not guaranteed) the extension of this chemistry to solid phase organic synthesis utilising phosphonate **234** and chemistry previously developed in the Steel laboratories should be undertaken (Scheme 150).



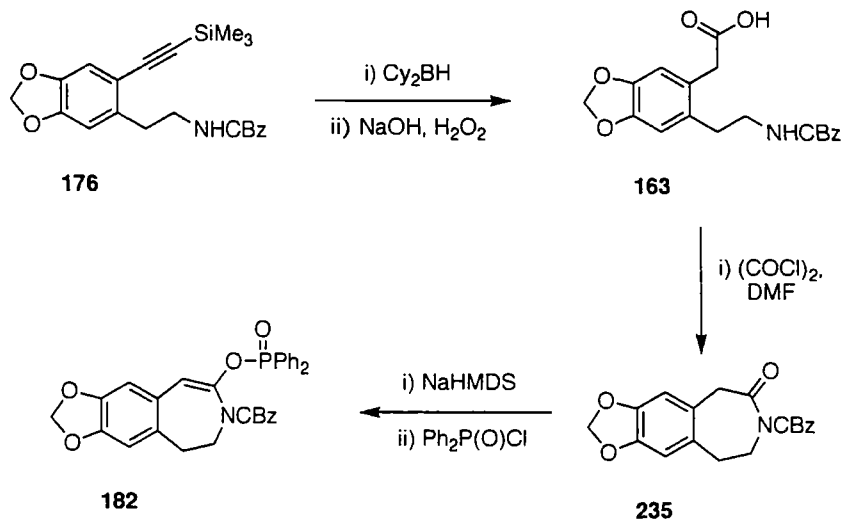
Scheme 150

6.3 Lennoxamine

The caprolactam model study indicated that the final step of the proposed synthesis, in which the five-membered lactam ring is formed, was viable. The benzazepine model study indicated that the required benzazepine vinyl phosphinate system exhibits low reactivity towards cross-coupling protocols, most likely as a result of conjugation of the C-O bond with the aromatic ring. Unsuccessful attempts to couple the final stannane, **193**, with a simple caprolactam phosphinate suggests that the sterically-hindered nature of the stannane will further complicate the key Stille reaction between **193** and **122**. Synthesis of stannane **193** is complete and proved trivial whilst synthesis of the phosphinate **122** requires only three further simple steps providing easy access to both the required fragments. It is expected that the cross-coupling of these two key fragments will be more difficult than first anticipated and prove to be the

decisive step in the synthesis. However, with thorough and careful investigation it is expected that this approach will provide a novel route to Lennoxamine through the use of a cross-coupling reaction of a lactam-derived vinyl phosphinate.

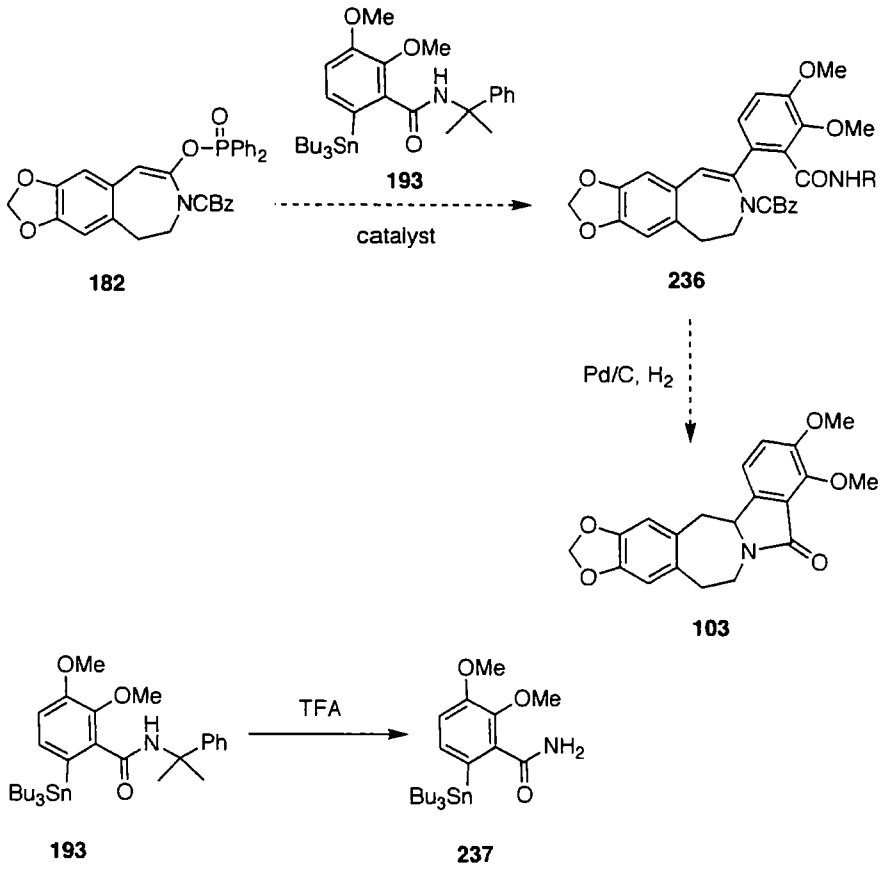
The final three steps in the synthesis of the phosphinate fragment needs to be carried out, these include the hydroboration/oxidation of alkyne **176** as described by Zwiefel *et al.*.[150] Subsequent formation of the acyl chloride will hopefully induce a spontaneous cyclisation reaction providing **235** from which phosphinate **182** will be formed using standard conditions (Scheme 151).



176 **163** **182** **235**

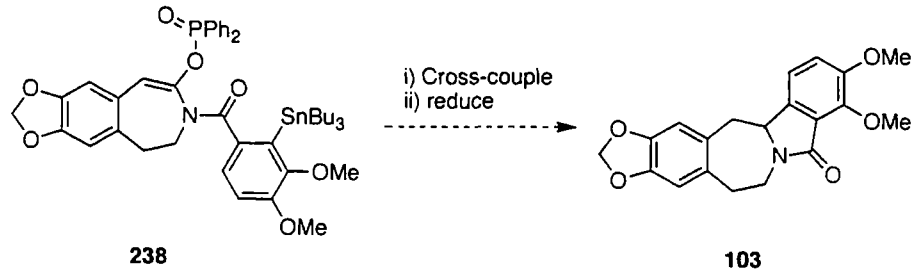
Scheme 151

The decisive cross-coupling step is shown in Scheme 152, if successful the product **236** should be readily converted to the natural product Lennoxamine **103** by treatment with Pd/C and H_2. If as suspected, the sterically hindered stannane moiety proves problematic, the bulky cumylamide group can be removed by treatment with TFA furnishing primary amide **237**. The cross-coupling of this compound can then be investigated (Scheme 152).



Scheme 152

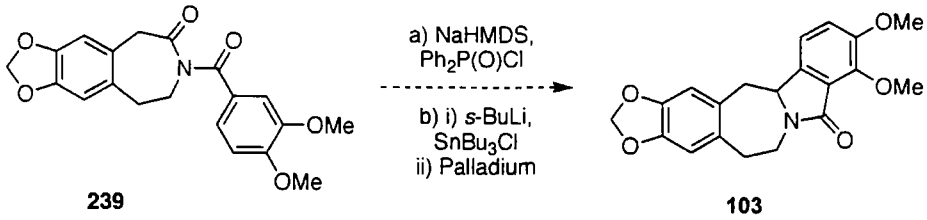
An alternative approach would be to carry out the cross-coupling reaction in an intramolecular fashion. Formation of the amide bond prior to cross-coupling would furnish an intermediate such as **238**. Following oxidative addition of the phosphinate to the catalyst the proximity of the stannane to the reactive centre should increase the likelihood of transmetallation occurring and the cross-coupling being successful (Scheme 153).



238 103

Scheme 153

A further advantage of this strategy is that the desired aromatic ring can be used as a protecting group during the synthesis of the benzazepine system **239**. The introduction of the phosphinate and stannane can be carried out at the end of the synthesis using benzazepine amide **239** as the DoM group to introduce the stannane. It might also be possible to carry out a one-pot stananylation/cross-coupling reaction (Scheme 154) as has been shown by Snieckus previously.[166]



239 103

Scheme 154

6.4 Sultams

ortho-Lithiation of cyclic aryl sulfonamides in the presence of phosphoryl chloride provides a novel, very simple entry to fused polycyclic sultams not easy to prepare by more standard methods. The yields for the formation of the sultams range from poor to moderate, the poor yield is partly due to the competing formation of the corresponding phosphinate as well as poor conversion of starting material. Unfortunately, the methodology was limited to seven-membered ring derivatives.

Future work should include a thorough optimisation of the reaction to improve the yields of the sultam product, inhibit the formation of the phosphinate and improve conversion of the starting material. A possible method of optimisation would be to employ a DoE approach like that discussed earlier in this thesis. Following a successful optimisation, applying this methodology to the synthesis of a natural product would provide an interesting project.

7 Experimental Section

7.1 General Experimental

All reactions were carried out under an argon or nitrogen atmosphere unless otherwise stated. Solvents were purified following established protocols. Petrol refers to petroleum spirit boiling in the 40-60 °C range. Ether refers to diethyl ether. Commercially available reagents were used as received unless otherwise stated. Flash column chromatography was performed according to the method of Still *et al.*[ref] using 200-400 mesh silica gel. Yields refer to isolated yields of products of greater than 95% purity as determined by ^{1}H and ^{13}C NMR spectroscopy or elemental analysis (Durham University Microanalytical Laboratory).

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films between KBr plates (liquids) or using an ATR attachment (ATR apparatus) on a Perkin-Elmer FT-IR 1600 spectrometer. Unless otherwise stated ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian Mercury-200, Varian Unity-300, Mercury-400, Varian Inova-500 or Varian-700 and are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant J (Hz), assignment). All coupling constants are $^{3}J_{HH}$ unless otherwise stated. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as the internal reference. ^{13}C NMR spectra were recorded at 101 MHz, 126 MHz or 176 MHz on Mercury-400, Varian Inova-500 or Varian-700, respectively, using the central resonance of (δ_C = 77.0 ppm) as the internal reference. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ_H = 0.00 ppm) and coupling constants are given in Hertz to the nearest 1 Hz. All ^{13}C spectra were proton decoupled. Assignment of spectra was carried out using DEPT, COSY, HSQC, HMBC and NOESY

experiments. Low-resolution electrospray mass spectra (ES) were obtained on a Micromass LCT Mass Spectrometer or a Thermo-Finnigan LTQ. High-resolution mass spectra (ES) were obtained on a Thermo-Finnigan LTQFT Mass Spectrometer in Durham University. All microanalysis results are given to within 0.5%.

7.2 Experimental Methods and Data

7.2.1 General Experimental Methods

NaHMDS Protocol for phosphinate formation:

To a cold solution (-78 °C) of the appropriate lactam (0.1 M, 1 eq) in dry THF was added NaHMDS (2 M 1.2 eq) slowly via syringe and the reaction mixture stirred at -78 °C for 1 h. Diphenylphosphonic chloride (1.2 eq) was added dropwise *via* syringe and the reaction mixture was stirred at -78 °C for an additional 2 h before warming to room temperature and quenching with H_2O. The resulting mixture was concentrated and the aqueous layer extracted into EtOAc (x 3). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated affording the crude product.

LDA/TMEDA Protocol for phosphinate formation:

To a cold solution (-78 °C) of the desired lactam (1 eq) and TMEDA (1.3 eq) in dry THF (0.08-0.1 M) was added a cold solution of LDA in dry THF (0.18 M, 1.3 eq). The resulting reaction mixture stirred at -78 °C for 2 h after which time a cold (-78 °C) solution of diphenylphosphonic chloride in dry THF (0.2–0.4 M, 1.2 eq) was added *via* cannula. The reaction mixture was stirred at -78 °C for 3 h then warmed to room temperature and quenched with aq. NH_4Cl. The THF was removed under reduced pressure and the aqueous layer extracted with EtOAc. The organic phase was washed with aq. $NaHCO_3$ brine then dried over $MgSO_4$ and concentrated under reduced pressure to give the crude material.

Suzuki protocol A:

A solution of phosphonite (1 eq), $NaHCO_3$ (3 eq), and boronic acid (1 eq) in DME/H_2O (7:3) was degassed *via* three freeze/pump/thaw cycles. $Pd(PPh_3)_4$ (0.05 eq) was added and the reaction mixture stirred at reflux (85 °C) for 1 h. The reaction mixture was cooled to room temperature, concentrated and extracted into EtOAc (x 3). The combined organics were washed with H_2O (x 3) then brine (x 3), dried over $MgSO_4$ and concentrated.

Suzuki microwave protocol:

The appropriate phosphinate (1 eq), boronic acid (1.1 eq), Na_2CO_3 (3 eq) and catalyst (0.05 eq) were placed in a microwave vial, the solvent (DME/H_2O/EtOH, [7:3:1]) was added and the vial sealed. The reaction was undertaken in a Biotage microwave reactor. Reaction parameters: Prestir = 10 s, reaction time = 300 s, temperature = 100 °C. The reaction was allowed to cool to room temperature, concentrated and extracted into EtOAc (x 3). The combined organics were washed with H_2O (x 3) then brine (x 3), dried over $MgSO_4$ and concentrated.

Thermal Stille protocol:

A solution of phosphinate (1.0 eq) and LiCl (2.5 eq) in THF was degassed by purging with argon for 10 min before $ArSnR_3$ (1.5 eq) and $Pd(PPh_3)_4$ (0.05 eq) were added. The mixture was heated at reflux for 2 h and cooled to room temperature. The solution was concentrated and extracted with EtOAc/(1 M aqueous KF), the organic phase was combined, dried over $MgSO_4$, filtered and concentrated.

General procedure for synthesis of amides.[129]

To a refluxing (70 °C) solution of the required amine (2 eq) in acetone was added 3-chloropropionylchloride (1 eq) as a solution in acetone and the reaction mixture stirred

at reflux for 1 h. After being cooled to room temperature, the resulting suspension was poured into a flask containing 5 M aq. HCl to achieve complete precipitation. The solid was collected by filtration and dried under reduced pressure. No purification was required unless otherwise stated.

Thermal protocol for the preparation of substituted quinolones.[129]

The appropriate amide (1 eq) was placed under an argon atmosphere and heated in an oil bath (methyl **49** - 130 °C, chloro **50** - 145 °C) until complete melting had occurred. Finely ground $AlCl_3$ (methyl 1.1 eq, chloro 2.0 eq) was added in small aliquots and the flask re-purged with argon. The reaction mixture was stirred for 24 h at elevated temperature after which it was allowed to cool to room temperature. 3 M aq. HCl was added dropwise [Care! Exothermic reaction] and the crude material was extracted with DCM then washed with brine. The organic phase was dried over $MgSO_4$, concentrated and dried under reduced pressure.

Microwave protocol for the preparation of substituted quinolones.

Methyl quinolinone **51**: $AlCl_3$ (1.1 eq), Ramp time = 3 min, hold time = 10 min, power = 75 W, set temperature = 150 °C, max temperature reached = 172 °C.

Chloro quinolinone **52**: $AlCl_3$ (2.0 eq), Ramp time = 3 min, hold time = 10 min, power = 75 W, set temperature = 170 °C, max temperature reached = 220 °C.

Amide (1 eq) and finely ground $AlCl_3$ were heated in an oil bath (140 °C) until melting occurred after which the reaction flask was transferred to a microwave reactor (see conditions above). The reaction mixture was allowed to cool to room temperature and 3 M aq. HCl added dropwise [Care! Exothermic reaction]. The crude material was extracted into DCM and washed with brine. The organic phase was dried over $MgSO_4$, concentrated and dried under reduced pressure.

General method for N-alkylsulfonyl protection of lactams:

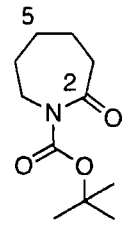
To a cold (0 °C) solution of lactam (0.34 M, 1.0 eq) in dry THF was added a solution of *n*-BuLi (1.6 M, 1.1 eq) *via* a syringe and the reaction mixture was stirred at 0 °C for 1 h (white precipitate (salt) forms). To this was added a cold (0 °C) solution of arylsulfonyl chloride (1.0 M, 1.3 eq) in dry THF *via* cannula. The reaction mixture was stirred at 0 °C until all the starting material was consumed. The reaction was warmed to room temperature and concentrated under reduced pressure, the crude material was taken into DCM, washed with water (x 3), dried over $MgSO_4$ and concentrated under reduced pressure.

General method for cyclisation of N-alkylsulfonyl protected lactams:

To a cold solution (-78 °C) of N-sulfonyl lactam (0.08 M, 1 eq) and TMEDA (1.3 eq) in dry THF was added a cold solution of LDA (1.3 eq) *via* cannula. The resulting reaction mixture was stirred at -78 °C for 2 h after which time a cold (-78 °C) solution of diphenylphosphonic chloride (0.2 M, 1.2 eq) in dry THF was added *via* cannula. The reaction mixture was stirred at -78 °C for 1 h then warmed to room temperature and quenched with aq. NH_4Cl. The mixture was concentrated under reduced pressure and the aqueous layer extracted with EtOAc. The organic phase was washed with aq. $NaHCO_3$ then brine, dried over $MgSO_4$ and concentrated affording crude material.

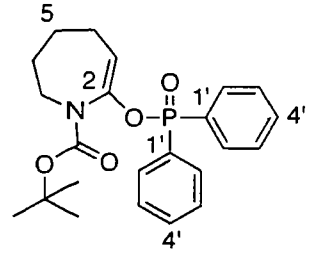
7.2.2 Experimental Methods and Data

N-(*tert*-Butyloxycarbonyl)-2-oxo-azepane **2**



To a solution of caprolactam (11.47 g, 0.10 mol) and DMAP (13.62 g, 0.11 mol) in dry THF (120 ml) was added a solution of di-*tert*-butyldicarbonate (24.33 g, 0.11 mol) in dry THF (60 ml). The reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated and extracted with EtOAc (150 ml). The organic phase was washed with 5% HCl (3 x 25 ml), brine (3 x 25 ml) and $NaHCO_3$ (3 x 25 ml), dried over $MgSO_4$ and concentrated. Kugelrohr distillation (50 °C, 0.4 mbar) afforded the title compound as a yellow oil (19.87 g, 93.17 mmol, 92%). ν_{max} (KBr) 1768 (CH_2C=O), 1716 (O=C-O), 1457, 1367, 1299, 1152 cm^{-1}. δ_H (500 MHz) 1.50 (9H, s, C(CH_3)$_3$), 1.72 (6H, m, 4-H_2, 5-H_2, 6-H_2), 2.62 (2H, m, 7-H_2), 3.75 (2H, m, 3-H_2). δ_C (125 MHz) 23.7 ((*C*H$_3$)$_3$), 28.3 (*C*-5), 28.9 (*C*-6), 29.5 (*C*-4), 39.7 (*C*-3) 46.4 (*C*-7), 83.0 (*C*(CH$_3$)$_3$), 153.1 (*C*-2), 176.0 (O*C*=O). *m/z* (ES^+) 236.1 (MNa^+), 449.1 ($2MNa^+$).

N-(*tert*-Butyloxycarbonyl)-4,5,6,7-tetrahydro-1*H*-azepin-2-yl-diphenylphosphinate **3**



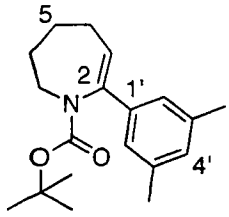
LDA/TMEDA Protocol for phosphinate formation:

The crude material was collected as a yellow/orange oil. Purification by flash chromatography ([4:1] pet. ether/Et_2O) and recrystallisation ([5:1] pet. ether/Et_2O) afforded the title compound as clear crystals (1.12 g, 2.71 mmol, 77%).

NaHMDS Protocol for phosphinate formation:

The crude material was collected as a yellow oil. Purification by flash chromatography ([4:1] DCM/EtOAc) afforded a colourless oil, which solidified on standing (1.80 g, 4.36 mmol, 89%). mp. 81-83 °C. Found; C, 66.70; H, 6.82; N, 3.22%; Calc. for $C_{23}H_{28}NO_4P$; C, 66.82; H, 6.83; N, 3.39%. ν_{max} (KBr) 2932 (C-H), 1703 (C=O), 1681 (enol ether), 1440 (P-Ph), 1356 (P=O), 1226 (P-O-Ar), 1159, 1131, 1059, 541, 524 cm^{-1}. δ_H (400 MHz) 1.44 (13H, m, $(CH_3)_3C$, 5-H_2, 6-H_2), 1.56 (2H, m, 4-H_2), 1.99 (2H, m, 7-H_2), 5.36 (1H, dt, J = 3 Hz, 7 Hz, 3-H), 7.38-7.58 (6H, m, Ar-H), 7.78-7.92 (4H, m, Ar-H). δ_C (100 MHz) 24.3 (C-5), 24.8 (C-6), 28.5 ($(C(CH_3)_3)$), 29.4 (C-4), 46.4 (C-7), 81.0 ($C(CH_3)_3$), 110.1 (C-3), 128.6 (d, J = 13 Hz, C-3'), 130.9 and 132.3 (d, J = 137 Hz, C-1'), 131.9 (d, J = 10 Hz, C-2'), 132.5 (C-4'), 144.9 (C-2), 153.4 (C=O). δ_P (162 MHz) 29.7. *m/z* (ES^+) 436.2 (MNa^+), 849.0 ($2MNa^+$).

N-(*tert*-Butyloxycarbonyl-2-(3',5'-Dimethylphenyl)-4,5,6,7-tetrahydroazepane **4a**

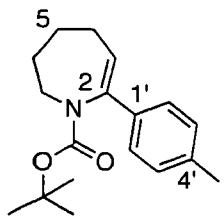


Suzuki protocol A:

Flash chromatography ([19:1] pet. ether/EtOAc) afforded the title compound as a white solid (83%). mp. 113-115 °C. G.C. analysis: 1 peak, R_t 22.35 min. ν_{max} (KBr) 2933, 1687 (C=O), 1391, 1357, 1161 cm^{-1}. δ_H (500 MHz) 1.10 (9H, s, $C(CH_3)_3$), 1.47 (2H, m, 7-H_2), 1.79-1.89 (2H, m, 6-H_2), 2.21-2.33 (10H, m, 3'-CH_3, 5'-CH_3, 4-H_2, 5-H_2), 5.85

(1H, t, J = 7 Hz, 3-*H*), 6.88 (1H, s, Ar-*H*), 6.92 (2H, s, Ar-*H*). δ_C (125 MHz) 21.5 (*C*-5), 24.4 (*C*-3', *C*-5'), 27.7 (*C*-4), 28.2 ((C(CH_3)$_3$), 28.7 (*C*-6), 48.2 (*C*-7), 79.9 (*C*(CH_3)$_3$), 122.8 (*C*-3), 123.1 (*C*-2'), 129.0 (*C*-4'), 137.7 (*C*-3'), 139.8 (*C*-2), 144.8 (*C*-1'), 153.9 (*C*=O). *m/z* (ES^+) 365 ($MNaMeCN^+$), 302 (MH^+), 246 (MH - $^tBu^+$). HRMS (ES^+) found MNa^+ 324.1934, $C_{19}H_{27}NO_2$ requires M^+ 324.1932.

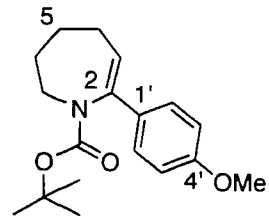
N-*tert*-Butyloxycarbonyl-2-(4'-methylphenyl)-4,5,6,7-tetrahydroazepane **4b**



Suzuki protocol A:

Purification by flash chromatography ([19:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.07 g, 0.24 mmol, 81%). mp. 95-97 °C. Found; C, 75.15; H, 8.88; N, 4.87%; Calc. for $C_{18}H_{25}NO_2$; C, 75.22; H, 8.77; N, 4.87%. ν_{max} (KBr) 2979, 2933, 2856 (C-H), 1687 (C=O), 1392, 1357, 1160, 813 cm^{-1}. δ_H (400 MHz) 1.10 (9H, s, C(CH_3)$_3$), 1.46 (4H, s, 5-H_2, 7-H_2), 1.83 (2H, m, 6-H_2), 2.27 (2H, m, 4-H_2), 2.33 (3H, s, 4'-CH_3), 5.83 (1H, t, J = 7 Hz, 3-*H*), 7.09 (2H, d, J = 9 Hz, 3'-*H*), 7.19 (2H, d, J = 9 Hz, 2'-*H*). δ_C (100 MHz) 21.4 (4'-CH_3), 24.5 (*C*-5), 27.7 (*C*-4), 28.2 ((C(CH_3)$_3$), 30.0 (*C*-6), 48.1 (*C*-7), 79.9 (*C*(CH_3)$_3$), 121.9 (*C*-3), 125.0 (*C*-2'), 128.9 (*C*-3'), 137.0 (*C*-1'), 137.2 (*C*-4'), 144.6 (*C*-2), 154.6 (*C*=O). *m/z* (ES^+) 311 (MH^+), 351 ($MNaMeCN^+$), 597 ($2MNa^+$). HRMS (ES^+) found MNa^+ 310.1776, $C_{18}H_{25}NO_2Na$ requires M^+ 310.1777.

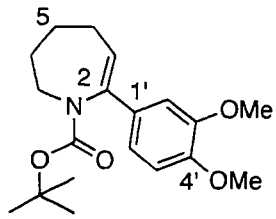
N-*tert*-Butyloxycarbonyl-2-(4'-Methoxyphenyl)-4,5,6,7-tetrahydroazepane **4c**



Suzuki protocol A:

Purification on a Horizon® column chromatography system ([9:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.06 g, 0.19 mmol, 99%). mp. 72-74 °C. Found; C, 71.22; H, 8.35; N, 4.64%; Calc. for $C_{18}H_{23}NO_3$; C, 71.26; H, 8.31; N, 4.62%. ν_{max} (KBr) 2935 (C-H), 1687 (C=O), 1509, 1392, 1357, 1248, 1160 cm^{-1}. δ_H (500 MHz) 1.11 (9H, s, C(C*H*$_3$)$_3$), 1.46 (4H, m, 5-*H*$_2$, 7-*H*$_2$), 1.81 (2H, m, 6-*H*$_2$), 2.28 (2H, m, 4-*H*$_2$), 3.80 (3H, s, O-C*H*$_3$), 5.76 (1H, t, J = 6 Hz, 3-*H*), 6.82 (2H, d, J = 9 Hz, 2'-*H*, 6'-*H*), 7.25 (2H, d, J = 9 Hz, 3'-*H*, 5'-*H*). δ_C (125 MHz) 24.5 (*C*-5), 27.6 (*C*-4), 28.2 ((C(*C*H$_3$)$_3$), 30.0 (*C*-6), 48.1 (*C*-7), 55.6 (O-*C*H$_3$), 79.8 (*C*(CH$_3$)$_3$), 113.6 (*C*-2'), 121.1 (*C*-3), 126.3 (*C*-3'), 132.6 (*C*-2), 144.3 (*C*-1'), 154.4 (*C*=O), 159.2 (*C*-4'). *m/z* (ES^+) 629 ($2MNa^+$).

N-*tert*-Butyloxycarbonyl-2-(3',4'-dimethoxyphenyl)-4,5,6,7-tetrahydroazepane **4d**

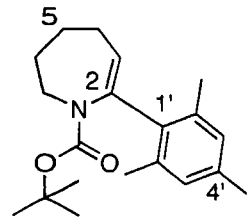


Suzuki protocol A:

Flash chromatography ([4:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.08 g, 0.24 mmol, 81%). mp. 95-97 °C. Found; C, 68.42; H, 8.26; N, 3.95%; Calc. for $C_{19}H_{27}NO_4$; C, 68.44; H, 8.16; N, 4.20%. ν_{max} (KBr) 2936, 1688 (C=O), 1515,

1266, 1249, 1160 (C-O-C), 1140, 1027 cm^{-1}. δ_H (400 MHz) 1.12 (9H, s, C(CH_3)$_3$), 1.46 (4H, s, 5-H_2, 7-H_2), 1.83 (2H, m, 6-H_2), 2.27 (2H, m, 4-H_2), 3.87 (6H, m, 3'-OCH_3, 4'-OCH_3), 5.78 (1H, t, J = 7 Hz, 3-H), 6.78-6.95 (3H, m, 3 x Ar-H). δ_C (100 MHz) 24.4 (CH_2), 27.5 (C-4), 28.2 (C(CH_3)$_3$), 29.9 (CH_2), 48.2 (C-7), 56.1 and 56.2 (3'-OCH_3, 4'-OCH_3), 79.9 (C(CH_3)$_3$), 108.5, 110.9 and 117.6 (3 x ArC-H), 121.3 (C-3), 133.1 (C-2), 144.4 (C-1'), 148.8 and 148.9 (C-OMe), 154.4 (C=O). *m/z* (ES^+) 688 ($2MNa^+$), 397 ($MNaMeCN^+$), 334 (MH^+), 278 (MH – $^tBu^+$).

