Strategic use of transition metals for selective C–H bond functionalisation

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy (PhD) in the Faculty of Engineering and Physical Science

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Abstract

The ability to selectively react C–H bonds in organic molecules is a field within synthetic chemistry that has grown substantively in the last few decades. The interest in this area emanates from the desire to maximise atom economy: this approach obviates the need for pre-functionalised starting materials and stoichiometric organometallic reagents. However, organic molecules typically contain many different C–H bonds with little difference in bond energy which can make selective functionalisation difficult to achieve.

Herein is described how ruthenium catalysis was shown to effect meta-bromination on substituted 2-phenylpyridines. This novel procedure shows a marked contrast to other transition metal catalysed bromination procedures which are selective for the ortho-position of the phenyl ring. It was shown that this methodology was compatible with more traditional palladium catalysed chemistries (Suzuki-Miyaura and Heck reactions) in the same pot which enabled the development of procedures for one-pot meta-arylation and meta-alkenylation. Mechanistic postulation on the meta-bromination procedure led to the discovery of several interesting new meta-selective C–H functionalisation reactions with ruthenium catalysis. The early investigations, together with the challenges faced, are described. Subsequent investigations into other halogenating agents with ruthenium catalysis showed that iodine monochloride gave interesting results, with switchable chemoselectivity through variance of catalyst giving ortho-chlorinated or ortho-iodinated products.

Also presented is a copper mediated coupling of electron rich arenes and toluene-like molecules to give (halo)diaryl methanes. This formal cross dehydrogenative coupling strategy tolerates a wide range of coupling partners for both the electron rich arene and the tolyl-component. Mechanistic studies suggest that the reaction proceeds via a copper mediated coupling of an in situ generated aryl bromide with a benzylic radical species.
Declaration

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Part of this work has been published in a peer reviewed journal:

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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>Alk</td>
<td>alkyl</td>
</tr>
<tr>
<td>APCI</td>
<td>atmospheric pressure chemical ionisation</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Ar(^F)</td>
<td>4-(CF(_3))C(_6)F(_4)</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>ATRA</td>
<td>atom transfer radical addition</td>
</tr>
<tr>
<td>BDE</td>
<td>bond dissociation energy</td>
</tr>
<tr>
<td>BHT</td>
<td>butylated hydroxytoluene</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2'-bipyridyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>'Bu</td>
<td>iso-butyl</td>
</tr>
<tr>
<td>&quot;Bu</td>
<td>nor-butyl</td>
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<tr>
<td>'Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic/catalyst</td>
</tr>
<tr>
<td>CDC</td>
<td>cross dehydrogenative coupling</td>
</tr>
<tr>
<td>CMD</td>
<td>concerted-metalation-deprotonation</td>
</tr>
<tr>
<td>cod</td>
<td>cycloctadiene</td>
</tr>
<tr>
<td>coe</td>
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<td>cyclopentyl methyl ether</td>
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<td>d</td>
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<tr>
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<td>DCM</td>
<td>dichloromethane</td>
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<tr>
<td>dF-ppy</td>
<td>2-(2',4'-difluorophenyl)-5-trifluoromethylpyridyl</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
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</tr>
<tr>
<td>DG</td>
<td>directing group</td>
</tr>
<tr>
<td>DMA</td>
<td>$N,N$-dimethylacetamide</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
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</tr>
<tr>
<td>DTBP</td>
<td>di-$tert$-butylperoxide</td>
</tr>
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<td>dtbbpy</td>
<td>4,4’-$tert$-butyl-$2,2'$-bipyridine</td>
</tr>
<tr>
<td>$\Delta$</td>
<td>heat</td>
</tr>
<tr>
<td>$e^-$</td>
<td>electron</td>
</tr>
<tr>
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<td>electron-donor-acceptor</td>
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<td>EDG</td>
<td>electron donating group</td>
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<tr>
<td>EI</td>
<td>electron impact</td>
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<tr>
<td>eq.</td>
<td>equivalents</td>
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<td>ESI</td>
<td>electrospray ionisation</td>
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<td>Et</td>
<td>ethyl</td>
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<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
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<td>gas chromatography</td>
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<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>het</td>
<td>heteroaromatic</td>
</tr>
<tr>
<td>HFIP</td>
<td>1,1,1,3,3,3-hexafluoropropanol</td>
</tr>
<tr>
<td>$h\nu$</td>
<td>photon</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
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<tr>
<td>HR</td>
<td>high resolution</td>
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<tr>
<td>$k$</td>
<td>rate constant</td>
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<tr>
<td>KIE</td>
<td>kinetic isotope effect</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
</tr>
<tr>
<td>LC</td>
<td>liquid chromatography</td>
</tr>
<tr>
<td>LR</td>
<td>low resolution</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>M</td>
<td>metal species</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
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<td>Mes</td>
<td>mesityl</td>
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<tr>
<td>min</td>
<td>minutes</td>
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<tr>
<td>m.p.</td>
<td>melting point</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>MS</td>
<td>mass spectrometry</td>
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<tr>
<td>MS</td>
<td>molecular sieves</td>
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<tr>
<td>MTBE</td>
<td>methy tert-butyl ether</td>
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<tr>
<td>µW</td>
<td>microwave</td>
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<tr>
<td>NBE</td>
<td>norbornene</td>
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<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
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<tr>
<td>Nf</td>
<td>nonafluyl</td>
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<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NiXantphos</td>
<td>4,6-bis(diphenylphosphino)phenoxyzine</td>
</tr>
<tr>
<td>NMM</td>
<td>N-methylmorpholine</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>Nu</td>
<td>nucleophile</td>
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<td>'Pr</td>
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<td>&quot;Pr</td>
<td>nor-propyl</td>
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<td>photoredox catalyst</td>
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<td>Pyr</td>
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<td>septet</td>
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<td>SET</td>
<td>single electron transfer</td>
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<tr>
<td>T</td>
<td>temperature</td>
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<tr>
<td>TBAB</td>
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</tr>
<tr>
<td>TBATB</td>
<td>tetrabutylammonium tribromide</td>
</tr>
<tr>
<td>TBATI</td>
<td>tetrabutylammonium triiodide</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyltriphenylsilyl</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>TBPB</td>
<td>tert-butylperoxybenzoate</td>
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<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(2,2,6,6-tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td>Tf</td>
<td>triflyl</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>TMATB</td>
<td>tetramethylammonium tribromide</td>
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<tr>
<td>TMEDA</td>
<td>tetramethylethylenediamine</td>
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<tr>
<td>tol</td>
<td>toluene</td>
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<tr>
<td>TS</td>
<td>transition state</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<tr>
<td>UV</td>
<td>ultraviolet</td>
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<tr>
<td>Val</td>
<td>valine</td>
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<tr>
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<td>visible</td>
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<tr>
<td>XPhos</td>
<td>2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl</td>
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“I suppose at one time in my life I might have had any number of stories, but now there is no other. This is the only story I will ever be able to tell.”

Donna Tartt, The Secret History
1. Introduction

1.1 Terminology

The terms “C–H activation” and “C–H functionalisation” have historically been used interchangeably and the exact definitions have been subject to much discussion and debate. Georgiy Shul’pin put forward an argument that activating a σ-bond implies “increasing the reactivity of this bond towards a reagent” and that ‘splitting’ of this bond was merely a consequence of activation. Organic chemists working in the field of transition metal catalysis, however, have often used “C–H activation” as a collective term for a process involving a transition metal catalyst which converts a C–H bond to a C–X bond (where X ≠ H).

Transition metal catalysed transformations of C–H bonds can be divided into two distinct pathways: 1) inner-sphere (or organometallic) mechanisms involve the cleavage of a C–H bond to form a distinct intermediate with a bond between the carbon centre and the metal (figure 1). Functionalisation then takes place on this intermediate either via an external reagent or one from the metal centre. 

![Figure 1: Inner-sphere C–H functionalisation](image)

2) Outer-sphere (or coordination) mechanisms do not produce any intermediate with a carbon-metal bond (figure 2). Typically, these reactions involve the formation of a metal complex in a high oxidation state containing ligand X. The reaction between this complex and the C–H bond of the substrate then proceeds either via direct insertion or via H-atom abstraction/radical rebound.
This mechanism is seen more with C(sp$^3$)–H bonds which are weaker as it is associated with a build-up of radical or cationic character at the carbon centre. Most biological oxidation reactions proceed via this type of mechanism for example.$^4$

It is important to note that plenty of C–H functionalisation techniques also exist that are not metal catalysed.$^5$ From herein, the naming convention that will be followed will be to refer to the step whereby metal insertion into the C–H bond occurs as “C–H activation”. C–H functionalisation will be used to describe the process as a whole i.e. the transformation from C–H bond into C–X bond (where X ≠ H).

1.2 Perspective

The area of C–H functionalisation can lay claim to some of the most powerful novel methodology that has been developed in organic synthesis in the past few decades. As the field has grown, a vast number of highly selective, high yielding metal catalysed transformations have been reported. The competitiveness of working on this topic reflects not only the thrill of the unexpected discovery and the excitement of exploring uncharted land, but also the desire for more efficient methods which can transform the way in which organic chemists do synthesis.$^6$

1.2.1 C–H functionalisation in total synthesis

Several representitive examples of the impact that C–H functionalisation has had on organic synthesis are presented below. What must now truly excite every retrosynthesiser is the potential to break bonds that were once thought unbreakable: the expansion of our synthetic toolbox allows us to be ever more creative in the art of total synthesis.$^7,8$
Morphine is probably one of the most synthesised molecules in history: and for good reason. Jon Ellman’s group last year reported the synthesis of a synthetic opioid, ent-ketorfanal, synthesised using their rhodium chemistry. Most previous syntheses of related semi-synthetic opioids rely on manipulations of morphionoid natural products which is somewhat restrictive as to what structures can be accessed. The approach that is taken is particularly pleasing to see as they demonstrate chemistry that has been developed extensively in their group on a more complex substrate to give the (non-regulated) enantiomer of opioid analgesic ketorfanol.

From structure 1 (prepared in 5 steps), a directed rhodium catalysed C–H activation takes place on the vinyl C–H bond conjugated to the imine directing group (scheme 1). Addition of this syn C–H bond to the alkyne gives an intermediate which can then undergo electrocyclisation with the torquoselectivity induced by the isopropylidene protected diol. Insequent in situ reduction of the enamine with sodium acetoxyborohydride gives the tetrahydropyridine product 2 in 69% yield. In just two further steps, ent-ketorfanol is produced. Their approach is also notable as a showcase for directed C–H activation because the imine directing group is incorporated in the final structure.

![Scheme 1: Rhodium C–H activation used by Ellman en route to ent-Ketorfanol](image)

Tetradotoxin 6 is an extremely potent neurotoxin which acts by way of blocking sodium channels and is most famously associated with the Japanese pufferfish (fugu) despite being isolated from many other animals. Moreover, it possesses a beautiful, if quite intimidating, carbon framework that has intrigued several ambitious chemists. Another fantastic example of C–H functionalisation, this time going via an outer-sphere mechanism, is the synthesis of (-)-tetradotoxin
from the group of Du Bois. Their route involves both a rhodium catalysed carbenoid and nitrenoid insertion.

![Scheme 2: Rhodium catalysed nitrenoid C–H insertion to produce an intermediate to (-)-tetrodotoxin](image)

The stereospecific C–H amination at the tertiary centre was accomplished in a particularly impressive 77% yield given the complexity of the substrate. The reaction proceeds via the formation of a rhodium nitrenoid species which then undergoes C–H insertion (scheme 2).

For one final example, we turn to a true milestone synthesis: perhaps the first example of palladium C–H activation used in total synthesis. Now 28 years previously, Trost and co-workers reported the total synthesis of ibogamine 8. Ibogamine is one of a number of similar structures that are thought may help with drug addiction although detailed studies are yet to be carried out. The enantiopure reactant for this impressive reaction is prepared in just three steps from tryptamine. Following C2 palladation on the indole structure, carbopalladation occurs before the resulting alkyl palladium species is reduced in situ to give a short synthesis of ibogamine without any use of protecting groups (scheme 3).

![Scheme 3: Palladium mediated C–H functionalisation as the final step in the synthesis of ibogamine](image)
This is a very brief sample of a huge field but hopefully shows the power of C–H functionalisation methodology and its potential for incorporation in extremely complex chemical systems. Rational design of precursors enables chemists to streamline their syntheses, which is very important as demand increases significantly for more efficient and shorter routes to targets.

Extensive reviews of this enormous field have been published\(^1\) and with the area growing every day it is sometimes difficult to know where to begin. Opinions vary as to where it all started and who lays claim to being the founding-fathers of this field. Outlined below is a brief introduction to directed ortho-C–H functionalisation before moving on to the area of directed strategies for targeting the meta-C–H bond of arene substrates. Finally, a short overview of benzylic C–H arylation is presented to put into context what follows in the latter part of the results and discussion.

### 1.2.2 Pioneering work: where it all began

It may be considered that ‘conventional’ directed ortho-C–H functionalisation is now well-trodden ground, yet challenges still remain. One of the seminal publications in the field was that by Murai and co-workers more than two decades ago.\(^{16}\) Here it was reported that aromatic ketones enable directed ortho-ruthenation which allows the addition of an aromatic C–H bond across a terminal olefin (scheme 4). This pioneering work was arguably, to an organic chemist, the first synthetically useful example of directed C–H cyclometallation being used to activate a C–H bond. Despite previous reports of cyclometallation reactions,\(^{17,18}\) here, the catalyst loading is as low as 2 mol%, with yields of products in a lot of cases almost quantitative.
In a highlight of Murai’s work, Goldman poses the following:

"The next question, of course, is how general these reactions are. What other functional groups (on either substrate) can be tolerated? What other types of olefin can be inserted into the C–H bond? More broadly... what other functional groups will act to 'direct' the functionalisation of specific C–H bonds?"

He rightly states that this will determine the impact that such chemistry has on organic synthesis and it is pertinent to observe that this publication itself highlights a large number of the challenges that existed in directed ortho-C–H functionalisation, most of which still exist although considerable progress has been made to address many of them.

1.2.3 Challenges and future paths

Although difficult to predict the exact direction that the C–H functionalisation community will take with their research in the coming years, outlined below are a few of the challenges that are already being addressed to further improve this area of organic synthesis.

1.2.3.1 Cross dehydrogenative coupling

One of the targets that chemists have set themselves is to move away from using pre-functionalised starting materials for not just one of the reactants, but both. In this way, chemists are trying to take two reactants with C–H bonds and selectively form a C–C bond between them. This has been termed cross dehydrogenative coupling (CDC). From an idealistic point of view it is easy to see why we would want to work towards this goal: if we used oxygen as the sole oxidant, the only by-product generated would be water.

As shown in scheme 5a, ortho-arylation of phenylpyridine derivatives catalysed by ruthenium and using arylbromides was first shown in 2001 by Oi and Inuoe. As an example of the progress made with this reaction, six years later, Sanford’s group reported a CDC using palladium catalysis to form similar products. Obvious disadvantages to this procedure are the use of large excesses of the arene component. This is still a common problem in many reports of CDC. A
related problem is being restricted to electronically biased substrates. Intrinsic mechanistic aspects of these reactions dictate that currently one of these factors needs to be present to favour heterocoupled rather than homocoupled products.

\[ \text{Scheme 5: Making progress on the road to CDC} \]

1.2.3.2 The drive for efficiency

When these reactions are taken from an academic lab into the industrial setting, it is important to address some more practical aspects that become far more significant when moving from milligram to decagram scales. Cost and sustainability issues are the driving factors to push for the lowest catalyst loading possible. It is desirable that the reactions be done at as low a temperature as possible: heating a solvent at a temperature considerably above its boiling point is still an all too common occurrence in this field and limits the ability to scale up the chemistry in a safe manner.

One recent example of a transition metal catalysed C–H functionalisation procedure that has been modified to make it more amenable to industrial use is that from Subok Chang and co-workers (scheme 6). Here they use 1,4,2-dioxazol-5-ones as a safer alternative to acyl azides. Notably in the later paper, they show that the reaction can be run at 0.5 mol% catalyst loading, in ethyl acetate (thus avoiding the use of the original undesirable chlorinated solvent) and with one third of the original reaction time. The reaction produces only carbon dioxide as a by-product and can be run under atmospheric conditions.
Another important contribution to the area of ‘going green’ is that from the research group of Larrosa. They show that stoichiometric silver salts which are required in a wide range of palladium catalysed C–H arylation procedures can often be replaced by tetralkylammonium salts.\(^{27}\) After determination that the role of the silver acetate was to regenerate Pd(OAc)\(_2\) from the PdI\(_2\) formed, it was found that tetramethylammonium acetate (which could be formed \textit{in situ} from tetramethylammonium chloride and potassium acetate) was capable of performing the same role. This has a substantial positive impact on cost reduction as well as simplifying work-up procedures.

