C–H Activation Reactions of Tetrahydropyridines

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Abstract

This thesis is presented as five chapters:

Chapter 1.0 is divided into two sections: the first is a review of palladium-catalysed C–C bond forming reactions. It covers palladium-catalysed cross-coupling reactions; C–H bond functionalisation; the Heck reaction and functionalisation of heteroaromatic C–H bonds. Secondly the use of tetrahydropyridines in organic synthesis is discussed, with a particular focus on methodology developed by the Craig group.

Chapter 2.0 discusses the research carried out during this studentship. It is divided into six sections and discusses the results obtained from research efforts into: our initial strategy for tetrahydropyridine synthesis; an S_N1 approach; an α,β-unsaturated lactam approach; synthesis of 3-methoxy aryl-substituted tetrahydropyridines; synthesis of heteroaromatic analogues and further elaboration of tricyclic tetrahydropyridines.

Chapter 3.0 details future work proposed within the areas described above.

Chapter 4.0 details the experimental procedures employed and spectroscopic data for the compounds discussed in chapter 2.0.

Finally, chapter 5.0 lists the references sourced in this thesis.

Declaration

I certify that all the work in this thesis is solely my own, except where explicitly stated and appropriately referenced. No part of the thesis has been submitted previously for a degree at this, or any other, university.

Contents

Acknowledgements

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Finally I would like to thank my parents, my sister Laura and my entire family, for supporting me in everything I do.

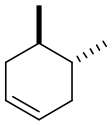
Abbreviations

Ac	acetyl
Ar	aryl
Boc	*tert*-butoxycarbonyl
Bu	butyl
BSA	*N,O*-bis(trimethylsilyl)acetamide
CAN	cerium(IV) ammonium nitrate
Cbz	carbobenzyloxy
CI	chemical ionisation
conc.	concentrated
Cy	cyclohexyl
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
dt	doublet of triplets
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	di*iso*butylaluminium hydride
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
EDG	electron-donating group
equiv.	equivalents
EI	electron impact
ESI	electronspray ionisation
Et	ethyl
EWG	electron-withdrawing group
h	hours
HTIB	hydroxy(tosyloxy)iodobenzene
Ind	indole

LDA	lithium di*iso*propylamide
m-	meta-
M	multiplet
Me	methyl
min	minutes
m.p.	melting point
MS	mass spectrum
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
o-	ortho-
p-	para-
Ph	phenyl
Piv	trimethylacetate
^{i}Pr	*iso*-propyl
q	quartet
rt	room temperature
s	singlet
sat.	saturated
SOMO	singly occupied molecular orbital
T	triplet
Td	triplet of doublets
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
Tol	tolyl
Ts	*para*-toluenesulfonyl
µw	microwave irradiation

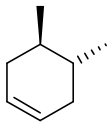
Stereochemical Notation

It should be noted that the Maehr convention for indicating relative and absolute stereochemistry has been used throughout this report.[1] Therefore, solid and broken lines are used to denote racemates, and solid and broken wedges denote absolute configuration. Narrowing of the wedges implies increasing distance from the reader in the latter case.



Racemate

Relative stereochemistry



Single enantiomer

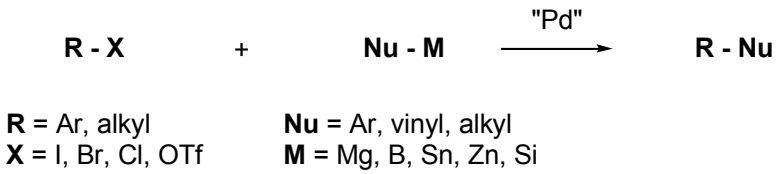
Absolute stereochemistry

1.0 Introduction

1.1.0 A Review of Palladium-catalysed C–C Bond Forming Reactions

1.1.1 Palladium-catalysed Cross-coupling Reactions

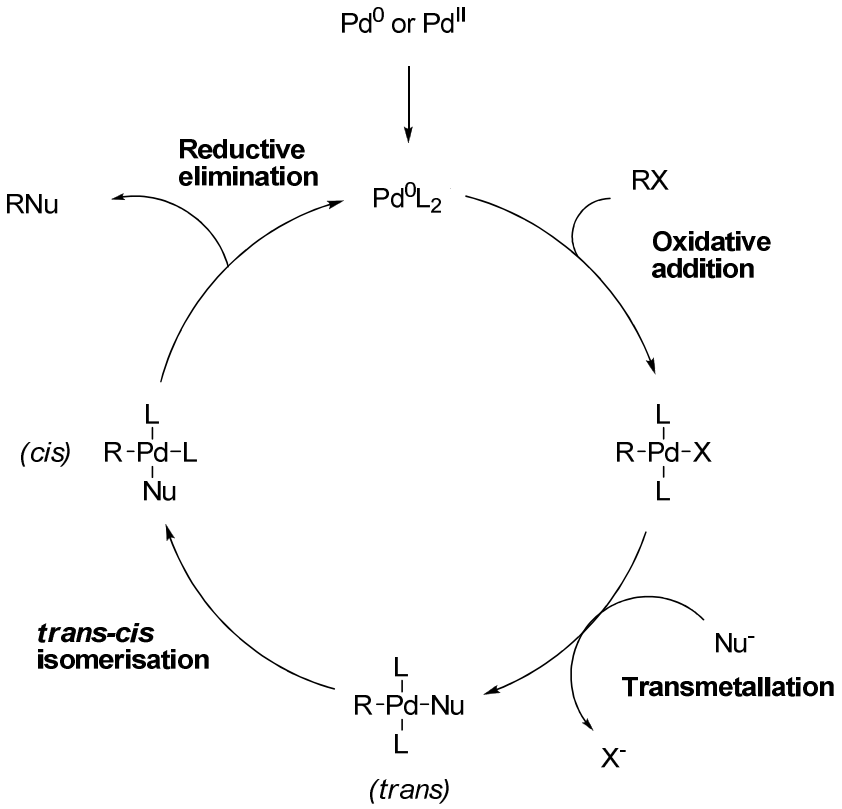
Over the past 40 years, transition metal catalysed cross-coupling reactions have become a standard bond-forming tool for synthetic chemists.[2] Typically, these processes involve the coupling of aryl or alkyl halides or pseudohalides with carbon-based nucleophile derivatives of magnesium (Kumada, Corriu),[3,4] boron (Suzuki, Miyaura),[5] tin (Stille–Migita),[6,7] zinc (Negishi),[8] or silicon (Hiyama)[9] (Scheme 1).



Scheme 1 *General scheme for Cross-coupling reactions*

A common feature of these catalytic processes is the formation of aryl or alkyl palladium(II) intermediates, which can be subsequently functionalised to form new carbon–carbon bonds.[10] The generally accepted catalytic cycle for cross-coupling reactions involves oxidative addition, transmetallation, *trans-cis* isomerisation (only with monodentate ligands), and finally reductive elimination (Scheme 2).[2]

The mechanism of oxidative addition of aryl iodides to zerovalent palladium is described by Fauvarque *et al*. as an aromatic nucleophilic substitution by the reactive bis-ligated $Pd(0)L_2$ 14-electron complex.[11] Alternatively, Amatore and Jutand proposed that the anions of the $Pd(II)Cl_2L_2$ precursor to $Pd(0)L_2$ could play a crucial role. It is believed that the tricoordinated anionic complex $Pd(0)L_2Cl^-$ is the active catalyst, which undergoes oxidative addition to give the pentacoordinated anionic complex $ArPdX(Cl)L_2$.[12]



Scheme 2 *General mechanism for cross-coupling reactions*

The choice of substrate has a well-defined effect on these coupling reactions, as electron-donating groups on the aryl halide often hinder oxidative addition. As a result, electron-rich aryl halides are often referred to as 'deactivated', whereas electron-poor aryl groups are considered 'activated'.[13] Furthermore, the various cross-coupling reactions show different functional group compatibilities. The Grignard reagents used in Kumada couplings only tolerate alkyl and alkoxy groups, hydrides and fluorides, whereas Negishi couplings also tolerate esters, nitro groups, secondary amines, ketones and aldehydes. In comparison, Suzuki and Stille cross-couplings tolerate most functional groups, except for acids. In most cases, free amines and/or alcohols often poison the metal catalyst *via* inter-/intramolecular ligation, or act as nucleophiles and therefore require protection. Bidentate ligands are often employed to overcome this as they create more robust catalytic systems, which are less prone to catalyst poisoning.[2]

In general, the role of the ligands is to stabilise the palladium species throughout the catalytic cycle, in order to prevent premature catalyst deactivation.[13] Their influence on the metal centre is thought to affect the course of the catalytic reaction in three ways: by changing the steric bulk around the metal centre, influencing the electronic properties of the metal and, for bidentate ligands, changing the bite angle preferred by the ligand.[14] In most cases, oxidative addition is considered to be the rate-determining step of the catalytic cycle and therefore ligands that can donate electrons to the metal centre are expected to accelerate this step, through generation of an electron-rich metal complex.[15] Moreover, it has also been found that the rate of reductive elimination is usually increased by the coordination of bulky ligands to the palladium centre.[16]

The ligands employed often also depend on the nature of the organohalide being used. In general, for more reactive iodides, relatively electron-rich monodentate phosphines, such as triphenylphosphine, are used.[17] For moderately reactive bromides, more sterically bulky electron-rich trialkylphosphines or Buchwald's biphenylphosphines have been employed.[18] Finally, for considerably less reactive chlorides or aryl halides containing one or two *ortho*-substituents, *N*-heterocyclic carbene ligands have been applied very successfully.[19] Aryl bromides and chlorides are often reluctant to undergo oxidative addition due to their stronger C–X bonds, particularly if the aryl group bears electron-rich substituents. They are however cheaper, more readily available and generally more robust than aryl iodides, making them attractive substrates to synthetic chemists.[13] In a study of the comparative reactivity of palladium(0) sources towards oxidative addition, it was found that halide additives could have a major impact on the activation of the catalyst. For example, the addition of lithium chloride or zinc chloride to $PdCl_2(PPh_3)_2$ led to a 3-fold acceleration of this often rate-determining oxidative addition step.[2]

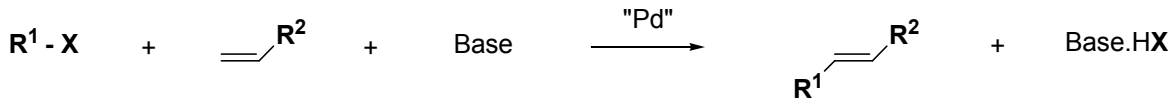
The often high catalytic activity of these different palladium species allows for extremely low catalyst loadings (as low as 0.1 mol%), which is very attractive from an industrial point of view.[17] In addition, ligand-free conditions have also been reported.[2] When using palladium(II) acetate as catalyst, immediate reduction to palladium(0) occurs in the form of palladium clusters that are stabilized by the anions present in solution. This phenomenon is often described as 'homeopathic palladium'. In large-scale production the use of ligand-free palladium is preferred as it is more cost effective and simplifies purification.

1.1.2 C–H Bond Functionalisation

Although cross-coupling is a very attractive method for the construction of carbon–carbon bonds, the prerequisite that both coupling partners are 'activated' can be viewed as extremely wasteful. Pre-activation requires the prior installation and subsequent disposal of stoichiometric metals and halides, which often requires several additional synthetic steps and can be time-consuming and economically inefficient.[17] An alternative approach is to consider a C–H bond as a functional group, analogous to a carbon–metal bond and therefore to use a pre-activated organo–halide as one coupling partner and a simple unactivated substrate as the other. This type of coupling may be considered to be one of the most environmentally benign transformations, as only one equivalent of a halide salt is produced as side product.[2] Several terms such as C–H (bond) activation, C–H (bond) functionalisation and cross-dehalogenative coupling have been used in the literature to describe this type of coupling. The term catalytic direct arylation is also employed, and is defined as the direct coupling of a nonactivated aryl C–H bond with an activated arene.[17]

1.1.3 The Heck Reaction

Palladium-catalysed arylation or vinylation of olefins under basic conditions was first reported by Mizoroki and Heck between 1971 and 1972 respectively.[20,21] Now commonly known as the Heck reaction, this fundamental reaction involves bond formation between two sp^2 carbon centres by an overall substitution of a C–H bond of an alkene with the aryl or vinyl group of an organo–halide. This methodology has been found to be very versatile and is applicable to a diverse range of organohalide species and olefinic coupling partners (Scheme 3).[13]

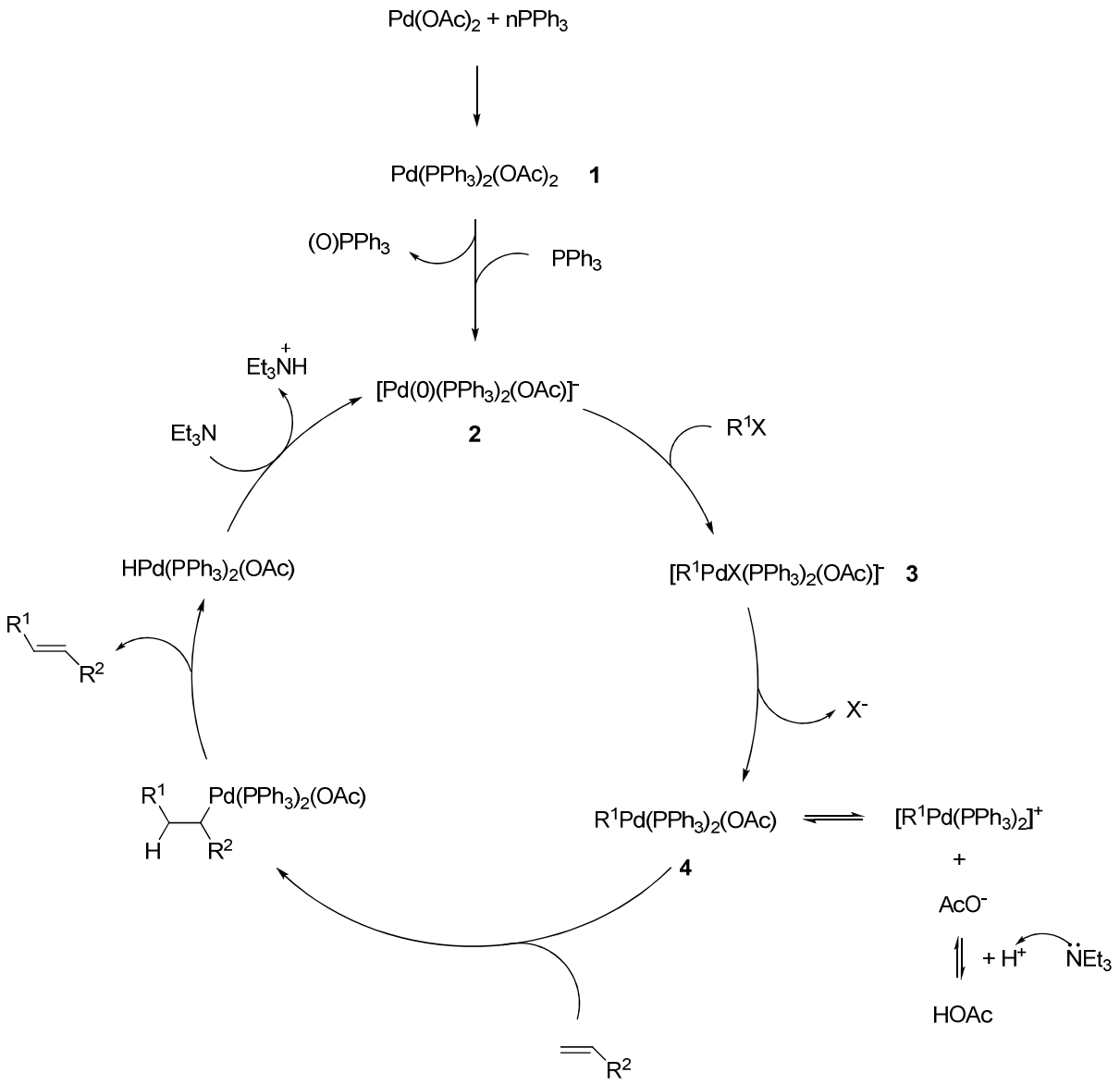


R1 = Ar, vinyl **R2** = EWG, EDG
X = I, Br, Cl, OTf, OTs, N_2^+

Scheme 3 *General scheme for the Heck reaction*

Usually, palladium salts such as palladium(II) acetate and palladium(II) chloride are employed in the Heck reaction. Coordination with donor ligands, such as triarylphosphines, is proposed to generate a 14-electron coordinatively unsaturated palladium(0) active species.[13] This catalytic precursor, PdL_2, then undergoes oxidative addition of R^1X to generate *cis*-R^1PdXL_2, which then isomerises to give the thermodynamically more stable *trans*-R^1PdXL_2 complex. Alkene insertion into the Pd–R^1 bond takes place following loss of a monodentate phosphine ligand and *syn*-addition to the neutral palladium complex, to form an unstable σ-bond. Rotation about this newly formed C–C bond and β-hydride elimination generates the new substituted alkene, which is expelled from the system. The active PdL_2 complex is regenerated following the addition of base, to remove HX from the system, and the cycle continues. According to current thinking, the exact mechanism in operation in a given reaction is dependent upon the ligand, the base, and the solvent used during the reaction.[22] Typically, inorganic bases such as sodium, potassium or caesium carbonate have been employed, in addition to potassium acetate, potassium *tert*-butoxide and caesium pivalate. Polar, aprotic solvents such as dimethylformamide, dimethylacetamide, acetonitrile, *N*-methyl-2-pyrrolidone and dimethyl sulfoxide are commonly used, although nonpolar solvents, toluene and xylene, have also been successfully employed.[17]

In the last decade, investigations by Amatore and Jutand have made vast contributions towards understanding the mechanisms of palladium-catalysed Heck and cross-coupling reactions.[12] They were the first group to propose that the initial complex formed on the addition of phosphine ligands to palladium(II) acetate in the Heck reaction, was in fact the unstable $Pd(PPh_3)_2(OAc)_2$ species **1** (Scheme 4). This complex then undergoes intramolecular reduction by ligated triphenylphosphine, to generate the unstable intermediate $[Pd(PPh_3)(OAc)]^-$. Subsequent coordination of a further molecule of triphenylphosphine results in formation of the active species $[Pd(PPh_3)_2(OAc)]^-$ (**2**), which is believed to initiate the catalytic cycle. As with the cross-coupling reactions described previously, oxidative addition of R^1X to this anionic complex proceeds rapidly to give anionic pentacoordinated complex $[R^1PdX(PPh_3)_2(OAc)]^-$ (**3**). Following the loss of halide anion X^-, the resulting neutral *trans*-$R^1Pd(PPh_3)_2(OAc)$ species **4** has been found to be the key reactive intermediate towards alkene insertion. It is clear from these results that the type of halide anion present plays an important role in determining the reactivity of this intermediate, in addition to the chosen catalyst, additives, substrate and reaction conditions.



Scheme 4 *Amatore and Jutand's proposed mechanism for the Heck reaction*

Additionally, Herrmann and Beller *et al*. were the first group to report the use of palladacycles as active catalysts in Heck reactions, *via* a palladium(0)-species.[23] An alternative palladium(II)/palladium(IV) catalytic cycle was reported by Milstein and co-workers for other cyclometallated palladium catalyst precursors.[24] Furthermore, Evans *et al*. have shown that the anionic palladium species, $[Pd_2X_6]^{2-}$ may be the active catalyst for phosphine-free Heck reactions.[25]

The Heck reaction has many applications, including natural product synthesis[26] and the production of fine chemicals on a multi-ton scale/year, such as the herbicide Prosulfuron™, the anti-inflammatory Naproxen™ and the anti-asthma agent Singulair™ (Figure 1).[27,28]

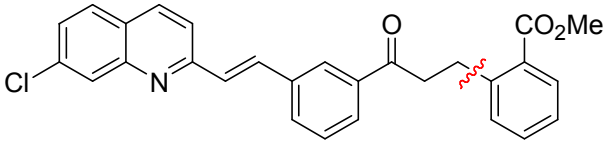
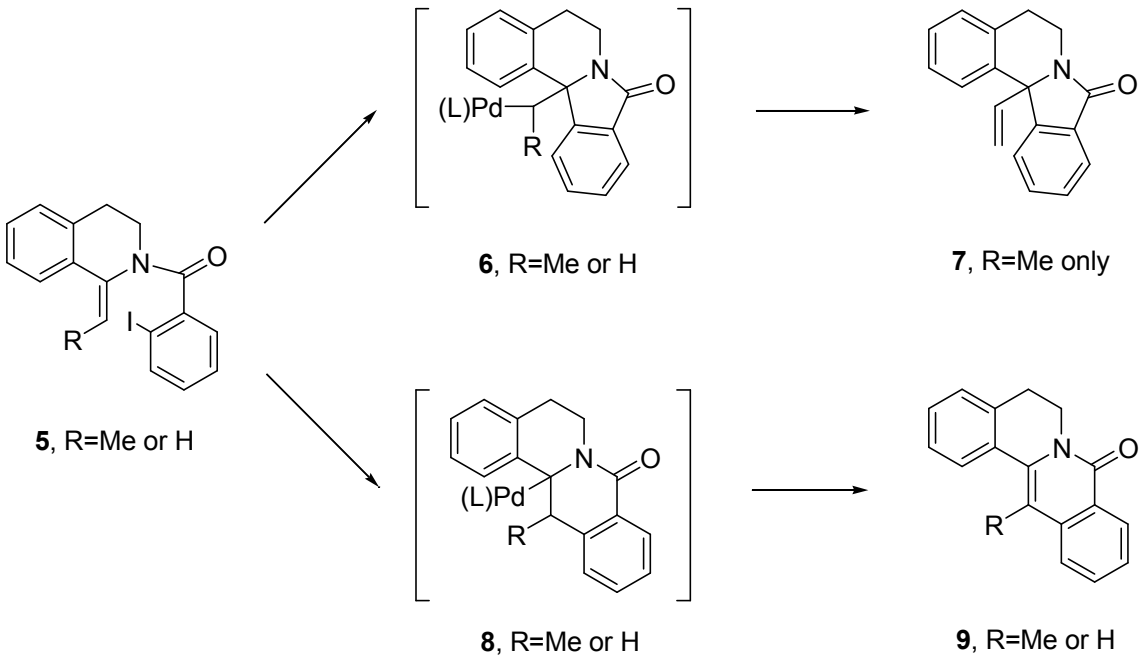


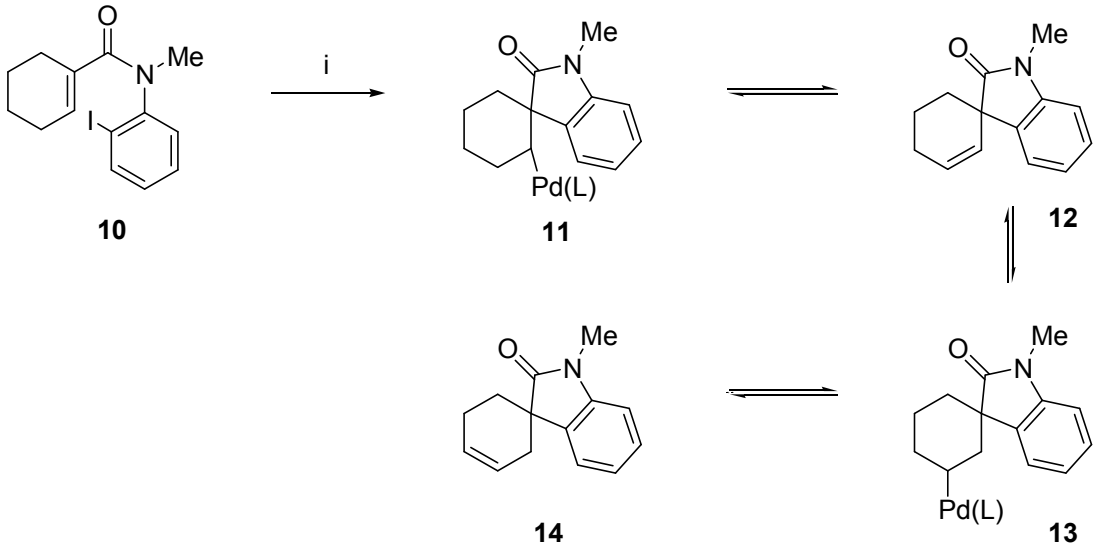
Figure 1 *Heck disconnection in ketone intermediate of Singulair™*

This methodology is also frequently applied in intramolecular mode to the construction of 5- and 6-membered rings.[29] Here, the choice of catalyst, base, reaction conditions and substrate permits manipulation of the reaction *via* the preferred 5-*exo*-trig or the alternative 6-*endo*-trig cyclisation pathways. For example palladium(II) acetate-catalysed cyclisation of **5** yields a mixture of **7** and **9** in a 10:1 ratio when R=Me, but **9** is isolated exclusively when R=H (Scheme 5).[30] This can be rationalised when you consider that when R=H, organopalladium intermediate **6** derived from 5-*exo*-trig cyclisation of **5**, lacks the necessary β-hydrogen to eliminate to product **7,** forcing the 6-*endo*-trig pathway *via* intermediate **8**.



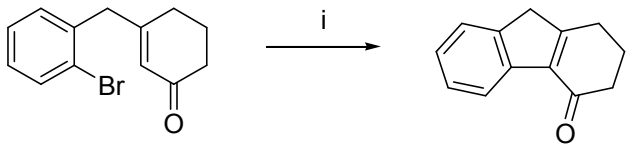
Scheme 5 *Reagents and conditions:* $Pd(OAc)_2$ (0.1 mol%), PPh_3 (0.2 mol%) , K_2CO_3 (2.0 equiv), $Et_4N^+Cl^-$ (1.0 equiv), MeCN, 80 °C, 1 h.

Double bond isomerisation is an issue in many Heck reactions, for example in the cyclisation of iodide **10** (Scheme 6).[31] Lactam **12** and its double bond isomer **14** are isolated in a 1:1 ratio, following treatment with palladium(II) acetate and triphenylphosphine. Isomer **14** is proposed to arise from re-addition of the Pd–H reductive elimination species to **12**, *via* intermediate **13**. Addition of silver nitrate to the reaction mixture suppresses this isomerisation by trapping the hydriodic acid generated in the reaction and therefore preventing re-addition of the Pd–H species. A 26:1 mixture of products **12** and **14** can then be obtained, in 70% yield.



Scheme 6 *Reagents and conditions:* i) $Pd(OAc)_2$ (3 mol%), PPh_3 (12 mol%), Et_3N (2.0 equiv), MeCN, reflux, 36 h.

An alternative way to control double bond isomerisation and also to improve regioselectivity in the Heck reaction, is through the incorporation of an α,β-unsaturated carbonyl moiety. Palladium-catalysed cyclisations of alkenyl and aryl halides containing a tethered α,β-unsaturated carbonyl, are highly regioselective (Scheme 7).[32]



Scheme 7 *Reagents and conditions:* i) $Pd(OAc)_2(PPh_3)_2$ (10 mol%), $NaHCO_3$ (2.0 equiv), DMF, 80 °C, 68%.

1.1.4 Functionalisation of Heteroaromatic C–H bonds

The use of cross-coupling reactions for the preparation of alkylated and arylated heteroaromatic compounds has seen a dramatic increase over the past two decades. This has been driven by the increasingly complex structures of new drugs containing one or more heterocyclic motif, and by the development of new catalysts and reaction conditions for even the most unreactive of heteroarenes.[2] In industry, these functionalisations play an important role in lead discovery chemistry, where fast and easy access to small focused libraries is essential, and where the preparation of large batches of drug candidates is required for clinical trials as well as for manufacturing.[33]

In recent years, many examples of palladium-catalysed cross-coupling reactions of aryl iodides and bromides with unfunctionalised heteroaromatic C–H bonds have been reported.[17] Direct arylation has been shown to be possible on (benzo)furans, (benzo)thiophenes, pyrroles, (benz)oxazoles, (benz)isoxazoles, (benz)imidazoles, (benzo)thiazoles, triazoles, indoles, indolizines, purines, pyrazines, quinolines, pyridine-*N*-oxides, and *N*-oxides of other heterocycles. The inherent electronic bias of the heterocycle, where the heteroatoms in the aromatic ring may be acting as directing groups, is often sufficient to control the regioselectivity of intermolecular direct arylation reactions (Figure 2). Other factors such as the steric and electronic nature of the catalyst employed, solvent, additives and nitrogen protecting groups have also been employed to alter the regioselectivity.

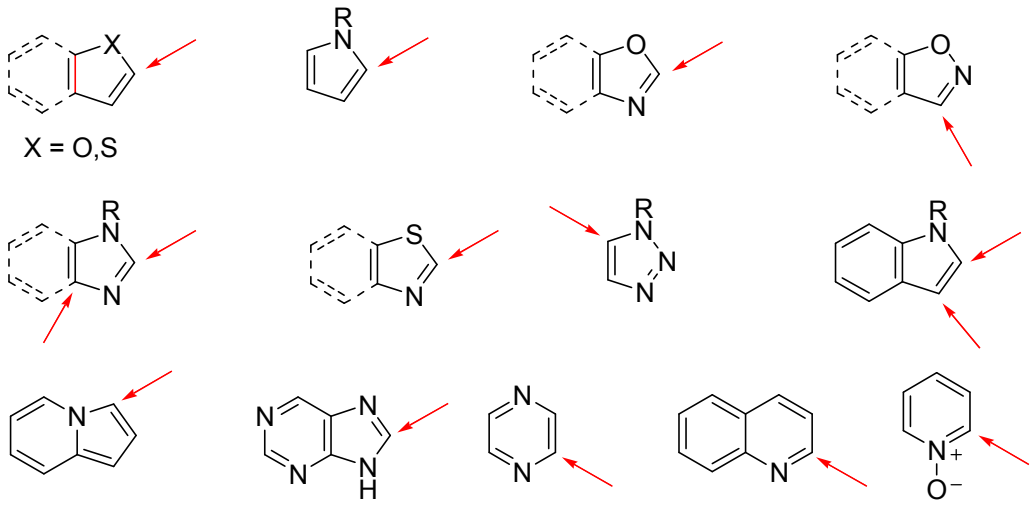
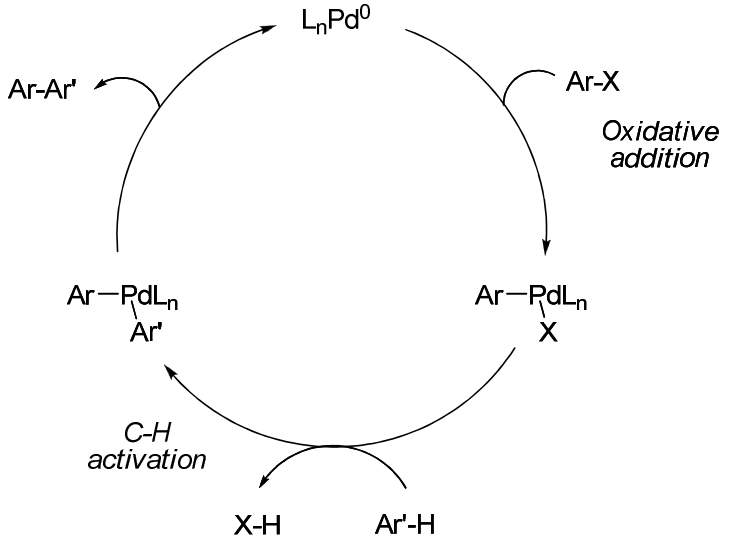


Figure 2 *Examples of heteroaromatic compounds used in direct arylation reactions, and their activated positions*

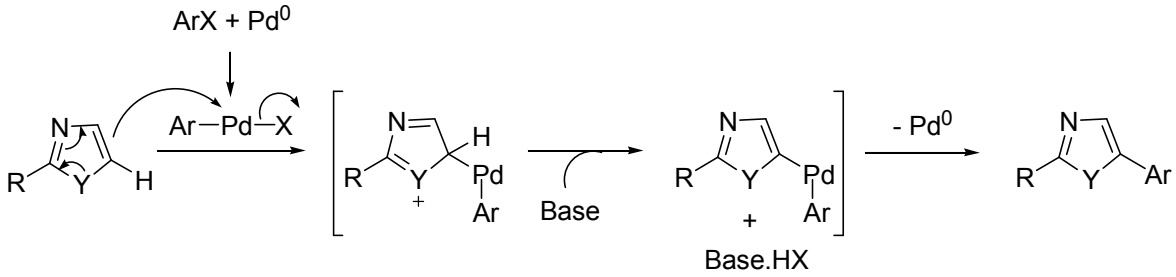
From a strategic perspective, replacement of the nucleophilic aryl organometallic component employed in classical cross-coupling reactions, is best done with electron-rich, π-nucleophilic aromatic compounds. It is therefore logical to assume that π-electron-rich heteroaromatics will exhibit a similar reactivity, which might mimic that of the organometallic at the transmetallation step of the catalytic cycle (Scheme 8).[34]



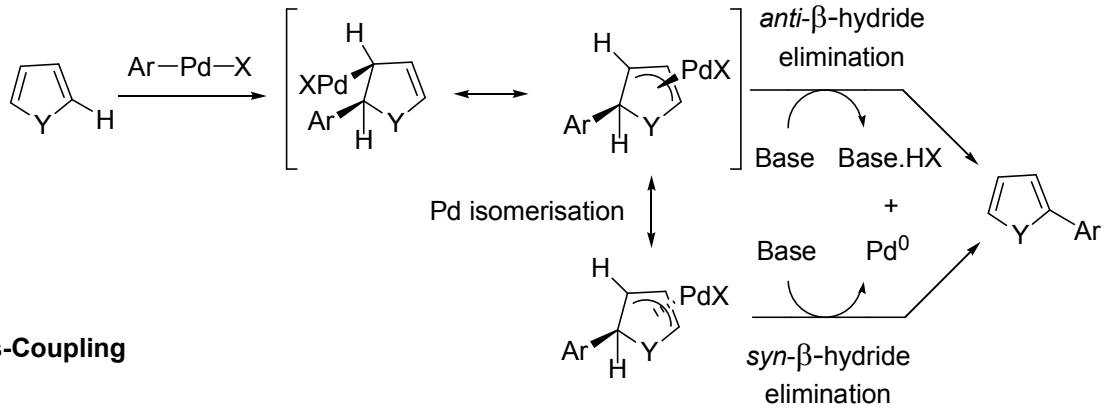
Scheme 8 *Catalytic cycle for arylation of electron-rich heterocycles*

Mechanistically, three possible pathways are proposed for the direct arylation of heteroaromatics: an electrophilic aromatic substitution; a Heck-type mechanism and a carbanion cross-coupling mechanism (Scheme 9).[17] Once again, the exact mechanism is dependent upon the substrate, catalyst, solvent and additives used. However, it is thought that the significant success achieved with the use of electron-rich heteroaromatic compounds can be attributed to the growing appreciation and application of electrophilic aromatic substitution reaction pathways in reaction design.[34]

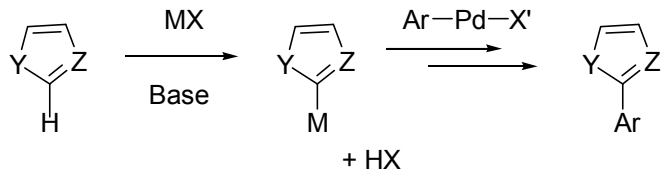
Electophilic Aromatic Substitution



Heck-Type Coupling



Cross-Coupling



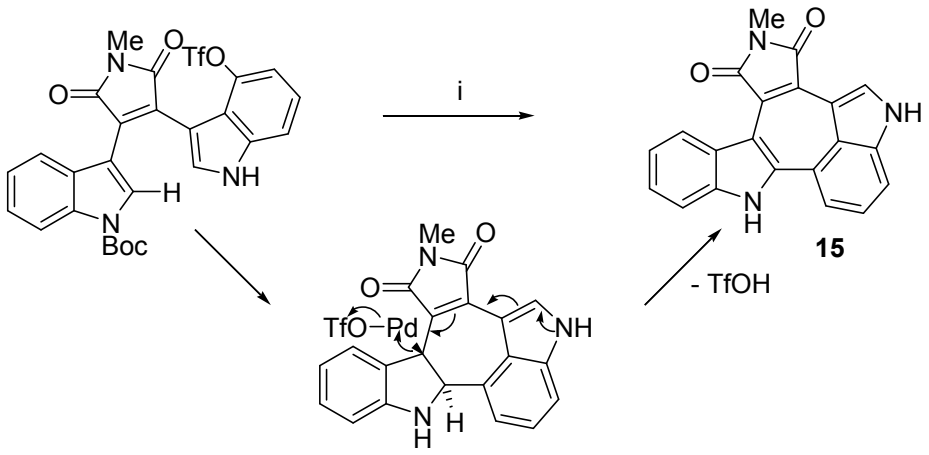
Scheme 9 *Proposed mechanistic pathways*

One of the first examples of direct arylation of heterocyclic arenes appeared in the early 1980's, when Ames and co-workers reported the first intramolecular direct arylation reaction involving pyridine.[35] Numerous other examples of arylation reactions of heteroaromatic substrates have since been reported and a comprehensive review on direct arylation of heteroaryl C–H bonds was published by Lautens and Alberico in 2007.[17]

This section of the review summarises some early reports of direct arylation according to heterocycle type and also discusses some more recent examples. Efforts have been made to focus on cases where reaction mechanism and regioselectivity have been extensively explored.

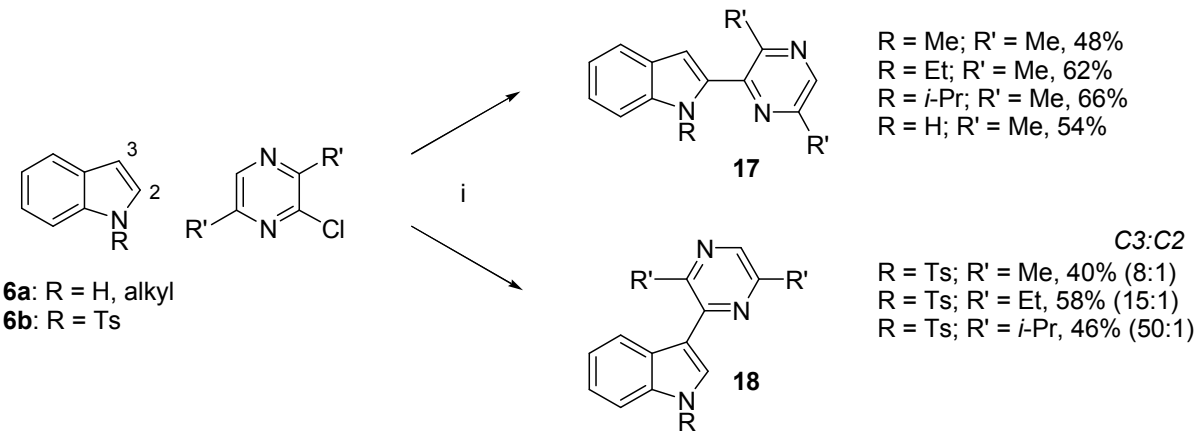
1.1.5 Aryl–Indolyl Bond Formation

Steglich and co-workers reported the intramolecular coupling of two indole fragments under palladium-catalysed conditions as the key step in the synthesis of slime mold alkaloid analogue, *N*-methylarcyriacyanin A (**15**).[36] The authors propose that cyclisation takes place *via* a carbopalladation/base-catalysed fragmentation pathway, as *syn*-elimination is not possible (Scheme 10). Alternatively, cyclisation could occur *via* a Heck-type coupling followed by *anti*-β-hydride elimination, or palladium isomerisation and *syn*-β-hydride elimination.



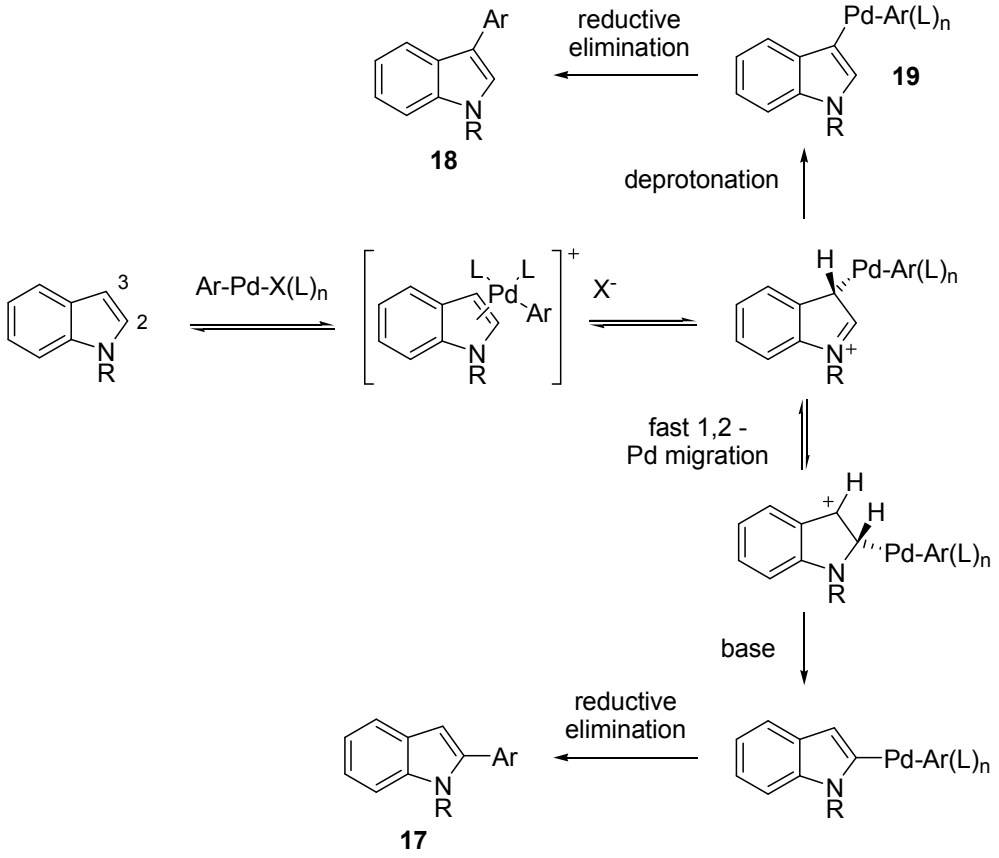
Scheme 10 *Reagents and conditions:* i) $Pd(OAc)_2$ (0.12 mol%), dppp (0.14 mol%), Et_3N, DMF, 110 °C, 18 h, 81%.

Ohta and co-workers reported the first intermolecular direct arylation of indole using chloropyrazines, and observed that the nature of the indole nitrogen protecting group had a profound effect on the regioselectivity of the reaction.[37] While the use of *N*-alkyl and *NH*-indoles **16a** gave the desired 2-pyrazinylindoles **17** in modest yields, *N*-tosylindole **16b** was found to favour the 3-pyrazinylindole product **18**. This C-3-selectivity was further increased with more sterically bulky pyrazine coupling partners (Scheme 11).



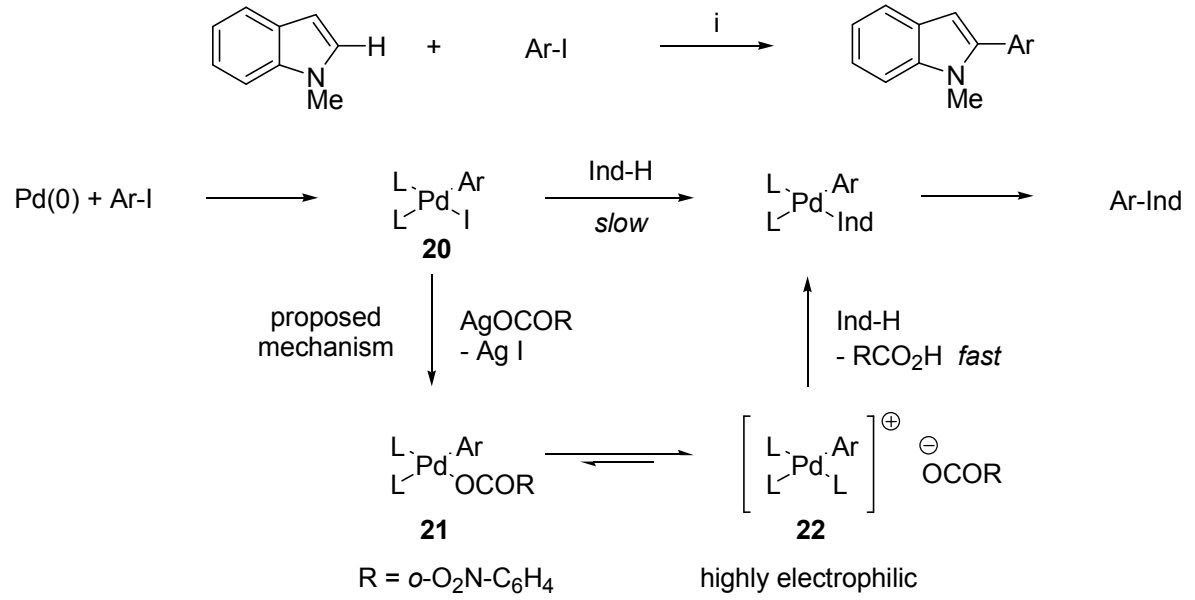
Scheme 11 *Reagents and conditions:* i) $Pd(PPh_3)_4$ (5 or 8.3 mol%), KOAc (1.2 equiv), DMA, reflux.

Mechanistic studies suggested that the reaction proceeds *via* initial electrophilic metallation at the 3-position, followed by 1,2-palladium migration, deprotonation, and reductive elimination (Scheme 12). Therefore, it is proposed that the poor regioselectivity associated with bulky aryl halides may be due to a slow 1,2-palladium migration, favouring deprotonation and subsequent formation of 3-metalloindole intermediate **19**. Reductive elimination of this intermediate would then provide the observed 3-arylindole product **18**.



Scheme 12 *Mechanisms of intermolecular direct arylation of indoles*

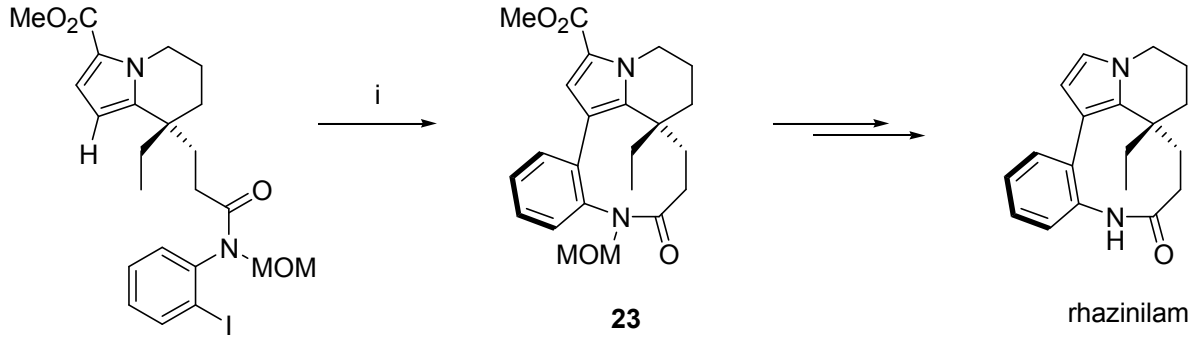
More recently, there has been an emphasis on the design of direct arylation reactions that can be performed under milder reaction conditions and at lower temperatures. Sanford *et al.* reported selective C-2 arylation of indoles, which could be carried out at room temperature *via* a proposed Pd(II)/Pd(IV) catalytic cycle.[38] Similarly, Larossa and co-workers developed an alternative ligand-free direct C-2 arylation of indoles with aryl iodides, at room temperature.[39] It was found that employing a silver salt to remove iodide from palladium(II) oxidative addition complex **20**, gave a cationic palladium species **22**, which was then more electrophilic towards carbopalladation (Scheme 13). Mechanistically, both a Pd(0)/Pd(II) and a Pd(II)/Pd(IV) are proposed. Additionally, in 2010 Djakovitch *et al.* reported site-selective palladium-catalysed C–H arylation of *NH*-indoles, on water.[40]



Scheme 13 *Reagents and conditions:* i) $Pd(OAc)_2$ (5 mol%), Ag_2O (0.75 equiv), *o*-O_2N-C_6H_4-CO_2H (1.5 equiv), DMF, 25 °C, 18 h.

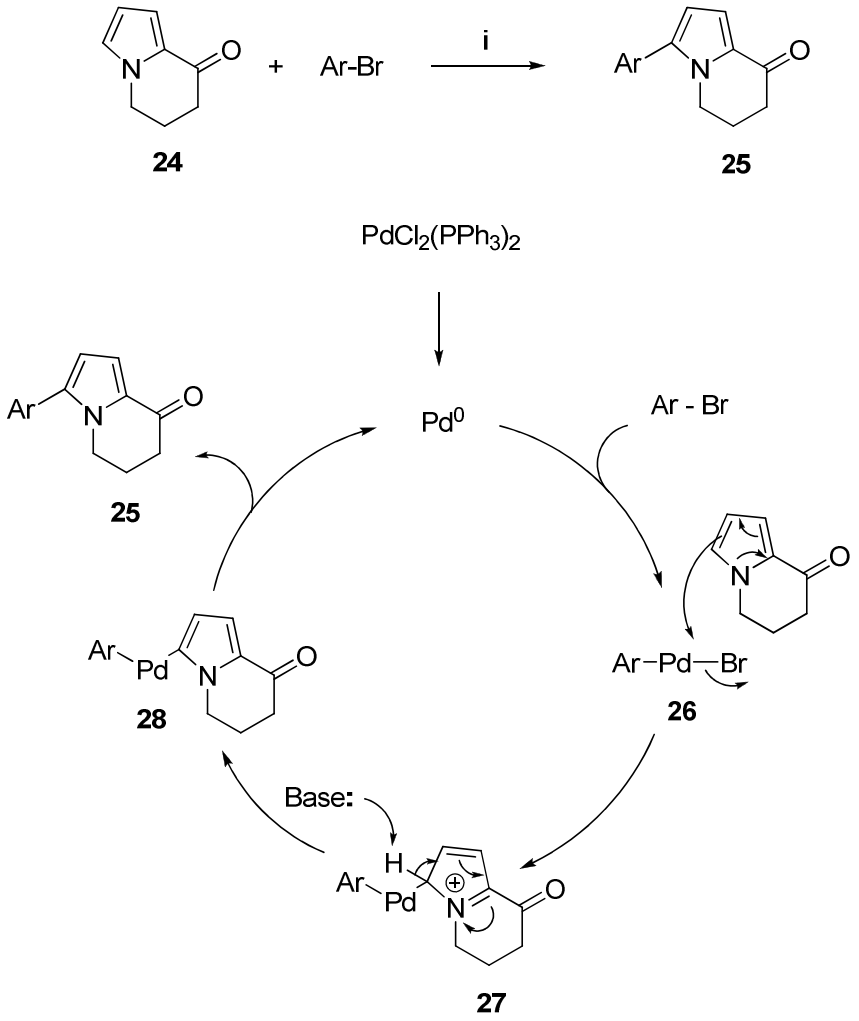
1.1.6 Aryl–Pyrrolyl Bond Formation

Intramolecular aryl–pyrrolyl bond formation was demonstrated by Trauner *et al.* during the total synthesis of (–)-rhazinilam.[41] Cyclisation of an aryl iodide onto the pyrrole ring took place following treatment with catalytic palladium and Buckwald's DavePhos ligand, to give the rhazinilam precursor **23** (Scheme 14).



Scheme 14 *Reagents and conditions:* i) $Pd(OAc)_2$ (10 mol%), DavePhos (13 mol%), K_2CO_3 (2.0 equiv), DMA, 145 °C, 12 h, 47%.

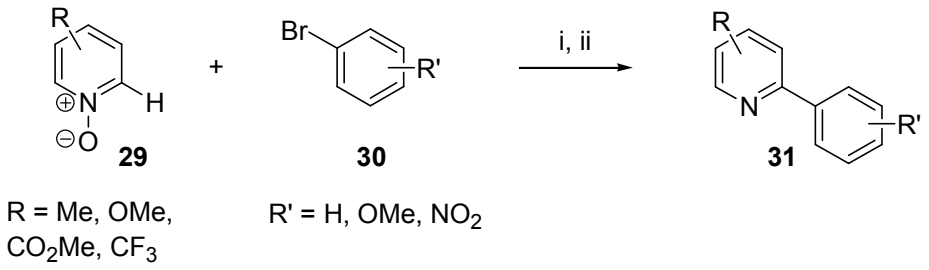
Regioselective, direct intermolecular arylation of pyrroles using ligand-free palladium catalysts has been reported by Doucet[42] and Jafarpour.[43] In addition, Lemaire and co-workers have developed a regioselective C-3 arylation of 8-oxo-5,6,7,8-tetrahydroindolizines **24**.[44] Treatment with a catalytic palladium(II) source, in the presence of potassium acetate base and water additive, gave good to excellent yields of 3-aryl-8-oxo-5,6,7,8-tetrahydroindolizines **25** (Scheme 15). Mechanistic studies led to the proposal of an electrophilic substitution pathway for these transformations. Following oxidative addition of aryl bromide, the 3-position of the pyrrole ring undergoes electrophilic attack by aryl-palladium species **26**, to form intermediate **27**. Deprotonation followed by reductive elimination of aryl(tetrahydroindolizinone)palladium(II) **28**, gave product **25** and the regenerated palladium(0) catalyst.



Scheme 15 *Reagents and conditions:* i) $PdCl_2(PPh_3)_2$ (0.5 mol%), KOAc (2.0 equiv), H_2O (0.2 equiv), NMP, 100 °C, 89 h.

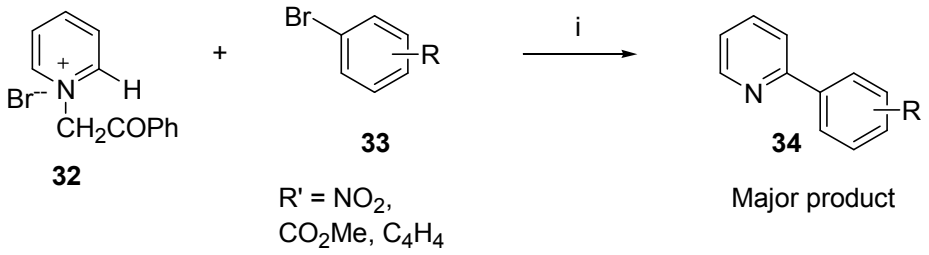
1.1.7 Aryl–Pyridyl Bond Formation

Direct arylation reactions with π-electron-deficient heteroarenes, such as pyridine, constitute a challenging transformation.[45] Fagnou *et al.* reported the regioselective preparation of 2-arylpyridines **31**, through the palladium-catalysed coupling of pyridine *N*-oxides **29** and aryl bromides **30** (Scheme 16). Both electron-rich and electron-poor pyridine *N*-oxides react exclusively at the C-2 position and tolerate sterically hindered, as well as electron-rich and electron-poor aryl bromides. Furthermore, deprotection to the corresponding 2-arylpyridines takes place under mild conditions and in high yields, *via* palladium-catalysed hydrogenolysis.



Scheme 16 *Reagents and conditions:* i) $Pd(OAc)_2$ (5 mol%), $^tBu_3P{\cdot}HBF_4$ (0.15 mol%), K_2CO_3 (2.0 equiv), toluene, 110 °C, 16 h; ii) Pd/C (10 mol%), $HCOONH_4$ (10.0 equiv), MeOH, rt.

