The University Of Sheffield.

Synthesis of Amino Acids using Organometallic Chemistry

A Dissertation Submitted for the Degree of Doctor of Philosophy

by

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of

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Contents

Declaration

This dissertation records the work carried out in the Department of Chemistry, University of Sheffield between October 2009 and September 2013 is original except where acknowledged by reference. No portion of this work is being, or has been submitted for a degree, diploma or any other qualification at any other university.

Acknowledgements

Undertaking my PhD has been both a challenging and rewarding experience that has only been made possible by the huge amount of support and guidance that I received from many people.

I would firstly like to thank my supervisor, Professor Richard Jackson, for giving me the opportunity to work in his group and for all the patient guidance, encouragement and support that he has provided over the past few years.

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Work wouldn't have been the same without trips to the tearoom with the Coldham group. A special thanks to Pauline and Sharon for maintaining my caffeine levels and always being there for a chat.

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There have been some very stressful moments in my PhD and I wouldn't have gotten through them so well without the help of my fellow PhD housemates Georgia, Jason and Lara. Thank you for making life thoroughly enjoyable.

Without the generosity of my boyfriend Alex (and his housemates), allowing me to live with him for free for the final stages of my PhD, life would have been more difficult. For that, putting up with my elevated stress levels, doing all my last minute proof reading and trying to keep things light, thank you very much.

Finally I would like to thank my Mum, Dad, Frances and Joseph for supporting and encouraging me all the way through my university career. I will be forever grateful for the emergency packages from my parents and grandma to 'keep the wolf at the door'.

Abbreviations

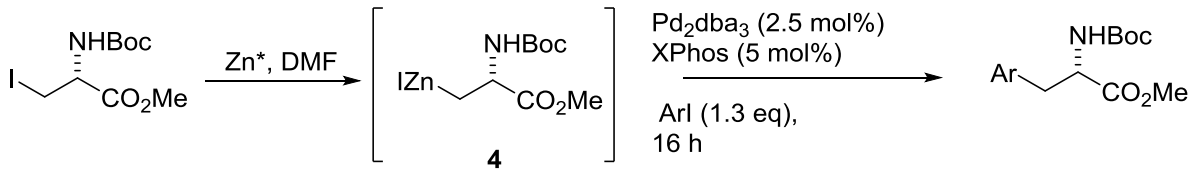
)))	Sonicate
Ac	Acetyl
Ar	Aryl
BQ	Benzoquinone
Boc	*tert*-Butyl carbamate
BSA	*N*, *O*-Bis-trimethylsilylacetamide
Bu	Butyl
cat.	Catalytic
Cy	Cyclohexyl
d	Doublet
Dba	Tris(dibenzylideneacetone)
DCB	Dichlorobenzene
dd	Doublet of doublets
DIBAL	Di-isobutyl aluminum hydride
DFT	Density Functional Theory
DG	Directing group
DMA	*N*, *N*-Dimethylacetamide
DMB	Dimethoxybenzyl
DMF	*N*, *N*-Dimethylformamide
dr	Diastereomeric ratio
ee	Enantiomeric excess
eq.	Equivalents

Et	Ethyl
FG	Functional group
h	Hour
Hz	Hertz
IR	Infra red
I	Iso
Im	Imidazole
J	Coupling constant in Hz
m	Meta
m	Multiplet
M	Metal
Me	Methyl
min	Minutes
m/z	Mass/Charge ratio
m.p.	Melting point
MS	Mass spectrometry
NMR	Nuclear Magnetic Resonance
o	Ortho
o/n	Over night
P	para
PG	Protecting group
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
Pv	Pivaloyl
Py	Pyridine

q	Quartet
R_f	Retention factor
rt	Room temperature
sm	Starting material
t	Triplet
TBAB	Tetra-*n*-butylammonium bromide
TBDMS	*Tert*-butyldimethylsilyl
Tert	Tertiary
THF	Tetrahydrofuran
TIPS	triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
tol	Tolyl
UV	Ultra Violet
Z	Benzyloxycarbonyl
Zn*	Activated zinc
δ	Chemical Shift
ν_{max}	Frequency maximum

Abstract

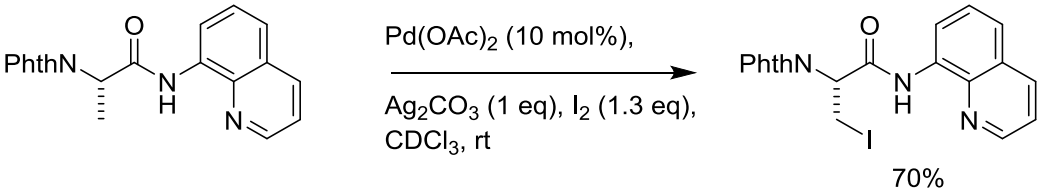
It has been established that a combination of Pd_2dba_3 and XPhos in a ratio of 2:1 is an efficient precatalyst for the Negishi cross-coupling reaction between the organozinc reagent **4** derived from iodoalanine and aromatic halides (Scheme 2.9). The yields from these reactions show improvement of 5-30 % on those previously obtained using SPhos.



Scheme 2.9: Negishi cross-coupling reaction of organozinc reagent 4 and aryl iodides

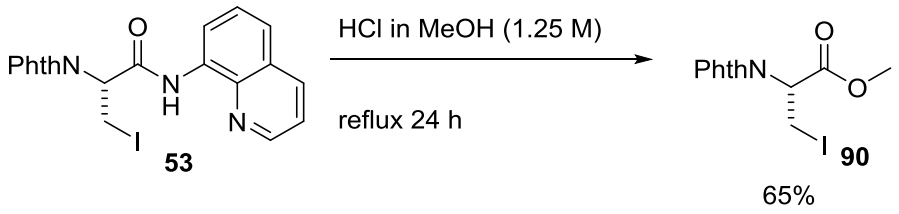
The use of Pd_2dba_3 and XPhos in the challenging cross-coupling reactions of organozinc reagent **4** and electron-rich halothiophenes has also had some success. Specifically reactions between thiophene halides with **4** have been achieved in yields of 50-65% compared to the low yields previously obtained using alternative phosphine ligands.

This thesis describes the development and successful scaling of the side chain, C-H activation and iodination reaction of alanine up to a 10 mmol scale, giving large scale reproducible results that were previously unobtainable (Scheme 3.24).



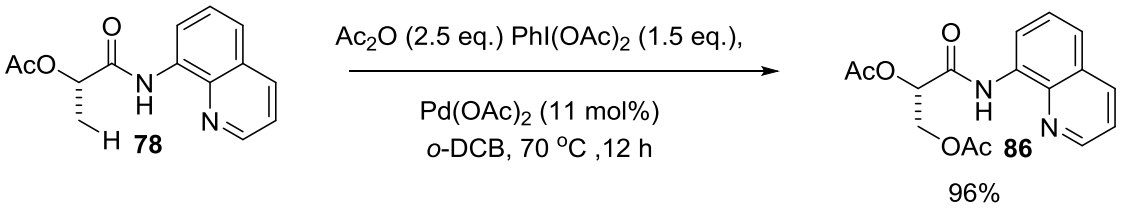
Scheme 3.24: Side chain iodination of alanine.

Cleavage of the 8-aminoquinoline group has successfully been achieved to afford the methyl ester (Scheme 3.81), from which phenylalanine derivatives can be synthesised using Negishi cross-coupling conditions.



Scheme 3.81: Removal of the 8-aminoquinoline group using conditions employed by Chatani and co-workers.

Lactic acid derivative **78** has successfully undergone a C-H activation and acetoxylation reaction to give the glyceric acid derivative **86** in excellent yield to give the first reported example of catalytic C-H activation on lactic acid derivatives (Scheme 3.68).

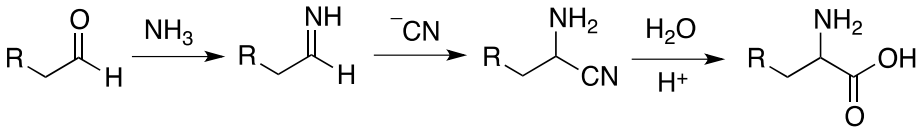


Scheme 3.68: Acetoxylation of lactic acid derivative 78.

1. Synthesis of α-Amino Acids

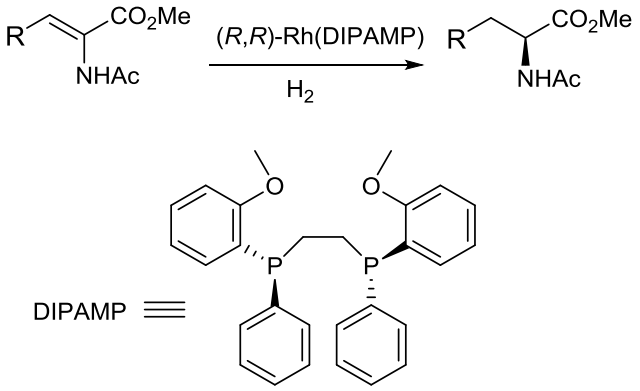
There has been much, well reviewed development in the synthesis of enantiopure α-amino acids; however it still poses an ongoing challenge within the field of organic chemistry. There are many general methods for synthesising enantiopure α-amino acids utilising chiral auxiliaries, chiral catalysts and the chiral pool.[1,2]

The first reported synthesis of an amino acid was the Strecker reaction which was discovered in 1850 on the formation of racemic alanine from acetaldehyde (Scheme 1.1).[3] The reaction proceeds by condensation of the aldehyde or ketone with ammonia to give an imine which then undergoes nucleophilic attack from a cyanide ion forming the α-amino nitrile. This can then be hydrolysed to give the desired amino acid product. More recently conditions have been developed allowing for the reaction to be carried out both catalytically and asymmetrically on a wide range of substrates with chirality being induced by the use of chiral catalysts, chiral auxiliaries or by chiral resolution of the racemic product.[4]



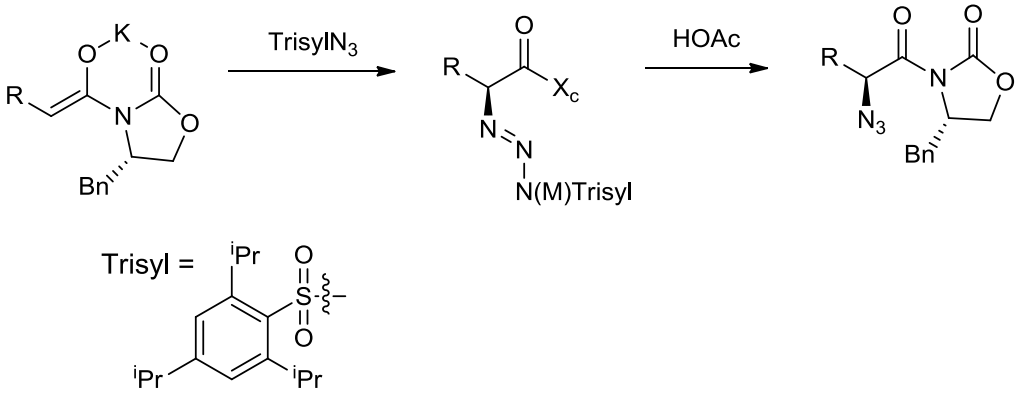
Scheme 1.1: Strecker synthesis of amino acids.

A second efficient route to enantiomerically pure amino acids is the catalytic asymmetric hydrogenation of the corresponding dehydroamino acids. This approach was originally pioneered by Knowles using α-acylaminoacrylic acids as substrates with chiral rhodium bisphosphine catalysts, for which he was awarded a part-share in the Nobel Prize in 2001 (Scheme 1.2). [5]



Scheme 1.2: Asymmetric hydrogenation of *α*-acylaminoacrylic acids.

A third approach for the synthesis of enantiopure amino acids is the electrophilic azidation of chiral imides, an example of which was developed by Evans and co-workers (Scheme 1.3). This method employs a chiral auxiliary to promote the diastereoselective formation of *α*–azido carboximides.[6]



Scheme 1.3: Azidation of chiral imides by Evans and co-workers.

A final route to the synthesis of amino acids is use of glycine *α*-anion equivalents, an example of which is the benzophenone imine **1** of a glycine alkyl ester (Figure 1.1). Following deprotonation the *α*-anion can undergo alkylation providing a simple method of accessing unnatural amino acids. In

this case the stereochemistry can be controlled by use of a chiral phase transfer catalyst such as compound **2**.[7]

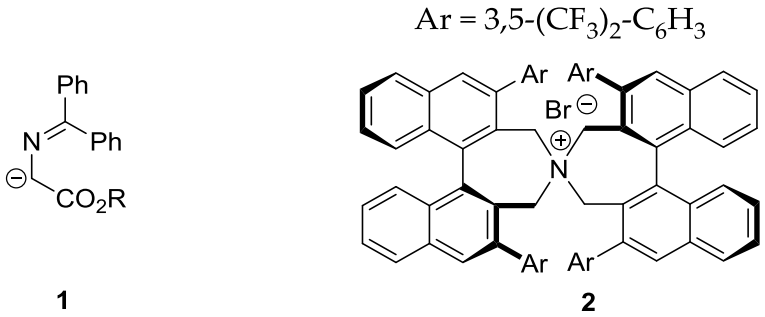
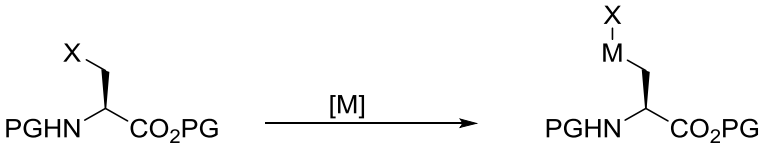


Figure 1.1: Glycine α-anion equivalent and chiral phase transfer catalyst.

A disadvantage of the methods discussed is the requirement for chirality to be induced in the resulting products. A simpler means of achieving the synthesis of enantiopure compounds would be to use naturally occurring amino acid starting materials from the chiral pool, allowing the already defined stereocentre to be carried through to the product. One way to achieve this is through the use of organometallic reagents derived from natural amino acids (Scheme 1.4).



Scheme 1.4: Organometallic reagent derived from natural amino acids

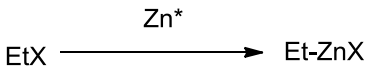
This thesis will focus on the formation of amino acid derived organometallic reagents for the synthesis of unnatural enantioenriched amino acids.

2. Development of Negishi Cross-Coupling Conditions

2.1 Introduction

2.1.1 Synthesis of Organozinc Reagents

Organozinc reagents can be made by two possible methods. The first uses a transmetallation reaction of an organometallic reagent such as a Grignard reagent, with a zinc halide. Nonetheless, owing to the Grignard reagent's relatively low functional group tolerance it has limited applicability. The second more preferable method is the direct insertion of elemental zinc into a carbon-halogen bond (Scheme 2.1). This was inadvertently discovered by Frankland in 1849 when the reaction between ethyl iodide and zinc metal produced diethylzinc.[8]



Scheme 2.1: Formation of diethylzinc by Frankland and co-workers.

Formation of an organozinc reagent can be difficult if the zinc is not first activated. This can be attributed to two main causes, the first being an outer oxide layer that is formed on the zinc on exposure to air. The second factor that can contribute to low reactivity of the zinc reagent is the particle size. Smaller particles have a larger surface area to mass ratio which allows more effective insertion of the zinc into the carbon-halogen bond.

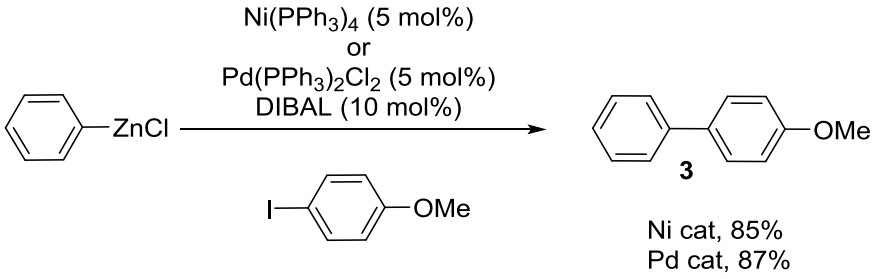
There are a number of techniques available for activating zinc such as washing with aqueous HCl, sonication and using a Zn-Cu couple.[9] A method employed by the Knochel group is the treatment of zinc powder with catalytic 1,2-dibromoethane followed by trimethylsilyl chloride in THF.[10] This has been subsequently modified by the Jackson group who established that trimethylsilyl chloride by itself in DMF produced effective conditions for the activation of zinc powder.[11]

An alternative method now routinely used in the Jackson group has been developed by Huo and co-workers.[12] This involves the use of catalytic iodine in DMF with zinc powder and works by small areas of exposed zinc metal on the surface reacting with the iodine in solution and forming zinc iodide. The zinc iodide goes into solution leaving a larger exposed surface area of zinc that can then insert into the desired carbon-halogen bond.

The high functionality tolerance of organozinc reagents does have a disadvantage in that they are relatively unreactive towards standard electrophiles in comparison with alternative organometallic species. This can be surmounted by the addition of a catalyst to the reaction which allows the organozinc reagents to undergo transmetallation.

2.1.2 Palladium Catalysed Negishi Cross-coupling

In 1977 the first organozinc cross-coupling was reported by Negishi and co-workers, who found that the reaction of phenylzinc chloride with 4-iodoanisole in the presence of either 5 mol% $Ni(PPh_3)_4$ or 5 mol% $Pd(PPh_3)_2Cl_2$ gave the biaryl **3** in 85% and 87% respectively (Scheme 2.2).[13]



Scheme 2.2: First organozinc cross-coupling.

Continuing from this, much research has been undertaken to further develop the Negishi cross-coupling reaction. The methodology has been extended to include organozinc reagents derived from sp^2, sp^3 and secondary carbon-halogen bonds.[14,15]

2.1.3 Mechanism

It is generally agreed that the Negishi cross-coupling reaction proceeds via three main steps; oxidative addition whereby the palladium inserts into the carbon–halogen bond, transmetallation where an alkyl group is transferred from the organozinc reagent onto the palladium centre, and reductive elimination to form the desired cross-coupled product. More recently however, DFT calculations undertaken by Wu and co-workers have suggested that there is a second transmetallation which accounts for the formation of homo-coupled and dehalogenation products as sometimes observed (Figure 2.1).[16]

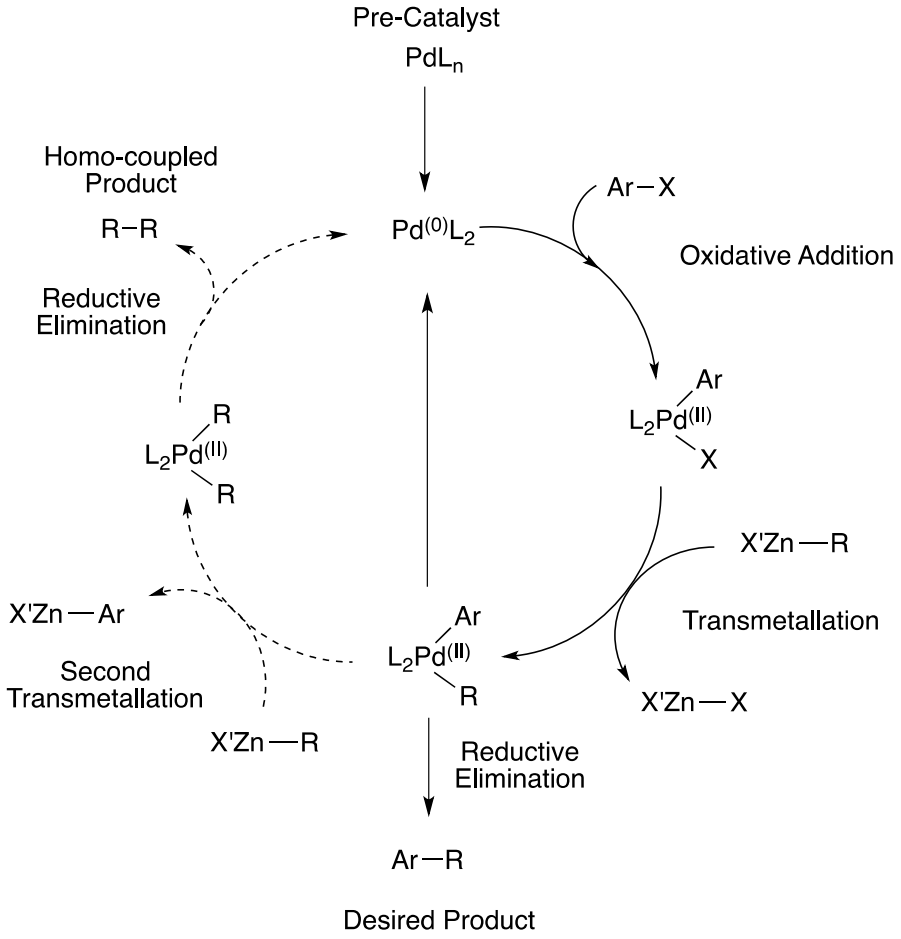
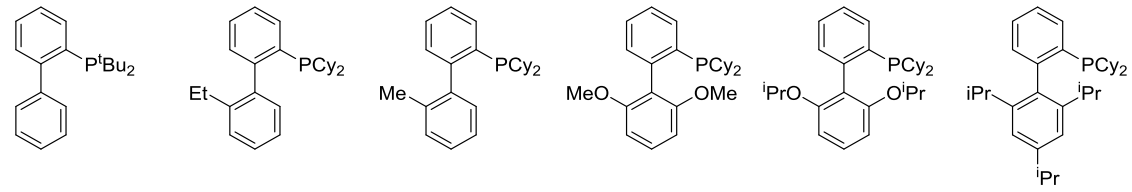


Figure 2.1: Mechanism for Negishi cross-coupling reactions.

2.1.4 Phosphine Ligands

Phosphine ligands were initially used as a way of solubilising and stabilising the palladium catalyst, however they have recently been developed to also increase the activity of the catalyst. Ligands can moderate both the steric and electronic environment surrounding the palladium centre. There are a large range of ligands that have been used in palladium catalysis. Electron rich, sterically crowded biaryl phosphine ligands developed by the Buchwald group[17] are some of the most commonly used as they have been found to produce more active catalysts in combination with a palladium source in a number of reactions (Figure 2.2).[18,19]



JohnPhos **SPhos** **RuPhos** **XPhos**

Figure 2.2: Biaryl phosphine ligands developed by Buchwald and co-workers.

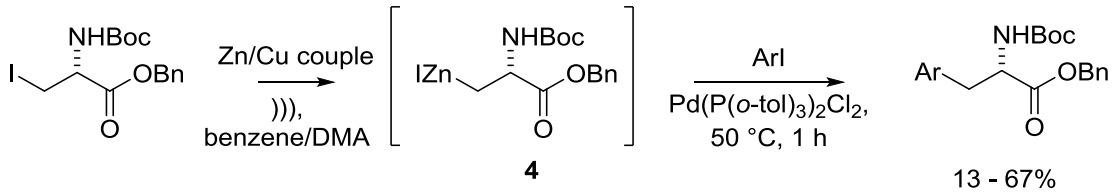
It is thought that the high activity of these phosphine ligands could be due to the enhancement of the oxidative addition step of the catalytic cycle owing to the high electron density on the ligand, which can be transferred to the palladium. In addition to this, it is possible that the rate of the reductive elimination step is improved by the increased steric bulk of the ligand. Due to this improved reactivity of the phosphine ligands, it means cross-couplings can be undertaken more effectively with lower loadings of palladium.

2.1.5 Jackson Group Development of Negish Cross-Coupling Conditions

The Jackson group has undertaken extensive development of Negishi cross-coupling conditions, primarily for the synthesis of phenylalanine derivatives. The coupling of iodoalanine derived organozinc reagent **4** with a range of aryl iodides has been optimised by varying the palladium source, the phosphine source and the method of zinc activation.

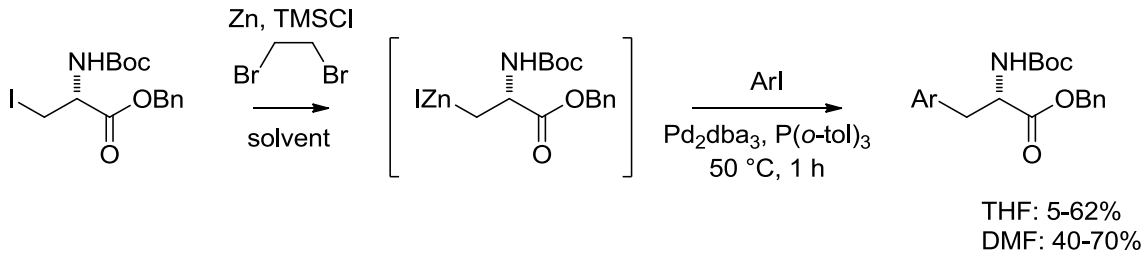
The first generation cross-coupling conditions were reported in 1989, using a zinc-copper couple in DMA and benzene under ultrasound irradiation to form organozinc reagent **4**.[20] The preformed Pd/phosphine catalyst, $PdCl_2(P(o\text{-}tol_3))_2$, was then added and **4** coupled with a range of aryl iodides (Scheme 2.3). Notably, the palladium source exists in oxidation state 2+

although the active catalytic species which takes part in the Negishi catalytic cycle is palladium in oxidation state 0. This means the palladium source must first be reduced before the cross-coupling can occur. The yields of these products were variable (13-67%, based on iodoalanine) with *ortho*-substituted aromatics proving problematic.



Scheme 2.3: The first generation of Jackson cross-coupling conditions.

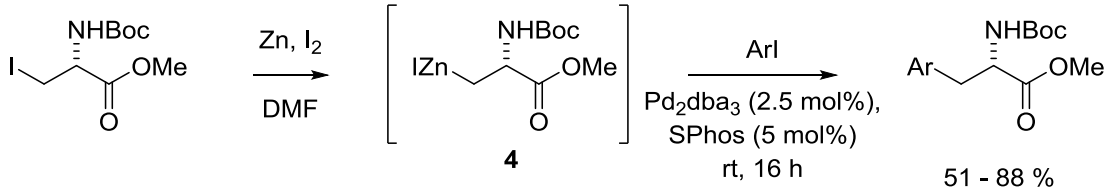
The second generation cross-coupling conditions were reported in 1992, altering not only the palladium source and the solvent but also the method of zinc activation (Scheme 2.4).[21] The palladium source was changed from $PdCl_2(P(o\text{-}tol_3))_2$ to $Pd_2(dba)_3$ obviating the need for the *in situ* reduction of the palladium to its active state. The phosphine ligand remained the same, but in this case was added separately in a 2:1 ratio to palladium. Zinc activation was achieved by a method developed by Knochel and coworkers using TMSCl and 1,2 dibromoethane.[10] Using THF was found to give improved yields compared with those previously obtained (5 - 62%). Subsequent work in the group found that using DMF instead of THF, again improved the yields (40-70%). This has been explained by the increased stability of the organozinc reagent in the presence of DMF compared to THF.[22]



Scheme 2.4: The second generation of Jackson cross-coupling conditions.

The third and final generation cross-coupling conditions arose through use of biaryl phophine ligands by Buchwald and co-workers (Figure 2.2) which have been found, in combination with a palladium source, to display high catalytic activity in a number of cross-coupling reactions.[23,24]

This work encouraged the Jackson group to undertake their own investigations into the use of SPhos and other Buchwald ligands in the Negishi cross-coupling of the organozinc reagent **4** and aryl halides (Scheme 2.5).[18] Zinc activation was achieved using the method developed by Huo and co-workers, using iodine and zinc powder.[12] The cross-coupling using a combination of $Pd_2(dba)_3$ with SPhos gave much improved yields, with the reaction proceeding at room temperature. It should also be noted that for some of the haloaromatics the catalyst loading could be dropped to 0.5 mol% and still produce comparable yields to the higher catalyst loading of 5 mol%. The lower yields observed tended to occur in couplings with either electron rich or *ortho*-substituted aromatics.



Scheme 2.5: The third generation of Jackson cross-coupling conditions.

It was discovered that the reaction worked better with a 1:1 ratio of phosphine to palladium, as opposed to the usual requirement for a 2:1 ratio. This may be because SPhos is able to act as a bidentate ligand forming a highly active catalyst for the cross-coupling reaction (Figure 2.3). Mixed-donor ligands, such as the P-O type ligands SPhos and RuPhos are hemilabile incorporating both hard donor sites (methoxy oxygen) and soft donor sites (arene carbons) in addition to the phosphorous centre. The stabilisation provided by the palladium-ligand species arises not only due to coordination of the phosphorus to palladium but also from extra stabilisation by either the *ipso*-carbon or the methoxy group. DFT calculations performed by Barder and co-workers have shown that the lowest energy conformation for the SPhos-palladium species changes when the palladium is oxidised from Pd(0) to Pd(II).[25] When the palladium is in oxidation state 0, there is an unusual coordination between the *ipso*-carbon of the bottom phenyl ring and the palladium centre. However, after oxidative addition, stabilisation occurs due to the coordination of the lone pairs on the oxygen to the palladium (II) centre (Figure 2.3). There is other spectroscopic evidence for this coordination behaviour including metal-ligand crystal structures and ^{31}P NMR data.[23,25]

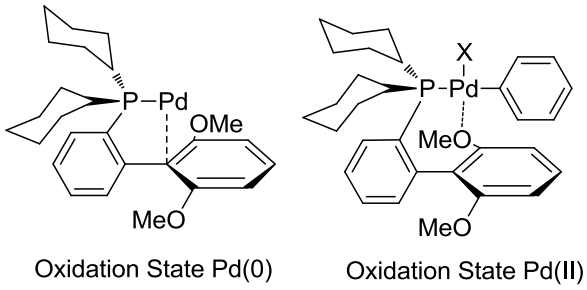
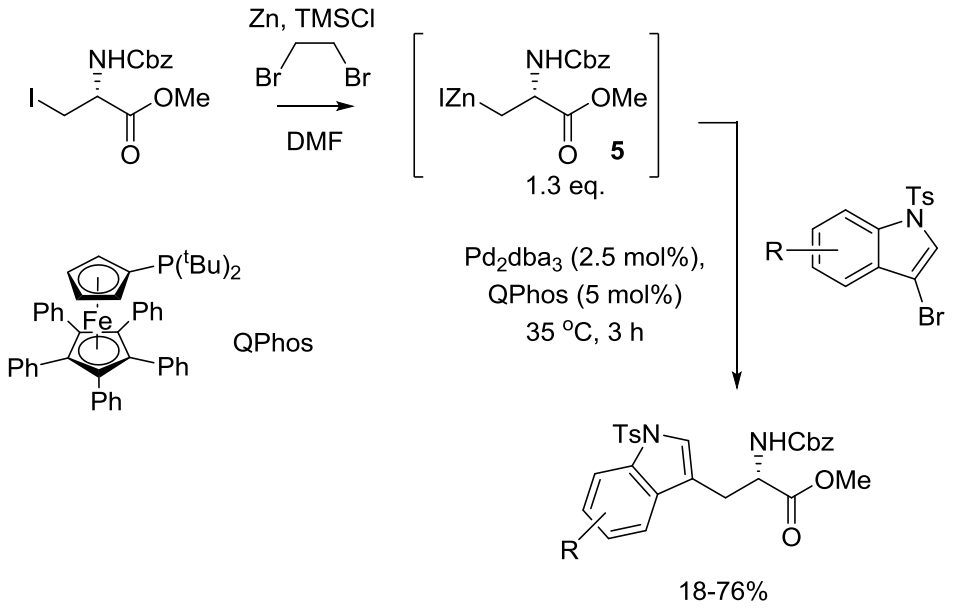


Figure 2.3: Lowest energy conformations for the SPhos-palladium species.

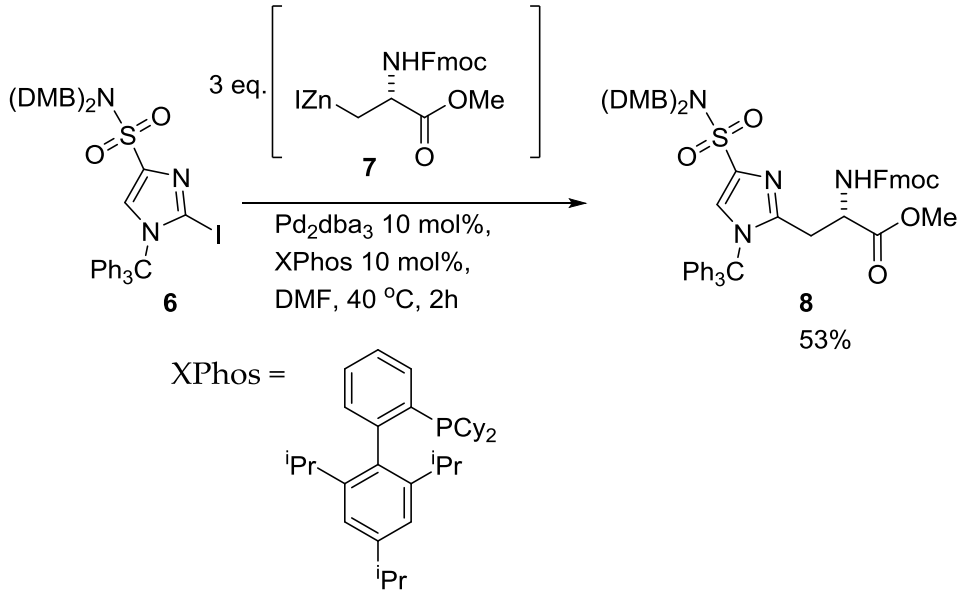
2.1.6 Negishi Cross-Coupling with Electron-Rich Electrophiles.

Negishi cross-coupling reactions with electon-rich electrophiles still pose a challenge due to the reduced reactivity of the palladium species towards transmetallation, however there has been some recent progress made in the area. Yokoyama and co-workers have developed Negishi cross-coupling conditions for the synthesis of electron rich tryptophan derivatives, using organozinc reagent **5** and substituted 3-bromoindoles (Scheme 2.6).[26] A series of Pd/phosphine combinations was applied to the coupling of 3-bromoindole to **5**, including the $Pd_2(dba)_3$/SPhos system developed by Jackson and co-workers which they reported to only give a moderate yield (43%) of the desired product. It was found that using QPhos with $Pd_2(dba)_3$ in a 1:1 ratio of phosphine to palladium and an excess of organozinc reagent **5** gave a yield of 66%. These conditions were applied to the synthesis of a range of substituted tryptophan derivatives giving yields of 18-76%.



Scheme 2.6: Synthesis of tryptophan derivatives using $Pd_2(dba)_3$/QPhos catalysed Negishi cross-coupling reaction.

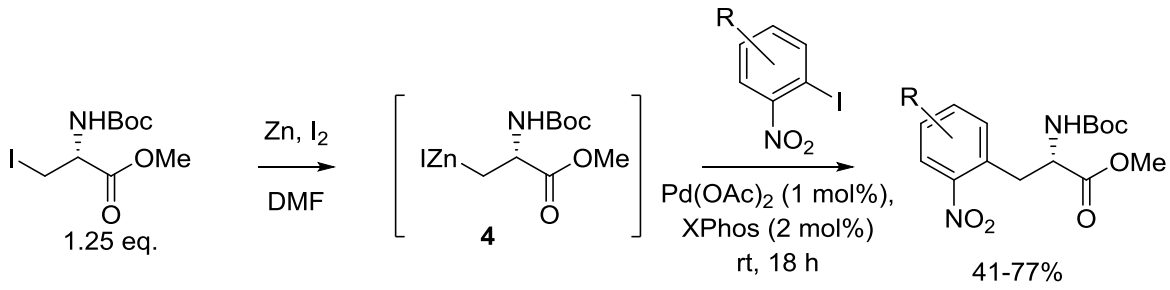
Hedberg and co-workers have reported the cross-coupling of 2-iodoimidazole **6** with iodoalanine derived organozinc reagent **7** (Scheme 2.7).[27] Initial attempts using a variety of palladium sources with triphenylphosphine and P(*o*-tol)$_3$ gave low yields. However, on using XPhos with 3-fold excess of **7**, a moderate yield of desired product **8** was obtained.



Scheme 2.7: Negishi cross-coupling of 2-iodoimidazole 6 with organozinc reagent 7.

2.1.7 Negishi Cross-Coupling Reactions with *Ortho*-Substituted Aromatics

Negishi cross-coupling reactions with *ortho*-substituted aromatics are more difficult due to steric hindrance. Recently Tuttle and co-workers have investigated Negishi cross-coupling reactions with organozinc reagent **4** and *ortho*-nitrobenzene derivatives which have traditionally been lower yielding (Scheme 2.8).[28] The cross-coupling reaction of organozinc reagent **4** and *ortho*-nitrobenzene was examined varying the phosphine ligands used (RuPhos, SPhos and XPhos) in a 2:1 ratio with $Pd(OAc)_2$. Of these XPhos was found to be the superior ligand, giving the highest yield of 92% when using 1.5:1 ratio of the organozinc reagent to the haloaromatic coupling partner. It should be noted that the organozinc reagent is not the limiting reagent in work that has been undertaken by the Jackson group.[18] The reaction conditions were applied to a range of substituted *ortho*-iodonitrobenzenes to give yields in the range of 41-77%.

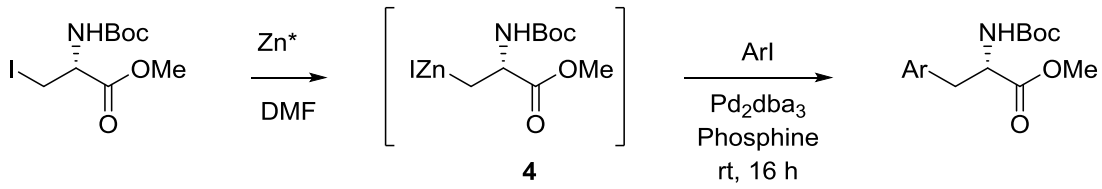


Scheme 2.8: Cross-coupling reaction of organozinc reagent 4 and *ortho*-nitrobenzene derivatives by Tuttle and co-workers.

2.2 Aims

Work previously carried out in the Jackson group has shown that using SPhos and Pd_2dba_3 in the Negishi cross-coupling reaction between organzinc reagent **4** and arylhalides gives higher yields of the desired products than previously reported.[18] However the yields of reactions with electron rich and *ortho*-substituted aromatics are still not ideal.

The first aim of the project is to carry out Negishi cross-coupling reactions between organozinc reagent **4** and a range of aromatic iodides using phosphine ligands XPhos or QPhos under standard conditions, to compare the yield with those previously obtained using SPhos (Scheme 2.9).



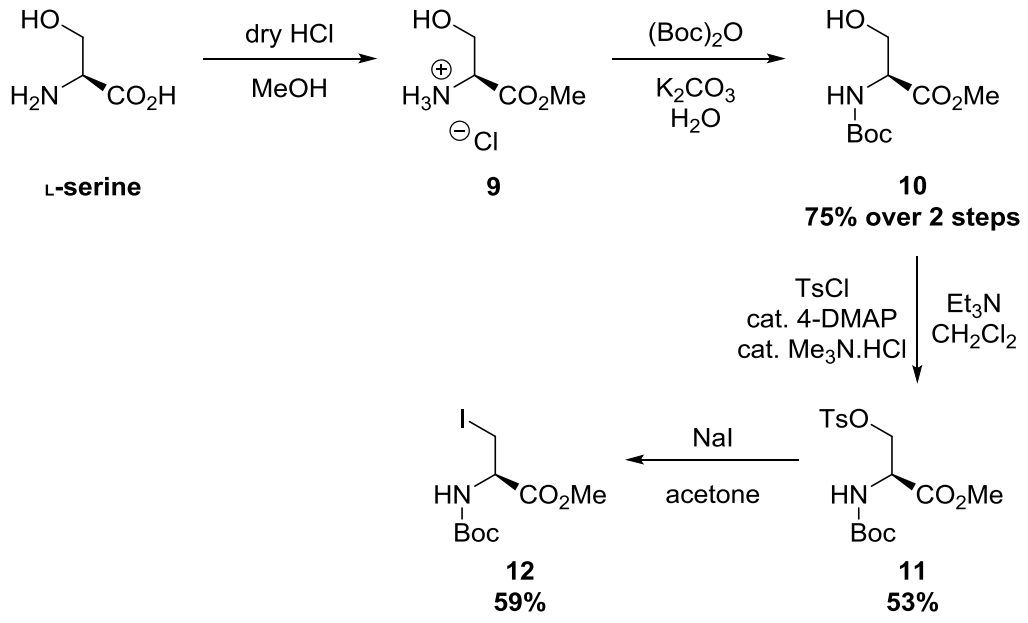
Scheme 2.9: Negishi cross-coupling of organozinc reagent 4 with aryl halides.

A subsequent aim is to investigate the use of XPhos and QPhos in the cross-coupling reaction between a variety of heterocycles and organozinc reagent **4.**

2.3 Results and Discussion

2.3.1 Synthesis of Iodoalanine.

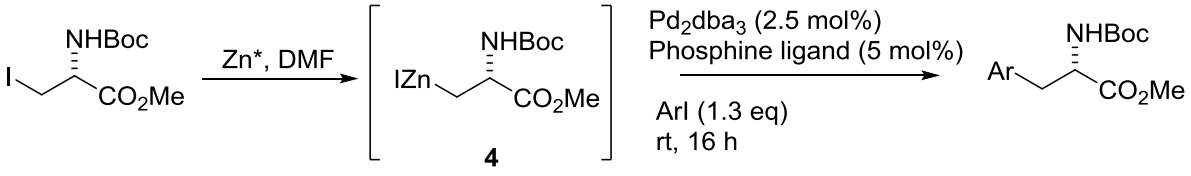
Organozinc precursor protected iodoalanine **12** was synthesised following the literature procedure.[18,29] *L*-Serine was converted to its methyl ester hydrochloride salt **9** by treatment with methanolic HCl (Scheme 2.10).[29] Boc protection of compound **9** using $(Boc)_2O$ in water, with K_2CO_3 as the base, gave *N*-Boc-L-serine methyl ester **10** in a 75% crude yield over two steps. Tosylation of the alcohol **10**, followed by a pseudo-Finkelstein reaction of the resulting tosylate **11** were carried out as reported by Jackson and co-workers,[18] yielding iodide **12** in a 24% overall yield from L-serine.