N-*tert*-Butyloxycarbonyl-2-(2',4',6'-trimethylphenyl)-4,5,6,7-tetrahydroazepane **4e**

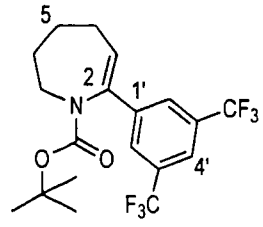


Suzuki protocol A:

Purification on a Horizon® column chromatography system ([19:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.12 mmol, 36%). mp. 56-58 °C. Found; C, 76.07; H, 9.39; N, 4.53%; Calc. for $C_{20}H_{29}NO_2$; C, 76.15; H, 9.27; N, 4.44%. ν_{max} (KBr) 2933 (C-H), 1681 (C=O), 1392, 1367, 1161, 853 cm^{-1}. δ_H (400 MHz) 1.07 (9H, s, C(CH_3)$_3$), 1.72-1.80 (2H, m, 5-H_2), 1.81-1.90 (2H, m, 6-H_2), 2.22 (6H, s, 2'-CH_3, 5'-CH_3), 2.25 (3H, s, 4'-CH_3), 2.29-2.39 (2H, m, 4-H_2), 3.81 (2H, t, J = 6 Hz, 7-H_2), 5.04 (1H, t, J = 5 Hz, 3-H), 6.79 (2H, s, 3'-H, 5'-H). δ_C (100 MHz) 21.1 (4'-CH_3), 21.5 (2'-CH_3), 24.1 (C-5), 27.8 (C-4), 27.9 (C-6), 28.1 (C(CH_3)$_3$), 49.8 (C-7), 80.2 (C(CH_3)$_3$), 122.7 (C-3), 128.7 (C-3'), 136.2 (C-4'), 136.7 (C-2'), 137.5 (C-1'), 140.9 (C-2), 154.4 (C=O). *m/z* (ES^+) 260 (MH - $^tBu^+$), 338 (MNa^+). Starting material was also recovered (0.02 g, isolated yield = 63%).

N-*tert*-Butyloxycarbonyl-2-(3',5'-bis[trifluoromethyl]phenyl)-4,5,6,7-tetrahydroazepane

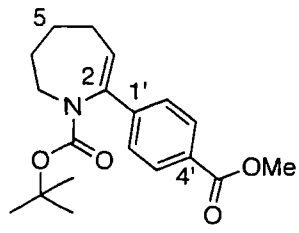
4f



Suzuki protocol A:

Purification on a Horizon® column chromatography system ([9:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.09 g, 0.21 mmol, 87%). mp. 52-54 °C. Found; C, 55.79; H, 5.30; N, 3.29%: Calc. for $C_{19}H_{21}NO_2F_6$; C, 55.75; H, 5.17; N, 3.42%. ν_{max} (KBr) 3019, 2936 (C-H), 1697 (C=O), 1357, 1222, 1209, 1182, 1170, 1020, 986, 901, 846, 794, 669 cm^{-1}. δ_H (500 MHz) 1.07 (9H, s, C(C*H*$_3$)$_3$), 1.46 (2H, m, 7-*H*$_2$), 1.60 (2H, broad, 5-*H*$_2$), 1.88 (2H, m, 6-*H*$_2$), 2.35 (2H, m, 4-*H*$_2$), 5.98 (0.79H, t, J = 7 Hz, 3-*H*), 6.17 (0.21H, t, J = 7 Hz, 3-*H*) 7,72 (2H, s, 2'-*H*), 7.75 (1H, s, 4'-*H*). δ_C (125 MHz) 23.9 (*C*-5), 27.95 (*C*-4), 27.99 (C(*C*H$_3$)$_3$), 29.4 (*C*-6), 48.5 (*C*-7), 80.7 (*C*(CH$_3$)$_3$), 120.8 (*C*-4'), 122.5 (*C*-3'), 125.4 (*C*-2'), 125.9 (*C*-3), 131.4-132.2 (2 x *C*F$_3$, q, J = 33 Hz), 142.3 (*C*-2), 142.7 (*C*-1'), 153.58 (*C*=O). HRMS (ES$^+$) found MNa$^+$ 432.1369, $C_{19}H_{21}NO_2F_6Na$ requires 432.1368.

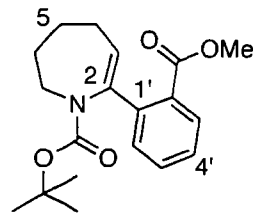
N-*tert*-Butyloxycarbonyl-2-(4'-Methoxycarbonylphenyl)-4,5,6,7-tetrahydroazepane **4g**



Suzuki protocol A:

Purification on a Horizon® column chromatography system ([85:15] DCM/EtOAc) afforded the title compound as a white solid (0.06 g, 0.17 mmol, 72%). mp. 102-104 °C. ν_{max} (KBr) 3019, 2936, 1715 (C=O), 1694 (C=O), 1608, 1437, 1280, 1223, 1209, 795, 669 cm^{-1}. δ_H (500 MHz) 1.06 (9H, s, C(CH_3)$_3$), 1.44 (2H, s, 7-H_2), 1.59 (2H, broad, 5-H_2), 1.84 (2H, m, 6-H_2), 2.30 (2H, m, 4-H_2), 3.89 (3H, s, O-CH_3), 5.96 (1H, t, J = 7 Hz, 3-*H*), 7.35 (2H, d, J = 9 Hz, 2'-*H*), 7.95 (2H, d, J = 9 Hz, 3'-*H*). δ_C (125 MHz) 24.2 (*C*-5), 27.9 (*C*-4), 28.2 (C(CH_3)$_3$), 29.8 (*C*-6), 48.1 (*C*-7), 52.3 (O-CH_3), 80.3 (C(CH$_3$)$_3$), 125.0 (*C*-3), 125.1 (*C*-2'), 129.0 (*C*-1'), 129.8 (*C*-3'), 143.9 (*C*-2), 144.6 (*C*-4'), 154.0 (N*C*=O), 167.2 (Ar*C*=O). HRMS (ES$^+$) found MNa$^+$ 354.1677, $C_{19}H_{25}NNaO_4$ requires M$^+$ 354.1676.

N-*tert*-Butyloxycarbonyl-2-(2'-Methoxycarbonylphenyl)-4,5,6,7-tetrahydroazepane **4h**

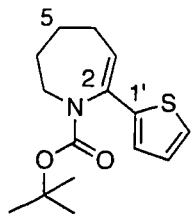


Suzuki protocol A:

The reaction was stirred for 18 h at 85 °C rather than 1 h. Purification by flash chromatography ([95:5], [6:4], [100:0] pet.ether/EtOAc) afforded the title compound as a white solid (0.60 mmol, 32%) and recovered starting material (0.19 mmol, 10%). δ_H (700 MHz) 1.02 (9H, s, C(CH_3)$_3$), 1.66 (2H, m, 5-H_2), 1.83 (2H, quint, J = 8 Hz, 6-H_2), 2.33 (2H, q, J = 8 Hz, 4-H_2), 3.64 (2H, broad, 7-H_2), 3.85 (3H, s, O-CH_3), 5.57 (1H, t, J = 8 Hz, 3-*H*), 7.27 (1H, m, 4'-*H*), 7.32-7.40 (2H, m, 5'-*H*, 6'-*H*), 7.42 (1H, m, 3'-*H*). δ_C (176 MHz) 23.9 (*C*-5), 27.9 (*C*-6), 28.0 (C(CH_3)$_3$), 28.3 (*C*-4), 49.8 (*C*-7), 52.4 (O-CH_3), 80.2 ((C(CH$_3$)$_3$), 123.0 (*C*-3), 127.1 (*C*-4'), 128.1 (*C*-3'), 129.8 (Ar*C*-H), 130.5 (Ar*C*-H), 130.7 (*C*-2'), 140.7 (*C*-1'), 143.5 (*C*-2), 153.8 (N*C*=O), 170.1 (Ar*C*=O). *m/z* (ES$^+$) 232.1

(M – Boc$^+$), 332.1 (MH$^+$), 354.1 (MNa$^+$), 685.3 (2MNa$^+$). HRMS (ES$^+$) found MH$^+$ 332.1859, $C_{19}H_{26}NO_4$ requires M$^+$ 322.1856, found MNa$^+$ 354.1674, $C_{19}H_{25}NO_4Na$ requires M$^+$ 354.1676. The desired product contained a small amount of impurity due to homocoupled boronic acid that could not be removed, approx 8% by ^{1}H NMR analysis.

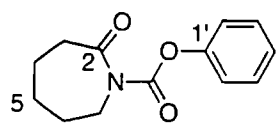
N-*tert*-Butyloxycarbonyl-2-Thiophen-2-yl-4,5,6,7-tetrahydroazepane **4i**



Suzuki protocol A:

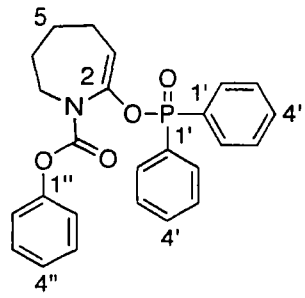
Purification by flash chromatography ([19:1] pet.ether/EtOAc, [4:1] DCM/EtOAc) afforded the title compound as a white solid (0.19 mmol, 38%). mp. 88-90 °C. ν_{max} (KBr) 2979, 2936, 1691 (C=O), 1388, 1367, 1255, 1163 cm^{-1}. δ_H (500 MHz) 1.40 (13H, m, 2 x C*H*$_2$, (C*H*$_3$)$_3$), 1.54 (2H, m, C*H*$_2$), 2.08 (2H, m, 4-*H*$_2$), 5.87 (1H, t, J = 7 Hz, 3-*H*), 6.81 (1H, m, 4'-*H*), 6.87 (1H, m, Ar-*H*), 6.97 (1H, m, Ar-*H*). δ_C (125 MHz) 24.3 (*C*-5), 27.4 (*C*-4), 28.0 (C(*C*H$_3$)$_3$), 29.8 (*C*-6), 47.5 (*C*-7), 79.4 (*C*(CH$_3$)$_3$), 122.0 (*C*-3), 122.7, 123.6 (*C*-2', *C*-3'), 127.1 (*C*-4'), 139.6 (*C*-2), 144.7 (*C*-1'), 153.6 (*C*=O). *m/z* (ES$^+$) 279.8 (MH$^+$), 302.2 (MNa$^+$), 580.9 (2MNa$^+$). HRMS (ES$^+$) found MNa$^+$ 302.1185, $C_{15}H_{21}NNaO_2S$ requires M$^+$ 302.1185. Starting material was also recovered (0.22 mmol, 44%).

N-(Phenyloxycarbonyl)-2-oxo-azepane **8**



To a cold (-78 °C) solution of caprolactam (1.06 g, 9.37 mmol) in dry THF (50 ml) was added *n*-BuLi (1.0 M, 11.24 ml, 11.24 mmol) dropwise *via* a syringe and the reaction mixture allowed to stir at -78 °C. After 2 h a cold (-78 °C) solution of phenyl chloroformate (2.93 g, 18.73 mmol) in dry THF (30 ml) was added *via* cannula and the resulting reaction mixture allowed to stir for an additional 3 h before warming to room temperature. The reaction was quenched with $NH_4Cl_{(aq)}$, concentrated and extracted with EtOAc (150 ml). The organic phase was washed with brine (3 x 50 ml), $NaHCO_3$ $_{(aq)}$ (3 x 50 ml), dried over $MgSO_4$ and concentrated affording the crude material as a yellow oil. Flash chromatography ([50:1], [19:1] DCM/EtOAc) followed by recrystallisation (pet. ether) afforded the title compound as clear crystals (1.17 g, 4.99 mmol, 53%). mp. 70-71 °C. Found; C, 66.90; H, 6.45; N, 5.90%; Calc. for $C_{13}H_{15}NO_3$; C, 66.94; H, 6.48; N, 6.00%. ν_{max}(KBr) 2938, 2861, 1778 (CH_2C=O), 1731 and 1715 (O=C-O), 1265, 1182 cm^{-1}. δ_H (500 MHz) 1.85 (6H, m, 4-*H*$_2$, 5-*H*$_2$, 6-*H*$_2$), 2.78 (2H, m, 3-*H*$_2$), 3.98 (2H, m, 7-*H*$_2$), 7.18-7.22 (2H, m, 3'-*H*, 5'-*H*), 7.23-7.29 (1H, m, 4'-*H*), 7.37-7.42 (2H, m, 2'-*H*, 6'-*H*). δ_C (125MHz) 23.8 (*C*-4), 28.9 (*C*-6), 29.4 (*C*-5), 39.7 (*C*-3), 46.9 (*C*-7), 121.8 (*C*-3'), 126.4 (*C*-4'), 129.6 (*C*-2'), 151.1 (*C*-1'), 153.4 (O*C*=O), 157.9 (*C*-2). *m/z* (ES^+) 234.1 (MH^+).

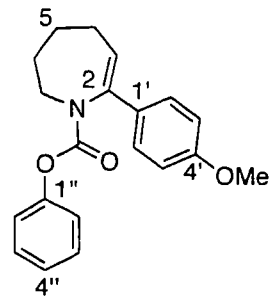
N-(Phenyloxycarbonyl)-4,5,6,7-tetrahydro-1*H*-azepin-2-yl diphenylphosphinate **9**



NaHMDS Protocol:

Purification by flash chromatography afforded the title compound as a white crystalline solid (1.74 g, 4.02 mmol, 79%). mp. 84-85 °C. Found; C, 69.29; H, 5.57; N, 3.12%; Calc. for $C_{25}H_{24}NO_4P$; C, 69.28; H, 5.58; N, 3.23%. ν_{max} (KBr) 3071, 2925, 1724 (C=O), 1685 (enol ether), 1441, 1375, 1351, 1322, 1197, 1126, 1093, 1057, 993, 871 cm^{-1}. δ_H (700 MHz) 1.35-1.6 (2H, broad, 5-*H*$_2$), 1.63-1.80 (2H, broad, 6-*H*$_2$), 2.08 (2H, m, 4-*H*$_2$), 3.10-3.60 (2H, broad, 7-*H*), 5.39-5.59 (1H, m, 3-*H*), 7.05 (2H, d, J = 8 Hz, 2''-*H*), 7.19 (1H, t, J = 8 Hz, 4''-*H*), 7.33 (2H, m, 3''-*H*), 7.42 (4H, m, 3'-*H*), 7.51 (2H, t, J = 7 Hz, 4'-*H*), 7.79-7.99 (4H, m, 2'-*H*). δ_C (175 MHz) 24.2 (*C*-5), 24.8 (*C*-4), 29.3 (*C*-6), 47.3 (*C*-7), 110.8 (*C*-3), 121.7 (*C*-2''), 125.7 (*C*-4''), 128.7, 128.8 (*C*-3'), 129.5 (*C*-3''), 131.0 (*C*-1'), and 131.9, 132.0 (*C*-2'), 132.7 (*C*-4'), 144.5 (*C*-2), 151.4 (*C*-1''), 152.6 (*C*=O). δ_P (283 MHz) 29.4. *m/z* (ES^+) 433.5 (MH^+). HRMS (ES^+) found MH^+ 434.1515, $C_{25}H_{25}NO_4P$ requires M^+ 434.1515, found MNa^+ 456.1332, $C_{25}H_{24}NNaO_4P$ requires M^+ 456.1335.

N-Phenyloxycarbonyl-2-(4'-methoxyphenyl)-4,5,6,7-tetrahydroazepane **10a**

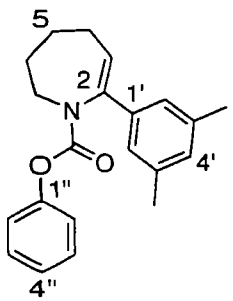


Suzuki protocol A:

Purification by flash chromatography ([9:1] pet. ether/EtOAc) afforded the title compound as a crystalline solid (0.06 g, 0.19 mmol, 81%). mp. 92-94 °C. Found; C, 73.78; H, 6.50; N, 4.13%: Calc. for $C_{20}H_{21}NO_3$; C, 74.28; H, 6.55; N, 4.33%. ν_{max} (ATR) 2931, 1710 (C=O), 1641, 1608, 1512, 1384, 1353, 1252, 1197, 1175, 1034, 812, 731 cm^{-1}. δ_H (500 MHz) 1.69 (2H, m, 7-*H*$_2$), 1.91-2.07 (4H, m, 5-*H*$_2$, 6-*H*$_2$), 2.40 (2H, m, 4-

H$_2$), 3.85 (3H, s, O-C*H*$_3$), 6.08 (1H, t, J = 6 Hz, 3-*H*), 6.78 (2H, m, 2 x Ar-*H*), 6.91 (2H, d, J = 9 Hz, 3'-*H*, 5'-*H*), 7.10 (1H, m, 4''-*H*), 7.22 (2H, m, 2 x Ar-*H*), 7.38 (2H, d, J = 9 Hz, 2'-*H*, 6'-*H*). δ_C (125MHz) 24.8 (*C*-5), 27.9 (*C*-4), 30.1 (*C*-6), 49.0 (*C*-7), 55.9 (O-*C*H$_3$), 114.1 (*C*-3'), 122.0 (Ar*C*), 123.0 (*C*-3), 125.2 (*C*-4''), 126.1 (*C*-2'), 129.7 (Ar*C*), 131.2 (*C*-1'), 143.7 (*C*-2), 151.8 (*C*-1''), 153.9 (*C*=O), 159.5 (*C*-4'). *m/z* (ES$^+$) 323.5 (MH$^+$). HRMS (ES$^+$) found MH$^+$ 324.1592, $C_{20}H_{22}NO_3$ requires M$^+$ 324.1594.

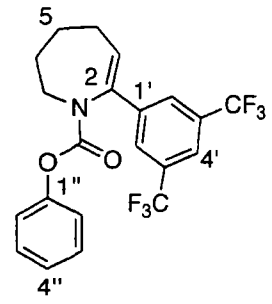
N-Phenyloxycarbonyl-2-(3',5'-dimethylphenyl)-4,5,6,7-tetrahydroazepane **10b**



Suzuki protocol A:

Purification by flash chromatography ([9:1], [1:1] pet.ether/EtOAc) afforded the title compound as a clear oil (69 mg, 0.21 mmol, 82%). ν_{max} (ATR) 2932, 1717 (C=O), 1382, 1352, 1196, 1170, 748, 688 cm^{-1}. δ_H (500 MHz) 1.97 (2H, m, C*H*$_2$), 2.34 (6H, m, Ar-C*H*$_3$), 2.42 (2H, q, J = 7 Hz, 4-*H*$_2$), 2.69 (1H, broad, 7-H*H*), 4.32-4.74 (1H, broad, 7-*H*H), 6.16 (1H, t, J = 7 Hz, 3-*H*), 6.75 (2H, d, J = 8 Hz, 2''-*H*$_2$), 6.96 (1H, s, 4'-*H*), 7.08 (2H, s, 2'-*H*$_2$), 7.11 (1H, t, J = 8 Hz, 4''-*H*), 7.24 (2H, t, J = 8 Hz, 3''-*H*$_2$). δ_C (125 MHz) 21.6 (Ar-*C*H$_3$), 24.4 (*C*-5 or 6), 27.6 (*C*-4), 30.0 (*C*-5 or 6), 48.9 (*C*-7), 121.9 (*C*-2''), 122.7 (*C*-2'), 124.1 (*C*-3), 125.4 (*C*-4''), 129.2 (*C*-3''), 129.7 (*C*-4'), 138.2 (*C*-3'), 138.3 (*C*-1'), 144.0 (*C*-2), 151.5 (*C*-1''), 153.7 (*C*=O). *m/z* (ES$^+$) 322.3 (MH$^+$), 339.3 (MH$_2$O$^+$) 665.6 (2MNa$^+$). HRMS (ES$^+$) found MNa$^+$ 344.1621, $C_{21}H_{23}NO_2Na$ requires M$^+$ 344.1621.

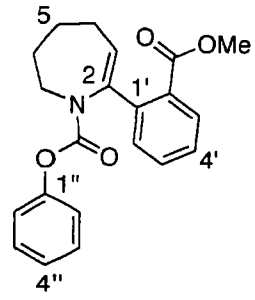
N-Phenyloxycarbonyl-2-(3',5'-bis[trifluoromethyl]phenyl)-4,5,6,7-tetrahydroazepane **10c**



Suzuki protocol A:

Purification by flash chromatography ([1:1] $CHCl_3$/pet. ether) afforded the title compound as a white solid (83 mg, 0.19 mmol, 69%). mp 111-113 °C. Found; C, 58.18; H, 3.99; N, 3.08%: Calc. for $C_{21}H_{17}NO_2F_6$; C, 58.74; H, 3.99; N, 3.26%. ν_{max} (ATR) 2948, 1712 (C=O), 1354, 1279, 1203, 1179, 1165, 1121, 1110, 978, 898, 754, 731, 683 cm^{-1}. δ_H (500 MHz) 1.59-1.90 (3H, broad, 5-H_2, 7-H*H*), 2.01 (2H, m, 6-H_2), 2.48 (2H, m, 4-H_2), 3.91 (1H, broad, 7-*H*H), 6.35 (1H, t, J = 7 Hz, 3-*H*), 6.74 (2H, d, J = 8 Hz, 2"-*H*, 6"-*H*), 7.13 (1H, t, J = 8 Hz, 4"-*H*), 7.25 (2H, t, J = 8 Hz, 3"-*H*, 5"-*H*), 7.08 (1H, s, 4'-*H*), 7.88 (2H, s, 2'-*H*, 6'-*H*). δ_C (125 MHz) 23.9 (*C*-5), 27.9 (*C*-4), 29.4 (*C*-6), 49.2 (*C*-7), 121.4 (*C*-2"), 121.7 (*C*-4'), 124.8 (*C*-2'), 125.8 (*C*-4"), 128.2 (*C*-3), 129.5 (*C*-3"), 129.6 (*C*-3'), 131.8-132.6 (2 x CF_3, q, J = 33 Hz), 140.8 (*C*-1'), 141.5 (*C*-2), 151.0 (*C*-1"), 153.1 (*C*=O). *m/z* (ES^+) 430.3 (MH^+) 447.3 (MH_2O^+) 493.3 ($MNaMeCN^+$), 881.5 ($2MNa^+$). HRMS (ES^+) found MH^+ 430.1237, $C_{21}H_{18}NO_2F_6$ requires 430.1236.

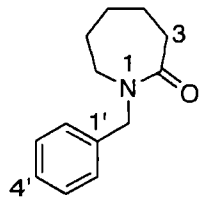
N-Phenyloxycarbonyl-2-(4'-methoxyphenyl)-4,5,6,7-tetrahydroazepane **10d**



Suzuki protocol A:

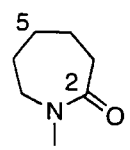
Purification by flash chromatography ([9:1] pet. ether/EtOAc) afforded the title compound as a clear oil (35 mg, 0.01 mmol, 37%). ν_{max} (ATR) 2954, 1725 (C=O), 1710 (C=O), 1381, 1263, 1200, 1086, 767, 732, 688 cm^{-1}. δ_H (500 MHz) 1.75 (2H, quint, J = 6 Hz, 5-H_2), 1.92 (2H, quint, J = 6 Hz, 6-H_2), 2.42 (2H, q, J = 6 Hz, 4-H_2), 3.76-3.94 (5H, m, 7-H_2, CH_3), 5.79 (1H, t, J = 6 Hz, 3-H_2), 6.64 (2H, d, J = 8 Hz, 2"-H 6"H), 7.07 (1H, m, 4"-H), 7.19 (2H, t, J = 8 Hz, 3"-H, 5"-H), 7.30 (1H, t, J = 8 Hz, 4'-H), 7.39 (1H, t, J = 8Hz, 5'-H), 7.45 (1H, d, J = 8 Hz, 6'-H), 7.52 (1H, d, J = 8 Hz, 3'-H). δ_C (125 MHz) 23.9 (*C*-5), 28.2 (*C*-4), 28.3 (*C*-6), 50.7 (*C*-7), 52.6 (*C*H_3), 121.5 (*C*-2"), 125.0 (*C*-3), 125.4 (*C*-4"), 127.6 (*C*-4'), 128.4 (*C*-3'), 129.2 (*C*-3"), 129.8 (*C*-6'), 130.6 (*C*-2') 130.9 (*C*-5'), 139.6 (*C*-1'), 142.5 (*C*-2), 151.2 (*C*-1"), 153.2 (N*C*=O), 170.0 (*C*O_2Me). *m/z* (ES^+) 352.3 (MH^+), 374.3 (MNa^+), 415.3 ($MNaMeCN^+$), 725.5 ($2MNa^+$). HRMS (ES^+) found MNa^+ 374.1362, $C_{21}H_{21}NO_4Na$ requires 374.1363.

N-Benzyl-2-oxo-azepane **11**



To a cold (0 °C) solution of caprolactam (1.02 g, 9.01 mmol, 1 eq) in dry THF (50 ml) was added *n*-BuLi (1.2 M, 10.85 ml, 13.02 mmol, 1.4 eq) dropwise and the mixture stirred at 0 °C for 1 h. To this was added a cold (0 °C) solution of benzyl bromide (1.86 g, 1.29 ml, 10.88 mmol, 1.2 eq) in dry THF (10 ml) *via* cannula and the reaction mixture stirred at 0 °C for 2 h before being warmed to room temperature and stirred for an additional 48 h. The reaction mixture was quenched with aq. NH_4Cl (30 ml) and extracted into EtOAc (3 x 25 ml). The combined organics were washed with brine (3 x 20 ml), dried over $MgSO_4$ and concentrated. Flash chromatography ([6:4], [100:0] pet. ether/Et_2O) afforded recovered starting material (0.11 g, 0.97 mmol, 11%) and the title compound as a yellow solid (1.24 g, 6.10 mmol, 68%). mp. 52-54 °C. Found; C, 76.79; H, 8.52; N, 6.80%: Calc. for $C_{13}H_{17}NO$; C, 76.81; H, 8.43; N, 6.89%. ν_{max} (KBr) 3031, 2936, 2858, 1626 (C=O), 1495, 1486, 1445, 1425, 1356, 1193 cm^{-1}. δ_H (500 MHz) 1.48 (2H, m, 6-*H*$_2$), 1.70 (4H, m, 4-*H*$_2$, 5-*H*$_2$), 2.61 (2H, m, 3-*H*$_2$), 3.29 (2H, m, 7-*H*$_2$), 4.59 (2H, s, PhC*H*$_2$), 7.22-7.36 (5H, m, Ar-*H*). δ_C (125 MHz) 23.7 (*C*-4), 28.4 (*C*-6), 30.2 (*C*-5), 37.4 (*C*-3), 49.1 (*C*-7), 51.3 (Ph*C*H$_2$), 127.5, 128.4, 128.8 (*C*-2', *C*-3', *C*-4'), 138.2 (*C*-1'), 176.2 (*C*-2). *m/z* (ES^+) 204.2 (MH^+).

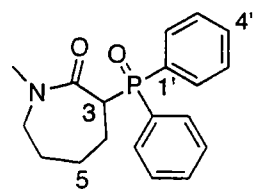
N-Methyl-2-oxo-azepane **12**



To a cold (0 °C) suspension of 95% NaH (0.51 g, 21.25 mmol, 1.2 eq) in dry THF (80 ml, 0.27 M) was added a cold (0 °C) solution of caprolactam (2.00 g, 17.67 mmol, 1 eq) in dry THF (60 ml) *via* cannula and the reaction mixture stirred at 0 °C for 1 h. Methyl iodide (1.1 ml, 17.67 mmol, 1 eq) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C for 1 h before warming to room temperature and stirring

for a further 24 h. The reaction was quenched with MeOH (20 ml), filtered through a plug of silica and washed through with diethyl ether (60 ml). The organics were concentrated to a yellow oil/solid. Purification by flash chromatography ([8:2] Et_2O/acetone) afforded recovered starting material (825 mg, 7.29 mmol, 41%) and the title compound as a pale yellow oil (1.14 g, 8.96 mmol, 51%). GC analysis, 1 peak R_t = 11.4 min. ν_{max} (KBr) 2935, 2859, 1621 (C=O), 1495, 1445, 1401, 1354, 1202, 1079, 841 cm^{-1}. δ_H (500 MHz) 1.55-1.62 (4H, m, 6-*H*$_2$, 4-*H*$_2$), 1.66 (2H, m, 5-*H*$_2$), 2.45 (2H, m, 3-*H*$_2$), 2.91 (3H, s, C*H*$_3$), 3.29 (2H, m, 7-*H*$_2$). δ_C (125 MHz) 23.5 (*C*-4), 27.8 (*C*-6), 30.1 (*C*-5), 36.0 (N*C*H$_3$), 37.1 (*C*-3), 51.6 (*C*-7), 176.2 (*C*-2). *m/z* (ES^+) 128.2 (MH^+). HRMS (ES^+) found MNa^+ 150.0889, $C_7H_{13}NNaO$ requires M^+ 150.0889.

