METAL CATALYSED CROSS-COUPLING REACTIONS OF HETEROCYCLES

KIRSTY ADAMS

A thesis submitted to the University of Huddersfield in partial fulfilment of the requirements for the degree of Doctor of Philosophy

The University of Huddersfield (in collaboration with EPSRC Pharmasyn Project)

November 2013

Copyright statement

ABSTRACT

This report describes two methodology studies dedicated towards development of metal catalysed cross-coupling reactions in the synthesis of novel heterocyclic compounds.

Firstly, a Heck-Mizoroki arylation reaction is reported for the direct functionalisation of tetrahydropyridines, towards the synthesis of kainoid analogues. Kainoids are a group of non-proteinogenic pyrrolidine dicarboxylic acids, which have attracted considerable interest because of their potent biological activity, including insecticidal, anthelmintic and neuroexcitatory properties. The ideal synthesis of kainoids would allow the ability to introduce various side chains at the C-4 position to access diverse pharmacologically active kainoid analogues. Tandem asymmetric Heck-Mizoroki arylation reaction and [2,3]-sigmatropic rearrangement provides a quick and efficient way to access these molecules. The Heck-Mizoroki arylation of 1-methyl-1,2,5,6-tetrahydropyridine and its hydrochloride salt is reported, with the arylation in the 3-position of the tetrahydropyridine as the major product. The reaction has been applied to a variety of substituted aryliodides, with promising results, demonstrating functional group tolerance of the method, however isolation and purification of the resulting compounds has remained challengeing. Diarylation of tetrahydropyridines has also been achieved.

Secondly, a new catalytic method for arylative spirocyclisation is reported, using stoichiometric Grignard reagents and iron(III) catalysts, to induce cyclisation of (2-iodo)benzyl ethers of furan in a highly stereoselective manner to produce novel functionalised spirocyclic compounds. Method optimisation and application of a variety of Grignard reagents is reported with aryl cross-coupling achieved in high yields. Alkyl- cross coupling has also been achieved with ethylmagnesium bromide Grignard reagent.

TABLE OF CONTENTS

Word Count: 30452

ACKNOWLEDGEMENTS

ABBREVIATIONS

δ	chemical shift
Δ	Reflux
5-PhNMTP	5-Phenyl-1-methyl-1,2,5,6-tetrahydropyidine
Ac	Acetyl
ADHD	Attention-deficit hyperactivity disorder
aq	aqueous
AMPA	2-Amino-3-(3-hydroxy-5-methyl-4-isoazoyl)-propionic acid
Ar	Aryl
Bn	Benzyl
br	broad
BTPP	*tert*-Butylimino-tri(pyrrolidino)phosphorane
^{n}Bu	*n*-Butyl
^{t}Bu	*tert*-Butyl
CNS	Central nervous system
CPAA	2-Carboxy-3-pyrrolidine-acetic acid
d	doublet
dbm	dibenzoylmethido
DCM	Dichloromethane
dd	double doublet
DMAc	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DNP	2,4-Dinitrophenyl
dpm	dipivaloylmethido
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
eq	equivalents of reagent
Et	Ethyl
Et$_3$N	Triethylamine
GC	Gas chromatography
GCMS	Gas Chromatography Mas Spectroscopy
HCl	Hydrochloric acid
HM	Heck-Matsuda
HPLC	High performance liquid chromatography
hrs	hours
Hz	Hertz

KO^{t}Bu	Potassium *tert*-butoxide
L	Unspecified Ligand
LCMS	Liquid Chromatography Mass Spectroscopy
LHMDS	Lithium hexamethyldisilazaide
M	Molar
m-	meta
m	multiplet
Me	Methyl
MeCN	Acetonitrile
mp	melting point
MPTP	1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine
MS	Molecular sieves
NMDA	*N*-Nethyl-D-aspartate
NMTP	*N*-Methyl-1,2,5,6-tetrahydropyidine
NMR	Nuclear Magnetic Resonance
NMP	N-Methyl-2-pyrrolidone
nOe	nuclear Overhauser effect
o-	ortho
OAc	Acetate
OTf	Trifluoromethanesulfonate
p-	para
Pd(118)	1,1'-Bis(di-tertbutylphosphino)ferrocene palladium dichloride
^{n}Pr	*n*-Propyl
^{i}PrO	*iso*propoxide
q	quartet
rt	room temperature
s	singlet
t	triplet
Tf$_2$O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TPPTS	3,3',3''-Phosphinidynetris(benzenesulfonic acid) trisodium salt
v	volume
w	weight

CHAPTER 1: INTRODUCTION

1.1 Cross-Coupling Reactions – General Overview

During the second half of the 20th century, transition metals have come to play an important role in organic chemistry, leading to the development of a large number of transition metal-catalysed reactions for creating organic molecules. Transition metals have a unique ability to activate various organic compounds and through this activation they can catalyse the formation of new bonds. The development of metal-catalysed cross-coupling over the last four decades has revolutionised carbon-carbon bond construction, allowing chemists to assemble complex molecular frameworks with a wide range of applications, including total synthesis of natural products,[1] medicinal chemistry,[2] and industrial process development[3] as well as chemical biology,[4] materials,[5] and nanotechnology.[6]

Table 1. Common cross-coupling reactions

R'-X + R-MX' →(catalyst) R-R' + MXX'

R = alkyl, aryl, vinyl, allyl, alkynyl, benzyl
R' = alkyl, aryl, vinyl, allyl, alkynyl, benzyl, acyl
X = I, Br, Cl, OTf, OTs
M = Mg, Zn, Cu, Sn, Si, B

substrate (organic electrophile) + coupling partner (organometallic nucleophile) → coupling product + metal halide or salt

Cross-Coupling Reactions	Catalyst	M	R	R'	X
Kumada-Corriu (1972)[7]	Ni or Pd	Mg	Aryl, alkyl, vinyl	Aryl, alkyl, vinyl	Cl, Br, I, OTs
Sonogashira (1975)[8]	Pd/CuI	Cu	Alkyne	Aryl, alkyl, vinyl	Br, I
Negishi (1977)[9]	Ni or Pd	Zn	Aryl, allyl, benzyl, propargyl	Aryl, alkyl, vinyl, alkynyl, benzyl, allyl	Cl, Br, I, OTs
Stille (1978)[10]	Pd	Sn	Aryl, vinyl, benzyl, alkynyl	Aryl, alkyl, vinyl, benzyl, allyl, acyl	Cl, Br, I, OTs
Suzuki (1979)[11]	Pd	B	Aryl, alkyl	Aryl, alkyl, alkynyl	Cl, Br, I, OTs
Hiyama (1988)[12]	Ni or Pd	Si	Aryl	Aryl, alkyl, vinyl	Br, I, OTs

With the exception of the Sonogashira cross-coupling which involves an alkyne, in general, cross-coupling reactions involve combining a substrate (organic electrophile) with a coupling partner (organometallic nucleophile) reacting in the presence of a substoichiometric transition metal catalyst,

most commonly palladium or nickel (typically 1-10 mol%), to form the desired coupling product and a metal halide/salt (Table 1).

1.2 Palladium Catalysed Cross-Coupling Reactions

Palladium-catalysed reactions have become a crucial part of organic synthesis, and have greatly improved the possibilities for chemists in the creation of sophisticated compounds.[13] Among palladium-catalysed transformations, the Heck reaction and related chemistry has become a vital and highly utilised tool for synthetic chemists, being recognised with the award of the Nobel prize in Chemistry in 2010, awarded jointly to Richard Heck, Ei-ichi Negishi and Akira Suzuki for the develoment of palladium-catalysed cross-couplings.

1.2.1 The Heck-Mizoroki Reaction

In the late 1960s,[14] Heck reported that olefins may be arylated in the presence of a stoichiometric amount of arylpalladium complex, generated *in situ* by reacting phenylmercury chloride with palladium(II) chloride or phenylmercury acetate with palladium acetate (Scheme 1).[15] In 1971, Mizoroki reported preliminary results on the palladium(II) chloride catalysed arylation of alkenes by iodobenzene **1** in the presence of potassium acetate as base (Scheme 2).[16]
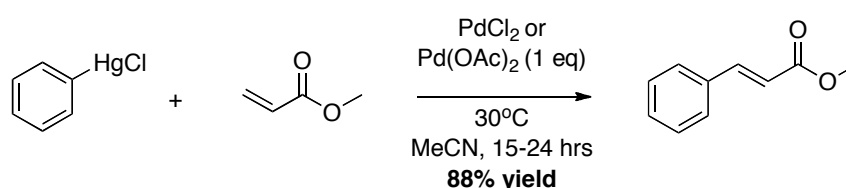
Scheme 1. *Heck's arylation of olefins by group VII metal aryls*
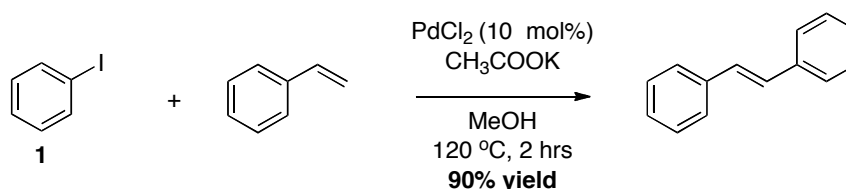
Scheme 2. *Mizoroki's arylation of olefins with aryl iodides catalysed by palladium*

The Heck-Mizoroki reaction is a cross-coupling reaction between aryl halides and olefinic compounds. In the presence of a base and substoichiometric amount of palladium(0) catalyst or palladium(II) pre-catalyst, olefinic compounds are formed, in which the aryl, benzyl or styryl group has replaced an alkenyl proton of the original olefin.[17] Since its discovery, this methodology has been found to be very versatile and applicable to a wide range of aryl species and a diverse range of olefins.

Heck-Mizoroki reactions may proceed through one of two mechanistic pathways: neutral mechanism and ionic mechanism (Scheme 4). Both mechanisms involve the same fundamental processes, initiated by pre-activation of the palladium species to generate a palladium(0) catalyst (**A**, Scheme 3), which

undergoes oxidative addition with an organohalide (**B**, Scheme 3). Association with the olefin (**C**, Scheme 3) and migratory insertion follows, producing an intermediate species (**D**, Scheme 3), which can then undergo β-hydride elimination to release the cross-coupled product (**E**, Scheme 3). In the presence of a base, the activated palladium(0) catalyst is regenerated (**A**, Scheme 3).
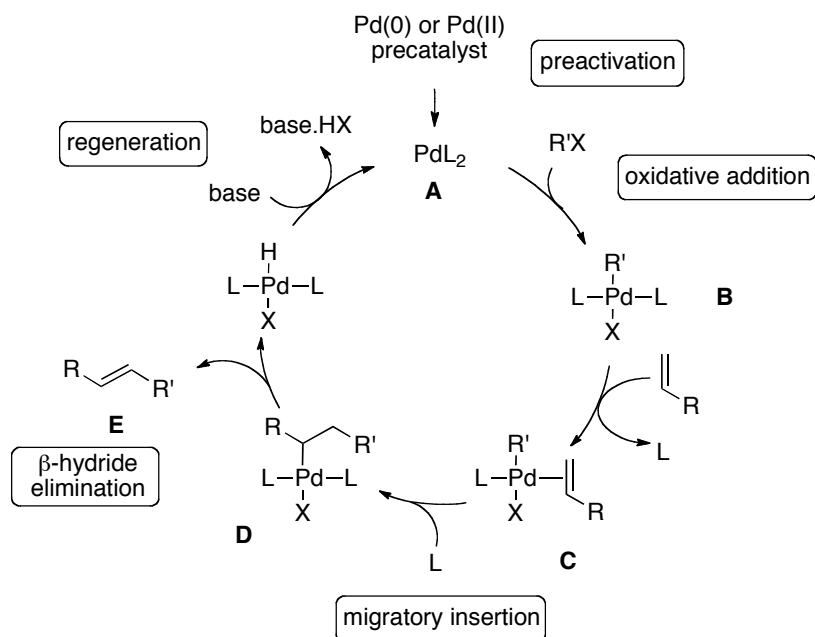
Scheme 3. *General Heck-Mizoroki Catalytic cycle*

By altering reaction conditions, one pathway may be accessed in preference to the other, for example the reaction of alkenyl and aryl halides may be directed into the cationic pathway by the addition of a silver or thallium salt, which acts as a halide scavenger (Scheme 4). Alkenyl and aryl triflates may progress through the neutral manifold by addition of tetrabutylammonium salts.[18]
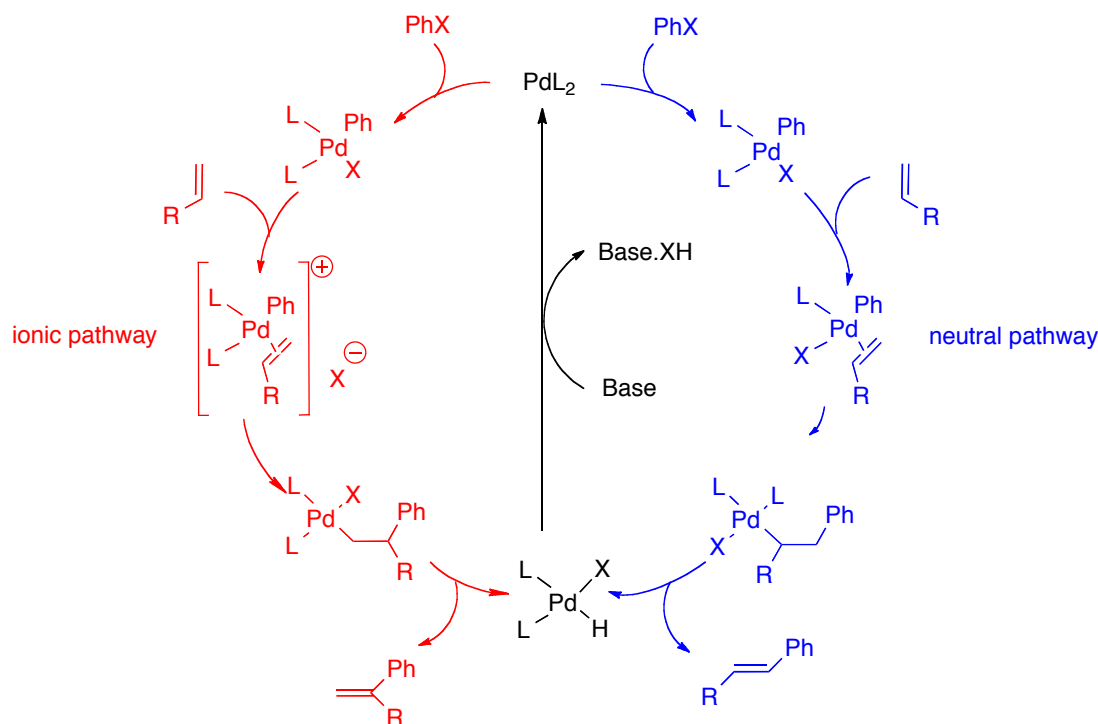
Scheme 4. *Neutral (blue) and Ionic (red) Heck reaction pathways*[19]

Heck-Mizoroki reactions have traditionally been carried out in polar aprotic solvents at high reaction temperatures (often >100 °C), in the presence of a stabilising ligand, which is often phosphine based, and a base to facilitate reductive elimination. Recent advances have however allowed for milder conditions to be developed resulting in many procedures utilising room temperature reactions.[20]

Jeffrey conditions, first reported in the 1980s[21] enabled reaction temperatures to be greatly reduced without the requirement for high catalyst loading, through the combination of a phase-transfer catalyst (a tetraalkylammonium salt) and insoluble base, resulting in an acceleration of the reaction rate. For example, iodobenzene (**1**) was successfully cross-coupled with methyl acrylate (**2**) in the presence of tetrabutylammonium chloride (**3**) in quantitative yield. In the absence of **3** only 2% of the cross-coupled product was obtained (Scheme 5).[22] The acceleration of reaction rate in the presence of tetraalkylammonium salts is reported as due to assistance of the salt in the regeneration of the zerovalent palladium catalyst by decomposition of the hydride-palladium species.
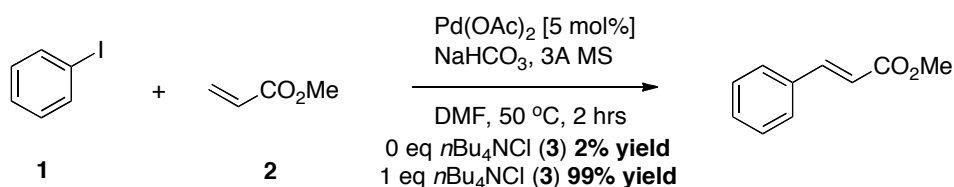
Scheme 5. *Jeffery Conditions*

In the presence of an organic base, Jeffery proposes a nucleophilic mechanism involving hydrogen bonding between the hydridopalladium halide and the ammonium salt (Scheme 6).[23]

11
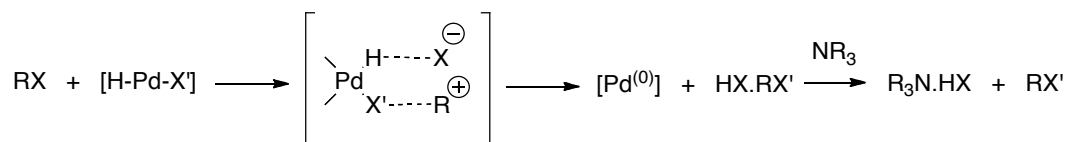
Scheme 6. Jeffery Conditions, where RX = tetraalkylammonium salt

The Heck-Mizoroki cross-coupling of heterocycles has been widely explored and applied to a large array of compounds of varying complexity. For example, Kaufmann utilized reductive Heck conditions in the synthesis of the alkaloid epibatidine (**4**, Scheme 7) utilising triphenylarsine ligand (**5**) in place of the more commonly applied phosphines.[24]   Under reductive Heck conditions, the saturated compound **4** was obtained in place of the standard Heck product, which would lead to a highly strained bridgehead olefinic system.
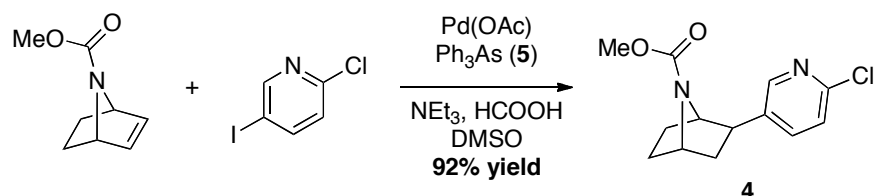
Scheme 7. Synthesis of epibatidine (4)

Triphenylarsine ligands are often utilized due to the observed increase in reaction rate.   Farina and Krishnan demonstrated that in the Suzuki reaction, rate accelerations as large as 10^3 may be observed when arsine ligands are applied in place of the corresponding phosphines.[25] This has been attributed to the soft $AsPh_3$ ligand being thermodynamically and kinetically more labile than PPh_3, which resulted in more rapid ligand dissociation in the rate determining transmetalation step.[26]

Cross-coupling reactions with heterocycles may also be achieved intramolecularly, and in the presence of water as demonstrated by Sinou, resulting in the formation of bicyclic compounds with migration of the double bond (Scheme 8).[27]
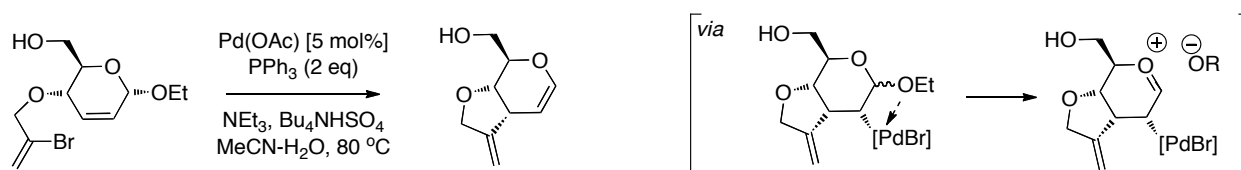
Scheme 8. Intramolecular Heck reaction

For the utilisation of aqueous solvent systems, hydrophilic ligands have been prepared such as triphenylphosphine trisulfonate (TPPTS, **6**) and monoguanidino phosphine (**7**) (Figue 1).[28] These have been applied to a range of cross-coupling reactions including intramolecular reactions of heterocyclic compounds resulting in a widening of reaction scope (Scheme 9).
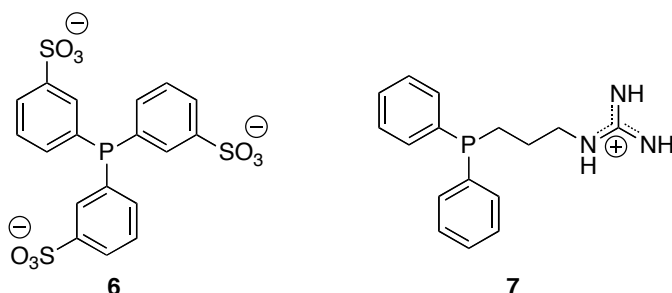
Figure 1. *Water soluble phosphine ligands*
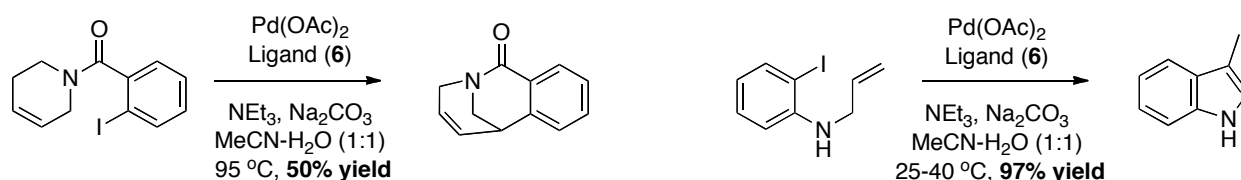
Scheme 9. *Aqueous Intramolecular Heck reaction of nitrogen hetoercycles with Ligand 6*[29]

Only limited Heck cross-couplings on *N*-alkyl heterocycles have been reported.[30] *N*-Acyl heterocycles have been more widely investigated, such as *N*-substituted 2,5-dihydropyrroles, which have been successfully cross-coupled with aryl halides (and triflates) in moderate to high yields (47-70%, Scheme 10).[31]

R = H, X = I,	**68% yield**
R = *o*-OMe, X = I,	**47% yield**
R = *p*-OMe, X = I,	**56% yield**
R = *m*-CF₃, X = I,	**63% yield**
R = *m*-SO₂Me, X = Br,	**70% yield**
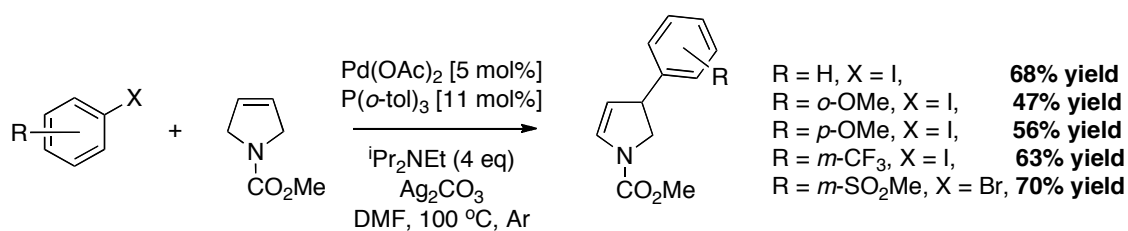
Scheme 10. *Heck reaction of pyrrolines*

1.2.2 The Heck-Matsuda Reaction

Heck reactions performed with arenediazonium salts are frequently referred to as the Heck–Matsuda (HM) reaction to acknowledge the extensive investigations carried out by the group of Matsuda in developing this methodology. The HM reaction, first reported by Tsutomu Matsuda in 1977,[32] is a palladium-catalysed arylation of olefins with arenediazonium salts in place of the traditionally used halides or triflates. The arylation of ethylene (**9**) may be achieved in good yields with a variety of substituted aryldiazonium tetrafluoroborate salts (**10**) at room temperature in only one hour (Scheme 11).[33]

R = Me, CH₂O, CO₂Et, Cl, Br, NO₂
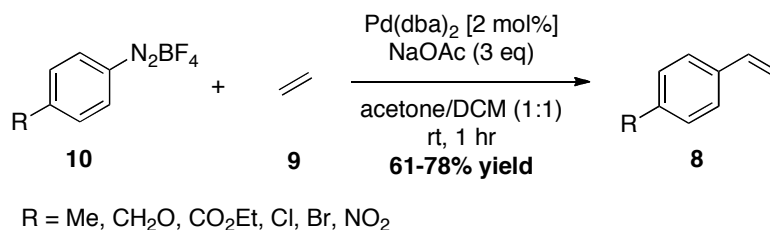
Scheme 11. *Heck-Matsuda reaction of ethylene (**9**) with functionalised diazonium tetrafluoroborates (**10**)*

Later, Matsuda evaluated different olefins and catalytic systems with arenediazonium salts, with highest yields obtained using $Pd_2(dba)_3$ as catalyst, NaOAc as base, and acetonitrile as solvent.[34]

Amongst the various arylating agents currently available for the Heck reaction, arenediazonium salts are among the least explored, despite offering some economic and environmental advantages when compared to traditional electrophiles (halides and triflates).

Reactions involving the diazonium salts are often more efficient than the Heck-Mizoroki reaction, requiring a reduced reaction time, providing the arylated products faster.[35] The efficiency and high reactivity of arenediazonium salts are related to the ease with which they undergo oxidative addition with zerovalent palladium at the $C–N_2^+$ bond,[36] generating highly reactive cationic palladium species during the catalytic cycle (Scheme 12). Consequently, the reactions can be carried out at milder temperatures.

Aryl halides may pass through a neutral or ionic Heck-Mizoroki mechanism (Scheme 4)[37] however, Heck reactions involving arenediazonium salts operate under a polar cationic mechanism, due to the $Pd–N_2$ bond being labile and easily ionizes after oxidative addition to liberate molecular nitrogen, leading to the cationic palladium species (Scheme 12).
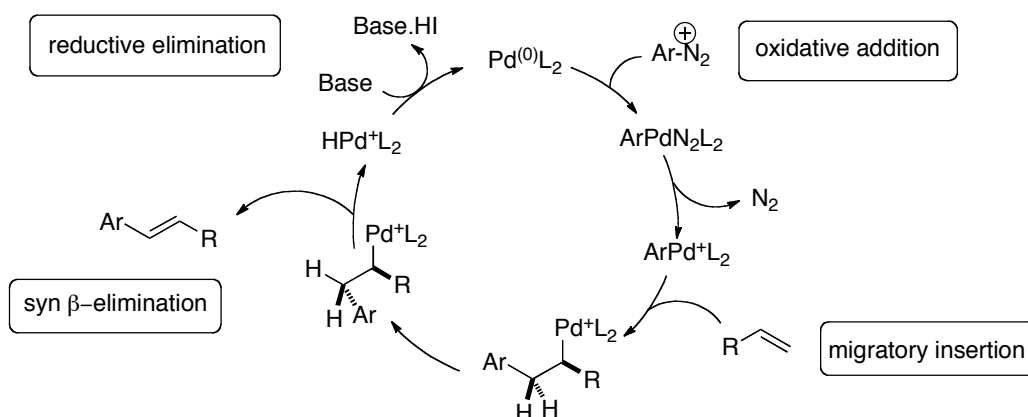
Scheme 12. *Mechanism of the Heck-Matsuda reaction*

In general terms, the catalytic cycle for the HM arylation reaction involves four steps; oxidative addition of Pd^0 with the arenediazonium salt resulting in a cationic palladium intermediate by elimination of N_2,

migratory insertion leading to the formation of a new C-C bond, *syn* β-hydride elimination to form the Heck adduct and palladium hydride, and reductive elimination to restore the active catalyst (Scheme 12).[38]

Although arenediazonium salts undergo oxidative addition with Pd with relative ease, the subsequent cationic intermediate is only weakly stabilised by the coordinating solvent (or acetate) and is therefore prone to aggregation, forming inactive palladium-black (Figure 2). Phosphanes are able to transfer an electron to arenediazonium salts, resulting in an arene radical, destabilising the cationic palladium intermediate. The HM reaction is therefore incompatible with phosphanes.
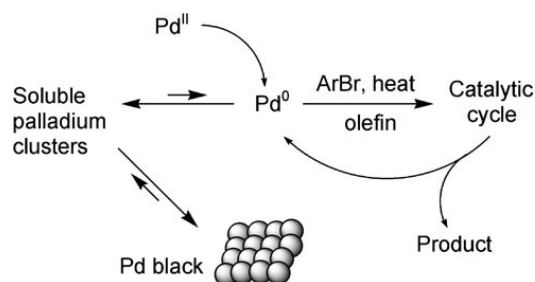
Figure 2. *Palladium black aggregation*[39]
Reproduced from ref. 39 with permission from The Royal Society of Chemistry.

Carbenes derived from imidazole, pyrazole and triazole derivatives have been reported to be good, stabilising ligands for palladium due to the ability for σ-donation, forming stable metal adducts.[40] These carbene complexes have high thermal stability, and are able to be used in place of phosphine ligands due to their nucleophilic behaviour. Carbene ligands are also inexpensive, and can be easily prepared from azolium salt precursors which are are stable in the presence of air and moisture.[41]

Song reported the cross-coupling of a range of olefins including methyl acrylate (**2**) (Scheme 13) with aryl diazonium tetrafluoroborates at room temperature in the presence of an imidazolium carbene; *N,N*-bis(2,6-diisopropylphenyl)dihydroimidazolium chloride and palladium(II) acetate (**11**, 2 mol %), giving products within 2 to 4 hours in 80–90% yields.[42]

R = H, **68% yield**   R = *o*-OMe, **70% yield**
R = *o*-Me, **66% yield**   R = *p*-OMe, **71% yield**
R = *m*-Me, **64% yield**   R = *p*-Br, **81% yield**
R = *p*-Me, **65% yield**
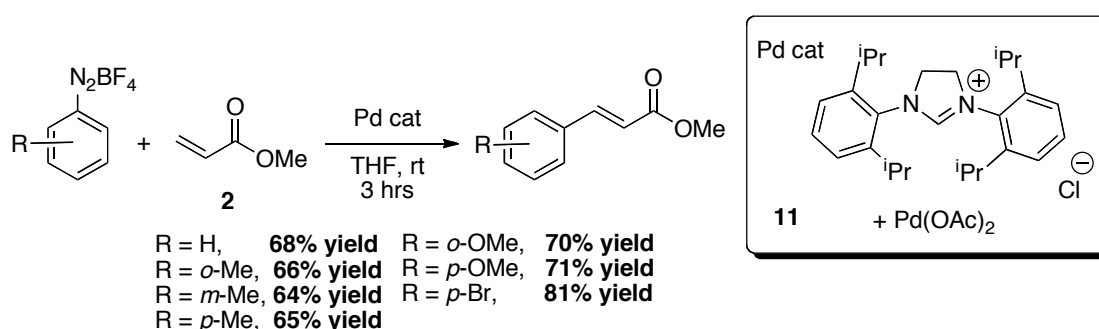
Scheme 13. *Heck-Matsuda reaction of methylacrylate (**2**) with functionalised diazonium tetrafluoroborates*

Heck-Matsuda reactions have also been applied to cross-coupling of heterocycles, such as in the synthesis of the alkaloid codonopsine (**12**), resulting in high yields of the target product under phosphine-

free conditions, eliminating the need for expensive ligands (Scheme 14).[43]
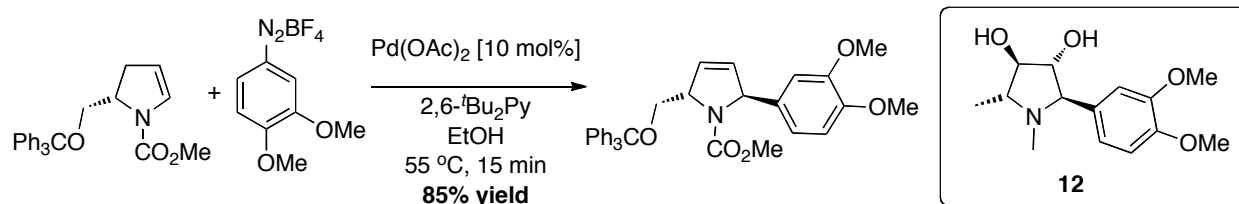
Scheme 14. *Heck-Matsuda Reaction in synthesis of codonopsine*

Correia reported the ligand-free Heck-Matsuda arylation of substituted acrylates using several arenediazonium tetrafluoroborates, without requiring anhydrous, inert conditions. This resulted in the synthesis of the corresponding substituted acrylates in moderate to high isolated yields (43-92%) irrespective of the electronic nature of the substituents on the arenediazonium tetrafluoroborates employed (Scheme 15).[44]
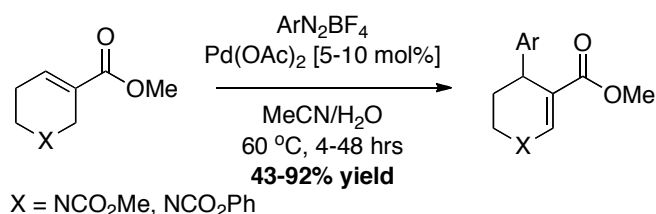
Scheme 15. *Heck-Matsuda Reaction*

Correia also reported asymmetric Heck-Matsuda arylations using chiral bisoxazoline ligands, with good to excellent yields (63–91%) in enantiomeric excesses from 60% to 84% ee (Scheme 16).[45]

R = 3-CF$_3$	**83%**	(84% ee)
R = 4-I	**76%**	(74% ee)
R = 3-NO$_2$	**74%**	(72% ee)
R = 4-NO$_2$	**63%**	(76% ee)
R = 4-OMe	**91%**	(70% ee)
R = 2-OMe	**76%**	(60% ee)
R = 4-Ph	**83%**	(60% ee)
R = 3-Cl, 4-OMe	**87%**	(74% ee)
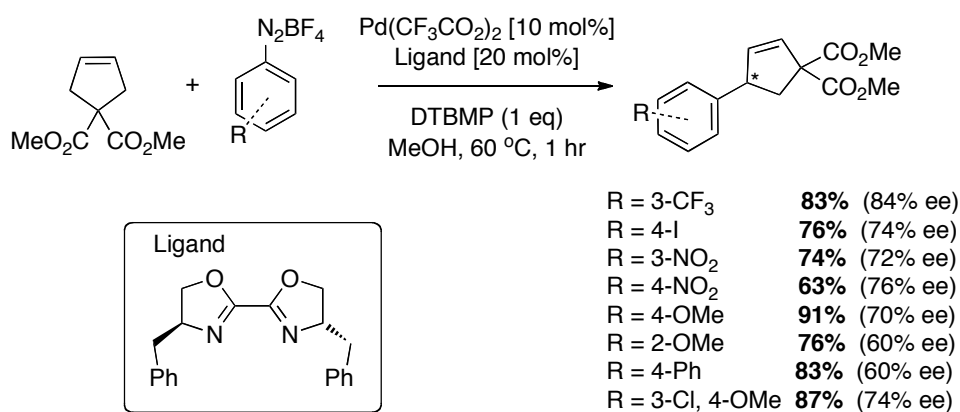
Scheme 16. *Asymmetric Heck-Matsuda Reaction*

1.3 Alternative Metal Catalysts for Cross-Coupling Reactions

As described, metal complexes have become essential for organic synthesis, allowing access to a wide variety of fast, efficient, clean and selective processes.[46] The demand for metal-based reagents, especially those which can be used catalytically in processes such as cross-coupling, or which can be recovered and recycled is continuing to increase. Many catalysts have a high toxicity and are often

expensive, as they are derived from heavy or rare metals. Both the expense and toxicity of these reagents are drawbacks for large scale application, increasing the cost of production and requiring thorough purification to remove any trace metals from product streams. Replacing materials with metals of higher natural abundance, particularly in applications that use large amounts of catalysts is highly beneficial. Due to the increased abundance, these materials are often less susceptible to supply fluctuations and therefore cheaper.[47]

Although palladium loadings in catalytic processes can be very low and so the financial cost of the catalyst is not a significant facter in the overall process, palladium is not an abundant metal, and therefore has limited supply. One of the most abundant metals on Earth is iron (second to aluminium, iron abundance in Earth's crust is 5.0% by weight, palladium 0.015% by weight). Although iron is inexpensive and environmentally benign, it is only recently that iron-catalysed processes have begun to be investigated. This includes cross-coupling reactions, with some very efficient processes recently being reported,[48] which have been shown to be able to compete with other more commonly used metals.

The interest in iron catalysis may be attributed to the fact that iron salts are inexpensive, readily accessible, generally nontoxic and environmentally benign. Despite the advances in iron-catalysed cross-coupling, mechanistic understanding remains largely unknown due to the actual active catalytic species usually being generated *in situ* as ill-defined but highly sensitive and short-lived entities.

Various oxidation states for the catalytic species have been reported including Fe(-II)/Fe(0), Fe(0)/Fe(II) and Fe(I)/Fe(III). Other mechanisms not based on redox processes have also been reported, applying nucleophilic organoferrate complexes of a different composition as the intermediates, based on principles governing organocopper chemistry.[49] Overall, the chemistry of iron represents an under-investigated area of organometallic research.

Since the discovery of the reaction of compounds with the general formula RMgX with carbonyl compounds by Grignard in 1900,[50] efforts have been devoted to investigating the reactivity of such species and to develop new applications in the synthesis of natural and synthetic compounds. Grignard reagents continue to be synthetic tools of high importance for organic chemists and are frequently used in the laboratory.[51] In addition, numerous industrial applications have also been reported, such as in the synthesis of the nonsteroidal anti-inflamatory drug Naproxen (Scheme 17).[52] The introduction of transition metal catalysts has greatly expanded the reactivity of Grignard reagents and therefore their utility in organic synthesis.
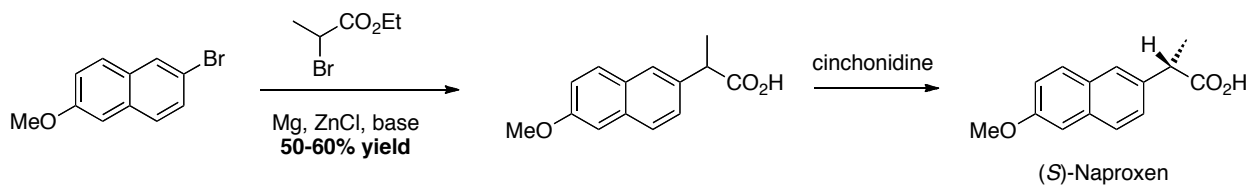
Scheme 17. Grignards in the synthesis of Naproxen

As early as 1972 Corriu and Kumada independently developed nickel-catalysed coupling reactions of Grignard reagents with alkenyl halides (Scheme 18 and Scheme 19 respectively).[53] However, the year before, Kochi had shown that iron salts could be used as catalysts for the same purpose (Scheme 20).[54] These early iron-catalysed cross-couplings were performed with vinyl bromide derivatives and alkylmagnesium reagents, with catalytic iron(II) or iron(III) salts.

$$R = 4\text{-}OMeC_6H_4$$
$$R = 4\text{-}MeC_6H_4$$
$$R = 3\text{-}OMeC_6H_4$$
$$R = 4\text{-}BrC_6H_4$$
$$R = 2,4\text{-}di\text{-}MeC_6H_3$$
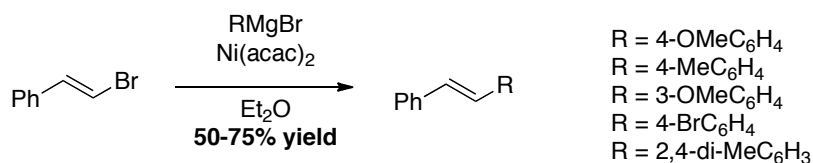
Scheme 18. Corriu's nickel-cataysed coupling with Grignards

Scheme 19. Kumada's nickel-cataysed coupling with Grignards

Scheme 20. Kochi's iron catalysed cross-coupling with Grignards

Important contributions in the cross-coupling of alkenyl halides with organometallic species were made by Cahiez, who greatly increased the scope of the reaction by demonstrating the possibility, in the presence of iron acetylacetonate (**13**), of the cross-coupling of alkenyl iodides, bromides and chlorides with Grignard reagents. Cahiez first recognised the advantages associated with the use of *N*-methyl-pyrrolidinone (NMP, **14**) in the iron-catalysed vinylation process leading to high yields, with *ca.* 80% yields of the cross-coupling products compared to the same reaction in THF, where less than 5% yield was obtained (Scheme 21).[55] The discovery of this solvent effect had significant consequences in the development of the process.
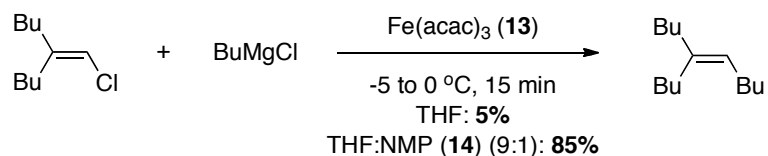
Scheme 21. Effect on reaction yield by incorporation of NMP co-solvent

NMP as a co-solvent suppresses the formation of side products formed through halogen-hydrogen reduction. It also allows alkenyl halides to react readily with a variety of aryl and alkyl Grignard reagents to afford highly substituted olefins with retention of configuration and drastically improved yields.[56] The polar nature of **14** is believed to help stabilise the iron organometallic species in the catalytically active species.[57]

Cahiez also investigated the nature of the iron salt used as catalyst, and observed no difference by replacing Fe(acac)$_3$ (**13**) with Fe(dpm)$_3$, Fe(dbm)$_3$ or FeCl$_3$. However, in the absence of **14** the catalyst deeply influences the course of the reaction. In the absence of NMP, Fe(dpm)$_3$ and Fe(dbm)$_3$ were found to be more efficient catalysis than Fe(acac)$_3$, and lowest yields obtained with FeCl$_3$,[58] again suggesting that **14** has a stabilising effect on the iron-organometallic species.