Scheme 2.10: Synthesis of protected iodoalanine

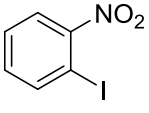
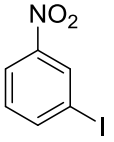
2.3.2 Negishi Cross-Couplings using XPhos

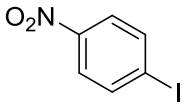
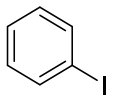
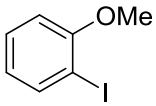
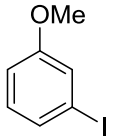
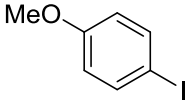
Tuttle and co-workers have shown XPhos to be a superior ligand compared to SPhos and RuPhos in the $Pd(OAc)_2$ catalysed cross-coupling of a range of substituted *ortho*-iodonitrobenzenes with an iodoalanine derived organozinc reagent (Scheme 2.8, page 15). The activity of the XPhos/Pd_2dba_3 catalyst was investigated modifying conditions previously developed in the Jackson group using SPhos. Thus iodoalanine derived organzinc reagent **4** was subjected to the 'high loading' cross-coupling conditions using Pd_2dba_3 (2.5 mol%) and XPhos (5 mol%) with a range of aryl iodides (Scheme 2.9).



Scheme 2.9: Negishi cross-coupling of organozinc reagent 4 with aryl halides.

Table 2.1: High catalyst loading cross-coupling using XPhos.

Entry	ArI	Product	SPhos[a]	XPhos[b]
1[c]		**13**	66	79
2[c]		**14**	53	84

Entry	ArI	Product	SPhos[a]	XPhos[b]
3[c]		**15**	51	83
4		**16**	79	84
5		**17**	66	69
6		**18**	71	75
7		**19**	76	78

[a]Yields obtained previously in the group.[18] [b] Reaction carried out using 2.5 mol% Pd_2dba_3 and 5 mol% XPhos. [c] Organozinc reagent removed from excess zinc.

Initially the cross-coupling of 2-nitro iodobenzene with **3** was carried out to give a direct comparison of the result obtained by Tuttle and co-workers. The desired product **13** was obtained in 79% compared to the 95% reported by Tuttle and co-workers (Table 2.1, Entry 1). This difference in yield can partly be attributed to equivalents of organozinc reagent used. Whereas Tuttle and co-workers used an excess (1.5 eq) this reaction was carried out with **4** as the limiting reagent due to relative cost compared with its coupling partners. More interesting was the notable increase in yield on using XPhos compared to SPhos using the same conditions. With this result in hand, the reaction conditions were applied to the coupling of **4** with 3-nitro and 4-nitro

iodobenzenes (Entries 3 and 4). Pleasingly both reactions gave their respective products **14** and **15** in high yields, exceeding those previously achieved using SPhos by about 30%.

The reaction conditions were further applied to the coupling of **4** with iodobenzene and the relatively electron rich iodoanisoles (Entries 4-7). In all cases the yields were comparable if not slightly improved to those previously seen using SPhos.

The success of the high catalyst loading conditions for the cross-coupling between **4** and the aryl iodides discussed prompted investigation into use of the lower loadings of Pd_2dba_3 (0.25 mol%) and XPhos (0.5 mol%) (Table 2.2).

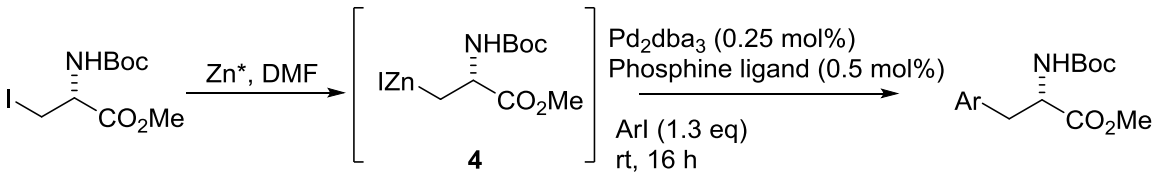
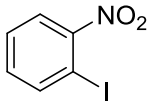
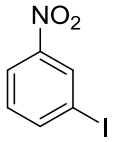
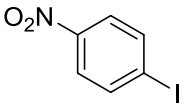
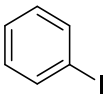
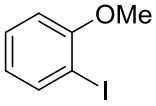
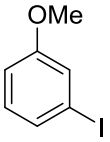
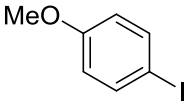


Table 2.2: Low loading cross-coupling using XPhos.

Entry	ArI	Product	SPhos[a]	XPhos[b]
1[c]		**13**	49	59
2[c]		**14**	34	67

Entry	ArI	Product	SPhos[a]	XPhos[b]
3[c]		**15**	38	74
4		**16**	80	81
5		**17**	8	48
6		**18**	67	70
7		**19**	65	68

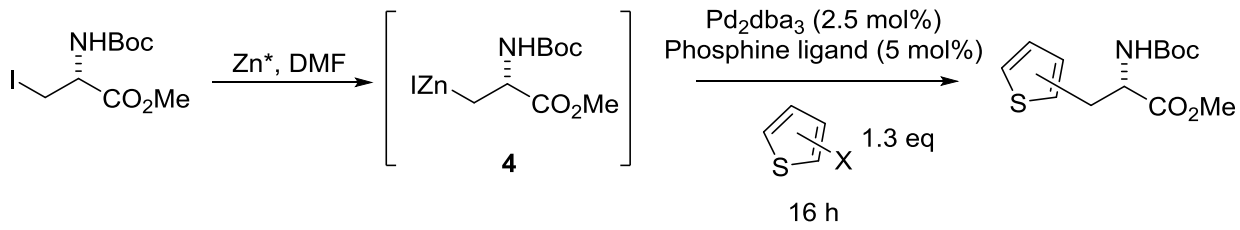
[a]Yields obtained previously in the group.[18] [b] Reaction carried out using 0.25 mol% Pd_2dba_3 and 0.5 mol% XPhos. [c] Organozinc reagent removed from excess zinc.

The cross-coupling reaction between organozinc reagent **4** and nitro iodobenzenes using low loadings of catalyst were used initially (Table 2.2, Entries 1-3). The yields for the reactions using XPhos were higher than those previously found using SPhos, particulary for the *meta-* and *para-* substituted nitrobenzene products **13**, **14** and **15**.

The low catalyst loading conditions were also applied to iodobenzene and the iodoanisoles. As before the desired products were generally obtained in comparable yields to those found using SPhos. However the reaction

between the *ortho*-substituted iodoanisole saw a notable increase in yield of **17** from 8% with SPhos to 40% with XPhos. These results suggest that XPhos forms a more active catalyst with Pd_2dba_3 than SPhos working well at both high and low catalyst loading.

The success of XPhos in the coupling of **4** with the aryl halides discussed previously led to the investigation of the Negishi cross-coupling of **4** with more challenging electron rich heterocycles. In particular, work in the Jackson group has recently looked at the cross-coupling reaction of halothiophenes with organozinc reagent **4** (Scheme 2.11).[30]



Scheme 2.11: Negishi cross-coupling of organozinc reagent 4 with halothiophenes.

Efforts to couple 2-iodothiophene with organozinc reagent **4** using the high loading SPhos (5 mol%)/Pd_2dba_3 (2.5 mol%) conditions developed in the Jackson group were unsuccessful, and only protonation of the organozinc reagent was observed (Table 2.3, Entry 1)[30]. However heating the reaction to 70 °C yielded 6% of desired product **20** (Entry 2). It has been shown by Buchwald and co-workers that biaryl phosphine ligands with a larger steric bulk form palladium complexes that are stable at higher temperatures. The reaction was repeated using RuPhos at 70 °C and 22% of product **20** was isolated (Entry 3). The low yields of these reactions could be attributed to the electron rich nature of thiophene.

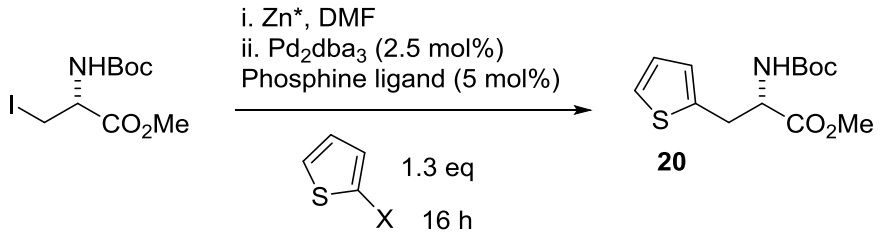
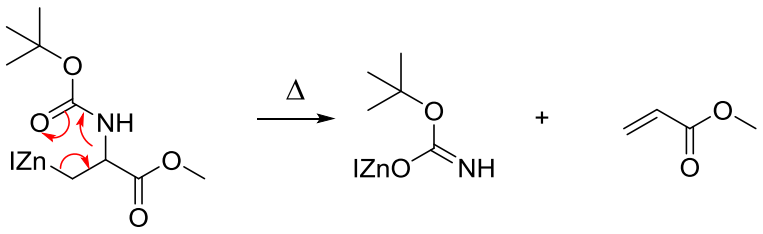


Table 2.3: High catalyst loading Negishi cross-coupling reaction of 2-halothiophenes with organzinc reagent 4.

Entry	X	Temperature (°C)	Ligand	Additive	Yield (%)
1	I	rt	SPhos	-	0[a]
2	I	70	SPhos	-	6[a]
3	I	70	RuPhos	-	22[a]
4	I	50	RuPhos	TBAB	50[a]
5	I	rt	XPhos	-	31
6	I	50	XPhos	-	49
7	I	50	XPhos	TBAB	29
8	Br	50	RuPhos	-	4
9	Br	50	XPhos	-	44

Reaction carried out using 2.5 mol% Pd_2dba_3 and 5 mol% XPhos with the organozinc reagent removed from excess zinc. [a]Yields obtained by another member of the Jackson Group.[30]

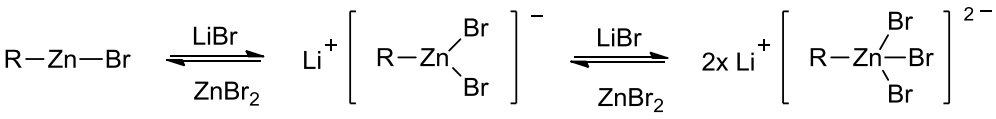
Reactions at higher temperatures than 70 °C were not successful due to the degradation of the organozinc reagent. This is thought to occur by an intramolecular elimination of the carbamate group (Scheme 2.12).



Scheme 2.12: Intramolecular elimination of the organzinc reagent.

The use of additives was also investigated in the Jackson group as they are thought to promote the transmetallation step of a cross-coupling reaction.[31] Knochel and co-workers have previously reported that using LiCl additives not only helps zinc insertion into the carbon-halogen bond but also promotes transmetallation of the resulting organozinc species.[32,33] The use of a range of halide additives was explored in the Jackson group and it was found on addition of 1.8 eq. of TBAB the isolated yield increased to 50% (Table 2.3, Entry 4).[30]

The exact mechanism of how halide additives promote the transmetallation is still unclear. Organ and co-workers have suggested that the halide additive binds to the organozinc reagent to form a higher order zincate species which is more active towards transmetallation (Scheme 2.13).[31]

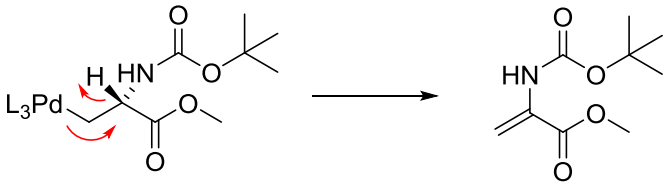


Scheme 2.13: Reaction of LiBr with the organozinc reagent.

The use of XPhos in this reaction was investigated to see if the formation of the cross-coupled product could be further promoted. The reaction was first carried out at room temperature giving an increased yield of 31% (Table 2.3,

Entry 5). Previously heating had lead to an increase in yield, so the reaction was carried out at 50 °C using XPhos. Pleasingly this again gave an increased yield of 49% (Entry 6).

The main by-product of these Negishi cross-coupling reactions is alanine which arises from the protonation of the organozinc reagent. Interestingly in the higher yielding reactions involving the coupling of the halothiophenes, dehydroalanine was also formed. This could be a result of *β*-hydride elimination after transmetallation of the organozinc reagent with the palladium complex (Scheme 2.14).



Scheme 2.14: Mechanism for *β*-Hydride elimination

With both the use of XPhos and the additive TBAB independently leading to an increased yield of the desired cross-coupled product **20**, the next step was to try combining the two. Thus, a reaction using XPhos and TBAB was carried out giving product **20** in 29% yield (Table 2.3, Entry 7). Although the yield was still better than the yields achieved using either SPhos or RuPhos without additives, it shows that the reaction using XPhos works better without the presence of TBAB and *vice versa*.

Cross-coupling of organozinc reagent **4** and 2-bromothiophene was also investigated. Again it was found that using RuPhos at 50 °C yielded very small amounts of the desired product (Table 2.3, Entry 8). However, on using

XPhos instead at 50 °C product **20** was obtained in 44% yield, comparable with the yield achieved with 2-iodothiophene (Entry 9).

Cross-coupling of 3-halothiophenes was next examined. Previously 3-bromothiophene had been found to couple with organozinc reagent **4** in 51% yield using RuPhos at 50 °C (Table 2.4, Entry 1). On applying the same conditions but using XPhos a small improvement in the yield was seen with the product being formed in 60% (Entry 2). The cross-coupling of 3-iodothiophene was also investigated, firstly using RuPhos, giving product **21** in 48% yield. The reaction was then carried out using XPhos both at room temperature and 50 °C, both of which saw a small increase in the yield of **21**.

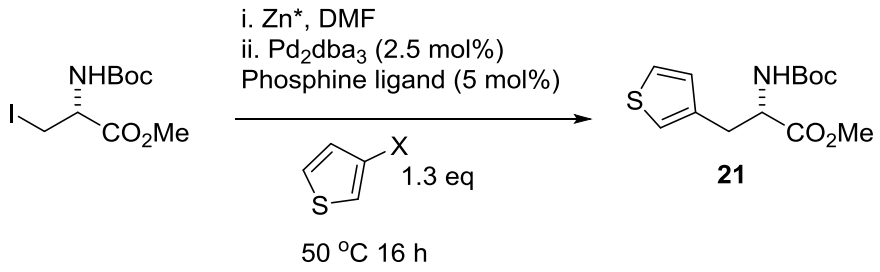


Table 2.4: High catalyst loading Negish cross-coupling reaction of 3-halothiophenes with organozinc reagent 4.

Entry	X	Temperature (°C)	Ligand	Yield (%)
1	Br	50	RuPhos	51[a]
2	Br	50	XPhos	60
3	I	50	RuPhos	48
4	I	50	XPhos	65
5	I	rt	XPhos	55

Reaction carried out using 2.5 mol% Pd_2dba_3 and 5 mol% XPhos with the organozinc reagent removed from excess zinc. [a]Yields obtained by another member of the Jackson Group.[30]

Interestingly, these results show that the bromothiophenes couple in comparable yields to those of the corresponding iodothiophenes, even though the oxidative addition of palladium (0) with the latter is easier. However the results also show that the 2- position of thiophene is less reactive towards Negishi cross-coupling conditions than the 3- position.

Having successfully coupled the halothiophenes with organozinc reagent **4** at higher catalyst loadings (Pd_2dba_3 (2.5 mol%), XPhos (5 mol%)) the effect of reducing the catalyst loading (Pd_2dba_3 (0.25 mol%), XPhos (0.5 mol%)) was investigated (Table 2.5). In the case of both the 3-bromo and 3-iodo thiophenes, the product was obtained in moderate yields of 50% and 55% respectively. For the 2-bromo and 2-iodo thiophenes, the corresponding products were formed in significantly lower yields compared to the 3-substituted thiophene as previously observed. In all cases a drop of around 15% from the yields obtained at higher catalyst loading was observed. These results suggest that the lower catalyst loading conditions are less suitable for reactions with 2-halothiophenes.

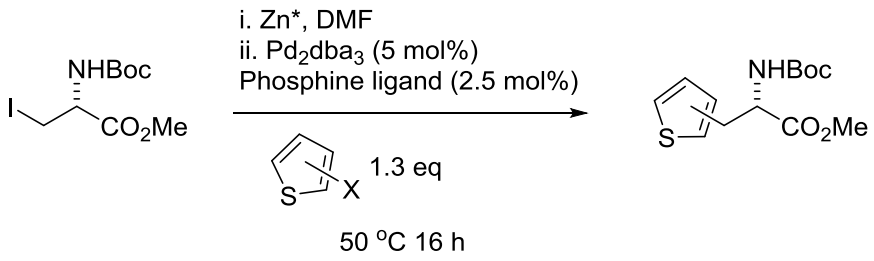


Table 2.5: Low catalyst loading Negishi cross-coupling reactions of halothiophenes with organozinc reagent 4.

Entry		Yield (%)
1	3-Br	50
4	3-I	55
2	2-Br	26
3	2-I	30

Reaction carried out using 0.25 mol% Pd_2dba_3 and 0.5 mol% XPhos with the organozinc reagent removed from excess zinc.

Following the investigations of coupling halothiophenes with organozinc reagent **4**, the effect of using the XPhos phosphine ligand in the cross-coupling of **4** with a range of other heteroaromatic halides was explored (Table 2.6).

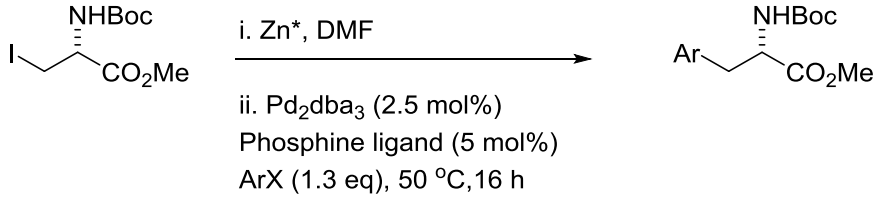
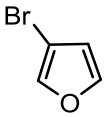
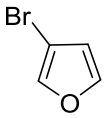
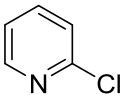
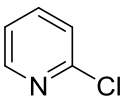
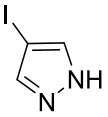
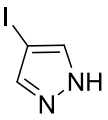
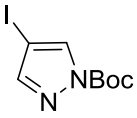
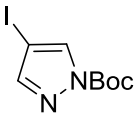


Table 2.6: High catalyst loading Negish cross-coupling reaction of heteroaromatics with organozinc reagent 4.

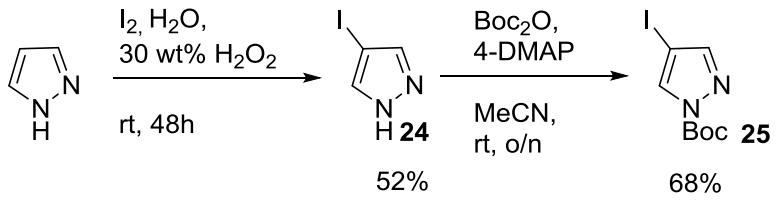
Entry	ArX	Product	Ligand	Yield (%)
1		**22**	RuPhos	32[a]
2		**22**	XPhos	29
3		**23**	RuPhos	19[a]
4		**23**	XPhos	11
5		**26**	RuPhos	0
6		**26**	XPhos	0
8		**27**	RuPhos	0
7		**27**	XPhos	~4

Reaction carried out using 2.5 mol% Pd_2dba_3 and 5 mol% XPhos. [a]Yields obtained by another member of the Jackson Group.[18,30]

Previously, electron rich 3-bromofuran has been successfully cross-coupled with iodoalanine derived organozinc reagent **4** in 32% yield catalysed by Pd_2dba_3 and RuPhos.[30] The reaction was repeated using XPhos to see if the yield of **22** could be further increased, however a similar yield of 29% was obtained.

Using the RuPhos/ Pd_2dba_3 conditions developed within the Jackson group it has been shown that the electron poor heterocycle, 2-bromopyridine, reacted to give **23** an excellent yield of 73%. However the same reaction using 2-chloropyridine not surprisingly gave the product in a much reduced yield of 19%. Attempting the reaction of 2-chloropyridine and **4** using XPhos saw a further reduction in yield to 11% (Table 2.6, Entry 4). These results demonstrate that oxidative addition is still a challenge with the stronger carbon-chlorine bonds and that in this case the XPhos/Pd_2dba_3 catalyst is not more active than the RuPhos/Pd_2dba_3 system. This could possibly be because oxidative addition is favoured by an electron rich palladium centre, which is provided more by the presence of RuPhos ligands than XPhos.

The Negishi cross-coupling reactions of electron rich heteroaromatics with organozinc reagent **4** was further investigated, looking at the pyrazole derived 4-iodopyrazole **24** and *N*-Boc 4-iodopyrazole **25** (Scheme 2.15).

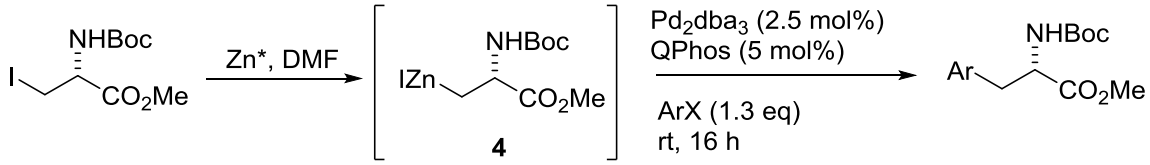


Scheme 2.15: Synthesis of 4-iodopyrazoles

Firstly, reactions of 4-iodopyrazole **24** with organozinc reagent **4** in the presence of XPhos and RuPhos were attempted, but only protonated by-product alanine was isolated (Table 2.6, Entries 5 and 6). To check that the protonation was not being caused by the free N-H proton of the pyrazole, *N*-Boc 4-iodopyrazole **25** was subjected to the cross-coupling conditions using RuPhos and XPhos. In the case of RuPhos, again only the protonated by-product was isolated. The reaction of XPhos also led to mainly protonated material, however there was evidence for a very small amount of the coupled product **27** in the ^{1}H NMR spectra although this could not be isolated by column chromatography cleanly. These results are not entirely surprising as pyrazoles are much more electron rich than any of the other heteroaromatics discussed in this chapter. There are no examples of Negishi cross-coupling reactions in the literature involving iodopyrazoles as the electrophile but there are examples of use in the opposite role as the organzinc reagent precursor.[34]

2.3.3 Negishi Cross-Couplings using QPhos

QPhos has been shown to be a suitable ligand in the Pd_2dba_3 catalysed cross-coupling reaction of organozinc reagent **4** with 3-haloindoles (Scheme 2.6, page 13).[26] The Pd_2dba_3/QPhos catalysed cross-coupling reaction of organozinc reagent **4** with some of the previously examined heteroaromatic halides was investigated (Scheme 2.16).



Scheme 2.16: Negishi cross-coupling of organozinc reagent 4 with heteroaromatic halides.

Yokoyama and co-workers found that for the Pd_2dba_3/QPhos catalysed cross-coupling of 3-haloindoles with organozinc reagent **5**, 3-bromoindoles produced higher yields of the coupled products than 3-iodoindoles. Thus reactions using heteroaromatic bromides, 2-bromothiophene and 3-bromofuran were investigated (Table 2.7, Entries 1 and 2). The cross-coupling reaction of **4** with 2-bromothiophene gave the product **20** in 25% yield. Although this is an improvement on the product yield obtained using RuPhos, this is notably less than the 45% gained using XPhos. The reaction of 3-bromofuran using QPhos gave 22% of the coupled product **22**, lower than the yields obtained using RuPhos and XPhos.

In addition to the coupling of heteroaromatic bromides, the reaction of 2-chloropyridine was also examined to see if the electron rich nature of QPhos could help overcome the difficulties of the oxidative addition of palladium(0) into the carbon-chlorine bond. The desired product **23** was obtained in 13% yield (Table 2.7, Entry 3), suggesting that the Pd_2dba_3/QPhos catalyst is not active enough to overcome the challenges of oxidative addition with carbon-chlorine bonds.

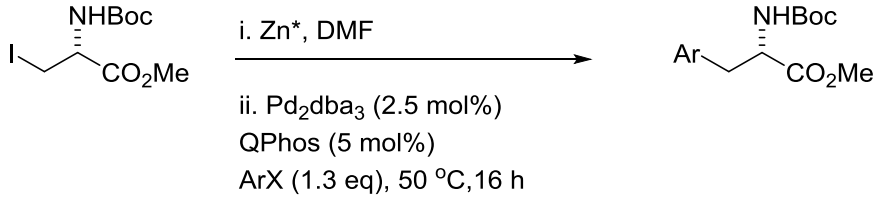
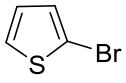
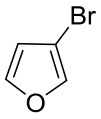
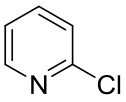


Table 2.7: High catalyst loading Negishi cross-coupling reactions using QPhos.

Entry	ArX	Product	RuPhos Yield (%)	XPhos Yield (%)	QPhos Yield (%)[a]
1		**20**	4	49	25
2		**22**	32[b]	29	22
3		**23**	19[b]	11	13

[a]Reaction carried out using 2.5 mol% Pd_2dba_3 and 5 mol% QPhos. [b]Yields obtained by another member of the Jackson Group.[18,30]

2.4 Conclusion

It has been established that using a combination of Pd_2dba_3 and XPhos in a ratio of 1:2 is an efficient precatalyst for the Negishi cross-coupling reaction between the organozinc reagent **4** derived from iodoalanine and aromatic halides. This has been demonstrated at both high (5 mol%) and low (0.5 mol%) catalyst loadings. In several instances the use of XPhos with Pd_2dba_3 has been shown to give improved results to those previously obtained using SPhos with Pd_2dba_3. This improvement has been particularly evident in the low catalyst loading reactions of *ortho*-substitued iodoanisole and the nitrobenzene iodides with organozinc reagent **4**.

The use of Pd_2dba_3 and XPhos in the challenging cross-coupling reactions of organozinc reagent **4** and electron-rich heteroaromatic halides has also had some success. Specifically reactions between 2-iodothiophene and 3-bromothiophene with **4** have been achieved in modest to good yields compared to those previously obtained using alternative phosphine ligands. Interestingly yields were not largely affected by altering the halide from iodide to bromide, but were affected on changing the position of the halide on the thiophene ring. Expanding the use of Pd_2dba_3 and XPhos in the cross-coupling reaction of the even more electron-rich imidazole and **4** was unsurprisingly not successful. This displays the limitations still present in the Negishi cross-coupling of electron rich aromatics.

Initial investigations using Pd_2dba_3 and QPhos in the cross-coupling reaction of heteroaromatic bromides and 2-chloropyridine with organozinc reagent **4** have been carried out. In general QPhos was found to be an inferior phosphine ligand to XPhos. This factor combined with its relative cost

compared to XPhos makes QPhos unsuitable for use in the Negishi cross-coupling reactions investigated here.

3. C-H Activation of Side Chain Amino Acids

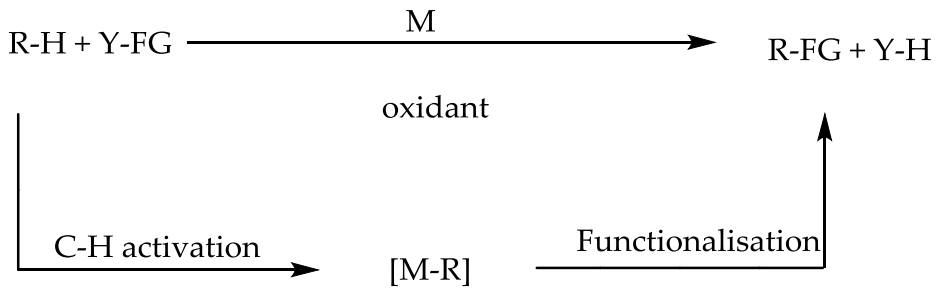
3.1 Introduction

3.1.1 C-H Activation

Until recently, the reactions of alkanes have been principally limited to that of radical and other oxidation processes, often relying on harsh conditions and generating multiple products.[35] The hampering of the synthetic development of alkane reactions can be attributed to two fundamental issues: the inert nature of the C-H bond and the difficulty in selectively functionalising a specific C-H bond in a compound containing multiple C-H bonds.[36]

Over the past decade, C-H activation has become an area of significant interest within the field of organic chemistry. The ability to functionalise unactivated C-H bonds offers the possibility of new disconnection strategies rivalling traditional approaches. Such advances could subsequently provide a facile and economical route for the conversion of hydrocarbon feedstocks into synthetically useful and industrially important compounds.[36]

One of the most widely investigated methods for C-H activation is the selective functionalisation of C-H bonds using organometallic systems. Such reactions occur by metal induced cleavage ('activation') of the C-H bond leading to the formation of a C-M bond. This provides a far more reactive intermediate, facilitating functionalisation at the carbon centre under much milder conditions (Scheme 3.1).[37]



Scheme 3.1: Metal induced activation of C-H bonds.

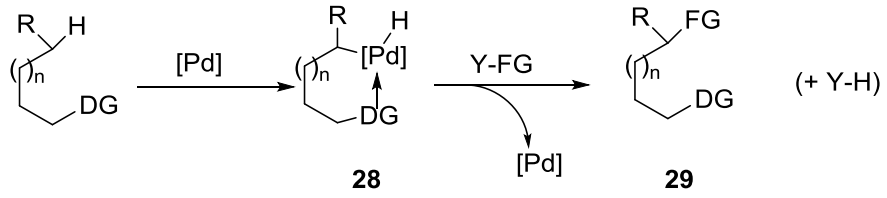
Catalytic C-H activation methods have been successfully applied to both sp^3 and sp^2 C-H bonds.[38] However, due to the low reactivity of the sp^3 C-H bond compared to that of the sp^2 C-H bond, activation of the latter is easier and has thus been more extensively investigated. In particular, the activation of arenes and heteroarenes has been the subject of several reviews.[35,39-41]

Various transition metal catalysts such as those containing Ru,[42] Rh,[43] Re,[44] Ir,[45] Cu[46] and Pd[47] have been used to promote C-H activation. However, palladium complexes have proven to be one of the most versatile catalysts for such transformations. In addition to promoting C-H activation with both sp^3 and sp^2 centres,[48] palladium catalysts have also shown to assist the formation of many new bonds such as carbon-carbon,[49] carbon-halogen[50] and carbon-oxygen.[51] Palladium complexes have been shown to work with a wide variety of directing groups and are also air and moisture stable.[52]

The following review aims to focus principally on the palladium catalysed activation of otherwise unreactive sp^3 C-H bonds. For a broader coverage of this field, there are several reviews that can be examined.[35,36,39-41,53-56]

3.1.2 Directing Groups

In the majority of sp^3 C-H activation reactions, easily cleavable directing groups containing heteroatoms are incorporated into the starting material. The addition of such groups allows reactions to proceed under milder conditions. The reaction proceeds via coordination of a heteroatom to a palladium catalyst, facilitating insertion of the palladium into a specific C-H bond. The subsequently formed palladacycle **28** can then be functionalised at carbon to give **29** (Scheme 3.2).[57,58]



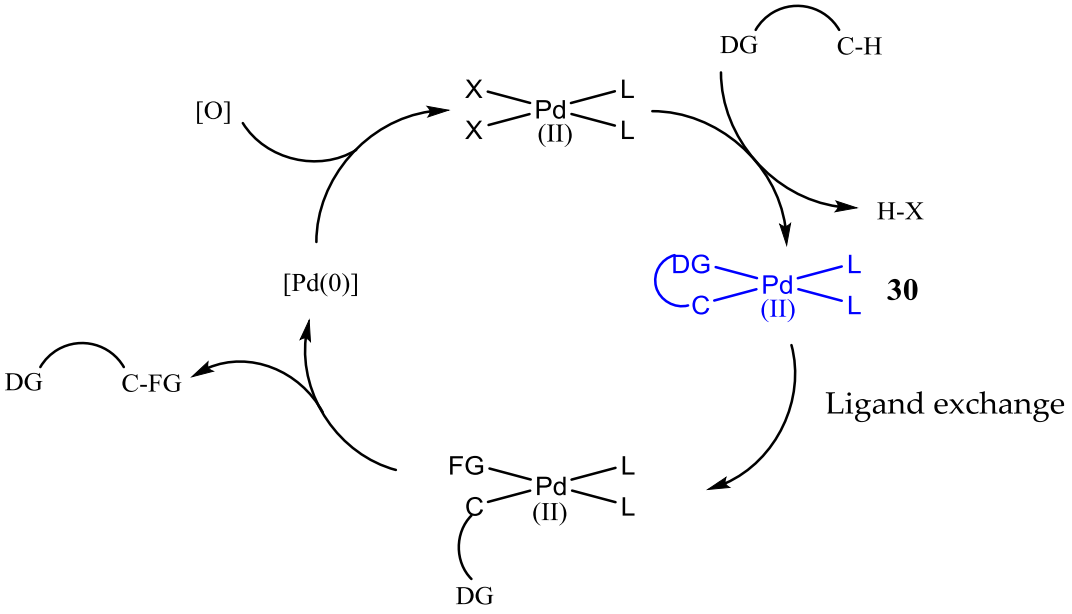
Scheme 3.2: C-H activation using a directing group.

Several functional groups have been shown to be effective at directing C-H activation, including pyridines, imines, oxime ethers, nitrogen heterocycles and amides containing relatively basic oxygen atoms.[59,60]

3.1.3 Mechanistic Pathways of Sp^3 C-H Activation.

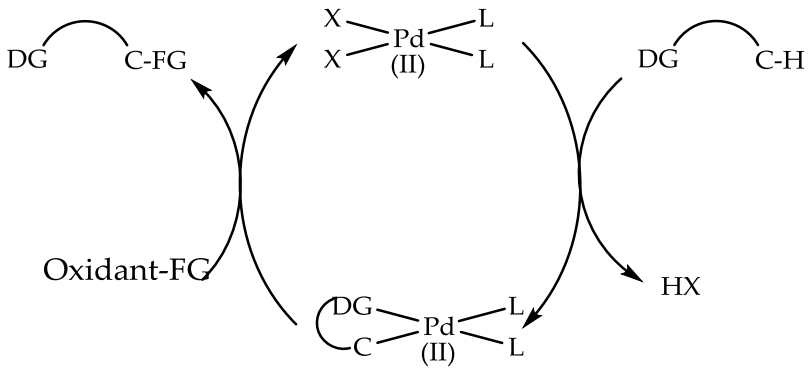
There are several proposed mechanistic pathways for directing group induced C-H activations, all of which are thought to proceed through cyclopalladated intermediates related to **30** (Scheme 3.3).[61] Although passing through a similar intermediate, the mechanistic pathways can be divided into 2 groups based on the way in which functionalisation of the substrate proceeds. The first is where functionalisation occurs reductively via

processes such as reductive elimination and β-hydride elimination. In this case the cycle is Pd(II)/Pd(0) and the Pd(II) must be regenerated.



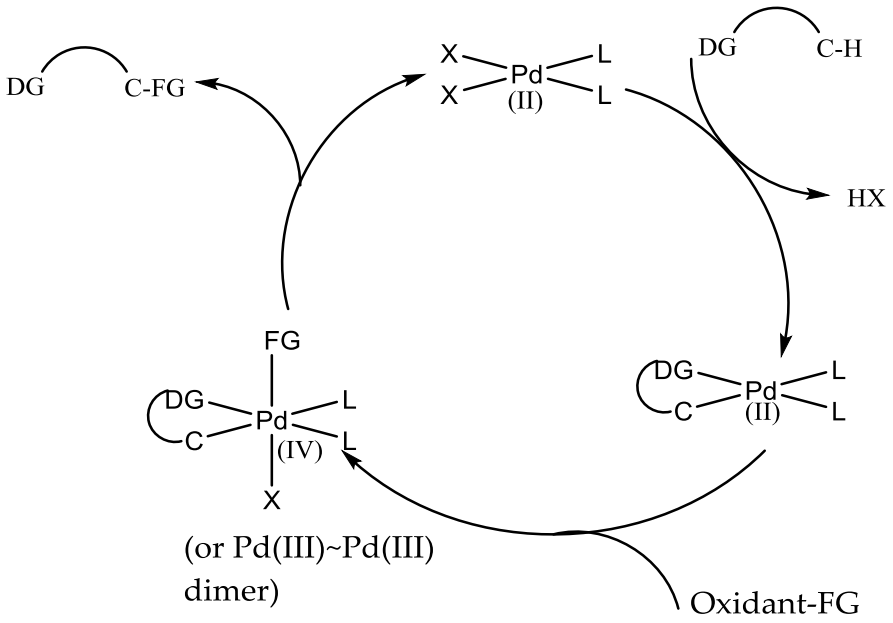
Scheme 3.3: Proposed Pd(II)/Pd(0) catalytic cycle for C-H activation

The second class of C-H activation mechanistic pathway achieves functionalisation via electrophilic addition to the palladacycle. The first example of this goes via direct cleavage of the Pd-C bond leading to the oxidation state of the metal centre remaining unchanged (Scheme 3.4).



Scheme 3.4: Proposed Pd(II)/Pd(II) catalytic cycle for C-H activation

The second example involves electrophilic addition of the functional group to the palladacycle via an oxidative process to generate a Pd(IV) intermediate (Scheme 3.5). Release of the newly functionalised product returns the palladium to its catalytically active oxidation state.

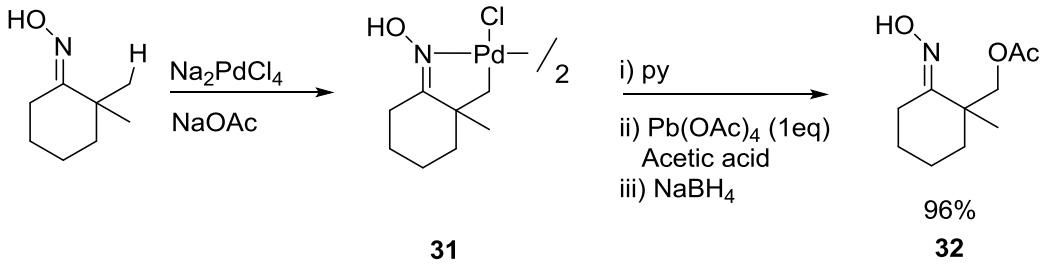


Scheme 3.5: Proposed Pd(II)/Pd(IV) catalytic cycle for C-H activation

3.1.4 Carbon-Oxygen Bond Formation

An early example of chelate-directed C-H activation at an sp^3 centre was reported by Shaw and co-workers in 1978.[62] Studies showed that simple ketone derivatives, such as oximes and *N*,*N*-dimethylhydrazones when treated with stoichiometric amounts of Li_2PdCl_4 and sodium acetate formed isolable palladacycle dimers (Scheme 3.6). In this system the oxime acts as a directing group with the nitrogen coordinating to the palladium, forming palladacycle dimer **31** thus facilitating the C-H activation.

The reaction conditions were further developed by Baldwin and co-workers in 1985 to allow for functionalisation of the palladacycle.[63] It was established that addition of pyridine to a cyclopalladated species such as **31** formed a further complex, which could then be oxidised with lead(IV) acetate in acetic acid, followed by reduction with sodium borohydride, to form a new C-O bond leading to acetoxy oxime **32**.

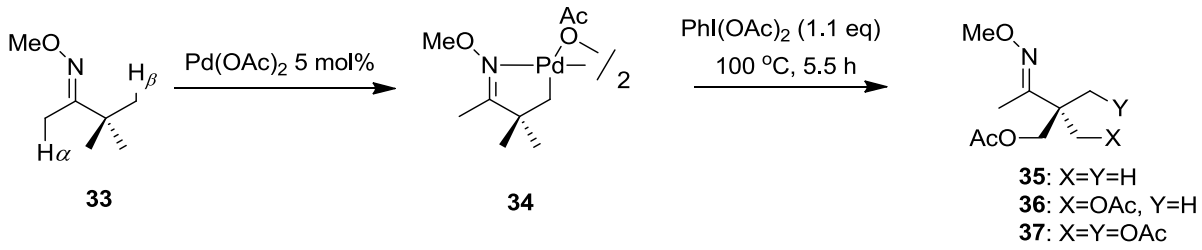


Scheme 3.6: Acetoxylation of oximes by Baldwin and co-workers.

Despite the significance of this C-H activation/functionalisation method, the requirement for stoichiometric amounts of palladium made it economically impractical. It was therefore necessary to find a method that allowed the palladium to be recycled in situ making the reaction catalytic. During the reaction Pd(II) is converted into Pd(0) which is unreactive in these systems, so an obvious solution was to introduce a stoichiometric oxidant that could convert the Pd(0) by-product back to the useful Pd(II) reactant.