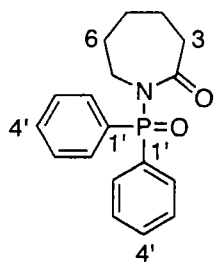
N-Methyl-2-oxo-3-(diphenylphosphoryl)-4,5,6,7-tetrahydroazepane **15**



To a cold solution (-78 °C) of N-methyl caprolactam **12** (314 mg, 2.47 mmol, 1 eq) in dry THF (15 ml, 0.16 M) was added a cold solution of LDA (1.0 eq). The resulting reaction mixture was stirred at -78 °C for 2 h after which time a cold (-78 °C) solution of diphenylphosphonic chloride (0.64 g, 0.52 ml, 2.72 mmol, 1.1 eq) in dry THF (5 ml) was added *via* cannula. The reaction mixture was stirred at -78 °C for 3 h before warming to room temperature and quenching with aq. NH_4Cl. The mixture was concentrated under reduced pressure and the aqueous layer extracted with EtOAc (x 3). The combined organics were washed with aq. $NaHCO_3$ then brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography ([7:3] Et_2O/acetone) afforded the title compound as a white solid (390 mg, 1.19 mmol, 48%).

ν_{max} (KBr) 2937, 1639 (C=O), 1438, 1401, 1193, 1146, 1118, 548, 521 cm^{-1}. δ_H (400 MHz) 1.46 (1H, m, 6-H*H*), 1.59 (2H, m, 4-H*H*, 5-H*H*), 1.75 (1H, m, 6-*H*H), 1.98 (1H, m, 5-*H*H), 2.18 (1H, m, 4-*H*H), 2.86 (3H, s, N-C*H*$_3$), 3.44 (1H, m, 7-H*H*), 3.60 (1H, m, 7-*H*H), 3.74 (1H, m, 3-*H*), 7.41 (6H, m, 2'-H, 4'-*H*, 6'-*H*), 7.77 (2H, m, 3'-*H*, 5'-*H*), 8.03 (2H, m, 3'-*H*, 5'-*H*). δ_C (100 MHz) 24.1 (d, J = 3 Hz, *C*-4), 26.7 (*C*-6), 28.2 (d, J = 10 Hz, *C*-5), 36.2 (*C*H$_3$), 49.42-48.70 (d, J = 73 Hz, *C*-3), 50.4 (*C*-7), 128.44-128.32 (d, J = 12 Hz, 1 x *C*-2', *C*-6'), 128.70-128.58 (d, J = 12 Hz, 1 x *C*-2', *C*-6'), 131.59-130.58 (d, J = 101 Hz, 1 x *C*-1'), 131.53-131.43 (d, J = 10 Hz, 1 x *C*-3', *C*-5'), 131.75 (d, J = 3 Hz, 1 x *C*-4'), 131.98 (d, J = 3 Hz, 1 x *C*-4'), 133.58-132.58 (d, J = 100 Hz, 1 x *C*-1'), 132.74-132.65 (d, J = 10 Hz, 1 x *C*-3', *C*-5'), 171.0 (*C*=O). δ_P (162 MHz) 35.0. *m/z* (ES^+) 327.6 (MH^+). HRMS (ES^+) found MH^+ 328.1462, $C_{19}H_{23}NO_2P$ requires M^+ 328.1461.

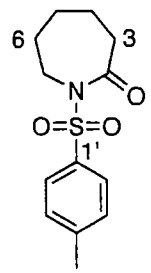
N-Diphenylphosphoryl-2-oxo-azepane **17**



To a cold solution (-78 °C) of N-benzyl caprolactam **11** (400 mg, 1.97 mmol, 1 eq) in dry THF (20 ml, 0.1 M) was added a cold solution of LDA (1.0 eq). The resulting reaction mixture was stirred at -78 °C for 2 h after which time a cold (-78 °C) solution of diphenylphosphonic chloride (559 mg, 0.45 ml, 2.36 mmol, 1.2 eq) in dry THF (5 ml) was added *via* cannula. The reaction mixture was stirred at -78 °C for 7 h before warming to room temperature and quenching with aq. NH_4Cl. The mixture was concentrated under reduced pressure and the aqueous layer extracted with EtOAc

(x 3). The combined organics were washed with aq. $NaHCO_3$ then brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography ([6:4] DCM/EtOAc) afforded the title compound as a yellow solid (232 mg, 0.74 mmol, 38%). ν_{max} (KBr) 2937, 1664 (C=O), 1437, 1395, 1197, 1125 cm^{-1}. δ_H (500 MHz) 1.72 (2H, m, 4-*H*$_2$), 1.76-1.90 (4H, m, 5-*H*$_2$, 6-*H*$_2$), 2.59 (2H, m, 3-*H*$_2$), 3.94 (2H, m, 7-*H*$_2$), 7.19-7.60 (6H, m, 6 x Ar-*H*), 7.79-7.89 (4H, m, 4 x Ar-*H*). δ_C (125 MHz) 23.3 (*C*-4), 29.4 (*C*-5), 30.0 (*C*-6), 38.9 (*C*-3), 43.6 (*C*-7), 128.5-129.0 (6 x Ar-*C*), 131.7-132.1 (4 x Ar-*C*), 180.0 (*C*=O). δ_P (161 MHz) 33.9. *m/z* (ES^+) 314.2 (MH^+), 336.2 (MNa^+). Starting material was also recovered (149 mg, 37%).

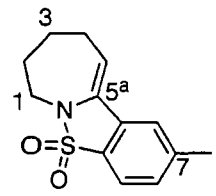
N-([4'-Methylphenyl]sulfonyl)-2-oxo-azepane **19**



Genral method for N-arylsulfonyl protection of lactams:

Purification by flash chromatography ([85:15], [4:1], [65:35] pet. ether/EtOAc) afforded the title compound as a white solid (1.10 g, 4.12 mmol, 46%). mp 117-120 °C. Found; C, 58.11; H, 6.28; N, 4.92%; Calc. for $C_{13}H_{17}NO_3S$; C, 58.40; H, 6.41; N, 5.24%. ν_{max} (KBr) 2941, 2861, 1697 (NC=O), 1597, 1353 (SO_2), 1168 (SO_2), 1123, 1088, 813, 549, 535 cm^{-1}. δ_H (500 MHz) 1.64-1.76 (4H, m, 4-*H*$_2$, 5-*H*$_2$), 1.81 (2H, m, 6-*H*$_2$), 2.41 (3H, s, 4'-C*H*$_3$), 2.53 (2H, t, J = 6 Hz, 3-*H*$_2$), 4.01 (2H, t, J = 5 Hz, 7-*H*$_2$), 7.29 (2H, d, J = 9 Hz, 3'-*H*, 5'-*H*), 7.87 (2H, d, J = 9 Hz, 2'-*H*, 6'-*H*). δ_C (125 MHz) 21.9 (4'-*C*H_3), 23.2 (*C*-4), 29.4 (C5), 29.6 (*C*-6), 39.0 (*C*-3), 46.7 (*C*-7), 128.8 (*C*-2'), 129.5 (*C*-3'), 136.8 (*C*-4'), 144.7 (*C*-1'), 175.1 (*C*-2). *m/z* (ES^+) 268.0 (MH^+).

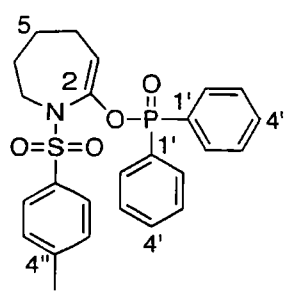
1,2,3,4-Tetrahydro-7-methylazepino[1,2-b][1,2]benzothiazole-10,10-dioxide **20**



General method for the cyclisation of N-alkylsulfonyl lactams:

Purification by flash chromatography ([85:15] DCM/EtOAc) afforded the title compound as a white solid (0.19 g, 0.76 mmol, 41%) and phosphonite (0.13 g, 0.28 mmol, 15%). mp 112-114 °C. ν_{max} (KBr) 3027, 2936, 1666, 1610, 1464, 1305, 1178, 1146, 1061, 941 cm^{-1}. δ_H (500 MHz) 1.79 (2H, m, 3-*H*$_2$), 1.98 (2H, m, 2-*H*$_2$), 2.42 (5H, m, 4-*H*$_2$, 7-C*H*$_3$), 3.57 (2H, t, J = 6 Hz, 1-*H*$_2$), 5.78 (1H, t, J = 7 Hz, 5-*H*), 7.29 (1H, d, J = 8 Hz, 8-*H*), 7.41 (1H, s, 6-*H*), 7.64 (1H, d, J = 8 Hz, 9-*H*). δ_C (125 MHz) 22.2 (7-*C*H$_3$), 27.0 (*C*-3), 27.3 (*C*-4), 28.9 (*C*-2), 45.3 (*C*-1), 106.3 (*C*-5), 120.8 (*C*-6), 121.1 (*C*-9), 128.9 (*C*-10), 130.6 (*C*-8), 132.4 (*C*-5''), 135.9 (*C*-5'), 144.1 (*C*-7). *m/z* (ES^+) 249.6 (MH^+) HRMS (ES^+) found MH^+ 250.0896, $C_{13}H_{16}NO_2S$ requires M^+ 250.0896.

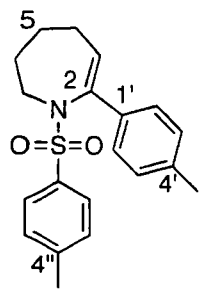
N-[(4''-Methylphenyl)-sulfonyl]-4,5,6,7-tetrahydro-1H-azepin-2-yl diphenylphosphinate **21**



NaHMDS Protocol:

The crude material was collected as a yellow soild. Purification on a Horizon® column chromatography system ([19:1], [9:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.80 g, 1.71 mmol, 73%). ν_{max} (KBr) 3056, 2947, 2914, 2848, 1672, 1595, 1440, 1343, 1230, 1160, 1031, 993, 953, 869 cm^{-1}. δ_H (400 MHz) 1.34 (2H, quint, J = 6 Hz, 5-*H*$_2$), 1.65 (2H, quint, J = 6 Hz, 6-*H*$_2$), 1.85 (2H, q, J = 6 Hz, 4-*H*$_2$), 2.35 (3H, s, 4"-C*H*$_3$), 3.19 (2H, m, 7-*H*$_2$), 5.52 (1H, dt, J_P = 2 Hz, J_H = 8 Hz, 3-*H*), 7.07 (2H, d, J = 8 Hz, 3"-*H*, 5"-*H*), 7.41-7.47 (4H, m, Ar-*H*), 7.52-7.57 (2H, m, 4'-*H*), 7.67 (2H, d, J = 8 Hz, 2"-*H*, 6"-*H*), 7.78-7.86 (4H, m, Ar-*H*). δ_C (100 MHz) 21.9 (4"-*C*H$_3$), 24.1 (*C*-5), 24.4 (*C*-4), 30.1 (*C*-6), 49.6 (*C*-7), 113.6 (d, J = 3 Hz, *C*-3), 127.7 (*C*-2"), 128.8 (d, J = 10 Hz, *C*-3'), 129.8 (*C*-3"), 130.3 and 131.6 (d, J = 130 Hz, *C*-1'), 132.4 (d, J = 10 Hz, *C*-2'), 132.8 (*C*-4'), 138.4 (Ar*C*), 143.8 (Ar*C*), 143.9 (d, J = 10 Hz, *C*-2). δ_P (162MHz,) 33.0. *m/z* (ES^+) 468.2 (MH^+), 490.3 (MNa^+), 956.8 ($2MNa^+$). HRMS (ES) found MH^+ 468.1398, $C_{25}H_{27}N_1O_4S_1P_1$ requires M^+ 468.1393, found MNa^+ 490.1214, $C_{25}H_{26}N_1O_4S_1P_1Na_1$ requires M^+ 490.1212.

N-[(4"-Methylphenyl)sulfonyl]-2-(4'-methylphenyl)-4,5,6,7-tetrahydro-azepane **22**

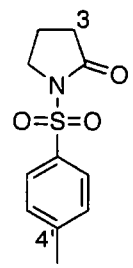


Suzuki protocol A:

The reaction mixture was degassed by passing a stream of nitrogen through it prior to adding the catalyst. Purification on a Horizon® column chromatography system ([19:1] DCM/EtOAc) afforded the title compound as a white solid (110 mg, 0.32 mmol, 43%). ν_{max} (ATR) 2938, 2918, 1440, 1334, 1150, 1087, 1058, 950, 814, 763, 704 cm^{-1}. δ_H

(400 MHz,) 1.43 (2H, m, 5-H_2), 1.83 (2H, quint, J = 6 Hz, 6-H_2), 2.06 (2H, q, J = 6 Hz, 4-H_2), 2.34 (3H, s, CH_3), 2.41 34 (3H, s, CH_3), 6.04 (1H, t, J = 6 Hz, 3-H), 7.04 (2H, d, J = 8 Hz, 2 x Ar-H), 7.18 (4H, d, J = 8 Hz, 2 x Ar-H), 7.55 (2H, d, J = 8 Hz, 2 x Ar-H). δ_C (100 MHz) 19.8 (CH_3), 20.2 (CH_3), 22.3 (C-5), 25.3 (C-4), 28.6 (C-6), 49.3 (C-7), 124.7 (ArC-H), 126.1 (ArC-H) 126.9 (C-3), 127.4 (ArC-H) 127.9 (ArC-H), 134.4 (ArC), 136.2 (C-2), 137.4 (ArC), 141.6 (ArC), 141.7 (ArC). *m/z* (ES^+) 342.3 (MH^+), 359.4 (MH_2O^+), 700.6 ($2MH_2O^+$). HRMS (ES^+) found MH^+ 342.1523, $C_{20}H_{24}NO_2S$ requires 342.1522, found MNa^+ 364.1342, $C_{20}H_{23}NO_2SNa$ requires 364.1342. Starting material was also recovered (114 mg, 0.24 mmol, 33%).

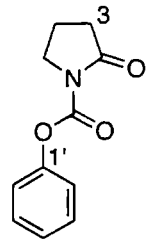
N-[(4'-methylphenyl)sulfonyl]pyrrolidin-2-one **24**



General method for N-alkylsulfonyl protection of lactams:

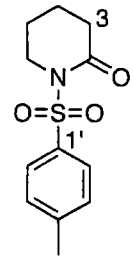
The crude material was collected as a pale brown/orange solid. Purification by flash chromatography ([7:3] pet. ether/EtOAc) afforded the title compound as a white solid (2.33 g, 9.74 mmol, 65%). mp. 139-141 °C. ν_{max} (ATR) 3028, 1737 (C=O), 1598, 1359 (NSO_2), 1238, 1217, 1169 (NSO_2), 1121, 957, 662, 596, 558 cm^{-1}. δ_H (500 MHz) 2.06 (2H, t, J = 8 Hz, 4-H_2), 2.39-2.47 (5H, m, 4'-CH_3, 3-H_2), 3.88 (2H, t, J = 7 Hz, 5-H_2), 7.33 (2H, d, J = 8 Hz, 3'-H), 7.91 (2H, d, J = 8 Hz, 2'-H). δ_C (125 MHz) 18.4 (C-4), 21.2 (CH_3), 32.5 (C-3), 47.5 (C-5), 128.3 (C-2'), 129.9 (C-3'), 135.3 (C-1'), 145.5 (C-4'), 173.7 (C=O). *m/z* (ES^+) 240 (MH^+). HRMS (ES^+) found MH^+ 240.0691, $C_{11}H_{14}NO_3S$ requires M^+ 240.0689, found MNa^+ 262.0509, $C_{11}H_{13}NO_3SNa$ requires M^+ 262.0508.

N-(Phenyloxycarbonyl)pyrrolidin-2-one **25**



To a cold solution (-78 °C) of pyrrolidinone (0.56 g, 6.58 mmol, 1 eq) in dry THF (10 ml, 0.66 M) was added *n*-BuLi (1.6 M, 4.9 ml, 7.90 mmol, 1.2 eq) dropwise *via* a syringe. The reaction mixture was allowed to stir at -78 °C for 1 h then $Ph_2P(O)Cl$ (2.06 g, 13.16 mmol, 2 eq) was added as a cold solution in dry THF (4 ml). The reaction mixture was stirred for 1.5 h at -78 °C, warmed to room temperature and stirred for an additional 0.5 h then quenched with H_2O. The THF was removed under reduced pressure and the aqueous phase extracted with EtOAc (x 3); the combined organics were washed with H_2O, dried over $MgSO_4$ and concentrated to give a pink solid. Purification by flash chromatography afforded the title compound as a white solid (1.01 g, 4.94 mmol, 75%). mp. 119-120 °C. Found; C, 64.33; H, 5.39; N, 6.81%; Calc. for $C_{11}H_{11}NO_3$; C, 64.38; H, 5.40; N, 6.83%. ν_{max} (ATR) 2977, 1779 (OC=O), 1697 (NC=O), 1490, 1458, 1379, 1288, 1188, 1163, 1020, 988, 751, 693 cm^{-1}. δ_H (700 MHz) 2.10 (2H, quint, J = 8 Hz, 4-*H*$_2$), 2.60 (2H, t, J = 8 Hz, C*H*$_2$), 3.93 (2H, t, J = 8 Hz, C*H*$_2$), 7.16 (2H, d, J = 8 Hz, 2'-*H*), 7.23 (1H, t, J = 8 Hz, 4'-*H*), 7.37 (2H, t, J = 8 Hz, 3'-*H*). δ_C (125 MHz) 17.8 (*C*-4), 33.1 (*C*H$_2$), 46.9 (*C*H$_2$), 121.7 (*C*-2'), 126.4 (*C*-4'), 129.6 (*C*-3'), 150.3 (*C*-1'), 150.5 (O*C*=O), 174.1 (*C*-2). *m/z* (ES^+) 206.1 (MH^+), 223.1 (MH_2O^+), 433.2 ($2MNa^+$).

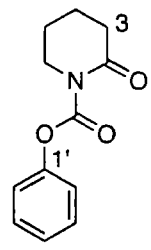
N-[(4'-methylphenyl)sulfonyl]piperidin-2-one **29**



General method for N-alkylsulfonyl protection of lactams:

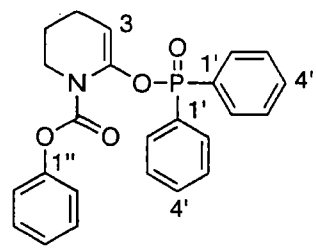
The crude material was collected as a clear oil which solidified on standing. Purification by flash chromatography ([7:3] pet. ether/EtOAc) afforded the title compound as a white solid (2.02 g, 7.9 mmol, 33%). mp. 136-138 °C. Found; C, 56.87; H, 5.97; N, 5.37%; Calc. for $C_{12}H_{15}NO_3S$; C, 56.90; H, 5.97; N, 5.53%. ν_{max} (KBr) 2958, 1691 (C=O), 1457, 1354 (NSO_2), 1283, 1171 (NSO_2), 1089, 969, 830, 577, 549 cm^{-1}. δ_H (400 MHz) 1.74 (2H, quint, J = 6 Hz, 4-*H*$_2$), 1.87 (2H, quint, J = 6 Hz, 5-*H*$_2$), 2.28-2.48 (5H, m, 3-*H*$_2$, 4'-C*H*$_3$), 3.88 (2H, t, J = 6 Hz, 6-*H*$_2$), 7.28 (2H, d, J = 8 Hz, 3'-*H*, 5'-*H*), 7.87 (2H, d, J = 8 Hz, 2'-*H*, 6'-*H*). δ_C (100 MHz) 20.6 (*C*-4), 21.9 (C4'-*C*H_3), 23.5 (*C*-5), 34.3 (*C*-3), 47.2 (*C*-6), 128.9 (*C*-2'), 129.5 (*C*-3'), 136.3 (*C*-1'), 145.0 (*C*-4'), 170.5 (*C*=O). *m/z* (ES^+) 254.1 (MH^+), 276.1 (MNa^+), 308.1 ($MNaMeOH^+$), 529 ($2MNa^+$). HRMS (ES^+) found MH^+ 254.0847, $C_{12}H_{16}NO_3S$ requires M^+ 254.0845, found MNa^+ 276.0666, $C_{12}H_{15}NO_3SNa$ requires M^+ 276.0665.

N-(Phenyloxycarbonyl)piperidin-2-one **30**



To a cold (-78 °C) solution of valerolactam (2.37 g, 23.91 mmol, 1 eq) in dry THF (80 ml) was added *n*-BuLi (1.2 M, 26.1 ml, 31.32 mmol, 1.3 eq) dropwise *via* a syringe and the reaction mixture allowed to stir at -78 °C. After 2 h a cold (-78 °C) solution of freshly distilled phenyl chloroformate (7.48 g, 47.77 mmol, 2 eq) in dry THF (14 ml) was added *via* cannula. The resulting reaction mixture was allowed to stir for 12 h before warming to room temperature. The reaction was quenched with aq. NH_4Cl, concentrated and extracted with EtOAc (3 x 50 ml). The organic phase was washed with brine (3 x 50 ml), aq. $NaHCO_3$ (3 x 50 ml), dried over $MgSO_4$ and concentrated. Purification by flash chromatography ([19:1] DCM/EtOAc) followed by recrystallisation ([10:1] pet. ether/EtOAc) afforded the title compound as a white solid (2.94 g, 13.42 mmol, 56%). mp. 114-116 °C. Found; C, 65.49; H, 5.99; N, 6.18%; Calc. for $C_{12}H_{13}NO_3$; C, 65.74; H, 5.98; N, 6.39%. ν_{max} (KBr) 3007, 2961, 1780 (C=O), 1714 (C=O), 1417, 1356, 1226, 1149, 824 cm^{-1}. δ_H (500 MHz) 1.93 (4H, m, 4-H_2, 5-H_2), 2.63 (2H, t, J = 6 Hz, 3-H_2), 3.87 (2H, t, J = 6 Hz, 6-H_2), 7.20 (2H, d, J = 8 Hz, 2'-H_2), 7.26 (1H, t, J = 8 Hz, 4'-H_2), 7.40 (2H, t, J = 8 Hz, 3'-H_2). δ_C (125 MHz) 20.8 (*C*-4), 22.9 (*C*-5), 35.3 (*C*-3), 47.2 (*C*-6), 121.7 (*C*-2'), 126.3 (*C*-4'), 129.7 (*C*-3'), 151.0 (*C*-1'), 153.3 (O*C*=O), 171.5 (*C*-2). *m/z* (ES^+) 220.1 (MH^+), 461.1 ($2MNa^+$).

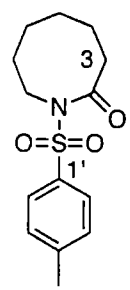
1-(Phenyloxycarbonyl)-4,5,6-trihydro-piperidin-2-diphenylphosphinate **32**



NaHMDS Procedure:

Purification by flash chromatography ([9:1] DCM/EtOAc) afforded the title compound as a clear oil which solidified on standing (1.27 g, 3.03 mmol, 61%). mp. 97-100 °C. Found; C, 68.61; H, 5.50; N, 3.31%; Calc. for $C_{24}H_{22}NO_4P$; C, 68.73; H, 5.29; N, 3.34%. ν_{max} (KBr) 3063, 2955, 1731 (C=O), 1677 (enol ether), 1439, 1364, 1345, 1207, 1175, 1131, 837, 545, 531 cm^{-1}. δ_H (400 MHz) 1.75 (2H, quint, J = 6 Hz, 5-*H*$_2$), 2.12 (2H, m, 4-*H*$_2$), 3.49 (2H, t, J = 6 Hz, 6-*H*$_2$), 5.23 (1H, dt, $^4J_{HP}$ = 2 Hz, J = 6 Hz, 3-*H*), 7.09 (2H, dd, ^4J = 1 Hz, J = 8 Hz, 3"-*H*, 5"-*H*), 7.22 (1H, t, ^4J = 1 Hz, J = 8 Hz, 4"-H), 7.31-7.43 (6H, m, 6 x Ar-*H*), 7.50 (2H, tq, J = 8 Hz, ^4J = 2 Hz, 4'-*H*), 7.86-7.93 (4H, m, 3'-*H*, 5'-*H*). δ_C (100 MHz) 21.8 (*C*-5), 23.0 (*C*-4), 46.0 (*C*-6), 101.1 (d, J = 5 Hz, *C*-3), 121.8 (*C*-3"), 125.9 (*C*-4"), 128.7 (d, J = 13 Hz, *C*-3'), 129.6 (*C*-2"), 130.2 and 131.5 (d, J = 138 Hz, 132.1 (d, J = 11 Hz, *C*-2'), 132.7 (d, J = 3 Hz, *C*-4'), 139.8 (d, J = 8 Hz, *C*-2), 151.2 (*C*-1"), 152.5 (*C*=O). δ_P (162 MHz) 31.1. *m/z* (ES^+) 420.1 (MH^+), 442.1 (MNa^+), 861.3 ($2MNa^+$).

N-[(4'-methylphenyl)sulfonyl]-2-oxoazocine **35**

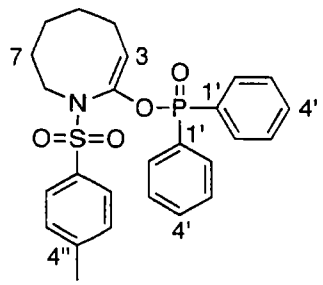


General method for N-alkylprotection of lactams:

Purification by flash chromatography ([7:3] pet. ether/EtOAc) afforded the title compound as a white solid (3.46 g, 12.30 mmol, 80%). mp 116-118 °C. Found; C, 59.64; H, 6.82; N, 4.79%; Calc. for $C_{14}H_{19}NO_3S$; C, 59.76; H, 6.81; N, 4.98%. ν_{max} (KBr) 2938, 1687 (C=O), 1448, 1358 (NSO_2), 1211, 1167 (NSO_2), 1119, 1083, 814, 683, 634, 542 cm^{-1}. δ_H (500 MHz) 1.46 (2H, qt, J = 6 Hz, 6-*H*$_2$), 1.54 (2H, qt, J = 6 Hz, 5-*H*$_2$), 1.75

(2H, qt, J = 6 Hz, 4-*H*$_2$), 1.87 (2H, qt, J = 6 Hz, 7-*H*$_2$), 2.41 (3H, s, 4'-C*H*$_3$), 2.48 (2H, m, 3-*H*$_2$), 4.06 (2H, t, J = 6 Hz, 8-*H*$_2$), 7.28 (2H, d, J = 9 Hz, 3'-*H*, 5'-*H*), 7.90 (2H, d, J = 9 Hz, 2'-*H*, 6'-*H*). δ_C (125 MHz) 21.9 (4'-*C*H$_3$), 23.9 (*C*-6), 26.3 (*C*-5), 28.7 (*C*-4), 31.3 (*C*-7), 36.6 (*C*-3), 46.3 (*C*-8), 129.2, 129.4 (*C*-2', *C*-3'), 136.6 (*C*-1'), 144.8 (*C*-4'), 175.1 (*C*=O). *m/z* (ES$^+$) 282.1 (MH$^+$).