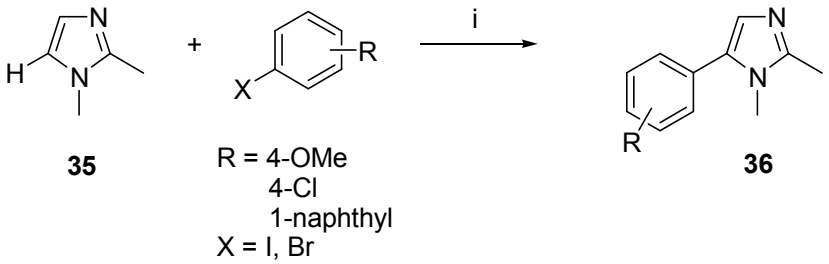
More recently, Wang and co-workers reported a novel palladium-catalysed C-2 arylation of *N*-phenacylpyridinium bromide **32** (Scheme 17).[46] The carbonyl group of the *N*-phenacyl substituent regioselectively activates the *ortho*-C–H bond of pyridine, *via* coordination to palladium. Following arylation, the *N*-phenacyl group is spontanously eliminated as acetophenone and 2-arylpyridine **34** is obtained as the major product as a mixture with 2,6-diarylpyridine. However, employing bromobenzenes **33** with strongly electron-withdrawing or sterically bulky substituents, resulted in mono-arylated pyridine **34** as a single product. Kinetic isotope effect studies suggested that this arylation takes place *via* a C–H bond activation pathway.



Scheme 17 *Reagents and conditions:* i) $Pd(OAc)_2$ (5 mol%), PPh_3 (0.15 equiv), K_2CO_3 (3.0 equiv), toluene, reflux, 16 h.

1.1.8 Alternative Nitrogen-Containing Heteroaromatics

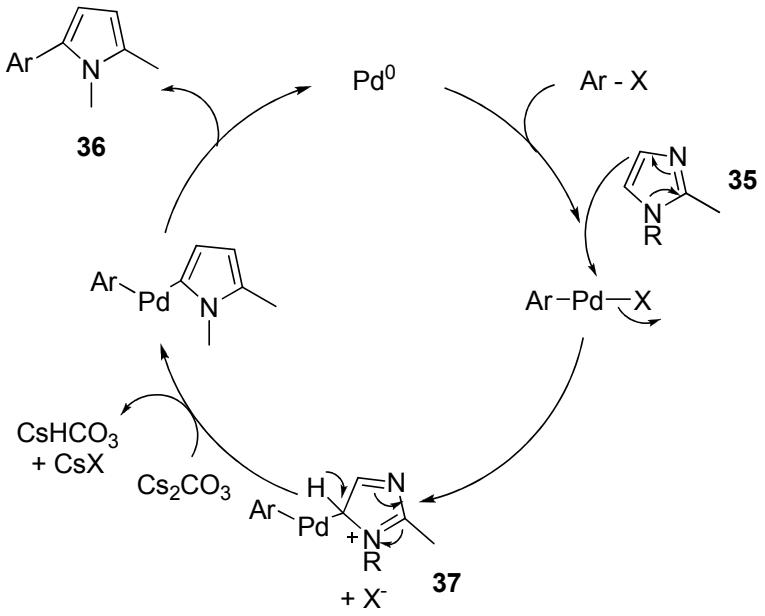
Numerous other nitrogen-containing five- and six-membered heterocyclic ring systems have been shown to undergo direct arylation.[17] Miura and co-workers reported regioselective C-5 intermolecular palladium-catalysed arylation of a variety of azoles **35**.[47] The scope of the reaction was found to be fairly broad, affording good to excellent yields for a variety of electron-rich, electron-poor, and sterically-hindered aryl iodides and bromides. The methodology was extended to oxazoles, benzoxazoles, thiazoles and benzothiazoles (Scheme 18).



Scheme 18 *Reagents and conditions:* i) $Pd(OAc)_2$ (5 mol%), PPh_3, Cs_2CO_3, DMF, 140 °C.

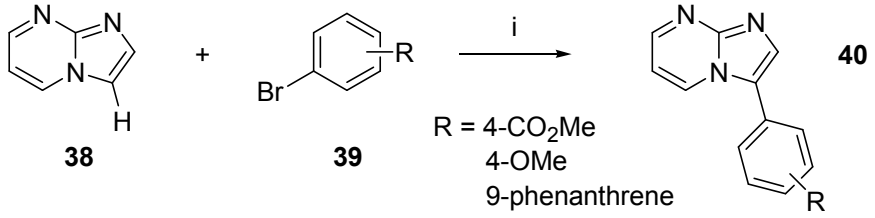
The authors also discovered that for *N*-methylimidazole and thiazole, the selectivity of the C–H bond undergoing arylation could be controlled by altering the catalyst system used. Under palladium-catalysed conditions, arylation of the azole occurred preferentially at the C-5 position, followed by a subsequent arylation at the C-2 position. However, employing a copper iodide additive in the absence of palladium exclusively gave the C-2 arylated product.[47] It was proposed that this copper-mediated arylation occurs *via* a Cu(I)/base-assisted nucleophilic substitution of the aryl iodide.

For the palladium-catalysed arylation process, the authors propose that the reaction proceeds *via* initial oxidative addition of palladium(0) to the aryl halide, followed by nucleophilic attack of azole **35** to afford σ-azole/arylpalladium(II) adduct **37**. Base-mediated deprotonation followed by reductive elimination then affords the arylated product **36** (Scheme 19).[47]



Scheme 19 *Proposed mechanism for arylation of C-5 azoles*

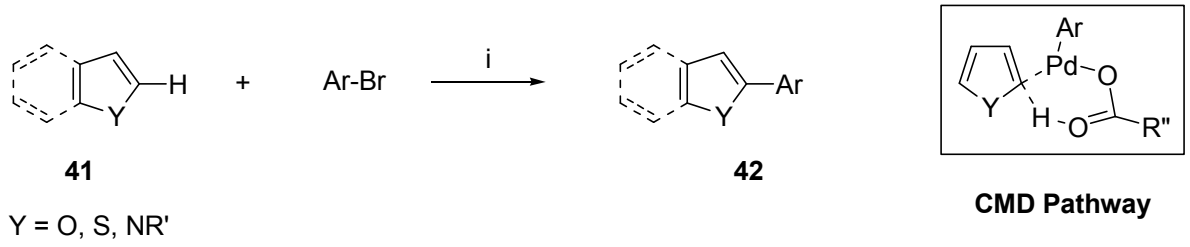
The direct arylation of a variety of other related nitrogen-containing fused heterocyclic ring systems has also been reported.[17] Li *et al.* described the intermolecular palladium-catalysed direct arylation of imidazo[1,2-*a*]pyrimidines **38** with a range of aryl bromides **39** (Scheme 20).[48] In general, coupling with electron-deficient aryl bromides led to higher yields than coupling with their electron-rich counterparts. Furthermore, coupling was found to occur exclusively at the π-rich 3-position, which suggests that an electrophilic aromatic substitution mechanism is occurring, similar to the one described above (Scheme 19).



Scheme 20 *Reagents and conditions:* i) $Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%), Cs_2CO_3 (2.0 equiv), dioxane, 100 °C, 12-36 h.

More recently, Fagnou *et al.* reported broadly applicable reaction conditions for the palladium-catalysed direct arylation of a range of heteroaromatic compounds **41** with aryl bromides (Scheme 21).[49] Uniquely, their methodology employed a stoichiometric ratio of

both coupling partners and insoluble carbonate base, in addition to a sub-stoichiometric amount of pivalic acid. A concerted metallation-deprotonation pathway (CMD) is proposed, whereby potassium pivalate generated *in situ* acts as a soluble proton transfer reagent from the arene and palladium catalyst to the insoluble carbonate base resulting in acceleration of direct arylation.[50]



41

Y = O, S, NR'

42

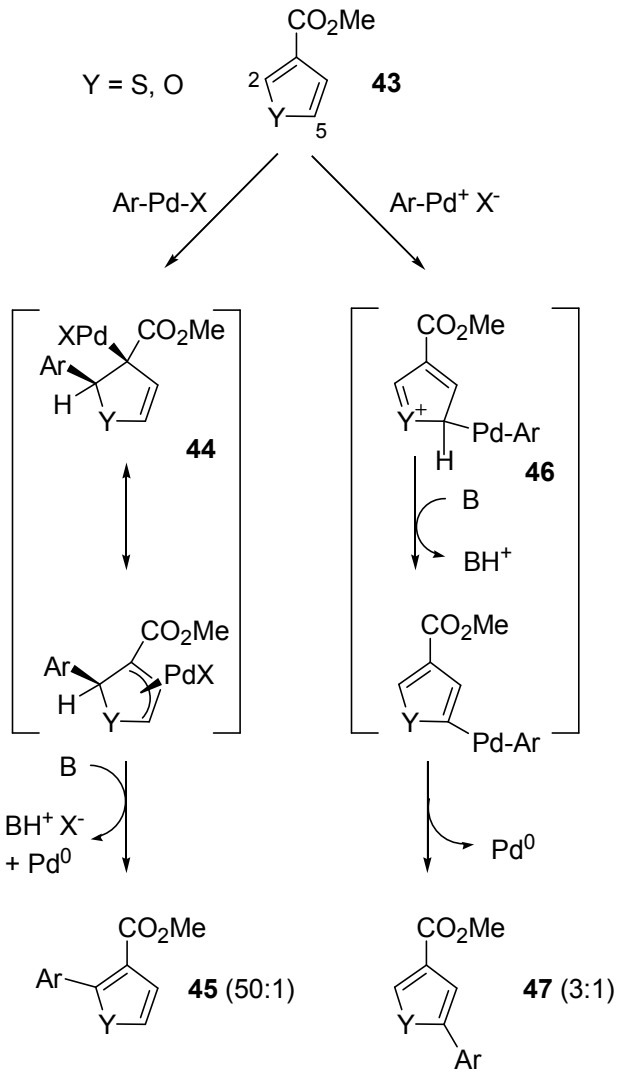
CMD Pathway

Scheme 21 *Reagents and conditions:* i) $Pd(OAc)_2$ (2 mol%), $PCy_3{\cdot}HBF_4$ (4 mol%), PivOH (30 mol%), K_2CO_3 (1.5 equiv), DMA, 100 °C.

1.1.9 Aryl–Furyl and Aryl–Thiophenyl Bond Formation

Ohta and co-workers reported the first catalytic direct C-2 arylation of furan, thiophene, benzothiophene, and benzofuran in 1990.[51] Almost all electron-poor aryl bromides used in their study gave the desired products in modest yields, whereas those lacking an electron-withdrawing group were found to give little or no arylated products.

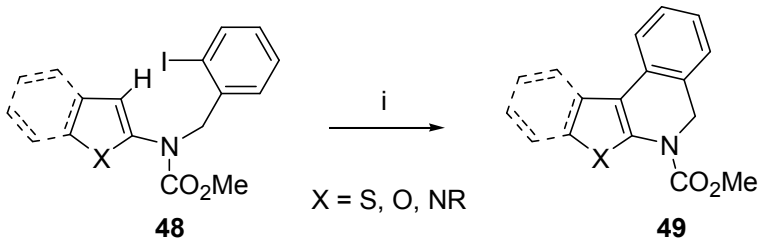
More recently, Sharp *et al.* discovered that the most important factors influencing the regiochemistry of direct arylation of activated 3-(methoxycarbonyl)thiophenes **43** with electron-poor aryl bromides, were a combination of solvent and catalyst type (Scheme 22).[52] The authors propose that in the presence of a nonpolar solvent such as toluene and a phosphine-ligated palladium catalyst, σ-bonded palladium-(II) species **44** is favoured, which promotes a Heck-type reaction to give the C-2 arylated product **45**. However, employing a polar aprotic solvent such as NMP with a phosphine-free palladium catalyst is likely to promote ionisation of Pd–X, to give a cationic palladium species which undergoes an electrophilic substitution at the more electron-rich C-5 position to give cationic intermediate **46**. Base-promoted deprotonation and reductive elimination of the palladium(II) species therefore affords the C-5-arylated product **47**.



Scheme 22 *C-2 vs. C-5 arylation of 3-(methoxycarbonyl)thiophenes and furans*

The regioselective arylation of 3-(methoxycarbonyl)furans was also reported. Again, use of a nonpolar solvent and phosphine-ligated palladium catalyst favoured the C-2-arylated product, while use of a polar aprotic solvent such as NMP and Pd/C favoured the formation of the C-5-arylated product.[52]

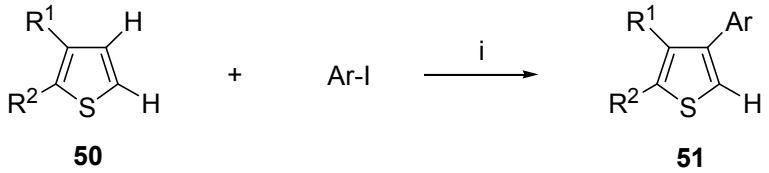
Becalli and co-workers investigated the microwave-assisted intramolecular cyclisation of carbamates of heterocycles such as furans, thiophenes and indoles (**48**) to afford polycyclic fused systems **49** (Scheme 23).[53] Both aryl- and vinyl halides can be employed for the synthesis of a variety of nitrogen-containing heterocycles. An electrophilic substitution pathway is once again considered the most plausible mechanism for this transformation.[54]



48 **49**

Scheme 23 *Reagents and conditions:* i) $Pd(OAc)_2$ (10 mol%), PPh_3 (1.0 equiv), KOAc (2.0 equiv), DMA, 100 °C, μw, 1 h.

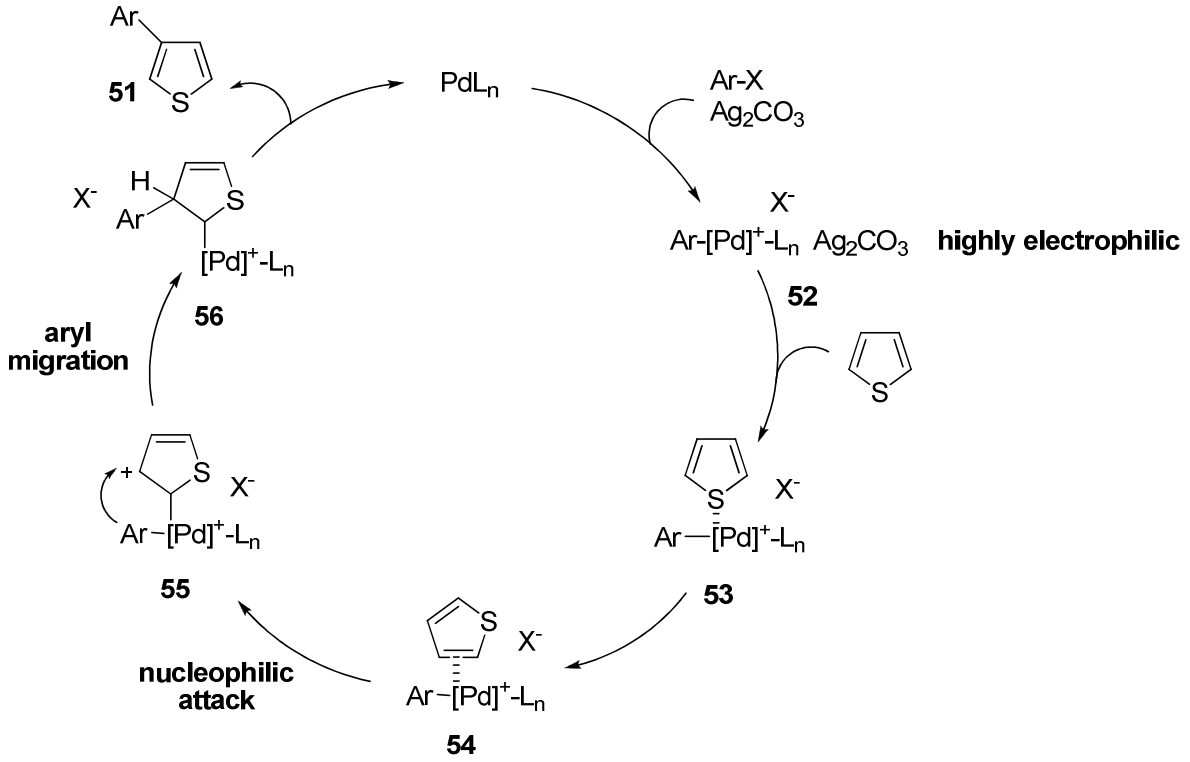
Finally, Itami *et al.* reported the first general catalytic system for the β-selective arylation of thiophene C–H bonds (Scheme 24).[55] Both electron-rich and electron-deficient aryl groups could be installed on the thiophene ring at the β-position and the observed selectivity was found to override the influence of *ortho*-/*para*- and *meta*-directing groups on the heteroaromatic **50**. The observed regioselectivities are thought to be the result of catalyst control and the highly electron-withdrawing phosphine $P[OCH(CF_3)_2]_3$, was found to be the best ligand for β-selective arylation.



50 **51**

Scheme 24 *Reagents and conditions:* i) $PdCl_2$ (5 mol%), $P[OCH(CF_3)_2]_3$ (10 mol%), Ag_2CO_3 (1.0 equiv), *m*-xylene, 130 °C, 12 h.

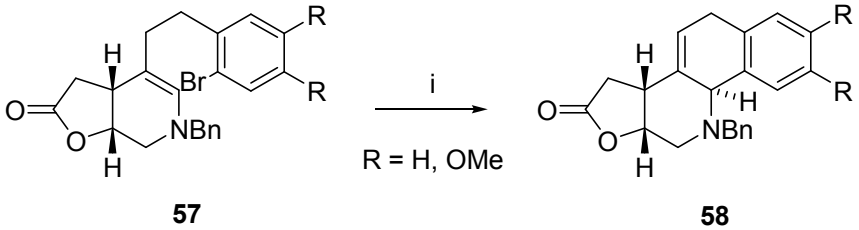
The proposed mechanism involves silver-mediated generation of a cationic and electrophilic aryl palladium complex **52**, following oxidative addition. Co-ordination of the thiophene to this complex gives intermediates **53** and/or **54** and σ-bond formation gives palladium(II) species **55**. Migration of the aryl group from palladium to the cationic β-position affords aryl–palladium intermediate **56**, and subsequent proton abstraction eliminates palladium to give β-aryl thiophene **51** (Scheme 25).[55]



Scheme 25 *Proposed catalytic cycle for β-arylation of thiophenes*

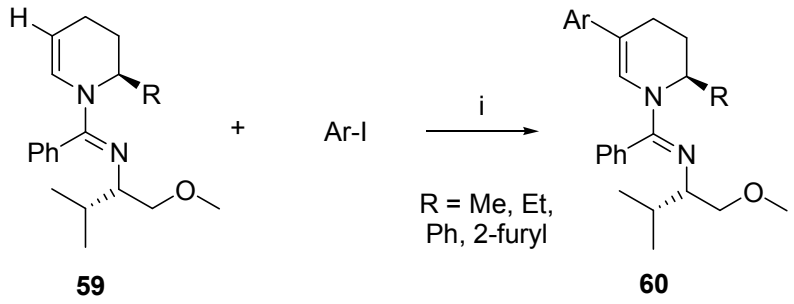
1.1.10 Direct Arylation of Tetrahydropyridines

To date, few examples exist of direct arylation reactions of tetrahydropyridines and cyclic enamines. Aurrecoechea and co-workers reported the intramolecular palladium-catalysed cyclisation of tetrahydropyridines **57** with a tethered aryl-halide functionality at the β-carbon of the enamine, to give polycyclic products **58** (Scheme 26).[56] A highly regio- and stereoselective Heck-type coupling of the electron-rich enamine double bond was found to take place *via* a 6-*endo*-trig pathway and the major product displayed an exocyclic alkene moiety on the piperidine ring.



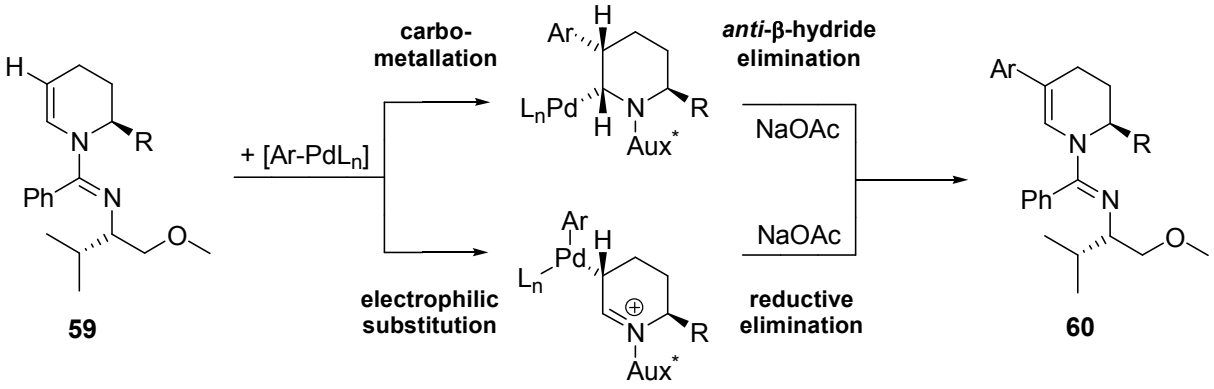
Scheme 26 *Reagents and conditions:* i) $Pd(OAc)_2$ (5 mol%), P(*o*-tolyl)$_3$ (10 mol%), TlOAc (1.1 equiv), DMF, 120 °C, 3.5-6 h.

Charette *et al.* reported a highly regioselective intermolecular β-arylation of 1,2,3,4-tetrahydropyridines **59**, in 2008 (Scheme 27).[57] The issue of regioselectivity in this arylation reaction is thought to have been overcome by employing a silver phosphate additive, which also abstracts halogen anions to generate a cationic palladium species.[58] β-Arylation was successful for a range of aryl iodides bearing electron-rich and electron-poor substituents, although the latter required longer reaction times. Heteroaryl iodides also gave the desired β-arylated product **60** in moderate yields. Furthermore, highly functionalised piperidines are accessible from these arylation products *via* a diastereoselective hydrogenation or a tandem epoxidation–nucleophilic ring opening sequence.



Scheme 27 *Reagents and conditions:* i) $PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mol%), Ag_3PO_4 (0.6 equiv), NaOAc (1.2 equiv), DMF, 150 °C, 6-24 h.

Two possible mechanisms are proposed to account for the regioselectivity observed in the arylation reaction: (i) a Heck-type carbo-palladation followed by an *anti*-β-hydride elimination, and (ii) an electrophilic substitution from the enamine, followed by deprotonation and reductive elimination (Scheme 28).[57]



Scheme 28 *Proposed mechanisms for the arylation of 1,2,3,4-tetrahydropyridines*

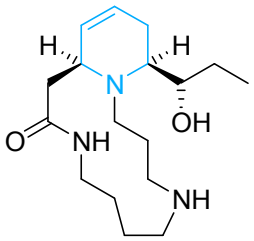
1.1.11 Conclusions

Transition metal-catalysed reactions are very attractive for the synthesis and substitution of heteroaromatic substrates.[2] Catalytic aromatic C–H activation and direct arylation have recently received significant attention and are emerging as valuable and efficient tools for these C–C bond forming processes.[50] Unlike traditional palladium-catalysed cross coupling reactions, the direct arylation of a heterocyclic core eliminates the need for establishing a reactive functionality through halogenation or stoichiometric metallation prior to C–C coupling, resulting in fewer reaction steps and reduced waste.[59]

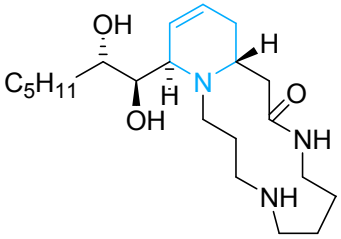
Over the last 20 years, the development of new catalyst systems for direct arylation has grown considerably to enable the formation of a wide range of aryl–aryl, aryl–heteroaryl, and heteroaryl–heteroaryl bonds, as illustrated in this review. More recently, studies have focused on developing milder, lower temperature and ligand-free direct arylation reactions. It is expected that direct arylation will become a valuable tool for diverse academic and industrial applications in the future.[17]

1.2.0 Tetrahydropyridines in Organic Synthesis

Nitrogen-containing heterocyclic compounds are commonly used as scaffolds in designing biologically active compounds.[60] Tetrahydropyridine units are present in many naturally occuring products. (+)-Palustrine **61** is a toxic component of the horsetail plant *Equisetum paluster* L., isolated in 1948, which results in loss of appetite, weight loss and milk secretion in cows, and (+)-cannabisativine **62** is an alkaloid, which was isolated from *Cannibis sativa* L. in 1975 (Figure 3).[61,62]



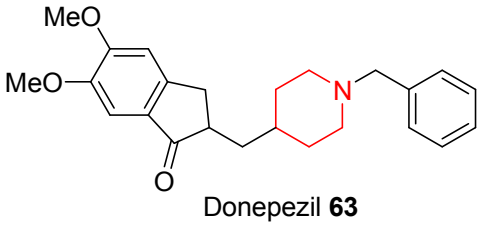
(+)-palustrine **61**



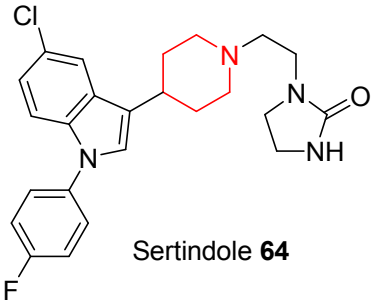
(+)-cannabisativine **62**

Figure 3 *Natural products containing a tetrahydropyridine motif*

The piperidine ring is one of the most common motifs present in natural products and biologically active molecules.[63] Two commercial products which possess this simple ring system and exhibit interesting pharmaceutical properties include: Aricept (donepezil **63**), an acetylcholinesterase inhibitor employed in the treatment of Alzheimer's disease and Serdolect (sertindole **64**), a non-selective 5-HT/D_2 antagonist used in the treatment of schizophrenia (Figure 4).[60]



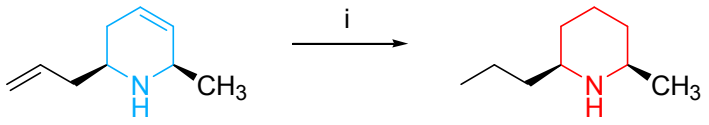
Donepezil **63**



Sertindole **64**

Figure 4 *Commercial products containing a 1,4-disubstituted piperidine ring*

Manipulation of the tetrahydropyridine double bond allows for easy access to highly substituted piperidines.[64] Therefore, these unsaturated heterocycles are often seen as key intermediates in the synthesis of chiral piperidine analogues. Hydrogenation of tetrahydropyridine **65** over Raney nickel in acetic acid, gave (±)-dihydropinidine **66**, a 2,6-disubstituted piperidine alkaloid isolated from the Mexican bean weevil, *Epilachna varivestis* (Scheme 29).[65]

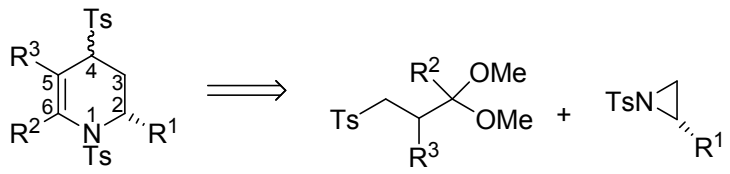


65 (±)-Dihydropinidine **66**

Scheme 29 *Reagents and conditions:* i) H_2 (100 atm), Ni, AcOH, 100 °C, 10 h, 71%.

1.2.1 Synthesis of 1,2,3,4-tetrahydropyridines

Research in the Craig group over the past fifteen years has focused on the novel reactivity of 1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines **67**. These compounds are readily assembled in enantiomerically pure form from arylsulfonyl-substituted acetals **68** and amino acid-derived *N*-tosylaziridines **69**, by lithiation of **68**, nucleophilic ring-opening of **69** and cyclocondensation of the resulting adducts (Scheme 30).[66-70]



67 **68** **69**

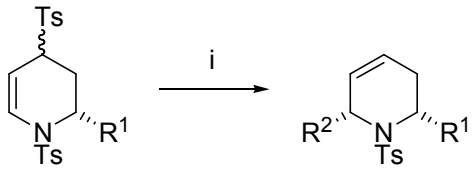
67a-e R^1 = CH_2Ph, *i*-Pr, *i*-Bu, $CH_2OTBDPS$, $CH_2(4\text{-}C_6H_4OMe)$; R^2 = H; R^3 = H, 50-91%[67,68]
67f-h R^1 = CH_2Ph, Me, *i*-Pr; R^2 = Me; R^3 = H, 72-100%[67,68]
67i R^1 = CH_2Ph; R^2 = H; R^3 = Me, 100%[68]
67j R^1 = Me; R^2 = $C_{11}H_{23}$; R^3 = H, 82%[67]
67k R^1 = $C_{12}H_{25}$; R^2 = H; R^3 = H, 62% over 3 steps[69]
67l R^1 = H; R^2 = H; R^3 = H, 90%[70]

Scheme 30 *1,2,3,4-Tetrahydropyridines synthesised by the Craig group*

It has been demonstrated that these nitrogen heterocycles enter into a variety of bond-forming reactions including S_N1' and S_N1 reactions; Lewis acid- and Brønsted acid-catalysed cyclisation; C-4 alkylation; *syn*-dihydroxylation; reduction and desulfonylation; nucleophilic addition reactions and Diels–Alder reactions.

1.2.2 S_N1' Reactivity

Tetrahydropyridines **67** undergo ionisation upon treatment with a Lewis acid to give a conjugated iminium species, which reacts with carbon nucleophiles in a 1,2-sense. Dialkyltetrahydropyridines **70** were formed exclusively as 2,6-*syn*-isomers; the complete stereoselectivity of these transformations, regardless of the configuration at C-4, confirms that these reactions proceed *via* an S_N1' mechanism. The conjugated iminium species are therefore intercepted exclusively from the α-face and nucleophilic attack takes place along the more hindered axial trajectory. It is proposed that this selectivity arises due to steric strain between the incoming nucleophile and the tosyl group on nitrogen, which is positioned on the β-face of the ring due to repulsive interactions with the axial C-2 substituent. The three substituents therefore adopt pseudo-axial orientations so as to minimise these interactions. Axial attack may also be a result of the stereoelectronic preference for a more chair-like transition-state (Scheme 31, Figure 5).[67]



67 **70**

70a-d R^1 = CH_2Ph, *i*-Pr, *i*-Bu, CH_2OSiPh_2*t*-Bu; R^2 = Me, 66-99%
70e-h R^1 = CH_2Ph, *i*-Pr, *i*-Bu, CH_2OSiPh_2*t*-Bu; R^2 = Et, 70-99%
70i-k R^1 = CH_2Ph, *i*-Pr, *i*-Bu; R^2 = CH_2CHCH_2, 89-99%
70l R^1 = CH_2Ph; R^2 = CH_2CO*t*-Bu, 99%

Scheme 31 *Reagents and conditions:* i) **70a-d:** Me_3Al (1.1-3.0 equiv), PhMe, rt, 0.5-2.0 h; **70e-h:** Et_2AlCl (1.1-2.2 equiv), PhMe, rt, 0.5-2.0 h; **70i-k:** $SnCl_4$ (2.0 equiv), $TMSCH_2CHCH_2$ (2.0 equiv), CH_2Cl_2, –78 ºC, 30 min, then rt, 1 h**;** **70l:** $SnCl_4$ (2.2 equiv), $TBSOC(CH_2)$*t*-Bu (2.2 equiv), CH_2Cl_2, –78 ºC, 30 min, then rt, 30 min.

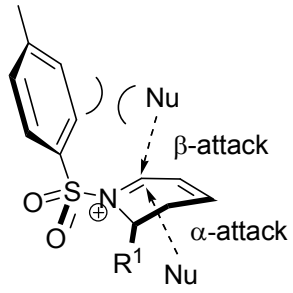


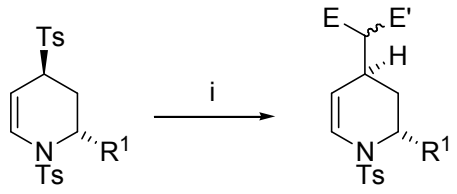
Figure 5 *Nucleophilic attack at the iminium centre*

1.2.3 S_N1 Reactivity

Tetrahydropyridines **67** also undergo stereoselective S_N1 reactions with soft carbon nucleophiles in the presence of a Lewis acid, to give 4-substituted tetrahydropyridines **71**, the products of 1,4-attack.[71] Treatment of tetrahydropyridines **67** with tin tetrachloride, dimethyl malonate and bis(trimethylsilyl)acetamide additive in dichloromethane gave the desired tetrahydropyridines **71** in good yield as mixtures of C-4 epimers.

Tin tetrachloride is thought to initially activate the C-4 tosyl leaving group generating a conjugated iminium species and releasing a chloride ion. This anion then attacks bis(trimethylsilyl)acetamide to give chlorotrimethylsilane and the conjugate base of *N*-(trimethylsilyl)acetamide. Subsequent proton exchange then generates the nucleophilic tin(IV) enolate *in situ*, which intercepts the conjugated iminium in a 1,4-sense. Interestingly, replacing the bis(trimethylsilyl)acetamide additive with *N*,*N*-di*iso*propylethylamine gave reproducible results, provided an extra equivalent of tin tetrachloride was added.

The stereoselectivity is variable; whereby tetrahydropyridines **67** bearing less sterically demanding C-2-substituents showed almost no selectivity, but for bulkier C-2-substituents the *anti*-product was the major isomer. Methyl acetoacetate and ethyl nitroacetate were also investigated as nucleophilic partners, and the products of both reactions showed complete 2,4-*anti*-selectivity (Scheme 32).[71]

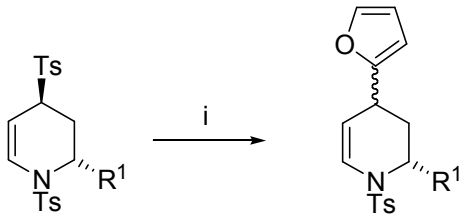


67 . **71**

71a-b R^1 = Me, CH_2*i*-Pr; E = E' = CO_2Me, 65-100%, 45:55 (*anti:syn*)
71c R^1 = CH_2OAc; E = E' = CO_2Me, 80%, 50:50
71d-e R^1 = $CH_2OTBDPS$, *i*-Pr; E = E' = CO_2Me, 88-100%, >98:2
71f-g R^1 = *i*-Pr; E = CO_2Me; E' = COMe, NO_2, 84-94%
71h R^1 = $CH_2OTBDPS$; E = E' = CO_2Me, 90%, >98:2

Scheme 32 *Reagents and Conditions:* i) **71a-g:** Nucleophile (3.0 equiv), $SnCl_4$ (3.0 equiv), BSA (3.0 equiv), CH_2Cl_2,, –78 ºC, 1 h, then rt, 16 h; **71h**: Nucleophile (3.0 equiv), $SnCl_4$ (4.0 equiv), *i*-PrNEt (3.0 equiv), CH_2Cl_2,, –78 ºC, 1 h, then rt, 16 h.

Intermolecular nucleophilic substitution with aromatic nucleophiles was also investigated using these established conditions. However, only treatment with furan gave 1,4-addition product **72**. It is thought that this lack of reactivity is due to the loss of aromaticity necessary for the substitution (Scheme 33).[70]

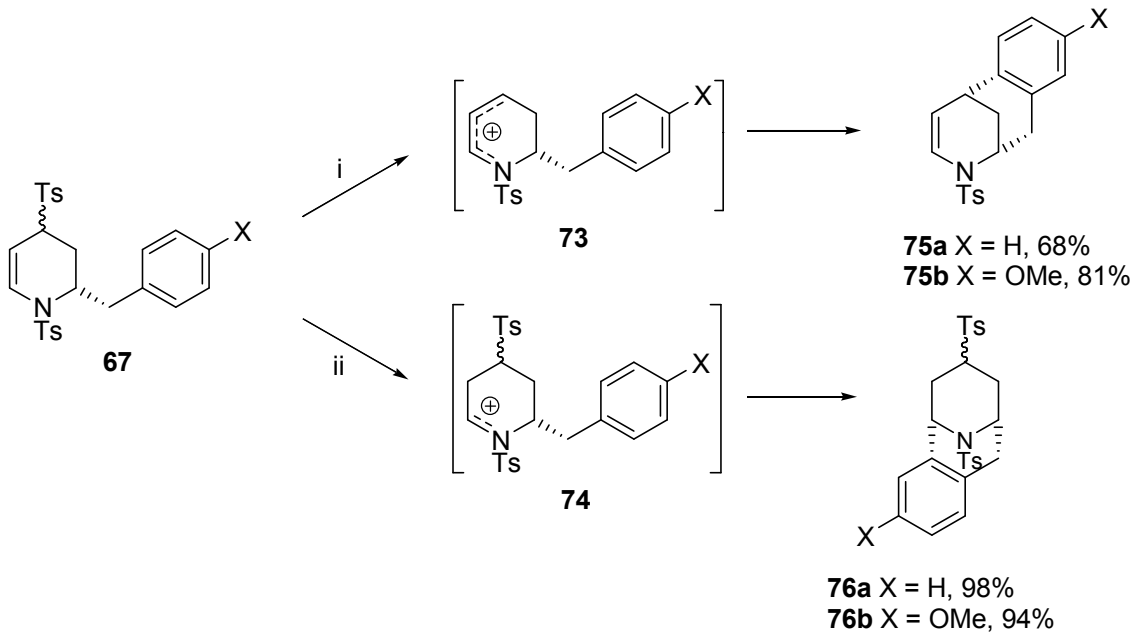


67 **72** R^1 = *i*-Pr, 84%, 1:1

Scheme 33 *Reagents and Conditions:* i) Furan (3.0 equiv), $SnCl_4$ (3.0 equiv), BSA (3.0 equiv), CH_2Cl_2,, –78 ºC, 1 h, then rt, 24 h.

1.2.4 Lewis acid- and Brønsted acid-catalysed cyclisation

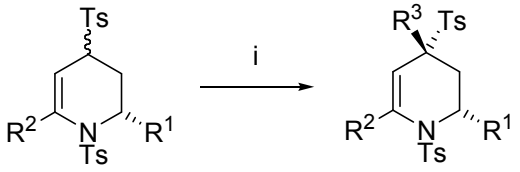
Tetrahydropyridines **67** possessing aromatic R^1 groups at the C-2 position, can react intramolecularly through ionisation followed by cyclisation, to give tricyclic products **75** and **76**. Two different cationic species, **73** and **74** can be formed by *N*-assisted loss of the tolylsulfinate ion and protonation respectively, which lead to competing cyclisation pathways. Treatment of **67** with tin tetrachloride in dichloromethane gave benzomorphan analogue **75**, through interception of cation **73** at the C-4 position. Conversely, Brønsted acid-catalysed cyclisation reactions of **67** with catalytic sulfuric acid in dichloromethane yielded tropane analogue **76** through interception of iminium ion **74** at the C-2 position (Scheme 34).[72]



Scheme 34 *Reagents and Conditions:* i) $SnCl_4$ (2.2 equiv), CH_2Cl_2, –78 ºC → rt, 1 h; ii) H_2SO_4 (cat), CH_2Cl_2, rt, 30 min.

1.2.5 C-4 Alkylation

Treatment of tetrahydropyridines **67** with lithium di*iso*propylamide at –78 ºC generates a red-orange lithio-anion at the C-4 position, α- to the sulfone group, which has been shown to react readily with electrophiles such as iodomethane and 1-bromo-2-propene. These reactions are completely selective for the 2,4-*anti*-diastereomers **77** (Scheme 35).[67,68]



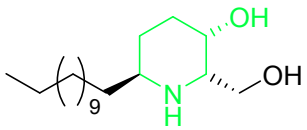
67 **77**

77a $R^1 = CH_2Ph$; $R^2 = H$; $R^3 = Me$, 69-91%[67,68]
77b $R^1 = CH_2Ph$; $R^2 = Me$; $R^3 = Me$, 65%[67]
77c $R^1 = i\text{-}Pr$; $R^2 = H$; $R^3 = Me$, 99%[68]
77d $R^1 = CH_2Ph$; $R^2 = H$; $R^3 = CH_2CHCH_2$, 85%[67]

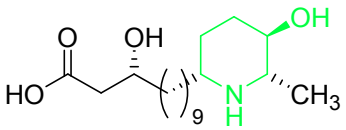
Scheme 35 *Reagents and conditions:* i) a) LDA (1.1 equiv), THF–TMEDA (10:1), –78 ºC, 30 min; b) MeI (2.2 equiv) or $BrCH_2CHCH_2$ (1.1 equiv), –78 ºC → rt, 1 h.

1.2.6 Synthesis of hydroxypiperidines

Hydroxylated piperidines are naturally occurring products which exhibit a wide range of important bioactivities. Recently reported total syntheses of 2,6-substituted piperidin-3-ol containing alkaloids, include: (–)-3-*epi*-deoxoprosopinine **78**, a *Prosopis* alkaloid possessing analgesic, anaesthetic and antibiotic activity and (–)-morusimic acid D (**79**), isolated from the white ripened fruit of *M. alba*, grown in Turkey (Figure 6).[64,73]



(-)-3-*epi*-Deoxoprosopinine **78**

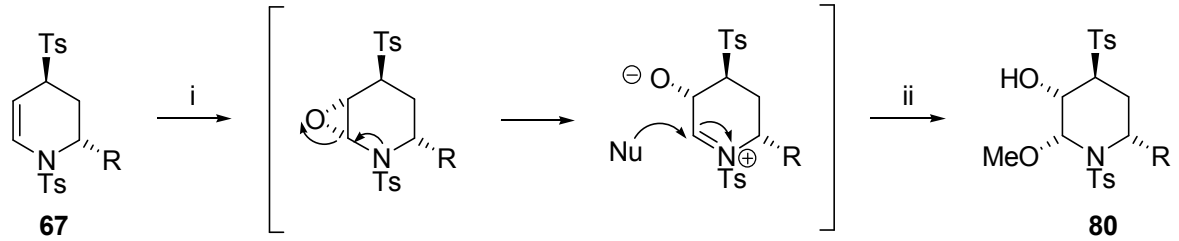


(-)-morusimic acid D (**79**)

Figure 6 *2,6-substituted piperidin-3-ol containing alkaloids reported in the literature*

1.2.6.1 Epoxidation of the C-5–C-6 enamide double bond

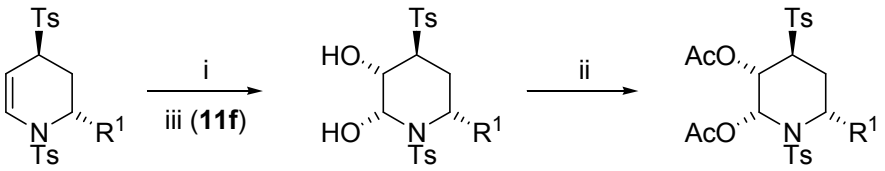
α-Methoxy,β-hydroxypiperidines **80** were synthesised as single diastereomers, following epoxidation of the C-5–C-6 enamide double bond with dimethyldioxirane and nucleophilic ring opening with methanol. The *cis*-selectivity was thought to arise from attack on the α-face, due to steric strain between the incoming nucleophile and the *N*-tosyl group on the β-face. Unfortunately, treatment with various carbon nucleophiles in the presence of Lewis acids did not result in carbon-carbon bond formation at the C-2 position, to give alternatively substituted hydroxypiperidines (Scheme 36).[69]



Scheme 36 *Reagents and conditions:* i) DMDO (0.08M in Me_2CO), 0 °C, 2 h; ii) MeOH, rt.

1.2.6.2 *Syn*-dihydroxylation of the C-5–C-6 enamide double bond

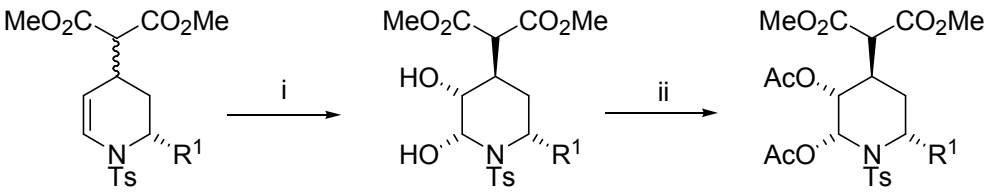
Dihydroxylation of C-2-substituted tetrahydropyridines **67** and C-4-substituted tetrahydropyridines **71** with osmium tetroxide and *N*-methylmorpholine-*N*-oxide occurs with complete stereoselectivity to give the corresponding *syn*-α, α diols **81** and **82** respectively. Diacetates **83** and **84** were accessed from **81** and **82** following treatment with acetic anhydride–triethylamine in the presence of 4-dimethylaminopyridine. Dihydroxylation was observed to take place *anti* to the C-4 tosyl group in all cases and it was therefore deduced that the tosyl group exerts complete control over the stereochemistry of the reaction (Schemes 37 and 38).[69-71,74]



67 **81** **83**

81a R^1 = CH_2OAc, 86%; **83a**, 71%
81b R^1 = *i*-Pr, 99%; **83b**, 99%
81c R^1 = *i*-Bu, 75%; **83c**, 99%
81d R^1 = Me, 57%; **83d**, 88%
81e R^1 = $C_{12}H_{25}$, 77%; **83e**, 99%
81f R^1 = H, 99%; **83f**, 61%

Scheme 37 *Reagents and Conditions:* i) OsO_4 (0.05 equiv), NMO (2.8 equiv), Me_2CO–H_2O (9:1), rt, 12 h; ii) Ac_2O (5.0 equiv), DMAP (0.1 equiv), Et_3N (5.0 equiv), CH_2Cl_2, rt, 5 h; iii) OsO_4 (0.05 equiv), NMO (2.8 equiv), THF–H_2O (19:1), rt, 96 h.

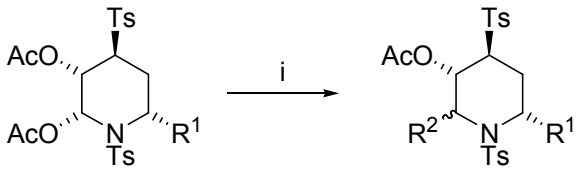


71 **82** **84**

82a R^1 = CH_2OAc; **84a**, 50% over two steps
82b R^1 = *i*-Pr; **84b**, 64% over two steps

Scheme 38 *Reagents and Conditions:* i) OsO_4 (0.05 equiv), NMO (2.8 equiv), Me_2CO–H_2O (9:1), rt, 12 h; ii) Ac_2O (5.0 equiv), DMAP (0.1 equiv), Et_3N (5.0 equiv), CH_2Cl_2, rt, 5 h.

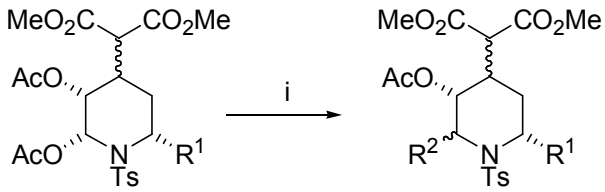
Lewis acid-mediated nucleophilic substitution reactions of **83** and **84** were investigated with allyltrimethylsilane, and with the *tert*-butyldimethylsilyl enol ethers derived from pinacolone and cyclohexanone, in the presence of tin tetrachloride in dichloromethane to give substitution products **85** and **86**. It was found that for bulky R^1 groups nucleophilic attack takes place on the β-face, *anti* to the C-2 substituent; whereas for less bulky R^1 groups attack takes place predominantly on the α-face, *syn* to the C-2 substituent, as the β-face is by default more sterically hindered due to the *N*-tosyl group. In both cases selectivity is maximised with a larger nucleophile (Schemes 39 and 40).[71,74]



83 **85**

85a-c R^1 = *i*-Pr; R^2 = allyl, 88%, 50:50; R^2 = *t*-BuCOCH$_2$, 90%, 15:85; R^2 = 1-cyclohexanone-2-yl, 83%, 0:100 (*syn:anti*)
85d-f R^1 = *i*-Bu; R^2 = allyl, 85%, 75:25; R^2 = *t*-BuCOCH$_2$, 92%, 85:15; R^2 = 1-cyclohexanone-2-yl, 90%, 100:0
85g R^1 = Me; R^2 =*t*-BuCOCH$_2$, 99%, 60:40
85h R^1 = CH$_2$OAc; R^2 = *t*-BuCOCH$_2$, 85%, 0:100
85i R^1 = $C_{12}H_{25}$; R^2 = *t*-BuCOCH$_2$, 72%, 45:55

Scheme 39 *Reagents and Conditions:* i) **85a-f:** Nucleophile (2.0-3.5 equiv), $SnCl_4$ (3.0 equiv), CH_2Cl_2, –78 ºC → rt, 2.5 h; **85g:** Nucleophile (2.0 equiv), $SnCl_4$ (3.0 equiv), CH_2Cl_2, –60 ºC → rt, 2.5 h; **85h:** Nucleophile (2.0 equiv), $TiCl_4$ (3.0 equiv), CH_2Cl_2, –40 ºC → rt, 2.5 h; **85i:** Nucleophile (2.0 equiv), $SnCl_4$ (3.0 equiv), CH_2Cl_2, –60 → 0 ºC, 40 min.



84 **86**

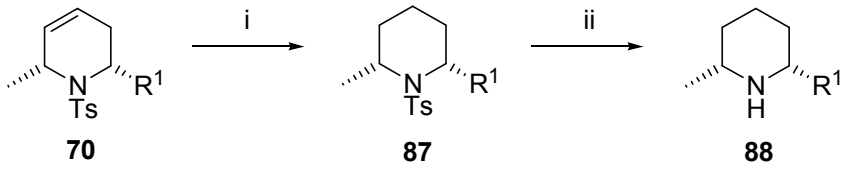
86a R^1 = *i*-Pr; R^2 = *t*-BuCOCH$_2$, 83%, 100:0 (*syn:anti*)
86b R^1 = CH$_2$OAc; R^2 = *t*-BuCOCH$_2$, 64%, 100:0

Scheme 40 *Reagents and Conditions:* i) **86a-b:** Nucleophile (3.0 equiv), $SnCl_4$ (3.0 equiv), CH_2Cl_2, –60 ºC → rt, 3 h.

1.2.7 Reduction and Desulfonylation

Piperidine **88** was accessed by reduction of the C-4–C-5 double bond of tetrahydropyridine **70**, followed by desulfonylation. The double bond in question was found to have a very low reactivity, and this was thought to be due to its doubly-hindered nature, as both the α- and β-faces are blocked by the axial C-6 substituent and the *N*-tosyl group respectively. Hydrogenation was achieved with one atmosphere of hydrogen in the presence of Wilkinson's catalyst to give **87**. Treatment with excess sodium amalgam in

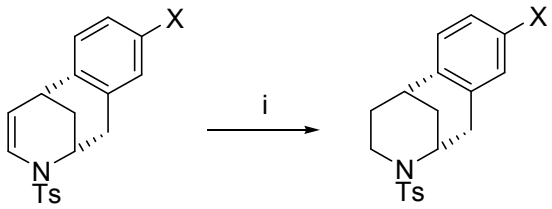
tetrahydrofuran–methanol under reflux, effected desulfonylation in high yield to give **88** (Scheme 41).[67]



87 R^1 = CH_2Ph, 87%; **88**, 66%

Scheme 41 *Reagents and Conditions:* i) H_2 (1 atm), $RhCl(PPh_3)_3$ (18 mol%), PhMe, rt, 72 h; ii) 6% Na–Hg (5.0 equiv), 1:1 THF–MeOH, reflux, 12 h.

Treatment of benzomorphan analogue **75** with triethylsilane and trifluoroacetic acid in dichloromethane resulted in reduction of the C-5–C-6 enamide double bond, to give piperidine **89**. This was thought to take place *via* acid-mediated ionisation, followed by trapping with an *in situ* hydride source (Scheme 42).[72]

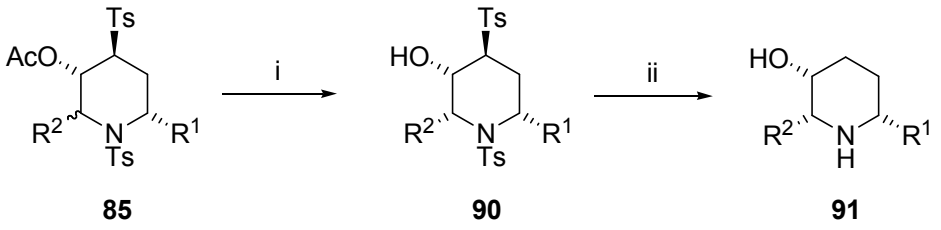


75a X = H
75b X = OMe

89a X = H, 97%
89b X = OMe, 92%

Scheme 42 *Reagents and Conditions:* i) Et_3SiH (1.1 equiv), CF_3CO_2H (2.0 equiv), CH_2Cl_2, rt, 1 h.

Julia olefination-type conditions using sodium amalgam were not suitable for the desulfonylation of all substrates, particularly as tetrahydropyridines **85** would be susceptible to reductive elimination of the C-5 acetate group in addition to the tosyl group. The C-5 oxygen functionality was therefore deactivated by conversion to the corresponding alcohol **90**. Brief treatment of this derivative with sodium naphthalide in tetrahydrofuran gave *syn*-dialkyl hydroxypiperidine **91** (Scheme 43).[74]



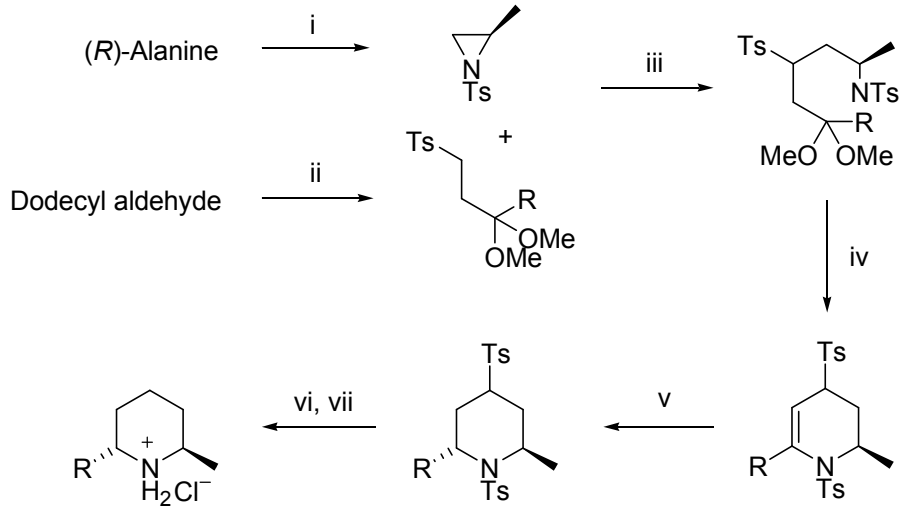
85 **90** **91**

90 R^1 = *i*-Bu, R^2 = allyl, 85%; **91**, 70%

Scheme 43 *Reagents and Conditions:* i) DIBAL-H (2.0 equiv), CH_2Cl_2 –78 ºC, 1 h, then rt, 1 h; ii) $NaC_{10}H_8$ (9.0 equiv), THF, –78 ºC, 5 min.

1.2.8 Total synthesis of (–)-Solenopsin A

The methodology developed for the preparation of enantiopure 2,6-piperidines as described above, was extended towards the synthesis of alkaloids. (–)-Solenopsin A (**92**) is isolated from the venom of the *Solenopsis saevissima* fire-ant and members of this class of compound are known to exhibit insecticidal and antibiotic properties.[75] The total synthesis was completed by the Craig group in 11 steps from a commercially available amino acid, in an overall yield of 11% (Scheme 44).[76]

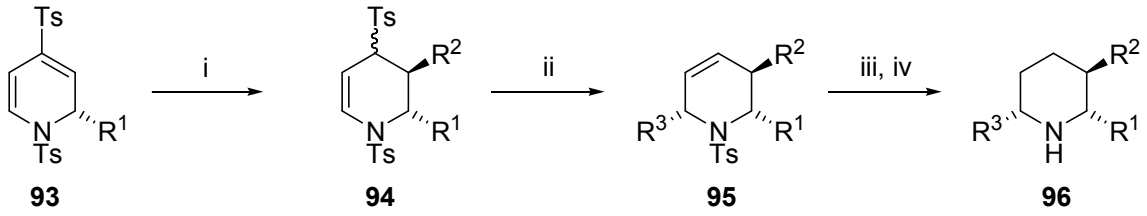


92, R=$C_{11}H_{23}$

Scheme 44 *Reagents and Conditions:* i) 3 steps, 58%; ii) 4 steps, 63%; iii) *n*-BuLi (1.1 equiv), THF–TMEDA, –78 °C → rt, 30 min, 51%; iv) H_2SO_4 (cat), CH_2Cl_2, rt, 10 min, 82%; v) Et_3SiH (10.0 equiv), TFA (2.0 equiv), CH_2Cl_2, rt, 30 min, 72%; vi) 6% Na-Hg, THF–MeOH (1:1), reflux, 16 h; vii) 4M HCl in dioxane, rt, 1 h, 61% (over 2 steps).

