Direct Arylation of Thiazoles

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A posse ad esse
From possibility to actuality

Declaration

This thesis was submitted in part fullfillment of the requirements for the degree of Doctor of Philosophy at the University of Edinburgh. Unless otherwise stated the work described in this thesis is origional and has not been submitted previously in whole or in any part for any other degree or qualification at this, or any other university.

Gemma L. Turner

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Abstract

An introduction to the thiazole ring system is presented together with a detailed, but non-exhaustive review of the rapidly emerging area of palladium-mediated directed arylation.

The direct arylation of thiazole is also discussed together with our attempts to improve the established methods. A high-yielding, mild protocol has been developed for the functionalisation of the most electron-rich carbon-hydrogen bonds in a number of heterocyclic ring systems, this represents the first example of a C-H activation reaction being accomplished in aqueous media and allows access to a diverse range of functionalised aryl heterocycles.

In addition, work towards functionalisation of the thiazole C4 position is described. A number of different approaches are discussed and our endeavors are recorded.

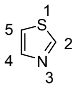
List of abbreviations

Å	angstroms
Ac	acetate
Ad	adamantyl
AIBN	azoisobutryonitrile
aq	aqueous
Ar	aryl substituent
atm	atmospheres
BP	boiling point
BQ	benzoquinone
cf	compare from
CF	concerted C-H functionalisation
Cy	cyclohexyl
d	doublet
dba	dibenzylidene acetone
DCM	dichloromethane
dd	doubled doublet
ddd	doubled doubled doublet
DG	directing group
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,1'-bis-(diphenylphosphino)butane
dppe	1,1'-bis-(diphenylphosphino)ethane
dppf	1,1'-bis-(diphenylphosphino)ferrocene
dppm	1,1'-bis-(diphenylphosphino)methane
dpppr	1,1'-bis-(diphenylphosphino)propane
dt	doubled triplet
E	electrophile
e^-	electron
EA	electrophilic addition
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarboiimide, water soluble carbodiimide
EI	electon impact ionisation
Equiv	equivalents
ES	electrospray ionisiation
Et	ethyl
FAB	fast atom bombardment ionisation
Fu	furyl
HATU	2-(1H-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate
HIV	human immunodeficiency virus

HOBt	hydroxy benzotriazole
HPLC	high pressure liquid chromatography
hr	hours
HRMS	high resolution mass spectrometry
^{i}Bu	iso-butyl
IR	infra-red spectroscopy
KIE	kinetic isotope effect
L	ligand
LC-MS	liquid chromatography - mass spectrometry
m	meta
M	metal
*m*CPBA	meta-chloroperbenzoic acid
Me	methyl
mes	mesityl
min	minutes
mol	moles
MP	melting point
MRSA	methicillin-resistent *Staphylococcus aureus*
MS	mass spectroscopy/molecular sieves
mw	microwave
NCS	N-chlorosuccinimide
NMP	N-methylpyrrolidinone
NMR	nuclear magnetic resonance
NSAID	non-steroidal anti inflamatory drug
o	ortho
O/N	overnight
OA	oxidative addition
p	para
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
quat	quaternary
RDS	rate determining step
RE	reductive elimination
R_f	retention factor
rt	room temperature
s	singlet
^{s}Bu	sec-butyl
sept	septet
T	temperature
t	triplet
TBAB	tetrabutyl ammonium bromide

TBAF	tetrabutyl ammonium fluoride
^{t}Bu	tert-butyl
Temp	temperature
Tf	triflate - SO_2CF_3
Th	thiazole
THF	tetrahydrofuran
tlc	thin layer chromatography
UV	ultra violet radiation
Δ	heating to reflux

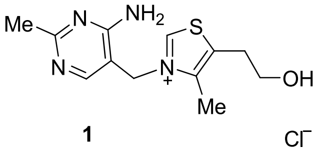
Contents



1. Introduction

1.1. Thiazoles

The thiazole ring system is found in a diverse range of natural products and functional materials. It plays a central role in the biochemistry of life, being incorporated into the structure of vitamin B1,[1] thiamin, **1**, which is vital for neural function and the metabolism of carbohydrate. Thiazoles are also found in a number of natural products,[2-5] are increasingly being incorporated into pharmaceutical compounds[2], and have wide use in flavourings and perfumes.[6] Major agrochemical compounds[7] have incorporated thiazoles for more than twenty years. They possess interesting electronic and optical properties[8] and as such have received considerable attention from material scientists.



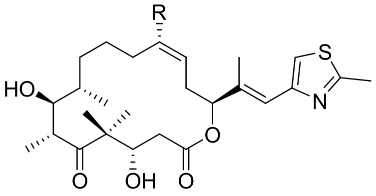
1

vitamin B1, thiamin

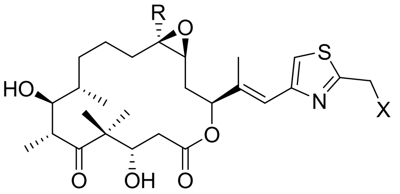
1.1.1. Use of thiazoles

Whilst many heterocycles are isolated in trace amounts from crude oil, thiazoles are not within this number;[5] they are however found in nature, generally in peptidic compounds.[2-5] There are a number of different types of thiazole natural products, perhaps the most well known are the epothilones, **2a-f**,[9,10] originally isolated from soil bacteria *Sorangium cellulosum,* they are microtubule polymerisation promoters and have a similar mechanism of action to Taxol.[2-5] Although structurally dissimilar they exhibit dramatically improved potency against multi-drug resistant tumour cell lines and as such have received considerable interest. In addition to this, and, in contrast to Taxol, multi kilogram quantities are available from fermentation which, when combined with precursor-driven directed evolution has allowed extensive studies of a number of analogues. Epothilone B, **2b**, is currently in Phase II trials by

Novartis and its lactam analogue is in Phase II/III trials by Bristol-Meyers Squibb.[2-5] 12,13-Deoxyepothilone B (Sloan-Kettering/Kosan/Roche) and C21-amino epothilone B (Bristol-Meyers Squibb) have also entered clinical trials.[2-5]

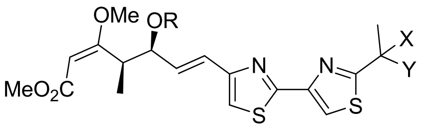


R = H	epothilone C	**2c**
R = Me	epothilone D	**2d**

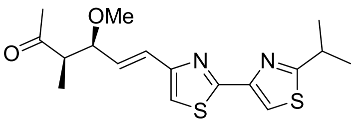


R = H, X = H	epothilone A	**2a**
R = Me, X = H	epothilone B	**2b**
R = H, X = OH	epothilone E	**2e**
R = Me, X = OH	epothilone F	**2f**

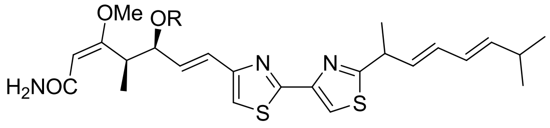
Myxobacteria have been recognised as a rich source of novel, bioactive compounds[9] including, but not limited to the promising anti tumour compounds the epothilones. Also of note are the cystothiazoles A-G, **3a-g**, [11-14] and myxothiazole, **4**,[9,15] each have a 2,4-linked bisthiazole motif and are isolated from the *Cystobacter fuscus* strain AJ-13278.[2-5]



R = Y = Me, X = H	cystothiazole A	**3a**
R = Y = Me, X = OH	cystothiazole B	**3b**
R = X = H, Y = Me	cystothiazole C	**3c**
R = H, X,Y = CH_2	cystothiazole D	**3d**
R = Me, X = H, Y = CH_2OH	cystothiazole F	**3f**
R = Me, X = Y = H	cystothiazole G	**3g**

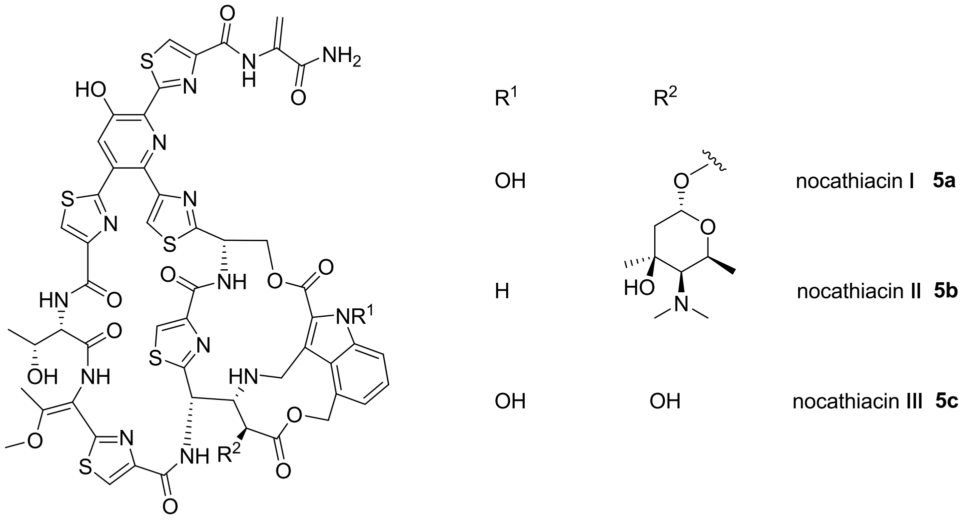


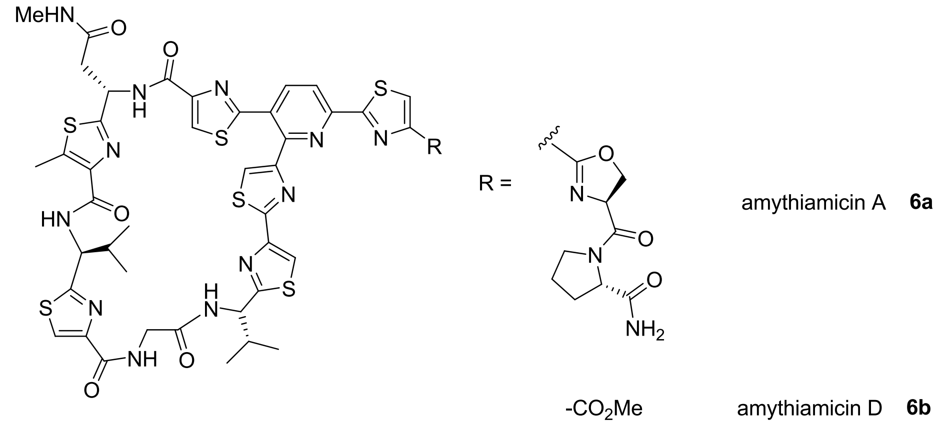
cystothiazole E **3e**



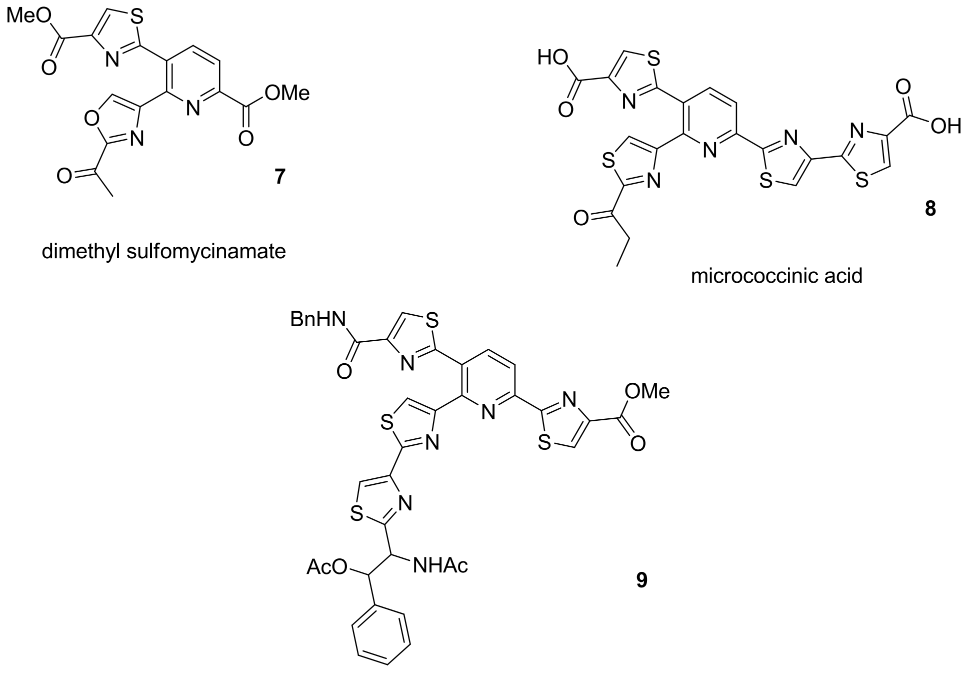
myxothiazole **4**

An important class of thiazole compounds are thiopeptide antibiotics. This family of antibiotics are sulfur-containing, highly modified cyclic peptides containing thiazole rings together with, in some cases, oxazoles, unusual or dehydro amino acids around a central tri- or tetra- substituted pyridine (or piperidine, dehydropiperidine, or imidazopiperidine) core in a macrocyclic array.[2-5] Worthy of note are the nocathiacins, **5a-c**, isolated from the culture broth of *Nocardia* sp. WW-12651(ATCC-202099).[16-18] They possess potent *in vitro* inhibitory activity against a wide range of gram-positive bacteria, including organisms such as methicillin-resistent *Staphylococcus aureus* (MRSA), multi-drug resistant *Enterococcus faecium,* and fully penicillin resistant *Streptococcus pneumoniae.* In addition they demonstrated excellent *in vivo* efficacy against a systemic *Staphylococcus aureus* infection in mice.





Amythiamicins such as amythiamicin A and D (**6a** and **b**), were first isolated from a strain of *Amycolatopsis* sp. MI481-42F4,[2-5] and were reported to be active against a wide spectrum of gram-positive bacteria including MRSA. More recently they have been reported to exhibit antimalarial activity against *Plasmodium falciparum*. A wide range of structurally related cyclic peptide compounds (thiostepton, siomycin, sulfomycin and micrococcin anitibiotics) which all contain a related pyridine core. There have been a vast number of reports on the syntheses of degradation products of these complex molecules. These degradation products include dimethyl sulfomycinamate, **7**,[19-22] micrococcinic acid, **8**,[23,24] and the core of GE2270A, **9**, Figure 1.1.1.[25-29] Each contain a pyridine ring substituted with thiazole rings and have been used to develop novel thiazole palladium chemistry.



7

dimethyl sulfomycinamate

8

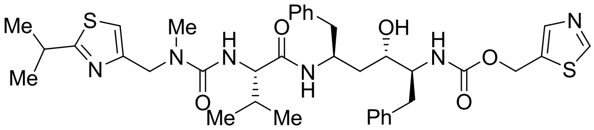
micrococcinic acid

9

degradation product of GE2270A

Figure 1.1.1 – Degradation products of peptidic antibiotic compounds

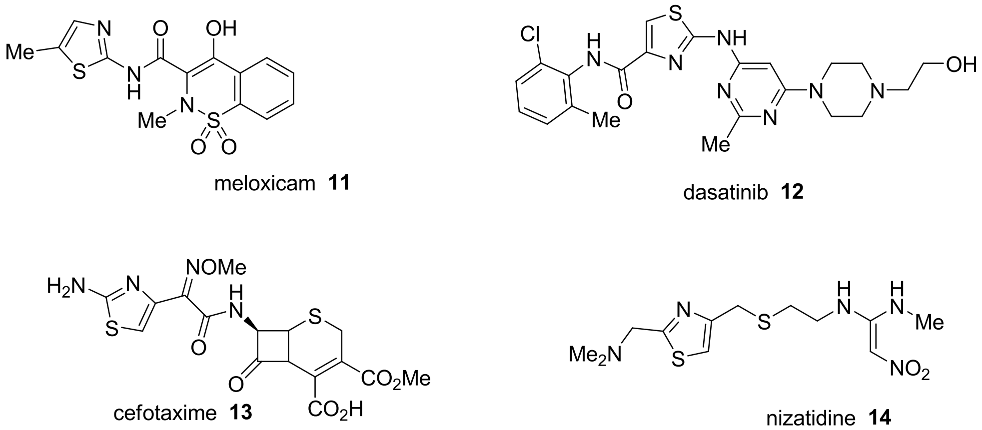
Thiazoles are convenient bio-isosteres for carbonyl or aromatic groups in the pharmaceuticl induxtry.[30] Carbonyl and aromatic groups can be quickly metabolised by the body, so replacement offers a better pharmacokinetic profile and increasing the concentration of drug reaching its point of action. As such, thiazole has been incorporated into ritonavir, **10**, an HIV1 protease inhibitor.[31] The thiazole groups have replaced ester and pyridine groups to ameliorate the pharmacokinetic problems. Ritonavir is perhaps the most well known thiazole drug and is unusual that it contains two thiazole units.



ritonavir

10

It is reasonably common to utilise thiazoles in drug substances as can be seen in Figure 1.1.2.



meloxicam **11**

dasatinib **12**

cefotaxime **13**

nizatidine **14**

Figure 1.1.2 – Thiazole pharmaceuticals

Meloxicam, **11**, is a non-steroidal anti-inflammatory compound (NSAID) developed by Boehringer Ingelheim and used to treat arthritis, dysmenorrhea, fever and also acts as an analgesic. It has a longer half-life *in vivo* than similar compounds enabling it to be administered in a once daily dose.[32]

Dasatinib, **12**, was developed by Bristol Myers Squibb as an ABL/SCR family tyrosine kinase inhibitor for the treatment of chronic myelogenous leukaemia and Philadelphia chromosome-positive acute lymphoblastic leukaemia.[33] It is currently being assessed for use in the treatment of metastatic melanoma.[34]

Cefotaxime, **13**, is a third generation cephalosporin antibiotic with broad spectrum activity against both gram positive and gram negative bacteria.[35]

Nizatidine, **14**, was developed by Eli Lilly, and is a histamine H_2 receptor antagonist that inhibits the production of stomach acid.[36] It is used in the treatment of peptic ulcer disease and gastroesophageal reflux disease.

Whilst there are a variety of drugs currently on the market with thiazole motifs[2] they are far outnumbered by agrochemicals,[7] preservatives and flavourings.[6]

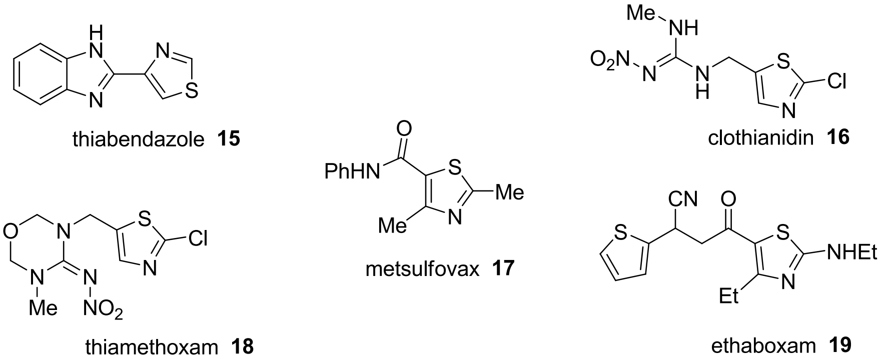


Figure 1.1.3 – Thiazole agrochemicals

A number of agrochemicals are shown in Figure 1.1.3. Thiabendazole, metsulfovax and ethaboxam are fungicides used to treat mould and blight.[7] Clothianidin and thiamethoxam are neonicitinoid insecticides,[7] both are used as seed treatments and to treat juvenile and mature crops.

The use of thiazoles in flavourings is widespread. The signature notes of a number of compounds, **20-31**, are described in Table 1.1.1.[6] They are used in the food industry to provide meaty and roasted flavours. In the perfumery industry several thiazoles are used to add "green" notes to scents.[6]

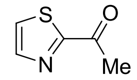
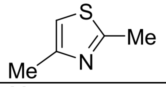
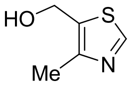
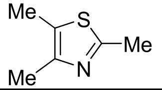
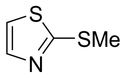
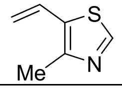
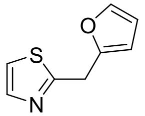
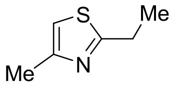
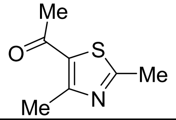
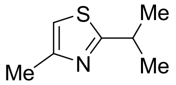
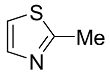
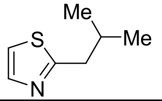
	Compound	Scent		Compound	Scent
20		Beef, nutty, grilled peanut.	**26**		Coffee, cocoa, roast barley, beef.
21		Meaty, nutty, yeast, milky.	**27**		Chocolate, green, nutty, cocoa, coffee, mouldy.
22		Onion like.	**28**		Mouldy, earthy, nutty.
23		Roasted potato, bread.	**29**		Nutty, roasted.
24		Roasted meat, sulfur, nutty.	**30**		Mouldy, earthy, tropical fruit, vegetable, meaty.
25		Shallot, vegetable, nutty, meaty.	**31**		Green grass, tomato leaf, vines.

Table 1.1.1 – Thiazole flavours and fragrances

Thiazoles are even finding applications for liquid crystals and light emitting materials.[37] The major drawbacks with regard to their use are the methods of preparation, which have barely changed since the 1880s.

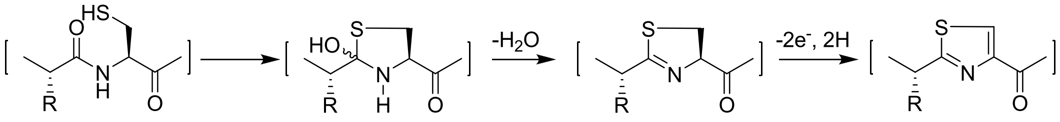
1.1.2. Synthesis, properties and reactions

The synthesis, properties and reactions of thiazole have been extensively reviewed in 2001 by Kikelj and Urleb.[38] A brief overview is described here, together with a more thorough discussion of the role of thiazoles in palladium cross-coupling reactions.

The thiazole ring system comprises a 5-membered aromatic heterocycle, substituted with a nitrogen and a sulfur atom, commonly in the 1,3 (thiazole) or 1,2 (iso-thiazole) positions. Whilst π-excessive, the nature of the heteroatoms leave the thiazole ring electron deficient, therefore less reactive than benzene to electrophilic substitution.

Biosynthesis

The thiazole ring is substituted in the C2 and C4 positions in natural products as a consequence of the biosynthesis of the rings. They are formed from cysteine residues that are enzymatically cyclised to thiazolines, **34**, followed by oxidation to form thiazoles (Scheme 1.1.1).[39]

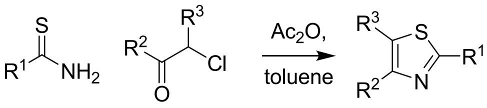


32 **33** **34** **35**

Scheme 1.1.1 – Biosynthesis of thiazoles

Chemical Synthesis

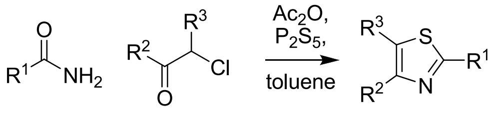
The most common method for preparing thiazoles was first developed by Hantzsch in 1889. (Scheme 1.1.2)[40] Whilst this method works well for some thiazoles, the yields are generally modest at best.



36 **37** **38**

Scheme 1.1.2 – Hantzsch synthesis

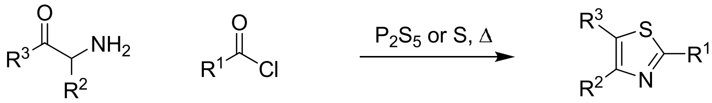
Modified conditions were developed by Erlenmeyer in 1947 which avoided the need to pre-form the thioamide, (Scheme 1.1.3).[41] Again, this method suffers from moderate yields.



39 40 38

Scheme 1.1.3 – Erlenmeyer's conditions

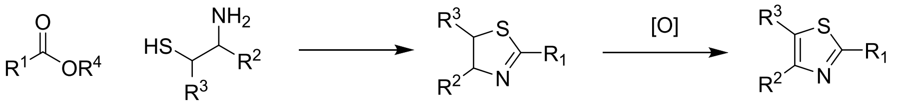
A modification of the Robinson Gabriel oxazole synthesis involves the reagents being heated in the presence of phosphorus pentasulfide or sulfur to give the thiazole product, **38** (Scheme 1.1.4).



41 **42** **38**

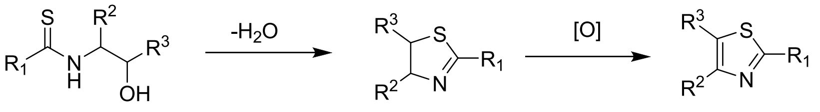
Scheme 1.1.4 – Modified Robinson Gabriel conditions

Alternative syntheses involve the formation of thiazolines, **45,** followed by oxidation to give the thiazole products (Scheme 1.1.5 and Scheme 1.1.6).[15,22,42-45]



43 **44** **45** **38**

Scheme 1.1.5

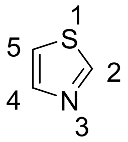


46 **45** **38**

Scheme 1.1.6

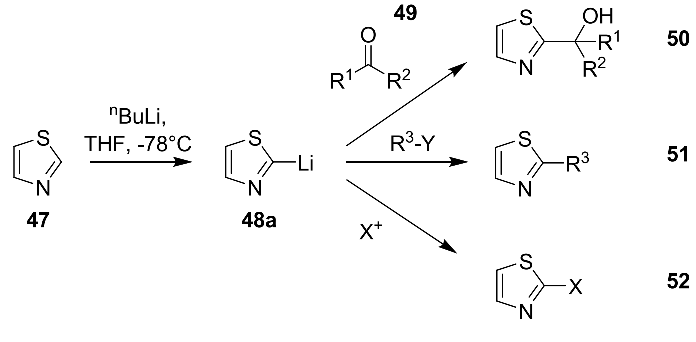
There are a wide variety of different syntheses of thiazoles but they generally take place at elevated temperatures under harsh conditions, often leading to many by-products. As such they are unsuitable for the diversity-orientated synthesis applied to discovery programs used in industry today. For a reaction to be practical for combinatorial chemistry it should be clean, quick and mild, as well as allowing coupling of several different components to easily incorporate diversity into a library of compounds. A more subtle point is that condensation reactions involve the synthesis of appropriately functionalised precursor molecules where the incorporated functionality is destroyed in order to construct the azole ring. The modern approach of chemists in industry has diverged from this and now the underlying ethos is never to destroy functionality but always to create it. Functionalisation of a core molecule to build up a larger structure is more convenient and allows a greater range of compounds to be produced.

Reactions and Properties



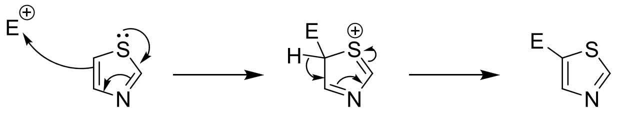
Thiazoles are electron deficient and as such react more slowly than benzene with electrophiles. The azoles are numbered as shown above.

The C2 position is electron poor and acidic (pK_a ~ 29.5)[46] due to the proximity of the two heteroatoms. The ring can easily be metallated here using a lithium reagent, as such this provides easy access to 2-substituted thiazoles (Scheme 1.1.7).



Scheme 1.1.7 - Metallation of thiazoles

The C5 position is the most electron-rich as a consequence of the resonance structures, it is here that the molecule will react with electrophiles (Scheme 1.1.8).[47,48]



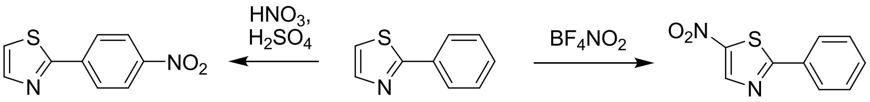
47 **53** **54**

Scheme 1.1.8 - Electrophilic addition to azoles

The C4 position is neither electron-rich nor electron poor and as such will only react under forcing conditions when the others are blocked.[48]

Whilst electrophilic substitution occurs in thiazole rings it is slower than for benzene, this is a consequence of two factors. Firstly that the heteroatoms are electron-withdrawing and secondly that electrophilic reagents are commonly acidic or used with acids. A Lewis or Bronsted acid will complex with the ring nitrogen and this further deactivates the ring towards electrophilic substitution.[47]

In the case of 2-phenyl thiazole, **51a**, under standard nitration conditions, protonation of the nitrogen leads to substitution in the benzene ring, **51b**, (Scheme 1.1.9). Switching to less acidic conditions allows nitration to occur in the C5 position, **54**.



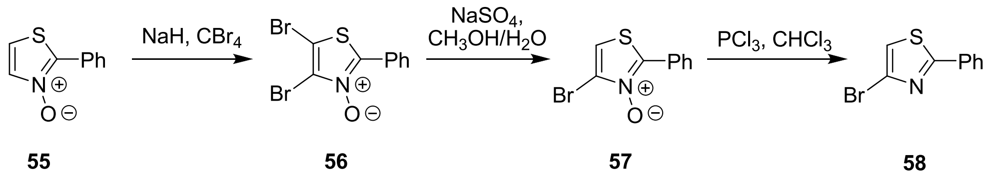
51b **51a** **54**

Scheme 1.1.9 - Nitration of thiazoles

Halogenation of thiazoles is also possible, although regioselectivity is a major problem. Substitution at the 5-position occurs reasonably well although it is often accompanied by some substitution at the 4-position giving 4,5-dihalothiazoles.[47] Electrophilic substitution at the 2-position is notoriously difficult, having only been achieved under forcing nitration and mercuration conditions. In order to selectively introduce a halogen at the 2- or 4-position, hydroxy-halogen exchange must be carried out or, in the case of C2 either diazotization or deprotonation followed by the reaction with an electrophilic halogen.[48]

Thiazole rings are also susceptible to oxidation, the *N*-oxides of thiazoles are well-characterised[48] and their reactivity towards electrophiles has been studied.[48] They are easily prepared from the corresponding thiazoles and *m*CPBA, peracetic acid, permaleic acid or trifluoroperacetic acid albeit in relatively poor yields (up to 52%).[48] Reactions can be carried out on the *N*-oxide or on the *O*-methylated and acylated compounds, with methylation and acylation occurring in excellent yields.[48] Reduction of the *N*-oxides can be successfully carried out using phosphorus trichloride in chloroform quantitatively.

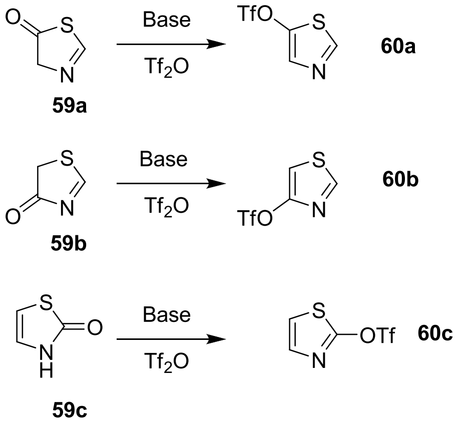
N-Oxides are stable for months when kept cool and dry. *N*-oxidation activates the 2-position for electrophilic attack due to delocalisation of the oxygen negative charge. In contrast the positive charge in the ring deactivates positions 4 and 5 to electrophilic attack. All of the ring hydrogens are rendered more acidic compared to the parent thiazoles, hence the proton at C2 is easily abstracted using sodium hydride and the anion will react with a range of electrophiles. When C2 is blocked, C5 is deprotonated over C4; whilst this should allow regioselective substitution at C5, the enhanced acidity of C4 when an electron withdrawing substituent is present at C5 leads to a mixture of mono and di-substituted products.



Scheme 1.1.10 – Route to 4-bromothiazoles

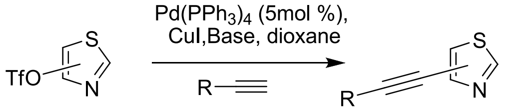
Whilst the pattern of reactivity is similar to the parent thiazole, it is possible in this way to form the 4,5-disubstituted thiazole, **56**, then to selectively remove the substituent at C5 leaving a substituent at C4, **58,** (Scheme 1.1.10).

The ability to synthesise halothiazoles is a prerequisite for their use in palladium cross-coupling chemistry. These reactions are some of the most useful reactions in the synthetic chemist's toolbox.[49-51] Palladium has been used with a variety of heterocycles for more than 20 years,[52] and there are thousands of examples of cross-couplings to pyridines, pyrroles, thiophenes, furans etc. However there is a sharp decline in the number of examples as the number of heteroatoms increases.[51] This means that compounds containing azole heterocycles are often constructed *via* multiple classical condensations rather than with concise palladium cross-couplings. Some isolated examples have been studied; Stille,[21,24] Negishi,[53] Suzuki[13] and Sonogashira,[54] couplings have all been attempted. However, only Panek's work on the Sonogashira protocol[14,55] looks systematically at the potential of the reaction. Panek envisaged using azole triflates, **60**, for the halide partner conveniently prepared from the corresponding thiazolones, (Scheme 1.1.11).



Scheme 1.1.11

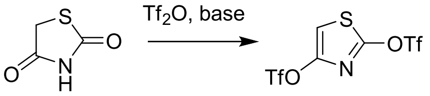
A range of terminal alkynes were coupled to thiazole triflates using catalytic palladium tetrakistriphenylphosphine and copper iodide, (Scheme 1.1.12).[54]



60 **61**

Scheme 1.1.12

The chemistry tolerated a variety of alkyl and aryl substituents on the azole ring as well as a variety of functional groups on the alkyne such as ethers, silyl ethers, alcohols and even free basic groups such as carbamates. The reactions proceed with good to excellent yields. A regioselective cross-coupling from the 2,4-ditrifloyl thiazole, **62** has been developed (Scheme 1.1.13).[14,55]

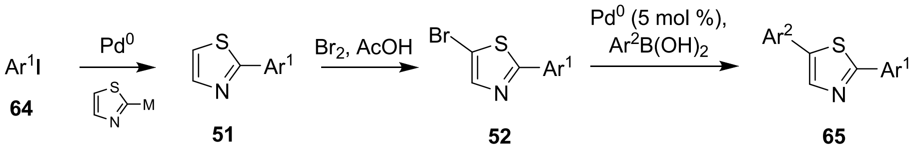


62 **63a**

Scheme 1.1.13

From the ditrifloylthiazole, **62**, it is possible to perform a selective Sonogashira at C2 then to utilise the monosubstituted product in a second successive palladium cross-coupling; (Sonogashira or a Stille coupling) to form a disubstituted thiazole.

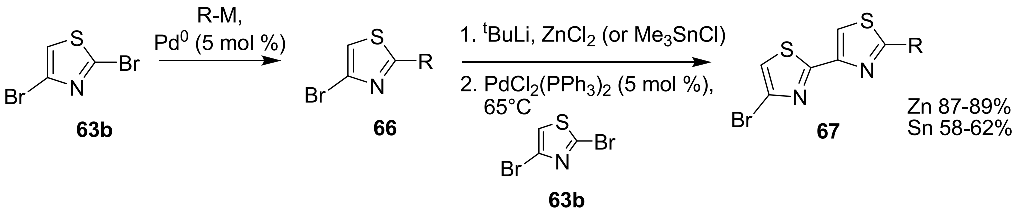
Some work has been done by several groups towards Stille, Suzuki and Negishi couplings to azoles to develop molecules with liquid crystalline properties.[56] Vachal and Toth demonstrated the use of thiazolyl zinc bromide and thiazolyl tributyl stannane in a series of reactions with aryl iodides in good yields to form 2-aryl thiazoles, **51**.[56] The products were then brominated using bromine in acetic acid and subjected to a Suzuki cross-coupling to form 2,5-diarylthiazoles, **65**, (Scheme 1.1.14).



64 **48** **51** **52** **65**

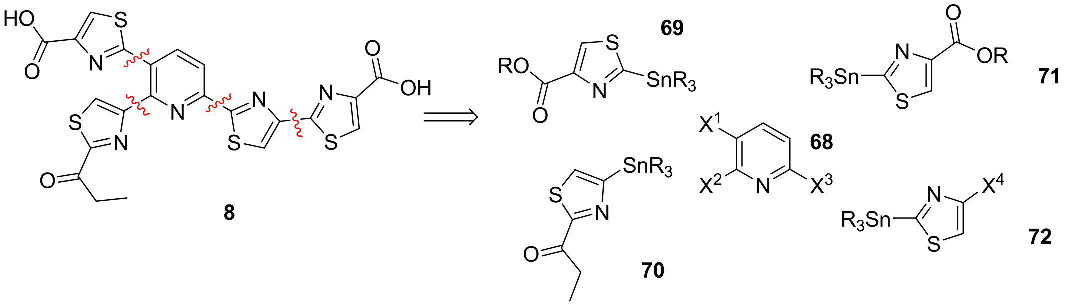
Scheme 1.1.14

In a similar vein, Bach and Heuser have investigated the regioselective coupling of 2,4-dibromothiazole, **63b**.[12,13,53,57] The C2 position is the most electron poor and reacts more quickly in palladium cross-coupling reactions than the C4 position. The two step process is detailed in Scheme 1.1.15. Selective coupling to C2 of 2,4-dibromothiazole gives the 2-substituted-4-bromothiazole, **66**. Lithium halogen exchange and transmetallation gives the zincate or stannane which then reacts with 2,4-dibromothiazole to provide the product, 2-substituted-4-bromo-2,4-bithiazoles, **67**.



Scheme 1.1.15

Most impressive of all the palladium cross-coupling reaction of thiazoles is Kelly's synthesis of micrococcinic acid, **8**. Micrococcinic acid was systematically constructed using consecutive Stille couplings between thiazoles, **69-72**.[24] Scheme 1.1.16 shows how the natural product was constructed from a triply orthogonal pyridine, **68**.



Scheme 1.1.16 Retrosynthesis of micrococcinic acid

Kelly's synthesis provided a concise, convergent route to the natural product and demonstrates the power of palladium cross-coupling in the field of azole heterocycles. This work was completed in 1991, yet this is one of the few examples of azole-azole palladium cross-couplings being used for the synthesis of multi-azole natural products.[12-14]

Whilst Suzuki, Stille and Negishi reactions are convenient in terms of regioselectivity one drawback is the need to preform the metallated partners. This demands uneconomical extra reaction steps particularly due to the use of stoichiometric metals. The compounds themselves may be toxic such as stannanes for the Stille reaction, which means that waste removal is expensive. The arylation of thiazole C-H, will be discussed in more detail in chapter 2.

1.2. The use of directing groups to facilitate palladium-mediated direct arylation reactions

Palladium has been utilised as a catalyst in a wide range of cross-couplings for close to 30 years. In that time, a vast number of coupling reactions have been envisaged and developed: Heck, Stille, Suzuki-Miyura, Kumada-Corriu, Hayashi, Negishi, and Sonagashira, to name but a few. In most of these examples a stoichiometric organometallic reagent is necessary, which is often not commercially available. The need to synthesise the precursor and convert it to the organometallic can be detrimental to an otherwise elegant synthesis. The reagent may be incompatible with some functionality and stoichiometric amounts of metal waste which can be highly toxic are generated. To address this there has been interest in developing "Direct Arylation" or "C-H Activation" chemistries. These circumvent the need to form a stoichiometric metallated partner, or may avoid the use of any preactivated compound by doing the simplest of reactions, the selective reaction between two C-H bonds forming a C-C bond.

Herein the literature regarding use of palladium to enable direct arylation in compounds bearing a chelating group is discussed, (until the end of March 2008). The review does not seek to cover the area of electronically directed arylations such as those seen by Fagnou[58-61] and Itami,[62] nor is the field of *ortho*-lithiation or deprotonation covered except where it seeks to explain the background of the current research (for further information on other types of C-H functionalisation please see the following reviews: non-directed arylation,[63] carbene insertions,[64] C-H oxidations,[65] palladacycles,[66] general C-H activation[67-69]).

1.2.1. Some Definitions

Before discussing this area in detail it may be helpful to provide some definitions and parameters for a number of terms that have been used recently to describe a number of transformations.

C-H Functionalisation

C-H functionalisation is the reaction of a C-H bond to form a carbon-heteroatom or carbon-carbon bond. This would usually be accomplished using a transition metal, therefore, a deprotonation with a strong base cannot be classified as a C-H functionalisation. In a similar manner, an electrophilic addition to an aromatic ring would not be classed as a C-H functionalisation reaction, nor are photochemical or radical processes, or those involving carbocations.

C-H Activation:

This is the specific mechanistic step when the C-H bond is cleaved during a C-H functionalisation reaction.

Direct arylation

A specific C-H functionalisation where the H of the C-H bond is replaced by an aryl or heteroaryl group.

Directed arylation

A specific example of a direct arylation where a temporary tether allows a formally intermolecular arylation to be achieved in an intramolecular fashion, giving a specific regioisomer as the product.

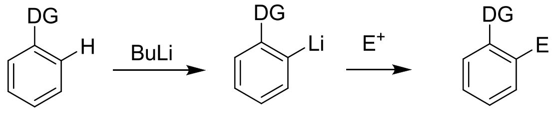
This methodology is particularly attractive from a green standpoint. The reaction partners in a traditional cross-coupling reaction require differential functionalisation in order to react. In a C-H activation reaction, only one reaction partner needs to be functionalised, which cuts out on a number of steps. This avoids the generation of potentially toxic metallated intermediates and prevents the necessary formation of stoichiometric amounts of toxic metal waste.

A directed C-H activation strategy can lead to different regioisomers to those available through the established methodologies, some of which would be very difficult to achieve by other methods.

1.2.2. Background and Concepts

One of the most challenging aspects of direct arylation and C-H activation chemistry is the question of regioselectivity. Each molecule contains a large number of carbon hydrogen bonds, determining which will react, and with what selectivity can be a difficult task. A possible solution to this question is the use of chelating groups to control and direct the metal catalyst to the C-H bond of choice. The initial research in this area has its roots in directed metallation and predates palladium cross-coupling.

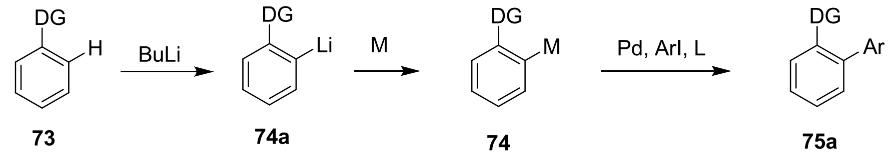
Ortho-lithiation was first reported independantly by Henry Gillman[70] in 1939 and Georg Wittig[71] in 1940. It has subsequently developed as one of the most useful protocols for the synthesis of *ortho*-substituted aromatic compounds, (Scheme 1.2.1).



73 **74a** **75**

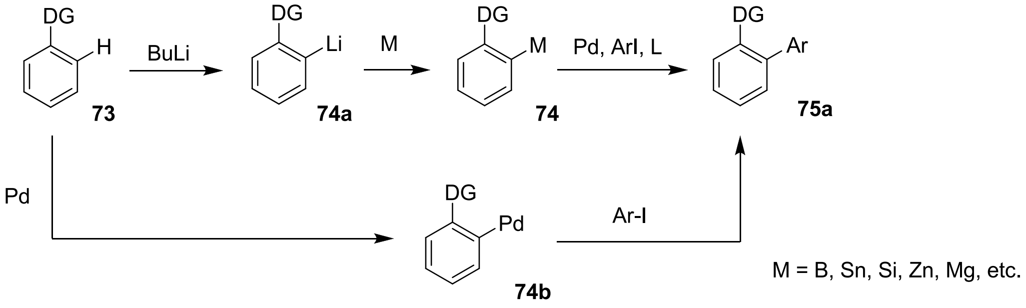
Scheme 1.2.1 – *Ortho*-lithiation

More recently *ortho*-lithiation has been used to prepare aromatic boronic acids, zincates, stannanes etc. **74**, used in palladium cross-coupling reactions. This method also provides a route to hindered aromatic compounds, (Scheme 1.2.2).



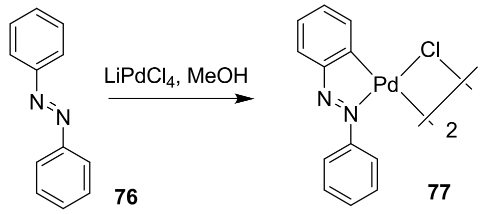
Scheme 1.2.2 – *Ortho*-lithiation – used in palladium cross-coupling

Directed arylation and C-H functionalisation reactions rely on a similar sequence . An aromatic compound with a suitable directing group can be functionalised using palladium and reacted with an arylhalide to form *ortho*-substituted aromatics, (Scheme 1.2.3). This replaces the deprotonation and transmetallation steps with a single C-H activation step.



Scheme 1.2.3 – C-H Activation as an alternative to *ortho*-lithiation and transmetallation

Early examples of this type of C-H activation can be seen in the stoichiometric formation of palladacycles. Cope *et al* reported the first synthesis of a palladacyclic compound, **77**, in 1965.[72] It was prepared simply by stirring the palladium salt with azobenzene at room temperature, (Scheme 1.2.4). There are numerous examples of the formation of palladacycles under mild conditions,[66] many are excellent catalysts for a range of different transformations.



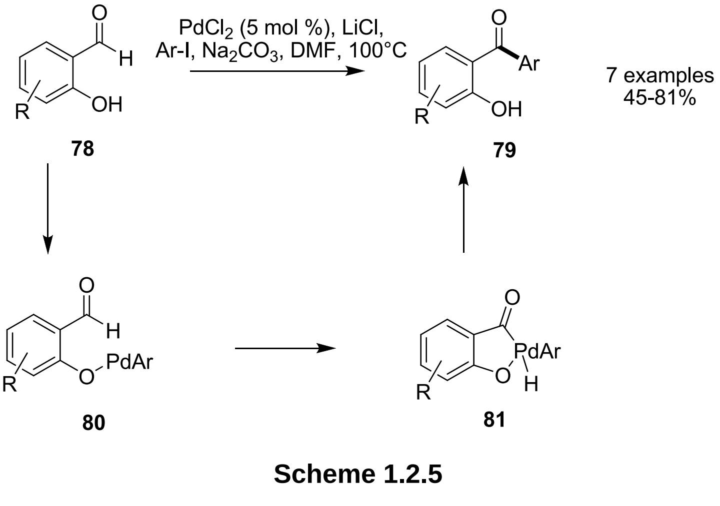
Scheme 1.2.4

The formation of palladacycles is possible at low temperatures, which has generated significant interest in developing a methodology where the formation of the palladacycle is the first step in a catalytic cycle. This approach forms the basis for a large proportion of the directed arylation chemistry currently in the literature.

1.2.3. Examples

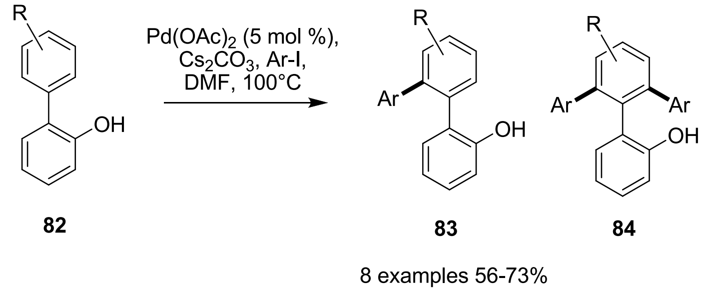
Phenol and alcohol directing groups

The pioneer in the area of intermolecular palladium-mediated directed arylation was Miura. Miura *et al* reported the first example of a palladium-mediated directed arylation in 1996.[73] The aldehyde C-H was arylated using the phenol oxygen as a chelating group to form a 5-membered palladacyclic intermediate, **81**, (Scheme 1.2.5).



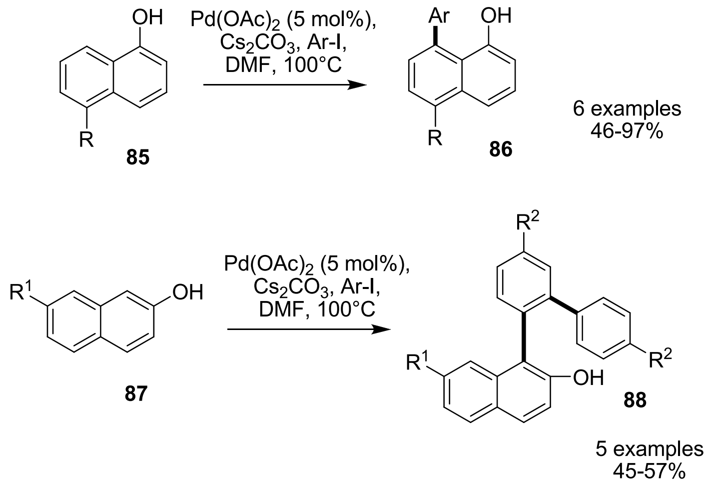
Scheme 1.2.5

Subsequently the reaction was found to be amenable to the arylation of C-H bonds in proximity to a phenolic oxygen,[74] (Scheme 1.2.6). Initially, they found mixtures of the mono **83**, and diarylated **84**, compounds, but by restricting the equivalents of both base and aryl iodide they were selectively able to form the mono-arylated product. This reaction proceeds through a similar mechanism (Scheme 1.2.5), but with a 6-membered palladacycle.



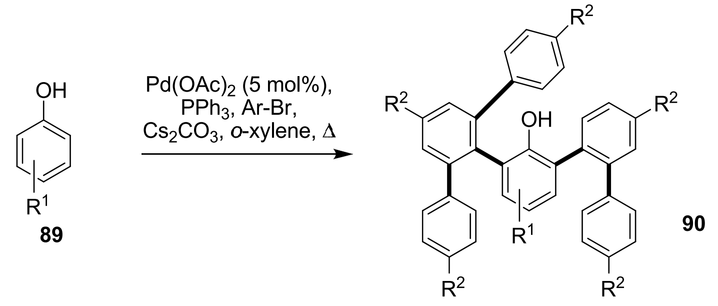
Scheme 1.2.6

In addition to the arylation of the biphenyl compounds they were able to arylate both 1- and 2-naphthol, **85** and **87**.[75] 1-Naphthol was arylated as expected giving the product arising from a 5-membered palladacycle. In the case of 2-naphthol, no 5-membered chelate is available, and arylation occurred α to the phenol, this product then being subsequently arylated, (Scheme 1.2.7).



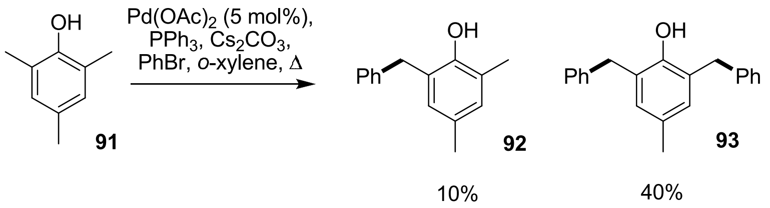
Scheme 1.2.7

The methodology can also be applied to the arylation of unsubstituted phenols. In Up tp five arylations can be performed in the presence of excess aryl bromide (Scheme 1.2.8).



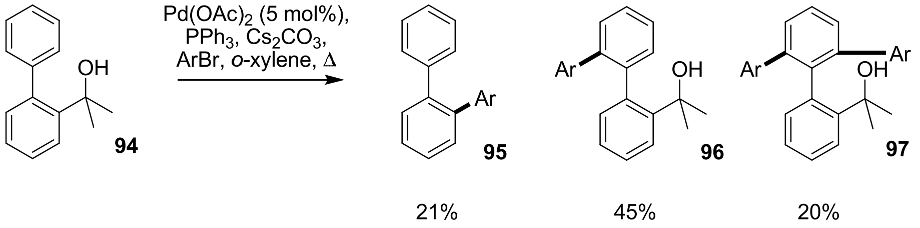
Scheme 1.2.8

Not only is this protocol suitable for the arylation of sp^2 C-H bonds, it can also be used to functionalise sp^3 bonds providing a mixture of the mono and diarylated compounds (**92** and **93** respectively, Scheme 1.2.9).



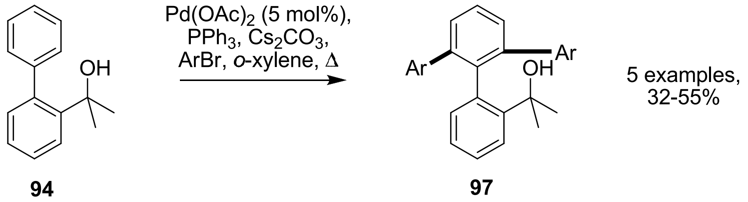
Scheme 1.2.9

Miura *et al* have shown that the directing group need not be phenolic in nature; a benzyl alcohol can also direct arylation to an aromatic ring, (Scheme 1.2.10). An alternative pathway leads to the loss of acetone from the substrate followed by arylation leading to a different class of products altogether, **95**.[76]



Scheme 1.2.10

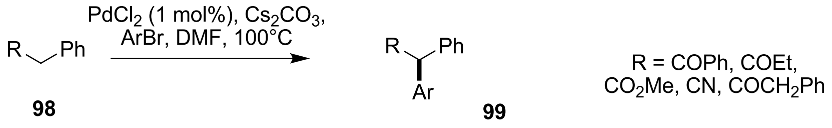
The reaction can also be driven to give the exclusively the diarylated product, **97**, (Scheme 1.2.11).[77]



Scheme 1.2.11

Aldehyde, ketone, acid, ester and enolate directing groups

Following their work on phenol directing groups, Miura *et al* developed conditions to selectively monoarylate a number of benzyl carbonyl compounds, (Scheme 1.2.12 and Table 1.2.1).