1-Tosyl-4,5,6,7,8-quintahydro-1*H*-azepin-2-yl diphenylphosphinate **36**

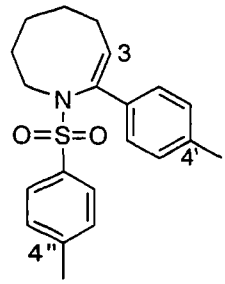


NaHMDS Method:

Purification on a Horizon® column chromatography system ([95:5], [9:1] $CHCl_3$/EtOAc) afforded the title compound as a gummy oil which solidified on standing (874 mg, 1.82 mmol, 51%). mp. 199-200 °C. HPLC, R_t = 6.02 min, 98.13%. ν_{max} (KBr) 2928, 2851, 1671, 1593, 1440, 1348, 1235, 1156, 1126, 1076, 1006, 961, 874, 829, 730 cm^{-1}. δ_H (400 MHz) 1.43-1.60 (6H, m, 5-*H*$_2$, 6-*H*$_2$, 7-*H*$_2$), 2.13 (2H, m, 4-*H*$_2$), 2.36 (3H, s, 4''-C*H*$_3$), 3.31 (2H, m, 8-*H*$_2$), 5.54 (1H, dt, $^4J_{HP}$ = 2 Hz, J = 8 Hz, 3-*H*), 7.09 (2H, d, J = 8 Hz, 3''-*H*, 5''-*H*), 7.38-7.45 (4H, m, Ar-*H*), 7.51-7.57 (2H, m, 4'-*H*), 7.63-7.70 (4H, m, Ar-*H*), 7.73 (2H, d, J = 8 Hz, 2''-*H*, 6''-*H*). δ_C (100 MHz) 21.9 (4''-*C*H$_3$), 26.2 (*C*-4), 26.9 (*C*-6), 27.2 (*C*-7), 28.8 (*C*-5), 50.3 (*C*-8), 119.3 (d, J = 4 Hz, *C*-3), 128.1 (*C*-2''), 128.9 (d, J = 13 Hz, *C*-3'), 129.8 (*C*-3''), 130.5 and 131.89 (d, J = 136 Hz, *C*-1'), 132.1 (d, J = 11 Hz, *C*-2'), 132.8 (d, J = 3 Hz, *C*-4'), 137.7 (Ar*C*), 138.5 (d, J = 10 Hz, *C*-2), 143.6 (Ar*C*). δ_P (162 MHz) 32.4. *m/z* (ES$^+$) 482.1 (MH$^+$), 980.4 (2MH$_2$O$^+$). HRMS (ES$^+$) found

MH^+ 482.1554, $C_{26}H_{29}N_1O_4S_1P_1$ requires M^+ 482.1550, found MNa^+ 504.1367, $C_{26}H_{28}N_1O_4S_1P_1Na_1$ requires M^+ 504.1369.

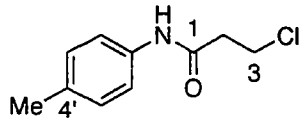
N-[(4"-Methylphenyl)sulfonyl]-2-(4'-methylphenyl)-4,5,6,7,8-quintahydro-1*H*-azocine **37**



Suzuki protocol A:

The reaction mixture was degassed by passing a stream of nitrogen through it prior to adding the catalyst. Purification on a Horizon® column chromatography system ([100:0], [95:5], [7:3] EtOAc/$CHCl_3$) afforded the title compound as a white solid (214 mg, 0.60 mmol, 58%). ν_{max} (KBr) 2924, 2855, 1691, 1447, 1340, 1155, 1118, 1086, 1010, 874, 815, 708 cm^{-1}. δ_H (400 MHz) 1.60 (4H, m, 5-*H*$_2$, 6-*H*$_2$), 1.72 (2H, m, 7-*H*$_2$), 2.31 (3H, s, C*H*$_3$), 2.36 (2H, m, 4-*H*$_2$), 2.40 (3H, s, C*H*$_3$), 3.63 (2H, m, 8-*H*$_2$), 6.39 (1H, t, J = 8 Hz, 3-*H*), 6.97 (2H, d, J = 8 Hz, Ar-*H*), 7.07 (2H, d, J = 8 Hz, Ar-*H*), 7.16 (2H, d, J = 8 Hz, Ar-*H*), 7.52 (2H, d, J = 8 Hz, Ar-*H*). δ_C (100 MHz) 21.0 (*C*H$_3$), 21.4 (*C*H$_3$), 26.5 (*C*-4), 27.0 (*C*-5 or 6), 27.4 (*C*-7), 28.3 (*C*-5 or 6), 52.6 (*C*-8), 125.7 (Ar*C*-H), 127.4 (Ar*C*-H), 128.8 (Ar*C*-H),129.1 (Ar*C*-H), 132.4 (*C*-3), 134.1, 137.3, 138.0, 138.2 and 142.7 (tertiary-*C*). m/z (ES^+) 356.3 (MH^+), 373.2 (MH_2O^+), 728.4 ($2MH_2O^+$). HRMS (ES^+) found MH^+ 356.1680, $C_{21}H_{26}NO_2S$ requires 356.1679, found MNa^+ 378.1498, $C_{21}H_{25}NO_2SNa$ requires 378.1498. Starting material was also recovered (164 mg, 0.34 mmol, 33%).

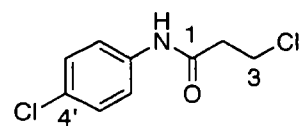
N-(4'-Methylphenyl)-3-chloropropanamide **49**



General procedure for synthesis of amides:

The title compound was obtained as an off-white solid (94%). mp. 119-121 °C. Found; C, 60.82; H, 6.16; N, 7.05%; Calc. for $C_{10}H_{12}ClNO$; C, 60.77; H, 6.12; N, 7.08%. ν_{max} (KBr) 3431 (N-H), 3326 (N-H), 3032 (Ar-H), 1682 (C=O), 1597, 1519 (C=O), 1405, 1311, 814 (C-Cl), 504 cm^{-1}. δ_H (500 MHz) 2.29 (3H, s, C*H*$_3$), 2.81 (2H, t, J = 7 Hz, 2-*H*$_2$), 3.85 (2H, t, J = 7 Hz, 3-*H*$_2$), 7.11 (2H, d, J = 9 Hz, 2'-*H*), 7.43 (2H, d, J = 9 Hz, 3'-*H*). δ_C (125 MHz) 19.8 (*C*H$_3$), 39.5 (*C*-2), 39.9 (*C*-3), 120.2 (*C*-2'), 129.1 (*C*-3'), 133.9 (*C*-4'), 135.9 (*C*-1'), 169.4 (*C*=O). *m/z* (ES^+) 220.1/222.1 [3:1] (MNa^+ Cl^{35}:Cl^{37}).

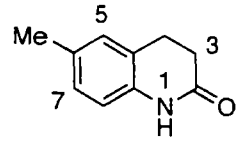
N-(4'-Chlorophenyl)-3-chloropropanamide **50**



General procedure for synthesis of amides:

The crude product was purified by recrystallisation (methanol/water [1:1]) and dried under reduced pressure affording the title compound as a white solid (84%). mp. 125-129 °C. δ_H (200 MHz) 2.82 (2H, t, J = 6 Hz, 2-*H*$_2$), 3.89 (2H, t, J = 6 Hz, 3-*H*$_2$), 7.31 (2H, d, J = 9 Hz, 2'-*H*), 7.75 (2H, d, J = 9 Hz, 3'-*H*). *m/z* (ES^+) 217.9/219.9 [3:1] (MH^+ Cl^{35}:Cl^{37}).

6-Methyl-3,4-dihydroquinolin-2(1H)-one **51**



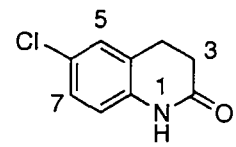
Thermal protocol for the preparation of substituted quinolones:

Flash chromatography ([1:1] pet. ether/EtOAc) afforded the title compound as a white solid (33%).

Microwave protocol for the preparation of substituted quinolones:

The title compound was obtained as a white solid with no need for further purification (96%). mp. 130-132 °C. Found; C, 74.33; H, 6.92; N, 8.67%; Calc. for $C_{10}H_{11}NO$; C, 74.52; H, 6.87; N, 8.69%. ν_{max} (KBr) 3406 (N-H), 1673 (C=O), 1507, 1364, 1233, 1193, 815 cm^{-1}. δ_H (500 MHz) 2.29 (3H, s, CH_3), 2.62 (2H, t, J = 7 Hz, 3-H_2), 2.92 (2H, t, J = 7 Hz, 4-H_2), 6.77 (1H, m, 5-*H*), 6.96 (2H, m, 7-*H*, 8-*H*), 9.52 (1H, b, N*H*). δ_C (125 MHz) 20.0 (CH_3), 25.6 (*C*-4), 31.1 (*C*-3), 115.8 (*C*-5), 123.7 (*C*-4^a), 128.2 (*C*-8), 128.8 (*C*-7), 132.8 (*C*-6), 135.2 (*C*-8^a), 172.7 (*C*-2). *m/z* (ES^+) 162.5 (MH^+), 203.5 ($MHMeCN^+$).

6-Chloro-3,4-dihydroquinolin-2(1H)-one **52**



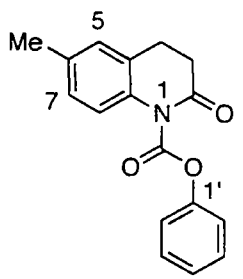
Thermal protocol for the preparation of substituted quinolones:

The title compound was obtained as a white solid with no need for further purification (96%).

Microwave protocol for the preparation of substituted quinolones:

The title compound was obtained as a white solid with no need for further purification (81%). mp. 164-165 °C. Found; C, 59.38; H, 4.47; N, 7.63%; Calc. for C_9H_8ClNO; C, 59.52; H, 4.44; N, 7.71%. ν_{max} (KBr) 3405 (N-H), 3206 and 3081 (amide), 1682 (C=O), 1493, 1361, 1195, 819 (Ar-Cl) cm^{-1}. δ_H (400 MHz) 2.63 (2H, t, J = 7 Hz, 3-H_2), 2.94 (2H, t, J = 7 Hz, 4-H_2), 6.79 (1H, d, J = 9 Hz, Ar-*H*), 7.12 (2H, m, Ar-*H*), 9.60 (1H, b, N*H*). δ_C (100 MHz) 25.4 (*C*-4), 30.5 (*C*-3), 117.0 (Ar*C*-H), 125.5 (*C*-4[a]), 127.7 (Ar*C*-H), 128.1 (Ar*C*-H), 128.2 (*C*-6), 136.2 (*C*-8[a]), 172.4 (*C*=O). *m/z* (ES^+) 182.5/184.5 (MH^+ Cl^{35}:Cl^{37}).

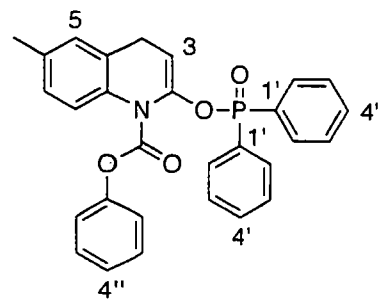
N-(Phenyloxycarbonyl)-6-Methyl-2-oxo-3,4-dihydroquinolin-2(1H)-one **53**



To a cold (-78 °C) solution of lactam **51** (0.32 g, 1.96 mmol) in dry THF (20 ml) was added *n*-BuLi (0.99 M, 2.38 ml, 2.36 mmol) dropwise and the reaction mixture stirred at -78 °C for 1 h. To this was added a cold solution of freshly distilled phenylchloroformate (0.46 g, 0.37 ml, 2.94 mmol) in dry THF (5 ml) *via* cannula and the reaction mixture stirred at -78 °C for 2 h before being warmed to room temperature. The reaction mixture was concentrated and extracted into EtOAc (3 x 5 ml). The organics were washed with brine, dried over $MgSO_4$, concentrated and dried under reduced pressure. Flash chromatography ([9:1], [8:2], [75:25] pet. ether/EtOAc) afforded the title compound as a white solid (1.38 g, 4.91 mmol, 60%). mp. 42-44 °C. Found; C, 72.31; H, 5.40; N, 4.91%; Calc. for $C_{17}H_{15}NO_3$; C, 72.58; H, 5.37; N, 4.98%. ν_{max} (KBr) 1783 (C=O), 1699 (C=O), 1505, 1494, 1283, 1237, 1195, 1160, 816 cm^{-1}. δ_H (500 MHz) 2.33

(3H, s, C*H*$_3$), 2.75 (2H, t, J = 8 Hz, 3-*H*$_2$), 2.98 (2H, t, J = 8 Hz, 4-*H*$_2$), 7.06 (1H, s, 5-*H*), 7.08 (1H, m, Ar-*H*), 7.15 (1H, d, J = 9 Hz, Ar-*H*), 7.28-7.32 (3H, m, 2'-*H*, 4'-*H*, 6'-*H*), 7.40-7.46 (2H, m, 3'-*H*, 5'-*H*). δ_C (125 MHz) 20.0 (*C*H$_3$), 25.8 (*C*-4), 33.8 (*C*-3), 119.5 (Ar*C*-H), 121.4 (*C*-2'), 126.8 (*C*-4'), 127.6 (Ar*C*), 128.2 (Ar*C*-H), 128.8 (*C*-5), 129.9 (*C*-3'), 134.6 (*C*-6), 135.2 (*C*-8[a]), 151.0 (*C*-1'), 152.2 (O*C*=O), 170.6 (N*C*=O). GCMS (EI) 1 peak, R_t = 23.4 min, *m/z* 281.1 (M^+), 188.1 (M^+ - PhO), 160.1 (M^+ - CO_2Ph).

N-(Phenyloxycarbonyl)-2-(diphenylphosphinoyloxy)-6-methylquinoline **54**

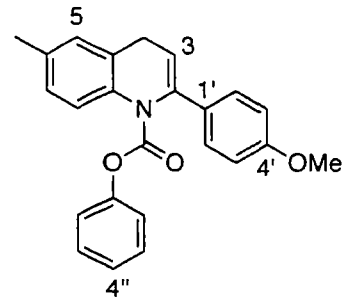


LDA/TMEDA protocol for phosphinate synthesis:

Purification by flash chromatography ([9:1] DCM/EtOAc) afforded an off-white solid (0.99 g, 2.06 mmol, 88%). This material required purification a second time and flash chromatography afforded the title compound as a white foam (0.52 g, 1.08 mmol, 46%). mp. 44-46 °C. ν_{max} (KBr) 3063, 2925, 1731 (C=O), 1681 (enol ether), 1593, 1494, 1439, 1337, 1317, 1223, 1191, 1131, 858, 820 cm^{-1}. δ_H (400 MHz) 2.28 (3H, s, *C*H$_3$), 3.23 (2H, m, 4-*H*$_2$), 5.60 (1H, dt, $^4J_{HP}$ = 2 Hz, J = 5 Hz, 3-*H*), 6.89 (1H, s, 5-*H*), 6.94 (1H, d, J = 9 Hz, 7-*H*), 7.14 (2H, m, 3''-*H*, 5''-*H*), 7.21-7.26 (2H, m, 8-*H*, 4''-*H*), 7.34-7.44 (6H, m, 2''-*H*, 6''-*H* 4 x 2'-*H*), 7.48-7.54 (2H, m, 2 x 4'-*H*), 7.86-7.93 (4H, m, 4 x 3'-*H*). δ_C (100 MHz) 21.1 (*C*H$_3$), 27.6 (*C*-4), 103.0 (d, J = 5 Hz, *C*-3), 121.8 (*C*-2''), 124.1 (*C*-8), 126.1 (*C*-4''), 126.8 (*C*-7), 127.8 (*C*-5), 128.8 (d, J = 13 Hz, *C*-3'), 129.7 (*C*-3''), 131.2 (Ar*C*), 132.1 (d, J = 10 Hz, *C*-2'), 132.6 (Ar*C*), 132.8 (d, J = 3 Hz, *C*-4'), 134.5

(Ar*C*), 135.8 (*C*-6), 141.0 (d, J = 9 Hz, *C*-2), 151.1 (*C*=O), 151.9 (*C*-1"). δ_P (162 MHz) 31.3. GCMS (EI) 1 Peak, R_t = 23.49 min, 281.1 (MH^+ - $C_{12}H_9OP$).

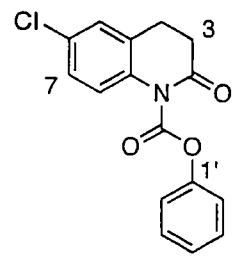
N-Phenyloxycarbonyl-2-(4'-methoxyphenyl)-6-methyl quinoline **55**



Suzuki protocol A:

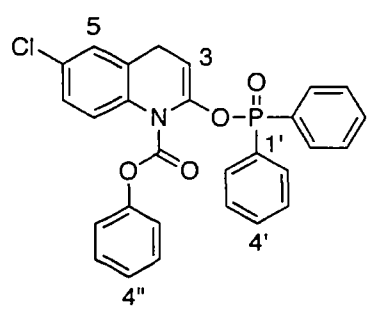
The crude material was collected as a dark red oil. Purification by flash chromatography ([1:1] pet. ether/$CHCl_3$) afforded a clear oil. This material required further purification and flash chromatography affording the title compound as an off-white solid. (31 mg, 8.4 x 10^{-5} mol, 24%). δ_H (300 MHz) 2.35 (3H, s, CC*H*$_3$), 3.41 (2H, d, J = 5 Hz, 4-*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 5.91 (1H, t, J = 5 Hz, 3-*H*), 6.80 (2H, d, J = 8 Hz, 2 x Ar-*H*), 6.91 (2H, d, J = 8 Hz, 2 x Ar-*H*), 7.01 (1H, s, 5-*H*), 7.06-7.15 (2H, m, 2 x Ar-*H*), 7.19-7.29 (2H, m, 2 x Ar-*H*), 7.45 (2H, d, J = 8 Hz, 2 x Ar-*H*), 7.80 (1H, d, J = 8 Hz, Ar-H).

N-(Phenyloxycarbonyl)-6-chloro-2-oxo-3,4-dihydroquinolin-2(1H)-one **56**



To a cold (0 °C) solution of lactam **52** (2.00 g, 11.0 mmol) in dry THF (80 ml, 0.14 M) was added *n*-BuLi (1.6 M, 8.3 ml, 13.2 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h before adding freshly distilled phenylchloroformate (3.45 g, 2.77 ml, 22.0 mmol) and stirring for an additional 2 h. The reaction was quenched with H_2O, warmed to room temperature and concentrated. The aqueous was extracted into EtOAc (3 x 10 ml) and the combined organics washed with brine, dried over $MgSO_4$, concentrated and dried under reduced pressure. Flash chromatography ([6:3:1] cyclohexane/$CHCl_3$/Et_2O) afforded the title compound as a white solid (3.04 g, 10.1 mmol, 92%). mp. 71-72 °C. Found; C, 63.76; H, 4.01; N, 4.68%; calc. for $C_{16}H_{12}NO_3Cl$; C, 63.69; H, 4.01; N, 4.64%. ν_{max} (KBr) 1783 (C=O), 1699 (C=O), 1505, 1494, 1283, 1237, 1195, 1160, 816 cm^{-1}. δ_H (500 MHz) 2.33 (3H, s, C*H*$_3$), 2.75 (2H, t, J = 7 Hz, 3-*H*$_2$), 2.98 (2H, t, J = 7 Hz, 4-*H*$_2$), 7.19-7.32 (6H, m, 5-*H*, 7-*H*, 8-*H*, 3 x Ar-*H*), 7.42-7.50 (2H, m, 2 x Ar-*H*). δ_C (125 MHz) 25.9 (*C*-4), 33.8 (*C*-3), 120.8 (Ar*C*-H), 121.2 (*C*-2'), 127.0 (*C*-4'), 127.9 (Ar*C*-H) 128.1 (*C*-5), 129.9 (*C*-4^a), 130.0 (*C*-3'), 130.9 (*C*-6), 135.8 (*C*-8^a), 150.9 (*C*-1'), 152.2 (O*C*=O), 170.0 (N*C*=O). *m/z* (EI) 281.1 (M^+), 188.1 (M^+ - PhO), 160.1 (M^+ - CO_2Ph).

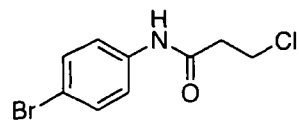
N-Phenyloxycarbonyl-2-(diphenylphosphinoyloxy)-3,4-dihydro-6-chloroquinolone **57**



LDA/TMEDA Protocol for phosphinate synthesis:

Purification by flash chromatography ([9:1] DCM/EtOAc) afforded the title compound as a white foam (236 mg, 0.47 mmol, 37%). δ_H (300 MHz) 3.24 (2H, m, 4-H_2), 5.59 (1H, dt, $^4J_{HP}$ = 2 Hz, J = 5 Hz, 3-*H*), 7.06-7.15 (4H, m, 4 x Ar-*H*), 7.24-7.30 (2H, m, 2 x Ar-*H*), 7.34-7.44 (6H, m, 6 x Ar-*H*), 7.49-7.55 (2H, m, 2 x Ar-*H*), 7.83-7.91 (4H, m, 4 x Ar-*H*). δ_C (100 MHz) 27.5 (*C*-4), 102.6 (d, J = 5 Hz, *C*-3), 121.6 (Ar*C*-H), 125.5 (Ar*C*-H), 126.2 (Ar*C*-H), 126.3 (Ar*C*-H), 127.1 (Ar*C*-H), 128.8 (d, J = 13 Hz, *C*-3'), 129.2 (Ar*C*), 129.7 (Ar*C*-H), 131.0 (Ar*C*), 132.0 (d, J = 10 Hz, *C*-2'), 132.9 (d, J = 3 Hz, *C*-4'), 134.6 (Ar*C*), 136.8 (Ar*C*), 140.9 (d, J = 9 Hz, *C*-2), 150.8 (*C*=O), 151.4 (*C*-1''). δ_P (162 MHz) 31.8.

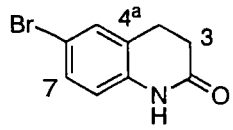
N-(4'-Bromophenyl)-3-chloropropanamide **60**



General procedure for synthesis of amides:

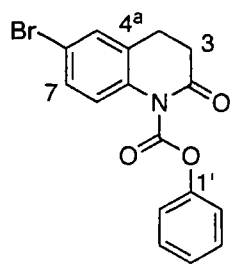
The title compound was obtained as a white solid (87%). mp. 122-124 °C. Found; C, 41.21; H, 3.47; N, 5.34%; Calc. for $C_9H_9BrClNO$; C, 41.17; H, 3.46; N, 5.15%. ν_{max} (KBr) 3430 (N-H), 1697 (C=O), 1591, 1515 (C=O), 1396, 1303, 1239, 1074, 1009, 826 (C-Br), 502 cm^{-1}. δ_H (500 MHz) 2.84 (2H, t, J = 7 Hz, 2-H_2), 3.86 (2H, t, J = 7 Hz, 3-H_2), 7.44 (2H, d, J = 9 Hz, 2'-*H*), 7.52 (2H, d, J = 9 Hz, 3'-*H*). δ_C (125MHz) 39.6 (*C*-2), 39.7 (*C*-3), 116.4 (*C*-4'), 121.6 (*C*-3'), 131.7 (*C*-2'), 137.8 (*C*-1'), 169.6 (*C*=O). m/z (ES^+) 262.0 (MH^+ Cl^{35}:Br^{79}), 264.0 (MH^+ Cl^{35}:Br^{81}), 266.0 (MH^+ Cl^{37}:Br^{81}), 303.0 ($MHMeCN^+$ Cl^{35}:Br^{79}), 305.0 ($MHMeCN^+$ Cl^{35}:Br^{81}), 307.0 ($MHMeCN^+$ Cl^{37}:Br^{81}).

6-Bromo-3,4-dihydroquinolin-2(1H)-one **6**



To a cold solution (0 °C) of 3,4-dihydroquinolin-2(1*H*)-one (2.00 g, 13.6 mmol, 1 eq) in DMF (43 ml, 0.32 M) was added a solution of N-bromosuccinimide (2.54 g, 14.3 mmol, 1.05 eq) in DMF (45 ml, 0.32 M) dropwise *via* a dropping funnel. The reaction mixture was stirred at 0 °C for 2 h before warming to room temperature and quenching with H_2O. The resultant solution was extracted with a 1:1 EtOAc/toluene mixture (3 x 75 ml) and the combined organics washed with H_2O and dried over $MgSO_4$. The crude material was recrystallised from EtOH affording the title compound as clear rod-like crystals (1.90 g, 8.41 mmol, 62%). δ_H (400 MHz) 2.62 (2H, t, J = 8 Hz, 3-*H*$_2$), 2.94 (2H, t, J = 8 Hz, 4-*H*$_2$), 6.76 (1H, d, J = 10 Hz, Ar-*H*), 7.24-7.28 (2H, m, 2 x Ar-*H*), 9.91 (1H, b, N*H*). δ_C (100 MHz) 25.5 (*C*-4), 30.8 (*C*-3), 115.8 (*C*-6), 117.6 (*C*-8), 126.0 (*C*-4^a), 130.8 and 131.1 (*C*-5 and *C*-7), 136.9 (*C*-8^a), 172.8 (*C*=O). *m/z* (ES$^+$) 267.0/269.0 [1:1] (MHMeCN$^+$ Br^{79}:Br^{81}), 452.9 (2MH$^+$).

N-(Phenyloxycarbonyl)-6-bromo-2-oxo-3,4-dihydroquinolin-2(1H)-one **63**

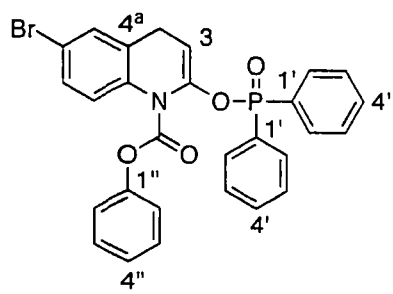


To a cold (-78 °C) solution of **61** (2.00 g, 8.85 mmol) in dry THF (50 ml, 0.18 M) was added LDA dropwise (Aldrich 1.8 M, 6.4 ml 11.5 mmol) and the reaction mixture stirred for 30 min. Phenylchloroformate (2.77 g, 17.70 mmol) was added dropwise *via* syringe

and the reaction mixture stirred at -78 °C for 1 h before being warmed to room temperature. The reaction was quenched with H_2O and concentrated and the aqueous phase extracted into EtOAc (x 3). The organics were washed with brine, dried over $MgSO_4$, concentrated and dried under reduced pressure. Purification on a Horizon® column chromatography system ([6:3:1] cyclohexane/$CHCl_3$/Et_2O) afforded the title compound as a white solid (2.82 g, 8.15 mmol, 92%). HPLC R_t = 5.86 min, 98.8% no impurity greater than 1.20%. ν_{max} (ATR) 1789 (C=O), 1702 (C=O), 1483, 1295, 1277, 1218, 1890, 1128, 1076, 998, 873, 825, 750, 691 cm^{-1}. δ_H (400 MHz) 2.77 (2H, t, J = 7 Hz, 3-*H*$_2$), 3.00 (2H, t, J = 7 Hz, 4-*H*$_2$), 7.16 (1H, d, J = 10 Hz, Ar-*H*), 7.26-7.33 (3H, m, 2'-*H*, 4'-*H* & 6'-*H*), 7.38-7.47 (4H, m, 5-*H*, 3'-*H*, 5'-*H*, Ar-*H*). δ_C (100 MHz) 25.7 (*C*-4), 33.4 (*C*-3), 118.4 (*C*-6), 121.2 (Ar*C*-H), 121.4 (*C*-3'), 127.0 (*C*-4'), 130.0 (*C*-4^a), 130.1 (*C*-2'), 130.8 & 131.2 (2 x Ar*C*-H), 136.3 (*C*-8^a), 151.1 (*C*=O), 152.1 (*C*-1'), 170.0 (*C*-2). *m/z* (ES^+) 346.2/348.2 [1:1] (MH^+ Br^{79}:Br^{81}).

N-Phenyloxycarbonyl-2-(diphenylphosphinoyloxy)-3,4-dihydro-6-bromoquinolone

64

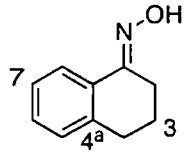


NaHMDS Protocol for the formation of phosphinates:

Purification on a Horizon® column chromatography system ([97:3] DCM/EtOAc) afforded the title compound as a white crystalline solid (2.45 g, 4.49 mmol, 77%). HPLC R_t = 6.55 min, 98.1% no impurity greater than 1.0%. ν_{max} (ATR) 1736 (C=O), 1673 (enol ether), 1591, 1479, 1439, 1333, 1305, 1186, 1129, 1073, 964, 848, 728, 690 cm^{-1}. δ_H

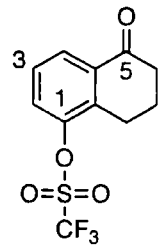
(400 MHz) 3.25 (2H, m, 4-*H*$_2$), 5.60 (1H, dt, J = 5 Hz, $^4J_{HP}$ = 2 Hz, 3-*H*), 7.14 (2H, d, J = 8 Hz, 2'-*H*, 6'-*H*), 7.21-7.29 (4H, m, 5-*H*, 7-*H*, 8-*H*, 4'-*H*), 7.36-7.45 (6H, m, 2 x 2"-*H*, 2 x 6"-*H*, 3'-*H*, 5'-*H*), 7.50-7.56 (2H, m, 2 x 4"-*H*), 7.85-7.92 (4H, m, 2 x 3"-*H*, 2 x 5"-*H*). δ_C (100 MHz) 27.6 (*C*-4), 102.7 (d, J = 4 Hz, *C*-3), 119.6 (*C*-6), 121.8 (*C*-2"), 126.0 (Ar*C*-H), 126.5 (Ar*C*-H), 129.1 (d, J = 13 Hz, *C*-3'), 129.4 (Ar*C*-H), 129.9 (*C*-3"), 130.2 (Ar*C*-H), 131.2 (Ar*C*), 132.3 (d, J = 11 Hz, *C*-2'), 133.1 (*C*-4"), 135.2 (Ar*C*), 137.6 (Ar*C*), 141.1 (d, J = 9 Hz, *C*-2), 151.0 (*C*=O), 151.5 (*C*-1"). δ_P (162 MHz) 33.5. m/z (ES$^+$) 546.1/548.1 [1:1] (MH$^+$ Br^{79}:Br^{81}).