1.2.9 Nucleophilic Addition Reactions

Treatment of 2-substituted dihydropyridine **93** with a range of organometallic reagents effected nucleophilic addition to give 2,3-*anti*-tetrahydropyridines **94** as mixtures of C-4 epimers (*syn*- or *anti*- with respect to the C-3 substituent). This selectivity at the C-3 position is thought to arise from axial nucleophilic attack at the vinylic sulfone β-carbon atom, *anti* with respect to the C-2 substituent. S_N1 reaction of this more highly substituted substrate takes place upon treatment with trimethylaluminium in dichloromethane to give 2,6-*syn*-trisubstituted tetrahydropyridine **95**, in accordance with previous stereoselectivity observed. Hydrogenation of the C-4–C-5 double bond was achieved as before with Wilkinson's catalyst and desulfonylation occurred following treatment with sodium naphthalide to generate trisubstituted piperidine **96** (Scheme 45).[77]



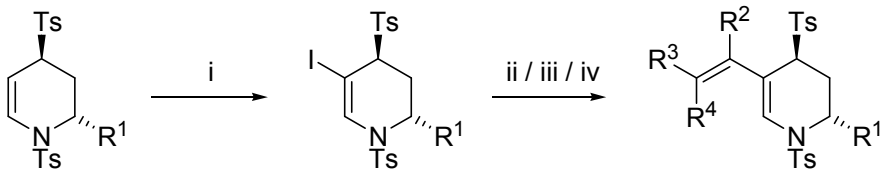
94a $R^1 = CH_2Ph$; R^2 = allyl, 95%, 77:23 (*syn:anti*)
94b $R^1 = CH_2Ph$; R^2 = Me, 95%, 24:76
94c $R^1 = CH_2Ph$; R^2 = Ph, 95%, 30:70
94d $R^1 = CH_2Ph$; $R^2 = PhSO_2CH_2$, 95%, 26:74
94e $R^1 = CH_2Ph$; R^2 = *n*-Bu, 95%, 17:83
94f $R^1 = CH_2Ph$; $R^2 = NCCH_2$ 95%, 7:93
94g $R^1 = CH_2Ph$; $R^2 = CH_3(CH_2)_5CC$, 17% (**23g** 63%), 100:0
95 $R^1 = CH_2Ph$; $R^2 = R^3$ = Me, 85% (over 2 steps)
96 $R^1 = CH_2Ph$; $R^2 = R^3$ = Me, 85% (over 2 steps)

Scheme 45 *Reagents and Conditions:* i) **94a-f:** R^2Li (1.2-4.0 equiv), THF, –78 ºC, 15 min-1 h; **94g:** 1-heptyne (4.0 equiv), MeLi (3.0 equiv), THF, –78 ºC, 15 min, then –30 ºC, 15 min, then –78 ºC, 1 h, then –30 ºC, 1 h; ii) Me_3Al (2.0 equiv), CH_2Cl_2, rt, 1 h; iii) H_2 (1 atm), $RhCl(PPh_3)_3$ (18 mol%), PhMe, rt, 10 h; iv) $NaC_{10}H_8$ (10.0 equiv), DME, –60 ºC, 45 min.

1.2.10 Formation of Dienes

Introduction of a C-5-alkenyl substituent was achieved using palladium(0)-catalysed Cross coupling reactions of a C-5-iodo derivative of tetrahydropyridine **67**. This enabled investigations into Diels–Alder reactions of 1,3-dienes possessing an embedded tetrahydropyridine motif. Iodo-tetrahydropyridine **97** was generated from tetrahydropyridine **67** following treatment with *N*-iodosuccinimide and hydroxyl(tosyloxy) iodobenzene in dichloromethane. A variety of palladium(0)-catalysed coupling methods were then investigated for the functionalisation of this modified tetrahydropyridine core.

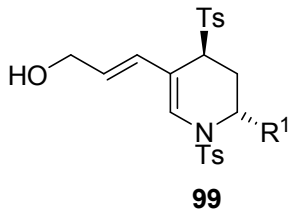
Stille reactions with vinylstannanes and Suzuki reactions with vinylboronic acids enabled access to a wide range of diverse 1,3-dienes **98** in good to excellent yields. Suzuki coupling was chosen as the preferred method for the majority of these substrates, as it avoids the use of organostannanes, there is a large range of commercially available boronic acids and scale up was facile. Moderate success was also achieved from the cross-coupling of Grignard reagents, but Heck coupling, cross-metathesis, dialkyl cuprates and alkyl zinc reagents failed to yield the desired dienes. Some time was also spent exploring the synthesis of oxygenated dienes **99**, but in these cases Heck, Suzuki and Stille coupling all proved unsuccessful (Scheme 46, Figure 7).[70,78]



67 **97** **98**

98a-b R^1 = *i*-Pr ; R^2 = H, Me; R^3 = H; R^4 = H, 18-89%
98c-o R^1 = *i*-Pr ; R^2 = H; R^3 = Ph, 4-C_6H_4Cl, 4-C_6H_4F, 4-$C_6H_4CF_3$, 4-$C_6H_4CH_3$, Me, Bu, Hex, -CH_2Cl, furan, thiophene, benzofuran, benzothiophene; R^4 = H, 8-88%
98p R^1 = *i*-Pr ; R^2 = H, Me; R^3 = H; R^4 = Me, 83%

Scheme 46 *Reagents and Conditions*: i) NIS (1.1 equiv), PhI(OH)(OTs) (0.1 equiv), CH_2Cl_2, reflux, 16 h; ii) **98a-b:** $Bu_3SnCH{=}CH_2$ (1.1 equiv), $Pd_2(dba)_3$ (0.06 equiv), P(2-furyl)$_3$ (0.12 equiv), DMF, 70 ºC, 16 h; iii) **98a-b:** vinylmagnesium bromide, $Pd(PPh_3)_4$, toluene, 0 ºC → rt, 16 h; iv) **98a-p:** $R^3(R^4)CH{=}C(R^2)B(OH)_2$ (2.5 equiv), $Pd(PPh_3)_4$ (0.05 equiv), Na_2CO_3 (10 equiv), dioxane, 80 ºC, 16 h.

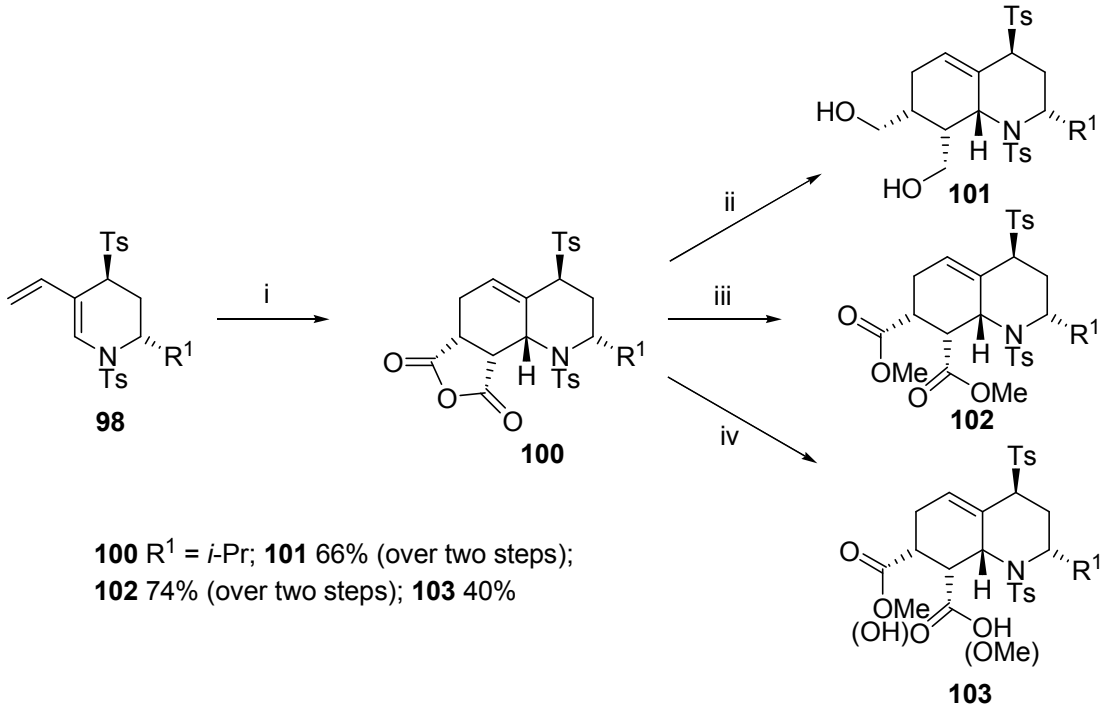


99

Figure 7 *Oxygenated diene **99** not isolated*

1.2.11 Diels–Alder Reactions

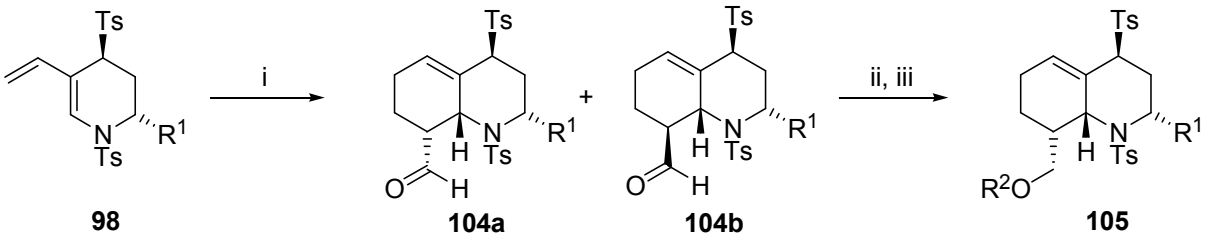
It has been shown that these tetrahydropyridine dienes enter into completely stereo- and regioselective Diels–Alder reactions with a range of dienophiles. Heating an equimolar mixture of diene **98** and maleic anhydride in deuterated chloroform gave cycloadduct **100** in quantitative yield. Treatment of this adduct with lithium aluminium hydride in tetrahydrofuran or with trimethylsilyldiazomethane in methanol–dichloromethane gave the corresponding diol **101** and dimethyl diesters **102** and **103** respectively. Formation of cycloadduct **100** indicates a preference for *endo*-approach of the dienophile to the α-face of diene **98**, whereby it is *syn* to the C-2 substituent and therefore *anti* to the large *N*-tosyl group (Scheme 47).[69,78]



100 R^1 = *i*-Pr; **101** 66% (over two steps);
102 74% (over two steps); **103** 40%

Scheme 47 *Reagents and Conditions:* i) Maleic anhydride (1.0 equiv), $CDCl_3$, 65 ºC, 2 h; ii) $LiAlH_4$ (4.0 equiv), THF, reflux 1.5 h; iii) $TMSCHN_2$ (4.0 equiv), MeOH–CH_2Cl_2 (1.5:1), rt, 2 h; iv) $TMSCHN_2$ (2.0 equiv), MeOH–CH_2Cl_2 (1.5:1), rt, 2 h.

Reaction of diene **98** with acrolein gave an inseparable mixture of cycloaddition products **104a** and **104b**. Treatment with lithium aluminium hydride and then 3,5-dinitrobenzoyl chloride enabled separation and gave 3,5-dinitrobenzoate ester **105** as the major isomer (Scheme 48).[69,78]

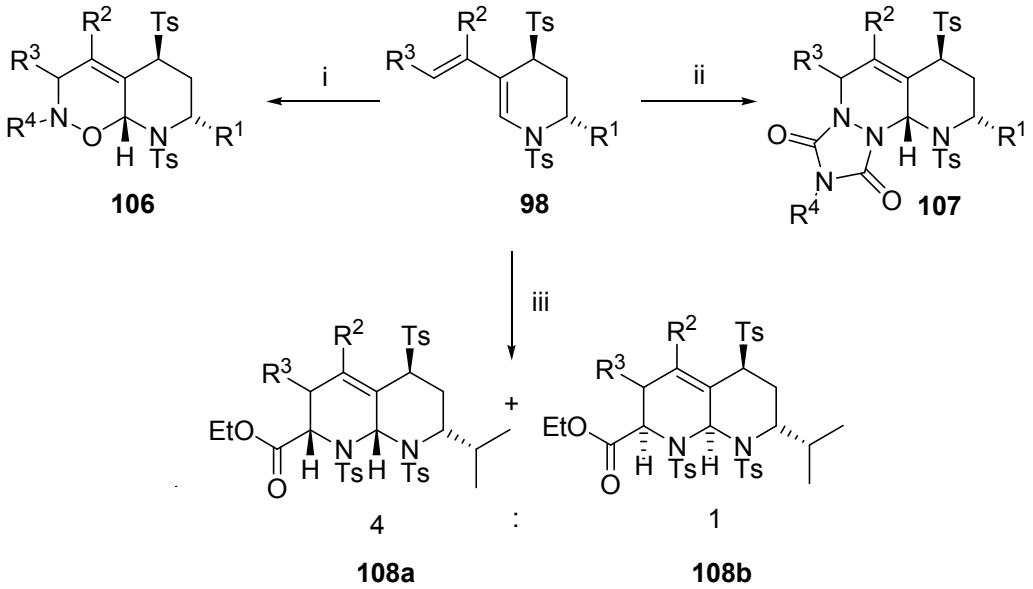


104a+b R^1 = *i*-Pr, 79%, 82:18 (*syn*:*anti*)
105 R^1 = *i*-Pr; R^2 = 3,5-$C_6H_3(NO_2)_2CO$, 51% (over two steps)

Scheme 48 *Reagents and Conditions:* i) acrolein (1.2 equiv), $CDCl_3$, 53 ºC, 24 h; ii) $LiAlH_4$ (1.35 equiv), THF, rt, 30 min; iii) 3,5-$C_6H_3(NO_2)_2COCl$ (1.3 equiv), Et_3N (2.0 equiv), DMAP (0.05 equiv), CH_2Cl_2, 0 ºC, 20 min.

Hetero-Diels–Alder reactions of dienes **98** with nitroso dienophiles and 4-alkyltriazoline-3,5-diones in dichloromethane gave cycloadducts **106** and **107** respectively, whereby approach of the dienophile occurred exclusively *syn* to the C-2-substituent. Reaction of diene **98** with activated *N*-tosylimine gave a mixture of two cycloadducts **108a** and **108b**, again where the major product seen was the result of the dienophile approaching *syn* to the C-2-substituent and therefore *anti* to the *N*-tosyl group (Scheme 49).

No cycloaddition product was observed following reaction of unactivated *N*-tosylimine dienophiles, even at elevated temperatures. This was thought to be due to a lack of reactivity of both the diene and the dienophile. Attempts to manipulate these hetero-Diels–Alder products through reduction of either the nitrogen–oxygen bond or the carbon–carbon double bond and detosylation proved mostly unsuccessful due to steric restraints and the relative stability of the cycloadducts.[70,78]



106a-c R^1 = *i*-Pr; R^2 = R^3 = H; R^4 = Cbz, Boc, Ph, 70-98%
106d-f R^1 = *i*-Pr; R^2 = Me; R^3 = H; R^4 = Cbz, Boc, Ph, 55-88%
106g-i R^1 = *i*-Pr; R^2 = H; R^3 = Ph; R^4 = Cbz, Boc, Ph, 22-73%
107a-b R^1 = *i*-Pr; R^2 = R^3 = H; R^4 = Ph, Me, 25-77%
107c R^1 = *i*-Pr; R^2 = Me; R^3 = H; R^4 = Ph, 58%
107d R^1 = *i*-Pr; R^2 = H; R^3 = Ph; R^4 = Ph, 58%
108a+b R^1 = *i*-Pr; R^2 = R^3 = H, 55%, 4:1 (*syn:anti*)

Scheme 49 *Reagents and Conditions:* i) $R^4N{=}O$ (1.0 equiv), CH_2Cl_2, rt, 1-48 h; ii) 4-alkyltriazoline-3,5-dione (1.0 equiv), CH_2Cl_2, rt; iii) tosylimino-acetic acid ethyl ester (1.1 equiv), CH_2Cl_2, rt, 24 h, then reflux, 48 h.

1.2.12 Conclusions

Work within the Craig group has shown that 1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines can enter into a variety of C–C bond forming reactions to access highly substituted chiral piperidines.[66-70] The methodology developed was successfully applied to the total synthesis of nitrogen heterocycle-containing natural products such as (–)-solenopsin A.[76]

In addition, it was demonstrated that C-5 derivatives of these tetrahydropyridines can be successfully employed as dienes in Diels–Alder reactions and that these reactions proceed with good regio- and stereoselectivity with a range of dienophiles, including maleic anhydride and acrolein.[69] Furthermore, hetero-Diels–Alder reactions of these dienes with nitroso and 4-alkyltriazoline-3,5-dione dienophiles proved completely stereoselective.

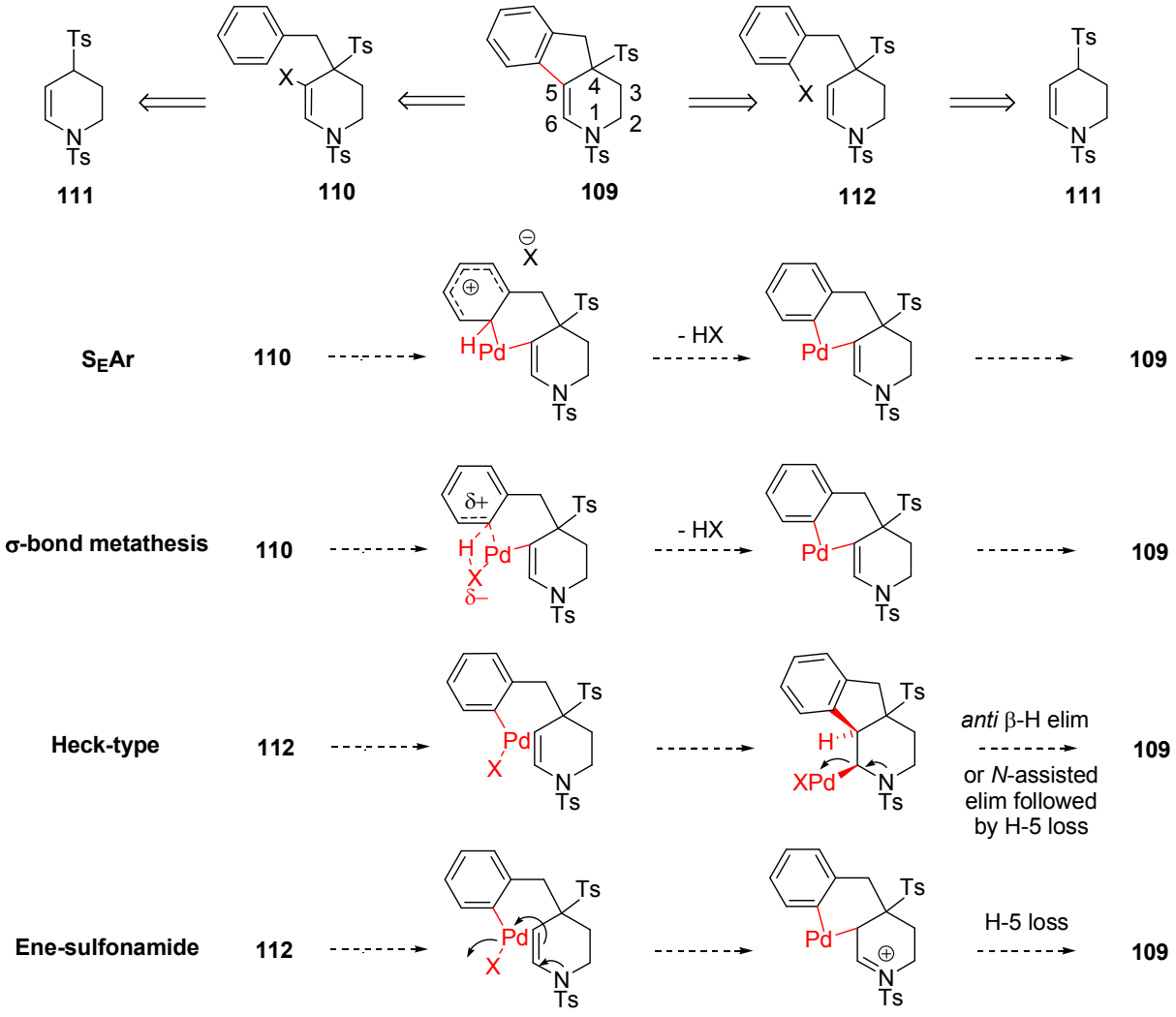
2.0 Results and Discussion

2.1.0 Aim of the Work

We wished to develop new modes of reactivity of 1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines **3**, to include palladium-catalysed carbon–carbon bond forming reactions and direct C–H activation processes.

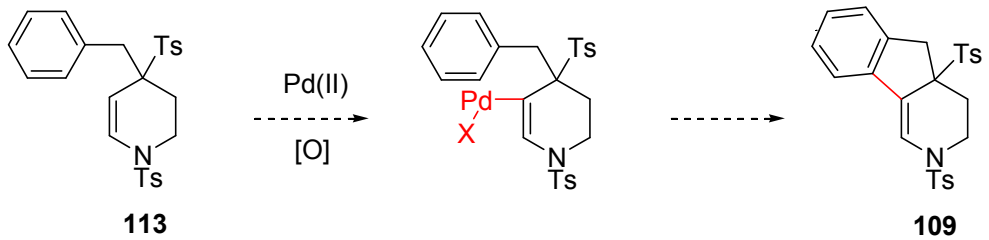
It was hoped that tricyclic system **109** could be accessed from bifunctional substrate **110**, readily available from **111** following C-4 alkylation and C-5 halogenation (Scheme 50).[67,69] We proposed that cyclisation would take place *via* a catalytic direct arylation of tetrahydropyridine **110**, wherein a non-activated aryl C–H bond is intramolecularly directly coupled with the activated electron-rich ene–sulfonamide, under catalytic conditions. We wished to evaluate whether the palladium insertion product of **110** was sufficiently electrophilic for direct interception by electron-rich arenes *via* electrophilic aromatic substitution or sigma-bond metathesis.

We also wished to investigate direct intramolecular coupling reactions of haloaryl-substituted tetrahydropyridine **112** in the presence of palladium(0) to give tricycle **109**. Analogue **112** was expected to cyclise *via* a Heck-type mechanism or one where the ene–sulfonamide intercepted the initial oxidative addition intermediate.[17]



Scheme 50 *Proposed mechanistic pathways for catalytic direct arylation*

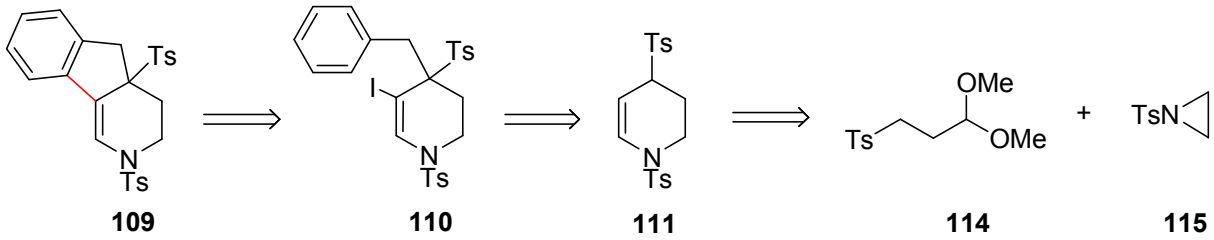
Finally, we wished to assess whether direct palladation of the C-5 position was possible and whether coupling of unactivated arene **113** could be effected in an overall oxidative process by treatment with a transition metal catalyst in conjunction with an oxidant to access tricycle **109** (Scheme 51).[79]



Scheme 51 *Access to tricycle **109** in an overall oxidative process*

2.2.0 Initial Strategy for Tetrahydropyridine Synthesis

Previous work within the Craig group has shown that 1,4-bis(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine **111** can be readily assembled from aryl-sulfonyl substituted acetal **114** and *N*-tosylaziridine **115** (Scheme 52).[66] Nucleophilic ring-opening of **115** with the lithiated anion of **114**, followed by cyclocondensation of the resulting adduct, gives the desired tetrahydropyridine **111**.[67] We proposed that tricycle **109** could be accessed from cyclisation precursor **110** following C-4 alkylation and C-5 halogenation of **111**.

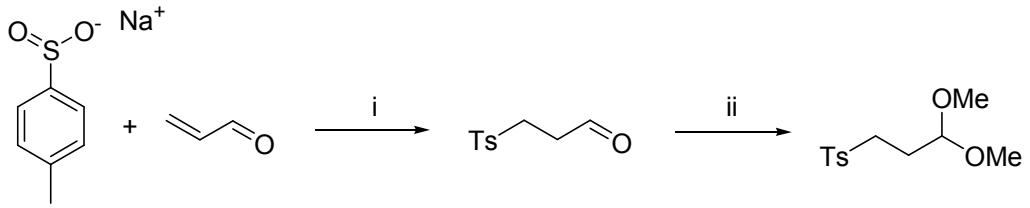


109 **110** **111** **114** **115**

Scheme 52 *Retrosynthetic analysis of tricyclic systems*

2.2.1 Synthesis of tetrahydropyridine 111

A two-step synthesis of acetal **114** employed methodology previously used by the group, whereby addition of sodium *p*-toluenesulfinate (**116**) to acrolein (**117**), followed by treatment of crude aldehyde product **118** with trimethyl orthoformate, gave acetal **114** in 87% yield (Scheme 53).[80]

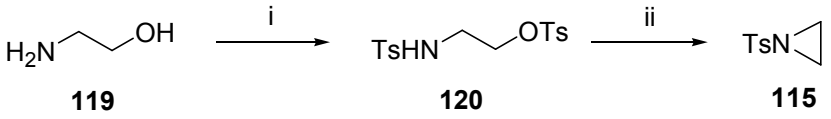


(**116**) (**117**) **118** **114**

Scheme 53 *Reagents and conditions:* i) AcOH (1.0 equiv), H_2O–THF, 0 ºC → rt, 16 h, 88%; ii) $CH(OMe)_3$ (2.0 equiv), *p*-TsOH (0.03 equiv), MeOH, 50 ºC, 16 h, 87%.

Treatment of ethanolamine (**119**) with toluene-4-sulfonyl chloride, triethylamine and 4-dimethylaminopyridine in dichloromethane at –5 °C, gave the desired bis-tosylated product **120** in 73% yield (Scheme 54).[81,82] Aziridine **115** was then obtained in quantitative yield upon treatment with 50% aqueous sodium hydroxide in dichloromethane, without the need for purification of the crude material.[83]

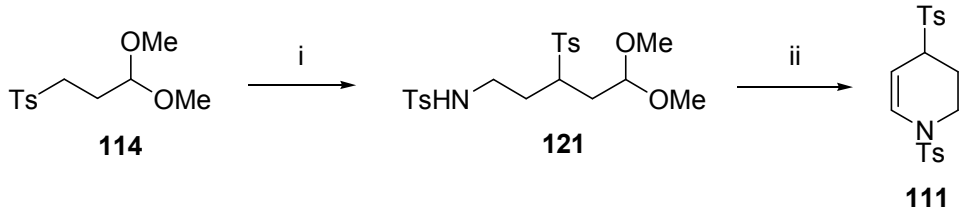
Aziridine **115** was found to be susceptible to polymerisation; steps taken to reduce this problem included short reaction times (30 min), drying with sodium sulfate instead of magnesium sulfate and taking care not to overheat the product during solvent evaporation.



Scheme 54 *Reagents and Conditions:* i) TsCl (2.0 equiv), DMAP (0.15 equiv), Et_3N (2.0 equiv), CH_2Cl_2, –5 → 0 °C, 2.5 h, 73%; ii) NaOH (50% w/w in H_2O, 5.3 equiv), CH_2Cl_2, rt, 30 min, 100%.

Cyclocondensation substrate **121** was obtained in one step from acetal **114** and aziridine **115**: treatment of **114** with *n*-butyllithium to form the corresponding tosyl anion, followed by addition to **115** gave ring-opened adduct **121** in 82% yield (Scheme 55).[67] Tetramethylethylenediamine was used as a co-solvent and binds to the lithium cation, thereby providing a more nucleophilic tosyl anion.[84]

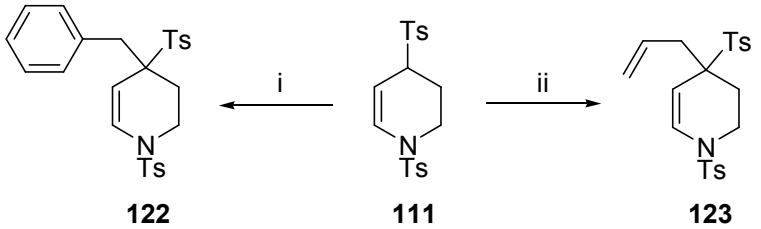
A range of cyclisation conditions were investigated to effect cyclocondensation of adduct **121**: treatment with sodium iodide and chlorotrimethylsilane in acetonitrile was found to be optimal, giving tetrahydropyridine **111** in 79% yield.[67] Iodotrimethylsilane is formed *in situ* and is proposed to act as a Lewis acidic catalyst and abstract one of the methoxy groups to form an oxonium ion intermediate, which undergoes subsequent nucleophilic attack.[85]



Scheme 55 *Reagents and conditions:* i) a) *n*-BuLi (1.1 equiv), THF–TMEDA, –78 ºC, 30 min; b) **114** (1.0 equiv), THF, –78 ºC → rt, 2 h; c) AcOH (1M in THF, 1.1 equiv), 82%; ii) NaI (3.0 equiv), TMSCl (3.0 equiv), MeCN, rt, 20 min, 79%.

2.2.2 Alkylation at the C-4 position

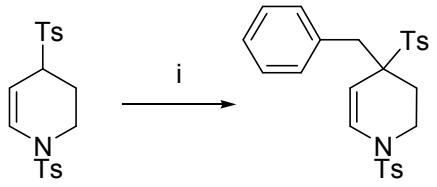
Previously our group has demonstrated that tetrahydropyridine substrates can be alkylated at the C-4 position with iodomethane and allyl bromide, under basic conditions.[67] Attempts to reproduce these results with tetrahydropyridine **111** proved to be moderately successful only with benzyl bromide and allyl bromide, to give alkylated tetrahydropyridines **122** and **123** respectively (Scheme 56). In contrast, only starting material was isolated following treatment of lithiated **111** with 1-bromo-2-propyne, benzaldehyde, chlorotrimethylsilane, methyl chloroformate, paraformaldehyde, iodomethane and dimethyl formamide.



122 **111** **123**

Scheme 56 *Reagents and conditions:* i) a) *n*-BuLi (1.2 equiv), THF–TMEDA, –78 ºC, 30 min; b) BnBr (2.5 equiv), –78 ºC → rt, 4 h, 36%; ii) a) *n*-BuLi (1.1 equiv), THF–TMEDA, –78 ºC, 30 min; b) CH_2CHCH_2Br (2.2 equiv), –78 ºC → rt, 2 h, 53%.

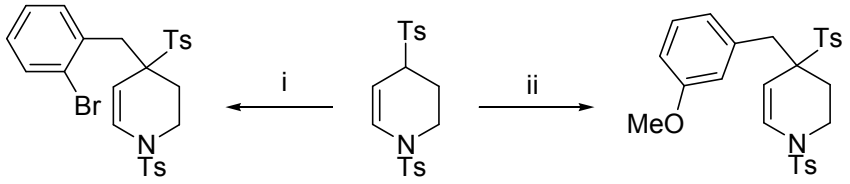
Subsequently, optimisation of the alkylation of **111** with benzyl bromide was performed. Various parameters were investigated, including: equivalents of base and electrophile used; use of a co-solvent to bind to the lithium cation; reaction concentration; temperature at which base was added to the reaction; deprotonation time prior to quenching; temperature at which the reaction was quenched with benzyl bromide and length of time the reaction was allowed to progress before work up. The optimal conditions required 1.1 equivalents of base, 1.0 equivalent of electrophile and the use of tetramethylethylenediamine as co-solvent (Scheme 57). The stability of the anion formed was investigated through the addition of base at different temperatures; it was concluded that lithio-**111** is unstable above –50 ºC. It was also noted that deprotonation at the C-4 position was very rapid, and no more than 15 min was needed between adding the base and quenching with the electrophile.



111 **122**

Scheme 57 *Reagents and conditions:* i) a) *n*-BuLi (1.1 equiv), THF–TMEDA, –78 ºC, 15 min; b) BnBr (1.0 equiv), –78 ºC → rt, 1 h, 76%.

These optimised conditions were applied to alkylation reactions with 2-bromobenzyl bromide and 3-methoxybenzyl bromide (Scheme 58). However, upon purification by column chromatography, a significant amount of starting material **111** was often isolated, which was inseparable from the desired alkylated products. Chromatography over base-washed silica gel was therefore required to prevent decomposition of tetrahydropyridines **124** and **125**.

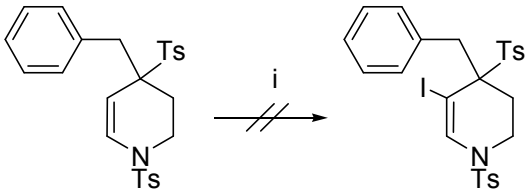


124 **111** **125**

Scheme 58 *Reagents and Conditions:* i) a) *n*-BuLi (1.1 equiv), THF–TMEDA, –78 ºC, 15 min; b) 2-bromobenzyl bromide (1.1 equiv), –78 ºC → rt, 1.5 h, 55%; ii) a) *n*-BuLi (1.1 equiv), THF–TMEDA, –78 ºC, 15 min; b) 3-methoxybenzyl bromide (1.0 equiv), –78 ºC → rt, 2 h, 45%.

2.2.3 Iodination at the C-5 position

A number of C-5 iodination conditions were explored for the preparation of cyclisation precursor **110**, which we expected to be more reactive in subsequent palladium-catalysed coupling reactions compared to other halogenated congeners (Scheme 59, Table 1).[72,86-90] Unfortunately, the desired product was not obtained. Instead, a by-product, thought to be elimination product **126**, was isolated under three different sets of iodination conditions, as a 1:1 mixture of geometric isomers (Table 1, entries 2-4, Figure 8). It was thought that the C-5 position was too sterically hindered to react with these bulky iodine reagents, due to the adjacent quaternary centre at C-4.

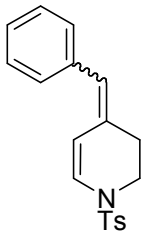


122 **110**

Scheme 59 *Reagents and conditions:* i) See Table 1.

Table 1 *Attempts to iodinate at the C-5 position of tetrahydropyridines **122***

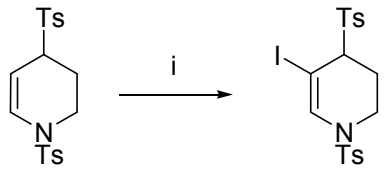
Entry	Reagents (equiv)	Solvent	Temp (°C)	Time (h)	Product (yield)
1[78]	NIS (1.1), HTIB (0.1), Et_3N (1.1 after 20 h)	CH_2Cl_2	Reflux	20	Decomposition
2[87]	I_2 (2.0), K_2CO_3 (3.2)	CH_2Cl_2	Rt	16	By-product **126**
3[88]	I_2 (3.0), Cs_2CO_3 (3.0)	1,4–dioxane	65	20	By-product **126**
4[89]	NIS (3.0)	THF	–78 → rt	16	By-product **126**
5[90]	ICl (1.5)	CH_2Cl_2	0 → rt	16	Decomposition



126

Figure 8 Elimination product **126**

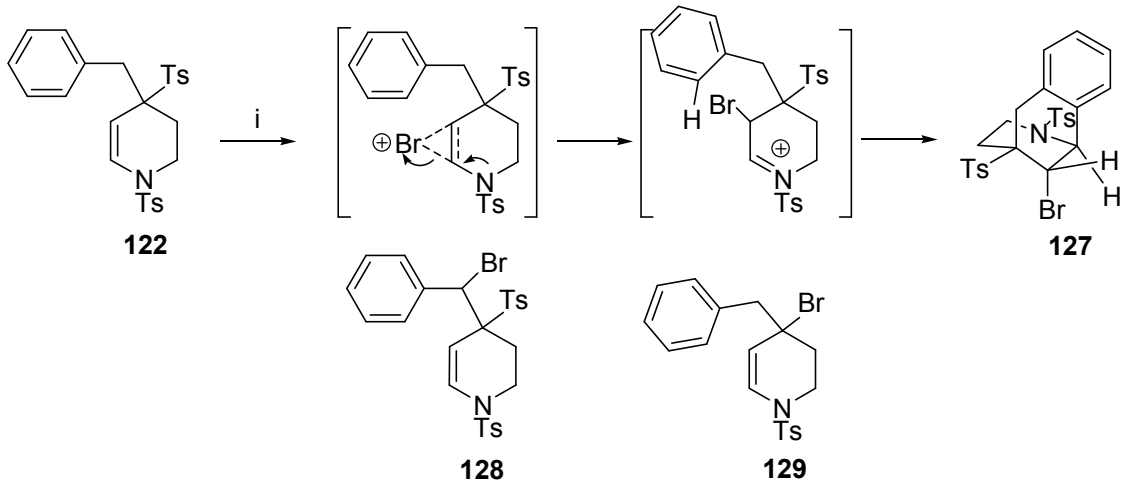
As previously described, 5-iodotetrahydropyridine **97** has been synthesised in our group, whereby there is no extra substitution at the C-4 position (Introduction, Scheme 46).[72] These conditions were used as the basis of a test reaction on tetrahydropyridine **111**, and desired iodide **97** was obtained in 79% yield (Scheme 60). However, as seen in Table 1 (entry 1), when the same conditions were applied to benzyl-substituted tetrahydropyridine **122,** no iodinated product was formed. These results confirm that steric hindrance prevents iodination of C-4 substituted tetrahydropyridine **122** at the C-5 position.



Scheme 60 *Reagents and conditions:* i) a) NIS (1.1 equiv), HTIB (0.1 equiv), CH_2Cl_2, reflux, 20 h; b) Et_3N (1.1 equiv), 79%.

2.2.4 Bromination at the C-5 position

In light of the findings described above, benzyl-substituted tetrahydropyridine **122** was treated with less sterically bulky bromine reagents, using a range of literature procedures.[69,91-98] Once again the desired bromide was not obtained, although interestingly a number of by-products were isolated (Table 2, entries 2-6). Unfortunately, it was not possible to elucidate the structures of all of these by-products following detailed spectroscopic analysis, although a number of possible structures have been proposed such as **127**, **128** and **129** (Scheme 61). Furthermore, it was observed that in general, addition of base was necessary in order to avoid decomposition of the substrate. It is thought that the base may be required to neutralise hydrogen bromide present in the reaction mixture.

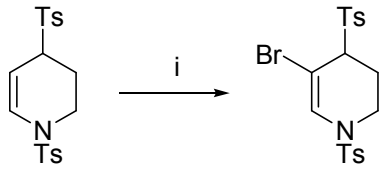


Scheme 61 *Reagents and Conditions:* i) See Table 2.

Table 2 *Attempts to brominate at the C-5 position of tetrahydropyridine* ***122***

Entry	Reagents (equiv)	Solvent	Temp (°C)	Time (h)	Product (yield)
1[91]	NBS (2.0)	THF	–78 → rt	16	Decomposition
2[92]	NBS (1.1), Et_3N (1.1 quench after 1 h)	$CHCl_3$	rt	17	**127** (79%)
3[94]	Br_2 (1.1)	CH_2Cl_2	–78 → rt	16	**128** (not isolated)
4[96]	Br_2 (2.5), EtN^iPr_2 (1.1)	CH_2Cl_2	–78 → rt	16	Unknown
5[98]	Br_2 (1.0)	AcOH	–20 → rt	2	**128** (not isolated)
6[69]	NBS (1.1), HTIB (0.1), Et_3N (1.1 after 20 h)	CH_2Cl_2	Reflux	20	**129** (62%)

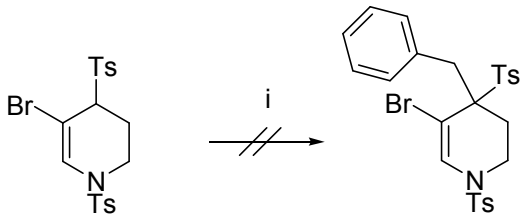
A selection of these brominating conditions were applied to unsubstituted tetrahydropyridine **111,** and the desired bromide **130** was obtained in 54% yield, following treatment with bromine in dichloromethane (Scheme 62).



111 **130**

Scheme 62 *Reagents and Conditions:* i) Br_2 (1.1 equiv), CH_2Cl_2, – 78 °C → rt, 16 h, 54%.

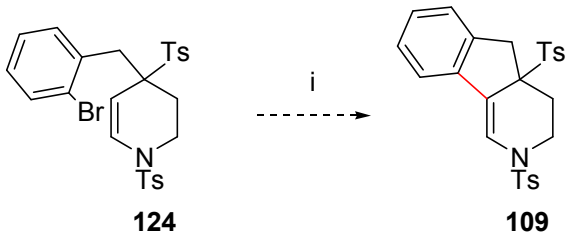
As we had not been able to obtain cyclisation precursor **110** *via* C-4 alkylation followed by C-5 halogenation, it was decided to reverse the order of elaboration to access substrate **110** through C-4 alkylation of bromide **130**. It was hoped that even with the bromine substituent in place, steric hindrance would be less of an issue when it came to installing the benzyl group. However, three attempts to treat tetrahydropyridine **130** with the established benzylating conditions, led only to decomposition through loss of bromide (Scheme 63).



Scheme 63 *Reagents and conditions:* i) a) *n*-BuLi (1.1 equiv), THF–TMEDA, –78 ºC, 20 min; b) BnBr (1.0), –78 ºC → rt, 20 h.

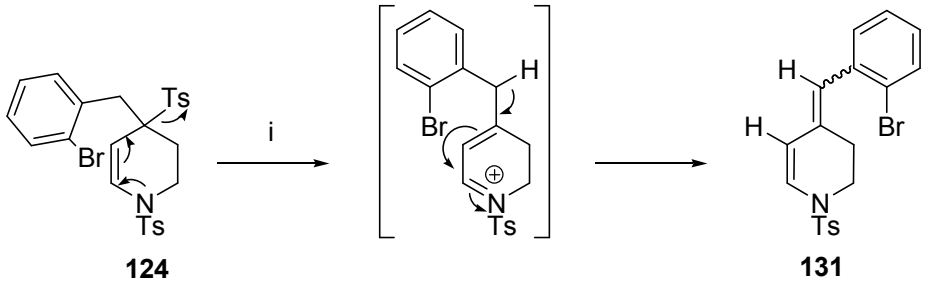
2.2.5 Palladium-catalysed arylation

We had proposed that tricycle **109** could be accessed *via* direct, catalytic arylation of tetrahydropyridine **110**, wherein a non-activated aryl C–H bond is intramolecularly coupled with the activated electron-rich ene–sulfonamide, under catalytic conditions. As we had not been able to synthesise cyclisation precursor **110**, it was hoped that we could still access this tricyclic system through palladium-catalysed arylation of tetrahydropyridine **124** (Scheme 64).



Scheme 64 *Reagents and conditions:* See Table 3.

Recent methodology by Charette and co-workers for the palladium-catalysed regioselective arylation of 1,2,3,4-tetrahydropyridines was applied to substrate **124**.[57] Unfortunately, no insertion product was observed for a range of catalytic systems investigated, even when treating our substrate with an equimolar amount of palladium (Table 3, entry 3).[99] Interestingly, elimination product **131** was isolated as a mixture of geometric isomers (Scheme 65).



124 **131**

Scheme 65 *Reagents and Conditions:* i) See Table 3.

Table 3 *Palladium-catalysed cyclisations*

Entry	Reagents (equiv)	Conditions	Product (yield, ***Z*** **:** ***E***)
1[57]	$PdCl_2$ (0.1), AgOTf (0.6), NaOAc (1.2)	DMF, 150 ºC, 16 h	**131** (28%, 4:3)
2	$PdCl_2$ (0.1), AgOTf (0.5), Et_3N (1.0)	DMF, 150 ºC, 16 h	**131** (64%, 5:4)
3	$PdCl_2$ (1.0), AgOTf (0.5), Et_3N (1.0)	DMF, 150 ºC, 16 h	**131** (62%, 4:3)
4	$Pd(OAc)_2$ (0.1), AgOTf (0.5), Et_3N (1.0)	DMF, 80 ºC, 12 h	**131** (4:1)
5[99]	$Pd_2(dba)_3$ (0.1), P(*o*-tolyl)$_3$ (0.2)	DMF, 80 ºC, 12 h	**131** (31%, 1:2)

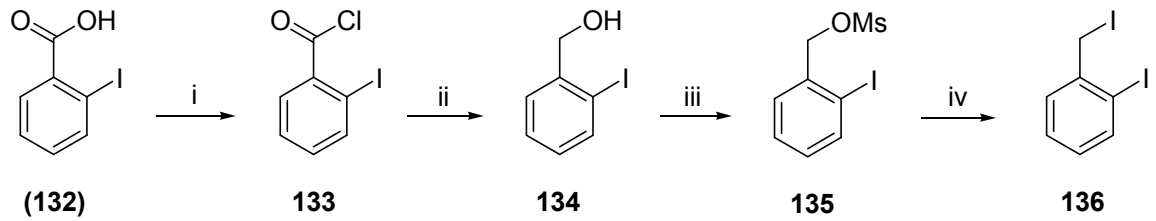
A series of test reactions was carried out on substrate **124** in the presence of solvent alone, base + solvent and palladium catalyst + solvent, in an attempt to determine the cause of elimination. The reactions were heated from 50 → 110 ºC over six hours and were analysed by TLC at hourly intervals. As may be seen from entries 1 and 2 of Table 4, elimination occurs at 90 ºC in the absence of palladium catalyst and at 70 ºC when palladium catalyst is present, as seen in entry 3. Strikingly, the presence of base does not appear to increase the rate of formation of elimination product **131**, although it does result in a change in the ratio of geometric isomers obtained. It can therefore be deduced that tetrahydropyridine **124** is thermally unstable, as even heating in a non-basic solvent such as 1,4-dioxane led to elimination, followed by decomposition (entry 4).

Table 4 Stability tests on tetrahydropyridine **124**

Entry	Substrate	Reagents (equiv)	Conditions	Elimination	Product (yield, ***Z*** **:** ***E***)
1	**124**	N/A	DMF, 50 → 110 ºC	90 ºC	**131** (50%, 3:2)
2	**124**	Et_3N (0.1)	DMF, 50 → 110 ºC	90 ºC	**131** (57%, 2:3)
3	**124**	$Pd(PPh_3)_4$ (0.1)	DMF, 50 → 110 ºC	70 ºC	**131** (50%, 1:2)
4	**124**	N/A	1,4-dioxane, 50 → 90 ºC	90 ºC	Decomposition

2.2.6 Alkylations with 2-iodobenzyl iodide

Our final investigation within this initial strategy was to revisit alkylation of tetrahydropyridine **111,** this time with 2-iodobenzyl iodide **136** as the alkylating agent. We hoped to evaluate whether the corresponding aryl iodide would be more reactive towards oxidative addition than the bromo-analogue had been. It was first necessary to synthesise 2-iodobenzyl iodide **136**, and this was prepared in four steps from commercially available 2-iodobenzoic acid (**132**). The acid was heated under reflux in thionyl chloride to give acid chloride **133**, which was used crude for the reduction with sodium borohydride to give benzyl alcohol **134**. Treatment with triethylamine and mesyl chloride in dichloromethane gave mesylate **135**, which was also used crude to isolate iodide **136** in 75% yield, following treatment with sodium iodide in acetonitrile and purification by column chromatography (Scheme 66).[100,101]

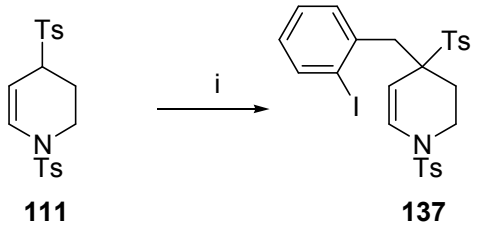


(132) **133** **134** **135** **136**

Scheme 66 *Reagents and Conditions:* i) $SOCl_2$ (6.9 equiv), reflux, 45 min, 95%; ii) $NaBH_4$ (3.9 equiv), THF, 0 °C, then reflux, 12.5 h, 81%; iii) MsCl (1.1 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 10 min, then rt, 1 h, 95%; iv) NaI (2.0 equiv), MeCN, reflux, 16 h, 75%.

Using our established alkylation conditions, tetrahydropyridine **137** was obtained in 61% yield (Scheme 67). As before for the bromoarylated derivative, some product was lost during

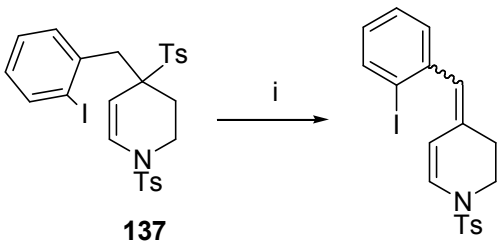
purification, which likely was due to decomposition during silica gel chromatography; degradation of the reaction mixture was observed by TLC analysis over time.



111 **137**

Scheme 67 *Reagents and Conditions:* i) a) *n*-BuLi (1.1 equiv), THF–TMEDA, –78 °C, 30 min; b) 2-iodobenzyl iodide (1.0 equiv), THF, –78 °C → rt, 16 h, 61%.

With 4-substituted tetrahydropyridine **137** in hand, it was decided to re-explore the cyclisation conditions previously investigated for the bromo-analogue. Once again, we expected this substrate to cyclise *via* a Heck-type mechanism or one where the ene–sulfonamide intercepted the initial oxidative addition intermediate. Unfortunately, no insertion product was observed and only elimination product **138** was identified as a mixture of geometric isomers by TLC and NMR analysis (Scheme 68).[99,102]



137 **138**

Scheme 68 *Reagents and Conditions:* i) $Pd_2(dba)_3$ (0.01 equiv), PPh_3 (0.02 equiv), Cs_2CO_3 (1.5 equiv), DMF, 80 °C, 16 h; or $Pd(PPh_3)_4$ (0.02 equiv), Cs_2CO_3 (1.5 equiv), DMF, 80 °C, 16 h.

2.2.7 Conclusions

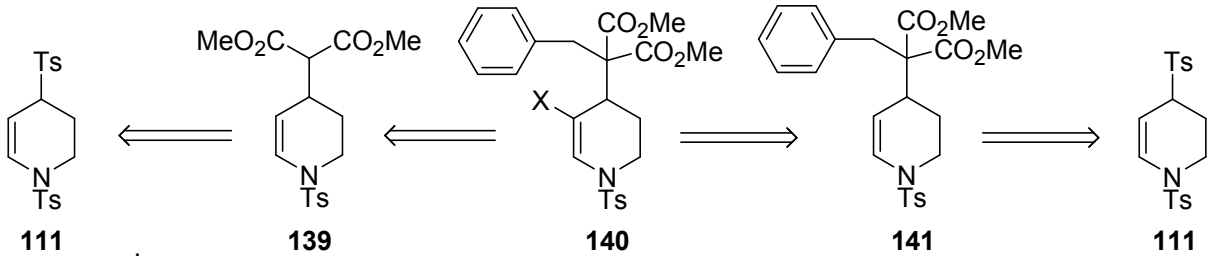
The synthesis of tetrahydropyridine **111** was successfully carried out using methodology previously established in the group and many of the steps were optimised. C-4 Alkylation was successful with benzyl bromide, 2-bromobenzyl bromide, 3-methoxybenzyl bromide and 2-iodobenzyl iodide as the electrophiles to give tetrahydropyridines **122**, **123**, **124** and **125** respectively. Steps were taken to prevent degradation of these acid sensitive derivatives during work up and purification.

Halogenation of tetrahydropyridine **122** proved to be unsuccessful and this was attributed to steric hindrance around the C-5 position due to an adjacent quaternary centre. Iodo- and bromo-derivatives of tetrahydropyridine **111** were obtained in good yields, and attempts were made to access cyclisation precursor **110** by reversing the order of addition of electrophile and halide, which also proved unsuccessful.

Attempts were made to isolate tricyclic systems following direct arylation of tetrahydropyridines **125** and **137** with a palladium catalyst, additive and base, but only elimination products **131** and **138** were observed.

2.3.0 S_N1 Approach

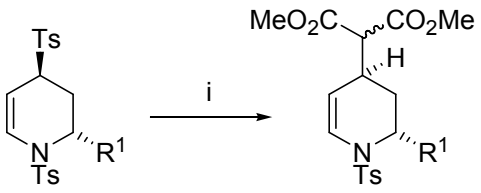
Attention next turned to the S_N1 chemistry of these tetrahydropyridine substrates, as previously described (Introduction, Scheme 32). It was hoped that we could use this methodology to access substitution product **139** and that this substrate would then undergo alkylation and halogenation to give cyclisation precursor **140**. It was proposed that the problem of steric hindrance at C-5 would be avoided as there would no longer be an adjacent congested quaternary centre at C-4. Furthermore, we hoped to observe a Thorpe–Ingold effect, whereby the presence of a gem-dimethyl ester group on a tetrahedral centre results in enhanced reactivity between the tetrahydropyridine ring and tethered arene.[103]
We also planned to alkylate the nucleophile prior to substitution (**141**), for a more convergent synthetic route (Scheme 69).



Scheme 69 *Proposed S_N1 route to cyclisation precursor*

2.3.1 Previous group methodology

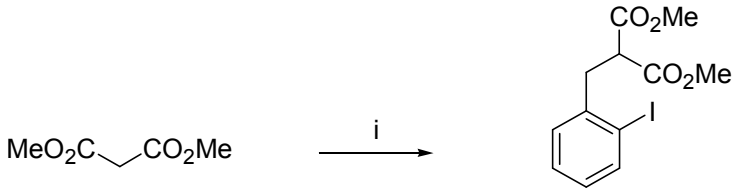
Previous work within the group has demonstrated that treatment of tetrahydropyridine **67** with tin tetrachloride, dimethyl malonate and **bis(trimethylsilyl)acetamide (BSA)** additive in dichloromethane gave the desired 4-substituted-tetrahydropyridine **71** in good yield as a mixture of C-4 epimers (Scheme 70).[71] Tin tetrachloride is thought to simultaneously activate the C-4 tosyl leaving group *via* formation of a conjugated iminium species and generate the nucleophilic enolate *in situ*. The stereoselectivity is variable whereby tetrahydropyridine **67** bearing less sterically demanding C-2-substituents showed almost no selectivity, whereas for bulkier C-2-substituents the *anti*-product was the major isomer.



67 . **71**

Scheme 70 *Reagents and Conditions:* i) Dimethyl malonate (3.0 equiv), $SnCl_4$ (3.0 equiv), BSA (3.0 equiv), CH_2Cl_2,, –78 ºC, 1 h, then rt, 16 h, 65-100%.

We wished to investigate this reactivity for tetrahydropyridine substrate **111**, with dimethyl malonate **(143)** and dimethyl 2-(2-iodobenzyl)malonate **144** as nucleophiles. Dimethyl 2-(2-iodobenzyl)malonate **144** was obtained in 95% yield, following treatment of dimethyl malonate **(143)** with sodium hydride, and reaction of the resulting enolate with 2-iodobenzyl iodide **136** (Scheme 71).[104]

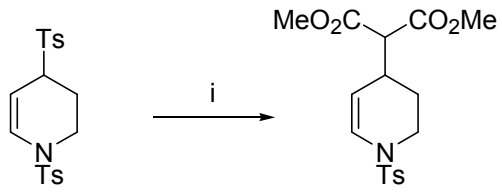


(143) **144**

Scheme 71 *Reagents and Conditions:* i) a) dimethyl malonate **(143)** (2.5 equiv), NaH (2.0 equiv), THF, 0 °C → rt, 30 min; b) 2-iodobenzyl iodide **136** (1.0 equiv), THF, rt, 20 h, 95%.