Mechanistic studies of the metal-catalysed (iron and cobalt) cross-coupling reaction of Grignard reagents with vinyl bromides have been carried out by Hoffmann,[59] in which an enantiomerically enriched chiral organomagnesium species was used (Scheme 22). With Fe(acac)$_3$ as catalyst, the transmetallation step was suggested to be a a single electron transfer (SET) process. This was based on observed partial racemisation of the final product.
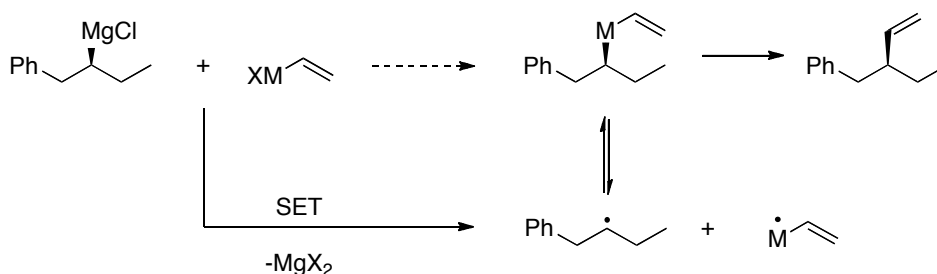
M = Co or Fe of unknown oxidation state

Scheme 22. Hoffman's mechanistic study of the metal-catalysed cross-coupling

Both Kochi[60] and Fürstner[61] have proposed catalytic cycles for the iron catalysed cross-coupling, from Fe(III) pre-catalyst where Fe(I) is the reported active species (Scheme 23, cycle A), and from Fe(II) pre-catalyst where Fe(-II) is the reported active species (Scheme 23, cycle B).
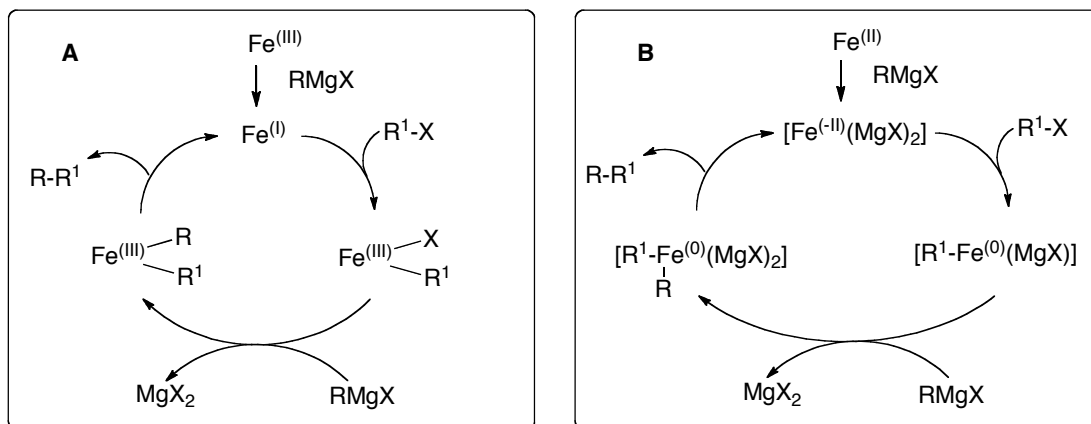
Scheme 23. *Kochi (**A**) and Fürstner (**B**) proposed iron catalysed cross-coupling catalytic cycles*

Fürstner conducted extensive investigations with a series of organoiron complexes and showed that Ph/MeMgBr and EtMgBr (and higher chains) exhibit significantly different behavior. They reported that in attempted cross-coupling reactions of aryl chlorides with EtMgBr (or higher alkyl Grignard reagents) in the presence of Fe(acac)$_3$ (**13**) or FeCl$_n$ (n = 2, 3) as precatalyst, the desired product was obtained in virtually quantitative yield within minutes, whereas MeMgBr failed to react (Scheme 24).
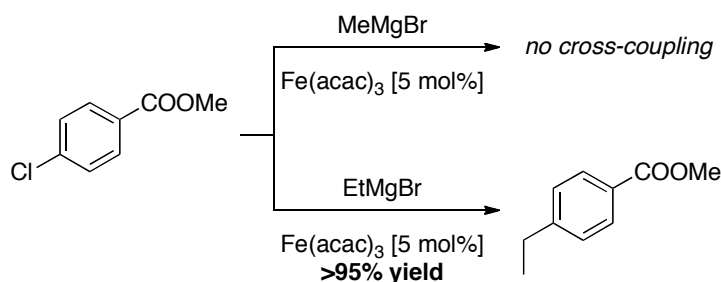
Scheme 24. *Behaviour of different Grignard reagents towards cross-coupling*

Fürstner characterised a number of iron complexes, and concluded that nucleophiles unable to undergo β-hydride elimination, such as MeLi, PhLi, or PhMgBr, rapidly reduce Fe(III) to Fe(II) and then exhaustively alkylate the metal centre, whereas higher chains form a different iron complex intermediate which undergoes cross-coupling.[62]

Iron-catalysed cross-coupling has been shown to be sensitive to steric hindrance exerted by α-substituents at the cross-coupling site. Fürstner examined the cross-coupling of a variety of cyclic alkenyl triflates and found a significant reduction in the reaction yield in the presence of a methyl substituent α- to the triflate (Table 2).[63]

Table 2. *Effect of an α-substituent on cross-coupling*

$$R^1\text{-OTf} \xrightarrow[\text{THF/NMP, -30 °C}]{\text{RMgX, Fe(acac)}_3} R^1\text{-R}$$

Entry	R^1X	RMgX	R-R^1	Yield (%)
1	(structure, OTf)	C$_4$H$_9$MgCl	(structure, C$_4$H$_9$)	80%
2	(structure, OTf)	C$_4$H$_9$MgCl	(structure, C$_4$H$_9$)	53%
3	(structure, OTf)	C$_{14}$H$_{29}$MgCl	(structure, C$_{14}$H$_{29}$)	67%
4	(structure, OTf)	C$_{14}$H$_{29}$MgCl	(structure, C$_{14}$H$_{29}$)	17%

1.3.1 Synthesis of Grignard Reagents

Grignard reagents are classically prepared by combining activated magnesium with an organic halide, in a suitable anhydrous ethereal solvent (such as THF or diethyl ether).[64] Magnesium metal is usually unreactive due to the formation of an oxide layer on its surface, and therefore is often activated by the addition of small amounts of iodine, 1,2-diiodoethane or 1,2-dibromoethane.   The ethereal solvent also acts to dissolve and stabilise the Grignard reagents, by forming Lewis acid base complexes (Scheme 25).

$$\text{Mg + RX} \xrightarrow{\text{Et}_2\text{O}} \text{RMgX} \qquad \left[\begin{array}{c} R \diagdown \quad :OEt_2 \\ Mg \\ X \diagup \quad :OEt_2 \end{array} \right]$$

Scheme 25. *Synthesis of Grignard reagents, with stablilisation from co-ordinating solvent*

The use of activated magnesium for the preparation of Grignard reagents is not always possible, since highly electrophilic functional groups inhibit the insertion of magnesium into the carbon-halogen bond.[65] Knochel's chemoselective magnesium-iodine exchange reaction provides an alternative route to these highly functionalised Grignard reagents.[66] The method has been extensively utilised in the synthesis of alkenyl-, aryl- and heteroarylmagnesium reagents which are not commercially available. The process involves exchange of a halide with isopropyl magnesium bromide (**15**) or chloride, to give the desired Grignard, which may then be utilised in subsequent cross-coupling reactions (Scheme 26). In this way, functional groups such as iodides, esters, imines, nitriles and nitro groups can be incorporated in a wide range of aromatic and heterocyclic organomagnesium reagents.
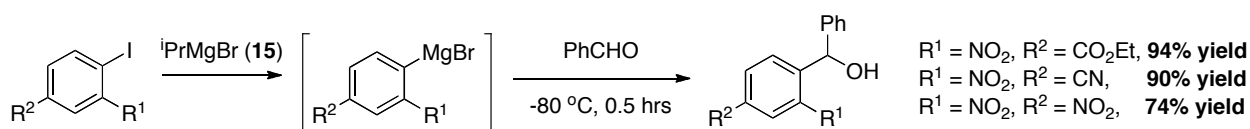
Scheme 26. *Knochel's magnesium iodine exchange reaction*

The magnesium-halogen exchange process occurs due to the position of the equilibrium lying in favour of the formation of the aryl Grignard over the alkyl Grignard as a result of the stability of the intermediate carbanion species. sp-Hybridised carbanions are of higher stability than sp^2-hydridised carbanions, which are of higher stability than sp^3-hybridised carbanions (Scheme 27).
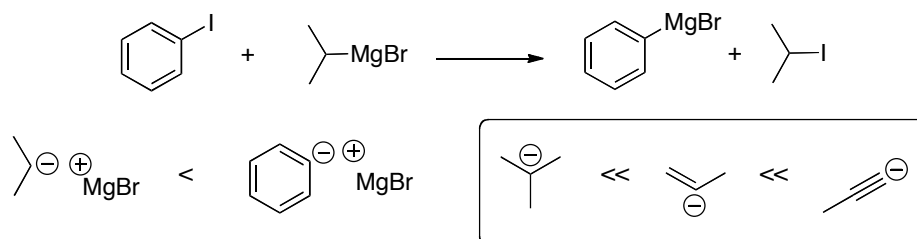
Scheme 27. *Stability of metal carbanions in the magnesium iodine exchange reaction*

Hence, the formation of aryl Grignards is the favoured process. The rate of magnesium-halogen exchange is also accelerated by electron-withdrawing groups on the aromatic ring, and is slowed by electron-donating groups.[67]

1.3.2 Metal-Catalysed Cyclisations in the Generation of Spirocycles

In 1900, Baeyer first introduced the term 'spirocyclane' to represent two rings which are connected through one atom to form a rigid tetrahedral center fused at a common quaternary carbon center (spiro carbon atom).[68] Spirocyclic structures have been found in a wide range of natural and clinically valuable compounds,[69] access to which may be achieved through synthetic construction of these spirocentres.

Spirocyclic compounds are named based on the number of carbon atoms in the ring structure, with the given prefix *spiro*[x.y], where x and y are the number of atoms in the links that make each ring, excluding the spirocentre itself, listed in increasing magnitude. For substituted spiroalkanes, the rings are numbered starting on the smallest ring attached to the spirocentre (for examples see Figure 3).

spiro[2.5]octane   spiro[4.5]decane
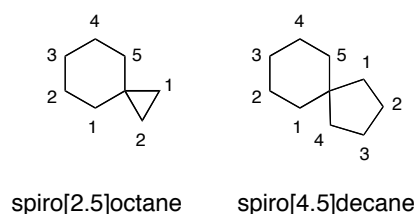
Figure 3. *Spiroalkane nomenclature*

The construction of spirocyclic centres can be categorised into four main synthetic approaches: alkylation,

rearrangement, cycloaddition and cleavage of bridged systems. Intramolecular alkylation of a tertiary carbon center is one of the most common methods of constructing spirocentres. Iwata[70] reported the stereoselective synthesis of spiro[5.5]undecane systems using Lewis acid promoted spiroannulation of acetals (Scheme 28). A tandem reaction involving ynamines was used by Ficini[71] during the synthesis of acoradiene (Scheme 29). Spiroannulation was employed by Brands and DiMichele to synthesise the functionalised pyrrolo[2,3-*i*]isoquinoline subunit of manzamine A (Scheme 30).[72]
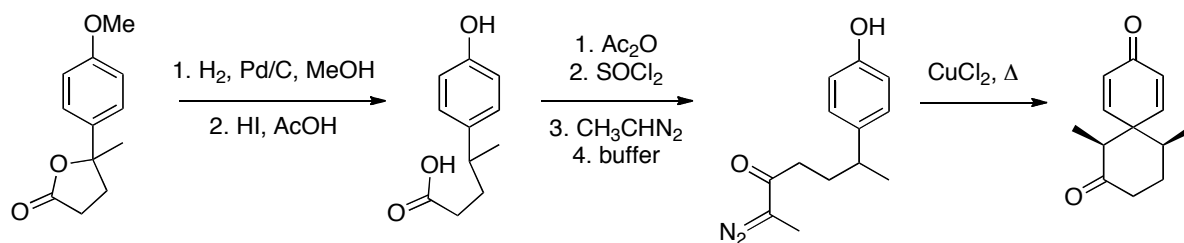
Scheme 28. *Iwata's stereoselective synthesis of spiro[5.5]undecane systems*
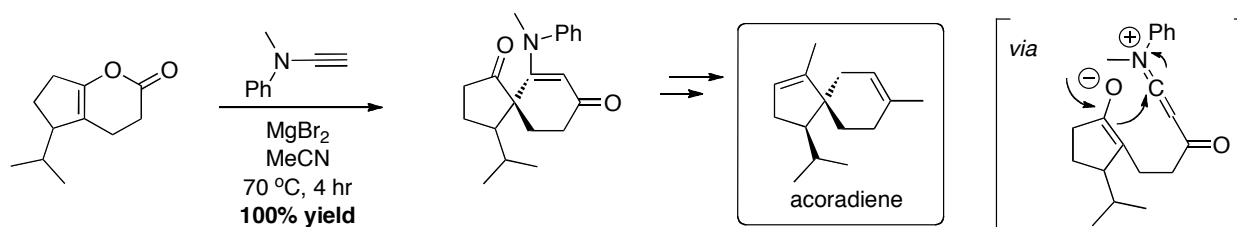
Scheme 29. *Ficini's spiroannelation reaction towards acoradiene synthesis*
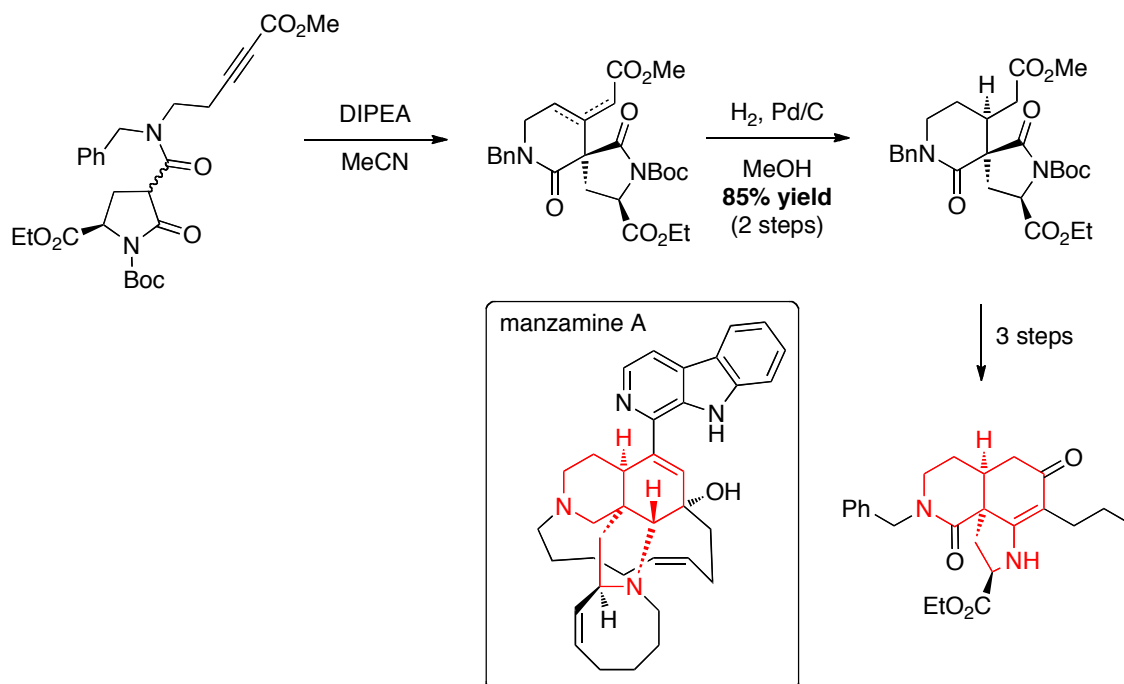
Scheme 30. *Brands and DiMichele's synthesis of functionalised pyrrolo[2,3-i]isoquinoline*

Heck reactions have also been employed in the generation of spirocenters. Overman reported a intramolecular palladium-catalysed Heck reaction of trienyl triflate in a bis-cyclisation, with excellent yield

and modest enantioselectivity (Scheme 31).[73]
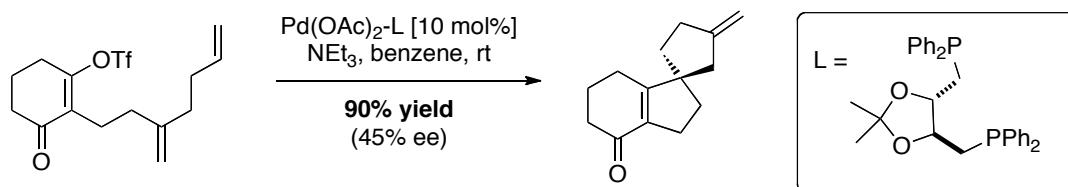
Scheme 31. *Overman's intramolecular Heck reaction*

Overman improved the enantioselectivity in the reported asymmetric synthesis of spiro-oxindoles from the corresponding aryl iodide, by palladium catalyzed cyclisations using the chiral ligand BINAP (Scheme 32).[74] Overman found that cyclisations also occurred with good enantioselectivity without incorporation of the silver salt (an HI scavenger).
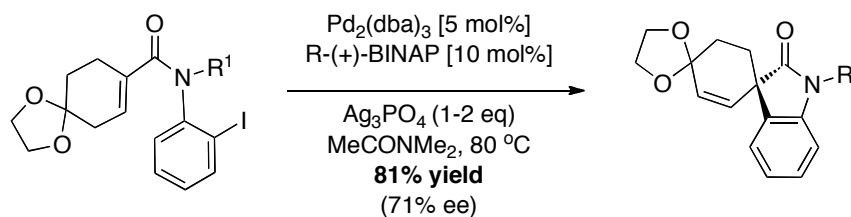
Scheme 32. *Overman's asymmetric intramolecular Heck cyclisation*

1.4 Project Goals

This project had two main aims, firstly to employ metal-catalysed processes in the development of a simplified method to functionalise nitrogen containing heterocycles, which may allow access to compounds of pharmaceutical interest. These functionalised compounds are intended for further application to rearrangement chemistry which has previously been developed in our group to access kainoids. In order to access these kainoids with the desired stereochemistry, exploitation of quaternary cyclic nitrogen centres were investigated in an attempt to access single enantiomers of quaternary ammonium salts. When these salts are applied to the developed rearrangement chemistry, access to kainoid analogues with controled facial selectivity can be achieved, implimenting desired stereochemistry.

Through investigations into metal catalysed cross-coupling reactions, more economically viable and lower toxicity metals were investigated, predominantly iron. Althought the cross-coupling reaction of primary interest was not successful in the presence of iron, a second arylative-spirocyclisation reaction was developed which is also reported herein.

1.5 Kainic Acid and Analogues as Target Molecules

In the mammalian central nervous system (CNS), glutamic acid (**16**) is the primary excitatory neurotransmitter.[75] Abnormalities in glutamatergic transmission at synapses in the brain have been linked to a wide range of CNS disorders which includes Huntington's, Alzheimer's and Parkinson's

diseases.[76] The development of glutamate mimics which may regulatate these abnomalities has become a challenging synthetic target for chemists in the potential treatment of symptoms associated with these disorders.

Amino acids bind to cellular trans-membrane proteins, leading to a conformational change of the receptor protein, which stimulates a signal within the cell *via* secondary messengers. The mode of action of the secondary messenger determines receptor type as ionotropic or metabotropic. Ionotropic receptors rapidly activate cation specific ion channels (Na^+, K^+ and Ca^{2+}), whereas metabotropic receptors are large, single-membrane proteins coupled *via* G proteins to intracellular signaling enzymes or ion channels in comparatively slower processes.[77]

The ionotropic receptors can be divided into three subgroups, named according to their agonists: kainic acid (**17**), *N*-methyl-D-aspartate (NMDA, **18**) and 2-amino-3-(3-hydroxy-5-methyl-4-isoazoyl)-propionic acid (AMPA, **19**) receptors (Figure 4).

(L)-Glutamic Acid **16** Kainic Acid **17** NMDA **18** AMPA **19**
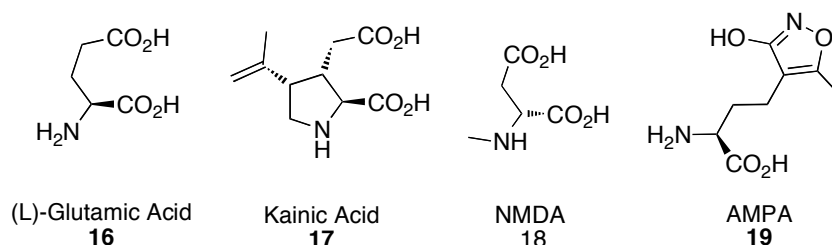
Figure 4. *Glutamic acid and ionotropic receptors*

Kainic acid (**17**) is the parent member of the kainoid amino acid family;[78] a group of non-proteinogenic pyrrolidine dicarboxylic acids, with three asymmetric centres at positions 2, 3 and 4 of the pyrrolidine ring. Kainic acid (**17**, originally known as digenic acid) was first isolated in 1953 from the Japanese marine algae *Digenea simplex*.[79] Kainoids have attracted considerable interest largely because of their potent biological activity, in particular their insecticidal, anthelmintic and neuroexcitatory properties.[80] Kainate analogues are therefore compounds of pharmacological interest.

Trans-2-carboxy-3-pyrrolidine-acetic acid (CPAA **20**) is an important conformationally restricted glutamate analogue bearing a pyrrolidine dicarboxylic acid structure,[81] which represents the common amino acid moiety in many naturally occurring members of the kainoid family, including kainic acid **17**,[82] the acromelic acids **21** and domoic acid **22**[83] (Figure 5).
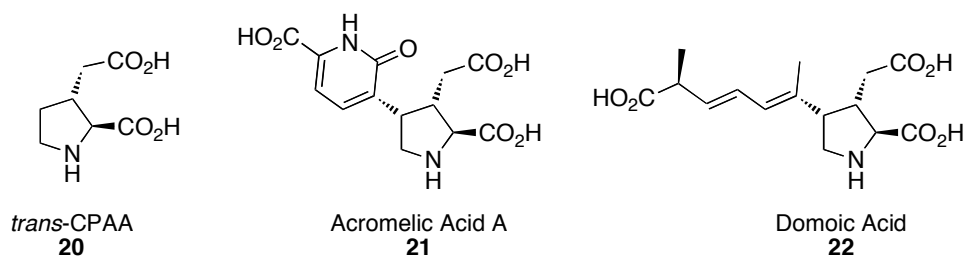
Figure 5. *CPAA (**20**), acromelic acid A (**21**) and domoic acid (**22**)*

Acromelic acid A (**21**) is a potent neuroexcitatory amino acid member of the kainoid family, which was first isolated from the poisonous fungi *Clitocybe acromelalga Ichimura* (Japanese name, *Dokusasako*) by Shirahama, who isolated 110 mg from 16.2 kg of fungus.[84]

Synthesis of the kainoid amino acids represents a considerable challenge, as the synthesis is required to address the formation of a pyrrolidine-2-carboxylic acid with defined stereochemistry at three adjacent chiral centres of the ring, bearing *cis*-stereochemistry at the 3 and 4 positions.   In addition an ideal synthesis would allow the ability to introduce various side chains at the C-4 position to afford various functionalised kainoid analogues.

Since first being isolated, numerous groups have investigated the synthesis of acromelic acid A (**21**) and analogues, including Takano, who reported the synthesis of **21** in 1987 *via* 12 steps, starting from (*S*)-O-benzylglycidol employing intramolecular [1,3]-dipolar addition as the key reaction (Scheme 28),[85] Benetti utilised tandem Michael reaction methodology to synthesise **21** in 1993 (Scheme 29),[86] and Baldwin reported the total synthesis *via* 13 steps in 9% yield in 1998 from commercially available *trans*-4-hydroxy-L-proline (Scheme 30).[87]
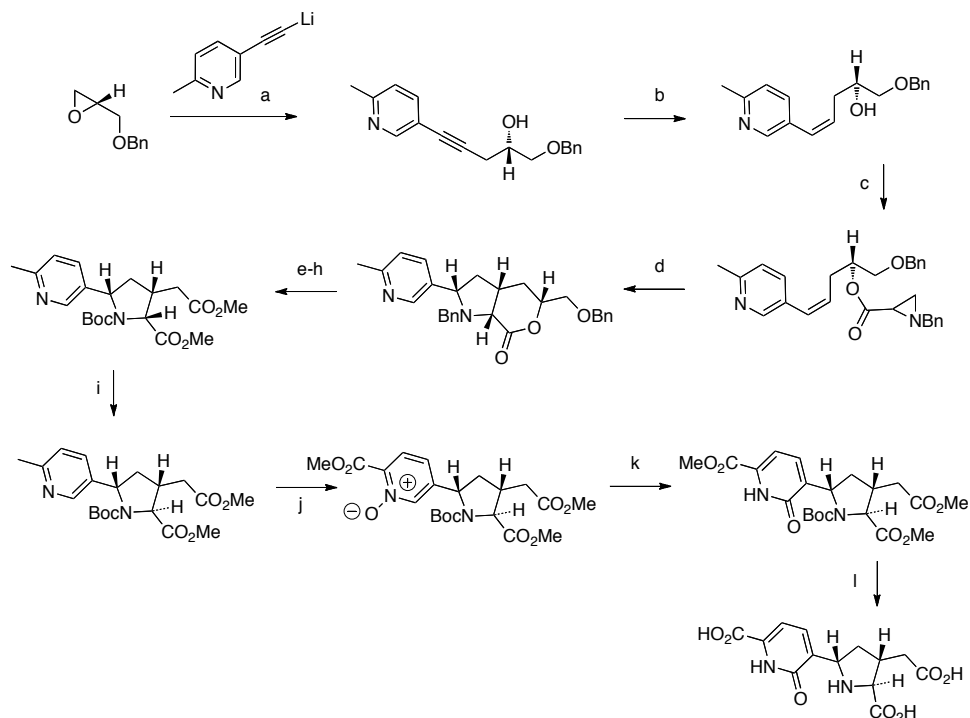
(a) THF-HMPA, -70 °C to rt, 8 hrs; (b) H₂/Lindlar catalyst, benzene, quinoline, rt, 24 hrs; (c) BrCH₂CHBrCOCl, NEt₃, DCM, 0 °C, 2 hrs, then C₆H₅CH₂NH₂, 0 °C, 2 hrs; (d) 200 °C, 1.7% in o-C₆H₄Cl₂, 1.5 hrs; (e) H₂/10%Pd-C, MeOH-HCl, rt, 3 days; (f) (Boc)₂O, 3N NaOH-dioxane (1:1), rt, 1 hrs, NaIO₄₍aq₎, 0 °C, 15 min, then KMnO₄₍aq₎, 0 °C, 2 hrs; (g) conc H₂SO₄, MeOH, reflux, 24 hrs; (h) (Boc)₂O, NEt₃, DCM, rt, 15 mins; (i) NaH, DBU, benzene, rt, 5 hrs; (j) mCPBA, DCM, rt, 24 hrs; (k) (CF₃CO)₂O, DMF, rt, 45 hrs; (l) KOH, TFA[88]

Scheme 33. *Takano's synthesis of acromelic acid A from (S)-O-benzylglycidol*
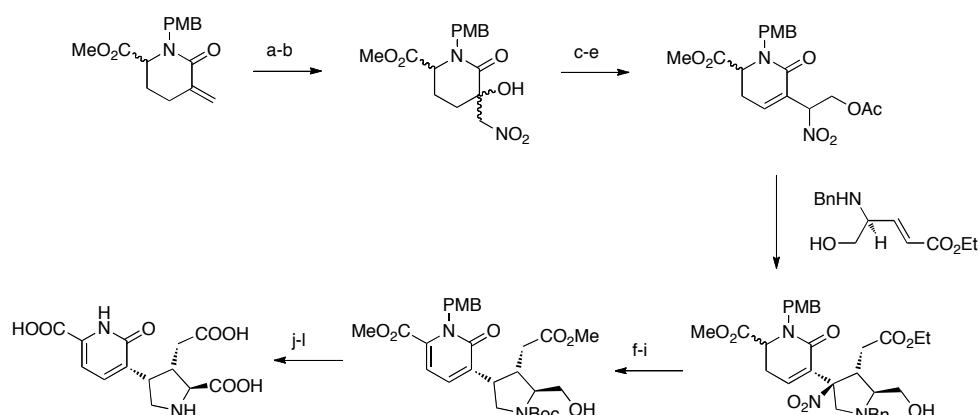
(a) O₃, DCM/pyridine; (b) MeNO₂, C₅H₁₁N (72% yield); (c) MeSO₂Cl, NEt₃ (82% yield); (d) CH₂O, NEt₃; (e) Ac₂O, H⁺ (90% yield); (f) Pd(PPh₂)₄, PPh₃, HCO₂NH₄; (g) TBDMSCl, NEt₃ (63% yield); (h) ACE-Cl then (Boc)₂O (77% yield); (i) NaOMe, MeOH; (j) Jones reagent then CH₂N₂ (72% yield); (k) CAN, MeCN/H₂O (50% yield); (l) KOH then TFAA (71% yield)

Scheme 34. *Benetti's synthesis of acromelic acid A*
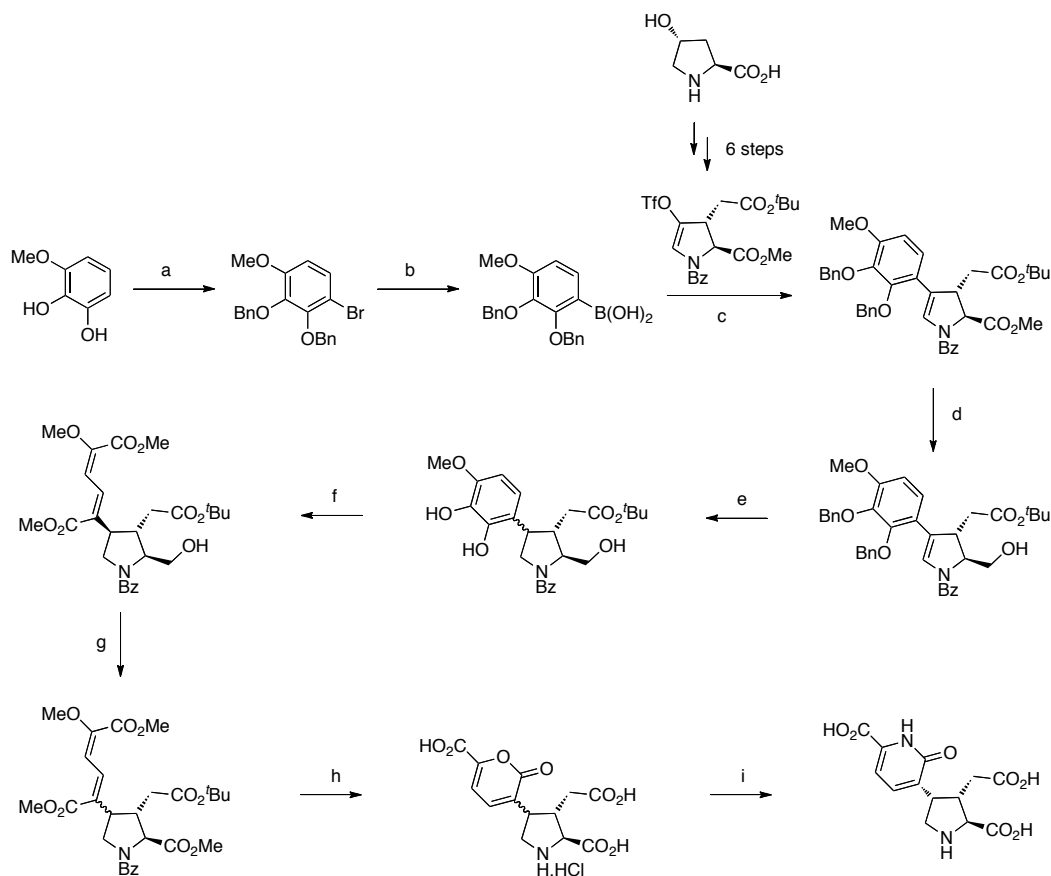
(a) NBS, AcOH, rt, then BnBr, K₂CO₃, DMF, rt; (b) ⁿBuLi, THF, -78 °C, then B(OMe)₃, -78°C to 0°C, then NH₄(aq); (c) Pd(Ph₃)₄, DME, 2M Na₂CO₃(aq), LiCl, Δ (67% yield); (d) NaBH₄, MeOH, 0 °C (78% yield); (e) H₂, catalyst, solvent; (f) Pd(OAc)₄, MeOH, 0 °C (95% yield); (g) CrO₃, conc. H₂SO₄, acetone, H₂O then CH₂N₂, Et₂O, rt (54% yield); (h) 6M HCl(aq), 100 °C; (i) NH₃(aq), rt, ion-exchange chromatography (quant. yield), actovated charcole, cellulose chromatography (60% yield);

Scheme 35. *Baldwin's total synthesis of acromelic acid A in 13 steps (9% yield) from trans-4-hydroxy-L-proline.*[89]

Each of these routes involves multiple complex processes, resulting in extended linear syntheses. Within this group, a method has been reported for the [2,3]-rearrangement of tetrahydropyridneyilds. Development of methodology to allow direct functionalisation of tetrahydropyridines by cross-coupling combined with [2,3]-rearrangement would enable a convergent synthesis to access a wide variety of analogues, with potential for a reduction in the length of the synthetic process.

1.5.1 Tetrahydropyridines - Overview

There are three isomeric tetrahydropyridines; 1,2,5,6-tetrahydropyridine (**23**), 1,4,5,6-tetrahydropyridine (**24**) and 3,4,5,6-tetrahydropyridine (**25**) (Figure 6).
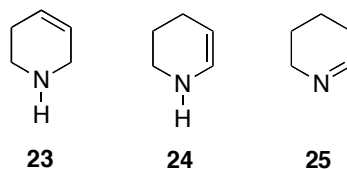
Figure 6. *Isomeric tetrahydropyridines*

The ground state conformation of all tetrahydropyridines confirmed by x-ray analysis is the half chair form. 1,2,5,6-tetrahydropyridines (**23**) can exist in two half chair conformations, with the nitrogen substituent in the axial or equatorial positions (Figure 7).[90]
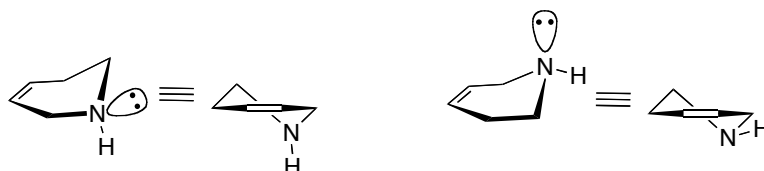
Figure 7. *Half-chair conformation of **23** with axial and equatorial NH*

Since the discovery of the neurotoxic properties of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP, **26**), extensive research has been, and continues to be conducted on the synthesis and pharmacological properties of the compound and its analogues. The aim is to develop an extensive database for structure-activity relationship (SAR) studies, leading towards a potential Parkinson's disease treatment. Parkinson's disease is a progressive neurodegeneration of the nigrostriatal dopaminergic neuron and is characterised by symptoms such as tremor, rigidity and poor balance.[91] Studies have shown that MPTP is a potent neurotoxin in the dopaminergic system, producing Parkinson's-like symptoms.[92] The effects of **25** have been attributed to the oxidation of the molecule by monoamine oxidase (MAO) A and B. Through an oxidative biological cascade **26** is converted to MPP+, which accumulates in the central nervous system. MPP+ is taken into the dopaminergic neurons and inhibits the production of cellular ATP in the mitochondria resulting in cell death (Scheme 36).[93]
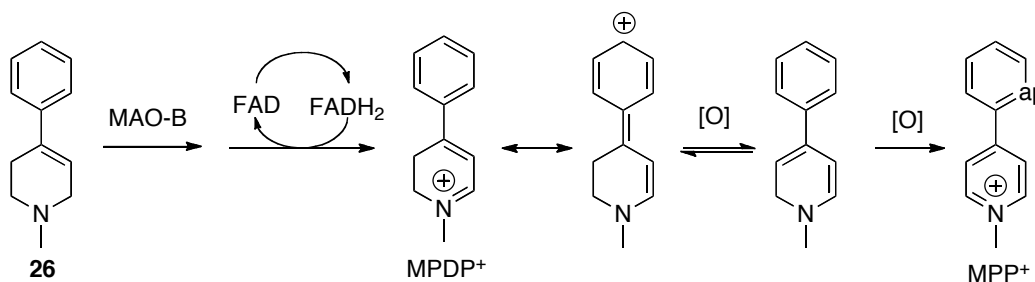
Scheme 36. *Catalytic oxidation of MPTP by MAO-B*

Some synthetic analogues of MPTP have been shown to have affinity for MAO-B enzyme active site, and a number have been shown to display high potency for the enzyme. These compounds have displayed significant pharmacological effects and demonstrated medicinal value that include dopaminergic, nicotinic and muscarinic receptor agonist/antagonist action.[94] Molecules containing tetrahydropyridines have also

been examined for their uses as analgesics, anti-inflammatory agents, antipsychotic and nerve gas antidotes.
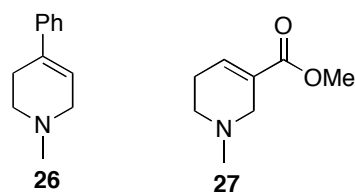
Figure 8. MPTP (**26**) and Arecoline (**27**)

Alzheimer's Disease (AD) and senile dementia of the Alzheimer's type (SDAT) are associated with a loss of neurone receptor activity in the brain.[95] The effects of the disease are irreversible and believed to be a result of impaired cholinergic transmission and a depletion of acetylcholine in the forebrain. In an attempt to replace the acetylcholine function of AD patients, muscarinic receptor agonists have been employed as therapeutic agents. Arecoline (methyl 1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate, **27**, Figure 8) is an alkaloid natural product found in the areca nut, the fruit of the areca palm (*Areca catechu*). Arecoline is known to be a partial agonist of muscarinic acetylcholine receptors. Owing to its muscarinic agonist properties, arecoline has been examined for its clinical application to AD treatment. Administered intravenously, arecoline shows modest verbal and spatial memory improvement in AD patients,[96] however due to its possible carcinogenic properties, and the low affinity of the ligand at muscarinic receptors, development of a more potent candidate for AD treatment is necessary.

Our group has demonstrated that analogues of acromelic acid (**21**) may be accessed *via* the Sommelet-Hauser [2,3] sigmatropic rearrangement of tetrahydropyridines. A sigmatropic rearrangement is defined as migration in an uncatalysed intramolecular process, of a σ-bond adjacent to one or more π-systems, to a new position in a molecule, with the π-system becoming reorganised in the process.[97] The order of a rearrangement is expressed in the form [a,b], where a and b refer to the number of atoms on either side of the bond broken. Thus, in Scheme 37, a [3,3]-sigmatropic rearrangement is shown.[98]
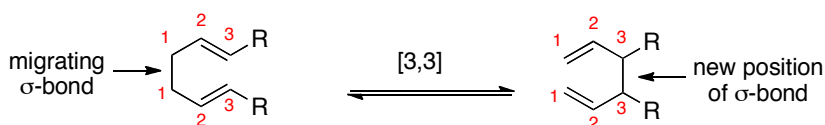
Scheme 37. *Example of a sigmatropic rearrangement*

The Sommelet-Hauser rearrangement consists of the rearrangement of benzyl quaternary ammonium salts. The [2,3]-rearrangement is a concerted process proceeding through a five membered, 6π electrocyclic transition state. Sigmatropic rearrangements are not confined to entirely carbon systems,[99] with [2,3]-rearrangements often involving a heteroatom.[100] [2,3]-Sigmatropic rearrangements proceed *via* a highly reactive ylid (a species bearing a positively charged heteroatom connected to a carbon atom possessing an unshared pair of electrons).[101] These ylid intermediates may be generated *via* treatment

of a salt with a base, or by use of a metal catalyst, to trigger decomposition of a diazo species to the corresponding electrophilic metal carbenoid. Tautomeric proton transfer to rearomatise the ring results in the Sommelet-Hauser [2,3]-rearranged product (Scheme 38).[102]
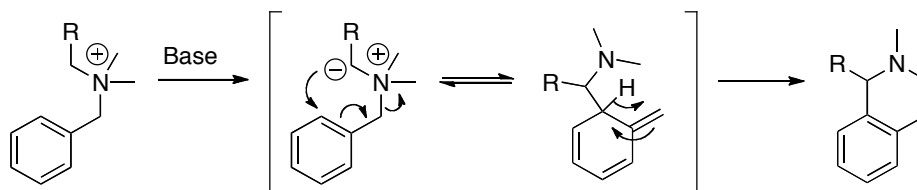
Scheme 38. *Mechanism of Sommelet-Hauser [2,3] rearrangement*

[2,3]-Sigmatropic rearrangement of tetrahydropyridinium ylids was first reported in 1973 by Ollis, who carried out rearrangements of benzoyl stabilised ylids in boiling benzene to give *cis*-2-benzoyl-3-vinyl pyrrolines **28** (Scheme 39).[103]
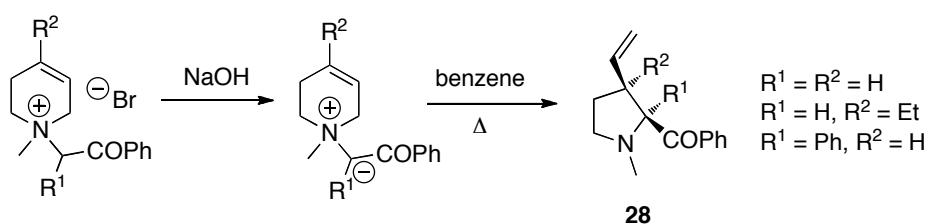
Scheme 39. *Ollis's [2,3] rearrangement of benzoyl-stabilised cyclic ylids*

Our group has investigated [2,3] rearrangements of 1-methyl-1,2,5,6-tetrahydropyridines (NMTP **29**) and the effect of substituents, to provide an alternative pathway for the synthesis of constrained amino acids.[104] Under the reaction conditions, pyrrolidine carboxylic esters (**30**) may be accessed with trace amounts of the acyclic diene (methyl 3-aza-3-methyl-octa-5,7-dienoate, **31**) also obtained. It was reported that [2,3]-rearrangement of NMTP esters (**32**) could be achieved in moderate to good yields with a variety of substituted methyl esters, with both those containing electron withdrawing and electron donating characteristics (Table 3), with low yields of the acyclic dienes **31a-j** produced due to the stability of the ammonium ylids formed.[105]

Table 3. *Pyrrolidine carboxylic acids via NMTP ester rearrangement*

Entry	R	Product	Yield **30** (%)	Yield **31** (%)
1	H	**a**	58	0
2	CO$_2$Me	**b**	79	0
3	Ph	**c**	71	3
4	1-Naphthyl	**d**	89	0
5	4-MeO-C$_6$H$_4$	**e**	28	25
6	4-NO$_2$-C$_6$H$_4$	**f**	48	0
7	4-Cl-C$_6$H$_4$	**g**	32	11
8	3-Cl-C$_6$H$_4$	**h**	43	9
9	4-F-C$_6$H$_4$	**i**	58	0
10	3-F-C$_6$H$_4$	**j**	36	0

Rearrangement could proceed either by an *endo* or *exo* process. However, as shown in Scheme 40, the *endo* route results in secondary orbital interaction between the olefin and the carbonyl, which stabilises the transition state. As a result, the reaction is highly selective, giving one diastereoisomer; the more favoured *endo* product **30**.[106]
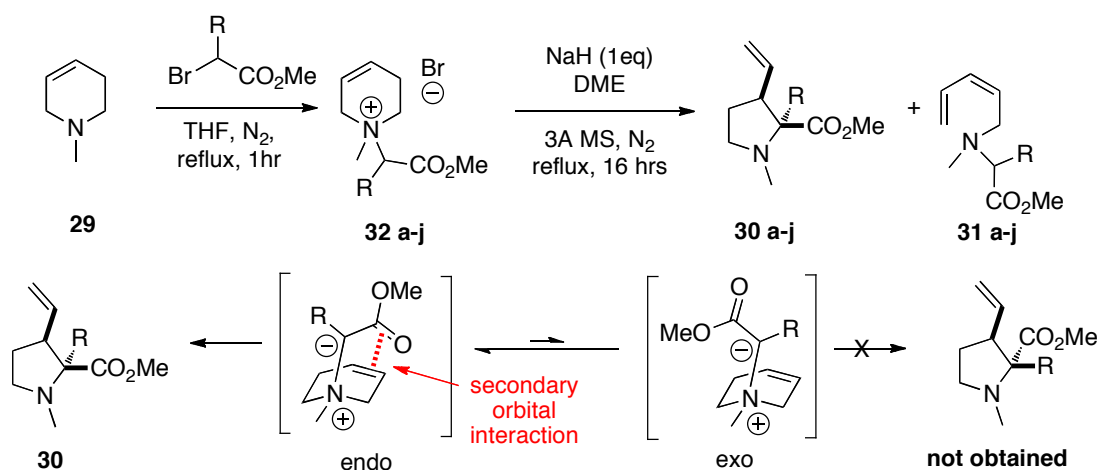
Scheme 40. *Optimised salt formation and rearrangement of NMTP **29**, where R=H.*

Prior to the application of the developed [2,3]-rearrangement to synthesise pyrrolidine carboxylic acids,

access to tetrahydropyridines are required.