\subsection*{1.2.3.3 A precious commodity}

As well as moving to lower catalyst loadings, there is also a big drive towards using less-precious metals as catalysts. Two groups who have made notable contributions to rhodium catalysed directed C–H functionalisation are that of Jon Ellman and that of Frank Glorius. Both have more recently published work to show that cobalt catalysis can perform many of the same reactions that they initially developed with rhodium (scheme 7).\(^{28,29}\) It has also been noted that cobalt is a more active catalyst for some C–H activation reactions than rhodium.\(^{30}\)
Sustainability worries together with the high price of transition metals (particularly, rhodium, iridium and palladium) highlight the importance of this aspect of chemistry.

1.2.3.4 Widening the scope

Finally, one of the limitations of this chemistry and indeed a large proportion of newly published methods, in not just this field but organic chemistry as a whole, is the limitation of the scope of the reaction under the published conditions. It will be seen that this is a problem that is prevalent throughout the work described later in this thesis and is an all-too familiar menace.

1.3 A change of direction: going meta

Over time and given the understanding that chemists have developed regarding different methods of directed cyclometallation, new challenges have been sought regarding selective functionalisation of aromatic substrates. With directed ortho-C–H activation well established, attention turned to a slightly more distant challenge: the C–H bond at the position meta to the directing group. Clearly innovation and a new set of tactics would be needed to allow such a change in selectivity and the considerable efforts and achievements in this field are outlined below.

* At the time of writing (20/03/2016) the costs of transition metals (per troy ounce) were as following: Rh $710; Ir $520; Pd $595; Ru $42 (source Johnson Matthey).
1.3.1 Large templating groups for meta-C–H functionalisation

When it had come to targeting meta-C–H activation, it seemed obvious to explore whether it would be possible to use the same strategy as for ortho-C–H activation: using a directing group to position the metal catalyst for C–H mettallation but this time at the meta-position. This strategy was evidently not without numerous challenges and posed many questions: the over-riding one being whether it would even be possible to invoke a transition state of the size and geometry that would be required to insert the metal at this position.

The group of Jin Quan Yu answered this in the affirmative, reporting in 2012 how a large template with a nitrile group could provide a weak ‘end-on’ coordination to palladium and allow meta-olefination of benzyl ether and hydrocinnamic acid derivatives (scheme 8).

The authors state that the nitrile group is key to their approach as it obviates the additional strain that would otherwise be present in the pre-transition state. It is important to note that for metallacycles of ring size greater than seven, a cyclophane-like transition state is proposed which is considerably less rigid and ordered (structure 24, scheme 8). The flexibility thus provided by the nitrile directing group is important and the fact that it is weakly coordinating is also thought to help with the palladation event as the palladium species is more electrophilic.

Following this first publication in 2012, the same group reported that a similar meta-olefination procedure could be carried out on α-phenoxyacetic acid
derivatives (figure 3b). They then further showed that the same template was amenable to meta-arylation when using aryl boronic acid esters (figure 3a). Tan and co-workers reported the use of a more easily cleaved silyl directing group to carry out meta-olefination which arguably started to make this approach more attractive as a practical method in organic synthesis (figure 3f).

Attaching a template first to anilines and benzamines (figure 3d) and then indolines and indoles (figure 3i) allowed further expansion of the substrate scope of this reaction. Olefination of phenylacetic acid derivatives at the meta-position was recounted using a similar directing group which is now commercially available (figure 3g). Development of simpler and commercially available directing groups, which also tend to provide more selectivity for mono-functionalised products over di-functionalised, has been the main contribution by Maiti and co-workers (figure 3h). Recently, Li’s group has reported meta-selective olefination and acetoxylation on benzoic acid derivatives with this being the first example to use this approach on electron deficient aromatic rings (figure 3j).

Figure 3: Examples of templating groups reported in the literature for meta-C–H functionalisation
Finally, Yu’s group has demonstrated that a template with a pyridine moiety as the co-ordinating group can be used for meta-olefination and -iodination (figure 3e). This is the first example of such a templating group having the nitrile group replaced with a different group. New templates that have emerged have widened the scope of the transformations that are possible with this approach and the templates themselves have evolved to become more efficient, more selective and more readily cleaved. In recognition of the markable contribution made by Yu’s group, these meta-directing templates are now often dubbed ‘Yu-turns’.  

Although some chemists characterise this approach as inelegant and impractical, and these criticisms can certainly be accepted as valid, the work itself must be put into context of the time at which it was published: the field was in its infancy and these studies were forgetive. It would seem likely that further significant developments in the use of large templating directing groups are not far away.

### 1.3.2 Copper catalysed meta-arylation with iodonium salts

The group of Matthew Gaunt published an unusual copper-catalysed procedure in 2009 whereby acetanilides 26 react with diaryl iodonium salts 27 under relatively mild conditions to give meta-arylated products 30. This notable piece of work was the first significant piece of transition metal catalysed directed meta-C–H functionalisation and is an important milestone for the area, not least because the directing group is considerably more versatile than many other examples that have been reported since.

![Scheme 9: Copper catalysed meta-C–H arylation](image)

The authors’ proposed mechanism is outlined in scheme 9 but further computational work was done in the groups of Yu-Xue Li and Yun-Dong Wu who suggested a slightly different mechanism. Following coordination of a Cu(III)
species to the carbonyl group, electrophilic attack on the copper species from the aromatic ring occurs at the ortho-position. The phenyl group bound to the copper is then transferred to the meta-position of the aromatic ring via a Heck-like four-membered-ring transition state.

In an ensuing publication, Gaunt’s group disclosed that α-aryl acetamides, the corresponding Weinreb amides, α-arylketones and α-aryl esters were all competent substrates for this uniquely powerful method for meta-arylation. Furthermore, they observed at slightly elevated temperatures that some substrates could undergo the reaction in good yields without addition of metal catalyst.

1.3.3 Double directing group strategies
Another strategy that has been envisaged to enable meta-C–H functionalisation is the use of two directing groups within the reactive system and this has been carried out in a number of different ways.

1.3.3.1 Norbornene as a transient mediator
Marta Catellani’s research group showed that norbornene (NBE) 32 can shuttle palladium to the C–H bond ortho to that of a C–X bond following oxidative addition. This efficacious reaction is now frequently referred to as the ‘Catellani reaction’. Together with the group of Mark Lautens, they have developed this to become an extremely powerful methodology for double functionalisation of aryl halides. Other groups have capitalised on this potent chemistry to synthesise a whole host of different structures (figure 4). Further, the total synthesis of (+)-linoxepine 35, which used the Catellani reaction as a key step, was carried out by Lautens’ group. The total synthesis of rhazinal 36 has also been performed using this reaction as a significant step.
Jin Quan Yu’s group successfully combined the idea of using norbornene’s ability to shuttle palladium one carbon further around the ring but with the initial step now not as an oxidative addition reaction, but as a directed ortho-C–H activation from phenylacetic acid derivatives 44 (figure 5). This powerful reaction gives meta-arylated, -alkylated and -benzylated products in good to excellent yields and opens the door to switching reactivity between ortho and meta solely by introducing norbornene as a co-catalyst (scheme 10).
In order to suppress unwanted side reactions in this system, extensive screening of pyridine based ligands was necessary. It was found that electron rich pyridine ligands favoured the formation of the meta-methylated product with methyl iodide as the coupling partner. Ethyl iodide was significantly less reactive and so more equivalents of the reagent were necessary. The more reactive electrophile, benzyl bromide worked well under the reaction conditions as did electron-deficient, ortho-substituted aryl iodides.

Scheme 10: Yu’s doubly directed palladium catalysed meta-C–H functionalisation methodology
Clearly this work is a landmark achievement in the field but it would be remiss not to highlight the areas which could be improved: namely it would be desirable to avoid the use of excess silver reagents and the directing group used requires prior preparation and further manipulation to give more synthetically useful products.

Guangbin Dong’s group published work using a very similar tactic just shortly after Yu’s group.\(^{51}\) They showed that simple dimethyl benzylamines \(^{47}\) react together with aryl iodides in the presence of an astounding range of reagents: palladium catalyst, triphenylarsine ligand, silver acetate and what they refer to as an ‘acetate cocktail’ (caesium, lithium and copper acetates together with acetic acid) all in chlorobenzene to give the meta-arylated products (scheme 11). Through a range of control experiments, it has been shown that all additives are necessary to give the products in good to excellent yields although understandably, the role of each one has yet to be rationalised. Like Yu’s work, the scope of the aryl iodides is limited to those with an electron-deficient ortho substituent and also a large excess of a silver reagent is used. It is worth noting that it is hard to prevent double meta-arylation on substrates without a pre-existing meta-substituent. Despite the complicated reaction set-up, it must be pointed out that this methodology is nevertheless very powerful with the benzylamines easily converted to benzyl chlorides or the corresponding benzaldehydes in one step.

\[
\begin{align*}
\text{Scheme 11: Dong’s take on the directed Catellani reaction} \\
\text{Notedly, Yu and co-workers have since disclosed in their subsequent communication that by using 2-carbomethoxynorbornene } 52 \text{ as the transient mediator, the substrate scope is markedly widened (scheme 12).}^{52}\text{ In contrast to previously, less-reactive alkyl iodides containing a broad range of functional groups can react to give the meta-substituted compounds. The broadening in scope of aryl }
\end{align*}
\]
iodides is similarly impressive with the restriction to ortho-substitution now having been lifted and electron rich aryl iodides also now reacting to give products in good to excellent yields.

Scheme 12: Yu’s more recent developments in the field
1.3.3.2 Carbon dioxide as a traceless director

Phenols are extremely common motifs in organic chemistry appearing frequently in natural products, drugs and materials.\(^{53}\) Electronic factors typically determine that they react at the ortho and para positions. Larrosa and co-workers showed that it was possible to over-ride this reactivity profile by temporary introduction of a carboxylic acid directing group ortho to the alcohol (structure 54, figure 6).\(^{54}\) After directing palladation to the position ortho to the newly installed carboxylic acid (but meta relative to the original phenol compound), C–H functionalisation occurs before the resulting carboxylic acid decarboxylates \textit{in situ}. This leaves an overall meta-arylated phenol via what they term a ‘traceless directing group strategy’ (scheme 13).

![Figure 6: The concept of using carbon dioxide as a traceless directing group](image)

Despite the use of high temperatures and pressures, the utility of this procedure is undeniable, allowing access to a substitution pattern that would otherwise be very hard to achieve. This is shown by synthesising a \(\gamma\)-Secretase Inhibitor 57 in 41\% overall yield and just three steps rather than the previously reported eight steps and 6\% overall yield.\(^{55}\)

![Scheme 13: The Larrosa group’s one-pot meta-C–H arylation of phenols](image)
1.3.3.3 Ruthenium catalysed meta-functionalisation

Chris Frost and co-workers discovered the reaction of aryl-sulfonyl chlorides with phenyl pyridine under ruthenium catalysis to give the meta-substituted products in 2011. Where palladium had been shown to give ortho-sulfonlated products, Frost’s group observed that switching the metal catalyst to ruthenium switched the selectivity to give the meta-sulfonated products (scheme 14). Although the substrate scope was very limited in terms of what substitution was allowed on the aromatic ring and the directing group was limited to pyridine, this was clearly a significant piece of work.

![Scheme 14: Ruthenium catalysed meta-sulfonation of phenylpyridines](image)

In seeking an explanation to this selectivity, it was interesting to look back at the reactivity profile of some organo-ruthenium complexes. Wright et al. had reported in the late 1990s that ruthenium and osmium complexes with phenyl pyridine ligands could be brominated and nitrated in the position para to the ruthenium centre (scheme 15).

![Scheme 15: Bromination and nitration of organoruthenium and organoosmium complexes](image)
In this way it can be thought that ruthenium is acting as a directing group itself in the catalytic system. After directed ortho-metallation, the cyclo-ruthenated species is now highly pre-disposed to react at the centre para to the metal, but overall meta to the pyridine directing group. Subsequent proto-deruthenation would give the meta-substituted phenyl pyridine.

In 2013, Lutz Ackermann’s research group published an article which revealed that under ruthenium catalysis, secondary alkyl halides gave meta-alkylated products \(65\) (scheme 16). Unlike Frost’s report, it was disclosed that the directing group scope included pyrazolyl-, imidazolyl-, and benzimidazolyl-substituted arenes and there was more tolerance in terms of pre-existing substitution on the aromatic ring. The same group had reported two years previously that reaction of primary alkyl halides under extremely similar conditions gave the ortho alkylated products.\(^{59}\)

![Scheme 16: Ruthenium catalysed meta-alkylation of phenylpyridines with secondary alkyl halides](image)

Then, in 2015, Frost’s group\(^{61}\) (scheme 17) and subsequently Ackermann’s group\(^{62}\) reported that the meta-alkylated product is also observed when the reaction is carried out using tertiary alkyl halides. Although not a significant step in terms of substrate scope development, both groups proposed for the first time that the reaction was proceeding via a radical mechanism whereas before it had been postulated that it could have been via an electrophilic aromatic substitution mechanism.

![Scheme 17: Ruthenium catalysed meta-alkylation of phenylpyridines with tertiary alkyl halides](image)
Significantly, the report from Ackermann for the first time showed that a cleavable directing group could be used offering access to meta-alkylated anilines 70 (scheme 18). Also, it is suggested that the use of amino-acid derived ligands is significant to enable higher conversion in these reactions with the phenyl pyridine substrates run at a slightly lower temperature than for the reactions carried out by Frost’s group.

![Scheme 18: Ruthenium catalysed meta-alkylation of pyrimidine protected anilines with tertiary alkyl halides and subsequent directing group cleavage](image)

Outlined below is Ackermann’s proposed mechanism (figure 7) which is similarly in line with the Frost group’s thoughts. Reversible ortho cyclo-ruthenation is followed by radical addition to the cyclo-ruthenated intermediate. It is proposed that the ruthenium in this reaction is playing two roles – not just that of a directing group but that it is also responsible for the generation of the radical via single electron transfer.

It is notable that Ru(II) to Ru(III) cycles for generation of radicals are well known for Kharasch reactions and this fits broadly with the suggestion outlined in figure 7. After radical addition to the cyclo-ruthenated intermediate, electron transfer can take place between the radical and a Ru(III) species thereby regenerating Ru(II) and leaving the cationic species bound to the ruthenium. Rapid removal of the proton rearomatises this species before de-ruthenation releases the product. Deuterium labelling studies led the researchers carrying out this work to suggest that the proto-demetallation involves abstraction of a proton from the alkyl halide reactant 66, to generate alkene 76, although it is unclear how this fits in with other ruthenium catalysed reactions.
Following publication of the work described in section 2.1 of this thesis, another research group also published a method for ruthenium catalysed meta-bromination. Using N-bromosuccinimide as the brominating agent, [Ru(p-cymene)Cl$_2$]$_2$ catalyst and DMA as solvent, they showed that it was possible to effect meta-bromination on phenyl pyridine derivatives (scheme 19). Pyrimidine, isoquinoline and substituted pyrazoles also worked as directing groups albeit with varying degrees of success. To show the utility of this methodology, they carried out the synthesis of drug molecule Vismodegib 78 in five steps and 47% overall yield.

Scheme 19: Ruthenium catalysed meta-bromination towards the synthesis of Vismodegib
They also make some interesting observations regarding mechanism with results suggesting that two phenylpyridine molecules could be bound to the ruthenium centre in the catalytically active species 80. They postulate a mechanism which involves oxidative addition of NBS 84 to Ru(II) to give a Ru(IV) species 81 although there is little evidence to support this specific step. The outline of their proposal is detailed in figure 8.

![Diagram](image-url)

**Figure 8:** Huang’s proposed mechanism for meta-bromination

### 1.3.4 Hydrogen bonding bifunctional ligands

Recently, an elegant piece of work by Kanai and co-workers has described a methodology for meta-borylation which utilises a ligand 88 which contains both a bipyridyl moiety, which binds to the iridium centre, and also a urea moiety, which interacts with the amide directing group on the aromatic ring through a hydrogen bonding interaction (intermediate 86, scheme 20). This ensures the correct spatial arrangement of the metal with respect to the directing group to allow overall meta C–H borylation.
1.3.5 Non-directed meta-functionalisation

A few different methods for functionalisation of more distal C–H bonds have not relied on directing groups, but rather on the electronics or steric of the arene. It could be argued that this is still directed, just in a different way, however a distinction is drawn here. An overview of two of the most significant contributions to this area is presented below.