However, treatment of a solution of tetrahydropyridine **111**, BSA and dimethyl malonate **(143)** in dichloromethane with tin tetrachloride, resulted in only decomposition. It was therefore decided to investigate forming the enolate and conjugated iminium species separately. Solutions of dimethyl malonate **(143)** and BSA in dichloromethane and tetrahydropyridine **111** in dichloromethane were treated with tin tetrachloride at –78 °C and stirred for 30 minutes. The conjugated iminium solution was then added to the enolate solution and the reaction mixture stirred at room temperature overnight to isolate tetrahydropyridine **139** in only 10% yield (Scheme 72).

Applying the same conditions to dimethyl 2-(2-iodobenzyl)malonate **144** resulted in no reaction and **144** was recovered in 62% yield.



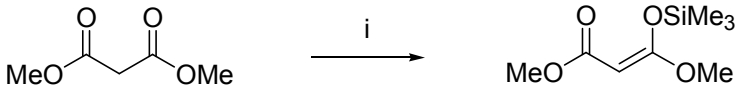
111 . **139**

Scheme 72 *Reagents and Conditions:* i) a) Dimethyl malonate (**143**) (1.5 equiv), BSA (1.5 equiv), $SnCl_4$ (1.5 equiv), CH_2Cl_2,, –78 ºC, 30 min; b) **111** (1.0 equiv), $SnCl_4$ (1.5 equiv), –78 ºC, 30 min; c) (**143**) + **111**, –78 ºC → rt, 17 h, 10%.

2.3.2 Silyl ketene acetal formation

The group had previously demonstrated that tetrahydropyridines undergo ionisation following treatment with tin tetrachloride, we were therefore concerned that our enolate species may not have been forming *in situ* and therefore decided to pre-form and isolate the enolate species as silyl ketene acetal **145** (Scheme 73). Two different literature procedures were followed to form (Z)-methyl 3-methoxy-3-(trimethylsilyloxy)acrylate **145**, however isolation proved very difficult.[105,106] In each case, chlorotrimethylsilane was base-washed with triethylamine prior to addition.

When an anhydrous work-up was carried out, crude NMR analysis confirmed that only the starting dimethyl malonate **(143)** was present. Therefore, it was suspected that the product was sensitive to atmospheric moisture and so the reaction mixture was instead centrifuged by way of a work-up and distilled. Silyl ketene acetal **145** was isolated as a mixture with malonate **143**, but despite fractionally distilling this mixture, separation was not achieved and successive distillations resulted in decomposition to the starting material. A 3:1 selectivity for the desired product was the optimum ratio observed despite a selectivity of 9:1 reported in the literature.[105]



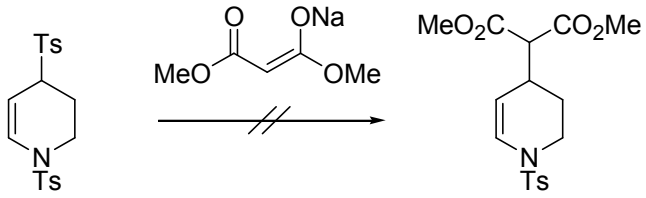
(143) **145**

Scheme 73 *Reagents and Conditions:* i) a) (**143**) (1.0 equiv), NaH (1.2 equiv), THF, 0 °C; b) TMSCl (2.0 equiv), 0 °C → rt, 16 h, **143:145** (3:1).

It was thought that silyl ketene acetal **145** would be more stable and possibly easier to isolate with a bulkier silyl group, so chlorodiphenylmethylsilane was investigated as an alternative silylating agent. Attempts to separate the product from starting material and unreacted silylating agent by fractional distillation, proved unsuccessful and therefore this bulkier silyl ketene acetal was not isolated.[107]

2.3.3 *In-situ* enolate formation

As we had been unable to isolate (Z)-methyl 3-methoxy-3-(trimethylsilyloxy)acrylate **145**, attempts were made to form the sodium enolate *in-situ* and then react this nucleophile with the pre-formed conjugated iminium species to give 4-(dimethyl malonate)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine **139** (Scheme 74).



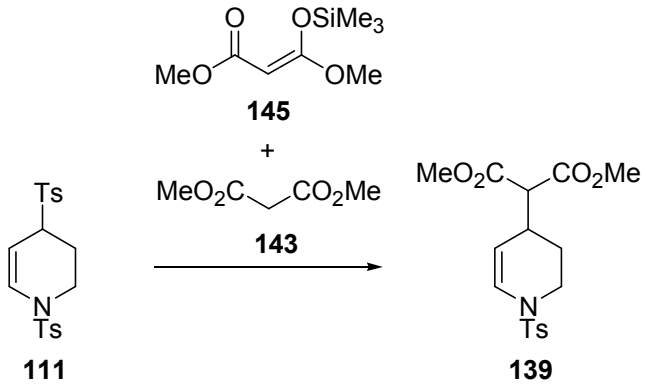
111 **139**

Scheme 74 *Attempt to form the enolate in-situ*

The enolate was formed following treatment of a suspension of sodium hydride in tetrahydrofuran with a solution of dimethyl malonate **(143)** in tetrahydrofuran at 0 °C. Formation was deduced to have taken place due to the exothermic effervescence observed upon addition of **(143)**. The conjugated iminium species was formed following addition of a range of hard and soft Lewis acids (tin tetrachloride, boron trifluoride, silver triflate, palladium(II) acetate, copper(II) acetate and copper(II) triflate) to solutions of tetrahydropyridine **111**, in tetrahydrofuran at –78 °C. In each case no reaction was observed and only starting material was isolated. It was unknown whether the enolate was being quenched before the conjugated iminium species was added, or if the iminium species was not forming. It was also thought that tetrahydrofuran might have been too co-ordinating a solvent, hence hindering substitution.

2.3.4 Using the silyl ketene acetal: malonate mixture

In light of the above, it was decided to use the isolated mixture of **145** and **143** as the nucleophilic reactant in the formation tetrahydropyridine **139**, as both separation of the **145** and **143** and forming the enolate *in situ* had proved unsuccessful (Scheme 75). Once again, a range of different Lewis acids were investigated to effect this substitution: the use of boron trifluoride and zinc chloride resulted in the recovery of starting material, whereas addition of titanium tetrachloride at –78 °C, 0 °C and room temperature resulted in decomposition. Finally a solution of tetrahydropyridine **111** and an excess of a 10:7 ratio of the **145:143** enolate mixture, was stirred at –78 °C in dichloromethane for 30 minutes. Tin tetrachloride was then added and the reaction mixture stirred at –78 °C for a further hour before warming to room temperature. As previously observed, only 10% of tetrahydropyridine **139** was isolated.

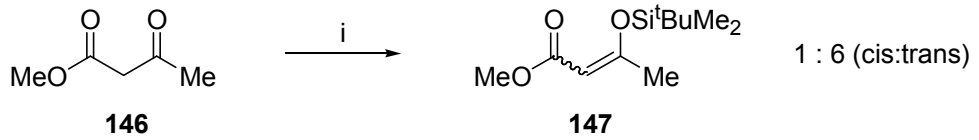


Scheme 75 *Reagents and Conditions:* i) a) **145:143** (10:7) (3.0 equiv), CH_2Cl_2, –78 °C, 30 min; b) $SnCl_4$ (1.1 equiv), –78 °C, 1 h → rt, 1.5 h, 10%

2.3.5 β-Keto ester approach

We still believed that pre-forming the enolate species was key to the success of this desired substitution reaction. It was proposed that forming the silyl enol ether of a β-keto ester would provide a much more stable nucleophile than that of dimethyl malonate, which could then be used to carry out the desired S_N1 substitution. Silyl enol ether **147** was isolated in 70% yield, following treatment of methyl acetoacetate **146** with 1,8-diazabicyclo[5.4.0]undec-7-ene and *tert*-butyldimethylsilyl chloride in toluene at 80 °C (Scheme 76).[108] The product was isolated

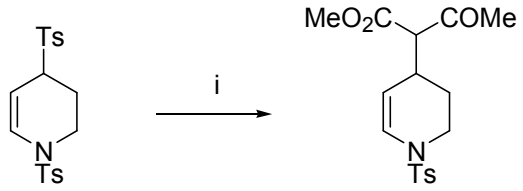
in a 1:6 mixture of cis:trans, in accordance with the literature, and was even stable to column chromatography.



146 **147**

Scheme 76 *Reagents and conditions:* i) DBU (1.2 equiv), TBDMSCl (1.1 equiv), toluene, 80 °C, 16 h, 70%.

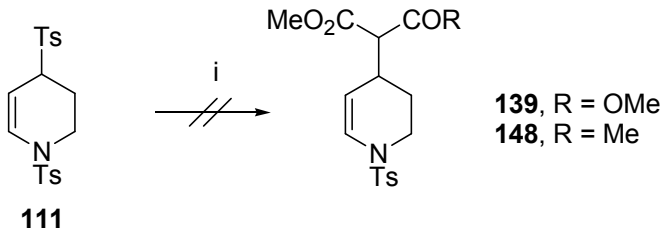
Tin tetrachloride, boron trifluoride and zinc chloride in dichloromethane were investigated as Lewis acids in order to effect the desired transformation, at temperatures ranging from –78 °C to room temperature. Limited success was achieved, with the desired product **148** being obtained in very poor yield (14%), following treatment of tetrahydropyridine **111** and silyl enol ether **147** with tin tetrachloride at room temperature (Scheme 77).



111 **148**

Scheme 77 *Reagents and Conditions:* i) a) **111** (1.0 equiv), **147** (1.0 equiv), CH_2Cl_2, rt; b) $SnCl_4$ (1.0 equiv), rt, 15 h, 14%.

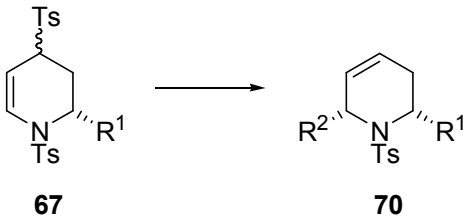
The final attempts to access the desired S_N1 products involved treatment of a solution of tetrahydropyridine **111** in dichloromethane with either dimethyl malonate or methyl acetoacetate followed by tin tetrachloride at room temperature. After stirring for 2.5 hours, triethylamine was added and the reaction mixture was stirred for a further 2 hours. Unfortunately no reaction was seen to occur in either case and only starting material was isolated (Scheme 78).



Scheme 78 *Reagents and Conditions:* i) a) dimethyl malonate/methyl acetoacetate (1.0 equiv), $SnCl_4$ (1.0 equiv), CH_2Cl_2, rt, 2.5 h; b) Et_3N (1.0 equiv), 2 h.

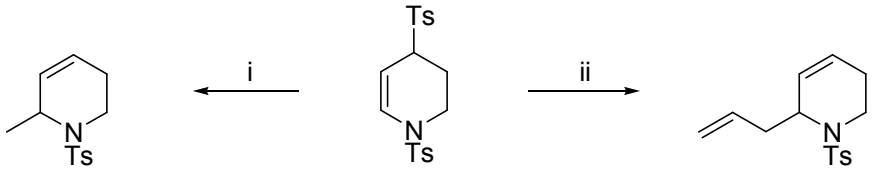
2.3.6 Investigating S_N1' reactivity

It has previously been demonstrated in the Craig group that dialkyltetrahydropyridines **70** are formed exclusively as 2,6-*syn* isomers following treatment of C-2-substituted tetrahydropyidines **67** with a Lewis Acid, to give a conjugated iminium species, which then reacts with hard carbon nucleophiles in a 1,2-sense.[67] The complete stereoselectivity of these transformations, regardless of the configuration at C-4, confirms that these reactions proceed via an S_N1' mechanism (Scheme 79).



Scheme 79 *S_N1' approach to di-substituted tetrahydropyridines*

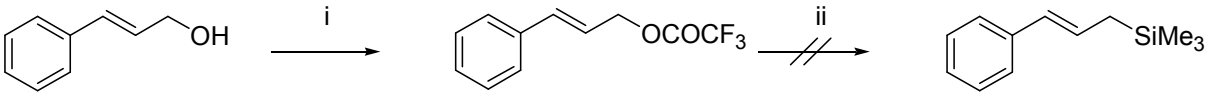
These substitutions had never been carried out on non-C-2-substituted substrates and it was thought that by investigating this S_N1' reactivity we would be able to determine whether or not the desired conjugated iminium intermediate was being formed, and whether this could be the reason for the lack of S_N1 reactivity. Treatment of tetrahydropyridine **111** with trimethyl aluminium and also allyltrimethylsilane in conjunction with tin tetrachloride, gave the desired substitution products **149** and **150** respectively (Scheme 80).[67]



149 **111** **150**

Scheme 80 *Reagents and Conditions:* i) Me_3Al (2.0 equiv), toluene, rt, 1 h, 73%; ii) $CH_2CHCH_2SiMe_3$ (2.2 equiv), $SnCl_4$ (2.2 equiv), CH_2Cl_2, −78 °C, 20 min, then rt, 1 h, 36%.

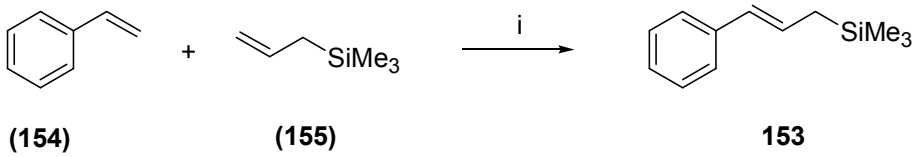
Following successful S_N1' substitution with these nucleophiles, it was proposed that employing a bulky silane reagent, i.e. one containing an aryl group, might force the reaction in a 1,4-sense to give the desired S_N1 substitution. Work was therefore undertaken to synthesise cinnamyl trimethylsilane **153**. Trifluoroacetate **152** was obtained in good yield (80%) following treatment of cinnamyl alcohol (**151**) with triethylamine, 4-dimethylaminopyridine and trifluoroacetic anhydride (Scheme 81).[109] However, various conditions explored for the subsequent silylation, using hexamethyldisilane and a palladium source, proved unsuccessful.[110-112]



151 **152** **153**

Scheme 81 *Reagents and Conditions:* i) Et_3N (1.38 equiv), DMAP (0.10 equiv), $(CF_3CO)_2O$ (1.18 equiv), CH_2Cl_2, 0 °C → rt, 80%; ii) $(SiMe_3)_2$ (2.0 equiv), $Pd(OAc)_2$/ $Pd_2(dba)_3$ (0.030 equiv), THF/toluene, rt, 16 h, no reaction.

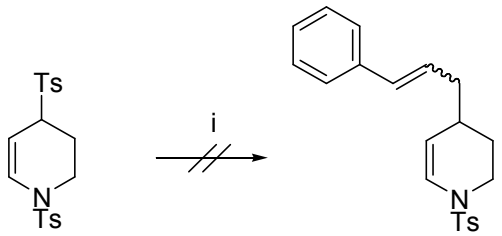
A different approach was also investigated whereby cinnamyl trimethylsilane **153** was synthesised by cross-metathesis of styrene **(154)** and allyl trimethylsilane **(155)**. Grubbs second generation catalyst was used and the reaction mixture heated under reflux in dichloromethane for 24 hours.[113] The reaction did not reach completion and it proved difficult to separate the product from the starting styrene by column chromatography. Silane **153** was finally isolated by Kügelrohr distillation in only 24% yield (Scheme 82).



(154) **(155)** **153**

Scheme 82 *Reagents and conditions:* i) styrene (1.0 equiv), allyl trimethylsilane (1.5 equiv), Grubbs II (0.15 equiv), CH_2Cl_2, reflux, 24 h, 24%.

Unfortunately, treatment of a dichloromethane solution of tetrahydropyridine **111** and silane **153** with tin tetrachloride at –78 °C, did not result in the formation of any substitution product (Scheme 83).[67]



111 **156**

Scheme 83 *Reagents and Conditions:* i) Tetrahydropyridine **111** (1.0 equiv), silane **153** (2.0 equiv), $SnCl_4$ (2.0 equiv), CH_2Cl_2, –78 °C, 1.5 h, then rt, 1.5 h, decomposition.

2.3.7 Conclusions

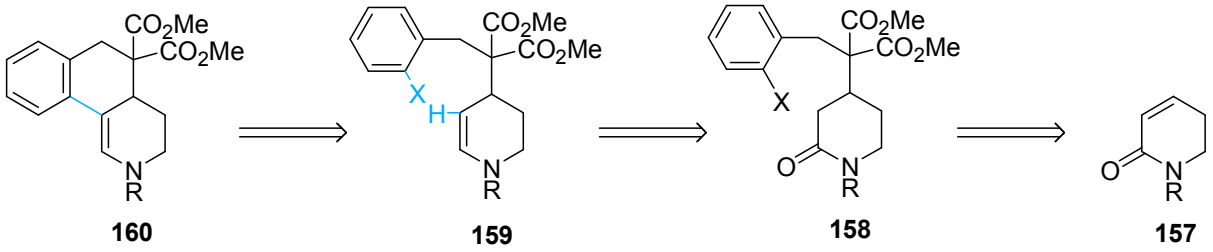
Unfortunately, the S_N1 methodology previously established in the group was unsuccessful for our non-C-2 substituted tetrahydropyridine **111**.[71] Various other attempts to effect the desired substitution through pre-forming the nucleophilic species included: silyl ketene acetal formation, *in-situ* enolate formation and β-keto ester formation, but tetrahydropyridines **139** and **148** were isolated in only 10% and 14% yield respectively.

It was suspected that the desired conjugated iminium intermediate required for substitution to take place was not being formed. However, investigations of S_N1' reactivity, *via* the same intermediate, gave C-2 substitution products **149** and **150**, following treatment with trimethylaluminium and allyltrimethylsilane respectively.[67] Subsequent attempts to force this substitution to occur at the C-4 position with bulky silane reagent **153,** unfortunately did not result in any C-2 or C-4 substitution product.

A possible explanation for the lack of $S_N1$reactivity of our substrate is the absence of a C-2 substituent. This loss of steric bulk on the tetrahydropyridine ring may have resulted in a reduction in the rate of intermediate iminium formation, as the corresponding relief of steric strain that occurred in the rate-determining ionisation step may have been less pronounced.

2.4.0 α,β-Unsaturated lactam approach

At this point in time we decided it was necessary to develop a new substrate in order to demonstrate the desired direct arylation. We planned to first generate α,β-unsaturated lactam **157**, which we expected to behave as a good Michael acceptor towards 1,4-addition with an halo-aryl-substituted nucleophile. Reduction of the lactam would give cyclisation precursor **159**, followed by direct arylation under catalytic conditions to give tricycle **160** (Scheme 84).

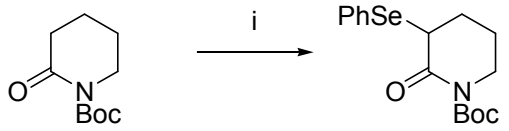


Scheme 84 *Access to desired tricyclic system from lactam **157***

2.4.1 Synthesis of α,β-unsaturated lactam 157

2.4.1.1 Work towards Boc-protected lactam 161

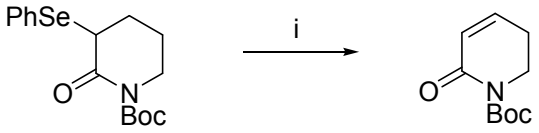
Boc-protected α,β-unsaturated lactam **161** was isolated following selenoxide elimination of 1-Boc-2-piperidone (**162**) (Scheme 85). A range of literature selenylation conditions were investigated: of the different bases used, it was suspected that *n*-butyl lithium was too nucleophilic for this transformation and that more hindered bases, such as sodium hexamethyldisilazide and lithium di*iso*propylamide were more suitable.[114-116] However, by-product formation, thought to be the result of di-selenylation, was observed, even with only 1.0 equivalent of phenylselenyl chloride. Changing the order of addition, so that the pre-formed enolate was rapidly added to a solution of the electrophile *via* cannula, significantly reduced by-product formation, and the desired α-phenyl selenylated lactam **163** was obtained in 87% yield.



162 **163**

Scheme 85 *Reagents and Conditions:* i) a) *i*-Pr_2NH (1.0 equiv), *n*-BuLi (1.0 equiv), THF, –78 °C, 30 min; b) (**162**) (1.0 equiv), THF, –78 °C, 30 min; c) added to PhSeCl (1.5 equiv), THF, –78 °C → rt, 2.5 h, 87%.

α,β-Unsaturated lactam **161** was obtained in consistently good yields following oxidation with sodium periodate and elimination with sodium bicarbonate (Scheme 86).[117]

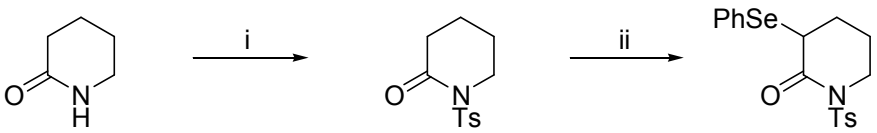


163 **161**

Scheme 86 *Reagents and Conditions:* i) $NaIO_4$ (2.3 equiv), $NaHCO_3$ (1.2 equiv), MeOH-H_2O, rt, 16 h, 75 %.

2.4.1.2 Work towards tosyl-protected lactam 164

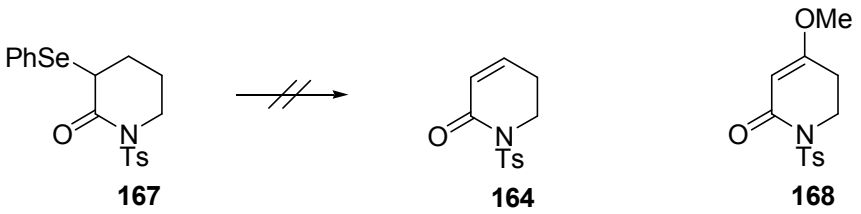
In addition to Boc-protected lactam **161**, it was desirable to prepare the tosyl-derivative from δ-valerolactam **(165)**. Treatment with *n*-butyllithium and tosyl chloride followed by trituration with toluene gave lactam **166** in 56% yield.[118] A variety of conditions were investigated to effect selenylation of **166**, and *n*-butyl lithium was found to be the preferred base with only 1.2 equivalents of phenylselenyl chloride required (Scheme 87).[115,116]



165 **166** **167**

Scheme 87 *Reagents and Conditions:* i) a) *n*-BuLi (1.07 equiv), THF, –78 °C, 30 min; b) TsCl (1.07 equiv), THF, –78 → 0 °C, 16 h, 56%; ii) a) *n*-BuLi (1.12 equiv), THF, –78 °C; b) **166** (1.0 equiv), THF, 15 min; PhSeCl (1.2 equiv), THF, –78 °C → rt, 1.5 h, 59%.

Oxidation of lactam **167** and elimination to give lactam **164** was not as successful (Scheme 88). A range of conditions were investigated, including those employed for lactam **163**.[115,117,119,120] However the tosyl-protected lactam was found to be water-insoluble, and by-product **168** was obtained following treatment with sodium periodate and sodium bicarbonate. Treatment with *m*-chloroperoxybenzoic acid and hydrogen peroxide resulted in decomposition.

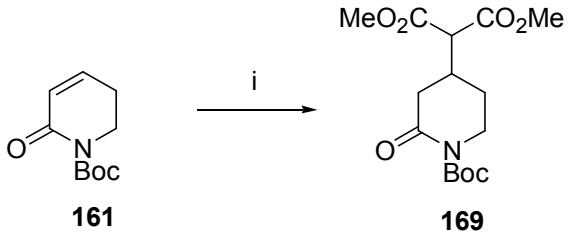


Scheme 88 *Oxidative elimination was unsuccessful; by-product **168***

2.4.2 1,4-Michael addition

2.4.2.1 1,4-Addition with dimethyl malonate

1,4-Michael addition to α,β-unsaturated lactam **161** was investigated with dimethyl malonate and a range of sub-stoichiometric bases: triethylamine, potassium *tert*-butoxide and sodium hydride.[121,122] The desired Michael addition product **169** was isolated in an optimum yield of 87% (Scheme 89).

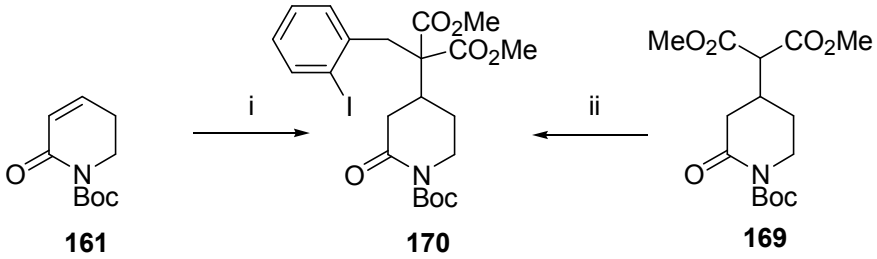


Scheme 89 *Reagents and Conditions:* i) a) NaH (0.1 equiv), dimethyl malonate (1.0 equiv), THF, 0 °C → rt, 10 min; b) **161** (1.0 equiv), THF, rt, 18 h, 87%.

It was proposed that this malonate addition product could be arylated through alkylation of **169** with 2-iodobenzyl iodide **136**, or following treatment of lactam **161** with an aryl-substituted malonate and sub-stoichiometric base, to give lactam **170** (Scheme 90). It was found that Michael addition to lactam **161** with malonate **144** and sub-stoichiometric

sodium hydride gave the desired product in 63% yield.[123] However, this result was not reproducible on a multi-gram scale; despite using an excess of both malonate **144** and base, the reaction failed to reach completion and the starting lactam and product were very difficult to separate by column chromatography.

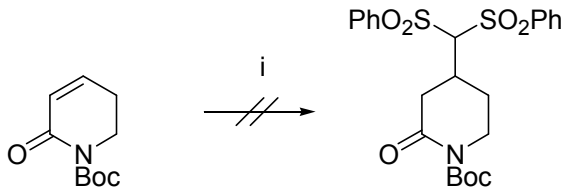
For the generation of **170**, a range of alkylation conditions with 2-iodobenzyl iodide **136** were investigated on malonate addition product **169**. Employing sodium hydride or potassium *tert*-butoxide as base in tetrahydrofuran resulted in incomplete reaction, or decomposition in the form of elimination of dimethyl malonate to give the starting lactam **161**. It was discovered that pre-mixing lactam **169** and iodide **136** in dimethylformamide and then adding this solution to hexane-washed and dried sodium hydride gave the desired lactam **170** in 98% yield after only 2 hours. Monitoring the reaction time was very important for this transformation, as if the reaction was left for too long elimination occurred again to give unsaturated lactam **161**.



Scheme 90 *Reagents and Conditions:* i) a) NaH (0.1 equiv), malonate **144** (1.0 equiv), THF, 10 min; b) **161** (1.0 equiv), THF, 0 °C → rt, 16 h, 63%; ii) NaH (1.0 equiv), 0 °C; malonate **169** (1.0 equiv), iodide **136** (1.0 equiv), DMF, 0 °C → rt, 2 h, 98%.

2.4.2.2 Michael addition with sulfone nucleophiles

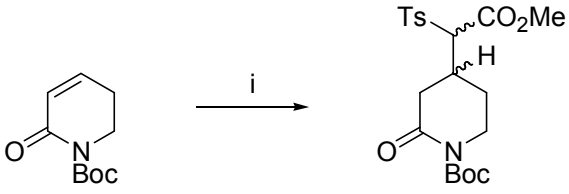
It was decided to also explore the reactivity of bis-sulfone nucleophiles with lactam **161**, using the methodology previously applied to the malonate addition products (Scheme 91).[123] In this case however, no reaction was observed following treatment with sub-stoichiometric and equimolar potassium *tert*-butoxide or sodium hydride. It is thought that the bis-sulfone was too hindered a nucleophile for 1,4-addition.



161 **171**

Scheme 91 *Reagents and Conditions:* i) a) NaH (0.1-1.0 equiv)/KO*t*-Bu (0.1 equiv), bis-sulfone (1.0 equiv), THF, 0 °C → rt, 10 min; b) **161** (1.0 equiv), THF, rt, 16 h, no reaction.

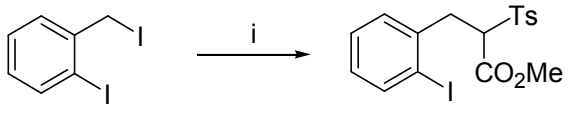
Methyl-*p*-tosyl acetate was therefore investigated as an alternative sulfone nucleophile. Michael addition of lactam **161** was effected following treatment with the sodium enolate of methyl-*p*-tosyl acetate, to isolate lactam **172** in 60% yield, as a 1:1 mixture of inseparable diastereomers (Scheme 92).[123]



161 **172**

Scheme 92 *Reagents and Conditions:* i) a) NaH (1.0 equiv), THF, 0 °C; methyl-*p*-tosyl acetate (1.0 equiv), THF, 0 °C, 45 min; b) lactam **161** (1.0 equiv), THF, 0 °C → rt, 19 h, 60%

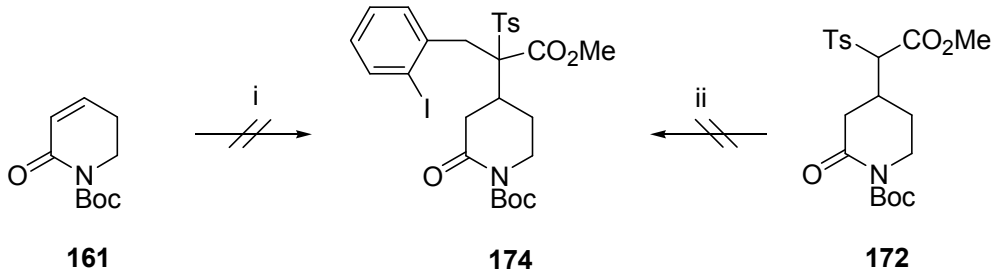
Aryl-substituted methyl-*p*-tosyl acetate **173** was isolated in 90% yield under the same conditions used to synthesise aryl-substituted malonate **144**: following deprotonation of methyl-*p*-tosyl acetate with sodium hydride and then quenching with 2-iodobenzyl iodide **136** (Scheme 93).[104]



136 **173**

Scheme 93 *Reagents and Conditions:* i) a) NaH (2.0 equiv), THF, 0 °C, methyl-*p*-tosyl acetate (2.5 equiv), 0 °C, 15 min; b) 2-iodo-benzyl iodide **136** (1.0 equiv), THF, 0 °C → rt, 16 h, 90%.

Efforts to generate lactam **174**, by 1,4-addition of the sodium enolate of aryl-substituted methyl-*p*-tosyl acetate **173** (formed by treatment of **173** with sodium hydride and DBU) to α,β-unsaturated lactam **161**, were unsuccessful (Scheme 94).[123,124] Alkylation of addition product **172** with 2-iodobenzyl iodide **136** also proved to be ineffective, resulting in either no reaction or decomposition. This lack of reactivity is once again thought to be the result of steric hindrance arising from the quaternary centre in **174**.

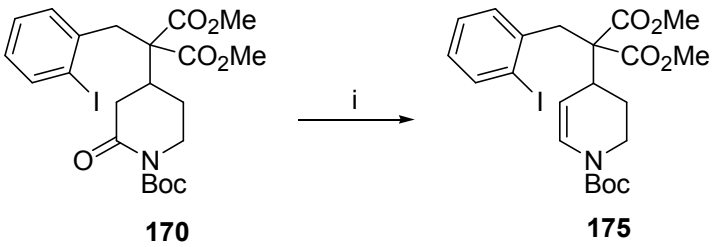


Scheme 94 *Reagents and Conditions:* i) a) NaH (0.1-1.0 equiv)/DBU (0.1 equiv), LiCl (1.0 equiv), **173** (1.0 equiv), THF, 0 °C → rt, 10 min; b) **161** (1.0 equiv), THF, rt, 20 h, no reaction; ii) NaH (1.0-2.0 equiv), THF, 0 °C; lactam **172** (2.5 equiv), THF, 0 °C → rt, 10 min; iodide **136** (1.0 equiv), THF, rt, 44 h, decomposition.

2.4.3 Reduction of the lactam functionality

2.4.3.1 Reduction of alkylated product 170

A one-pot reduction and elimination of lactam **170** was envisaged to give tetrahydropyridine **175** (Scheme 95). Treatment with sodium borohydride followed by acidification with a 2 M ethanolic hydrochloric acid solution, gave the corresponding ethoxide. Following neutralisation and washing with dichloromethane, heating under reflux in toluene effected elimination to give the desired cyclisation precursor **175** in only 33%.[125] Di*iso*butylaluminium hydride was investigated as an alternative reducing agent, and the optimal reaction conditions were found to be treatment with 1.0 equivalent at –78 °C.[126] Following isolation of the corresponding lactamol, dehydration was effected by treatment with 12.0 equivalents of 1 M aqueous hydrochloric acid solution, giving tetrahydropyridine **175** in 83% yield.

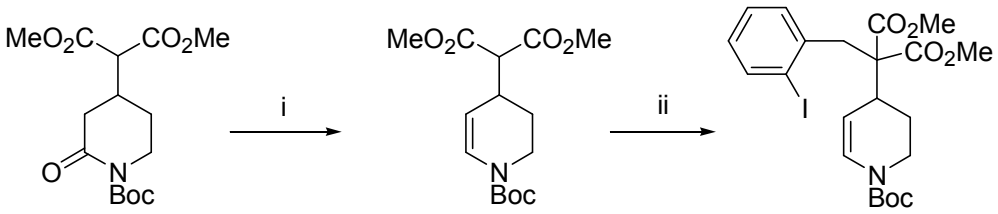


170 **175**

Scheme 95 *Reagents and Conditions:* i) a) DIBAL-H (1.0 equiv), THF, –78 °C, 2 h; Rochelle's salt, Et_2O, rt, 16 h; b) 1M $HCl_{aq.soln}$ (12.0 equiv), CH_2Cl_2, rt, 20 h, 83%.

2.4.3.2 Alternative route towards cyclisation precursor 175

An alternative route to cyclisation precursor **175** was also investigated, which would enable easier manipulation of the aryl side-chain, and iodination of the ene–carbamate prior to alkylation. Reduction of addition product **169** using the previously established di*iso*butylaluminium hydride conditions, gave ene–carbamate **176** in excellent yield (92%).[126] Subsequent alkylation with 2-iodobenzyl iodide **136**, where the two substrates were pre-mixed prior to deprotonation as before, gave **175** in 87% yield without the need for purification (Scheme 96). Reversing the order of these two transformations in this way gave consistently higher yields, and it was anticipated that more diverse substrates would be easier to access, as alkylation with the relevant aryl halide would now be the final step.



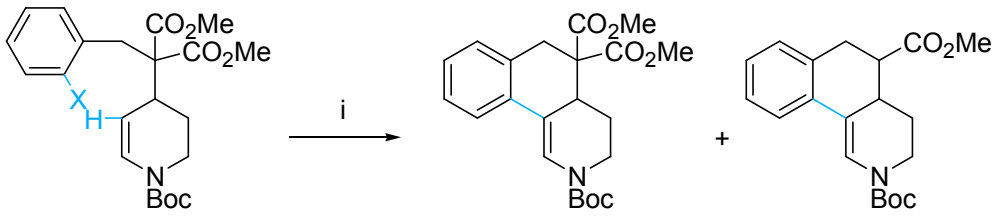
169 **176** **175**

Scheme 96 *Reagents and Conditions:* i) a) DIBAL-H (1.0 equiv), THF, –78 °C, 2 h; Rochelle's salt, Et_2O, rt, 16 h; b) 1M $HCl_{aq.soln}$ (8.0 equiv), CH_2Cl_2, rt, 2 h, 92%; ii) NaH (1.0 equiv), DMF, 0 °C; malonate **176** (1.0 equiv), 2-iodobenzyl iodide (1.0 equiv), DMF, 0 °C → rt, 1 h, 87%.

2.4.4 Palladium-catalysed arylation

Some time was spent optimising the direct arylation of tetrahydropyridine **175** to give tricycle **176** (Scheme 97, Table 5). Treatment with catalytic tetrakis(triphenylphosphine) palladium(0) and potassium acetate in dimethylacetamide under microwave irradiation at 140 °C for ten minutes, gave the desired product in 70% yield on a 9 mg scale (entry 1).[53] Repeating these conditions on a larger scale was found to give a disappointingly lower yield and resulted also in the isolation of monoester **177**.

A range of other catalytic systems were investigated with a palladium(II) source (entries 2-4): resulting in mixtures of **176** and **177**, decomposition and isolation of a second unidentified by-product respectively.[34,57,127] Employing the conditions from entry 1 with palladium(II) acetate in conjunction with triphenylphosphine ligand, gave tricycle **176** in 82% yield together with only 7% of monoester **177** (entry 5). Attempts were made to reduce the reaction time in order to minimise the formation of monoester, but this resulted in a reduced yield of tricycle **176**. It was thought that the hydrogen iodide eliminated upon cyclisation could be responsible for the loss of one of the ester groups and so an excess of base was added in order to neutralise this, and again attempts were made to reduce the reaction time (entry 6). However, increased levels of heating were required and a higher proportion of monoester **177** was isolated (21%).



175 **176** **177**

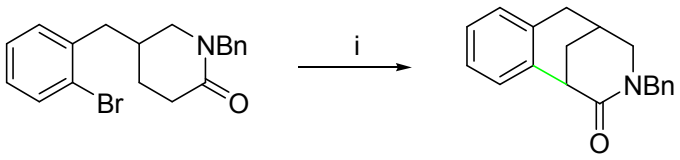
Scheme 97 *Reagents and Conditions:* i) See Table 5

Table 5 Reaction conditions investigated to effect direct arylation of tetrahydropyridine **175**

Entry	Pd source (equiv)	Reagents and Conditions (equiv)	Product (yield)
1[53]	$Pd(PPh_3)_4$ (0.1)	KOAc (2.0), DMA, 140 °C in microwave, 10 min	**176** (70%)
2[34]	$Pd(OAc)_2$ (0.05)	PPh_3 (0.05), K_2CO_3 (3.0), PivOH (0.3), DMA, 50 → 120 °C, 8 h; 120 °C, 16 h	**176** and **177** (not isolated)
3[57]	$PdCl_2(PPh_3)_2$ (0.1)	AgOTf (0.6), NaOAc (1.2), DMF, 200 °C in microwave, 10 min	Decomposition
4[127]	$Pd(OAc)_2$ (0.1)	KOAc (2.75), TBAB (1.2), DMF, 180 °C in microwave, 9 min	**177** (4%) and unknown
5[53]	$Pd(OAc)_2$ (0.1)	PPh_3 (1.0), KOAc (2.0), DMA, 140 °C in microwave, 10 min	**176** (82%) and **177** (7%)
6	$Pd(OAc)_2$ (0.1)	PPh_3 (1.0), KOAc (3.0), DMA, 140 °C in microwave, 3 min; 140 °C in microwave, 5 min; 140 °C in microwave, 5 min	**176** (39%) and **177** (21%)

2.4.5 α-Arylation of *N*-substituted 2-piperidones

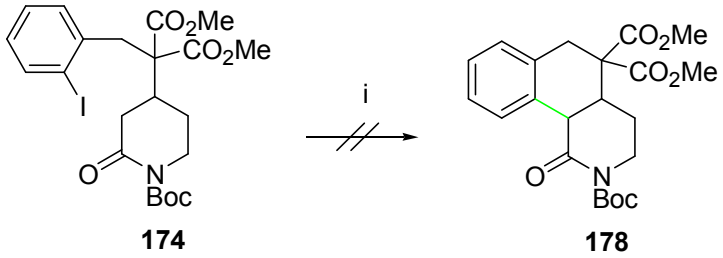
The intramolecular Buchwald–Hartwig α-arylation of *N*-substituted 2-piperidones substituted with a 2-bromobenzyl group in the 5-position, has previously been reported by Maier *et al.*[128] This methodology employed a base, palladium catalyst and ligand and required the formation of an intermediate zinc enolate in order to increase the reactivity of the enolate (Scheme 98).



Scheme 98 *Reagents and Conditions:* i) NaHMDS (4.0 equiv), $ZnCl_2$ (4.0 equiv), $Pd(dba)_2$ (10 mol%), $^tBu_3P$ (15 mol%), THF, 0 → 65 °C, 12 h.

It was desirable to apply this methodology to effect α-arylation of lactam **174**, as an alternative route towards our tricyclic structure (Scheme 99, Table 6). Potassium *tert*-butoxide and lithium di*iso*propylamide were investigated as the source of base (entries 1 and 2 respectively), with tetrakis(triphenylphosphine) palladium(0) as the chosen palladium

source.[129] Elimination was observed to occur and aryl malonate **144** was isolated along with α,β-unsaturated lactam **161** and unreacted starting material **174**. As a result, we decided to study the effect of just base on lactam **174**, without generating the corresponding zinc enolates or adding a catalyst (entries 3 and 4). Elimination was again observed to occur, although more readily with lithium di*iso*propylamide than with potassium *tert*-butoxide. Two new unidentified products were also isolated, which were inseparable from unsaturated lactam **161**. Finally, lactam **174** was treated with an excess of lithium di*iso*propylamide (entry 5) in an attempt to force formation of the desired enolate over elimination. However, after only 5 min the presence of aryl malonate was detected by TLC and crude NMR analysis.



174 **178**

Scheme 99 *Reagents and Conditions:* i) See Table 6

Table 6 Attempts at α-arylation of *N*-Boc 2-piperidone **174**

Entry	Base (equiv)	Reagents and Conditions (equiv)	Product (yield)
1[129]	KO^{t}Bu (0.91)	Lactam **174** (1.0), THF, –20 °C, 20 min; $ZnCl_2$ (1.1), –20 °C, 20 min; $Pd(PPh_3)$ (0.05), 65 °C, 4 h.	Aryl malonate **144** (4%) and **174** : **161** (5:1)
2[129]	LDA (0.91)	Lactam **174** (1.0), THF, –20 °C, 20 min; $ZnCl_2$ (1.1), –20 °C, 20 min; $Pd(PPh_3)$ (0.05), 65 °C, 20 min.	Aryl malonate **144** : **174** (1:1)
3	KO^{t}Bu (1.0)	Lactam **174** (1.0), THF, –20 °C → rt, 2.5 h; KO^{t}Bu (1.0), rt, 4 h.	Aryl malonate **144** (50%) and **161** + unknown
4	LDA (1.0)	Lactam **174** (1.0), THF, –20 °C → rt, 6.5 h.	Aryl malonate **144** (54%) and **161** + unknown
5	LDA (2.0)	Lactam **174** (1.0), THF, –20 °C, 0 °C, 5 min.	Aryl malonate **144**

2.4.6 Conclusions

Lactam **174** was successfully synthesised following α-phenyl selenylation and oxidative elimination of 1-Boc-2-piperidone and subsequent 1,4-addition with dimethyl malonate and alkylation with benzyl bromide. Attempts were also made to isolate the tosyl-analogue, but selenoxide elimination was unsuccessful and alternative routes to the *N*-tosyl lactam were not investigated.

1,4-Addition with sulfone nucleophiles such as bis(phenylsulfonyl)methane and methyl-*p*-tosyl acetate and subsequent alkylation were also unsuccessful. This was thought to be due to steric hindrance resulting from the desired formation of a crowded quaternary centre.

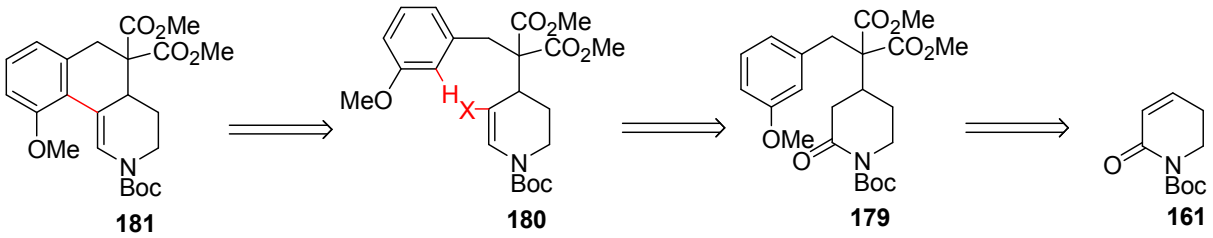
Reduction of the lactam functionality gave cyclisation precursor **175** in excellent yield and direct arylation was effected with a palladium(II) source to give our desired tricyclic substrate. This cyclisation is proposed to occur *via* a Heck-type mechanism or a *N*-assisted interception of the initial oxidative addition intermediate by the ene–carbamate. Our route towards these arylation substrates was successfully re-designed to make it more convergent and allow for alkylation with alternatively substituted arenes and heteroarenes.

Finally, α-arylation of our lactam substrate was also investigated, however this proved unsuccessful as elimination of aryl-substituted dimethyl malonate resulted.

2.5.0 3-Methoxy aryl-substituted tetrahydropyridines

Following on from successful direct arylation with 2-iodobenzene, we decided to explore coupling reactions of arenes with alternative, non-halogen based activating groups, such as a 3-methoxy group. The regioselectivity of intramolecular direct arylation is strongly influenced by the electronics of the arene being functionalised. For example, the reaction is expected to occur *ortho* or *para* to an electron-donating group, *via* a proposed electrophilic aromatic substitution pathway.[17] Furthermore, nitrogen- and oxygen-coordinating functional groups can be employed to direct the arylation. As arene–transition metal interactions tend to be rather weak, these groups can be used to hold the arene within the co-ordination sphere of the metal.[54]

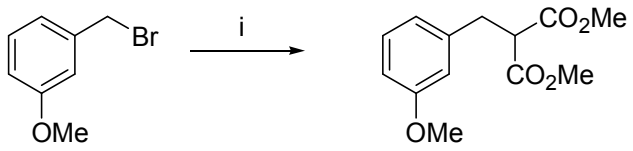
We proposed that α,β-unsaturated lactam **161** could undergo 1,4-Michael addition with 3-methoxybenzyl-substituted malonate to give **179**, and subsequent reduction and C-5 halogenation would give tetrahydropyridine **180.** We then hoped that this substrate would undergo direct arylation to give tricylic structure **181**, the product of *ortho*-arylation (Scheme 100).



Scheme 100 *Proposed route to alternatively substituted tetrahydropyridines*

2.5.1 Michael addition with 3-methoxy aryl-substituted malonate

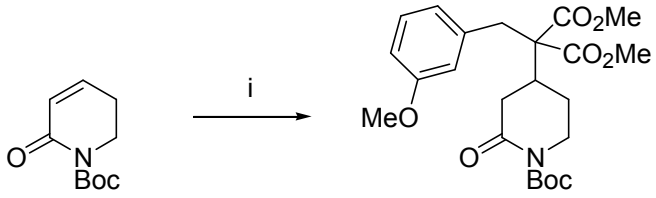
Our investigations began with the 1,4-addition of 3-methoxy aryl-substituted malonate to α,β-unsaturated lactam **161**. This was prepared following treatment of the sodium enolate of dimethyl malonate with 3-methoxybenzyl bromide (**182**). The desired aryl-substituted malonate **183** was obtained in 86% yield, following purification by Kügelrohr distillation and column chromatography (Scheme 101).[130]



182 **183**

Scheme 101 *Reagents and Conditions:* i) a) NaH (2.0 equiv), THF, 0 °C, dimethyl malonate (2.5 equiv), 0 °C → rt, 30 min; b) 3-methoxybenzyl bromide (1.0 equiv), rt, 3 h, 86%.

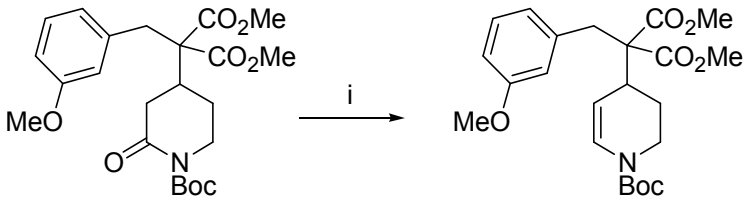
1,4-Addition was effected under the conditions described for 2-iodoaryl-substituted malonate **144**, in satisfactory yield (65%) (Scheme 102).[123] This transformation appears to be reproducible and no problems were observed with separating the product from any unreacted starting material by column chromatography.



161 **179**

Scheme 102 *Reagents and Conditions:* i) a) NaH (0.1 equiv), malonate 1**83** (1.3 equiv), THF, 0 °C, 10 min; b) lactam **161** (1.0 equiv), THF, 0 °C → rt, 16 h, 65%.

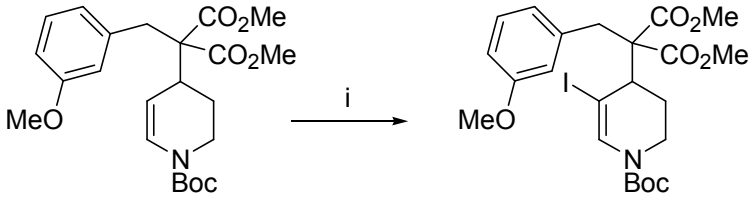
With the desired malonate addition product in hand, reduction of the lactam was effected following treatment with di*iso*butylaluminium hydride at –78 °C, giving the corresponding lactamol. Elimination with 1 M aqueous hydrochloric acid gave tetrahydropyridine **184** in 78% yield (Scheme 103).[126]



179 **184**

Scheme 103 *Reagents and Conditions:* i) a) DIBAL-H (1.0 equiv), THF, –78 °C, 1.5 h; Rochelle's salt, Et_2O, rt, 16 h; b) 1M $HCl_{aq.soln}$ (4.0 equiv), CH_2Cl_2, rt, 2.5 h, 78%.

It was next desirable to iodinate at the C-5 position of tetrahydropyridine **184** to give cyclisation precursor **180.** Iodination conditions previously employed in the group, involving treatment of a dichloromethane solution of the tetrahydropyridine substrate with *N*–iodosuccinimide and hydroxyl(tosyloxy) iodobenzene under overnight reflux, gave desired halide **180** in a disappointingly low yield of 15% (Scheme 104).[72] We had hoped to avoid the problem of steric hindrance at the C-5 position by removing the adjacent crowded quaternary centre at C-4. However, it was thought that steric hindrance continued to be the reason for our lack of reactivity.

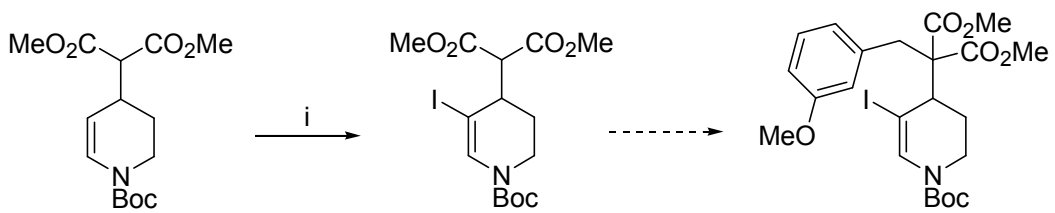


184 **180**

Scheme 104 *Reagents and Conditions:* i) a) NIS (1.1 equiv), HTIB (0.1 equiv), CH_2Cl_2, reflux, 22 h; b) Et_3N (1.1 equiv), 15%.

2.5.2 Investigating iodination prior to alkylation

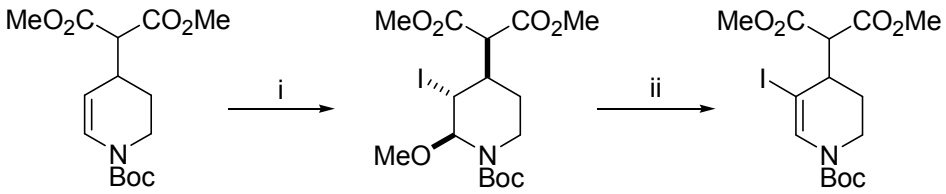
In light of the findings described above, it was decided to synthesise iodide **185** prior to alkylation with 3-methoxybenzyl bromide, as an alternative route towards cyclisation precursor **180** (Scheme 105). Treatment of malonate addition product **176** with *N*–iodosuccinimide and hydroxyl(tosyloxy) iodobenzene according to the above conditions, gave iodide **185** in only 25% yield.[72]



176 **185** **180**

Scheme 105 *Reagents and Conditions:* i) a) NIS (1.1 equiv), HTIB (0.1 equiv), CH_2Cl_2, reflux, 22 h; b) Et_3N (1.1 equiv), 25%.

A two-step route *via* iodo-methoxyamine **186** was therefore investigated as an alternative way to access iodide **185** (Scheme 106). Ene–carbamate **176** was treated with *N*–iodosuccinimide and methanol in dichloromethane at –78 °C, and intermediate **186** was isolated in 96% yield without the need for purification.[131]



176 **186** **185**

Scheme 106 *Reagents and Conditions:* i) NIS (1.2 equiv), MeOH (1.2 equiv), CH_2Cl_2, –78 °C, **176** (1.0 equiv), 1.5 h, 96%; ii) See Table 7.

A considerable amount of time was spent investigating the elimination of methanol from **186** to give iodide **185** (Table 7). Heating **186** in toluene with a trace amount of trifluoroacetic acid gave iodide **185** in 38% yield along with 45% of ene–carbamate **176** (entry 1).[132] A mixture of product and ene–carbamate **176** was isolated upon heating **186** with 1 M aqueous hydrochloric acid in toluene (entry 2). No reaction was observed using sub-stoichiometric hydrochloric acid in 2 M diethyl ether solution, and using an equimolar amount led to decomposition.

A series of Lewis Acids were also investigated to effect elimination of methanol: treatment with zinc chloride and an excess of magnesium chloride gave only iodomethoxyamine **186** starting material after prolonged reaction times. The use of aluminium trichloride and tin tetrachloride led to rapid decomposition.

Employing known dehydrating agents, dihydropyran and 2-methoxypropene, also failed to isolate any elimination product and upon increasing the equivalents of reagents used, only decomposition was observed.

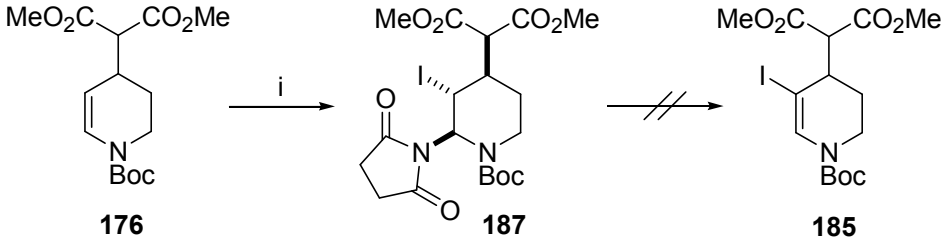
We therefore decided to return our attention to trifluoroacetic acid, but found that addition to a solution of intermediate **186** in dichloromethane resulted in incomplete elimination (entry 3). However, the addition of pre-activated 4 Å molecular sieves improved this

conversion significantly, by assisting the elimination of methanol, and iodide **185** was isolated in an optimum yield of 72% (entry 4). This reaction unfortunately continued to be very capricious, and its success lay in a very delicate balance between trifluoroacetic acid stoichiometry added and reaction concentration. For example, if four equivalents or more were added in one portion, unidentified by-products were also formed (entries 5). Furthermore, the reaction was found to require immediate purification by column chromatography following work up, as well as base-washing of the silica gel.

Table 7 Attempts to access iodide **185** from iodo-methoxyamine **186**

Entry	Reagents and Conditions (equiv)	Product (yield)
1[131]	TFA (0.09), toluene, 90 °C, 1 h; Et_3N (0.15)	**185** (38%) and **176** (45%)
2	1M $HCl_{aq.soln}$ (4.0), toluene, 90 °C, 1 h; Et_3N (0.15)	**185:176** (1:2)
3	TFA (0.09), CH_2Cl_2, rt, 1 h; Et_3N (0.15), rt, 16 h	**185:186** (10:7)
4	TFA (3.0), 4Å MS, CH_2Cl_2, rt, 16 h; TFA (1.0), 1.5 h; Et_3N (4.0)	**185** (72%) and **186** (10%)
5	TFA (4.0), 4Å MS, CH_2Cl_2, rt, 19 h; Et_3N (4.0)	**185** (53%)+by-products

Our attention therefore returned to direct iodination of tetrahydropyridine **176**. Of the alternative iodinating conditions explored, decomposition resulted following treatment with iodine and pyridine and also with iodinemonochloride. Interestingly, employing *N*-iodosuccinimide and pyridine indicated formation of iodide **185** by TLC analysis, but instead gave addition product **187** in excellent yield (Scheme 107).