98 **99**

Scheme 1.2.12

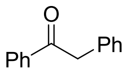
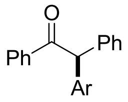
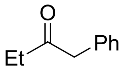
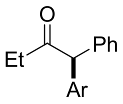
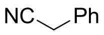
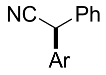
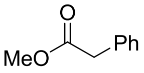
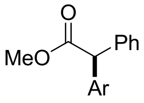
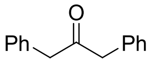
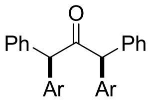
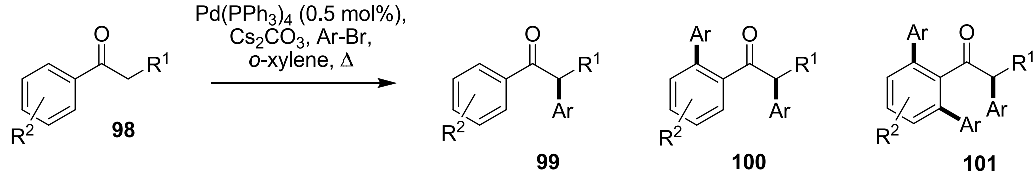
Substrate **98**	Ar-X	Product **99**	Isolated Yield
	Ph-I		90
	4-$MeOC_6H_4I$		93
	4-ClC_6H_4I		82
	1-naphthyl		75
	Ph-I		53
	Ph-Br		96
	Ph-I		72
	Ph-I		18
	Ph-Br		47
	Ph-I		56
	Ph-I		59

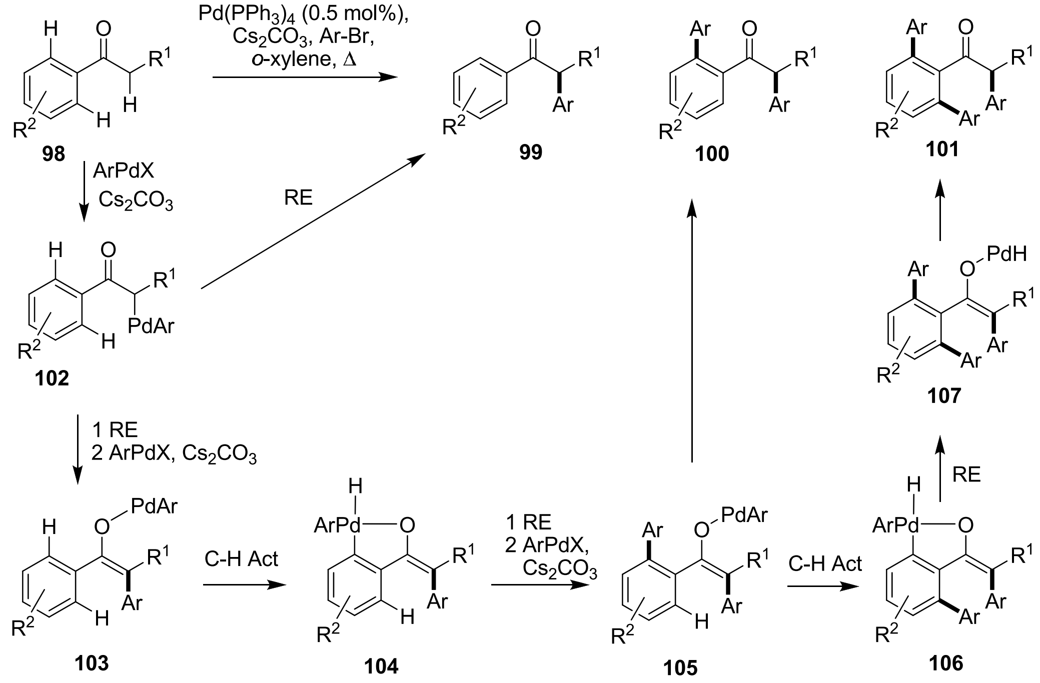
Table 1.2.1

Strictly speaking, these are not examples of directed arylation, but by changing the solvent from dimethylformamide to *o*-xylene and increasing the temperature, a directed arylation took place in the aryl ring, **100** and **101**, (Scheme 1.2.13).[78]



Scheme 1.2.13

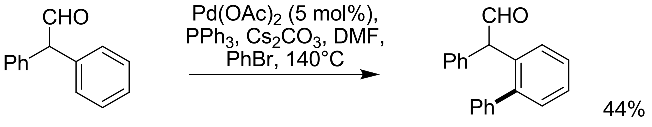
The reaction could be driven to provide the triarylated product, **101**, in good yields by switching the solvent and increasing the time, (7 examples 25-59% yield).



Scheme 1.2.14

Whilst the mechanism for arylation at the acidic position α to the carbonyl is well-understood,[79,80] the directing effect of the carbonyl group is less so. Miura *et al* proposed a mechanism (Scheme 1.2.14),[81] where the palladium enolates, **103** and **105,** form 5-membered palladacycles, **104** and **106**.

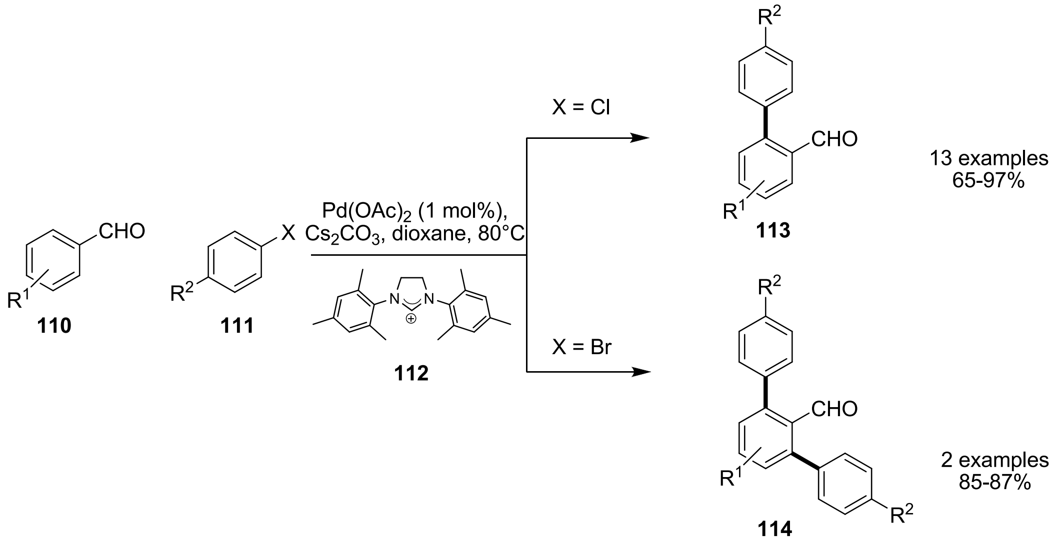
Further examples of this reaction have shown this to be a concise and mild route to α-aryl carbonyl compounds[81-83] including aldehydes, (Scheme 1.2.15).[84]



108 **109**

Scheme 1.2.15

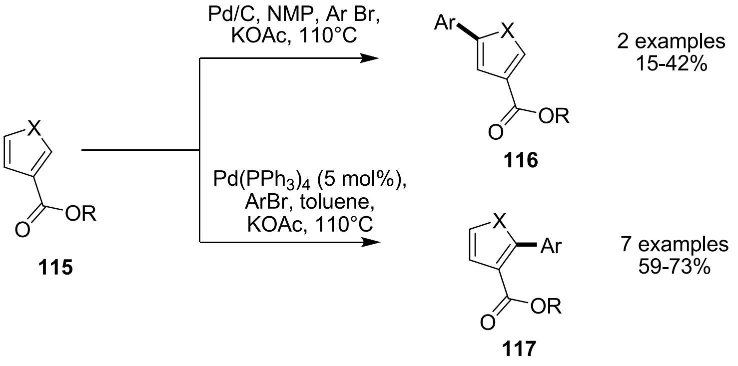
However, unlike the majority of examples detailed above, the arylation takes place by a 6-membered palladacycle. 5-Membered palladacycles are thought to be more stable than 6-membered palladacycles[67] although both are capable of promoting direct arylation.



110 **111** **112** **113** **114**

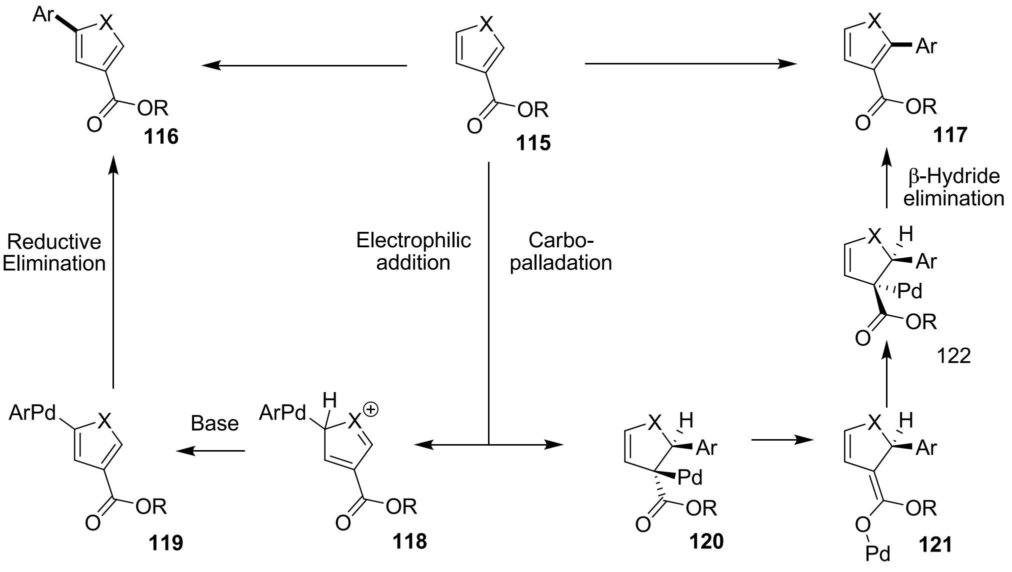
Scheme 1.2.16

Guerbuz *et al* have reported a different aldehyde directing group strategy more recently.[85] Using substituted benzaldehydes the *ortho*-position of the ring is selectively arylated. By using aryl chlorides or bromides they are able to selectively obtain the mono, **113**, or diarylated, **114**, compounds respectively, (Scheme 1.2.16). Meanwhile, an ester directing group strategy has been developed for the regioselective arylation of 3-carbalkoxyfurans and thiophenes, **115**, by Sharp *et al* (Scheme 1.2.17).[86]



Scheme 1.2.17

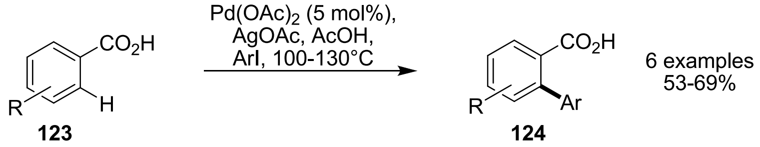
The selectivity can be explained by two different mechanistic pathways, (Scheme 1.2.18).



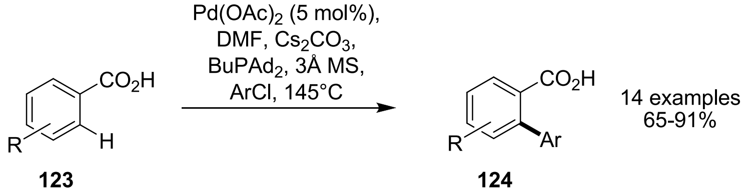
Scheme 1.2.18

The formation of the 5-arylated product goes through an electrophilic addition mechanism, *via* **118** and **119**. However, in the case of the 2-arylated compound, Sharp *et al* propose a Heck mechanism. Carbo-palladation of **115** gives **120**, isomerisation of intermediate **120** by way of a palladium enolate, **121**, gives **122**. Syn-elimination of the palladium hydride from **122** provides the product and regenerates palladium (0). The selectivity is explained in terms of the solvents employed. *N*-Methylpyrollidone (NMP) is a polar solvent and can stabilise the ionic intermediates in the electrophilic addition mechanism. Toluene isfar less polar so the reaction proceeds by the only other mechanism available.

More recently, Daugulis *et al* have reported the arylation of benzoic acids with both aryl iodides (Scheme 1.2.19) and aryl chlorides (Scheme 1.2.20).[87]

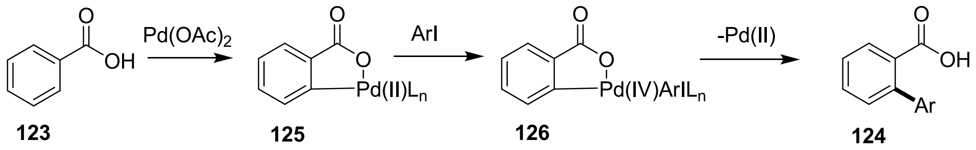


Scheme 1.2.19

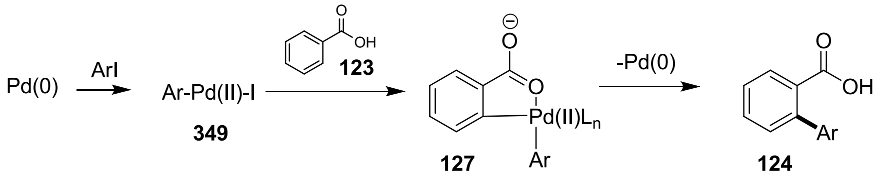


Scheme 1.2.20

A mechanistic investigation was carried out in addition to the development of these conditions. There are a number of different mechanistic pathways available in these reactions. They propose that the most likely mechanisms for aryl iodides are a palladium (II) to palladium (IV) catalytic cycle (Scheme 1.2.21), or a palladium (0) to palladium (II) catalytic cycle (Scheme 1.2.22). Both of these mechanisms proceed via a 5-membered palladacycle, **125** or **127**.

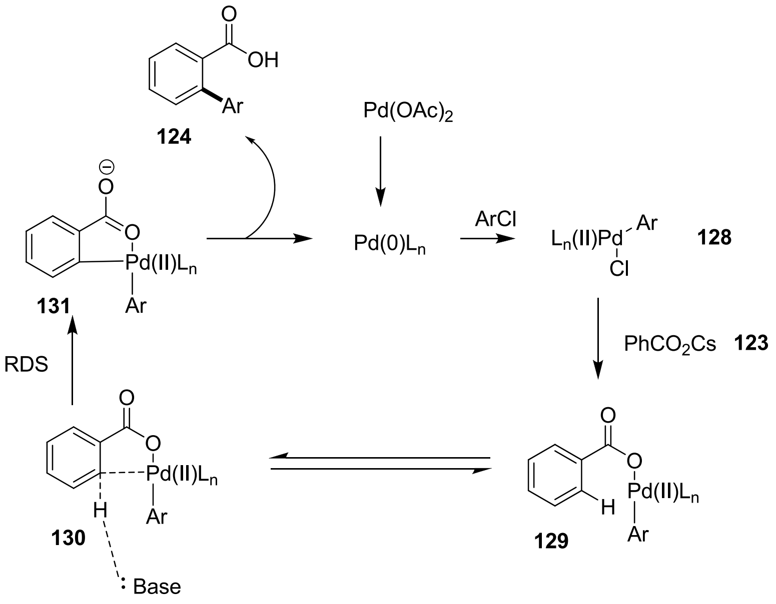


Scheme 1.2.21 – Palladium (II) to palladium (IV) mechanism



Scheme 1.2.22 – Palladium (0) to palladium (II) mechanism

The reactions were repeated using a palladium (0) or palladium (II) source in the absence of AgOAc to establish the mechanism in operation. In the case of the palladium (0) source, no conversion was observed, however with the palladium (II) source, one turnover of the palladium occurred, lending support to the palladium (II) to palladium (IV) mechanism.

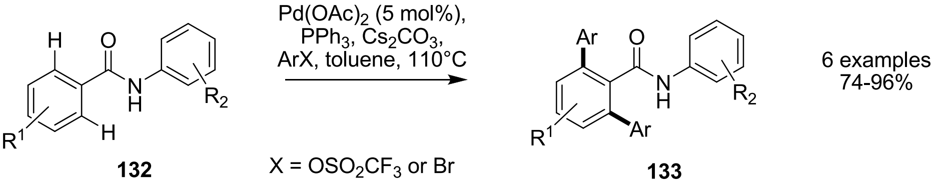


Scheme 1.2.23

The reaction of aryl chlorides was noted to work well for both electron-rich and electron-poor benzoic acids. This is unusual as the palladation step is usually favoured by electron-donating groups on the aromatic ring.[88] Fagnou reported a reversal in this pattern, where a more electron-deficient ring is arylated more readily.[58,89] Daugulis *et al* therefore determined the intra- and intermolecular kinetic isotope effect, which provided further evidence for a different C-H palladation mechanism to that seen with aryl iodides. It is thought that a concerted C-Pd bond formation, C-H deprotonation step, **130**,[90] is the C-H activation mechanism occurring with aryl chlorides, (Scheme 1.2.23).

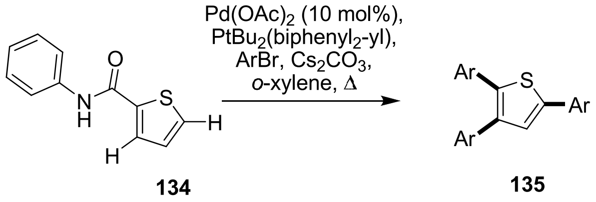
Amides

As with the directing groups discussed above, Miura *et al* led the field in the development of amide directing groups.[91] An extension of their work on the arylation of ketones and other carbonyl compounds was published in 2000. Mulitple arylations were performed on benzanilides, **132**, at the *ortho*-positions of the aryl ring to give **133**, (Scheme 1.2.24). Arylation occurs through a 5-membered palladacycle; arylation of the other aryl ring however, would occur by co-ordination through the amide carbonyl to give a less-favoured 6-membered palladacycle.



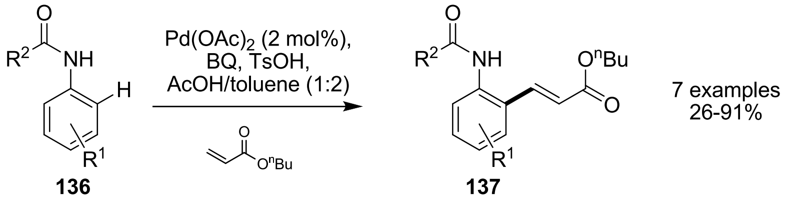
Scheme 1.2.24

Multiple arylation of thiophenes and thiazoles, **134**, was reported in 2002, (Scheme 1.2.25).[92,93] This unusual reaction involves a decarbamoylation step in which palladium and base mediates the cleavage of the amide bond, followed by the decarboxylation and subsequent arylation of the empty position.



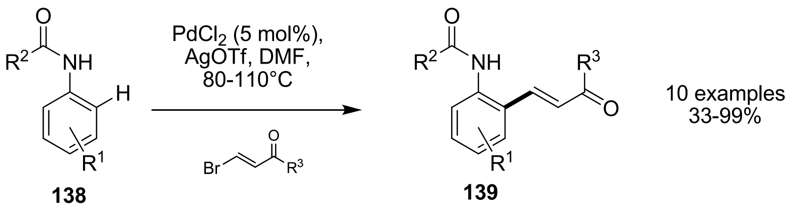
Scheme 1.2.25

De Vries *et al* use amide-directing groups to accomplish a Fujiwara-Moritani reaction at room temperature using benzoquinone as re-oxidant, (Scheme 1.2.26).



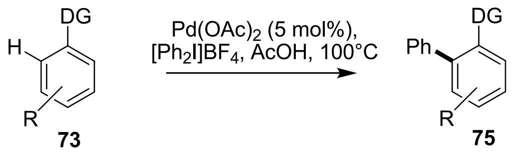
Scheme 1.2.26

A related paper from Daugulis *et al* descibes the reaction between arylanilides, **138**, and halo-olefins negating the need for a re-oxidant, (Scheme 1.2.27).[94]



Scheme 1.2.27

Sanford *et al* have described a versatile protocol for the arylation of a number of different aryl amides using hypervalent iodine reagents, (Scheme 1.2.28 and Table 1.2.2).[95] Hypervalent iodine reagents give good conversions and yields by way of a palladium (II)–(IV) catalytic cycle. Unfortunately, only the diphenyliodonium salt compound is commercially available



Scheme 1.2.28

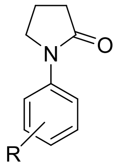
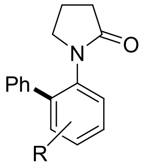
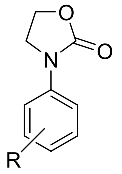
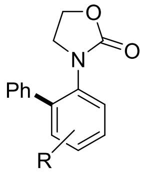
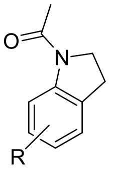
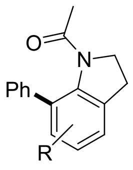
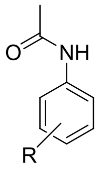
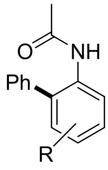
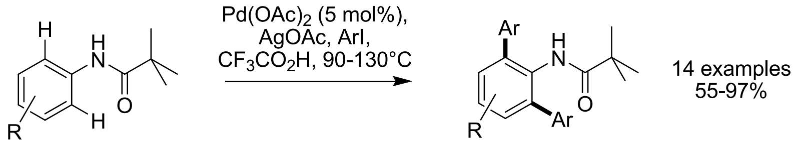
Substrate 73	Product 75	Yield %
		75-84
		83
		49
		67

Table 1.2.2 – Sanford's amide direction

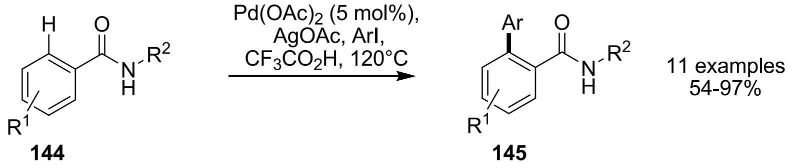
In response to this, Daugulis *et al* have developed conditions that allow the use of aryl iodides with a silver acetate oxidant, (Scheme 1.2.29).[96,97] As this is a palladium (II)-(IV) catalytic cycle, aryl iodides with bromo substituents can be used, allowing for further elaboration of the products.



142 **143**

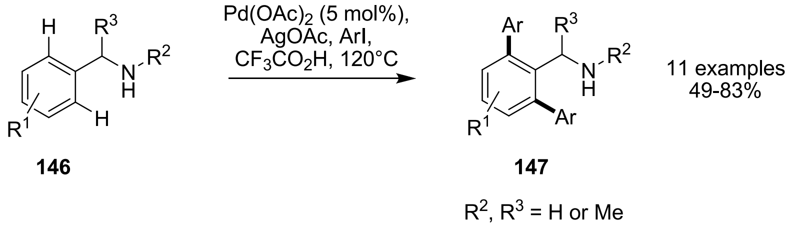
Scheme 1.2.29

By making a subtle change in the directing group selective monoarylation was achieved. Instead of an anilide, they used a benzamide, **144**, (Scheme 1.2.30).[98] These conditions are tolerant of bromides as well as electon withdrawing and donating groups on the aryl iodide. The mono arylated products, **145**, can themselves be further arylated to give differentially substituted 2,6-diaryl benzamides.



Scheme 1.2.30

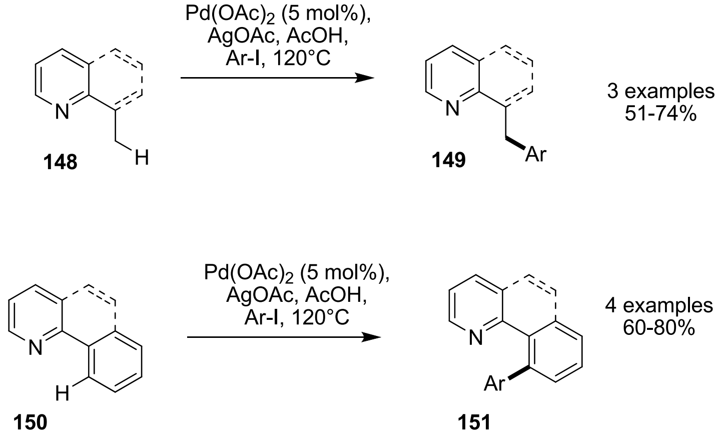
Daugulis *et al* have also investigated whether amines can be used as a directing group.[99] Amines are generally regarded as being catalyst poisons, despite this they were able to successfully arylate with a range of aryl iodides. Notably iodide and bromide were tolerated on the aryl iodide, (Scheme 1.2.31).



Scheme 1.2.31

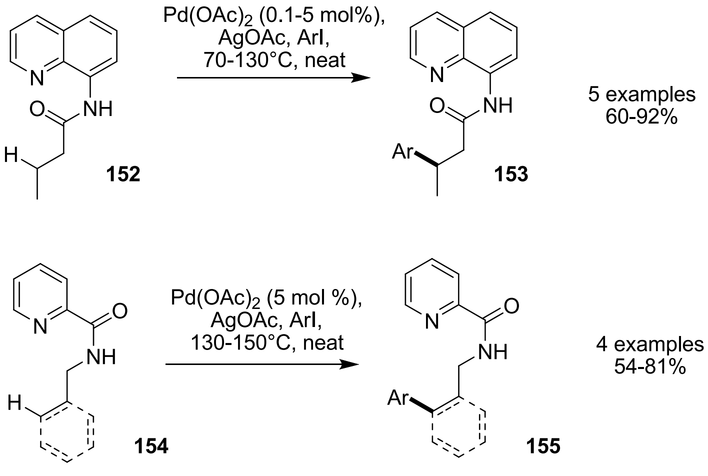
Pyridines

Daugulis *et al* have utilised a pyridine ring to arylate both *sp*^{2} and *sp*^{3} C-H bonds.[100] Selective monoarylation was achieved using an oxidative protocol. The reactions proceed more quickly with electron-rich aryl iodides which suggests the reaction proceeds through a palladium (II)-(IV) catalytic cycle, (Scheme 1.2.32).



Scheme 1.2.32

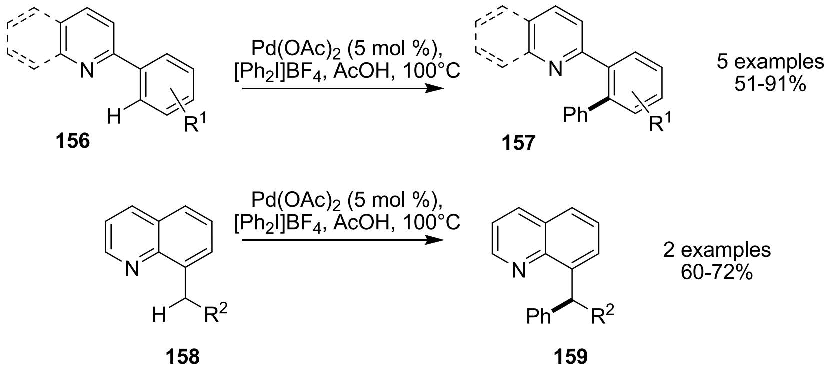
In addition to the arylation of pyridines they have also invented a strategy to incorporate a directing group into simple molecules through amide bond formation, (Scheme 1.2.33).[101]



Scheme 1.2.33

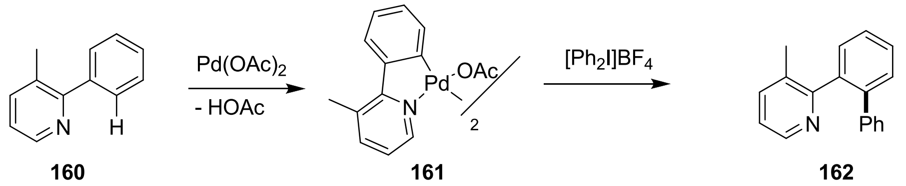
The quinoline group allows *β*-arylation of a simple carboxylic acid, (conversion of **152** to **153)**. In a similar fashion, the picolinamide-directing group enables the functionalisation of an alkyl amine, **154**. Both of these amides are easily cleaved providing the arylated acids and amines respectively.

Sanford *et al* have also used pyridines to direct arylation to specific *sp*^{2} and *sp*^{3} C-H bonds.[95] A number of different pyridine and quinoline compounds were arylated using an oxidative protocol, (Scheme 1.2.34).



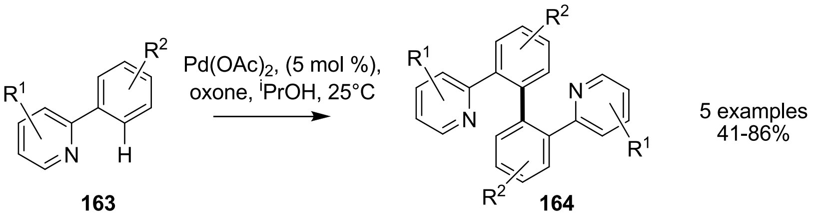
Scheme 1.2.34

A number of mechanistic experiments were conducted in order to determine the reaction mechanism. Stoichiometric palladium acetate was reacted with a phenylpyridine, **160**, to give the bridged dimeric palladacycle, **161**. **161** was then treated with phenyliodide but no product was formed. Treating the same compound with diphenyliodonium tetrafluoroborate gave full conversion of the palladacycle to the product, **162**. This indicated that the reaction is likely proceding through a palladium (II)-(IV) catalytic cycle, (Scheme 1.2.35).



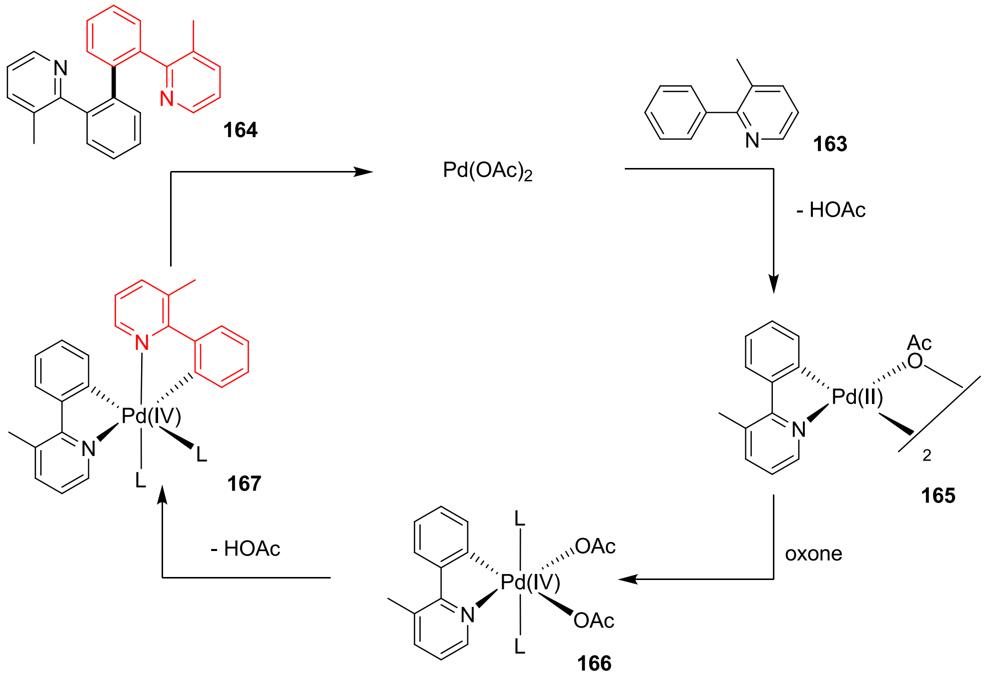
Scheme 1.2.35

Sanford *et al* have reported a highly impressive double C-H activation reaction more recently, (Scheme 1.2.36).[102]



Scheme 1.2.36

An extensive and highly detailed mechanistic study was also carried out to determine the nature of the C-H activation steps. The evidence pointed to an initial palladium (II) cyclopalladation to give **165**, followed by oxidation to palladium (IV), **166**. This species can then undergo a further cyclopalladation to give **167** before reductively eliminating the product, **164**, and regenerating palladium (II), Scheme 1.2.37.

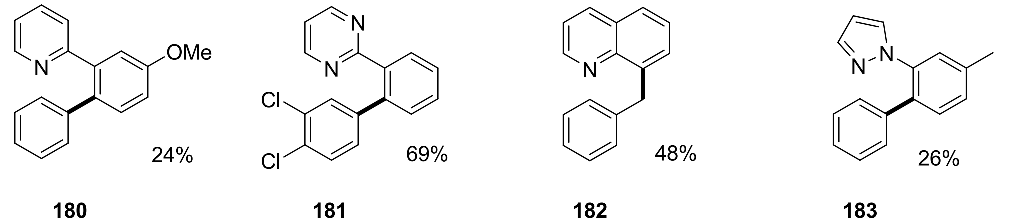


Scheme 1.2.37

Subsequent to this highly impressive double C-H activation/dimerisation reaction, a cross double C-H activation reaction has been reported using a similar protocol, (Scheme 1.2.38).[103]

Scheme 1.2.38

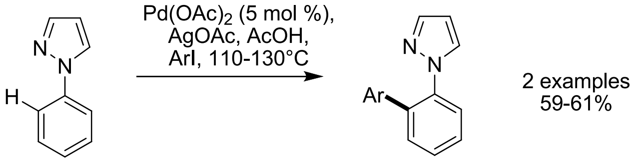
The separate nature of the 2 C-H activation steps, (one at palladium (II) the other at palladium (IV)) allows an effective cross-coupling because homocoupleing of the two substrates is avoided. These conditions have been applied to a number of other directing groups in good yields, (Scheme 1.2.39).



Scheme 1.2.39

Other heterocycles

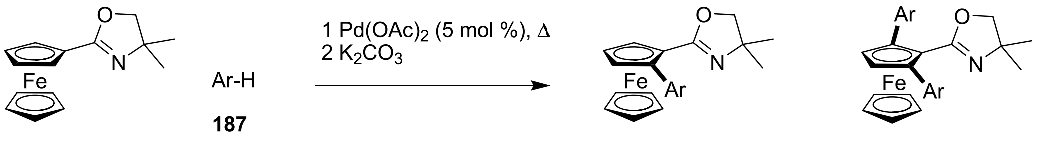
Whilst pyridines are the most commonly used heterocyclic directing group, a number of other heterocycles have been used to direct arylation. Daugulis has demonstrated that *N*-phenylpyrazoles, **184**, are effective directing groups, (Scheme 1.2.40).[100]



184 **185**

Scheme 1.2.40

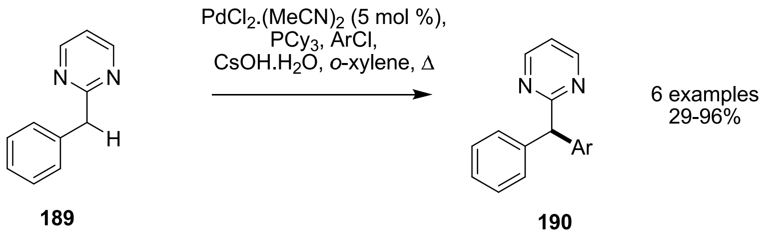
You *et al* have utilised an oxazoline to functionalise ferrocene, **186**, in the pursuit of planar-chiral ligands.[104] In this case, rather than using an aryl halide, arenes have been used in a double C-H activation process, (Scheme 1.2.41).



186 **187** **188** **189**

Scheme 1.2.41

Oshima *et al* have reported the arylation of *sp*^{3} C-H bonds using a pyrimidine directing group, **189**.[105] Using aryl chlorides in refluxing *o*-xylene they are able to form triarylmethanes, **190**, in good yields, (Scheme 1.2.42).



189 **190**

Scheme 1.2.42

These conditions can be applied to a range of different heterocycles, a number of which also show a directing effect, Table 1.2.3. Even the weakly basic benzoxazole and benzothiazole give the desired products in good yields.

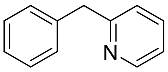
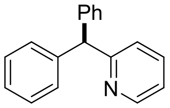
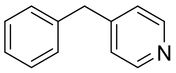
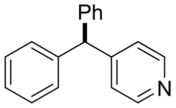
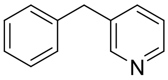
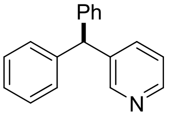
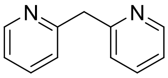
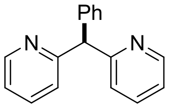
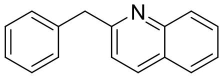
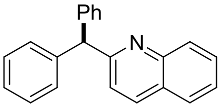
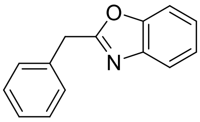
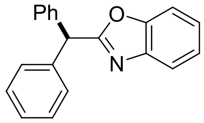
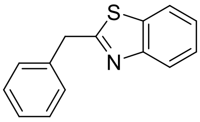
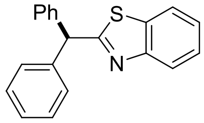
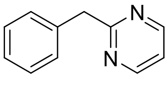
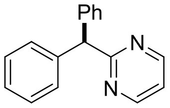
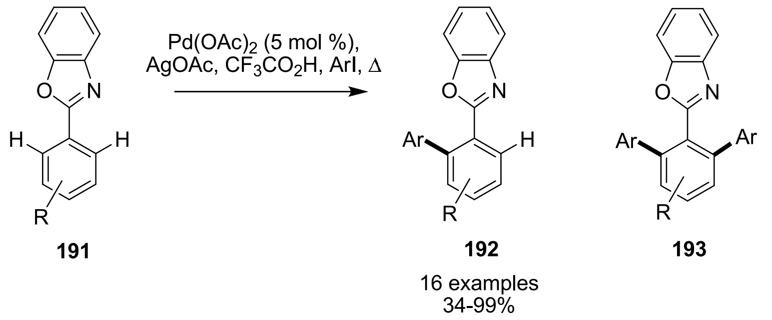
Substrate **189**	Product **190**	Yield %
		87
		92
		<1
		91
		91
		71
		82
		86

Table 1.2.3

Benzoxazole, **191**, has also been shown to direct arylation by Wu *et al*, (Scheme 1.2.43).[106] Despite initial problems with diarylation, they prepared 16 examples of the monoarylated product, **192**, in good yields.

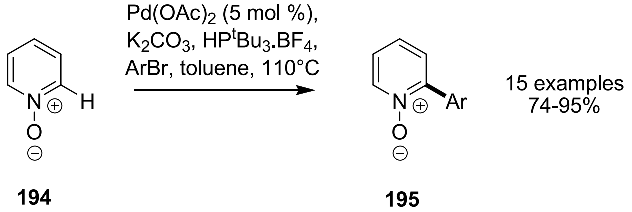


Scheme 1.2.43

The reaction works particularly well when electron-donating groups are present on the aryl iodide and on the aryl ring. Bromo and chloro substituents are also tolerated, which allows for further elaboration of the products.

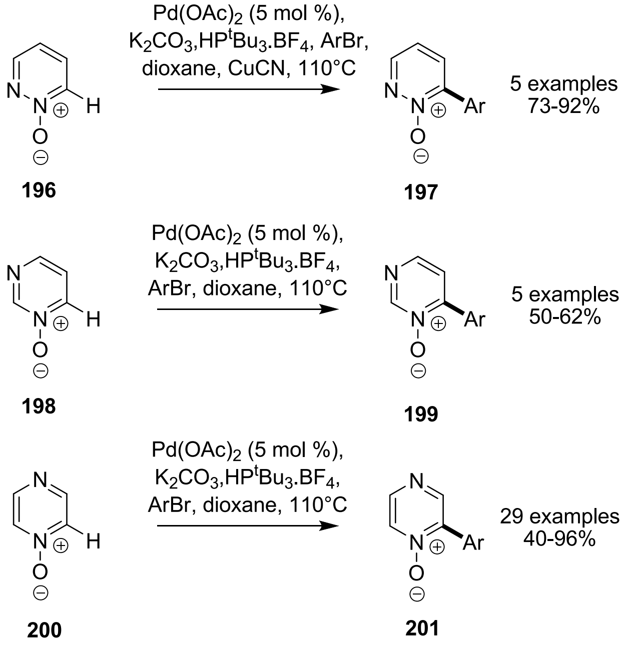
Pyridine N-oxides

The synthesis of 2-arylpyridines is far from straightforward since 2-halopyridines can poison palladium catalysts by forming a dimeric palladacycle.[107] In addition, boronic acids and esters in the 2-position are susceptible to protodeboronation,[107] which renders them of no use in Suzuki cross-coupling reactions. Fagnou's alternative, of pyridine *N*-oxide-directed arylation at pyridine C2,[107] represents a leap forward in the palladium chemistry of pyridine compounds, (Scheme 1.2.44). Pyridine *N*-oxides are conveniently prepared from pyridines using *m*CPBA and can be reduced to the free pyridines by reaction with palladium on carbon in a formic acid/methanol solution.



Scheme 1.2.44

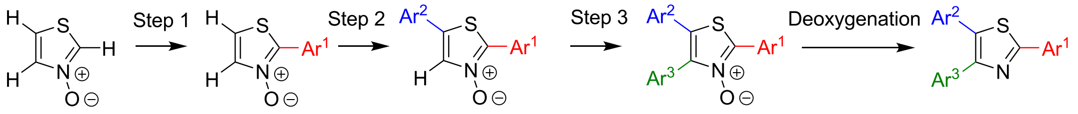
Fagnou extended the scope of this reaction by showing that diazine *N*-oxides, **196**, **198** and **200** are arylated under similar conditions, (Scheme 1.2.45).



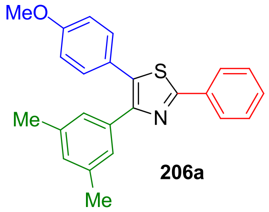
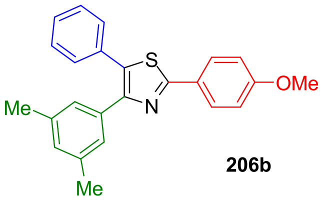
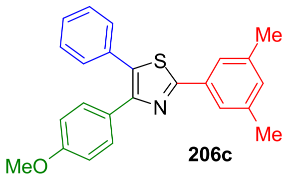
Scheme 1.2.45

However, the free N in the ring showed a tendency to poison the palladium catalyst in some cases. The reactions proceeded much more smoothly when 10 mol % of a copper (I) salt such as bromide or cyanide was added.

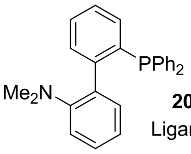
Fagnou *et al* have expanded this methodology to the arylation of thiazoles.[108] Whilst the C2 and C5 position of thiazoles can be arylated without the need for a directing group, arylation at the C4 position is notoriously difficult. By synthesising thiazole *N*-oxide, not only is arylation at C2 and C5 more facile, but they also reported one of only two examples of arylation at the thiazole C4 position, (Scheme 1.2.46).[93,108]



202 **203** **204** **205** **206**

Step	 **206a**	 **206b**	 **206c**
1	84	69	76
2	86	80	85
3	59	64	84
Deoxygenation	72	66	64

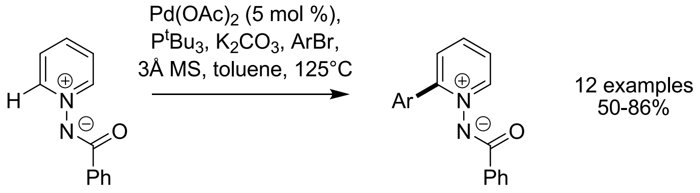
Conditions:
Step 1 - ArI, $Pd(OAc)_2$ (5 mol %), Ligand 1, Cs_2CO_3, pivalic acid, CuBr, toluene, 25°C
Step 2 - ArBr, $Pd(OAc)_2$ (5 mol %), $HP^tBu_3.BF_4$, K_2CO_3, toluene, 70°C
Step 3 - ArBr, $Pd(OAc)_2$ (5 mol %),PPh_3, K_2CO_3, Toluene, 110°
Deoxygenation - Zn powder, NH_4Cl, THF



207
Ligand 1

Scheme 1.2.46

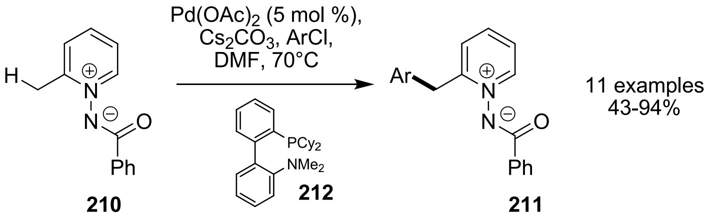
In addition to pyridine *N*-oxides, *N*-iminopyridinium ylides, **208**, can be used to arylate a pyridine ring, (Scheme 1.2.47).[109,110]



208 **209**

Scheme 1.2.47

The reaction conditions are tolerant of electron-donating and electron-withdrawing substituents on the aryl bromide. Furthermore, heteroaryl bromides such as 2- and 3-bromopyridine can be used in the reaction with no detrimental effects. This methodology is also applicable to the arylation of sp^3 C-H bonds, (Scheme 1.2.48).



210 **212** **211**

Scheme 1.2.48

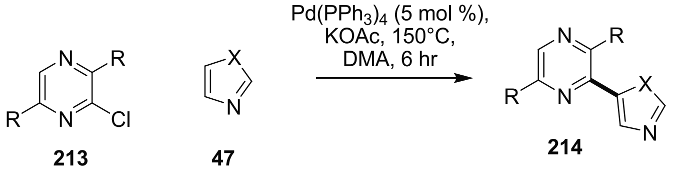
The products can be easily converted back to pyridines, reduced to piperidines, or elaborated in a number of different ways, which provides a convenient route to highly functionalised pyridine and piperidine compounds.

2. Arylation at thiazole C5

2.1. Precedents

The direct arylation of thiazole has been covered in a number of recent reviews.[61,67,111-115] The most salient and relevant examples are discussed here:

Direct arylation of an azole ring was first accomplished in 1989 by Ohta *et al.*[116] The impressive foray into the direct arylation of thiazole, oxazole and imidazole yielded astounding results, both in terms of conversion and selectivity. Taking thiazole and oxazole in dimethylacetamide, together with tetrakistriphenylphosphino palladium and potassium acetate, a heterocyclic chloride could be coupled at the C5 position of the azole ring in yields of up to 83%, (Scheme 2.1.1).

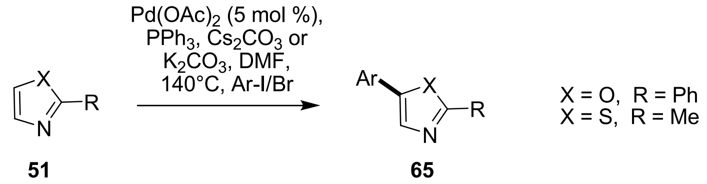


X	R	Yield
O	Me	52
O	Et	65
O	^{i}Bu	83
S	Me	43
S	Et	59
S	^{i}Bu	68

Scheme 2.1.1 Ohta's chloropyrazine arylations

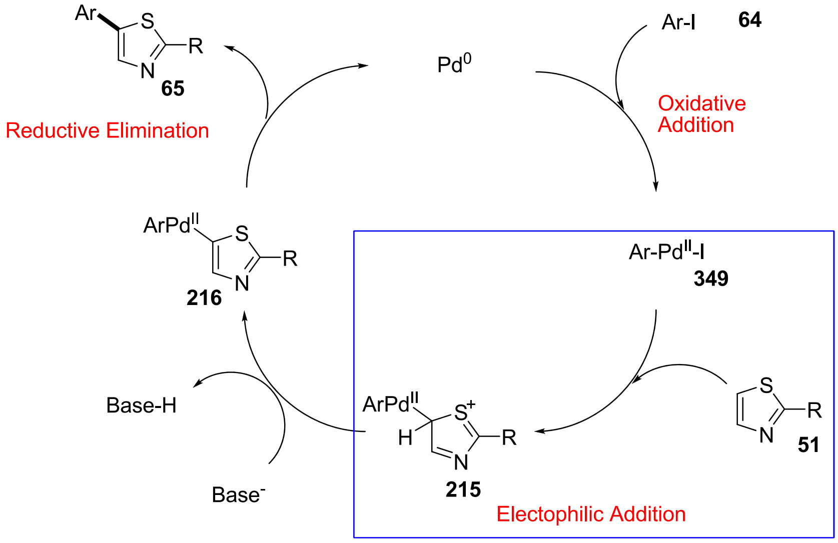
This should have marked the beginning of research into the direct functionalisation of these molecules. That was not the case, in 1998 Miura's *et al* developed the methodology put forward by Ohta.[117] This expanded the range of substrates to aryl iodides and bromides, and investigated the regioselectivity with other substituents on the azole ring. A number of other variables were investigated, including bases. The research was comprehensive for the direct arylation of imidazoles, but there were only a limited number of examples where thiazole and substituted thiazoles were functionalised. Crucially, they discovered that the regioselectivity could be reversed when copper (I) iodide was used as an additive, switching the preferred position of substitution from C5 to C2.

Preliminary results showed that caesium carbonate was the most effective base for both oxazoles and thiazoles, (Scheme 2.1.2). Potassium carbonate was ineffective with an aryl iodide, whereas, it was equally effective for aryl bromides. This was explained in terms of the solubilities of the inorganic salts in dimethylformamide; potassium iodide is particularly soluble in dimethylformamide, whereas potassium bromide is much less so. They proposed that the solubility of the iodide ion was causing the reaction to be less efficient, this was confirmed by adding a small amount of potassium iodide to the aryl iodide/caesium carbonate reaction, causing the reaction to stall.



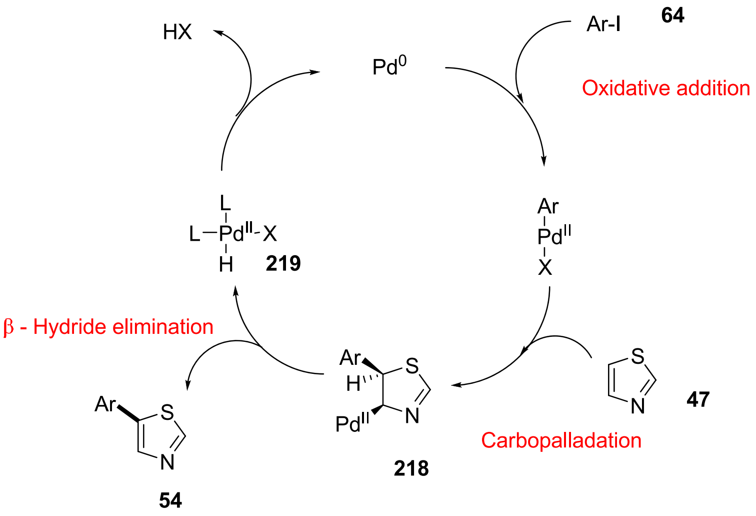
Scheme 2.1.2 - Miura's conditions

The 5-substituted azole ring was the only product isolated from the reaction which is consistent with an electrophilic mechanism (Scheme 2.1.3).



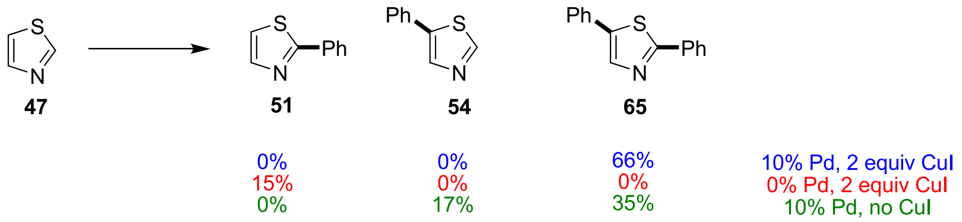
Scheme 2.1.3 Miura's proposed catalytic cycle[117]

Oxidative addition of the aryl halide, **64**, to palladium followed by electrophilic addition of the aryl palladium, **349**, to thiazole **51** gives intermediate **215**. Deprotonation of **215** to regain the aromaticity gives intermediate **216** which can then undergo reductive elimination to give the substituted product, **65**, and re-form palladium (0). Substitution at C5 is the only observed product, this supports an electophilic addition mechanism. If the mechanism followed a "Heck" type mechanism, (*via* carbopalladation followed by β-hydride elimination),[118] some substitution at C4 would be expected. The Heck mechanism, (Scheme 2.1.4), is also unlikely in this case as it would require a formal anti-elimination of the *β*-hydrogen (conversion of **218** to **54**) which would be unusual but not unprecedented.[119,120]



Scheme 2.1.4 – "Heck-type" mechanism for arylation of thiazole

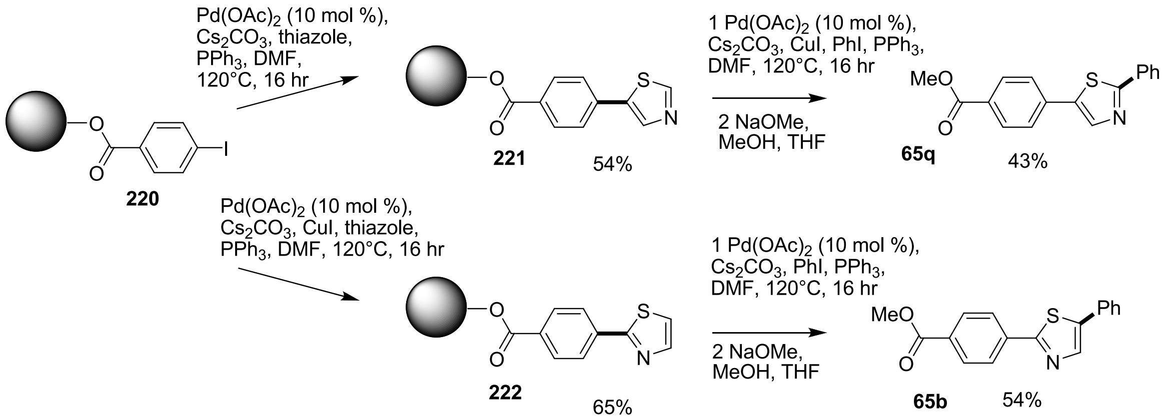
Miura *et al* further investigated the regioselectivity of their reaction by using thiazole, introducing the possibility of arylation at C2 or C5. This led to a mixture of products, (namely the expected 5-phenylthiazole, **54**, and also 2,5-diphenylthiazole, **65**) although overall yields were poor, (Scheme 2.1.5). When two equivalents of copper (I) iodide had been added to the reaction with 2-methylthiazole an increase in the yield was observed. Using copper (I) iodide with thiazole gave exclusively 2-methyl-5-phenylthiazole in a shorter reaction time.



Scheme 2.1.5 – Effect of Copper on regioselectivity

The reaction was repeated omitting palladium acetate to establish whether copper (I) was catalysing the reaction. Only the 2 substituted thiazole, **51**, was obtained in 15% yield. The copper may have two functions: firstly, since it is soft, it may help to prevent the sulphur in the thiazole ring from ligating the palladium;[117] secondly it may partially metallate at the acidic C2 position directing substitution, in analogy to its role in the Sonagashira reaction.[121]

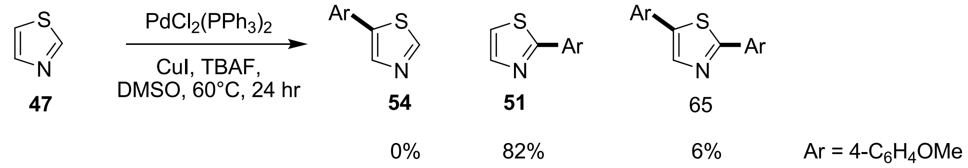
Kondo *et al* immobilized iodobenzoate on solid support and applied Miura's conditions to the selective synthesis of 2- or 5-arylated thiazoles, (Scheme 2.1.6).[122]



Scheme 2.1.6 – Kondo's solid supported route to substituted thiazoles

Diarylation was not observed under these conditions, yields of the 2- or 5-aryl thiazoles were 65% and 54% after cleavage. The products were further arylated using a solution phase aryl iodide providing a route to 2,5-diarylthiazoles. Unfortunately high temperatures and long reaction times were still required.