One of the first examples of Pd-catalysed ligand-directed C-H bond oxygenation was achieved by Sanford and co-workers in 2004 on sp^2 centres.[64] This process involved the use of $PhI(OAc)_2$ as a stoichiometric oxidant in combination with catalytic $Pd(OAc)_2$. These conditions were subsequently applied to the unactivated sp^3 C-H bonds of oxime and pyridine derivatives.[59] Initial studies looked into the β-functionalisation of

pinacolone *O*-methyl oxime **33** used 5 mol% of $Pd(OAc)_2$ and 1.1 equivalents of $PhI(OAc)_2$ (Scheme 3.7). Formation of the palladacycle dimer **34** followed by oxidation afforded a mixture of the mono-, bis- and tris-acetoxylated products **35**, **36** and **37**. Increasing the oxidant loading to 4.5 equivalents gave the tris-acetoxylated oxime as the major product in a 59% yield. Significantly no reaction took place at the more acidic α-C-H bonds which would typically display increased reactivity towards electrophilic C-H activation.



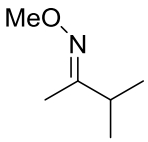
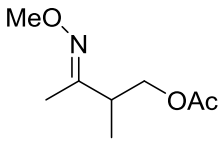
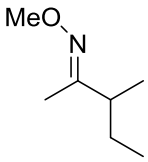
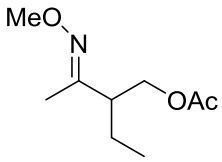
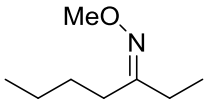
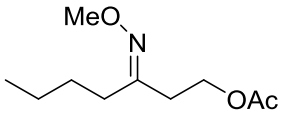
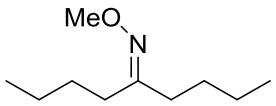
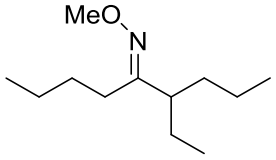
33 **34**

Scheme 3.7: Acetoxylation of *O*-methyl oxime 33 by Sanford and co-workers.

Functionalisation of a range of *O*-methyl substituted oximes was examined, using the same catalytic conditions, in order to explore the regioselectivity of the reaction (Table 3.1). Entry 2 showed a preference for reaction at the primary position over the secondary. This can be explained by a strong steric preference for a reaction at the least hindered position. In addition, the results showed (Entries 2-3) that the activation occurs at the β- over the γ- and δ-position. The rationalisation for this lies in the preference for the formation of a 5-membered palladacycle rather than a 6- or 7-membered analogue. Entries 4-5 show that in the absence of a primary β-C-H bond, no reaction takes place. The branched substrates were found to give higher yields than the linear ones (Entries 2-3). This is most likely due to the requirement for co-planarity between the reacting C-H bond and the oxime

which is more easily achieved in branched substrates which favour the bulkier substituent pointing away from the oxime.

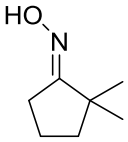
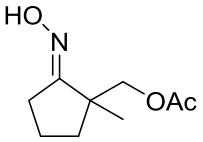
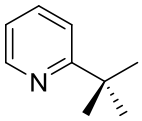
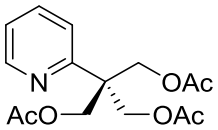
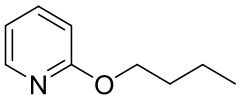
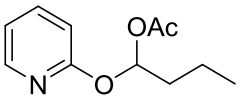
Table 3.1: Selectivity of Pd(II)/PhI(OAc)$_2$ catalysed sp^3 C-H bond oxidation.

Entry	Substrate	Major Product	Yield (%)
1			74
2			78
3			39
4		No reaction	0
5		No reaction	0

The substrate scope was further extended to a wider range of oximes (Table 3.2). The substrate in entry 1 had previously been shown to be unreactive toward stoichiometric cyclopalladation reactions, however under catalytic conditions the acetoxylated product was obtained in good yield. Pyridine directing groups (Entries 2-3) were also successfully exploited and have been

shown to furnish the mono-, bis- and tris- acetoxylated product in good yield. Interestingly the introduction of a linking heteroatom in entry 3 provided a route for activation at a secondary sp^3 C-H centre.

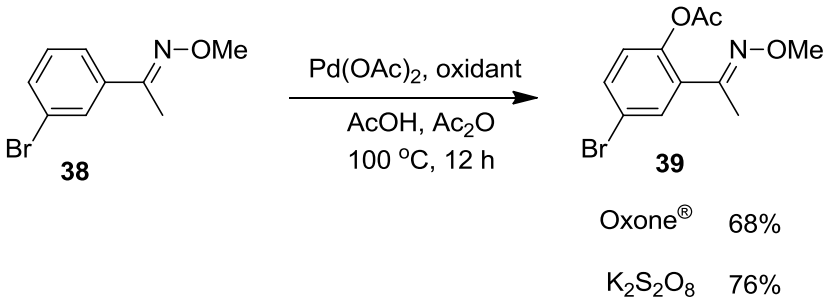
Table 3.2: Substrate scope of Pd(II)/$PhI(OAc)_2$ catalysed sp^3 C-H bond oxygenation.

Entry	Substrate	Product	Yield (%)
1			61
2			63
3			41

The aforementioned work done by Sanford and co-workers provides a catalytic, ligand-directed C-H activation method that proceeds with good yields and with high levels of regioselectivity. Nevertheless, $PhI(OAc)_2$ is an expensive oxidant and produce a stoichiometric amount of PhI. Thus investigations were undertaken to establish a greener mode of oxidation that would in turn be more practical for large scale synthesis.[60]

Previous work had suggested that the C-H activation and oxygenation of oximes occurred via a Pd(IV) acetoxy intermediate where the acetoxy ligand was obtained from the $PhI(OAc)_2$ oxidant.[65] Thus it was postulated that if an

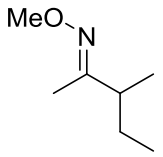
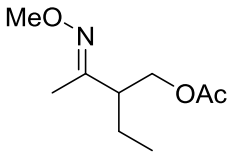
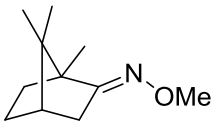
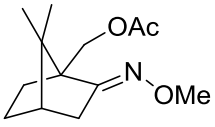
external source was used to provide the acetoxy ligand, then an alternative oxidant such as a peroxide could be used. A variety of oxidants were examined in the presence of acetic acid in the reaction with the sp^2 centre of oxime ether **38**. They were all found to provide the oxygenated product **39**, with Oxone® and $K_2S_2O_8$ giving the best results (Scheme 3.8).



Scheme 3.8: Varying the oxidant in the acetoxylation of *O*-methyl oxime 38 by Sanford and co-workers

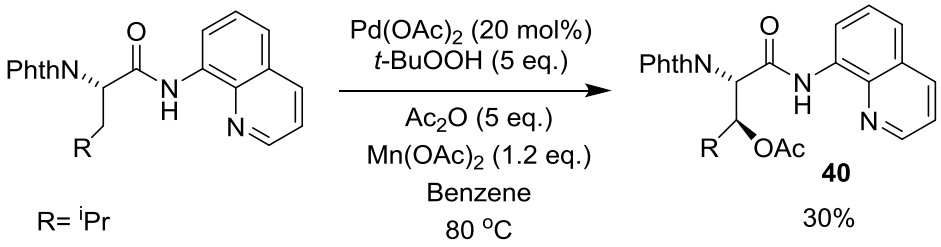
Oxone® was selected for further trials on a range of substrates due to its low cost and safe nature. Of particular interest, it was shown to act as a terminal oxidant for sp^3 C-H bonds in the same manner as the previously utilised $PhI(OAc)_2$ (Table 3.3). In addition to this it was found to have good functional group tolerance.

Table 3.3: Pd(II)/ Oxone® catalysed acetoxylation of sp^3 C-H bonds.

Entry	Substrate	Product	Yield (%)
1			45
2			63

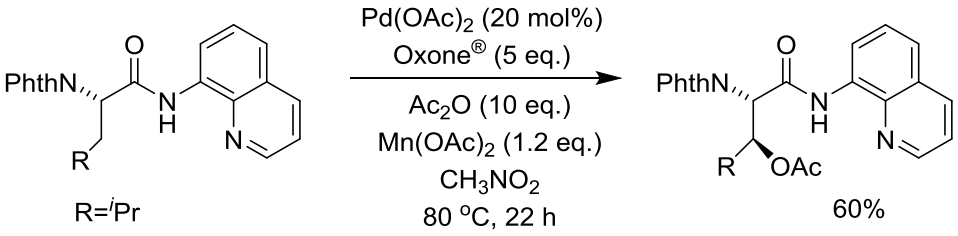
Building on the work developed by Sanford, Corey and co-workers sought to make the methodology applicable to the functionalisation of α-amino acids such as leucine, alanine, β-methyl alanine and phenylalanine.[66] Until this point, acetoxy functionalistion at the β-position of amino acids had not been achieved. The suitability of a range of *N*-phthaloyl-α-amino acid amide derivatives was investigated. Derivatives containing an 8-aminoquinoline directing group (which had previously been employed by Daugulis and co-workers and will be discussed at a later point)[67] were determined to be the most promising.

Initial studies looked at the palladium catalysed acetoxylation using either *t*-BuOOH with Ac_2O or $PhI(OAc)_2$ with Ac_2O. These conditions had previously been shown to work with a series of substrates; however the reaction afforded none of the desired oxidised product. On addition of $Mn(OAc)_2$ to the reaction with *t*-BuOOH, conversion to the product **40** was observed (Scheme 3.9).



Scheme 3.9: Acetoxylation of α-amino acid derivatives by Corey and co-workers.

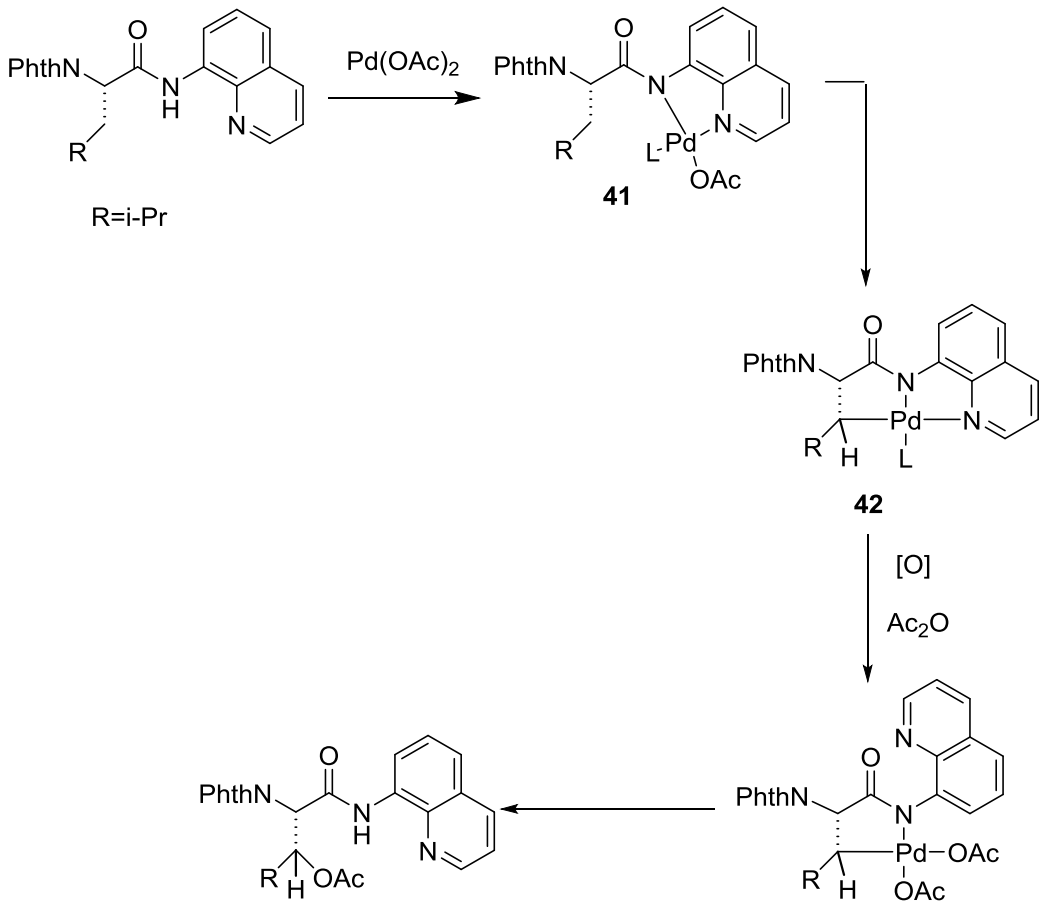
It was found that replacement of $Mn(OAc)_2$ with AgOAc, $Cu(OAc)_2$ or $Co(OAc)_2$ gave none of the desired product. However, the use of Oxone® instead of *t*-BuOOH with $Mn(OAc)_2$ was shown to give an improved yield (Scheme 3.10) proving Oxone® to be the superior oxidant in this case.



Scheme 3.10: Acetoxylation of α-amino acid derivatives by Corey and co-workers.

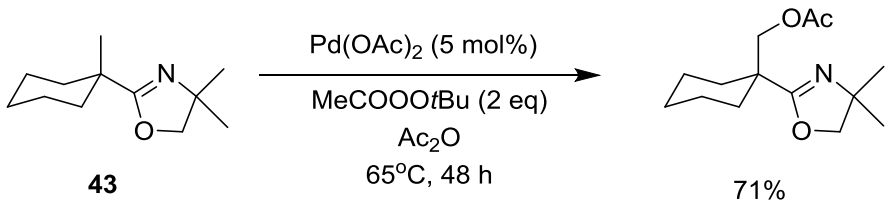
A suggested role for the $Mn(OAc)_2$ additive is as a precursor to the oxidised derivative $Mn_3O(OAc)_2$ which possesses Lewis acid characteristics. Coordination of $Mn_3O(OAc)_2$ to the acetoxy ligand increases the positive charge on the Pd of the first intermediate **41** lowering the barrier for insertion into the C-H bond and facilitating the formation of palladacycle **42** (Scheme 3.11). Oxone® was found to be an efficient oxidant as it promoted rapid oxidation of Pd(II) species **42**, allowing for β-acetoxylation. At a slower rate of oxidation, decomposition routes such as β-H elimination or Pd-C homolysis could take precedence. Nitromethane was used as solvent due to

its non-coordinating, polar nature which maximises the electrophilicity of the palladium species.



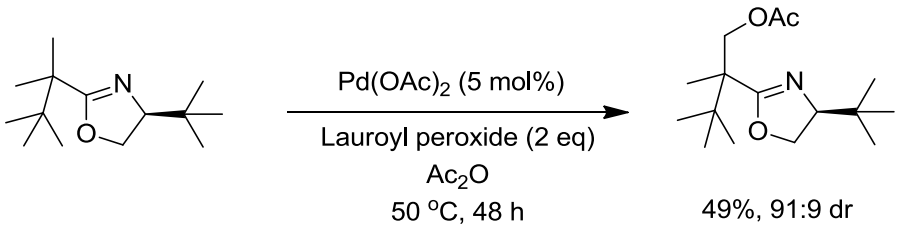
Scheme 3.11: Proposed mechanism for the acetoxylation of *α*-amino acid derivatives by Corey and co-workers.

Yu and co-workers have also reported the palladium catalysed oxidation of unactivated methyl groups utilising oxazoline directing groups (Scheme 3.12).[68] Initial work showed that use of the peroxyester MeCOOO^{t}Bu as the stoichiometric oxidant and Ac_2O as a promoter was efficient in the regeneration of the Pd(II) catalyst. Acetoxylation of **43** was shown to occur in good yield.



Scheme 3.12: Acetoxylation of methyl groups by Yu and co-workers.

A wide range of substrates were oxidised, with the reaction conditions found to tolerate imides, esters and chlorides. The conditions were then altered in order to induce diastereoselective acetoxylation, by using a chiral oxazoline, but it was found that the oxidant MeCOOO^{t}Bu was not compatible. This was due to the α-H now present in the oxazoline which could allow oxidation to the oxazole. Thus the oxidants lauroyl and benzoyl peroxide were employed on a range of substrates containing prochiral methyl groups. Moderate to good diastereoselective enrichments of 56:44-91:9% were observed (Scheme 3.13).

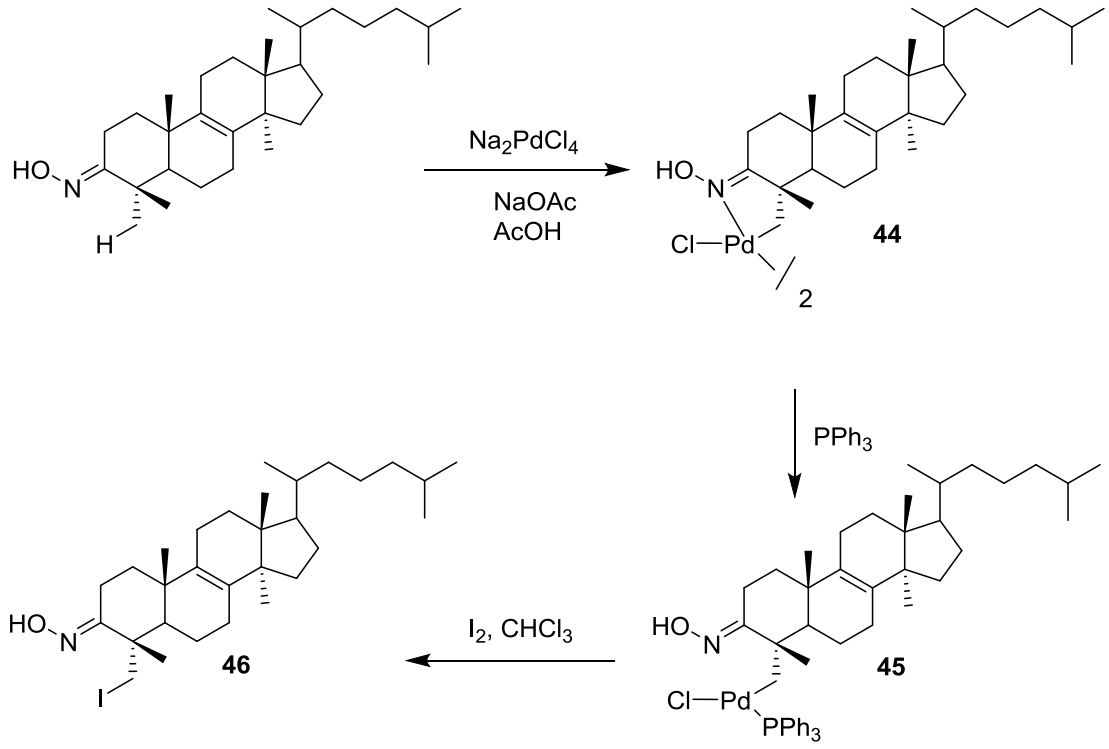


Scheme 3.13: Diastereoselective acetoxylation of methyl groups by Yu and co-workers.

3.1.5 Carbon-Halogen Bond Formation

Carbon-halogen bond formation provides a synthetically useful stepping stone to various other functionalities. One of the first examples of C-H activation followed by halogenation was reported by Sutherland and co-

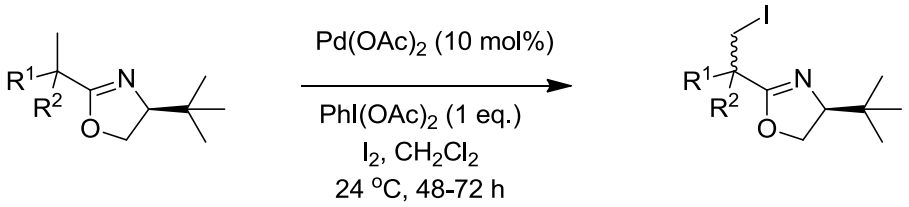
workers.[69] Previously developed conditions using stoichiometric amounts of Na_2PdCl_4 in addition to NaOAc, and AcOH were employed for the formation of the lanost-8-en-3-one cyclopalladated dimer **44**.[62] The dimer was then reacted with triphenylphosphine to furnish the monomer **45** as a crystalline solid. Further reaction of the monomer **45** with iodine yielded the iodinated product **46** (Scheme 3.14).



Scheme 3.14: Iodination of Lanost-8-En-3-One by Sutherland and co-workers.

More recently Yu and co-workers have reported the chemoselective and asymmetric, catalytic iodination of methyl groups located at the α- position of saturated aliphatic acids.[70] The C-H activation in these systems was again mediated by σ- chelating auxiliaries such as oxazolines (Scheme 3.15). Both AgOAc and $PhI(OAc)_2$ were shown to be capable of converting the

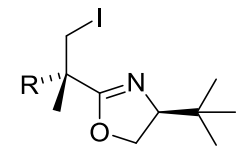
unreactive PdI_2 by-product back to $Pd(OAc)_2$, with the latter furnishing slightly better yields.



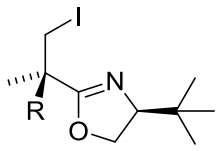
Scheme 3.15: Iodination of methyl groups by Yu and co-workers.

A range of substrates derived from the corresponding carboxylic acids and (*S*)-tert-leucinol was examined (Table 3.4). The selective activation of primary over secondary C-H bonds was conclusively demonstrated by entry 2 in which only the *β*-C-H of the R=Me was activated. Interestingly, this entry was also found to display a moderate degree of diastereoselectivity (63:37). This encouraged investigation into the asymmetric iodination of various prochiral substrates. Entries 3 and 4 were accessed with significant diastereoselectivity.

Table 3.4: **Pd(II)/PhI(OAc)$_2$ catalysed monoiodination of methyl groups.**



Major diastereoisomer



Minor diastereoisomer

Entry	R	Yield (%)	dr
1	Me	92	N/A

Entry	R	Yield (%)	dr
2	Et	88	63:37
3	^{t}Bu	83	91:9
4	OTBDMS	62	93:7

The increase in diastereoselectivity from entries 2 to 3 can be explained by looking at the steric repulsion (Figure 3.1).[71] When R^1 is larger than the Me group, **47** is favoured over **48**. This minimises any steric interaction between the R^2 group at the stereogenic centre of the oxazoline directing group and therefore the selectivity of the C-H activation can be controlled, particularly when both R^1 and R are sterically bulky.

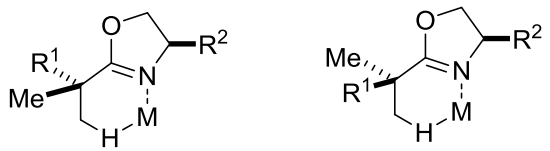
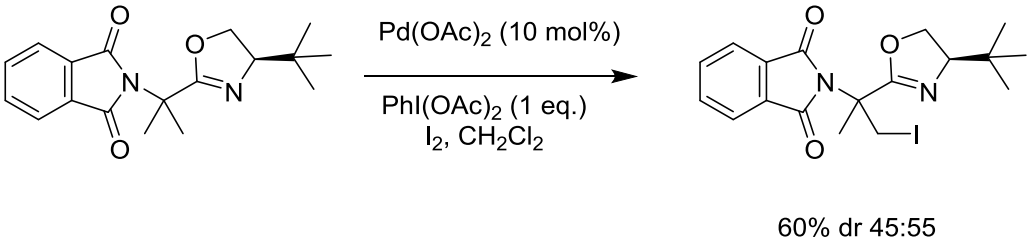


Figure 3.1: Model for the diastereoselective iodination of amino acid derivatives by Yu and co-workers.

Continuing from this the substrate range was extended. The diastereoselective iodination conditions were found to tolerate a number of functional groups including halides, esters, ethers and imides. In particular use of the phthalimide protecting group was investigated, which had been successfully applied in related work carried out by Corey and co-workers (Scheme 3.16). Only a small amount of diastereoselectivity was observed

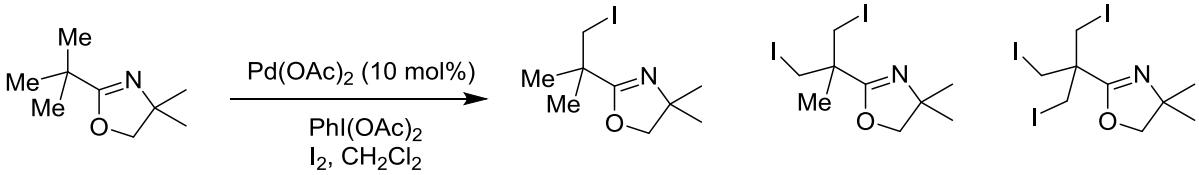
suggesting the phthalamide group is not bulky enough to induce high levels of selectivity.



Scheme 3.16: Diastereoselective iodination of amino acide derivatives by Yu and co-workers.

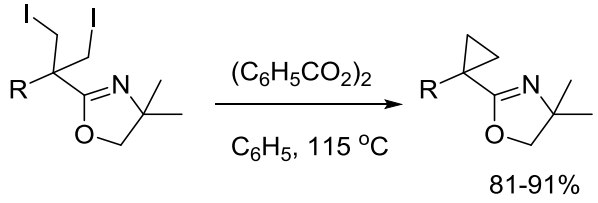
Yu and co-workers discovered that by variation of the oxazoline and oxidant/iodine loadings, multiple C-H activations could occur, thus yielding not only the mono- but the bis- and tris- iodinated products as well (Table 3.5).[72]

Table 3.5: **Pd(II)/PhI(OAc)$_2$ catalysed mono, bis- and tris- iodinationion of 2-(*tert*-Butyl)dimethyloxazoline.**



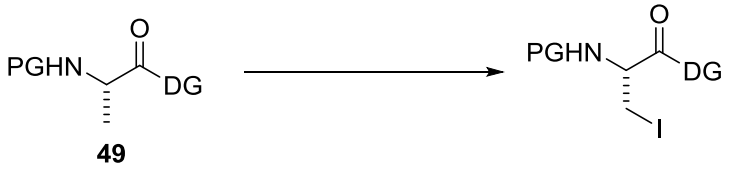
PhI(OAc)$_2$/I$_2$ (eq.)	Time (h)	Yield (%)	Yield (%)	Yield (%)
1.0	2.5	10	70	5
2.0	24	0	2	90

Formation of the bis-iodinated product provides an intermediate in the transformation of gem-methyl groups into cyclopropanes (Scheme 3.17).



Scheme 3.17: Synthesis of cyclopropanes by Yu and co-workers.

More recently, related studies have been undertaken within the Jackson group. The initial aims of this project were to perform a C-H activation on the *β*-methyl group of *L*-alanine **49**, followed by the formation of a carbon iodine bond (Scheme 3.18).[73]

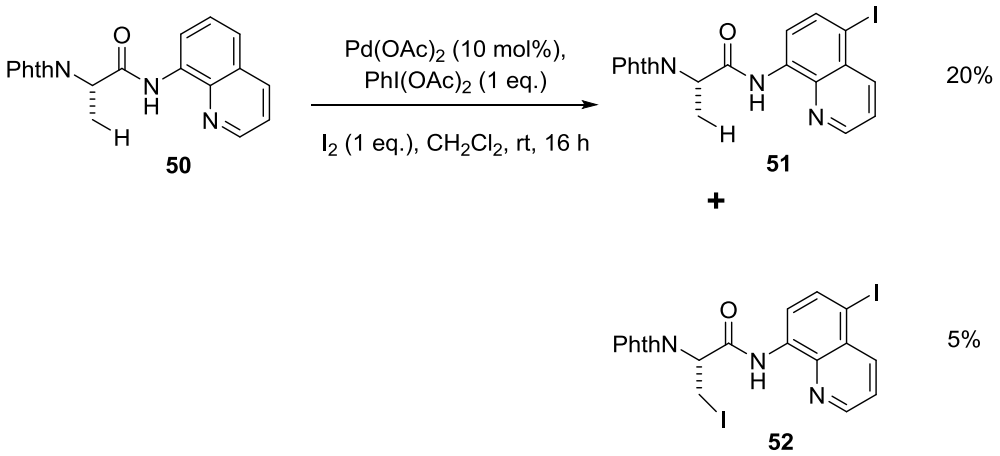


Scheme 3.18: Iodination of alanine

As already described, Corey and co-workers have successfully developed a method for the C-H activation and subsequent acetoxylation of *α*-amino acids (Page 47, Scheme 3.10).[66] In particular the phthalimide protected *L*-alanine, in combination with an 8-aminoquinoline directing group was found to be a suitable substrate for such reactions. Thus it was deduced that **50** might also be exploited in a C-H activation/iodination process using the conditions developed by Yu and co-workers.[70,71]

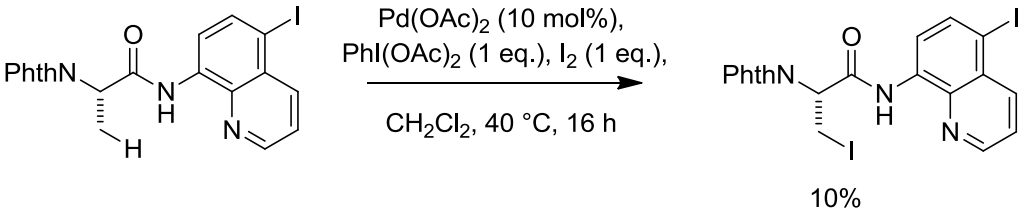
Initial results found that using Yu's conditions, substrate **50** formed two products: the mono iodinated product at the aromatic position **51** and the bis-iodinated product **52** (Scheme 3.19). It had been noted in the literature

that a combination of iodine and $PhI(OAc)_2$ could iodinate aromatic substrates, due to the formation of acetyl hypoiodite.[74] This was tested by reacting substrate **50** in the presence of $PhI(OAc)_2$ and iodine and not surprisingly aromatic iodide product **51** was formed in 80% yield. However, the presence of bis-iodinated product **52** from the reaction with palladium showed that C-H activation was taking place, thus the 8-aminoquinoline was an effective directing group.



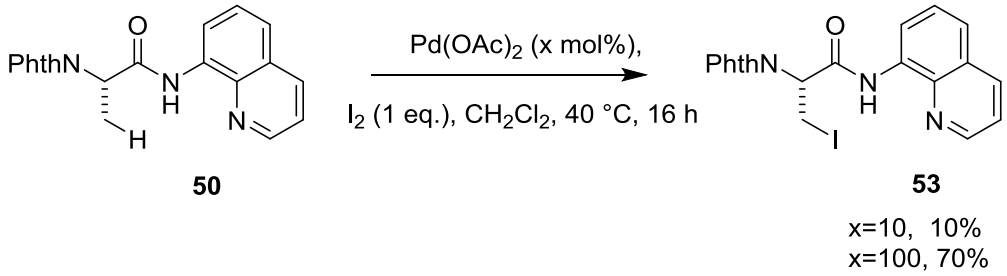
Scheme 3.19: Work towards the side chain iodination of alanine by Jackson and co-workers.

The conditions were varied in an effort to try and improve the yield of the bis-iodinated product **52**. Screening of solvents and temperature found that the reaction at 40 °C in CH_2Cl_2 gave the best conversion to the bis-iodinated product (Scheme 3.20). However, it became apparent that the reaction was stoichiometric in Pd, suggesting that $PhI(OAc)_2$ was not a suitable reagent for converting $PdI(OAc)$ back to $Pd(OAc)_2$.



Scheme 3.20: Work towards the side chain iodination of alanine by Jackson and co-workers.

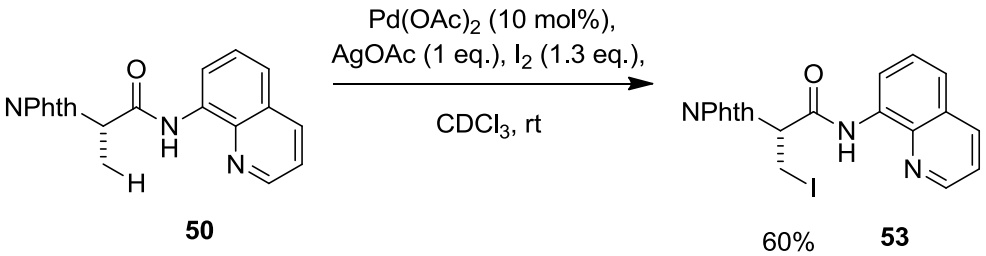
The inability of $PhI(OAc)_2$ to regenerate $Pd(OAc)_2$ was confirmed when the reaction was repeated in the absence of $PhI(OAc)_2$ (Scheme 3.21). This time the reaction produced the desired mono-iodinated product **53** in 10% yield, a stoichiometric amount relative to Pd, proving that $PhI(OAc)_2$ was only involved in the aromatic iodination, and not in the regeneration of the Pd(II) catalyst. The reaction was repeated using $Pd(OAc)_2$ and **50** in a 1:1 ratio giving **53** in 70% confirming that the reaction was stoichiometric in terms of $Pd(OAc)_2$.



Scheme 3.21: Work towards the side chain iodination of alanine by Jackson and co-workers.

It was apparent that an alternative to the $PhI(OAc)_2$ was needed. Yu and co-workers had reported the use of AgOAc as a suitable additive in similar processes, so the reaction was repeated with the AgOAc in place of $PhI(OAc)_2$ (Scheme 3.22).[71] These conditions were found to produce the desired mono-iodinated product. However to obtain higher yields of

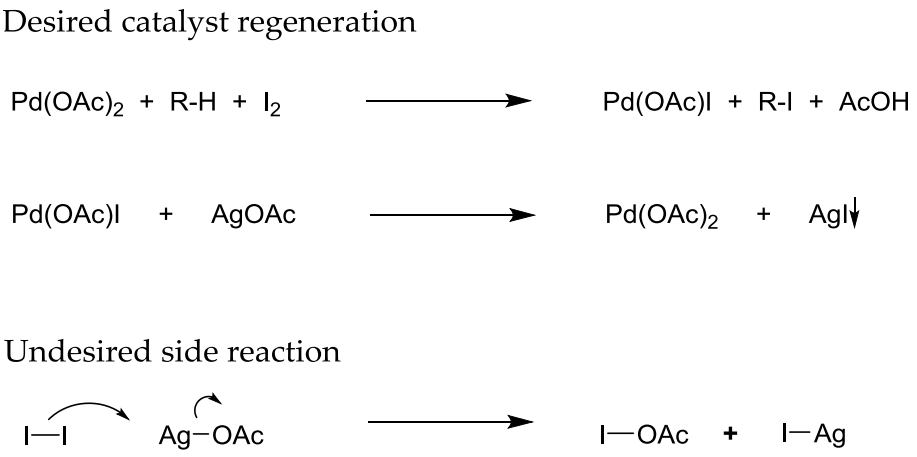
product **53** the reaction vessel had to be unsealed and the initial concentration of **50** in solvent had to be carefully controlled to subdue the formation of by-products **51** and **52**. The best yield obtained was 60% after 24 hours starting at 0.1 M concentration on a 0.14 mmol scale, but the use of an open reaction vessel meant the reproducibility of these results proved difficult due to variable solvent evaporation. The reactions were carried out in deuterated solvent, in order to monitor the conversion of **50** to **53** and the presence of any possible intermediates.



50 60% **53**

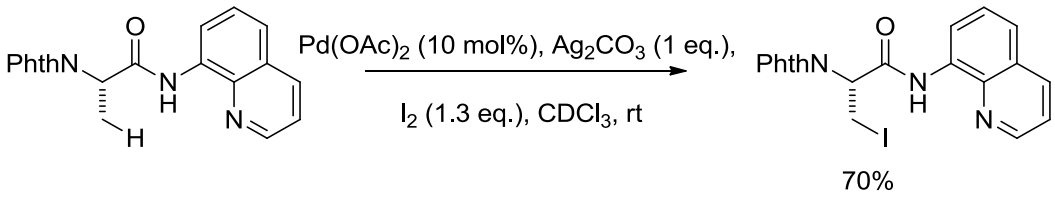
Scheme 3.22: Side chain iodination of alanine by Jackson and co-workers.

The effect of AgOAc on by-product formation can be understood by examining the intermediates in the reaction. After one catalytic turnover forming the C-I bond the $Pd(OAc)_2$ is converted to intermediate Pd(OAc)I (Scheme 3.23). The AgOAc reacts with the Pd(OAc)I thus regenerating the $Pd(OAc)_2$ catalyst, with the formation of AgI. Simultaneously AcOI is formed by the reaction of AgOAc with I_2, which then iodinates the aromatic system of the starting material, forming the unwanted by-product. This process was inhibited by controlling the initial concentration of the reaction, it was found going above 0.1 M lead to more aromatic iodination.



Scheme 3.23: The effect of AgOAc on by-product formation.

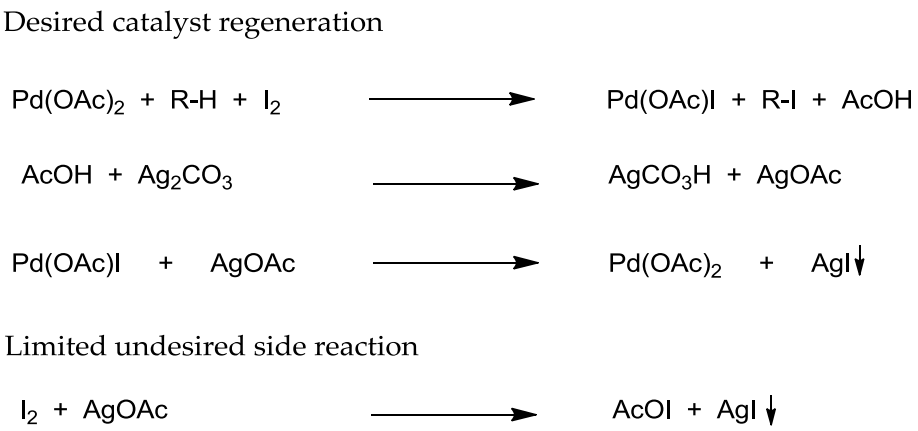
Ag_2CO_3 was then investigated as an alternative additive. In addition to giving an improved yield of the desired product, it gave much less of the bis-iodinated product and the reaction could be carried out in a closed system and was more reproducible (Scheme 3.24). Despite this, the reaction was only found to work on 0.14 mmol scale, and efforts to increase the scale were unsuccessful.



Scheme 3.24: Side chain iodination of alanine by Jackson and co-workers

It appears likely that this improvement is due to the lower solubility of Ag_2CO_3 in $CDCl_3$ compared to AgOAc. It can be explained by looking at the reaction stoichiometrically in Pd (Scheme 3.25). As the C-H activation occurs, only then is AcOH generated. The AcOH can then react with the Ag_2CO_3 to form AgOAc. The AgOAc then goes into solution and reacts with the Pd(II)

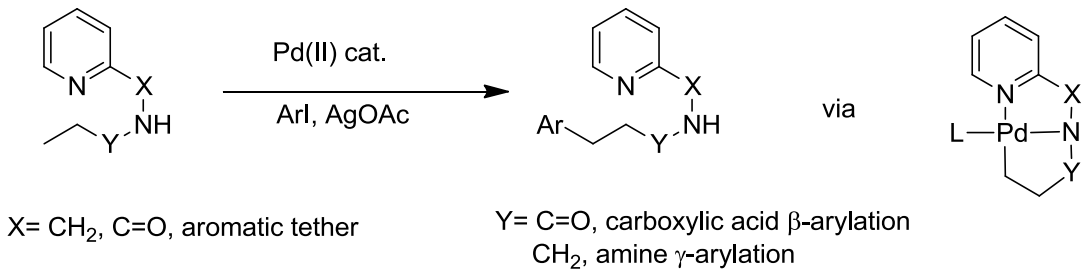
intermediate to regenerate $Pd(OAc)_2$ thus limiting the formation of the undesired hypoiodite species.



Scheme 3.25: The effect of Ag_2CO_3 on by-product formation.

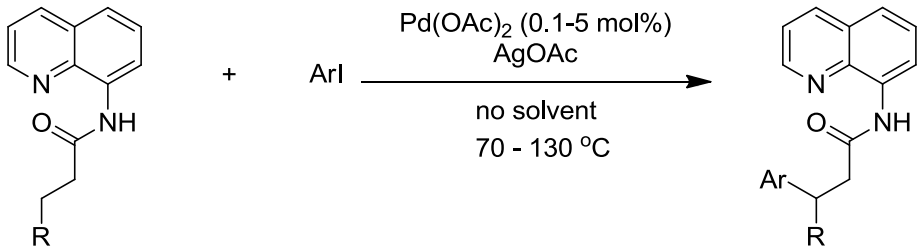
3.1.6 Carbon-Carbon Bond Formation

Selective, catalytic activation of C-H bonds, followed by the formation C-C bonds is an important goal for synthetic chemistry and is an area that is under developed. Daugulis and co-workers designed a system for the palladium catalysed arylation of acetanilide derivatives and pyridines using a $Pd(OAc)_2$ catalyst with stoichiometric AgOAc.[75] They were then able to extend this to unactivated sp^3 bonds using a chelating pyridine functionality to facilitate the C-H activation step (Scheme 3.26).[76]



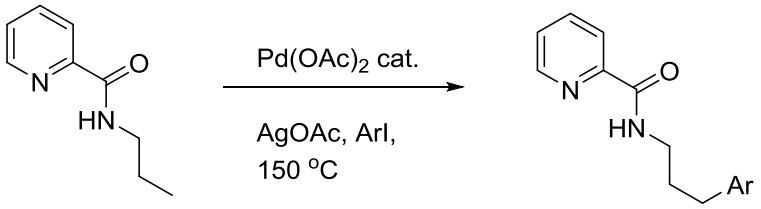
Scheme 3.26: Arylation of acetanilide derivatives by Daugulis and co-workers.