1.3.5.1 Ligand controlled palladation

In contrast to previous strategies for ortho-olefination for benzoic acids and anilides, Yu’s group reported their discovery of a meta-olefination for electron deficient aromatic systems (scheme 21). Key to the success of this reaction is the use of novel rationally-designed 2,6-dialkyl substituted pyridine ligands. Pyridine ligands are known to be one of the most efficient ligands when using molecular oxygen as an oxidant to turn over Pd(0). However, due to the strength of the Pd-N bond, displacement by an electron-deficient arene in electrophilic palladation mechanism is not possible. In order to weaken the strength of this bond, pyridine ligands with a sufficient balance of steric repulsion were designed. If the ligand was too sterically bulky then Pd(0) would be precipitated from the reaction but without sufficient steric bulk, the palladation of these substrates could not occur. Their optimised conditions are as follows: a pyridine ligand with branched alkyl side...
chains 91 (20 mol%) with Pd(OAc)$_2$ (10 mol%) and one equivalent of acetic anhydride in the arene substrate as a solvent (20 – 30 eq.) at 90 °C under one atmosphere of oxygen. In general *meta*-*para*-functionalisation is around 80:20 in terms of selectivity.

![Scheme 21: Palladium catalysed meta-alkenylation on electron deficient arenes](image)

One criticism that is partially addressed is the use of large excesses of the arene substrate. An example is carried out with only five equivalents of arene in ethyl acetate as solvent which results in a modest reduction in yield. No concrete conclusions were drawn over the origin of *meta*-selectivity however it is believed that electrophilic substitution patterns together with the stronger acidity of the *meta*-C–H bond are likely influences.

1.3.5.2 Borylation and silylation under steric control

An area that is slightly distinct from the other methodologies reviewed here is iridium and rhodium catalysed borylation and silylation. This work warrants comment nonetheless due to the power it is capable of wielding.$^{69,70}$ The first publication in this area came from the research group of Smith III and describes how using low loadings of a few different iridium catalysts with a bidentate ligand with various different stoichiometries of arene substrate and B$_2$Pin$_2$ under thermal conditions gives borylated arenes (scheme 22).$^{71}$

The substitution pattern appears to arise solely from steric factors with the least sterically hindered C–H bond being transformed. Many advances have been made in this area since with the groups of John Hartwig and Norio Miyaura being notable contributors.$^{69,70}$
From Smith III and Maleczka’s initial publication where the arene substrate was used as the solvent, a number of modifications to the catalytic species and ligand have been made to allow the reaction to be performed under much milder conditions than initially reported.\(^\text{72,73}\) Extensive screening of Ir(I) precatalysts revealed \([\text{Ir(OMe)}(\text{cod})]\_2\) to be the most active and in combination with dtbpy ligand, it was possible to form arylboronates in good yields at room temperature with a stoichiometric ratio of \(\text{B}_2\text{Pin}_2\) to arene (scheme 23).\(^\text{74}\) 1,2-Disubstituted compounds possessing different substituents give mixtures of products however, regardless of the functional groups, in all cases 1,3-disubstituted or 1,2,3-trisustituted arenes will give the 1,3,5-trisubstituted or 1,2,3,5-tetrasubstituted arenes as products, respectively.

In 2014, it was reported that rhodium catalysed C–H silylation of arenes could be carried out with high control of site selectivity (scheme 24).\(^\text{75}\) Key to the
success of these reactions was the use of 2,2’-biphenylphosphine ligand 94. With the arene as the limiting reagent, [Rh(coe)_{2}(OH)]_{2} catalyst and HSiMe(OTMS)$_{2}$ as the silyl source, a wide range of aromatics and heteroaromatics could be functionalised.

It has since been disclosed that a combination of [Ir(cod)(OMe)]$_{2}$ with 2,4,7-trimethylphenanthroline can catalyse a similar silylation procedure but with greater tolerance of functional groups. This has enabled late-stage functionalisation of a number of pharmaceutical compounds.

### 1.3.6 The future outlook for meta

It can be seen that a number of different strategies for meta-C–H functionalisation have already been employed with varying degrees of success with some extremely creative work on show. It seems likely with the continuing interest in this area that the number of methods will grow rapidly. In all likelihood, at some point we will see development of Yu’s large directing groups such that they can be formed catalytically in situ (intermediate 97, figure 9).
The use of transient mediators is obviously a significant development in this area and the number of transformations that it is possible to carry out will grow as will the range of directing groups. More discussion of where the ruthenium community is headed will be deliberated over later in this thesis once the results from our research group have been presented.
1.4 Targeting a weakness: the move to benzylic

Whereas aryl C–H bond activation requires the breaking of one of the strongest C–H bonds that exists, benzylic C–H bonds are considerably weaker ~110 vs 90 kcal mol\(^{-1}\) (figure 10).\(^{77}\) It is therefore perhaps surprising on first inspection that, for oxidative addition type mechanisms at least, transition metal catalysed C–H activation is far more proliferate for aryl C–H bonds. However, it has been shown that arene pre-coordination to the metal can provide an additional driving force to lower the energy of oxidative addition to aryl C–H bonds.\(^{78}\) Furthermore, the metal carbon bond strength is significantly stronger with aryl carbons (vs alkyl) such that this compensates for initially breaking a stronger bond.\(^{79}\)

<table>
<thead>
<tr>
<th>R–H</th>
<th>BDE / kcal mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>\begin{center} \includegraphics[width=0.2\textwidth]{image.png} \end{center}</td>
<td>112.9</td>
</tr>
<tr>
<td>\begin{center} \includegraphics[width=0.2\textwidth]{image.png} \end{center}</td>
<td>110.7</td>
</tr>
<tr>
<td>Me–O–H</td>
<td>104.6</td>
</tr>
<tr>
<td>Me–H</td>
<td>101.1</td>
</tr>
<tr>
<td>Me–Me</td>
<td>98.6</td>
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<tr>
<td>Me–Me</td>
<td>96.5</td>
</tr>
<tr>
<td>\begin{center} \includegraphics[width=0.2\textwidth]{image.png} \end{center}</td>
<td>89.7</td>
</tr>
<tr>
<td>Me–O</td>
<td>89.4</td>
</tr>
<tr>
<td>R–H</td>
<td>88.8</td>
</tr>
</tbody>
</table>

Figure 10: Selected C–H bond-dissociation energies

As a result of this, selective approaches are required especially for substrates which contain both aromatic and benzylic protons. Outlined below are some strategies that have been used to either take advantage of the inherent weakness of benzylic C–H bonds, or to overcome the preferential formation of a carbon metal bond with an aryl rather than benzylic carbon centre.
1.4.1 Palladium catalysed arylation

A number of reports of palladium catalysed benzylic C–H arylation have emerged in the last decade and a half. It is noteworthy that almost all of these examples rely on substrates where the $pK_a$ of the benzylic C–H bond is (significantly) lowered compared to that of toluene itself (see figure 11). In the cases where this is not true, strong bases are required for deprotonation at the benzylic carbon centre.

![Figure 11: Selected $pK_a$s of tolyl C–H bonds in DMSO](image)

The first report in this area came from the group of Mashiro Miura in the late 1990s. Taking a two-fold excess of toluene substrates with a para-nitro group and reacting them at 140 °C with an aryl bromide and caesium carbonate as a base under the action of palladium catalysis gave the diaryl methane products in moderate to excellent yields (scheme 25). The doubly arylated product was rarely observed which the authors attribute to steric factors. It is important to note that this report is restricted to benzylic substrates containing a para-nitro group. This reduces the $pK_a$ of the benzylic proton significantly.

![Scheme 25: Palladium catalysed benzylic arylation of para-nitrotoluenes](image)
Whilst substrate scope was limited by the requirement of an ‘activating group’ in this case, a number of other contributions have been made since then expanding the possibilities of what is achievable regarding palladium catalysed benzylic arylation. Oshima and co-workers reported the arylation of aryl(azaaryl)methanes 102 with aryl chlorides under palladium catalysis (scheme 26).\textsuperscript{82}

\begin{equation}
\begin{array}{c}
\text{Het-Ar} = \text{2-pyrimidyl, 2-pyridyl, 4-pyridyl, 2-quinolyl, 2-benzoxazoyl, 2-benzothiazoyl etc.}
\end{array}
\end{equation}

\textbf{Scheme 26: Palladium catalysed benzylic arylation of aryl(azaaryl)methanes}

Using caesium hydroxide as base, a number of different substrates were arylated. A clear trend is observed with regards to $pK_a$ with those substrates reported as ineffective substrates under the reaction conditions, diphenylmethane, 2-picoline and 3-benzylpyridine, all having a $pK_a$ which suggests that hydroxide would not be able to deprotonate the benzylic proton.

\textbf{Scheme 27: Palladium catalysed benzylic arylation of benzylsulfones}

The same researchers have also disclosed that it is possible to arylate benzylsulfones 105 under very similar conditions (scheme 27).\textsuperscript{83} Optimisation studies showed that in this case, palladium $\pi$-allyl dimer catalyst, tricyclohexylphosphine ligand and potassium tert-butoxide as the base in refluxing toluene gave the best conversion. A tentative mechanistic suggestion is made: deprotonation at the benzylic position by the base gives $\alpha$-tosylbenzylpotassium.
This could transmetallate with aryl-palladium(II) species which, followed by reductive elimination, would give the product and regenerate the palladium(0) catalyst. The authors note that the benzylic proton of the product should be more acidic than that of the starting material. They do not observe formation of $p$-tolyl triphenylethyl sulfone, however, which could plausibly be due to increased steric bulk.

Keith Fagnou and co-workers published an impressive paper on arylation of azazine and diazine N-oxides. It was shown that choice of base enables control of $sp^2$ vs $sp^3$ arylation on these systems under palladium catalysis (scheme 28). With a strong base (sodium tert-butoxide) and XPhos ligand, under microwave conditions, $sp^3$ arylation takes place whereas with potassium carbonate and $P^tBu_3$, $sp^2$ arylation occurs. This switchable methodology has been shown in divergent and sequential reaction sequences.

![Scheme 28: Fagnou’s switchable methodology for palladium catalysed $sp^2$/sp$^3$ arylation of azazines](image)

Song, Xie and Huang’s groups reported the preparation of 9,9-diarylfluorenes via a palladium catalysed benzylic C–H functionalisation (scheme 29). Although a seemingly quite a specialist scope for the substrates, it is asserted that these moieties are particularly important in materials including polymers and composite materials. In previous examples, steric arguments have been invoked for highly substituted benzylic carbons being comparatively unreactive. So, it is notable here that it is possible to form a congested quaternary centre using this chemistry. Yields are largely good although the scope of both reactants is narrow.
Finally, the group of Patrick Walsh at the University of Pennsylvania has made a number of contributions to this area. They have taken a number of different approaches which focus on either lowering the acidity of the benzylic C–H bond or using stronger bases to enable deprotonation on less acidic substrates.

One early approach was that of chromium complexation (scheme 30). Detailed studies have shown that Cr(CO)$_3$ is “hermaphroditic” in that it is capable of stabilising both cation and anions at the benzylic position. It was thought that the ability to temper the generated benzylic cation in this case would allow new reactivity to be accessed.

With the preformed tricarbonylchromium-complexed toluene component 112, the arylated product 113 was formed using [PdCl$_2$(PPh$_3$)$_2$] catalyst, LiN(SiMe$_3$)$_2$ base in THF at 55 – 60°C. It was possible to expose the reaction to air and light before purification, resulting in decomplexation of the tricarbonylchromium, to give the ‘free’ product.

More recently it was found that NiXantphos could play a key role in deprotonative cross-couling reactions to form triarylmethanes (scheme 31). Initial screening happened upon NiXantphos as an important ligand and further optimisation allowed reaction conditions to be changed from refluxing dioxane to room temperature in cyclopentylmethyl ether (CPME).
Scheme 31: NiXantphos as a ligand to allow efficient, room-temperature formation of triarylmethanes

This research was further extended such that aryl chlorides could be used in place of the corresponding bromides. This was notable for being the first report of oxidative addition of aryl chlorides with a palladium complex based on a bidentate triarylpophosphate. It is believed that the reason behind this is the formation of a heterobimetallic Pd(K-NiXantphos) based catalytic system.

Further contributions from this group on palladium catalysed diarylmethane synthesis include the use of benzylic phosphonates and azaarylmethylamines.

1.4.2 Radical (hetero)arylation
As outlined earlier in this section, due to the comparative weakness of benzylic C–H bonds, radical approaches to benzylic C–H functionalisation have good potential to be selective. It is worth noting though that caution should be exercised in taking bond dissociation energy as a measure of radical stability as has been previously reported.

A stylish approach to 4-pyridination of benzylic C–H bonds was recently described by the group of Inoue (scheme 32). Taking inspiration from the well-known Minisci reaction, they use UV light with one equivalent of benzoquinone to cleave benzylic C–H bonds and generate the resulting benzylic C–H radical. Ipsso attack on 4-cyanopyridine followed by expulsion of HCN generates the products in a highly selective manner. It should be noted that although the substrate scope of the benzylic partner is broad, the pyridine component is restricted exclusively to 4-cyanopyridine 116.
Shi and co-workers reported a CDC iron catalysed arylation of benzylic C–H bonds of diarylmethanes.\(^6\) Using iron(II) chloride as the catalyst and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant in 1,2-dichloroethane solvent gave the products 121 in excellent yield (scheme 33). It is noteworthy that the arene substrate scope is generally limited to molecules that have an electron donating group para to the reactive C–H bond and an electron withdrawing group at the meta position. The reactant containing the benzylic C(sp\(^3\))–H component is used in six-fold excess with respect to the arene component and is limited to diaryl methanes.

A large intramolecular kinetic isotope effect (6.0) is observed for diphenylmethane suggesting that the breaking of the benzylic C–H bond is involved in the rate determining step. Isolation of the homocoupled product 123a resulting from diphenylmethane also suggests that this component is oxidised to the corresponding radical 122a. The proposed mechanism by which this reaction proceeds is outlined in figure 12: SET assisted by the iron(II) catalyst generates the benzylic radical 122a which can be further oxidised to the cation 124a. Subsequent Friedel-Crafts reaction gives intermediate 125a which is then rearomatised to give the product and regenerate the free iron(II) species.
Figure 12: Shi’s proposed mechanism for the iron CDC formation of triarylmethanes

Chen and co-workers showed that $N,N$-dimethylcarbamoyl protected indoles 126 could be used instead of the electron rich (methoxy-)arenes under virtually identical conditions (scheme 34).\textsuperscript{97} Electron donating groups on the indole ring were detrimental to reactivity whereas electron withdrawing groups seemed beneficial. This is in contrast to the pattern observed with substitution on the aromatic rings of the diarylmethane component. Here it is suggested that electron withdrawing groups destabilise the proposed benzyl cation intermediate. The mechanistic outline is largely in line with what Shi and co-workers proposed in their original publication.

Scheme 34: Iron chloride catalysed CDC between diarylmethanes and indoles

A similar piece of work appeared a few years hence by Song and co-workers using somewhat similar conditions to those previously reported (FeCl$_2$ catalyst and
DDQ as the oxidant in DCE). A double CDC coupling of 1,3-dicarbonyl compounds 129 and arylmethanes 128 is reported to take place in an analogous way to the work reported by Shi et al. (scheme 35).

![Scheme 35: Iron chloride catalysed CDC formation of diarylmethanes](image)

The idea of using a transition metal catalyst together with a strong oxidant for benzylic radical generation was also exemplified by Duan and co-workers (scheme 36). With catalytic copper(II) acetate (5 mol%) in the presence of tert-butylperoxy benzoate (two equivalents) and using a substituted toluene as the solvent, a CDC reaction with coumarins 131 could occur.

![Scheme 36: Copper acetate catalysed CDC between coumarins and substituted toluenes](image)

Some background reaction is observed without the use of the copper catalyst (15% isolated product) however the oxidant is necessary for any reaction to occur. As a general trend, more electron-deficient substituents on the toluene component 132 deliver the product in lower yield. A number of other heterocyclic compounds were also amenable to the benzylation procedure including 1-methyl-2-quinolinones, 2-phenyl-4-chromone and 2-methyl-1,4-naphthoquinone. In terms of postulated mechanism, radical traps were noted to prevent the reaction from taking place. An intermolecular KIE experiment gave a value of 2.2, however independent reactions with toluene and deuterated toluene established a KIE = 0.71 which indicates that the cleavage of the benzylic C–H bond is not involved in the rate determining step. The
researchers indicate their belief that the reaction proceeds as follows: thermal or copper catalysed decomposition of the peroxide generates the tert-butoxy radical which abstracts a benzylic hydrogen atom thus generating the benzylic radical; subsequent attack of this species onto the coumarin is followed by oxidation by copper(II) species to generate a cation and a copper(I) species; assequest loss of a proton forms the product.

### 1.4.3 Directed arylation

Several cases of directed benzylic arylation have been reported whereby C–H activation is directed to take place at the benzylic position of the substrate. This is another approach that can be used to overcome the inherent preference for aryl C–H bonds.