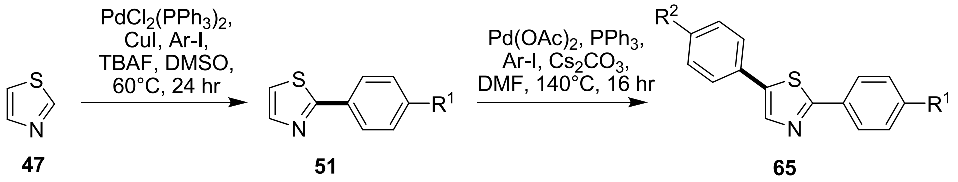
Whilst investigating the fluorescent properties of thiazole compounds in 2003, Mori *et al* devised a similar catalytic system for the arylation of thiazole. Tetrbutylammonium fluoride was used to accelerate the reaction and reduce the temperature, (Scheme 2.1.7).[8]

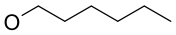
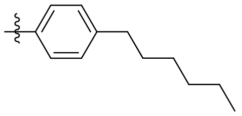


Scheme 2.1.7 Mori's selective 2-arylation

Regioselective C2 substitution (**51**) was achieved with only 2 mol % of copper (I) iodide, however, only two examples of this reaction were reported.

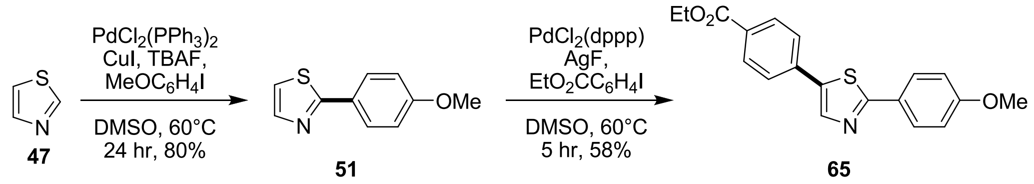
Several 2,5-diarylthiazoles, **65**, were constucted using their conditions[8] and Miura's,[117] (Scheme 2.1.8). The products were analysed for liquid crystalline characteristics, 2,5-diarylthiazoles have a wide temperature range in which they exhibit liquid crystalline behaviour.[8]



R^1	R^2	Yield **65**
OMe	Me	69%
OMe	MeO	94%
OMe	CN	62%
OMe		76%
NMe_2		39%
NMe_2	CN	26%

Scheme 2.1.8 – Mori's synthesis of 2,5-diarylthiazoles

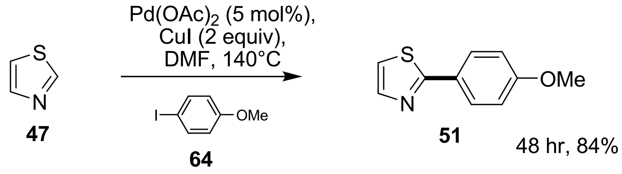
With a reliable proceedure for arylation at thiazole C2, Mori then developed a reduced temperature protocol for 5-arylation. This was accomplished by the use of a silver salt as an additive in the reaction, namely silver fluoride, (Scheme 2.1.9).[37]



Scheme 2.1.9 - Mori's improved 5-arylation

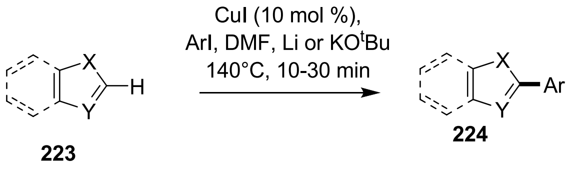
This modification of the reaction was milder and far quicker. Previously reactions had taken at least twenty-four hours to reach completion; with silver fluoride the reaction was finished in five hours, albeit with an attenuated yield of 58%. The use of 2-anisylthiazole constitutes a particularly good substrate for the electrophilic addition mechanism proposed by Miura, (Scheme 2.1.3) yet the yield was only 58%. As the only thiazole example, the potential applicability of these conditions for the arylation of other thiazoles can therefore be questioned.

Whilst investigating this reaction there have been several further publications in this area. Bellina *et al* were able to successfully arylate thiazole in the C2 position using a base and ligand free protocol, (Scheme 2.1.10).[123,124] 2-anisylthiazole was the sole product isolated from a reaction using stoichiometric copper in place of palladium.[117] This method was demonstrated to be applicable to a wide range of other heterocycles in good yields, however the high temperature remains a drawback.



Scheme 2.1.10 - Bellina's thiazole 2-arylation

In 2007 Daugulis reported the arylation of a number of heterocycles with aryl iodides using a catalytic copper based system.[125] Not only did they successfully arylate thiazole, they were also able to arylate a wide range of heterocycles in a remarkably short reaction time, (Scheme 2.1.11).

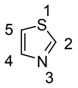


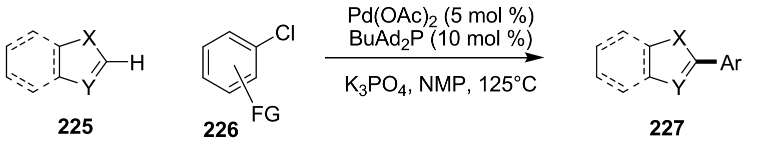
16 examples yields 55-91%

Scheme 2.1.11 - Daugulis's copper mediated system

A number of mechanistic experiments were conducted, including the reaction of 4,5-dimethylthiazole with deuterated phenyl iodide. When potassium tert-butoxide was used a proton was incorporated into the ortho position of the phenyliodide. This may suggest a benzyne-type intermediate was generated. This, however, was not observed when lithium tert-butoxide was used. In further support of this mechanism, when 4-iodotoluene was used in place of phenyliodide and using potassium tert-butoxide, a mixture of meta and para-tolylthiazoles are obtained.

The use of aryl chlorides in place of aryl iodides and bromides is becoming more common in cross-coupling reactions. Not only are aryl chlorides more generally available, but they are considerably cheaper and their use is considered to be greener, as there is a higher proportion of the mass of the substrate incorporated into the product. Daugulis *et al* have expanded the purview of their arylation of electron-rich heterocycles to include the use of aryl chlorides.[126] These were found to be unreactive under the copper conditions.[125] Brief investigation of a palladium-based system quickly led them to identify conditions for the transformation, (Scheme 2.1.12).





225 **226** **227**

17 examples, 52-86% yield

Scheme 2.1.12 - Daugulis's aryl chloride arylation conditions

Despite the advances reported since Mori's silver catalysed system was published, there remains a need to develop a general mild protocol for the arylation of thiazole at the C5 position. Daugulis's palladium conditions did arylate at the C5 position of the thiazole ring but they only reported two examples. Mori's silver fluoride conditions remain the only example of thiazole C5 coupling at a temperature less than 100°C.

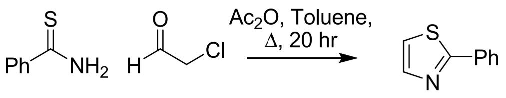
2.2. Optimisation studies

The drawbacks associated with the above studies prompted us to investigate the potential of the methods in place, with a view to optimisation and amelioration of the conditions.

It was felt that the conditions developed by Mori, utilising silver fluoride could be significantly improved upon in terms of both scope and yield. The use of two equivalents of silver fluoride, a particularly expensive silver salt (£44.50 for 5 g from Sigma-Aldrich), is prohibitive for large scale use of these conditions.

To avoid the potential confusion of 2, 5 or 2,5-diarylation it was decided to utilise a 2-substituted thiazole. 2-Phenylthiazole, **51a**, was selected due to the neutral electron-donating ability of the phenyl group (compare with anisyl in Mori's example, Scheme 2.1.9)[37] to enable a methodology to be developed with wide applicability.

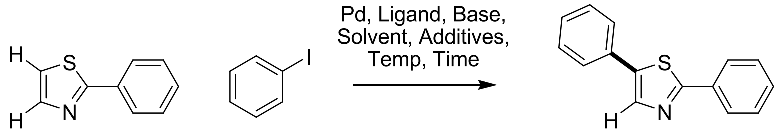
2-Phenylthiazole was synthesised by a classic Hantzsch synthesis from thiobenzamide, **36a**, and α-chloroacetaldehyde hydrate, **37a**, (Scheme 2.2.1). This method involved isolating the hydrate of the aldehyde from an aqueous solution using calcium chloride, proving to be time consuming and impractical on a small scale. The use of large amounts of acetic anhydride to remove the water and drive the reaction to completion, required considerable amounts of base to quench and neutralise, leading to excessive volumes and emulsions during the workup.



36a **37a** **51a**

Scheme 2.2.1 – Hantzsch synthesis of 2-phenylthiazole

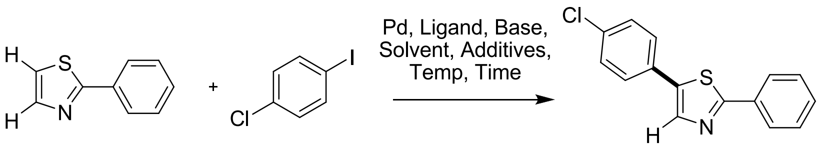
It was found that the reaction could be run using aqueous chloroacetaldehyde in ethanol negating the need for the acetic anhydride altogether, and greatly simplifying the procedure. Furthermore this led to higher yields and cleaner reactions, especially on a smaller scale.



51a **64a** **65a**

Scheme 2.2.2 – Model system for optimisation

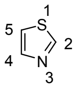
Using Miura's conditions ($Pd(OAc)_2$, PPh_3, Cs_2CO_3, Ar-I, Scheme 2.1.2) as a starting point, several variables were examined including temperature and solvent, immediately revealing a serious problem. 2-Phenylthiazole and 2,5-diphenylthiazole have identical R_f values in ethyl acetate/hexane mixtures and extremely close R_f in dichloromethane or toluene tlc systems. Despite a variety of differing solvent systems being used it was not possible to isolate the product from the reaction mixture without losing significant amounts to mixed fractions during column chromatography. A different aryl iodide was chosen to carry out the optimisation studies. Iodotoluene formed a product that co-eluted with 2-phenylthiazole however, whilst 4-chloroiodobenzene also gave a 2,5-diarylthiazole product that was close running with 2-phenylthiazole, it was possible to separate them.



51a **64b** **65b**

Scheme 2.2.3 – The improved model system

With substrate that was reasonably easy to purify it was decided to optimise the system for chloroiodobenzene and 2-phenylthiazole, (Scheme 2.2.3). Samples of the starting materials and products were also run by HPLC to allow *in situ* monitoring of the reaction to provide a quantitative method of analysis.



Starting from Miura's conditions, in dimethylformamide, the temperature was increased from room temperature in 10°C increments to determine at which point the reaction proceeds. The reaction does not start until above 100°C and, at this temperature it took more than a week for the reaction to reach completion. The reaction was repeated in toluene at 100°C but the conversion was poor by HPLC and the reaction profile messy, isolated yield 18%.

Temp /°C	Time to reach end point[1]/hr
20	No reaction
30	No reaction
40	No reaction
50	No reaction
60	No reaction
70	No reaction
80	No reaction
90	No reaction
100	>144
110	144
120	120
130	96
140	72
150	48 – yield 59%

Table 2.2.1 – Initial findings with regard to temperature

Despite the use of elevated temperatures, the reactions proceed slowly and fail to reach completion. Our initial hopes to use HPLC as a method to assess the success of each reaction were thrown aside at this point, as there were a large number of side reactions. A number of the side products have a very high UV response and skew the conversions measured by HPLC. HPLC was instead used as a guide to the success of the reaction. Products from reactions deemed to be successful were

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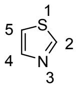
[1] The reactions do not proceed to completion. The time here measures the time until the reaction irreversibly stalls (measured by HPLC).



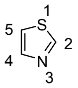
isolated and subjected to column chromatography to quantify the results. In some cases there were large disparities between the conversion (measured by HPLC) and isolated yield.

We next began to investigate the use of additives in the reaction such as silver fluoride and tetrabutylammonium fluoride, both shown to be promoters by Mori.[8,37] In addition to increasing the rate, they are able to significantly reduce the temperature necessary for C-H activation at the C5 position of the thiazole ring.

Using two equivalents of silver fluoride with palladium acetate (5 mol %), triphenylphosphine (10 mol %), caesium carbonate (2 equiv), 2-phenylthiazole (1 equiv) and 4-chloroiodobenzene (1.2 equiv) in dimethylformamide at 60°C for 24 hr the product was isolated in 60% yield constituting a large drop in the temperature needed to conduct the reaction. It was then repeated using acetonitrile rather than dimethylformamide. Acetonitrile is a superior solvent in terms of removing it from the reaction mixture and purification of the product. The reaction was carried out at 60°C for 48 hours and the product isolated in 73% yield following column chromatography. Whilst the reaction was slower in acetonitrile, it gave an increase in the yield, it was also noted that the purification was more straightforward.

Although Mori's work had suggested that using tetrabutylammonium fluoride could be nearly as effective as using a silver salt, it was found that this did not apply to our reaction system. Furthermore, the reaction was slow and formed a number of unknown impurities without a trace of product being seen.

The silver cation was obviously crucial to the reaction. Being aware of the reported effect of iodide, it was decided to investigate a number of silver salts to determine if silver fluoride was the most effective.



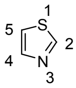
Silver Salt	Yield **65b**	Time /days
AgF	80	2
Ag_2O	17	5
$AgOSO_2CF_3$	30	1
Ag_2CO_3	41	3
Ag_2CO_3 (on celite)	67	5
Ag_2CO_3 (on celite)[a]	87	5
AgF[b]	0	2
AgF[c]	63	2
Conditions: $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), 2-phenylthiazole (50 mg, 1 equiv), 4-chloroiodobenzene (1.2 equiv), Cs_2CO_3 (2 equiv), silver salt (2 equiv of Ag^+), CH_3CN (5 mL), 60°C. **a** No Cs_2CO_3, **b** No $Pd(OAc)_2$, **c** 1 equiv AgF		

Table 2.2.2 – Investigation of the effect of silver salts

Whilst silver fluoride works well for the reaction it is expensive, it would be beneficial to be able to use a cheaper silver salt; the results of the screen are shown in Table 2.2.2. Silver oxide hardly affected the reaction at all, after five days very little product was observed. The use of silver triflate led to a number of side products. Silver carbonate reacted cleanly but slowly; after a prolonged reaction time silver carbonate on celite gave a 67% yield. When the reaction was repeated omitting the caesium carbonate and using silver carbonate on celite as both base and silver salt, the reaction gave an 87% yield in five days. This was a significant increase over using the caesium carbonate, silver carbonate combination.

To try and discover the role of the silver salt, the reaction was repeated without palladium to investigate whether the silver cation alone could be mediating this transformation. After two days no reaction had been seen but when palladium acetate was added, the reaction began.

Reducing the amount of silver fluoride demands longer reaction times to obtain high yields; this is not too surprising because the use of silver or thallium salts to accelerate Heck-type reactions is well precedented.[127-129] The silver cation is a



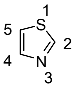
halophile causing silver iodide or bromide to precipitate out of the reaction mixture and therefore be unavailable to ligate the palladium. It is thought that this gives a cationic palladium species which is a more active catalyst, it would seem likely that this is the role of the silver salt. A cationic palladium species would be expected to undergo an electrophilic addition to the thiazole more readily than a neutral palladium complex. Whilst the fluoride counter ion is not necessarily contributing to the increase in rate it is a poor ligand to the palladium and as such does not interfere with the cationic palladium. Silver fluoride is also particularly soluble in acetonitrile when compared to other silver salts so this should increase the rate of precipitation of silver iodide.

The fact that the yield is higher using silver carbonate without caesium carbonate is possibly due to the relative solubilities of caesium iodide and silver iodide. Since silver iodide is less soluble than caesium iodide there would be less iodide in solution to ligate the palladium. It is also feasible that in the case of caesium carbonate and silver fluoride, ion exchange occurs forming caesium fluoride and silver carbonate. This is supported by the decrease in respective yields when different bases are used. Sodium and potassium iodide are both particularly soluble in acetonitrile compared to both caesium and silver iodides and a corresponding decrease in the yield is seen in these cases, (Table 2.2.3).

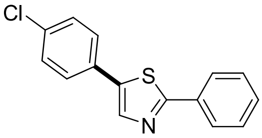
Base	Silver Salt	Conversion to **65b**%	Time /hr
Cs_2CO_3	-	0	72
Cs_2CO_3	AgF	75	72
-	AgF	60	72
K_2CO_3	AgF	15	72
Na_2CO_3	AgF	10	72
KOAc	AgF	18	72

Table 2.2.3 – The effect of different bases.

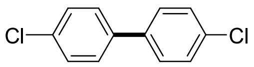
Despite the reasonable yields achieved so far, the reaction was still very slow, generally taking five days to reach completion. To accelerate the reaction, the use of



microwave heating was investigated. Using $Pd_2(dba)_3$ we obtained the results shown in Table 2.2.4. The reaction was complete in only two hours at 100°C. Unfortunately on isolation it proved to be a mixture of two compounds, the expected product, 2-phenyl-5-(4-chlorophenyl)thiazole, **65b**, and 4,4-dichlorobiphenyl, **227**, this was the first time the biphenyl compound had been observed, it co-runs with the product by HPLC. Method development was attempted in order to separate the peaks but with the columns available this proved to be impossible. The isolated yields of each respectively was 24% and 46%.



65b



227

Time /min	Temperature /°C	Conversion %
5	60	13
10	60	22
40	60	29
5	100	16
10	100	20
30	100	23
120	100	95
240	100	95

Table 2.2.4 – Conversion using microwave heating

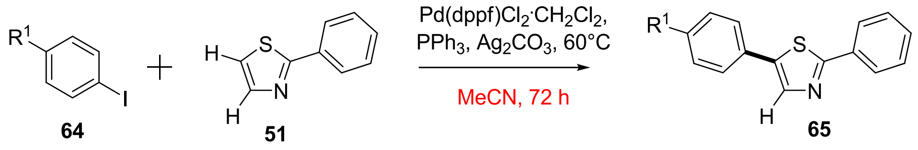
As the proportion of biphenyl could not be determined by HPLC, it was decided to investigate different palladium sources to see how this would affect the reaction. It had already been seen that $Pd_2(dba)_3$ was a slightly more active catalyst than palladium acetate although both were slow. A number of different palladium sources were used and the conversions measured by HPLC, see Table 2.2.5.

Pd Source	Time /hr	Conversion into **65b** /%
$Pd(OAc)_2$	72	39
$Pd_2(dba)_3$	72	42
$PdCl_2(dppf)\ CH_2Cl_2$	72	81
$PdCl_2(PPh_3)_2$	72	63
$PdCl_2$	48	76
$PdCl_2{\cdot}CH_3CN$	120	66
$PdCl_2(dppe)$	120	40
$Pd(PPh_3)_4$	120	69
Conditions: Pd (5 mol %), PPh_3 (10 mol %), CH_3CN (5 mL), Ag_2CO_3 (2 equiv), 2-phenylthiazole (1 equiv), 4-chloroiodobenzene (1.2 equiv)		

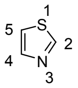
Table 2.2.5 – Investigation of palladium sources

The use of $PdCl_2(dppf){\cdot}CH_2Cl_2$ provided excellent conversion (isolated yield 79%), palladium chloride also had a very clean reaction profile and reached complete conversion in under two days but unfortunately led to some homocoupling of the aryl iodide.

It was interesting to note that in the case of $PdCl_2(dppf){\cdot}CH_2Cl_2$ the addition of extra ligands was necessary to ensure continued catalyst turnover. Without extra triphenylphosphine the conversion falls to 43%, comparable with $Pd_2(dba)_3$. With these conditions in hand it was decided to attempt the coupling of other aryl iodides to the 2-phenylthiazole core, (Scheme 2.2.4 and Table 2.2.6).



Scheme 2.2.4 - General library scheme



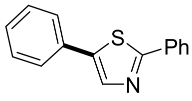
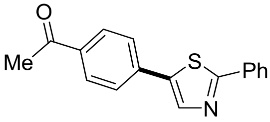
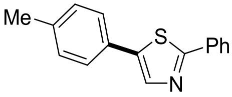
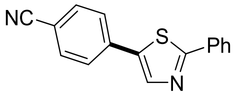
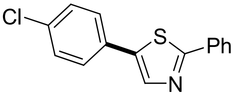
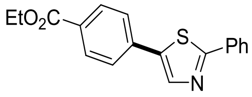
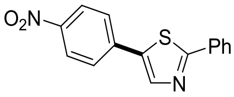
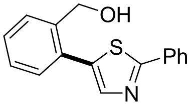
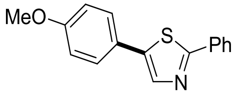
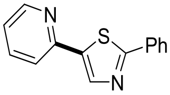
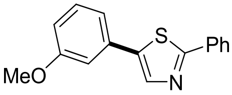
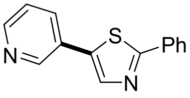
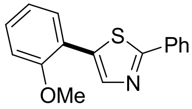
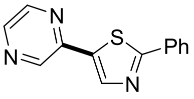
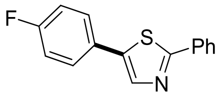
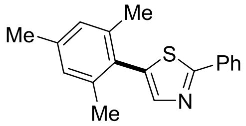
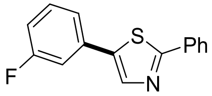
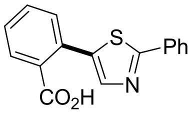
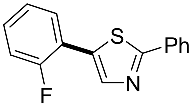
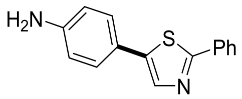
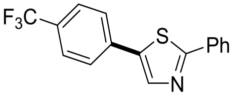
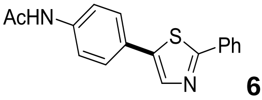
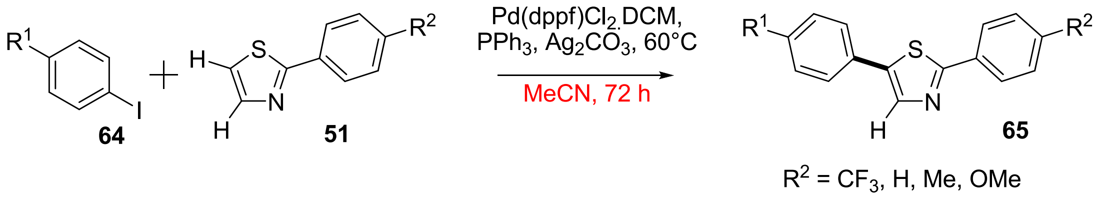
Compound	Yield		Compound	Yield
 **65a**	79		 **65l**	94
 **65c**	74		 **65m**	88
 **65b**	81		 **65n**	53
 **65d**	62		 **65p**	65
 **65e**	78		 **291a**	57
 **65f**	53		 **65q**	36
 **65g**	71		 **65r**	0
 **65h**	89		 **65s**	0
 **65i**	65		 **65t**	0
 **65j**	59		 **65u**	0
 **65k**	62		 **65v**	0

Table 2.2.6 – Reactions in CH_3CN

A large number of different aryl iodides are viable in the reactions and overall yields were moderate to good. A number of failures were, however, observed. The pyridine, (**291a** and **65q**) and pyrazine (**65r**) heteroaryliodides reacted poorly or not at all. This is probably due to their ability to coordinate to the palladium reducing the efficiency of the catalytic cycle. Similar reasoning can be applied to the iodobenzoic acid (**65t**) and the iodoanilines (**65u** and **65v**) that were attempted. Iodomesitylene, **65s**, also failed under these conditions demonstrating unfavourable steric effects. This can also be seen in the ortho-substituted aryliodides which demonstrated a noticable reduction in yields over their para-substituted analogues.

In order to lend further support to the electrophilic substitution mechanism put forward by Miura[117] we looked at different aryl groups in the thiazole 2-position. To examine the electronic effects at the thiazole C2 position *para* -CF_3, -Me and MeO- aromatic groups were chosen, (Scheme 2.2.5 and Table 2.2.7).



Scheme 2.2.5 – General scheme for library synthesis

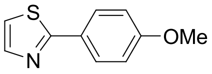
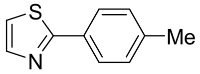
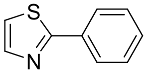
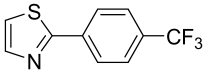
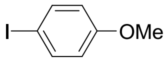
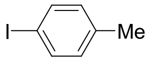
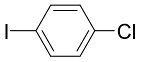
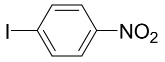
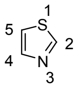
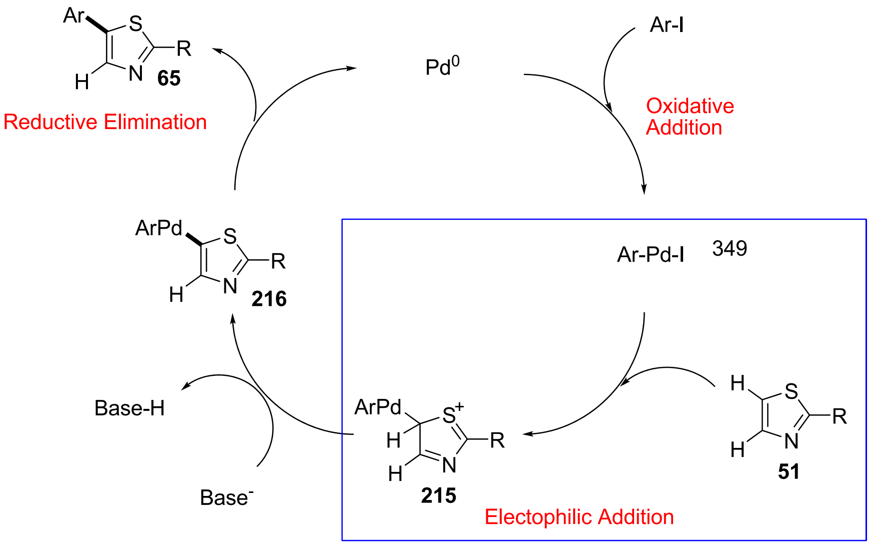
	 **51c**	 **51d**	 **51a**	 **51e**
	73	77	78	74
	96	93	74	32
	98	85	81	63
	64	69	62	12

Table 2.2.7 – Effect of *para*-substituents at thiazole C2 showing isolated yields of 2,5-diarylthiazoles

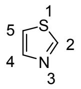


Before analysing these results it is worth looking again at the four discrete steps in Miura's proposed mechanism, (Scheme 2.2.6). Looking at each, together with the data collected we can dismiss the oxidative addition step as the rate determining step. Oxidative addition of aryl iodides is facile at room temperature so cannot be the rate determining step. Likewise, there is no evidence to suggest that the reductive elimination is the rate determining step. If it was, the electronic nature of the aryl iodide would affect the rate; a more electron-rich aryl iodide would give a more electron-rich palladium species, which would undergo more facile reductive elimination. Likewise bulky electron-rich ligands would promote the reaction. Overall, no real trend was seen with regard to the aryl iodide employed in the reaction.



Scheme 2.2.6 – Miura's proposed mechanism

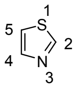
This leaves two possible rate determining steps in the reaction sequence; electrophilic addition of the thiazole to the aryl palladium and deprotonation of the aryl thiazole intermediate to regain the aromaticity. Dealing with the former first, the concentration of base in the reaction mixture is such that it is unlikely that this is the rate determining step. In addition the restoration of the thiazole aromaticity should cause this step to be favourable, leaving the electrophilic addition as the rate determining step. Indeed this would seem to be confirmed by Mori's silver fluoride



conditions,[37] presumably giving a cationic aryl palladium species and greatly accelerating the reaction.

The results in Table 2.2.7 showed that the actual situation is not quite as straightforward as might be expected. Considering the reaction of 4-iodoanisole with the four 2-arylthiazoles shows essentially the same yield across electron-donating and withdrawing substituents. This is likely to be due to slow oxidative addition of palladium (0) to 4-iodoanisole masking the substituent effect on the thiazole. Looking at 4-chloroiodobenzene and 4-iodotoluene there is a definite correlation between the electron-donating ability of the substituent at thiazole C2 and the yield of product isolated, 4-iodonitrobenzene also does not adhere to the expected pattern. Oxidative addition of 4-iodonitrobenzene is known to be very fast and it is assumed that it may be consumed in side reactions before being able to react with the thiazole substrate. From these results it is obvious that the electrophilic addition is an important event in the mechanism but that it is not always the rate determining step. In the case of very electron-donating aryl iodides (poor substrates) the slow oxidative addition may even be the rate determining step.

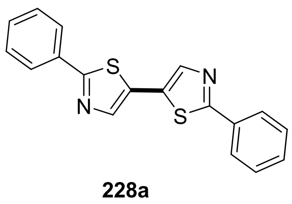
Despite these positive results we remained dissatisfied with the time that the reactions needed to reach completion, to improve this we decided to look at a number of factors. This further investigation of the variables was started whilst on CASE placement at Syngenta and initially it was found that the reaction was entirely unreproducible and completely failed. A systematic approach identified two main problems, firstly the purity of the starting material. In Edinburgh purification of the starting material was accomplished by reduced pressure distillation. At Syngenta, even after distillation under reduced pressure, the material, whilst appearing clean by NMR, failed to react. After passing the material through a plug of silica gel, it was substantially more active in the reaction. It was also found, however, that purification by column chromatography was not an acceptable alternative; a highly coloured impurity co-eluted and again, the material was unreactive in the palladium cross-coupling reaction.



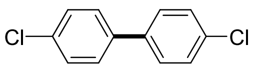
The second of the problems encountered at Syngenta was due to the solvent. Dry acetonitrile purchased from Aldrich was not sufficiently dry to effect the transformation, nor when it had been further dried and stored, over activated molecular sieves. Syngenta policy dictated that solvent stills were an unacceptable method for drying solvents, however, all other avenues having been explored and found wanting, a compromise was reached. Acetonitrile distilled from calcium hydride can be stored over 3Å molecular sieves and under nitrogen for approximately fourteen days before reaction efficiency is significantly compromised.

With these results in hand, it was found that the reaction was more reliable and reproducible. This allowed an accurate and trustworthy HPLC method to be introduced to gauge product amounts. Together with LC-MS this allowed a large amount of data to be generated about the reaction and the associated variables.

Investigation of the variables commenced with a brief look at the reaction temperature, followed by ligand properties to further modify the steric and electronic environment around the aryl-palladium. At temperatures in excess of 80°C we began to see a side reaction occurring in preference to our desired reaction. This led to the formation of homocoupled aryl iodide, **227**, (as seen in the microwave studies) together with a degree of homocoupling of the thiazole compound, **228a**, described in detail by Mori.[130]



228a



227

Until this point it had been determined that the addition of extra ligand was important to the reaction, but it had not been discovered whether there was a significant effect dependent on the ligand used. We had looked at a number of different palladium sources, some of which contained ligands, and noticed no real advantage except in the case of Pd(dppf)Cl_2. In light of the mechanistic implications it was thought that electronic modification of the arylpalladium species might lead to accelerated reaction times. A small screen of available ligands showed some interesting trends. These reactions were carried out with palladium acetate, to prevent possible interference of any ligands already present on palladium. The catalyst and ligand were stirred in dry, degassed acetonitrile for 10 min prior to adding the remaining reagents. The reactions were then heated to 60°C for three hours, the time being kept short to avoid unrepresentative results if a reaction was substantially accelerated. The results are depicted in Figure 2.2.1 and the nature of the ligands in Table 2.2.8.

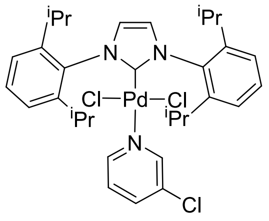
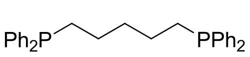
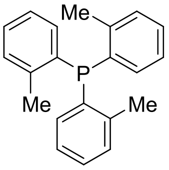
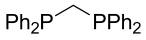
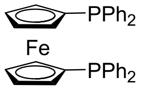
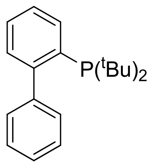
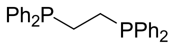
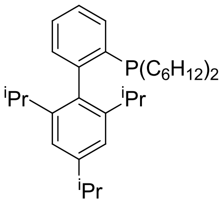
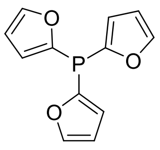
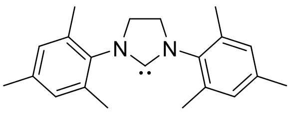
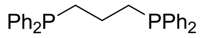
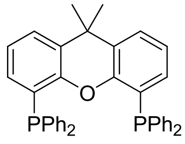
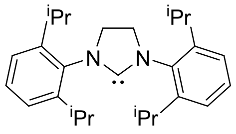
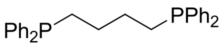
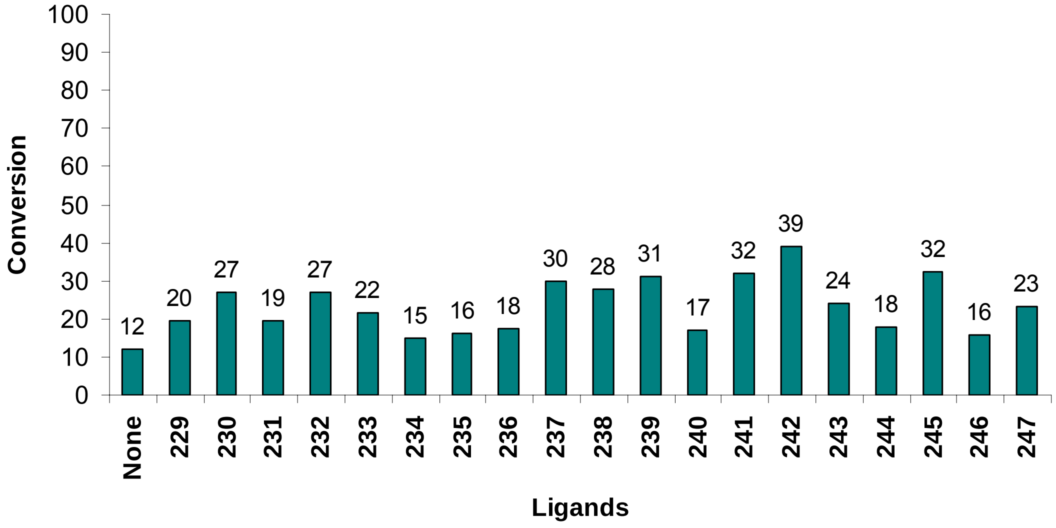
PPh_3 **229**	PBu_3 **234**	 **239**	 **244**
 **230**	$HP^tBu_3.BF_4$ **235**	 **240**	 **245**
231 $P(C_6H_{12})_3$	 **236**	 **241**	 **246**
 **232**	 **237**	 **242**	 **247**
$P(C_6F_5)_3$ **233**	 **238**	 **243**	

Table 2.2.8 - Ligands used in the screen

Figure 2.2.1 - Conversion at 3 hours for different ligands

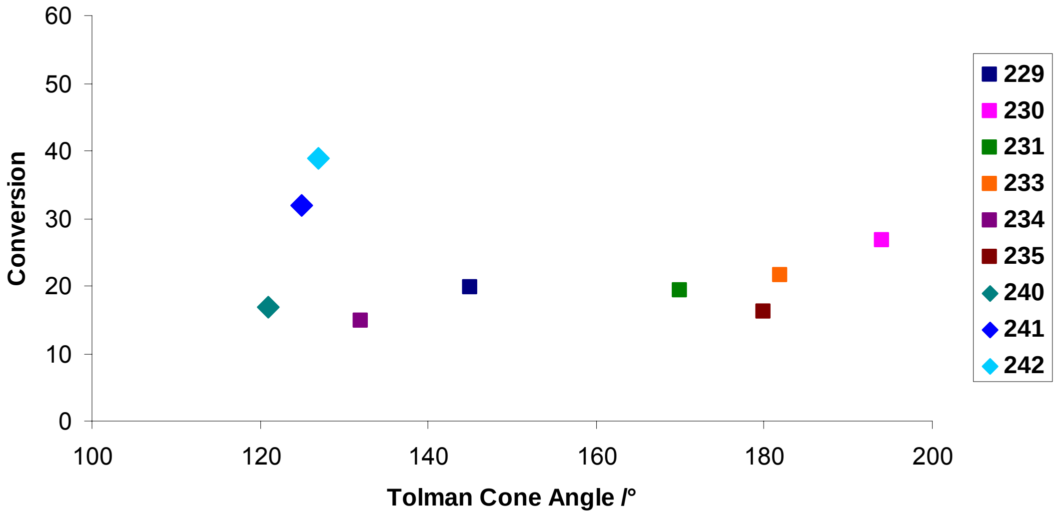


Only a small ligand effect was observed. However, in every case the use of a ligand did cause some improvement in conversion.

The effects of the ligands themselves can be broken down into a number of variables; sterics, electronics and bite angle for the bidentate ligands.

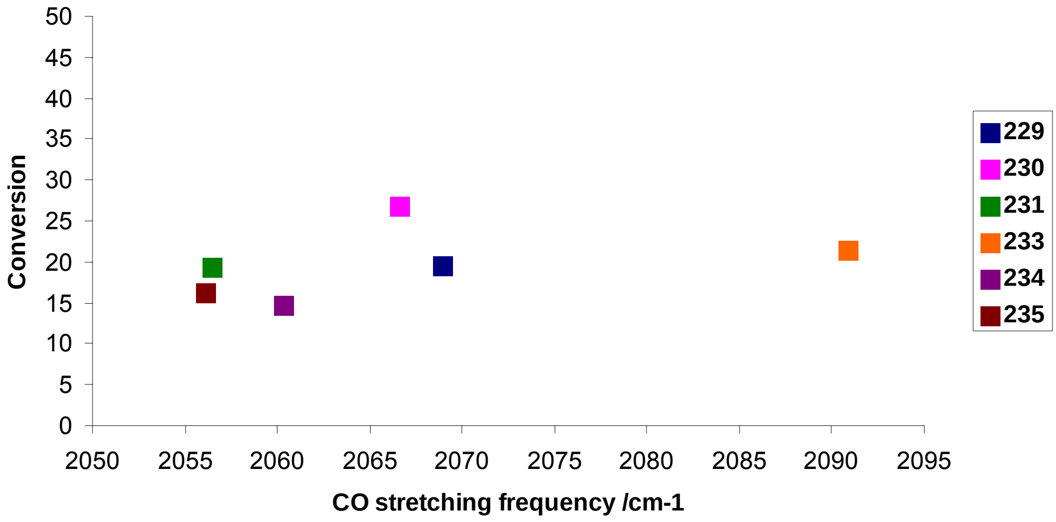
The steric effects of the ligands can be quantified by the Tolman cone angles,[131] a plot of cone angle against conversion shows that the more sterically encumbered the ligand (and therefore the metal centre) the higher the conversion, (Figure 2.2.2). Dppm, dppe and dppp are substantially more active than the monodentate ligands, but even within these two classes of ligands it can be seen that the conversion increases with cone angle. A more sterically bulky ligand promotes faster reductive elimination.[132]

Figure 2.2.2 – Steric factors



Whilst cone angle is an intuitive method to quantify the steric effects of a particular ligand it is more difficult to identify a method to measure a ligand's electronic contribution to a metal complex. This is traditionally done by measuring the C≡O stretch (by infrared spectroscopy) of the ligand whilst part of a $Ni(CO)_3L$ complex.[131] The values associated with a number of the investigated ligands have been plotted against the conversion in Figure 2.2.3.

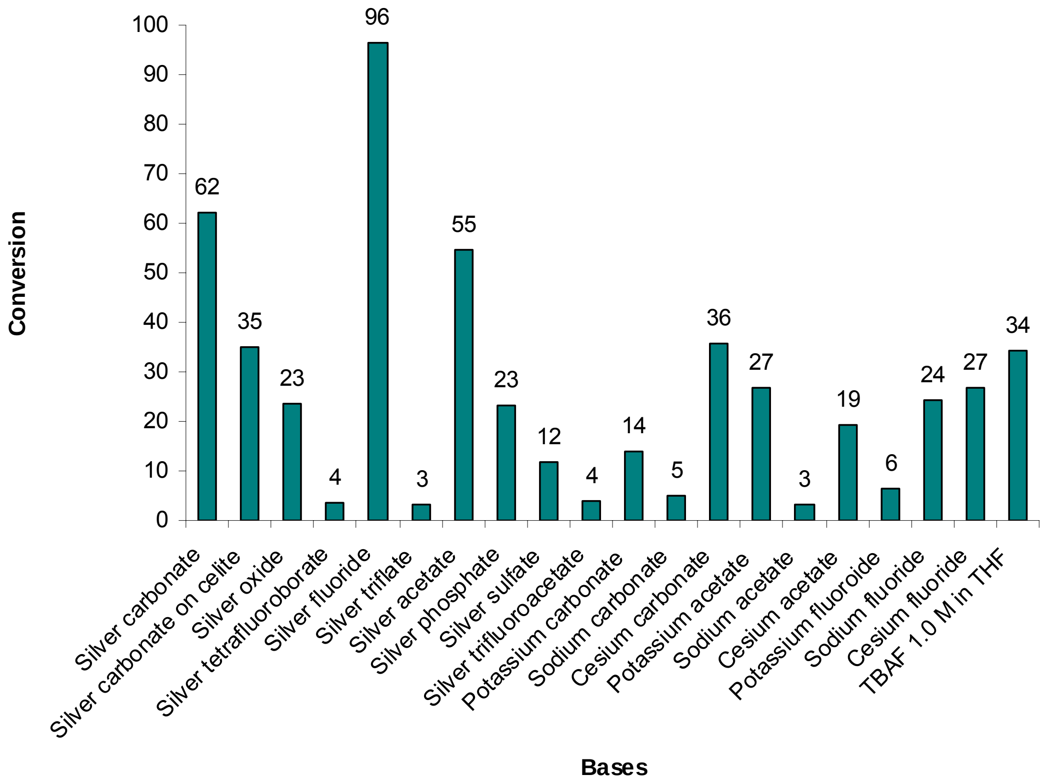
Figure 2.2.3 - Electronic Contributions



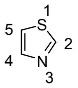
There is a positive correlation between the stretching frequency and the conversion, i.e. an increase in the conversion for less electron-donating ligands. This supports an electrophilic addition mechanism, whereby an electron-poor palladium species would react faster than an electron-rich one.

The next variable returned to was the nature of the silver salt. As a marked counter-ion effect had been observed it was appropriate to screen a wider range, especially with the more reliable procedure now in place. Also investigated were a number of other additives and different bases, (Figure 2.2.4, conditions: 2-phenylthiazole, Pd(dppf)Cl_2·CH_2Cl_2, PPh_3, CH_3CN, 4-ClC_6H_4I, 60 °C, 24 hr).

Figure 2.2.4 – The effect of different additives and bases



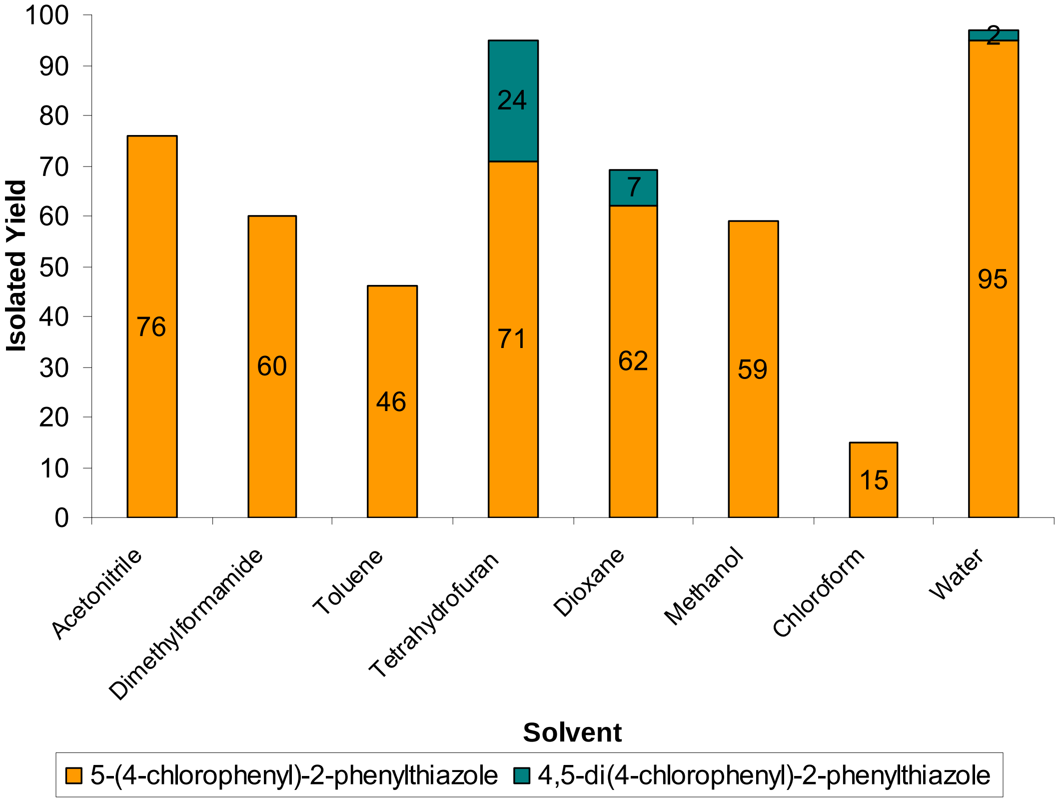
Silver fluoride was confirmed as the best silver salt followed by silver carbonate and silver acetate; the efficiency of silver acetate was a surprising result. It had been

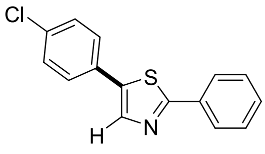


assumed that an effective silver salt would have a non-coordinating anion. From these results is not always necessary, but the silver salt should also be basic. Of the other bases used, caesium carbonate and potassium acetate were shown to be good choices, although less efficient than the silver carbonate, fluoride and acetate. This was in contrast to earlier work, which had shown caesium carbonate and potassium acetate to both cause the reaction to stall. This may be due to the cleaner starting material which has been shown to be more active in the reaction. In addition some of the results here do not match up with the earlier screen of silver salts. This is probably because the original screen was done with a number of old pots of silver salts. Silver salts degrade to silver over time and with exposure to light. A common solution to this is the immobilisation of silver carbonate on celite to improve its lifetime with regard to decomposition. This would explain why in the initial screen, (see Table 2.2.2), silver carbonate on celite was more active than silver carbonate.

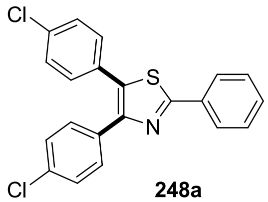
Whilst repeating the 5-arylation a curious result was observed. The reaction was flooded with water when the condenser broke and left to stir at room temperature over the weekend. On recovering the starting material the following Monday there was also a small amount of product obtained, 7%. This was surprising as the use of wet solvent had usually lead to poor conversion at 60°C and the reaction had never been observed at room temperature. This led to investigation of a number of common solvents. The results are shown in Figure 2.2.5. Tetrahydrofuran and dioxane had curious results where not only was the expected product seen but also small amounts of 4,5-diarylation which is entirely unprecedented in the absence of a directing group.[93] These two results will be discussed in more detail in chapter 3. However, the most important and unexpected result was in the case where the reaction was run in water and displayed a startling efficiency. It should be noted that Figure 2.2.5 shows isolated yields, not simply conversions and that the reaction in water was complete where as all of the others showed some 2-phenylthiazole remaining.

Figure 2.2.5 – Solvent effects on arylation at thiazole C5 – 72 hr at 60°C





65b



248a

With this rather surprising result in hand, the reaction was repeated to confirm the result, and three other 2,5-diarylthiazoles were made to see if this was a general effect. The results are shown in Table 2.2.9 and are quite spectacular. The increase in yield was also accompanied by much cleaner reactions that had reached completion; as there was no remaining 2-phenylthiazole the purification was significantly improved.

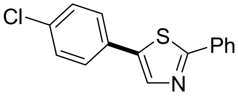
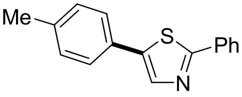
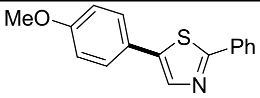
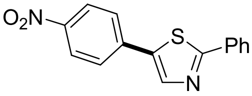
Compound **65**	Yield in CH_3CN	Yield in H_2O
 **65b**	81	95
 **65c**	74	87
 **65e**	78	88
 **65d**	62	67
Conditions: 2-phenylthiazole, Pd(dppf)Cl_2·CH_2Cl_2 (5 mol %), PPh_3 (10 mol %), Ar-I (1.2 equiv), Ag_2CO_3 (2 equiv), CH_3CN (5 mL) or H_2O (5 mL), 60°C, 72 hr.		

Table 2.2.9 - Comparison of the reaction in acetonitrile and water

We next turned our attention to the timescale needed for the reactions to reach completion and to try and understand the effect that the water was having on the reaction. Figure 2.2.6 shows conversion with time, demonstrating a significant increase in rate between acetonitrile and water. Somewhat surprisingly, the neat rate is quite similar to the rate in water. As the reagents are, only sparingly soluble in water, it is assumed that water is acting as an "anti-solvent" essentially allowing the reaction to be conducted neat but retaining stirring and efficient heat transfer.

Figure 2.2.6 – Conversion measured as a function of time at 60°C

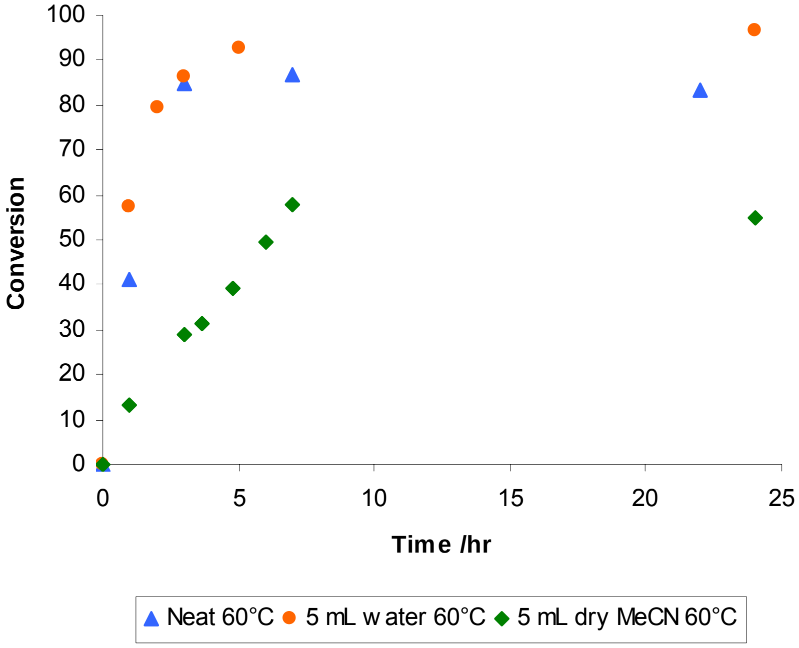
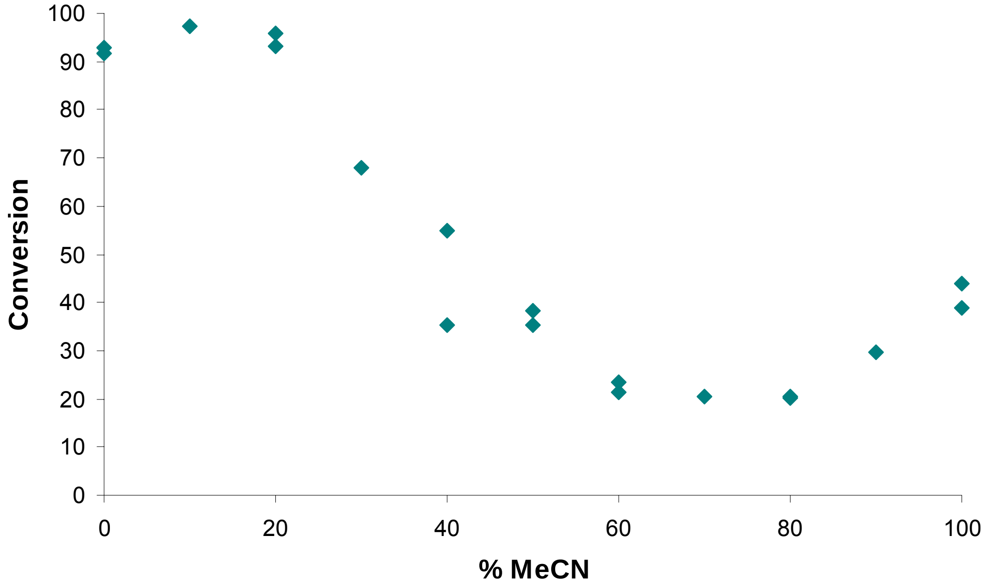
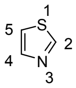


Figure 2.2.7 – Conversion in mixed water acetonitrile systems



A mixed aqueous/organic single phase system was also investigated to see if it would confer any advantage over the water system. Stirring was often poor and the



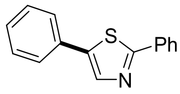
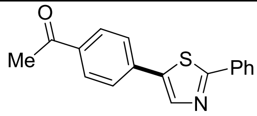
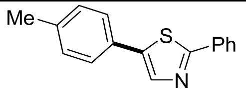
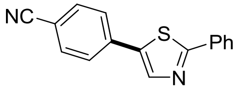
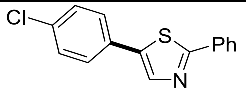
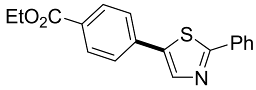
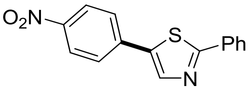
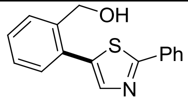
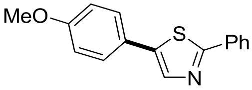
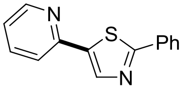
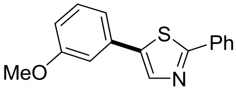
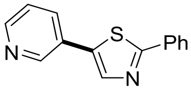
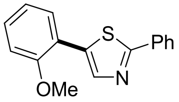
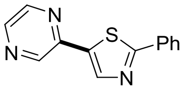
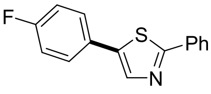
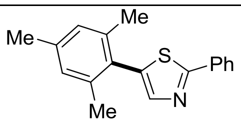
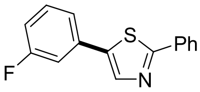
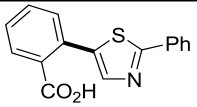
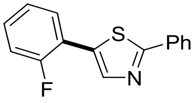
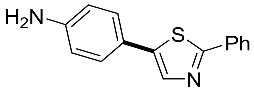
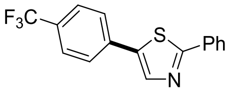
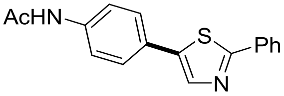
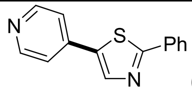
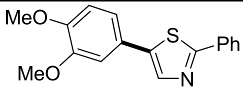
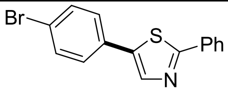
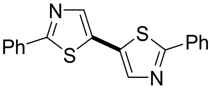
reagents would adhere to the side of the flask, thus necessitating mechanical agitation with dichloromethane to remove the solids at the end of the reaction. Differing proportions of water and acetonitrile were combined and the conversion measured after five hours, see Figure 2.2.7.