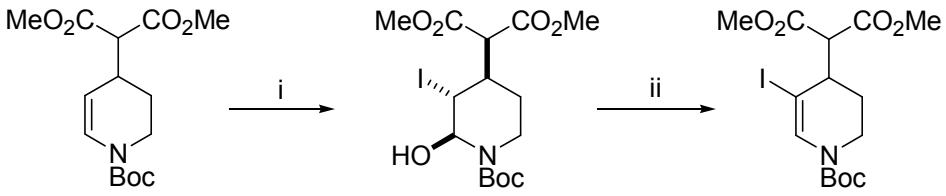


Scheme 107 *Reagents and Conditions:* i) NIS (1.0 equiv), CH_2Cl_2, 1.5 h; pyridine (1.0 equiv), rt, 3 h, 89%.

Given that product formation had only been previously observed following treatment with *N*-iodosuccinimide and hydroxyl(tosyloxy) iodobenzene, it was decided to investigate different reaction conditions with these reagents in order to determine at which point the desired iodide was formed. Interestingly, longer reaction times at higher temperatures resulted in a higher proportion of addition product **187**, as determined by crude ^{1}H NMR analysis, but purification by column chromatography gave only iodide **185**, in very low yield (5%). Alternative sub-stoichiometric sources of acid were also investigated: addition product **187** was once again observed to form with trifluoroacetic acid and decomposition resulted with *para*-toluenesulfonic acid.

The observations above led to the conclusion that addition product **187** decomposed on exposure to silica gel to give iodide **185**. Tetrahydropyridine **176** was therefore treated with *N*-iodosuccinimide and hydroxyl(tosyloxy) iodobenzene to give the addition product, then stirred over silica gel to aid elimination to the desired iodide, followed by a triethylamine quench and then the addition of more silica gel. The reaction failed to reach completion and dry loading onto silica gel, followed by column chromatography, gave iodide **185** in only 29% yield.

Our third and final attempt to isolate iodide **185** investigated the formation of iodo-alcohol **188,** which we hoped would undergo dehydration to give the desired product. Treatment of a solution of ene–carbamate **176** in tetrahydrofuran and water with *N*-iodosuccinimide at 0 °C, gave the desired iodo-alcohol in quantitative yield.[133] A solution of this intermediate in dichloromethane was then added to activated 4 Å molecular sieves and treated with trifluoroacetic acid. Pleasingly, iodide **185** was isolated following column chromatography in 89% yield (Scheme 108). As previously observed for this substrate, it was necessary to base wash the silica gel with triethylamine prior to chromatography.

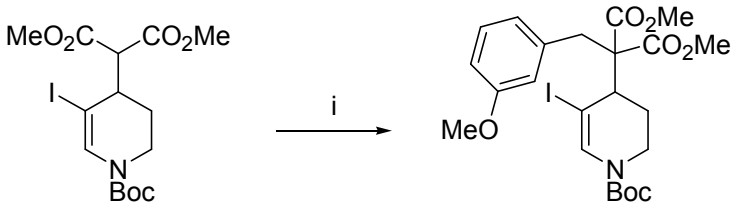


176 **188** **185**

Scheme 108 *Reagents and Conditions:* i) NIS (2.0 equiv), H_2O–THF, 0 °C → rt, 4 h; ii) a) TFA (1.0 equiv), 4 Å MS, CH_2Cl_2, rt, 2 h; b) Et_3N (1.0 equiv), rt, 1 h, 89% over two steps.

2.5.3 Alkylation with 3-methoxybenzyl bromide

Alkylation of iodide **185** with 3-methoxylbenzyl bromide was effected according to previously established conditions, whereby pre-mixing the alkylating agent with the malonate substitution product prior to addition to sodium hydride, gave superior yields (Scheme 109). Reaction concentration was found to be an important consideration and a molarity of 0.2, as well as a slight excess of sodium hydride were required to give optimum yields.



185 **180**

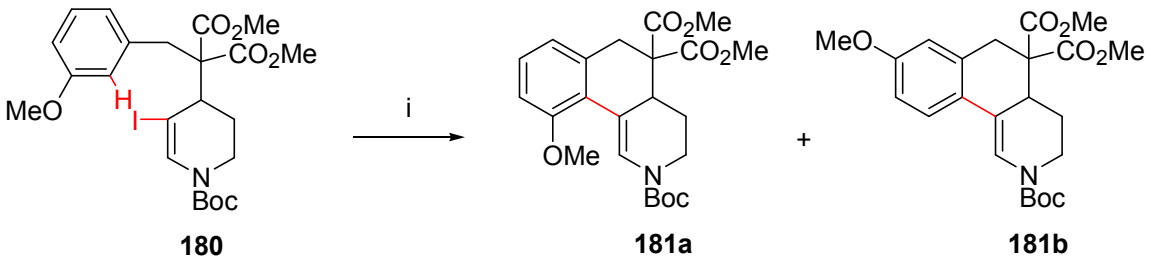
Scheme 109 *Reagents and Conditions:* i) a) NaH (1.2 equiv), DMF, 0 °C; b) iodide **185** (1.0 equiv), 3-methoxybenzyl bromide (1.0 equiv), DMF, 0 °C → rt, 12.5 h, 83%.

2.5.4 Palladium-catalysed arylation

Our previously optimised palladium-catalysed arylation conditions were initially investigated for this substrate, but incomplete reaction was observed and the product was not isolated (Scheme 110, Table 8, entry 1).[53] The use of a bulkier ligand, tri(*ortho*-tolyl)phosphine, in conjunction with the same palladium(II) source, failed to promote any direct arylation and only starting material was isolated (entry 2).

The desired product was formed in very low yield following treatment with tris(dibenzylideneacetone)dipalladium(0) and tri(*ortho*-tolyl)phosphine, however 57% of starting material was also recovered (entry 3). Investigations with alternative ligands failed to improve conversion and unidentified by-products were also isolated (entries 4-5).

Treatment with pre-formed palladium(0) source, tetrakis(triphenylphosphine) palladium(0), gave tricycles **181a** and **181b** in a moderate yield of 31%, as an inseparable mixture of isomers following cyclisation *ortho*- and *para*- to the methoxy substituent (entry 6). Employing dimethylformamide as an alternative solvent, at a higher temperature, did not improve conversion or selectivity (entry 7). Finally the use of sodium carbonate as an alternative base did not result in any product formation (entry 8).



180 **181a** **181b**

Scheme 110 *Reagents and Conditions:* i) See Table 8

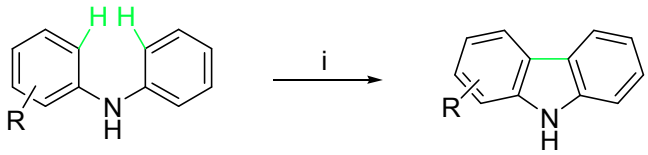
Table 8 Attempts to effect direct arylation of tetrahydropyridine **180**

Entry	Reagents (equiv)	Conditions	Product (yield)
1[53]	$Pd(OAc)_2$ (0.1), PPh_3 (1.0), KOAc (2.0)	DMA, 140 °C µw, 10 min x 2	Incomplete reaction
2	$Pd(OAc)_2$ (0.1), P(*o*-tolyl)$_3$ (1.0), KOAc (2.0)	DMA, 140 °C µw, 10 min	**180** (77%)
3	$Pd_2(dba)_3$ (0.05), P(*o*-tolyl)$_3$ (0.25), KOAc (2.0)	DMA, 120 °C µw, 10 min; 140 °C µw, 10 min	**181a** (7%) and **180** (57%)
4	$Pd_2(dba)_3$ (0.05), dppf (0.5), KOAc (2.0)	DMA, 140 °C µw, 20 min	Decomposition
5	$Pd_2(dba)_3$ (0.05), PPh_3 (0.5), KOAc (2.0)	DMA, 140 °C µw, 10 min x 2	**181a+b** + **180** + side products
6	$Pd(PPh_3)_4$ (0.1), KOAc (2.0)	DMA, 120 °C µw, 10 min	**181a+b** (31%)
7	$Pd(PPh_3)_4$ (0.1), KOAc (2.0)	DMF, 140 °C µw, 10 min x 2	**181a+b** + side products
8	$Pd(PPh_3)_4$ (0.1), Na_2CO_3 (2.0)	DMA, 140 °C µw, 10 min	No reaction

2.5.5 Intramolecular oxidative arylation

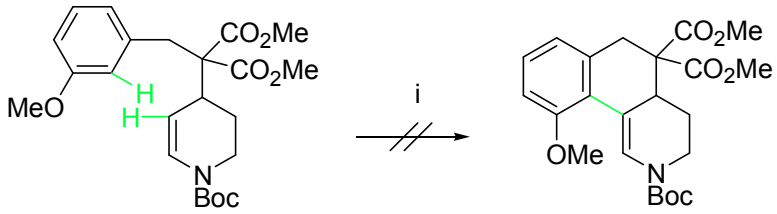
Palladium(II)-catalysed cross-coupling reactions of arenes are generally dependent on pre-activation of either one or both of the two aromatic carbon fragments. As this can often involve extra synthetic steps, excessive waste generation and unwanted by-products, increased attention is being turned to replacing one or both of the pre-activated substrates with a simple arene.[17]

Intramolecular palladium(II)-catalysed oxidative biaryl synthesis under air has been described by Fagnou *et al*, whereby two unactivated aromatic compounds are directly coupled without the need for pre-activation (Scheme 111).[134] These reactions employ an atmosphere of air at ambient pressure as the terminal oxidant, thereby avoiding the need for stoichiometric metal oxidants. In addition to palladium(II) acetate, pivalic acid is thought to act as a co-catalyst and play a key role in the cleavage of one of the C-H bonds.



Scheme 111 *Reagents and Conditions:* i) $Pd(OAc)_2$ (3 mol%), K_2CO_3 (10 mol%), air, PivOH, 110 °C, 14 h, 72-95%.

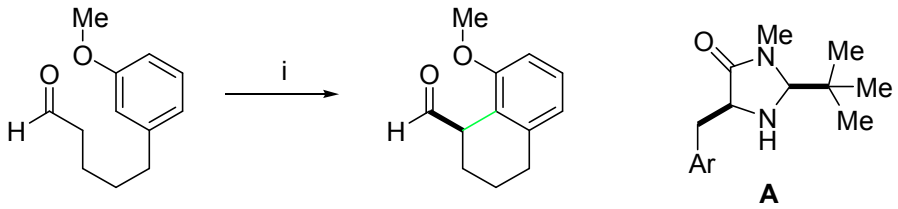
Unfortunately, oxidative coupling was not achieved for tetrahydropyridine **184** under these conditions and only starting material was recovered (Scheme 112). Furthermore, Heck-type cyclisation conditions were also applied to unactivated substrate **184**, in the hope that the aryl C–H bond *ortho* to the methoxy group would be sufficiently activated by electron donation for coupling to occur.[53] However, once again no reaction was observed to take place.



184 **181**

Scheme 112 *Reagents and Conditions:* i) $Pd(OAc)_2$ (0.1 equiv), K_2CO_3 (0.1 equiv), PivOH (8.8 equiv), air, 120 °C, 16 h, no reaction; $Pd(OAc)_2$ (0.1 equiv), PPh_3 (1.0 equiv), KOAc (2.0 equiv), DMA, 140 °C in microwave, 10 min, no reaction.

Enantioselective α-arylation of aldehydes *via* Organo-SOMO catalysis is well established in the literature by MacMillan *et al*.[135] A single-electron oxidant is applied to an enamine (formed from an aldehyde and amine catalyst **A**) to create a 3π-radical cation species, which then cyclises intramolecularly and asymmetrically (Scheme 113). Base and water additives are thought to facilitate re-aromatisation *via* proton loss and hydrolysis of the resultant iminium species respectively.



A

Scheme 113 *Reagents and Conditions:* i) CAN (2.5 equiv), $NaHCO_3$ (5.0 equiv), H_2O (1.0 equiv), MeCN, –78 → –20 °C, 24 h.

It was decided to also apply this methodology to the oxidative arylation of ene–carbamate **184**, employing cerium(IV) ammonium nitrate as the oxidant under a range of conditions: with or without H_2O additive or base (Table 9, entries 1-3).[135-137] In each case however, no reaction was observed and only starting material was recovered.

Table 9 Attempts to arylate using Organo-SOMO catalysis

Entry	Reagents and Conditions (equiv)	Product (yield)
1[137]	**184** (1.0), THF, –78 °C; H_2O (2.0), CAN (2.0), –78 → –30 °C, 4 h; –30 °C → rt, 20 h.	No reaction observed
2[135]	CAN (2.5), $NaHCO_3$ (5.0), MeCN, –78 °C; H_2O (1.0), **184** (1.0), –78 → –20 °C, 2.5 h; –20 °C → rt, 20 h.	No reaction observed
3[136]	CAN (2.5), $NaHCO_3$ (1.5), THF, –50 °C; **184** (1.0), –50 → –20 °C, 2.5 h; –20 °C → rt, 20 h.	No reaction observed

2.5.6 Conclusions

Methoxy-analogue **184** was successfully isolated following 1,4-addition with 3-methoxybenzyl malonate and subsequent reduction. Attempts to iodinate at the C-5 position proved unsuccessful so a variety of methods for the iodination of non-arylated tetrahydropyridine **176** were explored. In these experiments attempts were made to isolate the desired iodide *via* a methoxy-iodide intermediate and also an *N*-iodosuccinimide adduct, with limited success.[131] Synthesis of hydroxy-iodide intermediate **188** and subsequent elimination of water, gave iodide **185** in excellent yield.[133]

Alkylation with 3-methoxybenzyl bromide gave our desired cyclisation precursor and direct arylation was effected following treatment with tetrakis(triphenylphosphine) palladium(0) to give tricycle **181** in 31% yield as a mixture of *ortho*- and *para*-substituted isomers. A variety of different parameters were investigated in an attempt to optimise this transformation, such as type of ligand, base and solvent, though little improvement was observed. It is thought that steric hindrance from the methoxy group may have been restricting arene metalation from taking place, rather than assisting it.

Intramolecular oxidative arylation was investigated for non-iodinated tetrahydropyridine **184**, however despite literature precedent no reaction was observed to take place.[134] Organo-SOMO catalysis with cerium(IV) ammonium nitrate was also explored, however once again no arylation occurred.[135] It is thought that the enamide double bond in our system is less electron rich than those described in the literature, due to the electron withdrawing Boc protecting group on the nitrogen.

2.6.0 Synthesis of heteroaromatic analogues

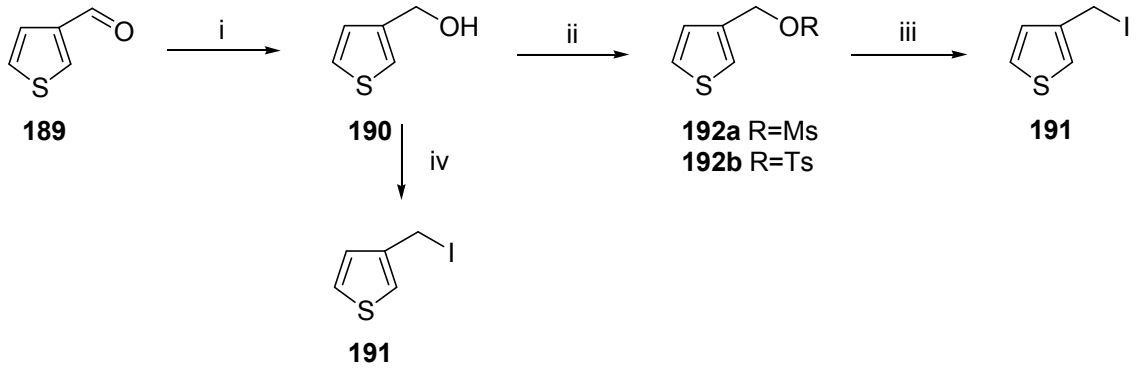
Due to the convergent nature of the route we had developed towards arylated tetrahydropyridines we were now able to introduce differently substituted aryl groups into our system. Heteroaryl-heteroaryl bonds are prominent in the substructures of many natural products, pharmaceutical agents and electronic materials.[138] Therefore, our attention was next turned to the synthesis of heteroaromatic analogues possessing π-electron-rich arenes such as thiophene and furan joined at the three position and 1-methylindole joined at the two position.

2.6.1 Synthesis of thiophene analogue

2.6.1.1 Synthesis of 3-(iodomethyl)thiophene 191

Alcohol **190** was readily available in high yield from the corresponding aldehyde (**189**), *via* sodium borohydride reduction in methanol (Scheme 114).[139] Two possible routes towards iodide **191** were proposed, whereby the alcohol could be converted into a good leaving group and then undergo iodide substitution or where the alcohol could be directly substituted.

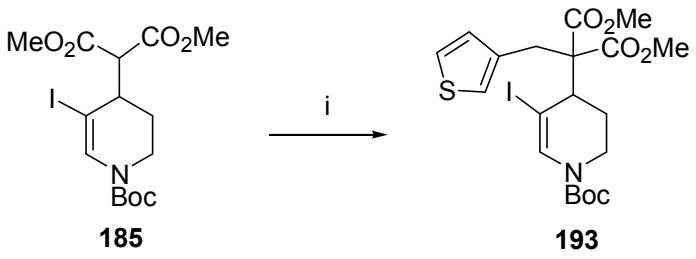
Attempts to form mesylate **192a** met with limited success, as it proved very difficult to determine whether the reaction was complete by TLC analysis; iodide **191** was isolated in only 44% yield over two steps *via* this intermediate. Formation of the corresponding tosylate **192b** was found to be no more successful and in this case no product was isolated. However, treatment of alcohol **190** with iodine, triphenylphosphine and imidazole gave the desired alkylating agent **191** in an acceptable yield of 51%. Furthermore, the iodide was found to be stable to purification by column chromatography, but could only be stored in the fridge for two to three weeks before decomposing.



Scheme 114 *Reagents and Conditions:* i) $NaBH_4$ (1.0 eqviv), MeOH, 0 °C → rt, 84%; ii) MsCl (1.1 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C → rt, 30 min → 1 h, incomplete reaction; or TsCl (1.0 equiv), Et_3N (1.5 equiv), DMAP (0.15 equiv), CH_2Cl_2, rt, 55 h, no reaction; iii) NaI (3.0 equiv), MeCN, rt, 22 h, 44% (over two steps from mesylate **192a**); iv) I_2 (1.0 equiv), PPh_3 (1.0 equiv), imidazole (1.1 equiv), CH_2Cl_2, rt, 4.5 h, 51%.

2.6.1.2 Alkylation with 3-(iodomethyl)thiophene 191

Applying our previously established alkylation conditions to iodide **185** and 3-(iodomethyl)thiophene **191** gave our desired cyclisation precursor **193** in 72% yield (Scheme 115). Once again reaction concentration was found to be a very important consideration: 0.4 M gave optimum conversion. Separation of the product and unreacted starting material by column chromatography proved difficult, but this was overcome by eluting with 5% ethyl acetate–toluene.

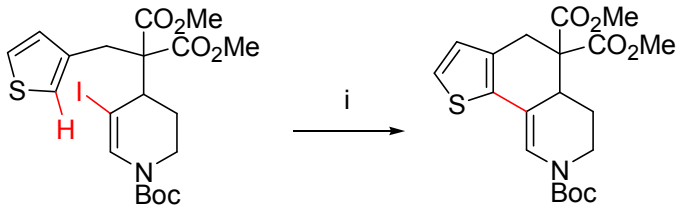


Scheme 115 *Reagents and Conditions:* i) a) NaH (1.1 equiv), DMF, 0 °C; b) iodide **185** (1.0 equiv), **191** (1.0 equiv), DMF, 0 °C → rt, 22 h, 72%.

2.6.1.3 Palladium-catalysed arylation

Pleasingly, cyclisation of thiophene analogue **193** occurred much more readily than for methoxy analogue **180**, to give tricycle **194** (Scheme 116). Treatment with tetrakis(triphenylphosphine) palladium(0) and potassium acetate gave the desired product in 61% yield, however evidence of monoester formation was detected after prolonged heating. The combination of palladium(II) acetate and triphenylphosphine appeared to give superior conversion and arylation product **194** was isolated in 72% yield.[53]

As previously illustrated in figure 2, it was expected that arylation would take place at the more electron-rich C-2 position, as opposed to the alternative C-4 position.[17] This prediction was confirmed by ^{1}H NMR spectroscopy, whereby the broad singlet corresponding to H_{Ar} at the C-2 position in the starting material, was not present in the product.



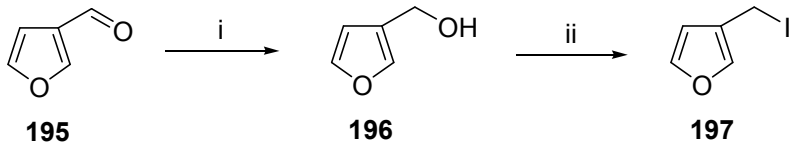
193 **194**

Scheme 116 *Reagents and Conditions:* i) $Pd(OAc)_2$ (0.1 equiv), PPh_3 (1.0 equiv), KOAc (2.0 equiv), DMF, 120 °C μw, 20 min, 72%.

2.6.2 Synthesis of furan analogue

2.6.2.1 Synthesis of 3-(bromomethyl)furan 199

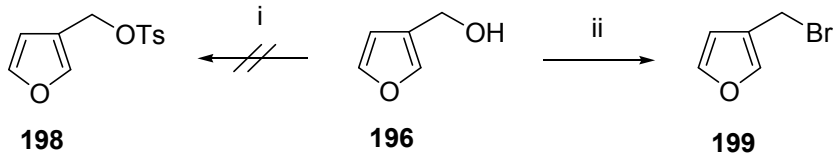
The furan derivative proved rather more difficult to handle than the corresponding thiophene, due to its extremely volatile nature. Alcohol **196** was isolated following reduction of aldehyde **195** with sodium borohydride, but great care had to be taken when concentrating the crude product under reduced pressure, following work up.[139] Direct iodination was effected using the same conditions previously described, to give iodide **197** in 56% yield (Scheme 117). The product was stable to column chromatography, but was unfortunately extremely unstable in concentrated form and spontaneously and exothermically decomposed on standing.



195 **196** **197**

Scheme 117 *Reagents and Conditions:* i) $NaBH_4$ (1.0 eqviv), MeOH, 0 °C → rt, 82%; ii) I_2 (1.0 equiv), PPh_3 (1.0 equiv), Imidazole (1.1 equiv), CH_2Cl_2, rt, 2.5 h, 56%.

Our attention therefore turned to the synthesis of alternative alkylating agents, such as tosylate **198** and bromide **199** (Scheme 118). Treatment of alcohol **196** with triethylamine, tosyl chloride and dimethylaminopyridine did not result in any tosylated product, however stirring with phosphorus tribromide at room temperature gave bromide **199** in 89% yield.[140] It was not necessary to purify the bromide prior to the subsequent alkylation step. However, it was found that the stability of this alkylating agent was greatly improved following neutralisation of any hydrogen bromide present in solution with potassium carbonate.

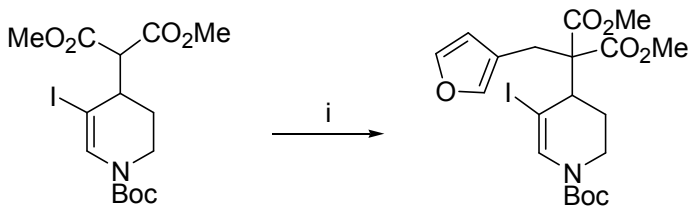


198 **196** **199**

Scheme 118 *Reagents and Conditions:* i) Et_3N (1.5 equiv), TsCl (1.0 equiv), DMAP (0.15 equiv), CH_2Cl_2, rt, 3 h, no product isolated; ii) PBr_3 (2.0 equiv), CH_2Cl_2, rt, 16 h, 89%.

2.6.2.2 Alkylation with 3-(bromomethyl)furan 199

Applying the previously established alkylation conditions to iodide **185** and 3-(bromomethyl)furan **199**, gave the desired cyclisation precursor in excellent yield (Scheme 119). Once again reaction concentration was found to be a very important consideration and a molarity of 0.5 gave optimum conversion. Furthermore, an excess of base and alkylating agent were used where possible, in order to maximise the consumption of starting material and alkylation was found to be most successful when bromide **199** was used immediately following isolation.

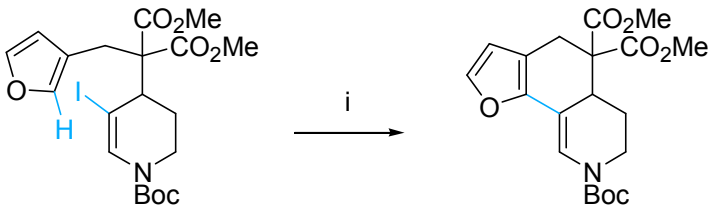


185 **200**

Scheme 119 *Reagents and Conditions:* i) a) NaH (1.6 equiv), 0 °C; b) iodide **185** (1.0 equiv), bromide **199** (2.05 equiv), DMF, 0 °C → rt, 64 h, 91%.

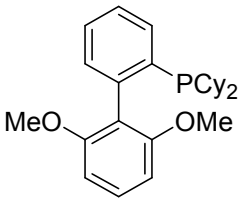
2.6.2.3 Palladium-catalysed arylation

Palladium-catalysed arylation to give tricycle **201** did not appear to occur as readily as for the thiophene substrate and our previously optimised conditions using palladium(II) acetate, triphenylphosphine and potassium acetate gave only 33% of our desired product (Scheme 120, Table 10, entry 1).[53] Heating in the microwave at a higher temperature resulted in significant monoester formation, as did treatment with tetrakis(triphenylphosphine) palladium(0) and potassium acetate after prolonged heating (entries 2 and 3). Screening alternative phosphine ligands revealed that using tri(*ortho*-tolyl)phosphine and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos (**B**), Figure 9) also resulted in mixtures of starting material, desired product and monoester (entries 4 and 6) However, employing 1,1'-bis(diphenylphosphino)ferrocene as ligand gave the highest level of starting material consumption, with no observed formation of the monoester product, to afford tricycle **201** in 58% (entry 5). As for the thiophene analogue, arylation was confirmed to occur at the C-2 position of the heteroarene by ^{1}H NMR analysis, whereby H_{Ar} at the C-4 position was present in both the starting material and the product.



200 **201**

Scheme 120 *Reagents and Conditions:* i) See Table 10.



B

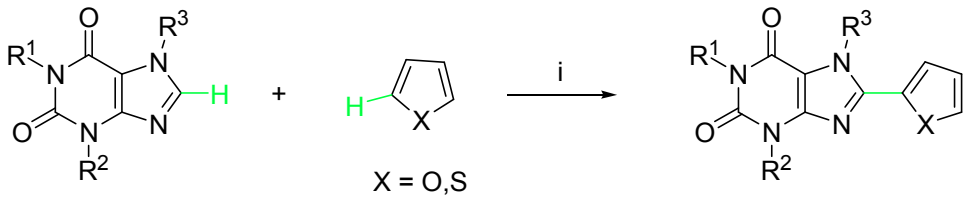
Figure 9 SPhos ligand

Table 10 Palladium-catalysed arylation of furan analogue

Entry	Reagents and Conditions (equiv)	Product (yield)
1[53]	$Pd(OAc)_2$ (0.1), PPh_3 (1.0), KOAc (2.0), DMF, 120 °C μw, 15 min x 2	**201** (33%)
2	$Pd(OAc)_2$ (0.1), PPh_3 (1.0), KOAc (2.0), DMF, 140 °C μw, 10 min	**201** (28%) and **monoester** (17%)
3	$Pd(PPh_3)_4$ (0.1), KOAc (2.0), DMF, 120 °C μw, 10 min; 15 min; 140 °C μw, 15 min	**201:monoester** (1:1)
4	$Pd(OAc)_2$ (0.1), P(*o*-tolyl)$_3$ (1.0), KOAc (2.0), DMF, 120 °C μw, 10 min x 2	**200:201:monoester**
5	$Pd(OAc)_2$ (0.1), DPPF (1.0), KOAc (2.0), DMF, 140 °C μw, 20 min	**201** (58%)
6	$Pd(OAc)_2$ (0.1), S–PHOS (1.0), KOAc (2.0), DMF, 140 °C μw, 20 min; 150 °C μw, 20 min	**201:monoester** (1:1)

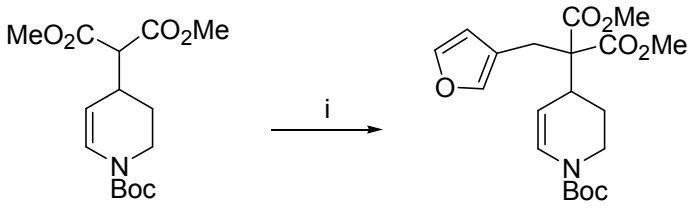
2.6.2.4 Palladium-catalysed oxidative coupling

There have been many reports on transition metal-catalysed direct oxidative heteroarylation of heteroarenes in recent years. Work by You *et al.* demonstrates that catalytic oxidative C–H/C–H cross-coupling of various *N*-containing heteroarenes with π-electron-rich five membered rings, takes place without the need for pre-activation of either coupling partner (Scheme 121).[138] Their catalytic system comprises palladium(II) acetate as catalyst and copper(II) acetate hydrate as oxidant, to regenerate the palladium(II) species. It is proposed that the 5-membered heteroarene undergoes a regioselective electrophilic C–H substitution by palladium(II) acetate and then the heterocoupling intermediate is formed through a concerted metalation–deprotonation process.



Scheme 121 *Reagents and Conditions:* i) $Pd(OAc)_2$ (2.5 mol%), $Cu(OAc)_2 \bullet H_2O$ (1.5 equiv), pyridine (1.0 equiv), 1,4-dioxane, 120 °C, 20 h.

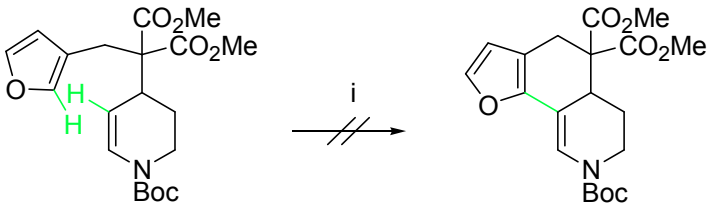
It was first necessary to alkylate non-iodinated tetrahydropyridine **176** in order to isolate our cyclisation pre-cursor **202**. This was only attempted once following addition of a pre-stirred mixture of tetrahydropyridine **176** and bromide **199** in dimethylformamide, to dried sodium hydride (Scheme 122). The desired alkylated product was obtained in a moderate yield of 45%, due to difficulty experienced separating the product and unreacted starting material by column chromatography.



176 **202**

Scheme 122 *Reagents and Conditions:* i) a) NaH (1.5 equiv), 0 °C; b) iodide **176** (1.0 equiv), bromide **199** (1.2 equiv), DMF, 0 °C → rt, 24 h, 45%.

A variety of catalytic systems were investigated to effect this twofold C–H functionalisation, including the conditions described above (Table 11, entry 1).[138] Unfortunately, no arylation product was observed and in each case only starting material **202** was isolated (Scheme 123). Alternative oxidants were explored, such as silver carbonate, silver acetate and *tert*-butyl benzoyl peroxide (entries 3, 4 and 7 respectively), without success.[141-143] Fagnou's conditions were also re-investigated (entry 6).[134]



202 **203**

Scheme 123 *Reagents and Conditions:* i) See Table 11.

Table 11 Palladium-catalysed oxidative coupling conditions

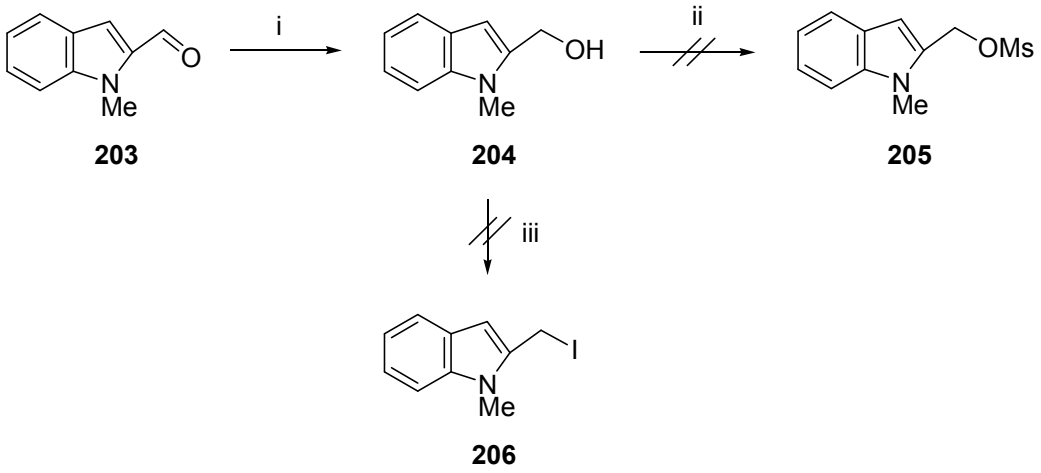
Entry	Reagents and conditions (equiv)	Product (yield)
1[138]	$Pd(OAc)_2$ (0.1), $Cu(OAc)_2•H_2O$ (1.5), pyridine (1.0), 1,4-dioxane, 100 °C, 18 h	**202** (32%)
2[79]	$Pd(OAc)_2$ (0.1), $Cu(OAc)_2$ (1.7), DMF, 120 °C μw, 10 min; 140 °C μw, 20 min	**202** (30%)
3[141]	$Pd(OAc)_2$ (0.1), Ag_2CO_3 (1.5), AcOH (1.0), DMF–DMSO (95:5), 160 °C μw, 45 min	**202** (3%)
4[142]	$Pd(OAc)_2$ (0.1), AgOAc (2.0), pyridine (4.0), DMF, 120 °C, 16 h	**202** (not isolated)
5	$Pd(OAc)_2$ (0.1), $Cu(OAc)_2$ (3.0), AcOH, 100 °C, 64 h	**202** (not isolated)
6[134]	$Pd(OAc)_2$ (0.1), K_2CO_3 (0.1), PivOH, air, 110 °C, 5 h; 120 °C, 12 h	**202** (not isolated)
7[143]	$Pd(OAc)_2$ (0.1), *t*-BuOOBz (0.9), MeCN–AcOH, 120 °C μw, 40 min	**202** (not isolated)

2.6.3 Synthesis of indole analogue

2.6.3.1 Work towards 2-(iodomethyl)-1-methylindole 206

Synthesis of 2-(iodomethyl)-1-methylindole **206** was also investigated, directly from alcohol **204** and via mesylate **205** (Scheme 124).[139] Direct iodination proved unsuccessful using our previously employed conditions and this was thought to be due to the highly electron-rich

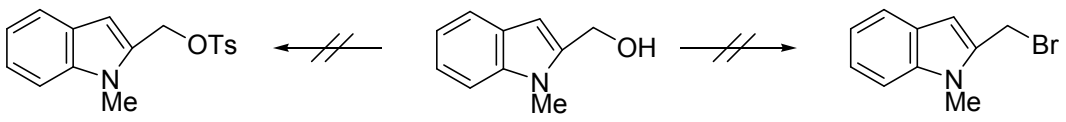
nature of the indole ring. Furthermore, treatment of alcohol **204** with mesyl chloride and triethylamine failed to isolate mesylate **205**.



203 **204** **205** **206**

Scheme 124 *Reagents and Conditions:* i) $NaBH_4$ (1.0 eqviv), MeOH, 0 °C → rt, 96%; ii) MsCl (1.1 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C → rt, 15 h, decomposition; iii) I_2 (1.0 equiv), PPh_3 (1.0 equiv), imidazole (1.1 equiv), CH_2Cl_2, rt, 20 h, decomposition.

Our attention therefore turned to the synthesis of tosylate **207** (Scheme 125). A variety of conditions were investigated using a range of different bases (triethylamine, pyridine and sodium hydride) and toluenesulfonyl sources (*p*-toluenesulfonyl chloride and *p*-toluenesulfonic anhydride). However, in each case only decomposition was observed.[144,145] Similarly, attempts to form bromide **208** using the same conditions as for the furan analogue proved unsuccessful. Alternative literature bromination conditions employing lithium bromide, methanesulfonyl chloride and triethylamine, and also carbon tetrabromide and triphenylphosphine, also gave only decomposition products.[140,146,147]

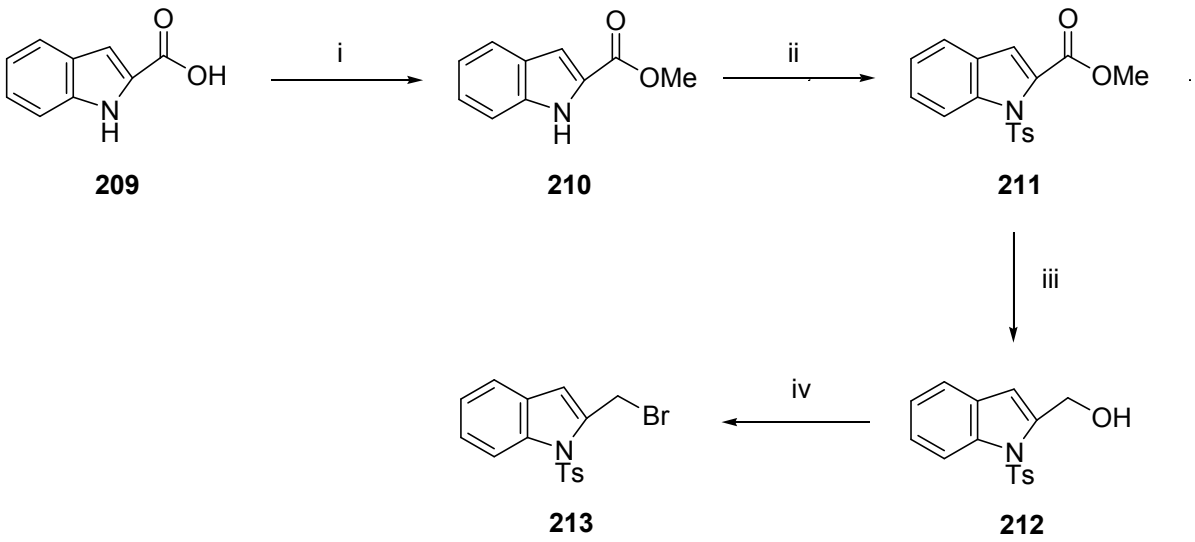


207 **204** **208**

Scheme 125 *Attempts to form tosylate **207** and bromide **208** were unsuccessful*

It was suggested by Bélanger *et al*. that 2-bromomethyl-1-methyl-1*H*-indole **208** was too unstable to isolate and therefore we turned our attention to the synthesis of the more stable

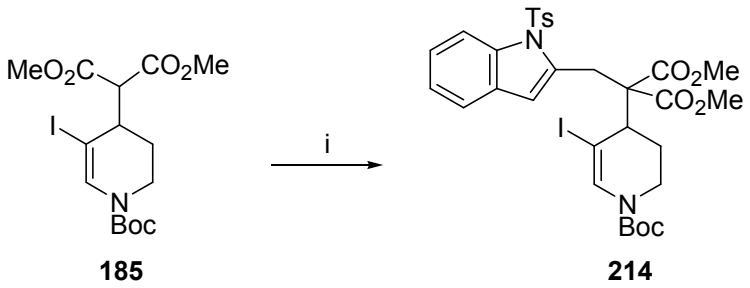
tosyl protected indole (Scheme 126).[146] Initial studies looked at investigating direct *N*-tosylation of commercially available 1*H*-Indole-2-carboxylic acid **209** with tosyl chloride and either sodium hydride or *n*-butyl lithium, however in each case it proved difficult to *N*-tosylate in the presence of the carboxylic acid.[148,149] Acid **209** was therefore esterified with conc. sulfuric acid and methanol to give methyl ester **210** in excellent yield. Subsequent *N*-tosylation with sodium hydride and tosyl chloride gave the desired tosyl-protected indole **211** in satisfactory yield, however the reaction did not reach completion and it was difficult to fully separate the product from the unreacted starting material by column chromatography. Finally, reduction of ester **211** with lithium aluminium hydride gave alcohol **212** and bromination with phosphorus tribromide gave the desired bromide **213** in excellent yield, without the need for purification.[148]



Scheme 126 *Reagents and Conditions:* i) H_2SO_4 (35 drops), MeOH, reflux, 21.5 h, 93%; ii)a) NaH (1.3 equiv), 0 °C; ester **210** (1.0 equiv), DMF; b) TsCl (1.3 equiv), DMF, 0 °C → rt, 24 h, 69%; iii) $LiAlH_4$ (2.4 equiv), THF, 0 °C → rt, 1.5 h, 90%; iv) PBr_3 (2.0 equiv), CH_2Cl_2, rt, 1 h, 94%.

2.6.3.2 Alkylation with 2-bromomethyl-1-tosyl-1*H*-indole 213

Alkylation with 2-bromomethyl-1-tosyl-1*H*-indole **213** proved much more sluggish than with our corresponding thiophene and furan alkylating agents. Attempts to improve this reactivity included employing potassium hydride as base, however this led to decomposition. Adding an extra 1.5 equivalents of sodium hydride as the reaction progressed optimised the yield of tetrahydropyridine **214** to 57% (Scheme 127).



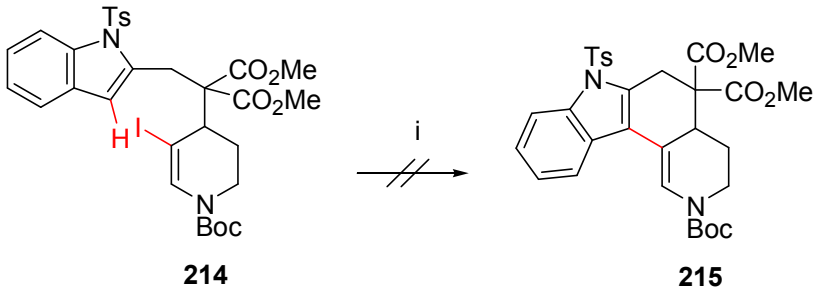
185 **214**

Scheme 127 *Reagents and Conditions:* i) a) NaH (1.5 equiv), 0 °C; b) iodide **185** (1.0 equiv), bromide **213** (1.4 equiv), DMF, 0 °C → rt; c) NaH (1.5 equiv), rt, 3 h, 57%.

2.6.3.3 Palladium-catalysed arylation

A variety of different conditions were investigated to effect palladium-catalysed arylation of cyclisation precursor **214** (Scheme 128, Table 12). Interestingly, treatment with palladium(II) acetate and either triphenylphosphine or SPhos gave elimination product **216** (Scheme 129, entries 1 and 2).[53] This was thought to result from decarboxylation of one of the ester groups, followed by nitrogen-assisted elimination of the indole malonate.

Employing 1,1'-bis(diphenylphosphino)ferrocene as our ligand gave what was initially believed to be arylated product **215**, however it was later thought to be either an isomer or an adduct of the desired product (entry 3). Exploring a different catalyst, tetrakis(triphenylphosphine) palladium(0), gave this same unknown (entry 4); a different base (silver carbonate) resulted in decomposition (entry 5) and finally the absence of a ligand source resulted in no reaction taking place (entry 6).[150,151] Unfortunately, it was not possible to optimise this transformation or successfully characterise our unknown product during the time period of this research.

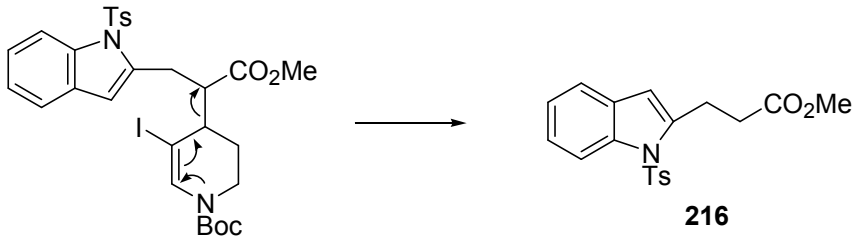


214 **215**

Scheme 128 *Reagents and Conditions:* i) See Table 12

Table 12 Palladium-catalysed arylation of indole analogue

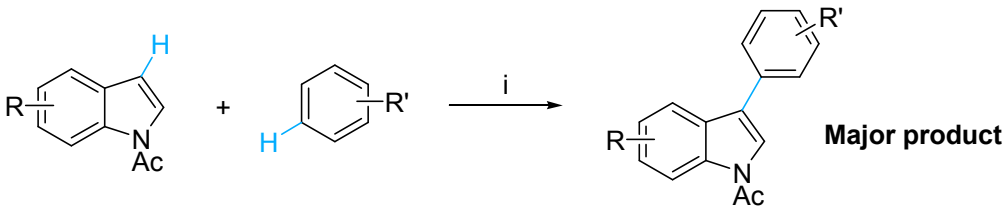
Entry	Reagents and conditions (equiv)	Product (yield)
1	$Pd(OAc)_2$ (0.1), PPh_3 (1.0), KOAc (2.0), 140 °C μw, 20 min	**216** (15%)
2	$Pd(OAc)_2$ (0.1), S–PHOS (1.0), KOAc (2.0), DMF, 140 °C μw, 20 min	**216** (28%)
3	$Pd(OAc)_2$ (0.1), DPPF (1.0), KOAc (2.0), 140 °C μw, 30 min	Unknown
4	$Pd(PPh_3)_4$ (0.1), KOAc (2.0), DMF, 140 °C μw, 20 min	Unknown
5[150]	$Pd(OAc)_2$ (0.2), PPh_3 (0.4), Ag_2CO_3 (2.0), DMF, 100 °C μw, 1 h	Decomposition
6[151]	$Pd(OAc)_2$ (0.1), K_2CO_3 (3.0), 1,4-dioxane, 100 °C, 20 h	No reaction



Scheme 129 Elimination of indole malonate **216**

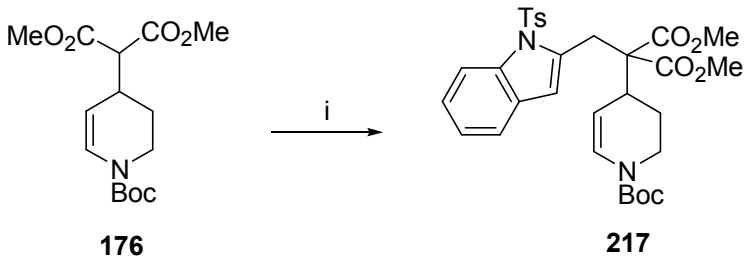
2.6.3.4 Palladium-catalysed oxidative coupling

The catalytic cross-coupling of unactivated indoles and benzenes with a palladium catalyst, in conjunction with a copper oxidant has been described in the literature by Fagnou *et al.* (Scheme 130).[79] An inversion in catalyst selectivity is required, whereby the catalyst must react with one arene in the first step of the catalytic cycle and then react exclusively with the other arene in the second step. This is proposed to take place *via* either an electrophilic aromatic metallation mechanism or a concerted proton transfer–metallation pathway. Furthermore, the selectivity for arylation of the indole was found to be influenced by the choice of oxidant and the use of an acidic solvent: silver acetate favours arylation at the 2-position and copper acetate in an acidic medium favours arylation at the 3-position.



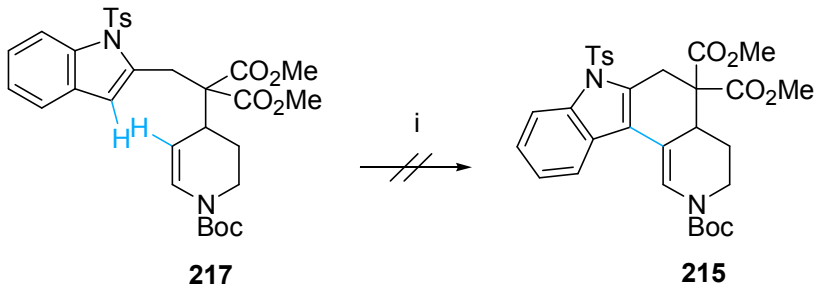
Scheme 130 *Reagents and Conditions:* i) Benzene (30.0 equiv), $Pd(TFA)_2$ (10 mol%), 3-nitropyridine (10 mol%), cesium pivalate (40 mol%), $Cu(OAc)_2$ (3.0 equiv), PivOH, microwave, 140 °C.

We were interested in exploring this methodology for our indole-substituted tetrahydropyridine substrate. Once again, alkylation with 2-bromomethyl-1-tosyl-1*H*-indole **213** was very sluggish and extended reaction times were only able to give a moderate yield of 47%. Increasing the equivalents of base and alkylating reagent resulted in a decrease in yield, possibly due to competing side-reactions (Scheme 131).



Scheme 131 *Reagents and Conditions:* i) a) NaH (1.2 equiv), 0 °C; b) **176** (1.0 equiv), bromide **213** (1.1 equiv), DMF, 0 °C → rt, 60 h, 47%.

As previously observed with our furan analogue, investigation of a range of different catalytic conditions failed to isolate oxidative arylation product **215** (Scheme 132, Table 13). A variety of stoichiometric oxidants were explored, such as copper acetate (entries 1 and 2), silver acetate (entry 3), *tert*-butyl benzoyl peroxide (entry 4) and silver carbonate (entry 5).[143,152,153] A range of polar and acidic solvents were also employed, but in each case only starting material was recovered, or decomposition observed.



217 **215**

Scheme 132 *Reagents and Conditions:* See Table 13

Table 13 Palladium-catalysed oxidative coupling conditions

Entry	Reagents and conditions (equiv)	Product (yield)
1	$Pd(OAc)_2$ (0.1), $Cu(OAc)_2$ (1.7), AcOH, 160 °C µw, 26 min; 160 °C µw, 1 h; 160 °C µw, 2 h	Decomposition
2[143]	$Pd(OAc)_2$ (0.1), $Cu(OAc)_2$ (1.8), DMF–DMSO (9:1), 120 °C µw, 40 min; 140 °C µw, 40 min	**217** (13%)
3[152]	$Pd(OAc)_2$ (0.1), AgOAc (3.0), PivOH (2.5), 150 °C µw, 30 min; 160 °C µw, 1 h	Decomposition
4[143]	$Pd(OAc)_2$ (0.1), *t*-BuOOBz (0.9), MeCN–AcOH, 120 °C µw, 40 min	**217** (not isolated)
5[153]	$Pd(OAc)_2$ (0.1), Ag_2CO_3 (1.5), pyridine (1.0), 1,4-dioxane, 100 °C, 7 h; rt, 16 h	**217** (not isolated)

2.6.4 Conclusions

Heteroaromatic analogues of our tricyclic structures were accessed with relative ease *via* the convergent route we had devised, whereby iodide **185** could be alkylated with a variety of heteroaromatic alkylating agents. 3-(Iodomethyl)thiophene **191** was readily available following iodination of the corresponding alcohol, and the desired cyclisation precursor was obtained in very good yield *via* alkylation. Direct arylation was then effected following treatment with palladium(II)acetate and triphenylphosphine.

3-(Iodomethyl)furan proved rather more difficult to isolate due to its extremely reactive nature, however the corresponding bromide was much more stable and gave excellent yields

for the alkylation of iodide **185**. Interestingly, direct arylation did not occur as readily as for the thiophene substrate, despite furans higher relative reactivity towards electrophilic aromatic substitution. This could have been due to the noticeably lower stability of the furan substrate. Furthermore, palladium-catalysed oxidative coupling was investigated, following alkylation of our non-iodinated tetrahydropyridine **176** with 3-(bromomethyl)furan. Unfortunately, no arylation product was observed and it was thought that the enamide double bond may have been too electron deficient due to the electron withdrawing *N*-Boc group.

Finally direct arylation of indole-substituted tetrahydropyridines was also investigated. 2-(Iodomethyl)-1-methylindole proved too reactive to isolate, however 2-bromomethyl-1-tosyl-1*H*-indole **213** was much easier to handle and was obtained in excellent yield from commercially available 1*H*-indole-2-carboxylic acid **209**. Alkylation of iodide **185** was very sluggish and this was thought to be due to the creation of a very sterically hindered quaternary centre. Furthermore, direct arylation proved difficult, possibly due to the electron deficient nature of the *N*-tosyl protected indole ring. Once again palladium-catalysed oxidative coupling was investigated, however no arylation was observed.

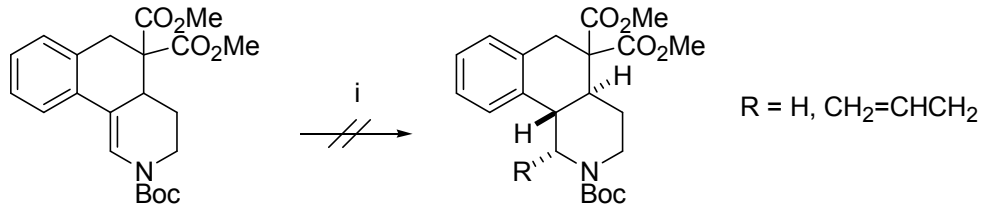
We would also have liked to have investigated direct arylation of pyridine joined at the 3-position, but we were unable to synthesise either 3-(iodomethyl)- or 3-(bromomethyl)- pyridine during this project. The corresponding alcohol was found to be very volatile and the pyridine ring itself very reactive, which made substitution at the methylene position difficult.

2.7.0 Further elaboration of tricyclic tetrahydropyridines

In the final phase of this project, it was considered attractive to investigate further elaboration of our tricyclic tetrahydropyridine systems, namely through manipulation of the C-5–C-6 double bond to give polysubstituted piperidines.

2.7.1. Reductions of the C-5–C-6 enamide bond

Reduction of the C-5–C-6 enamide double bond has previously been carried out in the group *via* ionisation with trifluoroacetic acid and treatment with triethylsilane as hydride source, to give substituted piperidines (Introduction, Scheme 42).[72] However, applying this methodology to tricycle **176** resulted in no reaction (Scheme 133, Table 14, entry 1). Using an *in-situ* nucleophilic trap, allyltrimethyl silane, following acid-catalysed ionisation also failed to give the desired piperidine **218** (entry 2). Furthermore, treatment with a stronger acid, trifluoro-methanesulfonic acid, resulted in decomposition of the starting material (entries 3 and 4).



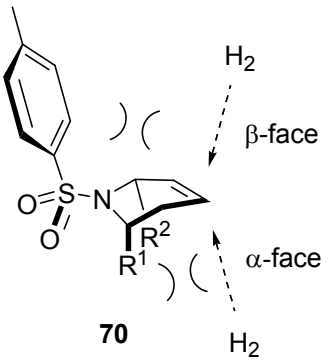
176 **218**

Scheme 133 *Reagents and Conditions:* i) See Table 14

Table 14 Reduction of the C-5–C-6 enamide double bond *via* ionisation

Entry	R	Reagents and Conditions (equiv)	Product (yield)
1[72]	H	**176** (1.0), Et_3SiH (1.1), CF_3CO_2H (2.0), CH_2Cl_2, rt, 20 h.	No reaction
2[72]	CH_2=$CHCH_2$	**176** (1.0), allyltrimethyl silane (2.2), CF_3CO_2H (2.2), rt, 20 h.	No reaction
3	H	**176** (1.0), Et_3SiH (1.1), CF_3SO_3H (2.0), CH_2Cl_2, rt, 30 min.	Decomposition
4	CH_2=$CHCH_2$	**176** (1.0), allyltrimethyl silane (2.2), CF_3SO_3H (2.2), rt, 30 min.	Decomposition

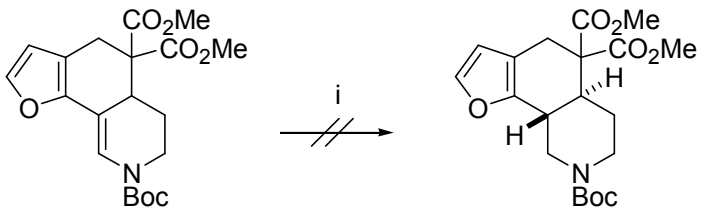
More forcing hydrogenation conditions have also previously been employed for the reduction of the C-4–C-5 double bond of S_N1' substitution products **70** (Introduction, Scheme 41). This double bond was found to have a very low reactivity as both the α- and β-faces are blocked by the axial C-2 and C-6 alkyl substituents and the *N*-tosyl group respectively (Figure 10).[67]



70

Figure 10 Doubly hindered nature of C-4–C-5 double bond

Unfortunately, heterogeneous hydrogenation of tetrahydropyridine **201** over Pd/C and $Pd(OH)_2/C$, and homogeneous hydrogenation using Wilkinson's catalyst and hydrogen at atmospheric pressure, failed to reduce the C-5–C-6 enamide double bond (Scheme 134).[67] It was therefore suspected that our system may also have been too sterically hindered, resulting in the low reactivity of the double bond.