1.5.2 Tetrahydropyridine Synthesis

Tetrahydropyridines have been synthesised from their *N*-alkylpyridinium salt precursors *via* sodium borohydride reduction in a protic solvent.[107]   This method has been utilised for the synthesis of pharmacologically interesting tetrahydropyridines (Scheme 41).

R = R$_1$ = H, R$_2$ = β-(3-indolyl)ethyl
R = H, R$_1$ = CH$_2$CO$_2$Me, R$_2$ = β-(3-indolyl)ethyl
R = CH$_2$CO$_2$Me, R$_1$ = H, R$_2$ = β-(3-indolyl)ethyl
R = H, R$_1$ = CH$_2$CO$_2$Me, R$_2$ = Me
R = CH$_2$CO$_2$Me, R$_1$ = H, R$_2$ = Me
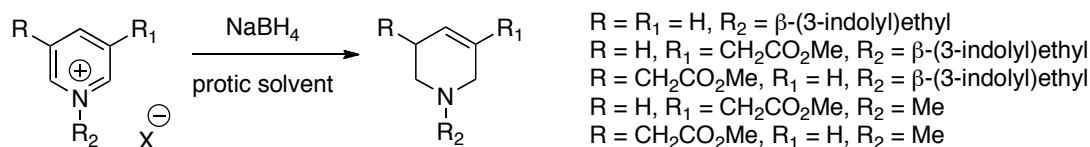
Scheme 41. Borohydride reduction of pyridinium salts

The reduction of pyridines and pyridinium salts with reducing agents of the complex hydride type is essentially a nucleophilic addition.   It is therefore much easier to reduce pyridines than benzenes. However, in simple pyridines it is difficult to achieve selective reduction.[108] Pyridinium is reduced by LiAlH$_4$ to a mixture of 1,2- and 1,4-dihydropyridines. With lithium triethylborohydride, pyridine is fully reduced to piperidine,[109] however if sodium borohydride is utilised as the reducing agent, tetrahydropyridines are synthesised.[110]

Lyle[111] carried out mechanistic studies on the sodium borohydride reduction of pyridinium ions in deuterium oxide. Initial attack of the hydride ion on a carbon adjacent to the positive charge was shown to occur to give the 1,2,5,6-tetrahydropyridine. Where bulky substituents were present (R, Scheme 42), steric hindrance resulted in initial attack occurring at the 4-position of the pyridinium ion, which resulted in isolation of the saturated piperidine.
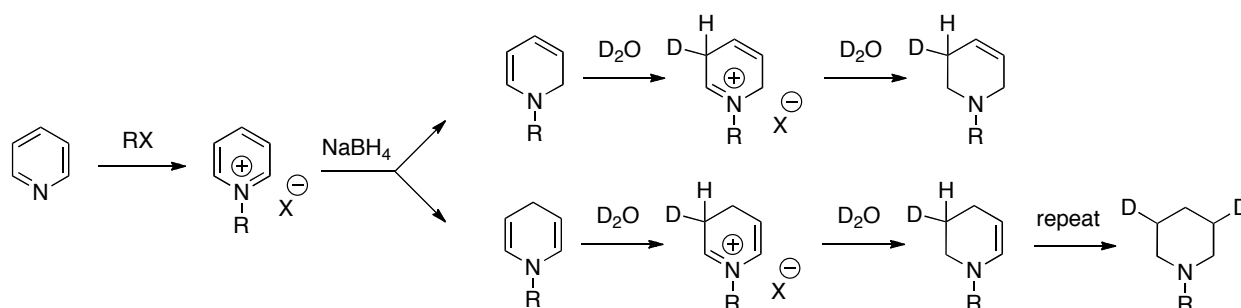
Scheme 42. Borohydride reduction of pyridinium salts

Control over the reduction process was demonstrated by changing the alkyl substituent. It was shown that as the alkyl group increased in size, the relative amount of piperidine isolated increased, with Me < Bu < Bn < ^{i}Pr, consistent with the hypothesis that the larger substituents sterically interfere with the approach of the hydride ion to the 2-position (Table 4).

Table 4. *Effect of substituent on pyridinium reduction*

R	Yield (%) tetrahydropyridine	Yield (%) piperidine
-CH$_3$	100	0
-(CH$_2$)$_3$CH$_3$	95	5
-CH$_2$Ph	88	12
-CH(CH$_3$)$_2$	72	28

Synthesis of a range of pyridinium salts enables access to a versatile library of tetrahydropyridines *via* borohydride reduction. Pyridinium salts are commonly synthesised *via* electrophilic reactions at the nitrogen center of pyridine (Scheme 43).[112]
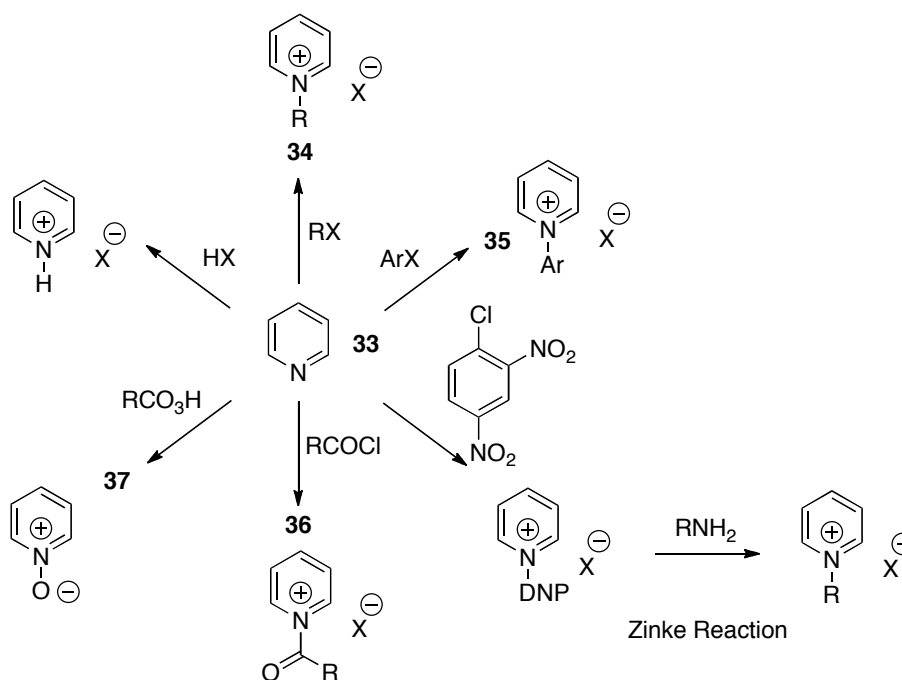
Scheme 43. *Electrophilic reactions of nitrogen*

Pyridine (**33**) is a good nucleophile and can be readily alkylated with alkyl halides, alkyl tosylates or dialkyl sulfates to give *N*-alkyl pyridinium salts (**34**), while activated haloarenes form *N*-aryl pyridinium salts (**35**). Pyridine (**33**) reacts readily but reversibly with acid chlorides and acid anhydrides yielding *N*-acyl pyridinium salts (**36**), which are highly reactive and sensitive to hydrolysis. Peroxy acids react with pyridine to give pyridine *N*-oxide (**37**) by an electrophilic oxygen transfer. *N*-Alkyl pyridinium halides of varying alkyl chain length (C$_8$ to C$_{20}$) have been successfully synthesised by Marek, who demonstrated the versatility of the method in the preparation of cationic surfactants from pyridine.[113]

For more complex substituents where steric hinderance or electronic factors may inhibit reactions of pyridine, the Zinke reaction may be applied. The Zinke reaction, first reported in 1903,[114] is an amine exchange process which provides an efficient approach to the preparation of *N*-aryl or *N*-alkyl pyridinium salts, where the alkyl groups can be primary, secondary or tertiary. The Zinke reaction converts *N*-(2,4-dinitrophenyl)pyridinium chloride salts (Zinke salts) to *N*-aryl or *N*-alkyl pyridinium salts by reaction with an appropriate aniline or alkyl amine[115] *via* a ring opening, *cis-trans* interconversion and ring closure.[116]

Where synthesis *via* the pyridinium salts is not suitable, tetrahydropyridines may also be accessed *via* ring closing metathesis. Grubbs' catalyst is a member of a family of well-defined ruthenium complexes capable of ring-closing both strained and unstrained olefins. This catalyst is commonly applied due to its diminished sensitivity to atmospheric oxygen and moisture, and increased tolerance of most functional groups including acids, alcohols, and aldehydes (Scheme 44).[117]
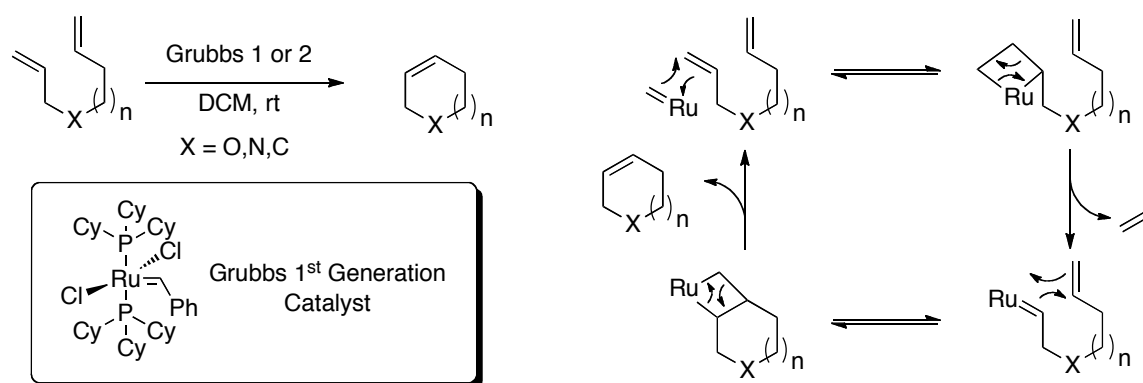
Scheme 44. *Grubbs ring closing methathesis*

Ring closing metathesis *via* Grubbs catalyst can efficiently generate five-,[118] six-,[119] and seven-membered[120] heterocycles and carbocycles at room temperature in good yields. However, Grubbs 1 is not effective for the cyclisation of amino dienes due to coordination of the nitrogen lone pair to the catalyst, in which case the corresponding hydrochloride salts are required (Scheme 45).[121]
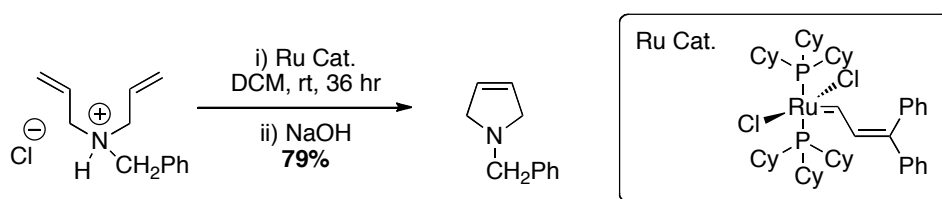
Scheme 45. *Cyclisation of amino diene salts*

Ring closing metathesis utilising Grubbs 1st generation catalyst has been used within our group for the synthesis of several tetrahydropyridines (Scheme 46).
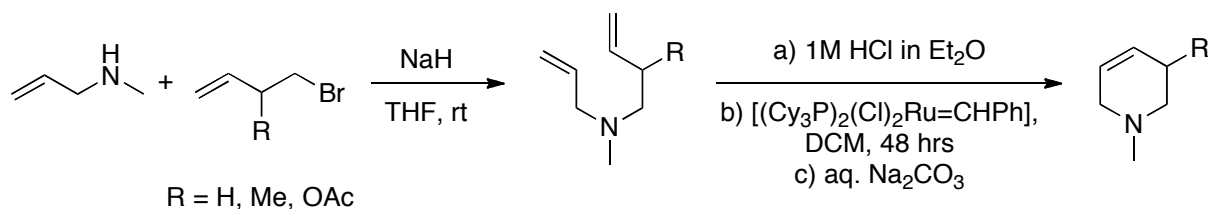
Scheme 46. *Synthesis of tetrahydropyridines via Grubbs ring closing metathesis*

1.5.3 Functionalisation of Tetrahydropyridines

Early structure-activity relationship studies of acromelic acid (**21,** Figure 9) analogues have shown that the nature of the C-4 substituent of the pyrrolidine is key to the resulting biological activity observed. When Shinozaki synthesised dihydrokainic acid **38** with an isopropyl C-4 substituent and therefore no π-electron density, no excitatory activity was observed.[122] Lehmann demonstrated that CPPA **20** with no C-4 substituent also does not show kainate selectivity.[123] Hashimoto prepared numerous acromelate analogues, some of which proved to be as potent as kainic acid (**39**[124] and **40-41**[125], Figure 9). However they obtained their best results with the methoxyphenyl analogue **42**, which proved to be 3 to 5 times more potent than acromelic acid A (**21**) in new born rat spinal motor neurons and 10 times more potent than kainic acid (**17**).[126]
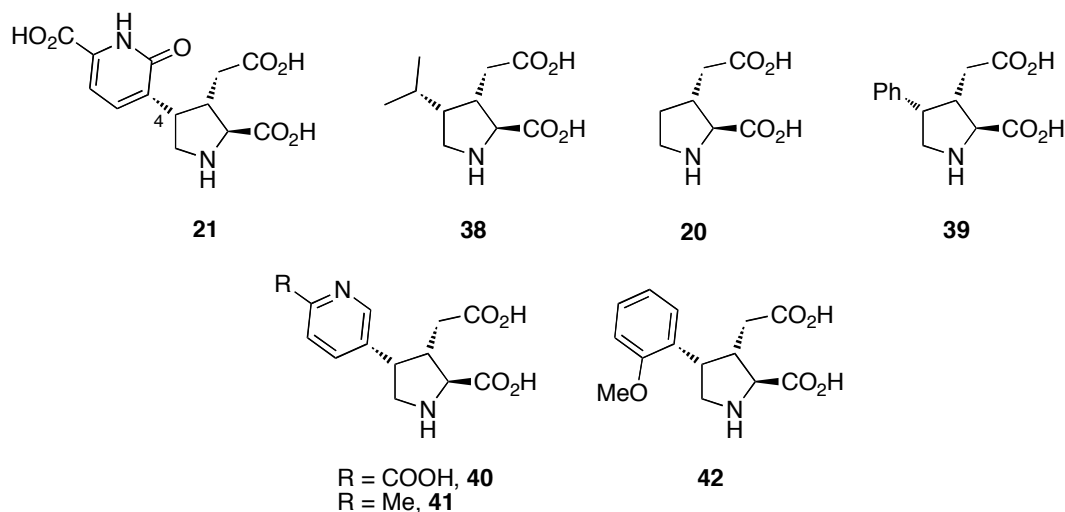
Figure 9. *Acromelate analogues*

The configuration of the C-4 substituent of the pyrrolidine ring has also been shown to influence the intensity of the excitatory response. Hashimoto demonstrated that in order to achieve maximum neuroexcitatory activity, the same absolute (4*S*) configuration as the natural products is required in the synthetic analogues.[127]

Aryl functionalisation at the C-4 position therefore represents a key synthetic target for acromelic acid (**21**) analogue synthesis. Direct functionalisation of *N*-methyl-1,2,5,6-tetrahydropyridine (**29**) through methods such as cross-coupling and subsequent [2,3]-sigmatropic rearrangement as previously described, could

allow access to these pharmacologically interesting compounds (Scheme 47).
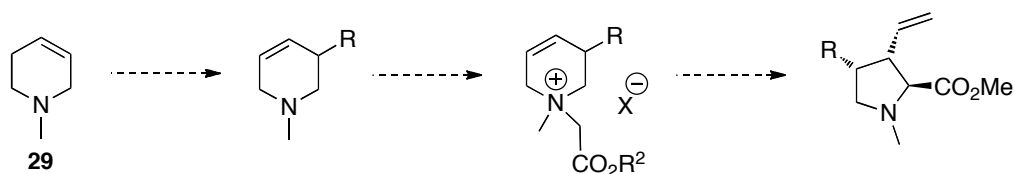
Scheme 47. *Direct functionalisation of N-methyl-1,2,5,6-tetrahydropyridine (**29**) and subsequent [2,3]-sigmatropic rearrangement*

Preparation of functionalised NMTPs is a laborious process, as is the corresponding synthesis of enantiomerically-pure NMTPs.[128] Therefore, direct functionalisation of tetrahydropyridines before rearrangement would be beneficial. One method to do this is *via* the Heck-Mizoroki reaction. Currently there is only one example reported of the Heck-Mizoroki reaction of tetrahydropyridines, which utilises *N*-propyl tetrahydropyridine (**43**). In a multi-vessel process, Hallberg[129] synthesised racemic 1-propyl-3-(-3-hydroxyphenyl)piperidine (**44**) from 1-propyl-1,2,5,6-tetrahydropyridine (**43**, Scheme 48), in 12% yield over the 2 steps through the tetrahydropyridine **45**, with a high preference for 3-arylation, over the 4-position.
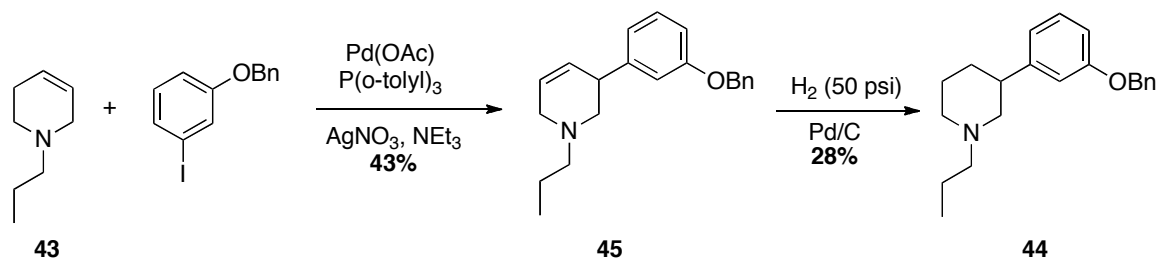
Scheme 48. *Hallberg's synthesis of 1-propyl-3-(-3-hydroxyphenyl)piperidine **45***

Previous work within our group has confirmed that this reaction can be utilised to arylate 1-methyl-1,2,5,6-tetrahydropyridine (NMTP **29**) with arylation occurring selectively at the 3 position (Scheme 49).[130]
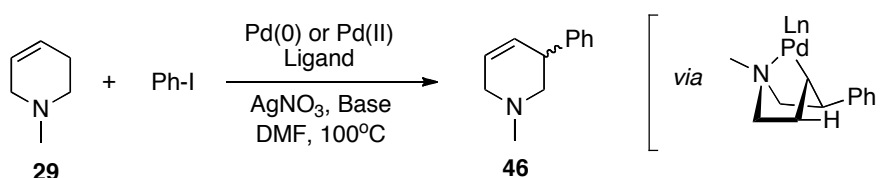
Scheme 49. *Heck-Mizoroki arylation of NMTP (**29**)*

The high regioselectivity found with these Heck arylations is due to the preference for addition to the 3-position rather than the 4-position, due to the *N*-chelation which presents both the olefin and amine functionality towards the palladium catalytic centre. The formation of stabilised 5-membered σ-palladium adducts by arylation of the 3-position occurs, in preference to the more strained 4-membered adduct which would be formed by arylation of the 4-position (Scheme 50).
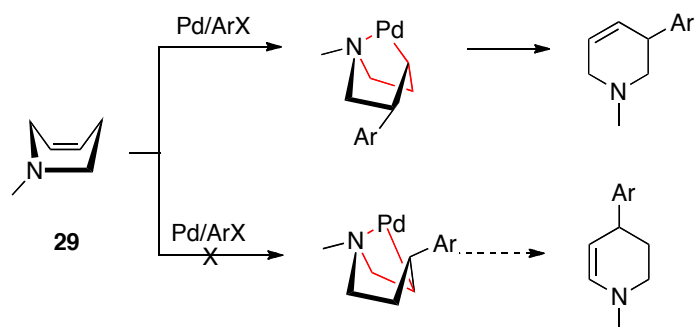
Scheme 50. *Formation of stabilised 5-membered σ-palladium adducts*

High regioselectivity is also obtained due to the insertion and elimination steps of the catalytic cycle being *syn*-processes. For β-hydride elimination to occur, rotation about the Cα-Cβ bond is required, which is not feasible. Therefore there is no competition between the β-hydride and β'-hydride elimination processes (Scheme 51). [131]
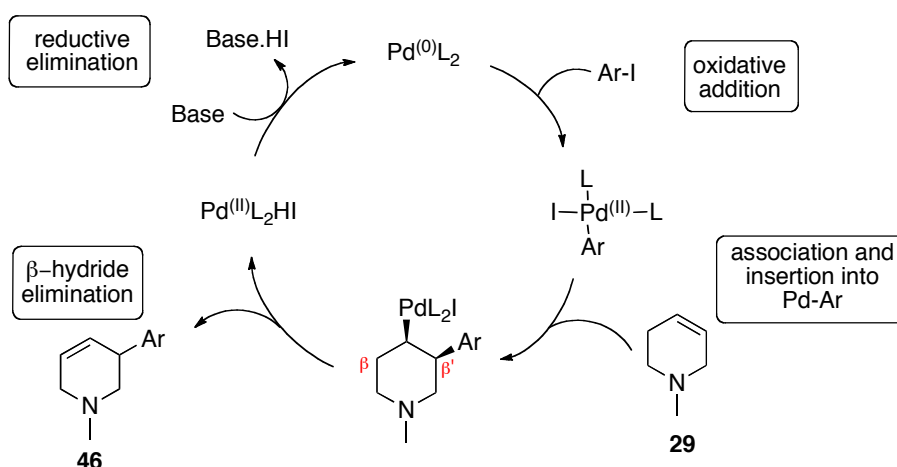
Scheme 51. *Four step catalytic cycle of Heck arylations leading to high regioselectivity*

Once the tetrahydropyridine has been arylated, further transformations and rearrangements may be carried out such as [2,3]-sigmatropic rearrangements towards the synthesis of pharmacologically interesting analogues of kainic acid (**17**).

1.5.4 Nitrogen Chirality in Quaternary Ammonium Salts

The formation of enantiomerically enriched compounds is an essential requirement for the synthesis of complex molecules. The use of an existing stereocentre to control the stereochemistry of subsequent transformations is an efficient route to introduce complexity into substrates. The literature has focused almost exclusively on the formation of optically enriched carbon centres. The use of enantiomerically pure heteroatom centres to control stereochemistry remains an underdeveloped area.

Preparation of *N*-chiral ylids would be an effective method to synthesise chiral pyrrolidines such as enantiomerically enriched kainic acid (**17**) derivatives *via* [2,3]-rearrangements.

When quaternary ammonium tetrahydropyridine salts are formed, the nitrogen atom forms an asymmetric centre resulting in a racemic mixture of the *R* and *S* enantiomers, which cannot be separated chromatographically. This asymmetry controls the facial selectivity in the [2,3]-rearrangement (Scheme 52).
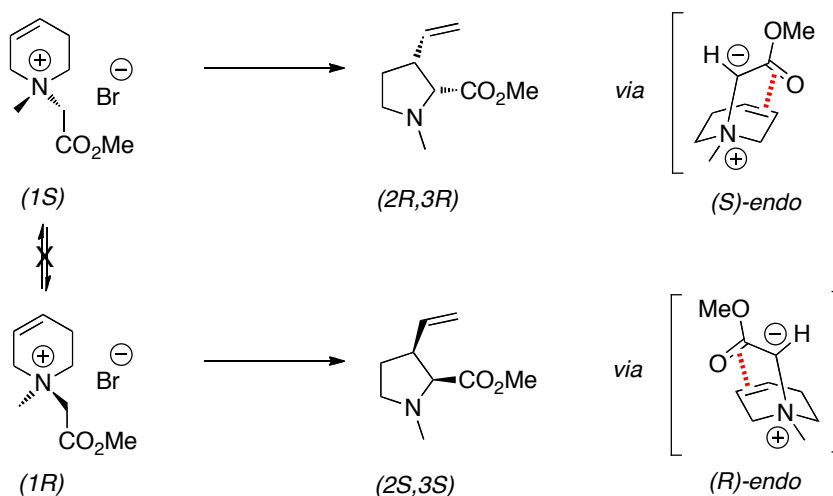
Scheme 52. *[2,3]-Rearrangement products from each ammonium salt enantiomer*

To control the selectivity, a single enantiomer of ammonium salt is required. Previously within our group, a chiral camphorsultam auxilary has been utilised in attempts to isolate a single diastereomer of ammonium salt. The ammonium salt (**47**) was isolated in 1:1 ratio of diastereoisomers, showing that in this instance, the chiral auxilaries has no influence over the stereochemistry of the quaternary nitrogen. However, [2,3]-rearrangement of the mixture gave the two corresponding diastereomeric pyrrolidines (**48a**) and (**48b**) with *cis* configuration, which were readily separable by column chromatography (Scheme 53).[132]
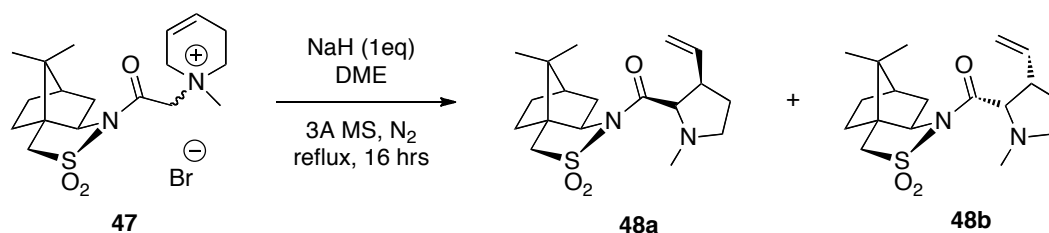
Scheme 53. *[2,3] Rearrangement of 47*

Mills has reported the synthesis of quaternary ammonium salts derived from 1-methyl-4-phenylpiperidine (**49**) and 4-hydroxy-piperidine (**50**), during their research into the tetrahedral configuration of nitrogen (Scheme 54).[133] For the hydroxyl substituted salt, the less soluble α-*trans* isomer could be isolated by crystallisation of the crude product.

Scheme 54. Mills' reported synthesis of quaternary ammonium salts

If a single enantiomer of ammonium tetrahydropyridine salt could be synthesised, the facial selectivity in the [2,3]-rearrangement may be controlled. A possible synthetic route to a single enantiomer could be developed, as shown by the retrosynthesis in Scheme 55, utilising manipulation of nitrogen chirality. The synthesis initiates from the formation of a quaternary ammonium salt. If racemic starting material were used, a racemic mixture of quaternary ammonium salts would be produced. When the hydroxyl and the benzyl ester are *cis* to each other, cyclisation would be induced to produce a lactone, which may then be separated from the *trans* quaternary ammonium salt. Ring opening and dehydration would result in a single enantiomer of ammonium tetrahydropyridine salt from which further functionalisation or [2,3]-rearrangement could be carried out towards the synthesis of kainoids (Scheme 55).

Scheme 55. Towards the synthesis of a single enantiomer of quaternary ammonium salts

CHAPTER 2: RESULTS AND DISCUSSION: DIRECT FUNCTIONALISATION OF NITROGEN CONTAINING HETEROCYCLES

2.1 The Heck-Mizoroki Arylation of Tetrahydropyridines

Previous work within our group has demonstrated that the Heck-Mizoroki reaction can be utilised to arylate 1-methyl-1,2,5,6-tetrahydropyridine (NMTP, **29**) with only the 3-aryl tetrahydropyridine (**46**) observed (Scheme 56).[130] Screening reactions were carried out which successfully optimised the reaction to produce 1-methyl-5-phenyl-1,2,5,6-tetrahydropyridine (5-PhNMTP, **46**).   Repetition of this previous work resulted in 63% isolated yield achieved, under standard Heck reaction conditions (phosphine ligand, silver source, base, polar aprotic solvent, Scheme 56).
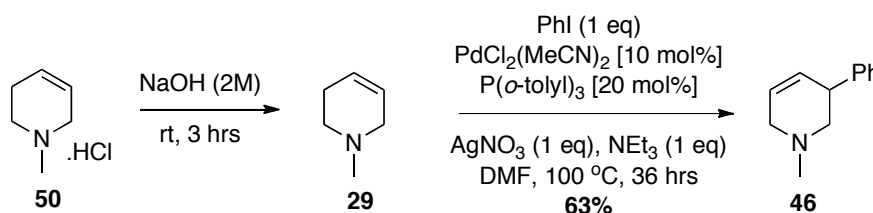
*Scheme 56. Optimised aryl Heck reaction of NMTP (**29**)*

1-Methyl-1,2,5,6-tetrahydropyridine (NMTP, **29**) was used, which was isolated *via* basification of the commercially available hydrochloride salt (NMTP.HCl, **50**). To obtain optimum yields, it was found that a large excess (4 equivalents) of **29** was required. This is due to its high volatility, therefore residing in the reaction headspace and reducing the amount of **29** available for cross-coupling.   Use of the non-volatile hydrochloride salt **50** would enable a reduction in the excess required, and eliminate the need to carry out the initial basification. The hydrochloride salt (**50**) would also enable the reaction to be investigated in a aqueous environment, eliminating the need for flammable, toxic solvent systems. Aqueous conditions would require assessment of the efficiency of water soluble ligands as potential substitutes for the P(*o*-tolyl)$_3$ ligand utilised in the previously optimised organic Heck arylation, and would allow for easier removal of the ligands from the reaction products during purification.

Initial Heck arylation reactions were therefore carried out using NMTP.HCl (**50**) with iodobenzene (**1**). It was found that the water soluble phosphine triphenylphosphine-3,3′,3′′-trisulfonic acid trisodium salt (TPPTS, **6**) was a suitable replacement phosphine ligand and that the reaction could be carried out in an acetonitrile/water solvent system (Scheme 67). TPPTS (**6**) has previously been used by Arai[134] in a nickel-catalysed Heck alkylation of styrene, methyl acrylate (**2**) and butyl acrylate with iodobenzene (**1**), with the Ni/TPPTS (**6**) catalyst phase immobilised on ethylene glycol film on silica support.
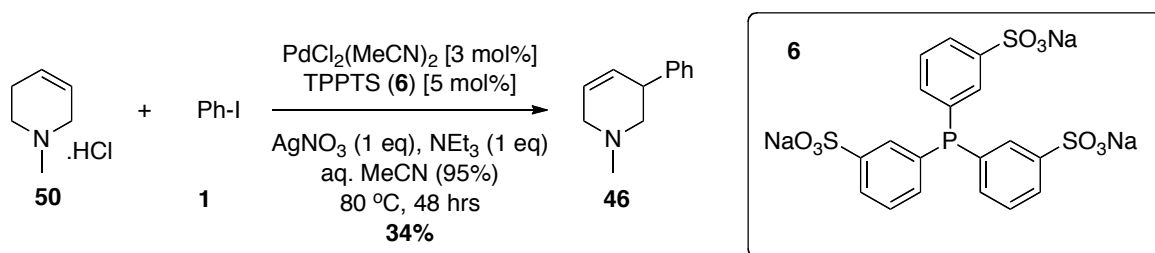
Scheme 57. Heck-Mizoroki reaction of NMTP.HCl (**50**) with iodobenzene (**1**) and TPPTS (**6**) ligand

In aqueous MeCN (5% H$_2$O) 1-methyl-5-phenyl-1,2,5,6-tetrahydropyridine **46** was obtained in 34% isolated yield, allowing for simplification of the reaction procedure, with a decrease in the excess of olefin (from 4 equivalents to 1.5 equivalents). The reaction was also carried out at a slightly lower temperature to that previously employed (80 ^{o}C *cf*. 100 ^{o}C), although extension of the reaction time (48 hrs *vs*. 36 hrs) was required to ensure completion.

To overcome the volatility of the NMTP, the reactions were also carried out in sealed screw-cap vials. However, when **29** was used, as previously found, 4 equivalents were still required to drive the reaction towards completion and maintain high yields.

The two original publications by Mizoroki[135] and Heck[1] described phosphine- and ligand-free reactions, and therefore in an attempt to further streamline the reaction, the procedure was carried out without inclusion of a silver salt or phosphine ligand (TPPTS **6**, Table 5).

Table 5. Heck-Mizoroki reaction of NMTP.HCl (**50**) with iodobenzene (**1**)

Entry	Silver Source	Ligand	Time (hrs)	Yield **46** (%)
1	AgNO$_3$	**6**	48	34
2	-	**6**	48	36
3	-	**-**	72	38

Silver salts are classically included in Heck-Mizoroki reactions to act as halide scavengers to drive the reaction towards the cationic pathway. Experimental investigation found that inclusion of a silver salt had a nominal effect on the reaction yield, and could therefore be excluded. Ligand-free conditions (Table 5, entry 3) were also found to successfully produce the desired product **46**, however the reaction time required extension to 72 hours, for comparable product yield (38%, *cf*. 36%). This phosphine-free method is

beneficial as the ligands used in the classical phosphine-assisted reactions are expensive, toxic and unrecoverable. Elimination of phosphine ligands and silver salts reduces the cost of the reaction, which is of consequence when reactions are scaled up, simplifying the process.

2.1.1 Development of the Heck-Mizoroki Reaction

The Heck-Mizoroki reaction of NMTP.HCl (**50**) was conducted in a 95:5 ratio of acetonitrile to water. If the proportion of acetonitrile in the solvent system can be reduced, the cost of the reaction can be decreased, and the reaction may be considered more "green". Variation of the solvent ratio was undertaken, using phosphine-free reaction conditions utilising 1-(benzyloxy)-3-iodobenzene (**51**) (Table 6).

*Table 6. Effect of solvent ratio on the Heck-Mizoroki reaction of NMTP.HCl (**50**).*

Entry	MeCN	H_2O	Yield 52 (%)
1	95	5	30
2	75	25	19
3	50	50	9
4	25	75	21
5	5	95	21

When 1-(benzyloxy)-3-iodobenzene (**51**) was utilised, 1-methyl-5-(3-(benzyloxy)phenyl)-1,2,5,6-tetrahydropyridine (**52**) was successfully synthesised and identified for each reaction solvent ratio as the sole product using ^{1}H NMR spectroscopy. The yields obtained varied, with entry 3, (50:50 MeCN:H_2O) resulting in the lowest yield (9%), and entry 1, (original 95:5) resulting in the highest yield (30%).

When the above screen was conducted with iodobenene (**1**), it was noted that when the water content of the reaction solvent was increased, multiple products were obtained, as demonstrated by multiple resonances corresponding to the *N*-methyl protons. Column chromatography isolated two of these products as the desired 1-methyl-5-phenyl-1,2,5,6-tetrahydropyridine (**46**), and also what appeared by ^{1}H NMR spectroscopy to be the product of a second Heck reaction, 1-methyl-3,5-diphenyl-1,2,5,6-tetrahydropyridine (**53**).

LC-MS analysis of the reaction mixture enabled confirmation of the presence of a compound with a molecular mass consistent with a doubly-arylated tetrahydropyridine. In an attempt to isolate increased

quantities of this compound in order to confirm its presence and define its structure, 1-methyl-5-phenyl-1,2,5,6-tetrahydropyridine **46** was reacted under the developed Heck-Mizoroki conditions with iodobenzene cross-coupling partner (Scheme 58).
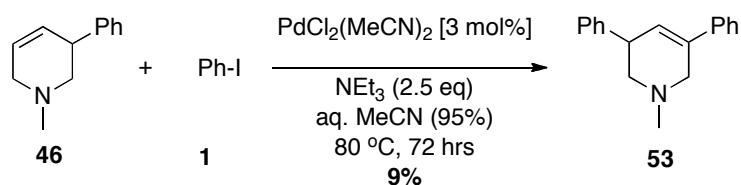
Scheme 58. *Heck reaction of 1-methyl-5-phenyl-1,2,5,6-tetrahydropyridine (**46**)*

The di-phenylated product (**53**) was successfully synthesised by a second Heck reaction of **46**, as a yellow oil in 9% isolated yield. ^{1}H NMR spectroscopy demonstrated the disappearance of one resonance corresponding to an alkene proton in the 5.5-6.5 ppm region, and an increase in the resonance corresponding to aromatic protons (Figure 10). The ability to further functionalise the tetrahydropyridine will allow for wider access to a greater library of compounds.
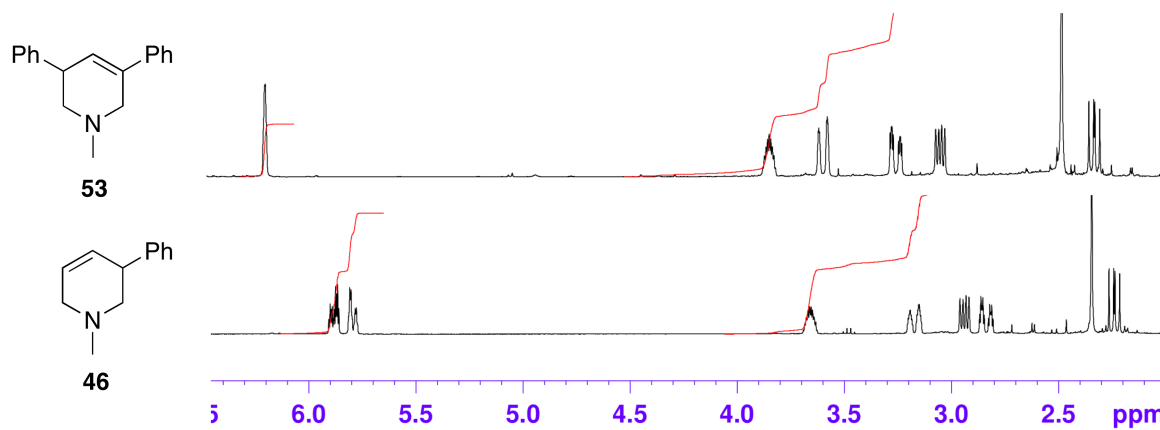
Figure 10. ^{1}*H NMR spectra showing fragments isolated from the aqueous Heck reaction of NMTP.HCl (**50**) with iodobenzene (**1**). Products **53** top, **46** lower spectrum*

2.1.2 Attempted Optimisation of the Heck-Mizoroki Arylation

With moderate reaction yields for the ligand and silver-free Heck-Mizoroki arylation of NMTP.HCl (**50**) achieved, the reaction components were further explored for reaction optimisation.

2.1.2.1 Palladium Catalyst

To assess the suitability of the palladium catalyst, five commercially available palladium sources were applied to the Heck-Mizoroki reaction of NMTP.HCl (**50**) and iodobenzene (**1**) in aqueous acetonitrile (Table 7).

44

Table 7. *Analysis of palladium catalyst*
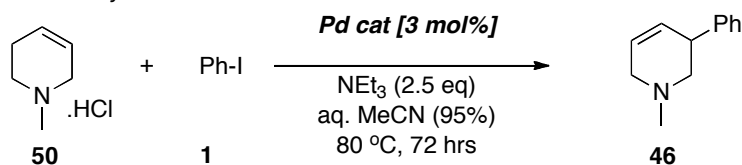
Entry	Pd catalyst	Yield **46** (%)
1	$PdCl_2(MeCN)_2$	31
2	$Pd(OAc)_2$	24
3	$PdCl_2(PPh_3)_2$	24
4	$Pd(dba)_2$	30
5	Pd(118)	0

It was observed that although $PdCl_2(MeCN)_2$ (Table 7, entry 1) and $Pd(dba)_2$ (Table 7, entry 4) gave the highest product yields (31% and 30% respectively), $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ (Table 7, entries 3 and 4 respectively) gave similar yields, suggesting that the reaction is relatively amenable to a variety of palladium catalysts. Only Pd-118 (1,1'-bis(di-tertbutylphosphino)ferrocene palladium dichloride, entry 4) was deemed unsuitable, as no product was detected, even at increased reaction time (96 hours).

By reaction monitoring, a reaction yield maximum of approximately 30% was apparent, suggesting the possibility that catalyst is no longer active after the three days at 80 ^{o}C required for the reaction. Addition of extra catalyst over the reaction period was therefore attempted, however this did not result in increased yield.

De Vries demonstrated that ligand-free $Pd(OAc)_2$ can be used as a catalyst in the Heck reaction of aryl bromides as long as catalyst loading is low (between 0.01 and 0.1 mol%). At higher concentrations palladium black formation was reported during the early stages of the reaction progression, which resulted in the prevention of full conversion, by removal of the active palladium from the catalytic cycle.[136] The palladium species aggregate to form initially soluble palladium clusters, which turn into insoluble palladium black.

In the Heck-Mizoroki arylation of NMTP (**29**), Pd black formation occurs rapidly. It is therefore feasible that a reduction in the catalyst loading may result in higher yield by reducing Pd black formation and increasing the palladium available in the catalytic cycle. A screen of catalyst loading was therefore conducted, with catalyst loading from 3 to 0.01 mol%, however product was only observed when 3 mol% was used. Lower loading failed to result in detection of any **46** by LCMS.
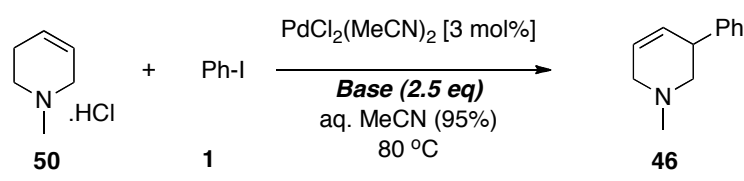
2.1.2.2 Assessment of the Role of Base

Although base-free Heck-Mizoroki reactions have been reported, in general the catalytic cycle requires a base present to reduce Pd(II) to Pd(0), and to facilitate reductive elimination, by neutralisation of the acid (HX) produced when the hydridopalladium(II) species is reduced to regenerate the active Pd(0) catalyst. A stoichiometric amount of base is needed, but in practice 2-5 molar equivalents are often used. Generally, hindered tertiary amines are chosen.[137]

The base in the arylation of NMTP.HCl (**50**) is not only required for reductive elimination to regenerate the active Pd(0) catalyst, but is also required initially for release of the free amine NMTP (**29**) from the HCl salt (**50**). As 1.5 equivalents of NMTP.HCl (**50**) are utilised, an initial 1.5 eq of base was predicted to be required, with another 1 eq of base for removal of the HI species. 2.5 equivalents have therefore been utilised predominantly. A screen of base charge from 1 to 4 equivalents was subsequently carried out. **46** was detected in each reaction, with a general increase in product observed with charge increase up to 3 equivalents. Above this level, no further increase was observed. The initially applied 2.5 equivalents of base was therefore applied to all further reactions, to ensure maximum yield without unnecessary excess wastage of reagents.