Two reports have been published using N-pyridyl benzylamines 135 and ruthenium catalysis differing only slightly in the conditions used: in one case aryl boronates are used as the arylating agent\(^\text{100}\) (scheme 37a); in the other case it is aryl bromides (scheme 37b).\(^\text{101}\) Both works suggest that the ruthenacycle formation is a reversible process.

\[ \text{Scheme 37: Directed ruthenium catalysed benzylic arylation} \]
The first publication also demonstrates that the pyridine motif can be removed from the amine via protection with a tert-butyloxycarbonyl group and then methylation of the pyridine moiety using methyl triflate and subsequent hydrolysis.

Zhang and Wen reported a directed CDC between the C2 position of indole and various substituted toluenes in 2015 (scheme 38). With conditions not so far removed from what we report for our synthesis of diarylmethanes (see section 2.8) they take N-pyrimidylindoles 137 with toluene solvent, catalytic copper(II) acetate and di-tert-butylperoxide. They found that yields with no C3 substitution on the indole were consistently below 50% due to homo-coupling of the starting material and so chose to investigate substitution at that position. Much better yields were obtained with bromine at the 3-position of the indole.

Scheme 38: Directed copper catalysed C2 benzylation of indoles

It is important to note that when the pyrimidine is replaced with a phenyl ring on the nitrogen of indole, no reaction is observed suggesting strongly that there must be some sort of directing effect from this group as shown for intermediate 139a (figure 13).
An impressive recent contribution in this area is from Jin Quan Yu’s team at Scripps, using a strategy that is sure to be dramatically expanded to other systems in the near future.\textsuperscript{103}

They initiated their studies with 2-methylbenzaldehyde, 4-iodoanisole and glycine as the amino acid reasoning that benzaldehydes are well known to readily form imine linkages. After extensive research, they found that it was optimum to use Pd(OAc)$_2$ catalyst, silver trifluoroacetate additive and addition of three equivalents of
water in an acetic acid/hexafluoroisopropyl alcohol solvent system (scheme 39). They postulated that water was required to reduce the concentration of imine intermediate 144 which when too high appeared to result in product decomposition. They were able to use this methodology for non-benzylic C(sp³)–H functionalisation as well, following some optimisation, and thus showed that by using L-tert-leucine as the ligand, it was possible to obtain chiral diarylmethanes 145 with excellent enantioselectivity.

1.4.4 Lighting up nickel chemistry

One final strategy that will be discussed, which is outside the realm of C–H functionalisation, is that of co-operative catalysis. It seems pertinent to discuss this area because it involves generation of a C(sp³) radical and subsequent cross-coupling with a transition metal, albeit under very different conditions to those mentioned in section 1.4.2.

This highly novel strategy, first published at the same time by Molander¹⁰⁴ and Macmillan¹⁰⁵, merges photoredox catalysis with transition metal catalysis. In both their cases they take an iridium photocatalyst and nickel transition metal catalyst and take advantage of available oxidation states of nickel being separated by only a single electron. One notable advantage to this chemistry is the ability to run the reactions under mild conditions at room temperature and they enable a number of C(sp²)–C(sp³) couplings that have previously been difficult to effect.

![Scheme 40: Co-operative catalysis: nickel and photoredox catalysts combine for a mild synthesis of diaryl methanes](image)

Here we focus on Molander’s synthesis of diarylmethanes from benzyltetrafluoroborate salts 146 and aryl bromides (scheme 40). Tetrafluoroborate salts have been known to generate carbon radicals 148 upon single-electron oxidation and it was reasoned that it would be possible to capture these radical species
(generated by a photocatalyst) with a Ni(II) species 149 (formed upon oxidative addition to an aryl bromide). Reductive elimination from Ni(III) intermediate 150 would give the product 147 and electron transfer from the reduced photocatalyst to the resulting Ni(I) regenerates both catalytic species (figure 14). Substrate scope for the transformation is broadly good with a number of heterocycles being tolerated together with protic functional groups such as amides, phenols and protected anilines.

Subsequent reports have shown that this nickel chemistry is amenable to a large number of other transformations with several different photocatalysts used depending upon the radical source.\(^{106}\)

Figure 14: Proposed mechanism for co-operative catalysis between nickel and iridium
2. Results and discussion

2.1 meta-Selective bromination

Given the precedent for halogenation on 2-phenylpyridine ligands of organoruthenium compounds, it was decided to investigate the possibility of carrying out a catalytic meta-bromination procedure. It goes without saying that aryl bromides are supremely versatile compounds which can undergo a large variety of different transformations. A vast number of methods for C–H ortho-bromination, and halogenation in general, have already undergone extensive development in the literature. Hence we were aiming to create a catalyst-controlled bromination system, where bromination of the same arene substrate could be directed to the ortho or meta position according to catalyst choice.

2.1.1 Reaction discovery and screening

Of the initial reactions carried out (table 1, entries 1 – 6), the most common electrophilic brominating agent, N-bromosuccinimide and bromine were selected together with tetrabutylammonium tribromide (TBATB) which is essentially a more convenient, easier to handle, solid form of bromine. We embarked upon our initial studies using the two precedented solvents for ruthenium catalysed meta-functionalisation: acetonitrile and 1,4-dioxane. Only traces of meta-brominated phenyl pyridine 77a were observed in all cases except for the reaction with TBATB in 1,4-dioxane (table 1, entry 6) where almost complete conversion to the desired product had occurred. A small screening of solvents showed that 1,4-dioxane was unique in allowing this reaction to happen (table 1, entries 5 – 9).
Intriguingly, pyridinium tribromide (table 1, entry 10) gave no conversion. The failure of pyridinium tribromide is notable as this reagent has been successfully used to stoichiometrically brominate organoruthenium complexes.\textsuperscript{58} Tetramethylammonium tribromide (TMATB) was tested to eliminate the possibility that the tetrabutylammonium cation could be undergoing Hoffman elimination to reprotonate the ruthenacycle in a way analogous to that proposed by Ackermann for tertiary alkyl halides.\textsuperscript{62} It was observed, however, that similar conversion occurred to when using TBATB (table 1, entry 11), which effectively dismisses this idea for the role of the tetrabutylammonium cation because the tetramethylammonium can not undergo Hoffman elimination.

\begin{table}[h]
\centering
\begin{tabular}{cccc}
\hline
entry & brominating agent & solvent & 13a:77a\textsuperscript{a} \\
\hline
1 & NBS & MeCN & >99:1 \\
2 & NBS & 1,4-dioxane & >95:5 \\
3 & Br\textsubscript{2} & MeCN & >99:1 \\
4 & Br\textsubscript{2} & 1,4-dioxane & >99:1 \\
5 & TBATB & MeCN & >99:1 \\
6 & TBATB & 1,4-dioxane & 5:95 \\
7 & TBATB & DMF & >99:1 \\
8 & TBATB & water & >99:1 \\
9 & TBATB & 1,4-dioxane/water (1:1) & >99:1 \\
10 & pyridinium tribromide & 1,4-dioxane & >99:1 \\
11\textsuperscript{b} & TMATB & 1,4-dioxane & 5:95 \\
\hline
\end{tabular}
\caption{meta-Bromination reaction discovery}
\end{table}

\textsuperscript{a} Ratio of starting material to product was determined from analysis of the 'H NMR of the crude reaction mixture. \textsuperscript{b} 4 equivalents of K\textsubscript{2}CO\textsubscript{3} were used. All reactions were carried out under inert atmosphere (see experimental section for further details).
Following the extremely promising initial results, investigations commenced to lower the catalyst loading whilst also investigating a few other species (table 2). It can be seen that lowering the catalyst loading significantly decreases the conversion of the starting material into the product (table 2, entries 1 – 3). The reaction does not proceed at all without a ruthenium catalyst (table 2, entry 4) although the triruthenium dodecacarbonyl catalyst works albeit poorly (table 2, entry 5). Even though there are not any reports using osmium catalysts in directed C–H activation literature, we decided to synthesise the osmium analogue of the ruthenium catalyst. This was on the grounds that organoosmium complexes previously described in the literature had shown increased reactivity compared to the analogous organoruthenium complexes. The osmium dichloride para-cymene dimer was synthesised without issue from the osmium trichloride trihydrate species with nine equivalents of α-terpinene in refluxing isopropanol.\textsuperscript{114} Disappointingly though, there was no reaction using either [OsCl\(_2\)(p-cymene)]\(_2\) or OsCl\(_3\).3H\(_2\)O as the catalytic species (table 2, entries 6 and 7).

Table 2: Catalyst screening

<table>
<thead>
<tr>
<th>entry</th>
<th>[M]</th>
<th>13a:77\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[RuCl(_2)(p-cymene)](_2) (5 mol%)</td>
<td>5:95</td>
</tr>
<tr>
<td>2</td>
<td>[RuCl(_2)(p-cymene)](_2) (2.5 mol%)</td>
<td>40:60</td>
</tr>
<tr>
<td>3</td>
<td>[RuCl(_2)(p-cymene)](_2) (1 mol%)</td>
<td>70:30</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>100:0</td>
</tr>
<tr>
<td>5</td>
<td>Ru(<em>3)(CO)(</em>{12}) (3 mol%)</td>
<td>90:10</td>
</tr>
<tr>
<td>6</td>
<td>[OsCl(_2)(p-cymene)](_2) (5 mol%)</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>7</td>
<td>OsCl(_3).3H(_2)O (15 mol%)</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Ratio of starting material to product was determined from analysis of the \(^1\)H NMR of the crude reaction mixture.
Table 3: Temperature and TBATB loading optimisation

Attempts to lower the equivalents of brominating agent (table 3, entry 3) or the temperature (table 3, entries 1 and 2) saw a significant reduction in conversion and so it was judged that the conditions, as they were in the original set of reactions, were optimal. It was noticed during the course of these experiments that yields were inconsistent unless air was rigorously removed from the reaction vessel. Oxygen is often disruptive of radical reactions which could be indicative that this reaction proceeds via a radical mechanism.

Control experiments revealed that without the potassium carbonate base, the reaction still proceeds but only to half conversion with the same reaction time (table 4, entry 1). Finally, without the carboxylic acid ligand, the reaction still proceeds in good conversion (table 4, entry 2) however it seemed that as a general trend, the conversion was 5 – 10% lower without and so it was decided to carry on using it in the reaction.

Table 3: Temperature and TBATB loading optimisation

<table>
<thead>
<tr>
<th>entry</th>
<th>(x eq.)</th>
<th>T °C</th>
<th>13a:77a*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>rt</td>
<td>100:0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>90</td>
<td>60:40</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>110</td>
<td>30:70</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>110</td>
<td>5:95</td>
</tr>
</tbody>
</table>

* Ratio of starting material to product was determined from analysis of the $^1$H NMR of the crude reaction mixture.
entry | [RuCl$_2$(p-cymene)]$_2$ | K$_2$CO$_3$ | MesCO$_2$H | 13a:77a$^a$
---|---|---|---|---
1 | Y | N | Y | 50:50
2 | Y | Y | N | 10:90
3 | Y | Y | Y | 5:95

$^a$ Ratio of starting material to product was determined from analysis of the $^1$H NMR of the crude reaction mixture.

Table 4: Control reactions

### 2.1.2 Substrate scope

With the optimised conditions in hand, we sought to explore the scope of substrates in the reaction (figure 15). We were pleased to find that both electron-donating (77b, 77c, 77d) and electron withdrawing groups (77e, 77f, 77g) in the para position of the aromatic ring were well tolerated, producing good to excellent yields of the brominated product. In cases where the para-substituent possesses significant steric bulk the reaction still proceeded, but at a slower rate, resulting in a low yield after 20 hours (77d). It should be noted that in low-yielding cases, the majority of the remaining material can be accounted for as starting material. The reaction is remarkably selective for the mono-brominated, rather than the di-brominated, product, despite using an excess of brominating agent. Over-bromination has been problematic in some previously reported examples of metal catalysed ortho-bromination.$^{109,111}$ The selectivity obtained in this meta-bromination relative to other transition metal-catalysed bromination methods is exemplified by the reaction of benzo[h]quinoline to give the 7-bromo compound 77j. It would not have been possible to selectively obtain this product using existing bromination methods, and presents a new C–Br bond at a useful site for further modification. It is worth noting that the 7-chloro analogue has been prepared in 13% overall yield via a nitration/reduction sequence followed by a Sandmeyer reaction.$^{115}$
Pleasingly, we were able to scale-up the reaction to a 5 mmol scale. By running the reaction for 65 hours but with half the catalyst loading (2.5 mol%), the isolated yield of 77a remained at 76% with 4% of the ortho-brominated product also isolated.

Disappointingly, a number of phenyl pyridine substrates either failed to react or reacted in a manner consistent with electrophilic aromatic substitution patterns on the substrates themselves (figure 16). It was observed that with methoxy groups on the phenyl ring (substrates 13n – 13q), the products observed were exclusively at the (unblocked) ortho and para positions relative to this group. This is strongly suggestive that in the case of electron rich substrates, electrophilic substitution occurs at a faster rate than the ruthenium catalysed reaction. Small quantities of the product 77i resulting from electrophilic aromatic substitution reaction was also observed in the substrate with a meta-methyl group. Adding a methyl group in either the ortho position of the aromatic ring or at the 3-position of the pyridine group resulted in isolation of solely starting material. It is postulated that it is important for the cycloruthenated intermediate to lie completely planar in order that the \( \pi \)-system is...
capable of interacting with the ruthenium orbitals to create a delocalised HOMO. In the case of the two substrates described (13k and 13m), steric clashing would make it unlikely that these substrates could form a planar cycloruthenated species which is the reason we ascribe to their lack of reactivity. Similarly, in the case of 2-(1-Naphthyl)pyridine 13r, we invoke the inability to form the planar cycloruthenated species as the reason for lack of reactivity. In the case of those compounds with para electron-withdrawing groups, only with a para-nitrile group were any traces of meta-brominated product 77t observed.

Figure 16: Unsuccessful substrates containing pyridine directing groups

It was hoped that other directing groups could be used to broaden the utility and scope of this novel transformation. Unfortunately, despite a large number of compounds being investigated, the efforts were to no avail (figure 17). Ackermann and co-workers had previously reported ortho-halogenation on benzamides but no product, either ortho or meta substituted, were observed under our reaction conditions. We reasoned that the use of a pyrazine directing group should allow the
planar, delocalised system analogous to that with the pyridine directing group to form. Again, however, none of desired product 152d was observed.

Figure 17: Unsuccessful substrates with different directing groups

Ackermann had reported that imine and pyrazole moieties were competent directing groups for meta-alkylation\(^5^9\) however no reaction was observed with aldimine or ketimine directing groups. The pyrazole directing group was brominated at the 4-position. Pyridine protected phenol 151h yielded only starting material under the reaction conditions. Ackermann recently reported that pyrimidine protected anilines were competent substrates for meta-alkylation with tertiary alkyl halides.\(^6^2\) In our reaction system, bromination was observed only in line with electrophilic aromatic substitution patterns. Azobenzene 151j did not react under the reaction
conditions whereas acetanilide, 1-phenylisoquinoline and 8-aminoquinoline amide all showed reactivity as expected from electrophilic aromatic substitution. Quinoline has been reported as binding to ruthenium and osmium to form a stoichiometric complex however no reaction was observed when using it as a substrate in our catalytic manifold.58

Dr Scott Cockroft (University of Edinburgh) performed some calculations based on finding the HOMO of the ruthenated intermediate together with the ionisation energies of the system (which quantifies the nucleophilicity).116 His results show that the HOMO of the system is delocalised over the phenyl ring, pyridine ring and the ruthenium centre suggesting the necessity for a planar system. With more electron deficient aromatic rings, the ionisation energy at the position para to the metal is higher implying a less nucleophilic system which provides a potential explanation for the lower reactivity.

Following some insightful discussions, we rationalised reasons for lack of reactivity in the ruthenium catalysed reactions as follows:

1) The directing group is too weak (i.e. lower $pK_{aH}$) or does not donate sufficient $\pi$-electron density;
2) The substrate is unable to form a planar intermediate (with delocalised $\pi$-system) upon cycloruthenation;
3) The substrate is too electron rich (and so electrophilic aromatic substitution reaction dominates);
4) The aromatic ring is too electron deficient.

2.1.3 One-pot chemistry

It was decided that in order to demonstrate the versatility of this methodology, we should develop facile one-pot processes to further manipulate the newly-installed bromide group in C–C bond forming reactions.

2.1.3.1 meta-Arylation

Following preliminary studies on carrying out a Suzuki-Miyaura reaction on the meta-brominated phenyl pyridine which were carried out by Andrew Lui, it was found simply by adding palladium acetate, triphenylphosphine, potassium carbonate, water and boronic acid 153a that the meta-arylated compound 154a could be isolated
in moderate yield (table 5, entry 2). The Suzuki reaction did not occur without water however (table 5, entry 1). Attempts to quench the excess brominating agent were futile – although presumably the boronic acid can react to give the corresponding aryl bromide (thus acting as a quenching agent in this way). Some of the biaryl was observed in the crude NMRs although never quantified. By increasing the excess of the boronic acid (table 5, entry 3), the yield was slightly increased although adding all the base in the first step seemed to have a more significant effect which is not so easily explained (table 5, entry 4). Attempts to carry out the meta-arylation by adding all reagents and reactants together before heating were unsuccessful with the complex mixture of products containing just traces of meta-arylated product 154a.