Initial investigations employed the pyridine-2-yl-methyl moiety to direct arylation. However this was found to be susceptible to C-H activation of the benzylic methylene group in some cases. As a result 8-aminoquinoline was utilised due to its lack of benzylic C-H bonds. *β*-Arylation successfully occurred on several carboxylic acid derivatives with high regioselectivity. Interestingly, it was found that secondary C-H bonds reacted more quickly than primary C-H bonds (Scheme 3.27).



Scheme 3.27: *β*-Arylation of carboxylic acid derivatives by Daugulis and co-workers.

A similar approach was found to be applicable for arylation of amine derivatives using 2-picolinic acids (Scheme 3.28). [76]



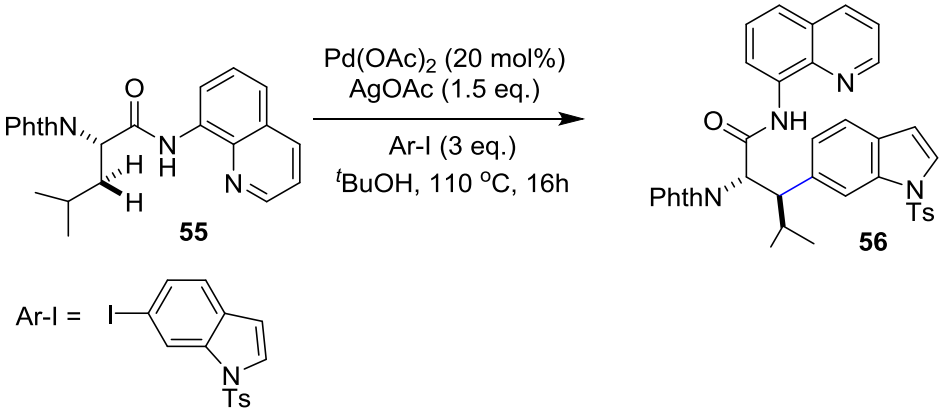
Scheme 3.28: Arylation of amine derivatives by Daugulis and co-workers.

Shortly thereafter, Corey and co-workers reported the synthesis of *β*-arylated leucine derivatives (Scheme 3.29).[66] Again using 8-aminoquinoline as the directing group to coordinate the palladium catalyst forming a palladacycle, a series of aryl groups with varying functionalities were successfully introduced in good yields with high diasteroselectivity.

Scheme 3.29: Arylation of Leucine derivatives by Corey and co-workers.

This strategy has since been implemented as a key step in the total synthesis of Celogentin C **54** carried out by Feng and co-workers in 2010 (Figure 3.2).[77] Stereoselective *β*-C-H activation took place on the Leu substrate **55** forming a palladacycle intermediate. This then presumably underwent cross-coupling with the iodoindole to provide the arylated product (Scheme 3.30). The core structure **56** underwent several further reactions to give the desired product

54. A similar route using the key C-H activation step was also reported by Hutton and co-workers shortly after.[78]



Scheme 3.30: Arylation of Leucine derivative 55 by Feng and co-workers.

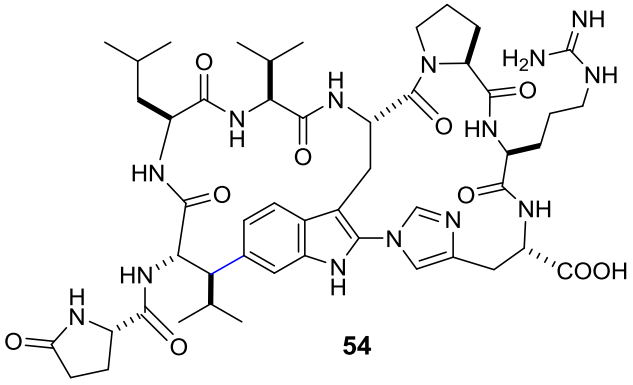
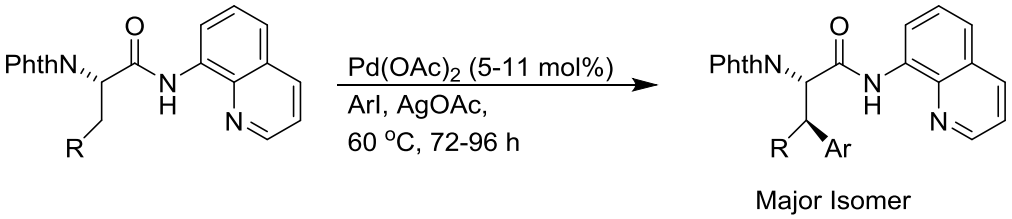


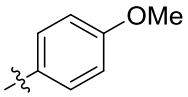
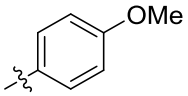
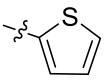
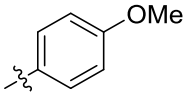
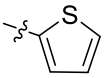
Figure 3.2: Celogentin C

Taking the lead from Corey and co-workers,[66] more recently Daugulis and co-workers have further extended the work to C-H activation followed by arylation to produce a range of unnatural amino acids using both low temperatures and low loadings of $Pd(OAc)_2$ (Scheme 3.31, Table 3.6).[79]



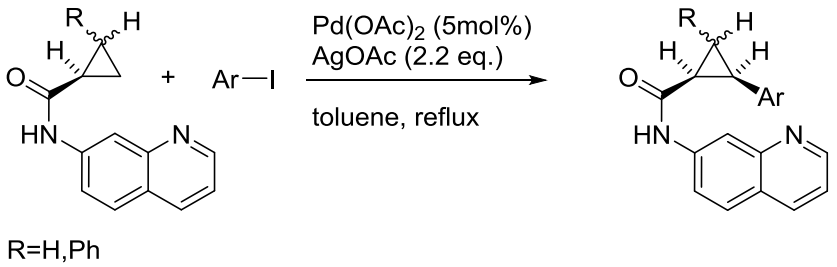
Scheme 3.31: Arylation of amino acid derivatives by Daugulis and co-workers.

Table 3.6: C-H activation and arylation to give unnatural amino acids.

Entry	R	Ar	Yield (%)	d.r.
1	H		81[a]	na
2	Ph		91	24:1
3	Ph		95	50:1
4	^{i}Pr		77	50:1
5	^{i}Pr		80	24:1

[a]Product doubly arylated

Babu and co-workers have reported the diastereoselective synthesis of mono- and diaryl cyclopropanecarboxamides using similar methodology (Scheme 3.32).[80] Once again 8-aminoquinoline was used to selectively direct $Pd(OAc)_2$ into the C-H bond of the cyclopropane ring forming a palladacycle that subsequently can be reacted with a range of aryl iodides. As seen previously AgOAc was also found to be the most suitable reagent for regeneration of the $Pd(OAc)_2$.



Scheme 3.32: Diastereoselective synthesis of mono- and diaryl cyclopropanecarboxamides by Babu and co-workers.

The scope of this cyclopropanecarboxamide arylation reaction was first examined where R=H, using a variety of aryl iodides containg both electron withdrawing and donating groups (Table 3.7). All substrates generally gave moderate to good yields of the corresponding diastereoslectively formed disubstitued cyclopropanes with cis stereochemistry.

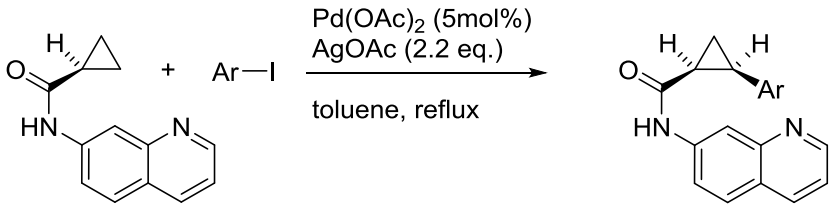
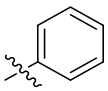
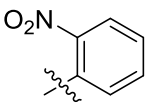
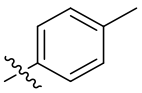
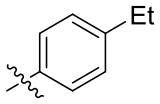
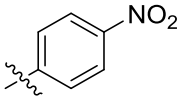
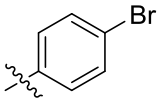
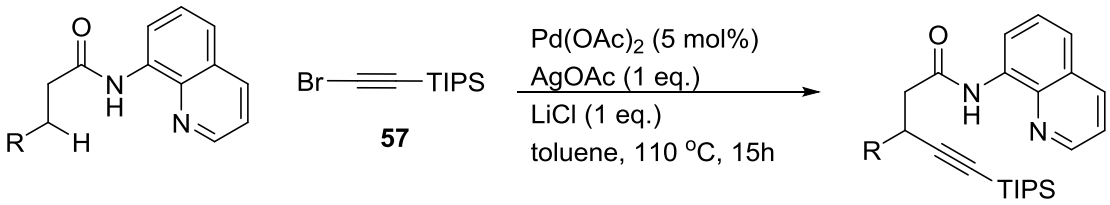


Table 3.7: Cyclopropanecarboxamide arylation reaction.

Entry	Ar	Yield (%)
1		69
2		28
3		69

Entry	Ar	Yield (%)
4		67
5		78
6		69

Chatani and co-workers have shown that the 8-aminoquinoline group can also be used to direct the sp^3 C-H activation and direct alkynylation using **57** on a range of aliphatic carboxylic acid derivatives (Scheme 3.33).[81] The reaction was found to be tolerant of a wide range of functional groups in addition to coping well with the presence of sterically demanding groups cyclohexyl and isopropyl (Table 3.8, Entries 1 and 2). However, whilst working well with secondary C-H bonds, the functionalisation of primary and tertiary C-H bonds occurs with much lower efficiency.

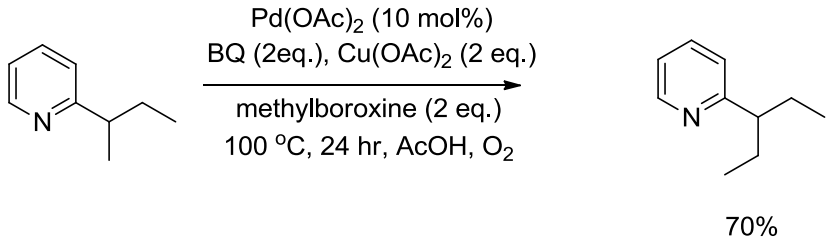


Scheme 3.33: Alkynylation on a range of aliphatic carboxylic acid derivatives by Chatani and co-workers.

Table 3.8: Pd-Catalyzed Direct Alkynylation of Aliphatic C-H Bonds with 57.

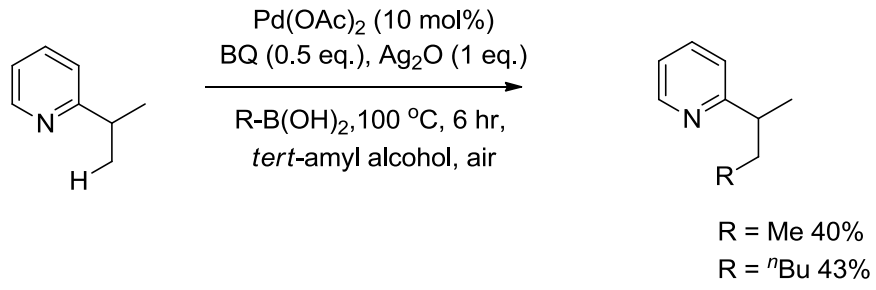
Entry	R	Yield (%)
1	^{i}Pr	64
2	Cy	66
3	OMe	60
4	CF_3	42
5	Ph	73

Yu and co-workers have developed a method for both sp^2 and sp^3 pyridine directed C-H activation followed by alkylation using either methylboroxine or alkyl boronic acids.[48] Using boroxine as an alkyl source, a mixture of $Cu(OAc)_2$ and benzoquinone oxidants were found to be suitable for the regeneration of the Pd(II) (Scheme 3.34). However, the boroxine was only viable for delivering a methyl group. Use of ethyl- or butyl-boroxines as coupling partners failed to give any of the desired alkylated products.



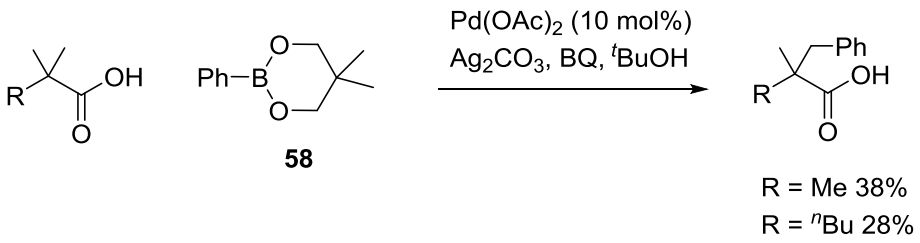
Scheme 3.34: Sp^3 alkylation by Yu and co-workers.

In an attempt to solve this problem a variety of boronic acids was examined applying the previously developed catalyst and oxidation method. However, these reactions were unsuccessful. A wider range of additives and solvents were investigated to try and promote the alkylation reaction. A mixture of Ag_2O and benzoquinone was found to provide moderate yields of the C-C coupling product (Scheme 3.35). Both these reaction conditions were found to be compatible with ether, alcohol and ester groups.



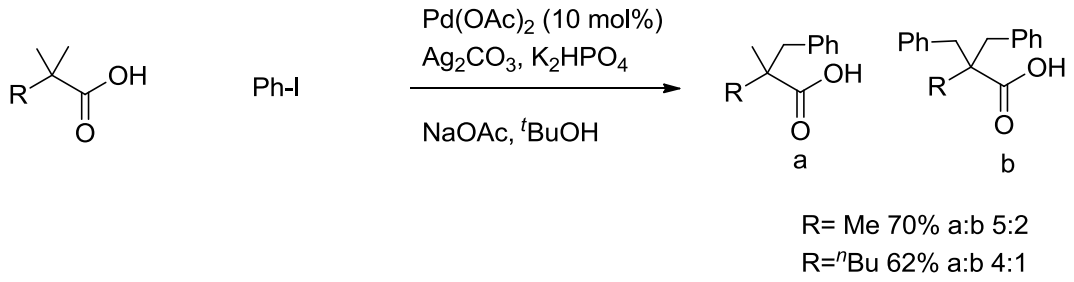
Scheme 3.35: Sp^3 alkylation by Yu and co-workers.

Subsequent work by the group provided examples of *β*-arylation of aliphatic acids with organoboron reagents.[38] The reaction proceeded via the *in situ* formation of a carboxylate which in turn acts as a directing group mediating the C-H activation (Scheme 3.36). Phenylboronate **58** was then reacted with the activated intermediate to form the arylated product. A range of substrates were found to react giving a modest yield.



Scheme 3.36: *β*-arylation of aliphatic acids by Yu and co-workers.

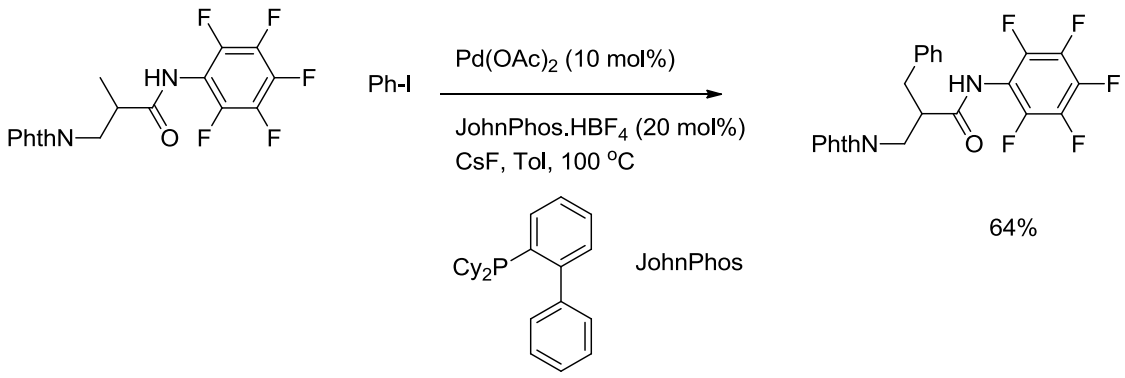
To demonstrate the generality of the C-H cleavage and C-C bond forming reactions, arylation was carried out using iodobenzene (Scheme 3.37). Alteration of the previous protocol by omitting the benzoquinone and adding NaOAc gave a good combined yield of the mono and diarylated products.



Scheme 3.37: *β*-arylation of aliphatic acids by Yu and co-workers.

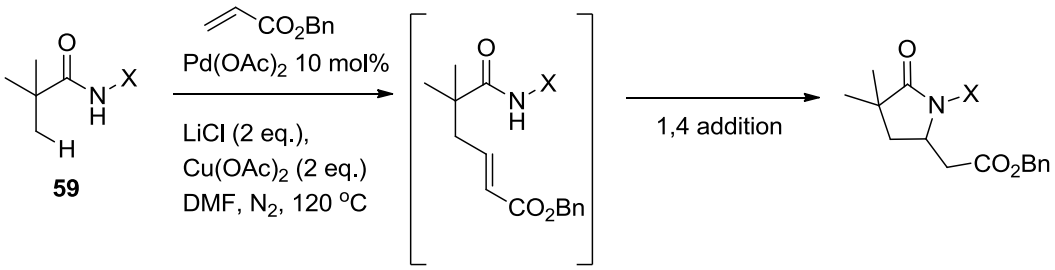
More recently Yu and co-workers have reported the *β*-arylation of *N*-pentafluoroamides.[82] It was suggested that installing an electron withdrawing group on the amide would reduce the nucleophilicity of the nitrogen atom. In addition to suppressing the possible Buckwald-Hartwig amination on addition of an aromatic iodide, this would also allow for easy deprotonation of the amide. The deprotonated amide would be free to coordinate to the palladium alongside the carbonyl oxygen, forming a palladacycle, thus promoting the C-H activation. It was found that using

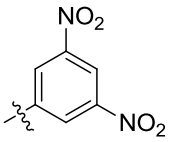
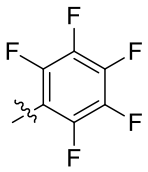
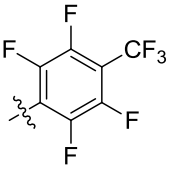
CONH-C_6F_5 as a directing group with Buchwald's cyclohexyl JohnPhos ligand and CsF as a base allowed for the formation of the arylated product when coupled with an aromatic iodide (Scheme 3.38). Both mono- and di-arylated products were observed depending on which substrate was used.



Scheme 3.38: *β*-Arylation of *N*-pentafluoroamides by Yu and co-workers.

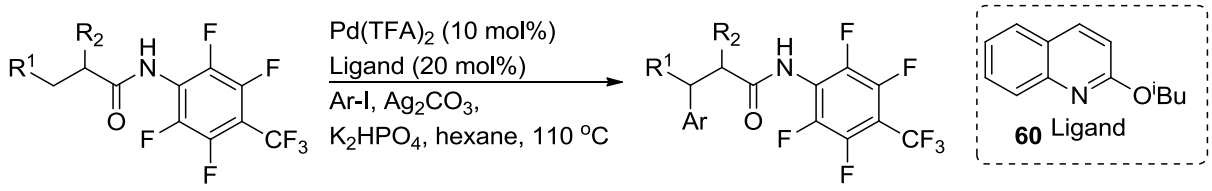
The reactivity of other electron-withdrawing directing groups was further examined.[83] It was found that sp^3 C-H *β*–olefination of N-arylpivalamide **59** with benzyl acrylate followed by an intramolecular 1,4 addition of the amide to the newly introduced acrylate led to the corresponding *γ*-lactam (Scheme 3.39). A range of *N*-aryl amides was investigated and it was found that electron withdrawing groups on the aromatic ring greatly improved the yields.



X =	OMe	Ph			
	0%	1%	47%	71%	88%

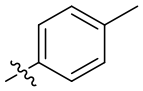
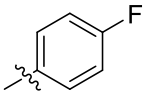
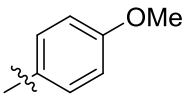
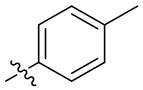
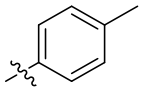
Scheme 3.39:*β*–Olefination of *N*-aryl amides by Yu and co-workers.

The possibility of arylation of acyclic and cyclic *β*-methylene sp^3 C-H bonds using electron withdrawing groups was further investigated (Scheme 3.40).[84] The amide coordinates to $Pd(O_2CCF_3)_2$ allowing for the formation of the palladacycle which then reacts with the aryl iodide to give the desired product. Ag_2CO_3 and K_2HPO_4 are then used to regenerate the active Pd(II) catalyst. In this case the addition of the ligand **60** was found to accelerate the reactions by coordinating to the Pd(II) centre and promoting the otherwise sluggish reductive elimination step. A range of *β*-arylated products in good yields was obtained (Table 3.9).



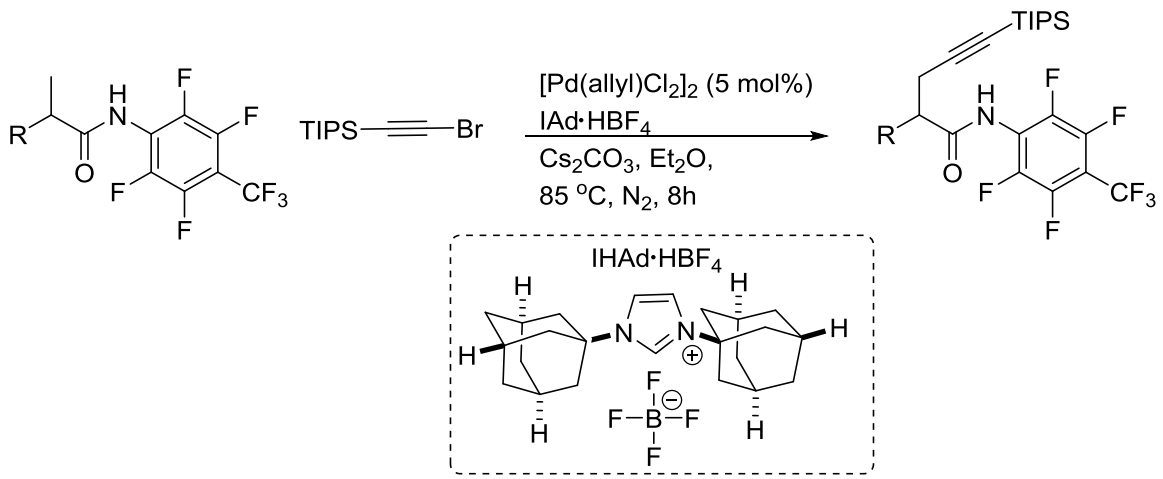
Scheme 3.40: *β*-Arylation of *N*-pentafluoroamides by Yu and co-workers.

Table 3.9: Arylation of methylene sp³ C–H bonds.

Entry	R^1	R^2	Ar	Yield (%)
1	Me	H		77
2	Me	H		71
3	Me	H		68
4	Et	H		55
5	Me	^{i}Pr		82 [a]

[a]Single diastereoisomer

Yu and co-workers have also investigated the alkynylation of sp³ *β*-C–H bonds in aliphatic amides using a Pd(0) catalyst in combination with the *N*-heterocyclic carbene IAd·HBF_4 (Scheme 3.41).[85] In this case the work focused on the activation of a primary C-H bond but again showed good functional group tolerance and gave the expected products in good yields (Table 3.10). One large drawback of this method is that the reaction is carried in Et_2O at 85 °C in a sealed vessel making it relatively dangerous.



Scheme 3.41: Alkynation of *N*-pentafluoroamides by Yu and co-workers.

Table 3.10: *β*-Alkynylation of carboxylic acid amides.

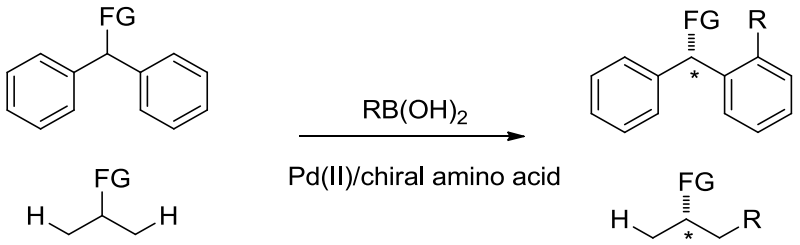
Entry	R	Yield (%)
1	^{n}Pr	81
2	H	62
3	Me	70
4	Et	78
5	Cy	70
6	CF_3	77
7	OBn	79

3.1.7 Enantioselective C-H activation

In recent years, C–H activation/functionalisation has emerged as a viable strategy for the synthesis of natural products as previously described. However in order to extend the scope of these transformations, the ability to perform C-H activations enantioselectively would be an advantage.

However, despite the success in asymmetric palladium catalysis, the enantioselective functionalisation of C-H bonds through palladium insertion has been for the most part unsuccessful.[55] Yu and co-workers have suggested two problems that have encumbered development in this area. The first is that the relatively high temperatures that are required in many C-H activation reactions make chiral recognition of the sp^3 carbon centre difficult. Secondly, the reaction requires an external chiral ligand to coordinate to the Pd(II) species in order to control the chemo-, regio- and stereoselectivity of insertion into the C-H bond. However, most commonly used chiral ligands can preferentially bind to the Pd(II) centre over the substrate or deactivate the Pd(II) towards cleavage of the desired C-H bond.[86]

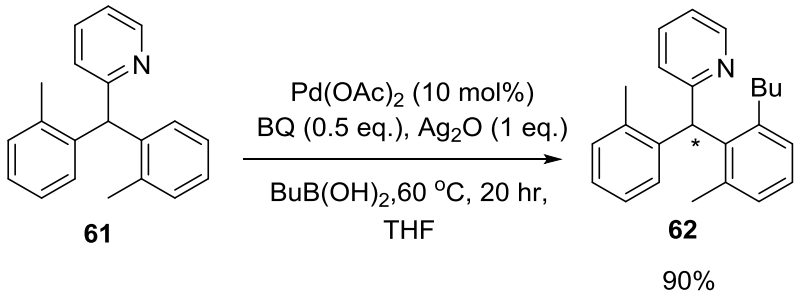
Yu and co-workers have undertaken pioneering work in the development of asymmetric activation of prochiral C(sp^2)-H and C(sp^3)-H bonds followed by C-C bond formation to give enantioenriched products (Scheme 3.42).[87]



Scheme 3.42: Asymmetric activation of prochiral C(sp^3)-H bonds by Yu and co-workers.

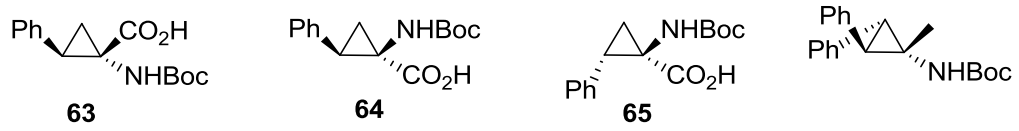
The initial goal was to find a suitable catalytic system that would work on the prochiral substrate, facilitating C-H activation and subsequent alkylation in a non-stereoselective manner. Previously developed conditions by the group using $Pd(OAc)_2$ in the presence of the additives benzoquinone and

Ag_2O followed by addition of the organoboron species, were found to convert starting material **61** to product **62** in excellent yield (Scheme 3.43).[48]



Scheme 3.43: Asymmetric activation of prochiral C(sp^3)-H bonds by Yu and co-workers.

Chiral carboxylates were employed as the ligand in the hope that along with the constrained conformation of the nitrogen coordinated palladium intermediate, asymmetric induction would occur. Enantiomeric excess' of up to 20% were obtained, leaving room for improvement. The low enantioselectivity observed was attributed to the relatively free rotation of the chiral moiety of the carboxylic acid ligand. Thus the use of chiral cyclopropane amino acid groups as ligands was examined (Figure 3.3). A marked improvement in the enantioselectivity of the product was observed. Interestingly, whilst the opposite enantioselectivities between **63** and **64** were expected, the switch of chiral induction between **64** and **65** suggested that the chirality of the α-carbon centre plays the dominant role.



46% yield
46% ee. (-)

71% yield
41% ee. (+)

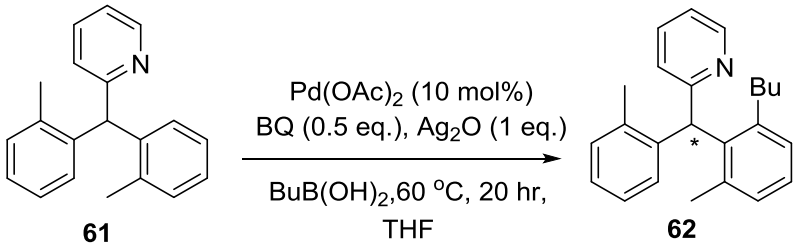
63% yield
42% ee. (-)

58% yield
racemic

Figure 3.3: Chiral ligands used activation of prochiral C(sp^3)-H bonds by Yu and co-workers.

Upon additional investigation, it was found that a wide range of monoprotected amino acids were even more effective chiral ligands for this enantioselective coupling reaction (Table 3.11). C-H activation/C-C coupling of **61** in the presence of Boc-*L*-leucine gave the alkylation product **62** in 90% ee. and 63% yield.

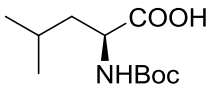
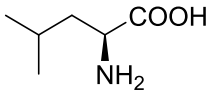
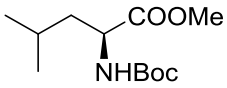
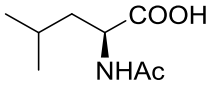
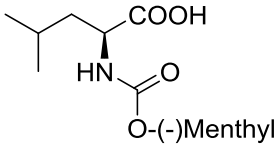
Systematic structural changes were made to the chiral ligand to probe the scope of the reaction. Removal of the Boc group on the ligand (Entry 2) lead to a full recovery of the starting material suggesting that an electron withdrawing group attached to the nitrogen is required in order to maintain the electrophilicity of the Pd(II) catalyst for C-H activation. Esterification of the carboxylic acid (Entry 3), resulted in complete loss of enantioselectivity of product **62**. Reduction of the size of the nitrogen protecting group from a Boc to a acetyl (Entry 4) also saw a decrease in the enantioselectivity. Changing the nitrogen protecting group to menthyl carbamate (Entry 5) gave again high enantioselectivity as well as a markedly improved yield.



61 **62**

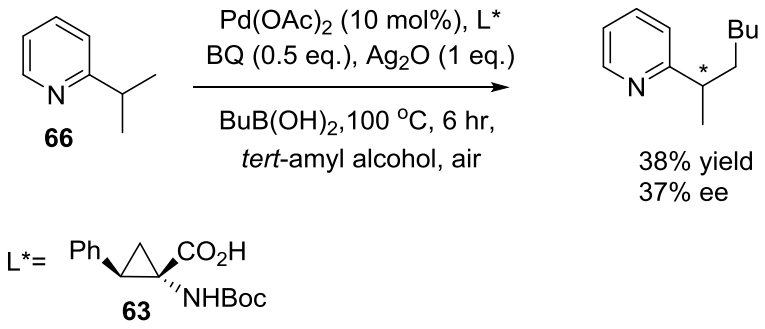
90%

Table 3.11: Influence of the ligand on enantioselectivity of the butylation of 61.

Entry	Ligand	Yield (%)	ee (%)
1		63	90
2		0	0
3		86	0
4		74	80
5		91	87

Using the conditions described above, in addition to a chiral ligand, the C-H activation and alkylation reaction was attempted on the sp^3 C-H bonds of **66** (Scheme 3.44). Poor selectivities were observed using the *L*-leucine derived ligands (10-15% ee). However an improved enantioselectivity of 37% was observed with the use of the cyclopropane amino acid **63**. This result

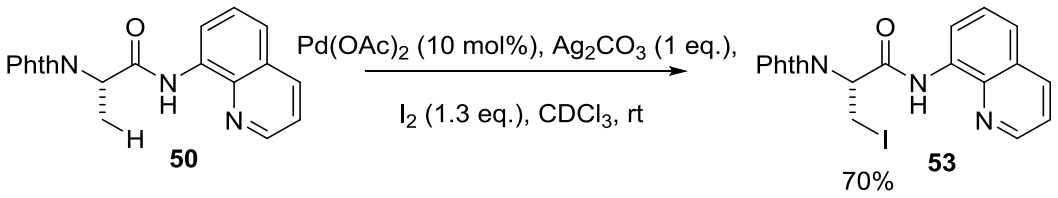
suggests that the chiral ligand could be further tuned for this class of C-H activation reaction.



Scheme 3.44: Alkylation of prochiral C(sp^3)-H bonds by Yu and co-workers.

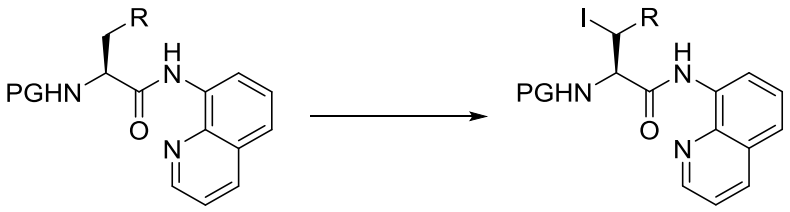
3.2 Aims

Previous work within the Jackson group has developed a method for the iodination of a phthaloylalanine derivative in the presence of an 8-aminoquinoline group using palladium catalysed C-H activation (Scheme 3.24). Unfortunately all efforts to scale up the reaction above a 0.14 mmol scale were unsuccessful.



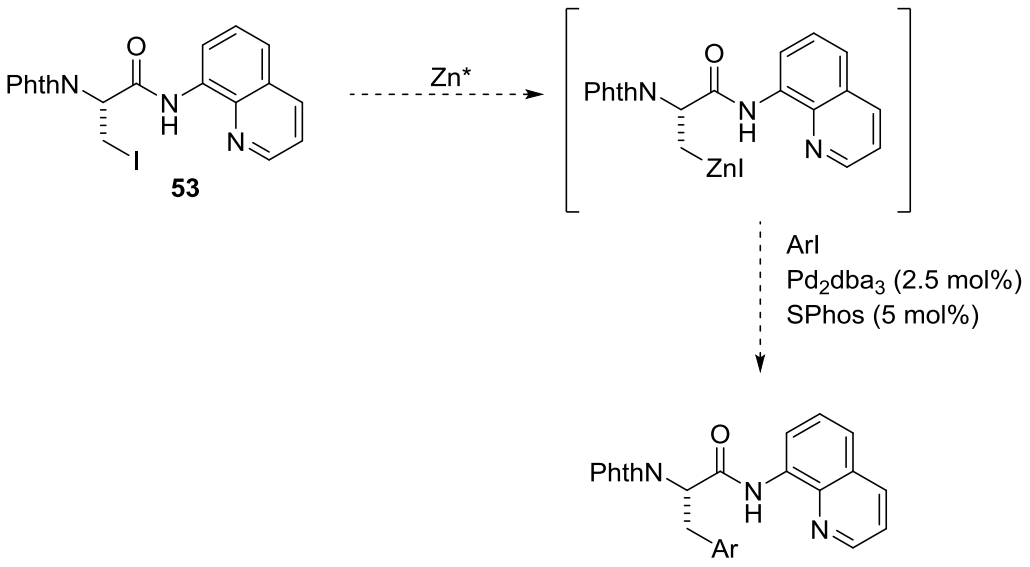
Scheme 3.24: Side chain iodination of alanine derivative 50.

The first aim of this project is to make this reaction scaleable and thus more useful as a synthetic tool. Subsequent aims include the side-chain iodination of a range of amino acid derivatives (Scheme 3.45).



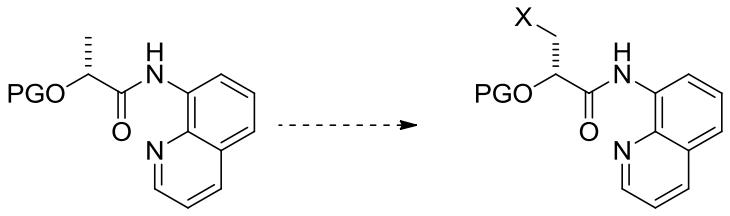
Scheme 3.45: Side chain iodination of amino acid derivatives

The second area of interest is to investigate the reactivity of iodide **53**, in particular employing Negishi cross-coupling conditions to synthesise phenyl alanine derivatives (Scheme 3.46). If successful this would represent a potentially general method for the functionalisation of the methyl side chain of alanine.



Scheme 3.46: Negishi cross-coupling of iodoalanine 53.

The third area of interest is to apply this approach to the C-H activation of lactic acid (Scheme 3.47). Initial investigations will apply the acetoxylation chemistry developed by Corey and co-workers and the iodination method already developed within the Jackson group.



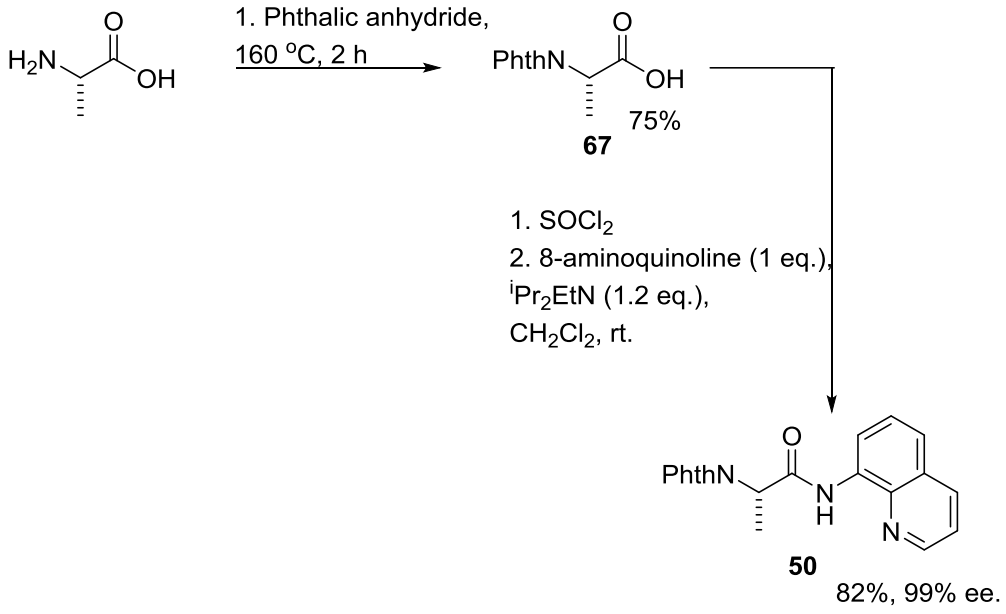
Scheme 3.47: Side chain iodination of lactic acid derivative.

3.3 Results and Discussion

3.3.1 Carbon-Iodine Bond Formation

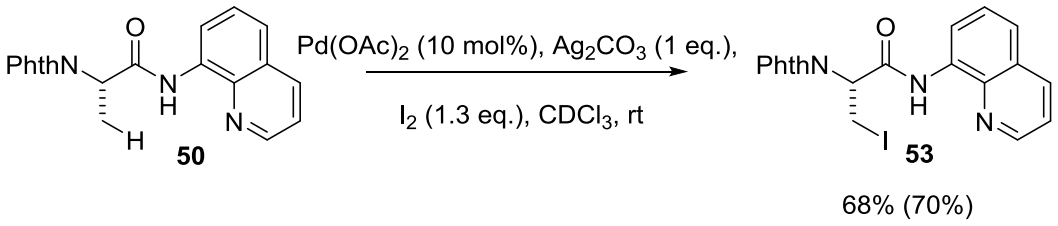
3.3.1.1 Alanine derivative

Initial work began with the synthesis of *N*-phthaloylalanine amide derivative **50**. *L*-Alanine was heated to 160 °C with phthalic anhydride to give phthaloyl protected alanine **67**. Using the method previously developed in the group compound **67** was converted to the corresponding acid chloride using thionyl chloride.[73] Subsequent removal of excess thionyl chloride and addition of 8-aminoquinoline and Hünig's base furnished the desired product in 82% yield and 99% ee. as determined by chiral HPLC (Scheme 3.48). It should be noted that previous synthesis of **50** in the Jackson group using NEt_3 instead of Hünig's base, as carried out by Corey and co-workers, caused racemisation of **50**.[66,73]



Scheme 3.48: Synthesis of alanine derivative 50.

With compound **50** in hand, it was decided to repeat the C-H activation/iodination reaction recently developed in the group on a 0.14 mmol scale (Scheme 3.24). Addition of iodine, catalytic $Pd(OAc)_2$ and stoichiometric Ag_2CO_3 gave the desired iodinated product **53** in 68% yield, comparable with previous results.[73]



Scheme 3.24: Side chain iodination of 50 on a 0.14 mmol scale.

With assurances that the reaction was reproducible on a small scale, it was decided to next look and see whether improvements could be made (Table 3.12). Use of an excess of Ag_2CO_3 was initially examined, but was found to hinder the reaction. Increasing the amount of iodine was examined to see if the yield of iodide **53** could be increased. Addition of 2 equivalents of iodine compared to the previous 1.3, saw an increase of 4% in yield. Although not a substantial increase, it was decided to use this amount for further reactions. The next component to be investigated was the loading of the Pd(II) catalyst. The previous reactions had employed 10 mol%, hence loadings of 5 and 1 mol% were examined and found to yield **53** in 66% and 56% respectively. From this, it suggested 5 mol% $Pd(OAc)_2$ could successfully be employed for this reaction.

Table 3.12: Optimisation of 0.14 mmol scale reaction.