Typically, triethylamine is the base of choice for Heck reactions, but inorganic bases such as potassium carbonate (K_2CO_3) and calcium carbonate ($CaCO_3$) have also been used under aqueous-phase transfer conditions.[138] Other tertiary amines such as *N,N*-diisopropylethylamine (Hünig's base, DIPEA, *i*-Pr$_2$NEt), 1,8-bis(dimethylamino)naphthalene (Proton Sponge), 2,2,6,6-tetramethylpiperidine (TMP) and the extremely hindered base 1,2,2,6,6-pentamethylpiperidine (PMP) are also commonly employed. A range of bases were therefore screened for suitability in the Heck arylation (Table 8).

Table 8. *Base screen*

Entry	Base	Yield (%)
1	none	0
2	NEt$_3$	25
3	TMP	29
4	MeCy$_2$N	39
5	K$_2$CO$_3$	44

It was observed that base was required in order for successful product formation under reaction conditions.

After 46 hours, all bases examined gave good yields particularly potassium carbonate (Table 8, entry 5). However, use of the insoluble inorganic base resulted in a heterogeneous reaction.

2.1.2.3 Attempted stabilisation of the Palladium catalyst
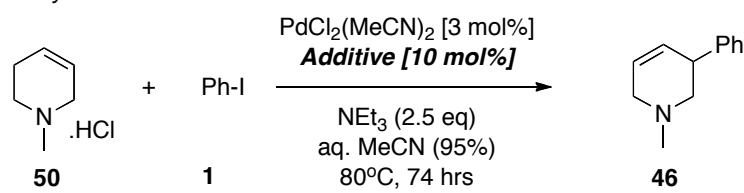
It has been widely reported that unless exceptionally mild reaction conditions are applicable, any Pd precursor will release underligated free Pd(0), which is the actual active species.[139] The released Pd species are unstable and likely to agglomerate forming Pd black and deactivate; therefore, stabilisation is crucial for reasonable catalytic activity (Figure 5).[39] Formation of large amounts of Pd black were observed in the Heck-Mizoroki arylation of NMTP (**29**).

Expensive and often sensitive ligands such as phosphines are often incorporated into palladium cross-coupling reactions to stabilise palladium against agglomeration. Less costly tetralkyl ammonium halides such as TBAB (tetrabutylammonium bromide) are also often utilized, as they have been reported to stabilize palladium catalysts and pre-catalysts.[140]

A range of phosphine ligands were applied to the Heck-Mizoroki arylation of NMTP (**29**) and were found to have negligible effect on reaction yield of 5-PhNMTP (**46**). With all of the phosphine ligands studied, (P(*o*-tolyl)$_3$, P(*m*-tolyl)$_3$, dppe, dppp, dppb, dppf, PPh$_3$, AsPh$_3$, (*R*)-BINAP) there appeared be be no increase in the reaction homogeneity, or a reduction in the Pd precipitate formation.

Two ammonium bromides were therefore also screened: tetrabutylammonium bromide (TBAB) and tetrahexylammonium bromide (THAB), and compared to the additive free reaction (Table 9). Under the reaction conditions, the yield remained roughly constant (32-38%) in the presence and absence of the additives. As found with the ligands study, there was no observed reduction in precipitated Pd.

Table 9. *Addition of quaternary ammonium bromides*

Entry	Additive	Yield (%)
1	None	32
2	TBAB	38
3	THAB	33

2.1.2.4 Assessment of Solvent

It has been demonstrated that Heck arylations are favoured in polar aprotic σ-donor type solvents, with DMF, DMAc and MeCN commonly favoured.[141] A range of solvents including polar aprotic, polar protic and non-polar were applied to the Heck-Mizoroki reaction of NMTP.HCl (**50**) and iodobenzene (**1**) with triethylamine base (Table 10). It was observed that aqueous acetonitrile, the solvent previously utilised, gave the highest yield, with the general trend showing aq. MeCN > MeCN > alcohols > Dioxan, DMF, THF, EtOAc, DMAc, Toluene.

Table 10. *Effect of solvent*

Entry	Solvent	Yield (%)
1	aq. MeCN (95%)	26
2	MeCN	18
3	DMF	8
4	THF	3
5	EtOAc	5
6	DMAc	5
7	MeOH	11
8	BuOH	17
9	Toluene	4
10	Dioxane	10

The NMTP.HCl salt (**50**) was shown to be soluble only in acetonitrile and methanol, with butanol only resulting in a homogeneous reation mixture upon heating.   All other reaction mixtures were heterogeneous, with large amounts of solid present in some solutions, particularly dioxan and toluene, potentially resulting in the observed lower yields if reaction components are unable to interact resulting in reduced cross-coupling.

2.1.2.5 Aryl-Halide Coupling Partner

Charette demonstrated that β-arylation of 1,2,3,4-tetrahydropyridines could be carried out with a variety of aryl halides in good yields and with complete selectivity at the β-position.[142] They reported that aryl iodides with electron rich substituents gave good regioselectivity and high yields (Table 10, entries 2-5, 71-85%), and that although those containing electron-withdrawing substituents also gave good selectivity, these required longer reaction time and gave slightly lower yields (Table 11, entries 6-10, 55-76%).

Table 11. *Charette's β-arylation of 1,2,3,4-tetrahydropyridines*

Reagents: ArI (3.0 eq), PdCl$_2$(dppf).CH$_2$Cl$_2$ [10 mol%], Ag$_3$PO$_4$ (0.6 eq), NaOAc (1.2 eq), DMF, 150 °C

Entry	Ar	Yield (%)	Entry	Ar	Yield (%)
1	Ph	84	8	3-Cl-C$_6$H$_4$	64
2	2-Me-C$_6$H$_4$	80	9	4-CO$_2$Et-C$_6$H$_4$	68
3	3-Me-C$_6$H$_4$	75	10	3-CF$_3$-C$_6$H$_4$	55
4	4-Me-C$_6$H$_4$	85	11	1-naphthyl	75
5	3,4-OCH$_2$O-C$_6$H$_4$	71	12	2-thiophene	46
6	4-F-C$_6$H$_4$	76	13	3-pyridine	32
7	3-Br-C$_6$H$_4$	68	14	2-benzofuran	50

Charette also reported that the arylation could be carried out under phosphine-free conditions with iodobenzene (**1**). In an attempt to confirm the suitability of our phosphine-free reaction, a range of aryl halides were employed (Table 12).

Table 12. *Effects of aryl halides on the Heck-Mizoroki reaction of NMTP.HCl (**50**). All yields reported from single reaction attempt with each iodide analogue. *Purified product obtained from aqueous workup without chromatographic purification*

Reagents: PdCl$_2$(MeCN)$_2$ [3 mol%], NEt$_3$ (2.5 eq), aq. MeCN (95%), 80 °C, 74 hrs

Entry	R	Product	Yield (%)	Entry	R	Product	Yield (%)
1	*m*-OBn	**52**	76*	10	*o*-OH	**62**	<5
2	*p*-OBn	**54**	<5	11	*o*-NH$_2$	**63**	15
3	o-Me	**55**	14	12	*p*-NH$_2$	**64**	0
4	m-Me	**56**	11	13	*o*-NO$_2$	**65**	<5
5	*p*-Me	**57**	7	14	*m*-NO$_2$	**66**	9
6	o-OMe	**58**	<5	15	*o*-CF$_3$	**67**	5
7	*m*-OMe	**59**	21	16	*m*-CF$_3$	**68**	19
8	*p*-OMe	**60**	7	17	*o*-CO$_2$H	**69**	0
9	*o*-napthyl	**61**	24	18	*p*-CO$_2$H	**70**	0

It was found that for most analogues, although product formation could clearly be detected by ^{1}H NMR analysis of the crude reaction mixtures, isolation of the products proved difficult. The purification techniques

applied generally resulted in only milligram quantities of the purified products obtained. Only the *meta*-benzyloxy analogue (Table 12, entry 1) was isolated in sufficiently pure form from reaction work-up, such that further purification was not required. This compound however gave variable reaction yields, initially high (Table 12, entry 1, 76%) but varying with repeated reactions (from 22-76% isolated yield), highlighting inherent problems with the reaction procedure and reliability.

With the exception of the *ortho/meta* carboxyl analogues and *para* amino (Table 12, entries 17, 18 and 12), product was obtained from all iodo analogues screened. Carboxy analogues (**69** and **70**) may have successfully been produced, however as the reaction workup required an acid extraction, isolation of the product from the aqueous phase would prove difficult, and therefore it cannot be definitively stated that cross-coupling did not occur.

It has been reported by Alami that the oxidative addition process of the catalytic cycle is generally found to be slower for *ortho*-substituted halides than the corresponding *meta*-substituted aryl halides due to steric hindrance.[143] Increased steric hindrance asserted by *ortho*-substituents may therefore also be a contributing factor to the generally lower amounts of product observed from cross-coupling of *ortho*-substituted arylhalides.

It is generally reported that oxidative addition of arylhalides is highly disfavoured when powerful electron donors such as -NH_2 or -OH reside on the aromatic ring.[144] This was observed, with low yields of product obtained from the deactivating analogues, (Table 12, *p*-NH_2 entry 12, *o*-/*m*-NO_2 entries 13 and 14 and *o*-CF_3 entry 15). The bulkier cross-coupling partners or those not containing heteroatoms or halides generally gave the highest yields (Table 12, *m*-OBn, *o*-napthyl, *o*/*m*/*p*-Me). This may again be due to difficulties in the product purification stages, or particularly in the case of the benzyloxy and napthyl, due to the steric bulk of the compounds resulting in reduction in the polarity of the compounds and reduction in the amount of by-product formation.

With several analogues, second arylated compounds (Figure 11) were isolated by preparative TLC, with quantities obtained typically <10mg (<5%) and therefore full analysis was not always possible. These compounds had analogous ^{1}H NMR spectra resonance patterns to the di-phenylated compound **53** isolated previously.
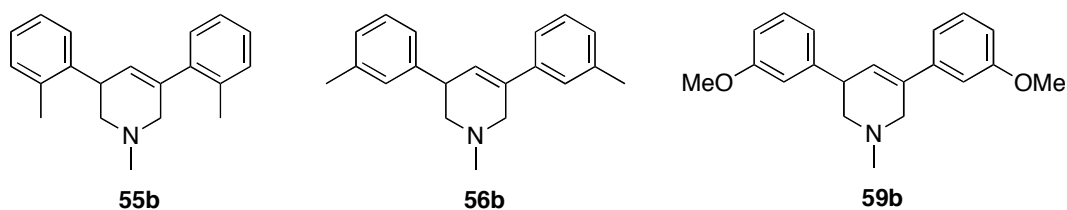
Figure 11. *Di-aryl analogues isolated in Heck-Mizoroki reaction*

The ability to conduct cross-coupling of NMTP.HCl in the presence of a variety of functional groups with varying electronic and steric properties, demonstrates the versatility of the reaction. With an improved purification method and use of in-line analysis, the scope of the reaction may be more fully explored. Several methods of product purification were examined, including silica column chromatography, silver nitrate column chromatography, alumina column chromatography and preparative TLC. In general products were only isolated by preparative TLC, and results obtained by repetition of reactions were often variable. Although analysis by LCMS and GC proved valuble in qualitatively analysing reactions, the low quantities of procuct isolated prevented the ability to calibtrate the instrumentation, and therefore quantification remained difficult.

2.1.2.6 Alternative Tetrahydropyridines

The scope of the reaction was further probed by synthesis of several alternative tetrahydropyridine analogues. These were synthesised by alkylation of pyridine and also *via* the Zinke reaction which proved to be higher yielding and more reproducible (Scheme 59).
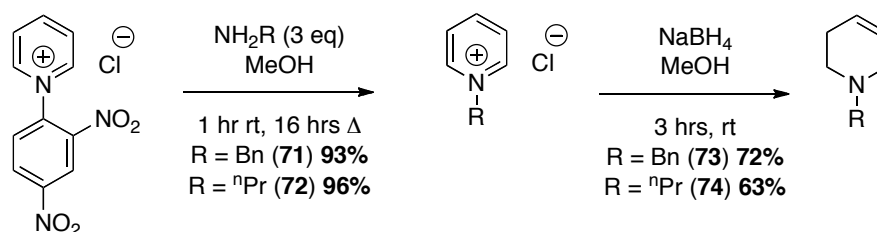
Scheme 59. Synthesis of alternate tetrahydropyridines

These tetrahydropyridines were subjected to the Heck-Mizoroki reaction under conditions described previously through method development (NEt$_3$ base, PdCl$_2$(MeCN)$_2$ catalyst, aq. MeCN solvent, 80 ^{o}C, 72 hours). Again as previously observed, the desired arylated products were believed to have been synthesised successfully by [1]HMR analysis, however poor isolation protocol resulted in the inability to obtain the products in their purified form at this time, emphasising the need for a more robust and reliable purification process or in-line analysis method.

2.1.2.7 GC Analysis for Reaction Profiling

In collaboration with Dr Matthew Stirling from IPOS, the reaction of NMTP.HCl (**50**) and Iodobenzene (**1**) was carried out in a screw cap tube, with an aliquot removed at set time intervals over 74 hours, which was then analysed by GCMS with comparison of reaction components to standards of known concentration. For quantification, biphenyl was incorporated as an internal standard. The mass balance was observed to be >90% throughout, demonstrating that the majority of the reaction products are volatile and observable by GC analysis. Although the desired reaction product was clearly observed, a large number of impurities were also formed at low level.

Graph 1. *Reaction profile by GCMS over time*
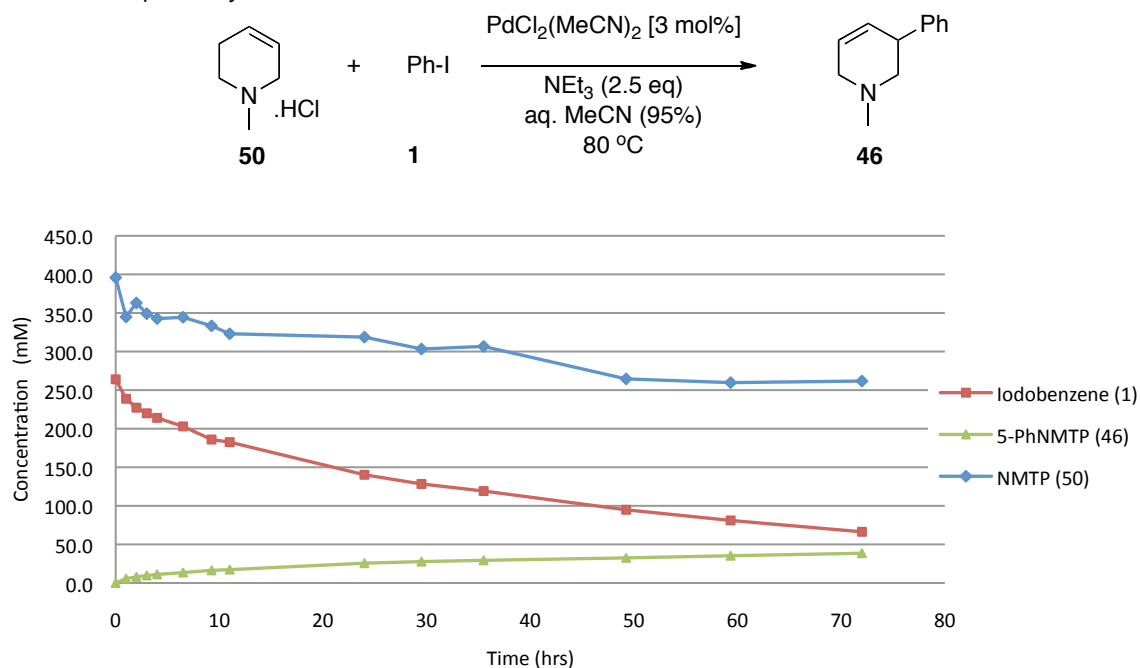
The reaction profiling data obtained indicated the formation of approximately 28% of the desired product over 74 hours, however, it was found that the rate of consumption of NMTP (**29**) and formation of product were effectively zero after approximately 50 hours. At this point the concentration of iodobenzene had significantly diminished, suggesting near-full consumption and therefore the reaction approaching end-point under the examined conditions (Graph 1).

The rate of consumption of iodobenzene (**1**) exceeded that of NMTP (**29**). With the formation of impurities, the high **1** consumption may be accounted for if the impurities are di- and tri-aryl NMTP derivatives, formed from sequential cross-coupling rections. The iodobenzene concentration appeared to continue to drop after both the NMTP and product concentrations reached a plateau and remained unchanged (at approx. 50 hours), indicating an alternative decomposition of iodobenzene (**1**) concurrently with the desired reaction. Both the desired product **46** and the unknown impurities were formed at a similar rate, both starting at t=0, suggesting that the impurities are not formed *via* a consecutive process but *via* an alternative reaction path.

The reaction profiling was repeated several times, with consistant results obtained, suggesting that the difficulties which had been observed previously with reproducibility and the subsequent low yields, was most likely an isolation and purification challenge and not inherently connected to the reaction success.

The formation of the desired product (5-PhNMTP, **46**) and the major impurities gave a good fit to 1st order kinetics over the first 32 hours (R^2 0.997 and 0.991 respectively).

The most interesting observation from reaction profiling by GCMS came from inspection of the impurities. Although the exact structures of the impurities could not be determined by GCMS data, the consistency of the 249 m/z molecular ion strongly suggested that all the major impurities were isomers of the disubstituted product **53**. The reaction mechanism is clearly complex, with several processes occurring simultaneously. The simultaneous production of both **46** and **53** from t=0, along with the greater reduction in **1** than **50** indicated the possibility that the monosubstituted product **46** may remain ligated to the palladium during loss of HI from the catalyst and reformation of Pd(0). A second iodobenzene (**1**) may oxidatively add to the palladium prior to dissociation of the product, resulting in formation of the disubstituted impurities **53**, as represented in blue in Scheme 60.

It had previously been observed that the di-phenylated product (3,5-PhNMTP, **53**) could be successfully synthesised by a separate Heck reaction of 5-PhNMTP (**46**), with iodobenzene (**1**). This reaction was repeated with inline analysis by GCMS. The reaction profile demonstrated that 5-PhNMTP is not stable under reaction conditions, and can itself act as a reactant, with the major reaction product identified as the di-PhNMTP (249 m/z). The reaction profile indicated immediate formation of products from t=0 hours, and a profile loosely matching the reaction of **50** with **1**, with rapid consumption of **46** and **1** in the first 10 hours, and negligible change in starting material concentration after 50 hours (Graph 2).
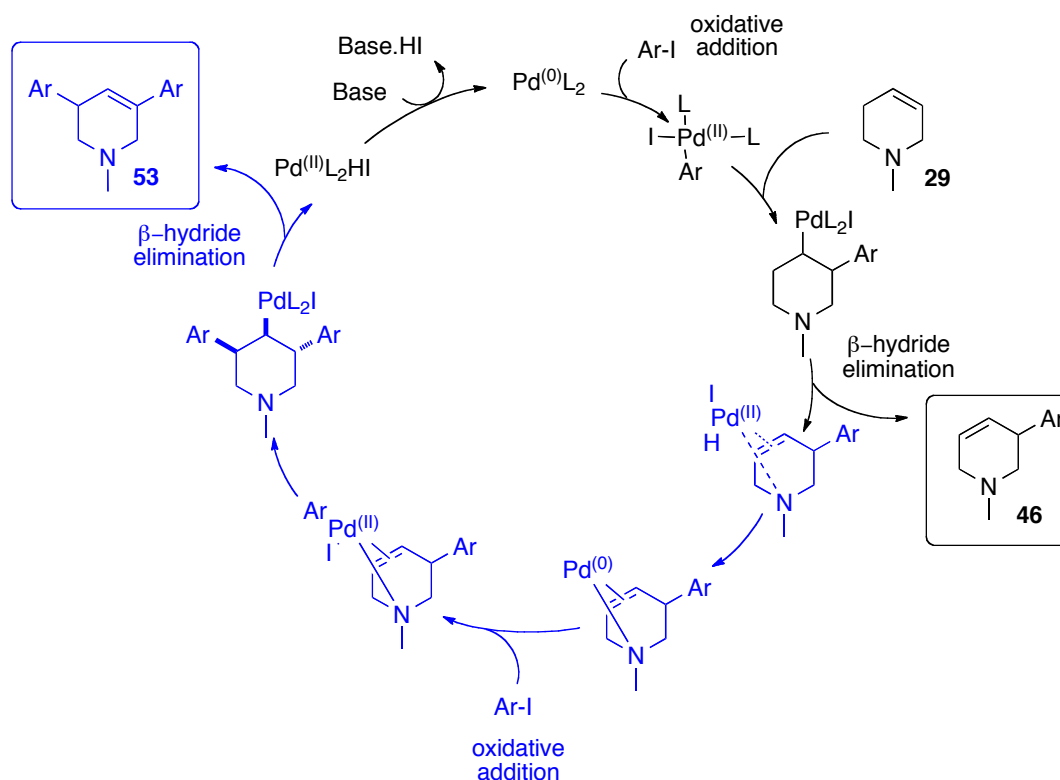
Scheme 60. *Possible reaction mechanism for concurrent formation of* ***46*** *and* ***53***

Graph 2. *Reaction profile by GCMS over time*
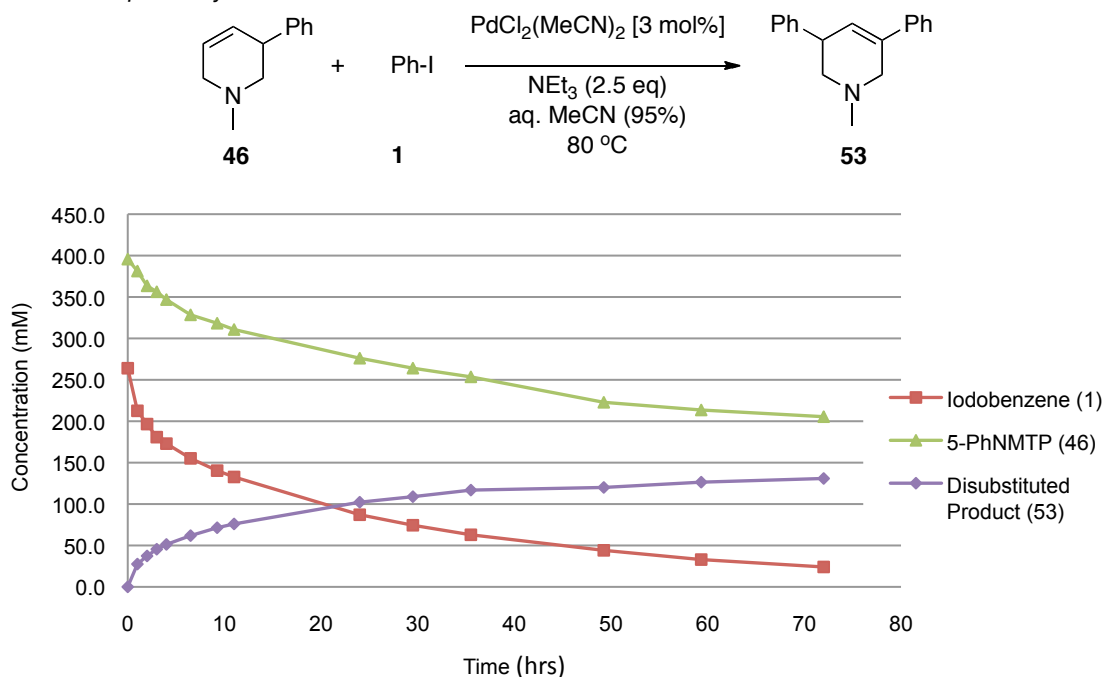
Under the standard reaction conditions of **50** with **1**, GCMS indicated an impurity peak at 15.95 minutes was observed with molecular ion 249 m/z, presumed to be the di-PhNMTP product **53**. This peak corresponded to only 3-8% of total reaction impurites. In the reaction of **46** with **1**, this peak is still observed, however it now corresponds to approximately 60% of total reaction impurites (by peak area). The total impurity profile for the reaction of **46** with **1** is much simpler than the standard reaction of **50** with **1**, indicating that although 5-PhNMTP (**46**) can act as a reagent, it is not the major source of the observed reaction impurities. Interestingly, in the case of **46**, a peak corresponding to a possible tri-PhNMTP product (325 m/z) was also observed, however the structure was unable to be confirmed.

2.1.3 Microwave Assisted Heck-Mizoroki Reaction

With a few exceptions, most Heck-Mizoroki reactions require reaction temperatures of 80-120 °C and reaction times ranging from hours to days for full conversion.[145] Attempts to reduce the reaction time by raising the temperatures are seldom effective due to decomposition of the catalytic system. Therefore, access to alternative and general synthetic procedures that permit fast coupling reactions is valuable.

Microwave-promoted synthesis is an area of increasing research interest. As well as being energy efficient, use of microwave heating has been shown to enhance the reaction rates and in many cases improve product yields.[146]

The application of microwaves as an efficient heating source for organic synthesis was recognised in the mid-1980s. Since then, numerous successful reactions with dramatically enhanced reaction rates have been reported. Very high yields and clean reactions have been obtained using small amounts of energy due to the superheating effect of microwaves.[147] Superheating occurs when a liquid or solvent is heated to a temperature above its normal boiling point. The possibility of employing milder and less toxic reagents and solvents offers a further advantage of use. The non-inert atmosphere conditions and simple experimental procedures of many microwave reactions offer additional convenience in chemical synthesis, especially for high-throughput applications.

By using closed microwave-transparent vessels, which can sustain higher pressures, the superheating effects are substantially magnified and it is possible to maintain solutions at temperatures much above their conventional reflux temperature.[148]
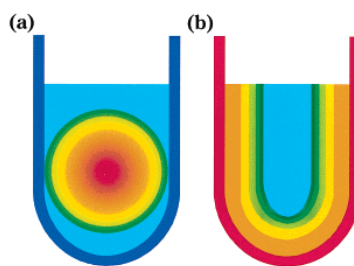
Figure 12. Diagram representing a) microwave in-situ heating and b) thermal wall heating, with red areas corresponding to the hottest areas, and blue the coolest areas.[149]
Reprinted with permission from Ref. 145, Copyright 2002, American Chemical Society.

The higher purity of products often observed after microwave irradiation can probably be largely attributed to the homogeneous *in-situ* heating (Figure 12). Microwave heating of closed reaction vessels is an energy efficient technique since only the reaction mixture is directly heated and not the reaction vessel. The heating procedure is also highly controlled since the energy input starts and stops immediately when the power is turned on or off, respectively.[150]

Microwave heating has been used for Heck reactions with a range of solvents and catalysts utilised.[151] Aqueous reaction conditions are also possible with microwave heating and offers a safe, economic, and environmentally friendly alternative in organic synthesis, as water is cheap, readily available, nontoxic and non-flammable.[152] In an investigation by Wang, microwave-mediated Heck couplings were rapidly performed in water under phase-transfer conditions (TBAB).[153] A mixture of water and acetonitrile was found by Villemine to be highly efficient for microwave-assisted Heck reactions utilising a water-soluble ligand.[154]

Initial investigations were carried out in an attempt to transfer the Heck-Mizoroki arylation to microwave synthesis. Triethylamine was predominantly utilised during microwave studies to ensure a homogeneous reaction mixture, in comparison to the heterogeneous reaction mixture obtained when K_2CO_3 is utilized as base.

It was found that at least 150 $^{\circ}$C heating for a minimum of 10 minutes was required for arylation to occur and resultant formation of 5-PhNMTP (**46**) to be detected by LCMS. In all reactions where the arylated product **46** was obsereved, masses corresponding to the di-phenyl Heck product **53**, [M+H]$^+$ 250 were also shown. However, a mass ion [M+H]$^+$ 176 was also observed, which is consistant with reduced 1-methyl-3-phenylpiperidine (**75**). This product increased in prevalence (by LCMS) as temperature and time increased (from 150 $^{\circ}$C to 200 $^{\circ}$C, 5 minutes to 20 minutes). At 200 $^{\circ}$C no **46** was observed and **75** was the major product. With increasing temperature, mass ion [M+H]$^+$ 252 was observed in increasing proportions, consistant with the presence of the reduced 3,5-PhNMTP (**76**, Figure 13).
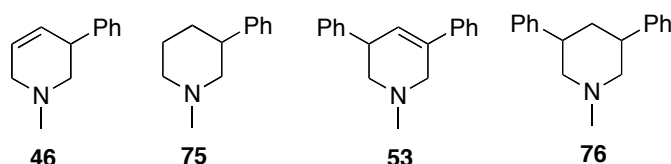
Figure 13. *nPhNMTP and reduced forms*

The presence of these reduced by-products results in difficulties in purification and isolation, as the reduced products (**75** and **76**) co-elute with the corresponding olefins (**46** and **53** respectively), preventing accurate evaluation of the reaction yields, and product separation. Therefore, yields were not obtained for the microwave reactions, and reaction progression was observed solely by peak area and LCMS analysis. Reduction of the olefinic products **46** and **53** to **75** and **76** respectively may be occurring due to L_nPd-H formed from reductive elimination during the Heck-Mizoroki reaction acting as a reducing agent at high temperatures.

When stock solutions of reaction components in aq. MeCN were prepared, all reagents were soluble and homogeneous at room temperature, however a palladium species rapidly precipitated out of solution. This solid was observed in both the stock solution over time and in the completed microwave reaction vessels. Decreasing catalyst charge from 3 mol% to 1 mol%, failed to reduce the precipitate formation. It was observed that for formation of 5-PhNMTP (**46**) by microwave reaction, palladium catalyst loading was required to be 1 mol% or higher. Even at this concentration, a Pd precipitate was observed. Lower concentrations of catalyst failed to give product.

Although it has been shown that microwave heating could be applied the cross-coupling of **1** and **50**, to

synthesise **46** (as shown by LCMS), the presence of the co-eluting reduced products resulted in inaccurate evaluation of product formation and yields which were unable to be calculated. As a consequence of the high amount of di-arylation, microwave synthesis was deemed an unsuitable method for rapid screening for reaction optimisation.

2.2 The Oxidative Heck Reaction

While the Heck-Mizoroki reaction has been highly utilised, providing desirable products, the overall process requires prefunctionalisation of the cross-coupling partner by formation of the required halide. An alternative process has been developed as a more efficient process; the Fujiwara–Moritani or Oxidative Heck reaction. This process enables direct coupling of an arene or boronic acid with an alkene, avoiding the use of halides.[155] Boronic acids are stable, of low toxicity, and a wide variety are commercially available. The relatively simple synthesis of further complex, non-commercially available boronic acids makes them useful and versatile reagents for cross-coupling.

The first example of a direct oxidative coupling of arenes with alkenes was described by Fujiwara and Moritani in 1967.[156] The reaction involved direct coupling of unfunctionalised arenes with methyl acrylate (Scheme 61, R = H). Although initially low yielding, this novel reaction opened a new area of palladium(II)-catalysed reactions.
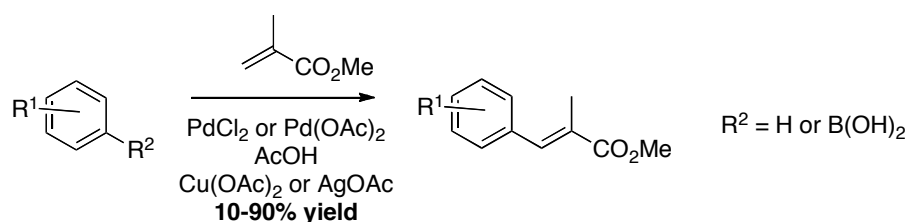
Scheme 61. *Fujiwara–Moritani Oxidative Heck Reaction with methyl acrylate*

The oxidative Heck mechanism involves use of a palladium catalyst (**A**, Scheme 62), which undergoes transmetallation with phenylboronic acid (**B**, Scheme 62). This species coordinates to the olefin to form an associated intermediate (**C**, Scheme 62), which undergoes an insertion to the olefin (**D**, Scheme 62). β-Hydride elminination and reductive elimination results in the cross-coupled product (**E**, Scheme 62). and a palladium(0) species (**F**, Scheme 62), from which the palladium(II) species (**A**, Scheme 62) is then regenerated in the presence of an oxidant.[157]

Scheme 62. *Oxidative Heck catalytic cycle*
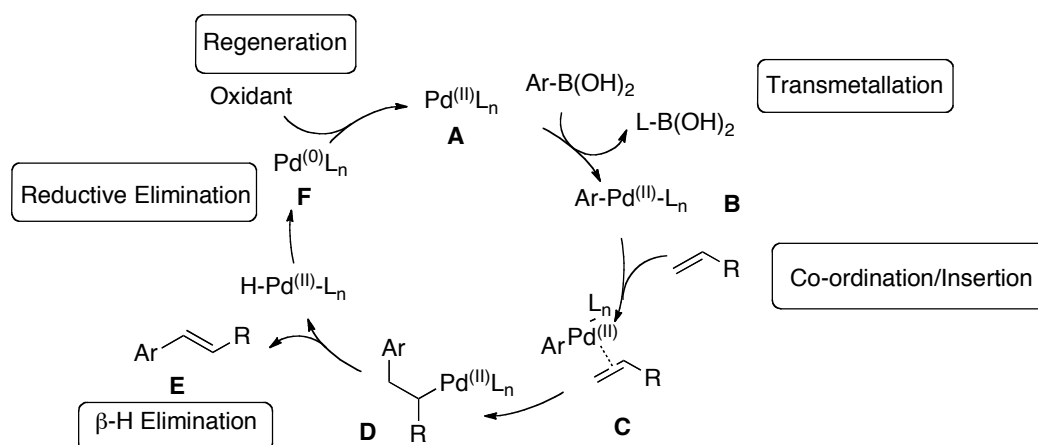
Although arylboronic acids or esters are most commonly employed in the oxidative Heck reaction, other arylating agents have also been reported, such as arylmercury compounds,[158] arylstannanes,[159] arylsilanes,[160] arylantimony compounds[161] and arylphosphonic acids.[162] However, these organometallic (or organometalloid) reagents are often unstable, and their byproducts highly toxic and difficult to remove.

The oxidative Heck reaction using organoboronic acids was first described in 1975 by Heck, using stoichiometric palladium acetate (Scheme 63).[163]

Scheme 63. *Oxidative Heck reaction using organoboronic acids as described by Heck*
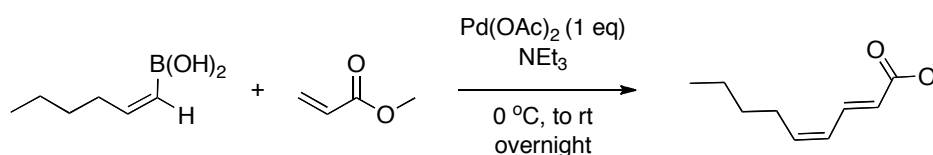
This coupling reaction did not receive much attention however until the mid 1990s, when Uemura reported the first sub-stoichiometric protocol using acetic acid as solvent, providing good yields of arylated olefins.[164] Since this, many such oxidative Heck methods have been reported, including ligand-modulated oxidative Heck reaction to facilitate the palladium reoxidation,[165] base-free oxidative Heck reactions,[166] and enantio- and regioselective reactions.[167] The wide availability of aryl boronic acids, their relative stability and the resultant non-toxic waste produced in the reactions, leads the oxidative Heck process to be one of great interest.

2.2.1 The Oxidative Heck Reaction of Tetrahydropyridines

In 2003, Jung developed a procedure where molecular oxygen was shown to act as an efficient palladium reoxidant (Scheme 64).[168]   It was found that reaction yield doubled when carried out under an O_2

atmosphere compared to in air (87% *cf.* 44%), and no product was isolated when performed under nitrogen. The use of oxygen gas for palladium recycling is inconvenient, expensive, and associated with dangerous handling, and is therefore not often applied to large-scale commercial applications, however for small-scale investigatory probing of a reaction, can be easily and safely applied.

$$Ph-B(OH)_2 \quad + \quad \diagup\diagdown CO_2{}^tBu \xrightarrow[\substack{O_2 \\ DMF, 50\ ^\circ C,\ 3\ hr \\ \textbf{87\% yield}}]{\substack{Pd(OAc)_2\ [10\ mol\%] \\ Na_2CO_3\ (2\ eq)}} Ph\diagup\diagdown CO_2{}^tBu$$
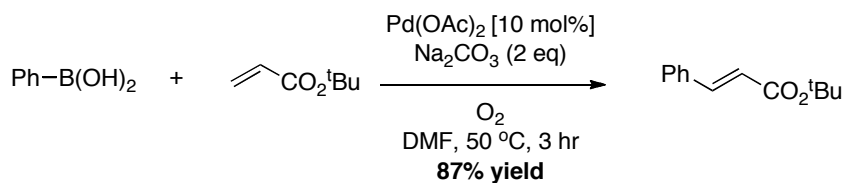
Scheme 64. *Use of oxygen reoxidant in Oxidative Heck reaction*

NMTP (**29**) and NMTP.HCl (**50**) were subjected to the oxidative Heck reaction, initially under conditions developed by Jung,[74] utilising molecular oxygen to facilitate the palladium reoxidation (Scheme 65).
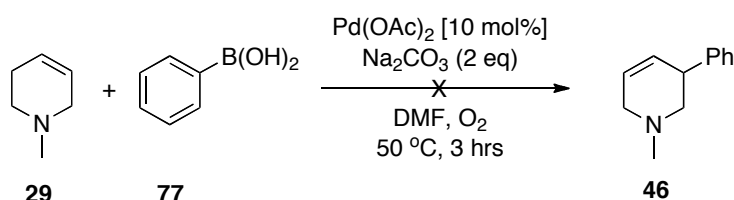
Scheme 65. *Oxidative Heck reaction with oxygen reoxidant*

Under Jung's conditions, **46** was not isolated. However, substantial amounts of a precipitated palladium species was observed within the reaction mixture and therefore oxygen facilitated reoxidation may not have been effective, resulting in the catalyst not being regenerated.

Prior to Jung's work with oxygen, Mori reported the use of a dedicated co-oxidant in the Oxidative Heck reaction.[169] Mori used Cu(OAc)$_2$ to regenerate Pd(II) from Pd(0), (Scheme 66). Copper(II) acetate and lithium acetate were found by Mori to realise the catalytic reaction successfully, with lithium acetate believed to enhance solubility of the copper(II) acetate.[170] Although high yielding, this method requires high reaction temperatures (100 $^\circ$C, DMF) and excess Cu(II), which results in the production of stoichometric metal salts.

$$Ph-B(OH)_2 \quad + \quad \diagup\diagdown COOBu \xrightarrow[\substack{LiOAc\ (3\ eq) \\ DMF, 100\ ^\circ C,\ 3\ hr \\ \textbf{84\% yield}}]{\substack{Pd(OAc)_2\ [10\ mol\%] \\ Cu(OAc)_2\ (2\ eq)}} Ph\diagup\diagdown COOBu$$
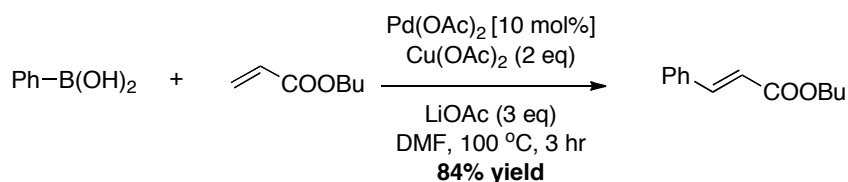
Scheme 66. *Mori's oxidative Heck protocol utilising Copper as a reoxidant*

Copper acetate is a commonly used re-oxidant. Gaunt reported the use of copper(II) acetate as re-oxidant in the C3-selective cross-coupling of indoles, in a solvent-controlled regioselective palladium-catalysed alkenylation by C-H functionalisation. They found that by changing the re-oxidant and solvent conditions, oxidative-Heck reactions may be tuned to occur selectively at the C3 or C2 positions (Scheme 67).[171]
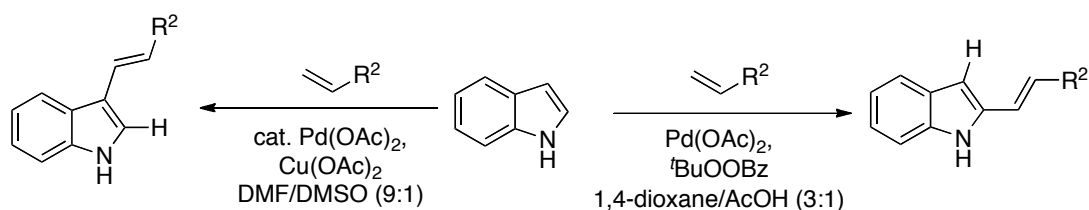
Scheme 67. *Tunable Oxidative Heck reaction of indoles*

As conditions developed by Jung's utilizing oxygen as the reoxidant were unsuccessful with NMTP, copper acetate was applied under conditions developed by Mori, to both NMTP (**29**) and NMTP.HCl (**50**), using phenyl boronic acid **77** (Scheme 68). Cross-coupling occurred to produce **46** from **50** after 4 hours, identified by ^{1}H NMR spectroscopy, but in poor yield. Extension of the reaction time to 24 hours did not result in higher yield (7%). Changing to acetonitrile as the solvent system gave comparable results to that of DMF (7% DMF, 6% MeCN), however yield decreased (3%) when water was used as the solvent.
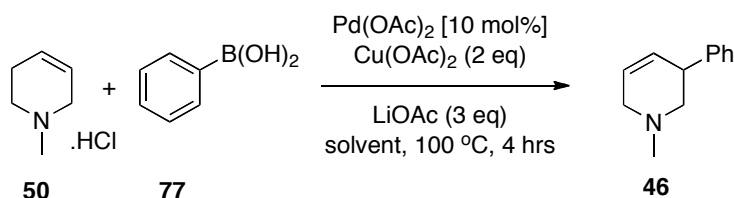
Scheme 68. *Oxidative Heck reaction with copper reoxidant, where solvent = DMF, MeCN or H₂O*

^{1}H NMR analysis of the oxidative Heck reaction product is comparable to that obtained under the developed Heck-Mizoroki conditions between iodobenzene and **50**, however the yield is significantly decreased (7%, *cf* 36%, 38% phosphine free). As previously suggested from reaction profiling, it is feasible that product was lost during purification and isolation, leading to the low yield.