<table>
<thead>
<tr>
<th>entry</th>
<th>(x eq.)</th>
<th>(y eq.)</th>
<th>(z eq.)</th>
<th>H2O</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>no</td>
<td>77a</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>yes</td>
<td>154a (44%)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>yes</td>
<td>154a (46%)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>yes</td>
<td>154a (69%)*</td>
</tr>
</tbody>
</table>

*Reaction carried out by Andrew Lui

Table 5: One-pot bromination/Suzuki-Miyaura reaction optimisation

Extensive optimisation was forgone on the basis that we were looking primarily to demonstrate the proof of concept that sequential transition metal catalysed reactions could be carried out in the same pot. The final conditions for meta-arylation (via one-pot bromination/Suzuki-Miyaura coupling) were using additional base in the first step and after running the bromination for 20 hours, water, Pd(OAc)2 (3 mol%), PPh3 (6 mol%), K2CO3 (y eq.), H2O, 110 °C, 15 h and a boronic acid or ester (3 eq.) were added and the reaction run for a further 15 hours. This one-pot meta-arylation procedure worked well for ortho-, meta- and para- substituted boronic acids and both electron withdrawing and electron-donating substituents were tolerated (154a – 154e) (figure
The reaction could be extended to heteroaromatic boronic esters, with the use of N-Boc-pyrrole-2-boronic acid MIDA ester proving effective for the synthesis of 154f in 64% yield. The cyclopentyl boronic acid did not give the desired meta-alkylated product 154g (although it should be noted that this can be prepared directly from the cyclopentenylbromide using ruthenium catalysis) and, similarly, 1-cyclopenten-1-ylboronic acid gave only traces of product 154h.

Inspiration was taken from Jeffery’s conditions for the Heck reaction which use a phase transfer catalyst (tetrabutylammonium salt), palladium diacetate catalyst and inorganic base under ‘ligandless conditions’. By simply adding Pd(OAc)$_2$ (3 mol%) and three equivalents of a suitable alkene, post-bromination, heating the reaction to 110 ºC allowed a one-pot bromination-Heck reaction to take place. Gratifyingly, this simple procedure worked well with the base (K$_2$CO$_3$) and phase transfer catalyst (TBATB) already present from the previous step (figure 19).

2.1.3.2 meta-Alkenylation

Figure 18: Substrate scope for the one-pot bromination/Suzuki-Miyaura methodology
Yields of alkenylated product over the two steps were good (155a and 155c), with the use of but-3-en-2-ol giving the alkylated ketone product 155b in 55% yield. In the case of ethyl acrylate, some product was observed resulting from both the Heck reaction but also a directed ortho-alkenylation much like that reported by Murai in his seminal work. Vinyl sulfone gave some product 155d but in a disappointingly low yield whilst the reaction seemed very sensitive to steric with methyl methacrylate not giving any of the desired meta-alkenylation product 155e.

2.1.4 Samarium reduction

To address one criticism that could be levelled at this chemistry as a whole – that of the restriction of the directing group - we wanted to demonstrate the ability to manipulate this to a more useful substrate. We successfully converted the pyridine directing group into the corresponding saturated heterocycle, piperidine.
reduction is a versatile entry point into functionalised piperidines which are heavily-exploited scaffolds in medicinal chemistry. Here, treatment of meta-brominated phenylpyridine with SmI\textsubscript{2}/H\textsubscript{2}O rapidly reduced the heteroarene, leaving the aryl bromide group intact for further manipulation (scheme 41).

### 2.2 Electrophile screening for meta-functionalisation

Following completion of the bromination project, and given at the time we had postulated that the reaction was going via attack of a nucleophilic organoruthenium intermediate onto an electrophilic species, investigations using other electrophiles under similar reaction conditions were commenced.

#### Table 6: Screening of electrophilic trifluoromethylating agents under ruthenium catalysed conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent</th>
<th>additive</th>
<th>solvent</th>
<th>base</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>157</td>
<td>-</td>
<td>1,4-dioxane</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>157</td>
<td>CuCl</td>
<td>1,4-dioxane</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>-</td>
</tr>
<tr>
<td>3*</td>
<td>157</td>
<td>-</td>
<td>DMF</td>
<td>Et\textsubscript{3}N</td>
<td>-</td>
</tr>
<tr>
<td>4*</td>
<td>157</td>
<td>-</td>
<td>DMF</td>
<td>NMM</td>
<td>-</td>
</tr>
<tr>
<td>5*</td>
<td>157</td>
<td>-</td>
<td>DMF</td>
<td>TMEDA</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>158a</td>
<td>-</td>
<td>1,4-dioxane</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>158a</td>
<td>CuCl</td>
<td>1,4-dioxane</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>-</td>
</tr>
<tr>
<td>8*</td>
<td>158a</td>
<td>-</td>
<td>DMF</td>
<td>Et\textsubscript{3}N</td>
<td>-</td>
</tr>
<tr>
<td>9*</td>
<td>158a</td>
<td>-</td>
<td>DMF</td>
<td>NMM</td>
<td>-</td>
</tr>
<tr>
<td>10*</td>
<td>158a</td>
<td>-</td>
<td>DMF</td>
<td>TMEDA</td>
<td>-</td>
</tr>
</tbody>
</table>

*no ligand used

The first focus was directed towards effecting a meta-trifluoromethylation given the interest in this functional group, not just by our research group, but also by the
pharmaceutical and agrochemical industries. Attempts with either Togni’s reagent or Umemoto’s reagent under the previously described conditions did not yield any product with or without copper additive (table 6, entries 1 – 2 and 6 – 7). The only product observed in the crude of these reactions was a coupled product resulting from the coupling of the iodobenzoic acid (resulting from the Togni reagent) with dioxane to form a new C–O bond.

Further to this, an interesting paper had been published which showed that amine bases were capable of reversibly forming an electron-donor-acceptor (EDA) complex 158ba with Umemoto’s reagent (scheme 42). Electron transfer then reduces Umemoto’s reagent which irreversibly generates the trifluoromethyl radical that can react with an electron rich (hetero-)aromatic. Attempts to amalgamate these conditions with our ruthenium chemistry however were unsuccessful with, again, only starting material returned after the reaction had been run (table 6, entries 3 – 5 and 8 – 9).

Attention next turned to a number of other electrophiles – diphenylsulphide and bis(pinacolato)diboron were similarly unreactive (table 7, entries 1 – 2). Selectfluor gave the dimerised phenylpyridine 161a (table 7, entry 3) and neither TBSCI nor TBDPSCI gave product although (table 7, entries 4 – 5), interestingly, these two were the only reactions where the ruthenacycle could clearly be identified in the 1H NMR of the crude reaction.
Our group has shown the Zhdankin reagent$^{123}$ **162** to be a useful source of azide radicals$^{124}$ and it has been demonstrated that this reagent is capable of performing C–H azidation on electron rich aromatics such as anilines under copper catalysis conditions.$^{125}$ Lamentably, the few attempts to use this reagent resulted in no product observed (table 8).

**Table 7**: Screening of electrophiles under ruthenium catalysis

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhS− SPh</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>B$_2$Pin$_2$</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Selectfluor</td>
<td><strong>161a</strong></td>
</tr>
<tr>
<td>4</td>
<td>TBSCl</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>TBDPSCl</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>entry</th>
<th>[Ru(p-cymene)Cl$_2$]$_2$</th>
<th>Cu(OAc)$_2$</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>N</td>
<td>Y</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 8**: The Zhdankin reagent with ruthenium
2.2.1 Triflyl chloride

With thoughts on Frost’s meta-aryl sulfonylation, it was noted that triflyl chloride 164 had been used in the literature as a trifluoromethylating agent under ruthenium(II) catalytic conditions. Furthermore this had been moulded into a fairly significant photoredox catalysed procedure. It was hoped that application of this reagent to our system would enact a meta-trifluoromethylation. Brief screening of conditions was abandoned after the third reaction gave only the ortho-chlorinated product 165a in around 50% conversion (table 9). Interestingly, no conversion was observed in acetonitrile or 1,4-dioxane and it was only in benzene that the reaction occurred. It should be noted that triflyl chloride is however known to be able to act as a mild chlorinating agent.

![Chemical structure](image)

Table 9: Reaction of triflyl chloride under the action of ruthenium catalysis

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>additive</th>
<th>13a:159a:165a&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>100:0:0</td>
</tr>
<tr>
<td>2</td>
<td>acetonitrile</td>
<td>-</td>
<td>100:0:0</td>
</tr>
<tr>
<td>3</td>
<td>benzene</td>
<td>-</td>
<td>50:0:50</td>
</tr>
<tr>
<td>4</td>
<td>benzene</td>
<td>AIBN</td>
<td>50:0:50</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratio determined by analysis of 1H NMR of crude reaction mixture
2.3 *meta*-Formylation

Following the publications from Frost and then Ackermann which suggested that ruthenium played an important role not only in *ortho*-C–H activation but also in radical generation of the coupling partner,\(^{61,62}\) our interest turned to reactants that were known to generate radical species under ruthenium(II) catalysed conditions. This also provided some explanation for the failure to obtain any positive results when screening electrophiles (section 2.2).

Attention turned to polychlorinated alkanes such as carbon tetrachloride and chloroform initially. Both of these substrates are known to generate carbon centred radicals and can be used to catalyse atom transfer radical additions (ATRA) to olefins.\(^{63,129}\) The first reactions carried out with chloroform gave a very positive result with the *meta*-formylated phenyl pyridine 167a appearing in the crude reaction mixture (table 10, entries 1 – 2). Presumably this resulted from `CCl\(_2\)H radical addition to give structure 168a and subsequent hydrolysis. Concomitantly, AIBN was used as an additive in a parallel reaction as it has been shown to reduce inactive Ru(III) species and aid catalyst turnover with chloroform in ATRA.\(^{129}\) However, no difference in conversion was noted in this case.

![Reaction diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>CHCl(_3) (x eq.)</th>
<th>base</th>
<th>additive</th>
<th>yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>K(_2)CO(_3)</td>
<td>-</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>K(_2)CO(_3)</td>
<td>AIBN (0.1 eq)</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>KOAc</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>K(_2)CO(_3)</td>
<td>H(_2)O (20 eq.)</td>
<td>nd</td>
</tr>
<tr>
<td>5(^b)</td>
<td>5</td>
<td>K(_2)CO(_3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>K(_2)CO(_3)</td>
<td>-</td>
<td>20%</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield unless otherwise indicated. \(^b\) no ligand used

**Table 10:** Reaction discovery with chloroform under the action of ruthenium catalysis
Upon switching to potassium acetate as base no product was observed - only starting material (table 10, entry 3). Adding water gave some product although this was not quantified because the conversion seemed lower from the $^1$H NMR (table 10, entry 4). Without addition of the carboxylate ligand, again, no product was observed (table 10, entry 5). When the first reaction was repeated but with five equivalents of chloroform, the product 167a was isolated from the reaction mixture in 20% yield (table 10, entry 6).

Given this extremely promising result, we embarked upon an optimisation journey in the hope of making this a high yielding and efficient reaction.† Given the overall transformation, we were very excited at the possibilities here. It was in 1876 that Karl Reimer and Ferdinand Tiemann observed that formylation of phenols was possible using chloroform under basic conditions. This reaction has since been developed for other electron rich (hetero)-aromatics though typically follows electrophilic aromatic substitution patterns for regioselectivity. It is clear that a meta-selective variant could be a huge asset to synthetic chemists.

\[
\text{13a} + \text{CHCl}_3 \xrightarrow{(x \text{ eq.})} \left[\text{RuCl}_2(p\text{-cymene})_2\right]_2 (5 \text{ mol%}) \quad \text{MesCO}_2\text{H} \quad 1,4\text{-dioxane} \quad \text{K}_2\text{CO}_3 (2 \text{ eq.}) \quad \text{solvent, 110 °C} \quad 20 \text{ h} \quad 167\text{a} \quad \text{CHO}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>CHCl$_3$ (x eq.)</th>
<th>ligand</th>
<th>solvent</th>
<th>yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>MesCO$_2$H</td>
<td>1,4-dioxane</td>
<td>21%</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>MesCO$_2$H</td>
<td>1,4-dioxane</td>
<td>b</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>MesCO$_2$H</td>
<td>toluene</td>
<td>traces</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>MesCO$_2$H</td>
<td>acetonitrile</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>MesCO$_2$H</td>
<td>DMA</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>Ad-CO$_2$H</td>
<td>1,4-dioxane</td>
<td>6%</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>Boc-Val-OH</td>
<td>1,4-dioxane</td>
<td>28%</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>Piv-Val-OH</td>
<td>1,4-dioxane</td>
<td>21%</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield unless otherwise indicated. $^b$ Complex mixture. $^c$ $^1$H NMR yield

Table 11: Ligand and solvent screen for the meta-formylation reaction

† This project was carried out with Danielle Bunting (D.L.B.).
To pursue this goal, optimisation studies were continued by increasing the equivalents of the reactant, since chloroform is readily available and inexpensive. Little increase in yield was seen (table 11, entry 1) but when increasing the equivalents further, an intractable mixture was obtained (table 11, entry 2). Changing the solvent to toluene showed some traces of compound, whereas none was seen with either acetonitrile or DMA. Upon trying other ligands, adamantane carboxylic acid gave a considerably lower yield but amino acid derived ligands Boc-Val-OH and Piv-Val-OH gave a yield similar to MesCO₂H (table 11, entries 6 – 8).

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>21$^b$%</td>
</tr>
<tr>
<td>2</td>
<td>AgSbF₆</td>
<td>21%</td>
</tr>
<tr>
<td>3</td>
<td>AgTFA</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>Ag₃PO₄</td>
<td>20%</td>
</tr>
<tr>
<td>5</td>
<td>AgOAc</td>
<td>14%</td>
</tr>
<tr>
<td>6$^c$</td>
<td>-</td>
<td>9%</td>
</tr>
</tbody>
</table>

$^a$ $^1$H NMR yield unless otherwise indicated. $^b$ Isolated yield. $^c$ Slow addition of phenylpyridine in dioxane over 4 h.

Table 12: Silver additives for meta-formylation

It was postulated that addition of silver salts may help to sequester chloride ions and thus improve catalyst turnover. However it can be seen that these largely had no impact on the reaction itself with only silver acetate appearing to slightly decrease the yield of the reaction (table 12, entries 1 – 5). Slow addition of the phenylpyridine substrate also resulted in less product being obtained (table 12, entry 6). Screening of bases showed that only K₃PO₄ gave comparable yields to potassium carbonate. Organic bases gave at most traces of products whilst although caesium and sodium carbonate gave some product, lithium carbonate did not.
Unfortunately, despite varying a large number of parameters including solvent, base, ligand and catalyst, no improvement was made on the best isolated yield of 28%. It is hoped that when further understanding of the mechanism of the reaction is elucidated (see figure 20 for our current proposal), it would be possible to return to this exciting reaction and educe a synthetically useful transformation.

2.4 Dual catalysis

It has already been mentioned that photoredox catalysis has been combined with nickel catalysis with this rapidly becoming a well-developed area (section 1.4.3). Previous to this, a number of other reports of cooperative catalysis have been reported.\textsuperscript{131,132,133}

2.4.1 Photocatalyst ligand modification

We were struck with one particular report from a paper by Corey Stephenson and co-workers on a photocatalyst deactivation pathway.\textsuperscript{134} Although at first this may seem

Figure 20: A plausible mechanism for meta-formylation
distinct from meta C–H functionalisation, it is possible to draw a number of similarities when looking at Ackermann’s proposed mechanism for ruthenium catalysed meta-tert-alkylation (figure 7). In that case, Ru(II) generates the carbon centred radical and becomes a Ru(III) species. This radical species then attacks a phenylpyridine bound to a ruthenium centre at the position para to the metal, before single electron transfer from a Ru(III) species and proton abstraction rearomatises the aryl ring. In the case of Ackermann’s chemistry, the binding of the phenylpyridine to the ruthenium catalyst is reversible via a C–H activation pathway.

![Figure 21: A plausible mechanism for functionalisation of Ir(ppy)$_3$](image)

Ir(ppy)$_3$ 177 is known to generate a carbon centred radical 176 from ethyl bromoacetate 175a$^{1,2}$ When excited under visible light radiation, the excited state of the catalyst can undergo single electron transfer to ethyl bromoacetate concomitantly forming Ir(IV) species. Presumably, this radical then attacks a phenyl pyridine ligand on the iridium catalyst, notably at the position para to the iridium metal (and meta to the pyridine group). This suggests that iridium can have the same directing effect as ruthenium. Single electron transfer from an Ir(IV) species to the phenyl pyridine
ligand (either inter- or intra-molecularly) then produces a cation which, through loss of a proton, rearomatises to form organoiridium complex 180 (figure 21).