The data obtained were in agreement with our original findings that wet acetonitrile was less efficient than dry acetonitrile. Interestingly it was also found that addition of a small amount of acetonitrile to the water reaction did increase the conversion slightly. This can be attributed to improved stirring over water alone as there will be increased solubility of the various organic components and therefore improved kinetics of transport throughout the aqueous phase.

With the improvement over the reactions in acetonitrile shown to be reproducible the original library of compounds was re-made using the water conditions. The results are shown in Table 2.2.10.

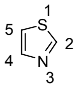
There was a significant advantage in the use of water as a solvent, not only in terms of yield but the considerable reduction in reaction time.

The absence of an organic solvent confers a green status on the reaction. Sharpless has extensively investigated the effect of water on reaction systems, dubbing certain reations as “on water” reactions.[133] The reaction mixture benefits from an anti-solvent effect whereby the effective concentration of the reaction is increased whilst maintaining efficient stirring and heat transfer.

Compound	Yield CH_3CN	Yield H_2O		Compound	Yield CH_3CN	Yield H_2O
 **65a**	79	87		 **65l**	94	97
 **65c**	74	97		 **65m**	88	98
 **65b**	81	95		 **65n**	53	>99
 **65d**	62	67		 **65p**	65	81
 **65e**	78	>99		 **291a**	57	71
 **65f**	53	88		 **65q**	36	>99
 **65g**	71	82		 **65r**	0	>99
 **65h**	89	>99		 **65s**	0	>99
 **65i**	65	99		 **65t**	0	0
 **65j**	59	82		 **65u**	0	0
 **65k**	62	>99		 **65v**	0	0
 **65w**	0	23		 **65x**	-	88
 **65y**	-	>99		 **228a**	61	>99

Conditions: 2-phenylthiazole (1 equiv), aryliodide (1.2 equiv), Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (5 mol %), PPh_3 (10 mol %), Ag_2CO_3 (2 equiv), CH_3CN 72 hr or H_2O 24 hr, Yields: average of 2 runs

Table 2.2.10 – Comparison of water and acetonitrile



Reduction of the quantity of organic solvent is obviously a desirable characteristic for green chemistry, however, it is not just the reaction solvent that should be considered. Aqueous chemistry cannot be considered green if large columes of organic solvent are necessary to extract the product out of the reaction mixture. In this case, only minimal solvent is needed to remove the product. The work up consists of firstly filtering the reaction mixture through celite to remove the insoluble salts, and washing the cake with acetone (5 mL) and dichloromethane (5 mL). The residue is concentrated to remove the acetone, then the aqueous residue extracted into dichloromethane (5 mL) and passed through a plug of silica gel to remove any unreacted aryl iodide. The need to remove the acetone and extract the product from the aqueous residue reduces the elegance of the procedure but proved to be unavoidable.

A property of the 2,5-diarylthiazole products is that they azeotrope with water, hence attempting to remove the water from the reaction mixture by distillation leads to the loss of the product. Indeed, during the reactions crystals of product were often observed around the top of the reaction tubes, see Figure 2.2.8. It was hoped that it might be possible to cleanly isolate the product from the reaction in this fashion and negate the need for organic solvents entirely, however, when this was attempted, not only was a poorer yield obtained compared to the work-up and extraction procedure, but not all the 2,5-diarylthiazoles azeotrope.

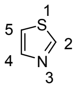
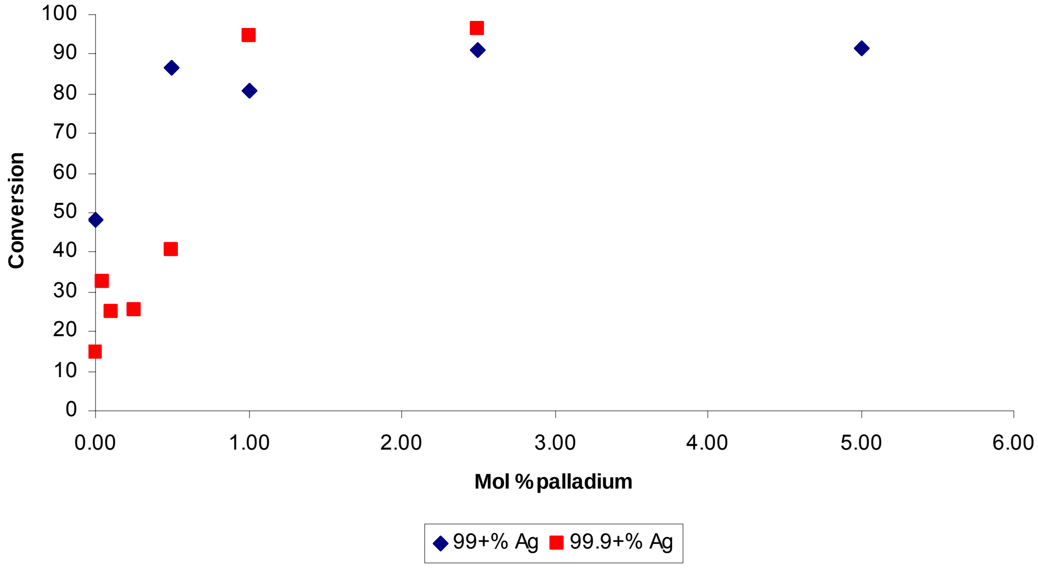


Figure 2.2.8 - Product crystals in water reactions

With the superior water conditions in hand the stoichiometry of the reaction was investigated. A catalyst loading of 5 mol % may be standard for small scale reactions, but only represents twenty turnovers for each molecule of catalyst. Gratifyingly, reducing the catalyst loading by a factor of ten did not significantly decrease the conversion after twenty-four hours at 60°C in water. This is a turnover number of at least two hundred. With this result in hand we further reduced the amount of added palladium and saw a corresponding drop off in the conversion which could be solved by longer reaction times. As a control experiment the reaction was also run with no added palladium, in new glassware, with a new stirrer bar. It was astounding to note that there was a 48% conversion to product, , see Figure 2.2.9.

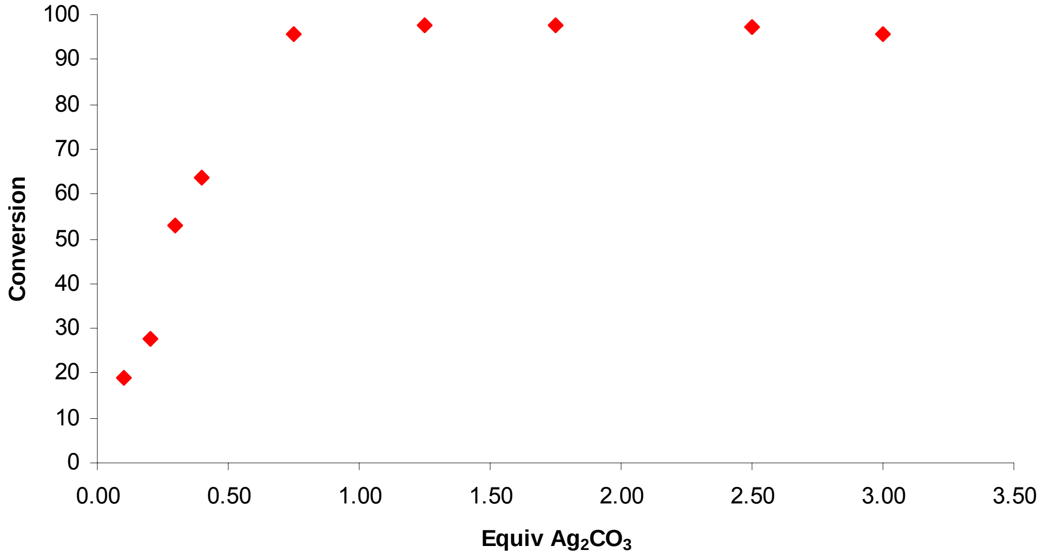
Investigating the purity of the silver carbonate employed (99% purity) it was decided to purchase a purer grade of silver carbonate (99.999%) and repeat the reaction, in this case there was only 15% conversion to the product, a substantial drop compared to the 99% pure silver salt. One of the major impurities in the finer grade silver was listed as palladium (Al 0.5, Ba 11.0, Ca 1.0, Cs 0.2, Fe 0.5, Ga 0.2, Pd 1.4, Sr 0.2, Th 0.8 and Zn 0.5 ppm) which could explain the conversion seen.

Figure 2.2.9 – Conversion after 5 hours against percentage Palladium



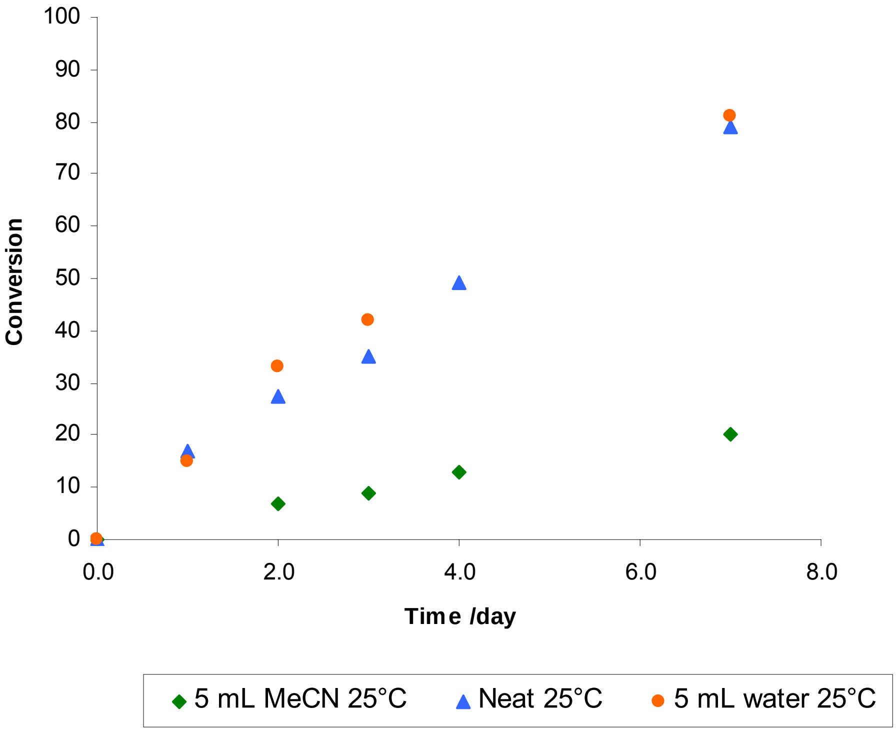
At four equivalents of silver cation, the amount of silver necessary in our reactions was obviously suboptimal. Looking at the number of equivalents necessary for the reaction showed a stoichiometric amount of silver to be a requirement, and ideally a slight excess, the number of equivalents of silver carbonate can safely be reduced to 0.75 with no detrimental effect on the reaction, see Figure 2.2.10.

Figure 2.2.10 – Equiv of Ag_2CO_3



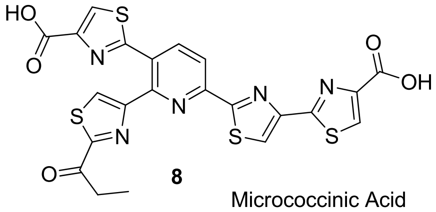
With these results in hand, it was wondered if the reaction could be accomplished at a reduced temperature. As such, a number of experiments were conducted at ambient temperature. It was, however, found that there is a significant decrease in the reaction rate as the temperature is reduced. Figure 2.2.6 shows the reaction to be substantially complete after only 5 hours at 60°C, whereas, at room temperature it takes a week to reach completion, (Figure 2.2.11).

Figure 2.2.11 – Conversion at Room temperature



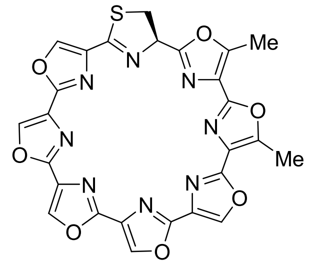
2.3. Arylation with other electrophiles

Ultimately it is hoped to be able to couple azole triflates to a thiazole or oxazole core and hence form multiple azole structures such as those in micrococcinic acid, **8**, and telomestatin, **249**. Micrococcinic acid was first synthesised in 1991 by Kelly *et al*[24] in a series of Stille reactions from a triply orthogonal pyridine core. This impressive synthesis perfectly demonstrated the power of palladium cross-couplings in the synthesis of this type of natural product. In an analogous fashion, it could be envisaged that micrococcinic acid could be constructed through a series of direct arylation reactions.



8

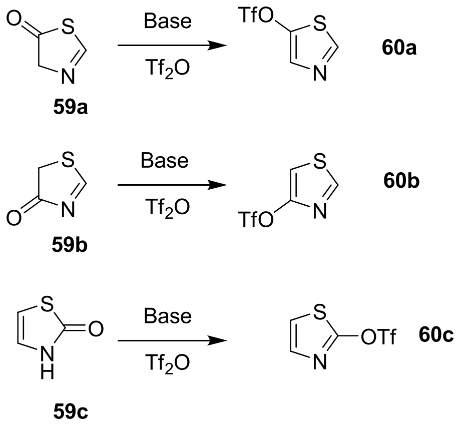
Micrococcinic Acid



249

Telomestatin

Azole triflates, **60**, are readily obtained from the related oxo compounds, **59**, as shown in Scheme 2.3.1. As such it was decided to make a preliminary investigation into the use of triflates and bromides as coupling partners.



Scheme 2.3.1 – Synthesis of azole triflates

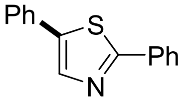
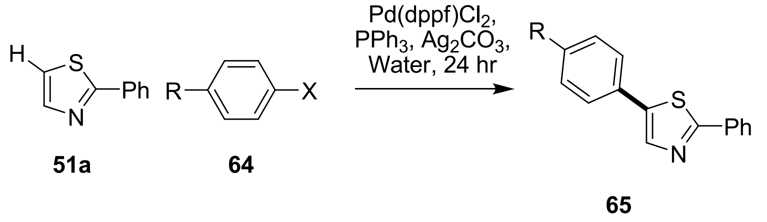
Ar-X	Conditions	Product	Yield
Ph-I	$Pd_2(dba)_3$, PPh_3, Cs_2CO_3, CH_3CN, AgF, 60°C 3 days	 **65a**	69
Ph-Br	$Pd_2(dba)_3$, PPh_3, Cs_2CO_3, CH_3CN, AgF, 60°C 3 days		0
Ph-OTf	$Pd(OAc)_2$, PPh_3, Cs_2CO_3, CH_3CN, AgF, 60°C 3 days		10
Ph-OTf	$Pd_2(dba)_3$, PPh_3, Cs_2CO_3, CH_3CN, 60°C 3 days		0

Table 2.3.1

The initial results are shown in Table 2.3.1, the initial screen was carried out before the purity of the starting material was identified as a crucial factor. Using iodobenzene the reaction proceeded as expected, but disappointingly no product was observed with bromobenzene. Reaction with phenyltriflate proceeded poorly giving a number of side reactions. The reaction was repeated without silver fluoride in an attempt to further investigate the role of the silver salt (if it is acting solely as a halophile then it should not be necessary in the reaction with phenyltriflate), but no conversion was seen. It seems likely that as well as serving a halophile function the silver may also bind to the sulfur of the thiazole ring and prevent it from binding to the palladium thereby retaining an active form of the catalyst. Before azole triflates can be coupled by this reaction further optimisation work needs to be carried out to couple thiazoles to other aryl triflates.

Once the reaction conditions were more fully understood this area was returned to. No significant improvement was seen in the case of aryl triflates however, it was discovered that arylbromides could indeed react in this transformation, (Scheme 2.3.2). Aryl bromides are more attractive than aryl iodides on a number of grounds. Firstly they are generally less expensive, secondly a wider variety are commercially available and thirdly, they can be considered to be greener on the basis that the bromide ion has a smaller molecular weight than iodide and that a larger proportion of the mass of the aryl halide is incorporated into the product making the process more atom efficient.



R	X = I 60°C	X = Br 80°C
Cl	95	46
Me	97	44
OMe	>99	38
NO_2	67	37
H	87	50

Scheme 2.3.2 – Reaction of aryl iodides and bromides with 2-phenylthiazole

Unfortunately aryl bromides are significantly less reactive than aryl iodides even at the slightly elevated temperature of 80°C. At temperatures higher than this there was significant amounts of homocoupling of the 2-phenylthiazole.

The reaction of 2-phenylthiazole with aryl chlorides was also attempted. However, even at 100°C no reaction was seen. Aryl chlorides are reluctant to undergo oxidative addition and usually require both high temperatures and bulky electron-rich ligands. Both aryl bromides and aryl chlorides may be shown to be valid reaction partners in the future with further optimisation of the reaction conditions.

2.4. Arylation of Other Heterocycles

We have described a powerful method of direct arylation that has been developed for the arylation of a range of 2-arylthiazoles. In order to demonstrate the power of such a method, and the generality of a mild aqueous arylation protocol, the application of it to a variety of other thiazoles and indeed other heterocyclic motifs has been investigated.

Various examples of direct arylation conditions have been reported in the literature.[108,111,124,134-141] In general, however, these conditions are only applicable to a limited number of heterocycles and of these they may not have good selectivity. Furthermore they often involve the use of high boiling solvents such as dimethylacetamide, dimethylformamide or dimethylsulfoxide which can be difficult to remove from reaction mixtures. In general there are few examples where the developed procedure has broad applicability over a wide range of compounds.

We sought to apply our conditions to the synthesis of a number of other aryl heterocycles. The results are shown in Figure 2.4.1, the conditions have been shown to not only be applicable to thiazoles, but also to oxazoles, thiophenes, benzothiophenes, benzoxazoles, benzimidazoles as well as benzofuran, although less effectively to a furan ring system. This is unsurprising as furan is less aromatic than thiophene with more di-ene character. The water chemistry has been further developed within the Greaney group by Stephan Ohnmacht and extended to the arylation of oxazoles.[137] As far as I am aware, the water conditions described above represent the first example of catalytic direct arylation being carried out in aqueous media. In addition this remains the only example of a general arylation protocol for the arylation of heterocycles that proceeds at a temperature less then 125°C.

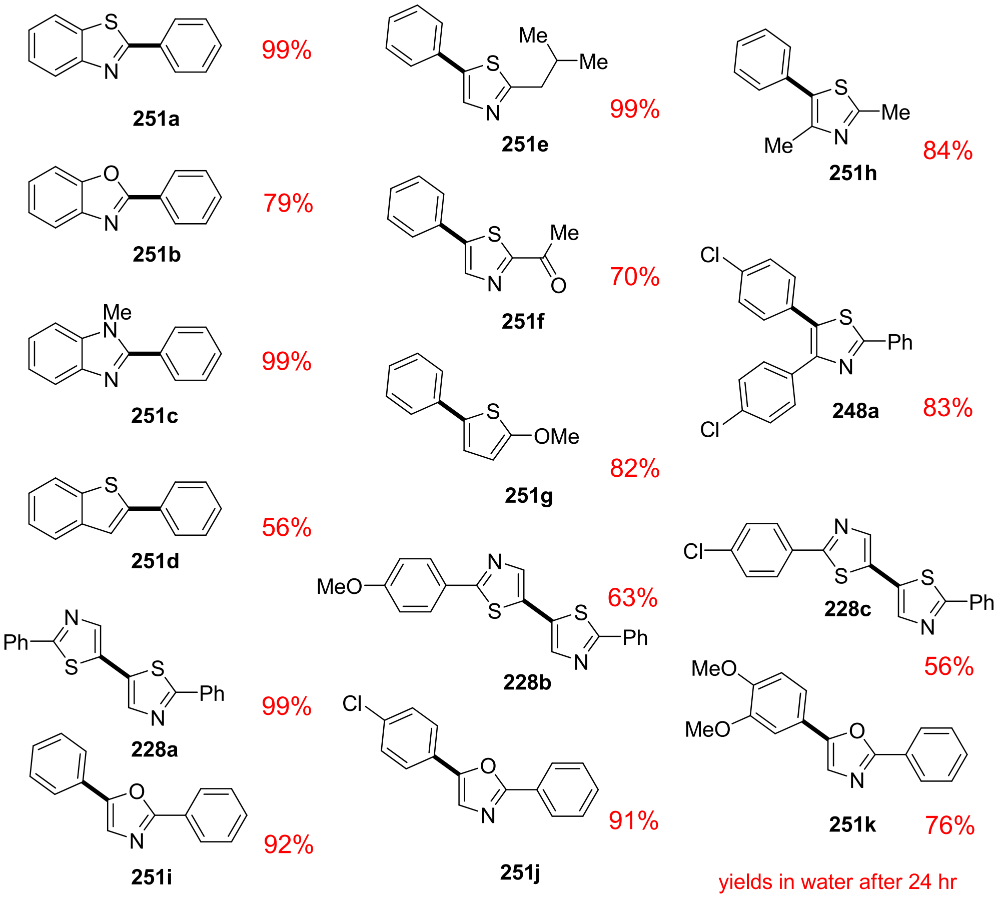
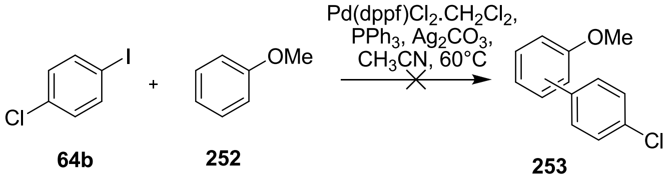


Figure 2.4.1 – Products from water conditions

2.5. Carbonylation and other C-H activations

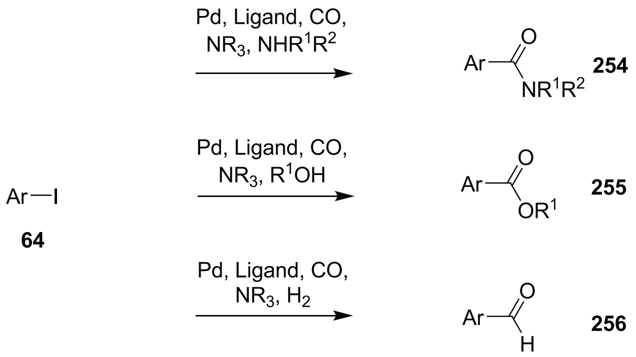
In addition to the arylation of other heterocycles, and in light of the recent advances in arylation at unactivated aryl C-H bonds,[61,62,142] it was attempted to apply the water conditions to the direct arylation of aryl C-H bonds in the absence of directing groups, (Scheme 2.5.1).



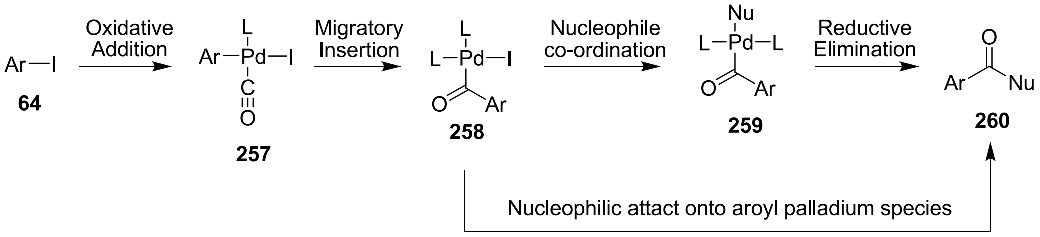
Scheme 2.5.1 – Initial attempts at direct arylation of unactivated CH bonds

Anisole (1 equiv) and iodochlorobenzene (1.2 equiv) were subjected to the previously developed conditions for 72 hr. After this time a new spot was seen by tlc, however, when the product was isolated it was determined to be the homocoupled aryl iodide. Following on from this, a large excess of anisole (20 equiv) was used, again at 60°C, but only homocoupled aryl iodide was recovered, although in much smaller amounts. Increasing the temperature to 100°C and conducting the reaction both under reflux in a sealed tube failed to provide any product other than homocoupled aryl iodide. As no reaction had been observed, attention was turned back to aspects of the direct arylation of thiazoles.

Carbonylation of aryl halides is a well documented area of palladium chemistry,[143] it is frequently used to introduce aldehydes, esters and amides in a convergent and atom economical sense, (Scheme 2.5.2). In other examples reaction of the aroyl palladium intermediate with a nucleophile can lead to the formation of ketones,[144,145] (Scheme 2.5.3).

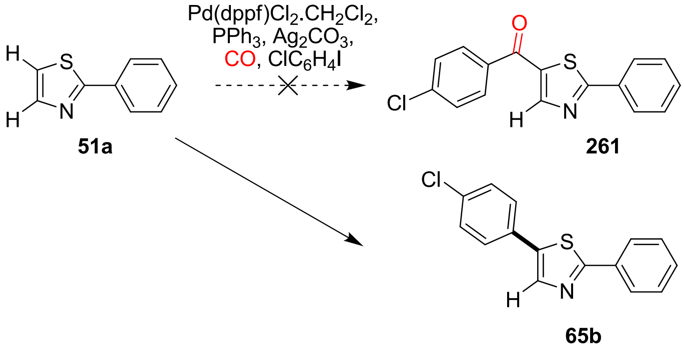


Scheme 2.5.2 – Carbonylations



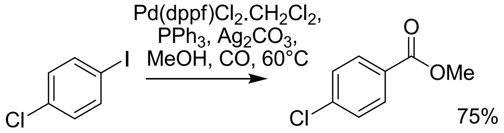
Scheme 2.5.3 – Carbonylation mechanism

It was envisaged that 2-phenylthiazole could be used as the nucleophile in a carbonylation reaction. Initially 2-phenylthiazole was subjected to the silver carbonate conditions in water, under one atmosphere of carbon monoxide supplied by balloon. After five hours only 5-(4-chlorophenyl)-2-phenylthiazole was isolated, (Scheme 2.5.4) and repeating the reaction in acetonitrile but for seventy-two hours, gave the same result.



Scheme 2.5.4

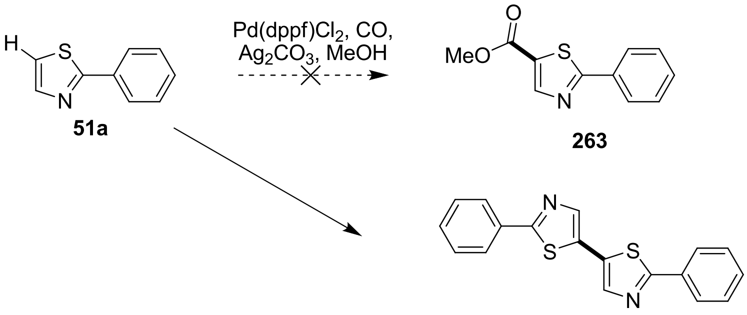
In order to further investigate the procedure 4-iodochlorobenzene was subjected to carbonylation conditions (Pd(dppf)Cl_2.CH_2Cl_2, triphenylphosphine, silver carbonate under one atmosphere of carbon monoxide in methanol), Scheme 2.5.5. This furnished the expected methyl-4-chlorobenzoate, **262**, in 75% yield proving the technique was not faulty.



64b **262**

Scheme 2.5.5

In addition to the attempted carbonylation-direct arylation we were also interested in a oxidative direct arylation-carbonylation sequence whereby 2-phenylthiazole could be carbonylated and then reacted with an alcohol to give **263** without the need for the thiazole to be pre-functionalised as a halide, (Scheme 2.5.6).



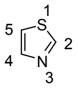
51a **263** **228a**

Scheme 2.5.6 – Oxidative carbonylation

In practice however, at 60°C in methanol only the thiazole dimer, **228a**, was isolated. It was thought that perhaps the problem lay in the carbon monoxide pressure. Unfortunately, no pressure vessels were available. As such this avenue of research was abandoned.

2.6. Conclusions

To summarise, a powerful, generally applicable method has been developed for the direct arylation of thiazoles. The conditions have also been shown to be applicable to a number of other heterocyclic motifs. It has been attempted to apply the conditions to electron-rich aromatic rings but further research is necessary to determine whether this is possible. In addition it has been attempted to incorporate a carbonylation into the direct arylation sequence. Preliminary reactions showed that this does not occur under our conditions in acetonitrile or water at 60°C. In a similar manner, attempted oxidative carbonylation of 2-phenylthiazole in methanol also failed to react in the expected manner.



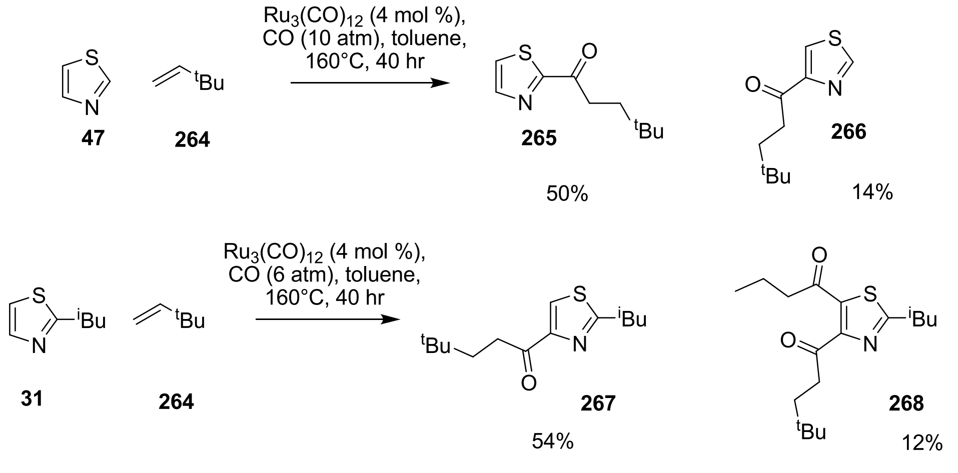
3. Arylation at thiazole C4

The prevalence of directing group chemistry in the literature has prompted the investigation and development of a directing group strategy for arylation of the thiazole C4 position.

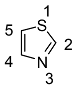
The work towards C-H activation at thiazole C5, described in chapter 2, has shown little inclination of the C4 position to react, even when it is the only unfunctionalised position left in the thiazole ring. It is envisaged that forcing conditions will be necessary to activate the C-H bond, and that the use of a directing group may also be necessary to effect a transformation.

3.1. Precedents and strategies

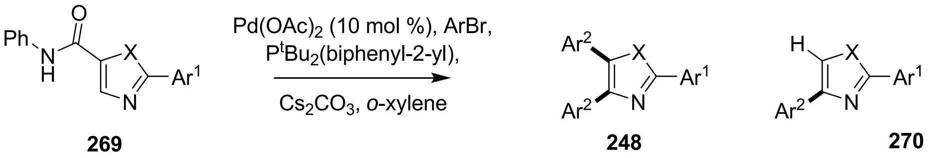
The first example of C-H activation at the thiazole C4 position was reported by Murai *et al* in 2000.[146] They used the nitrogen in the heterocycle to direct a ruthenium mediated carbonylation the the thiazole C4-H, (Scheme 3.1.1). Whilst highly impressive, the harsh conditions make this a prohibitive strategy for C-H activation.



Scheme 3.1.1 – Murai's thiazole C4-H functionalisation



The only example of palladium mediated substitution at C4 of an azole ring comes from Miura *et al*,[93] they use a sacrificial directing group to direct the palladation to C4, then decarbamoylation followed by cross coupling at C5 gives the 4,5-biarylated product, **248**, (Scheme 3.1.2).



X = S	86%	0%
X = O	33%	20%

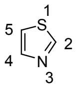
Scheme 3.1.2

For thiazole this proceeds with good yields, up to 86%, but is less successful with oxazole, only 33% although up to 20% of the 2-phenyl-4-aryl product, **270**, is formed as well. This is probably the most important result of this research. If the reaction can be stopped after the first arylation before the decarbamoylation, then this could be done in a separate step allowing access to 4-substiuted thiazoles and oxazoles.

On first inspection of the thiazole ring there are a number of possibilities for C-H activation at the C4 position. These can be divided into 3 main categories:

Directing group appended to N3
Directing group at C5
Non-directed arylation

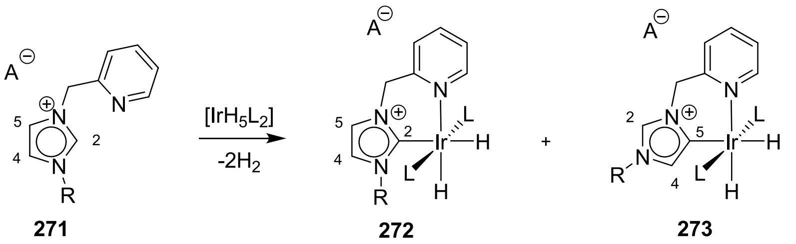
These catagories will be discussed in the subsequent sections.



3.2. Directing groups appended at N3

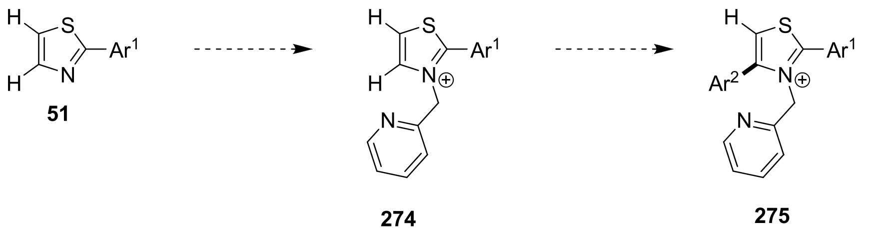
3.2.1. Quaternised thiazoles

It is well documented that the thiazole nitrogen can be quaternised to form a thiazolium salt.[147,148] Appending a directing group to the ring nitrogen was identified as being a way to incorporate a directing group that could easily be removed in a pseudo-deprotection/deactivation step. The use of a directing group in a similar way has been demonstrated by Crabtree *et al* in their synthesis of unusual imidazolium iridium carbenes, at the five position, **273**, as opposed to the usual two position, **272**.[149] In a thiazole analogy, this would correspond to an activation of the unreactive four position.



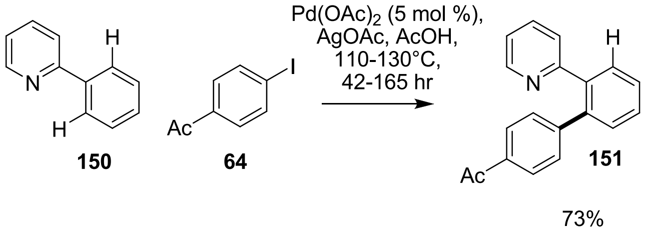
Scheme 3.2.1 Crabtree's unusual iridium carbenes, selectivity is controlled by the anion, A$^-$.

The first step in this strategy would be to incorporate a tethered pyridine into the thiazole motif, **274**, followed by a C-H activation step, (Scheme 3.2.1 and Scheme 3.2.2). An advantage to this approach is the deactivation of the thiazole ring by the quaternisation step. This should prevent the electrophilic addition mechanism from occurring at C5 by decreasing the electron density of the aromatic ring. In addition to the ease of incorporation of the directing group, it should be readily removed.

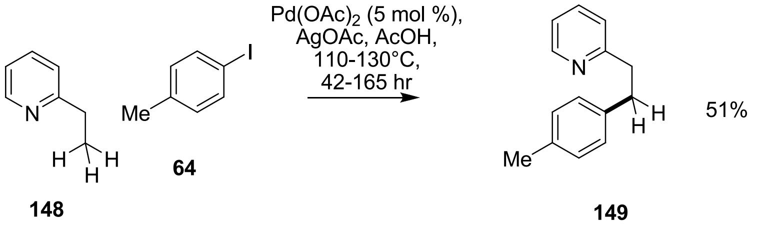


Scheme 3.2.2 Proposed reaction scheme with a methylpyridine group appended from the thiazole nitrogen

The use of pyridines as directing groups has been demonstrated by a number of groups in recent years.[95,100-102,111,150-154] Notably, Daugulis employed them, not only to arylate aromatic C-H bonds but also to effect an sp^3 C-H activation under unprecedentedly mild conditions, (Scheme 3.2.3 and Scheme 3.2.4).[100,101]

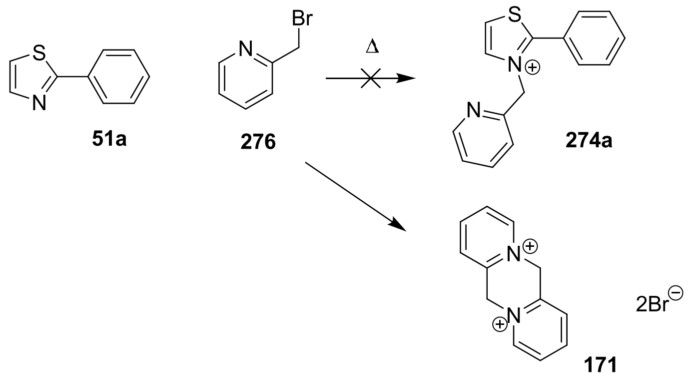


Scheme 3.2.3



Scheme 3.2.4

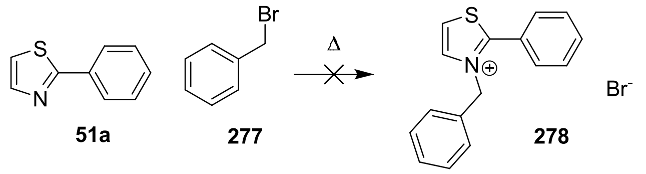
The synthesis of the quaternised thiazole was based on Tubaro's synthesis of the oxazole analogue,[155] 2-(bromomethyl) pyridine was isolated as the free base, then heated together with 2-phenylthiazole, both by conventional means and by microwave radiation, rather than leading to the expected product, a dimer of 2-(bromomethyl)pyridine, **171**, was obtained, (Scheme 3.2.5).



Scheme 3.2.5 – Reaction of 2-phenylthiazole and 2-bromomethylpyridine

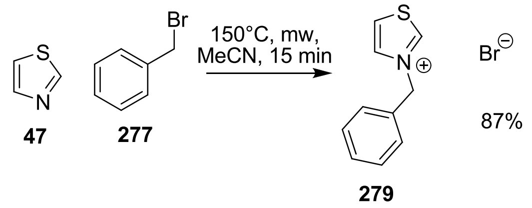
In hindsight this was to be expected, the pyridine nitrogen is far more nucleophilic than the thiazole nitrogen. The reaction was therefore repeated with the hydrobromide pyridine salt. Again, no product was isolated from the reaction.

It is known that 2-unsubstituted thiazoles can be quaternised with benzyl bromides[156-158] and that 2-phenylthiazole can be quaternised by methyl iodide.[159] In order to prove that 2-phenylthiazole can be quaternised by a group larger than methyl iodide, the reaction was repeated with benzyl bromide, (Scheme 3.2.6).



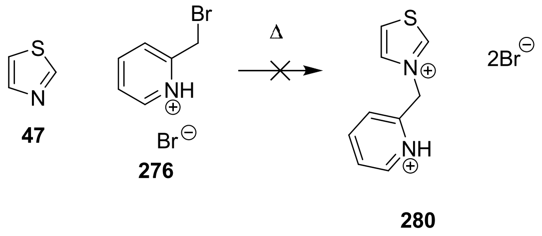
Scheme 3.2.6 – Attempted quaternisation of 2-phenylthiazole with benzyl bromide

Again, no product was formed, either under conventional or microwave heating. Since it has been documented that thiazole can be quaternised with benzyl bromide it was decided to replicate this as a model before attempting the reaction with 2-(bromomethyl)pyridine, (Scheme 3.2.7).



Scheme 3.2.7

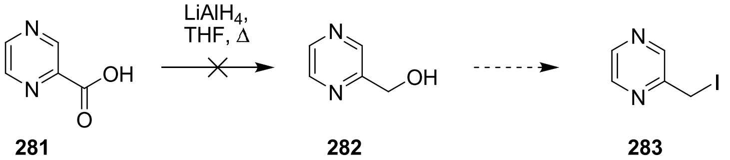
This reaction did provide the expected product. The reaction with 2-(bromomethyl)pyridine HBr salt was attempted but no product was isolated (Scheme 3.2.8). As the pyridine salt was positively charged, the reaction to form the doubly charged species would be disfavoured. Reacting with the free base again formed the dimer, **171**.



Scheme 3.2.8

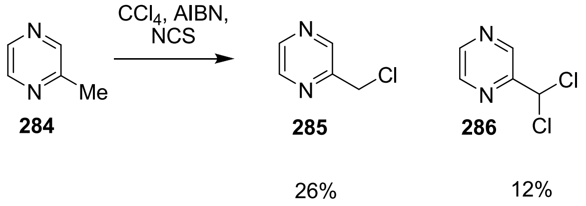
With the problem of the thiazole nitrogen nucleophilicity, it was decided that reaction with a less nucleophilic directing group might be an alternative.

A pyrazine group was chosen in place of the pyridine. 2-Halomethylpyrazines are not commercially available. The synthesis was approached as follows in Scheme 3.2.9.



Scheme 3.2.9 – Attempted synthesis of iodomethylpyrazine

The reduction of the acid proved impossible under lithium aluminium hydride conditions. Instead, radical chlorination of methylpyrazine was attempted, (Scheme 3.2.10).

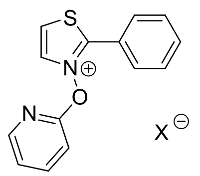


Scheme 3.2.10 – Formation of chloromethylpyrazine

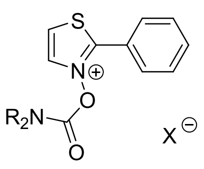
The desired compound was isolated as the major component of a mixture of mono, **285**, and dichlorinated compound, **286**. The crude mixture was reacted with thiazole but again, no product was isolated. As a 2-unsubstituted thiazole would give problems of C2 or C4 regioselectivity and potentially C2 carbene formation[158,160] together with the difficulties inherent in the preparation and purification of these quaternised thiazole compounds it was decided to abandon this strategy.

3.2.2. Thiazole N-oxides

Thiazole N-oxides are well characterised and the oxide can be easily reduced back to the thiazole ring. It was envisaged that directing groups could be attached to the thiazole nitrogen by way of an oxygen linker rather than a carbon linker. The following compounds were identified as targets.

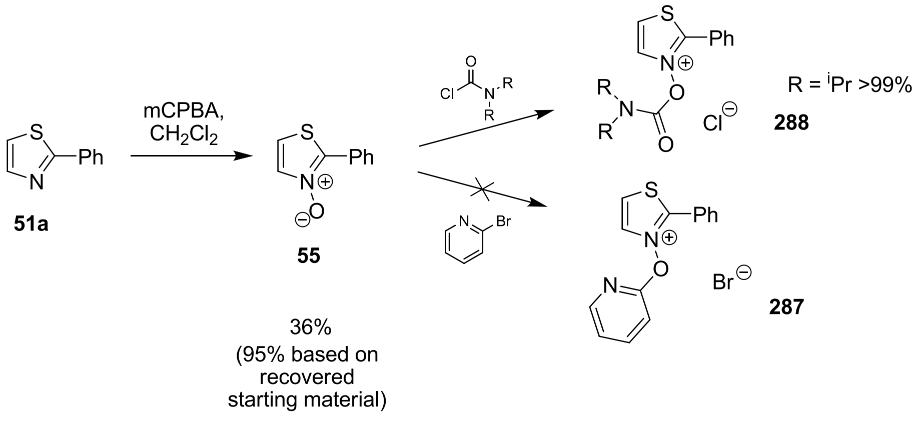


287



288

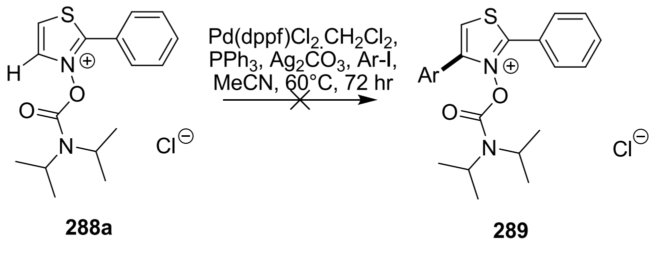
2-Phenylthiazole was successfully oxidised to 2-phenylthiazole-3-oxide, **55**, with *m*CPBA in CH_2Cl_2, (Scheme 3.2.11). The yield was relatively poor at only 36%, but the remainder of the starting material could be recovered and recycled.



Scheme 3.2.11 – N-oxide directing group strategies

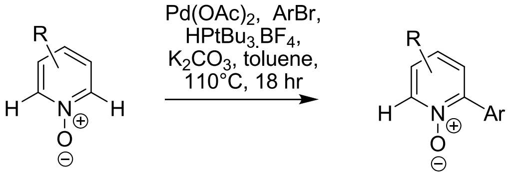
Unfortunately, under a number of conditions, (DMF, 150 °C, mw, 15 min; neat 150 °C, 2 hr; MeCN, reflux, 18 hr) the nucleophilic aromatic substitution with 2-bromopyridine did not yield the desired product, **287**.

An alternative to the pyridine directing group, a carbamate, could be attached through the N-oxide. This was prepared from 2-phenylthiazole-3-oxide in quantative yield, (Scheme 3.2.11). With this compound in hand, it was subjected to the acetonitrile conditions developed for arylation at the thiazole C5, (Scheme 3.2.12), no identifiable products were obtained.



Scheme 3.2.12

Following on from this a number of reactions were attempted in order to establish whether the compound would directly arylate at C4 in toluene, dioxane, methanol, DMF and DMSO. Of these conditions not a single one gave any identifiable products. A number of control reactions were therefore run with the capped thiazole-3-oxide, **289**; in acetonitrile at 60 °C the compound decomposed to an unidentifiable mixture. Similarly, it decomposed under both acidic and basic conditions, in the presence of water and with heating. As such, the compound was not suitable for directing arylation to the C4 position.

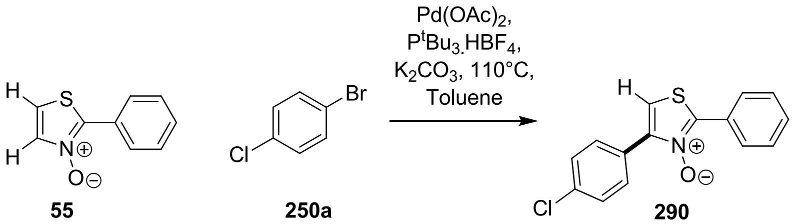


194 **195**

10 examples, yields 74-95%

Scheme 3.2.13 - Fagnou's pyridine N-oxide arylation

Following Fagnou's work on the arylation of pyridine N-oxides,[107,161] (Scheme 3.2.13) it was decided to investigate the arylation of 2-phenylthiazole-3-oxide. Applying Fagnou's conditions to 2-phenylthiazole-3-oxide did give a product albeit in low yield, (Scheme 3.2.14).

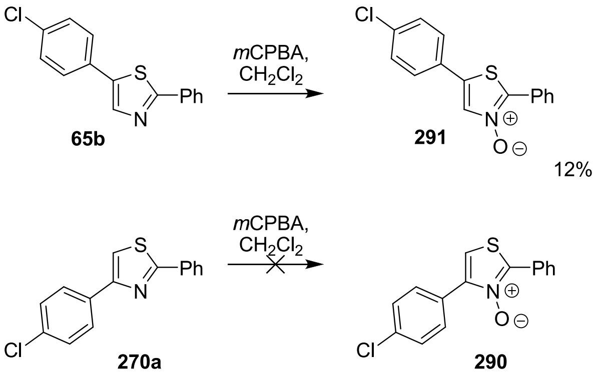


55 **250a** **290**

4% yield

Scheme 3.2.14 – Fagnou's conditions applied to 2-phenylthiazole-3-oxide

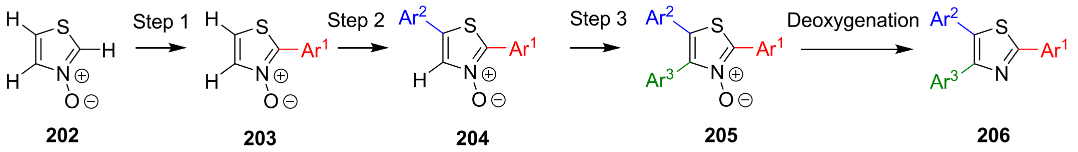
It proved difficult to purify the compound for characterisation. As such, it was attempted to make the expected compound by other means to compare the spectra. 4-(4-Chlorophenyl)-2-phenylthiazole, **270a**, and 5-(4-chlorophenyl)-2-phenylthiazole, **65b**, were oxidised with *m*CPBA in CH_2Cl_2, (Scheme 3.2.15). 4-(4-Chlorophenyl)-2-phenylthiaozle failed to give any product under these conditions. When the spectra (^1H, ^{13}C NMR) of the product from the directed arylation reaction was compared to 5-(4-chlorophenyl)-2-phenylthiazole-3-oxide, **291**, they were found to be identical. This shows that any directing effect of the N-oxide does not overcome the reactivity of the ring towards arylation at C5. This suggested that the C5 position may need to be blocked in order for arylation to occur at the C4 position. Attention was therefore turned towards incorporating a directing group at the C5 position of the ring.

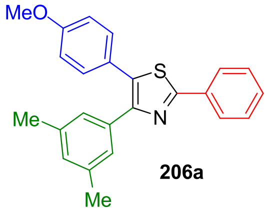
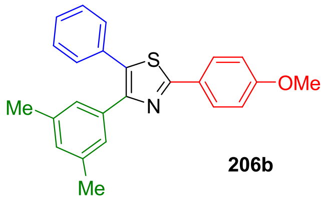
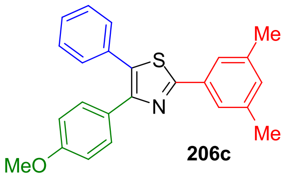


Scheme 3.2.15 – Oxidation of 2,5- and 2,4-diarylthiazoles

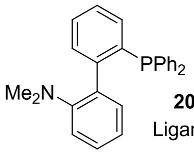
More recently this reaction has been reported by Fagnou *et al*[108] and, in order to get arylation at the C4 position of the thiazole ring the C5 position does need to be blocked. Their methodology provides an elegant and concise route to trisubstituted thiazoles in a convergent fashion, see Figure 3.2.1.

Figure 3.2.1 – Fagnou's thiazole N-oxide chemistry



Step	 **206a**	 **206b**	 **206c**
1	84	69	76
2	86	80	85
3	59	64	84
Deoxygenation	72	66	64

Conditions:
Step 1 - ArI, $Pd(OAc)_2$, Ligand 1, Cs_2CO_3, pivalic acid, CuBr, toluene, 25°C
Step 2 - ArBr, $Pd(OAc)_2$, $HP^tBu_3.BF_4$, K_2CO_3, toluene, 70°C
Step 3 - ArBr, $Pd(OAc)_2$,PPh_3, K_2CO_3, Toluene, 110°
Deoxygenation - Zn powder, NH_4Cl, THF



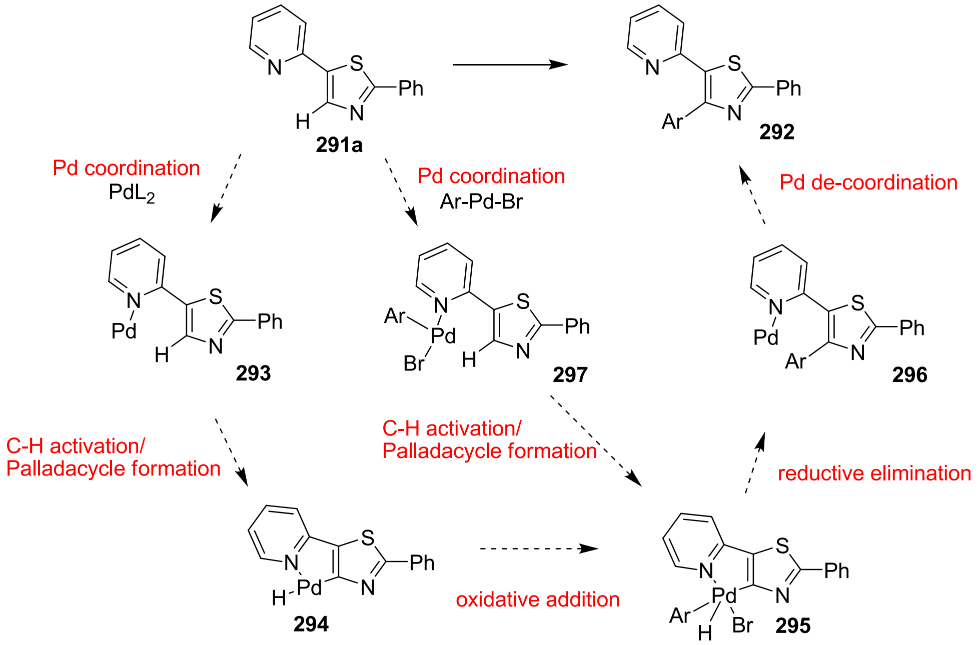
207
Ligand 1

3.3. Directing Groups at C5

3.3.1. Pyridine directing groups

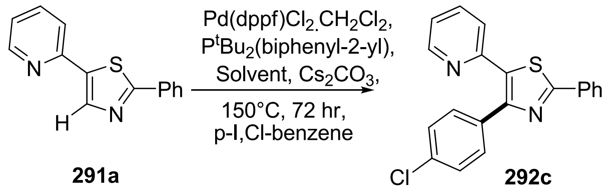
Chapter one described the use of a number of directing groups to promote direct arylation at specific C-H bonds. The most commonly employed directing group is the pyridine ring.[65,101] It is a known ligand for palladium and as such has shown considerable aptitude for the activation of C-H bonds.[65]

Initial interest was focussed on the arylation of 2-pyridyl-(2-phenylthiazol-5-yl), **291a**, systems in order to assess whether pyridine could, in fact, direct palladium catalysed arylation to the thiazole C4 position. It was envisaged that the reaction may proceed along the mechanism in Scheme 3.3.1; whereby initial coordination of the pyridine nitrogen to the palladium (**293** or **297**), would bring the palladium close enough to the thiazole C4-H bond to facilitate a C-H activation step, forming a five-membered palladacycle (**294** and **295**). A subsequent oxidative addition of an aryl halide followed by reductive elimination and decomplexation of the pyridine would give the expected product.