Entry	$Pd(OAc)_2$ (eq.)	Ag_2CO_3	I_2 (eq.)	Yield 53 (%)
1	0.1	1	1.3	68
2	0.1	1.3	1.3	59
3	0.1	1	2	72
4	0.05	1	2	66
5	0.01	1	2	54

Reactions carried out at 0.1 M concentration with respect to compound **50** in $CHCl_3$ at rt for 3 days.

Having undertaken this groundwork for the reaction, the issues of scalability were considered. Previous attempts at scaling had been unsuccessful meaning all reactions had been limited to a 0.14 mmol scale. In order for this iodination reaction to be a viable synthetic strategy it would be necessary to get the reaction working at least on a 1 mmol scale. To start with the scale was doubled to 0.3 mmol with respect to starting material **50** (Table 3.13).

The lower yield obtained (27%) suggests that 5 mol% Pd(II) loading was not feasible at this increased scale (Entry 1). Although use of 10 mol% Pd(II) loading did give an improved yield increase, it was still significantly less than the yields achieved on the smaller scale. Attempts at both lowering and increasing the temperature both saw reductions in yield.

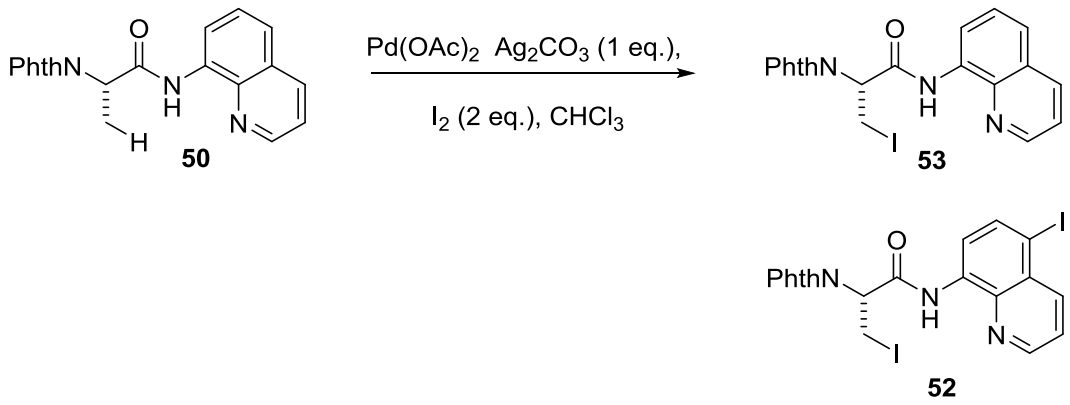


Table 3.13: Optimisation of 0.3 mmol scale reaction.

Entry	$Pd(OAc)_2$ (eq.)	Temp. (°C)	$CHCl_3$ (mL)	Concentration of 50 (M)	Yield 53 (%)	Yield 52 (%)
1	0.05	rt	3	0.1	23	[a]-
2	0.1	rt	3	0.1	51	[a]-
3	0.1	40	3	0.1	34	[a]-
4	0.1	0	3	0.1	38	[a]-
5	0.1	rt	2	0.15	59	[a]-
6[b]	0.1	rt	2	0.15	45	28

[a]Trace amount observed in ^1H NMR spectrum, [b]Solvent completely evaporated. Reactions carried out on 0.3 mmol scale with respect to compound **50** with 1 eq Ag_2CO_3 and 2 eq I_2 for 3 days.

The effect of increasing the concentration of the reaction was then investigated. Two reactions were carried out using 2 mL of solvent to give increased 0.15 M concentrations. In one of the cases the yield increased to 59% suggesting that concentration played a large role in the efficiency of these reactions. In the second case, the solvent evaporated completely. This interestingly led to almost complete consumption of the starting material. However, rather than just producing desired product **53**, bis-iodinated product **52** was also observed.

The scale of reaction was further increased using 0.6 mmol of starting material. Again, using 2 eq. I_2, 0.1 eq. $Pd(OAc)_2$ and 1 eq. Ag_2CO_3, a set of C-H activation/iodination reactions in which the concentration was varied were carried out (Table 3.14). For previous experiments the reaction time had been 3 days, however on monitoring the reactions via ^1H NMR spectroscopy, no further reaction of the starting material was seen up to 7 days.

It was found that by decreasing the volume of solvent from 6 to 3 mL (on a 0.6 mmol scale), thus increasing the concentration of reactants, the yield of the desired C-H activated product could be increased. However, upon decreasing the volume further, the yield of the unwanted bis-iodinated side product increased. It was therefore found that on a 0.6 mmol scale comparable yields to those previously obtained on a 0.14 mmol scale could be achieved, although isolation was complicated by the presence of the bis-iodinated by-product **52**.

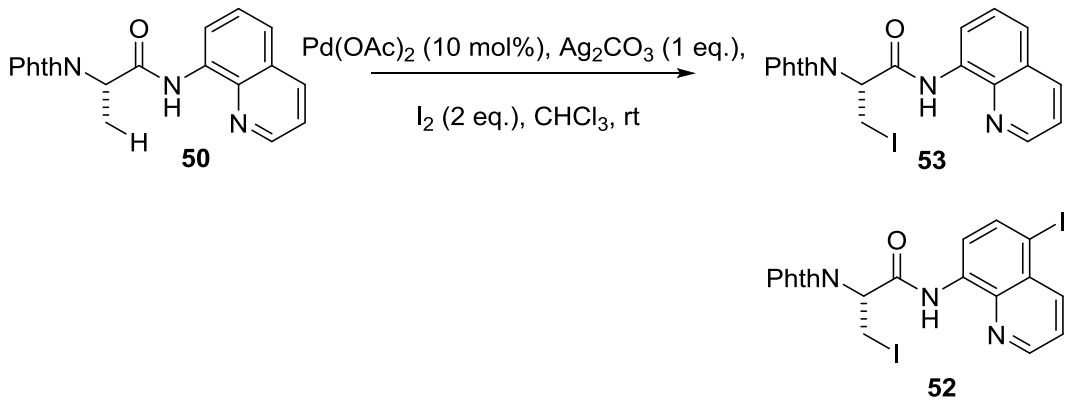


Table 3.14: Optimisation of 0.6 mmol scale reaction.

Entry	$CHCl_3$ (mL)	Concentration of 50 (M)	Yield 53 (%)	Yield 52 (%)	Total C-H activation (%)
1	6	0.1	41	-[a]	43
2	5	0.12	48	8	56
3	4	0.15	53	7	70
4	3	0.2	67	11	78
5	2	0.3	48	24	72
6	1	0.6	43	32	75

[a]Trace amount observed in ^1H NMR spectrum. Reaction carried out over 3 days. Reactions carried out on 0.6 mmol scale with respect to compound **50** with 1 eq Ag_2CO_3, 0.1 eq $Pd(OAc)_2$ and 2 eq I_2 for 7 days.

The initial aim was to get the C-H activation/iodination working at a 1 mmol scale. The optimum conditions for the 0.6 mmol scale were applied at the 1 mmol scale (Table 3.14, Entry 4). However on use of these conditions, the yield decreased significantly (Entry 1). It was again decided to try and increase the yield by increasing the reaction concentration. This was not as successful as it had been previously. Although the overall C-H activation and iodination of the side chain did noticeably increase, the unwanted aromatic iodination also increased concurrently.

Table 3.15: Optimisation of 1 mmol scale reaction.

Entry	$CHCl_3$ (mL)	Concentration of 50 (M)	Yield 53 (%)	Yield 52 (%)	Total C-H activation (%)
1	6	0.16	26	4	30
2	4	0.25	35	14	49
3	2	0.5	39	22	61
4	1	1	45	32	77

Reactions carried out on 1 mmol scale with respect to compound **50** with 1 eq Ag_2CO_3, 0.1 eq $Pd(OAc)_2$ and 2 eq. I_2 over 7 days.

It was next envisaged that by maintaining a low volume of solvent, but decreasing the loading of iodine, the extent of bis-iodination could be retarded. Reduction in the amount of iodine (from 2 to 1.5 eq.) gave 68% yield of desired product **53** in addition to 9% of by-product **52** (Table 3.16). Surprisingly, it was found that by decreasing the amount of iodine to 1.2 and 1.0 equivalents a huge decrease in yields, to 19 and 3% respectively, was observed.

Table 3.16: Optimisation of 1 mmol scale reaction.

Entry	I_2 (eq.)	Yield 53 (%)	Yield 52 (%)	Total C-H activation (%)
1	2	45	32	77
2	1.5	71	11	87
3	1.2	19	0	19
4	1	3	0	3

Reactions carried out on 1 mmol scale and 1 M concentration with respect to compound **50** with 1 eq. Ag_2CO_3 and 0.1 eq $Pd(OAc)_2$ over 7 days.

With the result obtained in entry 2, the reaction time was investigated. It was found that the reaction could be successfully carried out over 5 days rather than the 7 days used previously (Table 3.17).

Table 3.17: Optimisation of 1 mmol scale reaction.

Entry	Reaction time (d)	Yield 53 (%)	Yield 52 (%)	Total C-H activation (%)
1	7	71	11	82
2	5	68	9	77
3	3	38	6	44

Reactions carried out on 1 mmol scale and 1 M concentration with respect to compound **50** with 1 eq Ag_2CO_3, 0.1 eq $Pd(OAc)_2$ and 1.5 eq. I_2.

The scaleablility of the C-H activation/iodination was probed further and a reaction on a 2 mmol scale was carried out. Initial attempts using the optimised conditions developed on the 1 mmol scale were low yielding. However upon increasing the size of the reaction vessel, a comparable yield of 71% was obtained (Table 3.18). This is most likely due to the heterogeneous nature of the reaction. As the insoluble by-product AgI is formed, it forms a coating on the bottom of the reaction vessel if stirring is not adequate. This means that the sparingly soluble Ag_2CO_3 is unable to react at the surface of the reaction. By ensuring efficient stirring the reaction was found to successfully scale up to 10 mmol using the optimised conditions developed at the 1 mmol scale. In addition, at the larger scale where mechanical stirring could be employed, a large reduction in the reaction time can be observed (Entry 5).

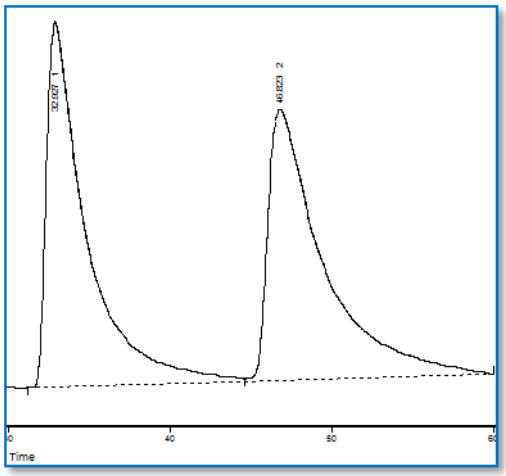
Table 3.18: Further scaling of reaction.

Entry	Scale (Mmol)	Reaction time (d)	Yield 53 (%)	Yield 52 (%)
1	1	5	68	9
2	2	7	67	11
3	4	7	66	7
4	10	9	69	8
[a]5	10	2	66	9

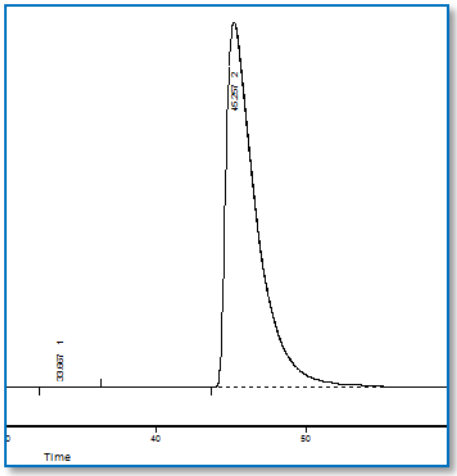
[a]Overhead stirring. Reactions carried out at 1 M concentration with respect to compound **50** with 1 eq. Ag_2CO_3, 0.1 eq. $Pd(OAc)_2$ and 1.5 eq. I_2.

The results presented above in Table 3.18, show that the original problem of scaleability of the C-H activation and iodination of alanine derivative **50** have been overcome. This has principaly been achieved by ensuring efficient stirring of the heterogeneous reaction mixture.

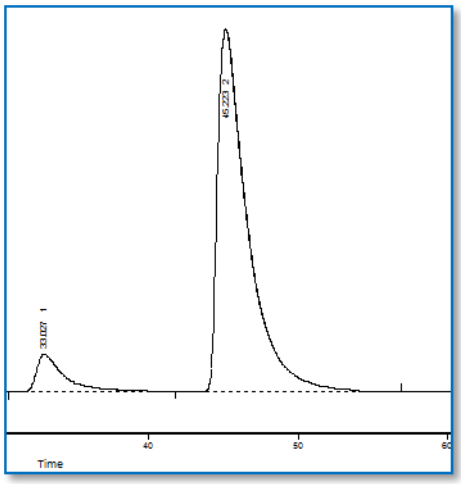
To ensure that the iodination reaction was occurring with no loss of the enantiopurity from starting material **50**, chiral HPLC conditions were developed (Figure 3.4). The conditions were first found for racemic iodide **53** showing clear separation of the 2 isomers with retention times of (*S*)-**53** 33.02 min, (*R*)-**53** 45.22 min. Iodide **53**, synthesised from enantiopure starting material, was then subjected to the same chiral HPLC conditions and pleasingly a peak for only one isomer was observed. To ensure that the peak corresponded to one of the isomers observed in the chromatogram of the racemic material, a mixture of racemic and enatiopure **53** were subjected to the developed HPLC conditions. As expected, 2 peaks were observed, with one peak being larger due to the addition of enantiopure **53**, thus proving that compound **53** has been synthesised enantioselectively in 99% ee.



Chiral HPLC chromatogram of racemic **53**.



Chiral HPLC chromatogram of enantiopure **53**.



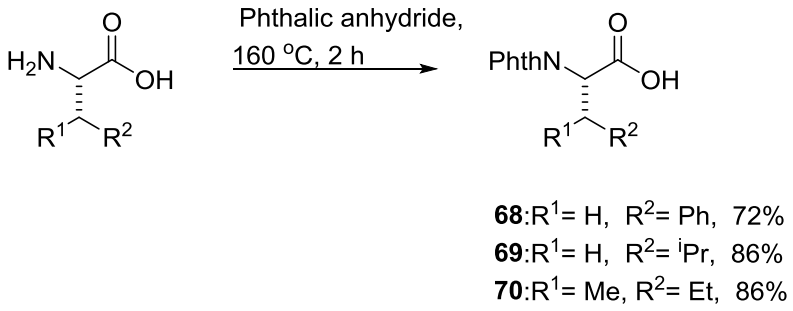
Chiral HPLC chromatogram of racemic and enantiopure **53** combined.

Figure 3.4: Chiral HPLC chromatogram of iodide 53. carried out on a Lux 3u cellulose-2 column using 20% *i*PrOH in hexane with a flow rate of 0.7 mL/min

3.3.1.2 Amino acid derivatives

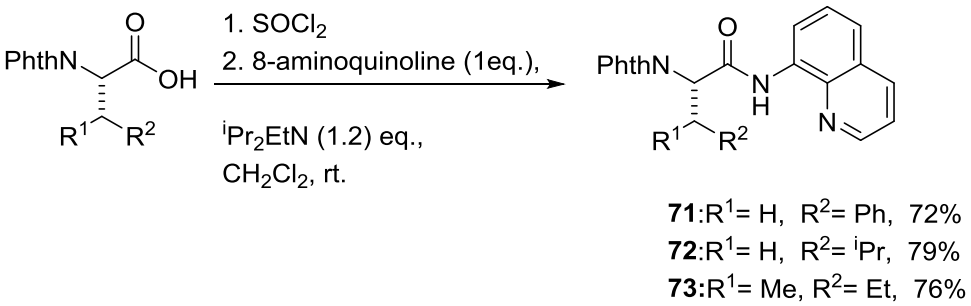
With a successful scaleable method for the C-H activation and subsequent iodination of alanine derivative **50** having been developed, the next step was to investigate application to other amino acid derivatives. So, phenylalanine, leucine and isoleucine were each heated with phthalic anhydride at 160 °C to

give the *N*-phthaloyl protected products **68**, **69** and **70** respectively in good yields (Scheme 3.49).



Scheme 3.49: *N*-Phthaloyl protection of amino acids.

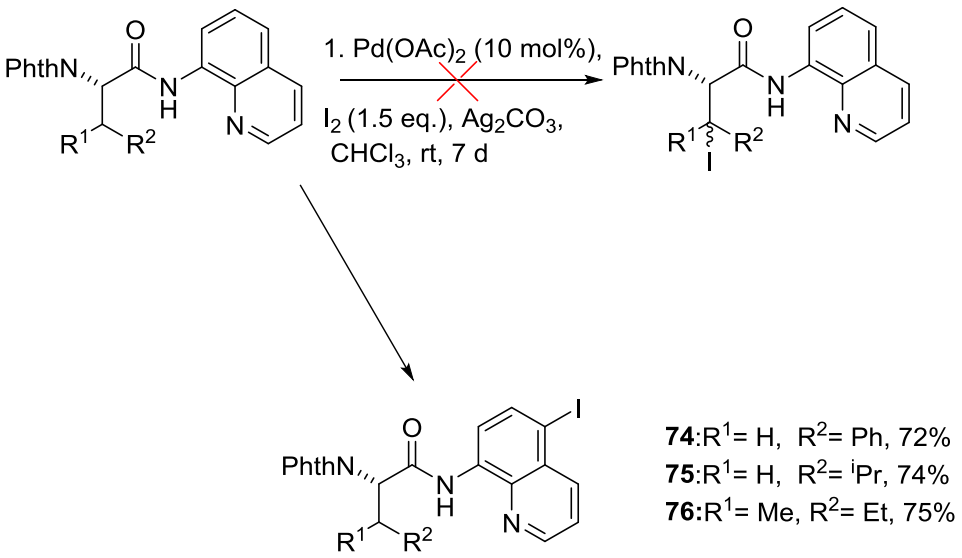
N-phthaloyl protected amino acids **68**, **69** and **70** were converted to the corresponding acid chlorides via the reaction with thionyl chloride. Subsequent removal of excess thionyl chloride and addition of 8-aminoquinoline and Hünig's base furnished the desired products **71**, **72** and **73** in good yields (Scheme 3.50).



Scheme 3.50: Synthesis of 8-aminoquinoline amide amino acid derivatives.

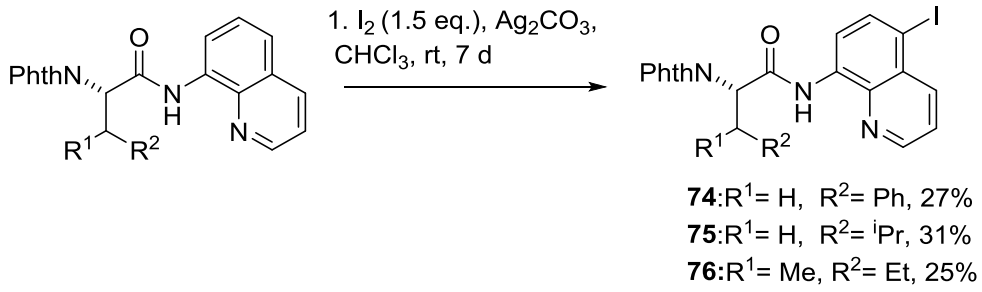
With compounds **71**, **72** and **73** in hand, each was subjected to the C-H activation/ iodination conditions developed for alanine derivative **50** on a 1 mmol scale (Scheme 3.51). Disappointingly none of the desired C-H activation product was obtained for any of the starting materials, rather the

aromatic iodination products **74**, **75** and **76** were isolated in 72, 74 and 75% yields respectively. This suggests that the larger side chains of **71**, **72**, and **73** compared to alanine derivative **50** hinder the C-H activation and iodination reaction, allowing the unwanted aromatic iodination to become the major reaction pathway.



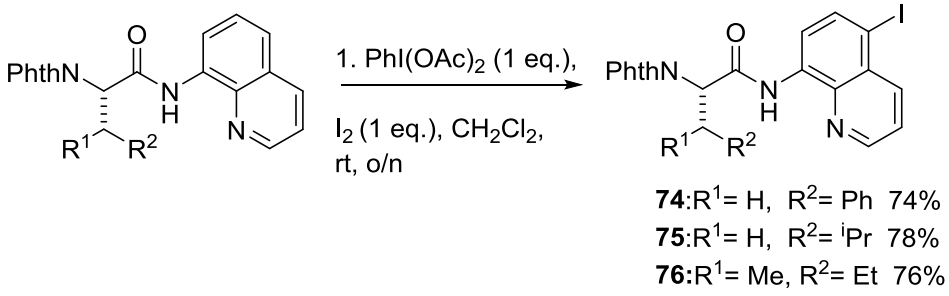
Scheme 3.51: Attempted side chain iodination of amino acid derivatives.

The reactions were repeated in the absence of $Pd(OAc)_2$ to see if the aromatic iodination still occurred (Scheme 3.52). This time, aromatic iodinated products **74**, **75** and **76** were isolated in reduced yield of 27, 31 and 25% respectively. This suggests that the presence of $Pd(OAc)_2$ enhances the unwanted aromatic iodination via the formation of AcOI as discussed previously (Page 59, Scheme 3.25), but some aromatic iodination is still occurring.



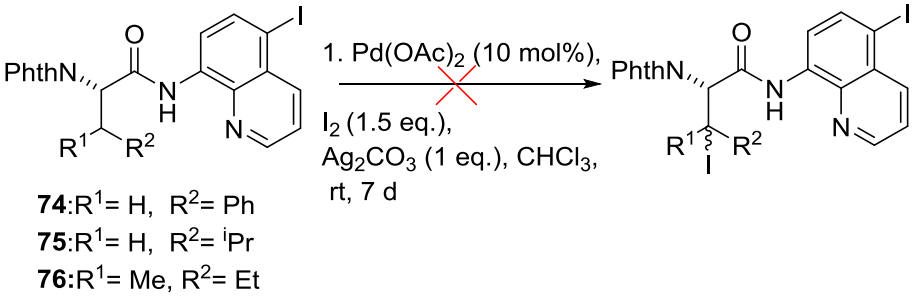
Scheme 3.52: Effect of Ag_2CO_3 and I_2 in the absence of $Pd(OAc)_2$ on aromatic iodination.

To see if C-H activation could be promoted, compounds **71**, **72** and **73** were subjected to standard aromatic iodination conditions to give products **74**, **75** and **76** respectively in good yields (Scheme 3.53). This blocks the reactive *para* site of the aromatic ring preventing the unwanted side reaction in subsequent C-H activation reactions.



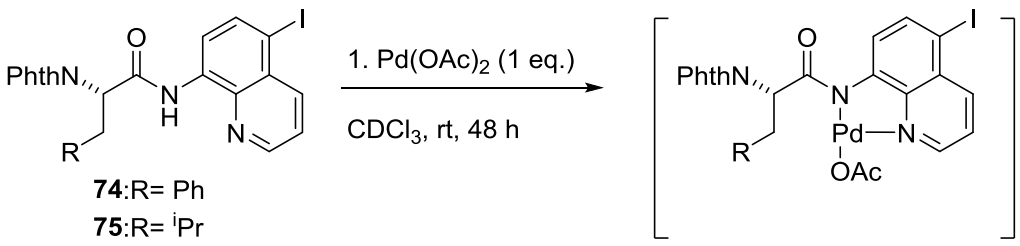
Scheme 3.53: Aromatic iodination of amino acid derivatives.

Compounds **74**, **75** and **76** were each treated with catalytic $Pd(OAc)_2$, iodine and Ag_2CO_3 on a 1 mmol scale, but again no C-H activation products were observed and the starting materials were recovered quantitatively (Scheme 3.54). This suggests that the larger side chains of **74**, **75** and **76** were still preventing C-H activation under these conditions.



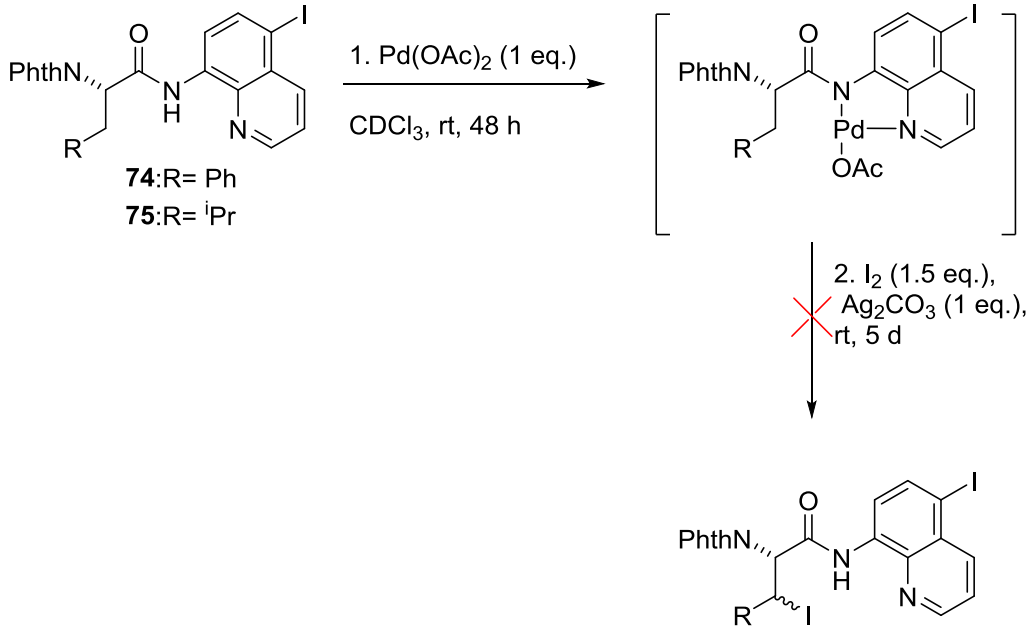
Scheme 3.54: Attempted side chain iodination of amino acid derivatives.

It was decided to focus efforts to achieve C-H activation on **74** and **75** rather than **76**, as Pd(II) insertion into secondary C-H bond compared to a tertiary C-H bond should be easier. In order to check that initial coordination of the 8-aminoquinoline group to $Pd(OAc)_2$ was occurring, compounds **74** and **75** were mixed with stoichiometric $Pd(OAc)_2$ in $CDCl_3$ and the resulting products observed by ^1H NMR spectroscopy (Scheme 3.55). For phenylalanine derived compound **74** the α-proton shifted from 5.46 to 5.71 and the CH_2 protons shifted from 3.76-3.85 to 4.03 and 4.72. For leucine derived compound **75** the α-proton shifted from 5.23 to 5.40 and the CH_2 protons shifted from 2.65 and 2.12 to 2.76 and 2.98. Work carried out previously in the Jackson group has shown similar changes to the proton shifts of alanine derivative **50** due to complexation with $Pd(OAc)_2$.[73] This suggests that the 8-aminoquinoline group of compounds **74** and **75** is also coordinating to $Pd(OAc)_2$.



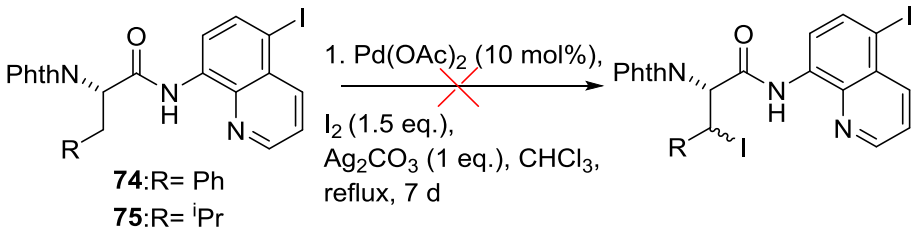
Scheme 3.55: Coordination of the 8-aminoquinoline group to Pd(II).

With evidence in hand that for both compounds **74** and **75** the initial 8-aminoqinoline-Pd(II) complex was being formed, the reaction mixtures were treated with I_2 and Ag_2CO_3 to try and induce the desired C-H activation and iodination reaction (Scheme 3.56). However again in neither case was evidence for C-H activation observed in the crude ^1H NMR spectrum and starting materials **74** and **75** were isolated quantitatively.



Scheme 3.56: Attempted side chain iodination of amino acid derivatives.

As a final attempt to promote C-H activation in compounds **74** and **75**, the reaction was repeated using the catalytic conditions but this time with heating at 62 °C to see if this could overcome the activation barrier and allow the desired reaction to take place. Disappointingly, again only starting materials **74** and **75** were isolated independently (Scheme 3.57). As many C-H activation reactions in the literature using these substrates require a high temperature to work,[66,79-81] heating the reaction to 100 °C in toluene was also carried out, but again no reaction took place.

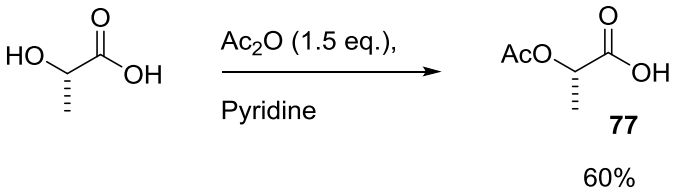


Scheme 3.57: Attempted side chain iodination of amino acid derivatives.

The iodination reactions of **74**, **75** and **76** have proved unsuccessful even though they been shown to undergo alternative $Pd(OAc)_2$ catalysed C-H activation reactions by Corey and co-workers.[66] In the case of Corey and co-workers a $Mn(OAc)_2$ derived Lewis acid was required to facilitate the dissociation of the acetate from the palladium to allow for the C-H activation to take place. The absence of a Lewis acid to assist the removal of the acetate group in the attempted iodination reactions of the more sterically demanding substrates **74**, **75** and **76** could be one reason why the reaction does not occur.

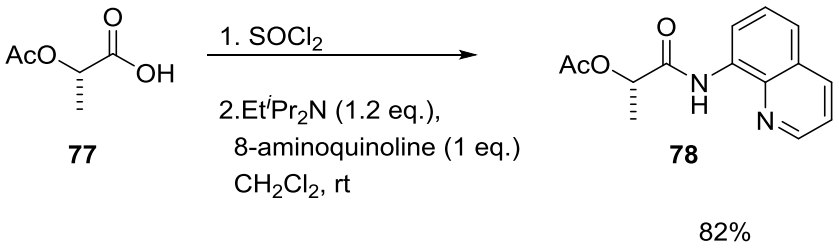
3.3.1.3. Lactic acid derivative

Having been unsuccessful applying the C-H activation conditions developed for alanine derivative **50** to other amino acid compounds, it was thought that the analogous lactic acid derivative might be suitable to undergo a similar C-H activation/iodination process. An acetyl group seemed an obvious starting point for protecting the alcohol group, due to its ease of attachment and removal, in addition to being stable to the conditions required to create the amide functionality. Acetylation was carried out in the presence of pyridine and acetic anhydride following a literature procedure (Scheme 3.58).[88] The crude product underwent vacuum distillation to give the pure product **77** as a colourless oil in 60% yield.



Scheme 3.58: Acetylation of lactic acid.

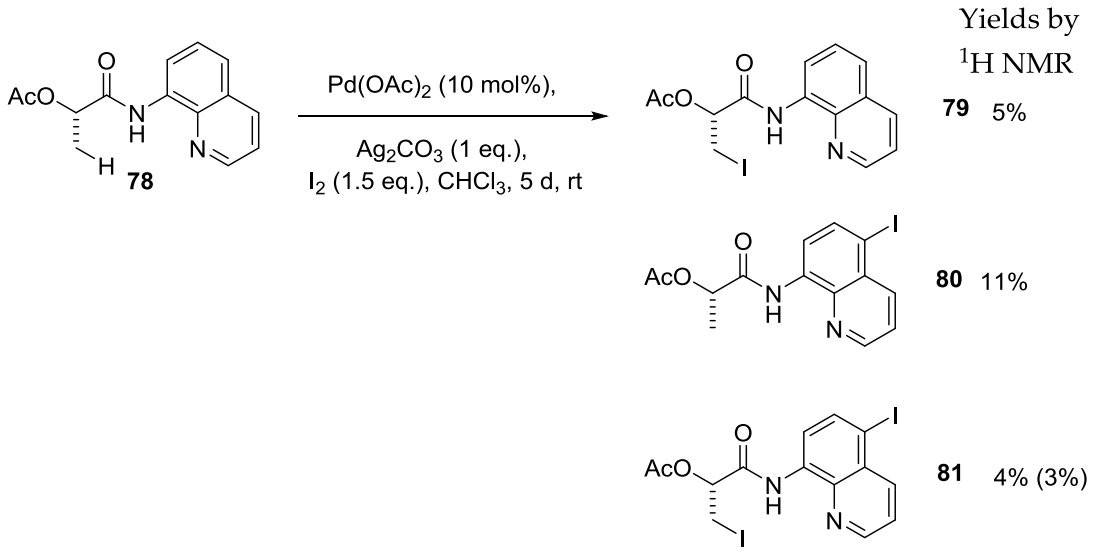
With the acetylated lactic acid **77** in hand, preparation of quinoline amide derivative **78** was carried out using the conditions developed for alanine derivative **50** to prevent racemisation. Thus compound **77** was converted to the corresponding acid chloride and subsequent reaction with the 8-aminoquinoline in the presence of Hünig's base gave desired product **78** in good yield (Scheme 3.59).



Scheme 3.59: Synthesis of 8-aminoquinoline amide lactic acid derivative.

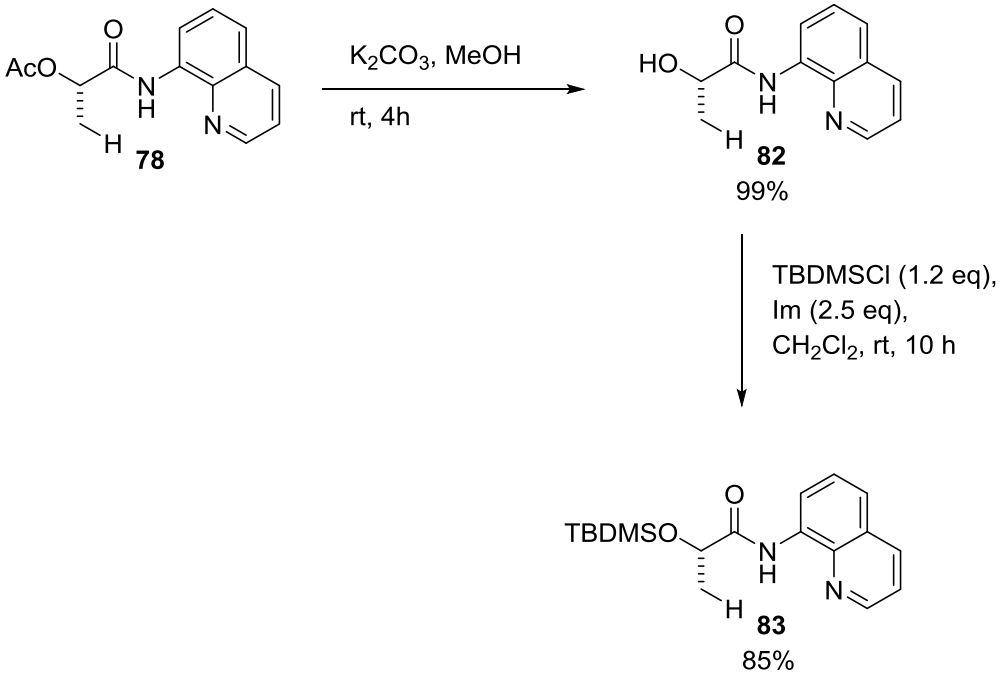
It was decided initially to investigate the C-H activation/ iodination reaction with compound **78**. The reaction was initially carried out using the conditions that had previously been found for alanine derivative **50** (Scheme 3.60). The ^{1}H NMR spectrum of the crude product showed a 5% conversion of **78** to the desired C-H activation product **79** as well as 11% of the unwanted aromatic iodination product **80**. These products could not be isolated separately as they ran with the same R_f value on a silica gel column. In addition to compounds **79** and **80**, bis-iodide **81** was also formed in 4%

yield by ^{1}H NMR spectroscopy and was isolated in 3% yield. The remaining material was accounted for by starting material.



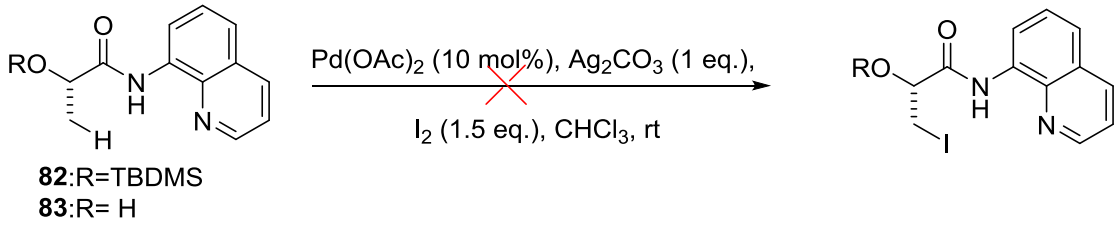
Scheme 3.60: Attempted C-H activation of lactic acid derivative 78.

To try and increase the yield of the reaction an alternative protecting group for the alcohol was considered. Yu and co-workers had previously shown a TBDMS protecting group to be suitable in C-H activation reactions.[70] Both the free alcohol and TBDMS protected derivatives **82** and **83** were synthesised in good yield (Scheme 3.61).



Scheme 3.61: Synthesis of lactic acid derivatives

Compounds **82** and **83** were each subjected to the catalytic $Pd(OAc)_2$, iodine and Ag_2CO_3 on a 1 mmol scale (Scheme 3.62). In both cases none of the desired product was observed but again there was evidence of aromatic iodination.



Scheme 3.62: Attempted C-H activation of lactic acid derivatives.

The iodination of acetyl protected compound **78** was further investigated as it had shown the most promising results. The amount of iodine in the reaction was increased to see if this would in turn increase the yield of C-H

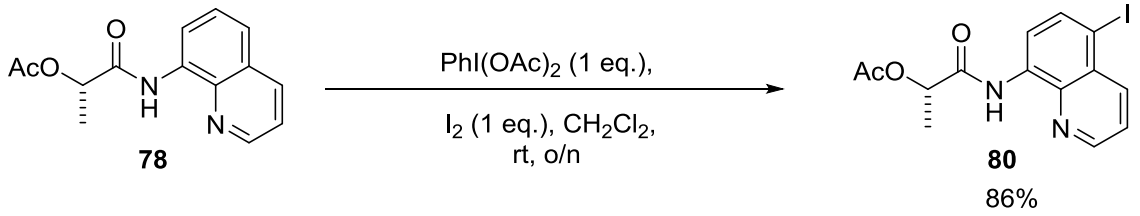
activated product (Table 3.19). The amount of iodine was increased incrementally from 1.5 to 3 equivalents, but rather than seeing an increase in product **79**, only the amount of aromatic iodination increased.

Table 3.19: Attempted optimisation of C-H activation/Iodination on a 1 mmol scale.

Entry	Iodine (eq.)	s.m 78 (%)	Mono-iodide 79 (%)[a]	Bis-iodide 81 (%)	Aromatic iodide 80 (%)[a]
1	1.5	81	5	3	6
2	2.0	48	4	6	37
3	2.5	35	2	8	49
4	3.0	33	2	8	51

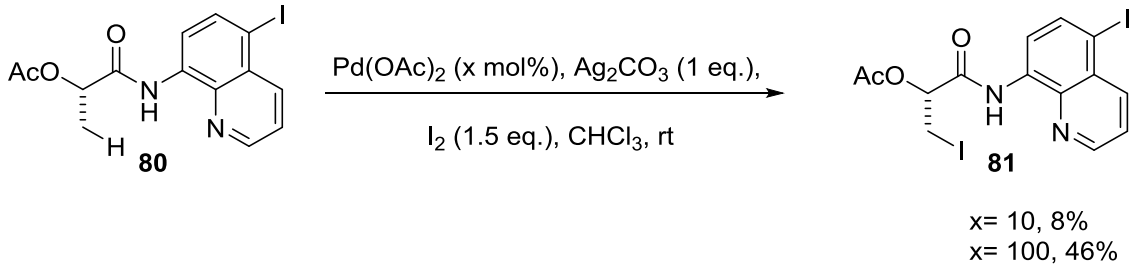
Reactions carried out on 1 mmol scale and 1 M concentration with respect to compound **78** with 1 eq Ag_2CO_3 and 0.1 eq $Pd(OAc)_2$ over 7 days. [a]Based on ^1H NMR of **79** and **80** combined.

In order to facilitate the C-H activation reaction it was necessary to prevent the unwanted aromatic iodination reaction from occurring. Thus compound **78** was transformed to **80** in good yield, blocking the *para* position of the aromatic ring by deliberate iodination using $PhI(OAc)_2$ and iodine, in the same way as shown previously with the amino acid derivatives (Scheme 3.63).



Scheme 3.63: Aromatic iodination of lactic acid derivative 78.

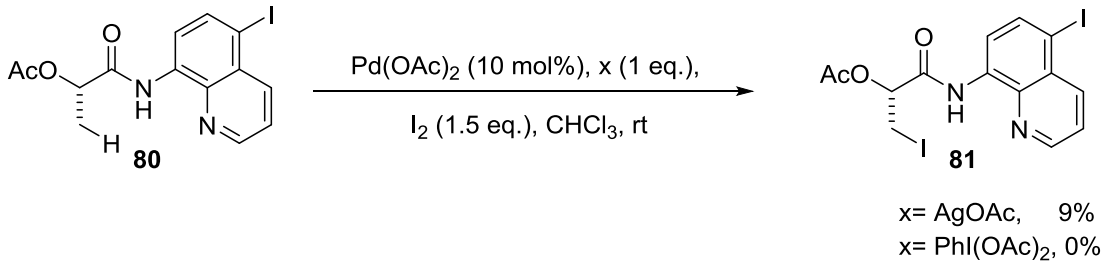
Compound **80** was subjected to the C-H activation conditions using 1.5 eq. of iodine and desired compound **81** was isolated in 8% yield (Scheme 3.64). The fact that with all the experiments the yield had not risen above 10% suggested that reaction was not catalytic and that Ag_2CO_3 was not regenerating the active Pd(II) catalyst. The reaction was repeated using a stoichiometric amount of $Pd(OAc)_2$ and product **81** was isolated in 46% yield suggesting that this may be the case.