Given this observation, we postulated that it may be possible to combine a photoredox catalyst for radical generation and a ruthenium catalyst for C–H activation to allow us to perform a number of different meta-C–H functionalisations (figure 22).

![Figure 22: A proposed mechanism for dual catalytic meta-functionalisation](image)

### 2.4.2 Screening for proposed dual-catalysis

A number of different photoredox/reagent systems were tried, some of which had already been reported by our group as being suitable for functionalisation of alkenes, thus we knew were capable of generating carbon centred radicals.\(^{135,136}\) It was hoped that by paring this with \([\text{Ru} (p\text{-cymene})\text{Cl}_2]\) catalyst and a base, we could combine the radical generation process with an ortho-C–H activation event which would
produce the required organoruthenium complex for overall meta-C–H functionalisation.‡

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R–X</th>
<th>photoredox cat.</th>
<th>base</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph$_2$I OTf$^-$</td>
<td>Ir(ppy)$_3$</td>
<td>K$_2$CO$_3$</td>
<td>$^a$</td>
</tr>
<tr>
<td>2</td>
<td>Ph$_2$I OTf$^-$</td>
<td>Ru(bpy)$_3$PF$_6$</td>
<td>K$_2$CO$_3$</td>
<td>$^a$</td>
</tr>
<tr>
<td>3</td>
<td>Umemoto’s reagent</td>
<td>Ir(ppy)$_3$</td>
<td>K$_2$CO$_3$</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Umemoto’s reagent</td>
<td>Ru(bpy)$_3$PF$_6$</td>
<td>K$_2$CO$_3$</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Umemoto’s reagent</td>
<td>Ir(ppy)$_3$</td>
<td>KOAc</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Umemoto’s reagent</td>
<td>Ru(bpy)$_3$PF$_6$</td>
<td>KOAc</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>bromoacetonitrile</td>
<td>Ir(ppy)$_3$</td>
<td>KOAc</td>
<td>-</td>
</tr>
<tr>
<td>8$^b$</td>
<td>bromoacetonitrile</td>
<td>Ir(ppy)$_3$</td>
<td>KOAc</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ ortho-Isomer of phenylpyridine was observed. $^b$ Without ruthenium catalyst.

Table 13: Screening of dual-catalytic conditions

Disappointingly, no meta-functionalised products were produced with the ortho-phenylated product being observed in the cases of using diphenyl iodonium triflate (table 13, entries 1 and 2). It has however been reported that this is observed under similar conditions but without the photoredox catalyst or light. Because we were unsure about the compatibility of heating the photoredox catalyst (despite previous reports) and being aware that the C–H activation mode of our ruthenium catalyst is not reversible at room temperature, we decided to investigate iridium as a C–H activation catalyst which has been reported to undergo C–H functionalisation reactions at room temperature. It was decided to switch to using Ir(dF-ppy)$_3$, given

$^4$ Danielle Bunting carried out a number of reactions on ruthenacycle 240 (see section 4.1) using several iridium photocatalysts and ethyl bromoacetate without any functionalisation on the phenylpyridine ligand being observed.
that this whole concept stemmed from the observation that Ir(ppy)$_3$ was known to react under photoredox conditions to give a catalyst that was less efficient: it seemed pertinent to rule this out by using a catalyst that had the reactive positions on the ligand blocked. Ir(dF-ppy)$_3$ is known to have similar reduction potentials to Ir(ppy)$_3$ and so was chosen as the most similar catalyst which was available to us. Unfortunately, none of product 182a was observed under these conditions with only 2-phenylpyridine 13a visible in the $^1$H NMR of the crude reaction mixture (scheme 43).

Scheme 43: Attempted meta-alkylation using iridium catalysts under visible light

Following these two attempts, we sought absolute confirmation that the intermediate metallacycles could undergo ligand functionalisation. By taking two equivalents of 2-phenylpyridine with either iridium or rhodium pentamethylcyclopentadiene dichloride dimers with sodium acetate at room temperature, it is possible to form the complexes 185. Taking these conditions with ethyl bromoacetate and catalytic Ir(dF-ppy)$_3$ added and irradiating with light overnight did not give complexes 184 returning only 185 instead (scheme 44).

Scheme 44: Attempted functionalisation of irida- and rhoda-cycles.
2.5 Mechanistic proposals

It is our belief that ruthenium catalysed meta-C–H functionalisation reactions proceed via a radical mechanism. When performing the reaction under the standard conditions, but with addition of three equivalents of TEMPO, no product was observed, with only starting material present in the NMR of the crude reaction mixture (Scheme 45).

Scheme 45: Radical trapping experiment

Indeed, upon turning our attention to substrates which were known to generate radical species under thermal Ru(II) catalysed conditions, we discovered several low yielding reactions giving meta-functionalised phenylpyridine species that have yet to be optimised.

Scheme 46: New meta-functionalisation reaction using carbon tetrachloride

Further to the formylation reaction detailed earlier, carbon tetrachloride and ethyl trichloroacetate \( \text{187} \) also reacted under the action of ruthenium catalysis to give meta-C–C bond formation (schemes 46 and 47). The products \( \text{186a} \) and \( \text{188a} \) isolated in both of these cases are a result of the addition of two molecules of the polychlorinated reactant, with formal elimination of chlorine, giving the products. It seems unlikely that these products would form via a non-radical mechanism.
We started to speculate, however, upon studying the mechanism proposed by Ackermann (figure 7), whether it was possible that in fact the electron transfer between the ruthenium centre and the phenylpyridine would be more likely to occur in an intramolecular sense, such that there was only one active catalytic species in the reaction. In their paper, Ackermann and co-workers perform some kinetic experiments and use the data to suggest that a second order dependence on ruthenium catalyst exists. Closer inspection of the data, however, casts some doubt over whether this is a valid conclusion to draw.

Furthermore, it is known that cyclometallation with 2-phenylpyridine occurs rapidly at room temperature, such that any active ruthenium species that are playing the role of radical generation are likely to be cyclometallated organoruthenium species. Therefore it seems plausible to suggest that single electron transfer could occur more quickly in an intramolecular sense analogous to what is known for example for complexes utilised as photoredox catalysts. What is not known though is the relative reactivity of a phenylpyridine ligand bound to a Ru(III) rather than a Ru(II) centre.

As a final comment and as previously stated, it is known that irradiating iridium photoredox catalysts with bromoethylacetate generates a carbon centred radical. Given the lack of reactivity with 2-phenylpyridine under ruthenium catalysed conditions (and also in stoichiometric experiments on the ruthenacycle itself performed by Danielle Bunting), it seems that there are two likely problems with combining this photoredox approach with C–H activation catalysis. Firstly, the carbon centre radical generated is not reactive enough. Given the range of radicals known in these processes span from tertiary alkyl radicals (nucleophilic) to bromine...
radicals (electrophilic), this would seem less likely.\textsuperscript{141} Secondly, the electron transfer steps are inefficient meaning that the iridium catalytic cycle is not completed. This could also be suggestive of an intramolecular electron transfer step. The combination of these factors has led to our suggestion for a plausible reaction mechanism (figure 23).

![Figure 23: A plausible mechanism](image_url)

If it is the case that the electron transfer step between catalysts is inefficient, there is exciting potential for future work in this area. Bimetallic linked complexes such as 195 have previously been reported in the literature\textsuperscript{142} (figure 24) and, to this end, one could imagine a photoredox catalyst linked \textit{via} a \pi-system to a C–H activation catalyst to enable a far more efficient electron transfer.
2.6 Origin of selectivity

An interesting question that must be posed regarding catalytic directed ruthenium chemistry is what exactly dictates the regioselectivity? This is a fundamentally important question that does not appear to have an obvious answer. Outlined in figure 25 is a proposed divergence from the same ruthenium(II) cyclometallated intermediate 196:

(i) Path A describes what is seen, for example, when R–X is an aryl halide. Oxidative addition gives ruthenium(IV) intermediate 197 from which reductive elimination is possible, forming a new C–R bond in the ortho position and regenerating the ruthenium(II) catalyst.

(ii) Path B is a plausible pathway from which it is possible to obtain the meta functionalised phenyl pyridine. Generation of a ruthenium(III) species 198 together with a radical could result in attack on the ligand. Several further steps (single electron transfer, base induced rearomatisation and protoderuthenation) would regenerate the ruthenium(II) catalyst and this time the meta-functionalised phenylpyridine 182.

This suggestion gives rise to another question of what might favour the respective pathways. For the example of primary alkyl halides (which give the ortho product) vs secondary and tertiary alkyl halides (which give the meta product), it could be reasoned that steric effects might drive the radical pathway. Of course, it could be
possible that a reactant could undergo oxidative addition to give 197 before transforming to the Ru(III)/radical pair 198 via homolytic cleavage of the R–Ru bond.

---

**Figure 25:** Postulated scheme to rationalise the divergence in reactivity for ruthenium catalysed reactions

Factors affecting which pathway is favoured could include: stability of the radical (R'); how reactive the radical is; how stable the respective ruthenacycles are; and how facile reductive elimination is. This divergence, of course, also opens opportunities: perhaps catalyst design could prevent reductive elimination (by addition of bulky ligands) and so favour the alternative pathway instead.

Further to the calculations that were carried out by Dr Scott Cockroft (section 2.1.2), it has also been reported by Coudret *et al.* that for the complex [Ru(bpy)2ppy]PF₆ 200, the HOMO was largely located on the phenyl group with a noticeably large coefficient on the carbon *para* to the one bound to the ruthenium centre.¹⁰⁷ They comment that the energy level of the HOMO is very close to that of the t₂g set of low spin Ru(II) which, if they were to react, would presumably result in oxidation of the metal centre rather than the ligand. This is not seen in their work, however, where they show that it was possible to carry out bromination and iodination under relatively mild conditions to give 201 (scheme 48). It is worth noting that NIS did not react at room temperature and caused degradation of starting material at reflux in MeCN.
Scheme 48: Selective bromination and iodination of [Ru(bpy)₂ppy]PF₆

2.7 *ortho*-Selective ruthenium chemistry

2.7.1 Background

During the course of our investigations in the group, we were interested in seeing if it was possible to carry out a procedure that was analogous to our bromination reaction but with an iodinating agent to obtain the *meta*-iodinated product. A number of different reagents were screened (table 14).

Table 14: Iodinating agents under ruthenium catalysed conditions
Simply switching from the tetrabutylammonium tribromide to the equivalent triiodide species did not give the meta-iodinated product \textit{202a}, but instead yielded the ortho-dimer product \textit{161a} (table 14, entry 1), which was also observed in this case of other oxidants such as Selectfluor and iodine (table 7, entry 3 and table 14, entry 2). \textit{N}-iodosaccarin and also gave some of \textit{161a} (table 14, entry 3). Taking \textit{N}-iodosuccinimide as the halogenating agent under the reaction conditions resulted in no reaction (table 14, entry 4). Barluenga’s reagent\textsuperscript{143} \textit{205} interestingly did give some iodinated product but in small quantities and at the ortho position of the phenyl ring (table 14, entry 5).

Next, our attention turned to mixed halogens: iodine monochloride and iodine monobromide. Both compounds are readily available and very cheap reagents, however, they prove less than straightforward to handle in the laboratory. Initial reactions showed that, like iodine, iodine monobromide gave dimeric product \textit{161a} only (table 14, entry 6). An interesting result was obtained however with iodine monochloride with 30\% of the ortho-chlorinated species \textit{165a} isolated (table 14, entry 7). This was somewhat unexpected, although some precedent was found to show that ICl can act as a chlorinating agent, despite traditionally being considered an iodinating agent.\textsuperscript{144}

Intrigued by this result, and with a dearth of ruthenium catalysed C–H halogenation work reported in the literature, we decided that this warranted some further investigation. As a consequence of iodine monochloride being difficult to accurately weigh on a small scale and safely handle, we made a complex that had been reported with 1,4-dioxane.\textsuperscript{145}

![Figure 26: Iodine monochloride complex with 1,4-dioxane](image)

Unlike other dioxane-halogen complexes which form 1:1 complexes, iodine monochloride typically forms a 1:2 complex \textit{206}, although this has been reported to be dependent on the method of synthesis.\textsuperscript{146} We took a known mass of ICl in dichloromethane and slowly added this to an equimolar quantity of 1,4-dioxane. An
orange solid precipitates (figure 26) and removal of volatiles gives a solid which can be weighed under air and kept in the freezer for months. One benefit to its use is that it generates no organic waste unlike with some other common halogenating agents. The relative stoichiometry of ICl:dioxane was confirmed to be 2:1 by elemental analysis.

2.7.2 Reaction discovery and optimisation

Upon commencing the investigation of this reaction, we found an extremely interesting result when screening catalysts. [Ru(p-cymene)Cl₂]₂ and Ru(PPh₃)₃Cl₂ both gave the ortho-chlorinated products 165a and 166a however upon switching to Ru₃(CO)₁₂, we observed solely the ortho-iodinated product 203a (table 15). Thus using a different ruthenium catalyst allowed us to completely reverse the chemoselectivity of the halogenating agent: something that, to the best of our knowledge, has yet to be reported.

\[
\text{[Ru(p-cymene)Cl₂]₂} \quad \text{MesCO₂H} \quad \text{N₂} \quad 50\% \quad 37:7:6:0
\]

\[
\text{Ru(PPh₃)₃Cl₂} \quad - \quad \text{N₂} \quad 62\% \quad 33:29:0:0
\]

\[
\text{Ru(PPh₃)₃Cl₂} \quad P(O)Ph₃ \quad \text{N₂} \quad 60\% \quad 32:28:0:0
\]

\[
\text{Ru(PPh₃)₃Cl₂} \quad PPh₃ \quad \text{N₂} \quad 68\% \quad 52:12:4:0
\]

\[
\text{Ru(PPh₃)₃Cl₂} \quad PPh₃ \quad \text{air} \quad 84\% \quad 42:42:0:0
\]

\[
[\text{Ru(p-cymene)Cl₂} ]₂ \quad - \quad \text{air} \quad 48\% \quad 41:5:2:0
\]

\[
[\text{Ru(p-cymene)Cl₂} ]₂ \quad PPh₃ \quad \text{air} \quad 73\% \quad 54:15:3:1
\]

\[
\text{Ru₃(CO)₁₂} \quad - \quad \text{N₂} \quad 76\% \quad 0:0:75:1
\]

* Ratios determined from ¹H NMR following column chromatography. b 3 mol% of catalyst was used. c One equivalent of 206 was used

Table 15: Iodine monochloride under ruthenium catalysed conditions
Initial experiments showed reasonable combined yield of ortho-chlorinated and ortho-dichlorinated compounds with Ru(PPh₃)₃Cl₂ with mesityl carboxylic acid ligand however upon removal of the ligand, the yield increased but with the selectivity for the mono-chlorinated product significantly diminished (table 15, entries 1 and 2). Triphenylphosphine oxide ligand appeared to have no effect compared to no ligand being present (table 15, entry 3). Addition of triphenylphosphine ligand, although only increasing the yield slightly, appeared to show higher selectivity for the mono-chlorinated product 165a (table 15, entry 4). Upon exposing the reaction to air rather than running it under inert (nitrogen) atmosphere the combined yield of chlorinated products increased significantly (table 15, entry 5). [Ru(p-cymene)Cl₂]₂ gave similar results to that of Ru(PPh₃)₃Cl₂ but with slightly lower yields (table 15, entries 6 – 7).

With these initial results in hand we decided to embark upon an optimisation for the chlorination reaction such that we could selectively obtain the mono-chlorinated product in good yield. The equivalents of complex used were investigated with little impact in yield decreasing from two equivalents of complex (four equivalents of ICl) to one equivalent of 206 (table 16).

<table>
<thead>
<tr>
<th>entry</th>
<th>complex (x eq.)</th>
<th>yield</th>
<th>165a:166a:203a:204a&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>87%</td>
<td>60:23:2:2</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>88%</td>
<td>54:34:0:0</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>74%</td>
<td>62:12:0:0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratios determined from <sup>1</sup>H NMR following column chromatography.

Table 16: Probing the effect of ICl stoichiometry on the chlorination reaction
Halving the catalyst loading from 5 to 2.5 mol% did not affect the outcome of the reaction however the conversion dropped significantly upon further reduction of the loading. Without any ruthenium catalyst present, no reaction was observed with only starting material present after twenty hours (table 17).

The phosphine loading appeared to make a significant difference to the reaction with 30 mol%, as originally tried, being optimal (table 18). Higher equivalents were trialed with the thought that the interaction between the phosphine and iodine monochloride could be significant for obtaining the chlorinated product however this was not the case (table 18, entries 3 – 4).
Finally, the temperature of the reaction was gradually lowered to see what effect this might have on the reaction (table 19). A regular drop in yield was observed with every 20 °C drop in temperature though it is still notable that the reaction proceeded in close to 50% yield at only 50 °C. This is in stark contrast to the meta-bromination procedure which is extremely inefficient at temperatures lower than reflux.