(1E)-3,4-Dihydronaphthalen-1(2H)-one oxime **90**



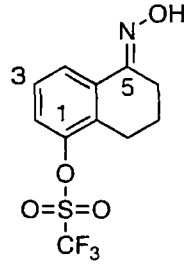
α-Tetralone (0.50 g, 3.42 mmol, 1 eq), zinc oxide (2 eq) and $NH_2OH.HCl$ (1.02 g, 14.73 mmol, 4.3 eq) were combined in a round-bottomed flask and heated (140 °C) with stirring for 1 h. The mixture was cooled to room temperature, diluted with EtOAc, filtered and the filtrate concentrated. Purification by flash chromatography ([95:5] pet. ether/EtOAc) afforded the title compound as an off-white solid (531 mg, 3.30 mmol, 88%). ν_{max} (ATR) 3050-3450 (O-H), 2959, 1414, 1249, 1211, 1137, 1103, 935, 877, 785, 714 cm^{-1}. δ_H (500 MHz) 1.91 (2H, quint, J = 6 Hz, 3-*H*$_2$), 2.79 (2H, t, J = 6 Hz, 4-*H*$_2$), 2.87 (2H, t, J = 6 Hz, 2-*H*$_2$), 7.18 (1H, d, J = 8 Hz, 5-*H*), 7.24 (1H, t, J = 8 Hz, 7-*H*), 7.30 (1H, dt, J = 8 Hz, $^4J_{HH}$ = 1 Hz, 6-*H*), 7.91 (1H, d, J = 8 Hz, 8-*H*). δ_C (100 MHz) 21.6 (*C*-3), 24.1 (*C*-2), 30.1 (*C*-4), 124.3 (*C*-8), 126.7 (*C*-7), 129.0 (*C*-5), 129.5 (*C*-6), 130.7 (*C*-8^a), 140.1 (*C*-4^a), 155.6 (C-1). *m/z* (ES$^+$) 162.1 (MH$^+$), 202.7 (MMeCN$^+$).

5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl trifluoromethanesulfonate **92**



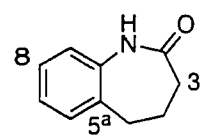
To a cold (0 °C) solution of 5-hydroxytetralone (495 mg, 3.05 mmol, 1 eq) in pyridine (5 ml, 0.61 M) was added triflic anhydride slowly (0.77 ml, 4.58 mmol, 1.5 eq). The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was diluted with Et_2O (25 ml) and quenched with H_2O. The aqueous phase was extracted with Et_2O (x 3) and the combined organics washed with H_2O (x 3) then aq. $CuSO_4$ (until all the pyridine was removed) then dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography ([95:5], [8:2] pet. ether/EtOAc) afforded the title compound as a yellow oil (880 mg, 2.99 mmol, 98%) that contained a minor impurity which could not be removed by chromatography. δ_H (400 MHz, CD_3OD) 2.12 (2H, quint, J = 8 Hz, 7-H_2), 2.63 (2H, t, J = 8 Hz, CH_2), 2.98 (2H, t, J = 8 Hz, CH_2), 7.41 (1H, t, J = 10 Hz, 3-H), 7.50 (1H, d, J = 10 Hz, Ar-H), 7.96 (1H, d, J = 10 Hz, Ar-H). δ_F (376 MHz, CD_3OD) -75.9.

(5E)-5-(Hydroxyimino)-5,6,7,8-tetrahydronaphthalen-1-yl trifluoromethanesulfonate **94**



Tetralone **92** (415 mg, 1.41 mmol, 1 eq), zinc oxide (230 mg, 2.82 mmol, 2 eq) and $NH_2OH.HCl$ (423 mg, 6.07 mmol, 4.3 eq) were combined in a round-bottomed flask and heated (120 °C) with stirring for 1 h. The mixture was cooled to room temperature, diluted with EtOAc and filtered and the filtrate concentrated. Purification by flash chromatography ([95:5], [9:1], [8:2] pet. ether/EtOAc) afforded the title compound as a white solid (400 mg, 1.29 mmol, 92%). mp. 126-128 °C. Found; C, 42.74; H, 3.43; N, 4.49%; Calc. for $C_{11}H_{10}F_3NO_4S$; C, 42.72; H, 3.26; N, 4.53%. ν_{max} (ATR) 3050-3450 (O-H), 2959, 1414, 1249, 1211, 1137, 1103, 935, 877, 785, 714 cm^{-1}. δ_H (500 MHz) 1.92 (2H, quint, J = 7 Hz, 7-*H*$_2$), 2.85 (4H, m, 6-*H*$_2$, 8-*H*$_2$), 7.24-7.32 (2H, m, 2-*H*, 3-*H*), 7.96 (1H, dd, J = 8 Hz, $^4J_{HH}$ = 2 Hz, 4-*H*), 8.32 (1H, broad, O*H*). δ_C (100 MHz) 20.5 (*C*-7), 23.3, 23.5 (*C*-6, *C*-8), 115.0-122.5 (q, $^1J_{CF}$ = 321 Hz, *C*F_3), 122.0 (Ar*C*-H), 124.4 (*C*-8), 127.6 (Ar*C*-H), 132.8 (*C*-4^a), 133.8 (*C*-5), 147.7 (*C*-8^a), 154.4 (*C*-1). δ_F (376 MHz) -74.0. *m/z* (ES^+) 309.9 (MH^+).

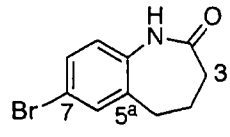
1,3,4,5-tetrahydro-2H-1-benzazepin-2-one **88**



A mixture of oxime **90** (2.41 g, 14.94 mmol, 1 eq) and polyphosphoric acid (10 x excess *w/w*) was heated (100 °C) with stirring (glass rod) for 15 min. Crushed ice was added and the mixture extracted with DCM (x 3), the combined organics were washed with H_2O, aq. $NaHCO_3$, H_2O then dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was filtered through a pad of silica affording the title compound as an off-white solid (2.17 g, 13.48 mmol, 90%). mp. 134-136 °C. Found; C, 74.51; H, 6.88; N, 8.69%; calc. for $C_{10}H_{11}NO$; C, 73.24; H, 6.74; N, 8.30%. ν_{max} (ATR) 1651 (C=O), 1490, 1383, 1290, 1157, 980, 761 cm^{-1}. δ_H (500 MHz) 2.24 (2H, quint,

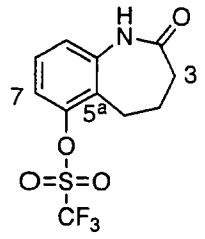
J = 7 Hz, 4-*H*$_2$), 2.37 (2H, t, J = 7 Hz, 3-*H*$_2$), 2.80 (2H, t, J = 7 Hz, 5-*H*$_2$), 7.03 (1H, d, J = 8 Hz, 9-*H*), 7.12 (1H, dt, J = 8 Hz, $^4J_{HH}$ = 1 Hz, 7-*H*), 7.18-7.26 (2H, m, 6-*H*, 8-*H*), 8.93 (1H, s, N*H*). δ_C (100 MHz) 28.9 (*C*-4), 30.6 (*C*-5), 33.1 (*C*-3), 122.1 (*C*-9), 125.8 (*C*-7), 127.7 (*C*-8), 130.0 (*C*-6), 134.5 (*C*-5^a), 138.3 (*C*-9^a), 176.1 (*C*=O). *m/z* (ES$^+$) 162.1 (MH^+), 184.1 (MNa^+). HRMS (ES$^+$) found MH^+ 162.0914, $C_{10}H_{12}NO$ requires M^+ 162.0913.

7-Bromo-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one **89**



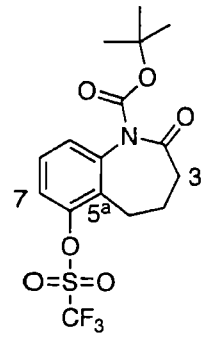
To a cold solution (0 °C) of benzazepine **88** (0.96 g, 5.94 mmol, 1 eq) in DMF (19 ml, 0.32 M) was added a solution of N-bromosuccinimide (1.27 g, 7.13 mmol, 1.2 eq) in DMF (22 ml, 0.32 M) dropwise *via* a dropping funnel. The reaction mixture was stirred at 0 °C for 2 h before warming to room temperature and quenching with H_2O. The resultant solution was extracted with a 1:1 EtOAc/toluene mixture (3 x 30 ml) and the combined organics washed with H_2O and dried over $MgSO_4$. Purification by flash chromatography afforded the title compound as a white solid (1.17 g, 4.86 mmol, 82%). mp. 163-164 °C. Found; C, 50.01; H, 4.21; N, 5.80%; calc. for $C_{10}H_{10}NOBr$; C, 50.02; H, 4.20; N, 5.83%. ν_{max} (ATR) 3047, 2938, 1659 (C=O), 1480, 1444, 1378, 1329, 1288, 1258, 1156, 1080, 922, 834 cm^{-1}. δ_H (700 MHz) 2.22 (2H, quint, J = 7 Hz, 4-*H*$_2$), 2.34 (2H, t, J = 7 Hz, 3-*H*$_2$), 2.75 (2H, t, J = 7 Hz, 5-*H*$_2$), 6.87 (1H, d, J = 8 Hz, 9-*H*), 7.33 (1H, dd, J = 8 Hz, $^4J_{HH}$ = 3 Hz, 8-*H*), 7.35 (1H, d, $^4J_{HH}$ = 3 Hz, 6-*H*), 8.52 (1H, br, N*H*). δ_C (176 MHz) 28.4 (*C*-4), 30.4 (*C*-5), 32.9 (*C*-3), 118.7 (*C*-7), 123.6 (*C*-9), 130.6 (*C*-8), 132.8 (*C*-6), 136.6 (*C*-5'), 137.3 (*C*-9'), 175.5 (*C*-2). GCMS, R_t = 20.7min, *m/z* (EI) 238.8/240.8 [1:1] (M^+ Br^{79}:Br^{81}).

2-Oxo-2,3,4,5-tetrahydro-1H-1-benzazepin-6-yl trifluoromethanesulfonate **95**



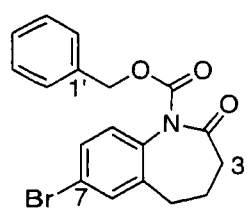
A mixture of oxime **94** (145 mg, 0.47 mmol) and polyphosphoric acid (10 x excess *w/w*) was heated (100 °C) with stirring (glass rod) for 15 min. Crushed ice was added and the mixture extracted with DCM (x 3), the combined organics were washed with H_2O, aq. $NaHCO_3$, H_2O then dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography ([9:1], [8:2] pet. ether/EtOAc) afforded the title compound as a clear oil (58 mg, 0.19 mmol, 40%). ν_{max} (ATR) 3224, 1682 (C=O), 1474, 1413, 1365, 1223, 1194, 1133, 1052, 1007, 956, 907, 869, 813, 735 cm^{-1}. δ_H (500 MHz) 2.33 (2H, quint, J = 7 Hz, 4-*H*$_2$), 2.41 (2H, t, J = 7 Hz, 3-*H*$_2$), 2.94 (2H, t, J = 7 Hz, 5-*H*$_2$), 7.09 (1H, d, J = 8 Hz, 9-*H*), 7.13 (1H, d, J = 8 Hz, 7-*H*), 7.32 (1H, t, J = 8 Hz, 8-*H*), 8.86 (1H, s, N*H*). δ_C (100 MHz) 23.9 (*C*-5), 27.7 (*C*-4), 33.0 (*C*-3), 115.0-122.6 (q, $^1J_{CF}$ = 321 Hz, *C*F_3), 118.7 (*C*-7), 122.0 (*C*-9), 128.1 (*C*-5^a), 128.5 (*C*-8), 140.8 (*C*-6), 148.0 (*C*-9^a), 175.5 (*C*=O). δ_F (188 MHz) -73.9. *m/z* (ES^+) 310.1 (MH^+). HRMS (ES^+) found MH^+ 310.0356, $C_{11}H_{11}NO_4F_3S$ requires M^+ 310.0355.

N-(tert-Butyloxycarbonyl)-2-oxo-6-([trifluoromethylsulfonyl]oxy)-2,3,4,5-tetrahydro-1H-1-benzazepine **98**



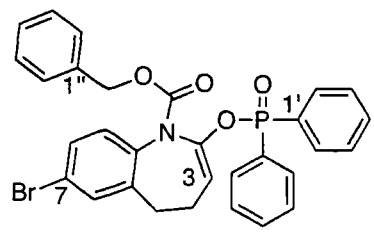
To a solution of benzazepine **95** (0.42 M, 241 mg, 0.78 mmol, 1 eq) and DMAP (105 mg, 0.86 mmol, 1.1 eq) in dry THF (2 ml) was added a solution of di-*tert*-butyldicarbonate (0.43 M, 187 mg, 0.86 mmol, 1 eq) as a solution in dry THF (2 ml) and the mixture stirred for 1 h at room temperature. The mixture was quenched with H_2O and the THF removed under reduced pressure. The aqueous layer was extracted with EtOAc (x 3) and the combined organics washed with H_2O, aq. $NaHCO_3$ then brine then dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography ([9:1], [8:2] pet. ether/EtOAc) afforded the title compound as a red oil (200 mg, 0.49 mmol, 63%). ν_{max} (ATR) 1777 (C=O), 1733 (C=O), 1461, 1418, 1365, 1208, 1133, 905, 846 cm^{-1}. δ_H (200 MHz) 1.47 (9H, s, $C(CH_3)_3$), 2.17-2.38 (4H, m, 2 x CH_2), 2.94 (2H, t, J = 7 Hz, CH_2), 7.14-7.42 (3H, m, 3 x Ar-*H*). δ_F (188 MHz) -73.9.

N-(Benzyloxycarbonyl)-7-bromo-2-oxo-2,3,4,5-tetrahydro-1H-1-benzazepine **100**



To a cold (-78 °C) solution of benzazepine **89** (0.42 M, 250 mg, 1.04 mmol, 1 eq) in dry THF (2.5 ml) was added LDA dropwise (Aldrich 1.6 M, 0.75 ml, 1.35 mmol, 1.3 eq) and the reaction mixture stirred for 30 min. Benzyl chloroformate (0.30 ml, 2.08 mmol, 2 eq) was then added dropwise *via* syringe and the reaction mixture stirred at -78 °C for 1 h before being warmed to room temperature. The reaction was quenched with H_2O, the THF removed under reduced pressure and the aqueous phase extracted into EtOAc (x 3). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography ([8:2] pet. ether/EtOAc) afforded the title compound as a white crystalline solid (234 mg, 0.63 mmol, 60%). mp. 94-96 °C. Found; C, 58.06; H, 4.43; N, 3.69%; calc. for $C_{18}H_{16}NO_3Br$; C, 57.77; H, 4.31; N, 3.74%. ν_{max} (ATR) 1773 (C=O), 1480, 1454, 1374, 1340, 1291, 1237, 1060, 1027, 958, 765, 744, 696 cm^{-1}. δ_H (500 MHz) 2.10 (2H, quint, J = 7 Hz, 4-*H*$_2$), 2.29 (2H, t, J = 7 Hz, 3-*H*$_2$), 2.77 (2H, t, J = 7 Hz, 5-*H*$_2$), 5.25 (2H, s, PhC*H*$_2$), 6.93 (1H, d, J = 8 Hz, 9-*H*), 7.31-7.38 (7H, m, Ar-*H*). δ_C (176 MHz) 27.2 (*C*-4), 29.3 (*C*-5), 34.8 (*C*-3), 69.2 (Ph*C*H$_2$), 121.8 (Ar*C*), 128.4, 128.5, 128.7, 128.8 (4 x Ar*C*-H), 130.6 (*C*-8), 132.2 (*C*-6), 135.1 (*C*-1'), 137.5 (*C*-5'), 137.9 (Ar*C*), 152.6 (O*C*=O), 172.1 (*C*-2). *m/z* (ES^+) 428.2/430.2 [1:1] ($MNaMeOH^+$ Br^{79}:Br^{81}), 437.3/439.3 [1:1] ($MNaMeCN^+$ Br^{79}:Br^{81}).

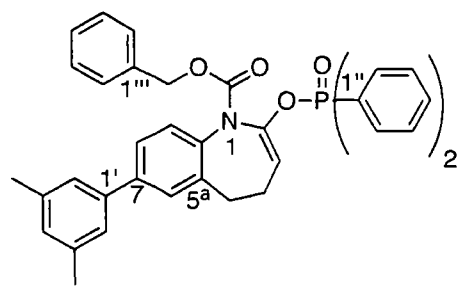
N-(Benzyloxycarbobonyl)-7-bromo-2-[(diphenylphosphoryl)oxy]-4,5-dihydro-1H-1-benzazepine **101**



NaHMDS Protocol for phosphinate synthesis:

Purification by flash chromatography ([5:3:2] pet. ether/$CHCl_3$/EtOAc) afforded the title compound as a clear oil (70 mg, 0.12 mmol, 42%). ν_{max} (ATR) 1720 (C=O), 1687, 1305, 1233, 1087, 1057, 989, 918, 831, 727, 693 cm^{-1}. δ_H (500 MHz) 2.13 (1H, m, 4-H*H*), 2.40-2.33 (2H, m, 4-*H*H, 5-H*H*), 2.98 (1H, m, 5-*H*H,), 5.12-5.24 (3H, m, 3-*H*, O-CH_2), 6.30 (1H, d, J = 8 Hz, 9-*H*), 7.14 (1H, dd, J = 8 Hz, $^4J_{HH}$ = 2 Hz, 8-*H*), 7.26 (1H, d, $^4J_{HH}$ = 2 Hz, 6-*H*), 7.27-7.42 (9H, m, Ar-*H*), 7.50 (2H, t, J = 8 Hz, 2 x 4'-*H*), 7.67-7.84 (4H, m, 2'-*H*, 6'-*H*). δ_C (125 MHz) 26.9 (*C*-4), 28.6 (*C*-5), 68.1 (O-*C*H_2), 108.3 (*C*-3), 121.8 (*C*), 128.2-128.6 (3 x Ar*C*-H), 128.8 (d, J = 13 Hz, *C*-3'), 129.5 (*C*-9), 129.9 (*C*-8), 131.5 (*C*), 131.7 (*C*-6), 132.1 (d, J = 10 Hz, *C*-2'), 132.6 (*C*-4'), 136.1 (*C*), 139.1 (*C*), 140.0 (*C*), 140.7 (d, J = 9 Hz, *C*-2), 153.9 (*C*=O). δ_p (283 MHz) 29.2. *m/z* (ES^+) 574.2/576.2 [1:1] (MH^+ Br^{79}:Br^{81}), 596.3/598.3 [1:1] (MNa^+ Br^{79}:Br^{81}). HRMS (ES^+) found MH^+ 574.0788, $C_{30}H_{26}NO_4PBr^{79}$ requires M^+ 574.0777, found MNa^+ 596.0603, $C_{30}H_{25}NO_4PBr^{79}Na$ requires M^+ 596.0597.

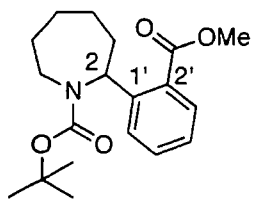
N-(Benzyloxycarbobonyl)-7-(3',5'-dimethylphenyl)-2-[(diphenylphosphoryl)oxy]-4,5-dihydro-1H-1-benzazepine **102**



A suspension of phosphinate **101** (60 mg, 0.10 mmol, 1 eq), 3,5-dimethylphenylboronic acid (17 mg, 0.11 mmol, 1.1 eq) and $NaHCO_3$ (26 mg, 0.31 mmol, 3 eq) in DME/H_2O (2 ml/0.6 ml) was degassed *via* three freeze/pump/thaw cycles. $Pd(PPh_3)_4$ was added and the reaction stirred at 85 °C for 2 h before cooling to room temperature. The DME was removed under reduced pressure and the aqueous extracted with EtOAC (x 3), the

combined organics were washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography ([5:3:2] pet. ether/$CHCl_3$/EtOAc) afforded the title compound as a pale yellow oil (23 mg, 0.04 mmol, 37%). ν_{max} (ATR) 1715 (C=O), 1685, 1304, 1270, 1087, 1055, 921, 829, 729, 697 cm^{-1}. δ_H (700 MHz) 2.20 (1H, m, 4-H*H*), 2.36 (6H, s, 2 x CH_3), 2.49-2.60 (2H, m, 4-*H*H, 5-H*H*), 3.06 (1H, m, 5-*H*H), 5.16-5.26 (3H, m, 2-*H*, OCH_2), 6.45 (1H, d, J = 8 Hz, 9-*H*), 6.98 (1H, s, 4'-*H*), 7.13 (2H, s, 2'-*H*), 7.21 (1H, dd, J = 8 Hz, $^4J_{HH}$ = 2 Hz, 8-*H*), 7.28-7.43 (10H, m), 7.51 (2H, t, J = 8 Hz, 4''-*H*), 7.70-7.88 (4H, m, 2''-*H*, 6''-*H*). δ_C (176 MHz) 21.6 (2 x CH_3), 27.3 (*C*-4), 29.4 (*C*-5), 68.1 (O-CH_2), 108.3 (d, J = 9 Hz, *C*-3), 125.3 (*C*-2'), 125.6 (*C*-8), 127.5 (Ar*C*-H), 127.8 (*C*-9), 128.4 (Ar*C*-H), 128.5 (Ar*C*-H), 128.6 (Ar*C*-H), 128.8 (d, J = 13 Hz, *C*-3''), 129.2 (*C*-4'), 131.0 (*C*), 132.0 (d, J = 11 Hz, *C*-2''), 132.5 (*C*-4''), 136.3 (*C*), 138.0 (*C*), 138.4 (*C*-3'), 139.5 (*C*), 140.7 (*C*), 140.8 (*C*), 141.6 (*C*-7), 154.4 (*C*=O). δ_P (283 MHz) 29.2. *m/z* (ES^+) 600.3 (MH^+), 622.4 (MNa^+). HRMS (ES^+) found MH^+ 600.2309, $C_{38}H_{35}O_4NP$ requires M^+ 600.2298.

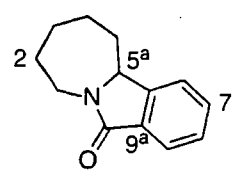
N-tert-Butyloxycarbonyl-2-[2'-(methoxycarbonyl)phenyl]azepane **127**



A flask containing 10% Pd/C (34 mg, 15% *w/w*) was purged with argon and a solution of **4h** (0.05 M, 172 mg, 0.52 mmol, 1 eq) in EtOH (10 ml) was introduced. The flask was evacuated and backfilled with hydrogen (x 3) then placed under a positive pressure of hydrogen with stirring. After 20 h the reaction flask was purged with argon and the reaction mixture was filtered through a pad of celite and washed through with EtOAc (x 3). The combined organics were concentrated under reduced pressure

affording a clear oil with no need for further purification (168 mg, 0.50 mmol, 97%). ν_{max} (ATR) 2926, 1719 (C=O), 1687 (C=O), 1397, 1253, 1157, 1075, 754 cm^{-1}. δ_H (700 MHz) 1.14 (9H, s, C(CH_3)$_3$), 1.29 (1H, m , 6-H*H*), 1.46-1.61 (3H, m, 3-H*H*, 4-H*H*, 5-H*H*), 1.78-1.94 (2H, m, 5-*H*H, 6-*H*H), 2.00 (1H, m, 4-*H*H), 2.31 (1H, m, 3-*H*H), 3.21 (1H, m, 7-H*H*), 3.87 (3H, s, OCH_3), 4.35 (1H, dd, J = 15 Hz, J = 6 Hz, 7-*H*H), 5.61 (1H, dd, J = 12 Hz, J = 5 Hz, 2-*H*), 7.23 (1H, t, J = 8 Hz, 4'-*H*), 7.28 (1H, d, J = 8 Hz, 6'-*H*), 7.43 (1H, t, J = 8 Hz, 5'-*H*), 7.83 (1H, d, J = 8 Hz, 3'-*H*). δ_C (176 MHz) 28.0 (*C*-4), 28.2 (C(CH_3)$_3$), 29.6 (*C*-6), 31.3 (*C*-5), 36.1 (*C*-3), 44.3 (*C*-7), 52.1 (O-CH_3), 58.9 (*C*-2), 79.5 (C(CH$_3$)$_3$), 152.6 (*C*-6'), 126.2 (*C*-4'), 127.4 (*C*-2'), 130.4 (*C*-3'), 132.6 (*C*-5'), 149.2 (*C*-1'), 156.1 (N*C*=O), 167.9 (O*C*=O). *m/z* (ES^+) 234.3 (MH^+ – Boc), 278.1 (MH^+ - ^{t}Bu), 334.1 (MH^+), 356.3 (MNa^+), 689.0 ($2MNa^+$). HRMS (ES^+) found MH^+ 334.2013, $C_{19}H_{28}NO_4$ requires M^+ 334.2013, found MNa^+ 356.1831, $C_{19}H_{27}NO_4Na$ requires M^+ 356.18323.

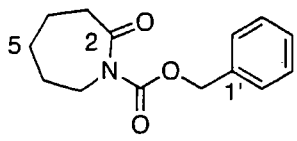
1,2,3,4,5,5^a-Hexahydro-5H-azepino[2,1-a]isoindol-10-one **126**



To a flask containing **127** (148 mg, 0.44 mmol, 1 eq) was added a 20% *v/v* solution of TFA/DCM (4 ml) and the reaction mixture stirred for 30 min. The reaction was quenched with H_2O and the aqueous phase extracted into DCM (x 3). The combined organics were washed with H_2O then brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography ([7:3], [100:0] pet. ether/EtOAc) afforded the title compound as a clear oil (80 mg, 0.40 mmol, 99%). mp. 46-49 °C. ν_{max} (ATR) 2923, 2851, 1674 (C=O), 1467, 1402, 1236, 1092, 1011, 757, 724, 689 cm^{-1}. δ_H (500 MHz) 1.52 (1H, m, 4-H*H*), 1.54-1.64 (2H, m, 3-H*H*, 4-*H*H), 1.70-

1.82 (3H, m, 2-H*H*, 3-*H*H, 5-H*H*), 1.94 (1H, m, 2-*H*H), 2.28 (1H, m, 5-*H*H), 3.44 (1H, m, 1-H*H*), 3.96 (1H, m, 1-*H*H), 4.60 (1H, m, 5^a-*H*), 7.39 (1H, d, J = 8 Hz, 6-*H*), 7.43 (1H, t, J = 8 Hz, 8-*H*), 7.52 (1H, t, J = 8 Hz, 7-*H*), 7.81 (1H, d, J = 8 Hz, 9-*H*). δ_C (125 MHz) 26.4 (*C*-4), 27.2 (*C*-2), 29.7 (*C*-3), 34.8 (*C*-5), 43.7 (*C*-1), 61.7 (*C*-5^a), 122.2 (*C*-6), 123.3 (*C*-9), 128.2 (*C*-8), 131.5 (*C*-7), 132.8 (*C*-9^a), 146.5 (*C*-5^b), 168.9 (*C*=O). *m/z* (ES^+) 202.1 (MH^+), 403.2 ($2MH^+$), 425.2 ($2MNa^+$). HRMS (ES^+) found MH^+ 202.1226, $C_{13}H_{16}NO$ requires M^+ 202.1226.