Scheme 3.3.1 – Possible mechanism for pyridine directed C-H activation

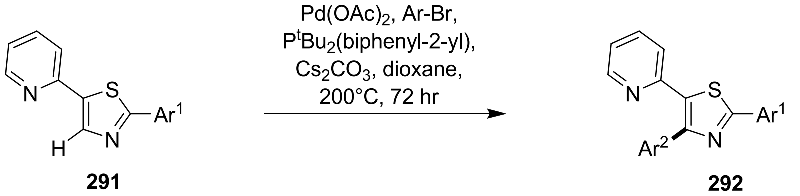
Daugulis and co-workers reported a pyridine mediated direct arylation of sp^2 and sp^3 C-H bonds.[100,101] Repeating their conditions, ($Pd(OAc)_2$, AgOAc, AcOH, 130 °C for 72 hr)[100] gave no product. However, using $Pd(dppf)Cl_2$. P^tBu_2(biphenyl-2-yl), Cs_2CO_3 in *o*-xylene at 150 °C gave the product in 64% yield.



Solvent	Yield /%
Toluene	55
o-Xylene	64
Dioxane	62

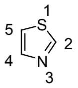
Scheme 3.3.2

The reaction was repeated in dioxane and toluene in sealed vials at 150 °C giving the results shown in Scheme 3.3.2. Whilst the yield was lower in dioxane, the reaction was considerably cleaner. Further to the initial results it was also found that in the absence of additional ligands no reaction was observed and that the added ligand needed to be bulky and electron rich; presumably this encourages the reductive elimination step in the mechanism,[132] which would be expected to be slow as it destroys a stabilised palladacycle intermediate. Under these conditions it was also found that aryl bromides were more reactive than aryl iodides. By increasing the temperature to 200 °C the yields of with aryl bromides could be increased. A number of 5-pyridyl-2,4-diarylthiazoles were synthesised under the conditions shown in Scheme 3.3.3. The results are shown in Table 3.3.1.



Scheme 3.3.3 – General scheme for the synthesis of 5-pyridyl-2,4-diarylthiazoles

It can be noticed that where the substrate contains an aryl chloride the reaction, in general, proceeds less smoothly. It is likely that with the high temperatures and



electron rich ligands employed that there is a certain amount of oxidative addition occurring into the aryl-chloride bond.[162]

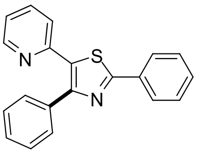
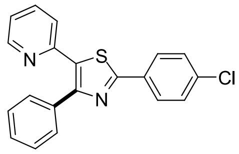
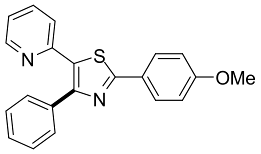
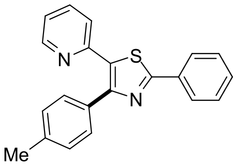
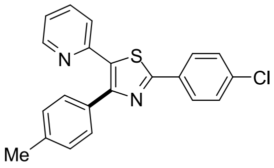
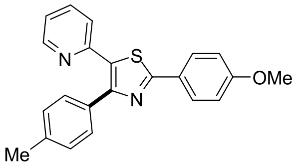
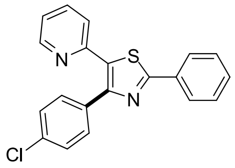
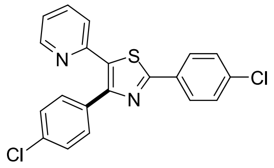
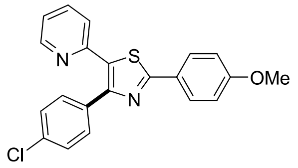
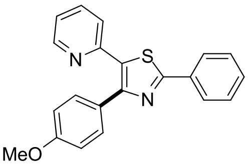
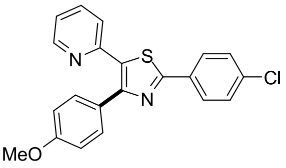
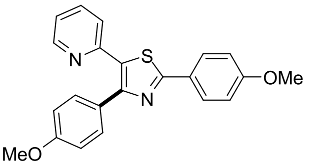
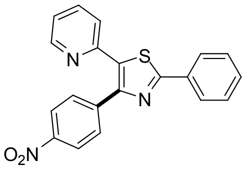
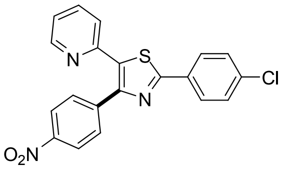
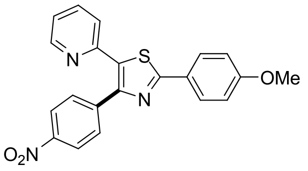
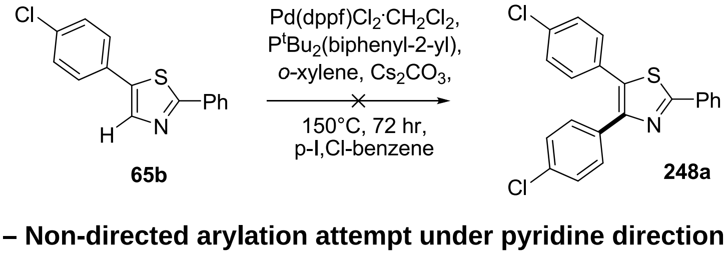
Compound **292a-e**	Yield	Compound **292f-j**	Yield	Compound **292k-p**	Yield
	88%		92%		56%
	70%		44%		41%
	64%		61%		36%
	44%		21%		22%
	88%		11%		56%

Table 3.3.1 – 5-Pyridyl-2,4-diarylthiazoles

In order to show that there is a directing effect, the reaction was repeated with 5-(4-chloro)-2-phenylthiazole, **65b**, but gratifyingly, no reaction was observed.

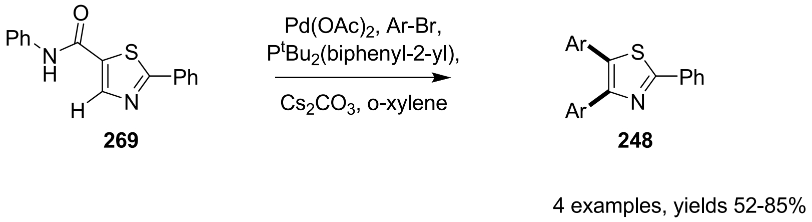


Scheme 3.3.4 – Non-directed arylation attempt under pyridine direction conditions

As the pyridine direction has shown directed arylation to work well for the arylation of the thiazole C4 position, it was decided to focus attention of the incorporation of a removable directing group at the C5 position.

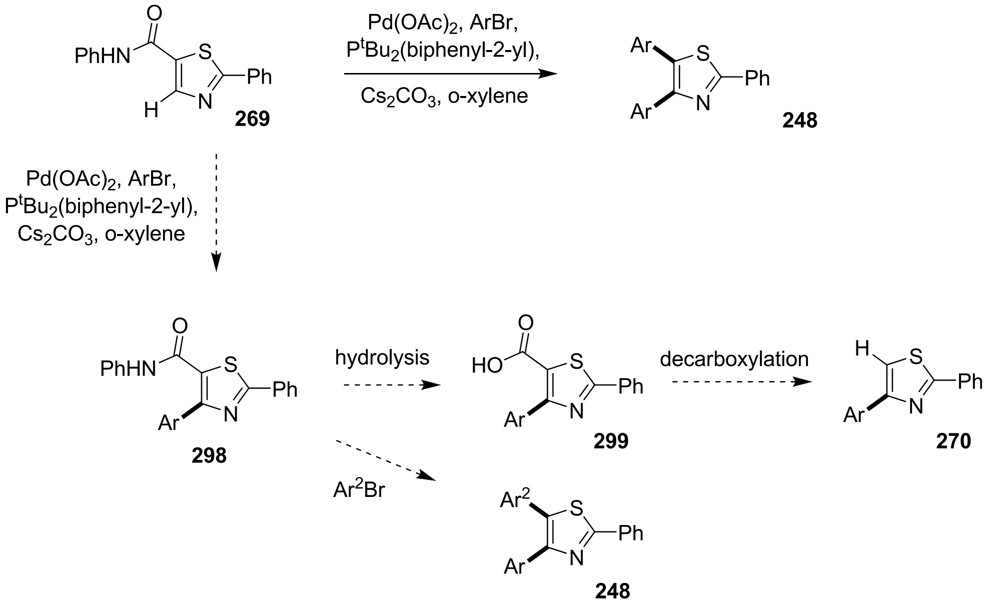
3.3.2. Phenyl amide

In 2003, Miura *et al* published the first example of a palladium mediated process for arylation of the thiazole C4 position, (Scheme 3.3.5).[93] This remained the only example of a palladium mediated C4 arylation of thiazole until Fagnou's thiazole N-oxide work was added to the area in 2008.[108]



Scheme 3.3.5 – Miura's 4,5-diarylation

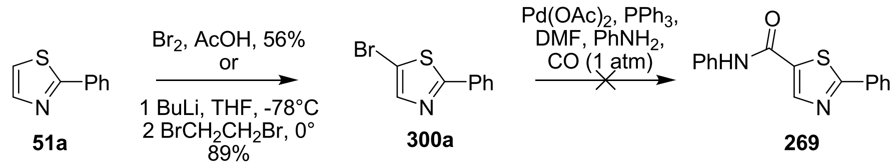
Miura's strategy utilises an amide in the C5 position of the thiazole to direct arylation to C4 before being lost in a separate step and arylation subsequently occurring at the C5 position as well.



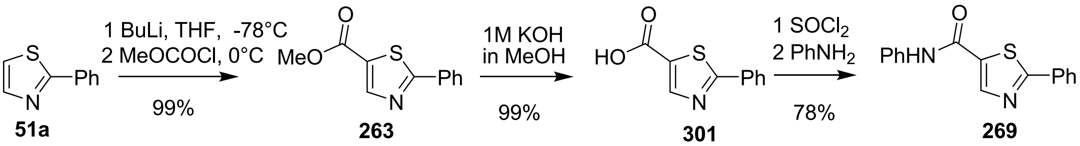
Scheme 3.3.6 – Proposed C4 arylation

If it could prove possible to separate these steps, then arylation of the thiazole C4 position would be feasible with a group in the C5 positions that could be readily removed or elaborated to provide more complex molecules, (Scheme 3.3.6).

The synthesis of the phenyl amide starting material was described by Miura,[93] however, in our hands the carbonylation of 5-bromo-2-phenylthiazole did not proceed well, (Scheme 3.3.7). Nevertheless, an alternative route to the amide was envisaged, (Scheme 3.3.8), which provided the material in good yield.



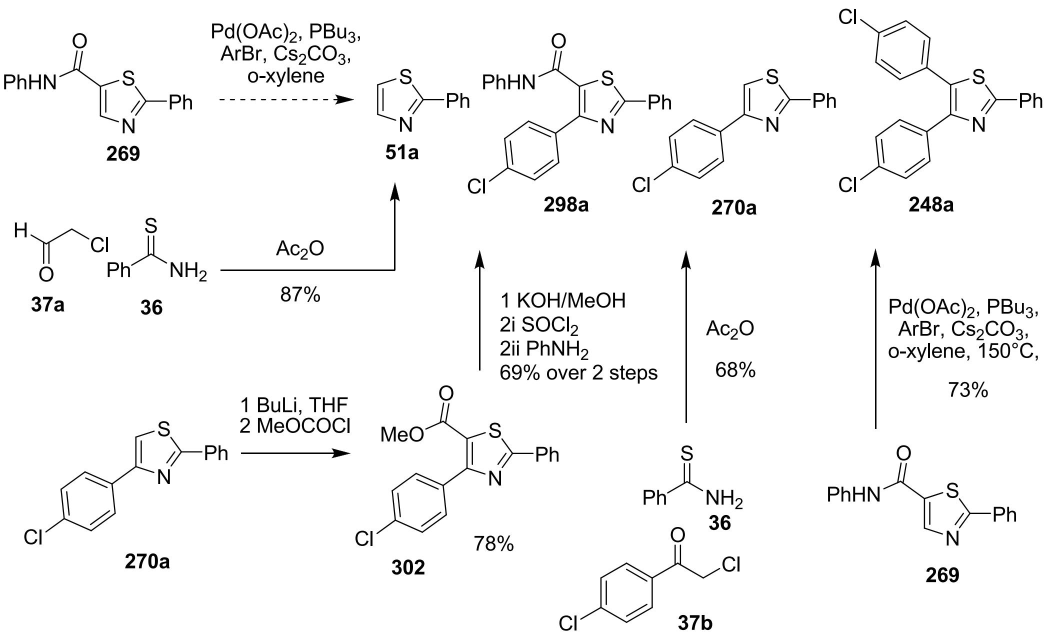
Scheme 3.3.7 – Carbonylation route to phenyl amide



Scheme 3.3.8 – Alternative route to phenyl amide

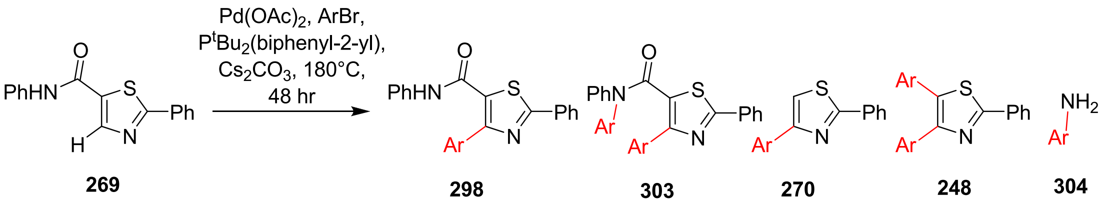
Before investigation of the stepwise arylation could be started, authentic samples of each of the potential products needed to be synthesised in order to allow the reactions to be monitored by HPLC. The syntheses are shown in

Scheme 3.3.9.



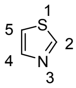
Scheme 3.3.9 – Synthesis of HPLC samples

Initally repeating Miura's conditions, but with tributylphosphine, at a lower temperature gave a mixture of diarylated product,**248**, and unreacted starting material, **269**, (see Table 3.3.2 for the optimisation conditions).



Scheme 3.3.10 – Possible arylation products

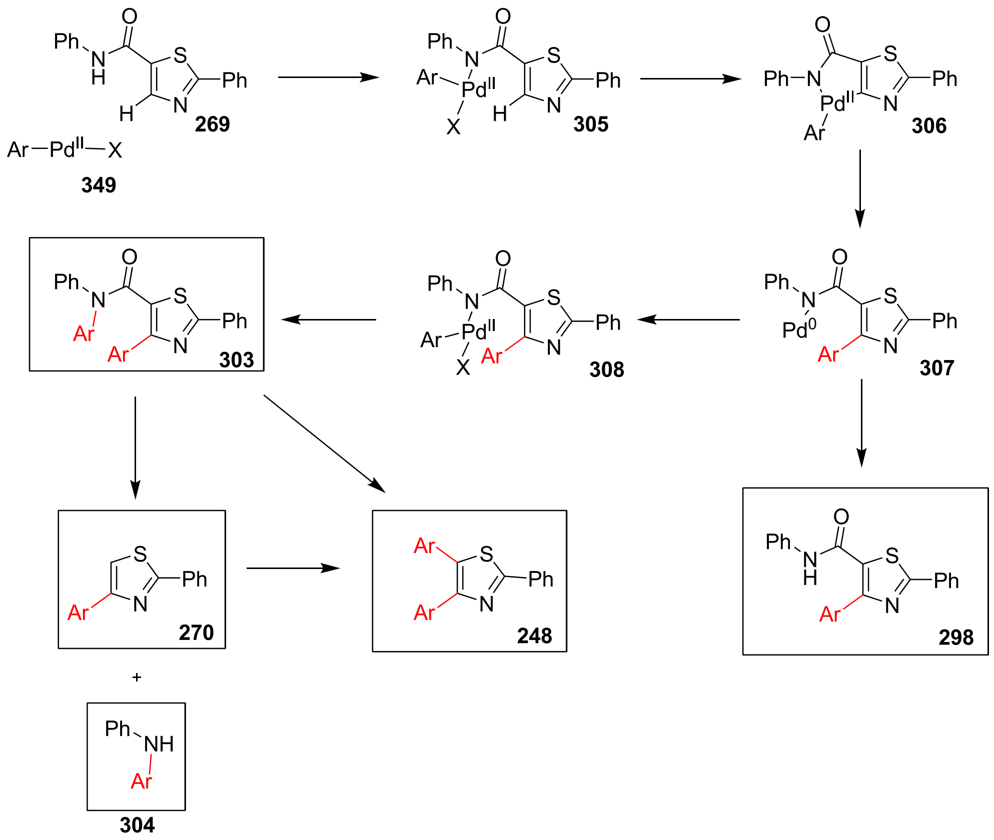
The number of possible products and intermediates in the reaction (Scheme 3.3.10) gave difficulties in identifying whether any desired products were formed. Whilst samples of the majority of the compounds had been made by other means, (Scheme 3.3.9), the compounds themselves proved difficult to separate by HPLC. Additionally, in the majority of cases the reaction solvent was *o*-xylene, itself a highly uv active compound, which masked the phenylamide starting material and the arylbromide in the HPLC traces.



Ar-X	Base	Ligand	Solvent	Temp /°C	Results
I	Cs_2CO_3	PBu_3	o-xylene	60	No reaction
I	Cs_2CO_3	PBu_3	o-xylene	80	No reaction
I	Cs_2CO_3	PBu_3	o-xylene	100	No reaction
I	Cs_2CO_3	PBu_3	o-xylene	120	Small amounts of **248**
I	Cs_2CO_3	PBu_3	o-xylene	150	Larger amounts of **248**
I	Cs_2CO_3	P^tBu_2(biphenyl-2-yl)	o-xylene	150	64% **248** isolated yield
Br	K_2CO_3	P^tBu_2(biphenyl-2-yl)	o-xylene	130	Trace of **298**
Br	K_2CO_3	none	o-xylene	130	Traces of **298** and **270**
Br	K_2CO_3	none	dioxane	160 mw	Reaction too dilute, failed to reach set temperature
Br	K_2CO_3	P^tBu_2(biphenyl-2-yl)	dioxane	160 mw	Traces of **298** + **303** reaction failed to reach set temperature
Br	K_2CO_3	P^tBu_2(biphenyl-2-yl)	dioxane	160	Traces of **298** + **303**
Br	Cs_2CO_3	P^tBu_2(biphenyl-2-yl)	dioxane	180	14% **270** large amounts of **269**
Br	Cs_2CO_3	P^tBu_2(biphenyl-2-yl)	o-xylene	180	Starting material consumed. 5% **270**, 60% **248**

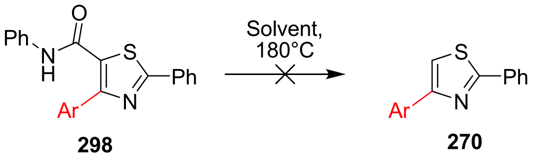
Table 3.3.2 – Optimisation C4 arylation using phenyl amide directing group

It was quickly seen that a high temperature was necessary to effect the C-H activation at C4. In addition, the reaction worked better with cesium carbonate than potassium carbonate, presumably due to the improved organic solubility. The use of a bulky, electron rich ligand such as 2-(di^{t}butylphosphino)-biphenyl-2-yl enhanced the reaction and prevented the deposition of metallic palladium. Presumably the bulky ligand promotes the the reductive elimination and collapse of the stable palladacyclic intermediate,[132] conversion of **306** to **307** in Scheme 3.3.11. In addition to the effect of base and ligand, there was a marked difference between the reaction being carried out in *o*-xylene or dioxane. In xylene the decarbamoylation step seemed to be favoured giving mainly the 4,5-diarylated product, **248**; in dioxane there was a much lower conversion of starting material, however, that which had reacted formed compounds **270** and **298**.



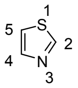
Scheme 3.3.11 – Proposed mechanism process

To determine the nature of the decarbamoylation step, **298** was heated in xylene at 180 °C overnight however, no decarbamoylation had taken place and only starting material remained, (Scheme 3.3.12).

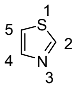


Scheme 3.3.12 – Decarbamoylation attempt

The amide, **298**, was also untouched in dioxane at 180 °C and in xylene in the presence of Cs_2CO_3, K_2CO_3, $Pd(OAc)_2$, PBu_3 and P^tBu_2(biphenyl-2-yl) individually

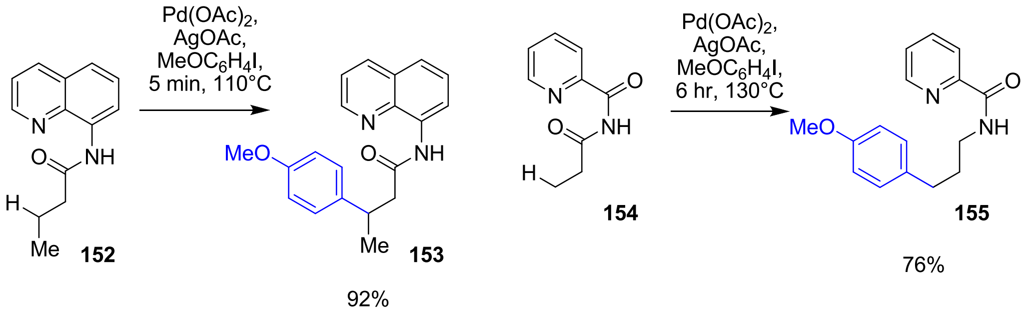


and in combinations akin to the reaction mixture. It was concluded that the decarbamoylation can only take place once the amide nitrogen has been arylated. With such high temperatures required to accomplish the C4-arylation, attention was turned to alternative amide directing groups that might cause the C4-H activation to be more facile.



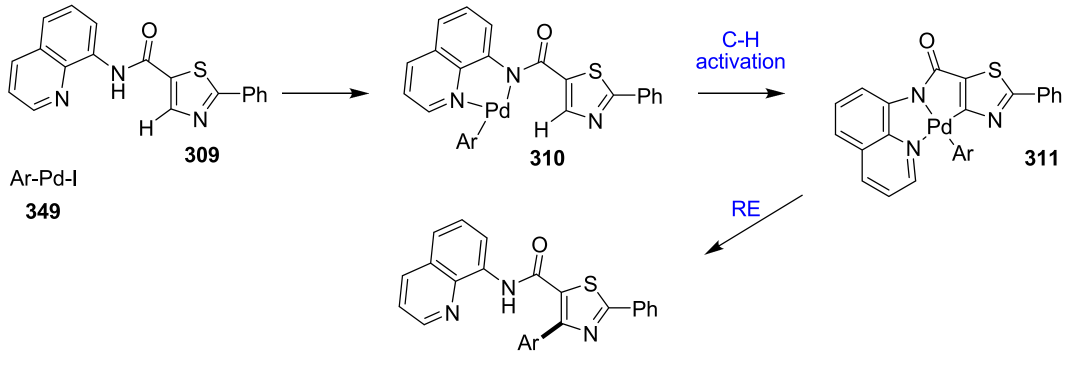
3.3.3. Quinoline amide

The concept of having a doubly chelating directing group was proposed by Daugulis and allowed direct arylation of sp^2 and sp^3 C-H bonds by incorporating a quinoline or picolinamide directing group through a tether,[101] (Scheme 3.3.13). Adding another chelation point to the amide, one that is better able to bind to the palladium should help to facilitate the C-H activation at the thiazole C4 position.



Scheme 3.3.13 – Daugulis' quinoline and picolinamide directing groups

In the case of thiazole C4 arylation, the incorporation of the quinoline amide would give the required five-membered palladacyclic ring system, **311**, (Scheme 3.3.14).



Scheme 3.3.14 – Doubly chelating directing group

Taking 2-phenylthiazole-5-carboxylic acid and reacting it with 8-aminoquinoline gave the required 2-phenyl-N-(quinolin-8-yl)thiazole-5-carboxamide, (Scheme

3.3.15). This compound proved to be exceptionally difficult to purify, being only sparingly soluble in almost all solvents. A number of different conditions were therefore attempted to identify which gave the cleanest reaction with the least need for further purification, see Table 3.3.3. Despite the yield not being the highest, the reaction with water soluble carbodiimide (EDCI) proved to give the cleanest material.

313 **301** **309**

Scheme 3.3.15 – Amide formation

Conditions	Yield of **309** /%
$SOCl_2$, Δ then 8-aminoquinoline, Et_3N, CH_2Cl_2	30
HATU, Et_3N, 8-aminoquinoline, CH_2Cl_2	38
EDCI, HOBt, Et_3N, 8-aminoquinoline, CH_2Cl_2	32

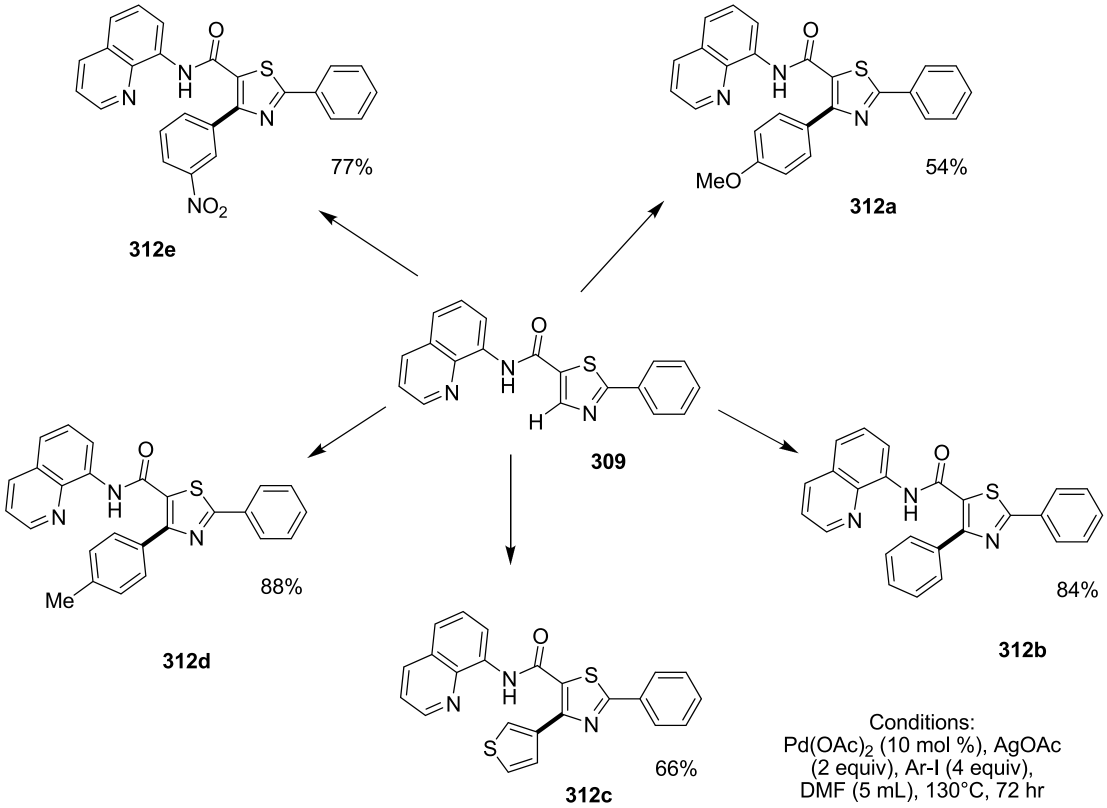
Table 3.3.3 – Conditions for amide formation

With the starting material in hand a brief screen of the variables was conducted, see Table 3.3.4. These conditions were based on Daugulis' original conditions. The arylation of thiazole C4 required more forcing conditions than the arylation of the amides used by Daugulis.

Conditions	Solvent	Equiv of AgOAc	Yield of **312a** %	Comments
110 °C, 24 hr	None	1.10	0	no reaction
130 °C, 4 hr	None	0.25	0	no reaction
130 °C, 24 hr	None	0.25	15	2.8:1 ratio of SM to prod
))) 2 hr	DMF	0.25	0	no reaction
150 °C, 5 min, mw	DMF	0.25	0	no reaction
130 °C, 72 hr	DMF	0.25	54	product formed but SM still present

Table 3.3.4 – Screen of variables for quinoline directing group

It was found that by adding extra palladium acetate at 24 hour intervals the reaction could be made to proceed further towards completion. These newly developed conditions were then applied to the synthesis of a number of 4-arylthiazoles, (Scheme 3.3.16).



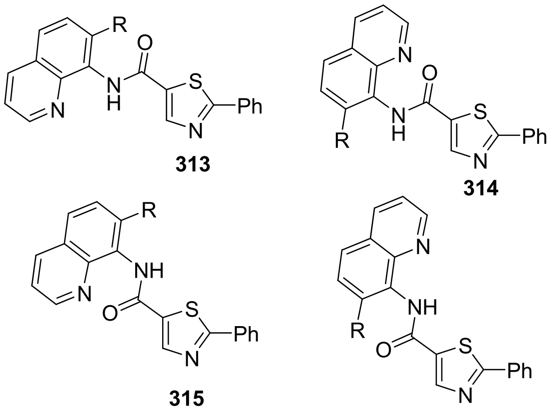
Conditions:
$Pd(OAc)_2$ (10 mol %), AgOAc (2 equiv), Ar-I (4 equiv), DMF (5 mL), 130°C, 72 hr

Scheme 3.3.16 – Quinoline amide results

The need to add extra palladium at intervals is detrimental to the overall appeal of the reaction. This is probably necessary due to the highly stabilised palladacyclic intermediates which may sequester the palladium. It is possible that this may be overcome by the use of bulky ligands which might help to break down the palladacyclic intermediate and turn over the catalyst, this warrants further investigation.

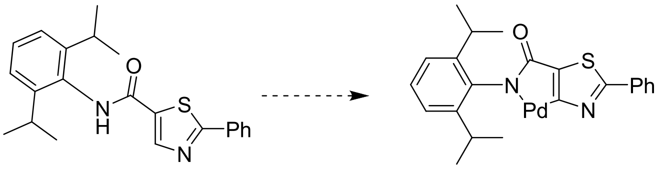
3.3.4. Other amides and mechanistic considerations

In both the case of the phenylamide and the quinoline amide the directed arylation reactions proceeded slowly despite the use of high temperatures. In order to improve these reactions it could be envisaged that the amide directing group could be engineered to provide more favourable characteristics for the reaction mechanism. For example: the quinoline amide, **309**, provides two chelating nitrogens there is no express reason for the chelated palladium complex to be aligned such that the thiazole C4-H bond would be in proximity to the palladium itself. By building in a certain amount of steric hindrance in the backbone of the directing group, it may be possible to bias the orientation of the chelating groups towards the C4-H bond, (Scheme 3.3.17 and Scheme 3.3.18).



313 **314** **315** **316**

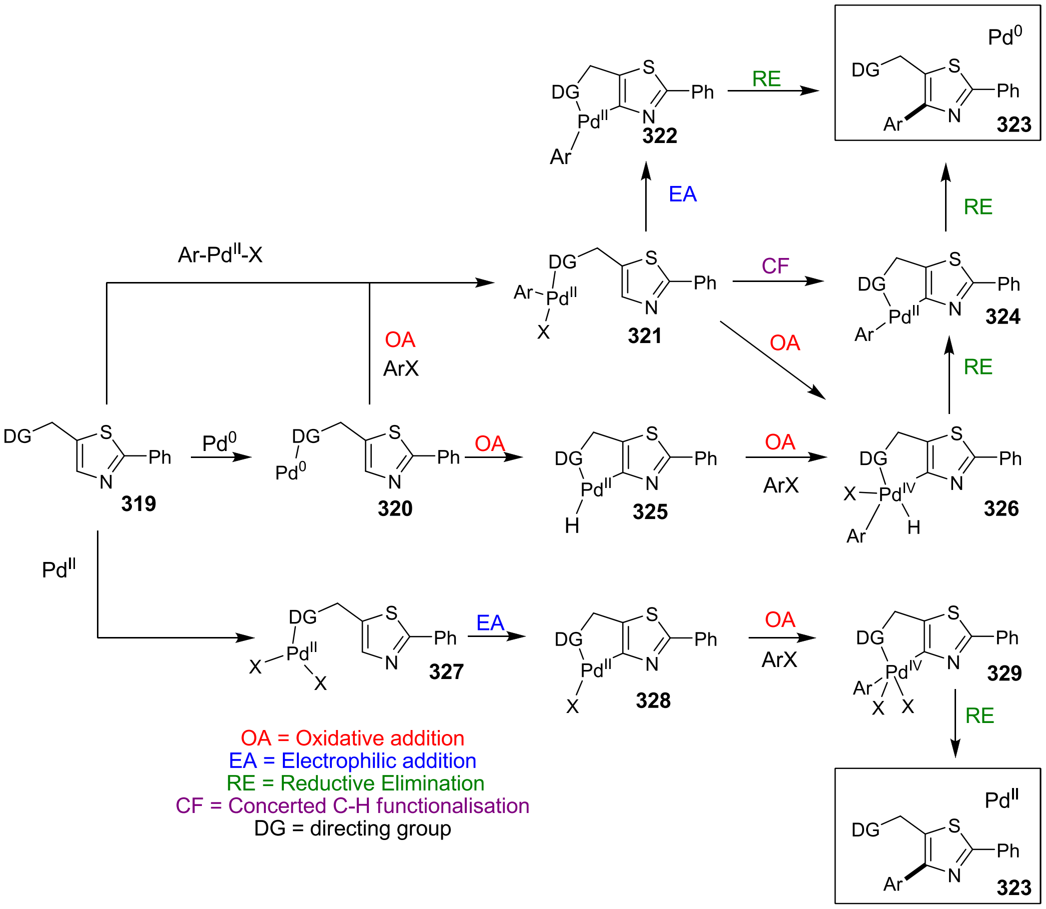
Scheme 3.3.17 – The various conformations of the quinoline amide



317 **318**

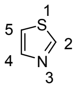
Scheme 3.3.18 – Steric bulk built into the directing group backbone

In addition this should cause some congestion around the palladium centre, promoting the reductive elimination of the product and therefore allowing the palladium catalyst to turn over. However, as in all palladium mechanisms, if this encourages reductive elimination it may discourage oxidative addition. In essence, if the oxidative addition occurs whilst the palladium is bound to the chelating groups (**320** to **321** or **328** to**329**) this may substantially hinder the reaction. If, however, oxidative addition occurs before coordination of the directing group to the palladium (**321** to**322**) then this may not be an issue, (Scheme 3.3.19).



Scheme 3.3.19 – Palladium oxidation states and possible mechanisms

There are a number of potential mechanisms that could be involved in the C-H activation step. Other mechanisms for C-H activation - metal carbene insertion[163] and radical-type metal processes are known processes for C-H functionalisation. In this case, however, neither is likely to be occurring. The possible mechanisms, are as follows in Table 3.3.5:



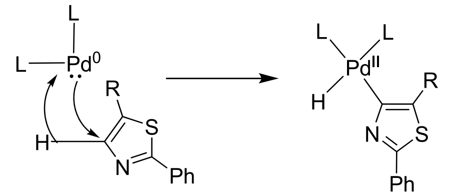
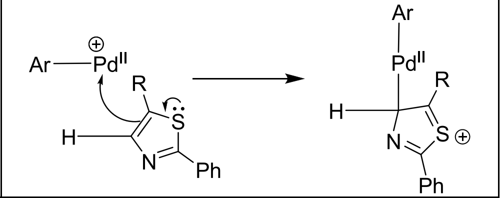
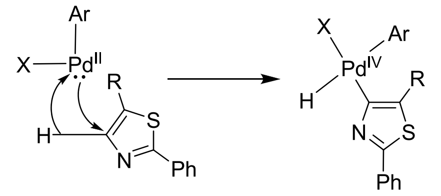
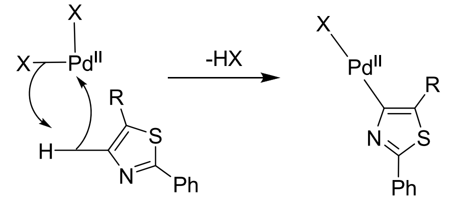
Oxidative addition of palladium (0) to the C4-H bond		Electrophilic addition of palladium (II) to thiazole C4
		
Oxidative addition of aryl palladium (II) to the C4-H bond		Concerted C-H functionalisation with no formal change in the oxidation state
		
X = I, Br, Cl, OAc etc. L = Ligands		

Table 3.3.5 – C-H activation mechanisms

The final option - deprotonation - can be discounted as Cs_2CO_3 is not a strong enough base to deprotonate the thiazole C4 proton (pK_a = 36.8).[46] The potential roles of the different C-H activation steps can been seen in Scheme 3.3.19. There are three main possibilities, a palladium (0) to palladium (II) mechanism, a palladium (0), (II), (IV) mechanism and a palladium (II) to (IV) mechanism.

In order to probe which mechanism might be in place, the stoichiometric synthesis of a number of intermediates was attempted, see Table 3.3.6. Despite the use of a number of common conditions[101] for the formation of palladacycles, none of the expected complexes were seen, although some evidence was observed in LCMS data that the complexes were formed in very small amounts but could not be isolated. It cannot, therefore, be concluded whether the proposed structures are or are not intermediates in the reaction.

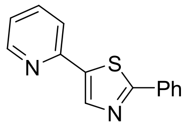
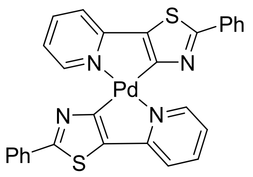
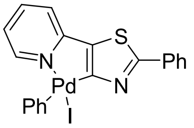
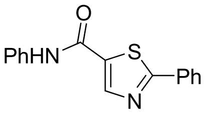
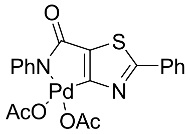
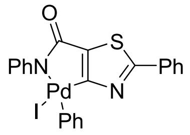
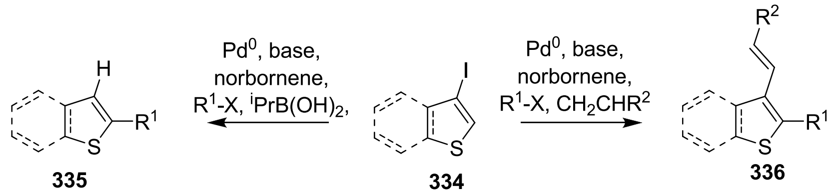
Substrate	Palladium	Conditions	Expected Product	Comments
 **291a**	Pd(OAc)$_2$	MeOH, 25 °C	 **330**	No reaction.
		AcOH, reflux		LCMS shows a small peak for palladium complexed to 2 pyridines, however, only unreacted starting material was isolated.
		CHCl$_3$, reflux		No reaction.
	PhPdI(PPh$_3$)$_2$	AcOH, reflux	 **331**	No recognisable products.
		CHCl$_3$, reflux		No recognisable products.
 **269**	Pd(OAc)$_2$	MeOH, K$_2$CO$_3$, 25 °C	 **332**	No reaction.
		AcOH, reflux		LCMS shows a small peak for the palladium complex, however, only unreacted amide was isolated.
		CHCl$_3$, reflux		No reaction.
	PhPdI(PPh$_3$)$_2$	AcOH, reflux	 **333**	No reaction.
		CHCl$_3$, reflux		Palladium black deposited. No recognisable products.
In all cases, the expected compound represents the simplest desired product. Each could form dimers and/or have bridging acetate ligands or could form solvent inclusion complexes.				

Table 3.3.6 – Stoichiometric palladacycle formation

Despite being unable to draw any mechanistic conclusions the directed arylation of thiazole has been shown to be possible using a number of directing groups, some of which can be readily elaborated or removed. Further research is needed in order to moderate the harsh conditions necessary and improve the catalyst turnover.

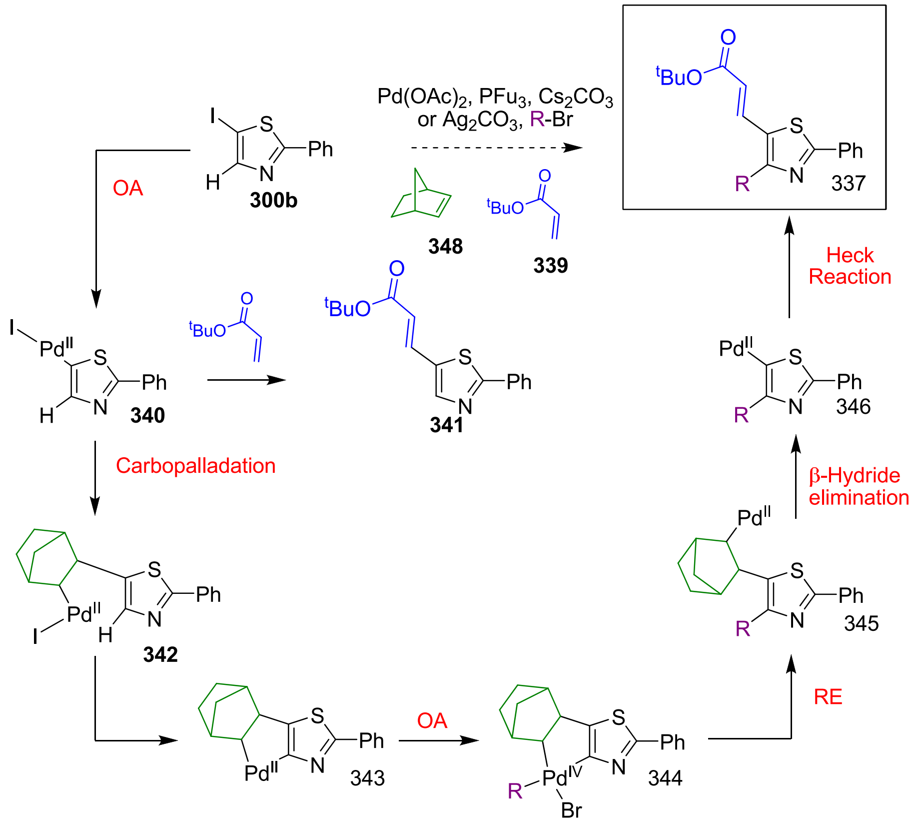
3.3.5. α-Alkylation via norbornene shuttle

An alternative way of introducing functionality to heteroaryliodides was reported by Lautens *et al* in 2006.[164] They were able to elaborate an iodothiophene by using methodology developed by Catellani *et al.*[165-167]



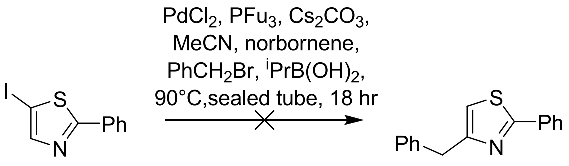
Scheme 3.3.20 – Lautens' thiophene alkylation

If this methodology could be adapted to the thiazole ring system it would provide a good route to 4,5-disubstituted thiazoles, **337**, (Scheme 3.3.21).



Scheme 3.3.21 – Proposed norbornene shuttle with thiazoles

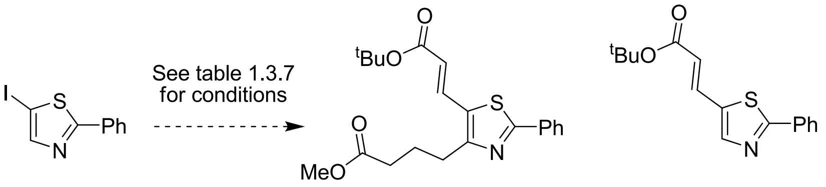
The investigation was started by repeating Lautens' conditions, (Scheme 3.3.22). None of the desired product was seen.



300b **347**

Scheme 3.3.22 – First attempt at norbornene shuttle

Following on from this, a different alkylbromide was chosen which was more reactive in the oxidation of palladium (II) to palladium (IV). It was hoped that trapping the final thiazol-5-yl palladium in a Heck reaction with tertiary butyl acrylate would give a product that would be easy to identify, (Scheme 3.3.23).



300b **337** **341**

Scheme 3.3.23

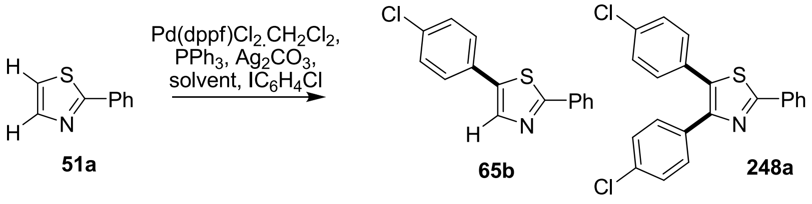
Conditions	**Results**
300b, $PdCl_2$, PFu_3, methyl 4-bromobutyrate, t-butyl acrylate, norbornene, DMF, Cs_2CO_3, 130 °C, 18 hr.	No identifiable products.
300b, $PdCl_2$, PFu_3, methyl 4-bromobutyrate, t-butyl acrylate, norbornene, toluene, Cs_2CO_3, 130 °C, 18 hr.	No identifiable products.
300b, $PdCl_2$, PFu_3, methyl 4-bromobutyrate, t-butyl acrylate, norbornene, DMF, Ag_2CO_3, 130 °C, 18 hr.	No identifiable products.

Table 3.3.7 – Norbornene shuttle attempts

Unfortunately, no product was formed in any of the reactions above, nor was the straight Heck product observed. Each reaction was a complex mixture of products from which no single product could be separated or identified. Having encountered these difficulties this research was put on one side whilst attention was focussed on other areas.

3.4. Non-directed arylation

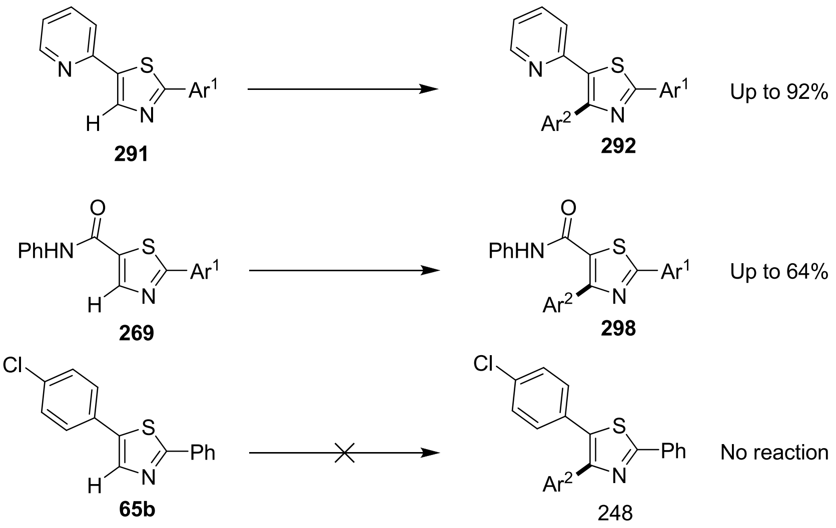
Whilst investigating solvent effects in the arylation of thiazole C5 (see chapter 2) it was noticed that a small amount of 4,5-diaryl thiazole was being produced in the case of tetrahydrofuran, dioxane and water, (Scheme 3.4.1).



Solvent:	Mono	Di
THF	71	24
Dioxane	62	7
Water	95	2

Scheme 3.4.1 – 5-arylation 4,5-diarylation results

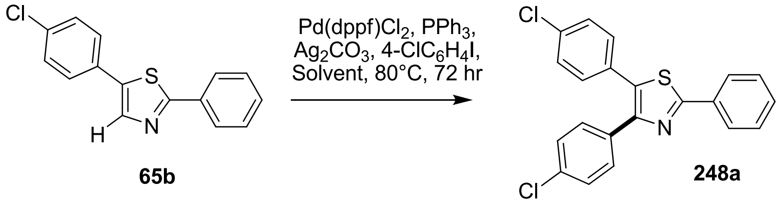
This was the first time **248** arising from double arylation had been observed. In spite of this, when control reactions had been run during the directed arylation attempts with pyridine and amide directing groups, arylation did not occur at C4 when 5-(4-chlorophenyl)-2-phenylthiazole, **65b**, was used in place of the directing groups, (Scheme 3.4.2). It was therefore concluded that arylation at the C4 position was highly dependant on the nature of the solvent, ligands and perhaps many other variables as well. Taking 5-(4-chlorophenyl)-2-phenylthiazole, **65b**, and subjecting it to the 5-arylation conditions in tetrahydrofuran, dioxane and water with an excess of aryl iodide it was hoped to be able to successfully arylate at the C4 positions. However, this proved not to be the case at 60 °C, in fact, the results demonstrated during the 5-arylation in tetrahydrofuran and dioxane proved to be unreproducible.



Conditions: Pd(OAc)$_2$, Ar^{2}Br, P^{t}Bu$_2$(biphenyl-2-yl), Cs$_2$CO$_3$, xylene or dioxane, 180°C, 48 hr

Scheme 3.4.2 – Directed arylation control reactions

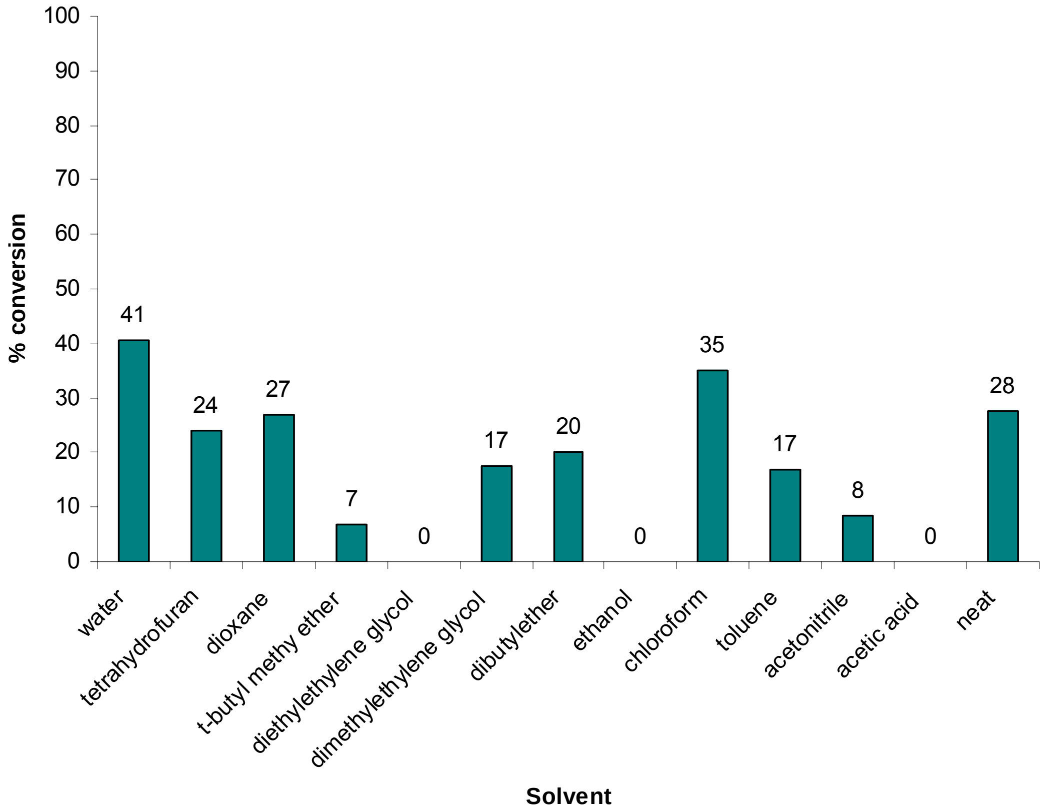
A brief solvent screen was therefore carried out to determine whether the transformation would take place in any common solvent at the slightly increased 80 °C, (Scheme 3.4.3 and Figure 3.4.1).



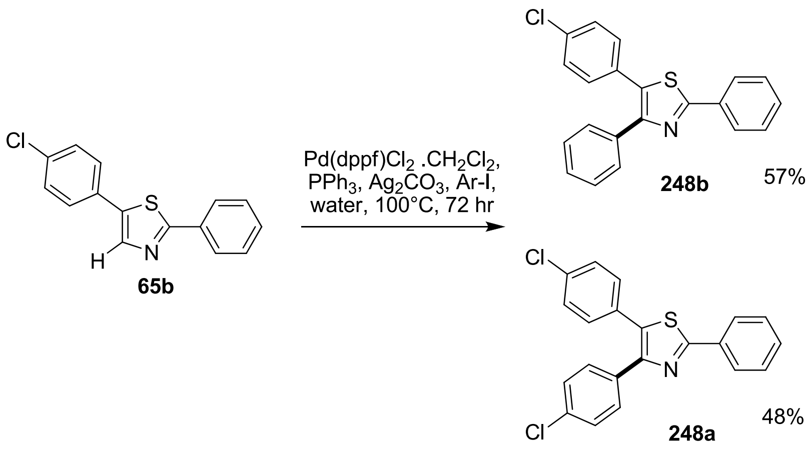
Scheme 3.4.3 – Conditions for solvent screen

The solvent screen confirmed that water was, in fact, the best reaction solvent.

Figure 3.4.1 – Solvent screen for non-directed arylation



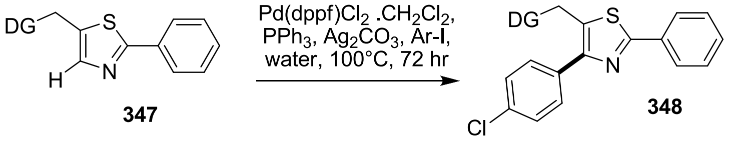
Despite water being identified as the optimum solvent for the transformation the conversion remained at only 41%, even after seventy-two hours at 80 °C. Increasing the temperature to 100 °C improved both the conversion and yield, (Scheme 3.4.4).



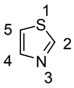
Scheme 3.4.4 – 4-Arylation with iodobenzene and 4-chloroiodobenzene

The reaction at thiazole C4 at 100 °C is a large step forwards in the arylation of unreactive C-H bonds. Even Fagnou's 4-arylation of the activated 2,5-diarylthiazole N-oxide[108] requires temperatures of over 100 °C. If this method can be proved to be general over a wider range of substrates this would provide an attractive route to 2,4,5-triarylthiazoles, **248**, without the need to oxidise and then reduce the thiazole nucleus.

In addition, the application of these conditions to the directing groups used previously, (Scheme 3.4.5 and Table 3.4.1), showed that not only are the water based conditions applicable to the arylation of thiazole at the C5 position, but that there is the potential for them to enable arylation at the C4 position, both in the absence and presence of a directing group. Whilst the yields remain moderate at best, with further optimisation and mechanistic insight it is hoped to be able to significantly improve the methodology.