<table>
<thead>
<tr>
<th>entry</th>
<th>PPh₃ (y mol%)</th>
<th>yield</th>
<th>165a:166a:203a:204a&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>65%</td>
<td>56:9:0:0</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>74%</td>
<td>62:12:0:0</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>48%</td>
<td>40:8:0:0</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>28%</td>
<td>26:2:0:0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratios determined from <sup>1</sup>H NMR following column chromatography.

<sup>b</sup> Yield determined via <sup>1</sup>H NMR using an internal standard

Table 18: The effect of triphenylphosphine loading on the chlorination reaction
Ratios determined from \textsuperscript{1}H NMR following column chromatography

Table 19: How temperature affects the yield of chlorination

<table>
<thead>
<tr>
<th>entry</th>
<th>T °C</th>
<th>yield</th>
<th>165a:166a:203a:204a$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>110</td>
<td>74%</td>
<td>62:12:0:0</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>67%</td>
<td>59:8:0:0</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>54%</td>
<td>49:5:0:0</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>46%</td>
<td>42:4:0:0</td>
</tr>
</tbody>
</table>

$^a$ Ratios determined from \textsuperscript{1}H NMR following column chromatography

Our attention next turned to the iodination procedure with triruthenium dodecacarbonyl as a catalyst (table 20). Our first hit with this reaction was with 3 mol\% of catalyst using one equivalent of the iodine monochloride complex. This gave the ortho-iodinated product 203a in a good yield of 75\% with just 1\% of the di-iodinated product 204a being observed. Running the reaction under air appeared to slightly decrease the yield (table 20, entry 2). Upon reducing the temperature to 90 °C, the yield dropped insignificantly, however, further lowering gave drastically lower yields (table 20, entries 3 – 5). It is thought that these values could be anomalous as not all of the starting material was recovered from these reactions. The loading of the catalyst was reduced to 1 mol\%, however, this resulted in a fairly significant drop in isolated yield to 53\% (table 20, entry 6). Without any catalyst present, only starting material was recovered from the reaction (table 20, entry 7).
Compared to the chlorination conditions, the iodination procedure proved to be cleaner, yielding far less of the di-halogenated product. Therefore, we took these conditions and changed the halogenating agent to the IBr:dioxane complex and then I₂ itself. With the equivalents of “I⁺” kept constant, it was intriguing to note that both other reagents gave the ortho-iodinated product. However the yields decreased as the polarity of the reagent decreased (table 21).

Table 20: Optimisation of the iodination reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>Ru₃(CO)₁₂ (x mol%)</th>
<th>T (°C)</th>
<th>yield</th>
<th>165a:166a:203a:204a&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>110</td>
<td>76%</td>
<td>0:0:75:1</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
<td>110</td>
<td>59%</td>
<td>0:0:59:0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>90</td>
<td>71%</td>
<td>0:0:71:0</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>70</td>
<td>22%</td>
<td>0:0:22:0</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>50</td>
<td>19%</td>
<td>0:0:19:0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>110</td>
<td>53%</td>
<td>0:0:53:0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>110</td>
<td>0%</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratios determined from ¹H NMR following column chromatography. <sup>b</sup> Reaction run under air atmosphere. <sup>c</sup> Yield determined via ¹H NMR using an internal standard.
### Table 21: ortho-Iodination with iodine, iodine monobromide and iodine monochloride

<table>
<thead>
<tr>
<th>entry</th>
<th>iodinating agent</th>
<th>yield</th>
<th>203a:203b*</th>
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</thead>
<tbody>
<tr>
<td>1b</td>
<td>206</td>
<td>76%</td>
<td>0:0:75:1</td>
</tr>
<tr>
<td>2</td>
<td>2(IBr.dioxane)</td>
<td>35%</td>
<td>0:0:35:0</td>
</tr>
<tr>
<td>3</td>
<td>2I₂</td>
<td>23%</td>
<td>0:0:23:0</td>
</tr>
</tbody>
</table>

*Isolated yields. b Reaction performed by Lucas Frederic.

2.7.3 Substrate scope

With both chlorination and iodination reactions optimised on phenylpyridine, investigation into the scope of the reaction is on going and has yet to be completed at the time of writing. Preliminary investigations into the iodination reaction were carried out by Lucas Frédéric. It can be seen that, disappointingly, mixtures of iiodinated and chlorinated products are obtained for a number of the substrates (figure 27). There appear to be two clear trends. Firstly, electron rich arenes (compound 13n), as with the meta-bromination, have a faster background reaction leading to regioselectivity patterns that would be expected from electrophilic aromatic substitution. Secondly, iodine monochloride appears to react less chemoselectively with electron deficient arenes (compound 13e, 13f and 13g). It was surprising to find that benzo(h)quinoline was not reactive under the reaction conditions.

With it becoming clear that the electronics of the aromatic ring would need to be carefully balanced, our attention turned to directing groups in the hope that we might find that the reaction was more general than previous ruthenium investigations (figure 28). Initial studies showed that pyrazine and oxazoline directing groups together with pyridine protected phenol gave no product under either reaction conditions.
Gratifyingly however, isoquinoline 151n gave the desired products under the respective conditions, with the ortho-chloro compound 207n obtained in excellent 78% yield and the ortho-iodo product 208n in an acceptable 40% yield. This was a somewhat interesting result, given that under the conditions used for meta-bromination, only a background bromination at the 4-position of the isoquinoline was observed (figure 17, compound 152n). No halogenation at this position was seen under either iodination or chlorination conditions.
2.7.4 Origins of selectivity

2.7.4.1 Iodine monochloride

Several reports of unexpected reactivity of iodine monochloride have been disclosed previously, typically where chlorination occurs on substrates when iodination had been expected.\(^\text{144}\)

One particularly intriguing study, carried out by Kochi and co-workers, tries to rationalise the different reactivity that various electron rich aromatics have with iodine monochloride (figure 29).\(^\text{147}\) Furthermore, an interesting result is shown in scheme 47, whereby just changing the solvent can drastically switch chemoselectivity between chlorination and iodination. In attempting to explain this result, the authors perform a series of experiments including UV-vis spectroscopy. They show that ICl forms a charge transfer complex with electron rich arenes.
Subsequent electron transfer forms a reactive triad of the aromatic radical cation, chloride anion and iodine radical. They reason that selectivity between acetonitrile and dichloromethane can be explained as following: in a non-polar solvent (DCM), collapse of the chloride anion and the radical cation is favoured; in more polar solvents such as acetonitrile, the charged species are better stabilised and separated and hence radical combination between iodine and the aromatic radical cation can occur (scheme 49).

Scheme 49: The effect of solvent on halogenation of electron rich aromatics with iodine monochloride

It is difficult to draw any incisive insight from this work and apply it to the work described in this chapter because this work does not involve any transition metal species. However, the observation that a reactive triad of chloride anion, iodine radical and arenium cation is produced is potentially noteworthy. This could be one explanation for a divergence in reactivity. Jin Quan Yu’s laboratory some time ago published results of ortho-C–H functionalisation using a copper catalyst and nucleophiles including chloride (scheme 50). This demonstrates some precedent for such a reaction on 2-phenylpyridine with a transition metal catalyst.

One suggestion for our system is that the more electron rich catalyst Ru(PPh$_3$)$_3$Cl$_2$ can undergo electron transfer to reduce iodine monochloride. This generates the radical cation, ICl$^+$, which fragments as previously shown into an iodine radical concomitantly forming [Ru(III)]Cl$_n$. Electron transfer between the Ru(III) centre and arene (analogous to that in scheme 48) would generate the arenium and Ru(II). Attack of chloride bound on the arenium would give the ortho-chlorinated species after rearomatisation. To the best of our knowledge, there are no reports of Ru$_3$(CO)$_{12}$ acting as a catalyst for Kharasch type reactions where a Ru(III)
species is generated. This could explain the difference in reactivity between the two catalysts.

![Scheme 50: Yu’s copper catalysed ortho-chlorination reaction](image)

2.7.4.2 Palladium catalysed iodination

One detailed mechanistic study carried out by Musaev, Yu and co-workers examined the two plausible mechanisms for their directed palladium catalysed iodination reactions.\(^{149}\) Computational calculations suggested that there were two possible pathways for the reaction to occur. The first was a redox neutral, concerted Pd(II)/Pd(II) electrophilic mechanism (path (a), figure 30). The other pathway would be oxidative addition to [Pd(II)] to form a [Pd(IV)] species 217 followed by reductive elimination (path (b), figure 30). They found that, in the majority of cases, the electrophilic mechanism is favoured, with the exception of when a strong directing group is combined with a C(sp\(^3\))–H substrate.

When considering the two pathways in the context of iodine monochloride for our system, an analogous electrophilic mechanism would have to solely give iodinated product due to the dipole moment of the reagent. Contrastingly, if iodine monochloride were to undergo oxidative addition to a ruthenium centre, the rate of reductive elimination of C–I vs C–Cl bond would determine the product formed which could give a divergence in product formation depending on the electronics of the metal centre.
Despite Ru$_3$(CO)$_{12}$ being a Ru(0) catalyst, upon cyclometallation, it would form a Ru(II) species. Cyclometallated intermediates from the two different catalysts (Ru$_3$(CO)$_{12}$ and Ru(PPh$_3$)$_3$Cl$_2$) would predictably have different electronic properties. Carbonyl ligands are π-acidic and undergo a significant degree of back-bonding from the metal centre. In contrast, triphenylphosphine is a stronger σ-donor resulting in more electron density on the metal centre. A more electron rich centre (i.e. with phosphine rather than carbonyl ligands) should better stabilise higher oxidation states at the metal. It is plausible that these differing electronics could affect the reductive elimination step from a Ru(IV) intermediate.

2.7.4.3 Mechanistic experiments
Notedly, it was found that ortho-chlorinated product was produced in small quantities when using BHT as a radical inhibitor (scheme 51), whereas the iodination reaction was completely inhibited in the presence of BHT (scheme 52).
Though far from definitive, this could be suggestive of two different mechanisms occurring i.e. these results would be at odds with the theory that the two pathways differ only in a reductive elimination step.

To try to further our understanding of the mechanisms of these transformations, intramolecular kinetic isotope experiments were carried out with substrate 13aa for both iodination and chlorination reactions (scheme 53). This type of experiment is most useful for ruling out the potential that C–H bond cleavage takes place during the rate-determining step. In both the cases, here, a primary kinetic isotope effect is seen but this is not necessarily reflective of C–H bond cleavage occurring in the rate-determining step. Perhaps the most interesting thing to note is that the recovered starting material 13ab from the chlorination reaction is ‘enriched’ in deuterium. This suggests that for this reaction, C–H bond cleavage is reversible.
2.7.4.3 Transition metal control of reagent chemoselectivity

Finally, one notable example of switchable reactivity in transition metal C–H functionalisation was disclosed by Vy Dong’s group in 2009. It was demonstrated that under palladium catalysis, aryl sulfonyl chlorides can react in 1,4-dioxane to give the ortho-sulfonylated product. However, upon switching to DMF and using CuCl₂ as a co-catalyst, the chemoselectivity changed to give the ortho-chlorinated product instead (scheme 54). Although no detailed suggestion is presented for why this change occurs, the authors mention that it is known that aryl sulfonyl chlorides can react with DMF to form amidinium arenesulfonate salts and that this could play a part in the reactivity patterns that are observed.

Scheme 53: Kinetic isotope effects as determined by intramolecular competition experiments

Scheme 54: Switching the chemoselectivity of tosyl chloride under transition metal catalysis
2.7.5 Future work

Additional investigations into the scope of both of these reactions will follow in the hope of finding a range of substrates in which it is possible to control chemoselectivity solely by ruthenium catalyst choice. To further probe the origin of the selectivity for the two reactions, more kinetic isotope experiments should be carried out. The only method for conclusively telling whether the C–H bond cleavage occurs during the rate determining step is to perform two separate reactions and measure the rates of reaction (scheme 55).

![Scheme 55: KIE determined from two parallel reactions](image)

It should be seen, too, if conversion between the two compounds occurs under either set of conditions. By subjecting the ortho-chlorinated compound to the iodination conditions, and the ortho-iodinated compound to the chlorination conditions we could rule out this possibility (scheme 56).

![Scheme 56: Checking for interconversion between chlorinated and iodinated compounds](image)
2.8 Copper mediated synthesis of (halo)diaryl-methanes

Methods for affecting benzylic arylation have been described in section 1.4. The majority of these reactions require strong base and are carried out under palladium catalysis. These reactions conditions also tend to demand a pre-functionalised starting material (aryl halide or aryl organometallic) and given that our group has been interested in developing CDC reactions, we sought to apply this to the synthesis of diarylmethanes. Dr Thomas Storr (T.E.S.) initiated this project in our research group and carried out some of the work described below including the optimisation.

2.8.1 Reaction discovery

![Reaction diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>copper salt</th>
<th>yield of 222a (%)</th>
<th>yield of 223 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)₂</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)₂</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)₂.H₂O</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>CuSO₄</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CuSO₄.H₂O</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>CuO</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Cu(BF₄)₂.H₂O</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>CuBr₂</td>
<td>0</td>
<td>49</td>
</tr>
<tr>
<td>9</td>
<td>CuCl₂</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>10</td>
<td>CuF₂</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Cu(acac)₂</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 22: Screening of copper salts to mediate a CDC formation of diarylmethanes

After screening of a large number of transition-metals (Pd, Pt, Cu, Ir, Ru) and photoredox catalysts (organometallic and organic) under both base promoted and
radical conditions, a positive result was finally obtained when subjecting trimethoxybenzene to the conditions outlined above (table 22, entry 8).

Using 1,3,5-trimethoxybenzene 221a as a limiting reagent, with two equivalents of copper(II) bromide, 4.5 equivalents of di-tert-butyl peroxide and para-xylene 132a as the solvent and coupling partner at 110 °C for 18 hours gave the halobenzylated product 223 as the major product in 49% yield. Also isolated were the mono- and di-brominated trimethoxybenzene substrates (231a and 232a) which accounted for the remainder of the starting material. This reaction has promoted the formation of both the desired C(sp²)–C(sp³) bond together with bromination of a C(sp²)–H bond of the electron rich aromatic. This is in stark contrast to what had previously been reported in our group where 1,3,5-trimethoxybenzene 221a with potassium persulfate and palladium acetate catalyst in para-xylene 132a and trifluoroacetic acid promoted the formation of a C(sp²)–C(sp²) bond (scheme 57) to form biaryl 224a. 152a

Scheme 57: CDC of 1,3,5-trimethoxybenzene and para-xylene to form a biaryl

Further optimisation of the copper promoted reaction was carried out in an attempt to boost the moderate yield however it was not possible to make any significant gains. It was considered worthwhile to pursue this methodology regardless because of its novelty and potential in carrying out a difficult transformation. It was also noted that a number of products from the reaction bear a striking resemblance to some marine natural products some of which possess a number of biological actions (see section 2.8.3). 153,154,155,156,157
2.8.2 Substrate scope

With conditions in hand, attention turned to exploring the scope and limitations of this chemistry and what type of chemical space it would be possible to access with this novel procedure. Regarding hydrocarbons, all isomers of xylene were tolerated well under the reaction conditions (223a – 223c) as were mesitylene (223d), prehenitine (223e), durene (223f) and tert-butylmethyl benzenes (223h, 223i) (figure 31).

![Diagram of the reaction](image)

*Figure 31: exploring the substrate scope of the toluene components*

It was noted that use of Luperox® 101 as the peroxide seemed to increase the yields slightly and so this general procedure was used for the majority of following experiments that were carried out on this project. *para*-Bromotoluene and *para*-chlorotoluene worked in fairly poor yields, to give structures 223g and 223j.
respectively, though they provide useful handles for further functional group manipulation. It was notable that toluene itself did not react to give any cross-coupled products. An explanation for this phenomenon has yet to be unraveled. The product 223l was not observed with cyclohexane and, similarly, saturated heterocycles did not work as coupling partners.

Investigation of how substitution at the benzylic position would affect reactivity revealed that it was possible to form tertiary carbon centres in poor to moderate yields when using a secondary benzylic coupling partner. Using Luperox® 101, the synthesis of triphenylmethane 225a was accomplished in 40% yield with diphenylmethane as the starting material. 1,4-Diethylbenzene generated 225b in 41% yield and indane gave the product 225c in 27% yield. When using fluorene as the starting material, fifteen equivalents were used with benzene as a co-solvent. This gave the product 225d in 22% yield. What is notable is that in this case, the des-halo product is obtained which is in contrast to all other substrates.

![Chemical Structures and Reactions](image)

* denotes reactions carried out by T.E.S.