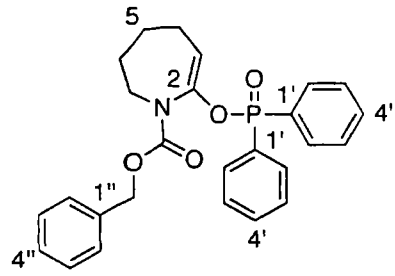
N-(Benzyloxycarbonyl)-2-oxo-azepane **129**



To a cold (-78 °C) solution of caprolactam (0.44 M, 2.00 g, 17.66 mmol) in dry THF (40 ml) was added *n*-BuLi (2.5 M, 9.2 ml, 22.97 mmol) dropwise *via* a syringe and the reaction mixture allowed to stir at -78 °C. After 30 min benzyl chloroformate was added slowly (6.03 g, 5.04 ml, 18.73 mmol) and the resulting reaction mixture allowed to stir for 1 h before warming to room temperature. The reaction was quenched with aq. NH_4Cl, concentrated and extracted with EtOAc (3 x). The organic phase was washed with brine (3 x), aq. $NaHCO_3$ (3 x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography ([4:1] DCM/EtOAc) afforded the title compound as a clear oil (2.25 g, 9.11 mmol, 52%). ν_{max} (ATR) 2932, 1767 (CH_2C=O), 1707 (O=C-O), 1378, 1264, 1163, 1014, 959, 736, 696 cm^{-1}. δ_H (500 MHz) 1.70-1.81 (6H, m, 4-H_2, 5-H_2, 6-H_2), 2.69 (2H, m, 3-H_2), 3.85 (2H, m, 7-H_2), 5.28 (2H, s, CO_2CH_2), 7.28-7.39 (3H, m, 3'-*H*, 4'-*H*), 7.43 (2H, m, 2'-*H*), 7.37-7.42. δ_C (125 MHz) 23.7, 28.9 and 29.4 (*C*-4, *C*-5, *C*-6), 39.7 (*C*-3), 46.6 (*C*-7), 68.8 (CO_2CH_2), 128.1, 128.4 and 128.8 (3 x Ar*C*-H), 135.8 (*C*-1'), 154.5 (O*C*=O), 175.9 (*C*-2). *m/z* (ES^+) 270.2 (MNa^+),

517.0 ($2MNa^+$). HRMS (ES^+) found MNa^+ 270.1101, $C_{14}H_{17}NO_3Na$ requires M^+ 270.1101.

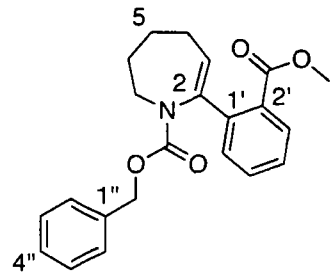
N-(Benzyloxycarbonyl)-4,5,6,7-tetrahydro-1H-azepin-2-yl diphenylphosphinate **130**



NaHMDS Protocol for phosphinate formation:

Purification by flash chromatography ([4:1] DCM/EtOAc) and recrystallisation ([9:1] pet. ether/EtOAc) afforded the title compound as a crystalline solid (1.13 g, 2.53 mmol, 58%). mp. 83-85 °C. Found; C, 69.55; H, 5.81; N, 3.18%; Calc. for $C_{26}H_{26}NO_4P$; C, 69.79; H, 5.86; N, 3.13%. ν_{max} (ATR) 2936, 1701 (C=O), 1672 (enol ether), 1441, 1395, 1345, 1327, 1285, 1241, 1168, 1121, 1057, 1016, 886, 763, 728, 694 cm^{-1}. δ_H (700 MHz) 1.29-1.55 (2H, broad, 5-H_2), 1.61 (2H, m, 6-H_2), 1.98 (2H, m, 4-H_2), 3.00-3.20 (2H, broad, 7-H_2), 5.00-5.20 (2H, m, OCH_2), 5.39-5.51 (1H, m, 3-*H*), 7.25-7.45 (9H, m, 9 x Ar-*H*), 7.49 (2H, t, J = 7 Hz, 4'-*H*), 7.63-7.97 (4H, m, 4 x Ar-*H*). δ_C (176 MHz) 24.2 (*C*-5), 24.7 (*C*-4), 29.4 (*C*-6), 47.1 (*C*-7), 67.6 (O*C*H_2), 110.9 (*C*-3), 128.2 (Ar*C*-H), 128.3 (Ar*C*-H), 128.6 (d, J = 13 Hz, *C*-3'), 128.7 (Ar*C*-H), 132.0 (d, J = 10 Hz, *C*-2'), 132.5 (*C*-4'), 136.5 (*C*-1'), 144.2 (*C*-2), 151.3 (*C*-1"), 154.1 (*C*=O). δ_P (283 MHz) 29.0. *m/z* (ES^+) 448.3 (MH^+), 917.3 ($2MNa^+$).

N-Benzyloxycarbonyl-2-(2'-methylbenzoate)-4,5,6,7-tetrahydro-azepane **131**



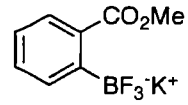
Suzuki protocol A (boronic acid):

The same protocol was employed except that the reaction mixture was stirred at 95 °C for 18 h during which time the catalyst decomposes. Purification by flash chromatography ([8:2], [6:4] pet. ether/EtOAc) afforded the title compound as a colourless oil (81 mg 0.22 mmol, 20%).

Suzuki protocol A (trifluoroborate salt):

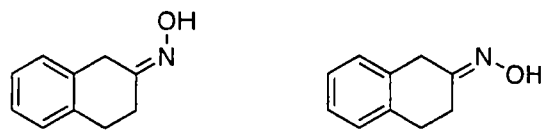
The same protocol was employed except that the reaction mixture was stirred at 85 °C for 3 h. Purification by flash chromatography ([8:2], [6:4] pet. ether/EtOAc) afforded the title compound as a colourless oil (71 mg 0.20 mmol, 58%). ν_{max} (ATR) 2930, 1726 (C=O), 1698 (C=O), 1398, 1254, 1162, 1112, 1085, 1022, 757, 696 cm-1. δ_H (700 MHz) 1.64 (2H, m, 5-*H*$_2$), 1.85 (2H, t, J = 6 Hz, 6-*H*$_2$), 2.30 (2H, q, J = 6 Hz, 4-*H*$_2$), 3.70 (2H, broad, 7-*H*$_2$), 3.79 (3H, s, C*H*$_3$), 4.82 (2H, s, OC*H*$_2$), 5.66 (1H, t, J = 6 Hz, 3-*H*), 6.68 (2H, d, J = 8 Hz, 2"-*H*, 6"*H*), 7.11 (2H, t, J = 8 Hz, 3"-*H*, 5"-*H*), 7.16 (1H, t, J = 8 Hz, 4"-*H*), 7.22-7.36 (3H, m, 3 x Ar-*H*), 7.38 (1H, d, J = 8 Hz, 6'-*H*). δ_C (176 MHz) 23.8 (*C*-5), 28.2 (*C*-4), 28.3 (*C*-6), 50.6 (*C*-7), 52.5 (*C*H$_3$), 67.6 (O*C*H$_2$), 124.8 (*C*-3), 127.3 (Ar*C*-H), 127.7 (*C*-4"), 127.9 (*C*-2"), 128.2 (*C*-3"), 128.3 (*C*-6'), 129.4 (Ar*C*-H), 130.60 (Ar*C*-H), 130.64 (C-2'), 136.1 (*C*-1"), 139.5 (*C*-1'), 142.5 (C-2), 154.8 (N*C*=O), 170.0 (*C*O$_2$Me). *m/z* (ES$^+$) 366.3 (MH$^+$), 753.6 (2MNa$^+$). HRMS (ES$^+$) found MNa$^+$ 388.1518, $C_{22}H_{23}NO_4Na$ requires 388.1519.

Methyl 2-(potassiumtrifluoroborate)benzoate **139**



To a solution of boronic acid (0.52 M, 944 mg, 5.24 mmol, 1 eq) in MeOH (10 ml) was added a saturated solution of aq. KHF_2 (2 ml) and the reaction mixture stirred for 15 min. The precipitate was collected by filtration and washed with cold MeOH (0 °C). Recrystallisation from MeCN afforded the title compound as white needle crystals (955 mg, 3.95 mmol, 75%). mp. 284-285 °C. ν_{max} (ATR) 1704 (C=O), 1436, 1297, 1253, 1182, 1138, 1087, 944 cm^{-1}. δ_H (700 MHz, $(CD_3)_2SO$) 3.64 (3H, s, OCH_3), 7.08 (1H, dt, J = 8 Hz, $^4J_{HH}$ = 1 Hz, Ar-*H*), 7.15 (1H, d, J = 8 Hz, Ar-*H*), 7.19 (1H, t, J = 8 Hz, Ar-*H*), 7.43 (1H, d, J = 8 Hz, Ar-*H*). δ_C (125 MHz, $(CD_3)_2SO$) 51.9 (CH_3), 125.5 (Ar*C*), 126.4 (Ar*C*), 128.9 (Ar*C*), 133.3 (Ar*C*), 133.4 (Ar*C*), 137.3 (Ar*C*), 172.9 (*C*=O). δ_B (225 MHz, $(CD_3)_2SO$) 2.5. δ_F (658 MHz, $(CD_3)_2SO$) -137.4. *m/z* (ES^-) 203.0 ($M\text{-}K^-$).

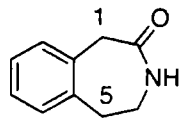
(*Z*/*E*)-3,4-Dihydronaphthalen-2(1H)-one oxime **143/144**

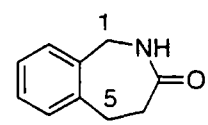


To a solution of *β*-tetralone (1.5 M, 1.72 g, 11.76 mmol, 1 eq) in EtOH (8 ml) was added a solution of $NH_2OH.HCl$ (1.43 g, 20.60 mmol, 1.75 eq) and NaOAc (0.97 g, 11.77 mmol, 1 eq) in water (6 ml). The reaction mixture was stirred at 85 °C for 30 min then cooled to room temperature. The EtOH was removed under reduced pressure and the aqueous phase extracted with EtOAc (x 3), the combined organics were washed with H_2O then brine, dried over $MgSO_4$ and concentrated to give a red oil. Purification by flash chromatography ([9:1], [8:2] pet. ether/EtOAc) afforded a mixture of the title

compounds as a pale yellow oil (1.79 g, 11.12 mmol, 94%). δ_H (400 MHz) 2.50 (2H, t, J = 6 Hz, C*H*$_2$), 2.65 (2H, t, J = 6 Hz, C*H*$_2$), 2.72-2.84 (4H, m, 2 x C*H*$_2$), 3.46 (2H, s, C*H*$_2$), 3.76 (2H, s, C*H*$_2$), 6.99-7.15 (8H, m, 8 x Ar-*H*), 9.08-9.71 (2H, broad, 2 x O-*H*). LCMS, 1 peak (R_t = 2.14 min), *m/z* (ES^+) 162.1 (MH^+), 203.1 ($MHMeCN^+$).

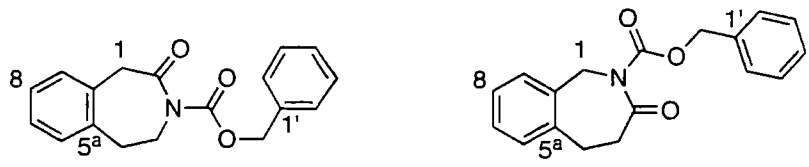
1,3,4,5-Tetrahydro-2H-3-benzazepin-2-one **145** and 1,2,4,5-tetrahydro-3H-2-benzazepin-3-one **146**





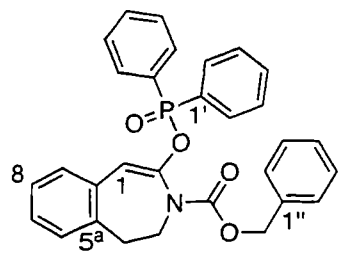
A 1:1 mixture of oximes **143** and **144** (1.13 g, 7.02 mmol, 1 eq) and polyphosphoric acid (11 g, 10 x *w/w*) was heated at 100 °C for 10 min with stirring (glass rod). Crushed ice was added and the mixture allowed to cool to room temperature. The aqueous phase was extracted with DCM (x 3) and the combined organics washed with H_2O, aq. $NaHCO_3$, H_2O and brine then dried over $MgSO_4$ and concentrated affording a mixture of the title compounds as a brown solid (752 mg, 4.67 mmol, 66%). The crude material is unstable to chromatography. ν_{max} (ATR) 3199 (N-H), 3056, 2895, 1666 (C=O), 1476, 1447, 1405, 1160, 743 cm^{-1}. δ_H (300 MHz) 2.78 (2H, t, J = 7 Hz, C*H*$_2$), 3.04-3.16 (4H, m, 2 x C*H*$_2$), 3.55 (2H, q, J = 7 Hz, 4-*H*$_2$ isomer **A**), 3.83 (2H, s, 1-*H*$_2$ isomer **A**), 4.34 (2H, d, J = 6 Hz, 1-*H*$_2$ isomer **B**), 7.01-7.30 (8H, m, 8 x Ar-*H*). *m/z* (ES^+) 162.2 (MH^+), 184.2 (MNa^+).

N-Benzyloxycarbonyl 2-oxo-1,2,4,5-tetrahydro-3H-3-benzazepine **147** and N-benzyloxycarbonyl 3-oxo-1,3,4,5-tetrahydro-2H-2-benzazepine **148**



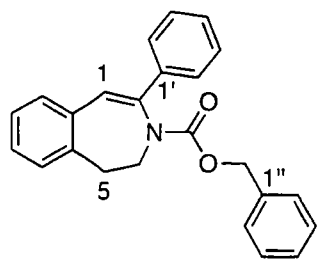
To a cold (-78 °C) solution of **145** and **146** (0.2 M, 447 mg, 2.78 mmol, 1 eq) in dry THF (14 ml) was added LDA (1.7 ml, 3.05 mmol, 1.1 eq) dropwise and the reaction mixture stirred for 30 min. Benzyl chloroformate (0.79 ml, 5.55 mmol, 2 eq) was added as a cold solution in dry THF (4 ml) and the reaction mixture stirred for 1 h before warming to room temperature and quenching with H_2O. The THF was removed under reduced pressure and the aqueous phase extracted with EtOAc (x 3). The combined organics were washed with aq. NH_4Cl, aq. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and concentrated to give a dark brown oil. Purification by flash chromatography ([8:2] pet. ether/EtOAc) afforded the mixture of two isomers as a light brown oil (350 mg, 1.19 mmol, 43%). δ_H (400 MHz) 3.10 (2H, t, J = 6 Hz, C*H*$_2$), 3.18-3.33 (4H, m, 2 x C*H*$_2$), 4.05 (2H, s, C*H*$_2$), 4.29 (2H, t, J = 6 Hz, C*H*$_2$), 5.02 (2H, s, C*H*$_2$), 5.25 (2H, s, C*H*$_2$), 5.29 (2H, s, C*H*$_2$), 7.04-7.47 (18H, m, 18 x Ar-*H*). LCMS, 1 peak (R_t = 5.41 min), *m/z* (ES^+) 296.2 (MH^+), 359.2 ($MNaMeCN^+$), 613.4 ($2MNa^+$).

N-Benzyloxycarbonyl 2-[(diphenylphosphoryl)oxy]-4,5-dihydro-3H-3-benzazepine **149**



To a [1:1] mixture of lactam isomers **147** and **148** (0.2 M, 329 mg, 1.12 mmol, 1 eq) in dry THF (5.5 ml) at -78 °C was added NaHMDS (1 M, 1.3 ml, 1.33 mmol, 1.2 eq) *via* syringe. The reaction mixture was stirred at -78 °C for 1 h, diphenylphosphonic chloride (0.23 ml, 1.23 mmol, 1.2 eq) was then added dropwise *via* syringe and the reaction mixture was stirred for an additional 2 h. The reaction mixture was allowed to warm to room temperature, H_2O added and the THF removed under reduced pressure. The aqueous phase was extracted with EtOAc (x 3) and the combined organics washed with brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography ([65:35] pet. ether/EtOAc) afforded the title compound as a light yellow oil (250 mg, 0.51 mmol, 45%). δ_H (200 MHz) 2.82 (2H, t, J = 7 Hz, 4-*H*$_2$), 3.55 (2H, t, J = 7 Hz, 5-*H*$_2$), 5.11 (2H, s, PhC*H*$_2$), 6.26 (1H, d, $^4J_{HP}$ = 2 Hz, 1-*H*), 7.01-7.22 (5H, m, 5 x Ar-*H*), 7.22-7.60 (10H, m, 10 x Ar-*H*), 7.73-7.93 (4H, m, 4 x Ar-*H*). δ_P (81 MHz) 31.4. *m/z* (ES^+) 496.3 (MH^+), 1008.5 ($2MH_2O^+$), 1014 ($2MHNa^+$).

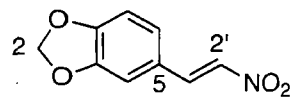
N-Benzyloxycarbonyl 2-phenyl-4,5-dihydro-3H-3-benzazepine **154**



A solution of phosphinate **149** (73 mg, 0.15 mmol, 1 eq), LiCl (31 mg, 0.73 mmol, 5 eq), $PdCl_2(PPh_3)_2$ (5 mg, 7 x 10^{-6} mol, 0.05 eq) and Bu_3SnPh (0.07 M, 0.15 mmol, 1 eq) in dry THF (2 ml) was degassed by three freeze/pump/thaw cycles. The reaction mixture was heated at reflux for 24 h before cooling to room temperature. A saturated aqueous solution of KF (1 ml) was added and the mixture stirred for 1 h. The mixture was filtered and the filtrate extracted with EtOAc (x 3). The combined organics were washed with

H_2O, dried over $MgSO_4$ and concentrated. Purification by flash chromatography ([9:1] pet. ether/EtOAc) afforded the title compound as a white solid (13 mg, 3.7×10^{-5} mol, 25%). mp. 122-123 °C. ν_{max} (ATR) 1694 (C=O), 1627, 1447, 1399, 1338, 1268, 1232, 1104, 997, 800, 762, 696 cm^{-1}. δ_H (700 MHz) 3.24 (2H, t, J = 6 Hz, C*H*$_2$), 4.06 (2H, t, J = 6 Hz, C*H*$_2$), 4.88 (2H, broad, PhC*H*$_2$), 6.44 (1H, s, 1-*H*), 6.56-6.74 (2H, broad, 2 x Ar-*H*), 7.08-7.16 (3H, broad, 3 x Ar-*H*), 7.17 (1H, dt, J = 7 Hz, $^4J_{HH}$ = 1 Hz, 7-*H*), 7.21 (1H, t, J = 7 Hz, 8-*H*), 7.23-7.28 (3H, m, 6-*H*, 9-*H*, 3 x Ar-*H*), 7.29-7.36 (3H, m, 3'-*H*, 5'-*H*, 4'-*H*), 7.47 (2H, d, J = 7 Hz, 2'-*H*, 6'-*H*). δ_C (176 MHz) 36.4 (*C*-5), 48.6 (*C*-4), 67.7 (Ph*C*H$_2$), 121.7 (*C*-1), 125.9 (*C*-2'), 126.5 (*C*-8), 127.2 (*C*-7), 127.7 (Ar*C*), 127.8 (Ar*C*), 128.0 (*C*-4'), 128.3 (Ar*C*), 128.7 (*C*-3'), 130.6 (*C*-6), 132.3 (*C*-9), 134.4 (*C*-9[a]), 136.0 (*C*-1''), 138.1 (*C*-5[a]), 140.3 (*C*-1'), 141.0 (*C*-2), 152.0 (*C*=O). *m/z* (ES^+) 356.3 (MH^+), 378.3 (MNa^+), 733.0 ($2MNa^+$). HRMS (ES^+) found MH^+ 356.1647, $C_{24}H_{22}NO_2$ requires 356.1645, found MNa^+ 378.1465, $C_{24}H_{21}NO_2Na$ requires 378.1465.

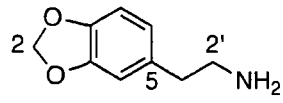
5-[(E)-2'-nitrovinyl]-1,3-benzodioxole **160**



A mixture of piperonal (3.00 g, 19.98 mmol, 1 eq), nitromethane (13 ml, 0.24 mol, 12 eq), ammonium acetate (3.32 g, 43.07 mmol, 2.2 eq) and acetic acid (3.3 ml, 57.65 mmol, 3 eq) was sonicated for 3 h at room temperature. The excess nitromethane was removed under reduced pressure and the residue partitioned between DCM and H_2O. The aqueous was extracted with DCM and the combined organics washed with H_2O (x 3) and brine (x 3), dried over $MgSO_4$ and concentrated. Recrystallisation from EtOH afforded the title compound as an off-white precipitate (2.62 g, 13.75 mmol, 69%). mp. 152-154 °C. Found; C, 55.72; H, 3.81; N, 7.05%; Calc. for $C_9H_7NO_4$; C, 55.96; H, 3.65; N, 7.25%. ν_{max} (ATR) 1628 (C=C), 1603, 1493 (NO_2),

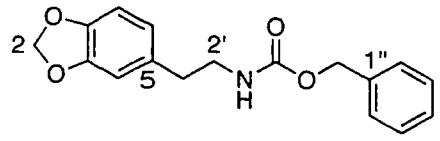
1455, 1333 (NO_2), 1267, 1104, 1034, 967, 923, 814 cm^{-1}. δ_H (500 MHz) 6.06 (2H, s, 2-*H*$_2$), 6.87 (1H, d, J = 8 Hz, 7-*H*), 7.00 (1H, d, $^4J_{HH}$ = 2 Hz, 4-*H*), 7.08 (1H, dd, J = 8 Hz, $^4J_{HH}$ = 2 Hz, 6-*H*), 7.47 (1H, d, J = 14 Hz, 2'-*H*), 7.92 (1H, d, J = 14 Hz, 1'-*H*). δ_C (125 MHz) 102.3 (*C*-2), 107.2 (*C*-4), 109.3 (*C*-7), 124.4 (*C*-5), 126.9 (*C*-6), 135.6 (*C*-2'), 139.4 (*C*-1'), 149.0 (*C*-3^a), 151.6 (*C*-7^a). GCMS, 1 peak (R_t = 19.20min), *m/z* (EI) 193.0 (M^+), 146.0 (M-NO_2^+).

2-(1,3-Benzodioxol-5-yl)ethanamine **158**[ref]



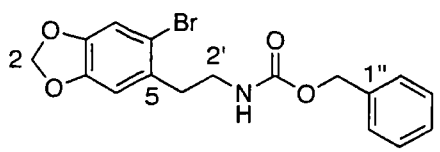
To a cold (0 °C) solution of $LiAlH_4$ (4.0 M, 597 mg, 15.73 mmol, 4 eq) in dry THF (4 ml) was slowly added a solution of nitroalkene **160** (759 mg, 3.93 mmol, 1 eq) in dry THF (30 ml). The reaction was stirred at reflux for 5 h before being cooled to room temperature then to 0 °C, 3 M aq. NaOH (1.5 ml) was added then H_2O (2 ml) then EtOAc (100 ml) and the mixture allowed to stir for 30 min. The mixture was filtered through celite and the layers separated, the organic layer was dried over $MgSO_4$ and concentrated affording the title compound as a yellow oil without the need for purification (630 mg, 3.82 mmol, 97%). ν_{max} (ATR) 2894, 1501, 1486, 1440, 1242, 1035, 926, 807 cm^{-1}. δ_H (500 MHz) 2.66 (2H, t, J = 7 Hz, 1'-*H*$_2$), 2.92 (2H, t, J = 7 Hz, 2'-*H*$_2$), 5.93 (2H, s, 2-*H*$_2$), 6.64 (1H, dt, J = 8 Hz, $^4J_{HH}$ = 2 Hz, Ar-*H*), 6.69 (1H, d, $^4J_{HH}$ = 2 Hz, 4-*H*), 6.74 (1H, d, J = 8 Hz, Ar-*H*). δ_C (125 MHz) 40.0 (*C*-1'), 43.9 (*C*-2'), 101.1 (*C*-2), 108.5 (*C*-7), 109.4, 121.9 (*C*-4, *C*-6), 133.8 (*C*-5), 146.1, 147.9 (*C*-7^a, *C*-3^a). *m/z* (ES^+) 149.1 (M–NH_2^+), 166.1 (MH^+), 207.1 ($MMeCN^+$).

Benzyl [2-(1,3-benzodioxol-5-yl)ethyl]carbamate **161**



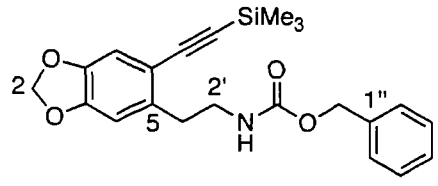
To a cold (0 °C) solution of amine **160** (1.0 M, 632 mg, 3.83 mmol, 1 eq) and NEt_3 (0.59 ml, 4.21 mmol, 1.1 eq) in dry THF (3.8 ml) was added a cold (0 °C) solution of benzyl chloroformate (1.1 ml, 7.66 mmol, 2 eq) *via* cannula. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with H_2O and the organics removed under reduced pressure. The aqueous phase was extracted with EtOAc (x 3) and the combined organics washed with H_2O then brine, dried over $MgSO_4$and concentrated. Purification by flash chromatography ([9:1], [8:2] pet. ether/EtOAc) afforded the title compound as an off-white solid (585 mg, 1.96 mmol, 51%). mp. 72-74 °C. ν_{max} (ATR) 3321 (N-H), 3063, 2889, 1680 (C=O), 1541, 1495, 1444, 1243, 1189, 1033, 925 cm^{-1}. δ_H (500 MHz) 2.74 (2H, t, J = 7 Hz, 1'-*H*$_2$), 3.42 (2H, q, J = 7 Hz, 2'-*H*$_2$), 4.77 (1H, broad, NH), 5.10 (2H, s, PhC*H*$_2$), 5.93 (2H, s, 2-*H*$_2$), 6.62 (1H, d, J = 8 Hz, 6-*H*), 6.68 (1H, s, 4-*H*), 6.74 (1H, d, J = 8 Hz, 7-*H*), 7.28-7.41 (5H, m, Ar-*H*). δ_C (125 MHz) 36.0 (*C*-1'), 42.6 (*C*-2'), 66.9 (Ph*C*H$_2$), 101.1 (*C*-2), 108.6 (*C*-7), 109.3 (*C*-4), 121.9 (*C*-6), 127.2 (Ar*C*), 128.4 (Ar*C*), 128.8 (Ar*C*), 132.7 (*C*-5), 136.8 (*C*-1"), 146.4, 148.1 (*C*-7^a, *C*-3^a), 156.5 (*C*=O). *m/z* (ES^+) 300.1 (MH^+), 322.1 (MNa^+). HRMS (ES^+) found MH^+ 300.1232, $C_{17}H_{18}NO_4$ requires 300.1230.

Benzyl [2-(6-bromo-1,3-benzodioxol-5-yl)ethyl]carbamate **162**



To a cold (0 °C) solution of amide **161** (0.32 M, 450 mg, 1.51 mmol, 1 eq) in dry DCM (5 ml) was added a cold (0 °C) solution of N-bromosuccinamide (295 mg, 1.66 mmol, 1.1 eq) in dry DCM (5 ml) *via* cannula. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with H_2O and extracted with EtOAc/toluene [1:1] (5 x 20 ml) and the combined organics washed with water (5 x 20 ml), dried over $MgSO_4$ and concentrated. Purification by flash chromatography ([8:2] pet. ether/EtOAc) afforded the title compound as an off-white crystalline solid (403 mg, 1.06 mmol, 71%). mp. 80-82 °C. Found; C, 54.22; H, 4.31; N, 3.71%; Calc. for $C_{17}H_{16}NO_4Br$; C, 53.99; H, 4.26; N, 3.70%. ν_{max} (ATR) 3420 (N-H), 3336 (N-H), 2948, 2896, 1702 (C=O), 1503, 1477, 1231, 1115, 1037, 933 cm^{-1}. δ_H (500 MHz) 2.88 (2H, t, J = 7 Hz, 1'-*H*$_2$), 3.42 (2H, q, J = 7 Hz, 2'-*H*$_2$), 4.83 (1H, broad, NH), 5.14 (2H, s, PhC*H*$_2$), 5.96 (2H, s, 2-*H*$_2$), 6.70 (1H, s, 4-*H*), 6.99 (1H, s, 7-*H*), 7.29-7.40 (5H, m, Ar-*H*). δ_C (125 MHz) 36.4 (*C*-1'), 41.2 (*C*-2'), 66.9 (Ph*C*H$_2$), 101.9 (*C*-2), 110.7 (*C*-4), 113.1 (*C*-7), 114.8 (*C*-6), 128.4, 128.8 (Ar*C*), 131.3 (*C*-5), 136.8 (*C*-1"), 147.4, 147.7 (*C*-7^a, *C*-3^a), 156.6 (*C*=O). *m/z* (ES^+) 378.1/380.1 [1:1] (MH^+ Br^{79}:Br^{81}). HRMS (ES^+) found MH^+ 378.0337, $C_{17}H_{17}NO_4Br^{79}$ requires M^+ 378.0336, found NNa^+ 596.0603, $C_{30}H_{25}NO_4PBr^{79}Na$ requires M^+ 596.0597.