Scheme 3.4.5 – Conditions for directed arylations in water



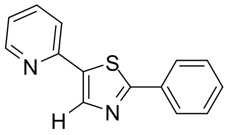
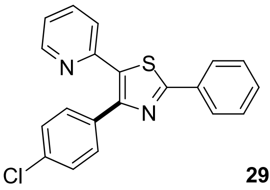
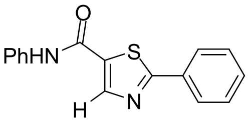
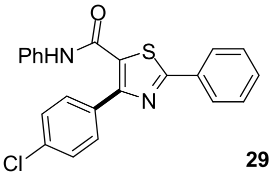
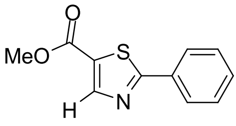
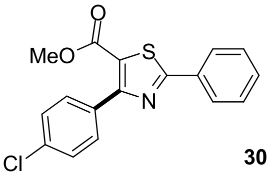
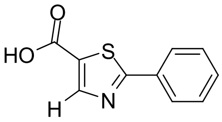
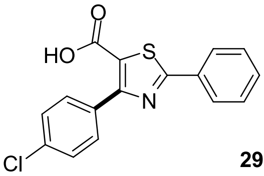
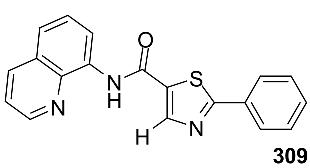
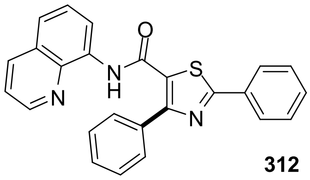
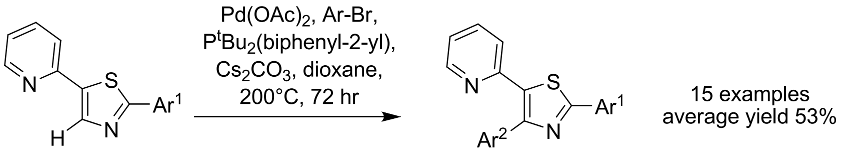
Substrate	Product	Yield %
 **291**	 **292**	29
 **269**	 **298**	19
 **263**	 **302**	24
 **301**	 **299**	No reaction
 **309**	 **312**	38

Table 3.4.1 – Application of water conditions to directed arylations

3.5. Conclusions

A number of directing group strategies have been developed which allow the arylation of the thiazole C4 position under fairly mild conditions. In each case, it has been determined that the C5 position must be blocked in order to prevent arylation at that position.

Pyridine directing groups worked well, albeit requiring temperatures in excess of 180 °C to effect the transformation.

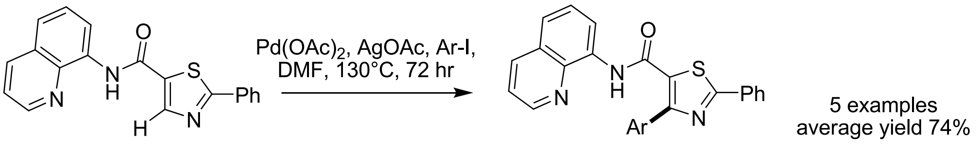


291 **292**

Scheme 3.5.1 – Pyridine direction (see Table 3.3.1)

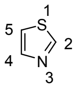
The phenyl amide directing group was of particular interest as it is potentially removable, giving a convenient route to 2,4-diarylthiazoles. However, the amide is partially decarbamoylated during the reaction and as such, with a complex mixture of products it was difficult to optimise the conditions to form a single product.

Attention was then turned to an amide directing group with more than one nitrogen to chelate to the palladium metal. This was accomplished using 8-aminoquinoline, (Scheme 3.5.2). This method required the use of 10 mole % percent of palladium, presumably due to the chelating properties of both the starting material and product.



309 **312**

Scheme 3.5.2 – Quinoline amide direction (see Table 3.4.1)



Further to that, an attempt to alkylate at the C4 position using norbornene as an internal tether and directing group, furnished none of the desired product.

With the newly discovered water conditions for the arylation of the thiazole C5 position a small amount of 4,5-diarylation was observed. These conditions were applied to 2,5-diarylthiazoles and it was gratifying to note that at 100 °C there was a significant conversion to product. In addition, these conditions could be applied to the substrate incorporating directing groups at the C5 position. The arylation at the thiazole C4 position at 100 °C constitutes a significant improvement over Fagnou's[108] arylation of thiazole N-oxides, removing the need to pre-functionalise the thiazole as its N-oxide.

In conclusion, several strategies for the direct arylation of the thiazole C4 position have been investigated and proven to be effective methods for the functionalisation of the C-H bond at the thiazole C4 position.

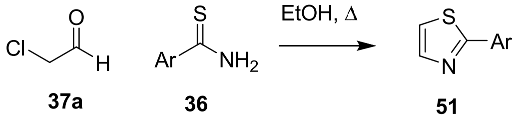
4. Experimental

General Methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 360 MHz instrument at 25 °C unless otherwise stated and are calibrated to residual solvent peaks ($CDCl_3$ 7.26 ppm and 77.0 ppm). The data is reported as chemical shift (ppm), then the interpretation of the peak with relevant coupling constants reported in Hertz. ^{19}F NMR spectra were recorded on a Brucker 250 MHz instrument at 25°C. Infra-red spectra were recorded on a JASCO FT/IR-460 using sodium chloride disks or a PerkinElmer Spectrum One FT-IR Universal ATR sampling accessory instrument as a thin film. Melting point measurements were obtained from a Gallencamp apparatus and are reported uncorrected. Electrospray high resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using a Finnigan MAT 900 XTL double focussing mass spectrometer. FAB HRMS was carried out by the University of Edinburgh using a Kratos MS50 instrument, EI mass spectrometry was carried out on a JEOL GcmateII; Samples were introduced either by Direct Heated Probe or via GC from an Agilent 6890 using a Chrompack CPSil5 low bleed MS column. The data is recorded as the ionisation method followed by the calculated and measured masses. T.L.C. was performed on Merck $60F_{254}$ aluminium backed silica plates and visualised by uv light (both 254 nm and 365 nm). The compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure. Acetonitrile and tetrahydrofuran were dried by distillation from calcium hydride and sodium respectively, other dry solvents were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com. Cs_2CO_3 was stored under vacuum at 70°C. $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ was purchased from Strem Chemicals, Inc. All other chemicals were purchased from a chemical supplier and used as received unless otherwise stated.

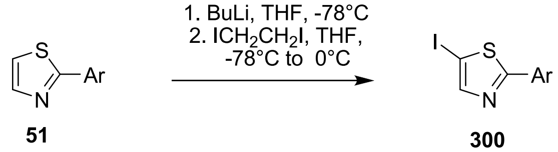
General procedures

General procedure A: Synthesis of 2-substituted thiazoles



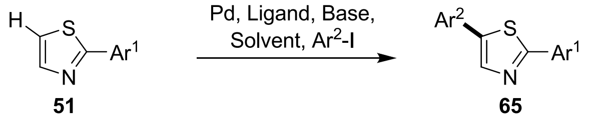
The thioamide, **36** (5.0 g, 1 equiv) was dissolved in ethanol (25 mL, 5 mLg^{-1}) and chloroacetaldehyde, **37a** (monohydrate as 50% solution in water, 1.2 equiv) was added and the solution heated to reflux. The reaction was monitored by T.L.C., when the starting material was consumed (approximately 2 hr), the ethanol was removed *in vacuo*. The residue was partitioned between water (25 mL, 5 mL g^{-1}) and CH_2Cl_2 (25 mL, 5 mL g^{-1}), the aqueous phase extracted with CH_2Cl_2 (25 mL, 5 mL g^{-1}) and the organics washed with brine (sat. aq., 25 mL, 5 mL g^{-1}) then dried over $MgSO_4$ and concentrated *in vacuo*. Purification was achieved by column chromatography or reduced pressure distillation.

General procedure B: Iodination of 2-aryl thiazoles at C5



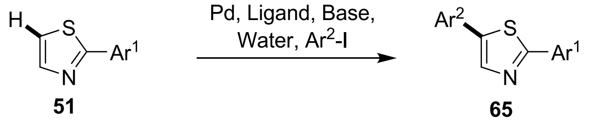
2-Arylthiazole, **51** (1 equiv) was dissolved in dry tetrahydrofuran (15 mL g^{-1}) under N_2 and cooled to -78°C To this was added ^{n}BuLi (1.1 equiv) dropwise and the reaction left to stir for 5 min. 1,2-Diiodoethane (1.2 equiv) was dissolved in tetrahydrofuran (15 mL g^{-1} of starting material) and added slowly to the solution, this was stirred at -78 °C for 15 min then warmed to 0°C, quenched by the addition of NH_4Cl (sat.aq., 15 mL g^{-1}) and diluted with Et_2O (15 mL g^{-1}). The phases were separated and the aqueous phase extracted with Et_2O (15 mL g^{-1}), the organics were washed with brine (sat. aq., 15 mL g^{-1}), dried over $MgSO_4$ and concentrated *in vacuo*. Purification was achieved by column chromatography.

General procedure C: 5-Arylation with 2-arylthiazole and aryl halide in dry solvents



Ag_2CO_3 (2 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (5.0 mol %), PPh_3 (10.0 mol %) and aryl halide (1.2 equiv) were dissolved in dry solvent (4 mL) under N_2. 2-Arylthiazole, **51** (100 mg, 1 equiv) was added as a solution in dry solvent (1 mL), and the solution heated to 60°C for 3 days under N_2. The reaction mixture was filtered through a pad of celite, washed with CH_2Cl_2 and acetone then concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure D: 5-Arylation with 2-arylthiazole and aryl halide on water



Aryl halide (1.2 equiv), Ag_2CO_3 (2 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (5.0 mol %), PPh_3 (10.0 mol %) and 2-arylthiazole, **51** (1 equiv, typical scale 100 mg) were combined[2] and then suspended in deionised water (5 mL) and the suspension heated to 60°C for 24 hr. The reaction mixture was filtered through a pad of celite, washed with acetone (5 mL) and CH_2Cl_2 (5 mL) then carefully concentrated *in vacuo*.[3] CH_2Cl_2 (5 mL) and brine (5 mL) were added to the resultant solid and water mixture and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (5 mL) and the organics concentrated *in vacuo*. The crude product was purified by column chromatography.

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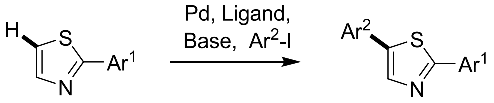
[2] As 2-phenylthiazole is insoluble in water it is important to ensure that it is placed directly on the mixture of solids and not on the sides of the reaction vessel as the water will not “wash” it into the reaction as an organic solvent would.

[3] Some of the 2,5-diarylthiazole products azeotrope with water, hence it is important to remove only the CH_2Cl_2 and acetone by distillation and not the water also. During the reaction with some aryl halides, crystals of product can be seen to form at the top of the reaction vessel.

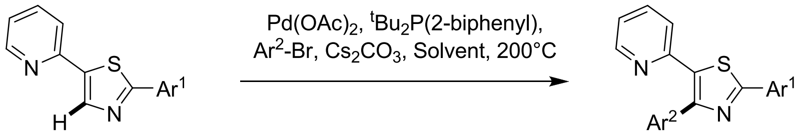
General procedure E: 5-Arylation with 2-arylthiazole and aryl halide neat



51 **65**

Ag_2CO_3 (2 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5.0 mol %), PPh_3 (10.0 mol %), aryl halide (2 equiv) were combined, shaken to mix thoroughly then 2-arylthiazole, **51** (100 mg, 1 equiv) was added and the mixture heated to 60°C for 24 hr.[4] CH_2Cl_2 was added to the reaction mixture which was filtered through a pad of celite, washed with CH_2Cl_2 and acetone then concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure F: Direct arylation at C4



291 **292**

2-(2-Arylthiazol-5-yl)-pyridine, **291** (1 equiv), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (5.0 mol %), ${}^tBu_2P$(biphenyl-2-yl) (10.0 mol %) and aryl bromide (2 equiv) were combined in a microwave vial (2 mL). Anhydrous solvent (xylene, dimethylformamide, dimethylsulfoxide or dioxane) (1 mL) was added and the vial was sealed and heated to 200°C for 72 hr. The reaction mixture was filtered through celite and washed through with CH_2Cl_2 (10 mL), concentrated *in vacuo*, dry loaded onto SiO_2 and purified by column chromatography.

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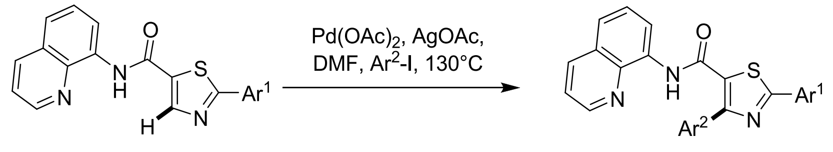
[4] The reaction is a melt for the first several hours and stirs well but as more product forms it begins to set into a solid cake.

General Proceedure G: Direct arylation of quinoline amide

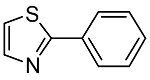


309 **312**

Quinoline amide, **309** (1 equiv), Pd(OAc)$_2$ (5.0 mol %), AgOAc (2 equiv), dimethylformamide (5 mL) and aryl iodide (4 equiv) were heated together under N$_2$ at 130°C for 24 hr. Further Pd(OAc)$_2$ (2 mol %) was added in two portions over a period of 48 hr. The reaction was then partitioned between CH$_2$Cl$_2$ and water, the organics washed twice with water, then brine, dried over MgSO$_4$ and concentrated *in vacuo*. The product was isolated following purification by column chromatography.

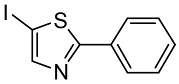
Specific examples

2-Phenylthiazole[48] **51a**



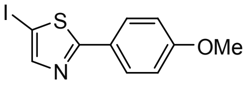
Following general procedure A, using thiobenzamide (22.00 g, 0.160 mol, 1 equiv) the title compound was obtained by reduced pressure distillation as a colourless oil (25.06 g, 96% yield). BP 82°C at 0.4 mmHg; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.00-7.95 (2H, m), 7.86 (1H, d, *J* = 3.3, ThC_4-**H**), 7.47-7.40 (3H, m), 7.31 (1H, d, *J* = 3.3, ThC_5-**H**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 168.38 (quat, Th**C**$_2$), 143.63 (CH, Th**C**$_4$-H), 133.52 (quat), 129.96 (CH), 128.93 (2 CH), 126.53 (2 CH), 118.80 (CH).

5-Iodo-2-phenylthiazole **300b**



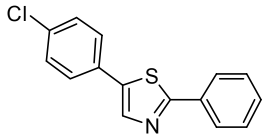
Following general procedure B, using 2-phenylthiazole, (2.00 g, 0.012 mol, 1 equiv) the title compound was obtained following purification by column chromatography (0-10% ethyl acetate/iso-hexane) and obtained as a brown solid (2.68 g, 75% yield). MP ($CHCl_3$) 101°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.86-7.83 (3H, m), 7.42-7.38 (3H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 173.24 (quat, T**C**$_2$), 151.19 (CH, ThC_4-H), 132.68 (quat), 130.21 (CH), 128.82 (2CH), 126.17 (2CH), 70.12 (quat, TC_5-I); IR (thin film, cm^{-1}) ν_{max} 3054, 2987, 1421, 1265, 896, 739, 705; HRMS (EI) calculated for $[C_9H_7INS]^+$ 286.9266, found 286.9259.

5-Iodo-2-(4-methoxyphenyl)thiazole **300c**



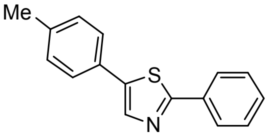
Following general procedure B, using 2-anisylthiazole, (300 mg, 1.569 mmol, 1 equiv), the title compound was obtained following purification by column chromatography (0-10% ethyl acetate/iso-hexane) as a yellow solid (334 mg, 67% yield). MP ($CHCl_3$) 105-106°C; ^{1}H NMR (360 MHz, $CDCl_3$) 7.83-7.80 (3H, m), 6.97-6.93 (2H, m), 3.86 (3H, s, OC**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 173.46 (quat, Th**C$_2$**), 161.42 (quat, **C**$_{Ar}$-OCH_3), 151.15 (CH, Th**C**$_4$-H), 127.91 (2CH), 126.00 (quat), 114.38 (2CH), 68.49 (quat, Th**C**$_5$-I), 55.42 (O**C**H_3); IR (thin film, cm^{-1}) ν_{max} 1607, 1475, 1410, 1257, 1177, 1110, 1034, 807, 666; HRMS (EI) calculated for $[C_{10}H_8INOS]^+$ 316.9372, found 316.9382.

5-(4-Chlorophenyl)-2-phenylthiazole **65b**



Following general procedure D, using 2-phenylthiazole, (100 mg, 0.620 mmol, 1 equiv) and iodochlorobenzene (178 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) gave the title compound as a yellow solid (160 mg, 95% yield). MP (Et_2O) 137°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.92 (1H, s, ThC_4-**H**), 7.90-7.87 (2H, m), 7.47-7.45 (2H, m), 7.39-7.37 (3H, m), 7.32-7.30 (2H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.49 (quat, Th**C**$_2$), 139.44 (CH, Th**C**$_4$-H), 137.94 (quat), 134.10 (quat), 133.45 (quat), 130.16 (CH), 129.88 (quat), 129.28 (2CH), 128.99 (2CH), 127.77 (2CH), 126.36 (2CH); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 1265, 1095, 896, 739, 705; HRMS (ES +ve) Calculated for $[C_{15}H_{10}{}^{35}ClNS+H]^+$ 272.0295, found 272.0293.

5-(4-Methylphenyl)-2-phenylthiazole[168,169] **65c**



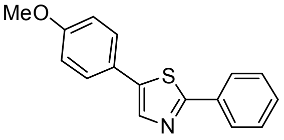
Following general procedure D, using 2-phenylthiazole (200 mg, 1.240 mmol, 1 equiv) and iodotoluene (325 mg, 1.488 mmol, 1.2 equiv), purification by column chromatography (toluene) gave the title compound as a yellow oil (281 mg, 90% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.99-7.96 (3H, m), 7.51-7.42 (5H, m), 7.23-7.21 (2H, m), 2.39 (3H, s, C**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 166.53 (quat, T**C**$_2$), 139.35 (quat), 138.62 (CH, Th**C**$_4$-H), 138.23 (quat), 133.65 (quat), 129.79 (CH), 129.68 (2CH), 128.85 (2CH), 128.44 (quat), 126.45 (2CH), 126.22 (2CH), 21.16 (CH_3).

5-(4-Nitrophenyl)-2-phenylthiazole **65d**

Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 4-iodonitrobenzene (185 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (2% ethyl acetate/hexane) gave the title compound as a yellow solid (108 mg, 62% yield). MP ($CHCl_3$) 173°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.30-8.26 (2H, m), 8.16 (1H, s, Th**C**$_4$-H), 8.00-7.97 (2H, m), 7.76-7.73 (2H, m), 7.51-7.48 (3H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 169.50 (quat, Th**C**$_2$), 147.11 (quat, **C**$_{Ar}$-NO2), 141.44 (CH, Th**C**$_4$-H), 137.78 (quat), 136.55 (quat), 133.10 (quat), 130.74

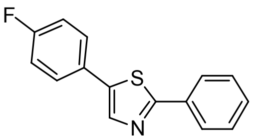
(CH), 129.13 (2CH), 126.88 (2CH), 126.58 (2CH), 124.56 (2CH); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 1596, 1520, 1422, 1340, 1265, 896, 739, 706; HRMS (EI) calculated for $[C_{15}H_{10}N_2O_2S]^+$ 282.0463, found 282.0462.

5-(4-Methoxyphenyl)-2-phenylthiazole **65e**



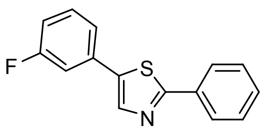
Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 4-iodoanisole (174 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (2% ethyl acetate/hexane) gave the title compound as a colourless solid (129 mg, 78% yield). MP (EtOH) 85-87°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.90-7.86 (2H, m), 7.84, (1H, s, ThC_4-**H**), 7.48-7.44 (2H, m), 7.38-7.35 (3H, m), 6.90-6.86 (2H,m), 3.77 (3H, s, OC**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 166.11 (quat, Th**C**$_2$), 159.65 (quat), 139.09 (quat), 138.05 (CH, Th**C**$_4$-H), 133.62 (quat), 129.70 (CH), 128.95 (2CH), 128.82 (2CH), 127.84 (2CH), 126.13 (quat), 114.40 (2CH), 55.25 (OCH_3); IR (thin film, cm^{-1}) ν_{max} 3049, 2960, 2837, 1609, 1533, 1489, 1453, 1255, 1034, 827, 761, 738, 689, 631; HRMS (FAB) calculated for $[C_{16}H_{13}NOS+H]^+$ 268.0796, found 268.0795.

5-(4-Fluorophenyl)-2-phenylthiazole **65h**



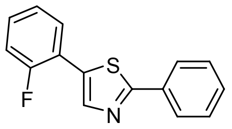
Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol) and 4-iodofluorobenzene (165 mg, 0.744 mmol), purification by column chromatography (CH_2Cl_2) afforded the title compound as a colourless solid (141 mg, 89% yield). MP (Et_2O) 124°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.97-7.94 (3H, m), 7.56-7.52 (2H, m), 7.45-7.42 (3H, m), 7.12-7.07 (2H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.01 (quat, Th**C**$_2$), 162.68 (quat, d, *J* = 248.6, **C**$_{Ar}$-F), 138.92 (CH, Th**C**$_4$-H), 137.99 (quat), 133.37 (quat), 129.97 (CH), 128.87 (2CH), 128.20 (2CH, d, *J* = 8.1, **C**HCHCF), 127.43 (quat, d, *J* = 3.5, **C**$_{Ar}$CHCHCF), 126.19 (2CH), 116.02 (2CH, d, *J* = 21.9, **C**HCF); ^{19}F NMR (235 MHz, $CDCl_3$) δ_F -114 (1F, s); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 1534, 1505, 1489, 1453, 1423, 1265, 1237, 1159, 896, 834, 739, 705; HRMS (ES +ve) calculated for $[C_{15}H_{10}FNS+H]^+$ 256.0591, found 256.0591.

5-(3-Fluorophenyl)-2-phenylthiazole **65i**



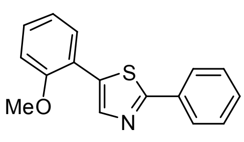
Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 3-iodofluorobenzene (165 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (10-20% ethyl acetate/hexane) afforded the product as a yellow solid, (103 mg, 65% yield). MP (EtOH) 112-114°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.02 (1H, s, ThC_4-**H**), 7.98-7.95 (2H, m), 7.47-7.43 (3H, m), 7.38-7.35 (2H, m), 7.30 (1H, m), 7.03 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.70 (quat, Th**C**$_2$), 163.00 (quat, d, *J* = 246.9, **C**$_{Ar}$-F), 139.75 (CH, Th**C**$_4$-H), 137.82 (quat, d, *J* = 2.6, Th**C**$_5$CCHCF), 133.39 (quat, d, *J* = 8.3, **C**CHCF), 133.38 (quat), 130.65 (CH, d, *J* = 8.6, **C**HCHCF), 130.19 (CH), 128.97 (2CH), 126.37 (2CH), 122.30 (CH, d, *J* = 2.8, **C**HCHCHCF), 115.05 (CH, d, *J* = 21.2, **C**HCF), 113.41 (CH, d, *J* = 23.0, **C**HCF); ^{19}F NMR (235 MHz, $CDCl_3$) δ_F -113.0 (1F, s); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 2305, 1610, 1585, 1421, 1265, 896, 738; HRMS (EI) calculated for $[C_{15}H_{10}FNS]^+$ 255.0518, found 255.0509.

5-(2-Fluorophenyl)-2-phenylthiazole **65j**



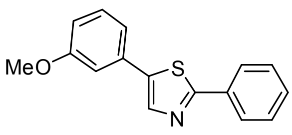
Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 2-iodofluorobenzene (165 mg, 0.744 mmol, 1 equiv), purification by column chromatography (10-20% ethyl acetate/hexanes) afforded the title compound as a yellow solid (93 mg, 59% yield). MP (EtOH) 92-94°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.19 (1H, d, *J* = 1.2, TC_4-**H**), 8.01-7.98 (2H, m), 7.63 (1H, ddd, *J* = 1.9, 7.6, 7.9, C**H**CHCF), 7.49-7.43 (3H, m), 7.31 (1H, m), 7.22-7.15 (2H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.93 (quat, d, *J* = 3.4, Th**C**$_2$), 158.90 (quat, d, *J* = 250.5, **C**$_{Ar}$-F), 141.95 (CH, d, *J* = 7.3), 133.44 (quat), 131.98 (quat, d, *J* = 4.2), 130.09 (CH), 129.47 (CH, d, *J* = 8.4), 128.94 (2CH), 128.89 (CH), 126.38 (2CH), 124.63 (CH, d, *J* = 3.4), 119.41 (quat, d, *J* = 13.6), 116.32 (CH, d, *J* = 22.1, **C**HCF); ^{19}F NMR (235 MHz, $CDCl_3$) δ_F -113.00 (1F, s); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 1422, 1264, 896, 748; HRMS (EI) calculated for $[C_{15}H_{10}FNS]^+$ 255.0518, found 255.0526.

5-(2'-Methoxyphenyl)-2-phenylthiazole **65g**



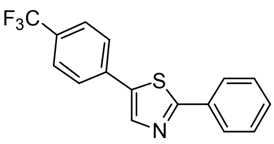
Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 2-iodoanisole (174 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) afforded the title compound as a yellow solid (118 mg, 71% yield). MP ($CHCl_3$) 58-60°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.24 (1H, s, ThC$_4$-**H**), 8.03-8.00 (2H, m), 7.67 (1H, dd, *J* = 1.7, 7.6), 7.46-7.41 (3H, m), 7.32 (1H, ddd, *J* = 1.7, 7.6, 8.3), 7.02 (2H, ddd, *J* = 1.3, 7.6, 15.1), 3.95 (3H, s, OC**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.37 (quat, Th**C**$_2$), 155.37 (quat, **C**$_{Ar}$OMe), 141.25 (CH, Th**C**$_4$), 134.15 (quat), 133.87 (quat), 129.63 (CH), 129.19 (CH), 128.82 (2CH), 128.33 (CH), 126.22 (2CH), 121.00 (CH), 120.41 (quat), 111.46 (CH), 55.51 (O**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 3053, 1479, 1465, 1265, 1025, 982, 896, 740, 705; HRMS (EI) calculated for $[C_{16}H_{13}NOS]^+$ 267.0718, found 267.0728.

5-(3'-Methoxyphenyl)-2-phenylthiazole **65f**



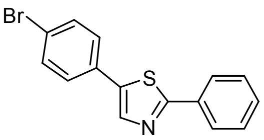
Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 3-iodoanisole (174 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) afforded the title compound as a colourless solid (87 mg, 53% yield). MP ($CHCl_3$) 69-70°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.01 (1H, s, ThC$_4$-**H**), 7.99-7.96 (2H, m), 7.45-7.43 (3H, m), 7.33 (1H, t, *J* = 7.9, C**H**CHCOCH$_3$), 7.17 (1H, ddd, *J* = 1.0, 1.7), 7.13 (1H, dd, *J* = 1.7, 2.3), 6.89 (1H, ddd, *J* = 1.0, 2.6, 8.3), 3.86 (3H, s, C**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.12 (quat, Th**C**$_2$), 159.96 (quat, **C**$_{Ar}$OCH$_3$), 139.27 (CH, Th**C**$_4$-H), 139.07 (quat), 133.57 (quat), 132.56 (quat), 130.09 (CH), 129.97 (CH), 128.91 (2CH), ,126.29 (2CH), 119.13 (CH), 113.63 (CH), 112.31 (CH), 55.29 (CH$_3$); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 1600, 1579, 1478, 1457, 1422, 1265, 1209, 1170, 896, 738, 705; HRMS (EI) calculated for $[C_{16}H_{13}NOS]^+$ 267.0718, found 267.0720.

2-Phenyl-5-((4-trifluoromethyl)phenyl)thiazole **65k**



Following general procedure C using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 4-iodobenzotrifluoride (203 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) gave the title compound as a colourless solid (117 mg, 62% yield). MP (Et_2O) 154°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.10 (1H, s, ThC$_4$-**H**), 8.01-7.97 (2H, m), 7.73-7.67 (4H, m), 7.51-7.46 (3H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 168.40 (quat, Th**C**$_2$), 140.36 (CH, Th**C**$_4$-H), 137.48 (quat), 134.88 (quat), 133.33 (quat), 130.41 (CH), 130.04 (quat, q, J = 32.7, **C**$_{Ar}$CF$_3$), 129.05 (2CH), 126.71 (2CH), 126.47 (2CH), 126.12 (2CH, q, J = 3.7, **C**HCCF$_3$), 123.93 (quat, q, J = 272.0, **C**F$_3$); ^{19}F NMR (235 MHz, $CDCl_3$) δ_F -63.9 (3F, s); IR (thin film, cm^{-1}) ν_{max} 3399, 1996, 1614, 1425, 1326, 1265, 1110, 1070, 896, 832, 739; HRMS (EI) calculated for $[C_{16}F_3H_{10}NS]^+$ 305.0486, found 305.0498.

5-(4-Bromophenyl)-2-phenylthiazole **65y**

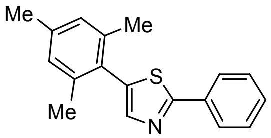


Following general procedure D using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 4-iodobromobenzene (211 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (10-20% ethyl acetate/hexane) gave the title compound as a pale yellow solid (196 mg, >99%). MP (EtOH) 146-148°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.99 (1H, s, Th**C**$_4$-H), 7.97-7.94 (2H, m), 7.55-7.51 (2H, m), 7.47-7.42 (5H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.50 (quat, Th**C**$_2$), 139.46 (CH, Th**C**$_4$-H), 137.94 (quat), 133.43 (quat), 132.20 (2CH), 130.31 (quat), 130.15 (CH), 128.98 (2CH), 127.99 (2CH), 126.35 (2CH), 122.16 (quat); IR (thin film, cm^{-1}) ν_{max} 3076, 1525, 1478, 1449, 1426, 1398, 1163, 1070, 979, 822, 760, 686, 629; HRMS (EI) calculated for $[C_{15}H_{10}NS^{79}Br]^+$ 314.9717, found 314.9718.

2-Phenylthiazol-5-yl-2-benzyl alcohol **65p**

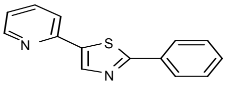
Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 2-iodobenzylalcohol (174 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) gave the title compound as a yellow oil (108 mg, 65% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.94-7.91 (2H, m), 7.84 (1H, s, ThC$_4$-**H**), 7.60-7.57 (1H, m), 7.44-7.40 (4H, m), 7.38-7.30 (2H, m), 4.72 (2H, s, C**H$_2$**OH); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 168.39 (quat, Th**C$_2$**), 142.03 (CH, Th**C**$_4$-H), 138.82 (quat), 136.18 (quat), 133.26 (quat), 130.78 (CH), 130.04 (CH), 129.70 (quat), 128.98 (CH), 128.91 (2CH), 128.85 (CH), 127.83 (CH), 126.32 (2CH), 62.84 (CH_2); IR (thin film, cm^{-1}) ν_{max} 3349, 1478, 1455, 1422, 1265, 982, 737, 703, 636; HRMS (EI) calculated for $[C_{16}H_{13}NOS]^+$ 267.0718, found 267.0728.

5-(2,4,6-Trimethylphenyl)-2-phenylthiazole **65s**



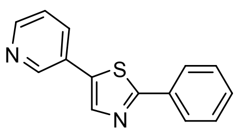
Following general procedure D, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 2,4,6-trimethyliodobenzene (183 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) afforded the title compound as a yellow oil (173 mg, quantitative yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.03-8.00 (2H, m), 7.58 (1H, s, ThC$_4$-**H**), 7.50-7.43 (3H, m), 6.99 (2H, s, C$_{Ar}$**H**CCH$_3$), 2.36 (3H, s, *p*-C**H$_3$**), 2.20 (6H, s, 2 *o*-C**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 168.46 (quat, Th**C**$_2$), 142.22 (CH, Th**C**$_4$-H), 138.59 (quat), 138.38 (2 quat), 135.53 (quat), 133.72 (quat), 129.83 (CH), 128.91 (2CH), 128.31 (2CH), 126.81 (quat), 126.26 (2CH), 21.06 (CH_3, p-**C**H$_3$), 20.78 (2CH$_3$, 2 o-**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 2918, 1456, 978, 851, 761, 689, 635; HRMS (EI) calculated for $[C_{18}H_{17}NS]^+$ 279.1082, found 279.1080.

2-(2-Phenylthiazol-5-yl)pyridine **291a**



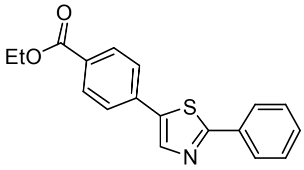
Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 2-iodopyridine (153 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) gave the title compound as a colourless solid (84 mg, 57% yield). MP ($CHCl_3$) 99-101°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.59 (1H, m), 8.27 (1H, s, ThC$_4$-**H**), 8.01-7.99 (2H, m), 7.71-7.67 (2H, m), 7.48-7.43 (3H, m), 7.20 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 169.27 (quat, Th**C**$_2$), 150.47 (CH), 149.78 (CH, Th**C**$_4$-H), 140.44 (quat), 140.01 (quat), 136.70 (CH), 133.48 (quat), 130.21 (CH), 128.93 (2CH), 126.38 (2CH), 122.47 (CH), 119.47 (CH); IR (thin film, cm^{-1}) ν_{max} 3053, 2984, 1584, 1466, 1450, 1434, 1420, 1265, 1162, 779, 738, 705; HRMS (ES +ve) calculated for $[C_{14}H_{10}N_2S+H]^+$ 239.0637, found 239.0636.

3-(2-Phenylthiazol-5-yl)pyridine **65q**



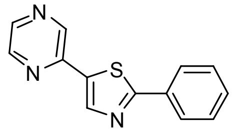
Following general procedure D using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 3-iodopyridine (153 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (10-20% ethyl acetate/hexane) gave the title compound as a pale yellow solid (148 mg, quantitative yield). MP (CH_2Cl_2) 90-91°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.87 (1H, d, *J* = 2.3, py), 8.57 (1H, dd, *J* = 1.6, 4.8, py), 8.06 (1H, s, ThC$_4$-**H**), 7.98-7.96 (2H, m), 7.87 (1H, ddd, *J* = 1.6, 2.3, 7.9, py), 7.48-7.44 (3H, m), 7.35 (1H, ddd, *J* = 0.7, 4.8, 7.9, py); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 168.15 (quat, Th**C**$_2$), 149.06 (CH, Th**C**$_4$-H), 147.30 (CH), 140.02 (CH), 135.07 (quat), 133.42 (CH), 133.14 (quat), 130.22 (CH), 128.89 (2CH), 127.49 (quat), 126.32 (2CH), 123.63 (CH); IR (thin film, cm^{-1}) ν_{max} 1561, 1522, 1467, 1450, 1415 1150, 1022, 974, 958, 843, 803, 759, 705; HRMS (EI) calculated for $[C_{14}H_{10}N_2S]^+$ 238.0565, found 238.0558.

Ethyl 4-(2-phenylthiazol-5-yl)benzoate **65n**



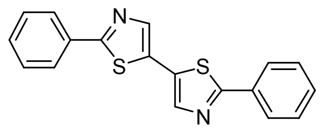
Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and ethyl iodobenzene-4-carboxylate (205 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) gave the title compound as a colourless solid (122 mg, 53% yield). MP ($CHCl_3$) 119-120°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.11-8.08 (3H, m), 8.00-7.97 (2H, m), 7.67-7.64 (2H, m), 7.49-7.45 (3H, m), 4.42 (2H, q, *J* = 7.1, C**H$_2$**CH$_3$), 1.44 (3H, t, *J* = 7.1, CH$_2$C**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 168.08 (quat, Th**C**$_2$), 165.84 (quat, **C**O$_2$Et), 140.21 (CH, Th**C**$_4$-H), 137.87 (quat), 135.42 (quat), 133.20 (quat), 130.22 (2CH and CH), 129.72 (quat), 128.89 (2CH), 126.29 (2CH), 126.05 (2CH), 61.01 (CH_2), 14.23 (CH_3); IR (thin film, cm^{-1}) ν_{max} 3054, 2987, 1714, 1608, 1531, 1452, 1425, 1368, 1266, 1185, 1155, 1109, 1022, 981, 896, 851; HRMS (EI) calculated for $[C_{18}H_{15}NO_2S]^+$ 309.0824, found 309.0827.

(2-Phenylthiazol-5-yl)pyrazine **65r**



Following general procedure D using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and iodopyrazine (153 mg, 0.744 mmol, 1.2 equiv), and purification by column chromatography (10-50% ethyl acetate/hexane) gave the title compound as a pale yellow solid (148 mg, quantitative yield). MP ($CHCl_3$) 159-161°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.98 (1H, d, J = 1.6, C**C**HN), 8.53 (1H, dd, J = 1.6, 2.6, **C**HCHNC), 8.45 (1H, d, J = 2.6, **C**HNC), 8.36 (1H, s), 8.01-7.98 (2H, m), 7.47-7.43 (3H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 170.51 (quat, Th**C**$_2$), 146.80 (quat), 144.25 (CH), 142.92 (CH), 141.66 (CH), 141.08 (CH), 136.56 (quat), 133.20 (quat), 130.61 (CH), 129.02 (2CH), 126.59 (2CH); IR (thin film, cm^{-1}) ν_{max} 1526, 1469, 1449, 1418, 1406, 1316, 1167, 1011, 848, 754, 683, 633; HRMS (EI) calculated for $[C_{13}H_9N_3S]^+$ 239.0517, found 239.0514.

2-Phenyl-5-(2-phenylthiazol-5-yl)thiazole **228a**



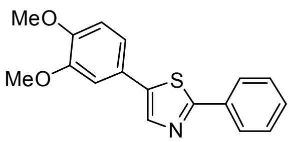
Following general procedure D, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 5-iodo-2-phenylthiazole (214 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (1-5% acetone/CH_2Cl_2) afforded the title compound as a yellow solid (198 mg, quantitative yield). MP ($CHCl_3$) 182°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.97-7.93 (6H, m), 7.48-7.44 (6H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.60 (2 quat, 2Th**C**$_2$), 141.12 (2CH, 2Th**C**$_4$-H), 133.11 (2 quat), 130.41 (2CH), 129.05 (4CH), 128.40 (2 quat), 126.48 (4CH); IR (thin film, cm^{-1}) ν_{max} 3019, 2400, 1479, 1417, 1216, 1149, 975, 929, 770; HRMS (ES +ve) calculated for $[C_{18}H_{12}N_2S_2+H]^+$, 321.0515 found 321.0512.

2'-(4-Methoxyphenyl)-2-phenyl-[5,5']bithiazolyl **228b**

Following general procedure D, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 5-iodo-2-anisylthiazole (236 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (1-5% acetone/CH_2Cl_2) afforded the title compound as a yellow solid (123 mg, 56% yield). MP ($CHCl_3$) 155-157°C; ^{1}H

NMR (360 MHz, $CDCl_3$) δ_H 7.95-7.92 (2H, m), 7.89-7.86 (4H, m), 7.47-7.44 (3H, m), 6.98-6.94 (2H, m), 3.85 (3H, s, OC$\mathbf{H_3}$); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.54 (quat, Th$\mathbf{C}_2$), 167.27 (quat, Th$\mathbf{C}_2$), 161.43 (quat, $\mathbf{C}_{Ar}OCH_3$), 140.92 (CH, Th$\mathbf{C}_4$-H), 140.85 (CH, Th$\mathbf{C}_4$-H), 133.15 (quat), 130.31 (CH), 129.01 (2CH), 128.61 (quat), 127.99 (2CH), 127.36 (quat), 126.43 (2CH), 126.03 (quat), 114.38 (2CH), 55.40 (O**C**H_3); IR (thin film, cm^{-1}) ν_{max} 1607, 1482, 1435, 1417, 1258, 1033, 846, 831, 763, 689, 629; HRMS (EI) calculated for $[C_{19}H_{14}N_2S_2O]^+$ 350.0548, found 350.0552.

2-Phenyl-5-(3,4-dimethoxy)thiazole **65x**

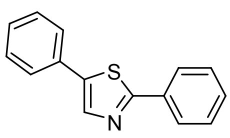


Following general procedure D using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv), 3,4-dimethyliodobenzene (197 mg, 0.744 mmol, 1.2 equiv) and purification by column chromatography (10-20% ethyl acetate/hexane), the title compound was isolated as a pale yellow solid (162 mg, 88% yield). MP ($CHCl_3$) 108-110°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.93-7.90 (2H, m), 7.88 (1H, s, ThC_4-**H**), 7.43-7.36 (3H, m), 7.10 (1H, m), 7.03 (1H, m), 6.82 (1H, m), 3.90 (3H, s, OC$\mathbf{H_3}$), 3.89 (3H, s, OC$\mathbf{H_3}$); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 166.01 (quat, Th$\mathbf{C}_2$), 149.11 (quat, $\mathbf{C}_{Ar}OCH_3$), 149.03 (quat, $\mathbf{C}_{Ar}OCH_3$), 139.14 (quat), 138.08 (CH, Th$\mathbf{C}_4$-H), 133.47 (quat), 129.63 (CH), 128.72 (2CH), 126.00 (2CH), 123.96 (quat), 119.24 (CH), 111.30 (CH), 109.51 (CH), 55.76 (O**C**H_3), 55.72 (O**C**H_3); IR (thin film, cm^{-1}) ν_{max} 2937, 2836, 1533, 1507, 1491, 1455, 1256, 1238, 1145, 1026, 841, 763, 691, 629; HRMS (ES +ve) calculated for $[C_{17}H_{15}NO_2S+H]^+$ 298.0896, found 298.0893.

4-(2-Phenylthiazol-5-yl)benzonitrile **65m**

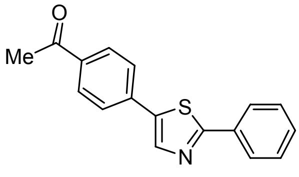
Following general procedure C, using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and iodobenzonitrile (205 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) afforded the title compound as a colourless solid (143 mg, 88% yield). MP (Et_2O) 183°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.12 (1H, s, ThC_4-**H**), 7.99-7.96 (2H, m), 7.70 (4H, s, $C_6\mathbf{H_4}CN$), 7.49-7.47 (3H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 168.94 (quat, Th$\mathbf{C}_2$), 140.91 (CH, Th$\mathbf{C}_4$-H), 136.93 (quat), 135.76 (quat), 133.08 (quat), 132.81 (2CH), 130.57 (CH), 129.04 (2CH), 126.77 (2CH), 126.46 (2CH), 118.43 (quat), 111.40 (quat); IR (thin film, cm^{-1}) ν_{max} 3055, 2223, 1996, 1601, 1532, 1488, 1449, 1422, 1265, 1168, 977, 896, 834, 737; HRMS (ES +ve) calculated for $[C_{16}H_{10}N_2S+H]^+$ 263.0637, found 263.0638.

2,5-Diphenylthiazole[170] **65a**



Following general procedure D, using 2-phenylthiazole (200 mg, 1.240 mmol, 1 equiv) and iodobenzene (303 mg, 1.488 mmol, 1.2 equiv), purification by column chromatography (0.5% ethyl acetate/hexane) gave the title compound as a colourless oil (255 mg 87% yield). ^{1}H NMR (360MHz, CDCl$_3$) δ_H 8.03 (1H, s), 8.00-7.97 (2H, m), 7.62-7.60 (2H, m), 7.47-7.32 (6H, m); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 166.95 (quat, Th**C**$_2$), 139.12 (quat), 139.02 (CH, Th**C**$_4$-H), 133.51 (quat), 131.21 (quat), 129.84 (CH), 128.94 (2CH), 128.81 (2CH), 128.12 (CH), 126.47 (2CH), 126.20 (2CH).

5-(4-Acetylphenyl)-2-phenylthiazole **65l**

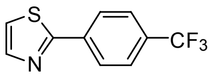


Following general procedure C using 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and 4-iodoacetophenone (183 mg, 0.744 mmol, 1.2 equiv), purification by column chromatography (CH$_2$Cl$_2$) gave the title compound as a yellow solid (163 mg, 94% yield). MP (CHCl$_3$) 147°C; ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.17 (1H, s, ThC$_4$-**H**), 8.06-8.01 (4H, m), 7.74-7.72 (2H, m), 7.53-7.49 (3H, m), 2.67 (3H, s, CH$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 196.98 (quat, **C**OCH$_3$), 168.34 (quat, Th**C**$_2$), 140.43 (CH, Th**C**$_4$-H), 137.79 (quat), 136.28 (quat), 135.76 (quat), 133.26 (quat), 130.32 (CH), 129.13 (2CH), 128.97 (2CH), 126.38 (2CH), 126.35 (2CH), 26.51 (**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 1681, 1603, 1420, 1265, 825, 738, 705, 590; HRMS (EI) calculated for $[C_{17}H_{13}NOS]^+$ 279.0718, found 279.0719.

2-(4-Methoxyphenyl)thiazole[171] **51c**

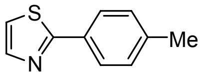
Following general procedure A, using 4-methoxythiobenzamide (859 mg, 6.000 mmol), purification by column chromatography (0-20% ethyl acetate/iso-hexane) gave the title compound as a colourless oil (792 mg, 81% yield). ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 7.92-7.88 (2H, m), 7.80 (1H, d, J = 3.3, ThC$_4$-**H**), 7.25 (1H, d, *J* = 3.3, ThC$_5$-**H**), 6.97-6.93 (2H, m), 3.85 (3H, s, OC**H$_3$**); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 168.28 (quat, Th**C**$_2$), 161.05 (quat, **C**$_{Ar}$OCH$_3$), 143.34 (CH, Th**C**$_4$-H), 128.00 (2CH), 126.55 (quat, ThC$_2$-**C**), 117.83 (CH, Th**C**$_5$-H), 114.25 (2CH), 55.36 (O**C**H$_3$).

2-(4-Trifluoromethylphenyl)thiazole **51e**



Following general procedure A using 4-trifluoromethylbenzamide (5.00 g, 0.024 mol), purification by column chromatography (0-20% ethyl acetate/iso-hexane) gave the title compound as a colourless solid (3.19 g, 37% yield). MP (CHCl$_3$) 74°C; ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.00-7.98 (2H, m), 7.85 (1H, d, *J* = 3.2, ThC$_4$-**H**), 7.63-7.61 (2H, m), 7.32 (1H, d, *J* = 3.2, ThC$_5$-**H**); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 166.21 (quat, Th**C**$_2$), 143.98 (CH, Th**C**$_4$-H), 136.49 (quat), 131.33 (quat, q, *J* = 36.7, **C**CF$_3$), 126.56 (2CH), 125.82 (2CH, q, *J* = 3.7, 2**C**HCCF$_3$), 123.80 (quat, q, *J* = 272.2, **C**F$_3$), 119.75 (CH, Th**C**$_5$-H); ^{19}F NMR (235 MHz, CDCl$_3$) δ_F -64.0 (3F, s); IR (thin film, cm^{-1}) ν_{max} 3122, 3054, 1616, 1485, 1421, 1326, 1265, 1170, 1129, 1109, 1067, 1019, 978, 848, 741, 706; HRMS (EI) calculated for $[C_{10}F_3H_6NS]^+$ 229.0173, found 229.0180.

2-(4-Methylphenyl)thiazole[172] **51d**

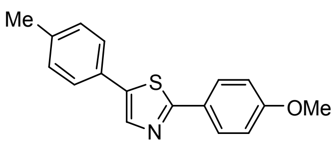


Following general procedure A using 4-methylthiobenzamide (2.00 g, 0.013 mol, 1 equiv), purification by column chromatography (0-20% ethyl acetate/iso-hexane) gave the title compound as a yellow oil (2.23 g, 91% yield). ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 7.88-7.84 (2H, m), 7.84 (1H, d, *J* = 3.3, ThC$_4$-**H**), 7.29 (1H, d, *J* = 3.3, ThC$_5$-**H**), 7.26-7.24 (2H, m), 2.40 (3H, s, C$_{Ar}$C**H$_3$**); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 168.58 (quat, Th**C**$_2$), 143.46 (CH, Th**C**$_4$-H), 140.19 (quat), 130.92 (quat), 129.60 (2CH), 126.46 (2CH), 118.30 (CH, Th**C**$_5$-H), 21.38 (C$_{Ar}$**C**H$_3$).

5-(4-Chlorophenyl)-2-(methoxyphenyl)thiazole **65aa**

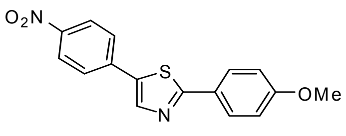
Following general procedure C, with 2-anisylthiazole (100 mg, 0.523 mmol, 1 equiv) and 4-iodochlorobenzene (150 mg, 0.627 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) afforded the title compound as a yellow solid (155 mg, 98% yield). MP ($CHCl_3$) 150°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.92 (1H, s, ThC$_4$-**H**), 7.90-7.86 (2H, m), 7.51-7.47 (2H, m), 7.37-7.34 (2H, m), 6.97-6.93 (2H, m), 3.85 (3H, s, OC**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.40 (quat, Th**C**$_2$), 161.22 (quat, C$_{Ar}$OCH$_3$), 139.15 (CH, Th**C**$_4$-H), 136.91 (quat), 133.80 (quat), 130.02 (quat), 129.19 (2CH), 127.83 (2CH), 127.60 (2CH), 126.39 (quat), 114.30 (2CH), 55.37 (O**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 3054, 1606, 1482, 1265, 1175, 1094, 896, 827, 743, 705; HRMS (EI) calculated for $[C_{16}H_{12}{}^{35}ClNOS]^+$ 301.0328, found 301.0315.

2-(4-Methoxyphenyl)-5-(4-methylphenyl)thiazole[8] **65ab**



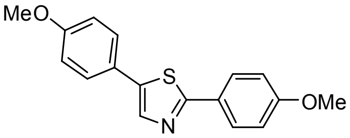
Following general procedure C, with 2-anisylthiazole (100 mg, 0.523 mmol, 1 equiv) and 4-iodotoluene (137 mg, 0.627 mmol, 1.2 equiv), purification by column chromatography (10-20% ethyl acetate/hexane) afforded the title compound as a yellow solid (141 mg, 96% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.89 (1H, s, ThC$_4$-**H**), 7.85-7.83 (2H, m), 7.53-7.49 (2H, m), 7.26-7.23 (2H, m), 6.95-6.91 (2H, m), 3.83 (3H, s, OC**H$_3$**), 2.39 (3H, s, C$_{Ar}$C**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 166.62 (quat, Th**C**$_2$), 161.05 (quat, **C**$_{Ar}$OCH$_3$), 138.43 (CH, Th**C**$_4$-H), 138.11 (quat), 129.72 (2CH), 128.68 (quat), 127.77 (2CH), 126.71 (quat), 126.44 (2CH), 114.29 (2CH), 55.40 (O**C**H$_3$), 21.22 (C$_{Ar}$**C**H$_3$), one quaternary not found.

2-(4-Methoxyphenyl)-5-(4-nitrophenyl)thiazole **65ac**



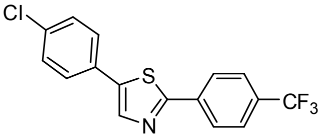
Following general procedure C, with 2-anisylthiazole (100 mg, 0.523 mmol, 1 equiv) and 4-iodonitrobenzene (156.2 mg, 0.627 mmol, 1.2 equiv), purification by column chromatography (10-50% ethyl acetate/hexane) afforded the title compound as a yellow solid (105 mg, 64% yield). MP ($CHCl_3$) 213°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.29-8.25 (2H, m), 8.11 (1H, s, ThC$_4$-**H**), 7.94-7.90 (2H, m), 7.75-7.71 (2H, m), 7.01-6.97 (2H, m), 3.88 (3H, s, OC**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 169.46 (quat, Th**C**$_2$), 161.72 (quat, **C**$_{Ar}$OCH$_3$), 146.92 (quat, C$_{Ar}$NO$_2$), 141.29 (CH, Th**C**$_4$-H), 137.99 (quat), 135.54 (quat), 128.14 (2CH), 126.68 (2CH), 126.03 (quat), 124.53 (2CH), 114.47 (2CH), 55.47 (O**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 3056, 2986, 1596, 1520, 1422, 1340, 1265, 896, 739, 706; HRMS (EI) calculated for $[C_{16}H_{12}N_2O_3S]^+$ 312.0569, found 312.0574.

2,5-Di(4-methoxyphenyl)thiazole[93] **65ad**



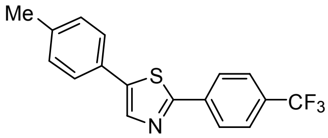
Following general procedure C, with 2-anisylthiazole (100 mg, 0.523 mmol, 1 equiv) and 4-iodochlorobenzene (150 mg, 0.627 mmol, 1.2 equiv), purification by column chromatography (10-20% ethyl acetate/hexane) afforded the title compound as a yellow solid (114 mg, 73% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.91-7.87 (2H, m), 7.85 (1H, s, ThC$_4$-**H**), 7.53-7.49 (2H, m), 6.98-6.92 (4H, m), 3.86 (3H, s, OC**H$_3$**), 3.84 (3H, s, OC**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 166.23 (quat, Th**C**$_2$), 161.01 (quat, **C**$_{Ar}$OCH$_3$), 159.62 (quat, **C**$_{Ar}$OCH$_3$), 138.22 (quat), 137.90 (CH, Th**C**$_4$-H), 127.85 (2CH), 127.72 (2CH), 126.74 (quat), 124.17 (quat), 114.48 (2CH), 114.29 (2CH), 55.40 (O**C**H$_3$), 55.38 (O**C**H$_3$).