Further optimisation of this oxidative Heck reaction is required. If comparable yields to the standard Heck-Mizoroki method can be obtained, this would provide a more rapid, cost-effective route to tetrahydropyridine functionalisation. This route is beneficial as it utilises the more widely available Pd(OAc)₂ catalyst, cheap copper oxidant and the wide variety of boronic acids commercially available, which would open the reaction to a wide scope of applications. Alternative oxidants could also be explored, such as benzoquinones reported by Van der Eycken in the catalytic oxidative Heck cyclisation for the construction of the azepinoindole framework (Scheme 69).[172]
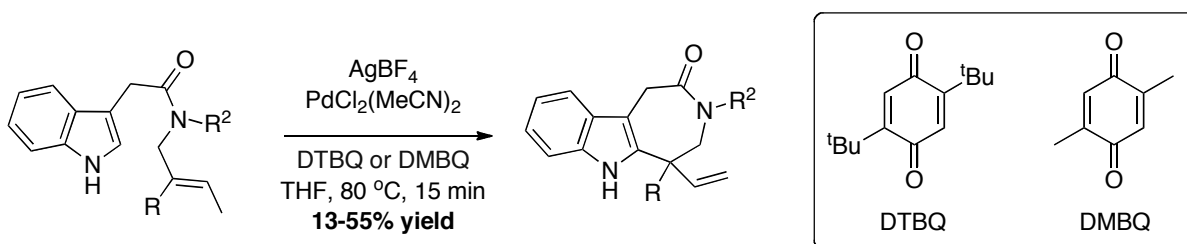
Scheme 69. Oxidative Heck intramolecular cyclisation of nitrogen heterocylces

2.3 Exploiting Nitrogen Chirality of Tetrahydropyridine Salts

When tetrahydropyridine ammonium salts are formed, a racemic mixture is usually produced which cannot be separated chromatographically. This asymmetry controls the face selectivity in the [2,3]-rearrangement reaction. To control the facial-selectivity, a single enantiomer of ammonium salt is required. Previously, attempts to isolate a single diastereoisomer through use of a chiral camphorsultam auxiliary failed, and therefore attention has been focused on an alternate route.

Synthesis of diastereomerically pure lactone **80** from racemic *N*-methyl-3-piperidinol (**78**) *via* racemic 3-hydroxy ammonium salt (1-ethoxycarbonylmethyl-3-hydroxy-1-methyl-piperidinium bromide, **79**) was investigated. **79** was isolated as a racemic oil (d.r. 1:1). Upon treatment of the salt with ethanolic HCl, the *cis*-isomer (**79a**) cyclised to give a mixture of the lactone (1-methyl-3-oxo-4-oxa-1-azonia-bicyclo[3.3.1]nonane bromide, **80**) and *cis* (**79a**) and *trans* hydroxy-ammonium salts (**79b**) as a yellow oil. Repeated crystallisation from aqueous ethanol gave the less soluble lactone (**80**) as colourless rod-like crystals in an isolated yield of 42% (Scheme 70), with structure confirmed by x-ray crystallography (Figure 14).[173]
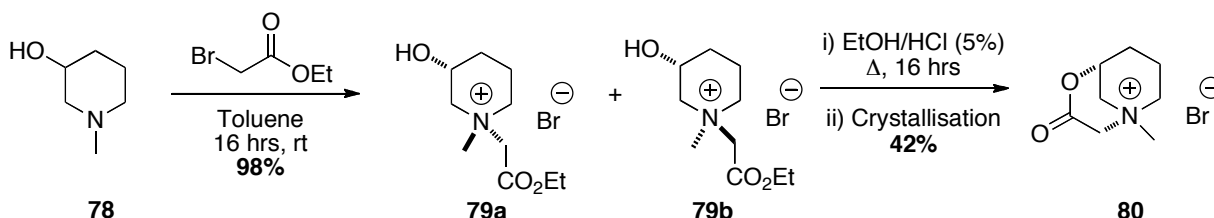
Scheme 70. Two step synthesis of lactone **80** from N-methyl-3-piperidinol **78**
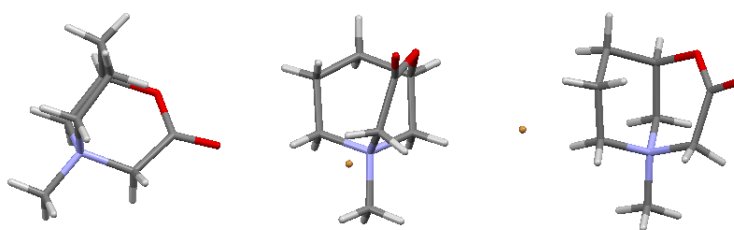
Figure 14. 3 Perspectives of the X-ray crystal structure of cyclised lactone salt **80**

Lactone ethanolysis subsequently led to a single diastereoisomer of ammonium salt **81** (Scheme 71).

Subsequent dehydration of the alcohol provides access to the tetrahydropyridines **82** and **83**.
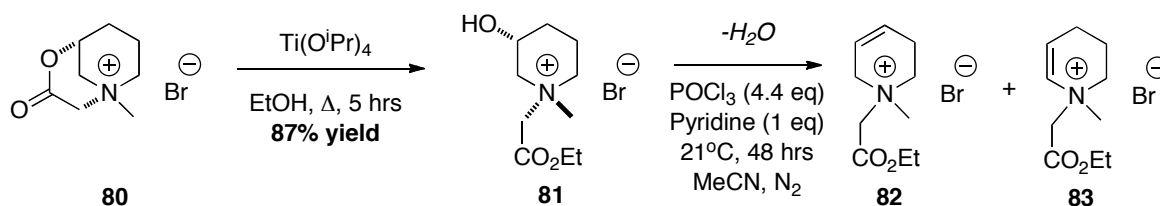
Scheme 71. *Towards the synthesis of a single diastereoisomer of ammonium salts*

Initially, dehydration was achieved with phosphorus(V) oxychloride and pyridine, with the two olefinic products observed (**82** and **83**), identifiable by the characteristic resonances of the cyclic olefinic protons 5.7-6.5 ppm in the ^{1}H NMR specta. To eliminate the requirement for the use of phosphorus oxychloride, the dehydration was conducted *in situ via* activation of the hydroxyl as a triflate.[174] This resulted, as observed with POCl$_3$, in the detection of the two isomeric olefins (**82** and **83**) in approximately equal amount (1:1 by ^{1}H NMR spectroscopy, Scheme 72). The reaction is efficient, but did not progress to completion, as the triflate (**84**) was still detectable in the reaction mixture. Extension of the reaction time did not decrease the ratio of triflate to olefins.
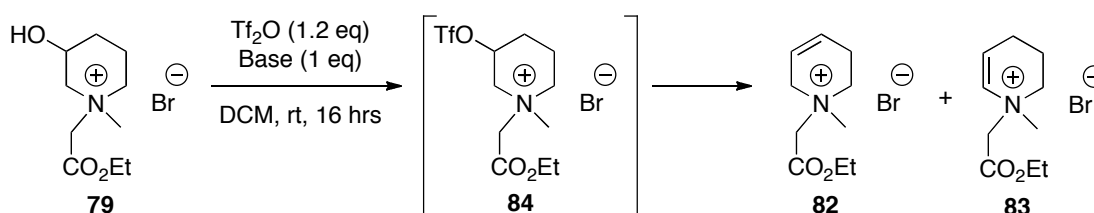
Scheme 72. *In situ dehydration via triflate*

In an attempt to distinguish between the steric environment of Hα and Hγ, in favour of the production of **82** by preferential elimination of the γ–hydride, pyridine was replaced with 2,6-di-*tert*-butyl-3-methyl pyridine (Scheme 73).
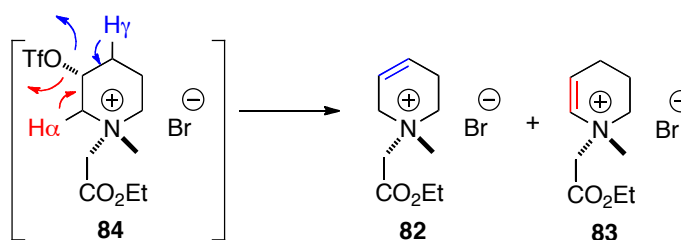
Scheme 73. *In situ dehydration via triflate*

Conducting the reaction in deuterated chloroform allowed for reaction sampling to be undertaken, resulting in visualisation of the olefin formation. The desired 1,2,5,6-tetrahydropyridine (**82**) was detected from 20 hours (9:1, triflate:olefin), and increased rapidly up to 44 hours (1:1, triflate:olefin) with no further change after this time. Throughout the monitoring process **83** was not detected by ^{1}H NMR analysis, demonstrating preferential elimination of the γ–hydride in the presence of 2,6-di-*tert*-butyl-3-methyl pyridine (Figure 15).
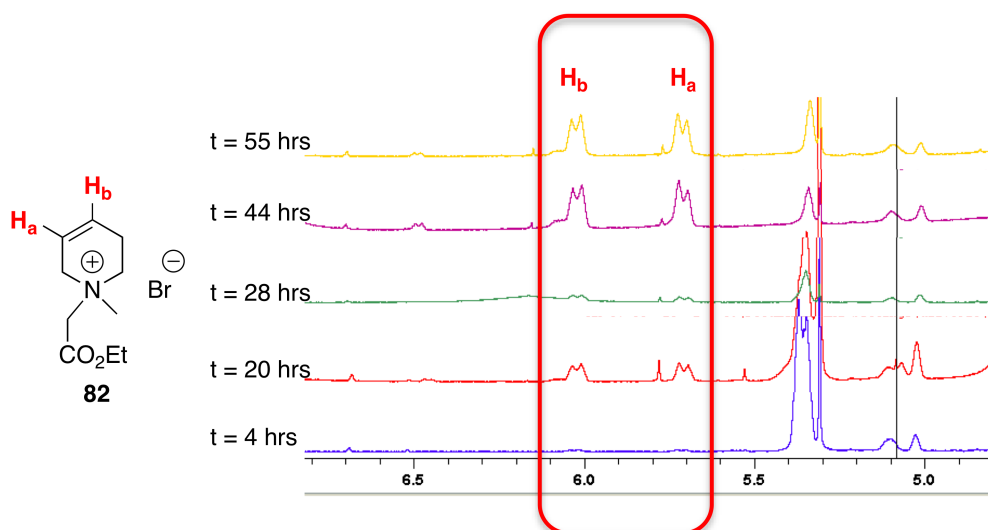
Figure 15. *In situ dehydration of quaternary ammonium hydroxyl salts via triflate with a bulky base, monitoring over 55 hours by ^{1}H NMR spectroscopy*

In an attempt to reduce the amount remaining **84** and increase conversion to the olefin (**82**), the amount of base and trifluoromethanesulfonic anhydride were increased. Increasing the amount of base without increasing the Tf$_2$O had no observable effect on the olefin:triflate ratio as observed by ^{1}H NMR spectroscopy. However, increasing both (base from 1 equivalent to 5 equivalents, trifluoromethanesulfonic anhydride from 1.2 equivalent to 4 equivalents) resulted in a single olefin detected by ^{1}H NMR analysis, with no starting material or triflate detected suggesting full conversion to the desired 1,2,5,6-tetrahydropyridine (**82**).

The requirement for 5 equivalents of 2,6-di-*tert*-butyl-3-methyl pyridine in the synthesis results in increased cost and reagent consumption. Therefore, a screen was conducted to find the lowest excess of triflate and base required to give full conversion, while maintaining a single olefin product (Table 13). Reaction mixtures were analysed by ^{1}H NMR spectroscopy to determine the ratio of compound **82**:**83**.

Results demonstrated that 3 equivalents of base and 2 equivalents of Tf$_2$O may be applied to generate a single olefin (**82**) with no starting material (**79**) or triflate (**84**) remaining. This is a significant reduction from the 5 equivalents of base and 4 equivalents of Tf$_2$O applied previously, providing a more cost-effective method and resulting in the formation of a single enantiomer of tetrahydropyridine salt **82** in high yield (83%).

Table 13. *Effect of altering base and triflic anhydride on olefin production*

Entry	[Base] (X eq)	[Tf$_2$O] (Y eq)	Ratio **82:83**
1	2.4	1.2	1:0.5
2	3	2	1:0
3	4	3	1:0
4	5	4	1:0
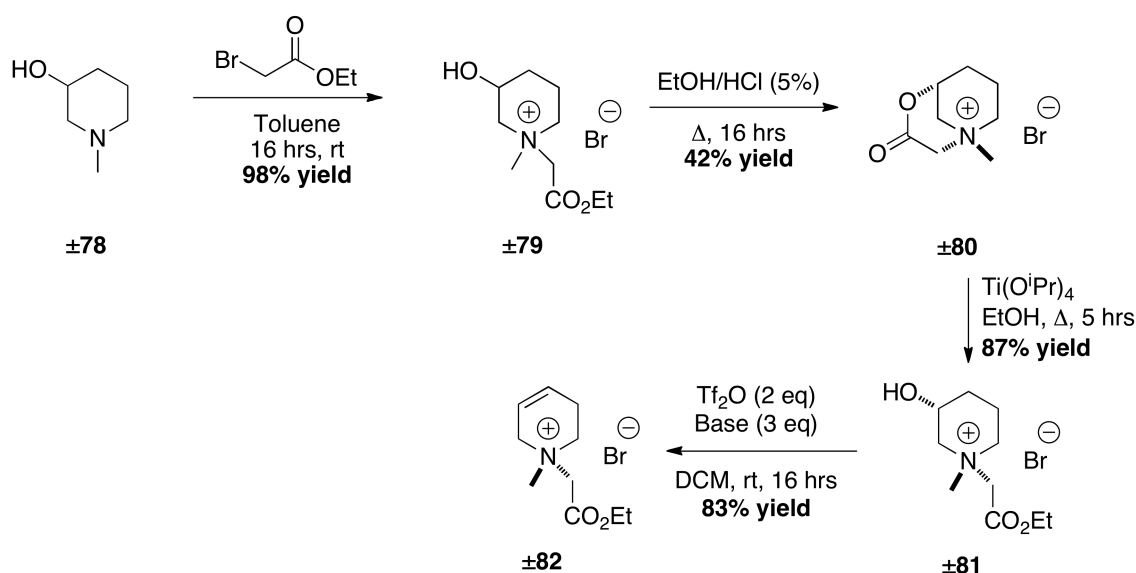
Scheme 74. *Route to single enantiomer of 1-ethoxycarbonylmethyl-1-methyl-1,2,5,6-tetrahydropyridine bromide (±82) from 1-methyl-3-piperidinol (±78)*

The route developed commenced with racemic starting material 1-methyl-3-piperidinol (**±78**), and resulted in **±82** in 29% yield over four steps. To enable the synthesis of optically pure products, a single enantiomer of **78** is required. Methylation of commercially available (*R*)-3-hydroxypiperidine (**85**) will give *(R)*-1-methyl-3-piperidinol (**86**) which may be employed into the developed synthesis to give (*S*)-1-ethoxycarbonylmethyl-1-methyl-1,2,5,6-tetrahydropyridine bromide (**82**, Scheme 75). This may then be applied to the developed direct functionalisation method or [2,3]-rearrangement to access kainoid-like structures of pharmaceutical interest.
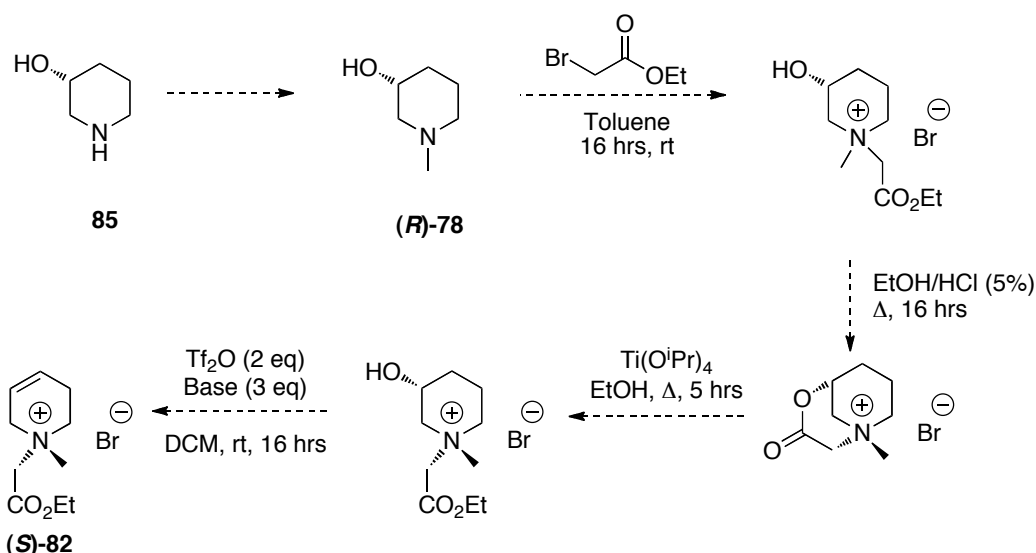
Scheme 75. Route to (S)-1-ethoxycarbonylmethyl-1-methyl-1,2,5,6-tetrahydropyridine bromide (**82**)

[2,3]-Rearrangement of **82** will give a pyrrolidine dicarboxylate with *cis* configuration at the C-2 and C-3 positions. In 2002, Karoyan reported the asymmetric synthesis of both the *cis-* and *trans*-3-prolinoglutamic acids in a diastereoselective and enantioselective manner *via* amino–zinc–enolate cyclisation.[81] The *trans* isomer was produced from the *cis* isomer by heating with water in a sealed tube, resulting in epimerisation at the 2 position (Scheme 76).
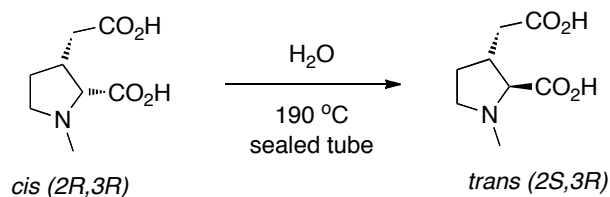
Scheme 76. Karoyan's inversion of stereochemistry

Epimerisation in this manner may be a valuable tool towards the synthesis of Acromelic acid A (**21**), if transferrable to the NMTPs under investigation (Scheme 77).
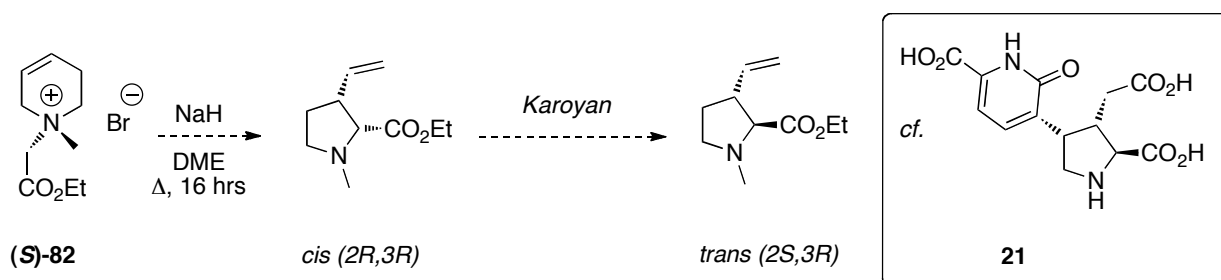
Scheme 77. Inversion of stereochemistry to obtain trans C2-C3 configuration

2.4 Conclusion and Future Work

As demonstrated, palladium-catalysed direct arylation of *N*-methyl-1,2,5,6-tetrahydropyridine **29** and the hydrochloride salt **50** is feasible under the reported streamlined phosphine- and silver-free conditions. A reduction in the excess of NMTP starting material required has been achieved, through use of the hydrochloride salt **50**. The reaction mechanism has been shown to be complex, and the arylated compounds produced difficult to purify utilising standard methods. The presence of the di-arylated products further emphasise the complexity of the catalytic processes involved. However, the reaction remains of great interest due to the difficulty in direct functionalisation of these highly polar nitrogen containing compounds.

Further probing of the reaction by in-line GCMS or LCMS may go further to explore the reaction process and lead to an improved method of purification and isolation. Once isolated, these compounds are clearly of interest in the telescoped route to 3-aryl-piperidines, or may be applied to the developed [2,3]-rearrangement to give coumpounds comprising of the pyrrolidine dicarboxylic acid structures found in kainoids, aided by the development of the route to a single diastereomer of quaternary ammonium salt to control the face selectivity.
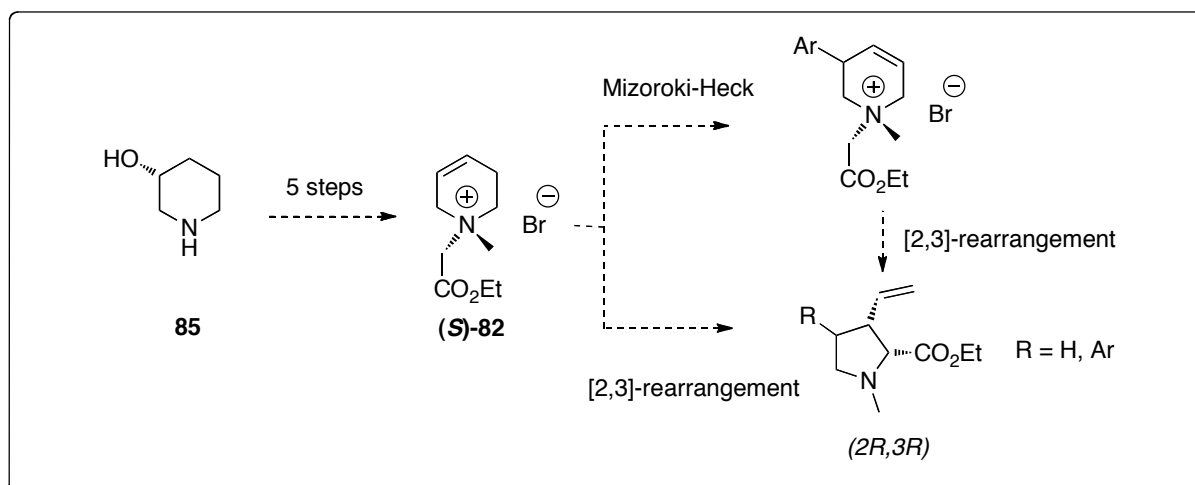
CHAPTER 3: EXPERIMENTAL: DIRECT FUNCTIONALISATION OF NITROGEN CONTAINING HETEROCYCLES

Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific, TCI UK or Lancaster Research Chemicals and were not purified except where stated. Solvents were purchased anhydrous and stored over molecular sieves, or distilled under nitrogen from an appropriate drying agent. THF, diethylether, DCM and acetonitrile were distilled from calcium hydride. Thin layer chromatography was performed on aluminum sheets coated with Merck silica gel 60 F_{254} with visualisation using potassium permanganate solution and/or scrutinised under 254 nm UV light. Column chromatography was performed using Silica 60 (35-70 microns) supplied by Fisher. Crude *N*-alkyl-5-aryl-1,2,5,6-tetrahydropyridines were purified by preparative thin layer chromatography utilising Analtech 1000mm plates (5% MeOH in EtOAc).

Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Ultrashield 400 Plus NMR spectrometer or Bruker Avance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) with the appropriate deuterated solvent. [1]H chemical shifts (δ_H) are expressed in parts per million (ppm) relative to tetramethylsilane (TMS), and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (*J*) are quoted in Hz and are rounded to the nearest 0.5 Hz. 13C chemical shifts (δ_C) are reported rlative to internal solvent peaks from the stated deuterated solvent. Mass spectrometry was performed using a Thermo Fisher Scientific Orbitrap XL or Bruker MicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using a PerkinElmer Spectrum RX1 FT-IR Spectrometer instrument on germanium ATR or a Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument; selected absorbance maxima are reported in wavenumbers (cm^{-1}). All melting points were obtained using a Stuart SMP10 melting point instrument and are uncorrected.

3.1 Heck Arylation of N-methyl-1,2,5,6-tetrahydropyridine

General Procedure for Heck-Mizoroki Arylation:

N-Alkyl-1,2,5,6-tetrahydropyridine (1.5 mmol, 1.5 eq), arylhalide (1.0 mmol, 1.0 eq), Pd(OAc)$_2$ (7 mg, 0.03 mmol, 0.03 eq), and NEt$_3$ (0.35 mL, 2.5 mmol, 2.5 eq) were combined in screw cap tubes with aq. MeCN (3 mL) and heated at 80 °C for 48 to 72 hours. The reaction mixture was then allowed to cool to room temperature before addition of Et$_2$O (15 mL) and filtration through Celite®. The filtrate was treated with 0.5M HCl (3 x 15 mL) and the combined aqueous layers were treated with sufficient NaOH (2M) for neutralisation (as shown by pH indicator paper), prior to further extracted with Et$_2$O (3 x 20 mL). The combined organic fractions were dried over Na$_2$SO$_4$ and concentrated *in vacuo* yielding the corresponding crude *N*-alkyl-5-aryl-1,2,5,6-tetrahydropyridine. Crude *N*-alkyl-5-aryl-1,2,5,6-tetrahydropyridines were purified by preparative thin layer chromatography utilising Analtech 1000mm plates (5% MeOH in EtOAc), or flash column chromatography (95:5 DCM:MeOH).

1-Methyl-5-phenyl-1,2,5,6-tetrahydropyridine (46)
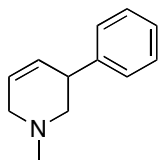
Iodobenzene (0.17 mL, 1.54 mmol, 1 eq), was used in the general method to yield 1-methyl-5-phenyl-1,2,5,6-tetrahydropyridine as a red oil (98 mg, 38%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.38 (dd, *J* 10.0 Hz 11.0 Hz, 1H, 6 -C<u>H</u>$_2$), 2.46 (s, 3H, -NC<u>H</u>$_3$), 2.95-3.06 (m, 1H, 2 -C<u>H</u>$_2$), 3.10 (q, *J* 6.5 Hz 12.0 Hz, 1H, 6 -C<u>H</u>$_2$), 3.35 (br.d, *J* 14.5 Hz, 1H, 2 –C<u>H</u>$_2$), 3.75-3.81 (m, 1H, 5 -C<u>H</u>), 5.86-5.90 (m, 2H, 3, 4 -C<u>H</u>=C<u>H</u>), 7.21-7.34 (m, 5H, Ar-<u>H</u>); ^{13}C NMR (100 MHz) δ_C 42.9 (5 -<u>C</u>H), 45.8 (-N<u>C</u>H$_3$), 54.3 (6 -<u>C</u>H$_2$), 60.8 (2 -<u>C</u>H$_2$), 126.2 (3 -<u>C</u>H), 126.5, 127.9, 128.4 (Ar-<u>C</u>), 128.4 (4 -<u>C</u>H), 143.5 (Ar-<u>C</u>); ν_{max} (thin film, cm^{-1}) 3028 (C=CH) 2966, 2936, 2917, 2869 (CH$_2$, C-H stretch), 2839, 2777 (N-CH$_3$), 1658, 1491 (Aromatic C=C), 1602 (C=C), 757 (mono-substituted phenyl), 699 (CH=CH *cis*); m/z (ES$^+$) calculated for C$_{12}$H$_{16}$N [M+H$^+$]; 174.1283, found 174.1277.

1-Methyl-5-(3'-benzyloxyphenyl)-1,2,5,6-tetrahydropyridine (52)
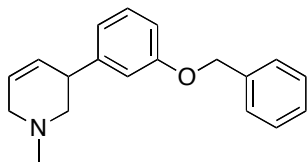
Benzyloxy-3-iodobenzene (0.310 g, 1 mmol) was used in the general method to yield 1-methyl-5-(3'-benzyloxyphenyl)-1,2,5,6-tetrahydropyridine (212 mg, 76 %); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.23 (dd, J 9.0 Hz 11.0 Hz, 1H, 6 -C$\underline{H}_2$), 2.33 (s, 3H, -NC$\underline{H}_3$), 2.79-2.84 (m, 1H, 2 -C$\underline{H}_2$), 2.93 (q, J 5.5 Hz, 1H, 6 -C$\underline{H}_2$), 3.16 (br d, J 16.5 Hz, 1H, 2 -C$\underline{H}_2$), 3.61-3.65 (m, 1H, 5 -C$\underline{H}$), 5.04 (s, 2H, -OC$\underline{H}_2$), 5.76-5.79 (m, 1H, 4 -C$\underline{H}$), 5.84-5.89 (m, 1H, 3 -C$\underline{H}$), 6.82-6.88 (m, 4H, Ar-$\underline{H}$), 7.20-7.24 (m, 5H, Ar-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 42.0 (5 -$\underline{C}$H), 45.2 (-N$\underline{C}$H$_3$), 53.7 (2 -$\underline{C}$H$_2$), 60.1 (6 -$\underline{C}$H$_2$), 69.9 (-O$\underline{C}$H$_2$), 125.1 (3 -$\underline{C}$H), 129.1 (4 -$\underline{C}$H), 112.8, 114.6, 120.5, 127.6, 128.3, 128.5, 129.4 (Ar -$\underline{C}$H), 137.0, 145.3, 159.0, (Ar-$\underline{C}$); ν_{max} (thin film, cm^{-1}) 3013 (C=CH) 2935 (CH$_2$, C-H stretch), 2870 (N-CH$_3$), 1656, 1448 (Aromatic C=C), 1597 (C=C), 1448 (C-N), 1315, 1157 (Ar-O-R), 777 (*meta* di-substituted benzene), 736 (mono-substituted phenyl) 696 (CH=CH *cis*); m/z (ES$^+$) calculated for C$_{19}$H$_{22}$NO [M+H]$^+$; 280.1701, found 280.1692.

1-Methyl-5-(4'-benzyloxyphenyl)-1,2,5,6-tetrahydropyridine (54)
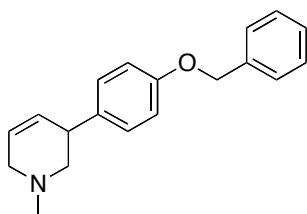
Benzyloxy-4-iodobenzene (0.310 g, 1 mmol) was used in the general method to yield 1-methyl-5-(4-benzyloxyphenyl)-1,2,5,6-tetrahydropyridine (10 mg, <5%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.20 (dd, J 9.0 Hz 11.0 Hz, 1H, 6 -C$\underline{H}_2$), 2.33 (s, 3H, -NC$\underline{H}_3$), 2.79-2.84 (m, 1H, 2 –C$\underline{H}_2$), 2.91 (q, J 5.5 Hz, 1H, 6 -C$\underline{H}_2$), 3.51 (d, J 16.0 Hz, 1H, 2 -C$\underline{H}_2$), 3.59-3.61 (m, 1H, 5 -C$\underline{H}$), 5.04 (s, 2H, -OC$\underline{H}_2$), 5.74-5.77 (m, 1H, 4 -CH_2), 5.83-5.87 (m, 1H, 3 -C$\underline{H}$), 7.03 (dd, J 8.5 Hz 9.0 Hz, 4H, Ar-$\underline{H}$), 7.27-7.43 (m, 5H, Ar-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 41.9 (5 -$\underline{C}$H), 45.7 (-N$\underline{C}$H$_3$), 54.2 (2 -$\underline{C}$H$_2$), 60.9 (6 -$\underline{C}$H$_2$), 60.0 (-O$\underline{C}$H$_2$), 125.8 (3 -$\underline{C}$H), 128.8 (4 -$\underline{C}$H), 114.7, 127.4, 127.9, 128.5, 128.7 (Ar-$\underline{C}$H), 135.9, 137.1, 157.5 (Ar-$\underline{C}$); Due to low quantities of product isolated, only partial characterization is reported.

1-Methyl-5-(*o*-tolyl)-1,2,5,6-tetrahydropyridine (55)

2-Iodotoluene (0.218 g, 1 mmol) was used in the general method to yield 1-methyl-5-(*o*-tolyl)-1,2,5,6-tetrahydropyridine (26 mg, 14%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.15 (dd, J 9.0 Hz 11.0 Hz, 1H, 6 -C$\underline{H}_2$), 2.35 (s, 3H, -NC$\underline{H}_3$), 2.37 (s, 3H, 2' -C$\underline{H}_3$), 2.81-2.86 (m, 1H, 2 -C$\underline{H}_2$), 2.95 (q, J 5.5 Hz, 1H, 6 -C$\underline{H}_2$), 3.21

(br d, *J* 17.0 Hz, 1H, 2 –C$\underline{H}_2$), 3.91-3.93 (m, 1H, 5 -C$\underline{H}$), 5.76 (br d, *J* 10.0 Hz, 1H, 4 -C$\underline{H}$), 5.88-5.91 (m, 1H, 3 -C$\underline{H}$), 7.10-7.19 (m, 4H, Ar-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 29.7 (2' -$\underline{C}H_3$), 38.8 (5 -$\underline{C}H$), 45.8 (-N$\underline{C}H_3$), 54.4 (2 -$\underline{C}H_2$), 59.3 (6 -$\underline{C}H_2$), 125.9 (4 -$\underline{C}H$), 128.8 (3 -$\underline{C}H$), 126.2, 126.3, 127.6, 130.2 (Ar-$\underline{C}H$), 135.7, 141.3 (Ar-$\underline{C}$); Due to low quantities of product isolated, only partial characterization is reported.

1-Methyl-5-(*m*-tolyl)-1,2,5,6-tetrahydropyridine (56)

3-Iodotoluene (0.218 g, 1 mmol) was used in the general method to yield 1-methyl-5-(*m*-tolyl)-1,2,5,6-tetrahydropyridine (20 mg, 11%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.22 (dd, *J* 9.0 Hz 11.0 Hz, 1H, 6 -C$\underline{H}_2$), 2.33 (s, 3H, -NC$\underline{H}_3$), 2.34 (s, 3H, 3' -C$\underline{H}_3$), 2.71-2.84 (m, 1H, 2 -C$\underline{H}_2$), 2.93 (q, *J* 5.5 Hz, 1H, 6 -C$\underline{H}_2$), 3.18 (dd, *J* 1.0 Hz 16.5 Hz, 1H, 2 -C$\underline{H}_2$), 3.62-3.66 (m, 1H, 5 -C$\underline{H}$), 5.77-5.80 (m, 1H, 4 -C$\underline{H}$), 5.85-5.90 (m, 1H, 3 -C$\underline{H}$), 7.04-7.21(m, 4H, Ar-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 21.4 (3' -$\underline{C}H_3$), 42.8 (5 -$\underline{C}H$), 45.8 (-N$\underline{C}H_3$), 54.4 (2 -$\underline{C}H_2$), 60.8 (6 -$\underline{C}H_2$), 127.2 (4 -$\underline{C}H$), 128.6 (3 -$\underline{C}H$), 124.9, 126.0, 128.3, 128.6 (Ar-$\underline{C}H$), 137.9, 143.5 (Ar-$\underline{C}$); Due to low quantities of product isolated, only partial characterization is reported.

1-Methyl-5-(*p*-tolyl)-1,2,5,6-tetrahydropyridine (57)
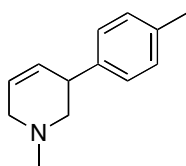
4-Iodotoluene (0.218 g, 1 mmol) was used in the general method to yield 1-methyl-5-(*p*-tolyl)-1,2,5,6-tetrahydropyridine (14 mg, 7%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.21 (dd, *J* 9.0 Hz 11.0 Hz, 1H, 6 -C$\underline{H}_2$), 2.32 (s, 3H, -NC$\underline{H}_3$), 2.34 (s, 3H, 4' -C$\underline{H}_3$), 2.79-2.85 (m, 1H, 2 -C$\underline{H}_2$), 2.93 (q, *J* 5.5 Hz, 1H, 6 -C$\underline{H}_2$), 3.17 (br d, *J* 16.5 Hz, 1H, 2 -C$\underline{H}_2$), 3.61-3.64 (m, 1H, 5 -C$\underline{H}$), 5.76-5.79 (m, 1H, 4 -C$\underline{H}$-), 5.83-5.89 (m, 1H, 3 -C$\underline{H}$), 7.11 (s, 4H, Ar-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 21.0 (4' -$\underline{C}H_3$), 42.4 (5 -$\underline{C}H$), 45.7 (-N$\underline{C}H_3$), 54.4 (2 –$\underline{C}H_2$), 60.9 (6 -$\underline{C}H_2$), 125.9 (4 -$\underline{C}H$), 127.8, 28.6 (Ar-$\underline{C}H$), 129.1 (3 -$\underline{C}H$), 136.0, 140.5 (Ar-$\underline{C}$); Due to low quantities of product isolated, only partial characterization is reported.

1-Methyl-5-(2'-methoxyphenyl)-1,2,5,6-tetrahydropyridine (58)

2-Iodoanisole (0.234 g, 1 mmol) was used in the general method to yield 1-methyl-5-(2'-methoxyphenyl)-1,2,5,6-tetrahydropyridine (6 mg, 3%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.20 (dd, *J* 7.9 Hz 11.0 Hz, 1H, 6 -C$\underline{H}_2$), 2.32 (s, 3H, -NC$\underline{H}_3$), 2.83-2.89 (m, 1H, 2 -C$\underline{H}_2$), 2.95 (q, *J* 5.5 Hz, 1H, 6 -C$\underline{H}_2$), 3.11 (br d, *J* 16.5 Hz,

1H, 2 -C<u>H</u>₂), 3.82 (s, 3H, -OC<u>H</u>₃), 4.09-4.13 (m, 1H, 5 -C<u>H</u>), 5.76 (dd, J 2.0 Hz 10.0 Hz, 1H, 4 -C<u>H</u>), 5.86-5.90 (m, 1H, 3 -C<u>H</u>), 6.85 (d J 8.5 Hz, 1H, Ar-<u>H</u>), 6.91 (t J 7.0 Hz, 1H, Ar-<u>H</u>), 7.17-7.21 (m, 2H, Ar-<u>H</u>); ^{13}C NMR (100 MHz) δ_C 35.3 (5 -<u>C</u>H), 4.45 (-N<u>C</u>H₃), 54.4 (2 -<u>C</u>H₂), 55.3 (-O<u>C</u>H₃), 58.8 (6 -<u>C</u>H₂), 126.0 (3 -<u>C</u>H), 128.4 (4 -<u>C</u>H), 110.2, 120.5, 127.3, 128.5 (Ar-<u>C</u>H), 131.1 (Ar-<u>C</u>), 157.0 (Ar-<u>C</u>); Due to low quantities of product isolated, only partial characterization is reported.

1-Methyl-5-(3'-methoxyphenyl)-1,2,5,6-tetrahydropyridine (59)
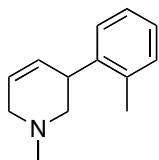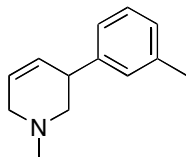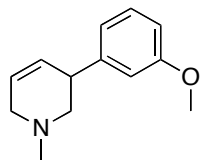

3-Iodoanisole (0.234 g, 1 mmol) was used in the general method to yield 1-methyl-5-(3'-methoxyphenyl)-1,2,5,6-tetrahydropyridine (43 mg, 21%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.24 (dd, J 9.0 Hz 11.0 Hz, 1H, 6 -C<u>H</u>₂), 2.34 (s, 3H, -NC<u>H</u>₃), 2.80-2.86 (m, 1H, 2 -C<u>H</u>₂), 2.94 (q, J 5.5 Hz, 1H, 6 -C<u>H</u>₂), 3.71 (br d, J 16.5 Hz, 1H, 2 -C<u>H</u>₂), 3.61-3.65 (m, 1H, 5 -C<u>H</u>), 3.80 (s, 3H, -OC<u>H</u>₃), 5.77-5.80 (m, 1H, 4 -C<u>H</u>), 5.85-5.90 (m, 1H, 3 -C<u>H</u>), 6.73-6.84 (m, 2H, Ar-<u>H</u>), 7.20-7.26 (m, 2H, Ar-<u>H</u>); ^{13}C NMR (100 MHz) δ_C 42.1 (5 -<u>C</u>H), 45.2 (-N<u>C</u>H₃), 53.9 (2 -<u>C</u>H₂), 55.1 (-O<u>C</u>H₃), 60.2 (6 -<u>C</u>H₂), 111.9, 112.7, 113.0, 120.3 (Ar -<u>C</u>H), 125.4 (3 -<u>C</u>H), 128.5 (*Ar-C*), 128.5 (4 -<u>C</u>H), 129.5 (Ar-<u>C</u>); ν_{max} (thin film, cm^{-1}) 3029 (C=CH) 2954 (CH$_2$, C-H stretch), 2836 (O-CH$_3$), 2779 (N-CH$_3$), 1671, 1453 (Aromatic C=C), 1599 (C=C), 1453 (C-N), 1315, 1156 (Ar-O-R), 768 (*meta* di-substituted phenyl), 680 (CH=CH *cis*); m/z (ES$^+$) calculated for C$_{13}$H$_{18}$NO [M+H]$^+$; 204.1383, found 204.1381.

1-Methyl-5-(4'-methoxyphenyl)-1,2,5,6-tetrahydropyridine (60)
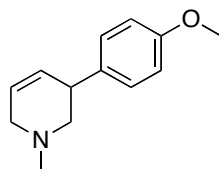
4-Iodoanisole (0.234 g, 1 mmol) was used in the general method to yield 1-methyl-5-(4'-methoxyphenyl)-1,2,5,6-tetrahydropyridine (16 mg, 7%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.21 (dd, J 9.0 Hz 11.0 Hz, 1H, 6 -C<u>H</u>₂), 2.34 (s, 3H, -NC<u>H</u>₃), 2.80-2.86 (m, 1H, 2 -C<u>H</u>₂), 2.92 (q, J 5.5 Hz, 1H, 6 -C<u>H</u>₂), 3.17 (br d, J 16.5 Hz, 1H, 2 -C<u>H</u>₂), 3.60-3.63 (m, 1H, 5 -C<u>H</u>), 3.79 (s, 3H, -OC<u>H</u>₃), 5.75-5.78 (m, 1H, 4 -C<u>H</u>), 5.83-5.88 (m, 1H, 3 -C<u>H</u>), 6.84 (d, J 8.5 Hz, 2H, Ar-<u>H</u>), 7.14 (d, J 8.5 Hz, 2H, Ar-<u>H</u>); ^{13}C NMR (100 MHz) δ_C 41.9 (5 -<u>C</u>H), 45.7 (-N<u>C</u>H₃), 54.4 (2 -<u>C</u>H₂), 55.2 (-O<u>C</u>H₃), 60.9 (6 -<u>C</u>H₂), 125.8 (3 -<u>C</u>H), 128.7 (4 -<u>C</u>H), 113.8, 128.8 (Ar-<u>C</u>H), 125.8, 135.6 (Ar-<u>C</u>); ν_{max} (thin film, cm^{-1}) 2935 (CH$_2$, C-H stretch), 2834, 2775 (N-CH$_3$), 1653, 1509 (Aromatic C=C), 1607 (C=C), 1245 (C-O), 668 (CH=CH *cis*); m/z (ES$^+$) calculated for C$_{13}$H$_{18}$NO [M+H]$^+$; 204.1383, found 204.1382.