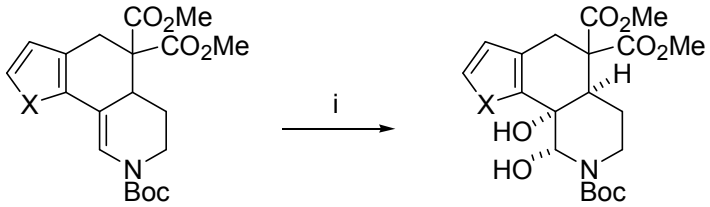
201 **219**

Scheme 134 *Reagents and Conditions:* i) H_2 (1 atm), 10% Pd–C (0.1 equiv)/ 20% $Pd(OH)_2/C$ (0.05 equiv), MeOH, rt, 3 h; 10% Pd–C (0.1 equiv)/ 20% $Pd(OH)_2/C$ (0.05 equiv), rt, 18 h, decomposition; or H_2 (1 atm), $RhCl(PPh_3)_3$ (0.18), toluene, rt, 96 h, no reaction.

2.7.2 Dihydroxylation of the C-5–C-6 enamide bond

Dihydroxylation of C-4-substituted tetrahydropyridines with osmium tetroxide and *N*-methylmorpholine-*N*-oxide has been previously shown to occur with complete stereoselectivity, to give the corresponding *syn*-α, α diol. Dihydroxylation was observed to take place *anti* to the C-4 tosyl group in all cases and it was therefore deduced that the tosyl group exerts complete control over the stereochemistry of the reaction (Introduction, Scheme 37).[74]

Pleasingly both thiophene and furan substituted tricyclic tetrahydropyridines (**194** and **201**) also underwent dihydroxylation following treatment with osmium tetroxide and *N*-methylmorpholine-*N*-oxide to give dihydroxypiperidines **220** and **221** respectively (Scheme 135).[70,74] Only one product was observed for each substrate, therefore it is once again believed that the reaction is under complete stereocontrol, this time from the concave face of the bis-fused cyclohexane rings. The yields were slightly disappointing, but unfortunately due to time constraints it was not possible to optimise these reactions or accurately assess the quality of the reagents used.



194 X=S
201 X=O

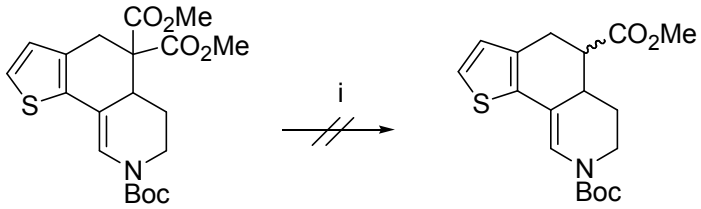
220 X=S
221 X=O

Scheme 135 *Reagents and Conditions:* i) X=S, OsO_4 (0.05 equiv), NMO (2.8 equiv), Me_2CO–H_2O (9:1), rt, 15 h, 63%; X=O, OsO_4 (0.05 equiv), NMO (2.8 equiv), THF–H_2O (9:1), rt, 6 h, 36%.

2.7.3 Krapcho Decarbalkoxylation

The decarbalkoxylation of geminal diesters, β-keto esters, and α-cyano esters has been reported in excellent yields by Krapcho *et al.* following heating with sodium chloride in wet dimethylsulfoxide at temperatures of 140-185 °C.[154] Water is thought to attack one carbonyl group of the diester, resulting in the elimination of carbon dioxide and an alcohol. The sodium chloride additive acts as a nucleophilic catalyst, as the presence of the chloride anion accelerates the rate of this decarbalkoxylation in less reactive substrates, through nucleophilic attack.

We had previously observed decarbomethoxylation of our substrates as a side reaction of direct arylation, so we expected it to be a facile transformation. Decarbomethoxylation of dimethyl diethylmalonate has been reported to proceed in excellent yield following treatment with water–dimethylsulfoxide and sodium chloride, lithium chloride and potassium cyanide.[154] Unfortunately, no elimination was observed for substrate **194** (Scheme 136, Table 15) and decomposition resulted after prolonged reaction times and high temperatures. Once again, due to time constraints this transformation was only attempted on a very small scale and a wide variety of metal salts, as well as alternative conditions remain uninvestigated.



194 **222**

Scheme 136 *Reagents and Conditions:* See Table 15

Table 15 Attempts to decarboxylate diester **194**

Entry	Reagents and conditions (equiv)	Product (yield)
1[154]	LiCl (2.0), H_2O (1.0), DMSO, 180 °C, 4 h; rt, 96 h	Decomposition
2[155]	NaCl (1.05), H_2O (2.0), DMSO, 180 °C μw, 1 h; 180 °C μw, 1 h	Decomposition
3[156]	LiCl (10.0), H_2O (2 drops), DMSO, 180 °C μw, 40 min	Decomposition

2.7.4 Conclusions

A variety of further elaborations of our tricyclic tetrahydropyridine core were investigated in order to access biologically interesting piperidines. Unfortunately, direct reduction of the C5–C6 enamide double bond proved unsuccessful *via* both acid-mediated ionisation and trapping with an *in-situ* nucleophile, and catalytic hydrogenation. It has previously been reported that highly substituted tetrahydropyridines are difficult to reduce, so we belief that steric hindrance may once again account for the low reactivity of our double bond.

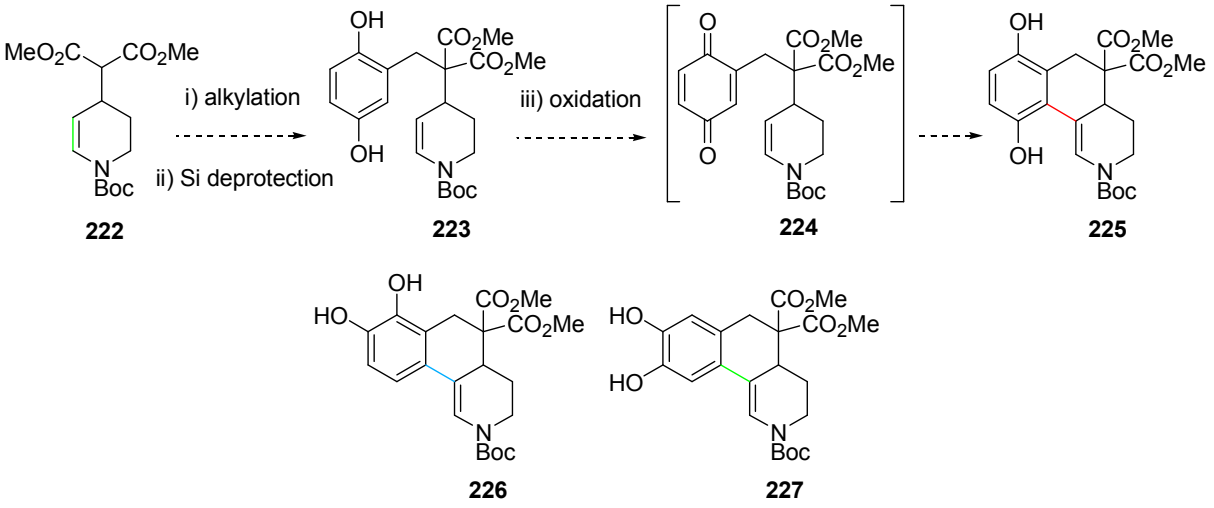
Pleasingly, dihydroxylation of thiophene- and furan-substituted tetrahydropyridines gave the desired diols **220** and **221**. Unfortunately it was not possible to optimise these transformations, however it is thought that the crowded nature of the ene–carbamate double bond may have been responsible for its low reactivity. An alternative route to 5,6-disubstituted piperidines could involve epoxide formation followed by nucleophilic ring opening, and this has previously been investigated by the group.

Decarbalkoxylation was investigated for thiophene arylation product **194**, but elimination of an ester group was not observed and after prolonged reaction times, decomposition resulted. It was not possible to fully evaluate the numerous conditions that have previously been employed for this kind of transformation, so future attempts could look at different metal salts or solvents.

3.0 Future Work

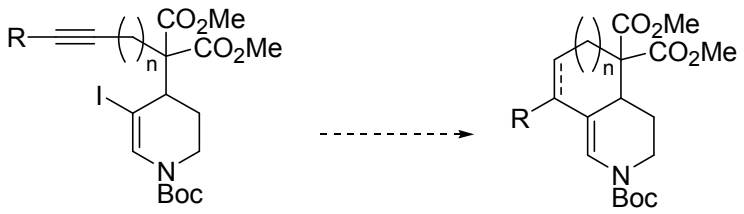
The dearomatisation of *ortho*- and *para*-substituted phenols to form cyclohexadienones using hypervalent iodine reagents such as phenyliodonium acetate, has been reported by Pelter *et al.*[157] Gaunt and co-workers have shown that this cyclohexadienone motif can be converted into highly functionalised chiral molecules *via* a catalytic asymmetric process.[158] *Para*-substituted phenol can undergo oxidative dearomatisation followed by a secondary amine-catalysed enantioselective desymmetrising Michael reaction, to isolate a range of polycyclic products.

It is proposed that this oxidative dearomatisation strategy could be applied to our ene–carbamate system, as an extension to the direct arylation studies reported in this thesis (Scheme 137). Tetrahydropyridine **222** could be alkylated with a silyl-protected 2,5-dihydroxybenzyl halide and undergo subsequent deprotection of the silyl-groups to isolate **223**. Treatment with an oxidant such as phenyliodonium acetate would give the substituted benzoquinone **224,** which could then undergo nitrogen-assisted Michael addition to give tricycle **225**. Alternative substitution patterns on the arene can also be envisaged to give arylated products **226** and **227**, via the isomeric *ortho*-quinones.
Additionally, Macmillan's Organo-SOMO catalysis methodology, which was previously investigated for our 3-methoxy analogue, could be applied to substrate **223**.[135] Once again a single-electron oxidant could be employed to create a 3π-radical cation species from the enamide, which would be expected to cyclise intramolecularly with the aryl radical formed.



Scheme 137 *Proposed oxidative dearomatisation–cyclisation reactions.*

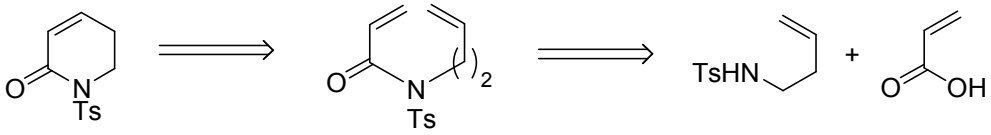
Cyclisation reactions with non-arene side chains, such as alkenes and alkynes **228** could also be investigated and the bifunctional substrates accessed could undergo further elaborations at the newly formed ring (Scheme 138). Beccalli and co-workers reported the use of vinyl halides in the intramolecular coupling of heteroaromatic-substituted carbamates to give a variety of nitrogen-containing heterocycles.[53]



228 **229**

Scheme 138 *Cyclisations with alkene and alkyne side chains*

Finally, it is highly desirable to re-investigate the synthesis of *N*-tosyl analogues of these substrates as these derivatives would greatly simplify NMR analysis due to the absence of rotamers generated by the freely rotating *N*-Boc group (Scheme 139). Furthermore, the degree of crystallinity imparted by the toluene-4-sulfonyl group would likely provide solid substrates, which would be easier to handle and allow for absolute stereochemical determination where required.[76]



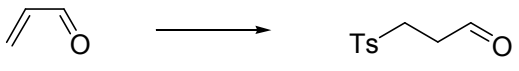
Scheme 139 *Proposed route alternative towards N-tosyl protected α,β-unsaturated lactam*

4.0 Experimental

All reactions were performed under an atmosphere of nitrogen unless otherwise stated. Melting points were determined using Stuart Scientific SMP1 melting point apparatus and are uncorrected. Infrared spectra were recorded on Mattson 5000 FTIR and Perkin–Elmer Spectrum RX FT-IR System spectrometers. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in $CDCl_3$ unless otherwise stated on a Bruker AV-400 spectrometer. Chemical shifts are in parts per million (ppm) and are referenced relative to the residual proton–containing solvent (^{1}H NMR: 7.26 ppm for $CDCl_3$; ^{13}C NMR: 77.0 ppm for $CDCl_3$). Mass spectra (CI, EI and ESI) were recorded using Micromass AutoSpec-Q or Micromass Platform II instruments. Elemental analyses were performed at the microanalytical laboratories of London Metropolitan University. Analytical thin layer chromatography (TLC) was performed on pre-coated Aluminium-backed Merck Silica gel 60 F_{254} plates. Visualisation was effected with ultraviolet light, potassium permanganate or vanillin as required. Flash column chromatography was performed using BDH (40-63 μm) silica gel or Isolute (30-90 μm) silica cartridges. Standard solvents were distilled under nitrogen prior to use; THF from sodium–benzophenone ketyl, CH_2Cl_2 and acetonitrile from CaH_2, toluene from sodium and dimethylformamide over molecular sieves. All other solvents used were reagent grade. Petrol refers to petroleum ether b.p. 40–60 °C and hexane refers to *n*-hexane b.p. 60-70 °C. All liquid reagents were distilled prior to use. Potassium acetate was recrystallised from AcOH and oven-dried at 120 °C for several days prior to use. *N*-iodosuccinimide was recrystallised from EtOAc and *n*-BuLi was titrated with diphenylacetic acid.

Microwave reactions were performed in a Biotage initiator.

3-(Toluene-4-sulfonyl)propanal 118



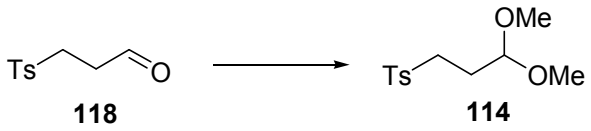
(**117**) **118**

To a colourless stirred solution of *p*-toluenesulfinic acid (25.5 g, 149.0 mmol, 1.0 equiv) in H_2O (128 mL) and THF (77 mL) at room temperature was added dropwise AcOH (8.70 mL, 149.0 mmol, 1.0 equiv). Acrolein (**117**) (20.0 mL, 298.0 mmol, 2.0 equiv) was then added at 0 ºC and the cloudy solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was then diluted with Et_2O and H_2O and the aqueous phase extracted with Et_2O. The combined organic layers were washed with H_2O, sat. $NaHCO_{3(aq)}$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield **118** (28.1 g, 88%) as a colourless oil, which was used crude in the next step.

R_f 0.3 (50% Et_2O–petrol); ν_{max} (film) 3063, 2929, 1724 (C=O), 1597, 1495, 1409, 1303 (SO_2), 1233, 1143 (SO_2), 1087, 1018, 816 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 9.77 (1H, s, CHO), 7.82 (2H, d, *J* 8.5 Hz, *ortho* $ArSO_2$), 7.41 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 3.45–3.38 (2H, m, CH_2Ts), 2.99 (2H, t, *J* 7.5 Hz, CH_2CHO), 2.49 (3H, s, $ArCH_3$); δ_C ($CDCl_3$, 101 MHz) 197.0 (CHO), 145.2 (*ipso* $ArSO_2$), 135.7 (*para* $ArSO_2$), 130.1 (*meta* $ArSO_2$), 128.1 (*ortho* $ArSO_2$), 49.2 (CH_2Ts), 36.7 (CH_2CHO), 21.7 ($ArCH_3$); *m/z* (CI) 230 $[M+NH_4]^+$, 139, 108, 91, 82 (Found: $[M+NH_4]^+$, 230.0860. $C_{10}H_{12}O_3S$ requires $[M+NH_4]^+$, 230.0851).

This data is in agreement with the published data for the compound.[80]

1,1-Dimethoxy-3-[toluene-4-sulfonyl]propane 114



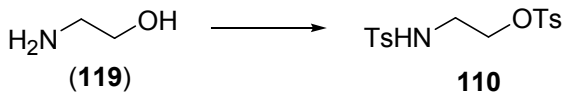
118 **114**

A solution of 3-(toluene-4-sulfonyl)propanal **118** (28.1 g, 132.0 mmol, 1.0 equiv), *p*-toluenesulfonic acid (0.760 g, 3.97 mmol, 0.03 equiv) and trimethyl orthoformate (28.9 mL, 265.0 mmol, 2.0 equiv) in MeOH (200 mL) was stirred at 70 ºC overnight. The dark yellow reaction mixture was diluted with Et_2O, washed with sat. $NaHCO_{3(aq)}$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting orange oil was purified by column chromatography (50 → 70% Et_2O–petrol) to isolate **114** (29.8 g, 87%) as colourless crystals.

R_f 0.26 (50% Et_2O–petrol); m.p. 30-32 °C (lit. 35.5-36.5 °C[80]); ν_{max} (film) 2940, 2834, 1598, 1495, 1443, 1383 (NSO_2), 1304 (NSO_2), 1235, 1193 (SO_2), 1145 (SO_2), 1087, 966, 923, 883, 817 cm^{-1}; δ_H ($CDCl_3$, 400 MHz); 7.81 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.38 (2H, d *J* 8.0 Hz, *meta*$ArSO_2$), 4.43 (1H, t, *J* 5.5 Hz, $CH(OMe)_2$), 3.32 (6H, s, OCH_3), 3.16 (2H, dt, *J* 4.5, 11.5 Hz, CH_2Ts), 2.47 (3H, s, $ArCH_3$), 2.07–1.97 (2H, m, $CH_2CH(OMe)_2$); δ_C ($CDCl_3$, 101 MHz) 144.8 (*ipso* $ArSO_2$), 136.0 (*para* $ArSO_2$), 129.9 (*meta* $ArSO_2$), 128.1 (*ortho* $ArSO_2$), 102.6 ($CH(OCH_3)_2$), 53.7 (OCH_3), 51.7 (CH_2Ts), 26.2 ($CH_2CH(OMe)_2$), 21.7 ($ArCH_3$); *m/z* (CI) 276 $[M+NH_4]^+$, 244 $[M+NH_4\text{-}CH_3OH]^+$, 227 $[M\text{-}OCH_3]^+$, 212 $[M+NH_4\text{-}C_2H_8O]^+$ (Found $[M+NH_4]^+$, 276.1276. $C_{12}H_{18}O_4S$ requires $[M+NH_4]^+$, 276.1270).

This data is in agreement with the published data for the compound.[80]

Bis(toluene-4-sulfonyl) aminoethanol 110



To a stirred solution of ethanolamine (**119**) (5.00 mL, 82.8 mmol, 1.0 equiv), DMAP (1.51 g, 12.4 mmol, 0.15 equiv) and toluene-4-sulfonyl chloride (31.6 g, 166.0 mmol, 2.0 equiv) in CH_2Cl_2 (150 mL) at –5 °C, was added Et_3N (23.0 mL, 166.0 mmol, 2.0 equiv). The resulting pale yellow solution was allowed to warm to 0 °C and stirred for 2 h. The resulting cloudy reaction mixture was then diluted with CH_2Cl_2 and sat. $NaHCO_{3(aq)}$ and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, sat. $NaHCO_{3(aq)}$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting pale yellow oil was purified by column chromatography (10 → 60% EtOAc–petrol) to isolate **110** (22.2 g, 73 %) as a colourless solid.

R_f 0.18 (30% EtOAc–hexane); m.p. 146-148 ºC; ν_{max} (film) 1597, 1494 , 1372 (NSO_2), 1309 (SO_2), 1266, 1176 (NSO_2) 1165 (SO_2), 1084, 1018, 918, 814 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.76 (2H, d, *J* 8.5 Hz, *ortho* $ArSO_2$), 7.72 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.37 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 7.32 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 4.98 (1H, t, *J* 6.5 Hz, NH), 4.07 (2H, t, *J* 5.0 Hz, CH_2OTs), 3.25 (2H, dd, *J* 5.5, 11.5 Hz, CH_2NHTs), 2.45 (3H, s, $ArCH_3$), 2.42 (3H, s, $ArCH_3$); δ_C ($CDCl_3$, 101 MHz) 145.4, 143.9 (*ipso* $ArSO_2$), 136.6, 132.3 (*para* $ArSO_2$), 130.1, 129.9 (*meta* $ArSO_2$), 128.0, 127.0 (*ortho* $ArSO_2$), 68.7 (OCH_2), 42.2 (NCH_2), 21.7, 21.6 ($ArCH_3$); *m/z* (CI) 387 $[M+NH_4]^+$, 251, 233, 215, 198, 174 (Found: $[M+NH_4]^+$, 387.1051. $C_{16}H_{19}NO_5S_2$ requires $[M+NH_4]^+$, 387.1048).

This data is in agreement with the published data for the compound.[83]

1-(Toluene-4-sulfonyl) aziridine 115

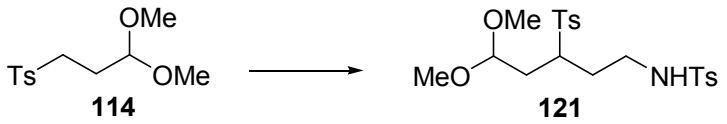
110 **15**

To a solution of bis(toluene-4-sulfonyl) aminoethanol **110** (18.7 g, 50.0 mmol, 1.0 equiv) in CH_2Cl_2 (300 mL) at room temperature was added NaOH (50% w/v in H_2O, 21.6 mL, 270.0 mmol, 5.3 equiv) and the gelatinous mixture was stirred rapidly. After 30 min, the reaction was diluted with H_2O and CH_2Cl_2. The organic phase was washed with H_2O, dried ($MgSO_4$) and concentrated under reduced pressure to yield **115** (9.94 g, 100%) as a colourless waxy solid.

R_f 0.47 (50% Et_2O–petrol); m.p. 60 °C (lit. 51 °C[83]); ν_{max} (film) 3108, 3069, 1596, 1491, 1444, 1398, 1316 (NSO_2), 1291, 1240, 1155 (SO_2), 1100, 1082, 1037, 1016, 906, 815 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.87–7.83 (2H, m, *ortho* $ArSO_2$), 7.37 (2H, d *J* 8.0 Hz, *meta* $ArSO_2$), 2.47 (3H, s, $ArCH_3$), 2.39 (4H, s, 2 x CH_2); δ_C ($CDCl_3$, 101 MHz) 144.7 (*ipso* $ArSO_2$), 134.9 (*para* $ArSO_2$), 129.8 (*meta* $ArSO_2$), 128.0 (*ortho* $ArSO_2$), 27.4 (CH_2), 21.7 ($ArCH_3$); *m/z* (CI) 215 $[M+NH_4]^+$, 198 $[M+H]^+$, 108, 91, 82 (Found: $[M+H]^+$, 198.0591. $C_9H_{11}NO_2S$ requires $[M+H]^+$, 198.0589).

This data is in agreement with the published data for the compound.[83]

_N_-5,5-dimethoxy-3-[toluene-4-sulfonyl]-toluene-4-sulfonamide 121

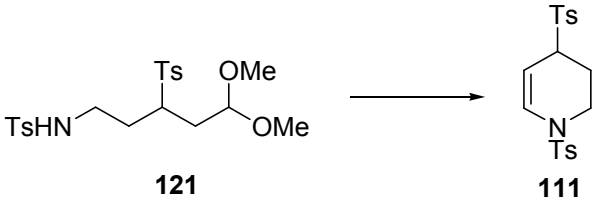


To a stirred solution of 1,1-dimethoxy-3-[toluene-4-sulfonyl]propane **114** (8.80 g, 34.1 mmol, 1.1 equiv) in THF (97 mL) and TMEDA (34 mL) at –78 ºC was added *n*-BuLi (2.36 M in hexanes, 14.4 mL, 34.1 mmol, 1.1 equiv). The resulting orange solution was stirred at –78 ºC for 20 min and 1-(toluene-4-sulfonyl) aziridine **115** (6.10 g, 31.0 mmol, 1.0 equiv) in THF (40 mL) was then added. The reaction was allowed to warm to room temperature and was stirred for 3 h before the resulting red solution was quenched with AcOH (1 M in THF, 34.1 mL, 34.1 mmol, 1.1 equiv). The mixture was diluted with H_2O and the aqueous phase extracted with Et_2O. The combined organic layers were then washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting orange oil was purified by column chromatography (10 → 60 % EtOAc–petrol) to yield **121** (10.1 g, 72%) as a colourless oil.

R_f 0.39 (50% Et_2O–petrol); ν_{max} (film) 2939, 1598, 1495, 1447, 1288, 1160 (NSO_2), 1127 (SO_2), 1084, 915, 816 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.73 (4H, dd, *J* 2.0, 8.5 Hz, *ortho* $ArSO_2$), 7.37 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 7.32 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 5.08 (1H, t, *J* 6.5 Hz, NH), 4.39 (1H, t, *J* 5.5 Hz, C*H*$(OCH_3)_2$, 3.31 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.20–3.02 (3H, m, NCH_2 and CHTs), 2.48 (3H, s, $ArCH_3$), 2.46 (3H, s, $ArCH_3$), 2.15–2.03 (2H, m, 1 x C*H*$_2$CH$(OMe)_2$ and 1 x C*H*$_2$CHTs), 1.85 (1H, dq, *J* 6.5, 13.0 Hz, C*H*$_2$CHTs), 1.73–1.67 (1H, m, C*H*$_2$CH$(OMe)_2$); δ_C ($CDCl_3$, 101 MHz) 145.1, 143.5 (*ipso* $ArSO_2$), 136.9, 134.0 (*para* $ArSO_2$), 130.0, 129.8 (*meta* $ArSO_2$), 128.9, 127.1 (*ortho* $ArSO_2$), 102.7 (*C*H$(OCH_3)_2$), 57.9 (CHTs), 54.8, 53.4 (OMe), 40.6 (NCH_2), 31.6 (*C*H_2CH$(OMe)_2$), 28.8 (*C*H_2CHTs), 21.7, 21.5 ($ArCH_3$); *m/z* (CI) 473 $[M+NH_4]^+$, 409, 392, 362, 330, 298, 266, 238, 189, 174, 144, 75, 52 (Found $[M+NH_4]^+$, 473.1784 $C_{21}H_{29}NO_6S_2$ requires $[M+NH_4]^+$, 473.1780).

This data is in agreement with the published data for the compound.[70]

1,4-Bis(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine 111

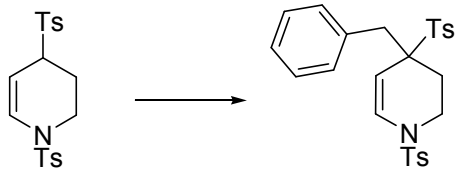


To a stirred solution of *N*-5,5-dimethoxy-3-[toluene-4-sulfonyl]-toluene-4-sulfonamide **121** (9.00 g, 19.8 mmol, 1.0 equiv) and NaI (8.89 g, 59.3 mmol, 3.0 equiv) in MeCN (200 mL) at room temperature was added TMSCl (7.50 mL, 59.3 mmol, 3.0 equiv). The dark orange suspension was stirred for 20 min, after which time the reaction mixture was quenched with sat. $NaHCO_{3(aq)}$, diluted with H_2O and the aqueous phase extracted with Et_2O. The combined organic layers were washed with sat. $Na_2S_2O_{3(aq)}$, sat. $NaHCO_{3(aq)}$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting dark brown solid was recrystallised from EtOAc–petrol to yield **111** (6.07 g, 79%) as a light brown solid.

R_f 0.31 (30% EtOAc –petrol); m.p. 164-166 °C (lit. 136-138 °C[5]); ν_{max} (film) 1644 (C=C), 1401, 1354, 1333 (NSO_2), 1303 (NSO_2), 1167 (SO_2), 1145 (SO_2), 1095, 941, 815, 708, 665 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.69 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.65–7.60 (2H, m, *ortho* $ArSO_2$), 7.33 (4H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 7.00 (1H, dd, *J* 1.5, 8.5 Hz, NC*H*CH), 4.95 (1H, dd, *J* 8.0, 4.0 Hz, NCHC*H*), 3.67-3.59 (1H, m, CHTs), 3.56–3.46 (1H, m, 1 x NCH_2), 3.36–3.23 (1H, m, 1 x NCH_2), 2.46 (3H, s, $ArCH_3$), 2.45 (3H, s, $ArCH_3$), 2.22–2.12 (1H, m, 1 x CHTsCH_2), 1.93 (1H, dddd, *J* 4.0, 6.5, 10.5, 14.5 Hz, 1 x CHTsCH_2); δ_C ($CDCl_3$, 101 MHz) 145.1, 144.3 (*ipso* $ArSO_2$), 134.6, 133.9 (*para* $ArSO_2$), 130.7 (CH*C*HNTs), 130.0, 129.8 (*meta* $ArSO_2$), 129.1, 127.0 (*ortho* $ArSO_2$), 97.3 (*C*HCHNTs), 57.3 (CTs), 40.1 (NCH_2), 21.7, 21.6 ($ArCH_3$), 21.5 (*C*H_2CTs); *m/z* (CI) 409 $[M+NH_4]^+$, 392 $[M+H]^+$, 257, 236, 209, 182, 164, 147, 82 (Found $[M+H]^+$, 392.1004. $C_{19}H_{21}NO_4S_2$ requires $[M+H]^+$, 392.0990).

This data is in agreement with the published data for the compound.[70]

(±)-4-Benzyl-1,4-bis(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine 122

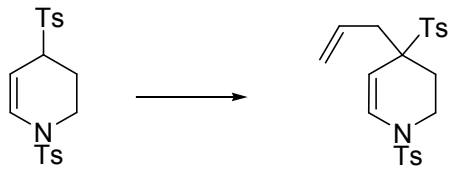


111 **122**

To a stirred solution of tetrahydropyridine **111** (0.300 g, 0.770 mmol, 1.0 equiv) in THF (16.1 mL) and TMEDA (5.3 mL) at –78 °C, was added *n*-BuLi (2.03 M in hexanes, 0.420 mL, 0.840 mmol, 1.1 equiv). The resulting dark orange solution was stirred at –78 °C for 15 min and benzyl bromide (0.090 mL, 0.77 mmol, 1.0 equiv) was then added and the reaction allowed to warm to 10 ºC over 1 h. The resulting dark yellow reaction mixture was quenched with H_2O and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting orange oil by column chromatography (10 → 20% EtOAc–petrol) gave **122** (0.280 g, 76%) as a colourless solid.

R_f 0.56 (30% EtOAc–petrol); m.p. 54-56 °C; ν_{max} (film) 3440, 1640 (C=C), 1598, 1401, 1357 (NSO_2), 1288, 1168, 1142 (SO_2), 1097, 948, 815, 738, 706, 673 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.73 (2H, dd, *J* 4.0, 8.0 Hz, *ortho* $ArSO_2$), 7.40 (2H, d, *J* 8.5 Hz, *ortho* $ArSO_2$), 7.35 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 7.27 (2H, d, *J* 8.5 Hz, *meta* $ArSO_2$), 7.16–7.08 (3H, m, H_{Ar}), 6.99–6.94 (3H, m, H_{Ar} and NC*H*CH), 4.92 (1H, d, *J* 8.5 Hz, NCHC*H*), 3.34–3.29 (1H, m,1 x NCH_2), 3.07 (1H, q, *J* 13.0 Hz, CH_2Ar), 2.75–2.67 (1H, m, 1 x NCH_2), 2.46 (3H, s, 1 x $ArCH_3$), 2.45 (3H, s, 1 x $ArCH_3$), 2.25–2.16 (1H, m, 1 x $CTsCH_2$), 1.79–1.70 (1H, m, 1 x $CTsCH_2$); δ_C ($CDCl_3$, 101 MHz) 145.2, 143.9 (*ipso* $ArSO_2$), 134.3, 134.2 (*para* $ArSO_2$), 132.4 (CH*C*HNTs), 131.4 (*ortho* $ArSO_2$), 130.6 (*meta* $ArSO_2$), 129.9, 129.6, 129.1 (C_{Ar}), 128.8 (*ipso* C_{Ar}), 128.3, 128.1 (C_{Ar}), 127.1 (*meta* $ArSO_2$), 126.8 (*ortho* $ArSO_2$), 101.7 (*C*HCHNTs), 64.3 (CTs), 40.0 (CH_2Ar), 39.9 (CH_2NTs), 25.3 (CH_2CTs), 21.7, 21.6 ($ArCH_3$); *m/z* (CI) 482 $[M+H]^+$, 343, 326, 257, 174, 147 (Found: $[M+H]^+$, 482.1490. $C_{26}H_{27}NO_4S_2$ requires $[M+H]^+$, 482.1460) (Found C, 64.95; H, 5.65; N, 2.91. $C_{26}H_{27}NO_4S_2$ requires C, 64.84; H, 5.65; N, 2.91%).

(±)-4-Allyl-1,4-bis(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine 123

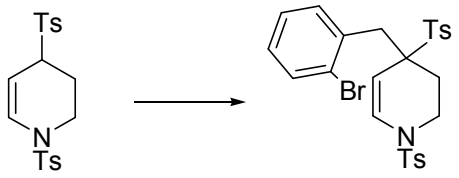


111 **123**

To a stirred solution of tetrahydropyridine **111** (0.200 g, 0.510 mmol, 1.0 equiv) in THF (10.2 mL) and TMEDA (2.6 mL) at –78 °C was added *n*-BuLi (1.82 M in hexanes, 0.310 mL, 0.560 mmol, 1.1 equiv). The resulting deep red solution was stirred for 45 min at –78 °C and allyl bromide (0.100 mL, 1.13 mmol, 2.2 equiv) was then added and the reaction allowed to slowly warm to room temperature over 2 h. The resulting dark orange reaction mixture was quenched with H_2O and the organic phase was extracted with Et_2O. The combined organic layers washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting yellow oil by column chromatography (20% EtOAc–petrol) gave **123** (0.116 g, 53%) as a colourless oil.

R_f 0.31 (30% EtOAc–petrol); ν_{max} (film) 2924, 2854, 1640 (C=C), 1598, 1464, 1358 (NSO_2), 1286, 1169, 1143 (SO_2), 939, 815 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.62 (4H, t, *J* 8.5 Hz, *ortho* $ArSO_2$), 7.33–7.26 (4H, m, *meta* $ArSO_2$), 7.03 (1H, d, *J* 8.5 Hz, NC*H*CH), 5.48–5.36 (1H, m, CH_2CH), 5.02 (2H, dd, *J* 9.0, 13.5 Hz, CH_2CH), 4.72 (1H, dd, *J* 1.0, 8.5 Hz, NCHC*H*), 3.56 (1H, dt, *J* 4.5, 12.0 Hz, 1 x NCH_2), 3.27 (1H, dt, *J* 3.5, 12.0 Hz 1 x NCH_2), 2.43 (3H, s, $ArCH_3$), 2.42 (3H, s, $ArCH_3$), 2.35 (2H, dd, *J* 9.0, 13.5 Hz, CH_2CHCH_2), 2.20–2.12 (1H, m, 1 x $CTsCH_2$), 1.83–1.73 (1H, m, 1 x $CTsCH_2$); δ_C ($CDCl_3$, 101 MHz) 145.0, 144.2 (*ipso* $ArSO_2$), 134.6, 132.6 (*para* $ArSO_2$), 131.2 (CH*C*HNTs), 130.5 (*ortho* $ArSO_2$), 129.9, 129.5 (*meta* $ArSO_2$), 127.0 (*ortho* $ArSO_2$), 120.2 (CH_2CH), 102.0 (*C*HCHNTs), 62.6 (CTs), 53.5 (CH_2CH), 40.2 (NCH_2), 39.0 ($CHCH_2$), 31.0 (CH_2CTs), 21.7, 21.6 ($ArCH_3$); *m/z* (CI) 449 $[M+NH_4]^+$, 293, 276, 174, 122 (Found $[M+Na]^+$, 454.1128. $C_{22}H_{25}NO_4S_2$ requires $[M+Na]^+$, 454.1123).

(±)-4-(2-Bromobenzyl-1,4-bis(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine 124

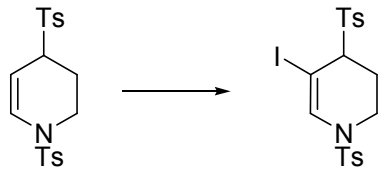


111 **124**

To a stirred solution of tetrahydropyridine **111** (0.500 g, 1.280 mmol, 1.0 equiv) in THF (8.7 mL) and TMEDA (3.6 mL) at –78 °C was added *n*-BuLi (2.33 M in hexanes, 0.610 mL, 1.410 mmol, 1.1 equiv). The resulting red–orange solution was stirred for 25 min at –78 °C, after which time 2-bromobenzyl bromide (0.352 g, 1.410 mmol, 1.1 equiv) in THF (2.0 mL) was added and the reaction was then allowed to slowly warm to room temperature over 1.5 h. The resulting deep red reaction mixture was quenched with H_2O and the aqueous phase was extracted with Et_2O. The combined organic layers washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting orange oil by column chromatography (5 → 15% EtOAc–petrol, 1% Et_3N) gave **124** (0.395 g, 55%) as a colourless solid.

R_f 0.45 (30% EtOAc–hexane); m.p. 74-76 °C; ν_{max} (film) 2926, 1640 (C=C), 1597, 1494, 1448, 1402, 1358 (NSO_2), 1288, 1169, 1142 (SO_2), 1089, 1031, 948, 815 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.72 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.41 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.38–7.34 (1H, m, H_{Ar}), 7.30 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 7.17 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 7.03–6.93 (4H, m, H_{Ar}, NC*H*CH), 4.98 (1H, d, *J* 8.5 Hz, NCHC*H*), 3.49 (1H, d, *J* 13.5 Hz, 1 x CH_2Ar), 3.43–3.34 (1H, m, 1 x NCH_2), 3.09 (1H, d, *J* 13.5 Hz, 1 x CH_2Ar), 2.89–2.82 (1H, m, 1 x NCH_2), 2.41 (3H, s, 1 x $ArCH_3$), 2.38 (3H, s, 1 x $ArCH_3$), 2.27 (1H, dt, *J* 6.0, 9.5, 1 x $CTsCH_2$), 1.79–1.70 (1H, m, 1 x $CTsCH_2$); δ_C ($CDCl_3$, 101 MHz) 145.2, 143.9 (*ipso* $ArSO_2$), 134.3, 134.2 (*para* $ArSO_2$), 133.0 (C_{Ar}), 132.5 (CH*C*HNTs), 131.7 (*ortho* $ArSO_2$), 130.6, 129.9 (*meta* $ArSO_2$), 129.6, 128.7 (C_{Ar}), 128.3 (*ipso* C_{Ar}), 127.1 (C_{Ar}), 126.8 (*ortho* $ArSO_2$), 126.0 (CBr), 101.4 (*C*HCHNTs), 64.9 (CTs), 40.0 (CH_2NTs), 39.0 (CH_2Ar), 25.2 (CH_2CTs), 21.7, 21.6 ($ArCH_3$); *m/z* (ESI) 625, 623, 584 $[M(^{81}Br)+Na]^+$, 582 $[M(^{79}Br)+Na]^+$, 407, 406 $[M(^{81}Br)-Ts]^+$, 404 $[M(^{79}Br)-Ts]^+$, 318 (Found: $[M+Na]^+$, 582.0367. $C_{26}H_{26}NO_4S_2Br$ requires $[M+Na]^+$, 582.0384) (Found C, 55.80; H, 4.56; N, 2.39. $C_{26}H_{26}NO_4S_2Br$ requires C, 55.71; H, 4.68; N, 2.50%).

5-iodo-1,4-bis(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine 97

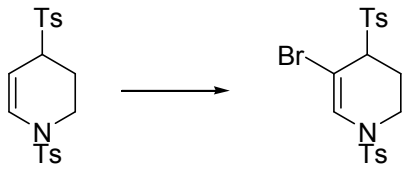


111 **97**

To a stirred solution of **111** (0.100 g, 0.260 mmol, 1.0 equiv) in CH_2Cl_2 (2.6 mL) was added NIS (0.062 g, 0.280 mmol, 1.1 equiv) and hydroxy(tosyloxy)iodobenzene (0.010 g, 0.026 mmol, 0.1 equiv). The resulting pink solution was heated under reflux for 20 h, after which time it was quenched with Et_3N (0.100 mL, 0.280 mmol, 1.1 equiv). The reaction mixture was then diluted with CH_2Cl_2, washed with sat. $Na_2S_2O_{3(aq)}$ and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting yellow oil by column chromatography (5 → 15% EtOAc–hexane) gave **97** (0.106 g, 79%) as a brown solid.

R_f 0.55 (30% EtOAc–hexane); m.p. 94-96 °C; ν_{max} (film) 2927, 1614 (C=C), 1597, 1494, 1456, 1365, 1324 (NSO_2), 1266, 1168 (NSO_2), 1094, 1018, 985, 957, 890, 815, 666 (C-I) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.70 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.65 (2H, t, *J* 7.0 Hz, *ortho* $ArSO_2$), 7.53 (1H, s, NC*H*CI), 7.34 (4H, dd, *J* 8.5, 10.5 Hz, *meta* $ArSO_2$), 3.84 (1H, dd, *J* 3.5, 12.5 Hz, CHTs), 3.78 (1H, d, *J* 5.5 Hz, 1 x NCH_2), 3.39 (1H, td, *J* 3.5, 13.0 Hz, 1 x NCH_2), 2.58 (1H, m, 1 x CHTsCH_2), 2.46 (3H, s, 1 x $ArCH_3$), 2.45 (3H, s, 1 x $ArCH_3$), 1.93 (1H, tt, *J* 5.0, 14.5 Hz, 1 x CHTsCH_2); δ_C ($CDCl_3$, 101 MHz) 145.5, 144.7 (*ipso* $ArSO_2$), 136.7 (CH*C*HNTs), 135.5, 134.1 (*para* $ArSO_2$), 130.1, 129.9 (*meta* $ArSO_2$), 129.5, 127.1 (*ortho* $ArSO_2$), 65.4 (CTs), 54.4 (C-I), 38.2 (NCH_2), 22.2 (*C*H_2CTs), 21.8, 21.7 ($ArCH_3$); *m/z* (CI) 535 $[M+NH_4]^+$, 409, 390, 362, 236, 174, 82 (Found: $[M+H]^+$, 517.9966. $C_{19}H_{20}NO_4S_2I$ requires $[M+H]^+$, 517.9957) (Found: C, 44.24; H, 4.01; N, 2.66. $C_{19}H_{20}NO_4S_2I$ requires C, 44.11; H, 3.90; N, 2.71%).

5-Bromo-1,4-bis(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine 130

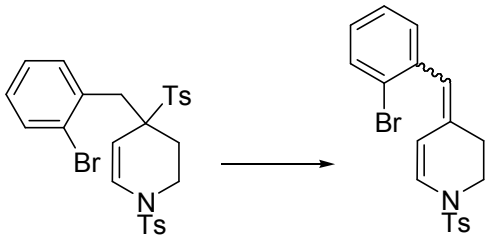


111 **130**

To a stirred solution of tetrahydropyridine **111** (0.050 g, 0.130 mmol, 1.0 equiv) in CH_2Cl_2 (0.7 mL), was added Br_2 (0.007 mL, 0.140 mmol, 1.1 equiv) at –78 ºC and the resulting orange solution allowed to warm to room temperature overnight. The reaction mixture was then diluted with CH_2Cl_2, washed with sat. $Na_2S_2O_{3(aq)}$ and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting orange oil was purified by column chromatography (5 → 15% EtOAc–petrol) to isolate **130** (0.033 g, 54%) as a yellow oil.

R_f 0.45 (30% EtOAc–petrol); ν_{max} (film) 2926, 1630 (C=C), 1596, 1363, 1321 (NSO_2), 1168 (NSO_2), 1095, 963, 814, 666 (C-Br) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.70 (4H, dd, *J* 8.0, 16.0 Hz, *ortho* $ArSO_2$), 7.38 (1H, s, NC*H*CBr), 7.37–7.31 (4H, m, *meta* $ArSO_2$), 3.84 (1H, d, *J* 5.0 Hz, NCH_2), 3.80–3.62 (1H, m, CHTs), 3.36 (1H, td, *J* 3.0, 13.5 Hz, 1 x NCH_2), 2.67 (1H, d, *J* 16.5 Hz, 1 x CHTsCH_2), 2.46 (3H, s, 1 x $ArCH_3$), 2.45 (3H, s, 1 x $ArCH_3$), 1.92 (1H, tt, *J* 5.0, 14.5 Hz, 1 x CHTsCH_2); δ_C ($CDCl_3$, 101 MHz) 145.4, 144.7 (*ipso* $ArSO_2$), 135.5, 134.0 (*para* $ArSO_2$), 131.5 (CH*C*HNTs), 130.1, 129.9 (*meta* $ArSO_2$), 129.3, 127.1 (*ortho* $ArSO_2$), 89.2 (CBr), 64.0 (CTs), 38.7 (NCH_2), 22.2 (CH_2CTs), 21.8, 21.7 ($ArCH_3$); *m/z* (CI) 489 $[M(^{81}Br)+NH_4]^+$, 487 $[M(^{79}Br)+NH_4]^+$, 472 $[M(^{81}Br)+H]^+$, 470 $[M(^{79}Br)+H]^+$, 327, 316 $[M(^{81}Br)+H\text{-}Ts]^+$, 314 $[M(^{79}Br)+H\text{-}Ts]^+$, 279, 255, 174, 162, 160, 139 (Found: $[M+H]^+$, 470.0089. $C_{19}H_{20}NO_4S_2Br$ requires $[M+H]^+$, 470.0095) (Found C, 48.58; H, 4.34; N, 2.88. $C_{19}H_{20}NO_4S_2Br$ requires C, 48.51; H, 4.29; N, 2.98%).

4-(2-Bromo-benzylidene)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine 131

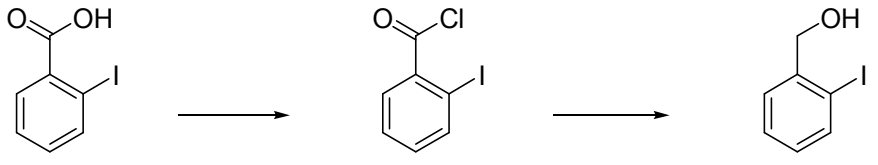


124 **131**

To a stirred suspension of (±)-4-(2-bromobenzyl-1,4-bis(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine **124** (0.050 g, 0.090 mmol, 1.0 equiv), $PdCl_2$ (0.002g, 0.009 mmol, 0.1 equiv) and AgOTf (0.012 g, 0.040 mmol, 0.5 equiv) in DMF (0.9 mL) in a sealed tube, was added Et_3N (0.012 mL, 0.090 mmol, 1.0 equiv) and the mixture was heated at 150 ºC for 16 h. The resulting black reaction mixture was filtered through a pad of silica, washing with EtOAc and the filtrate was then washed with H_2O and brine and dried ($MgSO_4$). Purification by column chromatography (5 → 10% EtOAc–petrol) isolated **131** (0.023 g, 64%, 5:4 mixture of cis:trans geometric isomers) as a yellow oil.

R_f 0.71 (30% EtOAc–petrol); ν_{max} (film) 2926, 1640 (C=C), 1598, 1464, 1355 (NSO_2), 1268, 1167 (SO_2), 1094, 1025, 947, 814 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.71 (2H, dd, *J* 3.0, 8.5 Hz, *ortho* $ArSO_2$), 7.58–7.55 (1H, m, H_{Ar}), 7.35 (2H, dd, *J* 3.5, 8.0 Hz, *meta* $ArSO_2$), 7.26 (1H, d, *J* 7.5 Hz, H_{Ar}), 7.15 (1H, dd, *J* 1.5, 7.5 Hz, H_{Ar}), 7.08 (1H, ddd, *J* 1.5, 4.0, 5.0 Hz, H_{Ar}), 6.83–6.80 (1H, m, NC*H*CH), [6.33 (1H, s, C*H*Ar), 6.09 (1H, s, C*H*Ar), mixture of geometric isomers], [5.77, (1H, d, *J* 8.5 Hz, NCHC*H*), 5.69 (1H, d, *J* 8.0 Hz, NCHC*H*), mixture of geometric isomers], 3.58–3.54 (1H, m, 1 x NCH_2), 3.40 (1H, dd, *J* 5.0, 7.5 Hz, 1 x NCH_2), 2.62–2.57 (2H, m, NCH_2CH_2), 2.45 (3H, s, $ArCH_3$); δ_C ($CDCl_3$, 101 MHz) 144.1 (*ipso* $ArSO_2$), 136.8 (*para* $ArSO_2$), 134.7 (*ipso* C_{Ar}), 134.6 (*C*CHAr), 132.7, 130.0 (C_{Ar}), 128.2 (*meta* $ArSO_2$), 127.8, 127.1 (C_{Ar}) 126.9 (CBr), 126.8 (N*C*HCH) 126.4 (*ortho* $ArSO_2$), 124.1, 123.2 (C*H*Ar), 112.3, 106.3 (*C*HCHNTs), 44.0, 43.5 (NCH_2), 30.3, 25.1 (NCH_2CH_2), 21.6 ($ArCH_3$); *m/z* (ESI) 406 $[M(^{81}Br)+H]^+$, 404 $[M(^{81}Br)+H]^+$, 338 (Found C, 56.55; H, 4.41; N, 3.41. $C_{19}H_{18}NO_2SBr$ requires C, 56.44; H, 4.49; N, 3.46%).

(2-Iodophenyl)methanol 134



(132) **133** **134**

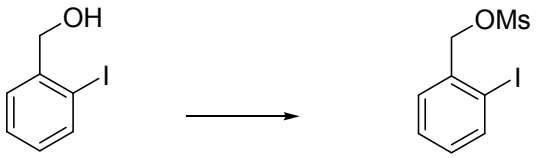
A stirred suspension of 2-iodobenzoic acid (**132**) (10.0 g, 40.3 mmol, 1.0 equiv) in $SOCl_2$ (20 mL) was heated under reflux for 45 min. The resulting yellow solution was allowed to cool to room temperature and then concentrated under reduced pressure to give 2-iodobenzoyl chloride **133** as a yellow oil, which was used crude in the next step.

To a stirred suspension of $NaBH_4$ (6.25 g, 165.0 mmol, 4.1 equiv) in THF (156 mL) at 0 °C, was added dropwise an ice-cold solution of **133** in THF (47 mL). After the effervescence had subsided, the reaction mixture was allowed to warm to room temperature and was then heated under reflux for 5 h. After cooling to room temperature, the reaction was quenched with H_2O and then stirred for 13 h. THF was removed under reduced pressure and the concentrate was diluted with H_2O and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers washed with H_2O, dried (Na_2SO_4) and concentrated under reduced pressure to isolate **134** (6.00 g, 64% over two steps) as a colourless solid, which was used crude in the next step.

R_f 0.77 (30% EtOAc–petrol); ν_{max} (film) 3216 (OH), 2361, 2340, 736 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.85 (1H, dd, *J* 1.0, 8.0 Hz, H_{Ar}), 7.48 (1H, dd, *J* 1.5, 7.5 Hz, H_{Ar}), 7.42–7.36 (1H, m, H_{Ar}), 7.02 (1H, td, *J* 1.5, 7.5 Hz, H_{Ar}), 4.70 (2H, s, CH_2), 2.07 (1H, br s, OH); δ_C ($CDCl_3$, 101 MHz) 142.6 (*ipso* C_{Ar}), 139.2, 129.3, 128.5 (C_{Ar}), 69.3 (CH_2); *m/z* (EI) 234 $[M]^+$, 105, 79, 77, 51 (Found: $[M]^+$, 233.9535. C_7H_7OI requires $[M]^+$, 233.9542).

This data is in agreement with the published data for the compound.[159]

2-Iodobenzyl methanesulfonate 135



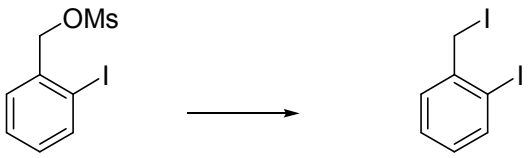
134 **135**

To a stirred solution of (2-iodophenyl)methanol **134** (6.00 g, 25.6 mmol, 1.0 equiv) and Et_3N (5.36 mL, 38.5 mmol, 1.5 equiv) in CH_2Cl_2 (128 mL) at 0 °C, was added dropwise methanesulfonyl chloride (2.23 mL, 28.2 mmol, 1.1 equiv) over a 10 min period. The pale yellow solution was then stirred at room temperature for 1 h. The resulting dark yellow solution was washed with aqueous HCl (2 M), sat. $NaHCO_{3(aq)}$ and brine, dried (Na_2SO_4) and concentrated under reduced pressure to isolate **135** (6.1 g, 76%) as a yellow oil, which was used crude in the next step.

R_f 0.40 (20% EtOAc–petrol); ν_{max} (film) 2361, 2340, 1355 (SO_2), 1175 (SO_2), 840, 750 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.89 (1H, d, *J* 8.0 Hz, H_{Ar}), 7.49 (1H, dd, *J* 1.5, 7.5 Hz, H_{Ar}), 7.43–7.38 (1H, m, H_{Ar}), 7.09 (1H, td, *J* 1.5, 7.5 Hz, H_{Ar}), 5.27 (2H, s, CH_2), 3.04 (3H, s, CH_3); δ_C ($CDCl_3$, 101 MHz) 139.8 (C_{Ar}), 136.0 (*ipso* (C_{Ar}), 131.0, 130.4, 128.8 (C_{Ar}), 98.7 (C-I), 75.0 (CH_2), 38.2 (CH_3); *m/z* (EI) 312 $[M]^+$, 217 $[M\text{-}OMs]^+$, 185 $[M\text{-}I]^+$, 107, 90, 78 (Found: $[M]^+$, 311.9319. $C_8H_9O_3SI$ requires $[M]^+$, 311.9317).

This data is in agreement with the published data for the compound.[100]

1-Iodo-2-(iodomethyl)benzene 136



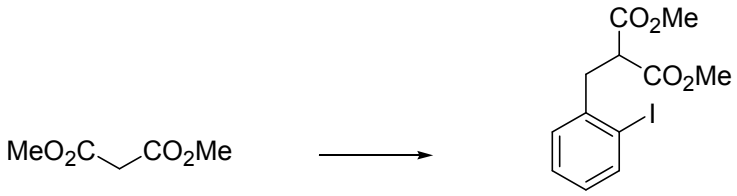
135 **136**

To a stirred solution of 2-iodobenzyl methanesulfonate **135** (6.0 g, 19.2 mmol, 1.0 equiv) in MeCN (95 mL) was added NaI (8.65 g, 57.7 mmol, 3.0 equiv) and the dark yellow suspension was stirred under reflux for 2 h. The resulting dark orange suspension was quenched with H_2O and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with H_2O, brine and sat. $Na_2S_2O_{3(aq)}$, dried (Na_2SO_4) and concentrated under reduced pressure to isolate **136** (7.37 g, quantitative) as a fluffy pale yellow solid, which was used crude in the next step.