5-(4-Chlorophenyl)-2-(4-trifluoromethylphenyl)thiazole **65ae**



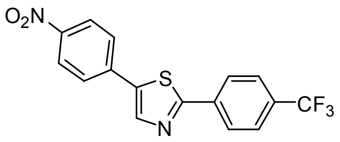
Following general procedure C, with 2-(4-trifluoromethylphenyl)thiazole (100 mg, 0.436 mmol) and 4-iodochlorobenzene (125 mg, 0.524 mmol), purification by column chromatography (0-4% acetone/CH_2Cl_2) afforded the title compound as a yellow solid (93 mg, 63% yield). MP ($CHCl_3$) 132°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.08-8.05 (2H, m), 8.03 (1H, s, ThC$_4$-**H**), 7.72-7.70 (2H, m), 7.55-7.53 (2H, m), 7.42-7.38 (2H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 165.39 (quat, Th**C**$_2$), 139.86 (CH, Th**C**$_4$-H), 139.25 (quat), 136.54 (quat), 134.58 (quat), 131.68 (quat, q, J = 32.8, **C**$_{Ar}$CF$_3$), 129.48 (quat), 129.41 (2CH), 127.89 (2CH), 126.54 (2CH), 126.03 (2CH, q, J = 3.6, 2**C**HCCF$_3$), 123.85 (quat, q, J = 272.2, C$_{Ar}$**C**F$_3$); ^{19}F NMR (235 MHz, $CDCl_3$) δ_F -64.0 (3F, s); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 1412, 1326, 1265, 1067, 896, 741, 706; HRMS (EI) calculated for $[C_{16}F_3H_9{}^{35}ClNOS]^+$ 339.0096, found 339.0083.

5-(4-Methylphenyl)-2-(4-trifluoromethylphenyl)thiazole **65af**



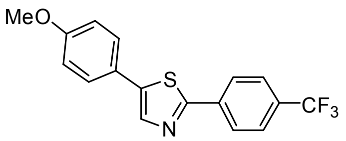
Following general procedure C, with 2-(4-trifluoromethylphenyl)thiazole (100 mg, 0.436 mmol, 1 equiv) and 4-iodotoluene (114 mg, 0.524 mmol, 1.2 equiv), purification by column chromatography (0-2% acetone/CH_2Cl_2) afforded the title compound as a yellow solid (44.6 mg, 32% yield). MP ($CHCl_3$) 179°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.08-8.06 (2H, m), 8.02 (1H, s, ThC$_4$-**H**), 7.72-7.69 (2H, m), 7.52-7.49 (2H, m), 7.25-7.23 (2H, m), 3.40 (3H, s, C$_{Ar}$C**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 164.55 (quat, Th**C**$_2$), 140.77 (quat), 139.15 (CH, Th**C**$_4$-H), 138.82 (quat), 136.83 (quat), 131.30 (quat, q, J = 32.7, **C**$_{Ar}$CF$_3$), 129.87 (2CH), 128.13 (quat), 126.67 (2CH), 126.44 (2CH), 125.97 (2CH, q, J = 3.7, **C**HC$_{Ar}$CF$_3$), 124.02 (quat, q, J = 272.3, C$_{Ar}$**C**F$_3$), 21.26 (CH$_3$, **C**$_{Ar}$CH$_3$); ^{19}F NMR (235 MHz, $CDCl_3$) δ_F -64.0 (3F, s); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 2253, 1421, 1325, 1265, 907, 728, 651; HRMS (EI) calculated for $[C_{17}F_3H_{12}NS]^+$ 319.0643, found 319.0643.

5-(4-Nitrophenyl)-2-(4-trifluoromethylphenyl)thiazole **65ag**



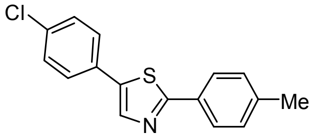
Following general procedure D with 2-(4-trifluoromethylphenyl)thiazole (100 mg, 0.436 mmol, 1 equiv) and 4-iodonitrobenzene (130 mg, 0.524 mmol, 1.2 equiv), purification by column chromatography (0-10% acetone/CH_2Cl_2) afforded the title compound as a yellow solid (121 mg, 79% yield). MP (EtOH) 175-176°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.31-8.28 (2H, m), 8.20 (1H, s, ThC$_4$-**H**), 8.11-8.08 (2H, m), 7.78-7.72 (4H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.31 (quat, Th**C**$_2$), 147.36 (quat), 141.73 (CH), 137.57 (quat), 137.30 (quat), 136.14 (quat), 132.17 (quat, q, J = 32.8, **C**$_{Ar}$CF$_3$), 127.06 (2CH), 126.76 (2CH), 126.13 (2CH, q, J = 3.6, 2**C**HC$_{Ar}$CF$_3$), 124.60 (2CH), 123.74 (quat, q, J = 272.4, C$_{Ar}$**C**F$_3$); ^{19}F NMR (235 MHz, $CDCl_3$) δ_F -64.0 (3F, s); IR (thin film, cm^{-1}) ν_{max} 1594, 1521, 1340, 1322, 1133, 1110, 1065, 845, 751, 688, 631; HRMS (EI) calculated for $[C_{16}H_9N_2O_2F_3S]^+$ 350.0337, found 350.0326.

5-(4-Methoxyphenyl)-2-(4-trifluoromethylphenyl)thiazole **65ah**



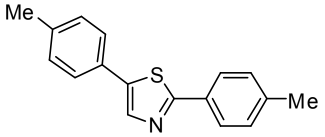
Following general procedure C, with 2-(4-trifluoromethylphenyl)thiazole (100 mg, 0.436 mmol, 1 equiv) and 4-iodoanisole (123 mg, 0.524 mmol, 1.2 equiv), purification by column chromatography (0-2% acetone/CH_2Cl_2) afforded the title compound as a yellow solid (108 mg, 74% yield). MP ($CHCl_3$) 160°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.07-8.04 (2H, m), 7.96 (1H, s, ThC_4-**H**), 7.71-7.69 (2H, m), 7.56-7.51 (2H, m), 6.98-6.94 (2H, m), 3.85 (3H, s, OC**H₃**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 164.09 (quat, Th**C**$_2$), 160.04 (quat, **C**$_{Ar}$OCH$_3$), 140.55 (quat), 138.60 (CH, Th**C**$_4$-H), 136.83 (quat), 131.31 (quat, q, *J* = 32.7, C$_{Ar}$CF$_3$), 128.09 (2CH), 126.38 (2CH), 125.95 (2CH, q, *J* = 3.8, 2**C**HC$_{Ar}$CF$_3$), 123.92 (quat, q, *J* = 272.2, C$_{Ar}$**C**F$_3$), 123.55 (quat), 114.60 (2CH), 55.39 (CH_3); ^{19}F NMR (250 MHz, $CDCl_3$) δ_F -64.0 (3F, s); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 1325, 1265, 1067, 896, 741, 706; HRMS (EI) calculated for $[C_{17}F_3H_{12}NOS]^+$ 335.0592, found 335.0588.

5-(4-Chlorophenyl)-2-(4-methylphenyl)thiazole **65ai**



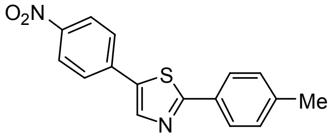
Following general procedure C with 2-(4-methylphenyl)thiazole (100 mg, 0.570 mmol, 1 equiv) and 4-iodonitrobenzene (154 mg, 0.646 mmol, 1.2 equiv), purification by column chromatography (10-20% ethyl acetate/hexane) afforded the title compound as a yellow solid (139 mg, 85% yield). MP ($CHCl_3$) 151°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.95 (1H, s, ThC_4-**H**), 7.85-7.83 (2H, m), 7.51-7.47 (2H, m), 7.38-7.34 (2H, m), 7.25-7.23 (2H, m), 2.39 (3H, s, C$_{Ar}$C**H₃**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.67 (quat, Th**C**$_2$), 140.44 (quat), 139.26 (CH, Th**C**$_4$-H), 137.38 (quat), 133.91 (quat), 130.80 (quat), 129.95 (quat), 129.64 (2CH), 129.20 (2CH), 127.66 (2CH), 126.25 (2CH), 21.41 (**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 1483, 1421, 1265, 896, 828, 747, 705; HRMS (EI) calculated for $[C_{16}H_{12}{}^{35}ClNS]$ 285.0379, found, 285.0380.

2,5-Di(4-methylphenyl)thiazole **65aj**



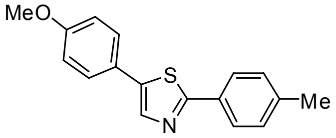
Following general procedure C, with 2-(4-methylphenyl)thiazole (100 mg, 0.570 mmol, 1 equiv) and 4-iodotoluene (141 mg, 0.646 mmol, 1.2 equiv), purification by column chromatography (10-20% ethyl acetate/hexane) afforded the title compound as a yellow solid (147 mg, 97% yield). MP ($CHCl_3$) 144°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.96 (1H, s, ThC_4-**H**), 7.87-7.84 (2H, m), 7.50-7.48 (2H, m), 7.26-7.21 (4H, m), 2.40 (3H, s, C**H₃**), 2.39 (3H, s, C**H₃**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 166.87 (quat, T**C**$_2$), 140.12 (quat), 138.88 (quat), 138.52 (CH, Th**C**$_4$-H), 138.19 (quat), 131.08 (quat), 129.71 (2CH), 129.60 (2CH), 128.61 (quat), 126.48 (2CH), 126.20 (2CH), 21.40 (**C**H_3), 21.21 (**C**H_3); IR (thin film, cm^{-1}) ν_{max} 3053, 2986, 1493, 1421, 1265, 896, 819, 741; HRMS (EI) calculated for [$C_{17}H_{15}NS$] 265.0925, found 265.0925.

5-(4-Nitrophenyl)-2-(4-methylphenyl)thiazole **65ak**



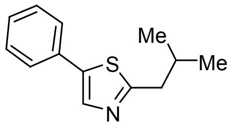
Following general procedure C with 2-(4-methylphenyl)thiazole (100 mg, 0.570 mmol, 1 equiv) and 4-iodonitrobenzene (171 mg, 0.646 mmol, 1.2 equiv), purification by column chromatography (10-50% ethyl acetate/hexane) afforded the title compound as a yellow solid (68 mg, 40% yield). MP ($CHCl_3$) 173°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.28-8.24 (2H, m), 8.12 (1H, s, ThC_4-**H**), 7.88-7.83 (2H, m), 7.74-7.70 (2H, m), 7.28-7.26 (2H, m), 2.41 (3H, s, C**H₃**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 169.67 (quat, Th**C**$_2$), 146.94 (quat), 141.31 (CH, Th**C**$_4$-H), 141.18 (quat), 137.84 (quat), 135.98 (quat), 130.42 (quat), 129.76 (2CH), 126.72 (2CH), 126.45 (2CH), 124.49 (2CH), 21.47 (**C**H_3); IR (thin film, cm^{-1}) ν_{max} 3055, 2986, 1598, 1519, 1434, 1347, 1328, 1264, 1109, 896, 840, 817, 738, 633; HRMS (EI) calculated for [$C_{16}H_{12}N_2O_2S$]$^+$ 296.0620, found 296.0620.

5-(4-Methoxyphenyl)-2-(4-methylphenyl)thiazole[173] **65al**



Following general procedure C with 2-(4-methylphenyl)thiazole (100 mg, 0.570 mmol, 1 equiv) and 4-iodoanisole (151 mg, 0.646 mmol, 1.2 equiv), purification by column chromatography (10-20% ethyl acetate/hexane) afforded the title compound as a yellow solid (124 mg, 77% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.89 (1H, s, ThC_4-**H**), 7.85-7.83 (2H, m), 7.53-7.49 (2H, m), 7.26-7.23 (2H, m), 6.95-6.91 (2H, m), 3.83 (3H, s, OC**H₃**), 2.39 (3H, s, C**H₃**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 166.40 (quat), 159.62 (quat), 139.99 (quat), 138.62 (quat), 137.95 (CH), 131.07 (quat), 129.55 (2CH), 127.83 (2CH), 126.11 (2CH), 124.04 (quat), 114.43 (2CH), 55.29 (OCH_3), 21.36 (CH_3).

2-Isobutyl-5-phenylthiazole[93] **251e**



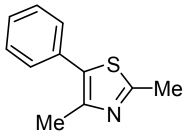
Following general procedure D with 2-isobutylthiazole (100 mg, 0.708 mmol, 1 equiv) and iodobenzene (173 mg, 0.850 mmol, 1.2 equiv), purification by column chromatography (0-5% ethyl acetate/hexane) gave the title compound as a colourless oil (153 mg, quantitative yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.82 (1H, s, ThC_4-**H**), 7.51 (2H, m), 7.37-7.33 (2H, m), 7.28 (1H, m), 2.86 (2H, d, *J* = 7.2, C**H₂**), 2.14 (1H, m, C**H**), 1.01 (6H, d, *J* = 6.6, 2C**H₃**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 169.46 (quat, Th**C**₂), 138.32 (quat), 137.44 (CH, Th**C**₄-H), 131.51 (CH), 128.85 (2CH), 127.79 (CH), 126.41 (2CH), 42.39 (**C**H₂), 29.67 (**C**H), 22.17 (2**C**H₃).

4,5-Di(4-chlorophenyl)-2-phenylthiazole[93] **248a**

Following general procedure D with 4-(4-chlorophenyl)-2-phenylthiazole (100 mg, 0.368 mmol, 1 equiv) and iodochlorobenzene (105 mg, 0.442 mmol, 1.2 equiv), purification by column chromatography (10% ethyl acetate/hexane) gave the title compound as a colourless solid (118 mg, 83% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.01-7.98 (2H, m), 7.55-7.51 (2H, m), 7.48-7.45 (3H, m), 7.35-7.29 (6H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 166.04 (quat, Th**C**₂), 149.89

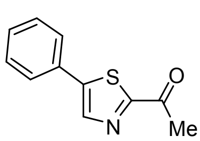
(quat), 134.45 (quat), 133.96 (quat), 133.30 (quat), 133.10 (quat), 131.95 (quat), 130.80 (2CH), 130.37 (2CH), 130.28 (CH), 130.27 (quat), 129.16 (2CH), 128.98 (2CH), 128.62 (2CH), 126.43 (2CH).

2,4-Dimethyl-5-phenylthiazole **251h**



Following general procedure D with 2,4-dimethylthiazole (100 mg, 0.884 mmol, 1 equiv) and iodobenzene (216 mg, 1.060 mmol, 1.2 equiv), purification by column chromatography (20% ethyl acetate/hexane) gave the title compound as a yellow oil (140 mg, 84% yield). ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 7.43-7.31 (5H, m), 2.70 (3H, s, ThC$_2$C**H$_3$**), 2.49 (3H, m, ThC$_4$C**H$_3$**); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 163.02 (quat, Th**C$_2$**), 146.86 (quat), 132.17 (quat) 131.18 (quat), 128.94 (2CH), 128.46 (2CH), 127.27 (CH), 18.93 (CH$_3$, ThC$_2$**C**H$_3$), 15.89 (CH$_3$, ThC$_4$**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 3057, 2922, 1601, 1494, 1438, 1377, 1250, 1180, 7589, 698; HRMS (FAB) calculated for $[C_{11}H_{11}NS+H]^+$ 190.0691, found 190.0690.

1-(5-Phenylthiazol-2-yl)ethanone **251f**

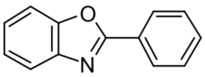


Following general procedure D with 2-acetylthiazole (100 mg, 0.786 mmol, 1 equiv) and iodobenzene (193 mg, 0.944 mmol, 1.2 equiv), purification by column chromatography (10% ethyl acetate/hexane) gave the title compound as a colourless solid (113 mg, 70% yield). MP (CHCl$_3$) 113-115°C; ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.13 (1H, s, ThC$_4$-**H**), 7.64-7.62 (2H, m), 7.47-7.41 (3H, m), 2.72 (3H, s, COC**H$_3$**); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 191.69 (quat, **C**OCH$_3$), 165.47 (quat, Th**C$_2$**), 147.10 (quat), 140.17 (CH), 130.47 (quat), 129.57 (CH), 129.32 (2CH), 127.19 (2CH), 25.67 (CH$_3$, COC**H$_3$**); IR (thin film, cm^{-1}) ν_{max} 1681, 1450, 1421, 1406, 1261, 1056, 1019, 760, 687; HRMS (FAB) calculated for $[C_{11}H_9NOS+H]^+$ 204.0483, found 204.0481.

2-Phenylbenzothiazole[174] **251a**

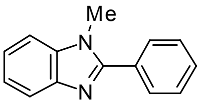
Following general procedure D with benzothiazole (100 mg, 0.740 mmol, 1 equiv) and iodobenzene (181 mg, 0.888 mmol, 1.2 equiv), purification by column chromatography (10% ethyl acetate/hexane) gave the title compound as a colourless solid (156 mg, quantitative yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.12-8.09 (3H, m), 7.89 (1H, m), 7.52-7.48 (4H, m), 7.38 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.96 (quat, N=**C**-S), 154.05 (quat), 134.97 (quat), 133.52 (quat), 130.87 (CH), 128.92 (2CH), 127.46 (2CH), 126.22 (CH), 125.09 (CH), 123.14 (CH), 121.53 (CH).

2-Phenylbenzoxazole[174] **251b**



Following general procedure D with benzoxazole (100 mg, 0.839 mmol, 1 equiv) and iodobenzene (206 mg, 1.007 mmol, 1.2 equiv), purification by column chromatography (20% ethyl acetate/hexane) gave the title compound as a colourless solid (130 mg, 79% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.26-8.23 (2H, m), 7.78 (1H, m), 7.55 (1H, m), 7.49-7.47 (3H, m), 7.33-7.31 (2H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 162.85 (quat, N=**C**-O), 150.60 (quat), 141.98 (quat), 131.34 (CH), 128.74 (2CH), 127.46 (2CH), 127.02 (quat), 124.94 (CH), 124.42 (CH), 119.87 (CH), 110.44 (CH).

N-Methyl-2-phenylbenzimidazole[175] **251c**



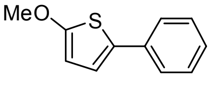
Following general procedure D with N-methylbenzimidazole (100 mg, 0.757 mmol, 1 equiv) and iodobenzene (185 mg, 0.908 mmol, 1.2 equiv), purification by column chromatography (50% ethyl acetate/hexane) gave the title compound as a colourless solid (157 mg, quantitative yield). ^{1}H NMR (360 MHz, $CDCl_3$), δ_H 7.83 (1H, m), 7.72-7.69 (2H, m), 7.49-7.44 (3H, m), 7.32-7.29 (3H, m), 3.74 (3H, s, NC**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 153.43 (quat, N-**C**=N), 142.62 (quat), 136.29 (quat), 129.87 (quat), 129.46 (CH), 129.14 (2CH), 128.40 (2CH), 122.50 (CH), 122.16 (CH), 119.46 (CH), 109.45 (CH), 31.37 (N**C**H$_3$).

2,5-Diphenyloxazole[176] **251i**

Following general procedure D with 2-phenyloxazole (100 mg, 0.689 mmol, 1 equiv) and iodobenzene (169 mg, 0.827 mmol, 1.2 equiv), purification by column chromatography (CH_2Cl_2) gave the title compound as a colourless solid (140 mg, 92% yield). ^{1}H NMR (360 MHz,

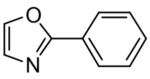
$CDCl_3$) δ_H 8.13-8.11 (2H, m), 7.74-7.72 (2H, m), 7.52-7.43 (6H, m), 7.35 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 161.13 (quat, Ox**C**$_2$), 151.24 (quat), 130.31 (CH, Ox**C**$_4$-H), 128.92 (2CH), 128.80 (2CH), 128.42 (CH), 128.00 (quat), 127.43 (quat), 126.26 (2CH), 124.18 (2CH), 123.43 (CH).

2-Methoxy-5-phenylthiophene[177] **251g**



Following general procedure D with 2-methoxythiophene (100 mg, 0.876 mmol, 1 equiv) and iodobenzene (214 mg, 1.051 mmol, 1.2 equiv), purification by column chromatography (5% ethyl acetate/hexane) gave the title compound as a colourless oil (136 mg, 82% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.55-7.53 (2H, m, Ph), 7.40-7.35 (2H, m, Ph), 7.26 (1H, m, Ph), 7.00 (1H, d, *J* = 4.0, Th), 6.22 (1H, d *J* = 4.0, Th), 3.94 (3H, s, OC**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 165.88 (quat, Th**C**$_2$OMe), 134.65 (quat) 130.13 (quat), 128.73 (2CH), 126.51 (CH), 124.76 (2CH), 120.48 (CH), 104.66 (CH), 60.08 (O**C**H$_3$).

2-Phenyloxazole[178] **51f**



Benzamide (5.00 g, 0.041 mol, 1 equiv) was dissolved in acetic anhydride (10 mL) under N_2. Chloroacetaldehyde monohydrate[5] (6.40 g, 0.082 mmol, 2 equiv) was added dropwise and the reaction mixture heated to 50 °C. The solution was further heated to reflux for 5 hr, then concentrated *in vacuo* to a brown oil. Water (40 mL) was added and the pH adjusted (to pH 8) with NaOH (1.0 M, ~40 mL). The product was extracted into CH_2Cl_2 (2 × 40 mL) then dried with brine (40 mL) and over $MgSO_4$, and finally concentrated to a brown oil. Purification by column chromatography (5% ethyl acetate/hexane) afforded the title compound as a brown oil (3.51 g, 59% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.12-8.08 (2H, m), 7.74 (1H, d, *J* = 0.7, OxC$_4$-**H**), 7.53-7.47 (3H, m), 7.18 (1H, d, *J* = 0.7, OxC$_5$-**H**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.76 (quat, O-**C**=N), 138.37 (CH, Ox**C**$_4$-H), 130.14 (CH), 128.35 (2CH), 128.21 (CH), 127.29 (quat), 126.14 (2CH).

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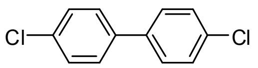
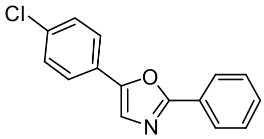
[5] Chloroacetaldehyde monohydrate was isolated from the commercially available aqueous solution (50%) by stirring for 1 hr with anhydrous calcium chloride (approximately 0.35 g per mL) and isolating the lower layer.

4,4'-Dichlorobiphenyl[179] **227**



4-Iodochlorobenzene (178 mg, 0.744 mmol, 1.2 equiv), Cs_2CO_3 (303 mg, 0.930 mmol, 1.5 equiv), $Pd_2(dba)_3$ (14 mg, 0.016 mmol, 0.025 equiv), PPh_3 (16 mg, 0.062 mmol, 0.10 equiv) and AgF (157 mg, 1.240 mmol, 2 equiv) were combined in MeCN (5 mL) together with 2-phenylthiazole (100 mg, 0.620 mmol, 1 equiv) and heated to 100 °C under microwave radiation for 2 hr. The reaction mixture was filtered through celite, washed with CH_2Cl_2 and acetone and concentrated *in vacuo*. Following chromatography (5% ethyl acetate/hexane) the product was isolated as a colourless solid, (77 mg, 92% yield[6]). ^1H NMR (360 MHz, $CDCl_3$) δ_H 7.44-7.30 (8H, q t, *J* = 9.1, 4.3); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 138.83 (2 quat), 134.14 (2 quat), 129.44 (4CH), 128.62 (4CH).

5-(4'-Chlorophenyl)-2-phenyloxazole[180] **251j**



Following general procedure C using 2-phenyloxazole (100 mg, 0.689 mmol, 1 equiv), 4-iodochlorobenzene (197 mg, 0.827 mmol, 1.2 equiv), Cs_2CO_3 (337 mg, 1.033 mmol, 1.5 equiv), $Pd_2(dba)_3$ (16 mg, 0.017 mmol, 0.025 equiv), PPh_3 (18 mg, 0.069 mmol, 0.10 equiv) and AgF (175 mg, 1.378 mmol, 2 equiv), were heated at 60 °C for 120 hr. Following purification by column chromatography (2% ethyl acetate/hexane) the title compound was isolated as a colourless solid (76 mg, 43% yield). ^1H NMR (360 MHz, $CDCl_3$) δ_H 8.05-8.01 (2H, m), 7.59 (2H, m), 7.43-7.33 (6H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 161.78 (quat, O-**C**=N), 150.67 (quat), 134.59 (quat), 130.93 (CH, Ox**C**$_4$-H), 129.63 (2CH), 129.27 (2CH), 127.63 (quat), 126.90 (quat), 126.74 (2CH), 125.81 (2CH), 124.22 (CH).

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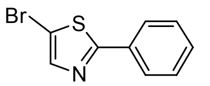
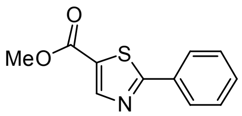
[6] Calculated with respect to iodochlorobenzene.

2-Phenyl-5-bromothiazole[181] **300a**



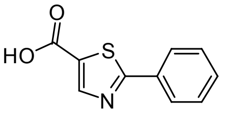
Sodium acetate (5.10 g, 0.062 mol, 2 equiv) and 2-phenylthiazole (5.00 g, 0.031 mol, 1 equiv) were dissolved in glacial acetic acid (25 mL) and bromine (1.59 mL, 0.031 mol, 1 equiv) was added dropwise. After 2 hr starting material remained and further bromine (3.18 mL, 0.062 mol, 2 equiv) was added and the reaction was left to stir for 3 days. Sodium thiosulfate (30 mL) was added to quench the unreacted bromine followed by NaOH (1.0 M, ~40 mL) to adjust to pH 9 and the aqueous phase was extracted into CH_2Cl_2 (200 mL). The organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow solid. Purification by column chromatography (2% ethyl acetate/hexane) gave the title compound as a colourless solid (4.02 g, 54% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 7.87-7.84 (2H, m), 7.73 (1H, s, ThC$_4$-**H**), 7.44-7.41 (3H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 169.42 (quat, Th**C**$_2$), 144.76 (CH, Th**C**$_4$-H), 132.99 (quat), 130.31 (CH), 128.95 (2CH), 126.12 (2CH), 108.44 (quat, Th**C**$_5$-Br).

Methyl 2-phenylthiazole-5-carboxylate **263**



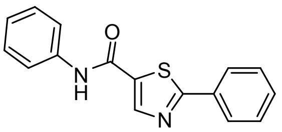
2-Phenylthiazole (200 mg, 1.240 mmol, 1 equiv) was dissolved in tetrahydrofuran (5 mL) at -78°C. ^{n}BuLi (0.775 mL, 1.6 M in hexanes, 1.240 mmol, 1 equiv) was added dropwise causing the colourless solution to become pale yellow. This was stirred at -78°C for 15 min followed by dropwise addition of methylchloroformate (115 μL, 1.490 mmol, 1.2 equiv). After a further 15 min at -78°C no reaction was observed and the reaction was warmed to ambient temperature and stirred for 30 min. $NH_4Cl_{(sat.aq)}$ (20 mL) was added together with ethyl acetate (20 mL) and the phases separated. The aqueous phase was extracted with ethyl acetate (20 mL), then the combined organics were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by recrystallisation from diethylether gave the title compound as a colourless solid (266 mg, yield 98%). MP (Et_2O) 102°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.21 (1H, s, ThC$_4$-**H**), 7.78-7.74 (2H, m), 7.25-7.11 (3H, m), 3.70 (3H, s, OC**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 174.41 (quat), 162.77 (quat), 150.32 (CH, Th**C**$_4$-H), 133.87 (quat), 132.23 (CH), 130.13 (2CH), 129.53 (quat), 127.91 (2CH), 53.52 (CO$_2$**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 3399, 1996, 1708, 1518, 1454, 1313, 1254, 1150, 1092, 902, 751; HRMS (ES +ve) calculated for $[C_{11}H_9NO_2S+H]^+$ 220.0427, found 220.0426.

2-Phenylthiazole-5-carboxylic acid[182] **301**



Methyl 2-phenylthiazole-5-carboxylate (1.00 g, 4.561 mmol, 1 equiv) was dissolved in methanolic KOH (1.0 M, 10 mL) and heated to reflux for 10 min. The resulting potassium salt was recovered by filtration then CH$_2$Cl$_2$ (20 mL) and water (20 mL) were added to the solid and the pH of the aqueous layer adjusted to pH 2 with HCl (2.0 M, ~5 mL). The layers were separated and the organics dried over MgSO$_4$ and concentrated *in vacuo* to give the title compound as a white solid (0.94 g, quantitative yield). ^{1}H NMR (360 MHz, CD$_3$OD) δ_H 8.34 (1H, s, ThC$_4$-**H**), 7.98-7.95 (2H, m), 7.51-7.44 (3H, m); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 174.45 (quat), 163.55 (quat), 149.53 (CH, Th**C**$_4$-H), 133.68 (quat), 132.06 (CH), 129.93 (2CH), 127.51 (2CH). (One quaternary not found).

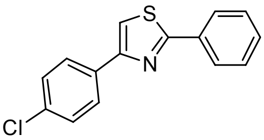
N,2-Diphenylthiazole-5-carboxamide[93] **269**



2-Phenylthiazole-5-carboxylic acid (3.00 g, 0.014 mol, 1 equiv) was suspended in thionyl chloride (25 mL) and heated to reflux for 45 min under N$_2$. Excess thionyl chloride was removed under vacuum and the last traces removed by a stream of dry N$_2$ being passed over the solid for 2 hr. The solid was then suspended in dry CH$_2$Cl$_2$ under N$_2$ and aniline (5.0 mL, 0.058 mmol, 4 equiv) was added dropwise with cooling. The suspension was concentrated *in vacuo* and the resultant solid stirred with diethyl ether (50 mL) overnight and the title compound collected by filtration as an off white solid (3.27 g, 81% yield). ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 10.48 (1H, s, N**H**), 8.69 (1H, s, ThC$_4$-**H**), 8.04-8.01 (2H, m), 7.74-7.72 (2H, d, *J* = 7.6), 7.55-7.53 (3H, m), 7.38 (2H, t, *J* = 7.9), 7.13 (1H, t, *J* = 7.4); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 170.71 (quat, **C**ONHPh), 158.39 (quat, Th**C**$_2$), 144.72 (CH, Th**C**$_4$-H), 138.28 (quat), 135.60

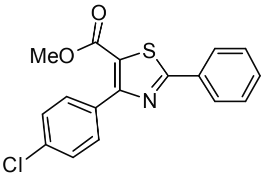
(quat), 132.45 (quat), 131.12 (CH), 129.32 (2CH), 128.71 (2CH), 126.47 (2CH), 124.07 (CH), 120.40 (2CH).

4-(4’-Chlorophenyl)-2-phenylthiazole **270**



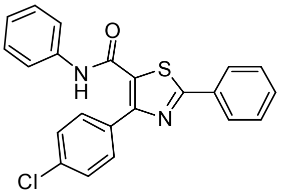
Thiobenzamide (5.00 g, 0.036 mol, 1 equiv) was dissolved in acetic anhydride (20 mL) and toluene (20 mL) and 4’-chloro-2-bromoacetophenone (10.20 g, 0.044 mol, 1.2 equiv) was added in portions. The solution was heated to reflux for 30 min then cooled to ambient temperature. Water was added and the pH was adjusted to pH 9 with NaOH (5.0 M, ~30 mL). The product was extracted into CH_2Cl_2 (2 × 100 mL), washed with brine (150 mL), dried over $MgSO_4$ and finally concentrated to a brown solid. Purification by column chromatography (2% ethyl acetate/hexane) provided the title compound as a yellow solid (5.35 g, 54% yield). MP (ethyl acetate) 130°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.05-8.02 (2H, m), 7.95-7.91 (2H, m), 7.50-7.39 (6H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 168.02 (quat, Th**C**$_2$), 154.96 (quat, Th**C**$_4$), 133.84 (quat), 133.49 (quat), 132.92 (quat), 130.11 (CH), 128.89 (2CH), 128.82 (2CH), 127.63 (2CH), 126.53 (2CH), 112.83 (CH); IR (thin film, cm^{-1}) ν_{max} 3054, 2986, 1476, 1440, 1265, 1091, 1055, 1014, 979, 897, 838, 739, 708; HRMS (EI) Calculated for $[C_{15}H_{10}{}^{35}ClNS]^+$ 271.0222, found 271.0216.

Methyl 4-(4’-chlorophenyl)-2-phenylthiazole-5-carboxylate **302**



4-(4’-Chlorophenyl)-2-phenylthiazole (1.00 g, 3.680 mmol, 1 equiv) was dissolved in tetrahydrofuran (50 mL) at -78 °C. ^{n}BuLi (2.30 mL, 1.6 M in hexanes, 3.680 mmol, 1 equiv) was added dropwise causing the colourless solution to become pale yellow. This was stirred at -78 °C for 15 min followed by dropwise addition of methylchloroformate (0.43 mL, 5.520 mmol, 1.5 equiv) causing a solid to precipitate. After a further 15 min at -78 °C the reaction mixture was warmed to ambient temperature causing the solid to dissolve and stirred for 15 min. The reaction was quenched by dropwise addition of $NH_4Cl_{(sat.aq)}$ (50 mL) together with ethyl acetate (50 mL) and the phases separated. The aqueous phase was extracted with ethyl acetate (2 × 50 mL) and the combined organics washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The yellow solid was recrystallised from diethylether to provide the product as a colourless solid (1.15 g, 95% yield). MP (Et_2O) 162°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.04-8.01 (2H, m), 7.83-7.80 (2H, m), 7.50-7.42 (5H, m), 3.85 (3H, s, OC**H₃**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 171.23 (quat, **C**O_2CH_3), 162.93 (quat, Th**C**$_2$), 160.80 (quat, Th**C**$_4$), 136.36 (quat), 133.70 (quat), 133.50 (quat), 132.41 (CH), 132.40 (2CH), 130.17 (2CH), 129.13 (2CH), 127.99 (2CH), 122.97 (quat), 53.54 (O**C**H_3); IR (thin film, cm^{-1}) ν_{max} 1996, 1731, 1481, 1429, 1325, 1272, 1141, 1079, 838, 763; HRMS (EI) calculated for $[C_{17}H_{12}{}^{35}ClNO_2S]^+$ 329.0277, found 329.0268.

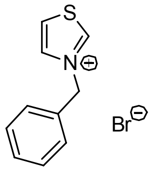
4-(4-Chlorophenyl)-N,2-diphenylthiazole-5-carboxamide **298**



Methyl 4-(4'-Chlorophenyl)-2-phenylthiazole-5-carboxylate (1.00 g, 3.030 mmol, 1 equiv) was dissolved in methanolic KOH (1.0 M, 20 mL) and heated to reflux for 10 min. The resulting potassium salt was recovered by filtration then CH_2Cl_2 (20 mL) and water (20 mL) were added to the solid and the pH of the aqueous layer adjusted to pH 2 with HCl (2.0 M, ~10 mL). The layers were separated and the organics dried over $MgSO_4$ and concentrated *in vacuo* to give the free acid in quantitative yield as a white solid. This was suspended in thionyl chloride (25 mL) and heated to reflux for 45 min under N_2. Excess thionyl chloride was removed under vacuum and the last traces removed by a stream of dry N_2 being passed over the solid for 2 hr. The solid was then suspended in dry CH_2Cl_2 under N_2 and aniline (2 mL, 22.7 mmol, 7.5 equiv) was added dropwise with cooling. The suspension was concentrated *in vacuo* and the resultant solid stirred with toluene (20 mL) overnight and the title compound collected by filtration as a cream solid and recrystallised from toluene to give an off white solid (1.04 g, 88% over two steps). MP (toluene) 164°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.03-8.00 (2H, m), 7.78-7.44 (2H, m), 7.55-7.45 (5H, m), 7.43 (1H, br s, N**H**), 7.32-7.30 (2H, m), 7.15-7.11 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 169.59 (quat, **C**O_2NHPh), 153.34 (quat, Th**C₂**), 142.27 (quat, Th**C**$_4$), 137.02 (quat), 136.09 (quat), 132.63 (quat), 132.13 (quat), 131.19 (CH), 130.98 (2CH), 130.12 (quat), 129.37 (2CH), 129.17 (2CH), 129.12 (2CH), 126.86 (2CH), 124.93 (CH), 119.65 (CH), 119.64 (CH); IR (thin film, cm^{-1})

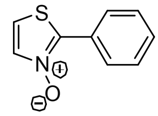
ν_{max} 3304, 1641, 1519, 1442, 1335, 1092, 890, 838, 753, 739; HRMS (ES+ve) calculated for $[C_{22}H_{15}{}^{35}ClN_2OS+H]^+$ 391.0666, found 391.0665.

3-Benzylthiazolium bromide[183] **279**



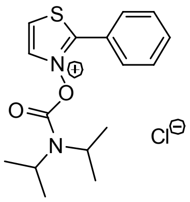
Thiazole (100 mg, 1.180 mmol, 1 equiv) and benzyl bromide (2.5 mL) were heated in a microwave for 15 min at 150°C. The solution was concentrated *in vacuo* and the solid triturated in cold MeCN (5 mL) and washed with Et_2O to give the product as a yellow solid (228 mg, 76% yield). ^{1}H NMR (360 MHz, CD_3OD) δ_H 10.24 (1H, m, ThC$_2$-**H**), 8.49 (1H, m, ThC$_4$-**H**), 8.31 (1H, m, ThC$_5$-**H**), 7.54-7.45 (5H, m), 5.83 (2H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 160.10 (CH, Th**C**$_2$-H), 138.34 (quat), 134.30 (CH), 130.93 (CH), 130.68 (2CH), 130.20 (2CH), 128.01 (CH), 59.64 (CH_2).

2-Phenylthiazole-3-oxide[181] **55**



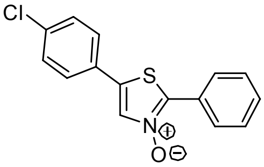
2-Phenylthiazole (1.00 g, 6.203 mmol, 1 equiv) was dissolved in ethyl acetate (6 mL) at ambient temperature and an ice cold solution of *m*CPBA (2.14 g, 12.406 mmol, 2 equiv) in ethyl acetate (3 mL) was added dropwise. The reaction was left to stir for 5 days at ambient temperature. The reaction mixture was partitioned between CH_2Cl_2 (50 mL) and NaOH (1.0 M, 50 mL). The combined aqueous layers were extracted with $CHCl_3$ (3 × 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (10 mL), loaded onto silica, washed with ethyl acetate (50 mL) to elute the remaining starting material (0.66 g, 66%) and then with ethyl acetate/methanol (1:1, 100 mL) to elute the product, which was obtained as a pale yellow oil that crystallised on standing (0.37 g, 34% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.27-8.24 (2H, m), 7.65 (1H, d, J = 4.0, ThC$_4$-**H**), 7.45-7.38 (3H, m), 7.24 (1H, d, J = 4.0, ThC$_5$-**H**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 143.49 (quat, Th**C**$_2$), 139.22 (CH, ThC$_4$-**H**), 130.39 (CH), 128.68 (2CH), 127.52 (quat), 126.67 (2CH), 115.00 (CH).

3-Diisopropylcarbamoyloxy-2-phenylthiazol-3-ium chloride **288**



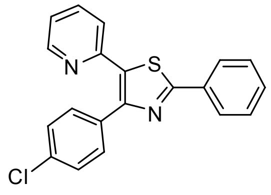
2-Phenylthiazole-3-oxide (200 mg, 1.129 mmol, 1 equiv) was dissolved in tetrahydrofuran (2 mL) at ambient temperature. Diisopropylcarbamoyl chloride (369 mg, 2.257 mmol, 2 equiv) was added as a solution in tetrahydrofuran (4 mL) dropwise and the reaction stirred at ambient temperature for 1 hr. The product was collected by filtration and washed with diethylether (50 mL) to give a white solid (383 mg, quantitative yield). MP (tetrahydrofuran) 136°C decomp.; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.97 (1H, d, J = 4.2, ThC$_4$-**H**), 8.72 (1H, d, J = 4.2, ThC$_5$-**H**), 7.71-7.63 (3H, m), 7.57-7.53 (2H, m), 4.22 (1H, sept, J = 6.7, C**H**), 3.56 (1H, sept, J = 6.7, C**H**), 1.79 (6H, d, J = 6.7, 2 C**H$_3$**), 1.10 (6H, d, J = 6.7, 2 C**H$_3$**); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 165.75 (quat, Th**C$_2$**), 147.15 (quat, **C**O$_2$N^{i}Pr$_2$), 134.39 (CH), 133.91 (CH), 129.68 (2CH), 129.17 (2CH), 126.54 (CH), 122.94 (quat), 48.69 (CH), 47.75 (CH), 20.61 ($2CH_3$), 19.69 ($2CH_3$); IR (thin film, cm^{-1}) ν_{max} 3398, 2976, 2717, 2476, 1780, 1631, 1539, 1453, 1430, 1374, 1303, 1203, 1155, 1114, 1036, 1015, 985, 924, 883, 859, 835, 764, 732; MS: this compound decomposed to 2-phenylthiazole-3-oxide under FAB, ES and EI conditions, as such HRMS was unobtainable.

5-(4’-Chlorophenyl)-2-phenylthiazole-N-oxide **291**



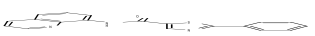
5-(4-Chlorophenyl)-2-phenylthiazole (1.00 g, 3.680 mmol, 1 equiv) was dissolved in CH_2Cl_2 (10 mL) at ambient temperature and an ice cold solution of *m*CPBA (1.81 g, 7.359 mmol, 2 equiv) in CH_2Cl_2 (5 mL) was added dropwise. The reaction was left to stir for 5 days at ambient temperature. The reaction mixture was partitioned between CH_2Cl_2 (50 mL) and NaOH (1.0 M, 2 × 25 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 50 mL),the organics were dried over $MgSO_4$ and concentrated *in vacuo*. Following purification by column chromatography (5% methanol/ethyl acetate) the title compound was isolated as a colourless solid (95 mg, 9% yield). MP ($CHCl_3$) 168°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.33-8.30 (2H, m), 7.92 (1H, s), 7.48-7.39 (7H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 143.12 (quat), 135.99 (CH), 134.67 (quat), 131.71 (quat), 130.60 (CH), 129.63 (2CH), 128.84 (2CH), 127.61 (quat), 127.35 (quat), 126.96 (2CH), 126.80 (2CH); IR (thin film, cm^{-1}) ν_{max} 3043, 1358, 1241, 1207, 820, 803, 747, 681, 648; HRMS (EI) calculated for $[C_{15}H_{10}{}^{35}ClNOS]^+$ 287.0166, found 287.0163.

5-(4'-Chlorophenyl)-4-(2'-pyridyl)-2-phenylthiazole **292c**



2-(2-Phenylthiazol-5-yl)pyridine (100 mg, 0.420 mmol) was dissolved in toluene (5 mL) together with Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (17 mg, 0.021 mmol), P(^{t}Bu)$_2$biphenyl (13 mg, 0.042 mmol), Cs_2CO_3 (410 mg, 1.259 mmol) and 4-iodochlorobenzene (200 mg, 0.839 mmol) and heated to reflux for 3 days. The reaction mixture was cooled to ambient temperature and filtered through celite. The filtrate was concentrated *in vacuo* and purified by column chromatography (30% Et_2O/hexanes) to afford the title compound as a pale yellow solid (94 mg, 64% yield). MP (Et_2O) 106°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.63 (1H, ddd, *J* = 1.1, 1.8, 4.9), 8.04-8.01 (2H, m), 7.61-7.58 (2H, m), 7.52 (1H, ddd, *J* = 1.8, 7.6, 8.1), 7.47-7.43 (3H, m), 7.41-7.37 (2H, m), 7.24 (1H, ddd, *J* = 1.1, 1.1, 8.1), 7.17 (1H, ddd, *J* = 1.1, 4.9, 7.6); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.55 (quat, Th**C**$_2$), 151.26 (quat), 151.05 (quat), 149.87 (CH), 136.26 (CH), 134.73 (quat), 134.51 (quat), 133.80 (quat), 133.39 (quat), 130.68 (2CH), 130.33 (CH), 128.94 (2CH), 128.86 (2CH), 128.50 (2CH), 122.40 (CH), 122.29 (CH); IR (thin film, cm^{-1}) ν_{max} 3398, 2067, 1996, 1709, 1519, 1456, 1313, 1254, 1151, 1093, 751; HRMS (EI) calculated for $[C_{20}H_{13}{}^{35}ClN_2S]^+$ 348.0488, found 348.0472.

2-Phenylthiazole-5-carboxylic acid quinolin-8-ylamide **309**



2-Phenylthizole-5-carboxylic acid (200 mg, 0.975 mmol, 1 equiv), was suspended in thionyl chloride (1.67 mL) and the mixture was refluxed for 45 min under nitrogen. Excess thionyl chloride was removed under vacuum and the last traces removed by a stream of dry nitrogen being passed over the solid for 2 hr. The solid was then suspended in CH_2Cl_2 (5 mL) under a nitrogen atmosphere and 8-aminoquinoline (560 mg, 3.898 mmol, 4 equiv) was added slowly with cooling. The suspension was then concentrated *in vacuo* and the resultant solid stirred with diethyl ether (4 mL) overnight and collected by filtration. The product was dissolved in CH_2Cl_2 to remove an insoluble impurity, purified by column chromatography (0-5% methanol/CH_2Cl_2) and recrystallised from chloroform to give the title compound as a green solid (82 mg, 30%).

Alternative Method

2-Phenylthiazole-5-carboxylic acid (100 mg, 0.487 mmol, 1 equiv), EDCI (112 mg, 0.585 mmol, 1.2 equiv), CH_2Cl_2 (5 mL), triethylamine (0.20 mL, 1.462 mmol, 3 equiv) and HOBt (66 mg, 0.487 mmol, 1 equiv) were stirred for 1 hr under nitrogen. 8-Aminoquinoline (78 mg, 0.536 mmol, 1.1 equiv) was added and the reaction stirred for a further 48 hr. The reaction was quenched by the addition of Na_2CO_3 (sat. aq., 10 mL), the phases separated and the organics dried over $MgSO_4$, the crude product was recrystallised from chloroform to give the title compound as a green solid (44 mg, 32%). MP ($CHCl_3$) 180°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 10.59 (1H, s, N**H**), 8.88 (1H, dd, *J* = 4.3, 1.8), 8.82 (1H, dd, *J* = 6.5, 2.3), 8.51 (1H, s, ThC$_4$-**H**), 8.20 (1H, dd, *J* = 8.3, 1.8), 8.05-8.03 (2H, m), 7.59-7.57 (2H, m), 7.52-7.48 (4H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 173.17 (quat, **C**ONHR), 159.65 (quat, Th**C**$_2$), 149.51 (CH, Th**C**$_4$-H), 145.66 (CH), 139.40 (quat), 137.50 (CH), 135.95 (quat), 135.02 (quat), 134.09 (quat), 132.09 (CH). 130.17 (2CH), 129.01 (quat), 128.45 (CH), 127.95 (2CH), 123.13 (CH), 122.89 (CH), 117.78 (CH); IR (thin film, cm^{-1}) ν_{max} 3019, 1663, 1531, 1217, 772, 669; HRMS (EI) calculated for $[C_{19}H_{13}N_3OS]^+$ 331.0774, found 331.0771.

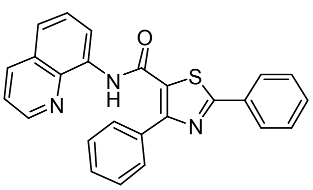
4-(4-Methoxyphenyl)-2-phenylthiazole-5-carboxylic acid quinolin-8-yl amide

312a

Following procedure G using 2-phenylthiazole-5-carboxylic acid quinolin-8-yl amide (100 mg, 0.302 mmol, 1 equiv) and 4-iodoanisole (283 mg, 1.207 mmol, 4 equiv). The title compound was isolated as a yellow solid (71 mg, 54%). MP ($CHCl_3$) 195°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 10.31 (1H, s, N**H**), 8.82 (1H, dd, *J* = 7.2, 1.4), 8.36 (1H, dd, *J* = 3.2, 1.8), 8.06 (3H, m), 7.70 (2H, dt, *J* = 9.0, 2.2), 7.58-7.44 (5H, m), 7.35 (1H, dd, *J* = 4.3, 8.3), 7.04 (2H, dt, *J* = 8.6, 2.2), 3.85

(3H, s, OC**H**$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 169.07 (quat, **C**ONHR), 160.74 (quat, Th**C**$_2$), 159.63 (quat), 155.54 (quat), 147.51 (CH), 138.28 (quat), 135.84 (CH), 134.177 (quat), 133. 03 (quat), 131.13 (2CH), 130.75 (CH), 130.08 (quat), 128.91 (2CH), 127.67 (quat), 127.21 (CH), 126.78 (2CH), 126.25 (quat), 121.68 (CH), 121.39 (CH), 116.38 (CH), 114.51 (2CH), 55.51 (O**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 3019, 2963, 1530, 1219, 1212, 1098, 1015, 784, 737, 669; HRMS (EI) calculated for $[C_{26}H_{19}N_3O_2S]^+$ 437.1193, found 437.1191.

2,4-Diphenylthiazole-5-carboxylic acid quinolin-8-yl amide **312b**



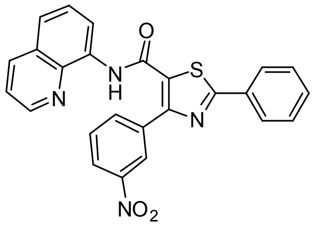
Following procedure G using 2-phenylthiazole-5-carboxylic acid quinolin-8-yl amide (100 mg, 0.302 mmol, 1 equiv) and iodobenzene (246 mg, 1.207 mmol, 4 equiv). The title compound was isolated, following column chromatography (0-10% ethyl acetate/hexane) as a yellow solid (103 mg, 84%). MP (CHCl$_3$) 142°C; ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 10.23 (1H, s, N**H**), 8.82 (1H, dd, *J* = 7.6, 1.4), 8.33 (1H, dd, *J* = 4.3, 1.8), 8.08-8.05 (3H, m), 7.81 (2H, dt, *J* = 6.1, 1.8), 7.55-7.46 (8H, m), 7.32 (1H, dd, *J* = 8.3, 4.3); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 169.34 (quat, **C**ONHR), 159.49 (quat, Th**C**$_2$), 155.63 (quat), 147.67 (CH), 138.37 (quat), 135.90 (CH), 134.15 (quat), 133.94 (quat), 133.04 (quat), 131.95 (quat), 131.95 (CH), 129.82 (2CH), 129.29 (CH), 129.09 (2CH), 129.01 (2CH), 127.72 (quat), 127.24 (CH), 126.88 (2CH), 121.83 (CH), 121.42 (CH), 116.48 (CH); IR (thin film, cm^{-1}) ν_{max} 3019, 1530, 1216, 756, 669; HRMS (EI) calculated for $[C_{25}H_{17}N_3OS]^+$ 407.1087, found 407.1080.

2-Phenyl-4-(4-methylphenyl)thiazole-5-carboxylic acid quinolin-8-yl amide **312d**

Following procedure G using 2-phenylthiazole-5-carboxylic acid quinolin-8-yl amide (100 mg, 0.302 mmol, 1 equiv) and 4-iodotoluene (263 mg, 1.207 mmol, 4 equiv). The title compound was isolated, following column chromatography (0-10% ethyl acetate/hexane) as a yellow solid (112 mg, 88%). MP (CHCl$_3$) 182°C; ^{1}H NMR (360 MHz, CDCl$_3$ δ_H 10.28 (1H, s, N**H**), 8.82

(1H, dd, *J* = 7.2, 1.4), 8.32 (1H, dd, *J* = 4.0, 1.4), 8.08-8.05 (3H, m), 7.70 (2H, dt, *J* = 8.2, 1.8), 7.55-7.46 (5H, m), 7.35-7.29 (3H, m), 2.46 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$), δ_C 169.14 (quat, **C**ONHR), 159.62 (quat, ThC_2), 155.87 (quat), 147.43 (CH), 139.28 (quat), 138.35 (quat), 135.89 (CH), 134.24 (quat), 133.08 (quat), 131.05 (quat), 130.81 (CH), 130.42 (quat), 129.74 (2CH), 129.68 (2CH), 128.97 (2CH), 127.72 (quat), 127.26 (CH), 126.85 (2CH), 121.76 (CH), 121.39 (CH), 116.48 (CH), 21.47 (CH_3); IR (thin film, cm^{-1}) ν_{max} 4214, 3019, 1530, 1219, 782, 735, 669; HRMS (EI) calculated for $[C_{26}H_{19}N_3OS]^+$ 421.1243, found 421.1246.

4-(3-Nitro-phenyl)-2-phenyl-thiazole-5-carboxylic acid quinolin-8-yl amide **312e**

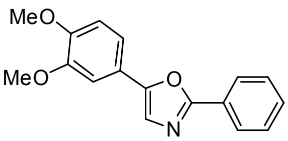


Following procedure G using 2-phenylthiazole-5-carboxylic acid quinolin-8-yl amide (100 mg, 0.302 mmol, 1 equiv) and 3-iodonitrobenzene (301 mg, 1.207 mmol, 4 equiv). The title compound was isolated, following column chromatography (0-90% ethyl acetate/hexane) as a yellow solid (105 mg, 77%). MP ($CHCl_3$) 219°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 10.15 (1H, s, N**H**), 8.81-8.79 (2H, m), 8.38-8.35 (2H, m), 8.17 (1H, dt, *J* = 7.9, 1.8), 8.12 (1H, dd, *J* = 8.3, 1.4), 8.09-8.05 (2H, m), 7.65-7.47 (6H, m), 7.38 (1H, dd, *J* = 8.3, 4.3); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 169.55 (quat, **C**ONHR), 158.68 (quat, ThC_2), 152.87 (quat), 148.48 (quat), 147.76 (CH), 138.07 (quat), 136.29 (quat), 135.78 (CH), 135.54 (quat),133.61 (quat),132.50 (CH), 131.22 (CH), 131.07 (quat), 129.77 (CH), 129.09 (2CH), 127.77 (CH), 127.27 (CH), 126.84 (2CH), 124.95 (CH), 123.78 (CH), 122.26 (CH), 121.61 (CH), 116.75 (quat); IR (thin film, cm^{-1}) ν_{max} 3019, 1529, 1216, 754, 669; HRMS (EI) calculated for $[C_{25}H_{16}N_4O_3S+H]^+$ 452.0938, found 452.0945.

2-Phenyl-4-thiophen-3-yl-thiazole-5-carboxylic acid quinolin-8-yl amide **312c**

Following procedure G using 2-phenylthiazole-5-carboxylic acid quinolin-8-yl amide (100 mg, 0.302 mmol, 1 equiv) and 2-iodothiophene (254 mg, 1.207 mmol, 4 equiv). The title compound was isolated, following column chromatography (0-10% ethyl acetate/hexane) as a white solid (82 mg, 66%). MP ($CHCl_3$) 176°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 10.44 (1H, s, N**H**), 8.85 (1H, dd, *J* = 7.2, 1.8), 8.57 (1H, dd, *J* = 4.0, 1.8), 8.12 (1H, dd, *J* = 8.3, 1.8), 8.07-8.04 (2H, m), 7.94 (1H, dd, *J* = 3.2, 1.3), 7.59-7.47 (6H, m), 7.44 (1H, dd, *J* = 5.4, 3.2), 7.40 (1H, dd, *J* = 8.3, 4.3); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 168.85 (quat, **C**ONHR), 159.45 (quat, Th**C**$_2$), 150.58 (quat), 147.90 (CH), 138.36 (quat), 135.99 (CH), 134.38 (quat), 134.08 (quat), 132.87 (quat), 130.84 (CH), 130.00 (quat), 128.94 (2CH), 128.55 (CH), 127.76 (quat), 127.25 (CH), 127.21 (CH), 126.79 (2CH), 126.39 (CH), 121.89 (CH), 121.49 (CH), 116.58 (CH); IR (thin film, cm^{-1}) ν_{max} 3295, 3016, 1649, 1529, 1216, 7545, 668; HRMS (EI) calculated for $[C_{23}H_{14}N_3OS_2]^+$ 413.0651, found 413.0651.