Scheme 3.64: Attempted C-H activation of lactic acid derivative 80.

It became apparent that an alternative to Ag_2CO_3 was required. The use of the more soluble AgOAc was investigated. On subjecting **80** to the modified C-H activation conditions, **81** was formed in 9% showing that the reaction was still not catalytic (Scheme 3.65). $PhI(OAc)_2$ has been shown in the literature to regenerate $Pd(OAc)_2$ in C-H activation iodination reactions on

other substrates,[70,71] thus it was tried as an alternative to Ag_2CO_3. On applying these modified conditions to **80**, this time none of the desired product was obtained and only a small amount of the starting material remained, according to the crude ^1H NMR spectrum. The use of $PhI(OAc)_2$ had lead to almost complete degradation of the starting material **80**. This is not completely surprising as the use of $PhI(OAc)_2$, $Pd(OAc)_2$ and I_2 reaction conditions with alanine derivative **50** has also been reported to lead to decomposition of the starting material, though to a lesser extent.[73]



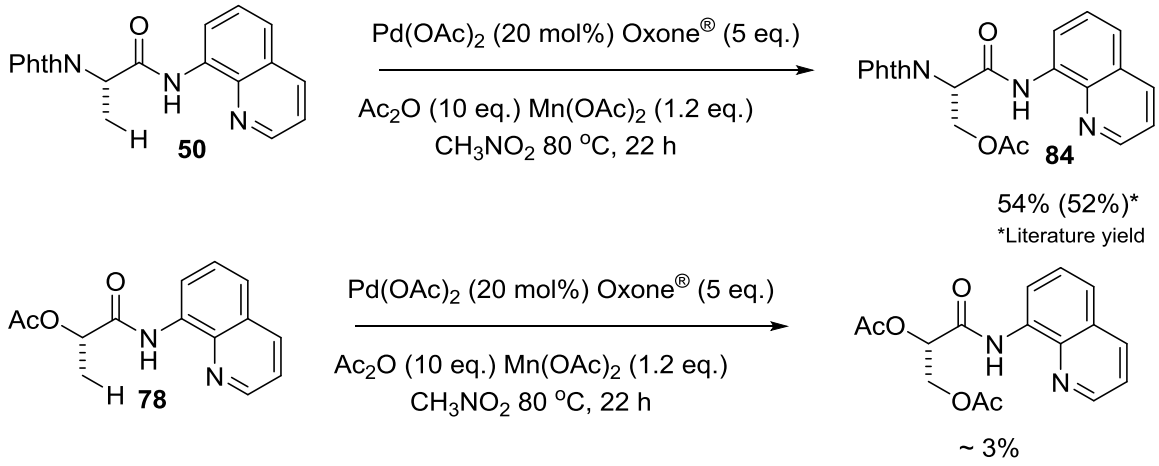
Scheme 3.65: Attempted C-H activation of lactic acid derivative 80.

3.3.2 Carbon-Oxygen Bond Formation

The side chain C-H activation/acetoxylation reaction reaction of amino acids has previously been demonstrated by Corey and co-workers.[66] Following on from this, investigations were carried out to see if the reaction conditions developed by Corey could be extended to lactic acid derivative **78**, with the view of providing a route to synthetically useful glyceric acid derivative.

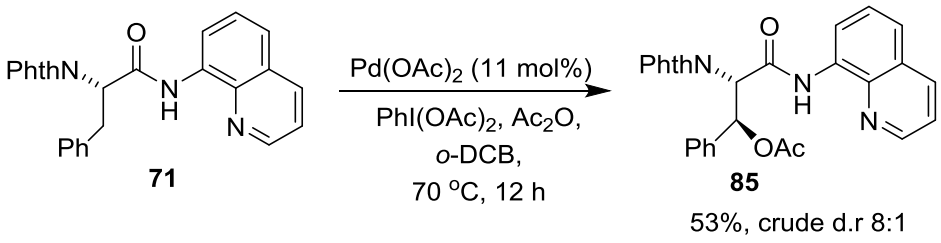
Initially Corey's reaction was repeated on alanine derivative **50** to check it worked in our hands. The reaction was carried out successfully to give **84,** in comparable yields to those reported by Corey (Scheme 3.66). However after subjection of compound **78** to these reaction conditions the ^1H NMR spectrum was inconclusive displaying multiple compounds present. This is

probably due to the harsh condition of the reaction which was not tolerated by the acetyl protecting group present in **78.**



Scheme 3.66: Acetoxylation reaction using conditions developed by Corey and co-workers.

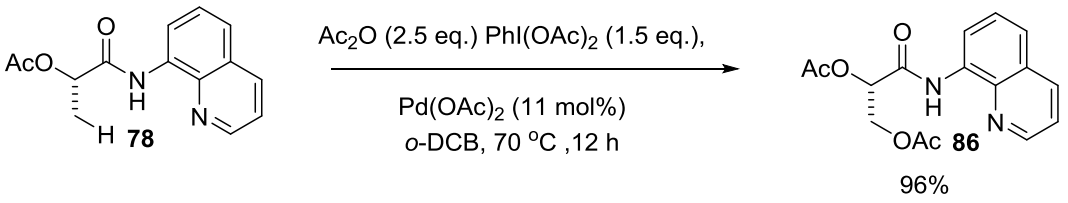
Recently, Daugulis and co-workers have reported the C-H activation and acetoxylation of phenylalanine **71** using $Pd(OAc)_2$, $PhI(OAc)_2$ and Ac_2O gave product **85** in moderate yield and dr. (Scheme 3.67).[79] Not only are these milder conditions than those employed by Corey but they also use a lower catalytic loading of $Pd(OAc)_2$



Scheme 3.67: Acetoxylation of phenylalanine derivative 71 by Daugulis and co-workers.

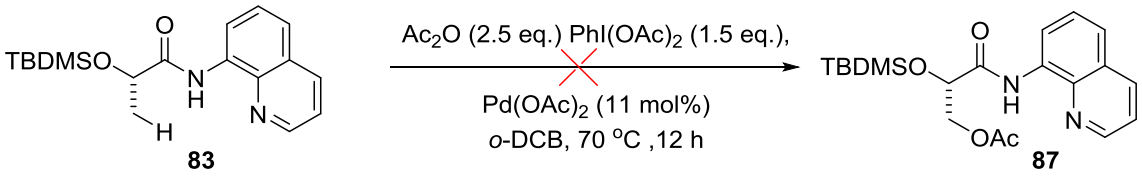
Following this success, lactic acid derivative **78** was subjected to the conditions developed by Daugulis (Scheme 3.68). Pleasingly the ^1H NMR

spectrum of the crude reaction material showed complete conversion of starting material **78** to desired product **86**. This was isolated in 96% yield providing the first reported example of the catalytic C-H activation of a lactic acid derivative.



Scheme 3.68: Acetoxylation of lactic acid derivative 78.

Continuing from this the C-H activation/ acetoxylation conditions were applied to TBDMS protected derivative **83** with the view of producing product **87** with two different protecting groups present (Scheme 3.69). However on carrying out the reaction only starting material was quantitatively retrieved and no evidence of C-H activation was observed.



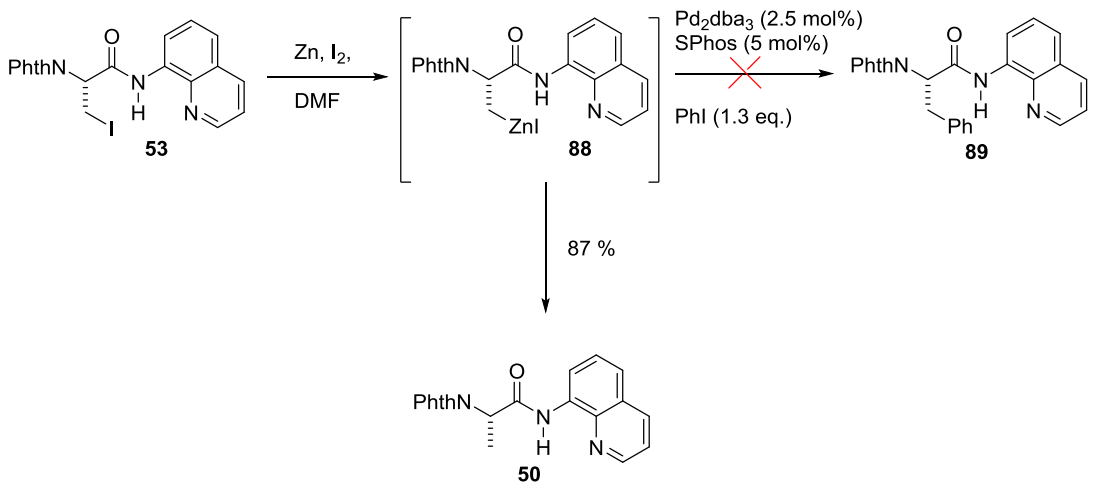
Scheme 3.69: Attempted acetoxylation of lactic acid derivative 83.

3.3.3 Reactions with Iodoalanine 53.

3.3.3.1 Negishi cross-coupling reaction

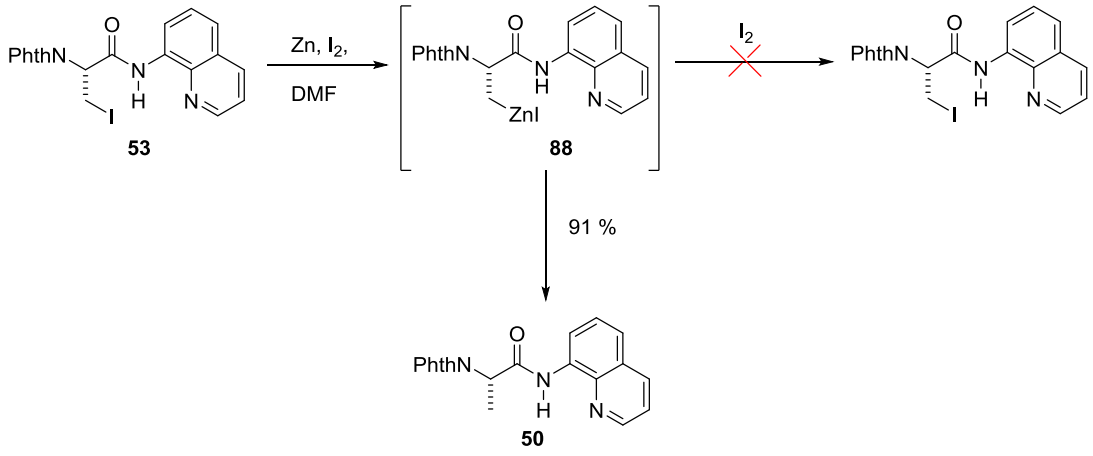
Much of the previous work in the Jackson group has focused on the preparation of enantiomerically pure non-natural amino acids via side chain modification.[18] Alkyl iodides derived from natural amino acids provide precursors to key organometallic intermediates required for carbon-carbon bond forming reactions. Whilst powerful, this approach is restricted by the range of suitable starting materials available. It would be a considerable advance if the range of available alkyl iodides could be increased.

With iodoalanine **53** in hand, it was decided to subject the compound to the standard cross coupling conditions developed in the Jackson group for the synthesis of phenylalanine derivatives (Scheme 3.70).[18] The zinc was activated using iodine in DMF and its insertion into **53** to form organozinc reagent **88** was monitored by TLC. Catalytic Pd_2dba_3 and SPhos were then added, in addition to iodobenzene. Disappointingly none of desired product **89** was observed by ^1H NMR spectroscopy. Following column chromatography, only compound **50** was isolated indicating that protonation of the organozinc reagent had occurred.



Scheme 3.70: Attempted Negishi cross-coupling of organozinc reagent 88 with iodobenzene.

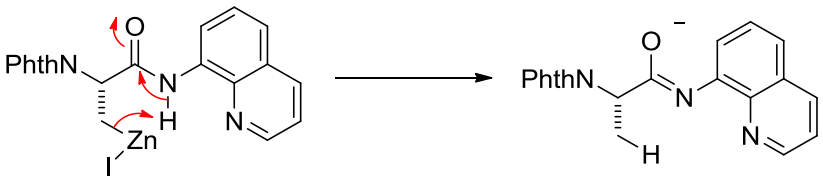
Attempts to trap organozinc reagent **88** were made. The zinc insertion was monitored by TLC until completion at which point the solution of **88** was removed from the excess zinc and quenched with iodine (Scheme 3.71). Again protonated product **50** was the only compound observed opposed to the desired regenerated iodoalanine **53**, suggesting rapid protonation of **88**.



Scheme 3.71: Attempted iodine quench of organozinc reagent 88.

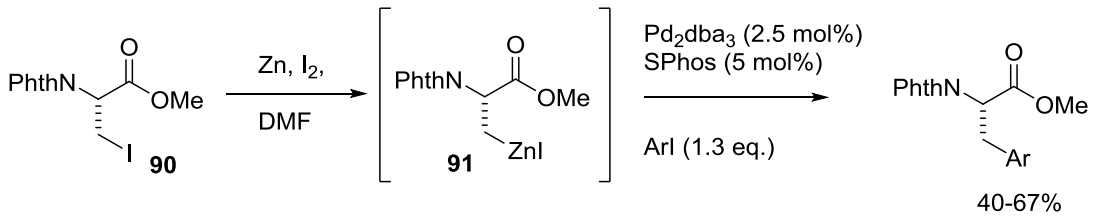
On examination of the structure of the organozinc reagent it can be seen that this rapid protonation may be due to the intramolecular protonation of the

carbon-zinc bond by the amide proton (Scheme 3.72). This is facilitated by the fact the organozinc reagent is set up to form a favourable five-membered ring transition state. A similar process has been reported previously in the Jackson group, with the self protonation of β-benzamido alkylzinc iodides.[89] This was studied kinetically and proven to be a first order reaction.



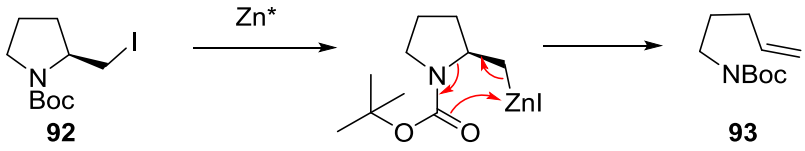
Scheme 3.72: Intramolecular protonation of the organozinc reagent.

Work recently carried out by Ashley Robinson in the Jackson group, has shown that it is possible to cross-couple organozinc reagent **91** derived from methyl ester **90** with a range of aryl halides in moderate to good yields (Scheme 3.73).[73] This supports the suggestion that the unwanted protonation is due to the NH proton of the amide.



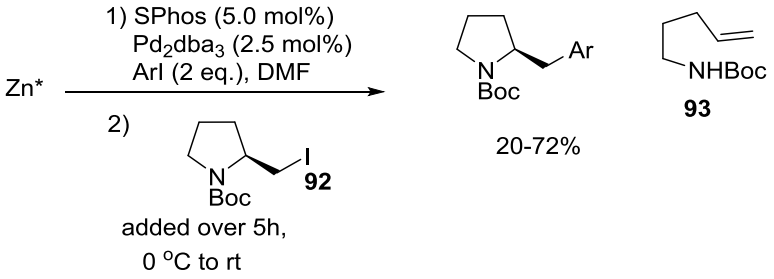
Scheme 3.73: Cross-coupling of organzinc reagent 91 with aryl halides carried out previously in the Jackson group.

A method has recently been developed in the group for the cross-coupling of proline derivatives.[90] Under standard conditions the organozinc reagent undergoes rapid elimination to give alkene product **93** as the major product (Scheme 3.74).



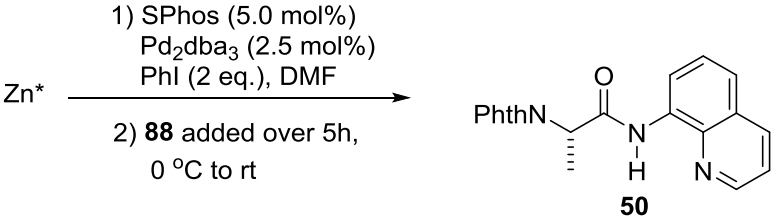
Scheme 3.74: Elimination of *β*-animoalkylzinc reagent.

In order to reduce this unwanted elimination a new cross-coupling method was developed (Scheme 3.75).[90] All reagents apart from proline iodide **92** are added to a solution of activated zinc. Compound **92** is then added in portions (10 mol%) over a period of time at low temperatures. This means that as the organozinc reagent is formed it can react directly with the palladium species formed from the oxidative addition step. Essentially the organozinc reagent is trapped *in situ* reducing the chance of undergoing elimination.



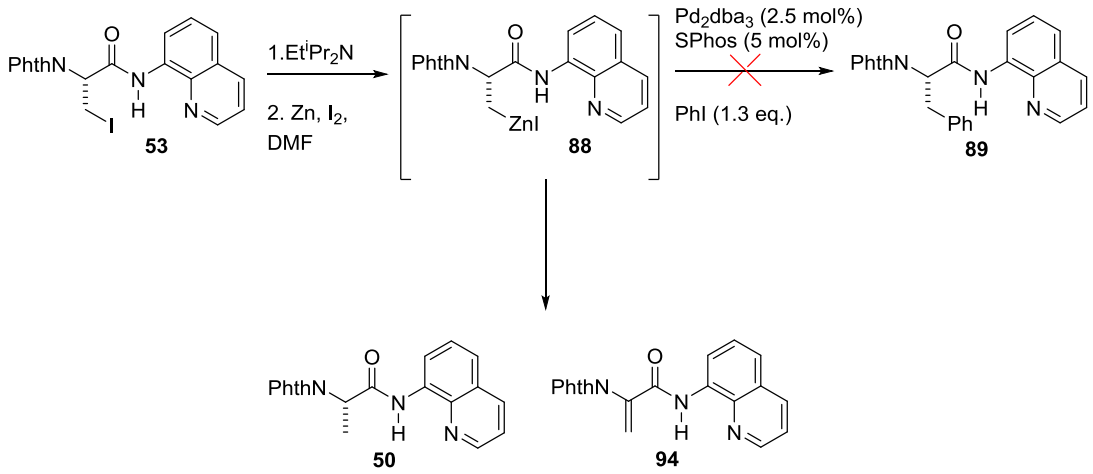
Scheme 3.75: Negishi cross-coupling of proline derivatives previously carried out in the Jackson group.

Although elimination is not a problem for organozinc reagent **88**, it was thought that the *in situ* trapping method could be used to prevent total protonation. However on carrying out this experiment, protonated product **50** was all that was formed, suggesting that degradation of the organozinc reagent is faster than transmetallation (Scheme 3.76).



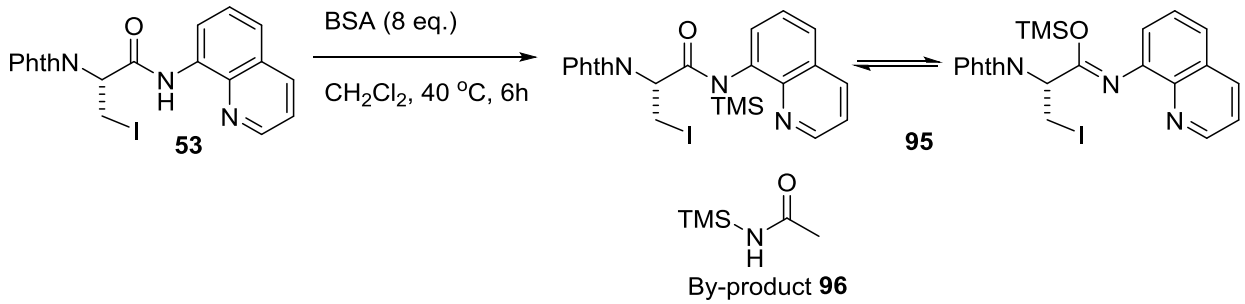
Scheme 3.76: Attempted Negishi cross-coupling of organzinc reagent 88 with iodobenzene.

As the proton on the nitrogen evidently seemed to be the problem, the next course of action was to try to remove it. A cross-coupling reaction was carried out with the addition of 1 eq. of Hünig's base to see if this would suppress the unwanted protonation of the zinc reagent (Scheme 3.77). However, this only led to a mixture of protonated product **50** and dehydroalanine **94** indicating that the base simply eliminates HI.



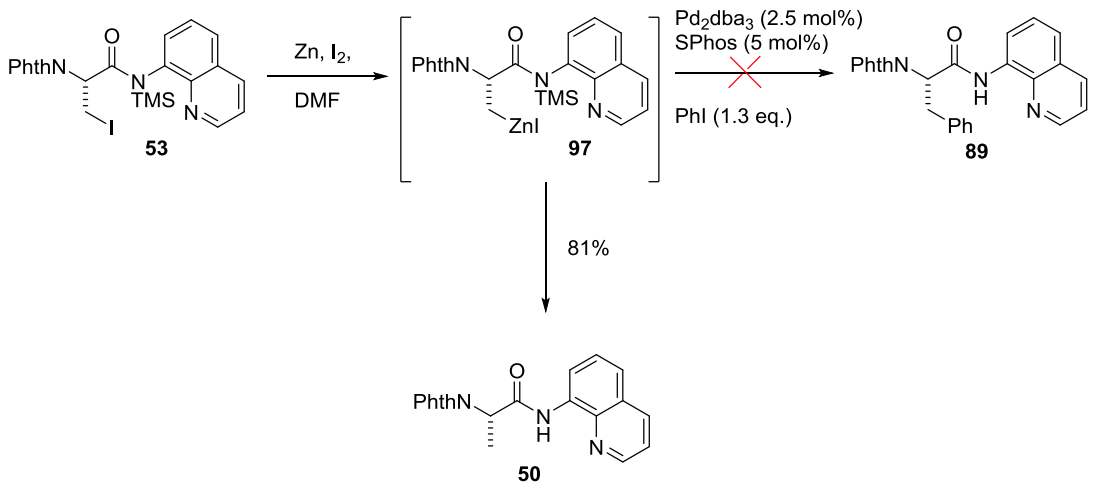
Scheme 3.77: Attempted Negishi cross-coupling of organzinc reagent 88 with iodobenzene.

As the use of base was unsuitable, the idea of temporarily protecting the nitrogen was considered. Introduction of the TMS protection group seemed suitable as the reaction conditions for addition (refluxing with bis(trimethylsilyl)acetamide in CH_2Cl_2) were mild and it could easily be removed in work-up on completion of the cross-coupling reaction. Thus compound **53** and an excess of BSA were refluxed in CH_2Cl_2 for 6 hours (Scheme 3.78). ^{1}H NMR spectroscopy of the resulting compound showed the disappearance of the NH proton and a shift in the position of the α–proton suggesting desired compound **95** had been formed.



Scheme 3.78: TMS protection of the 8-aminoquinoline amide.

Having removed the CH_2Cl_2, crude material **95** was transformed to organozinc reagent **97** and subjected to the cross-coupling conditions, but as before only protonated material **50** was isolated (Scheme 3.79). It was thought that the protic by-product **96** may also cause protonation of the organozinc reagent so the reaction was repeated, this time distilling off the excess BSA and by-product (50 °C/0.1 mbar) before compound **95** was subjected to the cross-coupling conditions. Disappointingly as before only protonated product **50** was formed, suggesting that the TMS protecting group is not stable enough to withstand the cross-coupling reaction. Overall these reactions have shown that compound **53** is not suitable for Negishi cross-coupling reactions.



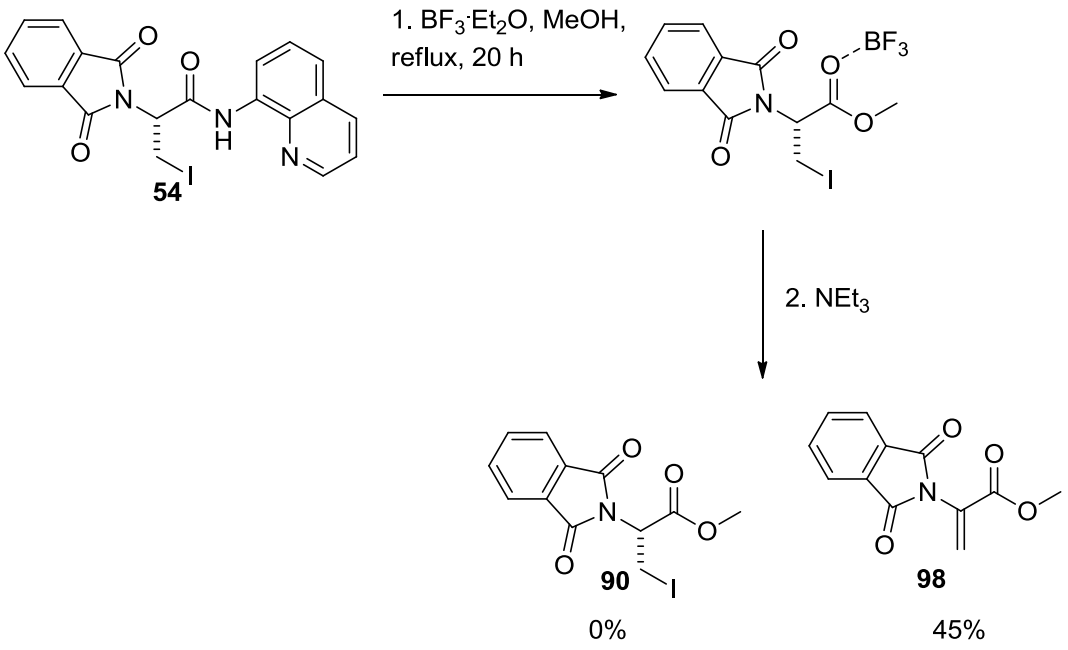
Scheme 3.79: Attempted Negishi cross-coupling of organozinc reagent 97 and iodobenzene.

3.3.3.2 Deprotection of compound 53

Compound **53** has been shown unsuitable for Negishi cross-coupling reactions due to the acidity of the NH proton. Conversely the methyl ester derivative **90** has successfully been converted into the respective organozinc reagent and been coupled with a range of aryl halides.[73] Thus it would be of synthetic use if **53** could be transformed to **90** by deprotection of the 8-aminoquinoline group.

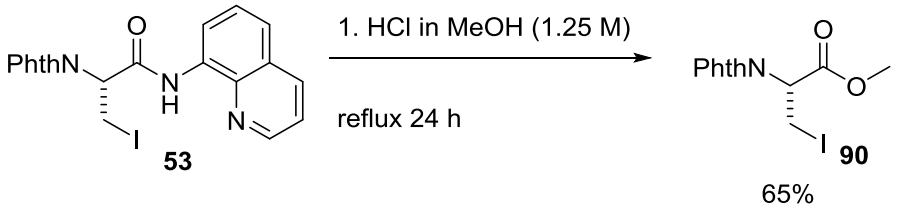
Daugulis and co-workers have successfully deprotected the 8-aminoquinoline group in a range of phenylalanine derivatives using $BF_3{\cdot}Et_2O$ in MeOH to give the corresponding methyl ester products.[79] Compound **53** was therefore subjected to the same conditions; however the desired methyl ester product was not formed (Scheme 3.80). The crude ^1H NMR spectrum showed the presence of several compounds but the major product isolated was eliminated methyl ester **98**. This suggested that the deprotection did work to some extent but it is likely the addition of NEt_3 used to break up the

borane complex caused the elimination of HI. The reaction was repeated this time using a K_2CO_3 wash rather than adding NEt_3. The crude ^1H NMR spectrum showed only a small amount of product **98** due to elimination of HI by the base work-up and the presence of new diastereotopic protons. However on carrying out column chromatography none of the desired product was isolated suggesting that K_2CO_3 was not strong enough to break up the borane complex.



Scheme 3.80: Removal of the 8-aminoquinoline group using conditions employed by Daugulis and co-workers.

It was apparent that an alternative method was needed which did not require the use of base. Chatani and co-workers have shown that refluxing aliphatic acid derivatives in methanolic HCl deprotects the 8-aminoquinoline group and gives the corresponding methyl ester (Scheme 3.81).[81] Pleasingly applying these conditions to compound **53** gave the desired product **90** in 65% yield.

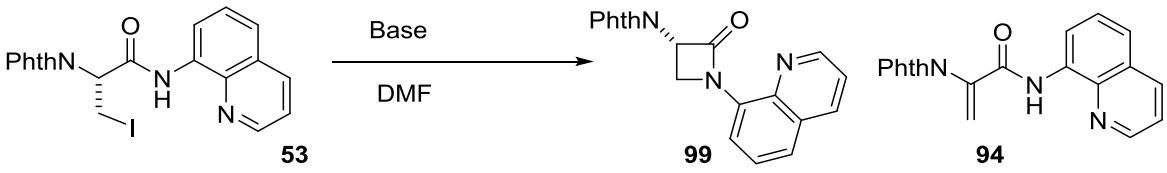


Scheme 3.81: Removal of the 8-aminoquinoline group using conditions employed by Chatani and co-workers.

This reaction means that a route from alanine to phenylalanine derivatives has now been established, using the methodology described in this thesis.

3.3.3.3 *β*-Lactam formation.

It was envisaged that iodoalanine **53** could be used to form the *β*-lactam derivative **99** in the presence of base (Scheme 3.82). However due to the acidity of the *α*–proton, the amount and strength of the base would have to be carefully considered to limit the formation of dehydroalanine **94** (Table 3.20). Initial results using dry DMF with a range of bases saw none of desired product **99** and small amounts of **94**. However on using 'wet' DMF with K_2CO_3, 73% yield of compound **99** was obtained (Entry 4). This presumably is due to small amounts of K_2CO_3 being solubilised by the water present in the DMF.



Scheme 3.82: *β*-Lactamisation of 53

Table 3.20: Effects of varying the base on the *β*-Lactamisation of 53.

Entry	Base (1.1 eq.)	Solvent	Yield 99 (%)	Yield 94 (%)
1	$NaHCO_3$	Dry DMF	0	Trace
2	$^{i}Pr_2EtN$	Dry DMF	0	13
3	K_2CO_3	Dry DMF	0	9
4	K_2CO_3	DMF	85	8
5	$NaHCO_3$	DMF	0	Trace
6	NaH	DMF	11	32

Reactions carried out on an 0.5 mmol scale and 0.1 M concentration with respect to compound **53** at rt for 6h.

In order to ensure reproducibility of results the amount of H_2O in the DMF required that allowed the *β*–lactamisation to occur whilst limiting the unwanted elimination reaction was investigated (Table 3.21). At higher water contents, lactamisation still occurred but the amount of eliminated product **100** also increased. It was found that reducing the water content to 0.05% in DMF gave the product **99** in 82% yield (Entry 4).

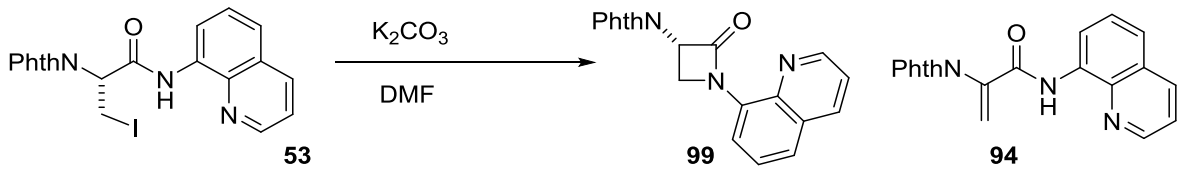


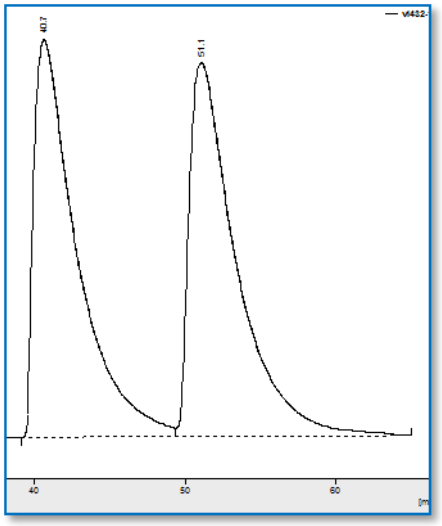
Table 3.21: *β*-Lactamisation of 53.

Entry	H_2O in DMF (%)	^1H NMR Yield 99 (%)	^1H NMR Yield 94 (%)
1	10	66	34
2	1	77	23
3	0.1	86	14
4	0.05	91 (82%)[a]	9

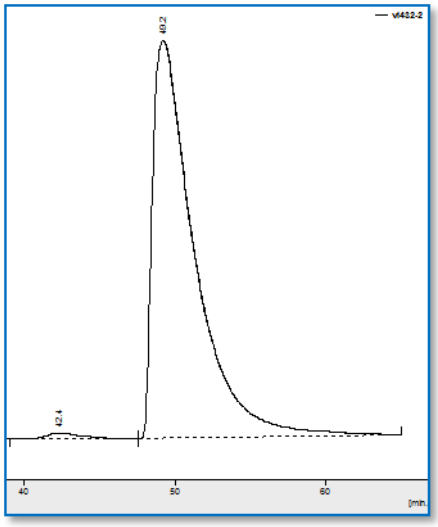
[a]Isolated yield. Reactions carried out on an 0.5 mmol scale and 0.1 M concentration with respect to compound **53** at rt for 6h.

There was concern that due to the presence of product **94** that there may be some epimerisation of product **99**. To ensure that the reaction was occurring with no loss of the enantiopurity from starting material **53**, chiral HPLC conditions were developed (Figure 3.5). The conditions were first found for racemic *β*-lactam **99** showing clear separation of the 2 isomers with retention times of (*R*)-**99** 41.33 min, (*S*)-**99** 49.89 min. *β*-lactam **99**, synthesised from enantiopure starting material, was then subjected to the same chiral HPLC conditions and pleasingly a peak for only one isomer was observed. To ensure that the peak corresponded to one of the isomers observed in the chromatogram of the racemic material, a mixture of racemic and enatiopure

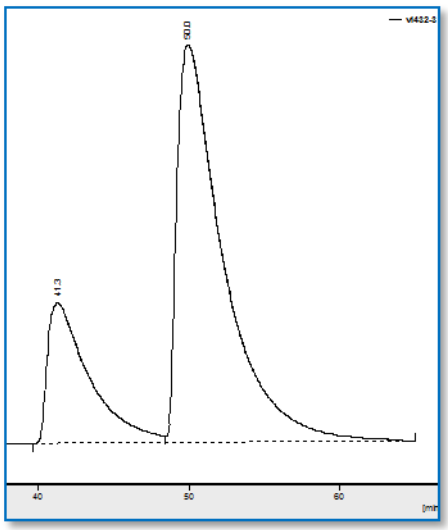
99 were subjected to the developed HPLC conditions. As expected, 2 peaks were observed, with one peak being larger due to the addition of enatiopure **99**, thus proving that **99** has been synthesised enantioselectively in 98% ee.



Chiral HPLC chromatogram of racemic **99.**



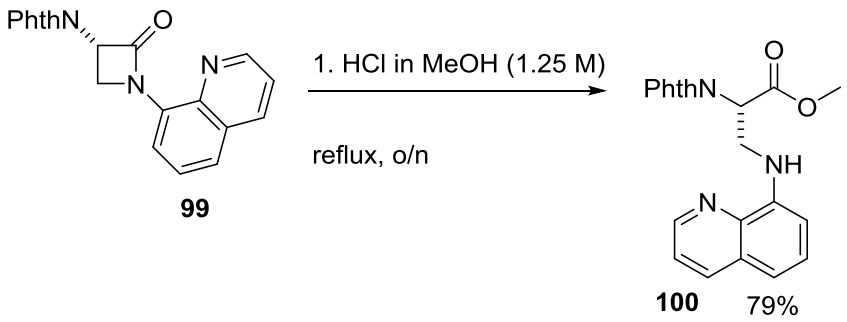
Chiral HPLC chromatogram of enantiopure **99.**



Chiral HPLC chromatogram of racemic and enantiopure **99** combined.

Figure 3.5: Chiral HPLC of *β*-lactam 99. carried out on a Lux 3u cellulose-2 column using 25% *i*PrOH in hexane with a flow rate of 1 mL/min

With β-lactam **99** in hand it was an obvious precursor to a β-aminoalanine derivative via a ring opening reaction, giving an indirect route to C-N bond formation. Thus compound **99** was refluxed in methanolic acid overnight to give the desired product **100** in 79% yield (Scheme 3.83).



Scheme 3.83: Ring opening of the β-lactam.

3.4 Conclusion

The $Pd(OAc)_2$ catalysed C-H activation and iodination of alanine derivative **50** has been successfully carried out on a 10 mmol scale. Application of the C-H activation iodination conditions to other amino acid derivatives was unsuccessful with unwanted aromatic iodination being the main product. Subjecting the aromatic iodinated amino acid derivatives to the same conditions still did not yield any of the desired products. This suggests that the increased size of the side chains in these amino acids compared to alanine is preventing the C-H activation from occurring.

The side chain iodination of lactic acid derivative **80** has shown promise with the desired product being formed in 8%. The reaction has proved not to be occurring catalytically, showing that Ag_2CO_3 is not suitable for the regeneration of the active Pd(II) catalyst in this instance. Initial investigations have been made into discovering an alternative to Ag_2CO_3 in order to make the reaction catalytic, however one has yet to be found.

Lactic acid derivative **78** has successfully undergone a C-H activation and acetoxylation reaction to give the glyceric acid derivative **86** in excellent yield. This provides the first reported example of a catalytic C-H activation on a lactic acid derivative.

The Negishi cross-coupling reaction of iodoalanine derived organozinc reagents with phenyl iodide has been unsuccessful. The reason for this is the presence of the NH proton which causes rapid intramolecular protonation of the organozinc reagent before transmetallation onto the palladium can occur. Attempts to remove the NH proton by TMS protection also did not lead to any of the desired cross-coupled product. A way around this is the use of the

iodoalanine methyl ester **90** which has previously been shown to undergo cross-coupling reactions with a range of aryl halides. The 8-aminoquinoline group of compound **53** was deprotected to give **90** in 65% yield.

Iodoalanine **53** has also been transformed into the *β*-lactam **99** in good yield when subjected to K_2CO_3 in 0.05% H_2O in DMF. The water allows a small amount of K_2CO_3 to go in solution and under these dilute conditions, the formation of the *β*-lactam is favoured over dehydroalanine**94**. *β*-lactam **99** was successfully ring opened to afford the *β*-aminoalanine derivative **100** in good yield.

4. Experimental

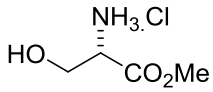
All moisture/air sensitive reactions were conducted under a nitrogen atmosphere in flame-dried or oven-dried glassware. All reagents used were purchased from commercial sources and used without further purification. Water is demineralised water. All solvents used were HPLC grade or distilled. Petroleum ether refers to the fraction which boils in the range 40-60 °C. Solvent evaporation under reduced pressure was performed using a Büchi rotary evaporator connected to a membrane pump. Purification was performed using flash chromatography apparatus and pressurised air, on silica gel for flash chromatography from BDH Lab or Davisil Fluorochem. Thin layer chromatography was performed using pre-coated plates (0.2 mm, Merck DC-alufolien Kieselgel 60 F_{254}), and compounds visualised by UV light (254 nm), ninhydrin solution (5% in MeOH) or $KMnO_4$.

^{13}C and ^{1}H Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AMX 400 at room temperature. Chemical shifts are referenced to residual solvent and are expressed in parts per million. ^{1}H NMR spectra are reported in the form: δ_H (integration, multiplicity, *J* value, assignment). Coupling constants are given in Hertz, and are corrected to the nearest 0.5 decimal place. ^{13}C NMR spectra were recorded at 101 MHz. High-resolution mass spectra were recorded using a Kratos MS 25 or MS 80 for electro impact (EI) or a MicroMass LCT operating in Electrospray (ES) mode. Infra-red spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer (ν_{max} in cm^{-1}) as thin films using NaCl plates. Wavenumbers are quoted to the nearest whole number. Melting points were determined using a Linkham HFS91 heating stage, used in conjunction with a TC92 controller and are uncorrected. Optical rotations were determined using an AA-10 Automatic Polarimeter, at 589nm. Resolution between

enantiomers was achieved using a Beckman system fitted with a Lux x 3u cellulose-2-column (250 mm x 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane: isopropanol as the mobile phase at ambient temperature and detection by UV absorbance at 254 nm.