R_f 0.92 (30% EtOAc–petrol); ν_{max} (film) 2361, 2339, 1576, 1559, 1466, 1437, 1265, 1212, 1159, 1013, 827, 757, 644 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.83 (1H, dd, *J* 1.0, 8.0 Hz, H_{Ar}), 7.50 (1H, dd, *J* 1.5, 7.5 Hz, H_{Ar}), 7.31 (1H, td, *J* 1.0, 7.5 Hz, H_{Ar}), 6.95 (1H, td, *J* 1.5, 7.5 Hz, H_{Ar}), 4.57 (2H, s, CH_2); δ_C ($CDCl_3$, 101 MHz) 141.4 (*ipso* C_{Ar}), 140.2, 129.8, 129.6, 129.0 (C_{Ar}), 99.8 (C-I), 12.3 (CH_2); *m/z* (EI) 344 $[M]^+$, 217 $[M\text{-}I]^+$, 90 $[M\text{-}2I]^+$, 63 (Found: $[M]^+$, 343.8558. $C_7H_6I_2$ requires $[M]^+$, 343.8559) (Found: C, 24.35; H, 1.74. $C_7H_6I_2$ requires C, 24.45; H, 1.76%).

This data is in agreement with the published data for the compound.[101]

Dimethyl 2-(2-iodobenzyl)malonate 144



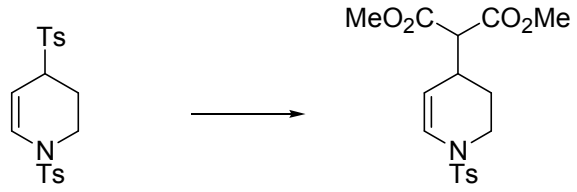
(143) **144**

To a stirred suspension of NaH (60% w/w in mineral oils, washed with hexane, 0.430 g, 18.1 mmol, 2.0 equiv) in THF (65 mL) at 0 °C, was added dimethylmalonate **(143)** (2.59 mL, 22.7 mmol, 2.5 equiv) and the colourless solution was stirred at room temperature for 30 min. A solution of 1-iodo-2-(iodomethyl)benzene **136** (3.12 g, 9.1 mmol, 1.0 equiv) in THF (65 mL) was then added via cannula and the resulting pale yellow solution stirred at room temperature for 16 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude oil was purified by column chromatography (5% EtOAc–petrol) to isolate **144** (2.73 g, 86%) as a pale yellow oil.

R_f 0.79 (30% EtOAc–petrol); ν_{max} (film) 2361, 2340, 1734 (C=O), 824, 754 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.83 (1H, d, *J* 8.0 Hz, H_{Ar}), 7.29–7.21 (2H, m, H_{Ar}), 6.96–6.89 (1H, m, H_{Ar}), 3.87 (1H, t, *J* 8.0 Hz, CH), 3.71 (6H, s, 2 x CH_3), 3.34 (2H, d, *J* 8.0 Hz); δ_C ($CDCl_3$, 101 MHz) 168.9 (C=O), 140.1 (*ipso* C_{Ar}), 139.7, 130.5, 128.8, 128.4 (C_{Ar}), 100.4 (C-I), 52.6, 52.5 (-CH(CO_2*Me*)$_2$) , 51.5 (-C*H*(CO_2Me)$_2$), 39.4 (CH_2); *m/z* (EI) 348 $[M]^+$, 317, 285, 257, 247, 221, 217, 161 (Found: $[M]^+$, 347.9861. $C_{12}H_{13}O_4I$ requires $[M]^+$, 347.9859) (Found: C, 44.55; H, 3.65. $C_{12}H_{13}O_4I$ requires C, 41.40; H, 3.76%).

This data is in agreement with the published data for the compound.[104]

4-(Dimethyl malonate)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine 139

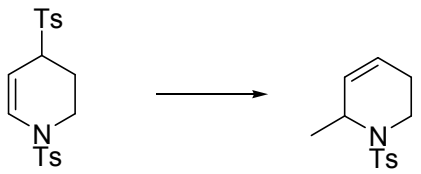


111 **139**

To a stirred solution of dimethyl malonate **(143)** (0.044 mL, 0.390 mmol, 1.5 equiv) and BSA (0.096 mL, 0.390 mmol, 1.5 equiv) in CH_2Cl_2 (0.65 mL) at –78 °C, was added $SnCl_4$ (1M in CH_2Cl_2, 0.390 mL, 0.390 mmol, 1.5 equiv) and the resulting pale yellow solution stirred at –78 °C for 30 min. Simultaneously, to a stirred solution of tetrahydropyridine **111** (0.100 g, 0.260 mmol, 1.0 equiv) in CH_2Cl_2 at –78 °C, was added $SnCl_4$ (1.0 M in CH_2Cl_2, 0.390 mL, 0.390 mmol, 1.5 equiv) and the resulting orange solution stirred at this temperature for 30 min. After this time, the tetrahydropyridine solution was added to the malonate solution via cannula at –78 °C and the reaction mixture allowed to warm to room temperature over 17 h. The resulting dark orange solution was quenched with sat. $NaHCO_{3(aq)}$ and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude orange residue by column chromatography (5 → 10% EtOAc–petrol) isolated **139** (9.1 mg, 10%) as a colourless oil.

R_f 0.50 (30% EtOAc–petrol); ν_{max} (film) 2361, 2340, 1734 (C=O), 1636 (C=C), 1436, 1340 (NSO_2), 1266, 1165 (SO_2) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.66 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.33 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 6.71 (1H, d, *J* 8.5 Hz, NC*H*CH), 4.85 (1H, dd, *J* 2.5, 8.5 Hz, NCHC*H*), 3.73 (3H, s, CO_2Me), 3.71 (3H, s, CO_2Me), 3.57–3.51 (1H, m, 1 x NCH_2), 3.22 (1H, t, *J* 9.5 Hz, 1 x NCH_2), 3.16 (1H, d, *J* 9.5 Hz, CHC*H*$(CO_2Me)_2$), 2.88–2.86 (1H, m, C*H*CH$(CO_2Me)_2$), 2.45 (3H, s, $ArCH_3$), 1.90–1.80 (1H, m, 1 x CH_2), 1.55–1.46 (1H, m, 1 x CH_2); δ_C ($CDCl_3$, 101 MHz) 168.1 (C=O), 143.9 (*ipso* $ArSO_2$), 134.7 (*para* $ArSO_2$), 129.8 (*meta* $ArSO_2$), 127.1 (*ortho* $ArSO_2$), 126.5 (CHNTs), 107.7 (*C*HCHNTs), 56.2 (-*C*H$(CO_2Me)_2$), 52.6 (-CH$(CO_2Me)_2$), 42.0 (NCH_2), 31.5 (*C*HCH$(CO_2Me)_2$), 25.0 (CH_2), 21.6 ($ArCH_3$); *m/z* (ESI) 775, 554, 390, 370, 368 $[M+H]^+$, 236 (Found: $[M+H]^+$, 368.1156. $C_{17}H_{21}NO_6S$ requires $[M+H]^+$, 368.1168).

6-Methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine 149

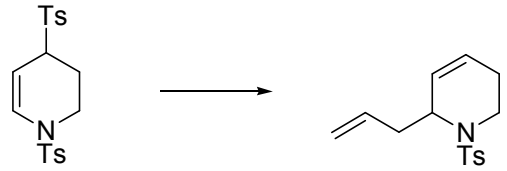


111 **149**

To a stirred suspension of tetrahydropyridine **111** (0.050 g, 0.130 mmol, 1.0 equiv) in toluene (1.7 mL) was added Me_3Al (0.130 mL, 0.260 mmol, 2.0 equiv). The resulting pale orange solution was stirred at room temperature for 1 h. The reaction mixture was then quenched with sat. $NaHCO_{3(aq)}$ and the aqueous phase extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude oil by column chromatography (20% Et_2O–petrol) isolated **149** (0.024 g, 73%) as a colourless residue.

R_f 0.29 (20% Et_2O–petrol); ν_{max} (film) 2928, 1648 (C=C), 1598, 1458, 1342, 1329 (NSO_2), 1213, 1160 (SO_2), 1105 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.72 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.27 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 5.65–5.58 (2H, m, C*H*C*H*), 4.43 (1H, br s, NC*H*CH_3), 3.86–3.81 (1 H, m, 1 x NCH_2), 3.14 (1 H, ddd, *J* 4.0, 12.0, 16.0 Hz, 1 x NCH_2), 2.42 (3H, s, $ArCH_3$), 1.94–1.79 (2H, m, CH_2CHCH), 1.28 (3 H, d, *J* 8.0, NCHCH_3); δ_C ($CDCl_3$, 101 MHz) 142.9 (*ipso* $ArSO_2$), 138.5 (*para* $ArSO_2$), 129.6 (*meta* $ArSO_2$), 129.5 (*C*HCH), 126.9 (*ortho* $ArSO_2$), 124.4 (CH*C*H), 49.5 (N*C*HCH_3, 37.8 (NCH_2), 23.7 (CH_2), 21.5 ($ArCH_3$), 20.4 (CH*C*H_3); *m/z* (ESI) 342, 318, 315, 252 $[M+H]^+$, 184, 153, 132 (Found $[M+H]^+$, 252.1059. $C_{13}H_{17}NO_2S$ requires $[M+H]^+$, 252.1058) (Found C, 62.14; H, 6.93; N, 5.45. $C_{13}H_{17}NO_2S$ requires C, 62.12; H, 6.82; N, 5.57%).

6-Allyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine 150

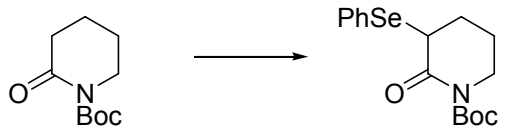


111 **150**

To a stirred solution of tetrahydropyridine **111** (0.050 g, 0.130 mmol, 1.0 equiv) and allyl trimethylsilane (0.046 mL, 0.290 mmol, 2.2 equiv) in CH_2Cl_2 (2.4 mL) at –78 °C was added $SnCl_4$ (1.0 M, 0.290 mL, 0.290 mmol, 2.2 equiv). The resulting yellow solution was stirred at –78 °C for 20 min and then warmed to room temperature for 1 h. The reaction mixture was then quenched with sat. $NaHCO_{3(aq)}$ and the aqueous phase extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude oil by column chromatography (20% Et_2O–petrol) isolated **150** (0.013 g, 36%) as a colourless residue.

R_f 0.33 (20% Et_2O–petrol); ν_{max} (film) 2924, 1643 (C=C), 1598, 1453, 1344, 1330 (NSO_2), 1212, 1159 (SO_2), 1095 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.72 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.27 (2H, d, *J* 8.0 Hz, *meta* $ArSO_2$), 5.86–5.69 (1H, m, C*H*CH_2), 5.67–5.64 (2H, m, C*H*C*H*), 5.12–5.08 (2H, m, CHCH_2), 4.38 (1H, br s, C*H*CH_2CHCH_2), 3.85 (1 H, dd, *J* 4.0, 16.0 Hz, 1 x NCH_2), 3.16 (1 H, ddd, *J* 4.0, 12.0, 16.0 Hz, 1 x NCH_2), 2.43 (3H, s, $ArCH_3$), 2.42–2.37 (2H, m, CHCH_2CHCH_2), 1.84–1.78 (2H, m, CH_2CHCH); δ_C ($CDCl_3$, 101 MHz) 143.0 (*ipso* $ArSO_2$), 138.6 (*para* $ArSO_2$), 134.3 (*C*HCH_2), 129.5 (*meta* $ArSO_2$), 127.4 (*C*HCH), 127.0 (*ortho* $ArSO_2$), 125.3 (CH*C*H), 117.7 (CH*C*H_2), 53.3 (N*C*HCH_2CHCH_2), 39.9 (*C*H_2CHCH_2), 38.5 (NCH_2), 23.1 (CH_2), 21.5 ($ArCH_3$); *m/z* (ESI) 341, 338, 282, 278 $[M+H]^+$, 236, 184, 132 (Found $[M+H]^+$, 278.1210. $C_{15}H_{19}NO_2S$ requires $[M+H]^+$, 278.1215) (Found C, 65.05; H, 6.84; N, 4.96. $C_{15}H_{19}NO_2S$ requires C, 64.95; H, 6.90; N, 5.05%).

2-Oxo-3-phenylselanyl-piperidine-1-carboxylic acid *tert*-butyl ester 163

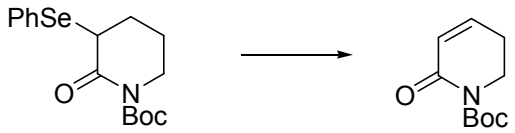


162 **163**

To a stirred solution of di*iso*propylamine (3.55 mL, 25.1 mmol, 1.0 equiv) in THF (40 mL) at –78 °C was added *n*-BuLi (2.30 M in hexanes, 10.9 mL, 25.1 mmol, 1.0 equiv). The pale yellow solution was stirred at –78 °C for 30 min, after which time a solution of tert-butyl 2-oxopiperidine-1-carboxylate **162** (5.00 g, 25.1 mmol. 1.0 equiv) in THF (40 mL) was added. The resulting bright yellow solution was stirred at –78 °C for 30 min and was then added to a solution of phenylselenyl chloride (7.22 g, 37.7 mmol, 1.5 equiv) in THF (40 mL). The dark yellow solution was stirred at –78 °C for 45 mins was then allowed to warm to room temp over 1.5 h. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure to isolate an orange oil. Purification by column chromatography (0 → 20% EtOAc–hexane) isolated **163** (7.70 g, 87%) as a pale orange oil.

R_f 0.42 (20% EtOAc–hexane); ν_{max} (film) 2978, 1766 (C=O), 1714 (C=O), 1578, 1477, 1393, 1368, 1296, 1250, 1147 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.69–7.67 (2H, m, H_{Ar}), 7.35–7.29 (3H, m, H_{Ar}), 4.01–3.98 (1H, m, CHSePh), 3.72–3.68 (1H, m, 1 x NCH_2) 3.65–3.62 (1H, m, 1 x NCH_2), 2.28–2.19 (1H, m, 1 x CHSePhCH_2), 2.09–1.98 (2H, m, 1 x CHSePhCH_2 and 1 x NCH_2CH_2), 1.82–1.73 (1H, m, 1 x NCH_2CH_2), 1.55 (9H, s, -$OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 170.1, 150.3 ($C{=}O_{Boc}$), 135.8, 130.2, 129.1, 128.6, 128.5 (C_{Ar}), 83.0 (-O$C(CH_3)_3$), 46.1 (NCH_2), 45.0 (CHSe), 28.7 (CHSePhCH_2), 28.0 (-OC(CH_3)$_3$), 21.2 (NCH_2CH_2); *m/z* (ESI) 378 $[M+Na]^+$, 319, 300 $[M+H-C_4H_8]^+$, 256 $[M+H-C_4H_8OCO]^+$ (Found $[M+Na]^+$, 378.0596. $C_{16}H_{21}NO_3{}^{80}Se$ requires $[M+Na]^+$, 378.0584) (Found C, 54.30; H, 6.02; N, 3.89. $C_{16}H_{21}NO_3{}^{80}Se$ requires C, 54.24; H, 5.97; N, 3.95%).

6-Oxo-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester 161

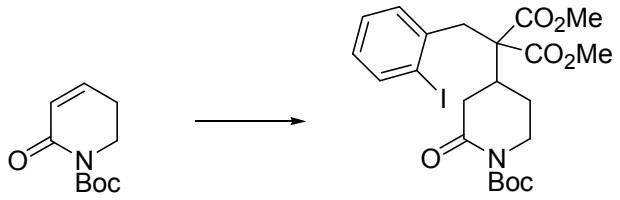


163 **161**

To a stirred solution of *tert*-butyl 2-oxo-3-(phenylselanyl)piperidine-1-carboxylate **163** (7.49 g, 21.1 mmol, 1.0 equiv) in MeOH (257 mL) and H_2O (43 mL) was added sodium periodate (10.40 g, 48.6 mmol, 2.3 equiv) and $NaHCO_3$ (2.13 g, 25.4 mmol, 1.2 equiv). The yellow solution was stirred at room temperature and after a few minutes extensive precipitation was observed. The reaction was left to stir overnight at room temp. The resulting pale yellow suspension was then diluted with sat. $NaHCO_{3(aq)}$ and the aqueous phase extracted with EtOAc. The combined organic layers were washed with H_2O, dried (Na_2SO_4) and concentrated under reduced pressure to isolate a yellow oil. Purification by column chromatography (0 → 20% EtOAc–hexane) using a combi flash companion isolated **161** (3.11 g, 75%) as a pale yellow oil.

R_f 0.23 (20% EtOAc–hexane); ν_{max} (film) 2982, 1766 (C=O), 1703 (C=O), 1476, 1392, 1369, 1314, 1232, 1161 (C-O), 1134, 822 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 6.79 (1H, dt, *J* 4.0, 9.5 Hz, CHCO), 5.97 (1H, dt, *J* 2.0, 10.0 Hz, C*H*CH), 3.87 (2H, t, *J* 6.5 Hz, NCH_2), 2.42 (2H, tdd, *J* 2.0, 4.0, 6.5 Hz, CH_2), 1.55 (9H, s, $-OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 163.7 ($C=O_{lactam}$), 152.7 ($C=O_{Boc}$), 143.4 (*C*HC=O), 126.4 (CH*C*H), 82.9 ($-OC(CH_3)_3$), 43.6 (NCH_2), 28.0 ($-OC(CH_3)$), 24.6 (CH_2); *m/z* (ESI) 418, 417 $[2xM+Na]^+$, 261 (Found $[2xM+Na]^+$, 417.1993. $C_{10}H_{15}NO_3$ requires $[2xM+Na]^+$, 417.2002) (Found C, 60.82; H, 7.73; N, 7.01. $C_{10}H_{15}NO_3$ requires C, 60.90; H, 7.67; N, 7.10%).

Dimethyl 2-(1-(*tert*-butoxycarbonyl)-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)-2-(2-iodobenzyl)malonate 170

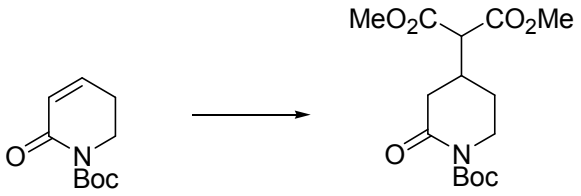


161 **170**

To a stirred suspension of NaH (60% w/w in mineral oils, washed with hexane, 4.88 mg, 0.120 mmol, 0.1 equiv) in THF (2 mL) at 0 °C, was added a solution of dimethyl 2-(2-iodobenzyl)malonate **144** (0.425 g, 1.22 mmol, 1.0 equiv) in THF (1 mL). The pale yellow solution was then stirred at 0 °C for 10 min, after which time a solution of *tert*-butyl 2-oxo-5,6-dihydropyridine-1(2H)-carboxylate **161** (0.2406 g, 1.22 mmol, 1.0 equiv) in THF (1.2 mL) was added. Effervescence was observed upon addition of the lactam and the resulting orange solution was stirred at room temp overnight. The dark brown reaction mixture was quenched with two drops of glacial acetic acid, diluted with Et_2O and washed with H_2O. The aqueous phase was then extracted with Et_2O and the combined organic layers washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (0 → 40% EtOAc–hexane) isolated **170** (0.417 g, 63%) as a pale yellow oil.

R_f 0.55 (30% EtOAc–hexane); ν_{max} (film) 2953, 1714 (C=O), 1504, 1434, 1368, 1156 (C-O), 1012 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.85 (1H, d, *J* 8.0 Hz, H_{Ar}), 7.29–7.27 (2H, m, H_{Ar}), 6.96–6.91 (1H, m, H_{Ar}), 3.90–3.85 (1H, m, 1 x NCH_2), 3.69 (6H, s, CO_2Me), 3.60–3.55 (1H, m, 1 x NCH_2), 3.53 (2H, s, CH_2Ar), 2.78–2.70 (2H, m, $CH_2C{=}O$), 2.65–2.61 (1H, m, $CH(CO_2Me)_2$), 2.24–2.19 (1H, m, 1 x CH_2), 1.71–1.59 (1H, m, 1 x CH_2), 1.55 (9H, s, $-OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 170.3, 170.2, (C=O), 152.4 ($C{=}O_{Boc}$), 143.9 (*ipso* C_{Ar}), 140.2, 139.8, 130.4, 129.1, 128.6 (C_{Ar}), 103.2 (C-I), 83.4 ($-OC(CH_3)_3$), 62.1 ($-C(CO_2Me)_2$), 53.0 ($-C(CO_2Me)_2$) 45.3 (NCH_2), 42.8 (CH_2Ar), 37.6 ($CH_2C{=}O$), 37.3 ($CHC(CO_2Me)_2$), 28.4 ($-OC(CH_3)_3$), 26.2 (CH_2); *m/z* (ESI) 568 $[M+Na]^+$, 468 $[M+Na-C_4H_8OCO]^+$, 446 $[M+H-C_4H_8OCO]^+$, 352 (Found $[M+Na]^+$, 568.0828. $C_{22}H_{28}NO_7I$ requires $[M+Na]^+$, 568.0808) (Found C, 48.54; H, 5.08; N, 2.63. $C_{22}H_{28}NO_7I$ requires C, 48.45; H, 5.17; N, 2.57%).

2-(1-*tert*-Butoxycarbonyl-2-oxo-piperidin-4-yl)-malonic acid dimethyl ester 169

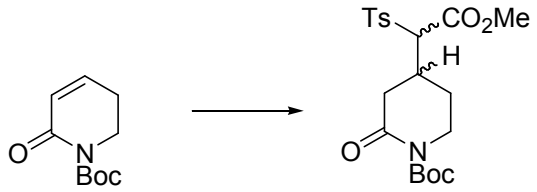


161 **169**

To a stirred suspension of NaH (60% w/w in mineral oils, washed with hexane, 0.039 g, 0.975 mmol, 0.1 equiv) in THF (20 mL) at 0 °C, was added dimethyl malonate (1.10 mL, 9.75 mmol, 1.0 equiv). The colourless solution was allowed to warm to room temperature and stirred for 10 min, after which time a solution of 6-oxo-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester **161** (1.90 g, 9.75 mmol, 1.0 equiv) in THF (30 mL) was added. The resulting pale orange solution was stirred at room temp for 18 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with Et_2O. The combined organic layers washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (10 → 40% EtOAc–petrol) isolated **169** (2.81 g, 87% as a mixture of rotamers) as a colourless solid.

R_f 0.22 (40% EtOAc–petrol); m.p. 72-72 ºC; ν_{max} (film) 2931, 1735, 1700 (C=O), 1598, 1436, 1369, 1329, 1267, 1159, 1105 (C-O), 1027 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 3.85 (1H, dt, *J* 4.5, 13.0 Hz, 1 x NCH_2), 3.77 (3H, s, CO_2Me), 3.76 (3H, s, CO_2Me), 3.59–3.53 (1H, m, 1 x NCH_2), 3.34 (1H, d, *J* 8.0 Hz, $CH(CO_2Me)_2$), 2.73–2.59 (2H, m, C*H*$CH(CO_2Me)_2$ and 1 x CH_2C=O), 2.43–2.34 (1H, m, 1 x CH_2C=O), 2.11–2.02 (1H, m, 1 x NCH_2CH_2), 1.67–1.57 (1H, m, 1 x NCH_2CH_2), 1.53 (9H, s, -$OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 169.3, 168.0 (C=O), 152.3 (C=O_{Boc}), 83.2 (-O*C*$(CH_3)_3$), 55.8 (-*C*$H(CO_2Me)_2$), 52.8, 52.7 (-$CH(CO_2Me)_2$), 45.0 (NCH_2), 38.6 (CH_2C=O), 32.4 ($CHCH(CO_2Me)_2$), 28.0 (-$OC(CH_3)_3$), 26.8 (NCH_2CH_2); *m/z* (ESI) 681, 393, 352 $[M+Na]^+$, 252 $[M+Na\text{-}C_4H_8OCO]^+$, 230 (Found $[M+Na]^+$, 352.1382. $C_{15}H_{23}NO_7$ requires $[M+Na]^+$, 352.1372) (Found C, 54.80; H, 7.15; N, 4.18. $C_{15}H_{23}NO_7$ requires C, 54.70; H, 7.09; N, 4.25%).

***tert*-Butyl 4-(2-methoxy-2-oxo-1-tosylethyl)-2-oxopiperidine-1-carboxylate 172**

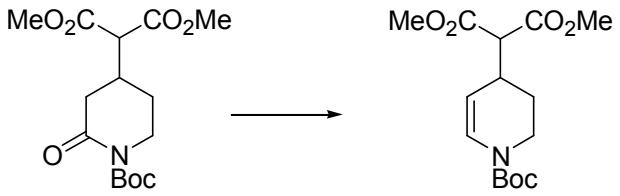


161 **172**

To a stirred suspension of NaH (60% w/w in mineral oils, washed with hexane, 0.020 g, 0.510 mmol, 1.0 equiv) in THF (2 mL) at 0 °C, was added a solution of methyl-*p*-toluenesulfonyl acetate (0.116 g, 0.510 mmol, 1.0 equiv) in THF (2 mL). The cloudy solution was then stirred at 0 °C for 45 min, after which time a solution of *tert*-butyl 2-oxo-5,6-dihydropyridine-1(2H)-carboxylate **161** (0.100 g, 0.510 mmol, 1.0 equiv) in THF (0.6 mL) was added. The resulting cloudy yellow suspension was stirred at room temp overnight. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with Et_2O. The combined organic layers washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (50% EtOAc–petrol) isolated **172** (0.130 g, 60% as a 1:1 mixture of diastereomers) as a colourless gum.

R_f 0.46 (50% EtOAc–petrol); ν_{max} (film) 2955, 1739, 1715 (C=O), 1651, 1597, 1496, 1323 (SO_2), 1146 (C-O), 1084 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.75 (4 H, dd, *J* 6.0, 8.0 Hz, *ortho* $ArSO_2$), 7.37 (4 H, d, *J* 8.5 Hz, *meta* $ArSO_2$), 3.92–3.88 (1 H, m, CHTs), 3.87–3.77 (1 H, m, 1 x NCH_2), 3.60 and 3.53 (3 H, s, CO_2Me), 3.54−3.45 (1 H, m, 1 x NCH_2), 2.97–2.91 (1 H, m, 1 x CH_2C=O), 2.80–2.68 (1 H, m, C*H*CHTs), 2.63–2.59 (1 H, m, 1 x CH_2C=O), 2.58–2.47 (3 H, m, 2 x CH_2C=O and 1 x CH_2CH), 2.46 (3 H, s, $ArCH_3$), 2.38–2.31 (1 H, m, 1 x CH_2C=O), 2.07–1.99 (1 H, m, 1 x CH_2CH), 1.88–1.67 (2 H, m, 1 x CH_2CH), 1.51 (18 H, 2 x s, -OC$(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 168.4, 168.3, 165.5, 165.4 ($C{=}O_{Esters}$), 152.1, 152.0 ($C{=}O_{Boc}$), 145.9 (*ipso* $ArSO_2$), 134.7, 134.5 (*para* $ArSO_2$), 129.9 (*meta* $ArSO_2$), 129.2, 129.1 (*ortho* $ArSO_2$), 83.5, 83.4 (-O*C*$(CH_3)_3$), 74.2, 73.9 (CHTs), 53.0 (-$CHCO_2$*Me*), 44.8, 44.7 (NCH_2), 39.1, 38.2 (*C*H_2C=O), 31.8, 31.6 (*C*HCHTs), 28.0 (-OC(*C*$H_3)_3$), 27.1, 26.3 (CH_2), 21.8 ($ArCH_3$); *m/z* (ESI) 448 $[M+Na]^+$, 370, 348 $[M+Na\text{-}C_4H_8OCO]^+$, 326 $[M+H\text{-}C_4H_8OCO]^+$ (Found $[M+Na]^+$, 448.1438. $C_{20}H_{27}NO_7S$ requires $[M+Na]^+$, 448.1406) (Found C, 56.48; H, 6.30; N, 3.36. $C_{20}H_{27}NO_7S$ requires C, 56.46; H, 6.40; N, 3.29%).

2-(1-*tert*-Butoxycarbonyl-1,2,3,4-tetrahydro-pyridin-4-yl)-malonic acid dimethyl ester 176



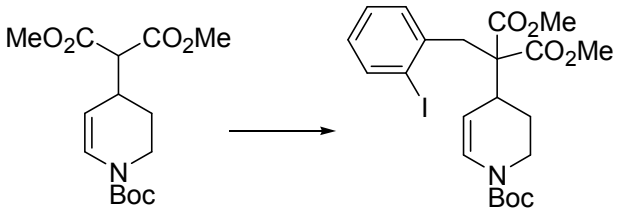
169 **176**

To a stirred solution of lactam **169** (2.29 g, 7.00 mmol, 1.0 equiv) in THF (70 mL) at –78 °C, was added DIBAL-H (1.0 M in hexane, 7.0 mL, 7.00 mmol, 1.0 equiv). The pale yellow solution was stirred at –78 °C for 2 h, after which time it was allowed to warm to room temperature and quenched with Rochelle's salt (70 mL). The biphasic mixture was then diluted with Et_2O (70 mL) and stirred at room temperature for 16 h. The aqueous phase was extracted with Et_2O and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure.

To a solution of the resulting colourless residue in CH_2Cl_2 (70 mL), was then added $HCl_{(aq)}$ (1.0 M, 56 mL, 56.0 mmol, 8.0 equiv) and the resulting biphasic mixture was vigorously stirred for 2 h. The reaction was then quenched with sat. $NaHCO_{3(aq)}$ and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (20 → 40% EtOAc–hexane) isolated **176** (2.01 g, 92% as a mixture of rotamers) as a colourless oil.

R_f 0.38 (30% EtOAc–petrol); ν_{max} (film) 2956, 1734, 1700 (C=O), 1650 (C=C), 1369, 1245, 1158 (C-O), 1124, 1003 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 6.94–6.79 (1H, m, CHNBoc), 4.79–4.67 (1H, m, C*H*CHNBoc), 3.78 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me), 3.74–3.61 (1H, m, 1 x NCH_2), 3.51–3.45 (1H, m, 1 x NCH_2), 3.31 (1H, d, *J* 9.5 Hz, $CH(CO_2Me)_2$), 3.04–2.97 (1H, m, C*H*$CH(CO_2Me)_2$), 2.03–1.90 (1H, m, 1 x NCH_2CH_2), 1.70–1.62 (1H, m, 1 x NCH_2CH_2), 1.51 (9H, s, $-OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 168.3 ($C=O_{Esters}$), 151.8 ($C=O_{Boc}$), 126.8, 126.5 (NCH), 105.0, 104.5 (NCH*C*H), 80.8, 80.7 ($-OC(CH_3)_3$) 56.3 ($CH(CO_2Me)_2$), 52.4 ($-CH(CO_2Me)_2$), 40.4, 39.4 (NCH_2), 32.0, 31.8 ($CHCH(CO_2Me)_2$), 28.1 ($-OC(CH_3)_3$), 25.4 (CH_2); *m/z* (ESI) 336, 314 $[M+H]^+$, 258, 214 $[M+H-C_4H_8OCO]^+$ (Found $[M+H]^+$, 314.1600 $C_{15}H_{23}NO_6$ requires $[M+H]^+$, 314.1604) (Found C, 57.65; H, 7.34; N, 4.35. $C_{15}H_{23}NO_7$ requires C, 57.50; H, 7.40; N, 4.47%).

2-(2-Iodo-benzyl)-2-(1-*tert*-butoxycarbonyl -1,2,3,4-tetrahydro-pyridin-4-yl)-malonic acid dimethyl ester 175

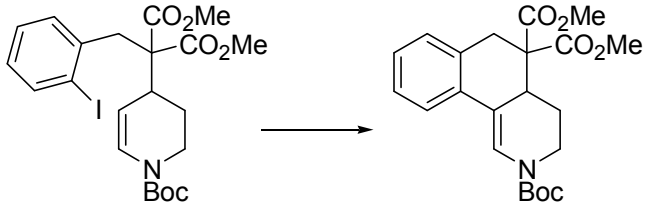


176 **175**

To a stirred suspension of NaH (60% w/w in mineral oils, washed with hexane, 0.013 g, 0.320 mmol, 1.0 equiv) in DMF (0.6 mL) at 0 °C, was added a pre-stirred solution of 2-(1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-pyridin-4-yl)-malonic acid dimethyl ester **176** (0.100 g, 0.320 mmol, 1.0 equiv) and 2-iodobenzyl iodide (0.110 g, 0.320 mmol, 1.0 equiv) in DMF (1.0 mL). The resulting yellow solution was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure to isolate **175** (0.148 g, 87% as a mixture of rotamers) as a colourless solid, which was used crude in the next step.

R_f 0.38 (30% EtOAc–petrol); m.p. 114-116 ºC; ν_{max} (film) 1730, 1700 (C=O), 1648 (C=C), 1364, 1245, 1166, 1119 (C-O), 746 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.77 (1H, dd, *J* 8.0, 1.0 Hz, H_{Ar}), 7.31 (1H, dd, *J* 8.0, 1.5 Hz, H_{Ar}), 7.18 (1H, td, *J* 7.5, 1.0 Hz H_{Ar}), 6.82 (1H, td, *J* 7.5, 1.5 Hz H_{Ar}), 6.81–6.79 (1H, m, CHNBoc), 5.05–4.93 (1H, m, C*H*CHNBoc), 4.07–3.93 (1H, m, 1 x NCH_2), 3.60 (3H, s, CO_2Me), 3.56 (3H, s, CO_2Me), 3.49 (2H, s, CH_2Ar), 3.17 (1H, td, *J* 12.5, 2.5 Hz, 1 x NCH_2), 3.11–3.06 (1H, m, C*H*C(CO_2Me)$_2$), 1.96–1.91 (1H, m, 1 x NCH_2CH_2), 1.82–1.72 (1H, m, 1 x NCH_2CH_2), 1.45 (9H, s, -OC(CH_3)$_3$); δ_C ($CDCl_3$, 101 MHz) 170.4, 170.3 ($C{=}O_{Esters}$), 152.1 ($C{=}O_{Boc}$), 140.2, 139.6, 130.5, 128.4, 128.0, (C_{Ar}), 126.8, 126.5 (CHNBoc), 105.4, 104.8 (*C*HCHNBoc), 102.8 (C-I), 80.9 (-O*C*(CH_3)$_3$), 61.7 (-*C*(CO_2Me)$_2$), 52.5, 52.4 (-C(CO_2*Me*)$_2$), 42.1 (CH_2Ar), 41.5, 41.1 (NCH_2), 37.9, 37.6 (*C*HC(CO_2Me)$_2$), 28.3 (-OC(*C*H_3)$_3$), 24.1, 22.7 (NCH_2*C*H_2); *m/z* (ESI) 552 $[M+Na]^+$, 530 $[M+H]^+$, 474 $[M-C_4H_8]^+$, 430 $[M-C_4H_8OCO]^+$ (Found $[M+H]^+$, 530.1037. $C_{22}H_{28}NO_6I$ requires $[M+H]^+$, 530.1040) (Found C, 50.02; H, 5.21; N, 2.56. $C_{22}H_{28}NO_6I$ requires C, 49.92; H, 5.33; N, 2.65%).

4,4a-Dihydro-3H,6H-benzo[h]isoquinoline-2,5,5-tricarboxylic acid 2-*tert*-butyl ester 5,5-dimethyl ester 176

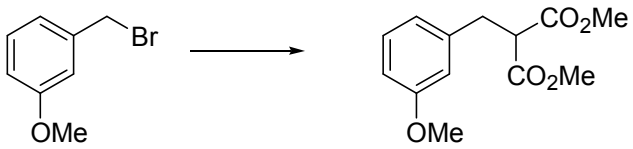


175 **176**

A suspension of 2-(1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-pyridin-4-yl)-2-(2-iodo-benzyl)-malonic acid dimethyl ester **175** (0.100 g, 0.190 mmol, 1.0 equiv), palladium(II) acetate (0.004 g, 0.019 mmol, 0.1 equiv), triphenylphosphine (0.050 g, 0.190 mmol, 1.0 equiv) and potassium acetate (0.037 g, 0.380 mmol, 2.0 equiv) in DMA (1.5 mL) was subjected to microwave irradiation at 140 °C for 10 min. Upon cooling to room temp, the resulting green suspension was diluted with brine and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (10% EtOAc–petrol) isolated **176** (0.0622 g, 82%) as a pale orange solid.

R_f 0.43 (20% EtOAc–petrol); m.p. 108-110 ºC; ν_{max} (film) 2956, 1734, 1705 (C=O), 1640 (C=C), 1435, 1389, 1237, 1164 (C-O), 1066 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.72–7.45 (2H, m, H_{Ar}), 7.16–7.02 (3H, m, H_{Ar} and CHNBoc), 4.26–4.10 (1H, m, 1 x NCH_2), 3.76 (3H, s, CO_2Me), 3.56 (3H, s, CO_2Me), 3.38–3.14 (3H, m, CH_2Ar and 1 x NCH_2), 3.08 (1H, ddd, *J* 11.5, 5.0, 2.5 Hz, C*H*C($CO_2Me)_2$), 2.42–2.33 (1H, m, 1 x CH_2), 2.00–1.97 (1H, m, 1 x CH_2), 1.57 (9H, s, -OC($CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 171.9, 169.7 ($C=O_{Esters}$), 152.2 ($C=O_{Boc}$), 133.1 (*ipso* C_{Ar}), 131.8, 129.0, 126.9, 125.9, 121.9, 121.1, 112.8 (5 x C_{Ar}, *C*CHNBoc and CHNBoc), 81.4, 81.2 (-O*C*($CH_3)_3$), 56.9 (-*C*($CO_2Me)_2$), 52.8, 52.2 (-C(CO_2*Me*$)_2$), 42.5, 41.5 (NCH_2), 39.2, 39.0 (*C*HC(CO_2*Me*$)_2$), 38.1 (CH_2Ar), 28.3 (-OC(*C*$H_3)_3$), 24.1, 23.9 (CH_2); *m/z* (ES) 424 $[M+Na]^+$, 419 $[M+NH_4]^+$, 402 $[M+H]^+$, 346 $[M+H-C_4H_8]^+$, 302 $[M+H-C_4H_8OCO]^+$. (Found $[M+H]^+$, 402.1914 $C_{22}H_{27}NO_6$ requires $[M+H]^+$, 402.19) (Found C, 65.74; H, 6.67; N, 3.34. $C_{22}H_{27}NO_6$ requires C, 65.82; H, 6.78; N, 3.49%).

2-(3-Methoxy-benzyl)-malonic acid dimethyl ester 183

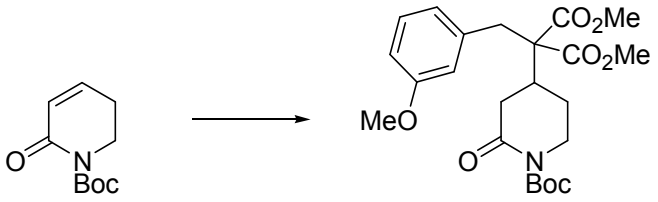


182 **183**

To a stirred suspension of NaH (60% w/w in mineral oils, washed with hexane, 0.686 g, 28.6 mmol, 2.0 equiv), in THF (100 mL) at 0 °C, was added dimethyl malonate (4.10 mL, 35.7 mmol, 2.5 equiv) and the colourless solution was stirred at room temperature for 30 min. 1-(bromomethyl)-3-methoxybenzene **182** (2.00 mL, 14.3 mmol, 1.0 equiv) was then added and the resulting colourless solution stirred at room temperature for 3 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Kugelrohr distillation and purification by column chromatography (0 → 50% EtOAc–hexane) isolated **183** (2.92 g, 81%) as a colourless oil.
R_f 0.45 (20% EtOAc–hexane); ν_{max} (film) 3002, 2953, 2838, 1740 (C=O), 1601, 1489, 1435, 1262, 1093 (C-O), 1048 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.22 (2H, t, *J* 8.0 Hz, H_{Ar}), 6.79–6.73 (2H, m, H_{Ar}), 3.81 (3H, s, ArOMe), 3.73 (6H, s, 2 x CO_2Me), 3.72–3.68 (1H, m, C*H*(CO_2Me)$_2$), 3.22 (d, *J* 8.0 Hz, CH_2); δ_C ($CDCl_3$, 101 MHz) 169.2 ($C{=}O_{Esters}$), 159.7 ($C{=}O_{Boc}$), 139.3 (*ipso* C_{Ar}), 129.6, 121.0, 114.4, 112.3 (C_{Ar}), 55.2 (ArOMe), 53.5 (*C*H(CO_2Me)$_2$), 52.6 (CH(CO_2*Me*)$_2$), 34.8 (CH_2); *m/z* (ESI) 316, 275 $[M+Na]^+$, 253 $[M+H]^+$, 221, 207 (Found: $[M+Na]^+$, 275.0904. $C_{13}H_{16}O_5$ requires $[M+Na]^+$, 275.0895) (Found C, 61.87; H, 6.34. $C_{13}H_{16}O_5$ requires C, 61.90; H, 6.39%).

This data is in agreement with the published data for the compound.[130]

2-(1-*tert*-Butoxycarbonyl-2-oxo-piperidin-4-yl)-2-(3-methoxy-benzyl)-malonic acid dimethyl ester 179

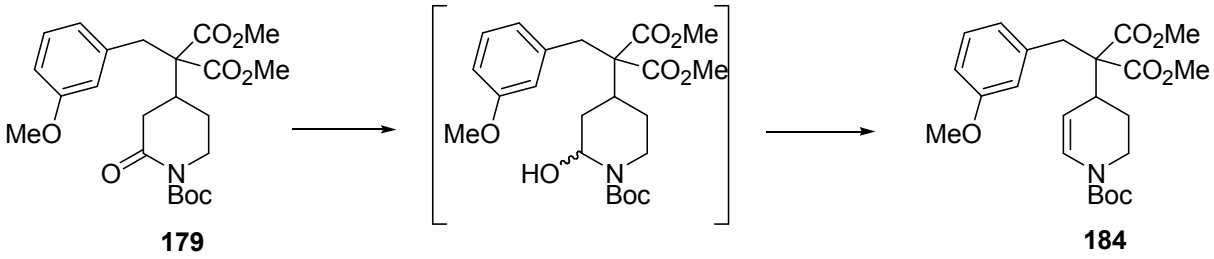


161 **179**

To a stirred suspension of NaH (60% w/w in mineral oils, washed with hexane, 4 mg, 0.100 mmol, 0.12 equiv) in THF (1 mL) at 0 °C, was added a solution of dimethyl 2-(3-methoxybenzyl)malonate **183** (0.256 g, 1.01 mmol, 1.25 equiv) in THF (1 mL). The colourless solution was then stirred at 0 °C for 10 min, after which time a solution of *tert*-butyl 2-oxo-5,6-dihydropyridine-1(2H)-carboxylate **161** (0.159 g, 0.810 mmol, 1.0 equiv) in THF (1 mL) was added. The resulting yellow solution was stirred at room temperature overnight. The reaction mixture was then quenched with a couple of drops of glacial acetic acid, diluted with EtOAc and washed with H_2O. The aqueous phase was then extracted with EtOAc and the combined organic layers washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (0 → 50% EtOAc–hexane) isolated **179** (0.234 g, 65%) as colourless oil.

R_f 0.26 (30% EtOAc–hexane); ν_{max} (film) 2954, 1769, 1714 (C=O), 1584, 1435, 1369, 1294, 1263, 1151, 1048 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.20 (1H, t, *J* 8.0 Hz, H_{Ar}), 6.80 (1H, dd, *J* 2.5, 8.0 Hz, H_{Ar}), 6.69–6.64 (2H, m, H_{Ar}), 3.85–3.77 (1H, m, 1 x NCH_2), 3.78 (3H, s, OMe), 3.72 (6H, 2 x s, 2 x CO_2Me), 3.50–3.43 (1H, m, 1 x NCH_2), 3.31–3.22 (2H, m, CH_2Ar), 2.89–2.80 (1H, m, 1 x CH_2C=O), 2.55–2.45 (2H, m, 1 x CH_2C=O and $CHC(CO_2Me)$, 2.25–2.19 (1H, m, 1 x CH_2NCH_2), 1.49-1.55 (10H, m, 1 x CH_2NCH_2 and -$OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 170.6, 170.4, 170.3 ($C=O_{Esters}$), 159.9 ($C=O_{Boc}$), 152.4, 137.2 (*ipso* C_{Ar}), 129.8, 122.5, 116.2, 112.8 (C_{Ar}), 83.5 (-$OC(CH_3)_3$), 62.3 (-$C(CO_2Me)_2$), 55.5 (ArOMe), 52.6 (-$C(CO_2Me)_2$), 45.4 (NCH_2), 39.3 (CH_2Ar), 37.5 (CH_2C=O), 35.4 ($CHC(CO_2Me)_2$), 28.4 (-$OC(CH_3)_3$), 26.1 (CH_2NCH_2); *m/z* (ESI) 472 $[M+Na]^+$, 450 $[M+H]^+$, 394 $[M+H-C_4H_8]^+$, 350 $[M+H-Boc]^+$ (Found: $[M+H]^+$, 450.2126. $C_{23}H_{32}NO_8$ requires $[M+H]^+$, 450.21) (Found C, 61.52; H, 6.88; N, 3.13. $C_{23}H_{31}NO_8$ requires C, 61.46; H, 6.95; N, 3.12%).

Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydropyridin-4-yl)-2-(3-methoxybenzyl) malonate 184



To a stirred solution of dimethyl 2-(1-(*tert*-butoxycarbonyl)-2-oxopiperidin-4-yl)-2-(3-methoxybenzyl)malonate **179** (0.104 g, 0.230 mmol, 1.0 equiv) in THF (2.7 mL) at –78 °C, was added DIBAL-H (1.2 M in toluene, 0.190 mL, 0.230 mmol, 1.0 equiv). The yellow solution was stirred at –78 °C for 2 h, after which time it was allowed to warm to room temperature and quenched with Rochelle's salt. The biphasic mixture was then diluted with Et_2O and stirred at room temperature for 16 h. The aqueous phase was extracted with Et_2O and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to isolate the corresponding lactamol.

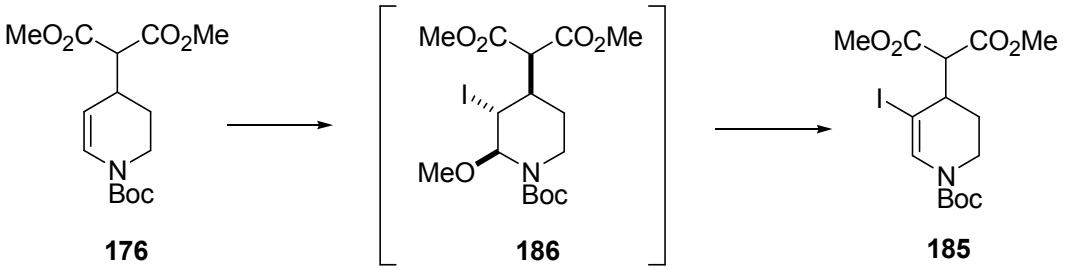
ν_{max} (film) 3433 (O-H), 2952, 1729, 1692 (C=O), 1601, 1433, 1367, 1264, 1169 (C-O), 1046 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.19–7.14 (1 H, m, H_{Ar}), 6.78–6.71 (3 H, m, H_{Ar}), 5.82 (1 H, s, C*H*OH), 3.87–3.82 (1 H, m, 1 x NCH_2), 3.77 (3 H, s, ArOMe), 3.69 (3 H, s, CO_2Me), 3.64 (3 H, s, CO_2Me), 3.30–3.22 (2 H, m, CH_2Ar), 3.17–3.11 (1 H, m, 1 x NCH_2), 2.69–2.62 (1 H, m, C*H*$C(CO_2Me)_2$), 2.21–2.17 (1 H, m, 1 x C*H*$_2$CHOH), 1.97–1.93 (1 H, m, 1 x C*H*$_2$$NCH_2$), 1.47 (9 H, s, -$OC(CH_3)_3$), 1.40–1.24 (2H, m, 1 x C*H*$_2$CHOH and 1 x C*H*$_2$$NCH_2$).

To a solution of the resulting colourless residue in CH_2Cl_2, was then added $HCl_{(aq)}$ (1 M, 1 mL, 1.0 mmol, 4.3 equiv). The biphasic mixture was vigorously stirred for 2.5 h, after which time the reaction was quenched with sat. $NaHCO_{3(aq)}$ and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (20% EtOAc–petrol) isolated **184** (0.078 g, 78%) as a colourless oil.

R_f 0.23 (20% EtOAc–hexane); ν_{max} (film) 2953, 1727, 1694 (C=O), 1649 (C=C), 1436, 1409, 1369, 1250, 1168 (C-O), 1124, 1058 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.19 (1 H, t, *J* 8.0 Hz, H_{Ar}), 6.95–6.66 (4 H, m, H_{Ar} and CHNBoc), 5.05–4.85 (1 H, m, C*H*CHNBoc), 4.03–3.84 (1 H, m,

1 x NCH_2), 3.79 (3 H, s, ArOMe), 3.72 (3 H, s, CO_2Me), 3.68 (3 H, s, CO_2Me), 3.37–3.27 (2 H, m, CH_2Ar), 3.21–3.17 (1 H, m, 1 x NCH_2), 2.97–2.86 (1 H, m, C*H*C$(CO_2Me)_2$), 2.18–2.13 (1 H, m, 1 x C*H*$_2$NCH_2), 1.77–1.61 (1 H, m, 1 x C*H*$_2$NCH_2), 1.51 (9 H, s, -OC$(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 170.5, 170.4 ($C{=}O_{Esters}$), 159.4 ($C{=}O_{Boc}$), 137.5 (*ipso* C_{Ar}), 129.1 (C_{Ar}), 126.5, 126.2 (CHNBoc), 122.3, 116.0, 112.3 (C_{Ar}), 105.2, 104.5 (*C*HCHNBoc), 80.8 (-O*C*$(CH_3)_3$), 62.2 (-*C*$(CO_2Me)_2$), 55.1 (ArOMe), 52.2, 52.1 (-C$(CO_2Me)_2$), 42.2, 41.1 (NCH_2), 38.7 (CH_2Ar), 36.1, 35.9 (*C*HC$(CO_2Me)_2$), 28.3 (-OC(*C*$H_3)_3$), 24.0 (*C*H_2NCH_2); *m/z* (ESI) 456 $[M+Na]^+$, 434 $[M+H]^+$, 378, 334 $[M+H–C_4H_8OCO]^+$, 221 (Found: $[M+Na]^+$, 456.1994. $C_{23}H_{31}NO_7$ requires $[M+Na]^+$, 456.1998). (Found C, 63.63; H, 7.18; N, 3.28. $C_{23}H_{31}NO_7$ requires C, 63.73; H, 7.21; N, 3.23%).

2-(1-*tert*-butoxycarbonyl-5-iodo-1,2,3,4-tetrahydro-pyridin-4-yl)-malonic acid dimethyl ester 185



To a stirred solution of NIS (0.198 g, 0.880 mmol, 1.2 equiv) and MeOH (0.021 mL, 0.880 mmol, 1.2 equiv) in CH_2Cl_2 (1.6 mL) at –78 °C, was added a solution of 2-(1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-pyridin-4-yl)-malonic acid dimethyl ester **176** (0.229 g, 0.730 mmol, 1.0 equiv). The resulting pale yellow solution was stirred at –78 °C for 1.5 h, after which time it was quenched with sat. $NaHCO_{3(aq)}$ and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers washed with sat. $Na_2S_2O_{3(aq)}$, dried ($MgSO_4$) and concentrated under reduced pressure to isolate **186** (0.329 g, 96%) as a yellow oil and a single isomer, which was used crude in the next step.

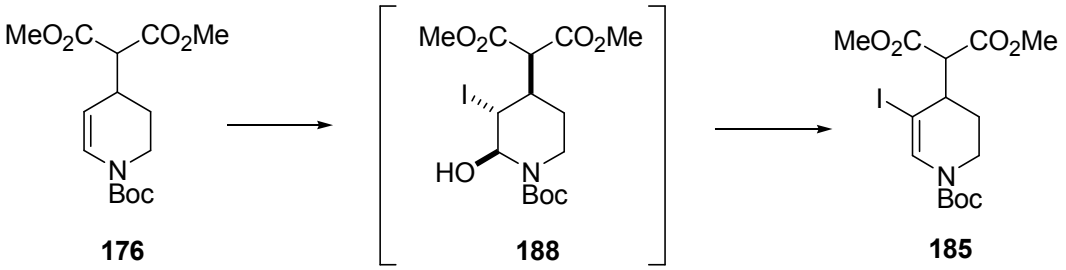
R_f 0.29 (30% EtOAc–petrol); ν_{max} (film) 2925, 1738, 1704 (C=O), 1410, 1293, 1259, 1163, 1070 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 5.63–5.48 (1H, m, CHOMe), 4.63–4.60 (1H, m, CHI), 4.06–3.86 (1H, m, 1 x NCH_2), 3.73 (3H, s, CO_2Me), 3.71 (3H, s, CO_2Me), 3.39–3.33 (1H, m, $CH(CO_2Me)_2$), 3.26–3.24 (3H, 2 x s, OMe), 3.06–2.90 (1H, m, 1 x NCH_2), 2.07–2.02 (1H, m, C*H*$CH(CO_2Me)_2$), 1.62–1.49 (1H, m, 1 x C*H*$_2NCH_2$), 1.46 (9H, s, -$OC(CH_3)_3$), 1.37–1.30 (1H, m, 1 x C*H*$_2NCH_2$); δ_C ($CDCl_3$, 101 MHz) 168.3, 168.2, 167.5 ($C=O_{Esters}$), 155.0, 154.5 ($C=O_{Boc}$), 86.8, 85.6 (*C*HOMe), 80.7, 80.4 (-O*C*$(CH_3)_3$), 58.2 (*C*$H(CO_2Me)_2$, 55.1, 54.9 (CHO*Me*), 52.8, 52.7 (-$CHCO_2$*Me*), 38.3, 37.4 (CHI), 37.0, 36.9 (NCH_2), 34.4, 34.4 (*C*$HCH(CO_2Me)_2$, 28.3, 28.3 (-$OC(CH_3)_3$), 25.3, 25.1 (*C*H_2NCH_2); *m/z* (ESI) 440 $[M+H\text{-}MeOH]^+$, 384 $[M+H\text{-}MeOH\text{-}C_4H_8]^+$, 340 $[M+H\text{-}MeOH\text{-}C_4H_8OCO]^+$, 213 $[M+H\text{-}MeOH\text{-}C_4H_8OCO\text{-}I]^+$.

To a stirred suspension of iodomethoxyamine **186** (0.394 g, 0.840 mmol, 1.0 equiv) and 4Å molecular sieves in CH_2Cl_2 (16 mL) at room temperature, was added TFA (0.19 mL, 2.52 mmol, 3.0 equiv). The yellow suspension was stirred at room temperature for 16 h, after which time TFA (0.7 mL, 0.909 mmol, 1.0 equiv) was added. The resulting pink suspension

was stirred for a further 1.5 h and the reaction mixture was then quenched with Et_3N (0.470 mL, 3.36 mmol, 4.0 equiv) to give an orange suspension. The reaction mixture was then filtered on a sinter funnel, washing with CH_2Cl_2 and the filtrate dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (5 →15 % EtOAc–petrol) isolated **185** (0.264 g, 72% (64% over two steps)) as an orange oil.

R_f 0.44 (30% EtOAc–petrol); ν_{max} (film) 2930, 1737, 1710 (C=O), 1629 (C=C), 1602, 1458, 1371, 1235, 1161 (C-O), 1069 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.51–7.34 (1H, m, CHNBoc), 3.89 (1H, d, *J* 6.0 Hz, $CH(CO_2Me)_2$), 3.81 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me), 3.71–3.59 (1H, m, 1 x NCH_2), 3.53–3.42 (1H, m, 1 x NCH_2), 3.16–3.11 (1H, m, $CHCH(CO_2Me)_2$), 2.28–2.11 (1H, m, 1 x CH_2NCH_2), 2.10–2.04 (1H, m, 1 x CH_2NCH_2), 1.51 (9H, s, $-OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 168.5, 167.9 ($C=O_{Esters}$), 150.8 ($C=O_{Boc}$), 134.6, 134.4 (CHNBoc), 81.9, 81.7 ($-OC(CH_3)_3$), 71.9 (C-I), 55.1 ($CH(CO_2Me)_2$), 52.8, 52.5 ($CH(CO_2Me)_2$), 40.6 ($CHCH(CO_2Me)_2$), 39.3, 38.3 (NCH_2), 28.2 ($-OC(CH_3)_3$), 25.0 (CH_2NCH_2); *m/z* (ESI) 462 $[M+Na]^+$, 457, 440 $[M+H]^+$, 384 $[M+H-C_4H_8]^+$, 340 $[M+H-C_4H_8OCO]^+$, 251 (Found $[M+H]^+$, 440.0571. $C_{15}H_{22}NO_6I$ requires $[M+H]^+$, 440.0570).