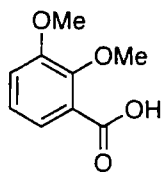
Benzyl (2-{6-[(trimethylsilyl)ethynyl]-1,3-benzodioxol-5-yl}ethyl)carbamate **181**



Aryl bromide **162** (203 mg, 0.54 mmol, 1 eq), $PdCl_2$ (5 mg, 0.03 mmol, 0.05 eq), PPh_3 (35 mg, 0.13 mmol, 0.25 eq) and $Cu(OAc)_2$ (5 mg, 0.03 mmol, 0.05 eq) were degassed by three freeze/pump/thaw cycles. To this was added NEt_3 (3 ml) that had been

degassed by three freeze/pump/thaw cycles and trimethylsilyl acetylene (63 mg, 0.64 mmol, 1.2 eq). The reaction mixture was stirred at reflux for 18 h then cooled to room temperature and the NEt_3 removed under reduced pressure. The residue was taken into DCM, filtered through a pad of silica gel and washed through with DCM (x 3) and the combined filtrates concentrated. Purification by flash chromatography ([8:2] hexanes/EtOAc) afforded the title compound as a brown oil (60 mg, 0.15 mmol, 28%). δ_H (400 MHz) 0.25 (9H, s, $SiMe_3$) 2.94 (2H, t, J = 7 Hz, 1'-H_2), 3.49 (2H, q, J = 7 Hz, 2'-H_2), 4.83 (1H, broad, NH), 5.11 (2H, s, PhCH_2), 5.96 (2H, s, 2-H_2), 6.67 (1H, s, 4-*H*), 6.90 (1H, s, 7-*H*), 7.29-7.40 (5H, m, Ar-*H*). *m/z* (ES^+) 396.2 (MH^+), 813.3 ($2MNa^+$). Starting material was also recovered (128 mg, 63%).

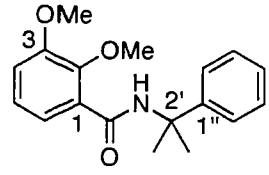
2,3-Dimethoxybenzoic acid **190**



To a solution of methyl-2,3-dimethoxybenzoate (3.78 g, 19.27 mmol, 1 eq) in THF/H_2O ([1:1], 15 ml) was slowly added a solution of LiOH (461 mg, 19.27 mmol, 1 eq) in THF/H_2O ([1:1], 15 ml). The reaction mixture was heated at reflux for 18 h before being cooled to room temperature and the THF removed under reduced pressure. The aqueous phase was extracted with EtOAc (3 x 10 ml) and the combined organics dried over $MgSO_4$ and concentrated affording recovered starting material (792 mg, 4.40 mmol, 21%). The aqueous phase was then cooled to 0 °C, acidified to pH 1 and quickly extracted into EtOAc (3 x 10 ml). The combined organics were dried over $MgSO_4$ and concentrated affording the title compound as a white crystalline solid without the need for purification (2.61 g, 14.34 mmol, 74%). mp. 112-114 °C, lit. 107-109 °C. ν_{max} (ATR) 3200-2400 (O-H), 1681, C=O), 1580, 1481, 1420, 1317, 1263,

1230, 1052, 999, 936 cm^{-1}. δ_H (400 MHz) 3.93 (3H, s, O-CH_3), 4.09 (3H, s, O-CH_3), 7.16 (1H, dd, J = 8 Hz, $^4J_{HH}$ = 2 Hz, Ar-*H*), 7.21 (1H, t, J = 8 Hz, 5-*H*), 7.73 (1H, dd, J = 8 Hz, $^4J_{HH}$ = 2 Hz, Ar-*H*), 11.37 (1H, broad, O*H*). δ_C (100 MHz) 56.4, 62.4, 117.7, 122.4, 124.0, 125.2, 148.5, 152.4, 166.0. *m/z* (ES^-) 181.3 (M^-).

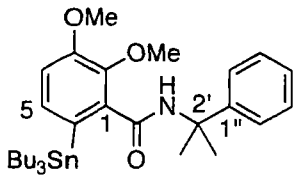
2,3-Dimethoxy-N-(2'-phenylpropan-2-yl)benzamide **192**



To a solution of acid **190** (778 mg, 4.27 mmol, 1 eq) and oxalyl chloride (0.72 ml, 8.55 mmol, 2 eq) in dry DCM (10 ml) was added two drops of DMF and the reaction mixture stirred at room temperature until no more effervescence was observed (approx 15 min). The DCM was removed under reduced pressure and the resulting acid chloride (yellow oil) taken into dry THF (5 ml). To this was slowly added a solution of DMAP (552 mg, 4.52 mmol, 1.1 eq) in dry THF (10 ml) and the reaction mixture stirred for 15 min. Cumylamine (578 mg, 4.27 mmol, 1 eq) was added dropwise and the reaction mixture stirred for 18 h. The precipitate was removed by filtration and the filtrate concentrated to a yellow oil. The crude material was filtered through a pad of silica gel ([6:4] pet. ether/EtOAc) affording the title compound as a yellow oil (1.17 g, 3.91 mmol, 92%). ν_{max} (ATR) 3367 (N-H), 2978, 1666 (C=O), 1578, 1525, 1472, 1263, 1063, 993, 758 cm^{-1}. δ_H (700 MHz) 1.80 (6H, s, 1'-H_3, 3'-H_3), 3.89 (3H, s, 3-OCH_3), 3.93 (3H, s, 2-OCH_3), 7.02 (1H, dd, J = 8 Hz, $^4J_{HH}$ = 1 Hz, 4-*H*), 7.12 (1H, t, J = 8 Hz, 5-*H*), 7.21 (1H, t, J = 8 Hz, 4''-*H*), 7.32 (2H, t, J = 8 Hz, 3''-*H*), 7.45 (2H, d, J = 8 Hz, 2''-*H*), 7.62 (1H, dd, J = 8 Hz, $^4J_{HH}$ = 1 Hz, 6-*H*). 8.41 (1H, s, N-*H*). δ_C (176 MHz) 29.5 (*C*-1', *C*-3'), 55.9 (*C*-2'), 56.3 (3-O*C*H_3), 61.5 (2-O*C*H_3), 115.3 (*C*-4), 123.0 (*C*-6), 124.7 (*C*-5), 125.0 (*C*-2''), 126.8 (*C*-4''), 128.0 (*C*-1), 128.6 (*C*-3''), 147.3, 147.5 (*C*-2, *C*-1''),

152.8 (*C*-3), 163.9 (*C*=O). *m/z* (ES^+) 300.2 (MH^+), 599.4 ($2MH^+$), 621.4 ($2MNa^+$). HRMS (ES^+) found MH^+ 300.1595, $C_{18}H_{22}NO_3$ requires M^+ 300.1594, found NNa^+ 322.1413, $C_{18}H_{21}NO_3Na$ requires M^+ 322.1414.

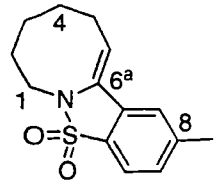
2,3-Dimethoxy-N-(2'-phenylpropan-2-yl)-6-(tributylstannyl)benzamide **193**



To a solution of amide **192** (160 mg, 0.54 mmol, 1 eq) and TMEDA (0.26 ml, 1.71 mmol, 3.2 eq) in freshly distilled THF (5 ml) at -78 °C was slowly added *s*-BuLi (0.6 M, 2.85 ml, 1.71 mmol, 3.2 eq) *via* syringe. The resulting yellow solution was stirred for 2 h at -78 °C and $SnBu_3Cl$ (0.32 ml, 1.18 mmol, 2.2 eq) was added dropwise. The reaction mixture was stirred at -78 °C for 15 min then allowed to warm to room temperature and stirred for 30 min. Saturated $NH_4Cl_{(aq)}$ was added and the THF removed under reduced pressure, the aqueous phase was extracted with EtOAc (x 3) and the combined organics washed with H_2O, dried over $MgSO_4$ and concentrated to a waxy white solid. Purification by flash chromatography ([9:1] pet. ether/EtOAc) afforded the title compound as a pale yellow oil (138 mg, 0.24 mmol, 44%). δ_H (700 MHz) 0.78-0.85 (15H, m, 3 x $SnCH_2$, 3 x CH_2CH_3), 1.23 (6H, sext, J = 8 Hz, CH_2CH_3), 1.38 (6H, quint, J = 8 Hz, $SnCH_2CH_2$), 1.81 (6H, s, 1'-H_3, 3'H_3), 3.89 (3H, s, 3-OCH_3), 3.90 (3H, s, 2-OCH_3), 7.02 (1H, d, J = 8 Hz, 4-*H*), 7.20 (1H, t, J = 8 Hz, 4"-*H*), 7.30 (2H, t, J = 8 Hz, 3"-*H*, 5"-*H*), 7.32 (1H, d, J = 8 Hz, 5-*H*), 7.43 (2H, d, J = 8 Hz, 2"-*H*, 6"-*H*), 8.67 (1H, s, N-*H*). δ_C (176 MHz) 12.3 ($SnCH_2$), 14.0 (CH_2CH_3), 27.7 (CH_2CH_3), 29.2 (*C*-1', *C*-3'), 29.5 ($SnCH_2CH_2$), 56.0 (*C*-2'), 56.2 (3-OCH_3), 61.4 (2-OCH_3), 114.8 (*C*-4), 125.1 (*C*-2"), 126.6 (*C*-4"), 128.4 (*C*-3"), 131.3 (*C*-1), 133.2 (*C*-5), 139.0 (*C*-6), 147.5 (*C*-1"),

148.2 (*C*-2), 152.8 (*C*-3), 165.2 (*C*=O). *m/z* (ES^+) 586.3/588.3/590.3 [1:1.7:2.3] (MH^+ Sn^{116}:Sn^{118}:Sn^{120}), 608.2/610.2/612.2 [1:1.7:2.3] (MNa^+ Sn^{116}:Sn^{118}:Sn^{120}). HRMS (ES^+) found MH^+ 590.2658, $C_{30}H_{48}NO_3Sn^{120}$ requires M^+ 590.2651, found NNa^+ 612.2474, $C_{30}H_{47}NO_3Sn^{120}Na$ requires M^+ 612.2470. Starting material was also recovered (60 mg, 38%).

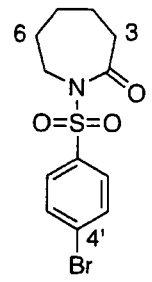
1,2,3,4,5-Quintahydro-8-methylazocine[1,2-b][1,2]benzothiazole-11,11-dioxide **207**



General method for the cyclisation of N-arylsulfonyl lactams:

Purification on a Horizon® column chromatography system ([8:2], [6:4] pet. ether/EtOAc) afforded the title compound as a clear oil (0.09 g, 0.34 mmol, 18%). ν_{max} (KBr) 3029, 2931, 1667, 1610, 1455, 1304, 1181, 1145, 1061, 940 cm^{-1}. δ_H (400 MHz) 1.71 (2H, m, 3-*H*$_2$), 1.79 (2H, m, 4-*H*$_2$), 2.02 (2H, quint, J = 7 Hz, 2-*H*$_2$), 2.46 (3H, s, 8-C*H*$_3$), 2.59 (2H, m, J = 7 Hz, 5-*H*$_2$), 4.02 (2H, t, J = 7 Hz, 1-*H*$_2$), 5.55 (1H, t, J = 9 Hz, 6-*H*), 7.30 (1H, d, J = 8 Hz, 8-*H*), 7.44 (1H, s, 7-*H*), 7.67 (1H, d, J = 8 Hz, 9-*H*). δ_C (100 MHz) 22.3 (8-*C*H$_3$), 22.5 (*C*-3), 23.6 (*C*-5), 28.6 (*C*-4), 30.5 (*C*-2), 40.3 (*C*-1), 100.6 (*C*-6), 120.9 (*C*-7), 121.1 (*C*-10), 128.9 (*C*-10^a), 130.6 (*C*-9), 132.1 (*C*-6^b), 134.0 (*C*-6^a), 143.9 (*C*-8). *m/z* (ES^+) 264.1 (MH^+), 286.1 (MNa^+), 318.1 ($MMeOHNa^+$), 549.3 ($2MNa^+$). HRMS (ES^+) found MH^+ 263.0985, $C_{14}H_{17}NO_2S$ requires M^+ 263.0980.

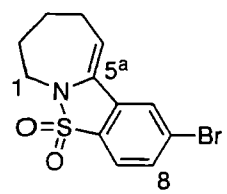
N-([4'-Bromophenyl]sulfonyl)-2-oxoazepane **208**



General method for N-arylsulfonyl protection of lactams:

Purification on the Horizon® automated chromatography system ([85:15], [7:3] cyclohexane/EtOAc) afforded the title compound as a white solid (1.43 g, 4.30 mmol, 49%). mp. 111-113 °C. ν_{max} (ATR) 2931, 2857, 1691 (NC=O), 1574, 1469, 1389, 1338 (SO_2), 1161 (SO_2), 1117, 1084, 1069, 1010, 960, 881, 820, 769, 743 (C-Br), 703 cm^{-1}. δ_H (400 MHz) 1.63-1.76 (4H, m, 4-*H*$_2$, 5-*H*$_2$), 1.76-1.84 (2H, m, 6-*H*$_2$), 2.52 (2H, m, 3-*H*$_2$), 3.99 (2H, m, 7-*H*$_2$), 7.62 (2H, d, J = 9 Hz, 3'-*H*, 5'-*H*), 7.84 (2H, d, J = 9 Hz, 2'-*H*, 6'-*H*). δ_C (100 MHz) 22.9 (*C*-4), 28.9 (*C*-5), 29.6 (*C*-6), 38.9 (*C*-3), 46.9 (*C*-7), 128.6 (*C*-4'), 130.1 (*C*-2'), 131.9 (*C*-3'), 138.7 (*C*-1'), 175.0 (*C*-2). *m/z* (ES^+) 332.2/334.2 [1:1] (MH^+ Br^{79}:Br^{81}). HRMS (ES^+) found MH^+ 331.9953, $C_{12}H_{15}NO_3SBr^{79}$ requires M^+ 331.9951.

1,2,3,4-Tetrahydro-7-bromoazepino[1,2-b][1,2]benzothiazole-10,10-dioxide **209**



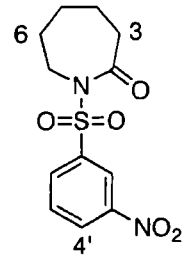
General method for the cyclisation of N-arylsulfonyl lactams:

Purification by flash chromatography ([85:15], [7:3] cyclohexane/EtOAc) afforded the title compound as a white solid (219 mg, 0.70 mmol, 46%). mp. 199-200 °C. Found; C,

46.25; H, 3.96; N, 4.38%; Calc. for $C_{12}H_{12}NO_2SBr$; C, 45.87; H, 3.85; N, 4.38%. ν_{max} (ATR) 2939, 2866, 1661, 1589, 1572, 1455, 1418, 1309, 1229, 1177, 1143, 1073, 1055 cm^{-1}. δ_H (400 MHz) 1.79 (2H, quint, J = 6 Hz, 3-*H*$_2$), 1.98 (2H, m, 2-*H*$_2$), 2.44 (2H, q, J = 6 Hz, 4-*H*$_2$), 3.58 (2H, m, 1-*H*$_2$), 5.79 (1H, t, J = 6 Hz, 5-*H*), 7.58-7.68 (2H, m, 8-*H*, 9-*H*), 7.76 (1H, s, 6-*H*). δ_C (100 MHz) 26.9 (*C*-4), 27.4 (*C*-3), 28.8 (*C*-2), 45.4 (*C*-1), 108.2 (*C*-5), 122.8 (*C*-9), 123.9 (*C*-6), 128.0 (Ar*C*), 130.3 (Ar*C*), 132.6 (*C*-8), 134.0 (*C*-5^b), 134.7 (*C*-5^a). *m/z* (ES^+) 314.2/316.2 (MH^+ Br^{79}:Br^{81}).

Crystal data: $C_{12}H_{12}BrNO_2S$, M = 314.20, orthorhombic, space group P bcn, a = 16.5525(3), b = 10.1393(2), c = 14.0826(3) Å, U = 2363.5(1) $Å^3$, F(000) = 1264, Z = 8, D_c = 1.766 mg m^{-3}, μ = 3.643 mm^{-1} (Mo-Kα, λ = 0.71073 Å), T = 120(1)K. 30330 reflections were collected on a Bruker SMART CCD 6000 diffractometer (ω-scan, 0.3°/frame) yielding 3450 unique data (R_{merg} = 0.0259). The SADABS absorption correction has been applied. The structure was solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL software. All non-hydrogen atoms (except the disordered ones) were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. Final $wR_2(F^2)$ = 0.0724 for all data (190 refined parameters), conventional R (F) = 0.0285 for 3450 reflections with $I \geq 2\sigma$, GOF = 1.145. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC.

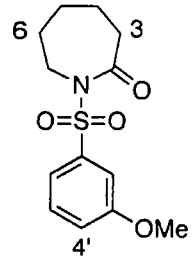
N-([3'-Nitrophenyl]sulfonyl)-2-oxo-azepane **210**



General method for N-arylsulfonyl protection of lactams:

Purification on the Horizon® automated chromatography system ([7:3], [1;1] cyclohexane/EtOAc) afforded the title compound as a white solid (0.20 g, 0.66 mmol, 15%). mp. 126-128 °C. Found; C, 48.28; H, 4.78; N, 9.31%; Calc. for $C_{12}H_{14}N_2O_5S$; C, 48.31; H, 4.73; N, 9.39%. ν_{max} (ATR) 2958, 2872, 1700 (NC=O), 1607, 1537, 1463, 1353 (SO_2), 1179 (SO_2), 1123, 1080 cm^{-1}. δ_H (400 MHz) 1.66-1.81 (4H, m, 4-*H*$_2$, 5-*H*$_2$), 1.81-1.90 (2H, m, 6-*H*$_2$), 2.55 (2H, m, 3-*H*$_2$), 4.06 (2H, m, 7-*H*$_2$), 7.35 (1H, t, J = 8 Hz, 5'-*H*), 8.34 (1H, d, J = 8 Hz, 6'-*H*), 8.43 (1H, d, J = 8 Hz, 4'-*H*), 8.75 (1H, s, 2'-*H*). δ_C (100 MHz) 23.2 (*C*-4), 29.5 (*C*-5), 29.9 (*C*-6), 39.0 (*C*-3), 46.2 (*C*-7), 124.0 (*C*-2'), 128.3 (*C*-4'/6'), 130.4 (*C*-5'), 134.8 (*C*-4'/6'), 142.0 (*C*-1'), 148.3 (*C*-3'), 175.5 (*C*-2). *m/z* (ES^+) 299.2 (MH^+), 316.2 (MH_2O^+), 614.2 ($2MH_2O^+$).

N-([3'-Methoxyphenyl]sulfonyl)-2-oxoazepane **212**

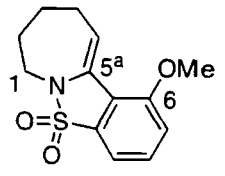


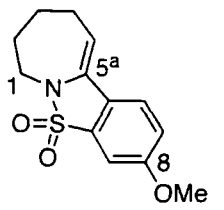
General method for N-arylsulfonyl protection of lactams:

Purification on the Horizon® automated chromatography system ([85:15], [7:3] cyclohexane/EtOAc) afforded the title compund as a clear oil (1.16 g, 4.11 mmol, 46%). ν_{max} (ATR) 2942, 2863, 1698 (NC=O), 1599, 1484, 1465, 1435, 1354 (SO_2), 1254, 1167 (SO_2), 1122, 1090, 1078, 1037, 577, 517 cm^{-1}. δ_H (400 MHz) 1.64-1.79 (4H, m, 4-*H*$_2$, 5-*H*$_2$), 1.85 (2H, m, 6-*H*$_2$), 2.55 (2H, m, 3-*H*$_2$), 3.86 (3H, s, OC*H*$_3$), 4.01 (2H, m, 7-*H*$_2$), 7.12 (1H, ddd, J = 8 Hz, $^4J_{HH}$ = 3 Hz, $^4J_{HH}$ = 1 Hz, 4'-*H*), 7.40 (1H, t, J = 8 Hz, 5'-*H*), 7.53 (2H, m, 2'-*H*, 6'-*H*). δ_C (100 MHz) 23.2 (*C*-4), 29.4 (*C*-5), 29.6 (*C*-6), 39.0 (*C*-3),

46.8 (*C*-7), 55.9 (OCH_3), 113.5 (Ar*C*-H), 120.2 (*C*-4'), 120.4 (Ar*C*-H), 129.9 (*C*-5'), 140.9 (*C*-1'), 159.6 (*C*-3'), 175.1 (*C*-2). *m/z* (ES^+) 284.2 (MH^+), 306.2 (MNa^+), 589.3 ($2MNa^+$). HRMS (ES^+) found MH^+ 284.0953, $C_{13}H_{19}NO_4S$ requires M^+ 284.0951.

1,2,3,4-Tetrahydro-6/8-methoxyazepino[1,2-b][1,2]benzothiazole-10,10-dioxide **213A** and **213B**



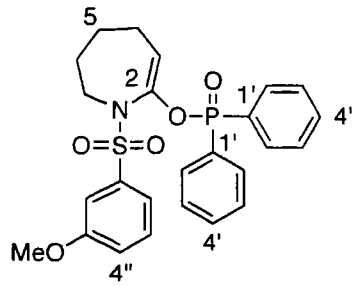


General method for the cyclisation of N-arylsulfonyl lactams:

Purification by flash chromatography ([9:1], [85:15], [1:1] pet. ether/EtOAc) afforded the title compounds as a mixture of isomers (31%). The initial fraction provided *1,2,3,4*-Tetrahydro-6-methoxyazepino[1,2-b][1,2]benzothiazole-10,10-dioxide **213A** as a colourless oil. (67 mg, 0.25 mmol, 25%). ν_{max} (ATR) 2941, 1727, 1647, 1595, 1485, 1440, 1304, 1273, 1212, 1171, 1158, 1044.cm^{-1}. δ_H (400 MHz) 1.81 (2H, quint, J = 6 Hz, 3-*H*$_2$), 1.95 (2H, quint, J = 6 Hz, 2-*H*$_2$), 2.44 (2H, q, J = 6 Hz, 4-*H*$_2$), 3.59 (2H, m, 1-*H*$_2$), 3.95 (3H, s, OCH_3), 6.52 (1H, t, J = 6 Hz, 5-*H*), 7.08 (1H, m, ArC-*H*), 7.34-7.44 (2H, m, 8-*H*, ArC-*H*). δ_C (100 MHz) 26.2 (*C*-3), 27.2 (*C*-4), 29.2 (*C*-2), 45.5 (*C*-1), 56.1 (OCH_3), 113.2 (Ar*C*), 114.5 (*C*-5), 114.7 (Ar*C*), 120.0 (*C*-5^b), 130.5 (*C*-8), 133.8 (*C*-9^a), 135.9 (*C*-5^a), 155.7 (*C*-6). *m/z* (ES^+) 266.2 (MH^+). HRMS (ES^+) found MH^+ 266.08454, $C_{13}H_{16}NO_3S$ requires M^+ 266.08483. Further elution then afforded 1,2,3,4-Tetrahydro-8-methoxyazepino[1,2-b][1,2]benzothiazole-10,10-dioxide **213B** as a colourless oil. (17 mg, 0.06 mmol, 6%). ν_{max} (ATR) 2941, 1726, 1664, 1611, 1495, 1464, 1441, 1303, 1274, 1168, 1056, 1027 cm^{-1}. δ_H (400 MHz) 1.80 (2H, quint, J = 6 Hz, 3-*H*$_2$), 1.98 (2H, m, 2-*H*$_2$), 2.42 (2H, q, J = 6 Hz, 4-*H*$_2$), 3.59 (2H, m, 1-*H*$_2$), 5.65 (1H, t, J = 6 Hz, 5-*H*),

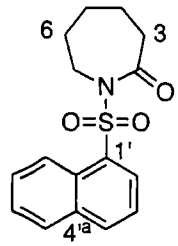
7.13 (1H, m, 7-*H*), 7.19 (1H, s, 9-*H*), 7.50 (1H, d, J = 9 Hz, 6-*H*). δ_C (100 MHz) 27.1, 27.2 (*C*-4, *C*-3), 28.9 (*C*-2), 45.4 (*C*-1), 56.1 (OCH_3), 103.3 (*C*-9), 104.9 (*C*-5), 122.0 (*C*-6), 122.3 (*C*-7), 124.9 (*C*-5[b]), 132.4 (*C*-9[a]), 135.7 (*C*-5[a]), 160.9 (*C*-8). *m/z* (ES^+) 266.2 (MH^+). HRMS (ES^+) found MH^+ 266.0848, $C_{13}H_{16}NO_3S$ requires M^+ 266.0845.

1-(3"-Methoxyphenyl)-4,5,6,7-tetrahydro-1H-azepin-2-yl diphenylphosphinate **214**



The pure material was collected as a clear oil (23%). ν_{max} (ATR) 3065, 2943, 1673, 1599, 1484, 1440, 1360, 1240, 1158, 1131, 1105, 1049 cm^{-1}. δ_H (500 MHz) 1.35 (2H. m, 5-H_2), 1.66 (2H, quint, J = 6 Hz, 6-H_2), 1.87 (2H, q, J = 7 Hz, 4-H_2), 3.19 (2H, m, 7-H_2), 3.67 (3H, s, 3"-OCH_3), 5.55 (1H, dt, J = 7 Hz, $^4J_{HP}$ = 3 Hz, 3-*H*), 7.00 (1H, m, Ar-*H*), 7.21 (1H, t, J = 8 Hz, 5"-*H*), 7.36 (1H, m, 2"-*H*), 7.38-7.46 (5H, m, 3'-*H*, 5'-*H*, Ar-*H*), 7.54 (2H, m, 4'-*H*), 7.81 (4H, m, 2'-*H*, 6'-*H*). δ_C (125 MHz) 23.9 (*C*-5), 24.3 (*C*-4), 30.0 (*C*-6), 49.5 (*C*-7), 55.7 (CH_3), 111.9 (*C*-2"), 113.9 (*C*-3), 119.5 and 119.7 (*C*-4", *C*-6"), 128.8 (d, J = 13 Hz, *C*-3'), 130.2 (*C*-5"), 129.9 and 131.2 (d, J = 130 Hz, *C*-1'), 132.2 (d, J = 11 Hz, *C*-2'), 132.7 (*C*-4'), 142.2 (*C*-1"), 143.6 (d, *C*-2), 160.0 (*C*-3"). δ_P (162 MHz) 31.4. *m/z* (ES^+) 484.2 (MH^+), 506.2 (MNa^+), 988.8 ($2MNa^+$). HRMS (ES^+) found MH^+ 484.1345, $C_{25}H_{27}NO_5PS$ requires M^+ 484.1342, found MNa^+ 506.1165, $C_{25}H_{26}NO_5PSNa$ requires M^+ 506.1162.

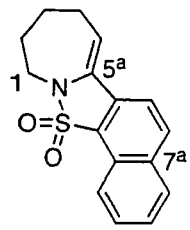
N-(1'-Napthylsulfonyl)-2-oxoazepane **215**



General method for N-arylsulfonyl protection of lactams:

Purification by flash chromatography ([7:3] pet. ether/EtOAc) afforded the title compound as a white solid (1.46 g, 4.81 mmol, 49%). mp. 132-134 °C. Found; C, 63.10; H, 5.61; N, 4.42%; Calc. for $C_{16}H_{17}NO_3S$; C, 63.34; H, 5.65; N, 4.62%. ν_{max} (ATR) 3028, 2944, 1699 (C=O), 1510, 1354 (NSO_2), 1210, 1165 (NSO_2), 1134, 880, 690, 506 cm^{-1}. δ_H (500 MHz) 1.71 (2H, quint, J = 6 Hz, 4-H_2), 1.77 (2H, quint, J = 6 Hz, 5-H_2), 1.98 (2H, quint, J = 6 Hz, 6-H_2), 2.47 (2H, m, 3-H_2), 4.26 (2H, m, 7-H_2), 7.59 (1H, t, J = 8 Hz, 6'-*H*), 7.62 (1H, t, J = 8 Hz, 3'-*H*), 7.66 (1H, t, J = 8 Hz, 7'-*H*), 7.95 (1H, d, J = 9 Hz, 5'-*H*), 8.10 (1H, d, J = 9 Hz, 4'-*H*), 8.35 (1H, d, J = 9 Hz, 8'-*H*), 8.53 (1H, d, J = 8 Hz, 2'-*H*). δ_C (125 MHz) 23.2 (*C*-4), 29.5 (*C*-5), 29.7 (*C*-6), 39.0 (*C*-3), 46.3 (*C*-7), 123.7 (*C*-8'), 124.5 (*C*-3'), 126.9 (*C*-6'), 128.4 (*C*-8^a), 128.5 (*C*-7'), 129.6 (*C*-5'), 133.1 (*C*-2'), 134.3 (*C*-4^a), 134.8 (*C*-1'), 135.3 (*C*-4'), 175.1 (*C*=O). *m/z* (ES^+) 304.1 (MH^+).