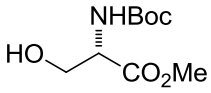
4.2 Chapter 2 Experimental

4.2.1 *L*-Serine methyl ester hydrochloride, 9



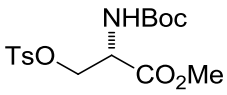
A 250 cm^3, three-necked round bottomed flask, containing a magnetic stirrer bar, was equipped with a dropping funnel, reflux condenser and glass stopper. The dropping funnel was charged with acetyl chloride (46 mL, 647 mmol) which was then added dropwise to MeOH (300 mL) at 0 °C for 10 min. *L*-serine (24.022 g, 229 mmol) was then added to the solution which was stirred for a further 5 min at 0 °C. The reaction was then heated at reflux for 2 h. After the solution had cooled to rt, the solvent was removed under reduced pressure to yield the crude *L*-serine methyl ester in quantative yield as a white solid (34.66 g); $[\alpha]_D^{25}$ +5.0 (*c* 2.0, MeOH), lit. value $[\alpha]_D^{25}$ +5.0 (*c* 2.0, MeOH);[29] δ_H (400 MHz, D_2O) 3.73 (3H, s, OCH_3), 3.88 (1H, dd, *J* 12.5, 4.0, CH_2), 3.97 (1H, dd, *J* 12.5, 4.0, CH_2), 4.15 (1H, t, *J* 4.0, CH); δ_C (101 MHz, D_2O) 53.7, 54.7, 59.2, 168.9. Spectroscopic data is consistent with that previously reported.[29]

4.2.2 *N*-(*tert*-butoxycarbonyl)-*L*-serine methyl ester, 10



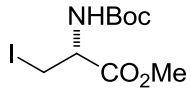
Crude *L*-serine methyl ester hydrochloride **9** (34.66 g, 223 mmol) was added to water (150 mL) at rt and left stirring to dissolve. Once fully dissolved, K_2CO_3 (30.82g, 223 mmol) and Boc_2O (49.13g, 223 mmol) were added and the solution was left to stir overnight. The product was then extracted with Et_2O and dried with $MgSO_4$. The solvent was then removed under reduced pressure to yield the crude *N*-(*tert*-butoxycarbonyl)-*L*-serine methyl ester as a thick, colourless oil (35.17g, 75% crude yield); $[\alpha]_D^{25}$ -18.1 (*c* 4.1, MeOH), lit. value -19.1 (*c* 4.07, MeOH);[91] δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, $C(CH_3)$), 3.82 (3H, s, OCH_3), 4.03–3.88 (2H, m, CH_2), 4.42 (1H, s, CH), 5.45 (1H, s, NH); δ_C (101 MHz, $CDCl_3$) 28.7, 53.0, 56.1, 63.8, 80.7, 156.2, 171.8. Spectroscopic data is consistent with that previously reported.[91]

4.2.3 *N*-(tert-butoxycarbonyl)-*O*-(p-toluenesulfonyl)- *L*-serine methyl ester, 11



Crude *N*-(*tert*-butoxycarbonyl)-*L*-serine methyl ester **10** (26.10 g, 119 mmol) was dissolved in dry CH_2Cl_2 (200 mL). 4-DMAP (0.71 g, 5.90 mmol), $Me_3N.HCl$ (1.10 g, 12.0 mmol) and *p*-TsCl (22.70 g, 119 mmol) were added to the solution at 0 °C. A dropping funnel was charged with Et_3N (17 mL, 119 mmol) dissolved in dry CH_2Cl_2 (50 mL) which was then added dropwise to the solution at 0 °C for 40 min. The resulting white slurry was stirred for 2 h at 0 °C before it was poured onto a mixture of ice (100 mL), water (100 mL) and 2 M HCl (50 mL). The aqueous layer was washed with CH_2Cl_2 (100 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure to yield the crude product as a white solid (35.89 g). The solid was dissolved in hot Et_2O (140 mL) and filtered to remove the insoluble white solid. The filtrate was allowed to cool to room temperature before being cooled to 0 °C. Crystallisation from petroleum ether (250 mL) at -20 °C overnight gave white crystals of *N*-(*tert*-butoxycarbonyl)-*O*-(*p*-toluenesulfonyl)-*L*-serine methyl ester (21.69 g, 53%): m.p. 70-72 °C, lit. value 74-76 °C;[92] $[\alpha]_D^{25}$ +2.2 (*c* 2.0, MeOH), lit. value $[\alpha]_D^{25}$ +3.0 (*c* 2.0, MeOH);[92] δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 2.48 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 4.31 (1H, dd, *J* 10.0, 3.0, CH_2), 4.42 (1H, dd, *J* 10.0. 3.0, CH_2), 4.57–4.48 (1H, m, CH), 5.32 (1H, d, *J* 8.0, NH), 7.38 (2H, d, *J* 8.0, ArH), 7.79 (2H, d, *J* 8.0, ArH); δ_C (101 MHz, $CDCl_3$) 21.7, 28.2, 52.9, 53.0, 69.5, 80.5, 128.0, 130.0, 132.4, 145.2, 155.0, 169.0. Spectroscopic data is consistent with that previously reported.[92]

4.2.4 *N*-(*tert*-butoxycarbonyl)-3-iodo-*L*-alanine methyl ester, 12



N-(*tert*-butoxycarbonyl)-*O*-(*p*-toluenesulfonyl)-*L*-serine methyl ester **11** (21.69 g, 65.93 mmol) was dissolved in acetone (160 mL) whilst being stirred. NaI (11.85 g, 79.10 mmol) was added and the flask was covered in aluminium foil. After stirring for 3 d, further NaI (2.96 g, 19.77 mmol) was added in one portion and the reaction was stirred for 1 d. The orange slurry was filtered through a sintered glass funnel, and the orange solid isolated was washed with acetone until the solid was colourless. The flask containing the filtrate was covered with aluminium foil to exclude light and the solvent was removed under reduced pressure at 0 °C. The solution was warmed to room temperature and the acetone was allowed to evaporate, producing a dark orange oil. The oil was then partitioned between Et_2O (150 mL) and 1 M $Na_2S_2O_3$ (60 mL). The organic layer was washed with $Na_2S_2O_3$ (40 mL) and brine (50 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure to yield the crude product as a pale yellow solid (16.95 g). The solid was dissolved in hot 40/60 petroleum ether (50 mL) before being cooled to 0 °C. The solution was then cooled further to -20 °C overnight, yielding *N*-(*tert*-butoxycarbonyl)-3-iodo-*L*-alanine methyl ester as a pale yellow solid. This solid was washed with cold petroleum ether, before being air dried and ground down to give a pale yellow powder (13.52 g, 59%); m.p. 41-45 °C, lit. value 45-47 °C;[92] $[\alpha]_D^{25}$ -3.6, *c* 3.0, MeOH (lit. -3.7, *c* 3.0, MeOH);[92] δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, $C(CH_3)_3$), 3.64–3.54 (2H, m, CH_2I), 3.82 (3H, s,

OCH_3), 4.58–4.50 (1H, m, CH), 5.38 (1H, d, *J* = 7.0, NH); δ_C (101 MHz, $CDCl_3$) 7.9, 28.3, 53.0, 53.7, 80.5, 154.8, 170.1. Spectroscopic data is consistent with that previously reported.[92]

General cross-coupling **Method A**:

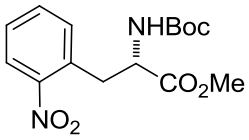
Zinc dust (190 mg, 3 mmol) was added to a flame dried, nitrogen purged side arm round bottom flask. Dry DMF (1 mL) was added via syringe followed by a catalytic amount of iodine (40 mg, 0.15 mmol). A colour change of the DMF was observed from colourless to yellow and back again. Iodoalanine **12** (329 mg, 1 mmol) was added immediately followed by a catalytic amount of iodine (40 mg, 0.15 mmol). The solution was stirred at rt and gave a noticeable exotherm. When the solution had cooled Pd_2dba_3 (22 mg, 0.025 mmol), phosphine ligand (0.05 mmol) and aryl halide (1.3 mmol) were added to the flask and left to stir at rt overnight, under positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column to afford the purified cross-coupled product.

General cross-coupling **Method B**:

Zinc dust (190 mg, 3 mmol) was added to a flame dried, nitrogen purged side arm round bottom flask. Dry DMF (1 mL) was added via syringe followed by a catalytic amount of iodine (40 mg, 0.15 mmol). A colour change of the DMF was observed from colourless to yellow and back again. Iodoalanine **12** (329 mg, 1 mmol) was added immediately followed by a catalytic amount of iodine (40 mg, 0.15 mmol). The solution was stirred at rt and gave a noticeable exotherm. In a separate flame dried nitrogen purged flask Pd_2dba_3 (11 mg, 0.0125 mmol), was added followed by dry DMF (0.5 mL). In a separate, flame dried nitrogen purged flask, phosphine ligand

(0.025 mmol) was added followed by dry DMF (0.5 mL). Once the zinc insertion has cooled the palladium solution (100 μL, 0.0025 mmol) and phosphine ligand solution (100 μL, 0.005 mmol) were added *via* syringe followed by aryl halide (1.3 mmol). The reaction was allowed to stir at rt overnight under positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column to afford the purified cross-coupled product.

4.2.5 (*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(2-nitrophenyl)-propanoate, 13



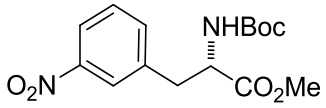
Following a variation of general cross-coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (24 mg, 0.05 mmol) and 1-iodo-2-nitrobenzene (323 mg, 1.3 mmol) gave, after purification by silica gel column (20% EtOAc in petrol) the title compound (195 mg, 79%) as a yellow solid.

Following a variation of general cross-coupling **Method B**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (2.4 mg, 0.005 mmol) and 1-iodo-2-nitrobenzene (323 mg, 1.3 mmol)

gave, after purification by silica gel column (20% EtOAc in petrol) gave the title compound (191 mg, 59%) as a yellow solid.

m.p. 78-80 ^{o}C, lit. value 83-84 ^{o}C; R_f 0.17 (20% EtOAc in petrol); $[\alpha]_D^{22}$ +27.8 (*c* 0.18, CH_2Cl_2), lit. value $[\alpha]_D^{22}$ +42.7 (*c* 0.19, CH_2Cl_2);[18] δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, $C(CH_3)_3$), 3.24 (1H, dd, *J* 13.5 and 8.5, CH_2), 3.55 (1H, dd, *J* 13.5 and 8.5, CH_2), 3.74 (3H, s, OCH_3), 4.69 (1H, dd, *J* 13.5 and 8.5, CH), 5.24 (1H, d, *J* 8.0, NH), 7.41 (2H, dd, *J* 12.0 and 8.0, ArH), 7.56 (1H, t, *J* 8.0 ArH), 7.96 (1H, d, *J* 8.0, ArH); δ_C (101 MHz, $CDCl_3$) 28.2, 35.6, 52.6, 54.0, 80.0, 125.0, 128.1, 131.8, 132.9, 133.0, 149.7, 155.0, 172.0. Spectroscopic data is consistent with that previously reported.[18]

4.2.6 (*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(3-nitrophenyl)-propanoate, 14



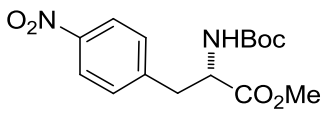
Following a variation of general cross-coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (24 mg, 0.05 mmol) and 1-iodo-3-nitrobenzene (323 mg, 1.3 mmol) gave, after purification by silica gel column (20% EtOAc in petrol) the title compound (178 mg, 84%) as a yellow solid.

Following a variation of general cross-coupling **Method B**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using

XPhos (2.4 mg, 0.005 mmol) and 1-iodo-3-nitrobenzene (324 mg, 1.3 mmol) gave, after purification by silica gel column (20% EtOAc in petrol) the title compound (217 mg, 67%) as a yellow solid.

m.p. 102-103 ^{o}C; R_f 0.16 (20% EtOAc in petrol); $[\alpha]_D^{22}$ +48.7 (*c* 1.0, $CHCl_3$), lit. value $[\alpha]_D^{22}$ +49.5 (*c* 0.19, CH_2Cl_2);[18] δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, $C(CH_3)_3$), 3.13 (1H, dd, *J* 14.0 and 6.0, CH_2), 3.31 (1H, dd, *J* 14.0 and 6.0, CH_2), 3.77 (3H, s, OCH_3), 4.64 (1H, dd, *J* 13.5 and 6.5, CH), 5.12 (1H, d, *J* 7.5, NH), 7.54-7.46 (2H, m, ArH), 8.02 (1H, s, ArH), 8.10-8.16 (1H, m, ArH); δ_C (101 MHz, $CDCl_3$) 28.2, 38.1, 52.5, 54.2, 80.3, 122.1, 124.3, 130.3, 135.6, 138.4, 148.3, 154.9, 171.6. Spectroscopic data is consistent with that previously reported.[18]

4.2.7 (*S*)-methyl 2-(tert-butoxycarbonylamino)-3-(4-nitrophenyl)-propanoate, 15



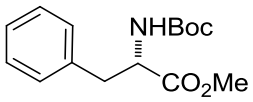
Following a variation of general cross-coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (24 mg, 0.05 mmol) and 1-iodo-4-nitrobenzene (323 mg, 1.3 mmol) gave, after purification by silica gel column (20% EtOAc in petrol) the title compound (240 mg, 83%) as a yellow solid.

Following a variation of general cross-coupling **Method B**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a

separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (2.4 mg, 0.005 mmol) 1-iodo-4-nitrobenzene (324 mg, 1.3 mmol), after purification by silica gel column (20% EtOAc in petrol) gave the title compound (172 mg, 74%) as a yellow solid.

m.p. 99-101 ^{o}C, lit. value 95-97 ^{o}C; R_f 0.15 (20% EtOAc in petrol); $[\alpha]_D^{21}$ +43.5 (*c* 1.06, CH_2Cl_2), lit. value $[\alpha]_D^{20}$ +30.4 (*c* 1.06, CH_2Cl_2);[18] δ_H (400 MHz; $CDCl_3$) 1.39 (9H, s, $(CH_3)_3$), 3.11 (1H, dd, *J* 13.5, 6.5, CH_2), 3.27 (1H, dd, *J* 13.5, 6.0, CH_2), 3.72 (3H, s, OCH_3), 4.62 (1H, dd, *J* 13.5, 6.5, CH), 5.16 (1H, d, *J* 8.0, NH), 7.31 (2H, d, *J* 8.5, ArH), 8.14 (2H, d, *J* 8.5, ArH); δ_C (101 MHz, $CDCl_3$) 28.2, 38.4, 52.5, 54.1, 80.3, 123.6, 130.2, 144.1, 147.1, 154.9, 171.6. Spectroscopic data is consistent with that previously reported.[18]

4.2.8 (*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate, 16



Following general cross-coupling **Method A** using SPhos (21 mg, 0.05 mmol) and iodobenzene (145 μL, 1.3 mmol) gave, after purification by silica gel column (5% EtOAc in toluene) gave the title compound (218 mg, 78%) as a yellow oil.

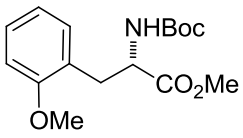
Following general cross-coupling **Method A** using iodobenzene (145 μL, 1.3 mmol) gave, after purification by silica gel column (5% EtOAc in toluene) the title compound (223 mg, 84%) as a yellow oil.

Following general cross-coupling **Method B** using SPhos (2.1 mg, 0.005 mmol) and iodobenzene (145 μL, 1.3 mmol) gave, after purification by silica gel column (5% EtOAc in toluene) the title compound (220 mg, 79%) as a yellow oil.

Following general cross-coupling **Method B** using XPhos (2.4 mg, 0.005 mmol) and iodobenzene (145 μL, 1.3 mmol) gave, after purification by silica gel column (5% EtOAc in toluene) the title compound (235 mg, 81%) as a yellow oil.

R_f 0.5 (30% EtOAc in petrol); $[\alpha]_D^{22}$ +46.0 (*c* 1.0, $CHCl_3$) , lit. value $[\alpha]_D^{22}$ +47.0 (*c* 1.0, $CHCl_3$);[18] δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 3.10 (2H, dd, *J* 14.0 and 6.0, CH_2), 3.75 (3H, s, OCH_3), 4.61 (1H, dd, *J* 14.0 and 6.0, CH), 5.00 (1H, d, *J* 8.0, NH), 7.15 (2H, d, *J* 7.0, ArH), 7.36-7.23 (3H, m, ArH); δ_C (101 MHz, $CDCl_3$) 18.6, 27.3, 28.3, 38.3, 52.2, 54.4, 79.9, 127.0, 128.5, 129.3, 136.1, 155.1, 172.3. Spectroscopic data is consistent with that previously reported.[18]

4.2.9 (*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(2-methoxyphenyl)-propanoate, 17

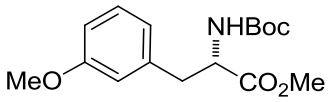


Following general cross-coupling **Method A** using XPhos (24 mg, 0.05 mmol) and 2-iodoanisole (169 μL, 1.3 mmol) gave, after purification by silica gel column (3% EtOAc in toluene) the title compound (213 mg, 69%) as an orange oil.

Following general cross-coupling **Method B** using XPhos (2.4 mg, 0.005 mmol) and 2-iodoanisole (169 μL, 1.3 mmol) gave, after purification by silica gel column (3% EtOAc in toluene) the title compound (148 mg, 48%) as an orange oil.

R_f 0.64 (30% EtOAc in toluene); $[\alpha]_D^{21}$ +13.6 (*c* 0.74, CH_2Cl_2) lit. value $[\alpha]_D^{20}$ +14.9 (*c* 0.68, CH_2Cl_2);[18] δ_H (400 MHz; $CDCl_3$) 1.39 (9H, s, $(CH_3)_3$), 3.13-3.02 (2H, m, CH_2), 3.71 (3H, s, OCH_3), 3.84 (3H, s, $ArOCH_3$), 4.52 (1H, dd, *J* 13.5, 7.5, CH), 5.26 (1H, d, *J* 7.5, NH), 6.89 (2H, dd, *J* 16.0, 8.0, ArH), 7.10 (1H, dd, *J* 7.5, 1.5, ArH), 7.27-7.21 (1H, m, ArH); δ_C (101 MHz; $CDCl_3$) 28.3, 32.8, 52.0, 54.0, 55.3, 79.5, 110.4, 120.6, 124.7, 128.4, 131.1, 155.3, 172.9. Spectroscopic data is consistent with that previously reported.[18]

4.2.10 (*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(3-methoxyphenyl)-propanoate, 18

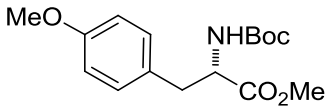


Following general cross-coupling **Method A** using XPhos (24 mg, 0.05 mmol) and 3-iodoanisole (155 μL, 1.3 mmol) gave, after purification by silica gel column (3% EtOAc in toluene) the title compound (216 mg, 75%) as an orange oil.

Following general cross-coupling **Method B** using XPhos (2.4 mg, 0.005 mmol) and 3-iodoanisole (155 μL 1.3 mmol) gave, after purification by silica gel column (3% EtOAc in toluene) the title compound (232 mg, 70%) as an orange oil.

R_f 0.46 (20 % EtOAc in toluene); $[\alpha]_D^{22}$ +43.5 (*c* 1.0, $CHCl_3$), lit. value $[\alpha]_D^{22}$ +46.1 (c 1.02, $CHCl_3$);[18] δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, $C(CH_3)_3$), 3.07 (2H, dd, *J* 14.0 and 6.0, CH_2), 3.73 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.59 (1H, dd, *J* 14.0 and 6.0, CH), 5.04 (1H, d, *J* 8.0, NH), 6.68 (1H, d, *J* 2.0, ArH), 6.72 (1H, d, *J* 7.5, ArH), 6.80 (1H, dd, *J* 8.0 and 2.0, ArH), 7.21 (1H, t, *J* 8.0, ArH); δ_C (101 MHz, $CDCl_3$) 28.3, 38.3, 52.2, 54.4, 55.1, 79.9, 112.5, 115.0, 121.6, 129.5, 137.5, 155.1, 159.7, 172.3. Spectroscopic data is consistent with that previously reported.[18]

4.2.11 (*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(4-methoxyphenyl)-propanoate, 19

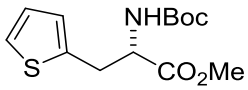


Following general cross-coupling **Method A** using XPhos (24 mg, 0.05 mmol) and 4-iodoanisole (303 mg, 1.3 mmol) gave, after purification by silica gel column (3% EtOAc in toluene) the title compound (216 mg, 78%) as a yellow oil.

Following general cross-coupling **Method B** using XPhos (2.4 mg, 0.005 mmol) and 4-iodoanisole (303 mg, 1.3 mmol) gave, after purification by silica gel column (3% EtOAc in toluene) the title compound (231 mg, 68%) as a yellow oil.

R_f 0.47 (15% EtOAc in toluene); $[\alpha]_D^{20}$ +50.0 (*c* 1.8, $CHCl_3$) lit. value $[\alpha]_D^{20}$ +50.0 (*c* 1.8, $CHCl_3$);[18] δ_H (400 MHz; $CDCl_3$) 1.42 (9H, s, $(CH_3)_3$), 3.02 (2H, dd, *J* 14.0, 6.0, CH_2), 3.71 (3H, s, OCH_3), 3.77 (3H, s, $ArOCH_3$), 4.54 (1H, dd, *J* 14.0, 6.0, CH), 5.04 (1H, d, *J* 8.0, NH), 6.83 (2H, d, *J* 8.5, ArH), 7.04 (2H, d, *J* 8.5, ArH); δ_C (101 MHz; $CDCl_3$) 28.3, 37.5, 52.2, 54.5, 55.2, 76.7, 77.0, 77.3, 114.0, 127.9, 130.3, 158.7, 172.4. Spectroscopic data is consistent with that previously reported.[18]

4.2.12 (*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(thiophen-2-yl)-propanoate, 20



Following a variation of general cross-coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (24 mg, 0.05 mmol) and 2-iodothiophene (145 μL, 1.3 mmol) at 50 °C gave, after purification by silica gel column (7% EtOAc in toluene) the title compound (140 mg, 49%) as a yellow oil.

Following a variation of general cross-coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (24 mg, 0.05 mmol) and 2-bromothiophene (125 μL, 1.3 mmol) at 50 °C gave, after purification by silica gel column (7% EtOAc in toluene) the title compound (126 mg, 44%) as a yellow oil.

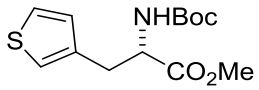
Following a variation of general cross-coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using QPhos (35 mg, 0.05 mmol) and 2-bromothiophene (125 μL, 1.3 mmol) at 50 ^{o}C gave, after purification by silica gel column (7% EtOAc in toluene) the title compound (71 mg, 25%) as a yellow oil.

Following a variation of general cross-coupling **Method B**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (2.4 mg, 0.005 mmol) 2-iodothiophene (145 μL, 1.3 mmol) at 50 ^{o}C gave, after purification by silica gel column (7% EtOAc in toluene) the title compound (86 mg, 30%) as a yellow oil.

Following a variation of general cross-coupling **Method B**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (2.4 mg, 0.005 mmol) 2-bromothiophene (125 μL, 1.3 mmol) at 50 ^{o}C gave, after purification by silica gel column (7% EtOAc in toluene) the title compound (74 mg, 26%) as a yellow oil.

$[[\alpha]_D^{20}$ +61 (*c* 1.0 $CHCl_3$); ν_{max}(film)/cm^{-1} 3375, 2974, 1740, 1715, 1506, 1436, 1391, 1366, 1247, 1215, 1166, 1060, 1018; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, $C(CH_3)_3$), 3.31-3.43 (2H, m, CH_2), 3.77 (3H, s, OCH_3), 4.67-4.57 (1H, m, CH), 5.18 (1H, d, *J* 7.5 NH), 6.82 (1H, d, *J* 3.0, ArH), 6.95 (1H, dd, *J* 5.0, 3.5, ArH), 7.19 (1H, d, *J* 5.0, ArH); δ_C (101 MHz, $CDCl_3$) 28.4, 32.4, 52.4, 54.2, 80.0, 124.7, 126.7, 127.0, 137.3, 155.0, 171.7; *m*/*z* (ES) Found: MH^+ 286.1119. $C_{13}H_{20}NO_4S$ requires MH^+ 286.1113.

4.2.13 (*S*)-methyl 2-{[(*tert*-butoxy)carbonyl]amino}-3-(thiophen-3-yl)-propanoate, 21



Following a variation of general cross-coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (24 mg, 0.05 mmol) and 3-iodothiophene (135 μL, 1.3 mmol) at 50 °C gave, after purification by silica gel column (7% EtOAc in toluene) the title compound (185 mg, 65%) as a yellow oil.

Following a variation of general cross-coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (24 mg, 0.05 mmol) and 3-bromothiophene (122 μL, 1.3 mmol) at 50 °C gave, after purification by silica gel column (7% EtOAc in toluene) the title compound (171 mg, 60%) as a yellow oil.

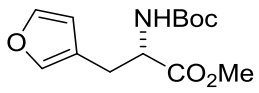
Following a variation of general cross-coupling **Method B**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (2.4 mg, 0.005 mmol) 3-iodothiophene (135 μL, 1.3 mmol) at 50 °C gave, after purification by silica gel column (7% EtOAc in toluene) the title compound (157 mg, 50%) as a yellow oil.

Following a variation of general cross-coupling **Method B**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a

separate flame dried, nitrogen purged side arm round bottom flask) using XPhos (2.4 mg, 0.005 mmol) 3-bromothiophene (122 μL, 1.3 mmol) at 50 °C gave, after purification by silica gel column (7% EtOAc in toluene) the title compound (143 mg, 50%) as a yellow oil.

$[\alpha]_D^{20}$ +48 (*c* 1.0 $CHCl_3$). ν_{max}(film)/cm^{-1} 3368, 3095, 2974, 2357, 1743, 1711, 1503, 1438, 1392, 1366, 1282, 1246, 1166, 1059, 1020; δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, $C(CH_3)_3$), 3.12-3.22 (2H, m, CH_2), 3.73 (3H, s, OCH_3), 4.58 (1H, dd, *J* 14.0, 6.0, CH), 5.1 (1H, d, *J* 8.0 NH), 6.88 (1H, d, *J* 5.0, ArH), 7.01 (1H, s, ArH), 7.27 (1H, dd, *J* 5.0, 3.0, ArH); δ_C (101 MHz, $CDCl_3$) 28.1, 32.6, 52.3, 55.0, 80.2, 122.7, 125.8, 128.2, 136.3, 155.1, 172.4; *m*/*z* (ES) Found: MH^+ 286.1118. $C_{13}H_{20}NO_4S$ requires MH^+ 286.1113.

4.2.14 (*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(furan-3-yl)- propanoate, 22

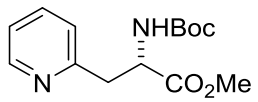


Following general cross-coupling **Method A** using XPhos (24 mg, 0.05 mmol) and 3-bromofuran (117 μL, 1.3 mmol) at 50 °C gave, after purification by silica gel column (3% EtOAc in toluene) the title compound (78 mg, 29%) as a yellow oil.

Following general cross-coupling **Method A** using QPhos (35 mg, 0.05 mmol) and 3-bromofuran (117 μL, 1.3 mmol) at 50 °C gave, after purification by silica gel column (3% EtOAc in toluene) the title compound (59 mg, 22%) as a yellow oil.

$[\alpha]_D^{23}$ +11 (*c* 1.0 $CHCl_3$), ν_{max} (film)/cm^{-1} 3359, 3108, 2975, 1740, 1721, 1504, 1437, 1395, 1363, 1238, 1211, 1166, 1059, 1021; δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, $C(CH_3)_3$), 3.24-3.10 (2H, m, CH_2), 3.76 (s, 3H, OCH_3), 4.61 (1H, dd, *J* 14.0, 5.5, CH), 5.06 (d, *J* 8.0, NH), 6.87 (1H, d, *J* 5.0, ArH), 7.02 (1H, d, *J* 2.5, ArH), 7.27 (1H, dd, *J* 5.0, 2.5, ArH); δ_C (101 MHz, $CDCl_3$) 28.2, 32.7, 52.1, 53.7, 80.3, 122.9, 126.1, 128.2, 136.0, 155.1, 172.3; Found: MH^+ 270.1191. $C_{13}H_{20}NO_4S$ requires MH^+ 270.1187.

4.2.15 Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-(pyridin-2-yl)-propanoate, 23



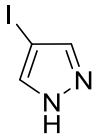
Following general cross-coupling **Method A** using XPhos (24 mg, 0.05 mmol) and 2-chloropyridine (123 μL, 1.3 mmol) at 50 °C gave, after purification by silica gel column (3% EtOAc in toluene) the title compound (31 mg, 11%) as a yellow oil.

Following general cross-coupling **Method A** using QPhos (35 mg, 0.05 mmol) and 2-chloropyridine (123 μL, 1.3 mmol) at 50 °C gave, after purification by silica gel column (3% EtOAc in toluene) the title compound (36 mg, 13%) as a yellow oil.

$[\alpha]_D^{22}$ +23 (*c* 1.0 $CHCl_3$), lit. value $[\alpha]_D^{23}$ +21.5 (*c* 1.0, $CHCl_3$);[93] δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 3.28 (1H, dd, *J* 4.5, 14.5, CH), 3.36 (1H, dd, *J* 6.0,

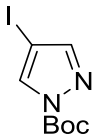
14.5, CH), 3.71 (3H, s, OCH_3), 4.66-4.75 (1H, m), 5.90 (1H, d, *J* 8.0, NH), 7.14-7.21 (2H, m, ArH), 7.63 (1H, dt, *J* 1.5, 4.0, ArH), 8.55 (1H, br s, ArH), δ_C (101 MHz, $CDCl_3$) 28.3, 39.2, 52.3, 53.0, 79.8, 121.9, 123.9, 136.9, 148.8, 155.5, 157.1, 172.4. Proton and carbon Spectroscopic data is consistent with that previously reported.[93]

4.2.16 4-iodo-1*H*-pyrazole, 24



To a mixture of pyrazole (25.53 g, 375 mmol) and iodine (47.6 g, 187.5 mmol) in H_2O (224 mL) was added 30 wt% H_2O_2 (26 mL). The reaction mixture was stirred for 48 h at room temperature, on which cold saturated sodium thiosulfate was added until the reaction mixture was colourless. The mixture was then vacuum filtered to give a brown solid, which was recystallised using hot H_2O to give the desired product as colourless needles (38.1 g, 52% yield); m.p. 108-109 °C, lit. m.p. 105-107 °C;[94] 246 δ_H (400 MHz, $CDCl_3$) 7.67 (2H, s, ArH), 10.29 (1H, s, NH); δ_C (101 MHz, $CDCl_3$) 56.6, 138.7. Spectroscopic data is consistent with that previously reported.[94]

4.2.17 *tert*-Butyl 4-iodopyrazol-1-yl carboxylate, 25



A solution of Boc_2O (5.6 g, 26 mmol) in MeCN (40 mL) was added to a mixture of 4-iodopyrazole (4.66 g, 24 mmol) and 4-DMAP (0.3 g, 2.4 mmol) and left to stir overnight at room temperature. The reaction mixture was then concentrated under reduced pressure and dissolved in EtOAc. The reaction mixture was then washed with 1M HCl, followed by water and brine. The organic layer was dried over $MgSO_4$, and the solvent removed under reduced pressure to give the product as an amorphous white solid (4.66 g, 68% yield); m.p. 66-70 °C; δ_H (400 MHz, $CDCl_3$) 1.65 (9H, s, $C(CH_3)_3$), 7.70 (1H, s, ArH), 8.15 (1H, s, ArH); δ_C (101 MHz, $CDCl_3$) 27.8, 61.2, 86.1, 134.9, 148.3, 171.3 .

4.3 Chapter 3 Experimental

Phthalimide protection of amino acids **Method A:**

The amino acid (100 mmol) and phthalic anhydride (14.8 g, 100 mmol) were heated at 160 °C for 2 h in a 250 mL round-bottom flask. After cooling to rt, the solid mixture was dissolved in the minimum the amount of boiling methanol. The filtrate was diluted with cold water until a white solid slowly appeared. The precipitate was collected and further washed with cold water.

8-Aminoquinoline amide formation **Method B:**

Starting material (20 mmol), thionylchloride (4.5 mL, 60 mmol) and 4 drops of DMF were heated in toluene at 80 °C for 3 h under nitrogen. The toluene and excess thionylchloride were removed by vacuum distillation and the remaining acid chloride was dissolved in anhydrous CH_2Cl_2 (10 mL).

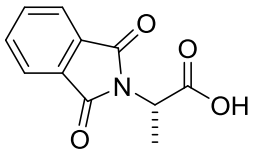
8-Aminoquinoline (2.88 g, 20 mmol) and Et^iPr_2N (4 mL, 26 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) and cooled to 0 ^oC. The acid chloride solution was added dropwise by cannula and the resulting reaction mixture was stirred overnight at rt. The reaction was then diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with 1 M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure to give the crude product.

Aromatic iodination **Method C:**

A solution of quinoline amide starting material (3 mmol) $PhI(OAc)_2$ (966 mg, 3.0 mmol) and iodine (756 mg, 3 mmol) in CH_2Cl_2 (24 mL) was stirred at

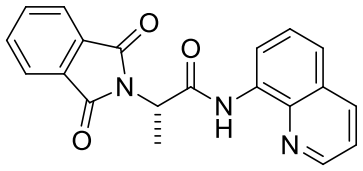
room temperature overnight. The reaction mixture was washed with $Na_2S_2O_3$, dried over $MgSO_4$ and the solvent removed under reduced pressure to give the crude product.

4.3.1 (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)propanoic acid, 67



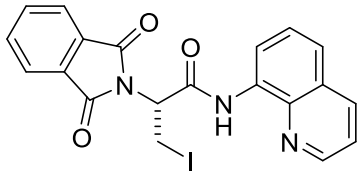
Following phthalimide protection of amino acids **Method A** using *L*-alanine (8.9 g, 100 mmol) gave the title compound at a white amorphous solid (16.4 g, 75%); m.p. 143-144 °C, lit. value 144-146 °C;[95] $[\alpha]_D^{20}$ -26.8 (*c* 2.6, EtOH), lit.value $[\alpha]_D^{20}$ -24.2 (*c* 2.6 , EtOH);[95] δ_H (400 MHz; $CDCl_3$) 1.48 (3H, d, *J* 7.5, CH_3), 4.98 (1H, q, 7.5, CH), 7.72 (2H, dd, *J* 5.5, 3.0, ArH), 7.84 (2H, dd, *J* 5.5, 3.0, ArH); δ_C (101 MHz; $CDCl_3$) 14.0, 47.2, 122.8, 131.8, 134.2, 167.3, 175.7. Spectroscopic data is consistent with that previously reported.[95]

4.3.2 (*S*)-2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-quinolin-8-yl-propionamide, 50



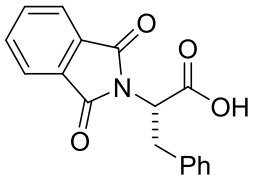
Following 8-aminoquinoline amide formation **Method B** using (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)propanoic acid **67** (4.4 g, 20 mmol) after purification by silica gel column chromatography (10% EtOAc in toluene) gave the product (5.6 g, 81%) as an amorphous cream solid; m.p. 190-192 °C, lit value 190-193 °C;[66] $[\alpha]_D^{22}$ + 1.2 (*c* 1.7, $CHCl_3$), lit. value $[\alpha]_D^{25}$ +1.05 (*c* 1.7, $CHCl_3$);[66] δ_H (400 MHz; $CDCl_3$) 2.00 (3H, d, *J* 7.5, CH_3), 5.30 (1H, q, *J* 7.5, CH), 7.46 (1H, dd, *J* 8.5, 4.5, ArH), 7.54 (1H, s, ArH), 7.55 (1H, d, *J* 3.0, ArH), 7.77 (2H, dd, *J* 5.5, 3.0 ArH), 7.92 (2H, dd, *J* 5.5, 3.0 ArH), 8.20 (1H, dd, *J* 8.5, 1.5 ArH), 8.72 (1H, dd, *J* 4.5, 1.5 ArH), 8.75 (1H, dd, *J* 5.5, 3.0 ArH), 10.37 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 15.5 , 50.1, 117.0, 121.6, 122.0, 123.6, 127.4 , 127.9, 132.0, 133.8, 134.2, 136.6, 138.4, 148.1, 167.3, 167.9. Spectroscopic data is consistent with that previously reported.[66]

4.3.3 (*R*)-2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-iodo-*N*-quinolin-8-yl-propionamide, 53



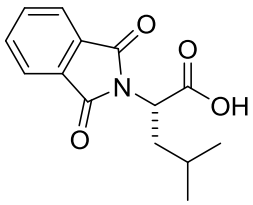
A solution of (*S*)-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-*N*-quinolin-8-yl-propionamide **50** (3.45 g, 10 mmol), $Pd(OAc)_2$ (225 mg, 1 mmol), I_2 (3.8 g, 15 mmol) and Ag_2CO_3 (2.76 g, 10 mmol) in CH_2Cl_2 (10 mL) was stirred overhead at room temperature for 50 h. The reaction mixture was filtered, extracted with CH_2Cl_2 (2 x 50 mL), washed with 10% $Na_2S_2O_3$ (50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified using silica gel column chromatography (5% EtOAc in toluene) to give the product (3.12 g, 66%) (>99% ee.) as a white solid (m.p. 112-114 °C); $[\alpha]_D^{20}$ +33 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3325, 2935, 1779, 1721, 1688, 1532; δ_H (400 MHz; $CDCl_3$) 4.18 (1H, dd, *J* 10.5, 5.0, C*H*HI), 4.30 (1H, dd, *J* 11.5, 10.5 CH*H*I), 5.38 (1H, dd, *J* 11.5, 5.0, CH), 7.43 (1H, dd, *J* 8.5, 4.0, ArH), 7.54 (1H, d, *J* 2.0, ArH), 7.55 (1H, s, ArH), 7.83 (2H, dd, *J* 5.5, 3.0, ArH), 7.98 (2H, dd, *J* 5.5, 3.0, ArH), 8.16 (1H, dd, *J* 8.5, 1.5, ArH), 8.64 (1H, dd, *J* 4.0, 1.5, ArH), 8.69 (1H, dd, *J* 5.5, 3.5, ArH), 10.38 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 0.8, 57.2, 117.0, 121.7, 122.4, 124.0, 127.9, 131.7, 133.5, 134.6, 136.4, 138.4, 140.4, 148.4, 164.0, 167.5; *m*/*z* (ES) Found: MH^+, 472.0169. $C_{20}H_{15}N_3O_3I$ requires MH^+ 472.0158; CSP-HPLC: Lux 3u cellulose-2 (20% *i*PrOH in hexane, 0.7 mL/min) (*S*)-**53** 33.02 min, (*R*)-**53** 45.22 min.