1-Methyl-5-napthyl-1,2,5,6-tetrahydropyridine (61)

Iodonapthalene (0.254 g, 1 mmol) was used in the general method to yield 1-methyl-5-napthyl-1,2,5,6-tetrahydropyridine (54 mg, 24%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.33 (s, 3H, -NC$\underline{H}_3$), 2.36 (dd, J 8.5 Hz 11.0 Hz, 1H, 6 -C$\underline{H}_2$), 2.88-2.94 (m, 1H, 2 -C$\underline{H}_2$), 3.11 (q, J 5.5 Hz, 1H, 6 -C$\underline{H}_2$), 3.21 (br d, J 17.4 Hz, 1H, 2 -C$\underline{H}_2$), 3.48-3.52 (m, 1H, 5 -C$\underline{H}$), 5.90-5.94 (m, 1H, 4 -C$\underline{H}$), 5.96-6.00 (m, 1H, 3 -C$\underline{H}$), 7.37-7.56 (m, 4H, napth-C$\underline{H}$), 7.69-7.80 (m, 1H, napth-$\underline{H}$), 7.84-7.87 (m, 1H, napth-$\underline{H}$), 8.14-8.16 (m, 1H, napth-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 38.2 (5 -$\underline{C}$H), 45.8 (-N$\underline{C}$H$_3$), 54.5 (2 -$\underline{C}$H$_2$), 59.8 (6 -$\underline{C}$H$_2$), 123.0, 125.1, 125.4, 125.6, 126.0, 126.4 (napth-$\underline{C}$), 127.0 (4 -$\underline{C}$H), 128.7 (napth-$\underline{C}$), 129.0 (3 -$\underline{C}$H), 131.5, 133.9, 139.3 (napth-$\underline{C}$); ν_{max} (thin film, cm^{-1}) 1653, 1507 (Aromatic C=C), 669 (CH=CH *cis*); m/z (ES$^+$) calculated for C$_{16}$H$_{18}$N [M+H]$^+$; 224.1439, found 224.1438.

1-Methyl-5-(2'-hydroxyphenyl)-1,2,5,6-tetrahydropyridine (62)
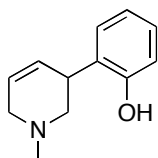
2-Iodophenol (0.220 g, 1 mmol) was used in the general method in aq. MeCN (3 mL, 95%) yielding 1-methyl-5-(2'-hydroxyphenyl)-1,2,5,6-tetrahydropyridine (<10 mg, <5%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.32 (td, J 12.7 Hz 3.7 Hz, 1H, 6 -C$\underline{H}_2$), 2.52 (s, 3H, -NC$\underline{H}_3$), 2.26-2.60 (m, 1H, 2 -C$\underline{H}_2$), 2.76 (dd, J 5.0 Hz 11.8 Hz, 1H, 5 -C$\underline{H}_2$), 3.02-3.04 (m, 1H, 2 -C$\underline{H}_2$), 3.36-3.41 (m, 1H, 5 -C$\underline{H}$), 4.95 (br. s, 1H, 2' -O$\underline{H}$), 5.72-5.79 (m, 2H, 3, 4 -C$\underline{H}$), 6.72-7.14 (m, 4H, Ar-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 42.8 (-N$\underline{C}$H$_3$), 44.3 (5 -$\underline{C}$H), 45.3 (6 -$\underline{C}$H$_2$), 56.0 (2 -$\underline{C}$H$_2$), 123.1 (3 -$\underline{C}$H), 127.0 (4 -$\underline{C}$H), 114.9, 118.3, 119.3, 127.8 (Ar-$\underline{C}$H), 128.4, 130.3, (Ar-$\underline{C}$); ν_{max} (thin film, cm^{-1}) 3068, 3039 (C=CH), 2994 (-OH), 2821 (N-CH$_3$), 1581 (Aromatic C=C), 1484 (C=C), 1457 (C-N), 1279 (O-H bending), 753 (*ortho* di-substituted phenyl); m/z (ES$^+$) calculated for C$_{12}$H$_{16}$NO [M+H]$^+$; 190.1232, found 190.1225.

1-Methyl-5-(2'-aminophenyl)-1,2,5,6-tetrahydropyridine (63)
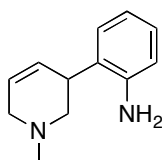
2-Iodoaniline (0.219 g, 1 mmol) was used in the general method in aq. MeCN (3 mL, 95%) yielding 1-methyl-5-(2-aminophenyl)-1,2,5,6-tetrahydropyridine (28 mg, 15%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.50 (dd, J 7.0 Hz 11.5 Hz, 1H, 6 -C$\underline{H}_2$), 2.55 (s, 3H, -NC$\underline{H}_3$), 2.87 (dd, J 5.0 Hz 10.6 Hz, 1H, 6 -C$\underline{H}_2$), 2.96-3.02 (m, 1H, 2 -C$\underline{H}_2$), 3.04-3.11 (m, 1H, 2 -C$\underline{H}_2$), 3.60-3.64 (m, 1H, 5 -C$\underline{H}$), 5.77-5.81 (m, 1H, 4 -C$\underline{H}$),

5.88-5.93 (m, 1H, 3 -C$\underline{H}$), 6.45-7.64 (m, 4H, Ar-$\underline{H}$); ν_{max} (thin film, cm^{-1}) 3058 (C=CH), 2924 (CH$_2$, C-H stretch), 2786 (N-CH$_3$), 1609 (NH$_2$), 1495, 1440 (Aromatic C=C), 1476 (C-N), 740 (*ortho* di-substituted phenyl), 695 (CH=CH *cis*); Due to low quantities of product isolated, only partial characterization is reported.

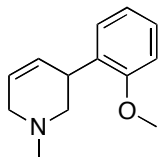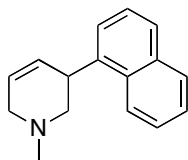### 1-Methyl-5-(2'-nitrophenyl)-1,2,5,6-tetrahydropyridine (65)
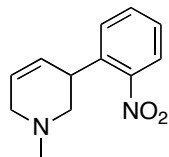
1-Iodo-2-nitrobenzene (0.249 g, 1 mmol, 1.0 eq) was used in the general method in aq. MeCN (3 mL, 95%) yielding 1-methyl-5-(2-nitrophenyl)-1,2,5,6-tetrahydropyridine (<10 mg, <5%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ$_H$ 2.34 (s, 3H, -NC$\underline{H}_3$), 2.46 (dd, *J* 6.2 Hz 11.4 Hz, 1H, 6 –C$\underline{H}_2$), 3.00 (d, *J* 5.4 Hz, 1H, 6 -C$\underline{H}_2$), 3.02-3.04 (m, 2H, 2 -C$\underline{H}_2$), 4.08-4.12 (m, 1H, 5 -C$\underline{H}$), 5.67-5.71 (m, 1H, 4 -C$\underline{H}$), 5.95-5.99 (m, 1H, 3 -C$\underline{H}$), 7.28-7.87 (m, 4H, Ar-$\underline{H}$); ^{13}C NMR (100 MHz) δ$_C$ 38.3 (5 -$\underline{C}$H), 45.5 (-N$\underline{C}$H$_3$), 54.0 (2 -$\underline{C}$H$_2$), 60.3 (6 -$\underline{C}$H$_2$), 126.4 (3 -$\underline{C}$H), 127.9 (4 -$\underline{C}$H), 125.0, 125.7, 126.7, 126.6, (Ar-$\underline{C}$H), 131.6, 130.8, (Ar-$\underline{C}$); ν_{max} (thin film, cm^{-1}) 2955, 2922 (CH$_2$, C-H stretch), 2853 (N-CH$_3$), 1660, 1459 (Aromatic C=C), 1580 (C=C), 1527, 1346 (NO$_2$), 1346 (C-N), 729 (*ortho* di-substituted phenyl), 695 (CH=CH *cis*); m/z (ES$^+$) calculated for C$_{12}$H$_{15}$N$_2$O$_2$ [M+H]$^+$; 129.1128, found 219.1126.

1-Methyl-5-(3'-nitrophenyl)-1,2,5,6-tetrahydropyridine (66)
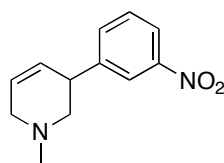
1-Iodo-3-nitrobenzene (0.249 g, 1.0 mmol, 1.0 eq) was used in the general method in aq. MeCN (3 mL, 95%), yielding 1-methyl-5-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine (20 mg, 9%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ$_H$ 2.31-2.36 (m, 1H, 6 -C$\underline{H}_2$), 2.34 (s, 3H, -NC$\underline{H}_3$) 2.89-3.01 (m, 2H, 2, 6 -C$\underline{H}_2$), 3.12 (br.d, *J* 17.4 Hz, 1H, 2 -C$\underline{H}_2$), 3.71-3.75 (m, 1H, 5 -C$\underline{H}$), 5.75-5.79 (m, 1H, 4 -C$\underline{H}$), 5.95-6.00 (m, 1H, 3 -C$\underline{H}$), 7.45-4.49 (m, 1H, Ar-C$\underline{H}$), 7.60-7.62 (m, 1H, Ar-C$\underline{H}$), 8.07-8.13 (m, 2H, Ar-C$\underline{H}$); ^{13}C NMR (100 MHz) δ$_C$ 42.6 (5 -$\underline{C}$H), 45.7 (-N$\underline{C}$H$_3$), 54.2 (2 -$\underline{C}$H$_2$), 60.0 (6 -$\underline{C}$H$_2$), 126.6 (4 -$\underline{C}$H), 126.6 (3 -$\underline{C}$H), 121.6, 122.8, 126.9, 129.2, (Ar-$\underline{C}$H), 134.5, 134.9 (Ar-$\underline{C}$); ν_{max} (thin film, cm^{-1}) 3033 (C=CH) 2976, 2917 (CH$_2$, C-H stretch), 2853 (N-CH$_3$), 1656, 1527 (Aromatic C=C), 1606 (C=C), 1527, 1349 (NO$_2$), 1349 (C-N), 737 (*meta* di-substituted phenyl), 687 (CH=CH *cis*); m/z (ES$^+$) calculated for C$_{12}$H$_{15}$N$_2$O$_2$ [M+H]$^+$; 219.1134, found 219.1127.

1-Methyl-5-(2'-(trifluoromethyl)phenyl)-1,2,5,6-tetrahydropyridine (67)
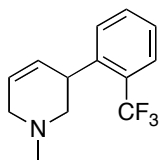
1-Iodo-2-(trifluoromethyl)benzene (0.272 g, 1 mmol) was used in the general method in aq. MeCN (3 mL, 95%) yielding 1-methyl-5-(2-(trifluoromethyl)phenyl)-1,2,5,6-tetrahydropyridine (11 mg, 5%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ$_H$ 2.27 (dd, J 7.8 Hz 11.3 Hz, 1H, 6 -C$\underline{H}_2$), 2.34 (s, 3H, -NC$\underline{H}_3$), 2.91-2.98 (m, 2H, 2, 6 -C$\underline{H}_2$), 3.15 (br.d, J 17.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.06-4.10 (m, 1H 5 -C$\underline{H}$), 567-5.70 (m, 1H, 4 -C$\underline{H}$), 5.90-5.95 (m, 1H, 3 -C$\underline{H}$), 7.49-7.63 (m, 4H, Ar-C$\underline{H}$); ^{13}C NMR (100 MHz) δ$_C$ 30.2 (5 –C$\underline{H}_2$), 45.5 (-NC$\underline{H}_3$), 54.1 (6 -C$\underline{H}_2$), 59.8 (2 -C$\underline{H}_2$), 126.4 (3 –C$\underline{H}$), 128.0 (4 -C$\underline{H}$), 123.6, 124.4, 125.6, 126.3 (Ar-C$\underline{H}$), 126.7, 131.2, (Ar-$\underline{C}$); ν$_{max}$ (thin film, cm^{-1}) 2978, 2918 (CH$_2$, C-H stretch), 2853 (N-CH$_3$), 1663, 1492 (Aromatic C=C), 1607 (C=C), 1311, 1159, 1161, 1036 (C-F), 1454 (C-N), 769 (*ortho* di-substituted phenyl), 709 (CH=CH *cis*); m/z (ES$^+$) calculated for C$_{13}$H$_{15}$NF$_3$ [M+H]$^+$; 242.1157, found 242.1150.

1-Methyl-5-(3-(trifluoromethyl)phenyl)-1,2,5,6-tetrahydropyridine (68)
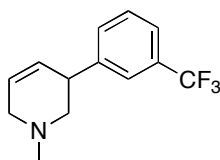
1-Iodo-3-(trifluoromethyl)benzene (0.272 g, 1.0 mmol, 1.0 eq) was used in the general method in aq. MeCN (3 mL, 95%), yielding 1-methyl-5-(3-(trifluoromethyl)phenyl)-1,2,5,6-tetrahydropyridine (46 mg, 19%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ$_H$ 2.26 (dd, J 8.4 Hz 11.2 Hz, 1H, 6 -C$\underline{H}_2$), 2.35 (s, 3H, -NC$\underline{H}_3$), 2.87-2.96 (m, 1H, 2, 6 -C$\underline{H}_2$), 3.17 (br.d, J 15.8 Hz, 1H, 2 -C$\underline{H}_2$), 3.68-3.73 (m, 1H 5 -C$\underline{H}$), 5.75-5.79 (m, 1H, 4 -C$\underline{H}$), 5.92-5.95 (m, 1H, 3 -C$\underline{H}$), 7.41-7.49 (m, 4H, Ar-C$\underline{H}$); ^{13}C NMR (100 MHz) δ$_C$ 42.5 (5 –C$\underline{H}_2$), 45.7 (-NC$\underline{H}_3$), 54.4 (2 -C$\underline{H}_2$), 60.2 (6 -C$\underline{H}_2$), 127.0 (3 -C$\underline{H}$), 127.2 (4 -C$\underline{H}$), 123.0, 123.6, 124.4, 128.8 (Ar-C$\underline{H}$), 131.0, 131.6, (Ar-$\underline{C}$); ν$_{max}$ (thin film, cm^{-1}) 2943 (CH$_2$, C-H stretch), 2787 (N-CH$_3$), 1662, 1490 (Aromatic C=C), 1613 (C=C), 1377, 1119, 1072 (C-F), 1447 (C-N), 767 (*meta* di-substituted phenyl), 701 (CH=CH *cis*); m/z (ES$^+$) calculated for C$_{13}$H$_{15}$NF$_3$ [M+H]$^+$; 242.1157, found 242.1148.

3.2 Diaryl *N*-Methyl Tetrahydropyridines

Diaryl *N*-methyl-1,2,5,6-tetrahydropyridines were isolated as by-products from the Heck arylation, isolated for identification purposes by ^{1}H NMR from preparative TLC (5% MeOH in EtOAc). Quantities obtained were typically <10mg (<5%) and therefore full analysis was not always possible.

1-Methyl-3,5-diphenyl-1,2,5,6-tetrahydropyridine (53)
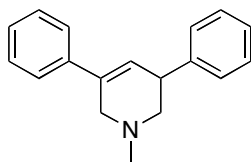
Iodobenzene (0.17 mL, 1.54 mmol, 1 eq), was used in the general method to yield 1-methyl-3,5-diphenyl-1,2,5,6-tetrahydropyridine as a yellow oil (14 mg, 9%) R_f 0.14. ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.31 (dd *J* 8.9 Hz 11.2 Hz, 1H, 2 -C$\underline{H}_2$), 2.46 (s, 3H, -NC$\underline{H}_3$), 3.02 (dd *J* 6.0 Hz, 11.0 Hz, 1H, 2- C$\underline{H}_2$), 3.23 (dq *J* 16.0 Hz 2.0 Hz 3.5 Hz 6.0 Hz, 6 -C$\underline{H}_2$), 3.57 (dt *J* 16.0 Hz 1.0 Hz 2.5 Hz, 6 -C$\underline{H}_2$), 3.80-.84 (m, 1H, 5 -C$\underline{H}$), 6.17 (d *J* 1.5 Hz, 1H, 4 -C$\underline{H}$), 7.18-7.47 (m, 10H, Ar-C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 29.7 (3 -$\underline{C}$), 43.2 (5 -$\underline{C}$H), 45.7 (-N$\underline{C}$H$_3$), 56.3 (6 -$\underline{C}$H$_2$), 60.4 (2 -$\underline{C}$H$_2$C), 125.2, 125.7, 126.7, 127.4, 128.1, 128.4, 128.5, 136.7, 143.6 (Ar-$\underline{C}$); ν_{max} (thin film, cm^{-1}) 3026 (C=CH) 2936, 2918 (CH$_2$, C-H stretch), 2783 (N-CH$_3$), 1675, 1493 (Aromatic C=C), 1600 (C=C), 753 (mono-substituted phenyl); m/z (ES$^+$) calculated for C$_{18}$H$_{20}$N [M+H$^+$]; 250.1596, found 250.1586.

1-Methyl-3,5-(*o*-tolyl)-1,2,5,6-tetrahydropyridine (55b)
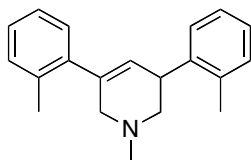
2-Iodotoluene (0.218 g, 1 mmol) was used in the general method to yield 1-methyl-3,5-(*o*-tolyl)-1,2,5,6-tetrahydropyridine (<5 mg, <5%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.26 (dd *J* 9.5 Hz 11.5 Hz, 1H, 2 -C$\underline{H}_2$), 2.41 (s, 9H, -NC$\underline{H}_3$, 2', 2'' -C$\underline{H}_3$), 2.86 (d, *J* 9.0 Hz, 1H, 6 -C$\underline{H}_2$), 3.02-3.06 (m, 1H, 2 -C$\underline{H}_2$), 3.32 (br d, *J* 16.0 Hz, 1H, 6 -C$\underline{H}_2$), 4.05-4.10 (m, 1H, 5 -C$\underline{H}$), 5.64 (s, 1H, 4 -C$\underline{H}$), 7.12-7.24, 7.44-7.49, 7.53-7.57, 7.64-7.69 (m, 8H, 2x C$_6\underline{H}_4$); Due to low quantities of product isolated, only partial characterization is reported.

1-Methyl-3,5-(*m*-tolyl)-1,2,5,6-tetrahydropyridine (56b)
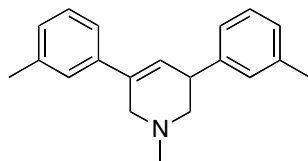
3-Iodotoluene (0.218 g, 1 mmol 1.0 eq) was used in the general method to yield 1-methyl-3,5-(*m*-tolyl)-

1,2,5,6-tetrahydropyridine (<10 mg, <5%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.28 (dd J 9.0 Hz 10.9 Hz, 1H, -2 -CH$_2$), 2.34 (s, 3H, -CH$_3$), 2.36 (s, 3H, -CH$_3$), 2.46 (s, 3H, -NCH$_3$), 3.02 (q, J 5.5 Hz, 1H, 6 -CH$_2$), 3.18-3.23 (m, 1H, 2 -CH$_2$), 3.56 (br d, J 15.5 Hz, 1H, 6 -CH$_2$), 3.76-3.80 (m, 1H, 5 -CH-), 6.15 (s, 1H, 4 -CH), 7.04-7.08, 7.17-7.23 (m, 8H, Ar-CH); Due to low quantities of product isolated, only partial characterization is reported.

1-Methyl-3,5-(3',3''-dimethoxyphenyl)-1,2,5,6-tetrahydropyridine (59b)
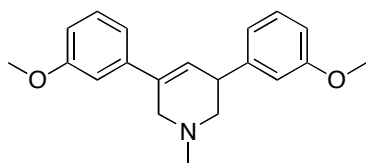
3-Iodoanisole (0.234 g, 1 mmol) was used in the general method to yield 1-methyl-3,5-(3',3''-dimethoxyphenyl)-1,2,5,6-tetrahydropyridine (<10 mg, <5%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.31 (dd J 9.0 Hz 11.0 Hz, 1H, 2 -CH$_2$), 2.46 (s, 3H, -NCH$_3$), 3.02 (q, J 5.5 Hz, 1H, 6 –CH$_2$), 3.18-3.24 (m, 1H, 2 -CH$_2$), 3.55 (br d, J 16.0 Hz, 1H, 6 -CH$_2$), 3.80 (s, 3H, -OCH$_3$), 3.81 (s, 3H, -OCH$_3$), 6.17 (s, 1H, 4 -CH), 6.77-7.01, 7.22-7.26 (m, 8H, Ar-CH); Due to low quantities of product isolated, only partial characterization is reported.

3.3 Synthesis of Pyridinium salts and corresponding Tetrahydropyridines

1-Methyl-pyridinium iodide[175]
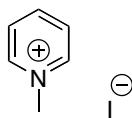
To a solution of pyridine (6.4 mL, 80 mmol, 1 eq) in THF (30 mL) was added dropwise Iodomethane (5.9 mL, 95 mmol, 1.5 eq) under N_2. The reaction mixture was stirred at room temperature for 13 hours after which time the resulting solid was triturated with light petroleum ether, filtered and washed with further light petroleum ether to give 1-methylpyridinium iodide as a pale yellow solid (11.87 g, 85%); mpt 117-118 $^{\circ}$C (Lit. 116-117 $^{\circ}$C); ^{1}H NMR (D$_2$O, 400 MHz) δ_H 4.30 (s, 3H, -NC$\underline{H}_3$), 7.96 (t J 7.0 Hz, 2H, 3, 5 -C$\underline{H}$), 8.44 (t J 8.0 Hz, 1H, 4 -C$\underline{H}$), 8.67 (d J 6.0 Hz, 2H, 2, 6 -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 48.2 (-NC$\underline{H}_3$), 128.0 (3, 5 -$\underline{C}$H), 145.0 (2, 6 -$\underline{C}$H), 145.3 (4 -$\underline{C}$H); ν_{max} (thin film, cm^{-1}) 3117, 3073, 3028, 2988 (C=CH), 2792 (N-CH$_3$), 1628 (C=N), 1482 (C-N); m/z (ES$^+$) calculated for C$_6$H$_8$N [M$^+$]; 94.0651, found 94.0648.

1-Methyl-1,2,5,6-tetrahydropyridine (29)[176]
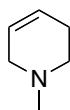
To a solution of 1-methylpyridinium iodide (2 g, 9.0 mmol, 1.0 eq) in NaOH (1M, 25 mL) was added sodium borohydride (0.51 g, 13.5 mmol, 1.5 eq) in two portions under N_2 at room temperature and stirred for 3 hours. The solution was washed with saturated sodium chloride solution and extracted with Et$_2$O. The organic layers were combined, dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo* to yield 1-methyl-1,2,5,6-tetrahydropyridine as a pale yellow oil (0.75 g, 85%). ^{1}H NMR (CDCl3, 400 MHz) δ_H 2.16-2.22 (m, 2H, 5 –C$\underline{H}_2$), 2.34 (s, 3H, -NC$\underline{H}_3$), 2.51 (t J 6.0 Hz, 2H, 6 -C$\underline{H}_2$), 2.90-2.92 (m, 2H, 2 -C$\underline{H}_2$), 5.63-5.69 (m, 1H, 3 -C$\underline{H}$), 5.71-5.76 (m, 1H, 4 –C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 25.9 (5 -$\underline{C}$H$_2$), 46.0 (-NC$\underline{H}_3$), 51.9 (6 -$\underline{C}$H$_2$), 56.5 (2 -$\underline{C}$H$_2$), 124.8 (4 –$\underline{C}$H), 125.2 (3 -$\underline{C}$H); ν_{max} (thin film, cm^{-1}) 2990, 2972, 2941, 2918 (CH$_2$, C-H stretch), 2783 (N-CH$_3$), 1658 (C=C), 1450 (C-N), 652 (CH=CH *cis*); m/z (ES$^+$) calculated for C$_6$H$_{12}$N [M+H$^+$]; 98.0970, found 98.0964.

1-Benzyl pyridinium chloride (71)[177]
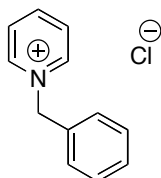
Benzylamine (0.32 mL, 3.0 mmol, 3 eq) was added to a stirred solution of *N*-(2,4-dinitrophenyl)pyridinium chloride (0.281 g, 1.0 mmol, 1 eq) in methanol (20 mL) under nitrogen at room temperature. After 2 hours

the resulting red mixture was heated to reflux for 18 hours, cooled, concentrated *in vacuo* and partitioned between H_2O (20 mL) and DCM (20 mL). The aqueous layer was washed repeatedly with DCM (20 mL) until no further colour was removed from the aqueous layer. The aqueous portion was concentrated *in vacuo* to give 1-benzylpyridinium chloride as a low melting point colourless solid (0.69 g, 93%); mpt <30°C; ^{1}H NMR (MeOD, 400 MHz) δ_H 5.89 (s, 2H, -C$\underline{H}_2$), 7.51 (dd *J* 6.0 Hz 19.5 Hz, 5H, Ar-C$\underline{H}$), 8.16 (t *J* 6.5 Hz, 2H, 3, 5 -C$\underline{H}$), 8.64 (t *J* 8.0 Hz, 1H, 4 -C$\underline{H}$), 9.11 (d *J* 6.0 Hz, 2H, 2, 6 -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 64.3 (-$\underline{C}H_2$), 128.3 (3, 5 -$\underline{C}H$), 128.5, 128.7, 128.8, 129.3, 129.6 (Ar-$\underline{C}H$), 133.2 (Ar-$\underline{C}$), 144.6 (2, 6 -$\underline{C}H$), 145.9 (4 -$\underline{C}H$); ν_{max} (solid, cm^{-1}) 3065 (C-H), 1630 (C=N), 1486 (C-N), 745 (C-H alkene); m/z (ES$^+$) calculated for $C_{12}H_{12}N$ [M]$^+$; 170.0970, found 170.0964.

1-Benzyl-1,2,5,6-tetrahydropyridine (73)[178]
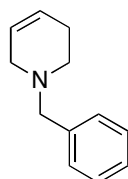
To a solution of 1-benzylpyridinium chloride (0.25 g, 1.21 mmol, 1 eq) in MeOH (20 mL) was added sodium borohydride (55 mg, 1.45 mmol, 1.2 eq) under N_2 at room temperature and stirred for 3 hours and partitioned between H_2O and DCM. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield 1-benzyl-1,2,5,6-tetrahydropyridine as an orange oil (0.151 g, 72%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.15 (br s, 2H, 5 -C$\underline{H}_2$), 2.55 (t *J* 5.5 Hz, 2H, 6 -C$\underline{H}_2$), 2.96 (br s, 2H, 2 -C$\underline{H}_2$), 3.57 (s, 2H, -C$\underline{H}_2$), 5.65 (d *J* 10.0 Hz, 1H, 3 -C$\underline{H}$), 5.74 (d *J* 10.5 Hz, 1H, 4 -C$\underline{H}$), 7.22-7.41 (m, 5H, Ar-C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 24.3 (5 -$\underline{C}H_2$), 49.6 (6 -$\underline{C}H_2$), 52.8 (2 -$\underline{C}H_2$), 62.9 (-$\underline{C}H_2$), 125.2 (3 -$\underline{C}H$), 125.3 (4 –$\underline{C}H$), 128.0, 128.2, 128.9 (Ar-$\underline{C}H$), 138.3 (Ar-$\underline{C}$); ν_{max} (thin film, cm^{-1}) 3028 (C-H aromatic), 2912 (C-H), 1659 (C=C), 1601, 1493 (C=C aromatic), 1453 (C-N), 653 (CH=CH *cis*);   MS m/z [M+H]$^+$ $C_{12}H_{16}N^+$ requires 174.1283 found 174.1283 (100%);

1-Propyl pyridinium chloride (72)[168]
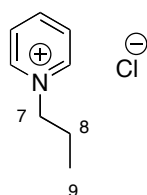
Propylamine (0.25 mL, 3.0 mmol, 3 eq) was added to a stirred solution of *N*-(2,4-dinitrophenyl)pyridinium chloride (0.281 g, 1.0 mmol, 1 eq) in methanol (20 mL) under nitrogen at room temperature. After 2 hours the resulting red mixture was heated to reflux for 18 hours, cooled, concentrated *in vacuo* and partitioned between H_2O (20 mL) and DCM (20 mL). The aqueous layer was washed repeatedly with DCM (20 mL) until no further colour was removed from the aqueous layer. The aqueous portion was concentrated *in vacuo* to give 1-propylpyridinium chloride as an orange oil (0.45 g, 96%); ^{1}H NMR (MeOD, 400 MHz) δ_H 1.03 (t *J* 7.o Hz, 3H, 9 -C$\underline{H}_3$), 2.08 (sext *J* 7.0 Hz, 2H, 8 -C$\underline{H}_2$), 4.64 (t *J* 7.5 Hz, 2H, 7 -C$\underline{H}_2$), 8.15 (t *J* 6.5

Hz, 2H, 3, 5 -C$\underline{H}$), 8.63 (t J 8.0 Hz, 1H, 4 -C$\underline{H}$), 9.04 (d J 6.0 Hz, 2H, 2, 6 -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 9.2 (9 -$\underline{C}$H$_3$), 24.4 (7 -$\underline{C}$H$_2$), 63.0 (6 -$\underline{C}$H$_2$), 128.0 (3, 5 -$\underline{C}$H), 144.5 (2, 6 -$\underline{C}$H), 145.5 (4 -$\underline{C}$H); ν_{max} (thin film, cm^{-1}) 3041, 2966, 2936 (C-H), 2878 (N-CH$_3$), 1633 (C=N), 1487 (C-N), 775 (C-H alkene); m/z (ES$^+$) calculated for C$_{18}$H$_{12}$N [M]$^+$; 122.0970, found 122.0964.

1-Propyl-1,2,5,6-tetrahydropyridine (74)[179]
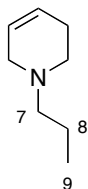
To a solution of 1-propylpyridinium chloride (0.20 g, 1.26 mmol, 1 eq) in MeOH (10 mL) was added sodium borohydride (57 mg, 1.52 mmol, 1.2 eq) under N$_2$ at room temperature and stirred for 3 hours and partitioned between H$_2$O and DCM. The organic layers were combined, dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo* to yield 1-propyl-1,2,5,6-tetrahydropyridine as an orange oil (99 mg, 63%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 0.91 (t J 7.0 Hz, 3H, 9 -NC$\underline{H}_3$), 1.55 (sext J 7.5 Hz, 2H, 8 -C$\underline{H}_2$), 2.18 (br s, 2H, 5 -C$\underline{H}_2$), 2.35 (t J 8.0 Hz, 2H, 7 -C$\underline{H}_2$), 2.54 (t J 5.5 Hz, 2H, 6 -C$\underline{H}_2$), 2.95 (s, 2H, 2 -C$\underline{H}_2$), 5.66 (d J 10.5 Hz, 1H, 3 -C$\underline{H}$), 5.73 (d J 11.0 Hz, 1H, 4 –C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 11.9 (9 -$\underline{C}$H$_3$), 17.0 (8 -$\underline{C}$H$_2$), 26.1 (5 -$\underline{C}$H$_2$), 50.0 (7 -$\underline{C}$H$_2$), 51.9 (2 -$\underline{C}$H$_2$), 60.2 (C6 -$\underline{C}$H$_2$), 125.1 (3 –$\underline{C}$H), 125.4 (4 –$\underline{C}$H); ν_{max} (thin film, cm^{-1}) 2958, 2928 (C-H stretch), 1663 (C=C), 1461 (C-N), 654 (CH=CH *cis*); MS m/z [M+H]$^+$ C$_8$H$_{16}$N$^+$ requires 126.1283 found 126.1276 (100%);

3.4 Manipulation of Nitrogen Chirality

1-Ethoxycarbonylmethyl-3-hydroxy-1-methyl-piperidinium bromide (79)[180]
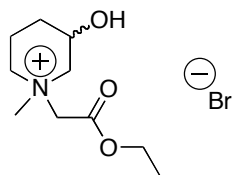
To a solution of 1-methyl-3-piperidinol (6.1 mL, 53.0 mmol, 1.0 eq) in toluene (80 mL) was added ethyl bromoacetate (7.90 mL, 71.0 mmol, 1.3 eq) and the reaction mixture left to stir at room temperature for 16 hours. The crude product was collected by filtration as a colourless solid (14.53 g, dr 1:1, 97%), diastereomeric ratio calculated from ^{1}H NMR spectrum by integration of the NC$\underline{H}_3$ resonances 3.21 *trans* and 3.32 *cis* ppm. Repeated crystallization from EtOH(aq) gave white solid 1-ethoxycarbonylmethyl-3-hydroxy-1-methyl-piperidinium bromide in a 2:1 *trans*:*cis* ratio, which was taken on for further lactonisation, and 1:3 *trans*:*cis* ratio in the liquor; mpt 150-152 ^{o}C; ^{1}H NMR (MeOD, 400 MHz) δ_H 1.22 (sext, *J* 3.5 Hz, 3H, –CH$_2$C$\underline{H}_3$), 1.60-1.67 (m, 1H, 4 -C$\underline{H}_2$), 1.76-1.86 (m, 2H, 5 -C$\underline{H}_2$), 2.05-2.15 (m, 1H, 4 -C$\underline{H}_2$), 3.24 (s, 3H, -NC$\underline{H}_3$), 3.51-3.66 (m, 2H, 2, 6 -C$\underline{H}_2$), 3.74-3.78 (m, 2H, 2, 6 -C$\underline{H}_2$), 4.07 (br t *J* 3.0 Hz, 1H, 3 -C$\underline{H}$), 4.16-4.23 (m, 2H, -C$\underline{H}_2$CH$_3$), 4.64 (dd *J* 16.5 Hz 119.0 Hz, 2H, -NC$\underline{H}_2$CO$_2$Et); ^{13}C NMR (MeOD, 100 MHz) δ_C 12.8 (-CH$_2$$\underline{C}H_3$), 16.3 (5 -$\underline{C}H_2$), 28.7 (4 -$\underline{C}H_2$), 50.2 (-N$\underline{C}H_3$), 60.4 (-N$\underline{C}H_2CO_2$Et), 61.9 (-CO$_2$$\underline{C}H_2CH_3$), 62.2 (3 -$\underline{C}$H), 63.7 (6 -$\underline{C}H_2$), 64.5 (2 -$\underline{C}H_2$), 164.4 (-$\underline{C}O_2$Et); ν_{max} (solid, cm^{-1}) 3257 (O-H), 2980 (C-H), 1736 (C=O), 1240, 1210 (C-N), 1077, 1042, 1025 (C-O); MS m/z [M-Br]$^{+\bullet}$ C$_{10}$H$_{20}$NO$_3$$^+$ requires 202.1438, found 202.1437.

(±)1-Methyl-3-oxo-4-oxa-1-azonia-bicyclo[3.3.1]nonane bromide (80)

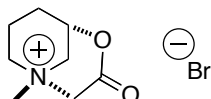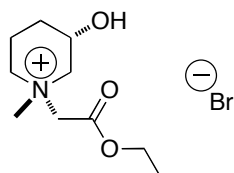A solution of 1-ethoxycarbonylmethyl-3-hydroxy-1-methyl-piperidinium bromide (8.0 g, 28.35 mmol, dr 1:1 *trans*:*cis*) in 5% HCl in EtOH (125 mL) was heated to reflux for 16 hours. Evaporation of the solvent left the crude product as a yellow oil which was a mixture of product, *cis*-1-ethoxycarbonylmethyl-3-hydroxy-1-methyl-piperidinium bromide and *trans*-1-ethoxycarbonylmethyl-3-hydroxy-1-methyl-piperidinium bromide. Nonane crystallized out of the crude reaction product on standing and was isolated by washing with cold EtOH to give as colourless needles (2.81 g, 42%); mpt 182 ^{o}C (decomposes); ^{1}H NMR (D$_2$O, 400 MHz) δ_H 1.84-2.16 (m, 4H, 3', 4' -C$\underline{H}_2$), 3.23 (s, 3H, -NC$\underline{H}_3$), 3.48-3.56 (m, 1H, 2' –CH$_2$), 3.66 (dd *J* 2.0 Hz, 12.0 Hz, 1H, 2' –CH$_2$), 3.78 (dd *J* 2.5 Hz, 13.5 Hz, 1H, 6 –C$\underline{H}_2$), 3.88 (br d *J* 13.5 Hz, 1H, 6 –C$\underline{H}_2$), 4.39 (d *J* 18.0 Hz, 1H, 2 -NCH$_2$CO), 4.49 (d *J* 18.0 Hz, 1H, 2 -NCH$_2$CO), 5.16 (br s, 1H, 5 -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 15.7, 25.4 (3', 4' –$\underline{C}$H$_2$), 55.8 (-N$\underline{C}$H$_3$), 57.3 (2' -C$\underline{H}_2$), 58.7 (6 -C$\underline{H}_2$), 64.4 (2 -N$\underline{C}$H$_2$CO), 73.2 (5 -$\underline{C}$H), 164.6 ($\underline{C}$O); ν_{max} (solid, cm^{-1}) 2929 (C-H), 1736 (C=O), 1236, 1216 (C-N), 1035 (C-O); MS m/z [M-Br]$^{+\bullet}$ C$_8$H$_{14}$NO$_2$ requires 156.1019, found 156.1017.

(1S, 3R)-1-Ethoxycarbonylmethyl-3-hydroxy-1-methyl-piperidinium bromide (81)[181]

To a solution of 1-methyl-3-oxo-4-oxa-1-azonia-bicyclo[3.3.1]nonane bromide (0.5 g, 2.0 mmol) in EtOH (30 mL) was added Ti(O*i*Pr)$_4$ (0.25 mL, 0.84 mmol, 0.4 eq) and the reaction heated to reflux for 5 hours. The reaction mixture was cooled and HCl (0.1 M, 50 mL, 5 mmol, 2.5 eq) added, filtered to remove any solid and concentrated *in vacuo* to yield *(1S,3R)*-1-methoxycarbonylethyl-3-hydroxy-1-methyl-piperidinium bromide as a yellow solid (0.492 g, 87%); mpt 152-154 °C; ^{1}H NMR (MeOD, 400 MHz) δ_H 1.33 (t *J* 7.0 HZ, 3H, –CH$_2$CH$_3$), 1.73-1.80 (m, 1H, 4 -CH$_2$), 1.88-1.94 (m, 2H, 5 -CH$_3$), 2.19-2.24 (m, 1H, 4 -CH$_2$), 3.35 (s, 3H, -NCH$_3$), 3.49-3.56 (m, 2H, 2, 6 -CH$_2$), 3.17-3.75 (m, 1H, 2 -CH$_2$), 3.88 (br dd *J* 4.5 Hz 13.0 Hz, 1H, 6 - CH$_2$), 4.18 (br t *J* 3.0 Hz, 1H, 3 -CH), 4.27-4.35 (m, 2H, -CH$_2$CH$_3$), 4.61 (dd *J* 17.0 Hz 119.0 Hz, 2H, - NCH$_2$CO$_2$Et); ^{13}C NMR (MeOD, 100 MHz) δ_C 12.8 (-CH$_2$CH$_3$), 16.2 (5 -CH$_2$), 28.5 (4 -CH$_2$), 51.4 (-NCH$_3$), 60.4 (-NCH$_2$CO$_2$Et), 62.0 (-CO$_2$CH$_2$CH$_3$), 62.5 (3 -CH), 62.6 (6 -CH$_2$), 63.5 (2 -CH$_2$), 164.9 (-CO$_2$Et); ν_{max} (solid, cm^{-1}) 3256 (O-H), 2976 (C-H), 1721 (C=O), 1242, 1215 (C-N), 1074, 1040, 1025 (C-O); MS m/z [M-Br]$^{+•}$ C$_{10}$H$_{20}$NO$_3$$^+$ requires 202.1438, found 202.1439.

1-Ethoxycarbonylmethyl-1-methyl-1,2,5,6-tetrahydropyridine bromide (82)[182]
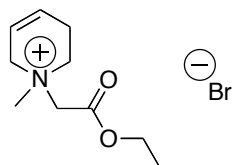
Trifluoromethanesulfonic anhydride (0.34 mL, 2.0 mmol, 2.0 eq) was added dropwise to a mixture of racemic 1-ethoxycarbonylmethyl-3-hydroxy-1-methyl-piperidinium bromide (0.282 g, 1.0 mmol, 1 eq) and 2,6-di-tertbutyl pyridine (0.616 g, 3.0 mmol, 3.0 eq) in DCM (5 mL) at 0 °C and stirred for 1 hour. The reaction mixture was warmed to room temperature and stirred for a further 16 hours. The reaction mixture was partitioned between DCM (10 mL) and H$_2$O (10 mL), and the aqueous layer concentrated *in vacuo* to give 1-ethoxycarbonylmethyl-1-methyl-1,2,5,6-tetrahydropyridine bromide as a yellow oil (0.220 g, 83%); ^{1}H NMR (MeOD, 400 MHz) δ_H 1.34 (t *J* 7.0 Hz, 3H, –CH$_2$CH$_3$), 2.54-2.60 (m, 2H, 5 –CH$_2$), 3.34 (s, 3H, -NCH$_3$), 3.61-3.85 (m, 2H, 6 –CH$_2$), 4.08-4.21 (m, 2H, 2 –CH$_2$), 4.33 (q *J* 7.5 Hz, 2H, -CH$_2$CH$_3$), 4.58 (dd *J* 2.0 Hz 14.0 Hz, 2H, -NCH$_2$CO$_2$Et), 5.75 (br dt *J* 2.0 Hz 10.5 Hz, 1H, 3 –CH) 6.04-6.09 (m, 1H, 4 –CH); ^{13}C NMR (100 MHz) δ_C 12.8 (–CH$_2$CH$_3$), 20.7 (5 –CH$_2$), 47.7 (-NCH$_3$), 57.8 (6 –CH$_2$), 58.2 (– CH$_2$CO$_2$Et), 59.9 (2 –CH$_2$), 62.4 (–CH$_2$CH$_3$), 118.8 (3 -CH), 124.6 (4 -CH), 164.5 (CO); ν_{max} (thin film, cm^{-1}) 1748 (C=O), 1222 (C-N), 1023 (C-O); MS m/z [M-Br]$^{+•}$ C$_{10}$H$_{18}$NO$_2$$^+$ requires 184.1332, found 184.1334.