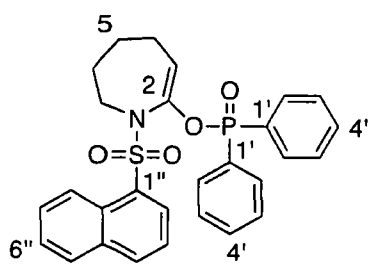
1,2,3,4-Tetrahydroazepino[1,2-b][1,2]napthathiazole-12,12-dioxide **216**



General method for the cyclisation of N-arylsulfonyl lactams:

Purification on the Horizon® column chromatography system ([8:2] pet. ether/EtOAc) afforded the title compound as a white solid (0.35 g, 1.23 mmol, 26%). mp. 183-186 °C. ν_{max} (ATR) 2930, 2868, 1657, 1626, 1592, 1512, 1288, 1154, 1131, 1074, 1005, 936, 826, 807, 761 cm^{-1}. δ_H (500 MHz) 1.83 (2H, quint, J = 6 Hz, 3-*H*$_2$), 2.05 (2H, m, 2-*H*$_2$), 2.50 (2H, q, J = 6 Hz, 4-*H*$_2$), 3.67 (2H, m, 1-*H*$_2$), 5.93 (1H, t, J = 6 Hz, 5-*H*), 7.57-7.63 (2H, m, 6-*H*, 9-*H*), 7.70 (1H, t, J = 8 Hz, 10-*H*), 7.91 (1H, d, J = 8 Hz, 8-*H*), 7.98 (1H, d, J = 9 Hz, 7-*H*), 8.37 (1H, d, J = 9 Hz, 11-*H*). δ_C (125 MHz) 27.0 (*C*-3), 27.6 (*C*-4), 29.0 (*C*-2), 45.5 (*C*-1), 108.5 (*C*-5), 117.3 (Ar*C*-H), 123.5 (*C*-11), 125.5 (*C*-11^a), 126.2 (*C*-11^b), 127.9 (Ar*C*-H), 128.9 (*C*-8), 129.4 (*C*-10), 131.2 (*C*-5^b), 133.5 (*C*-7^a), 134.0 (*C*-7), 136.5 (*C*-5^a). *m/z* (ES^+) 286.1 (MH^+), 308.1 (MNa^+), 340.1 ($MMeOHNa^+$), 593.3 ($2MNa^+$), 878.4 ($3MNa^+$). HRMS (ES^+) found MH^+ 286.0899, $C_{16}H_{16}NO_2S$ requires 286.0896. Phosphinate **217** (0.17 g, 0.34 mmol, 17%) and starting material (41%) were also isolated.

1-(1"-Napthylsulfonyl-4,5,6,7-tetrahydro-1H-azepin-2-yl-diphenylphosphinate **217**

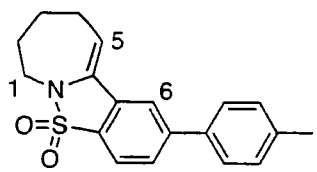


The pure material was isolated as a colourless oil. ν_{max} (KBr) 3064, 2943, 1672, 1440, 1338, 1226, 1200, 1160, 1133, 1097, 1062, 803 cm^{-1}. δ_H (500 MHz) 1.29 (2H, m, 5-*H*$_2$), 1.47 (2H, quint, J = 6 Hz, 6-*H*$_2$), 1.86 (2H, q, J = 7 Hz, 4-*H*$_2$), 3.26 (2H, m, 7-*H*$_2$), 5.64 (1H, dt, J = 7 Hz, $^4J_{HP}$ = 3 Hz, 3-*H*), 7.31-7.39 (5H, m, 3"-*H*, 3'-*H*, 5'-*H*), 7.46-7.59 (4H, m, 4'-*H*, 7"-*H*, 6"-*H*), 7.70 (4H, m, 2'-*H*, 6'-*H*), 7.90 (1H, d, J = 8 Hz, 5"-*H*), 7.98 (1H, d, J = 8 Hz, 4"-*H*), 8.25 (1H, m, 2"-*H*), 8.70 (1H, d, J = 8 Hz, 8"-*H*). δ_C (125 MHz) 23.9 (*C*-

5), 24.2 (*C*-4), 29.9 (*C*-6), 49.6 (*C*-7), 114.1 (*C*-3), 124.4 (*C*-3''), 125.5 (*C*-8''), 127.4 and 128.4 (*C*-6'', *C*-7''), 128.6 (d, J = 13 Hz, *C*-3'), 129.0 (*C*-5''), 129.6 (*C*-2''), 130.1 and 131.2 (d, J = 110 Hz, *C*-1'), 132.1 (Ar*C*), 132.2 (d, J = 10 Hz, *C*-2'), 132.6 (*C*-4'), 134.4 (*C*-4''), 134.5 (Ar*C*), 136.4 (Ar*C*), 143.6 (*C*-2). δ_P (162 MHz) 31.2. *m/z* (ES^+) 504.1 (MH^+), 526.1 (MNa^+), 1029.4 ($2MNa^+$). HRMS (ES^+) found MH^+ 504.1401, $C_{28}H_{27}NO_4PS$ requires M^+ 504.1393.

δ_C (100 MHz) 24.3 (*C*-5), 24.8 (*C*-6), 28.5 ((C(CH_3)$_3$), 29.4 (*C*-4), 46.4 (*C*-7), 81.0 (*C*(CH_3)$_3$), 110.1 (*C*-3), 128.6 (d, J = 13 Hz, *C*-3'), 130.9 and 132.3 (d, J = 137 Hz, *C*-1'), 131.9 (d, J = 10 Hz, *C*-2'), 132.5 (*C*-4'), 144.9 (*C*-2), 153.4 (*C*=O).

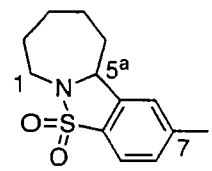
1,2,3,4-Tetrahydro-7-tolylazepino[1,2-b][1,2]benzothiazole-10,10-dioxide **223**



A mixture of *p*-tolylboronic acid (0.05 g, 0.37 mmol, 1 eq), $NaHCO_3$ (0.09 g, 1.10 mmol, 3 eq) and sultam **209** in a DME/H_2O (7:3) mixture was degassed by three freeze/pump/thaw cycles. $Pd(PPh_3)_4$ (0.02 g, 0.017 mmol, 0.05 eq) was added and the reaction mixture heated at 80 °C for 45 min. The mixture was allowed to cool to room temperature and concentrated under reduced pressure and the aqueous layer extracted with EtOAc (x 3). The organic phase was washed with H_2O then brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography ([9:1] pet. ether/EtOAc) afforded the title compound as an off-white solid (102 mg, 0.31 mmol, 86%). mp > 130 °C (sinters and decomposes). Found; C, 69.57; H, 5.87; N, 4.09%; Calc. for $C_{19}H_{19}NO_2S$; C, 70.12; H, 5.88; N, 4.30%. ν_{max} (ATR) 2940, 2920, 1622, 1393, 1291, 1173, 1142, 1067, 1005, 973, 829, 805, 701 cm^{-1}. δ_H (500 MHz) 1.83 (2H, quint, J = 6 Hz, 3-H_2), 2.01 (2H, m, 2-H_2), 2.43 (3H, s, 4'-CH_3), 2.48 (2H, s, J = 6 Hz, 4-H_2),

3.63 (2H, m, 1-*H*$_2$), 5.90 (1H, t, J = 6 Hz, 5-*H*), 7.30 (2H, d, J = 8 Hz, 3'-*H*), 7.50 (2H, d, J = 8 Hz, 2'-*H*), 7.68 (1H, dd, J = 9 Hz, $^4J_{HH}$ = 1 Hz, 8-*H*), 7.77 (1H, d, $^4J_{HH}$ = 1 Hz, 6-*H*), 7.82 (1H, d, J = 9 Hz, 9-*H*). δ_C (125 MHz) 21.4 (4'-*C*H$_3$), 27.0 (*C*-3), 27.3 (*C*-4), 28.9 (*C*-2), 45.3 (*C*-1), 106.7 (*C*-5), 118.9 (*C*-6), 121.7 (*C*-9), 127.5 (*C*-2'), 128.6 (*C*-8), 129.8 (*C*-7), 130.0 (*C*-3'), 132.8 (*C*-5^b), 136.0 (*C*-5^a), 136.8 (*C*-1'), 138.9 (*C*-4'), 146.6 (*C*-9^a). *m/z* (ES$^+$) 326.1 (MNa$^+$), 389.1 (MNaMeCN$^+$). HRMS (ES$^+$) found MH$^+$ 326.1208, $C_{19}H_{20}NO_2S$ requires M$^+$ 326.1209.

1,2,3,4,5-Quintahydro-7-methylazepino[1,2-b][1,2]benzothiazole-10,10-dioxide **224**



A solution of sultam **20** (0.05 g, 0.20 mmol, 1 eq) in EtOH (1 ml, 0.2 M) was added *via* cannula to a flask containing 10% Pd/C (7.5 mg, 15% *w/w*). The flask was placed under an atmosphere of H_2 and the reaction mixture stirred at room temperature overnight. The flask was flushed with argon and the suspension filtered through a pad of celite, washed through with EtOAc and concentrated under reduced pressure. Purification by flash chromatography ([8:2] pet. ether/EtOAc) afforded the title compound as a white solid (22 mg, 0.088 mmol, 44%). mp. 113-115 °C. ν_{max} (ATR) 2934, 2856, 1610, 1464, 1305, 1178, 1146, 1061, 941 cm^{-1}. δ_H (500 MHz) 1.57-1.90 (6H, m), 2.08 (1H, m, 2-H*H*), 2.28 (1H, m, 5-H*H*), 2.45 (3H, s, 7-*CH*$_3$), 3.29 (1H, ddd, $^2J_{HH}$ = 12 Hz, J = 8 Hz, J = 4 Hz, 1-H*H*), 3.68 (1H, ddd, $^2J_{HH}$ = 12 Hz, J = 8 Hz, J = 4 Hz, 1-*H*H), 4.47 (1H, dd, J = 10 Hz, J = 3 Hz, 5^a-*H*), 7.16 (1H, s, 6-*H*), 7.31 (1H, d, J = 8 Hz, 8-*H*), 7.66 (1H, d, J = 8 Hz, 9-*H*). δ_C (125 MHz) 22.1 (7-*C*H$_3$), 27.1, 27.6 (2 x *C*H$_2$), 27.7 (*C*-2), 36.3 (*C*-5), 42.5 (*C*-1), 62.3 (*C*-5^a), 121.1 (*C*-9), 124.3 (*C*-6), 130.3

(*C*-8), 132.0 (*C*-9[a]), 139.2 (*C*-5[b]), 143.9 (*C*-7). *m/z* (ES^+) 252.0 (MH^+), 503.1 ($2MH^+$), 525.1 ($2MNa^+$). HRMS (ES^+) found MH^+ 252.1060, $C_{13}H_{17}NO_2S$ requires M^+ 252.1858.

Experimental design Suzuki Greenhouse arrays

Two arrays of 24 Suzuki reactions were carried out employing Radleys Technology Greenhouse™ reactors. The identity of the phosphine ligands, bases and solvents were chosen from PCA models, two Pd sources and two temperatures were then included and the arrays were designed and generated using statistical experimental design software (Design Expert 7). In each case the reaction was carried out on a 0.05 mmol scale (phosphinate) employing 5 mol% catalyst, 10 mol% phosphine ligand, 3 Eq. base, and 1.5 ml of solvent (reaction molarity of 0.033 M w.r.t. phosphinate). Each vessel was also charged with an internal standard, biphenyl (0.025 mmol), to allow analysis of each reaction mixture by HPLC. The combinations of different conditions run at 75 °C are shown in Table 7 and those run at 55 °C in Table 8. Stock solutions of the phosphinate, boronic acid, phosphine ligands, Pd salts and biphenyl were prepared in THF which had been degassed by passing a stream of nitrogen gas through it. The appropriate quantity of each reagent was added to the relevant reaction vessel and the THF removed in the Genevac™. The appropriate base was added as either solid or liquid followed by the appropriate solvent, all the solvents were degassed prior to use by the same method as previously mentioned. The Greenhouse chamber was then evacuated and purged with nitrogen (x 3) and the reactions heated at the appropriate temperature for 18 h.

Run	Solvent	base	ligand	catalyst	Yield 61	Yield 69	Yield 70	Prod Yield	SM left	Yield 63
A1	toluene	NaOH	$P(OEt)_3$	$Pd_2(dba)_3$	89	0	11	3	N	0
A2	EtOH	NaOH	$P(OEt)_3$	$Pd(OAc)_2$	13	0	87	0	N	0
A3	^{i}PrOAc	Cs_2CO_3	P(pPh-OMe)$_3$	$Pd_2(dba)_3$	9	0	54	1	N	0
A4	dioxane	Cs_2CO_3	$P(cyhex)_3$	$Pd_2(dba)_3$	6	0	37	0	N	0
A5	NMP	KOAc	P(pPh-OMe)$_3$	$Pd_2(dba)_3$	100	0	0	0	N	0
A6	^{i}PrOAc	KOAc	P(pPh-OMe)$_3$	$Pd(OAc)_2$	1	87	1	0	N	32
B1	Diglyme	KH_2PO_4	$P(o\text{-}tol)_3$	$Pd_2(dba)_3$	0	1	0	4	Y	0
B2	Diglyme	NaOH	$P(o\text{-}tol)_3$	$Pd(OAc)_2$	86	0	14	0	N	0
B3	3-pentanone	K_2CO_3	PPh_3	$Pd_2(dba)_3$	0	53	1	10	N	55
B4	NMP	Cs_2CO_3	P(pPh-OMe)$_3$	$Pd(OAc)_2$	41	0	31	0	N	0
B5	3-pentanone	K_2CO_3	PPh_3	$Pd(OAc)_2$	2	70	2	21	min	20
B6	dioxane	KOAc	$P(cyhex)_3$	$Pd(OAc)_2$	1	85	3	0	N	22
C1	MeCN	KH_2PO_4	$P(o\text{-}tol)_3$	$Pd(OAc)_2$	1	1	4	3	Y	11
C2	toluene	KH_2PO_4	$P(OEt)_3$	$Pd(OAc)_2$	1	0	3	1	Y	0
C3	MeCN	NaOH	$P(o\text{-}tol)_3$	$Pd_2(dba)_3$	na	na	na	na	na	0
C4	DME	KOAc	$P(cyhex)_3$	$Pd_2(dba)_3$	6	60	5	0	N	40
C5	DME	Cs_2CO_3	$P(cyhex)_3$	$Pd(OAc)_2$	8	0	56	0	N	0
C6	EtOH	KH_2PO_4	$P(OEt)_3$	$Pd_2(dba)_3$	1	0	0	0	Y	0
D1	EtOH	NEt_3	$P(cyhex)_3$	$Pd_2(dba)_3$	1	0	0	4	Y	0
D2	Diglyme	NEt_3	$P(OEt)_3$	$Pd(OAc)_2$	1	0	0	1	Y	0
D3	DME	NEt_3	$P(o\text{-}tol)_3$	$Pd(OAc)_2$	1	1	0	14	Y	0
D4	3-pentanone	NEt_3	PPh_3	$Pd_2(dba)_3$	1	0	0	6	Y	0
D5	3-pentanone	NEt_3	PPh_3	$Pd(OAc)_2$	1	0	0	7	Y	0
D6	NMP	NEt_3	P(pPh-OMe)$_3$	$Pd_2(dba)_3$	1	0	5	4	Y	0

Table 7: DoE Array 75 °C

Run	Solvent	base	ligand	catalyst	Yield 61	Yield 69	Yield 70	Prod yield	SM left	Yield 63
A1	MeCN	Cs_2CO_3	$P(OEt)_3$	$Pd_2(dba)_3$	93	0	3	0	N	0
A2	toluene	Cs_2CO_3	$P(o\text{-}tol)_3$	$Pd_2(dba)_3$	15	11	3	27	Y	25
A3	NMP	NaOH	$P(cyhex)_3$	$Pd(OAc)_2$	na	na	na	na	N	0
A4	EtOH	Cs_2CO_3	$P(o\text{-}tol)_3$	$Pd(OAc)_2$	50	0	14	0	N	0
A5	EtOH	KOAc	$P(o\text{-}tol)_3$	$Pd_2(dba)_3$	20	1	2	8	Y	11
A6	toluene	KOAc	$P(o\text{-}tol)_3$	$Pd(OAc)_2$	0	65	1	33	min	29
B1	^{i}PrOAc	KH_2PO_4	$P(cyhex)_3$	$Pd(OAc)_2$	0	0	0	3	Y	0
B2	dioxane	NaOH	$P(pPh\text{-}OMe)_3$	$Pd_2(dba)_3$	75	0	25	0	N	0
B3	MeCN	KOAc	$P(OEt)_3$	$Pd(OAc)_2$	5	8	0	0	N	90
B4	^{i}PrOAc	NaOH	$P(cyhex)_3$	$Pd_2(dba)_3$	74	0	7	1	N	0
B5	DME	KH_2PO_4	$P(pPh\text{-}OMe)_3$	$Pd_2(dba)_3$	0	0	4	5	Y	25
B6	3-pentanone	K_2CO_3	PPh_3	$Pd(OAc)_2$	0	5	0	10	y	64
C1	Diglyme	Cs_2CO_3	$P(OEt)_3$	$Pd(OAc)_2$	83	0	17	0	N	0
C2	NMP	KH_2PO_4	$P(cyhex)_3$	$Pd_2(dba)_3$	1	0	0	2	Y	0
C3	3-pentanone	K_2CO_3	PPh_3	$Pd_2(dba)_3$	1	3	0	6	Y	75
C4	DME	NaOH	$P(pPh\text{-}OMe)_3$	$Pd(OAc)_2$	61	0	39	0	N	0
C5	Diglyme	KOAc	$P(OEt)_3$	$Pd_2(dba)_3$	20	1	1	1	N	80
C6	dioxane	KH_2PO_4	$P(pPh\text{-}OMe)_3$	$Pd(OAc)_2$	0	1	1	10	Y	10
D1	MeCN	NEt_3	$P(OEt)_3$	$Pd(OAc)_2$	0	0	0	1	Y	0
D2	iPrOAc	NEt_3	$P(pPh\text{-}OMe)_3$	$Pd_2(dba)_3$	0	0	5	6	Y	0
D3	dioxane	NEt_3	$P(o\text{-}tol)_3$	$Pd(OAc)_2$	0	2	0	14	Y	0
D4	3-pentanone	NEt_3	PPh_3	$Pd(OAc)_2$	0	0	0	10	Y	4
D5	toluene	NEt_3	$P(cyhex)_3$	$Pd_2(dba)_3$	0	0	0	2	Y	0
D6	3-pentanone	NEt_3	PPh_3	$Pd_2(dba)_3$	0	0	0	5	Y	0

Table 8: DoE Array 55 °C

Experimental Procedure for Suzuki Array Screening

The protocol used to carry out arrays of 24 Suzuki reactions using a Radley's Technologies Greenhouse Parallel Synthesiser is described in this Appendix. This procedure was adapted from one developed by Mr Ian B. Campbell of GlaxoSmithkline, Stevenage, UK and acknowledgement is made to him for the original protocol.

The conditions cover a range of catalysts, ligands, bases and solvents which have been employed regularly in Suzuki cross-coupling reactions. Arrays were carried out in a 24 array Greenhouse and followed by GC and GCMS. The reactions were carried out on 0.1 mmol scale using 3 mol% catalyst precursor, 6mol% ligand and 3 equivalents base together with 1 equivalent of dodecane as an internal standard exploring a total of 4 catalysts, 7 ligands, 10 bases, 8 solvents as described in the table below.

Entry	Catalyst	Ligand	Base	Solvent	% Yield by GC
A1	$Pd(PPh_3)_4$		Cs_2CO_3	DMF	N/A
A2	$Pd(PPh_3)_4$		K_3PO_4	DMF	23%
A3	$Pd(PPh_3)_4$		Na_2CO_3	DME / H_2O	no product
A4	$Pd(PPh_3)_4$		$NaHCO_3$	DME / H_2O	98%
A5	$Pd(PPh_3)_4$		$Ba(OH)_2$	DME / H_2O	72%
A6	$Pd(PPh_3)_4$		NaOH	DME / H_2O	<10%
B1	$Pd(OAc)_2$		K_2CO_3	DME / H_2O	17%
B2	$Pd(OAc)_2$	IMES	Et_3N	Toluene	<10%
B3	$Pd(OAc)_2$	IMES	Et_3N	DMF	<10%
B4	$Pd_2(dba)_3$	IMES	Et_3N	MeCN	<10%
B5	$Pd_2(dba)_3$	IMES	Et_3N	Dioxane / H_2O	11%
B6	$Pd(OAc)_2$	PPh_3	$NaHCO_3$	DME / H_2O	No product
C1	$Pd(OAc)_2$	$(2\text{-furan})_3P$	Et_3N	DMF	No product
C2	$Pd(OAc)_2$	Dppe	Et_3N	DMF	<10%
C3	$Pd(OAc)_2$	Dppb	Et_3N	DMF	<10%
C4	$Pd(OAc)_2$	Dppf	Et_3N	DMF	No product
C5	$Pd(OAc)_2$	$^tBu_2P(BiPh)$	K_3PO_4	EtOH / H_2O	44%
C6	$Pd(OAc)_2$	$^tBu_2P(BiPh)$	K_3PO_4	Toluene	<10%
D1	$Pd_2(dba)_3$		KOAc	Toluene/EtOH	31%
D2	$Pd_2(dba)_3$	IMES	Cs_2CO_3	Dioxane	<10%
D3	$Pd_2(dba)_3$	Dppf	Cs_2CO_3	DMF	No product
D4	$PdCl_2$(Binap)		$NaHCO_3$	DME / H_2O	46%
D5	$PdCl_2$(Binap)		K_3PO_4	DMF	14%
D6	$PdCl_2$(Binap)		CsF	THF / H_2O	63%

Table 9

Dispense List – The following stock solutions were prepared

A1	Enol Phosphinate **3a**	0.2 M in THF	
A1.5	Dodecane	0.2 M in THF	
A2	Boronic Acid **4a**	0.2 M in THF	
A3	$Pd(PPh_3)_4$	0.01 M in THF	11.55 mg/ml
A4	$Pd(OAc)_2$	0.01 M in THF	2.24 mg/ml
A5	$Pd_2(dba)_3$	0.01 M in THF	9.14 mg/ml
A6	$Pd(Binap)Cl_2$	0.01 M in THF	8.0 mg/ml
B1	IMES	0.01 M in THF	2.02 mg/ml
B2	dppm	0.01 M in THF	3.85 mg/ml
B3	$(2\text{-furan})_3P$	0.01 M in THF	2.32 mg/ml
B4	dppe	0.01 M in THF	3.98 mg/ml
B5	dppb	0.01 M in THF	4.26 mg/ml
B6	dppf	0.01 M in THF	5.54 mg/ml
B7	$^tBu_2P(BiPh)$	0.01 M in THF	2.98 mg/ml
C1	Na_2CO_3	1.0 M in H_2O	106 mg/ml
C2	$NaHCO_3$	1.0 M in H_2O	84 mg/ml
C3	NaOH	1.0 M in H_2O	40 mg/ml
C4	Et_3N		
C5	K_2CO_3	1.0 M in H_2O	138 mg/ml
C6	K_3PO_4	1.0 M in H_2O	203 mg/ml
C7	CsF	1.0 M in H_2O	151 mg/ml
D1	DMF		
D2	DME		
D3	PhMe		
D4	MeCN		

D5	Dioxane
D6	H_2O
D7	EtOH
D8	THF

Table A3- Solid Samples were preweighed

Cs_2CO_3	3 x 97.5 mg
K_3PO_4	3 x 60.9 mg
$Ba(OH)_2$	1 x 51.3 mg
KOAc	1 x 29.4 mg

Table A4- Protocol-

500 µl A1 to vessels A1 – D6	(24 dispenses)
500 µl A2 to vessels A1 – D6	(24 dispenses)
500 µl A3 to vessels A1 – A6	(3 dispenses)
500 µl A4 to vessels B1 – C6 (Not B4 and B5)	(10 dispenses)
500 µl A5 to vessels D1 – D3, B4 and B5	(5 dispenses)
500 µl A6 to vessels D4 – D6	(3 dispenses)
500 µl B1 to vessels B2 – B5 and D2	5 dispenses)
500 µl B2 to vessel B6	(1 dispense)
500 µl B3 to vessel C1	(1 dispense)
500 µl B4 to vessel C2	(1 dispense)
500 µl B5 to vessel C3	(1 dispense)
500 µl B6 to vessels C4 and D3	(2 dispenses)
500 µl B7 to vessels C5 and C6	(2 dispenses)

All the samples were then evacuated using a Genevac vacuum centrifuge operating at full power for 12 minutes

300 µl C1 to vessel A3 (1 dispense)

300 µl C2 to vessels A4, D4, and B6 3 dispenses)

300 µl C3 to vessel A1 (1 dispense)

50 µl C4 to vessels B2 – C4 NOT B6 8 dispenses)

300 µl C5 to vessel B1 (1 dispense)

300 µl C6 to vessel C5 (1 dispense)

300 µl C7 to vessel D6 (1 dispense)

1000 µl D1 to vessels A1, A2, B3, B7 – C4, D3, D5 9 dispenses)

700 µl D1 to vessel B1 (1 dispense)

700 µl D2 to vessels A3 – A6, B6 and D4 6 dispenses)

1000 µl D3 to vessels B2 and C6 (2 dispenses)

500 µl D3 to vessel D1 (1 dispense)

1000 µl D4 to vessel B4 (1 dispense)

500 µl D5 to vessel B5 (1 dispense)

1000 µl D5 to vessel D2 (1 dispense)

300 µl D6 to vessels A3 – A6, B1, B5, B6, C5, D4 and D6 10 dispenses)

700 µl D7 to vessel C5 (1 dispense)

700 µl D8 to vessel D6 (1 dispense)

Add Cs_2CO_3 97.5 mg to vessels A1, D2 and D3

Add K_3PO_4 60.9 mg to vessels A2, C6 and D5

Add $Ba(OH)_2$ 51.3 mg to vessel A5

Add KOAc 29.4 mg to vessel D1

Reaction array was then placed in the Greenhouse reactor and heated at 80 °C for 18 h and then analysed by GC and GCMS.

8 Appendix

Research conferences attended

'Modern Aspects of Stereochemistry', Stereochemistry at Sheffield. Dec. **2004**

'Modern Aspects of Stereochemistry', Stereochemistry at Sheffield. Dec. **2005**

'Modern Aspects of Stereochemistry', Stereochemistry at Sheffield. Dec. **2006**

'C-H Activation: Present and future', AstraZeneca, Charnwood, Loughborough, UK. Apr. **2007**.

'Modern Aspects of Stereochemistry', Stereochemistry at Sheffield. Jan. **2008**

Workshops attended

'Investigating Chemical Processes through Designed Experiments', University of Southampton, UK. Sept. **2006**.

Publications

John D. Harling, Patrick G. Steel, Tom M. Woods and Dmitry S. Yufit. 'Synthesis of benzothiazolines and napthathiazolines *via* ortho-lithiation, cyclisation and elimination of N-arylsulfonyl lactams'. *Org. Biomol. Chem.* 2007, *5*, 3472.

Jun Guo, John D. Harling, Patrick G. Steel, Tom M. Woods. 'Phosphinates as new electrophilic reagents for cross-coupling reactions'. *Org. Biomol. Chem.* 2008, *6*, 4053.

Patrick G. Steel, Tom M. Woods. 'Diversity cleavage strategies from phosphorus linkers' in 'Linker strategies in solid phase organic synthesis' Ed. P. J. H. Scott, *Wiley*, **2008**.

Oral presentations

'Phosphorus based electrophiles, new strategies for cross-coupling reactions'. Tom M. Woods. Invited speaker. *ACS National meeting.* New Orleans, USA. March **2008**.

'Phosphorus based electrophiles, new strategies for cross-coupling reactions'. Tom M. Woods. Invited speaker. *Organic reaction mechanisms postgraduate meeting*, Astrazeneca, Loughborough. Sept **2007**.

'Phosphorus based electrophiles, new strategies for cross coupling reactions'. Tom M. Woods. Invited speaker. *SCI postgraduate meeting*. University of Durham. March **2007**.

Poster presentations

'New synthetic transformations using phosphorus reagents'. Tom M. Woods. Poster presentation. *22nd Postgraduate Heterocyclic Symposium*. Organon, Newhouse, Scotland, UK. Sept. **2007**.

'New synthetic transformations using phosphorus reagents'. Tom M. Woods. Poster presentation. Department of chemistry, University of York, July **2007**.

'Phosphorus based electrophiles, new strategies for cross-coupling reactions'. Tom M. Woods. Poster presentation. *9th International SFB-Symposium*. Aachen, Germany. Oct. **2005**.

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