4.3.4 (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-phenylpropanoic acid, 68



Following phthalimide protection of amino acids **Method A** using *L*-phenylalanine (16.4 g, 100 mmol) gave the title compound at a white amorphous solid (20.9 g, 72%);[95] m.p. 181-183 °C, lit. value 182-183 °C;[95] $[\alpha]_D^{20}$ -209 (*c* 4.2, EtOH), lit.value $[\alpha]_D^{20}$ -212 (*c* 4.2 , EtOH); δ_H (400 MHz; $CDCl_3$) 3.42-3.6 (2H, m, CH_2), 5.12-5.19 (1H, dd, *J* 11.5, 5.0, CH), 7.08-7.18 (5H, m, ArH), 7.71-7.78 (4H, m, ArH); δ_C (101 MHz; $CDCl_3$) 34.1, 53.2, 122.8, 126.4, 128.1, 128.4, 131.1, 137.8, 134.2, 168.3, 171.5. Spectroscopic data is consistent with that previously reported.[95]

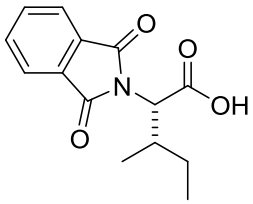
4.3.5 (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-4-methylpentanoic acid, 69



Following phthalimide protection of amino acids **Method A** using *L*-leucine (13.1 g, 100 mmol) gave the title compound at a white amorphous solid (22.4 g, 86%); m.p. 123-124 °C, lit. value 121-122 °C;[95] $[\alpha]_D^{21}$ -26 (*c* 1.0, EtOH), lit. value $[\alpha]_D^{20}$ -25.5 (*c* 1.0, EtOH);[95] δ_H (400 MHz; $CDCl_3$) 0.96 (3H, d, *J* 6.5, $CH(CH_3)_2$), 1.09 (3H, d, *J* 6.5, $CH(CH_3)_2$), 1.42-1.54 (1H, m, $CH(CH_3)_2$), 1.86

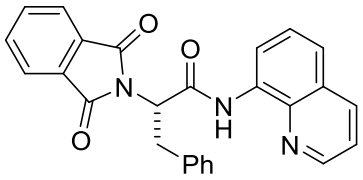
(1H, ddd, *J* 14.0, 10.0, 4.0, CH_2), 2.35 (1H, ddd, *J* 14.0, 11.5, 4.0, CH_2), 5.36 (1H, dd, *J* 11.5, 4.0, CH(CH_2)), 7.76 (2H, dd, *J* 5.5, 3.0, ArH), 7.88 (2H, dd, *J* 5.5, 3.0, ArH); δ_C (101 MHz; $CDCl_3$) 19.8, 23.1, 25.0, 37.0, 50.4, 123.0, 131.6 ,134.3, 167.9, 175.7. Spectroscopic data is consistent with that previously reported.[95]

4.3.6 (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-methylpentanoic acid, 70



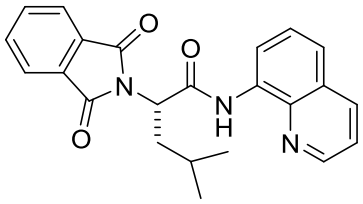
Following phthalimide protection of amino acids **Method A** using *L*-isoleucine (13.1 g, 100 mmol) gave the title compound at a white amorphous solid (21.9 g, 86%); m.p. 123-124 °C, lit. value 121-123 °C;[96] $[\alpha]_D^{21}$ -59 (*c* 1.0, MeOH), lit. value $[\alpha]_D^{20}$ -56 (*c* 1.0, MeOH);[96] δ_H (400 MHz; $CDCl_3$) 0.89 (3H, t, *J* 7.5, CH_2CH_3), 0.99-1.1 (1H, m CH_2), 1.14 (3H, d, *J* 6.5, $CHCH_3$), 1.49-1.59 (1H, m, CH_2), 2.41-2.52 (1H, m, CH), 4.63 (1H, d, *J* 8.0, CH), 7.85 (2H, dd, *J* 5.5, 3.0, ArH), 7.91 (2H, dd, *J* 5.5, 3.0, ArH); δ_C (101 MHz; $CDCl_3$) 9.9, 16.0, 25.6, 34.3, 56.7, 123.0, 131.5, 134.3, 167.9, 170.7. Spectroscopic data is consistent with that previously reported.[96]

4.3.7 (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-phenyl-*N*-(quinolin-8-yl)-propanamide, 71



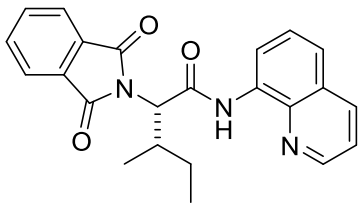
Following 8-aminoquinoline amide formation **Method B** using (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-phenylpropanoic acid **68** (5.9 g, 20 mmol) after purification by silica gel column chromatography (10% EtOAc in toluene) gave the product (7.1g, 75%) as an amorphous cream solid; m.p. 119-121 °C, lit value 120-122 °C;[66] $[\alpha]_D^{22}$ + 64 (*c* 0.8, $CHCl_3$), lit. value $[\alpha]_D^{25}$ +61.1 (*c* 0.8, $CHCl_3$);[66] δ_H (400 MHz; $CDCl_3$) 3.78-3.89 (2H, m, CH_2), 5.48 (1H, dd, *J* 10.0, 7.0 CH), 7.12-7.21 (5H, m, ArH), 7.43 (1H, dd, *J* 8.5, 4.5, ArH), 7.54 (1H, s, ArH), 7.55 (1H, d, *J* 3.0, ArH), 7.73 (2H, dd, *J* 5.5, 3.0 ArH), 7.85 (2H, dd, *J* 5.5, 3.0 ArH), 8.15 (1H, dd, *J* 8.5, 1.5 ArH), 8.64 (1H, dd, *J* 4.5, 1.5 ArH), 8.76 (1H, dd, *J* 6.5, 3.0 ArH), 10.37 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 34.8, 56.2, 116.9, 121.6, 122.0, 123.6, 127.0, 127.3, 127.9, 128.7, 129.0, 131.6, 133.8, 134.2, 136.3, 136.7, 138.0, 148.3, 167.9, 166.4. Spectroscopic data is consistent with that previously reported.[66]

4.3.8 (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-4-methyl-*N*-(quinolin-8-yl)-pentanamide, 72



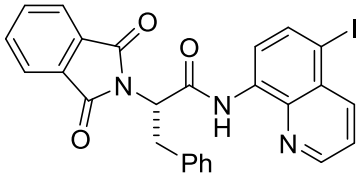
Following 8-aminoquinoline amide formation **Method B** using (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-4-methylpentanoic acid **69** (5.2 g, 20 mmol) after purification by silica gel column chromatography (10% EtOAc in toluene) gave the product (6.1 g, 79%) as an amorphous cream solid; m.p. 119-121 °C, lit value 190-193 °C;[66] $[\alpha]_D^{22}$ + 2.0 (*c* 1.8, $CHCl_3$), lit. value $[\alpha]_D^{25}$ +1.5 (*c* 1.8, $CHCl_3$);[66] δ_H (400 MHz; $CDCl_3$) 1.05 (3H, d, *J* 6.5, $CH(CH_3)_2$), 1.08 (3H, d, *J* 6.5, $CH(CH_3)_2$), 1.62-1.69 (1H, m, $CH(CH_3)_2$), 2.13 (1H, ddd, *J* 14.5, 9.5, 5.0, CH_2), 2.68 (1H, ddd, *J* 14.5, 11.5, 4.0, CH_2), 5.36 (1H, dd, *J* 11.5, 5.0, $CH(CH_2)$), 7.44 (1H, dd, *J* 8.5, 4.5, ArH), 7.52 (1H, s, ArH), 7.53 (1H, d, *J* 17.5, ArH), 7.78 (2H, dd, *J* 5.5, 3.0 ArH), 7.93 (2H, dd, *J* 5.5, 3.0 ArH), 8.20 (1H, dd, *J* 8.5, 1.5 ArH), 8.72 (1H, dd, *J* 4.5, 1.5 ArH), 8.70-8.75 (1H, m, ArH), 10.37 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 21.3, 23.3, 25.6, 37.4, 53.6, 116.7, 121.6, 121.9, 123.6, 127.3, 127.9, 131.9, 133.9, 134.2, 136.3, 138.5, 148.5, 167.4, 168.1. Spectroscopic data is consistent with that previously reported.[66]

4.3.9 (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-methyl-*N*-(quinolin-8-yl)pentanamide, 73



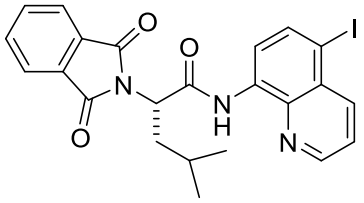
Following 8-aminoquinoline amide formation **Method B** using (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-methylpentanoic acid **70** (5.2 g, 20 mmol) after purification by silica gel column chromatography (10% EtOAc in toluene) gave the product (5.8 g, 76%) as an amorphous cream solid m.p; 143-145 °C, lit value 140-142 °C;[66] $[\alpha]_D^{22}$ -33 (*c* 1.7, $CHCl_3$), lit. value $[\alpha]_D^{25}$ -30.6 (*c* 1.3, $CHCl_3$);[66] δ_H (400 MHz; $CDCl_3$) 0.95 (3H, t, *J* 7.5, CH_2CH_3), 1.12-1.23 (1H, m CH_2), 1.20 (3H, d, *J* 6.5, $CHCH_3$), 1.51-1.67 (1H, m, CH_2), 3.06-3.14 (1H, m, CH), 4.80 (1H, d, *J* 11.0, CH), 7.47 (1H, dd, *J* 8.0, 4.5, ArH), 7.52 (1H, s, ArH), 7.53 (1H, s, ArH), 7.74 (2H, dd, *J* 5.5, 3.0 ArH), 7.90 (2H, dd, *J* 5.5, 3.0 ArH), 8.15 (1H, dd, *J* 8.0, 1.5 ArH), 8.72 (1H, dd, *J* 4.5, 1.5 ArH), 8.78 (1H, dd, *J* 4.5, 4.5 ArH), 10.64 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 10.4, 16.4, 25.7, 32.8, 62.1, 117.0, 121.6, 122.0, 123.7, 127.2, 127.9, 131.6, 134.2, 134.3, 136.2, 138.72, 148.55, 167.0, 168.3. Spectroscopic data is consistent with that previously reported.[66]

4.3.10 (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-*N*-(5-iodoquinolin-8-yl)-3-phenylpropanamide, 74



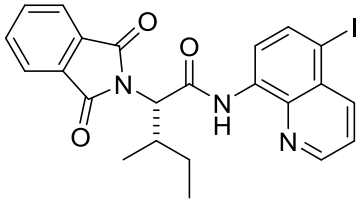
Aromatic iodination **Method C** using (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-phenyl-*N*-(quinolin-8-yl)-propanamide **71** (1.3 g, 3 mmol) after purification by silica gel column chromatography (5% EtOAc in toluene) gave the product (1.2 g, 74%) as an amorphous yellow solid m.p. 163-165 °C; $[\alpha]_D^{22}$ - 60 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3336, 3065, 2918, 1778, 1715, 1522, 1469, 1388, 1528; δ_H (400 MHz; $CDCl_3$) 3.76-3.85 (2H, m, CH_2), 5.46 (1H, dd, *J* 10.0, 6.5 CH), 7.12-7.32 (5H, m, ArH), 7.50 (1H, dd, *J* 8.5, 4.5, ArH), 7.74 (2H, dd, *J* 5.5, 3.0 ArH), 7.85 (2H, dd, *J* 5.5, 3.0 ArH), 8.01 (1H, d, *J* 8.5 ArH), 8.35 (1H, dd, *J* 8.5, 1.5 ArH), 8.53 (1H, d, *J* 8.5 ArH), 8.60 (1H, dd, *J* 4.5. 1.5), 10.33 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 34.8, 56.3, 90.0, 118.2, 123.2, 123.6, 127.0, 128.7, 129.0, 129.6, 131.6, 134.2, 134.8, 136.6, 138.2, 139.0, 140.7, 148.9, 166.5, 167.9; *m*/*z* (ES) Found: MH^+, 548.0446. $C_{26}H_{19}N_3O_3I$ requires MH^+ 548.0471.

4.3.11 (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-*N*-(5-iodoquinolin-8-yl)-4-methylpentanamide, 75



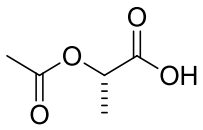
Aromatic iodination **Method C** using (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-4-methyl-*N*-(quinolin-8-yl)-pentanamide **72** (1.2 g, 3 mmol) after purification by silica gel column chromatography (5% EtOAc in toluene) gave the product (1.2 g, 78%) as an amorphous cream solid; m.p. 136-138 °C; $[\alpha]_D^{22}$ -13 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3339, 2959, 2931, 1778, 1709, 1522, 1472, 1382, 1316; δ_H (400 MHz; $CDCl_3$) 1.05 (3H, d, J 6.5, $CH(CH_3)_2$), 1.08 (3H, d, *J* 6.5, $CH(CH_3)_2$), 1.60-1.70 (1H, m, $CH(CH_3)_2$), 2.12 (1H, ddd, *J* 14.0, 9.5, 5.0, CH_2), 2.65 (1H, ddd, *J* 14.0, 11.5, 4.0, CH_2), 5.23 (1H, dd, *J* 11.5, 5.0, $CH(CH_2)$), 7.53 (1H, dd, *J* 8.5, 4.0, ArH), 7.79 (2H, dd, *J* 5.5, 3.0 ArH), 7.93 (2H, dd, *J* 5.5, 3.0 ArH), 8.07 (1H, d, *J* 8.5 ArH), 8.37 (1H, dd, *J* 8.5, 1.5 ArH), 8.51 (1H, d, *J* 8.5 ArH), 8.70 (1H, dd, *J* 4.0. 1.5), 10.35 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 21.3, 23.2, 25.6, 37.4, 53.7, 89.8, 118.1, 123.2, 123.7, 129.6, 131.8, 134.3, 134.9, 138.2, 139.1, 140.7, 149.0, 167.5, 168.1; *m*/*z* (ES) Found: MH^+, 514.0651. $C_{23}H_{21}N_3O_3I$ requires MH^+ 514.0628.

4.3.12 (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-*N*-(5-iodoquinolin-8-yl)-3-methylpentanamide, 76



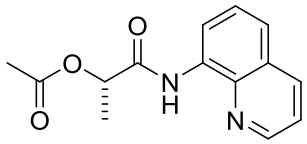
Aromatic iodination **Method C** using (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-methyl-*N*-(quinolin-8-yl)pentanamide **73** (1.2 g, 3 mmol) after purification by silica gel column chromatography (5% EtOAc in toluene) gave the product (1.1 g, 76%) as an amorphous cream solid; m.p. 134-136 °C; $[\alpha]_D^{22}$ - 48 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3339, 2972, 2927, 1771, 1715, 1525, 1472, 1378, 1067; δ_H (400 MHz; $CDCl_3$) 0.95 (3H, t, *J* 7.5, CH_2CH_3), 1.16-1.21 (1H, m CH_2), 1.19 (3H, d, *J* 6.5, $CHCH_3$), 1.51-1.59 (1H, m, CH_2), 3.02-3.12 (1H, m, CH), 4.79 (1H, d, *J* 11.0, CH), 7.56 (1H, dd, *J* 8.5, 4.0, ArH), 7.76 (2H, dd, *J* 5.5, 3.0 ArH), 7.91 (2H, dd, *J* 5.5, 3.0 ArH), 8.07 (1H, d, *J* 8.5 ArH), 8.37 (1H, dd, *J* 8.5, 1.5 ArH), 8.57 (1H, d, *J* 8.5 ArH), 8.87 (1H, dd, *J* 4.0. 1.5), 10.66 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 10.3, 16.3, 25.6, 32.8, 62.1, 90.0, 118.4, 123.2, 123.7, 129.6, 131.6, 134.3, 135.3, 138.1, 139.2, 140.6, 149.1, 167.4, 168.2; *m*/*z* (ES) Found: MH^+, 514.0606. $C_{23}H_{21}N_3O_3I$ requires MH^+ 514.0628.

4.3.13 (2*S*)-2-(acetyloxy)propanoic acid, 77



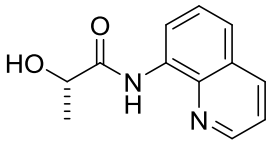
To a solution of *L*-lactic acid (90 w% in H_2O, 4.2 mL, 56 mmol) in pyridine (5.6 mL, 69 mmol) was added acetic acid (5.3 mL, 56 mmol) at 0 °C, followed by stirring at rt for 24 h. The reaction mixture was then poured onto ice water (25 mL), stirred for a further hour before being extracted in EtOAc (3 x 30 mL), washed with HCl (1 M, 3 x 30 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified via vacuum distillation (11 mmHg, 115 °C) to give the product as a colourless oil (4.89 g, 66%); $[\alpha]_D^{20}$ -50.9 (*c* 2.28, $CHCl_3$), lit. value[88] $[\alpha]_D^{21}$ -47.5 (*c* 2.28, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 1.51 (3H, d, *J* 7.0 CH_3), 2.11 (3H, s, CH_3), 5.08 (1H, q, *J* 7.0, CH), 10.75 (1H, s, COOH); δ_C (101 MHz; $CDCl_3$) 16.7, 20.51, 68.2, 170.8, 176.3. Spectroscopic data is consistent with that previously reported.[88]

4.3.14 (1*S*)-1-[(quinolin-8-yl)carbamoyl]ethyl acetate, 78



Following 8-aminoquinoline amide formation **Method B** using (2*S*)-2-(acetyloxy)propanoic acid **77** (2.6 g, 20 mmol) after purification by silica gel column chromatography (5% EtOAc in toluene) gave the product (4.16 g, 81%) as a cream amorphous solid; m.p 39-41 ^{o}C; $[\alpha]_D^{20}$ -95 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3344, 2927, 1745 (C=O), 1686 (C=O), 1528; δ_H (400 MHz; $CDCl_3$) 1.66 (3H, d, *J* 7.0, CH_3), 2.32 (3H, s, CH_3), 5.48 (1H, q, *J* 7.0, CH), 7.45 (1H, dd, *J* 8.5, 4.0, ArH), 7.52 (1H, s, ArH), 7.53 (1H, d, *J* 2.0, ArH), 8.15 (1H, dd, *J* 8.5, 1.5, ArH), 8.75 (1H, dd, *J* 3.5, 5.5, ArH), 8.81 (1H, dd, *J* 4.0, 1.5, ArH), 10.56 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 18.0, 21.1, 71.1, 116.6, 121.7, 122.1, 127.3, 127.9, 133.7, 136.4, 138.6, 148.5, 168.9, 169.0; *m*/*z* (ES) Found: MH$^+$, 259.1090. $C_{14}H_{15}N_2O_3$ requires MH$^+$ 259.1083.

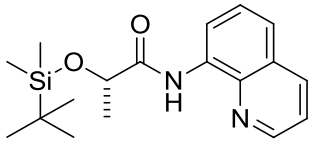
4.3.15 (2*S*)-2-hydroxy-*N*-(quinolin-8-yl)propanamide, 82



K_2CO_3 (1g) was added to a solution of (1*S*)-1-[(quinolin-8-yl)carbamoyl]ethyl acetate **78** (258 mg, 1 mmol) in MeOH (8 mL) at 0 ^{o}C. The resulting reaction mixture was then stirred at rt for 4 h. The reaction mixture was extracted in EtOAc (2 x 50 ml), washed with brine (50 ml), dried over $MgSO_4$ and the

solvent removed under reduced pressure. The crude product was then purified using silica gel column chromatography (40% EtOAc in toluene) to give the product as a yellow oil (215 mg, 99%); $[\alpha]_D^{20}$ -11 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3389, 3324, 1662 (C=O), 1528; δ_H (400 MHz; $CDCl_3$) 1.64 (3H, d, *J* 7.0, CH_3), 4.0 (1H, brs, OH), 4.57 (1H, q, *J* 7.0, CH), 7.40 (1H, dd, *J* 8.5, 4.0, ArH), 7.46 (1H, s, ArH), 7.47 (1H, d, *J* 4.5, ArH), 8.11 (1H, dd, *J* 8.5, 1.5, ArH), 8.73 (1H, dd, *J* 5.0, 4.5, ArH), 8.79 (1H, dd, *J* 4.0, 1.5, ArH), 10.79 (1H, s, NH). δ_C (101 MHz; $CDCl_3$) 21.3, 69.3, 116.8, 121.6, 122.1, 127.2, 128.0, 133.7, 136.3, 138.7, 148.5, 173.5; *m*/*z* (ES) Found: MH^+, 217.0932. $C_{12}H_{12}N_2O_2$ requires MH^+ 217.0925.

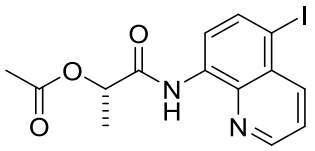
4.3.16 (2*S*)-2-[(tert-butyldimethylsilyl)oxy]-*N*-(quinolin-8-yl-propanamide, 83



To a solution of 2-hydroxy-*N*-(quinolin-8-yl)propanamide **82** (432 mg, 2 mmol) and imidazole (348 mg, 5 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added TBDMSCl (362 mg, 2.4 mmol). The reaction was stirred at room temperature for 10 hours. The reaction was diluted with CH_2Cl_2 (5 mL), and H_2O (10 mL) and further extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified using silica gel column chromatography (5% EtOAc in toluene) to give the product as a yellow oil (628 mg, 95%); $[\alpha]_D^{20}$ -74 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3344, 2927, 1686 (C=O), 1528, 1090; δ_H (400

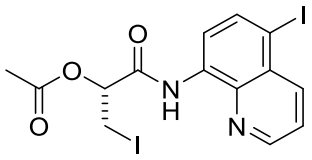
MHz; $CDCl_3$) 0.22 (6H, s, CH_3), 1.10 (9H, s, CH_3), 1.57 (3H, d, *J* 7.0, CH_3), 4.47 (1H, q, *J* 7.0, CH), 7.46 (1H, dd, *J* 8.5, 4.0, ArH), 7.54 (1H, s, ArH), 7.56 (1H, d, *J* 4.0, ArH), 8.17 (1H, dd, *J* 8.5, 1.5, ArH), 8.80 (2H, m, ArH), 11.17 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) -4.5 , 18.1, 25.7, 29.7, 70.7, 116.2, 121.6, 121.7, 127.3, 128.0, 134.3, 136.1, 139.0, 148.1, 173.1; *m*/*z* (ES) Found: MH^+, 331.1845. $C_{18}H_{26}N_2O_2Si$ requires MH^+ 331.1853.

4.3.17 (1*S*)-1-[(5-iodoquinolin-8-yl)carbamoyl]ethylacetate, 80



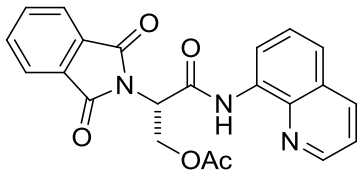
Aromatic iodination **Method C** using (1*S*)-1-[(quinolin-8-yl)carbamoyl]ethyl acetate **78** (0.77 g, 3 mmol) after purification by silica gel column chromatography (10% EtOAc in toluene) gave the product (0.99 g, 86%) as a pale yellow oil; $[\alpha]_D^{22}$ - 63 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3342, 2915, 2847, 1743, 1687, 1528, 1475, 1226; δ_H (400 MHz; $CDCl_3$) 1.67 (3H, d, *J* 7.0, CH_3), 2.33 (3H, s, CH_3), 5.48 (1H, q, *J* 7.0, CH), 7.58 (1H, dd, *J* 8.5, 4.5, ArH), 8.12 (1H, d, *J* 8.0 ArH), 8.42 (1H, dd, *J* 8.5, 1.5 ArH), 8.56 (1H, d, *J* 8.0 ArH), 8.87 (1H, dd, *J* 4.5. 1.5), 10.56 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 17.9, 21.1, 71.0, 89.1, 118.1, 121.7, 123.3, 127.9, 133.7, 136.4, 138.2, 148.5, 168.9, 169.0; *m*/*z* (ES) Found: MH^+, 385.0039. $C_{14}H_{14}N_2O_3I$ requires MH^+ 385.0049.

4.3.18 (1*R*)-2-iodo-1-[(5-iodoquinolin-8-yl)carbamoyl]ethyl acetate, 81



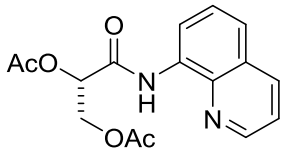
A solution of (1*S*)-1-[(5-iodoquinolin-8-yl)carbamoyl]ethylacetate **80** (384 mg, 1 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), I_2 (380 mg, 1.5 mmol) and Ag_2CO_3 (276 mg, 1 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 1 week. The reaction mixture was filtered, extracted with CH_2Cl_2 (2 x 5 mL), washed with 10% $Na_2S_2O_3$ (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified using silica gel column chromatography (10% EtOAc in toluene) to give the product (30 mg, 8%) as a pale yellow oil; $[\alpha]_D^{20}$ -14 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3333, 2921, 2853, 1749, 1687, 1528, 1475, 1213; δ_H (400 MHz; $CDCl_3$) 2.42 (3H, s, CH_3), 3.71 (1H, dd, *J* 11.0, 4.0, C*H*HI), 3.80 (1H, dd, *J* 11.0, 5.5 CH*H*I), 5.50 (1H, dd, *J* 5.5, 4.0, CH), 7.59 (1H, dd, *J* 8.5, 4.5, ArH), 8.13 (1H, d, *J* 8.0, ArH), 8.42 (1H , dd, *J* 8.5, 1.5 ArH), 8.55 (1H, d, *J* 8.0, ArH), 8.84 (1H, dd, *J* 4.5, 1.5, ArH), 10.65 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 3.3, 21.0, 73.0, 90.7,118.2, 123.4, 129.7, 134.1, 138.2, 139.2, 140.8, 149.24, 165.7, 168.2; *m*/*z* (ES) Found: MH^+, 510.9014. $C_{14}H_{13}N_2O_3I_2$ requires MH^+ 510.9016.

4.3.19 Acetoxy-*N*-Phthaloyl-*L*-alanine 8-aminoquinoline amide, 84



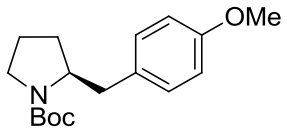
The named compound was prepared by a minor modification of the literature procedure.[54] A mixture of (*S*)-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-*N*-quinolin-8-yl-propionamide **50** (240 mg, 0.7 mmol), $Pd(OAc)_2$ (31 mg, 0.14 mmol), $Mn(OAc)_2$ (144 mg, 0.83 mmol), Oxone® (2.14 g, 3.5 mmol) and Ac_2O (0.7 mL, 7.0 mmol) in CH_3NO_2 (14 mL) was stirred at 80 °C under an air atmosphere. After 60 h the reaction mixture was filtered and washed with CH_2Cl_2 (2 x 15 mL). The solvent was removed under reduced pressure and the crude product purified by silica gel column chromatography (petrol-EtOAc, gradient from 0-100% EtOAc) to give the product (142 mg, 52%) as a light-brown amorphous solid; m.p. 179-180 °C, lit. value 182-185 °C; $[\alpha]_D^{20}$ +8.9 (*c* 1.7, $CHCl_3$), lit. value[66] $[\alpha]_D^{25}$ +8.2 (*c* 1.7, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 2.21 (3H, s, CH_3), 4.78 (1H, dd, *J* 11.5, 7.0, C*H*H), 5.15 (1H, dd, *J* 11.5, 7.5, CH*H*), 5.38 (1H, dd, *J* 7.5, 7.0, CH), 7.41 (1H, dd, *J* 8.5, 4.5, ArH), 7.49 (1H, d, *J* 5.5, ArH), 7.50 (1H, d, *J* 1.5, ArH), 7.76 (2H, dd, *J* 5.5, 3.0 ArH), 7.90 (2H, dd, *J* 5.5, 3.0, ArH), 8.13 (1H, dd, *J* 8.5, 1.5, ArH), 8.66 (1H, dd, *J* 4.5, 1.5, ArH), 8.68 (1H, dd, *J* 5.5, 1.5, ArH), 10.52 (1H, s, NH). δ_C (101 MHz; $CDCl_3$) 20.7, 52.9, 61.8, 117.0, 121.6, 122.2, 123.8, 127.3, 127.9, 131.8, 133.8, 134.4, 136.4, 138.4, 148.2, 164.4, 167.7, 170.2. Spectroscopic data is consistent with that previously reported.[66]

4.3.20 (1*S*)-2-(acetyloxy)-1-[(quinolin-8-yl)carbamoyl]ethyl acetate, 86



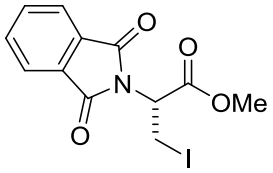
(1*S*)-1-[(quinolin-8-yl)carbamoyl]ethyl acetate **78** (130 mg, 0.5 mmol), $Pd(OAc)_2$ (13 mg, 0.058 mmol), $PhI(OAc)_2$ (242 mg, 0.75 mmol), acetic anhydride (131 mg, 1.28 mmol) and *o*-dichlorobenzene (1.4 mL) were added to a 10 mL round bottom flask and stirred at 70 °C for 12 h. The *o*-dichlorobenzene was removed by vacuum distillation and the crude product purified by silica gel column chromatography (20% EtOAc in toluene) to give the product (152 mg, 96%) as a cream amorphous solid; m.p 84-86 °C; $[\alpha]_D^{20}$ +14 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3339, 2959, 2921, 1747, 1691, 1437, 1488, 1232, 1210; δ_H (400 MHz; $CDCl_3$) 2.08 (3H, s, CH_3), 2.38 (3H, s, CH_3), 4.49 (1H, dd, *J* 12.0, 5.0 CH_2), 4.73 (1H, dd, *J* 12.0, 3.0 CH_2), 5.68 (1H, dd, *J* 5.0, 3.0 CH), 7.50 (1H, d, *J* 8.5, 4.0, ArH), 7.58 (1H, d, *J* 3.0, ArH), 7.59 (1H, s, ArH), 8.21 (1H, dd, *J* 8.5, 1.5, ArH), 8.77 (1H, dd, *J* 5.5, 3.0, ArH), 8.85 (1H, dd, *J* 4.0, 1.5, ArH), 10.56 (1H, s, NH); δ_C (101 MHz; $CDCl_3$) 20.6, 20.9, 63.1, 72.3, 116.8, 121.8, 122.4, 127.3, 128.0, 133.4, 136.4, 138.6, 148.6, 165.2, 169.4, 170.6; m/z (ES) Found: MH^+, 317.1128. $C_{16}H_{17}N_2O_5$ requires MH^+ 317.1137.

4.3.21 (*S*)-(+)-*tert*-Butyl 2-(4-Methoxybenzyl)pyrrolidine-1-carboxylate



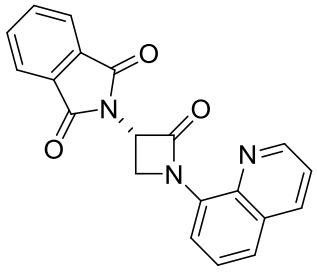
Zinc dust (190 mg, 3 mmol) was added to a flame-dried, nitrogen-purged, round bottom flask. Dry DMF (0.7 mL) was added via syringe, followed by iodine (40 mg, 0.15 mmol); the yellow colour rapidly faded. Pd_2dba_3 (22 mg, 0.025 mmol), SPhos (21 mg, 0.05 mmol), and 4-iodoanisole (468 mg, 2.0 mmol) were added to the flask, and the reaction mixture was cooled in an ice bath. The iodide 9 (311 mg, 1 mmol) in DMF (0.8 mL) was added in 10 portions, via syringe, over 5 h. The reaction mixture was allowed to warm to room temperature overnight. The crude product was purified using silica gel column chromatography (7% EtOAc in petroleum ether) to give the product as a colourless oil (159 mg, 55%); $[\alpha]_D^{25}$ -2.1 (*c* 1.04, $CHCl_3$), lit value $[\alpha]_D^{25}$ -2.4 (*c* 1.04, $CHCl_3$);[90] δ_H (400 MHz; $CDCl_3$) 1.43 (9H, s, $C(CH_3)_3$), 1.55-1.81 (4H, m, $2CH_2$), 2.54 (1H, dd, *J* 13.0, 9.0, CH), 2.88 (1H, dd, *J* 13.0, 3.5, CH), 3.11-3.19 (1H, m, CH), 3.21-3.31 (1H, m, CH), 3.73 (3H, s, OMe), 3.81-3.90 (1H, m, CH), 6.85 (2H, d, *J* 8.5, ArH), 7.07 (2H, d, *J* 8.5, ArH); δ_C (101 MHz; $CDCl_3$) 22.1, 28.6, 27.9, 45.8, 54.7, 57.9, 77.8,113.5, 129.7, 130.5, 153.1, 157.5, one peak obscured. Spectroscopic data is consistent with that previously reported.[90]

4.3.22 (2*R*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-iodopropanoate, 90



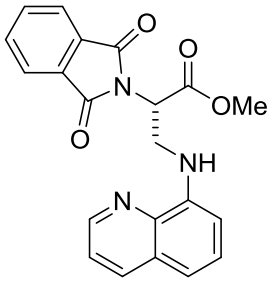
A solution of (*R*)-2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-iodo-*N*-quinolin-8-yl-propion-amide **53** (140 mg, 0.3 mmol) was refluxed in MeOH (3 mL, 1.25 M) for 24 h. The solvent was removed under vacuum and the crude product purified using silica gel chromatography (20% EtOAc in petrol) to give a white solid; m.p. 81-83 ^{o}C, lit. value 82-84 °C;[73] $[\alpha]_D^{25}$ -37.0 (*c* 1.0, $CHCl_3$), lit. value $[\alpha]_D^{20}$ -39.5 (*c* 1.0, $CHCl_3$);[73] δ_H (400 MHz; $CDCl_3$) 3.80 (3H, s, OCH_3), 3.93-4.00 (2H, m, CH_2), 5.10 (1H, dd, *J* 11.5, 5.0, CH), 7.83 (2H, dd, *J* 5.5, 3.0, ArH), 7.92 (2H, dd, *J* 5.5, 3.0, ArH); δ_C (101 MHz; $CDCl_3$) 0.3, 53.3, 54.0, 123.9, 131.7, 134.5, 166.8, 167.2; Found: MH^+, 358.9739. $C_{12}H_{10}NO_4I$ requires MH^+ 358.9733. Spectroscopic data is consistent with that previously reported.[73]

4.3.23 2-[(3*S*)-2-oxo-1-(quinolin-8-yl)azetidin-3-yl]-2,3-dihydro-1*H*-isoindole-1,3-dione, 99



(*R*)-2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-iodo-*N*-quinolin-8-yl-propion-amide **53** (236 mg, 0.5 mmol) and K_2CO_3 (75 mg, 0.55 mmol) were added to a solution of 0.5% H_2O in DMF (5 mL) and stirred at rt for 6 hours. The reaction mixture was then diluted with brine (100 mL), extracted with EtOAc (3 x 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material purified using silica gel column chromatography to give the product as a amorphous white solid (140 mg, 82%), (98% ee.); m.p. 163-165 °C; $[\alpha]_D^{20}$ -26 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3218, 2965, 2924, 1749, 1712, 1475, 1391, 830, 718; δ_H (400 MHz; $CDCl_3$) 4.76 (1H, dd, *J* 7.5, 3.0, CH_2), 5.09 (1H, dd, *J* 7.5, 6.0 CH_2), 5.71 (1H, dd, *J* 6.0, 3.0, CH), 7.42 (1H, dd, *J* 8.5, 4.0, ArH), 7.57 (1H, dd, *J* 8.0, 8.0 ArH), 7.62 (1H, dd, *J* 8.0, 1.5 ArH), 7.77 (2H, dd, *J* 5.5, 3.0, ArH), 7.90 (2H, dd, *J* 5.5, 3.0, ArH), 8.16 (1H, dd, *J* 8.5, 1.5, ArH), 8.55 (1H, dd, *J* 8.0, 1.5, ArH), 8.83 (1H, dd, *J* 4.0, 1.5, ArH); δ_C (101 MHz; $CDCl_3$) 52.0, 55.0, 117.0, 120.1, 121.4, 123.7, 123.9, 126.8, 128.9, 131.8, 134.4, 136.0, 140.4, 148.8, 164.2, 167.0; *m*/*z* (ES) Found: MH^+, 344.1044. $C_{20}H_{14}N_3O_3$ requires MH^+ 344.1035; CSP-HPLC: Lux 3u cellulose-2 (25% *i*PrOH in hexane, 1.0 mL/min) (*R*)-**99** 41.33 min, (*S*)-**99** 49.89 min.

4.3.24 methyl (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-[(quinolin-8-yl)amino]propanoate, 100



A solution of 2-[(3*S*)-2-oxo-1-(quinolin-8-yl)azetidin-3-yl]-2,3-dihydro-1*H*-isoindole-1,3-dione **99** (172 mg, 0.5 mmol) was refluxed in MeOH (6 mL, 1.25 M) overnight. The solvent was removed under vacuum and the crude product purified using silica gel chromatography (10% EtOAc in toluene) to give a brown solid; m.p 56-58 ^{o}C; (148 mg, 79%); $[\alpha]_D^{20}$ -40 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3361, 2915, 2846, 1743, 1715, 1519, 1385, 1260; δ_H (400 MHz; $CDCl_3$) 3.82 (3H, s, OCH_3), 4.21 (1H, ddd, *J* 14.5, 7.5, 8.5, CH_2), 4.32 (1H, ddd, *J* 14.5, 6.5, 6.0, CH_2), 5.32 (1H, dd, *J* 8.5, 6.0, CH), 6.53 (1H, dd, *J* 7.5, 6.5, NH), 6.86 (1H, d, *J* 8.0, ArH), 7.09 (1H, d, *J* 8.0, ArH), 7.33 (1H, dd, *J* 8.5, 4.0), 7.41 (1H, dd, *J* 8.0, 8.0, ArH), 7.73 (2H, dd, *J* 5.5, 3.0, ArH), 7.83 (2H, dd, *J* 5.5, 3.0, ArH), 8.04 (1H, dd, *J* 8.5, 1.5, ArH), 8.64 (1H, dd, *J* 4.0, 1.5, ArH); δ_C (101 MHz; $CDCl_3$) 29.7, 50.7, 52.9, 105.3, 115.0, 121.4, 123.6, 128.7, 129.1, 131.8, 134.3, 136.0, 143.5, 147.0, 167.6, 168.9; *m*/*z* (ES) Found: MH^+, 376.1285. $C_{21}H_{17}N_3O_4$ requires MH^+ 376.1297.

5. References

(1) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(2) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.

(3) Strecker, A. *Annalen der Chemie und Pharmacie* **1850**, *75*, 27.

(4) Kuethe, J. T.; Gauthier, D. R., Jr.; Beutner, G. L.; Yasuda, N. *J. Org. Chem.* **2007**, *72*, 7469.

(5) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

(6) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(7) Maruoka, K.; Ooi, T.; Kano, T. *Chem. Commun.* **2007**, 1487.

(8) Frankland, E. *Justus Liebigs Ann. Chem.* **1849**, 171.

(9) Smith, R. D.; Simmons, H. E. *Org. Synth.* **1961**, *41*, 72.

(10) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(11) Deboves, H. J. C.; Montalbetti, C. A. G. N.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1876.

(12) Huo, S. *Org. Lett.* **2003**, *5*, 423.

(13) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

(14) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.

(15) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532.

(16) Liu, Q.; Lan, Y.; Liu, J.; Li, G.; Wu, Y.-D.; Lei, A. *J. Am. Chem. Soc.* **2009**, *131*, 10201.

(17) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

(18) Ross, A. J.; Lang, H. L.; Jackson, R. F. W. *J. Org. Chem.* **2010**, *75*, 245.

(19) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(20) Jackson, R. F. W.; James, K.; Wythes, M. J.; Wood, A. *J. Chem. Soc., Chem. Commun.* **1989**, 644.

(21) Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397.

(22) Dexter, C. S.; Hunter, C.; Jackson, R. F. W.; Elliott, J. *J. Org. Chem.* **2000**, *65*, 7417.

(23) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(24) Kwong, F. Y.; Chan, A. S. C. *Synlett* **2008**, 1440.

(25) Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26*, 2183.

(26) Tanaka, M.; Hikawa, H.; Yokoyama, Y. *Tetrahedron* **2011**, *67*, 5897.

(27) Eerland, M. F.; Hedberg, C. *J. Org. Chem.* **2011**, *77*, 2047.

(28) Tuttle, J. B.; Azzarelli, J. M.; Bechle, B. M.; Dounay, A. B.; Evrard, E.; Gan, X.; Ghosh, S.; Henderson, J.; Kim, J.-Y.; Parikh, V. D.; Verhoest, P. R. *Tetrahedron Lett.* **2011**, *52*, 5211.

(29) Groselj, U.; Bevk, D.; Jakse, R.; Meden, A.; Pirc, S.; Recnik, S.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2004**, *15*, 2367.

(30) Lilley, M., Thesis, University of Sheffield, 2013.

(31) Achonduh, G. T.; Hadei, N.; Valente, C.; Avola, S.; O'Brien, C. J.; Organ, M. G. *J. Chem. Soc., Chem. Commun.* **2010**, *46*, 4109.

(32) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

(33) Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 5376.

(34) Schnurch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283.

(35) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879.

(36) Bergman, R. G. *Nature* **2007**, *446*, 391.

(37) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245.

(38) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

(39) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(40) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447.

(41) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.

(42) Chatt, J.; Davidson, J. M. *J. Chem. Soc., Chem. Commun.* **1965**, 843.

(43) Jones, W. D.; Feher, F. J. *Organometallics* **1983**, *2*, 562.

(44) Baudry, D.; Ephritikhine, M.; Felkin, H. *J. Chem. Soc., Chem. Commun.* **1980**, 1243.

(45) Bhalla, G.; Periana, R. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1540.

(46) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

(47) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716.

(48) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634.

(49) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(50) Hull Kami, L.; Anani Waseem, Q.; Sanford Melanie, S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.

(51) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, 5726.

(52) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285.

(53) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Eur. J. Org. Chem.* **2010**, *16*, 2654.

(54) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699.

(55) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

(56) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726.

(57) Ryabov, A. D. *Synthesis* **1985**, 233.

(58) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2009**, *110*, 1147.

(59) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542.

(60) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141.

(61) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191.

(62) Constable, A. G.; McDonald, W. S.; Sawkins, L. C.; Shaw, B. L. *J. Chem. Soc., Chem. Commun.* **1978**, 1061.

(63) Baldwin, J. E.; Najera, C.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1985**, 126.

(64) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.

(65) Maleckis, A.; Kampf, J. W.; Sanford, M. S. *J Am Chem Soc* **2013**, *135*, 6618.

(66) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391.

(67) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(68) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420.

(69) Carr, K.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1984**, 1227.

(70) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112.

(71) Giri, R.; Chen, X.; Hao, X.-S.; Li, J.-J.; Liang, J.; Fan, Z.-P.; Yu, J.-Q. *Tetrahedron: Asymmetry* **2005**, *16*, 3502.

(72) Giri, R.; Wasa, M.; Breazzano, S. P.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 5685.

(73) Robinson, S. A., Thesis, University of Sheffield, 2012.

(74) Kryska, A.; Skulski, L. *J. Chem. Res., Synop.* **1999**, 590.

(75) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657.

(76) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382.

(77) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958.

(78) Li, B. T. Y.; White, J. M.; Hutton, C. A. *Aust. J. Chem.* **2010**, *63*, 438.

(79) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188.

(80) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238.

(81) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984.

(82) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886.

(83) Yoo, E.-J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *132*, 17378.

(84) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570.

(85) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387.

(86) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.

(87) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882.

(88) Studte, C.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5451.

(89) Rilatt, I.; Jackson, R. F. W. *J. Org. Chem.* **2008**, *73*, 8694.

(90) Massah, A. R.; Ross, A. J.; Jackson, R. F. W. *J. Org. Chem.* **2010**, *75*, 8275.

(91) Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64.

(92) Jackson, R. F. W.; Perez-Gonzalez, M. *Org. Synth.* **2005**, *81*, 77.

(93) Walker, M. A.; Kaplita, K. P.; Chem, T.; King, D. H. *Synlett* **1997**, 740.

(94) Mezei, G.; Rivera-Carrillo, M.; Raptis, R. G. *Inorg. Chim. Acta* **2004**, *357*, 3721.

(95) Bose, A. K.; Greer, F.; Price, C. C. *J. Org. Chem.* **1958**, *23*, 1335.

(96) Casimir, J. R.; Guichard, G.; Briand, J.-P. *J. Org. Chem.* **2002**, *67*, 3764.