CHAPTER 4: RESULTS AND DISCUSSION: IRON CATALYSED ARYLATIVE SPIROCYCLISATION

4.1 Iron Catalysed Radical Cyclisations

Radical cyclisations are useful tools for the preparation of five-membered cyclic compounds,[183] often employing tributyltin hydride as a reagent. As a result of the toxicity of tin reagents and the difficulty in removing the residues from the products, alternative reagents have been extensively investigated recently, including the use of manganate and iron.[184]

Oshima demonstrated that trialkylmanganate salts and alkyl magnesium salts can initiate a radical cyclisation of halo acetals, allyl *o*-halophenyl ethers and diallyl iodoanilines in the presence of catalytic amounts of MnCl$_2$ or FeCl$_2$, *via* a single electron transfer process (Scheme 78).[185] Oshima proposed a radical intermediate formed by single-electron transfer from the electron-rich manganese to the substrate.
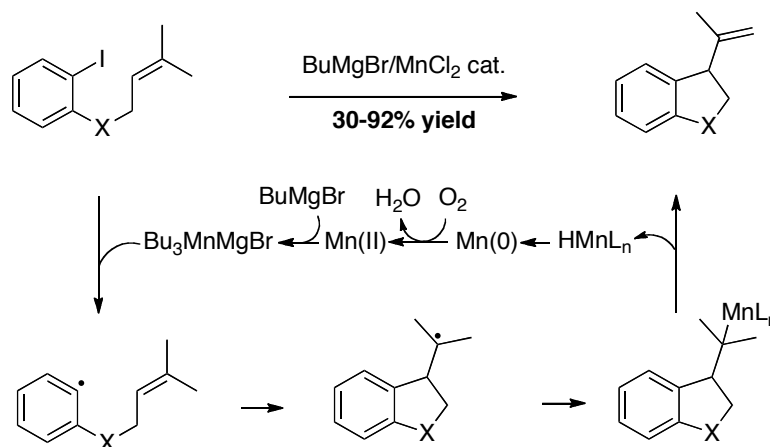
Scheme 78. *Mechanistic Grignard cross-coupling pathway, where X = O or NR*

In the case of the manganese-catalysed cyclisation, iodo-compounds are required, with the corresponding bromides not delivering in the desired cyclised products efficiently. The iron-catalysed reactions however, can be used to cyclise bromo ethers in fair to good yields (Scheme 79).[186]
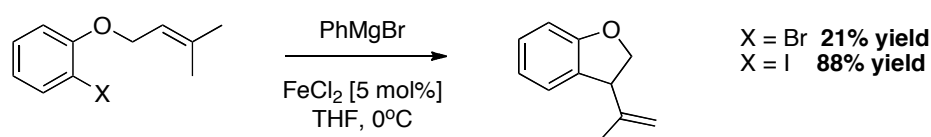
Scheme 79. *Cyclisation of bromo ethers in the presence of PhMgBr and iron(II) catalyst*

When using aromatic Grignard reagents, arylative capture results in the aromatic group being incorporated into the cyclised product. Thus, radical cyclisation and subsequent coupling with aromatic Grignard reagents can be achieved in a single operation. Alkyl Grignard species however, cannot be introduced in the products, leading to the reduced products as shown in Scheme 80, by Oshima.
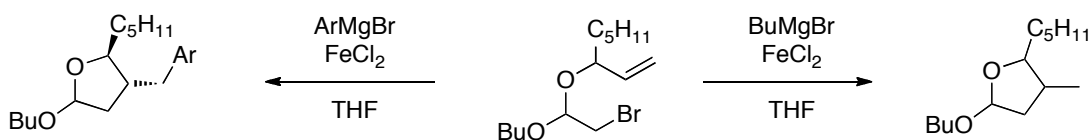
Scheme 80. *Cyclisation in the presence of aryl or alkyl Grignards*

4.2 Initial Investigations

Though there have been many well-designed studies into iron-mediated cross-coupling of Grignard reagents, to date there have been no reports describing a cyclisation-arylation cascade *via* spirocyclising capture of intermediate iron species. We postulated that a new catalytic method for arylative spirocyclisation would occur in the presence of stoichiometric Grignard reagents and iron(III) catalysts, to induce cyclisation of (2-iodo)benzyl ethers of furan in a highly stereoselective manner. The reaction would occur through oxidative addition of an iron species to the C-Hal bond, followed by an iron-mediated *exo*-cyclisation. The resultant organoiron intermediate captures an aryl group from the Grignard reagent, to give novel compounds containing spirocyclic centres (Scheme 81).
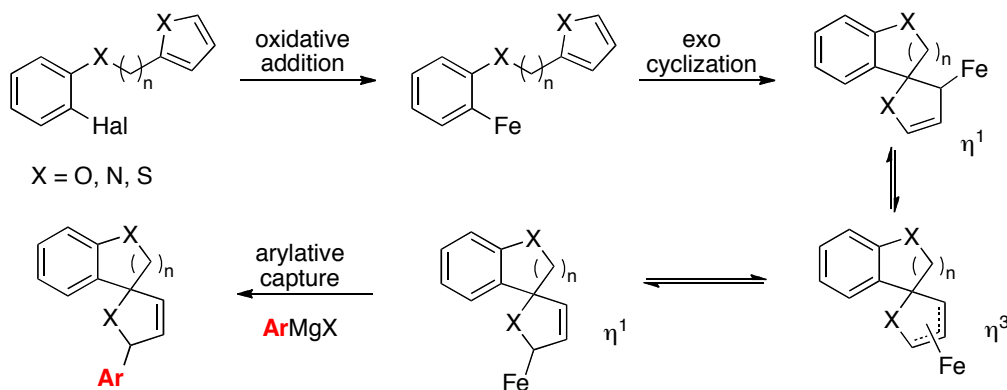
Scheme 81. *Proposed cyclisation-arylation cascade*

Following reported methods by Toste,[187] 2-[(2-Iodophenoxy)methyl]furan (**89**) was synthesised *via* activation of furfuryl alcohol (**90**) as the mesylate, and subsequent nucleophilic substitution with iodophenol (**91**). Initial cross-coupling of **89** with phenylmagnesium bromide in the presence of an iron catalyst (Fe(acac)$_3$) at room temperature, lead to the formation of the corresponding phenylated cyclised product 5'-phenyl-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (**88**) in moderate yield (41%, Scheme 82).
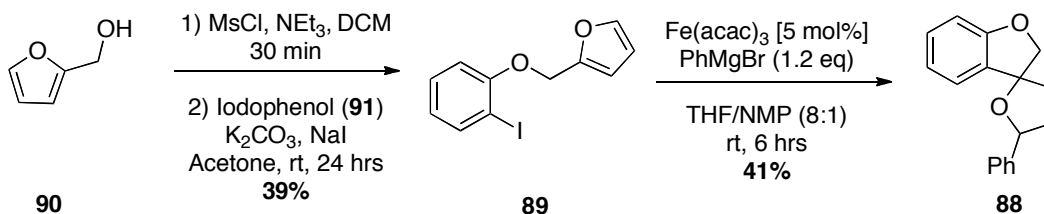
Scheme 82. *Synthesis of 5-phenyl-2H,5H-spiro[benzofuran-3,2'-furan] (**88**)*

The reaction mechanism is unknown, but likely involves radical process in a similar mannor to that

postulated by Oshima (Scheme 78), resulting in a cyclised intermediate, which may then undergo cross-coupling with the Grignard reagent (Scheme 83).
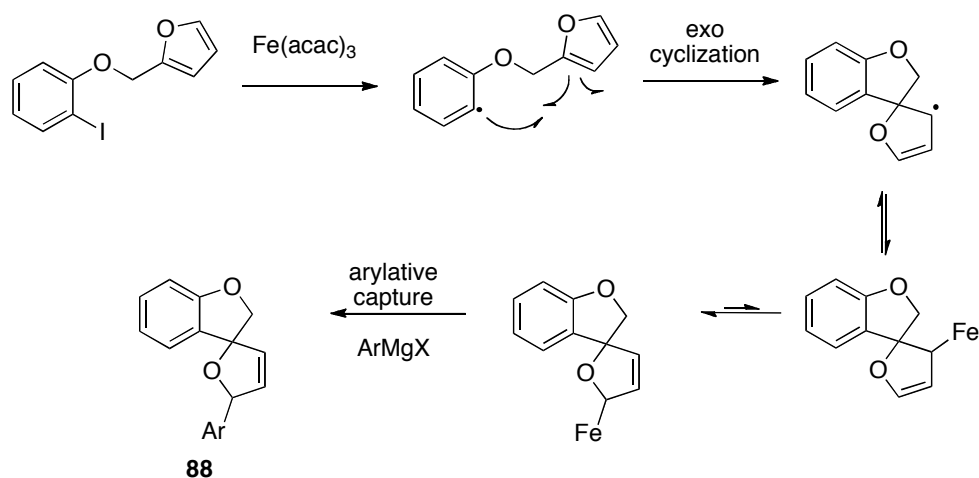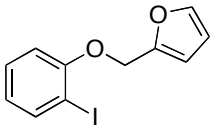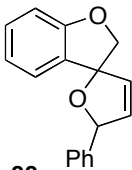
Scheme 83*. Postulated reaction mechanistic pathway for the formation of **88***

In an attempt to increase the isolated yield of **88**, reaction time was extended. This did not result in an increased yield, and therefore other reaction conditions were investigated for optimisation.

4.3 Solvent Effects

Grignard cross-coupling reactions are typically carried out in ethereal solvents such as diethyl ether, diisopropyl ether, dibutyl ether, tetrahydrofuran, and butyldiglyme. This is due to the nature of the RMgX reagent, which is polar and consequently requires a coordinating solvent to keep it in solution. Ethers are most suitable owing to the availability of lone-pair electrons for coordination to the magnesium ion and resulting solubilisation in organic media. Solvents with electrophilic sites such as acetonitrile, DMF, acetone, and ethyl acetate are unsuitable owing to their reactivity with RMgX.[188] Following the work of Cahiez into the advantages associated with the use of NMP (**14**) as a co-solvent, a variety of solvent systems were applied to the reaction in the presence of NMP (8:1, solvent:**14**, Table 14).

Table 14. *Solvent effect on synthesis of **88***

Entry	Solvent A	Solvent B	Yield **88** (%)
1	THF	NMP	41
2	Et$_2$O	NMP	63
3	DMF	NMP	0
4	DMPU	NMP	0
5	DMA	NMP	12
6	Dioxane	NMP	0

As expected, the ethereal solvents (Table 14, THF entry 1 and Et$_2$O entry 2) resulted in the highest yield of isolated product, with ether leading to the highest reaction yield and 100% conversion, with no starting material recovered. As expected, electrophilic solvents (Table 14, DMF entry 3 and DMPU entry 4) were unsuitable, with only starting material recovered.

The effect of the NMP co-solvent addition was examined to observe if an increase in NMP addition would affect the stability of the Grignard cross-coupling reagent in the ethereal solvent, and therefore affect the reaction yield (Table 15).

In both solvents examined, a normal distribution trend was observed with highest yields at 50:50 NMP:solvent (Table 15, entries 3 and 8 respectively). The highest yield achieved was in 50:50 NMP:Et$_2$O (Table 15, entry 8, 55%). Although a higher reaction yield had previously been achieved at 1:1 NMP:Et$_2$O ratio (Table 14, entry 2), consistently high yields were obtained with 1:1 NMP:Et$_2$O, where as with 1:8 yields appeared less reliable, with higher variation in reaction repeats. Therefore, the 1:1 NMP:Et$_2$O ratio was taken on for further reaction investigation and optimisation.

Table 15. *Effect of NMP co-solvent on synthesis of **88***
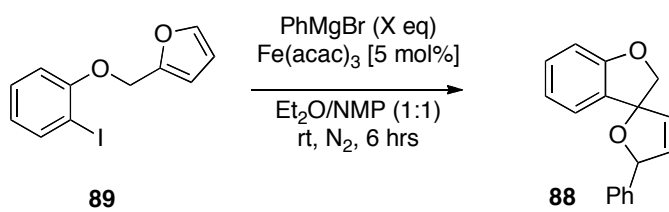
Entry	Solvent A	Solvent B	Ratio A:B	Yield **88** (%)
1	THF	NMP	0:100	9
2	THF	NMP	25:75	36
3	THF	NMP	50:50	44
4	THF	NMP	75:25	27
5	THF	NMP	100:0	30
6	Et$_2$O	NMP	0:100	27
7	Et$_2$O	NMP	25:75	37
8	Et$_2$O	NMP	50:50	55
9	Et$_2$O	NMP	75:25	27
10	Et$_2$O	NMP	100:0	19

4.4 Effect of Grignard

In the 1:1 NMP:Et$_2$O solvent system, 100% consumption of starting material was observed, however reaction yield remained modest. In an attempt to optimise the yield, the amount of Grignard was increased in an attempt to increase the yields of the desired product and avoid side-product formation (Table 16).

An increase in the excess of Grignard (1.2 eq to 2.4 eq) resulted in a higher isolated yield of **88**, (Table 16 entries 1 and 3, 73% *cf.* 63%). Under all conditions examined, full conversion was observed, with no starting material (**89**) recovered after 6 hours. With increased Grignard addition, 'clumped' solid was observed at the bottom of the reaction flask suggesting reaction end point. Although the amount of Grignard is in significant excess, the increase allows for higher reaction yield and is therefore beneficial.

Table 16. *Effect of increased excess of Grignard addition on synthesis of **88***
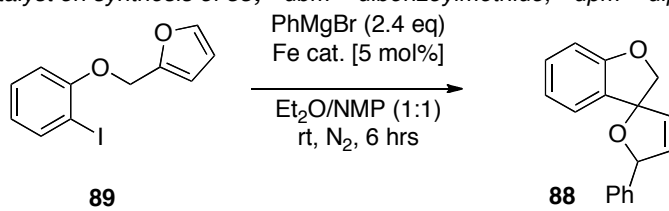
Entry	PhMgBr (X eq)	Yield **88** (%)	Conversion (%)
1	1.2	63	100
2	1.8	64	100
3	2.4	73	100

4.5 Iron Catalyst

In order to examine the influence of the iron catalyst, and to test the Cahiez hypothesis that the nature of the iron salt used as catalyst leads to no significant difference in the reaction yield in the presence of NMP, a range of iron(III) salts were applied to the reaction conditions. Although Iron(III) chloride (Table 17, entry 2) gave comparable results to that of Fe(acac)$_3$, salts bearing bulkier ligands were less productive in the reaction.

Table 17. *Effect of Iron Catalyst on synthesis of **88**; [a] dbm = dibenzoylmethido, [b] dpm = dipivaloylmethido*

Entry	Catalyst	Yield **88** (%)	Conversion (%)
1	Fe(acac)$_3$	73	100
2	FeCl$_3$	70	100
3	[a]Fe(dbm)$_3$	7	43
4	[b]Fe(dpm)$_3$	39	100
5	Fe$_2$(SO$_4$)$_3$	0	0

Iron(III) sulfate was the only catalyst examined which failed to result in conversion, however this may be due to the nature of the compound which commonly exists as the hydrate. Grignard reagents are highly water sensitive and therefore the presence of any hydrated catalyst may have resulted in deactivation of the Grignard and subsequent failure in the reaction. With the highest yield of **88** obtained with Fe(acac)$_3$,

this catalyst appears to be the most suitable from those examined, with FeCl$_3$ an appropriate substitute. Access to chiral Fe(acac)$_3$-like catalysts would in future allow for asymmetric varients of the reaction to be investigated, and therefore Fe(acac)$_3$ was applied to further reactions.

4.6 Reaction Scope

Once a robust method had been developed with phenylmagnesium bromide, a range of aryl Grignards were applied to the reaction conditions under optimised conditions; iron(III) catalyst [5 mol%], NMP:Et$_2$O (1:1) and excess Grignard (2.4 eq).   As FeCl$_3$ had previously been found to be comparable to Fe(acac)$_3$ catalyst with phenylmagnesium bromide, both were also examined with each of the aryl Grignard reagents examined.

4.6.1 Screening of Commercially Available Grignards

When using Fe(acac)$_3$ with sterically hindered mesitylmagnesium bromide (Table 18, entry 15), no coupling was observed. Molander reported the Grignard cross-coupling of aryl magnesium bromides with bromostyrene and found that arylated derivatives were not obtained from the reaction with mesitylmangesium bromide.   This was attributed to steric hinderance from the 3 methyl groups on benzene.[189]

With the *o*-methoxy reagent (Table 18, entry 8), coupling was also not observed, possibly due to steric interference, however the *o*-tolyl resulted in cross-coupling in moderate yield (76%, Table 18, entry 6). *Meta*-substituted reagents resulted in mixed results, with *m*-chlorophenyl and *m*-fluorophenyl (Table 18, entries 2 and 4 respectively) showing no or very little product formation, whereas *m*-methoxyphenyl (Table 18, entry 9, 88%) giving good yield. In general, all the *para*-substituted Grignards gave good to high yields (39-96%), supporting the theory of steric influence as found by Fürstner.

Isolated yields with FeCl$_3$ catalyst were generally slightly lower, but camparable to when Fe(acac)$_3$ was employed.   The only significant differences were found with the *p*-chlorophenyl and *m*-fluorophenyl analogues (Table 18, entries 3 and 4).   With Fe(acac)$_3$, *p*-chlorophenyl gave a moderate yield (49%), however with FeCl$_3$ no product was able to be isolated or detected by ^{1}H NMR spectroscopy. In a similar manner, *m*-fluorophenyl previously showed very low yields with Fe(acac)$_3$ (6%, Table 18, entry 4), however gave the highest yield of all the analogues examined with FeCl$_3$ (88%).

All reactions were conducted with commercially available Grignard cross-coupling reagents, and therefore relied on the suppliers for accuracy in the reagent strength and quality. Grignard reagents are notoriously difficult to store due to their rapid decomposition when exposed to air and therefore have a reduced shelf-life.   There was no discernable steric or electronic reason as to why the halo Grignards gave such

contrasting and unexpected results, based on the other results obtained, and it can therefore not be ruled out that the quality of the starting material may be a possible factor.

All products were isolated as predominantly a single diastereoisomer (>20:1 diastereoselectivity), as determined by NMR spectroscopy, demonstrating that the reaction is a steroeselevtive processs.

Table 18. *Reaction scope: Compatability of aryl Grignards*

Entry	R	Product	Yield (%) Fe(acac)$_3$	Yield (%) FeCl$_3$
1	C$_6$H$_5$	**88**	74	72
2	m-ClC$_6$H$_4$	**92**	0	0
3	p-ClC$_6$H$_4$	**93**	49	0
4	m-FC$_6$H$_4$	**94**	6	88
5	p-FC$_6$H$_4$	**95**	74	42
6	o-MeC$_6$H$_4$	**96**	76	34
7	p-MeC$_6$H$_4$	**97**	89	63
8	o-OMeC$_6$H$_4$	**98**	0	0
9	m-OMeC$_6$H$_4$	**99**	88	21
10	p-OMeC$_6$H$_4$	**100**	74	74
11	p-^{t}BuC$_6$H$_4$	**101**	52	41
12	p-OCF$_3$C$_6$H$_4$	**102**	39	55
13	p-PhC$_6$H$_4$	**103**	96	85
14	1-Napthyl	**104**	91	41
15	2,4,6-MeC$_6$H$_2$	**105**	0	0

4.6.2 Synthesis of Additional Aryl Grignards

The aryl Grignard screen demonstrated the robustness of the reaction, tolerating a variety of functional groups of differing electronic properties. In an attempt to further probe the reaction, a variety of additional non-commercially available Grignard reagents were attempted to be synthesised. Of particular interest to gain wider information as to the electronic tolerance of the reaction are the electron withdrawing *p*-

nitrophenyl and *p*-aryl methyl ester Grignards.

Nitro groups are electrophilic and therefore not suitable for preparation by activated magnesium, as the presence of the nitro group inhibits insertion of magnesium into the carbon-halogen bond.[190] Knochel's chemoselective magnesium-iodine exchange reaction has however been used to synthesise nitro Grignards and Grignards containing ester functional groups.[191]

Due to the instability of Grignards and difficulties associated with storage, the desired Grignards were generated *in situ* directly followed by arylative spirocyclisation with **89** and Fe(acac)$_3$ catalyst. As the Grignard is not isolated, it cannot be concluded as to whether both or one of the two steps in the process are unsuccessful. For this reason, *p*-methoxy was also included, as the arylative spirocyclisation reaction has been shown to be successful with this Grignard reagent in consistently high yields (Scheme 84).

Scheme 84. *Synthesis of Aryl Griganrds via magnesium-iodine exchange*
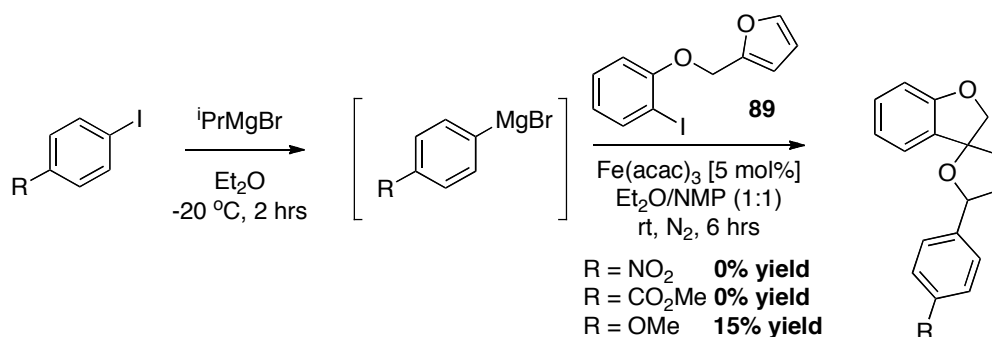
Only the *p*-(methoxycarbonyl)phenyl Grignard gave the desired product, though in lower yield than previously observed with the commercially produced Grignard (15% yield, *cf.* 74% Table 17, entry 10), showing that the magnesium-iodide exchange can be achieved for this analogue, though not as successfully as with the use of the commercially available Grignard..

Knochel has reported that whereas bromine-lithium exchange is a rapid process, occuring at low temperatures, bromine-magnesium exchange is considerably slower. This results in the exchange process requiring higher temperatures, which limits the application to sensitive functional groups. Knochel found that by incorporating lithium salts (LiCl), the exchange occurred at an increased rate with higher yields obtained (Scheme 85).[192] Further optimisation lead to the development of a range of commercially available Turbo Grignards, such as *i*PrMgBr.LiCl. Turbo Grignards have lead to the ability to convert a variety of sensitive, functionalised halides to their corresponding organometallic Grignard reagents.
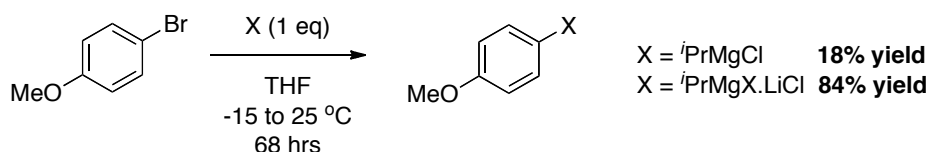
Scheme 85. Knochel's investigations into the developement of the Turbo Grignard iPrMgCl.LiCl

The sysnthesis of p-(Methoxycarbonyl)phenyl Grignard and indolyl Grignard were attempted from Turbo Grignard ^{i}PrMgCl.LiCl and the corresponding iodide and bromide respectively (Scheme 86 and 87).
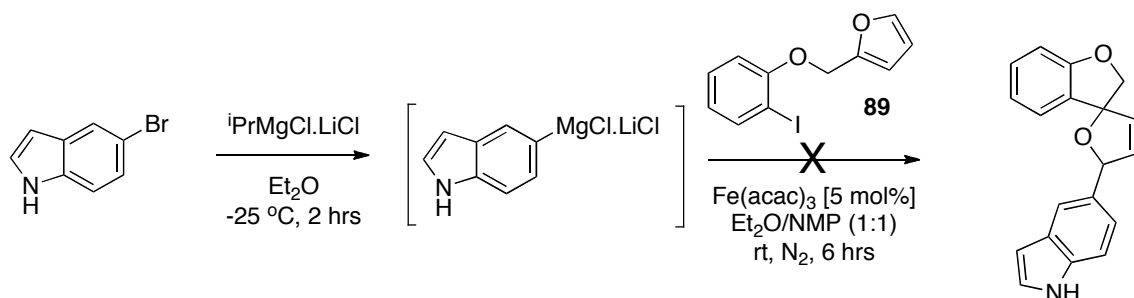
Scheme 86. Synthesis of Indolyl Grignard via Turbo Grignard
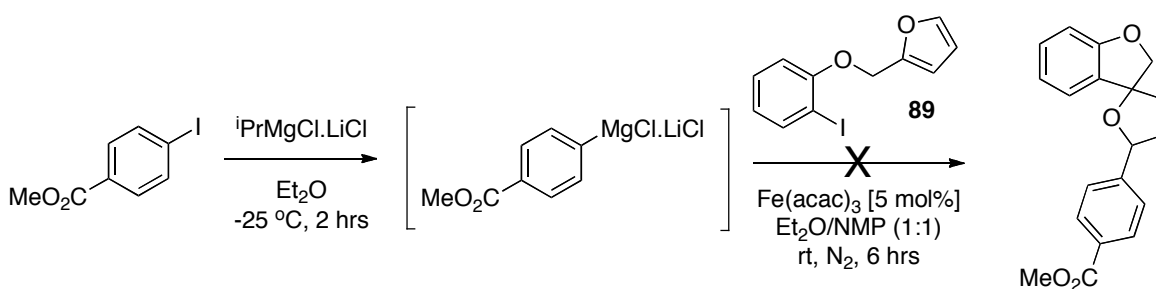
Scheme 87. Synthesis of p-(methoxycarbonyl) phenyl via Turbo Grignard

In both examples examined, the desired products were not observed by ^{1}H NMR spectroscopic analysis. Again, as the Grignard generation occurs *in situ*, the unsuccessful step in the process could not be identified. However, if successfully formed, magnesium chlorides would be produced. Commercially available magnesium chloride Grignard reagents were found to be incompatible with the spirocyclisation reaction, and therefore synthsis of Grignards in the manner is not ideal (Scheme 88).
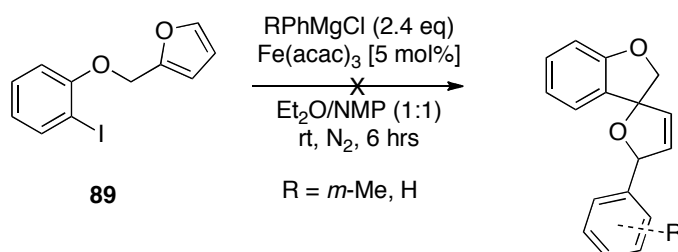
Scheme 88. Arylative spirocyclisation with aryl Grignard chlorides

4.7 Determining Product Structure

When products are examined by NMR spectroscopy in d$_6$-DMSO, the peak dispersion increased, which allows for nOe to be conducted on each environment. All products isolated were produced as predominantly a single diastereoisomer (>20:1 diastereoselectivity). nOe experiments were conducted to provide evidence for the structure of the major product. If the rings were in a *cis*-conformation, nOe would be observed between the proton at C-11 and the methylene protons at C-7, as demonstrated in Figure 16A. The lack of an nOe interaction between the C-11 proton and the C-7 protons can be visualised by nOe, as shown for the p-Me analogue **97** in Figure 17, which provides some evidence for the major product to be that of the isomer in which the aryl rings are in the *trans*-arrangement. Further work would be required to confirm the structure, by methods such as functionalisation of the olefin.

A　　　　　　　　　　　　　　　　　　　　　　　　　**B**
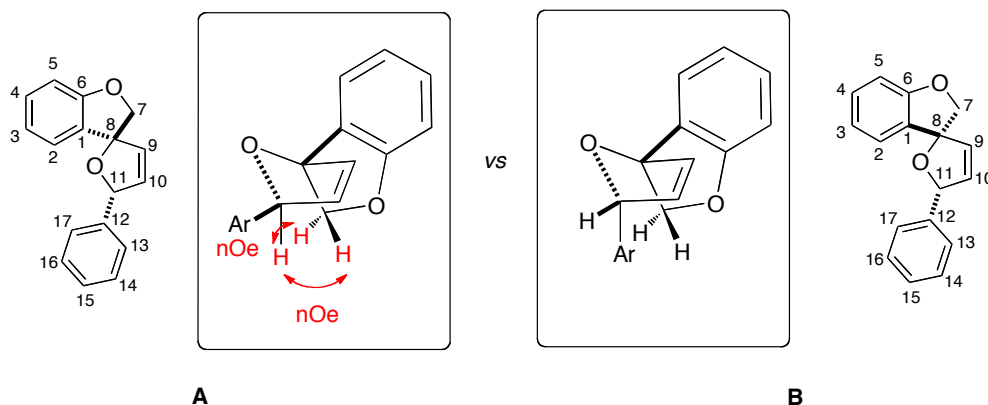
Figure 16. *Conformations of arylative cyclisation products, with aryl rings in A) cis- and B) trans-arrangement*
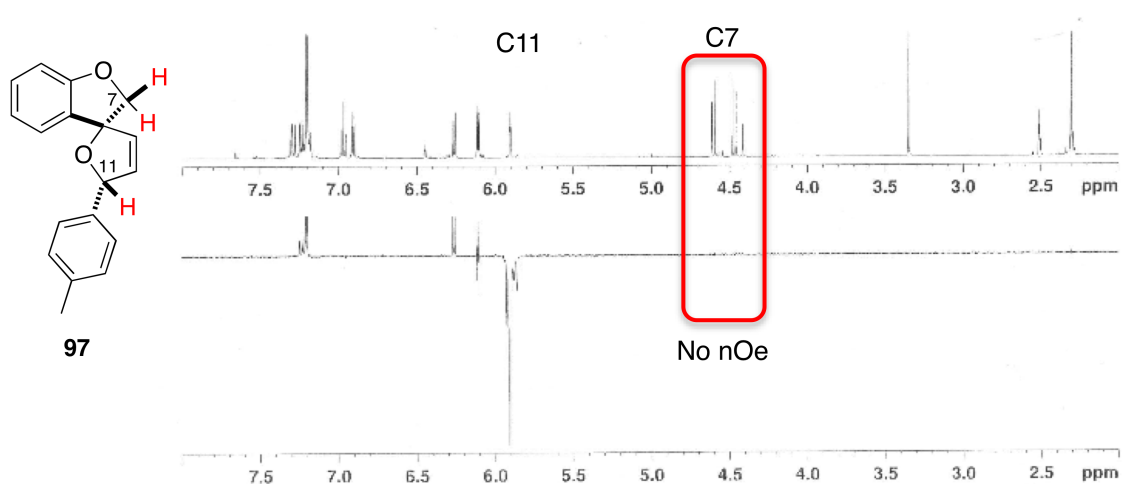
Figure 17. *nOe spectra of **97**, with irradiation at C-11.*

We suggest that the reaction proceeds through an intermediate σ-bonded aryl-iron species, which cyclises to give an allyl iron species **106** which can isomerise *via* **107** to the less hindered intermediate **108**. Reductive elimination results in 5'-phenyl-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] **88** (Scheme 89).
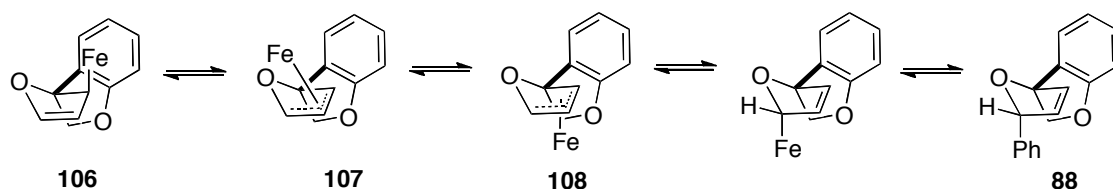
Scheme 89. *Postulated arylative spirocyclisation process*

4.8 Application of Alternative Grignard Reagents

The arylative spirocyclisation reaction has been shown to occur in moderate to high yields with a variety of aryl Grignards. The reaction may potentially also occur with alkyl- or heteroaryl-Grignards. Although Indole Grignard was unable to be synthesised, a variety of other alkyl- and heteroaryl-Grignards are commercially available, a few of which were applied to the reaction under the previously described reaction conditions developed (Table 19).

Table 19. *Reaction scope: Compatability of Grignards*

Entry	R	Product	Yield (%)
1	Me	**109**	0
2	Et	**110**	36
3	*i*Pr	**111**	0
4	2-Thienyl	**112**	0

Fürstner conducted extensive investigations into the series of organoiron complexes, showing that MeMgBr and EtMgBr (and higher chains) exhibit strikingly different behavior. They report that in attempted cross coupling reactions of aryl chlorides with EtMgBr the desired product is obtained in virtually quantitative yield within minutes, whereas MeMgBr fails to react (Scheme 90).[193]
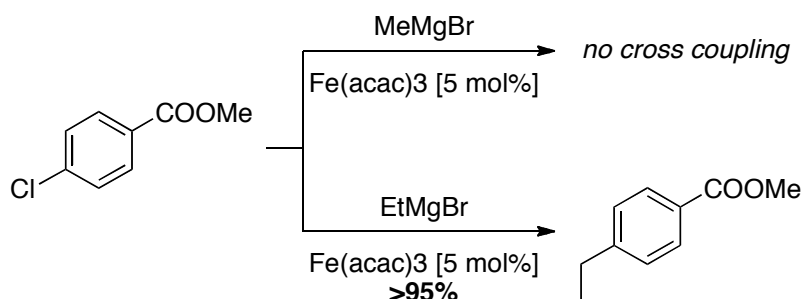
Scheme 90. *Behavious of different Grignards towards cross-coupling*

Application of MeMgBr and EtMgBr to the spirocyclisation reaction gave results in accordance with the work of Fürstner, with only EtMgBr resulting in cross-coupling (**110**), isolated in moderate yield (Table 19, entry 2). The thienyl compound failed to give the desired product **112** (entry 4, Table 18).

The reaction of *iso*propylmagnesium bromide with **89** did not result in spirocyclisation, instead giving quantitative formation of the de-iodinated product **113** (Scheme 91).

89 **113**
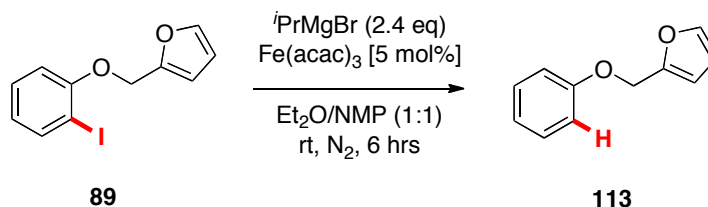
Scheme 91. Reaction of ^{i}PrMgBr with **89**

4.7 Conclusions and Future Work

Arylative spirocyclisation in the presence of stoichiometric Grignard reagents and iron(III) catalysts has been developed, to induce cyclisation of 2-[(2-Iodophenoxy)methyl]furan **89** in a highly stereoselective manner, to give novel compounds containing spirocyclic centres.   The reaction has proved highly versatile with application of a range of arylmagnesium bromide Grignard reagents of varying electronic and steric properties in good to excellent yields. Although initial examination of alkyl Grignards has not to date provided many compatible cross-coupling partners, further exploration is necessary, in particular examination of the applicability of heterocylic and heteroaryl Grignards such as furans and indoles. Alteration of the starting material would also enable access to a wider range of spirocyclic compound, for example variation of the chain length or heteroatoms.

CHAPTER 5: EXPERIMENTAL: IRON CATALYSED ARYLATIVE SPIROCYCLISATION

2-[(2-Iodophenoxy)methyl]furan (89)[187]
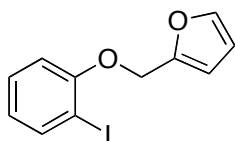
To a stirred solution of furfuryl alcohol in DCM (0.5 M, 57.4 mL, 30 mmol, 1 eq) and triethylamine (4.6 mL, 33 mmol, 1.1 eq) at 0 °C was added methanesulfonyl chloride (2.4 mL, 31.5 mmol, 1.05 eq) dropwise. The reaction mixture was maintained at 0 °C for 30 minutes and then poured into saturated aqueous NaHCO$_3$ (20 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo* to afford the crude product which was used without further purification.

To a solution of the crude product in acetone (30 mL) was added in succession iodophenol (3.05 g, 27 mmol, 0.90 eq), K$_2$CO$_3$ (8.29 g, 60 mmol, 2.0 eq) and NaI (0.44 g, 3 mmol, 0.1 eq). The reaction mixture was stirred for 24 hours and then concentrated *in vacuo*. To the crude residue was added water (20 mL) and DCM (20 mL). The aqueous and organic layers were separated and the aqueous layer extracted with DCM (2 x 20 mL). The combined organic layers were washed with NaOH (1M, 20 mL), dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo* to afford the crude product which was purified by column chromatography (Pet. Ether: EtOAc, 9:1, R$_f$ 0.40) to yield 2-[(2-iodophenoxy)methyl]furan as a yellow oil (3.13 g, 39%); ^{1}H NMR (CDCl$_3$, 400 MHz) δ^H 5.06 (s, 2H, C$\underline{H}_2$), 6.37 (br t *J* 1.5 Hz, 1H, 4 -C$\underline{H}$), 6.45 (d *J* 3.0 Hz, 1H, 3 -C$\underline{H}$), 6.73 (t *J* 7.5 Hz, 1H, 4' Ar -C$\underline{H}$), 6.94 (d *J* 8.0 Hz, 1H, 6' Ar -C$\underline{H}$), 7.28 (t *J* 7.5 Hz, 1H, 5' Ar -C$\underline{H}$), 7.44 (s, 1H, 5 -C$\underline{H}$), 7.77 (d *J* 8.0 Hz, 1H, 3' Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ^C 63.8 (-$\underline{C}$H$_2$), 87.23 (2 *quat.* $\underline{C}$), 110.5 (4 -$\underline{C}$H), 111.0 (3 -$\underline{C}$H), 113.4, 123.2, 129.3, 139.5 (Ar -$\underline{C}$H), 142.9 (5 -$\underline{C}$H), 149.8, 157.0 (1', 2' Ar -$\underline{C}$); ν_{max} (thin film, cm^{-1}) 1579 (C=C), 1502 (C=C aromatic) 1236 (C-O); m/z [C$_{11}$H$_9$O$_2$INa]$^+$ expected 322.9545, found 322.9538.

General Method for arylative spirocyclisation:

An oven dried flask was charged with 2-[(2-iodophenoxy)methyl]furan (0.300 g, 1.0 mmol, 1 eq) and Fe(III) catalyst (0.05 mmol, 5 mol%) and purged with nitrogen. Et$_2$O (2.5 mL) and NMP (2.5 mL) were then added and the flask evacuated and refilled with nitrogen (x 3). To the resulting solution was added arylmagnesium bromide (1M in THF or Et$_2$O, 2.4 mmol, 2.4 eq) dropwise over 30 min, and the resulting solution stirred for 6 hours at room temperature. The reaction mixture was diluted with ethyl acetate (25 mL) and the organic washed sequentially with aq. HCl (2M, 20 mL), water (20 mL) and brine (20 mL). The organic was then dried over MgSO$_4$, filtered and concentrated *in vacuo* to give the crude product which was purified by flash column chromatography (2% EtOAc in Hexane) to give the corresponding spirocyclic

compound.

5'-Phenyl-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (88)
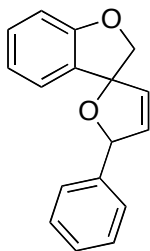
5'-Phenyl-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained as a pale yellow liquid (0.182 g, 73%) from phenyl magnesium bromide (1M in THF, 2.4 mL) following the general method; R_f 0.17 (2% EtOAc in Hex); ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ_H 4.50 (d *J* 10.5 Hz, 1H, 2 -C<u>H</u>$_2$), 4.61 (d *J* 10.5 Hz, 1H, 2 -C<u>H</u>$_2$), 5.95 (br s, 1H, 5' -C<u>H</u>), 6.12 (dd *J* 1.0 Hz 6.0 Hz, 1H, 3' -C<u>H</u>), 6.30 (d *J* 6.0 Hz, 1H, 4' -C<u>H</u>), 6.91 (d *J* 8.0 Hz, 1H, Ar -<u>H</u>), 6.97 (t *J* 7.5 Hz, 1H, Ar -<u>H</u>), 7.24 (d *J* 7.0 Hz, 1H, Ar -<u>H</u>), 7.28-7.34 (m, 4H, Ar -<u>H</u>), 7.39-7.52 (m, 2H, Ar -<u>H</u>); ^{13}C NMR (100 MHz) δ_C 80.1 (2 -<u>C</u>H$_2$), 87.1 (5' -<u>C</u>H), 95.9 (3 *quat.* -<u>C</u>), 110.7, 124.9, 125.5, 126.8, 128.2, 128.8 (Ar -<u>C</u>), 128.9 (3' -<u>C</u>H), 129.2 (Ar -<u>C</u>), 131.1 (4' -<u>C</u>H), 133.7, 141.6, 160.0 (Ar *quat.* -<u>C</u>); ν_{max} (thin film, cm[-1]) 1599 (C=C), 1492 (C=C aromatic) 1178 (C-O); m/z [C$_{17}$H$_{14}$O$_2$Na]$^+$ expected 273.0891, found 273.0888.

5'-(4-Chlorophenyl-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (93)
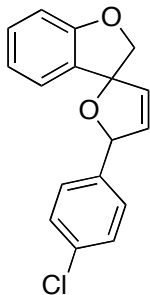
5'-(4-Chlorophenyl-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained as a pale yellow liquid (0.188g, 49%) from 4-chloromagnesium bromide (1M in Et$_2$O, 2.4 mL) following the general method; R_f 0.04 (2% EtOAc in Hex); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 4.41 (d *J* 10.5 Hz, 1H, 2 -C<u>H</u>$_2$), 4.48 (d *J* 10.5 Hz, 1H, 2 -C<u>H</u>$_2$), 5.84 (t *J* 2.0 Hz, 1H, 5' -C<u>H</u>), 5.88 (dd *J* 2.5 Hz 6.0 Hz, 1H, 3' -C<u>H</u>), 6.85 (dd *J* 2.0 Hz 8.0 Hz, 1H, 4' -C<u>H</u>), 6.79 (d *J* 8.0 Hz, 1H, Ar -<u>H</u>), 6.87 (dt *J* 1.0 Hz 7.5 Hz, 1H, Ar -<u>H</u>), 7.12-7.27 (m, 6H, Ar -<u>H</u>); ^{13}C NMR (100 MHz) δ_C 79.2 (2 -<u>C</u>H$_2$), 85.5 (5' -<u>C</u>H), 95.1 (3 -*quat.* C), 109.7, 120.0, 123.2, 126.8, 127.7 (Ar -<u>C</u>), 128.2 (3' -<u>C</u>H), 129.7 (Ar -<u>C</u>), 130.7 (4' -<u>C</u>H), 132.8, 138.3, 141.8, 159.0 (Ar *quat.* -<u>C</u>); ν_{max} (thin film, cm[-1]) 1597 (C=C), 1475 (C=C aromatic) 1177 (C-O); m/z [C$_{17}$H$_{13}$O$_2$^{35}ClNa]$^+$ expected 307.0502, found 307.0496.

5'-(3-Fluorophenyl)-2_H_,5'_H_-spiro[benzofuran-3.2'-furan] (94)

5'-(3-Fluorophenyl)-2_H_,5'_H_-spiro[benzofuran-3.2'-furan] was obtained synthesised as a pale yellow liquid (17 mg, 6%) from 3-fluoromagnesium bromide (1M in THF, 2.4 mL) following the general method; R_f 0.04 (2% EtOAc in Hex); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 4.52 (d J 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.68 (d J 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 5.83-5.90 (m, 2H, 3', 5' -C$\underline{H}$), 6.06 (d J 5.5 Hz, 1H, 4' -C$\underline{H}$), 6.79 (d J 8.0 Hz, 1H, Ar -C$\underline{H}$), 6.87 (t J 7.5 Hz, 1H, Ar -C$\underline{H}$), 7.10-7.24 (m, 6H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 80.2 (2 -$\underline{C}$H$_2$), 86.6 (C11- $\underline{C}$H), 96.3 (3 *quat.* -$\underline{C}$), 110.7, 113.2, 115.0, 121.1, 124.3 (Ar -$\underline{C}$), 127.7 (*quat.* Ar -$\underline{C}$), 129.2 (3' -$\underline{C}$H), 130.1, 130.2 (Ar -$\underline{C}$H), 130.8 (4' -$\underline{C}$H), 131.7 (Ar -$\underline{C}$), 143.6, 160.1, 164.2 (*quat.* Ar -$\underline{C}$); ^{19}F NMR (CDCl$_3$, 400 MHz) δ_F -112.5 (C$\underline{F}$); ν_{max} (thin film, cm^{-1}) 1592 (C=C), 1476 (C=C aromatic) 1179 (C-O); m/z [C$_{17}$H$_{13}$O$_2$FNa]$^+$ expected 291.0797, found 291.0792.