2-(1-*tert*-Butoxycarbonyl-5-iodo-1,2,3,4-tetrahydro-pyridin-4-yl)-malonic acid dimethyl ester 185

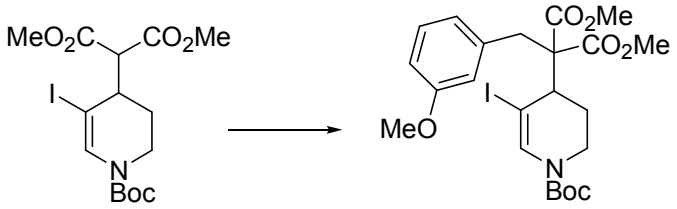


To a stirred solution of 2-(1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-pyridin-4-yl)-malonic acid dimethyl ester **176** (0.500 g, 1.600 mmol, 1.0 equiv) in THF (8 mL) and H_2O (8 mL) at 0 °C, was added NIS (0.720 g, 3.190 mmol, 2.0 equiv). The yellow solution was allowed to slowly warm to room temperature and stirred for 4 h. The resulting orange reaction mixture was quenched with sat. $Na_2S_2O_{3(aq)}$ and the aqueous phase extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure to isolate **188** as a yellow oil, which was used crude in the next step.
ν_{max} (film) 3424 (OH), 2955, 1737, 1702 (C=O), 1434, 1368, 1293, 1254, 1164, 1021 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 5.95–5.78 (1H, m, CHOH), 4.62–4.59 (1H, m, CHI), 4.33 (1H, d, *J* 8.0 Hz, 1 x NCH_2), 3.73 (3H, s, CO_2Me), 3.72 (3H, s, CO_2Me), 3.39–3.36 (1H, d, *J* 8.0 Hz, $CH(CO_2Me)_2$), 2.81–2.77 (1H, m, 1 x NCH_2), 2.35–2.24 (1H, m, 1 x C*H*$_2$$NCH_2$), 2.15–2.09 (1H, m, C*H*$CH(CO_2Me)_2$), 1.61–1.49 (1H, m, 1 x C*H*$_2$$NCH_2$), 1.44 (9H, s, -$OC(CH_3)_3$); *m/z* (ESI) 440 $[M+H-H_2O]^+$, 340 $[M+H-MeOH-C_4H_8OCO]^+$.

To a stirred suspension of iodohydroxyamine **188** and 4Å molecular sieves in CH_2Cl_2 (16 mL) at room temperature, was added TFA (0.120 mL, 1.60 mmol, 1.0 equiv). The pink suspension was stirred at room temperature for 2 h, after which time the reaction mixture was quenched with Et_3N (0.220 mL, 1.60 mmol, 1.0 equiv) to give an orange suspension. After stirring for a further 1 h at room temperature, the reaction mixture was then filtered on a sinter funnel, washing with CH_2Cl_2 and the filtrate dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (5 →15 % EtOAc–petrol; base-washed with Et_3N) isolated **185** (0.623 g, 89% over two steps) as a yellow oil.

The data was in agreement with that reported on page 153.

Dimethyl 2-(1-(*tert*-butoxycarbonyl)-5-iodo-1,2,3,4-tetrahydropyridin-4-yl)-2-(3-methoxybenzyl)malonate 180

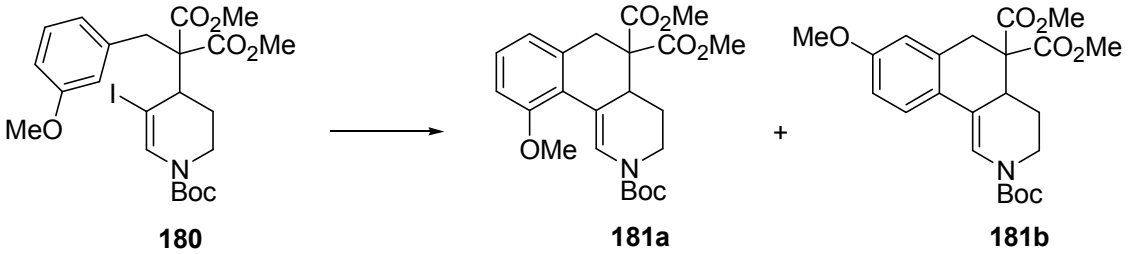


185 **180**

To a stirred suspension of NaH (60% w/w in mineral oils, washed with hexane, 0.018 g, 0.450 mmol, 1.2 equiv) in DMF (1 mL) at 0 °C was added a pre-stirred solution of iodide **185** (0.165 g, 0.380 mmol, 1.0 equiv) and 3-methoxybenzyl bromide (0.053 mL, 0.380 mmol, 1.0 equiv) in DMF (1 mL). The resulting yellow solution was allowed to warm to room temperature and stirred for 12.5 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (10 → 15% EtOAc–petrol) isolated **180** (0.176 g, 83%) as a colourless oil.

R_f 0.38 (30% EtOAc–petrol); ν_{max} (film) 2951, 1708 (C=O), 1624 (C=C), 1434, 1370, 1326, 1216, 1161 (C-O), 1048 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.56–7.39 (1 H, m, CHNBoc), 7.16 (1H, t, *J* 8.0 Hz, H_{Ar}), 6.83–6.75 (3 H, m, H_{Ar}), 3.78 (3 H, s, CO_2Me), 3.72–3.66 (1H, m, 1 x NCH_2), 3.66 (3 H, s, ArOMe), 3.60 (1H, d, *J* 16.0 Hz, 1 x $ArCH_2$), 3.55 (3H, s, CO_2Me), 3.44–3.32 (2 H, m, 1 x NCH_2 and $CHC(CO_2Me)_2$), 3.15 (1H, d, *J* 12.0 Hz, 1 x $ArCH_2$), 2.29–2.23 (1 H, m, 1 x CH_2NCH_2), 2.09–2.00 (1 H, s, 1 x CH_2NCH_2), 1.50 (9 H, s, $-OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 170.3, 169.8 ($C=O_{Esters}$), 159.2 ($C=O_{Boc}$), 151.5, 137.9 (*ipso* C_{Ar}), 135.1, 134.7 (CHNBoc), 128.9, 122.7, 116.0, 112.5 (C_{Ar}), 81.2 ($-OC(CH_3)_3$), 68.3 (C-I), 63.3 ($-C(CO_2Me)_2$), 52.1, 52.0 ($-C(CO_2Me)_2$ and ArOMe), 45.7 ($CHC(CO_2Me)_2$), 41.1 (CH_2Ar), 38.6, 37.9 (NCH_2), 28.3 ($-OC(CH_3)_3$), 26.5 (CH_2NCH_2); *m/z* (ESI) 582 $[M+Na]^+$, 560 $[M+H]^+$, 504 $[M+H-C_4H_8]^+$, 432 $[M-I]^+$, 332 $[M-C_4H_8OCO-I]^+$ (Found: $[M+Na]^+$, 582.0963. $C_{23}H_{30}NO_7I$ requires $[M+Na]^+$, 582.0965). (Found C, 49.45; H, 5.53; N, 2.47. $C_{23}H_{30}NO_7I$ requires C, 49.38; H, 5.41; N, 2.50%).

2-*tert*-Butyl 5,5-dimethyl 10-methoxy-4,4a-dihydrobenzo[h]isoquinoline-2,5,5(3H,6H)-tricarboxylate 181a and 181b



A suspension of dimethyl 2-(1-(*tert*-butoxycarbonyl)-5-iodo-1,2,3,4-tetrahydropyridin-4-yl)-2-(3-methoxybenzyl)malonate **180** (0.200 g, 0.360 mmol, 1.0 equiv), palladium tetrakis (triphenylphosphine) (0.042 g, 0.036 mmol, 0.1 equiv), and potassium acetate (0.070 g, 0.720 mmol, 2.0 equiv) in DMA (2.9 mL) was subjected to microwave irradiation at 120 °C for 10 min. Upon cooling to room temperature, the resulting dark green reaction mixture was diluted with H_2O and the aqueous phase extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (5 → 15% EtOAc–petrol) isolated **181a** and **181b** (0.0488 g, 31%) as an inseperable mixture.

R_f 0.25 (30% EtOAc–petrol); ν_{max} (film) 2958, 1734, 1701 (C=O), 1641 (C=C), 1439, 1389, 1354, 1245, 1164 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) [8.16–8.11 (1H, m, H_{Ar}), 7.58–7.38 (2 H, m, H_{Ar}), 7.07–6.62 (5H, m, H_{Ar} and CHNBoc) mixture of isomers], [4.26–4.02 (2H, m, 1 x NCH_2), 2 x isomers], [3.80–3.60 (18 H, 4 x s, 2 x $(CO_2Me)_2$ and 2 x ArOMe), 2 x isomers], [3.32–3.04 (8H, m, 1 x NCH_2, $ArCH_2$ and $CHC(CO_2Me)_2$), 2 x isomers], [2.47–2.31 (1 H, m, 1 x CH_2NCH_2), 2.22–2.12 (1 H, m, 1 x CH_2NCH_2), 2.03–1.90 (1 H, m, 1 x CH_2NCH_2), 1.77–1.62 (1 H, m, 1 x CH_2NCH_2), 2 x isomers], [1.56 (9 H, s, $(-OC(CH_3)_3)$, 1.5 (9 H, s, $(-OC(CH_3)_3)$, 2 x isomers]; δ_C ($CDCl_3$, 101 MHz) 171.6, 169.7 ($C=O_{Esters}$), 157.9, 156.1, 152.4 ($C=O_{Boc}$ and *ipso* C_{Ar}), 134.7, 133.2, 129.6, 127.3, 125.7, 121.3, 113.4, 112.3 (C_{Ar} and CHNBoc), 109.7 (C_{Ar}), 80.9 ($-OC(CH_3)_3$), 57.6 ($-C(CO_2Me)_2$), 55.3, 52.7, 52.3, 52.2 ($-C(CO_2Me)_2$ and ArOMe), 41.5 (NCH_2), 39.3, 38.6, 38.4, 37.3 ($CHC(CO_2Me)_2$ and $ArCH_2$), 29.4, 28.3 ($-OC(CH_3)_3$), 24.3, 24.0, 23.8 (CH_2NCH_2); *m/z* (ESI) 454 $[M+Na]^+$, 432 $[M+H]^+$, 375 $[M+H-C_4H_8]^+$, 332 $[M+H-C_4H_8OCO]^+$ (Found $[M+H]^+$, 432.2014. $C_{23}H_{29}NO_7$ requires $[M+H]^+$ 432.2022).

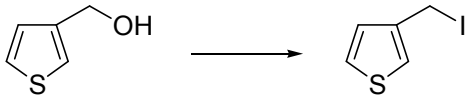
3-(Methanol)thiophene 190

189 **190**

To a stirred solution of thiophene-3-carboxaldehyde (**189**) (1.0 g, 9.09 mmol, 1.0 equiv) in MeOH (23 mL) at 0 °C was added $NaBH_4$ (0.344 g, 9.09 mmol, 1.0 equiv). The resulting orange solution was allowed to warm to room temperature and stirred for 19 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure to isolate **190** (0.873 g, 84%) as an orange oil, which was used crude in the next step.

R_f 0.60 (5% MeOH–CH_2Cl_2); ν_{max} (film) 3392 (OH), 2931, 1651, 1417, 1155, 1015 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.35 (1H, dd, *J* 3.0, 5.0 Hz, H_{Ar}), 7.26 (1H, s, H_{Ar}), 6.99 (1H, d, *J* 5.0 Hz, H_{Ar}), 4.72 (2H, s, CH_2), 1.88 (1H, br s, OH); δ_C ($CDCl_3$, 101 MHz) 142.3 (*ipso* C_{Ar}), 126.8, 126.3, 122.0 (C_{Ar}), 60.7 (CH_2); *m/z* (EI) 114 $[M]^+$, 113 $[M-H]^+$, 97 $[M-OH]^+$, 85 $[M+H-CH_2O]^+$ (Found $[M]^+$, 114.0137. C_5H_6OS requires $[M]^+$, 114.0139).

3-(iodomethyl)thiophene 191

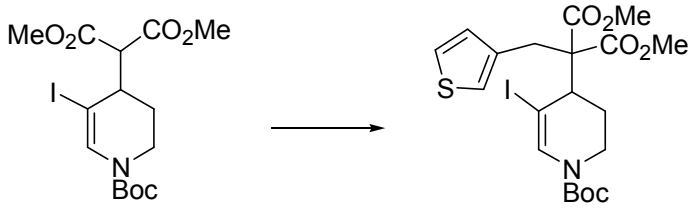


190 **191**

To a stirred solution of triphenylphosphine (2.44 g, 9.29 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at room temperature, was added I_2 (2.36 g, 9.29 mmol, 1.0 equiv). The brown solution was stirred at room temperature for 10 min, after which time imidazole (0.70 g, 10.2 mmol, 1.1 equiv) was added, followed by a solution of 3-(methoxyl)thiophene **190** (1.06 g, 9.29 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL). The resulting orange suspension was stirred at room temperature for 4.5 h. The reaction mixture was washed with sat. $Na_2S_2O_{3(aq)}$ and the combined organic layers washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (100% hexane) isolated **191** (1.059 g, 51%) as a brown oil.

R_f 1.0 (30% EtOAc–hexane); ν_{max} (film) 1652, 1590, 1484, 1437, 1181, 1120 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.33 (1H, d, *J* 4.5 Hz, H_{Ar}), 7.32 (1H, d, *J* 5.0 Hz, H_{Ar}), 7.14–7.13 (1H, m, H_{Ar}), 4.50 (2H, s, CH_2); δ_C ($CDCl_3$, 101 MHz) 132.6, 132.0, 128.9, 128.7 (C_{Ar}), 67.2 (CH_2); *m/z* (EI) 224 $[M]^+$, 223 $[M\text{-}H]^+$ (Found $[M]^+$, 223.9151. C_5H_5SI requires $[M]^+$, 223.9157).

Dimethyl 2-(1-(*tert*-butoxycarbonyl)-5-iodo-1,2,3,4-tetrahydropyridin-4-yl)-2-(thiophen-3-ylmethyl)malonate 193

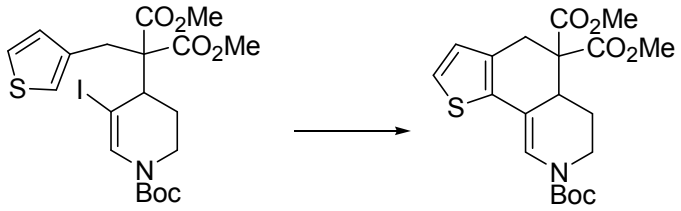


185 **193**

To dry NaH (60% w/w in mineral oils, washed with hexane, 0.114 g, 2.84 mmol, 1.1 equiv) at 0 °C, was added a pre-stirred solution of iodide **185** (1.13 g, 2.58 mmol, 1.0 equiv) and 3-(iodomethyl)thiophene **191** (0.580 g, 2.58 mmol, 1.0 equiv) in DMF (7 mL). The resulting yellow solution was allowed to warm to room temperature and stirred for 22 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (0 → 5% EtOAc–toluene) isolated **193** (1.01 g, 72%) as a yellow oil.

R_f 0.28 (20% EtOAc–hexane); ν_{max} (film) 2950, 1732, 1714 (C=O), 1622 (C=C), 1434, 1372, 1325, 1245, 1164 (C-O), 1126 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.57–7.39 (1H, m, CHNBoc), 7.17 (1H, dd, *J* 3.0, 5.0 Hz, H_{Ar}), 7.07 (1H, br s, H_{Ar}), 6.96 (1H, dd, *J* 1.0, 5.0 Hz, H_{Ar}) 3.70–3.67 (4H, s and m, CO_2Me and 1 x NCH_2), 3.61–3.58 (4H, s and m, CO_2Me and 1 x CH_2Ar), 3.42–3.36 (2H, m, 1 x NCH_2 and C*H*C(CO_2Me)$_2$), 3.27–3.24 (1H, m, 1 x CH_2Ar), 2.24–2.18 (1H, m, 1 x C*H*$_2$NCH$_2$), 2.08–2.01 (1H, m, 1 x C*H*$_2$NCH$_2$), 1.52 (9H, s, OC(CH_3)$_3$); δ_C ($CDCl_3$, 101 MHz) 170.0 ($C{=}O_{Esters}$), 137.9, 136.2 (*ipso* C_{Ar}), 135.2, 134.7 (CHNBoc), 129.8, 129.1, 128.2, 125.3, 124.6, 124.0 (C_{Ar}), 81.9 (-O*C*(CH_3)$_3$), 68.4 (C-I), 62.8 (-*C*(CO_2Me)$_2$), 52.3, 52.2 (-C(CO_2*Me*)$_2$), 46.6 (*C*HC(CO_2Me)$_2$), 38.8, 38.0 (NCH_2), 35.7 ($ArCH_2$), 28.2 (-OC(*C*H$_3$)$_3$), 24.9 (*C*H$_2$NCH$_2$); *m/z* (ESI) 574, 558 $[M+Na]^+$, 436 $[M+H-C_4H_8OCO]^+$, 196 (Found $[M+Na]^+$, 558.0418. $C_{20}H_{26}NO_6SI$ requires $[M + Na]^+$, 558.0423) (Found C, 45.02; H, 4.75; N, 2.68. $C_{20}H_{26}NO_6S$ I requires C, 44.87; H, 4.89; N, 2.62%).

8-*tert*-Butyl 5,5-dimethyl 6,7-dihydrothieno[3,2-h]isoquinoline-5,5,8(4H,5aH)-tricarboxylate 194

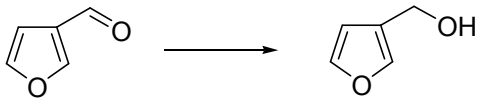


193 **194**

A suspension of dimethyl 2-(1-(*tert*-butoxycarbonyl)-5-iodo-1,2,3,4-tetrahydropyridin-4-yl)-2-(thiophen-3-ylmethyl)malonate **193** (0.342 g, 0.642 mmol, 1.0 equiv), palladium(II) acetate (0.014 g, 0.064 mmol, 0.1 equiv), triphenylphosphine (0.168 g, 0.642 mmol, 1.0 equiv) and potassium acetate (0.126 g, 1.280 mmol, 2.0 equiv) in DMF (3.2 mL), was subjected to microwave irradiation at 120 °C for 20 min. Upon cooling to room temperature, the reaction mixture was diluted with H_2O and the aqueous phase extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (10 → 20% EtOAc–hexane) isolated **194** (0.188 g, 72%) as an orange oil.

R_f 0.42 (30% EtOAc–petrol); ν_{max} (film) 2981, 1732, 1698 (C=O), 1650 (C=C), 1435, 1368, 1266, 1162 (C-O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.37–7.20 (1H, m, CHNBoc), 6.95 (1H, d, *J* 4.0 Hz, H_{Ar}), 6.73 (1H, t, *J* 4.0 Hz, H_{Ar}), 4.30–4.11 (1H, m, 1 x NCH_2), 3.81 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me), 3.46 (1H, d, *J* 16.0 Hz, 1 x $ArCH_2$), 3.19–3.00 (3H, m, 1 x NCH_2, 1 x $ArCH_2$ and C*H*C$(CO_2Me)_2$), 2.55–2.46 (1H, m, 1 x CH_2NCH_2), 1.98–1.97 (1H, m, 1 x CH_2NCH_2), 1.54 (9H, s, -OC$(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 171.8, 169.5 ($C{=}O_{Esters}$), 152.0 ($C{=}O_{Boc}$), 131.7, 131.5 (*ipso* C_{Ar}), 127.5, 127.2, 121.2, 121.0 (C_{Ar}), 120.1 (CHNBoc), 111.0, 110.4 (*ipso* C_{Ar}), 81.3 (-O*C*$(CH_3)_3$), 57.7 (-*C*$(CO_2Me)_2$), 52.8, 52.2 (-C$(CO_2Me)_2$), 42.4, 41.4 (NCH_2), 39.6, 39.3 (*C*HC$(CO_2Me)_2$), 34.6 (CH_2Ar), 28.3 (-OC(*C*$H_3)_3$), 23.9, 23.8 (*C*H_2NCH_2); *m/z* (ESI) 471, 466, 430 $[M+Na]^+$, 425, 352 $[M+H\text{-}C_4H_8]^+$, 308 $[M+H\text{-}C_4H_8OCO]^+$ (Found $[M+H]^+$, 408.1491. $C_{20}H_{25}NO_6S$ requires $[M + H]^+$, 408.1481) (Found C, 59.00; H, 6.09; N, 3.50. $C_{20}H_{25}NO_6S$ requires C, 58.95; H, 6.18; N, 3.44%).

3-(Methanol)furan 196

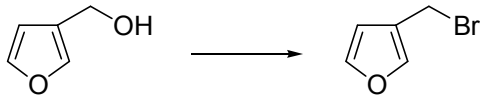


195 **196**

To a stirred solution of 3-furaldehyde (**195**) (1.0 g, 10.4 mmol, 1.0 equiv) in MeOH (26 mL) at 0 °C was added $NaBH_4$ (0.393 g, 10.4 mmol, 1.0 equiv). The resulting yellow solution was allowed to slowly warm to room temperature and stirred for 19 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure to isolate **196** (0.836 g, 82%) as a colourless oil, which was used crude in the next step.

R_f 0.56 (5% MeOH–CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 7.43–7.41 (2H, m, H_{Ar}), 6.45 (1H, s, H_{Ar}), 4.55 (2H, s, CH_2), 1.96 (1H, br s, OH); δ_C ($CDCl_3$, 101 MHz) 143.5, 139.9 (C_{Ar}), 125.1 (*ipso* C_{Ar}), 109.8 (C_{Ar}), 56.6 (CH_2) ; *m/z* (EI) 98 $[M]^+$, 97 $[M\text{-}H]^+$, 81 $[M\text{-}OH]^+$, 69 $[M+H\text{-}CH_2O]^+$ (Found $[M]^+$, 98.0367. $C_5H_6O_2$ requires $[M]^+$, 98.0368).

3-(Bromomethyl)furan 199

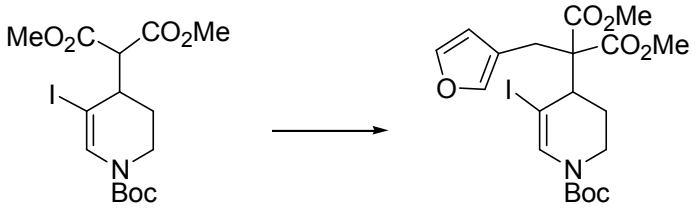


196 **199**

To a stirred solution of 3-(methanol)furan **196** (0.200 g, 2.04 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at room temperature was added phosphorus tribromide (0.380 mL, 4.08 mmol, 2.0 equiv). The resulting light brown solution was stirred at room temperature for 16 h. The reaction mixture was quenched with sat. $NaHCO_{3(aq)}$ and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a give **199** (0.308 g, 89%) as a brown oil which was taken on crude to the next step.

R_f 1.0 (30% EtOAc–hexane); δ_H ($CDCl_3$, 400 MHz) 7.51 (1H, s, H_{Ar}), 7.43 (1H, s, H_{Ar}), 6.48 (1H, s, H_{Ar}), 4.41 (2H, s, CH_2); δ_C ($CDCl_3$, 101 MHz) 143.8, 140.8 (C_{Ar}), 122.6 (*ipso* C_{Ar}), 110.9 (C_{Ar}), 23.6 (CH_2); *m/z* (EI) 162 $[M(^{81}Br)]^+$, 160 $[M(^{79}Br)]^+$, 82 $[M(^{81}Br)+H-^{81}Br]^+$, 81, 80 $[M(^{79}Br)+H-^{79}Br]^+$.

2-(1-(*tert*-Butoxycarbonyl)-5-iodo-1,2,3,4-tetrahydropyridin-4-yl)-2-(furan-3-ylmethyl) malonate 200

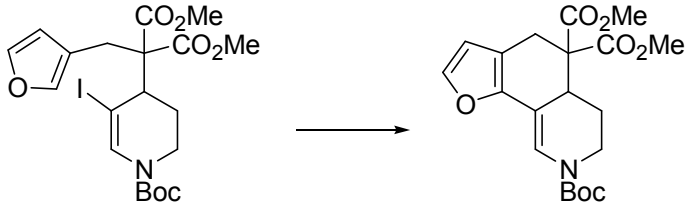


185 **200**

To dry NaH (60% w/w in mineral oils, washed with hexane, 0.156 g, 3.90 mmol, 1.6 equiv) at 0 °C was added a pre-stirred solution of iodide **185** (1.07 g, 2.44 mmol, 1.0 equiv) and 3-(bromomethyl)furan **199** (0.156 g, 3.90 mmol, 2.05 equiv) in DMF (4.9 mL). The resulting dark orange solution was allowed to warm to room temperature and stirred for 64 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (0 → 2.5% acetone–toluene) isolated **200** (1.15 g, 91%) as a yellow oil.

R_f 0.71 (5% acetone–toluene); ν_{max} (film) 2924, 1704 (C=O), 1634 (C=C), 1434, 1370, 1325, 1255, 1162, 1126 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.57–7.39 (1H, m, CHNBoc), 7.39–7.32 (1H, m, H_{Ar}), 7.27–7.19 (1H, m, H_{Ar}), 6.29 (1H, br s, H_{Ar}) 3.75–3.65 (7H, 2 x s and m, 2 x CO_2Me and 1 x NCH_2), 3.41–3.34 (3H, m, 1 x $ArCH_2$, 1 x NCH_2 and C*H*C(CO_2Me)$_2$), 3.11–3.00 (1H, m, 1 x NCH_2), 2.27–2.16 (1H, m, 1 x C*H*$_2$NCH$_2$), 2.07–1.98 (1H, m, 1 x C*H*$_2$NCH$_2$), 1.51 (9H, s, -OC(CH_3)$_3$); δ_C ($CDCl_3$, 101 MHz) 170.0, 168.5 ($C{=}O_{Esters}$), 150.8 ($C{=}O_{Boc}$), 142.2, 141.6 (C_{Ar}), 135.2, 134.7 (CHNBoc), 129.0, 128.2, 125.3 (C_{Ar}), 119.3 (*ipso* C_{Ar}), 112.4 (C_{Ar}), 82.0 (-O*C*(CH_3)$_3$), 68.4 (C-I), 62.4 (-*C*(CO_2Me)$_2$), 52.3, 52.2 (-C(CO_2*Me*)$_2$), 45.5 (*C*HC(CO_2Me)$_2$), 38.8, 38.0 ($ArCH_2$), 30.9 (NCH_2), 28.2 (-OC(*C*H$_3$)$_3$), 24.9 (*C*H$_2$NCH$_2$); *m/z* (ESI) 542 $[M+Na]^+$, 520 $[M+H]^+$, 505, 462, 252 (Found $[M+Na]^+$, 542.0643. $C_{20}H_{26}NO_7I$ requires $[M+Na]^+$, 542.0652) (Found C, 46.37; H, 4.91; N, 2.60. $C_{20}H_{26}NO_7I$ requires C, 46.25; H, 5.05; N, 2.70%).

6,7-Dihydro-4H,5aH-furo[3,2-h]isoquinoline-5,5,8-tricarboxylic acid 8-*tert*-butyl ester 5,5-dimethyl ester 201

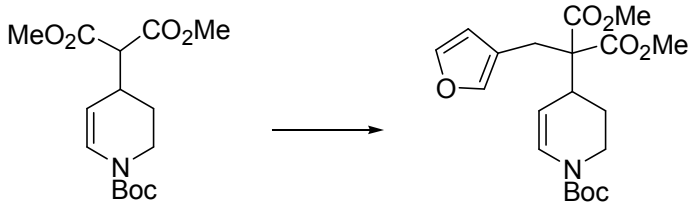


200 **201**

A suspension of 2-(1-(*tert*-butoxycarbonyl)-5-iodo-1,2,3,4-tetrahydropyridin-4-yl)-2-(furan-3-ylmethyl) malonate **200** (0.665 g, 1.28 mmol, 1.0 equiv), palladium(II) acetate (0.029 g, 0.128 mmol, 0.1 equiv), DPPF (0.710 g, 1.28 mmol, 1.0 equiv) and potassium acetate (0.250 g, 2.56 mmol, 2.0 equiv) in DMF (6.4 mL) was subjected to microwave irradiation at 140 °C for 20 min. Upon cooling to room temperature, the reaction mixture was diluted with H_2O and the aqueous phase extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (10 → 20% EtOAc–hexane) isolated **201** (0.289 g, 58%) as an orange oil.

R_f 0.52 (40% EtOAc–petrol); ν_{max} (film) 2956, 1734, 1702 (C=O), 1665 (C=C), 1440, 1369, 1250, 1161 (C-O), 1066 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.40–7.20 (2H, m, CHNBoc and H_{Ar}), 6.26 (1H, br s, H_{Ar}) 4.35–4.12 (1H, m, 1 x NCH_2), 3.82 (3H, s, CO_2Me), 3.63 (3H, s, CO_2Me), 3.31 (1H, d, *J* 15.5 Hz, 1 x $ArCH_2$), 3.16–2.90 (3H, 1 x NCH_2, 1 x $ArCH_2$ and $CHC(CO_2Me)_2$), 2.60–2.43 (1H, m, 1 x CH_2NCH_2), 1.86–1.74 (1H, m, 1 x CH_2NCH_2), 1.54 (9H, s, $-OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 171.7, 169.5 ($C=O_{Esters}$), 152.2 ($C=O_{Boc}$), 147.7 (*ipso* C_{Ar}), 142.7, 140.8, 118.2, 114.3, 111.7, 110.8 (C_{Ar} and CHNBoc), 81.3 ($-OC(CH_3)_3$), 58.2 ($-C(CO_2Me)_2$), 52.8, 52.5, 52.2 ($-C(CO_2Me)_2$), 42.4, 41.4(NCH_2), 39.0 ($CHC(CO_2Me)_2$), 31.3 ($ArCH_2$), 28.3 ($-OC(CH_3)_3$), 23.7 (CH_2NCH_2); *m/z* (ESI) 414 $[M+Na]^+$, 392 $[M+H]^+$, 336 $[M+H-C_4H_8]^+$, 292 $[M+H-C_4H_8OCO]^+$, 263 (Found $[M+Na]^+$, 414.1514. $C_{20}H_{25}NO_7$ requires $[M+Na]^+$, 414.1529).

2-(1-*tert*-Butoxycarbonyl-1,2,3,4-tetrahydro-pyridin-4-yl)-2-furan-3-ylmethyl-malonic acid dimethyl ester 202

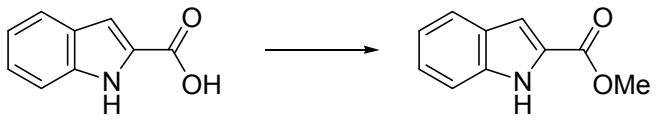


176 **202**

To dry NaH (60% w/w in mineral oils, washed with hexane, 0.038 g, 0.960 mmol, 1.2 equiv) at 0 °C was added a pre-stirred solution of tetrahydropyridine 1**76** (0.250 g, 0.880 mmol, 1.0 equiv) and 3-(bromomethyl)furan **199** (0.194 g, 1.21 mmol, 1.5 equiv) in DMF (1.6 mL). The resulting dark orange solution was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (0 → 5% EtOAc–toluene) isolated **202** (0.143 g, 45%) as a yellow oil.

R_f 0.42 (10% EtOAc–hexane); δ_H ($CDCl_3$, 400 MHz) 7.32–7.30 (1H, m, H_{Ar}), 7.22 (1H, s, H_{Ar}), 6.92–6.72 (1H, m, CHNBoc), 6.17 (1H, s, H_{Ar}), 4.92–4.80 (1H, m, C*H*CHNBoc), 3.71 (3H, s, CO_2Me), 3.68 (3H, s, CO_2Me), 3.21–3.09 (3H, m, $ArCH_2$ and 1 x NCH_2), 2.93–2.86 (1H, m, $CHC(CO_2Me)_2$), 2.12–1.95 (1H, m, 1 x CH_2NCH_2), 1.74–1.61 (1H, m, 1 x CH_2NCH_2), 1.47 (9H, s, $-OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 170.7, 170.6 ($C{=}O_{Esters}$), 142.7, 141.0 (C_{Ar}), 126.5 (CHNBoc), 118.9 (C_{Ar}), 111.7 (*C*HCHNBoc), 104.4 (*ipso* C_{Ar}), 80.1 ($-OC(CH_3)_3$), 61.4 ($-C(CO_2Me)_2$), 52.3, 52.2 ($-C(CO_2Me)_2$), 41.0 (NCH_2), 36.2 ($CHC(CO_2Me)_2$), 30.9 ($ArCH_2$), 28.3 ($-OC(CH_3)_3$), 23.8 (CH_2NCH_2); *m/z* (ESI) 416 $[M+Na]^+$, 394 $[M+H]^+$, 338 $[M+H-C_4H_8]^+$, 322, 294 $[M+H-C_4H_8OCO]^+$ (Found $[M+H]^+$, 394.1867. $C_{20}H_{28}NO_7$ requires $[M+H]^+$, 394.1866).

1*H*-Indole-2-carboxylic acid methyl ester 209

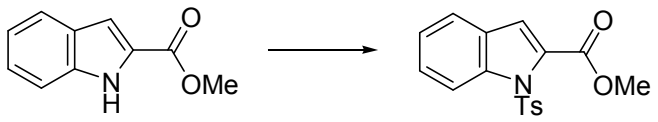


209 **210**

To a stirred solution of 1*H*-Indole-2-carboxylic acid (**14**) (1.14 g, 7.07 mmol, 1.0 equiv) in MeOH (12 mL) was added 35 drops of H_2SO_4 and the resulting yellow solution stirred under reflux for 21.5 h. The reaction mixture was quenched with sat. $NaHCO_{3(aq)}$ and the aqueous phase extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a give **210** (1.15g, 93%) as a pale yellow solid, which was taken on crude to the next step.

R_f 0.56 (5% MeOH–CH_2Cl_2); m.p. 150–153 °C; ν_{max} (film) 3319 (N-H), 2956, 1689 (C=O), 1529, 1439, 1316, 1255 (C-O), 1211, 748 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 8.95 (1H, br s, NH), 7.73 (1H, d, *J* 8.5 Hz, H_{Ar}), 7.46 (1H, d, *J* 8.5 Hz, H_{Ar}), 7.36 (1H, td, *J* 8.0, 1.0 Hz, H_{Ar}), 7.26 (1H, dd, *J* 2.0, 1.0 Hz, H_{Ar}), 7.19 (1H, t, *J* 7.5 Hz, H_{Ar}), 3.98 (3H, s, CO_2Me); δ_C ($CDCl_3$, 101 MHz) 162.4 ($C{=}O_{Ester}$), 136.8, 127.5, 127.1 (*ipso* C_{Ar}), 125.5, 122.7, 120.9, 111.9, 108.8 (C_{Ar}), 52.0 (CO_2*Me*); *m/z* (ESI) 393, 330, 176 $[M+H]^+$ (Found $[M+H]^+$, 176.0718. $C_{10}H_9NO_2$ requires $[M+H]^+$, 176.0712).

1-(Toluene-4-sulfonyl)-1*H*-indole-2-carboxylic acid methyl ester 211

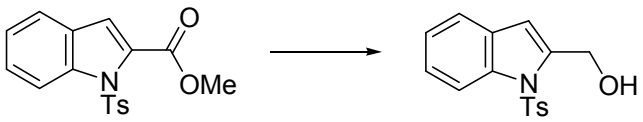


210 **211**

To dried NaH (0.340 g, 8.46 mmol, 1.3 equiv) at 0 °C, was added a solution of 1*H*-Indole-2-carboxylic acid methyl ester **210** (1.14 g, 6.51 mmol, 1.0 equiv) in DMF (16 mL). The orange solution was stirred at 0 °C until effervescence subsided, after which time a solution of toluene-4-sulfonyl chloride (1.61 g, 8.46 mmol, 1.3 equiv) in DMF (16 mL) was added. The resulting dark orange suspension was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was poured onto H_2O and the aqueous phase extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (5% Et_2O–toluene) isolated ester **211** (1.48 g, 69%) as a yellow solid.

R_f 0.61 (30% EtOAc–hexane); m.p. 68-72 °C; δ_H ($CDCl_3$, 400 MHz) 8.15 (1H, d, *J* 8.5 Hz, H_{Ar}), 7.94 (2H, d, *J* 8.5 Hz, *ortho* $ArSO_2$), 7.58 (1H, d, *J* 8.0 Hz, H_{Ar}), 7.49–7.43 (1H, m, H_{Ar}), 7.32–7.27 (3H, m, H_{Ar} and *meta* $ArSO_2$), 7.18 (1H, s, H_{Ar}), 3.96 (3H, s, CO_2Me), 2.40 (3H, s, $ArCH_3$); δ_C ($CDCl_3$, 101 MHz) 161.8 ($C{=}O_{Ester}$), 145.0, 138.3, 135.7, 131.4 (*ipso* C_{Ar}), 129.6 (*meta* $ArSO_2$), 128.2 (C_{Ar}), 127.4 (*ortho* $ArSO_2$), 124.1, 122.5, 116.9, 115.4 (C_{Ar}), 52.7 ($CO_2\mathit{Me}$), 21.7 ($ArCH_3$); *m/z* (ESI) 393, 330 $[M+H]^+$ (Found $[M+H]^+$, 330.0805. $C_{17}H_{15}NO_4S$ requires $[M+H]^+$, 330.0800) (Found C, 61.95; H, 4.41; N, 4.19. $C_{17}H_{15}NO_4S$ requires C, 61.99; H, 4.59; N, 4.25%).

[1-(Toluene-4-sulfonyl)-1H-indol-2-yl]-methanol 212

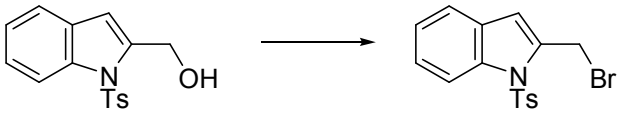


211 **212**

To a stirred solution of $LiAlH_4$ (2.0 M solution in hexane, 2.95 mL, 5.90 mmol, 2.4 equiv) in THF (10 mL) at 0 °C, was added a solution of 1-(Toluene-4-sulfonyl)-1*H*-indole-2-carboxylic acid methyl ester **211** (0.810 g, 2.46 mmol, 1.0 equiv) in THF (15 mL). The resulting yellow solution was stirred at 0 °C for 1.5 h, after which time the reaction mixture was slowly quenched with H_2O and allowed to warm to room temperature over 1 h. Rochelle's salt was added and the biphasic solution diluted with Et_2O and stirred at room temperature overnight. The aqueous phase was extracted with Et_2O and the combined organic layers washed with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure to isolate 2**12** (0.667 g, 90%) as an orange gum, which was taken on crude to the next step.

R_f 0.07 (30% EtOAc–hexane); ν_{max} (film) 3408 (O-H), 2925, 1739, 1597, 1453, 1369 (NSO_2), 1095, 1064, 748 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 8.09 (1H, d, *J* 8.0 Hz, H_{Ar}), 7.94 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.51 (1H, d, *J* 7.5 Hz, H_{Ar}), 7.37–7.20 (4H, m, 2 x H_{Ar} and *meta* $ArSO_2$), 6.66 (1H, s, H_{Ar}), 4.94 (2H, br s, CH_2OH), 2.35 (3H, s, $ArCH_3$); δ_C ($CDCl_3$, 101 MHz) 130.0 (*meta* $ArSO_2$), 126.4 (*ortho* $ArSO_2$), 125.0, 123.8, 121.2, 114.4, 111.3 (C_{Ar}), 58.6 (CH_2OH), 21.6 ($ArCH_3$); *m/z* (ESI) 338, 284 $[M+H-H_2O]^+$ (Found $[M+H-H_2O]^+$, 284.0735. $C_{16}H_{15}NO_3S$ requires $[M+H-H_2O]^+$, 284.0745).

2-Bromomethyl-1-(toluene-4-sulfonyl)-1H-indole 213

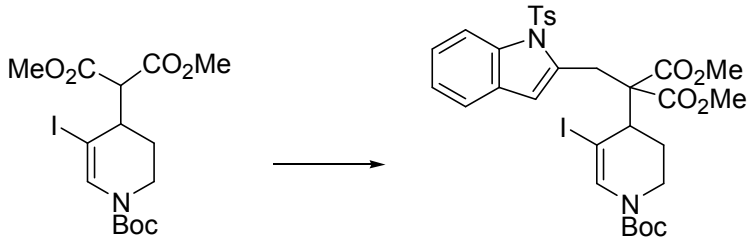


212 **213**

To a stirred solution of [1-(toluene-4-sulfonyl)-1H-indol-2-yl]-methanol **212** (0.300 g, 1.01 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at room temperature, was added phosphorus tribromide (0.190 mL, 2.02 mmol, 2.0 equiv). The resulting purple solution was stirred at room temperature for 1.5 h, after which time the reaction mixture was quenched with sat. $NaHCO_{3(aq)}$. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers washed with H_2O and brine, neutralised (K_2CO_3), dried (Na_2SO_4) and concentrated under reduced pressure to isolate **213** (0.346 g, 94%) as a dark red gum which was taken on crude to the next step.

R_f 0.42 (30% EtOAc–hexane); δ_H ($CDCl_3$, 400 MHz) 8.09 (1H, d, *J* 8.5 Hz, H_{Ar}), 7.81 (2H, d, *J* 8.5 Hz, *ortho* $ArSO_2$), 7.50 (1H, d, *J* 8.0 Hz, H_{Ar}), 7.36 (1H, t, *J* 8.0 Hz, H_{Ar}), 7.28–7.22 (3H, m, 1 x H_{Ar} and *meta* $ArSO_2$), 6.83 (1H, s, H_{Ar}), 5.04 (2H, br s, CH_2Br), 2.36 (3H, s, $ArCH_3$); δ_C ($CDCl_3$, 101 MHz) 129.8 (*meta* $ArSO_2$), 126.9 (*ortho* $ArSO_2$), 125.6, 123.9, 121.3, 114.9, 113.8 (C_{Ar}), 24.9 (CH_2Br), 21.4 ($ArCH_3$); *m/z* (ESI) 366 $[M(^{81}Br)+H]^+$, 364 $[M(^{79}Br)+H]^+$, 285 $[M(^{81}Br)+H-^{81}Br]^+$, 284 (Found $[M+H]^+$, 363.9995. $C_{16}H_{14}NO_2SBr$ requires $[M+H]^+$, 364.0007).

2-(1-*tert*-Butoxycarbonyl-5-iodo-1,2,3,4-tetrahydro-pyridin-4-yl)-2-[1-(toluene-4-sulfonyl)-1H-indol-2-ylmethyl]-malonic acid dimethyl ester 214

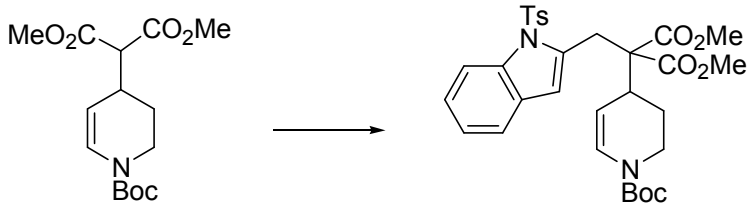


185 **214**

To dry NaH (60% w/w in mineral oils, washed with hexane, 0.021 g, 0.513 mmol, 1.5 equiv) at 0 °C was added a pre-stirred solution of iodide **185** (0.150 g, 0.342 mmol, 1.0 equiv) and 2-bromomethyl-1-(toluene-4-sulfonyl)-1H-indole **213** (0.170 g, 0.467 mmol, 1.37 equiv) in DMF (0.68 mL). The resulting dark brown solution was allowed to warm to room temperature and stirred for 16 h, after which time another spatula of NaH was added. After a further 3 h of stirring at room temperature, the reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (10 → 30% EtOAc–hexane) isolated **214** (0.141 g, 57%) as an orange gum.

R_f 0.25 (30% EtOAc–hexane); ν_{max} (film) 1730, 1705 (C=O), 1622 (C=C), 1452, 1365, 1324 (NSO_2), 1216, 1162 (C-O), 1124, 730 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 8.17 (1H, d, *J* 8.0 Hz, H_{Ar}), 7.65 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.46–7.40 (2H, m, CHNBoc and H_{Ar}), 7.28 (1H, d, *J* 8.0 Hz, H_{Ar}), 7.24–7.17 (3H, m, 1 x H_{Ar} and *meta* $ArSO_2$), 6.45 (1H, s, H_{Ar}), 4.06–3.72 (3H, m, NCH_2 and 1 x $ArCH_2$), 3.68 (3H, s, CO_2Me), 3.65 (3H, s, CO_2Me), 3.54–3.26 (2H, m, 1 x $ArCH_2$ and $CHC(CO_2Me)_2$), 2.36 (3H, s, $ArCH_3$), 2.03–1.92 (2H, m, CH_2NCH_2), 1.52 (9H, s, $-OC(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 170.0 ($C=O_{Esters}$), 144.8 (*ipso* $ArSO_2$), 136.8, 136.0 (CHNBoc), 129.8 (*meta* $ArSO_2$), 126.4 (*ortho* $ArSO_2$), 124.3, 123.6, 120.6, 114.8 (C_{Ar}), 81.8 ($-OC(CH_3)_3$, 61.3 ($-C(CO_2Me)_2$), 45.0 ($CHC(CO_2Me)_2$), 33.0 (NCH_2), 31.6 ($ArCH_2$), 28.2 ($-OC(CH_3)_3$), 22.7 (CH_2NCH_2), 21.4 ($ArCH_3$); *m/z* (ESI) 745 $[M+Na]^+$, 723 $[M+H]^+$, 623 $[M+H-C_4H_8OCO]^+$ (Found $[M+Na]^+$, 745.1069 $C_{31}H_{35}N_2O_8SI$ requires $[M+Na]^+$, 745.1057).

2-(1-tert-Butoxycarbonyl-1,2,3,4-tetrahydro-pyridin-4-yl)-2-[1-(toluene-4-sulfonyl)-1H-indol-2-ylmethyl]-malonic acid dimethyl ester 217

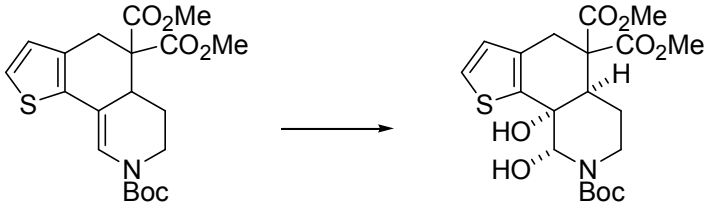


176 **217**

To dry NaH (60% w/w in mineral oils, washed with hexane, 0.0062 g, 0.156 mmol, 1.2 equiv) at 0 °C was added a pre-stirred solution of tetrahydropyridine **176** (0.041 g, 0.130 mmol, 1.0 equiv) and 2-bromomethyl-1-(toluene-4-sulfonyl)-1H-indole **213** (0.052 g, 0.143 mmol, 1.1 equiv) in DMF (0.26 mL). The resulting dark red solution was allowed to warm to room temperature and stirred for 60 h. The reaction mixture was then quenched with sat. $NH_4Cl_{(aq)}$ and the aqueous phase extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (0 → 5% EtOAc–toluene) isolated **217** (0.037 g, 47%) as a yellow oil.

R_f 0.20 (30% EtOAc–hexane); ν_{max} (film) 2951, 1734, 1703 (C=O), 160 (C=C), 1455, 1369 (NSO_2), 1248, 1222, 1174 (C-O), 1092, 754 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 8.17 (1H, d, *J* 8.0 Hz, H_{Ar}), 7.62 (2H, d, *J* 8.0 Hz, *ortho* $ArSO_2$), 7.42 (1H, d, *J* 8.0 Hz, H_{Ar}), 7.31–7.26 (1H, m, H_{Ar}), 7.24–7.18 (3H, m, 1 x H_{Ar} and *meta* $ArSO_2$), 6.95–6.74 (1H, m, CHNBoc), 6.53 (1H, s, H_{Ar}), 5.00–4.82 (1H, m, C*H*CHNBoc), 4.01–3.75 (3H, m, 1 x NCH_2 and $ArCH_2$), 3.71 (3H, s, CO_2Me), 3.70 (3H, s, CO_2Me), 3.22–3.09 (2H, m, 1 x NCH_2 and C*H*C($CO_2Me)_2$), 2.35 (3H, s, $ArCH_3$), 1.82–1.66 (2H, m, CH_2NCH_2), 1.50 (9H, s, -OC($CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 170.1 ($C{=}O_{Esters}$), 144.8 (*ipso* $ArSO_2$), 137.0, 136.5 (CHNBoc), 135.8 (*ipso* C_{Ar}), 129.8 (*meta* $ArSO_2$), 128.2 (*ipso* C_{Ar}), 126.4 (*ortho* $ArSO_2$), 124.4, 123.6, 120.5, 115.0, 111.5 (C_{Ar}), 104.4 (*C*HCHNBoc), 81.8 (-O*C*($CH_3)_3$, 60.5 (-*C*($CO_2Me)_2$), 52.6 (-C(CO_2*Me*$)_2$), 36.8 (*C*HC($CO_2Me)_2$), 30.5 (NCH_2), 28.3 (-OC(*C*$H_3)_3$), 23.7 (*C*H_2NCH_2), 21.6 ($ArCH_3$); *m/z* (ESI) 619 $[M+Na]^+$, 597 $[M+H]^+$, 541 $[M+H\text{-}C_4H_8]^+$, 497 $[M+H\text{-}C_4H_8OCO]^+$ (Found $[M+Na]^+$, 619.2086 $C_{31}H_{36}N_2O_8S$ requires $[M+Na]^+$, 619.2090).

9,9a-Dihydroxy-6,7,9,9a-tetrahydro-4H,5aH-1-thia-8-aza-cyclopenta[a]naphthalene-5,5,8-tricarboxylic acid 8-tert-butyl ester 5,5-dimethyl ester 220

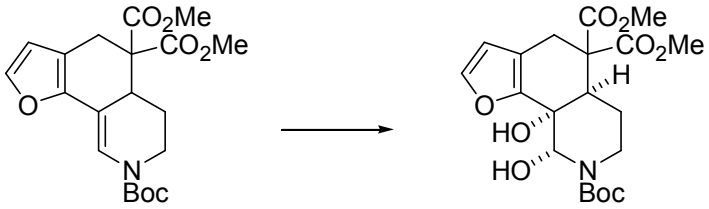


194 **220**

To a stirred solution of tricycle **194** (0.040 g, 0.0983 mmol, 1.0 equiv) and NMO (0.037 g, 0.275 mmol, 2.8 equiv) in acetone (0.9 mL) and H_2O (0.1 mL) at room temperature, was added OsO_4 (4% wt, 0.03 mL, 0.0049 mol, 0.05 equiv). The resulting orange solution was stirred at room temperature for 15 h, after which time it was quenched with sat. $Na_2S_2O_{5(aq)}$ at 0 °C. Stirring was continued for 1.5 h and the reaction mixture was then diluted with H_2O and the aqueous phase extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (60% EtOAc–hexane) isolated **220** (0.0275 g, 63%) as a yellow oil.

R_f 0.21 (60% EtOAc–petrol); ν_{max} (film) 3443 (C-O), 2957, 1735, 1679 (C=O), 1429, 1393, 1255, 1214, 1156 (C-O), 728 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.31 (1H, d, *J* 4.0 Hz, H_{Ar}), 6.91 (1H, d, *J* 4.0 Hz, H_{Ar}), 5.89 (1H, br s, C*H*OH), 3.81 (3H, s, CO_2Me), 3.79–3.66 (4H, m and s, 1 x NCH_2 and CO_2Me), 3.38–3.20 (3H, m, $ArCH_2$ and C*H*C(CO_2Me)$_2$), 2.96–2.85 (1H, m, 1 x NCH_2), 2.02–1.91 (1H, m, 1 x C*H*$_2$$NCH_2$), 1.38–1.28 (10H, m and s, 1 x C*H*$_2$$NCH_2$ and -OC(CH_3)$_3$); δ_C ($CDCl_3$, 101 MHz) 136.3 (*ipso* C_{Ar}), 133.9, 125.9 (*C*$_{Ar}$), 125.9 (*ipso* C_{Ar}), 80.9 (CHOH), 70.9 (*ipso* C-OH), 56.0 (-*C*(CO_2Me)$_2$), 53.0 (-C(CO_2*Me*)$_2$), 41.6 (*C*HC(CO_2Me)$_2$), 28.0 (-OC(*C*H_3)$_3$), 24.9 (NCH_2), 21.1 (*C*H_2NCH_2); *m/z* (ESI) 505, 464 $[M+Na]^+$, 424 $[M\text{-}OH]^+$, 324 $[M\text{-}OH\text{-}C_4H_8OCO]^+$ (Found $[M+Na]^+$, 464.1347. $C_{20}H_{27}NO_8S$ requires $[M + Na]^+$, 464.1355).

9,9a-Dihydroxy-6,7,9,9a-tetrahydro-4H,5aH-furo[3,2-h]isoquinoline-5,5,8-tricarboxylic acid 8-tert-butyl ester 5,5-dimethyl ester 221



201 **221**

To a stirred solution of tricycle **201** (0.100 g, 0.256 mmol, 1.0 equiv) and NMO (0.097 g, 0.717 mmol, 2.8 equiv) in THF (2.4 mL) and H_2O (0.13 mL) at room temperature, was added OsO_4 (4% wt, 0.08 mL, 0.0128 mol, 0.05 equiv). The resulting orange solution was stirred at room temperature for 6 h, after which time it was quenched with sat. $Na_2S_2O_{5(aq)}$ at 0 °C. Stirring was continued for 1 h and the reaction mixture was then diluted with H_2O and the aqueous phase extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (30 → 60% EtOAc–hexane) isolated **221** (0.0393 g, 36%) as an orange oil. δ_H ($CDCl_3$, 400 MHz) 7.36 (1H, br s, H_{Ar}), 6.29 (1H, s, H_{Ar}), 6.21 (1H, br s, C*H*OH), 3.79 (3H, s, CO_2Me), 3.63 (3H, s, CO_2Me), 3.51–3.36 (1H, m, NCH_2), 3.32–3.14 (3H, $ArCH_2$ and C*H*C(CO_2Me)$_2$), 2.89–2.70 (1H, m, NCH_2), 2.01–1.83 (1H, m, 1 x C$H_2$$NCH_2$), 1.53–1.34 (10H, s, -OC(CH_3)$_3$ and 1 x C$H_2$$NCH_2$); δ_C ($CDCl_3$, 101 MHz) 146.6 (*ipso* C_{Ar}), 143.2 (C_{Ar}), 119.0 (*ipso* C_{Ar}), 110.3 (C_{Ar}), 80.7 (-O*C*(CH_3)$_3$), 76.7 (CH-OH), 68.8 (-*C*(CO_2Me)$_2$), 53.0 (-C(CO_2*Me*)$_2$), 42.5 (*C*HC(CO_2Me)$_2$), 28.3 (-OC(*C*H_3)$_3$), 24.8 (*C*$H_2$$NCH_2$); *m/z* (ESI) 448 $[M+Na]^+$, 408 $[M-OH]^+$, 352 $[M-OH-C_4H_8]^+$, 308 $[M+H-C_4H_8OCO]^+$ (Found $[M+Na]^+$, 448.1578. $C_{20}H_{27}NO_9$ requires $[M+Na]^+$, 448.1584).

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