5-(3,4-Dimethoxy-phenyl)-2-phenyl-oxazole (Balsoxin)[170] **251k**



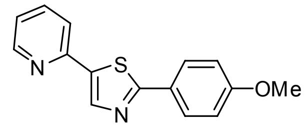
Following general procedure D using 2-phenyloxazole (50 mg, 0.344 mmol, 1 equiv) and 3,4-dimethoxyiodobenzene (109 mg, 0.413 mmol, 1.2 equiv), purification by column chromatography (5% ethyl acetate/hexane) gave the title compound as a colourless solid (73 mg, 76% yield); ^{1}H NMR (250 MHz, $CHCl_3$) δ 8.11-8.07 (2H, m), 7.50-7.44 (3H, m), 7.33 (1H, s), 7.30 (1H, dd, *J* = 8.4, 2.0), 7.19 (1H, d, *J* = 2.0), 6.93 (1H, d, *J* = 8.4), 3.90 (3H, s, OCH_3), 3.85 (3H, s, OCH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 160.47 (quat), 151.22 (quat), 149.38 (quat), 149.31 (quat), 130.09 (CH), 128.66 (CH), 127.48 (quat), 126.13 (CH), 122.24 (CH), 120.98 (quat), 117.22 (CH), 111.41 (CH), 107.37 (CH), 56.04 (CH_3), 55.85 (CH_3).

2-(2-(4-Chlorophenyl)thiazol-5-yl)-pyridine **291b**

Following general procedure D with 2-(4-chlorophenyl)thiazole (2.00 g, 0.010 mol, 1 equiv) and 2-bromopyridine (3.23 g, 0.020 mol, 2 equiv), purification by column chromatography (CH_2Cl_2) gave the title compound as a yellow solid (1.25 g, 45% yield). MP (toluene) 163°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.59 (1H, ddd, *J* = 4.9, 1.6, 1.0), 8.24 (1H, s, ThC$_4$-**H**), 7.93-7.89 (2H, m), 7.74-7.66 (2H, m), 7.43-7.39 (2H, m), 7.19 (1H, ddd, *J* = 6.9, 4.9, 1.6); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C

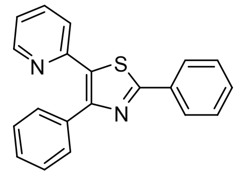
167.93 (quat, Th**C**$_2$), 150.43 (quat), 149.93 (CH, Th**C**$_4$-H), 140.55 (CH), 140.54 (quat), 136.78 (CH), 136.21 (quat), 132.11 (quat), 129.23 (2CH), 127.64 (2CH), 122.65 (CH), 119.54 (CH); IR (thin film, cm^{-1}) ν_{max} 1562, 1425, 1170, 824, 770, 734, 631; HRMS (EI) calculated for $[C_{14}H_9{}^{35}ClN_2S]^+$ 272.0170, found 272.0169.

2-(2-(4-Methoxyphenyl)thiazol-5-yl)-pyridine **291c**



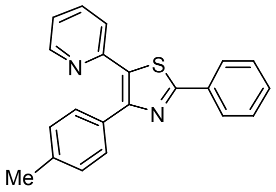
Following general procedure D with 2-(4-methoxyphenyl)thiazole (2.00 g, 0.010 mol, 1 equiv) and 2-bromopyridine (3.23 g, 0.020 mol, 2 equiv) and purification by column chromatography (CH_2Cl_2) gave the title compound as a yellow solid (1.73 g, 62% yield). MP (toluene) 129°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.59 (1H, ddd, *J* = 4.9, 1.6, .1.1), 8.22 (1H, s, ThC$_4$-**H**), 7.96-7.92 (2H, m), 7.74-7.67 (2H, m), 7.18 (1H, ddd, *J* = 6.7, 4.9, 1.8), 6.99-6.95 (2H, m), 3.87 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 169.34 (quat, Th**C**$_2$), 161.36 (quat,**C**$_{Ar}$OCH$_3$), 150.79 (quat), 149.84 (CH), 140.36 (CH), 139.12 (quat), 136.69 (CH), 128.58 (2CH), 126.58 (quat), 122.32 (CH), 119.42 (CH), 114.35 (2CH), 55.42 (O**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 1607, 1586, 1516, 1469, 1430, 1415, 1301, 1254, 1175, 1023, 825, 771, 733; HRMS (EI) calculated for $[C_{15}H_{12}N_2OS]^+$ 268.0665, found 268.0668.

2-(2,4-Diphenylthiazol-5-yl)-pyridine **292a**



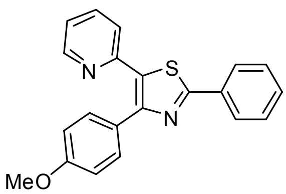
Following general procedure F using 2-(2-phenylthiazol-5-yl)-pyridine (100 mg, 0.420 mmol, 1 equiv) and bromobenzene (132 mg, 0.839 mmol, 2 equiv), purification by column chromatography (2% ethyl acetate/toluene) gave the title compound as a yellow oil (116 mg, 88% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.61 (1H, ddd, *J* = 4.9, 1.8, 1.0), 8.07-8.04 (2H, m), 7.67-7.64 (2H, m), 7.48-7.39 (7H, m), 7.22 (1H, dt, *J* = 8.0, 1.0), 7.12 (1H, ddd, *J* = 7.5, 4.9, 1.0); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.25 (quat, Th**C**$_2$), 152.41 (quat), 151.44 (quat), 149.62 (CH), 136.01 (CH), 135.35 (quat), 134.49 (quat), 133.49 (quat), 130.13 (CH), 129.25 (2CH), 128.92 (2CH), 128.80 (2CH), 128.50 (CH), 126.45 (2CH), 122.11 (CH), 122.07 (CH); IR (thin film, cm^{-1}) ν_{max} 3059, 1582, 1488, 1462, 1442, 1432, 771, 689, 666; HRMS (EI) calculated for $[C_{20}H_{14}N_2S]^+$ 314.0872, found 314.0874.

2-(4-(4-Methylphenyl)-2-phenyl)thiazol-5-yl)-pyridine **292b**



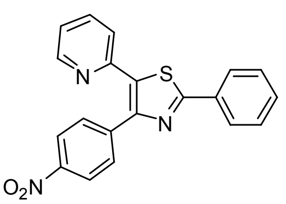
Following general procedure F using 2-(2-phenylthiazol-5-yl)-pyridine (100 mg, 0.420 mmol, 1 equiv) and bromotoluene (171 mg, 0.839 mmol, 2 equiv), purification by column chromatography (0-5% acetone/CH_2Cl_2) gave the title compound as a yellow gum (96 mg, 70% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.61 (1H, ddd, J = 4.9, 1.8, 1.1), 8.07-8.04 (2H, m), 7.56-7.53 (2H, m), 7.49-7.42 (4H, m), 7.27 (1H, ddd, J = 8.1, 1.1, 1.1), 7.24-7.22 (2H, m), 7.12 (1H, ddd, J = 7.5, 4.9, 1.0), 2.41 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.10 (quat), 152.56 (quat), 151.62 (quat), 149.58 (CH), 138.38 (quat), 135.98 (CH), 134.06 (quat), 133.56 (quat), 132.45 (quat), 130.07 (CH), 129.29 (2CH), 129.12 (2CH), 128.80 (2CH), 126.44 (2CH), 122.04 (CH), 122.02 (CH), 21.32 (CH_3); IR (thin film, cm^{-1}) ν_{max} 1583, 1495, 1461, 1432, 823, 779,688, 666; HRMS (EI) calculated for $[C_{21}H_{16}N_2S]^+$ 328.1029, found 328.1029.

2-(4-(4-Methoxyphenyl)-2-phenylthiazol-5-yl)-pyridine **292d**



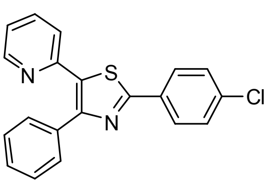
Following general procedure F using 2-(2-phenylthiazol-5-yl)-pyridine (100 mg, 0.420 mmol, 1 equiv) and bromoanisole (157 mg, 0.839 mmol, 2 equiv), purification by column chromatography (0-5% acetone/CH_2Cl_2) gave the title compound as a yellow oil (64 mg, 44% yield) together with recovered starting material (51 mg). ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.61 (1H, ddd, J = 4.9, 1.8, 1.0), 8.05-8.03 (2H, m),7.60-7.56 (2H, m), 7.48 (1H, m), 7.45-7.42 (3H, m), 7.27 (1H, dt, J = 8.1, 1.0), 7.13 (1H, ddd, J = 7.5, 4.9, 1.0), 6.97-6.93 (2H, m), 3.86 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 167.13 (quat, Th**C**$_2$), 159.85 (quat, **C**$_{Ar}OCH_3$), 152.30 (quat), 151.74 (quat), 149.65 (CH), 136.05 (CH), 133.63 (quat), 133.60 (quat), 130.58 (2CH), 130.11 (CH), 128.85 (2CH), 127.81 (quat), 126.47 (2CH), 122.05 (CH), 122.03 (CH), 114.05 (2CH), 55.29 (CH_3); IR (thin film, cm^{-1}) ν_{max} 1609, 1584, 1495, 1463, 1251, 1174, 1030, 836, 780, 665; HRMS (EI) calculated for $[C_{21}H_{16}N_2OS]^+$ 344.0978, found 344.0977.

2-(4-(4-Nitrophenyl)-2-phenyl)thiazol-5-yl)-pyridine **292e**



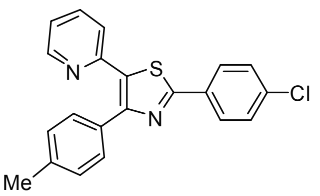
Following general procedure F using 2-(2-phenylthiazol-5-yl)-pyridine (100 mg, 0.420 mmol, 1 equiv) and bromonitrobenzene (170 mg, 0.839 mmol, 2 equiv), purification by column chromatography (0-15% acetone/toluene) gave the title compound as a yellow gum (133 mg, 88% yield). ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.66 (1H, ddd, *J* = 4.8, 1.8, 1.1), 8.26-8.22 (2H, m), 8.04-7.99 (2H, m), 7.85-7.81 (2H, m), 7.59 (1H, ddd, *J* = 8.0, 7.5, 1.8), 7.48-7.44 (3H, m), 7.27-7.23 (2H, m); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 168.00 (quat, Th**C$_2$**), 150.60 (quat), 150.07 (CH), 149.57 (quat), 147.49 (quat), 141.47 (quat), 136.63 (CH), 136.14 (quat), 132.98 (quat), 130.62 (CH), 130.13 (2CH), 129.02 (2CH), 126.50 (2CH), 123.74 (2CH), 122.99 (CH), 122.91 (CH); IR (thin film, cm^{-1}) ν_{max} 1582, 1517, 1345, 845, 761, 688, 665; HRMS (EI) calculated for $[C_{20}H_{13}N_3O_2S]^+$ 359.0723, found 359.0726.

2-(4-Phenyl-2-(4-chlorophenyl)thiazol-5-yl)-pyridine **292f**



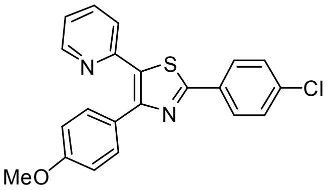
Following general procedure F using 2-(2-(4-chlorophenyl)thiazol-5-yl)pyridine (100 mg, 0.367 mmol, 1 equiv) and bromobenzene (115 mg, 0.733 mmol, 2 equiv), purification by column chromatography (1-5% acetone/toluene) afforded the title compound as a yellow oil (117 mg, 92%). ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.62 (1H, ddd, *J* = 4.9, 1.8, 1.0), 8.00-7.96 (2H, m), 7.64-7.62 (2H, m), 7.51-7.41 (6H, m), 7.22 (1H, dt, *J* = 8.1, 1.0), 7.12 (1H, ddd, *J* = 7.5, 4.9, 1.0); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 167.52 (quat, Th**C**$_2$), 150.36 (quat), 151.00 (quat), 149.97 (CH), 136.16 (CH), 134.77 (quat), 134.46 (quat), 133.93 (quat), 133.33 (quat), 131.78 (2CH), 129.42 (2CH), 128.92 (CH), 128.75 (2CH), 125.65 (2CH), 123.03 (CH), 122.42 (CH); IR (thin film, cm^{-1}) ν_{max} 1682, 1583, 1478, 1398, 1092,1012, 827, 700, 665; HRMS (EI) calculated for $[C_{20}H_{13}{}^{35}ClN_2S]^+$ 348.0483, found 348.0474.

2-(4-(4-Methylphenyl)-2-(4-chlorophenyl)thiazol-5-yl)-pyridine **292g**



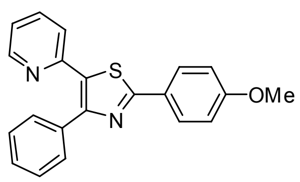
Following general procedure F using 2-(2-(4-chlorophenyl)thiazol-5-yl)pyridine (100 mg, 0.367 mmol, 1 equiv) and bromotoluene (125 mg, 0.733 mmol, 2 equiv), purification by column chromatography (1-5% acetone/toluene) afforded the title compound as a yellow oil (59 mg, 44% yield). ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.62 (1H, ddd, *J* = 4.9, 1.8, 1.0), 7.99-7.95 (2H, m), 7.53-7.46 (3H, m), 7.44-7.40 (2H, m), 7.27-7.22 (3H, m), 7.15, (1H, ddd, *J* = 7.5, 4.9, 1.0), 2.41 (3H, s); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 165.82 (quat, Th**C$_2$**), 152.76 (quat), 151.47 (quat), 149.67 (CH), 138.62 (quat), 136.15 (CH), 136.10 (quat), 134.42 (quat), 132.30 (quat), 132.12 (quat), 129.41 (2CH), 129.14 (2CH), 129.12 (2CH), 127.70 (2CH), 122.23 (CH), 122.13 (CH), 21.38 (CH$_3$); IR (thin film, cm^{-1}) ν_{max} 3050, 2921, 1750, 1584, 1455, 1092, 825, 779, 736; HRMS (EI) calculated for $[C_{21}H_{15}{}^{35}ClN_2S]^+$ 362.0639, found 362.0638.

2-(4-(4-Methoxyphenyl)-2-(4-chlorophenyl)thiazol-5-yl)-pyridine **292i**



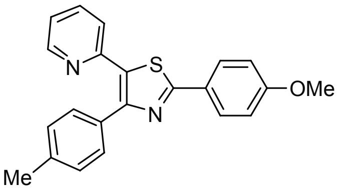
Following general procedure F using 2-(2-(4-chlorophenyl)thiazol-5-yl)pyridine (100 mg, 0.367 mmol, 1 equiv) and bromoanisole (137 mg, 0.733 mmol, 2 equiv), purification by column chromatography (1-5% acetone/toluene) afforded the title compound as a yellow oil (29 mg, 21% yield). ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.61 (1H, ddd, *J* = 4.9, 1.8, 1.0), 7.98-7.94 (2H, m), 7.58-7.54 (2H, m), 7.49 (1H, ddd, *J* = 8.0, 7.6, 1.8), 7.43-7.39 (2H, m), 7.27 (1H, ddd, *J* = 8.0, 1.0, 1.0), 7.14 (1H, ddd, *J* = 7.6, 4.9, 1.0), 6.97-6.93 (2H, m), 3.86 (3H, s); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 165.76 (quat, Th**C$_2$**), 159.95 (quat, **C$_{Ar}$**OCH$_3$), 152.44 (quat), 151.54 (quat), 149.68 (CH), 136.15 (CH), 136.08 (quat), 133.98 (quat), 132.11 (quat), 130.57 (2CH), 129.11 (2CH), 127.67 (2CH), 127.60 (quat), 122.19 (CH), 122.05 (CH), 114.12 (2CH), 55.32 (CH$_3$); IR (thin film, cm^{-1}) ν_{max} 1748, 1584, 1493, 1459, 1250, 1173, 1091, 1030, 833, 779; HRMS (EI) calculated for $[C_{21}H_{15}{}^{35}ClN_2OS]^+$ 378.0588, found 378.0587.

2-(4-Phenyl-2-(4-methoxyphenyl)thiazol-5-yl)-pyridine **292k**



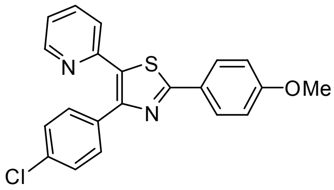
Following general procedure F using 2-(2-(4-methoxyphenyl)thiazol-5-yl)pyridine (100 mg, 0.373 mmol, 1 equiv) and bromobenzene (117 mg, 0.745 mmol, 2 equiv), purification by column chromatography (1-5% acetone/toluene) afforded the title compound as a yellow oil (112 mg, 87% yield); ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.60 (1H, ddd, *J* = 4.9, 1.8, 1.0), 8.01-7.97 (2H, m), 7.65-7.63 (2H, m), 7.46-7.39 (4H, m), 7.20 (1H, ddd, *J* = 8.1, 1.0, 1.0), 7.12 (1H, m), 6.98-6.94 (2H, m), 3.85 (3H, s); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 167.18 (quat, Th**C$_2$**), 161.26 (quat, **C$_{Ar}$**OCH$_3$), 152.24 (quat), 151.60 (quat), 149.58 (CH), 135.96 (CH), 135.50 (quat), 133.54 (quat), 129.26 (2CH), 128.59 (2CH), 128.45 (CH), 127.99 (2CH), 126.47 (quat), 121.96 (CH), 121.93 (CH), 114.18 (2CH), 55.32 (CH$_3$); IR (thin film, cm^{-1}) ν_{max} 2931, 1605, 1459, 1254, 1173, 1030, 833, 769, 701; HRMS (EI) calculated for [C21H16N2OS]$^+$ 344.0978, found 344.0976.

2-(4-(4-Methylphenyl)-2-(4-methoxyphenyl)thiazol-5-yl)-pyridine **292l**



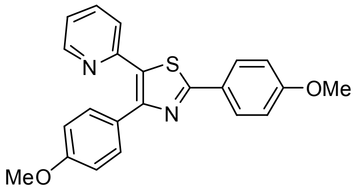
Following general procedure F using 2-(2-(4-methoxyphenyl)thiazol-5-yl)pyridine (100 mg, 0.373 mmol, 1 equiv) and bromotoluene (127 mg, 0.745 mmol, 2 equiv), purification by column chromatography (1-5% acetone/toluene) afforded the title compound as a yellow oil (75 mg, 56% yield); ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.60 (1H, ddd, *J* = 4.9, 1.8, 1.0), 8.00-7.96 (2H, m), 7.54-7.51 (2H, m), 7.46 (1H, ddd, *J* = 8.1, 7.5, 1.8), 7.26-7.21 (3H, m), 7.11 (1H, ddd, *J* = 7.5, 4.9, 1.0), 6.98-6.94 (2H, m), 3.86 (3H, s, OMe), 2.41 (3H, s, Me); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 168.15 (quat), 162.34 (quat), 153.52 (quat), 152.91 (quat), 150.66 (CH), 139.43 (quat), 137.05 (CH), 133.72 (quat), 130.40 (2CH), 130.23 (2CH), 130.17 (quat), 129.10 (quat), 127.68 (CH), 123.06 (CH), 122.95 (CH), 115.28 (2CH), 56.45 (CH$_3$, OMe), 22.44 (CH$_3$, C$_{Ar}$**C**H$_3$); IR (thin film, cm^{-1}) ν_{max} 1605, 1458, 1253, 1173, 825, 779; HRMS (EI) calculated for [$C_{22}H_{18}N_2OS$]$^+$ 358.1134, found 358.1130.

2-(4-(4-Chlorophenyl)-2-(4-methoxyphenyl)thiazol-5-yl)-pyridine **292m**



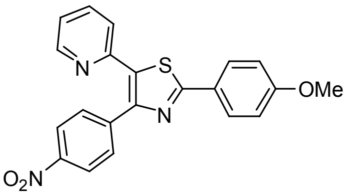
Following general procedure F using 2-(2-(4-methoxyphenyl)thiazol-5-yl)pyridine (100 mg, 0.373 mmol, 1 equiv) and bromochlorobenzene (127 mg, 0.745 mmol, 2 equiv), purification by column chromatography (1-5% acetone/toluene) afforded the title compound as a yellow oil (51 mg, 36% yield); ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.60 (1H, ddd, *J* = 4.9, 1.8, 1.0), 7.97-7.93 (2H, m), 7.60-7.56 (2H, m), 7.48 (1H, ddd, *J* = 8.0, 7.6, 1.8), 7.39-7.36 (2H, m), 7.21 (1H, ddd, *J* = 8.0, 1.0, 1.0), 7.13 (1H, ddd, *J* = 7.6, 4.9, 1.0), 6.97-6.93 (2H, m), 3.83 (3H, s); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 168.49 (quat), 162.48 (quat), 152.44 (quat), 151.90 (quat), 150.86 (CH), 137.24 (CH), 135.47 (quat), 135.01 (quat), 131.75 (2CH), 129.89 (2CH), 129.09 (2CH), 127.40 (quat), 123.28 (CH), 123.21 (CH), 115.34 (2CH), 56.45 (CH$_3$); IR (thin film, cm^{-1}) ν_{max} 2836, 1605, 1485,1458, 1254, 1173, 833; HRMS (EI) calculated for $[C_{21}H_{15}{}^{35}ClN_2OS]^+$ 378.0588, found 378.0588.

2-(2,4-Di(4-methoxyphenyl)thiazol-5-yl)-pyridine **292n**



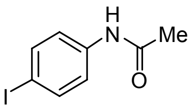
Following general procedure F using 2-(2-(4-methoxyphenyl)thiazol-5-yl)pyridine (100 mg, 0.373 mmol, 1 equiv) and 4-bromoanisole (139 mg, 0.745 mmol, 2 equiv), purification by column chromatography (1-5% acetone/toluene) afforded the title compound as a yellow gum (31 mg, 22% yield); ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.48 (1H, ddd, *J* = 4.9, 1.8, 1.0), 7.88-7.84 (2H, m), 7.48-7.44 (2H, m), 7.36 (1H, ddd, *J* = 8.0, 7.5, 1.8), 7.14 (1H, ddd, *J* = 8.0, 1.0, 1.0), 7.00 (1H, ddd, *J* = 7.5, 4.9, 1.0), 7.87-7.81 (4H, m), 3.74 (3H, s), 3.73 (3H, s); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 167.13 (quat, Th$\mathbf{C}_2$), 161.26 (quat, $\mathbf{C}_{\mathbf{Ar}}$OCH$_3$), 159.85 (quat, $\mathbf{C}_{Ar}$OCH$_3$), 152.30 (quat), 151.74 (quat), 149.65 (CH), 136.05 (CH), 133.63 (quat), 133.60 (quat), 130.58 (2CH), 130.11 (CH), 127.99 (2CH), 127.81 (quat), 122.05 (CH), 114.19 (2CH), 114.05 (2CH), 55.29 (CH$_3$), 55.31 (CH$_3$); IR (thin film, cm^{-1}) ν_{max} 3438, 2837, 1606, 1497, 1459, 1252,1173, 1031, 836; HRMS (EI) calculated for $[C_{22}H_{18}N_2O_2S]^+$ 374.1084, found 374.1088.

2-(4-(4-Nitrophenyl)-2-(4-methoxyphenyl)thiazol-5-yl)-pyridine **292p**



Following general procedure F using 2-(2-(4-methoxyphenyl)thiazol-5-yl)pyridine (100 mg, 0.373 mmol, 1 equiv) and 4-bromonitrobenzene (151 mg, 0.745 mmol, 2 equiv), purification by column chromatography (1-5% acetone/toluene) afforded the title compound as a yellow gum (81 mg, 56% yield); ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 8.65 (1H, ddd, *J* = 4.8, 1.8, 1.1), 8.25-8.21 (2H, m), 7.98-7.94 (2H, m), 7.85-7.81 (2H, m), 7.56 (1H, ddd, *J* = 8.0, 7.5, 1.8), 7.24-7.20 (2H, m, py), 6.99-6.95 (2H, m), 3.87 (3H, s, OMe); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 167.86 (quat, Th**C$_2$**), 161.62 (quat, **C$_{Ar}$**OCH$_3$), 150.82 (quat), 150.08 (CH), 149.35 (quat), 147.46 (quat), 141.72 (quat), 136.48 (2CH), 135.35 (quat), 130.15 (CH), 128.07 (2CH), 125.97 (quat), 123.74 (2CH), 122.76 (CH), 122.71 (CH), 114.36 (2CH), 55.41 (CH$_3$, OMe); IR (thin film, cm^{-1}) ν_{max} 1604, 1517,1458, 1344, 1253, 1172, 845; HRMS (EI) calculated for $[C_{21}H_{15}N_3O_3S]^+$ 389.0829, found 389.0826.

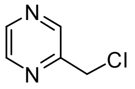
N-Acetyl-4-iodoaniline[184] **64**



Iodoaniline (2.00 g, 9.13 mmol, 1 equiv) was dissolved in AcOH (50 mL) and Ac$_2$O (1.04 mL, 10.96 mmol, 1.2 equiv) was added dropwise. The mixture was allowed to stir for 1 hr and then NaHCO$_3$ (sat. aq.) was added slowly until gas evolution ceased. The mixture was left to stir for a further 30 min and then CH$_2$Cl$_2$ (2 × 100 mL) was added to extract the product. The organic layer was washed with brine and dried over MgSO$_4$ before concentrating *in vacuo* to give the product as a purple solid. This was dissolved in CH$_2$Cl$_2$, filtered through silica which was washed with CH$_2$Cl$_2$/acetone (200 mL, 1:1) to give the product as a white solid (2.29 g, 96% yield. MP (CHCl$_3$) 184°C; ^{1}H NMR (360 MHz, CDCl$_3$) 7.60 (2H, d, *J* = 8.8), 7.28 (2H, d, *J* = 8.8), 2.12 (3H, s).

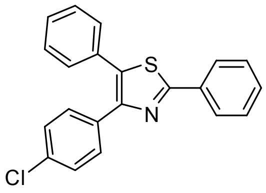
Chloromethylpyrazine[185] **285**

Methyl pyrazine (200 mg, 2.13 mmol), NCS (284 mg, 2.13 mmol) and AIBN (35 mg, 0.21 mmol) were dissolved in CCl$_4$ (10 mL) and heated to reflux for 48 hr. The mixture was cooled to room temperature, the solid succinimide was filtered off, the



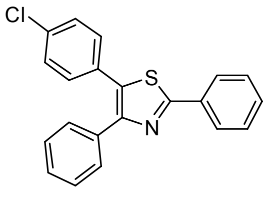
cake washed with further CCl_4 (10 mL) and the solvent removed *in vacuo* to give 148 mg of a mixture of unreacted methyl pyrazine, chloromethylpyrazine and 2,2-dichloromethylpyrazine in the molar ratio 6:3:1, (41.5 mg, 15% of the desired compound). This was used without further purification. ^{1}H NMR (360 MHz, $CDCl_3$), δ_H 8.73 (1H, s), 8.54-8.52 (2H, m), 4.66 (2H, s).

4-(4-Chlorophenyl)-2,5-diphenylthiazole **248c**



Following general procedure D using 4-(4-chloropehnyl)-2-phenylthiazole (100 mg, 0.368 mmol), iodobenzene (90 mg, 0.442 mmol), purification by column chromatography (0-5% acetone/toluene) gave the title compound as a colourless solid (149 mg, >99% yield). MP ($CHCl_3$) 108°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.03-8.00 (2H, m), 7.58-7.54 (2H, m), 7.48-7.44 (3H, m), 7.41-7.35 (5H, m), 7.30-7.27 (2H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 165.71 (quat, Th**C_2**), 149.45 (quat), 133.66 (quat), 133.45 (quat), 133.40 (2 quat), 131.75 (quat), 130.37 (2CH), 130.10 (CH), 129.56 (2CH), 128.92 (2CH), 128.86 (2CH), 128.46 (2CH), 128.39 (CH), 126.39 (2CH); IR (thin film, cm^{-1}) ν_{max} 3060, 1493, 1475, 1090, 1014, 981, 833, 760, 690; HRMS (EI) calculated for $[C_{21}H_{14}{}^{35}ClNS]^+$ 347.0530, found 347.0526.

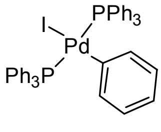
5-(4-Chlorophenyl)-2,4-diphenylthiazole **248b**



5-(4-Chlorophenyl)-2-phenylthiazole (136 mg, 0.500 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (21 mg, 0.025 mmol), triphenylphosphine (13 mg, 0.050 mmol), Ag_2CO_3 (276 mg, 1.000 mmol) were combined then iodobenzene (122 mg, 0.600 mmol) and water (5 mL) were added. The suspension was stirred at 100°C for 72 hr. The reaction was filtered through celite, washed first with acetone (10 mL) then with CH_2Cl_2 (10 mL) and the resultant mixture concentrated *in vacuo* being careful to removed only acetone and CH_2Cl_2 and not the water. The resultant oil was partitioned between water and CH_2Cl_2 and the phases separated, the organics dried over $MgSO_4$ and concentrated to a brown oil. This was dry loaded onto silica and purified by column chromatography (0-5% acetone/toluene) to give the title compound as a colourless solid (99 mg, 57% yield) MP ($CHCl_3$) 124°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ_H 8.03-

8.01 (2H, m), 7.61-7.58 (2H, m), 7.49-7.44 (3H, m), 7.34-7.32 (7H, m); ^{13}C NMR (90 MHz, CDCl$_3$) δ_C 165.75 (quat, Th**C$_2$**), 151.20 (quat), 134.65 (quat), 134.13 (quat), 133.45 (quat), 131.58 (quat), 130.80 (2CH), 130.58 (quat), 130.13 (CH), 129.10 (2CH), 128.98 (2CH), 128.92 (2CH), 128.39 (2CH), 128.04 (CH), 126.44 (2CH); IR (thin film, cm^{-1}) ν_{max} 3061, 1495, 1477, 1442, 1091, 983, 824, 762, 698; HRMS (EI) calculated for $[C_{21}H_{14}{}^{35}ClNS]^+$ 347.0530, found 347.0529.

Bis-triphenylphosphino phenyl palladium(II)iodide[186] **349**



Tetrakis triphenylphosphino palladium (1.00 g, 0.865 mmol) was dissolved in dry, degassed toluene (2.5 mL) under N$_2$ and iodobenzene (177 mg, 0.865 mmol) in toluene (2.5 mL) was added dropwise. The solution was stirred for 1 hr at room temp under N$_2$. The toluene was removed *in vacuo* to give a yellow solid. This was triturated with Et$_2$O to remove any PPh$_3$ and recrystallised from CH$_2$Cl$_2$/hexane to give the product as a yellow solid (701 mg, 97%). ^{1}H NMR (360 MHz, CDCl$_3$) δ_H 7.61-7.32 (30H, m), 6.71-6.67 (2H, m), 6.42-6.30 (3H, m).

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6. Appendices

6.1. Publications

Direct arylation of thiazoles on water

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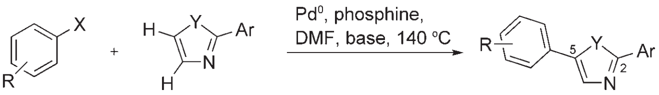
Direct Arylation of Thiazoles on Water**

*Gemma L. Turner, James A. Morris, and Michael F. Greaney**

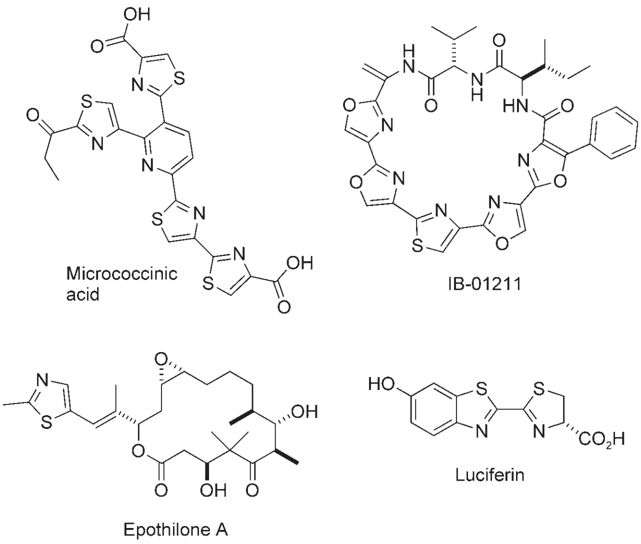
The intermolecular coupling of π-excessive heteroarenes with aryl halides is a principal reaction system in the rapidly growing area of transition-metal-catalyzed direct arylation.[1,2] The approach contrasts with traditional sp^2–sp^2 cross-coupling chemistry involving stoichiometric organometallic compounds, such as $ArB(OH)_2$, $ArSnR_3$, ArZnCl, as nucleophilic components. In direct arylation, formally unactivated C–H bonds are used as the functionalization site on the nucleophilic coupling partner. Regioselectivity between different C–H bonds is frequently high; in the absence of directing-group effects the 2-substituted heteroarenes shown in Scheme 1 undergo arylation at the most electron-rich 5-position through a postulated S_EAr mechanism.[3,4]



Scheme 1. Generalized intermolecular azole direct arylation. Y = O,S,NR.

Nearly all intermolecular (and many intramolecular) heteroarene direct arylations require harsh reaction conditions in terms of high temperatures and corresponding high-boiling solvents, such as dimethylformamide (DMF). Indeed, the reaction conditions developed by the groups of Ohta and Miura in their pioneering work on heteroarene direct arylations (anhydrous DMF, 140 °C, inorganic base, $Pd(OAc)_2$ plus phosphine ligand)[3a,5] have become the standard operating procedure, being heavily represented amongst existing reports.[1,6] Whilst these vigorous conditions may not cause undue difficulty in the functionalization of simple heteroarenes for medicinal chemistry screening programmes, they represent a serious limitation when applied to the synthesis of more-complex heteroarenes of the type found in natural products. With this in mind, we were interested in developing new ways of conducting heteroarene direct arylation that exemplify mildness and ease-of-use. We report herein our results on the direct arylation of thiazoles, featuring the first direct arylation system that works "on water".

Arylated and alkenylated thiazoles have vast application, being prominent components of biologically active natural products (Scheme 2) as well as agrochemicals, drug molecules, and novel optical materials. As a result, they have been popular substrates in direct arylation studies.[3a,7]



Scheme 2. Selected examples of bioactive thiazole-containing natural products.

We were aware at the outset of the report by Mori et al.[8] on the arylation of 2-anisylthiazole in DMSO under the relatively mild temperature of 60 °C in the presence of AgF, suggesting that there may be scope for developing a more general arylation methodology under mild conditions. We chose to study the arylation of 2-phenylthiazole (**1**) with *p*-chloroiodobenzene (**2a**).[9] The choice of a less-strongly electron-donating group in the 2-position (compared to anisyl) was made with a view to developing a robust arylation methodology that would have broad applicability.

Initial optimization studies established that the reaction could proceed in the more user-friendly acetonitrile as solvent at 60 °C over 3 days (Table 1), and that the cheaper Ag_2CO_3 could be employed as both silver source and base (2 equiv). The exact role of the silver additive in the reaction mechanism is unclear at this stage, however we note that an inhibitory effect of iodide has been recorded in a number of arylation

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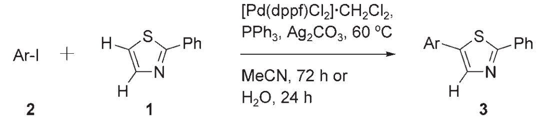
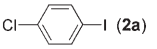
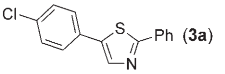
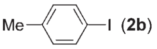
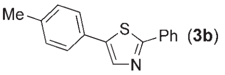
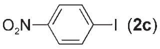
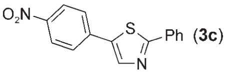
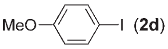
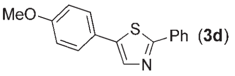
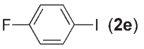
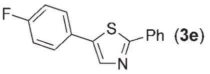
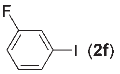
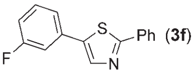
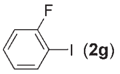
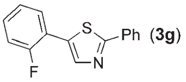
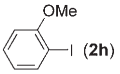
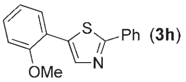
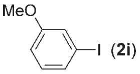
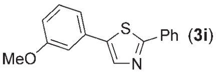
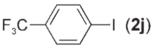
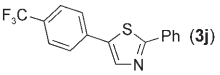
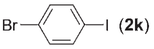
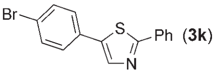
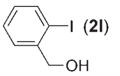
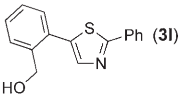
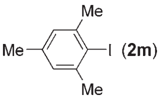
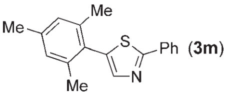
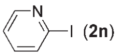
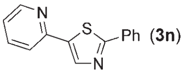
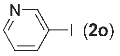
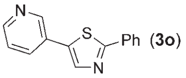
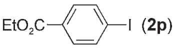
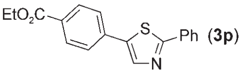
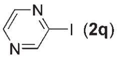
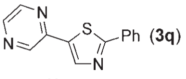
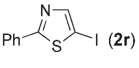
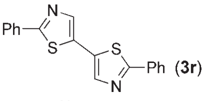
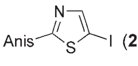
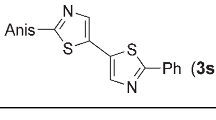
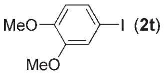
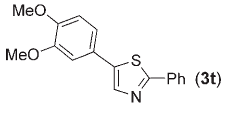
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Arylation of 2-phenylthiazole (**1**).



Entry	ArI[a] (**2**)	Product (**3**)	Yield in MeCN [%][b]	Yield in H_2O [%]
1	 (**2a**)	 (**3a**)	81	95
2	 (**2b**)	 (**3b**)	74	90
3	 (**2c**)	 (**3c**)	62	67
4	 (**2d**)	 (**3d**)	78	> 99
5	 (**2e**)	 (**3e**)	89	> 99
6	 (**2f**)	 (**3f**)	65	> 99
7	 (**2g**)	 (**3g**)	59	82
8	 (**2h**)	 (**3h**)	71	82
9	 (**2i**)	 (**3i**)	53	88
10	 (**2j**)	 (**3j**)	62	> 99
11	 (**2k**)	 (**3k**)	np	> 99
12	 (**2l**)	 (**3l**)	65	81
13	 (**2m**)	 (**3m**)	0	> 99
14	 (**2n**)	 (**3n**)	57	71
15	 (**2o**)	 (**3o**)	36	> 99
16	 (**2p**)	 (**3p**)	53	> 99
17	 (**2q**)	 (**3q**)	0	> 99
18	 (**2r**)	 (**3r**)	61	> 99
19[c]	 (**2s**)	 (**3s**)	0	56
20	 (**2t**)	 (**3t**)	np	88

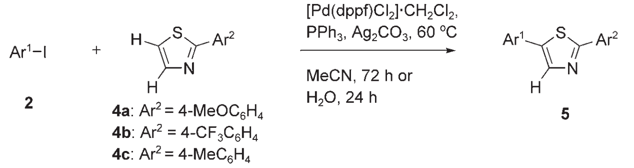
[a] See the Experimental Section for the reaction procedure. [b] np = not performed. [c] anis = 4-methoxyphenyl.

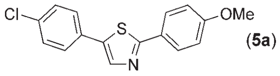
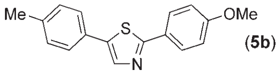
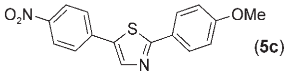
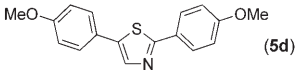
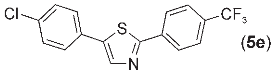
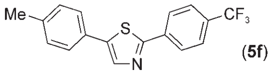
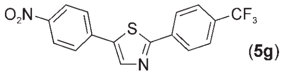
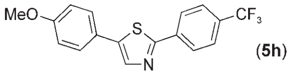
systems mandating the addition of Ag^+ sequestering agents.[2c,10] Arylation was entirely unsuccessful in the absence of Ag_2CO_3 under these conditions. We found a combination of $[Pd(dppf)Cl_2]\cdot CH_2Cl_2/PPh_3$, dppf = (diphenylphosphanyl)-ferrocene) to be an effective catalyst system, although there was good tolerance for a number of Pd salt/ligand combinations. Most importantly, the reaction is successful for a wide variety of electrophiles, effectively arylating **1** with the complete spectrum of aryl iodides. Both electron-rich (R = Me,OMe) and electron-poor (R = F,Cl,CF_3,CN,CO_2Et,COMe,NO_2) reacting partners coupled in generally good yields, with substitution being tolerated at each of the *o*, *m*, and *p*-positions. We were pleased to observe that certain heterocyclic iodides were viable for direct arylation, forming the pyridyl thiazoles **3n** and **3o** and the novel 5–5 linked symmetrical dithiazole **3r**; albeit in moderate yield. The only failures we observed in the system were the hindered mesityl iodide (**2m**) and the heterocyclic pyrazine (**2q**) and thiazole (**2s**) iodides, all of which completely failed to react to give the product. Aryl bromides were less-effective than iodides in every case, and triflates were not viable at all in the reaction.

We next varied the electronics of the thiazole substrate by changing the 2-phenyl substituent, studying the electron-withdrawing *p*-CF_3 (**4b**) group along with the electron-donating *p*-OMe (**4a**) and *p*-Me (**4c**) groups (Table 2 and the Supporting Information). The results are consistent with the S_EAr mechanism commonly put forward for direct arylation of the azole 5-position, with the electron-rich anisyl-substituted thiazole **4a** clearly providing the higher yields of arylation (64–98 %) when compared with the electron-poor substrate **4b** (12–74 %). The *p*-Me series produces comparable arylation yields (69–85 %) to the parent phenyl series (62–81 %, entries 1–4 in Table 1). Examining the electrophile, we observe that *p*-nitro-iodobenzene **2c** is somewhat anomalous, producing the lowest yields (**3c**, Table 1, **5c**,**g**, Table 2; 12–64 %). This result is likely due to the high reactivity of this iodide promoting deleterious side-reactions.

The reaction system compares very favorably with existing thiazole arylations,[7] working in higher yield for a far greater substrate range, embracing polarity differences across electrophile and nucleophile, being considerably milder at *T* = 60 °C, and using a simple and relatively inexpensive catalyst system. With this methodology in hand, we turned our attention to improving the reaction time, which at three days was sub-optimal. Interestingly, our reaction system appears dichotomous with the established Ohta/Miura con-

Table 2: Arylation of 2-aryl thiazoles.



Entry	Ar¹I[a]	Thiazole substrate[c]	Thiazole product	Yield in MeCN [%]	Yield in H₂O [%][b]
1	**2a**	**4a**	 (**5a**)	98	np
2	**2b**	**4a**	 (**5b**)	96	np
3	**2c**	**4a**	 (**5c**)	64	91
4	**2d**	**4a**	 (**5d**)	73	np
5	**2a**	**4b**	 (**5e**)	63	>99
6	**2b**	**4b**	 (**5f**)	32	>99
7	**2c**	**4b**	 (**5g**)	12	79
8	**2d**	**4b**	 (**5h**)	74	82

[a] See the Experimental Section for the reaction procedure. [b] np = not performed. [c] See the Supporting Information for the arylation of **4c**.

ditions as it did not respond well to increasing temperature; microwave heating of the reaction in excess of 100 °C, for example, lead to extensive homocoupling of the aryl iodide with little if any direct arylation.

A more productive approach was to change the solvent. A screen indicated that direct arylation was viable in each of THF, $CHCl_3$, dioxane, MeOH, and toluene. We were surprised to find, however, that water gave by far the best results of all—very clean conversions were observed after 24 h at 60 °C, with the arylated products being isolated in high yield. Repeating the arylations of the compounds in Table 1 and Table 2 in water resulted in substantially higher yields in every case. For some substrates, the difference was remarkable. The mesityl thiazole (**3m**, Table 1), which was not formed at all using acetonitrile, was produced in quantitative yield under aqueous conditions. Likewise, synthesis of the bithiazoles **3r** and **3s**, problematic in MeCN, was substantially improved. We extended the aqueous procedure to the novel pyrazine thiazole **3q** (Table 1) and the *p*-bromo compound **3k** (Table 1), featuring a versatile handle for further functionalization through cross-coupling. We also synthesized the 5-(3,4-dimethoxyphenyl)thiazole **3t**, the thio analogue of balsoxin, an oxazole natural product isolated from the plant *A. Balsamifera*.[11] The average yield using water as solvent was very high—90 % across the complete spectrum of aryl iodides used in the study.

Given the lack of solubility of reactants, reagents, and products in water, the system is an example of what Sharpless has termed an "on-water" reaction, whereby the organic components react in a heterogeneous aqueous suspension.[12,13] The benefits of conducting on-water chemistry can be substantial: increased efficiency and rate (as seen herein), convenient ease of operation, improved safety profile owing to the excellent heat capacity of water, in addition to the benefits of cost and of water as a green solvent. Work-up of the on-water reactions was straightforward, involving simple filtration, extraction, and concentration methods. In a number of cases (for example, thiazoles **3a**,**b**,**d**,**e**, and **j**) the product sublimed out of the aqueous mixture and could be isolated directly, without any extraction, washing, or further purification being necessary (see the Supporting Information).

A detailed examination of the arylation of thiazole **1** with *p*-chloroiodobenzene (**2a**) revealed the reaction to be complete in just 6 h at 60 °C with 5 mol % catalyst loading, compared to 72 h for the reaction in MeCN (Figure 1 A). The loading could be dropped to 0.5 mol % without significant penalty, providing product **3a** in an excellent 90 % yield after 24 h. Similarly, the equivalency of silver carbonate could be reduced to 0.5 molar equivalents (1 equiv of Ag^+, 92 % after 24 h). The reaction even proceeded to completion at room temperature, but only after a reaction time of 5 days.

The theoretical basis of rate acceleration both in and on water has been the subject of extensive investiga-

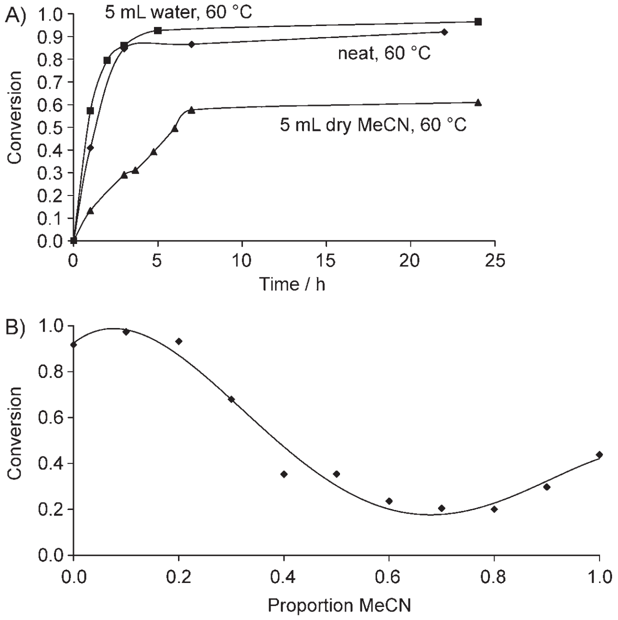
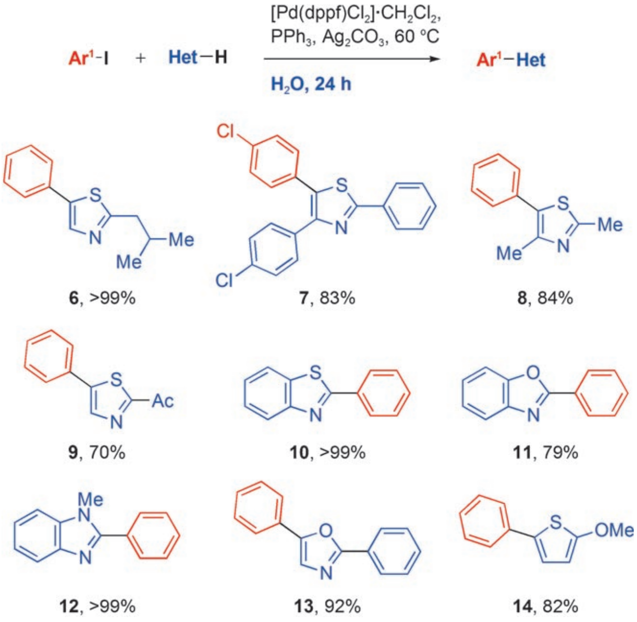


Figure 1. HPLC monitoring of the arylation of **1** with **2a**. A) Conversion over time for three methods. B) Conversion after 24 h in water/MeCN mixtures.

tion.[14,15] For the system at hand we note that running the reaction neat is nearly as effective as running it on water. This suggests that a substantial increase in the effective concentration of reactants and catalyst system is the main driving force for rate acceleration in an on-water reaction. Examining the relative ratio of water/MeCN in the reaction showed that whilst small amounts of MeCN were well tolerated, increasing the proportion of organic solvent led to a rapid decrease in yield, underlining the requirement for heterogeneity (Figure 1 B). Pending detailed mechanistic investigation, we hold this concentration effect as our principal hypothesis. From the point of view of synthetic expediency, the on-water method is to be recommended over running the reaction neat in all cases, owing to benefits of reproducibility and safety.

Having established high-yielding on-water arylation conditions for 2-aryl thiazoles, we were interested in exploring the scope of the methodology with alternative heterocyclic substrates. Initial results point to a versatile process for high-yielding direct arylation (Scheme 3). 2-Alkyl-substituted thiazoles were arylated in excellent yield (**6**) along with the more sterically hindered 2,4-disubstituted thiazoles (**7** and **8**) and the versatile 2-acyl thiazole (**9**). Moving away from thiazoles, the three parent benzazole heterocycles were effectively phenylated at the 2-position, with the benzimidazole and benzothiazole affording quantitative yields of product (**12** and **10**). 2-Phenyloxazole and 2-methoxythiophene were likewise efficiently functionalized at the 5-position (**13** and **14**).



Scheme 3. Direct arylation of five-membered heterocycles on water.

In conclusion, we have developed the first direct arylation methodology that takes place on water. The procedure is highly efficient, user-friendly, and has excellent generality, having been applied to the synthesis of heterocycles displaying diverse functionalities of relevance to medicinal, materials, and natural products chemistry. In addition, the reaction is carried out under conditions substantially milder than those commonly found in the literature for heteroarene arylation. Future work will look to apply this methodology to the synthesis of complex molecules.

Experimental Section

5-(4-Chlorophenyl)-2-phenylthiazole (**3a**):Representative procedure for cross-coupling in organic solvents: Ag_2CO_3 (342.1 mg, 1.240 mmol, 2 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (25.3 mg, 0.031 mmol, 5.0 mol %), PPh_3 (16.3 mg, 0.062 mmol, 10 mol %), 4-chloroiodobenzene (177.5 mg, 0.744 mmol, 1.2 equiv), and 2-phenylthiazole (100 mg, 0.620 mmol,1 equiv) were combined and dissolved in MeCN (5 mL) under N_2. The reaction was heated at 60 °C for 72 h and filtered through a pad of celite, washed with acetone (5 mL) and CH_2Cl_2 (5 mL), and concentrated under vacuum. The title compound is obtained following purification by column chromatography in 10 % EtOAc/hexane as a colorless solid (136.5 mg, 81 % yield). mp (Et_2O): 137 °C; ^1H NMR (360 MHz, $CDCl_3$): $\delta = 7.92$ (1 H, s), 7.90–7.87 (2 H, m), 7.47–7.45 (2 H, m), 7.39–737 (3 H, m), 7.32–7.30 ppm (2 H, m); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 167.49$, 139.44 (CH), 137.94, 134.10, 133.45, 130.16 (CH), 129.88, 129.28 (2 CH), 128.99 (2 CH), 127.77 (2 CH), 126.36 ppm (2 CH); IR (thin film): $\tilde{\nu}_{max} = 3054$, 2986, 1265, 1095, 896, 739, 705 cm^{-1}; HRMS (ES + ve): calculated for $[C_{15}H_{10}{}^{35}ClNS+H]^+$: 272.0295, found: 272.0293.

Representative procedure for cross-coupling on water: Ag_2CO_3 (342.1 mg, 1.240 mmol, 2 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (25.3 mg, 0.031 mmol, 5.0 mol %), PPh_3 (16.3 mg, 0.062 mmol, 10 mol %), and 4-chloroiodobenzene (177.5 mg, 0.744 mmol, 1.2 equiv) were combined and thoroughly mixed in the bottom of a quickfit testtube. 2-Phenylthiazole (100 mg, 0.620 mmol, 1 equiv) was added, followed by deionized water (5 mL), and the suspension heated to 60 °C for 24 h. The reaction mixture was then filtered through a pad of celite, washing the pad with acetone (10 mL) and CH_2Cl_2 (10 mL), and the organic solvents removed under vacuum. The resultant slurry was partitioned between CH_2Cl_2 (10 mL) and brine (5 mL), and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (10 mL) and the combined organic phases concentrated under vacuum. The crude product was purified by column chromatography in 10 % EtOAc/hexane to afford **3a** as a colorless solid (159.7 mg, 95 % yield).

Representative procedure for cross-coupling neat: Ag_2CO_3 (342.1 mg, 1.240 mmol, 2 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (25.3 mg, 0.031 mmol, 5.0 mol %), PPh_3 (16.3 mg, 0.062 mmol, 10 mol %), and 4-chloroiodobenzene (295.8 mg, 1.240 mmol, 2 equiv) were combined and shaken to mix thoroughly. 2-Phenylthiazole (100 mg, 0.620 mmol, 1 equiv) was then added and the mixture heated to 60 °C for 24 h. The reaction is a melt for the first several hours but as more product forms it begins to set into a solid cake. CH_2Cl_2 (10 mL) was added to suspend the reaction mixture which was mechanically broken down and filtered through a pad of celite, washed with CH_2Cl_2 (5 mL) and acetone (5 mL), then concentrated under vacuum. The crude product was purified by column chromatography in 10 % EtOAc/hexane to afford **3a** as a colorless solid (162.5 mg, 96 % yield).

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