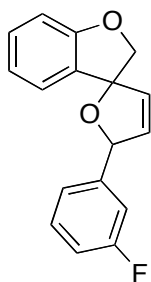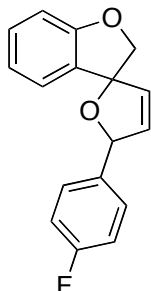**5'-(4-Fluorophenyl)-2_H_,5'_H_-spiro[benzofuran-3.2'-furan] (95)**

5'-(4-Fluorophenyl)-2_H_,5'_H_-spiro[benzofuran-3.2'-furan] was obtained as a pale yellow liquid (0.198 g, 74%) from 4-fluoromagnesium bromide (1M in THF, 2.4 mL) following the general method; R_f 0.04 (2% EtOAc in Hex); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 4.49 (d J 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.55 (d J 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 5.92 (t J 2.0 Hz, 1H, 5' -C$\underline{H}$), 5.95 (dd J 2.0 Hz 6.0 Hz, 1H, 3' -C$\underline{H}$), 6.11 (dd J 1.5 Hz 6.0 Hz, 1H, 4' -C$\underline{H}$), 6.86 (d J 8.0 Hz, 1H, Ar -C$\underline{H}$), 6.94 (dd J 1.0 Hz 7.5 Hz, 1H, Ar -C$\underline{H}$), 6.98-7.04 (m, 2H, Ar -C$\underline{H}$), 7.20-7.26 (m, 4H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 80.3 (2 -$\underline{C}$H$_2$), 86.6 (5' -$\underline{C}$H), 96.0 (3 *quat.* -C), 110.7, 115.5, 121.0, 124.3 (Ar -$\underline{C}$), 128.3 (*quat.* Ar -$\underline{C}$), 128.4 (3' -$\underline{C}$H), 129.2 (Ar -$\underline{C}$), 130.7 (4' -$\underline{C}$H), 131.9 (Ar -$\underline{C}$), 136.7, 160.1, 163.8 (*quat.* Ar -$\underline{C}$); ^{19}F NMR (CDCl$_3$, 400 MHz) δ_F -114.0 (C$\underline{F}$); ν_{max} (thin film, cm^{-1}) 1600 (C=C), 1476 (C=C aromatic) 1177 (C-O);m/z [C$_{17}$H$_{13}$O$_2$FNa]$^+$ expected 291.0797, found 291.0787.

5'-(*o*-Tolyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (96)
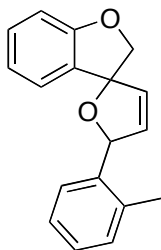
5'-(*o*-Tolyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained as a pale yellow liquid (0.200 g, 76%) from 2-methylmagnesium bromide (2M in THF, 1.2 mL) following the general method; R_f 0.14 (2% EtOAc in Hex); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.37 (s, 3H, -C$\underline{H}_3$), 4.58 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.78 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 5.92 (dd *J* 2.5 Hz 8.0 Hz, 1H, 3' -C$\underline{H}$), 6.15 (dd *J* 1.5 Hz 6.5 Hz, 1H, 5' -C$\underline{H}$), 6.19 (t *J* 2.0 Hz, 1H, 4' -C$\underline{H}$), 6.86 (d *J* 8.0 Hz, 1H, Ar -C$\underline{H}$), 6.93 (t *J* 7.5 Hz, 1H, Ar -C$\underline{H}$), 7.10-7.29 (m, 6H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 19.3 (-$\underline{C}$H$_3$), 80.4 (2 -$\underline{C}$H$_2$), 84.3 (5' -$\underline{C}$H), 95.8 (3 *quat.* -$\underline{C}$), 110.4, 121.1, 124.6, 126.0 (Ar -$\underline{C}$), 127.9 (3' -$\underline{C}$H), 128.5 (*quat.* Ar -$\underline{C}$), 129.2, 130.6 (Ar -$\underline{C}$), 130.7 (4' -$\underline{C}$H), 131.6 (Ar -$\underline{C}$), 135.5, 138.8, 160.2 (*quat.* Ar -$\underline{C}$); ν_{max} (thin film, cm^{-1}) 1598 (C=C), 1476 (C=C aromatic) 1178 (C-O); m/z [C$_{18}$H$_{16}$O$_2$Na]$^+$ expected 287.1048, found 287.1044.

5'-(*p*-Tolyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (97)

5'-(*p*-Tolyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained as a pale yellow liquid (0.235 g, 89%) from 4-methylmagnesium bromide (1M in THF, 2.4 mL) following the general method; R_f 0.06 (2% EtOAc in Hex); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.38 (s, 3H, -C$\underline{H}_3$), 4.46 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.55 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 5.91-5.94 (m, 2H, 3', 5' -C$\underline{H}$), 6.12 (t *J* 3.5 Hz, 1H, 4' -C$\underline{H}$), 6.56 (dd *J* 1.0 Hz 8.0 Hz, 1H, Ar -C$\underline{H}$), 6.93 (dt *J* 1.0 Hz 7.5 Hz, 1H, Ar -C$\underline{H}$), 7.14-7.19 (m, 4H, Ar -C$\underline{H}$), 7.22-7.27 (m, 2H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 21.2 (-$\underline{C}$H$_3$), 80.5 (2 -$\underline{C}$H$_2$), 87.3 (5' -$\underline{C}$H), 95.9 (3 *quat.* -$\underline{C}$), 110.7, 121.1, 124.4 (Ar -$\underline{C}$), 128.1 (*quat.* Ar -$\underline{C}$), 128.3 (3' -$\underline{C}$H), 128.9 (Ar -$\underline{C}$), 130.7 (4' -$\underline{C}$H), 132.2 (Ar -$\underline{C}$), 137.9, 160.2 (*quat.* Ar -$\underline{C}$); ν_{max} (thin film, cm^{-1}) 1598 (C=C), 1475 (C=C aromatic) 1177 (C-O); m/z [C$_{18}$H$_{16}$O$_2$Na]$^+$ expected 287.1048, found 287.1042.

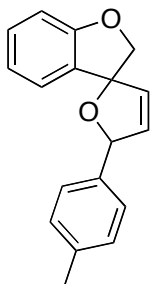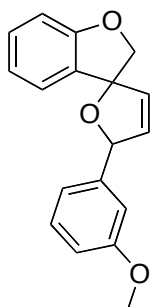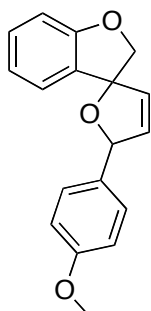**5'-(3-Methoxyphenyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (99)**

5'-(3-Methoxyphenyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained as a pale yellow liquid (0.246 g, 88%) from 4-methoxyphenylmagnesium bromide (1M in THF, 2.4 mL) following the general method, purified by flash column chromatography (activated basic alumina, 2% EtOAc in Hex); R_f 0.53 (20% EtOAc in Hex); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 3.78 (s, 3H, -OC$\underline{H}_3$), 4.47 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.58 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 5.94 (br d *J* 3.5 Hz, 2H, 3', 5' -C$\underline{H}$), 6.15 (t *J* 3.5 Hz, 1H, 4' -C$\underline{H}$), 6.80-6.87 (m, 3H, Ar -C$\underline{H}$), 6.94 (t 7.5 Hz, 1H, Ar -C$\underline{H}$), 7.21-7.35 (m, 4H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 55.2 (-OC$\underline{H}_3$), 80.4 (2 -C$\underline{H}_2$), 87.2 (5' -C$\underline{H}$), 96.1 (3 *quat.* -$\underline{C}$), 110.7, 112.2, 112.4, 118.8, 121.1, 124.4 (Ar -$\underline{C}$), 128.2 (*quat.* Ar -$\underline{C}$), 128.9 (3' -$\underline{C}$H), 129.6 (Ar -$\underline{C}$), 130.7 (4' -C$\underline{H}$), 132.1 (Ar -$\underline{C}$), 142.5, 159.9, 160.0 (*quat.* Ar -$\underline{C}$); ν_{max} (thin film, cm^{-1}) 1608 (C=C), 1475 (C=C aromatic) 1172 (C-O); m/z [C$_{18}$H$_{16}$O$_3$Na]$^+$ expected 303.0997, found 303.0991.

5'-(4-Methoxyphenyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (100)

5'-(4-Methoxyphenyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained as a pale yellow liquid (0.207 g, 74%) from 3-methoxyphenylmagnesium bromide (0.5M in Et$_2$O, 4.8 mL) following the general method, purified by flash column chromatography (activated basic alumina, 2% EtOAc in Hex); R_f 0.49 (20% EtOAc in Hex); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 3.79 (s, 3H, -OC$\underline{H}_3$), 4.39 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.46 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 5.93 (br s, 1H, 5' -C$\underline{H}$), 5.97 (d *J* 6.0 Hz, 1H, 3' -C$\underline{H}$), 6.14 (d *J* 6.0 Hz, 1H, 4' -C$\underline{H}$), 6.85-6.89 (m, 3H, Ar -C$\underline{H}$), 6.95 (t *J* 7.0 Hz, 1H, Ar -C$\underline{H}$), 7.20-7.30 (m, 4H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 55.3 (-OC$\underline{H}_3$), 80.5 (2 -C$\underline{H}_2$), 87.0 (5' -C$\underline{H}$), 95.7 (3 *quat.* -$\underline{C}$), 110.6, 114.1, 121.1, 124.4 (Ar -$\underline{C}$), 128.0 (3' -$\underline{C}$H), 128.2 (*quat.* Ar -$\underline{C}$), 129.0 (Ar -$\underline{C}$), 130.7 (4' -$\underline{C}$H), 132.2 (Ar -$\underline{C}$), 133.0, 159.6, 160.2 (*quat.* Ar -$\underline{C}$); ν_{max} (thin film, cm^{-1}) 1608 (C=C), 1475 (C=C aromatic) 1172 (C-O); m/z [C$_{18}$H$_{16}$O$_3$Na]$^+$ expected 303.0997, found 303.0992.

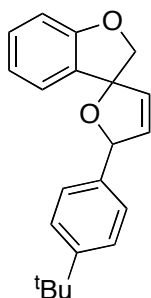**5'-(*tert*-Butyl)-phenyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (101)**

5'-(*tert*-Butyl)-phenyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained as a pale yellow liquid (0.1601 g, 52%) from 4-(*tert*-Butyl)phenylmagnesium bromide (0.5M in THF, 4.8 mL) following the general method; R_f 0.05 (2% EtOAc in Hex); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 1.30 (s, 9H, -C(C$\underline{H}_3$)$_3$), 4.47 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.57 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 5.91 (dd *J* 2.0 Hz 6.0 Hz, 1H, 3' -C$\underline{H}$), 5.93 (t *J* 2.0 Hz, 1H, 5' -C$\underline{H}$), 6.12 (dd *J* 1.5 Hz 6.0 Hz, 1H, 4' -C$\underline{H}$), 6.85 (d *J* 8.0 Hz, 1H, Ar -C$\underline{H}$), 6.92 (dt *J* 1.0 Hz 7.5 Hz, 1H, Ar -C$\underline{H}$), 7.20-7.24 (m, 6H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 31.5 (-C(C$\underline{H}_3$)$_3$), 34.6 (3 *quat.* -$\underline{C}$), 80.5 (2 -C$\underline{H}_2$), 87.3 (5' -C$\underline{H}$), 96.0 (*quat.* Ar -$\underline{C}$), 110.7, 121.1, 124.5, 125.6, 126.5 (Ar -$\underline{C}$), 128.4 (*quat.* Ar -$\underline{C}$) 128.9 (3' -C$\underline{H}$), 130.7 (4' -C$\underline{H}$), 132.2 (Ar -$\underline{C}$), 137.9, 151.2, 160.2 (*quat.* Ar -$\underline{C}$); ν_{max} (thin film, cm^{-1}) 2960 (C-H), 1599 (C=C), 1475 (C=C aromatic) 1177 (C-O); m/z [C$_{21}$H$_{22}$O$_2$Na]$^+$ expected 329.1517, found 329.1507.

5'-(4-Trifluoromethoxyphenyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (102)
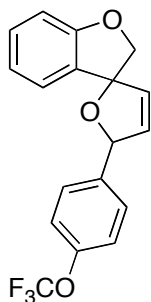

5'-(4-Trifluoromethoxyphenyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained as a pale yellow liquid (0.130 g, 39%) from 4-(trifluoromethoxy)phenylmagnesium bromide (0.5M in THF, 4.8 mL) following general the method; R_f 0.06 (2% EtOAc in Hex); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 4.42 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.49 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 5.83-5.90 (m, 2H, 3', 5' -C$\underline{H}$), 6.06 (d *J* 5.5 Hz, 1H, 4' -C$\underline{H}$), 6.79 (d *J* 8.0 Hz, 1H, Ar -C$\underline{H}$), 6.87 (t *J* 7.5 Hz, 1H, Ar -C$\underline{H}$), 7.10-7.24 (m, 6H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 52.5 (-OC$\underline{F}_3$), 79.2 (2 -C$\underline{H}_2$), 85.4 (5' -C$\underline{H}$), 95.2 (3 *quat.* -$\underline{C}$), 109.7, 120.1, 123.2, (Ar -$\underline{C}$), 126.4 (*quat.* Ar -$\underline{C}$), 126.8 (Ar -$\underline{C}$), 128.2 (3' -C$\underline{H}$), 129.8 (Ar -$\underline{C}$), 130.7 (4' -C$\underline{H}$), 138.5, 147.9, 159.1 (*quat.* Ar -$\underline{C}$); ^{19}F NMR (CDCl$_3$, 400 MHz) δ_F -62.5 (-OC$\underline{F}_3$); ν_{max} (thin film, cm^{-1}) 1598 (C=C), 1477 (C=C aromatic) 1259, 1165 (C-O); m/z [C$_{18}$H$_{13}$O$_3$F$_3$Na]$^+$ expected 357.0714, found 357.0707.

5'-(Biphenyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (103)
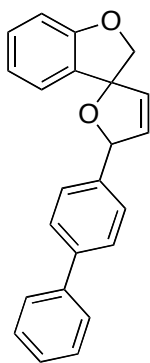
5'-(Biphenyl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained as a white solid (0.313 g, 96%) from 4-biphenylmagnesium bromide (0.5M in THF, 4.8 mL) following the general method; R_f 0.04 (2% EtOAc in Hex); mpt 82-83 ^{o}C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 4.47 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.59 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 5.89 (br d *J* 6.0 Hz, 1H, 3' -C$\underline{H}$), 5.96 (br s, 1H, 5' -C$\underline{H}$), 6.11 (br d *J* 6.0 Hz, 1H, 4' -C$\underline{H}$), 6.80 (d *J* 8.0 Hz, 1H, Ar -C$\underline{H}$), 6.93 (t *J* 7.0 Hz, 1H, Ar -C$\underline{H}$), 7.21-7.42 (m, 7H, Ar -C$\underline{H}$;), 7.54 (d J 8.0 Hz, 4H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 80.5 (2 -$\underline{C}$H$_2$), 87.2 (5' -$\underline{C}$H), 96.2 (3 *quat.* -$\underline{C}$), 110.8, 121.2, 124.5, 126.9, 127.3, 127.4, 127.5 (Ar -$\underline{C}$), 128.2 (*quat.* Ar -$\underline{C}$), 128.9 (3' -$\underline{C}$H), 129.1 (Ar -$\underline{C}$), 130.8 (4' -$\underline{C}$H), 132.2 (Ar -$\underline{C}$), 140.0, 140.8, 141.2, 160.3 (*quat.* Ar -$\underline{C}$); ν_{max} (thin film, cm^{-1}) 1598 (C=C), 1475 (C=C aromatic) 1176 (C-O); m/z [C$_{23}$H$_{18}$O$_2$Na]$^+$ expected 349.1204, found 349.1190.

5'-(Napthalen-1-yl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (104)
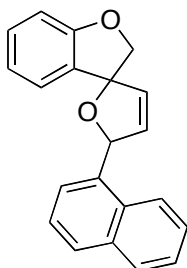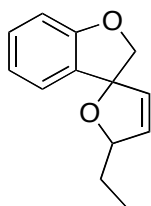

5'-(Napthalen-1-yl)-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained as a white solid (0.273 g, 91%) from 2-napthylmagnesium bromide (0.25M slurry in THF, 9.6 mL) following the general method; R_f 0.04 (2% EtOAc in Hex); mpt 98-99 ^{o}C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 4.68 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.55 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 6.03 (dd *J* 2.0 Hz 6.0 Hz, 1H, 4' -C$\underline{H}$), 6.15 (t *J* 2.0 Hz, 1H, 5' -C$\underline{H}$), 6.26 (dd *J* 1.5 Hz 6.0 Hz, 1H, 3' -C$\underline{H}$), 6.90 (d *J* 8.0 Hz, 1H, Ar -C$\underline{H}$), 6.98 (dt *J* 1.0 Hz 7.5 Hz, 1H, Ar -C$\underline{H}$), 7.26-7.38 (m, 2H, Ar -C$\underline{H}$), 7.40 (dd *J* 1.5 Hz, 8.0 Hz, 1H, Ar -C$\underline{H}$), 7.46-7.51 (m, 3H, Ar -C$\underline{H}$), 7.77 (d *J* 1.0 Hz, 1H, Ar -C$\underline{H}$), 7.82-7.86 (m, 2H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 80.4 (2 -$\underline{C}$H$_2$), 87.5 (5' -$\underline{C}$H), 96.2 (3 *quat.* -$\underline{C}$), 110.7, 121.1, 124.3, 124.4, 125.8, 126.1, 126.3, 127.7, 127.8, 128.0 (Ar -$\underline{C}$), 128.1 (*quat.* Ar -$\underline{C}$), 128.5 (4' -$\underline{C}$H), 129.1 (Ar -$\underline{C}$), 132.1 (3' -$\underline{C}$H), 133.2, 133.3, 138.2, 160.1 (*quat.* Ar -$\underline{C}$); ν_{max} (thin film, cm^{-1}) 1599 (C=C), 1476 (C=C aromatic) 1178 (C-O); m/z [C$_{21}$H$_{16}$O$_2$Na]$^+$ expected 323.1048, found 323.1039.

5'-Ethyl-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] (110)

5'-Ethyl-2*H*,5'*H*-spiro[benzofuran-3.2'-furan] was obtained in its crude form as an orange oil (0.061 g) from ethylmagnesium bromide (1M in THF, 2.4 mL) following the general method; R_f 0; ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 0.93 (t *J* 7.5 Hz, 3H, -C$\underline{H}_3$), 1.55-1.67 (m, 2H, -C$\underline{H}_2$), 4.39 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.48 (d *J* 10.5 Hz, 1H, 2 -C$\underline{H}_2$), 4.96 (dt *J* 2.0 Hz 5.5 Hz, 1H, 5' -C$\underline{H}$), 5.79 (dd J 2.0 Hz 6.0 Hz, 1H, 3' -C$\underline{H}$), 6.86 (dd *J* 1.0 Hz 6.0 Hz, 1H, 4' -C$\underline{H}$), 6.84-6.99 (m, 2H, Ar -C$\underline{H}$), 7.15-7.30 (m, 2H, Ar -C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 9.36 (-$\underline{C}H_3$), 29.3 (-$\underline{C}H_2$), 80.8 (2 -$\underline{C}H_2$), 86.9 (5' -$\underline{C}H$), 95.2 (3 *quat.* -$\underline{C}$), 110.5, 121.0, 124.4 (Ar -$\underline{C}$), 128.6 (3' -$\underline{C}H$), 129.5 (*quat.* Ar -$\underline{C}$), 130.5 (4' -$\underline{C}H$), 132.3 (Ar -$\underline{C}$), 160.0 (*quat.* Ar -$\underline{C}$); ν_{max} (thin film, cm^{-1}) 2964, 2933 (C-H), 1599 (C=C), 1476 (C=C aromatic) 1178 (C-O); m/z [C$_{13}$H$_{14}$O$_2$Na]$^+$ expected 225.0891, found 225.0886.

CHAPTER 6: REFERENCES

[1]   Heravi, M. M.; Hashemi, E. *Tetrahedron,* **2012**, *68*, 9145.

[2]   Yasuda, N. *J. Organomet. Chem.* **2002**, *253*, 279.

[3]   Miller, W. O.; Fray, A. H; Quatroche, J. T; Sturggill, C. D. *Org. Proc. Res. Dev.* **2007**, *11*, 359.

[4]   Li, J.; Chen, P. *ChemBioChem,* **2012**, *13*, 1728.

[5]   Cheng, Y-J.; Luh, T-Y. *J. Organomet. Chem.* **2004**, *689*, 4137.

[6]   Moussa, S.; Siamaki, A. R.; Gupton, B. F.; El-Shall, M.S. *ACS Catal.* **2012**, *2*, 145.

[7]   a) Corriu, R.; Masse, P. *J. Chem. Soc. Chem. Comm.* **1972**, 144; (b) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

[8]   Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

[9]   King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc. Chem Comm.* **1977,** 683**.**

[10]   Milstein, D.; Stille, J. K. *J. Am. Chem Soc.* **1978**, *100*, 3636.

[11]   a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 20, 3437; (b) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Comm.* **1979**, 866; (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[12]   Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.

[13]   "The Nobel Prize in Chemistry 2010 - Press Release", 19 Apr 2013 http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/press.html

[14]   Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.

[15]   Heck, R. F. *J. Am. Chem. Soc.* **1969**. *91*, 6707.

[16]   Mizoroki, T., Mori, K. and Ozaki, A. *Bull. Soc. Chem. Jpn.* **1971**, *44*, 581.

[17]   Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

[18]   Jeffery, T. *Tetrahedron*, **1996**, *52*, 10113.

[19]   Mo, J.; Liu, S.; Xiao, J. *Tetrahedron*, **2005**, *61*, 9902.

[20]   a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989; (b) Deshmukh, R.; Rajagopal, R.; Srinivasan, K. *Chem. Commun.* **2001**, 1544; (c) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.

[21]   Jeffery, T. *J. Chem. Soc. Chem. Commun.* **1984**, 1287.

[22]   Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.

[23]   Jeffery, T. *Tetrahedron,* **1996**, *52*, 10113.

[24]   a) Namyslo, J. C.; Kaufmann, D. E. *Synlett*, **1999**, 114; b) Yolacan, C.; Bagdatli, E.; Öcal, N.; Kaufmann, D. E. *Molecules,* **2006**, *11*, 603.

[25]   Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113,* 9585.

[26]   Choueiry, D.; Negishi, E-I. *Handbook of Organopalladium Chemistry for Synthesis*, Wiley & Sons, **2003**, p59.

[27]   a) Nguefack, J-F; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1997**, *62,* 6827; b) Nguefack, J-F.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1997**, *62*, 1341.

[28]   Dibowski, H.; Schmidtchen, F. P. *Tetrahedron*, **1995**, *51*, 2325.

[29]   Sollewijn Gelpke, A. E.; Veerman, J. J. N.; Schreuder Goedheijt, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. W; Hiemstra, H. *Tetrahedron*, **1999**, *55*, 6657.

[30]   a) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340; b) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011,** 133, 20146.

[31]   Sonesson, C.; Larhed, M.; Nyqvist, C.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 4756.

[32]   Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159.

[33]   Kikukawa, K.; Nagira, K.; Terao, N.; Wada, F.; Matsuda, T. *Bull. Chem. Soc. Jap.* **1979**, *52*, 2609.

[34]   Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron*, **1981**, *37*, 31.

[35]   Taylor, J. G.; Venturini Moro, A.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 1403.

[36]   Roglans, A.; Pla-Quitana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622.

[37]   Oestreich, M. *The Mizoroki–Heck Reaction,* **2009**, John Wiley & Sons, UK.

[38]   a) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 2514; b) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 4389.

[39]   de Vries, J. *J. Chem. Soc. Dalton Trans.* **2006**, 421.

[40]   a) Herrmann, W. A.; Köcher, C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162; (b) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. *Chem. Eur. J.* **1996**, *2*, 772; (c) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2371.

[41]   Herrmann, W. A.; Reisinger, C-P.; Spiegler, M. *Journal of Organometallic Chemistry,* **1998**, *557,* 93.

[42]   Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, *4*, 2079.

[43]   Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 2083.

[44]   Cezar Pastre, J.; Correia, C. R. D. *Org. Lett.* **2006**, *8*, 1657.

[45]   Correia, C. R. D.; Oliveira, C. C.; Salles, A. G.; Santos, E. A. F. *Tetrahedron Lett.* **2012**, *53*, 3325.

[46]   Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

[47]   National Research Council (US), *The Role of the Chemical Sciences in Finding Alternatives to Critical Resources: A Workshop Summary*, Chemical Sciences Roundtable Washington, **2012**

[48]   Kuzmina, O.; Steib, A.; Markiewicz, J.; Flubacher, D.; Knochel, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 494

[49]   a) Kauffmann, T. *Chem. Int. Ed.* **1996**, *35*, 386; (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.,* **2002**, *124*, 13856.

[50]   Grignard, V. C. R. *Acad. Sci.* **1900**, *130*, 1322.

[51]   Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents*, CRC Press, **1996**, 667.

[52]   a) Harrington, P. J.; Lodewijk, E. *Org. Process Res. Dev.* **1997**, *1*, 72; (b) Tissot-Croset, K.; Alexakis, A. *Tetrahedron Letters*, **2004**, *45*, 7375.

[53]   (a) Corriu, R. J. D.; Masse, J. *J. Chem. Soc., Chem. Commun.* **1972**, 144; (b) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

[54]   (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487; (b) Tamura, M.; Kochi, J. K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3063; (c) Tamura, M.; Kochi, J. K. *Synthesis,* **1971**, 303.

[55]   (a) Cahiez, G.; Avedissian, H. *Synthesis,* **1998**, 1199; (b) Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 53; (c) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett,* **2001**, 1901.

[56]   (a) Reddy, C; Knochel, P. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1700; (b) Fiandanese V.; Marchese, G.; Marinta, V.; Ronzini, L. *Tetrahedron Lett.* **1984**, *25*, 4805; (c) Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449.

[57]   Headström, A. *PhD Thesis, University of Gothenburg*, **2013**, *Iron-Catalysed C-C Coupling Reactions: Mechanistic Investigations.*

[58]   Neuman, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599.

[59]   Hölzer, B.; Hoffmann, R. *Chem. Commun.* **2003**, 732.

[60]   a) Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502; (b) Smith, R.; Kochi, J. K. *J. Organomet. Chem.* **2002**, *653*, 11.

[61]   Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856.

[62]   Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.

[63]   Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943.

[64]   Smith, M. B.; March, J. *March's Advanced Organic Chemistry; Reactions, Mechanisms and Structure*, 6th Ed. Wiley, **2007**, p 260.

[65]   Rottländer, M.; Boymond, L.; BeÂrillon, L.; LepreÃtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 767.

[66]   (a) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Anh Vu, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.

[67]   Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.

[68]   Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3771.

[69]   (a) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron,* **1996**, *52*, 12651; (b) Daly, J.; Karle, I.; Myers, C.; Tokuyama, T.; Waters, J.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870; (c) Sakabe, N.; Takada, S.; Okabe, K. *Chem. Commun. (London)* **1967**, 259.

[70]   a) Tanaka, T.; Okuda, O.; Murakami, K.; Yoshino, H.; Mikamiyama, H.; Kanda, A.; Iwata C. *Chem. Pharm. Bull.*, **1988**, *36*, 2872.

[71]   Ficini, J.; Revial, G.; Genet, J. P. *Tetrahedron Lett.* **1981**, *22*, 629.

[72]   Brands, K. M. J.; DiMichele, L. M. *Tetrahedron Lett.* **1998**, *39*, 1677.

[73]   Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.

[74]   Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571.

[75]   Greenamyre, J.; Porter, R. *Neurology*, **1994**, *44*, S7.

[76]   a) Rubinsztein, D.; Leggo, J.; Chiano, M.; Dodge, A.; Norbury, G.; Rosser, E.; Craufurd, D. *Proc.*

Natl. Acad. Sci. USA, **1997**, *94*, 3872; b) Doble, A. *Therapie*, **1995**, *50*, 319; (c) Cantrell, B. E.; Zimmerman, D. M.; Monn, J. A.; Kamboj, R. K.; Hoo, K. H.; Tizzano, J. P.; Pullar, I. A.; Farrell, L. N.; Bleakman, D. *J. Med. Chem.* **1996**, *39*, 3617.

[77] a) Balázs, R.; Bridges, R. J.; Cotman, C. W. *Excitatory amino acid transmission in Health and Disease;* Oxford University Press, **2006**, 1; b) Bleakman, D.; Lodge, D. *Neuropharmacology,* **1998**, *37*, 1187.

[78] Parsons, A. F. *Tetrahedron*, **1996**, *52*, 4149.

[79] Murakami, S.; Takemoto, T.; Shimizu, Z., J. *Pharm. Soc. Jpn.,* **1953**, *73*, 1026.

[80] McGeer, E. G.; Olney, J.; McGeer, P. *Kainic Acid as a Tool in Neurobiology*; Raven Press NY, **1978**, 17.

[81] Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **2002**, *43*, 253.

[82] Klotz, P.; Mann, A. *Tetrahedron Lett.* **2003**, *44*, 1927.

[83] Hampson, D.; Manalo, J. L. *Natural Toxins*, **1998**, *6*, 153.

[84] (a) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939; (b) Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *J. Am. Chem. Soc.* **1988**, *110*, 4807.

[85] Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1987**, *109*, 5523.

[86] Barco, A.; Benetti, S.; Pollini, G.; Spalluto, G.; Zanirato, V. *Gazz. Chim. It.* **1993**, *123*, 185.

[87] Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron Lett.* **1998**, *39*, 707

[88] Konno, K.; Hashimoto, K,; Ohfune, Y.; Shirahama. H.; Matsumoto, T. *Tetrahedron Lett.* **1986**, *27*, 607.

[89] Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron Lett.* **1998**, *39*, 707

[90] Bachrach, S. M.; Liu, M. *Tetrahedron Lett.* **1992**, *33*, 6771.

[91] Malaty, I.; Fernandez, H. *Ther. Clin. Risk Manag.* **2009**, *5*, 413.

[92] Nicotra, A; Parvez, S. *Toxicol.* **2000**, *153*, 157.

[93] a) Singer, T.; Ramsay, R. *FEBS Lett.* **1990**, *274*, 1; b) Cutillas, A.; Ambrosio, S.; Unzeta, M. *Neurosci. Lett.* **2002**, *329*, 165; b) Przedborski, S.; Vila, M. *Clinical Neuroscience Research*, **2001**, *1*, 407.

[94] Unger, E.; Mazzola-Pomietto, P.; Murphy, D.; Andrews, A. *J. Pharm. Exp. Therapeutics*, **2002**, *303*, 527.

[95] Tatsuoka, T. EU Patent, EP0460358 B1, **1997.**

[96] Mateeva, N. N.; Winfield, L. L.; Redda, K. K. *Curr. Med. Chem.* **2005**, *12*, 551.

[97] a) Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*; Academic Press: NY, **1970**, 114; b) Woodward, R. B.; Hoffman, R. *Angew. Chem. Int. Edit. Engl.* **1969**, *8*, 781.

[98] Smith, M. B; March, J. *March's Advanced Organic Chemistry*; John Wiley & Sons, Inc.: NY, **2001**, p1419.

[99]   Baldwin, J.; Urban, F. *J. Chem. Soc. Chem. Comm.* **1970**, 165.

[100] Clark, J. S. *Nitrogen Oxygen and Sulfur Ylide Chemistry* (Practical Approach in Chemistry Series), Oxford Press, **2002.**

[101] for reviews see; a) Li, A-H.; Dai, L-X.; Aggarwal, V. *Chem Rev.* **1997**, *97*, 2341; (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

[102] a) Sommelet, M. *Compt. Rend.* **1937**, *205*, 56; b) Kantor, S. W.; Hauser, C. R. *J. Am. Chem. Soc.* **1951**, *73*, 4122.

[103] Mageswaran, S.; Ollis, O.; Sutherland, I. *J. Chem. Soc. Chem. Comm.* **1973**, 656.

[104] Workman, J. *PhD Thesis, University of Reading*, **2004**, Sigmatropic Rearrangements; Studies Towards the Asymmetric Synthesis of Neuroexcitatory Amino-Acids.

[105] Sweeney, J. B.; Tavassoli, A.; Cartera, N. B.; Hayes, J. F. *Tetrahedron,* **2002**, *58*, 10113.

[106] Burns, B.; Coates, B.; Neeson, S.; Stevenson, P. *Tetrahedron Lett.* **1990**, *31*, 4351.

[107] a). Panouse, J. *Bull. Soc. Chim. France,* **1953**, D.60; b) Wenkert, E.; Massy-Westropp, R.A.; Lewis, R. *J. Am. Chem. Soc.* **1962**, *84*, 3732; c) Fry, E.; May, E. *J. Org. Chem.* **1961**, *26*, 2592.

[108] Gilchrist, T. *Heterocyclic Chemistry*, 3rd Ed., Addison Wesley Longman, **1992**, 150.

[109] Blough, B. E.; Carroll, F. I. *Tetrahedron Lett.* **1993**, *34*, 7239.

[110] Wenkert, E.; Dave, K. G.; Haglid, F.; Lewis, R. G.; Oishi, T.; Stevens, R. V.; Terashima, M. *J. Org. Chem.* **1968**, *33*, 747.

[111] Anderson, P. S.; Krueger, W. E.; Lyle, R. E. *Tetrahedron Lett.* **1965**, *6*, 4011.

[112] Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, Wiley-VCH, New York, **1995**, 272.

[113] Marek, J.; Stodulka, P.; Cabal, J.; Soukup, O.; Pohanka, M.; Korabecny, J.; Musilek, K.; Kuca, K. *Molecules,* **2010**, *15*, 1967.

[114] a) Zinke, T. *Justus Liebigs Ann. Chem.* **1903**, *330*, 361; b) Zinke, T. *Justus Liebigs Ann. Chem.* **1904**, *333*, 296.

[115] Li, J. J. *Name Reactions in Heterocyclic Chemistry,* John Wiley & Sons, **2004**, 355.

[116] Cheng, W-C.; Kurth, M. *Org. Prep. Proc. Int.* **2002**, 34, 585.

[117] for reviews see a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; b) Hoveyda, A.; Zhugralin, A. *Nature*, **2007**, *450*, 243; c) Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

[118] Castarlenas, R.; Vovard, C.; Fischmeister, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 4079.

[119] Sattely, E. S.; Cortez, G. A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526.

[120] Ghost, S.; Ghost, S.; Sarkar, N. *J. Chem. Sci.* **2006**, *118*, 223.

[121] a) Fu, G.; Nguyen, S. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856; b) Hyeok Hong, S.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508.

[122] Ishida, M.; Shinozaki, H. *Br. J. Pharmacol.* **1991**, *104*, 873.

[123] Tsai, C.; Schnider, J. A.; Lehmann, J. *Neurosci. Lett.* **1988**, *92*, 298.

[124] Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1991**, *23*, 2625.

[125] Konno, K.; Hashimoto, K.; Shirahama, H. *Heterocycles* **1992**, *33*, 303.

[261] (a) Hashimoto, K.; Horikawa, M.; Shirahama, H. *Tetrahedron Lett.* **1990**, *31*, 7047; (b) Itadani, S.; Takai, S.; Tanigawa, C.; Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **2002**, *43*, 7777.

[127] Hashimoto, K.; Horikawa, M.; Ishida, M.; Shinozaki, H.; Shirahama, H. *Bioorg. Med.* Chem. Lett. **1992**, 2, 743.

[128] Sançon, J. *PhD Thesis, University of Reading*, **2004**, *Expanding the Scope of the [2,3]-Sigmatropic Rearrangement of Cyclic Ammonium Ylids.*

[129] Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015.

[130] Tran, F. *PhD Thesis, University of Reading*, **2009**, *Catalytic Asymmetric Synthesis of Pyrrolidine Carboxylic Acids via Tandem Heck Reaction-[2,3]-Sigmatropic Rearrangement.*

[131] Shibasaki, M.; Vogl, E.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533.

[132] Travassoli, A. *PhD Thesis, University of Reading*, **1999**, Factors Affecting the [2,3]-sigmatropic Rearrangement of Didehydropiperidinium Ylids.

[133] Mills, W; Parkin, J; Ward, W. *J. Chem. Soc.* **1927**, 2613.

[134] Bhanage, B; Zhao, F; Chirai, M; Arai, M. *Catal. Lett.* **1998**, *54*, 195.

[135] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

[136] de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M. ; Henderickx, H. J. W.; de Vries, J. G.*Org. Lett.* **2003**, *5*, 3285.

[137] Heck, R. F.; Nolly, J. *J. Org. Chem.* **1972**, *37*, 2320.

[138] Jeffery, T.; Galland, J-C. *Tetrahedron Lett.* **1994**, *35*, 4103.

[139] a) Schmidt, A.; Al Halaiqa, A.; Smirnov, V. *Synlett*, **2006**, 2861; b) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553; c) Phan, N.; van der Sluys, M.; Jones, C. *Adv. Synth., Catal.* **2006**, *348*, 609.

[140] a) Proçkl, S. S.; Kleist, W.; Gruber, M. A.; Kçhler, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1881; b) Prockl, S. s.; Kleist, W.; Koçhler, K. *Tetrahedron,* **2005**, *61*, 9855.

[141] a) Spencer, A., *J. Organomet. Chem.* **1983**, *258*, 101; b) Borhade, S.; Waghmode, S. *Indian J. Chem.*, **2008**, *47B*, 1549; c) Islam, M.; Mondal, P.; Tuhina, K.; Roy, A. *J. Braz. Chem. Soc,* **2011**, *2*, 319; d) Charette, A.B.; *Electronic Encyclopedia of Reagents for Organic Synthesis (e-EROS)*, Wiley and Sons, Chichester, **2007**.

[142] Pelletier, G.; Larivée, A,; Charette, A. b. *Org. Lett.* **2008**, *10*, 4791.

[143] Alami, M.; Amatore, C.; Bensalem, S.; Choukchou-Brahim, A.; Jutand, A. *Eu. J. Inorg. Chem.* **2001**, *10*, 2675.

[144] Tsuji, J. *Palladium Reagents and Catalysts; Innovations in Organic Synthesis*, Wiley and Sons, New York, **1997**.

[145] Knowles, J.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31.

[146] Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron*, **2001**, *57*, 9225;

[147] Singh, B. K.; Kaval, N.; Tomar, S.; Van der Eycken, E.; Parmar, V. S. *Org. Proc. Res. Dev.* **2008**, *12*, 468.

[148] Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

[149] Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717.

[150] a) Larhed, M.; Hallberg, A. *Drug Discovery Today,* **2001**, *6*, 406; b) Strauss, C.; Trainor, R. *Aust. J. Chem.* **1995**, *48*, 1665; c) Elander, N.; Jones, J.; Lu, S.; Stone-Elander, S. *Chem. Soc. Rev.* **2000**, *29*, 239.

[151] a) Bergbreiter, D.; Furyk, S. *Green Chem.* **2004**, *6*, 280; b) Xie, X.; Lu, J.; Chen, B.; Han, J.; She, X.; Pan, X. *Tetrahedron Lett.* **2004**, *45*, 809; c) Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N.; Kappe, C. O. *Org. Proc. Res. Dev.* **2003**, *7*, 707; d) Vallin, K. S. A.; Emilsson, P.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6243 e) Diaz Ortiz, A.; Prieto, P.; Vazquez, E. *Synlett,* **1997**, 269; f) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582.

[152] Arvela, R. K.; Leadbeater, N. E.; Collins, M. J. *Tetrahedron*, **2005**, *61*, 9349.

[153] Wang, J.; Hu, Z.; Wei, B.; Bai, L. *J. Chem. Res.* **2000**, 484.

[154] Villemin, D.; Nechab, B. *J. Chem. Res.* **2000**, 429.

[155] a) Moritani, I.; Fujiwara, Y. *Synthesis*, **1973**, 524; b) Fujiwara,Y. *Handbook of Organopalladium Chemistry in Organic Synthesis Vol. 2,* Wiley, New York, **2002**, 2863; c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633; d) Fujiwara, Y.; Jia, C. *Pure Appl. Chem.* **2001**.

[156] a) Fujiwara, Y.; Noritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166; b) Moritani, I.; Fujiwara, Y.*Tetrahedron Lett.* **1967**, *8*, 1119.

[157] Sun, P.; Zhu, Y.; Yang, H.; Yan, H.; Lu, L.; Zhang, X.; Mao, J. *Org. Biomol. Chem.* **2012**, *10*, 4512.

[158] Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5531.

[159] Parrish, J. P.; Jung, Y. C.; Shin, S. I.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 7127.

[160] Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 7893.

[161] Matoba, K.; Motofusa, S.; Cho, C.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **1999**, *574*, 3.

[162] Inoue, A.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 1484.

[163] Dieck, H.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083.

[164] Cho, C.; Uemura, S. *J. Organomet. Chem.* **1994**, *465*, 85.

[165] Lindh, J.; Enquist, P-A.; Pilotti, A.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 7957.

[166] Yoo, K.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384.

[167] Penn, L.; Shpruhman, A.; Gelman, D. *J. Org. Chem.* **2007**, *72*, 3875.

[168] Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231.

[169] a) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A. *Org. Lett.* **2001**, *3*, 3313; (b) Hirabayashi, K.; Ando, J.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1409.

[170] Hirabayashi, K.; Ando, J.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1409.

[171] Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2005**, *44*,

3125.

[172] Donets, P.; Van der Eycken, E. *Synthesis*, **2011**, 2147.

[173] Chapman, H. University of Reading, **2007**, *Unpublished.*

[174] Schäfer, S.; Frey, W.; Hashmi, S.; Cmrecki, V.; Luquin, A.; Laguna, M. *Polyhedron,* **2010**, *29*, 1925.

[175] Kosower, E. M. *J. Am. Chem. Soc.* **1955**, *77*, 3883.

[176] Park, K.; Han, D.; Shin, D. Bull. *Korean. Chem. Soc. 1986, 7*, 201.

[177] Robertson, L.; Hartley, R. C. *Tetrahedron,* **2009**, *65*, 5284.

[178] Moriconi, E. J.; Misner, R. E. *J. Org. Chem.* **1969**, *34*, 3672.

[179] a) Grierson, D. S.; Harris, M.; Husson, H. P. *J. Am. Chem. Soc.* **1980**, *102*, 1064; b) Liberatore, F.; Casini, A.; Carelli, V. *J. Org. Chem.* **1975**, *40*, 559.

[180] Method adapted from Thut, C. C.; Bottini, A. T. *J. Am. Chem. Soc.* **1968**, *90*, 4752.

[181] Method adapted from Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis,* **1982**, 138.

[182] Method adapted from Zou, Y.; Chen, C-H.; Taylor, C.; Foxman, B.; Snider, B. *Org. Lett.* **2007**, *9*, 1825.

[183] Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

[184] (a) Studer, A.; Amrein, S. *Synthesis*, **2002**, 835; (b) Baguley, P.; Walton, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 3072.

[185] Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081.

[186] Hayashi, Y.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 63.

[187] Wang, Y-M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F.D. *J. Am. Chem. Soc.* **2011**, *133*, 12972 (SI Proc C).

[188] Westrum, L. *Fine Chemistry*, **2002**, 10.

[189] Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449.

[190] Rottländer, M.; Boymond, L.; BeÂrillon, L.; Lepretre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; QueÂguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 767.

[191] (a) Boudier, A.; Bromm, L.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Anh Vu, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.

[192] Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

[193] Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.