*a reaction carried out with 15 eq. of fluorene and benzene (1 ml) as solvent

Figure 32: Generation of tertiary benzylic centres

Next, attention turned to varying the electron rich aromatic arene (figure 33). After screening different 1,3,5-alkoxybenzenes, it was seen that the yield decreased as steric bulk increased which was somewhat unsurprising (226a – 226d). Following optimisation on 1,3,5-trimethoxybenzene, we were concerned that less electron rich aromatics would not work in the reaction. Gratifyingly, however, 1,3-dimethoxybenzene reacted under the conditions to give the bromodiarylmethane
product 226e in acceptable yield of 43%. When using 3,4,5-trimethoxytoluene, the hexasubstituted product 226f was generated although in a low yield of 12%. In contrast, 1,2,3-trimethoxybenzene gave cross-coupled product 226h but without bromination on the electron rich aromatic ring. This is suggestive that the methyl group in 132f means that the substrate is electron rich enough to undergo double bromination under the reaction conditions.

A number of other substrates investigated gave only the xylylated product without the bromination on the electron rich ring. 1,2,4,5-tetramethoxybenzene gave product 226i in 22% yield. 2-fluoro-1,3,5-trimethoxybenzene was xylylated in moderate yield to give 226ja however after analysis of the GCMS and NMR spectra, it was determined that the bromo-xylylated product 226jb was also produced in 8%
yield together with 4% of the doubly-xylylated product 226jc. 2-Nitro-1,3,5-trimethoxybenzene was by far the best substrate tested during the course of this project with 226g being obtained in an extremely good 76% yield. In the hope that a strong electron withdrawing group at the 2-position would provide us with the possibility of generating products in better yields, the 2-formyl-1,3,5-trimethoxybenzene was trialed in the reaction. 226k was obtained in a slightly disappointing 20% yield.

It should be noted that in very few cases does the reaction proceed without an electron-withdrawing group on the electron rich aromatic ring. Whether this be a second bromine or another group, it seems that this is predominantly a requirement for the coupling reaction to occur.

2.8.3 Vidalol A synthesis
It was previously mentioned that the products resulting from this reaction resemble a number of natural products that have been isolated from marine sponges.\textsuperscript{154,155} Vidalols A and B were isolated from Caribbean marine red alga \textit{Vidalia obtusaloba} in 1990.\textsuperscript{156} They both demonstrate carbonic anhydrase as well as phospholipase A\textsubscript{2} inhibition.

To date, Vidalol B 228 has been synthesised but Vidalol A 227 had remained unsynthesised despite one previous reported attempt.\textsuperscript{157} Preparation of substrate 132m to try under the reaction conditions was carried out by T.E.S. He then established that the formation of product 223m was possible under the reaction conditions using five equivalents of 132m with benzene as solvent (scheme 58). It was found that this reaction was reproducible with the yields varying between 12 and 19%. Thankfully, the majority of unreacted 132m could be recovered.
Attention next turned to the penta-demethylation to give the natural product 227. As mentioned, it has been reported in the literature that use of BBr₃ on 223m did not give the demethylated product.¹⁵⁷ Our first few attempts were also ambiguous, with the crude reaction mixture, when submitted to LCMS, always containing the mass of the product. It appeared that the material obtained was not particularly soluble in chloroform despite the NMR data from the isolation paper having been recorded in CDCl₃. Following several unsuccessful attempts where the starting material was consumed but no product was isolated, the same procedure was followed with a slight adjustment. After addition of the BBr₃ solution at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was then cooled again to 0 °C and a large excess of methanol was added. Unlike previous occasions, this mixture was then allowed to stir at room temperature for seven hours in the hope that this would encourage complete removal of the boron species from the product. After addition of water and rigorous extraction with ethyl acetate, the brown solid that was obtained was dissolved in deuterated acetone and the spectra recorded. It should be noted that observation of the five phenolic protons between 7.53 and 8.63 ppm is consistent with data for Vidalol B 228 obtained in (CD₃)₂CO where the phenolic protons are also visible.¹⁵⁷

Unfortunately, it has not yet proved possible to isolate Vidalol A from a number of unidentified impurities so no yield for this reaction has been obtained.
2.8.4 Mechanistic investigations

A series of experiments were carried out to deduce a plausible mechanism for this reaction. It was initially postulated that the reaction could be proceeding via a simple electrophilic aromatic substitution reaction where the electron rich aromatic was the nucleophile and the electrophile was the in situ generated benzylic bromide. The Wohl-Ziegler bromination is carried out under radical conditions\textsuperscript{158} so it was not implausible that a similar process could be occurring here.

\[(\text{H-}) \text{CuBr}_2 (1 \text{ eq.}) \xrightarrow{110 \degree C, 18 \text{ h}} \text{Br} \quad (25 \text{ eq.}) \]

in benzene with \((\text{BuO})_2 (4.5 \text{ eq.})\) without 14% 0%

\[\text{OMe} \text{OMe} \quad \text{Br} \text{OMe} \text{OMe} \]

\[\text{MeO} \text{H} + \text{Br} \quad \text{MeO} \text{H} \quad \text{MeO} \text{H} \]

221a 230a 223a

(1 eq.) (25 eq.) (25 eq.)

A: CuBr\textsubscript{2} (2 eq.)
B: (BuO)\textsubscript{2} (4.5 eq.)
C: no additives

Reactions performed by T.E.S.

It was shown however that only a small quantity of \(\alpha\)-bromo-\(\alpha\)-xylene 230a was produced under the reaction conditions. Heating this molecule with one equivalent of trimethoxybenzene 221a in benzene gave none of 223a even with the peroxide (scheme 59). Only traces of product were observed in the presence of copper(II) bromide (TLC analysis, not isolable) which we deemed sufficient evidence for ruling out this mechanism as the dominant process that occurred.

Given the precedent for using cupric halides as stoichiometric halogenating agents\textsuperscript{159}, it was unsurprising to find that the electron rich 1,3,5-trimethoxybenzene 221a forms both brominated and di-brominated products, 231a and 232a respectively, (in approximately 1:2 ratio respectively) when heated with copper(II) bromide both with and without the oxidant (scheme 60). Slightly higher mass balance was observed without the oxidant.
Subjecting the brominated and di-brominated products to the reaction conditions showed that both were competent substrates giving the desired product when using CuBr or CuBr$_2$ (scheme 61). This suggests that they are reaction intermediates rather than merely by-products.

Inconsequentially, to see whether it was possible to further promote C–C bond formation, the reaction was run under the standard conditions for twenty hours at which point one equivalent of copper(I) bromide was added to the reaction vessel (scheme 62). Upon heating for 24 further hours, 43% of the normally observed product 223a was observed however a considerable quantity of di-xylated product 233a was also observed (25%) suggesting that it is extremely likely that the C–C bond coupling process is copper promoted.
It was shown that when two equivalents of either radical trap TEMPO or galvinoxyl were added to the benchmark reaction, no product was observed (scheme 63).

Finally, when starting from 2-chloro-1,3,5-trimethoxybenzene 234a, two products, 235a and 223a, are obtained as an inseparable mixture of products. This is highly suggestive of a mechanism where bromination of the electron rich arene occurs first. In this case, there are two resulting carbon-halide bonds where the coupling can occur but it is more efficient at the C–Br bond resulting in more product seen with C–Cl bond remaining (scheme 64).

The proposed mechanism based on what we have observed during the course of the project is as follows: 1) copper(II) bromide (doubly) brominates the electron
rich aromatic; 2) the O–O bond in di-tertbutilperoxide undergoes thermal cleavage to generate two reactive tert-butyl radicals which can abstract a benzylic hydrogen atom thus generating a benzylic carbon radical species 141a;\textsuperscript{160} 3) a copper mediated coupling between aryl bromide 232a and benzylic radical 141a occurs to generate a new C(sp\textsuperscript{2})–C(sp\textsuperscript{3}) bond.

![Figure 35: A plausible mechanism for the copper mediated synthesis of halodiarylmethanes](image)

It is not know the exact mechanism by which this copper mediated coupling occurs but one plausible mechanism is that the benzylic radical could react with a copper(II) aryl species to generate a highly reactive copper(III) species\textsuperscript{161,162} which upon reductive elimination would give the coupled product 223a and generate copper(I) (see figure 13). As was mentioned in section 1.4.4, nickel is capable of catalysing a cross coupling reaction between an \textit{in situ} generated carbon centred radical and an aryl bromide (figure 14). Oxidative addition of Ni(0) to the aryl bromide forms a Ni(II) species which, upon reaction with the benyl radical, forms a Ni(III) intermediate. Reductive elimination forms the new C–C bond and generates Ni(I) which is then reduced by the photoredox catalyst. We cannot rule out an analogous mechanism with copper in this case. If such a mechanism is active for this
reaction, it should be possible to develop a catalytic variant of the reaction either with preformed aryl bromides or with an additional stoichiometric brominating agent in the reaction mixture.
3. Conclusions

3.1 Ruthenium

To compendiate, several new catalytic ruthenium manifolds have been discovered (figure 36). The first was an unprecedented meta-selective bromination procedure on substituted phenylpyridines using tetrabutylammonium tribromide as the brominating agent. The regioselectivity of this reaction is in stark contrast to other transition metal procedures previously reported which are selective for the ortho position. This chemistry was combined with palladium chemistry in one pot to allow access to meta-arylated and meta-alkenyalted products.163

We also discovered conditions to deliver meta-formylated phenylpyridine in a low yield using chloroform as a reagent under ruthenium catalysis. Hopefully, further optimisation could transform this into a synthetically useful reaction. Following this, reactions for ortho-chlorination and ortho-iodination, both using iodine monochloride were optimised with investigations into the substrate scope and mechanism currently ongoing within the group.

![Figure 36: A summary of developed ruthenium catalysed halogenation conditions](image)

A conclusive mechanistic explanation for the control of selectivity for C–H halogenation under ruthenium catalysis has yet to be elucidated. In particular, there is a noticeable disparity between bromination and iodination: no meta-iodinated products are obtained when using iodinating agents although the ortho regioisomer is
obtained in a number of cases. Furthermore, that the nature of the ruthenium catalyst can alter the chemoselectivity of reactions with iodine monochloride was unexpected. Future work will hopefully help to unravel the mysteries of these dichotomous results.

### 3.2 Copper

A novel approach to the synthesis of polysubstituted (halo)diarylmethanes was developed (scheme 65). This protocol employs stoichiometric copper(II) halides which play two roles: both as a halogenating agent for the more electron rich arene and also as a mediator for the new C–C bond formation step. We propose that the reaction proceeds through coupling of a benzylic radical species and the *in situ* generated aryl halide.

![Scheme 65: A summary of the copper mediated synthesis of diarylmethanes](image)

Despite the moderate yields, it is hoped that additional research into the nature of the C–C bond formation step could see this methodology inspire development of copper mediated couplings of radical species with aryl bromides on more general systems (figure 37).

![Figure 37: The potential for a copper catalysed cross coupling of radicals with aryl bromides](image)
4. Experimental

4.1 General remarks

Nuclear Magnetic Resonance (NMR) spectra were recorded on 500 or 400 MHz Bruker NMR spectrometers in CDCl₃ or (CD₃)₂CO at 298 K. All chemical shift values are reported in parts per million (ppm) relative to the solvent signal (¹H NMR: δ = 7.26 ppm, ¹³C NMR: δ = 77.16 ppm for CDCl₃; ¹H NMR: δ = 2.05 ppm, ¹³C NMR: δ = 29.8 ppm (CD₃)₂CO) with coupling constant (J) values reported to the nearest 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), septet (sept.), multiplet (m), broad singlet (br s) and combinations thereof. NMR spectra were assigned with the aid of 2-D Correlation and DEPT-135 spectra where appropriate.

TLC: Macherey-Nagel, TLC plates Alugram® Sil G/UV254. Detection under UV light at 254 nm. Chromatography: Separations were carried out on Silica gel (Sigma Aldrich, 40-63 µm, 60 Å) or using Biotage Snap Ultra cartridges on a Biotage Isolera automated columning machine. High resolution mass spectrometry was performed on a Waters QTOF with ESI/APCI ionisation and a Thermo Finnigan MAT95XP (EI). Melting points were determined using a Buchi M565 melting point apparatus. Elemental analysis was performed using Therm Scientific Flash 2000 instrument (CHNS) and Metrohm potentiometric autotitrator (halogens).

Reactions were carried out under N₂ using pre-dried glassware which was cooled under vacuum unless otherwise stated. Anhydrous THF was distilled from sodium/benzophenone ketyl immediately before use. Dichloromethane and toluene were distilled over calcium hydride. Other solvents were purchased in anhydrous quality and used as received. Reagents were either purchased directly from commercial suppliers or prepared according to literature procedures. Potassium carbonate was dried under vacuum before being weighed. Yields of all the compounds refer to isolated compounds. SmI₂ was prepared by Dr Nico Kern according to literature procedure.¹⁶⁴
4.2 Starting material syntheses

General procedure A

Typical synthesis: To the boronic acid (3.0 mmol, 1.5 eq), palladium acetate (6.7 mg, 0.030 mmol, 0.015 eq) and potassium carbonate (553 mg, 4.0 mmol, 2.0 eq) was added ethanol (9 ml), water (3 ml) and 2-bromopyridine (192 µl, 2.0 mmol, 1.0 eq). After heating at 80 °C for 20 hours, water was added and the mixture extracted three times with ethyl acetate. The combined organic layers were washed with brine, concentrated, dried over MgSO₄ and purified by flash column chromatography (ethyl acetate, hexane mixtures).

13c, N-(4-(pyridin-2-yl)phenyl)acetamide<sup>165</sup>

![Chemical structure of 13c](image)

Synthesised according to general procedure A. Off white solid, 299 mg, 71%;

<sup>1</sup>H NMR (500 MHz, CDCl₃): 8.68 – 8.64 (m, 1H), 7.98 – 7.93 (m, 2H), 7.73 (app td, \( J = 7.6, 1.8 \text{ Hz, 1H} \)), 7.69 (app dt, \( J = 8.1, 1.2 \text{ Hz, 1H} \)), 7.64 – 7.60 (m, 2H), 7.49 (br s, 1H), 7.20 (ddd, \( J = 7.2, 4.9, 1.4 \text{ Hz, 1H} \)), 2.19 (d, \( J = 1.3 \text{ Hz, 3H} \)); <sup>13</sup>C NMR (125 MHz, CDCl₃): \( \delta \) 168.5, 156.9, 149.7, 138.8, 136.9, 135.3, 127.7, 122.0, 120.3, 119.9, 24.9.

13d, 2-(4-(tert-butyl)phenyl)pyridine<sup>166</sup>

![Chemical structure of 13d](image)

Synthesised according to general procedure A. Yellow oil, 271 mg, 86%;
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.68 (d, $J = 4.8$ Hz, 1H), 7.94 (d, $J = 8.5$ Hz, 2H), 7.73 – 7.71 (m, 2H), 7.51 (d, $J = 8.5$ Hz, 2H), 7.22 – 7.18 (m, 1H), 1.37 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.6, 152.2, 149.7, 136.8, 136.7, 126.7, 125.8, 121.9, 120.4, 34.8, 31.4.

13e, 2-(4-fluorophenyl)pyridine$^{167}$

Synthesised according to general procedure A. White solid, 299 mg, 86%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.61 (ddd, $J = 4.8$, 1.9, 1.0 Hz, 1H), 7.94 – 7.89 (m, 2H) 7.68 (ddd, $J = 8.0$, 7.4, 1.9 Hz, 1H), 7.61 (dd, $J = 7.9$, 1.2, 1.0 Hz, 1H), 7.16 (ddd, $J = 7.4$, 4.8, 1.2 Hz, 1H), 7.12 – 7.06 (m, 2H); $^{19}$F NMR (100 MHz, CDCl$_3$): $\delta$ -113.2; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 163.7 (d, $J_{C-F} = 247$ Hz), 156.6, 149.8, 136.9, 135.7 (d, $J_{C-F} = 3.4$ Hz), 128.8 (d, $J_{C-F} = 8.5$ Hz), 122.2, 120.4, 115.8 (d, $J_{C-F} = 22.0$ Hz).

13g, 2-(4-chlorophenyl)pyridine$^{168}$

Synthesised according to general procedure A. White solid, 197 mg, 69%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.69 (ddd, $J = 4.9$, 1.8, 1.0 Hz, 1H), 7.94 (d, $J = 8.6$ Hz, 2H), 7.76 (ddd, $J = 8.0$, 7.3, 1.8 Hz, 1H), 7.70 (ddd, $J = 8.0$, 1.1, 1.0 Hz, 1H), 7.45 (d, $J = 8.6$ Hz, 1H), 7.27 – 7.22 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.1, 149.7, 137.8, 136.9, 135.1, 128.9, 128.2, 122.4, 120.4.
13h, 4-methyl-2-phenylpyridine$^{169}$

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{C} \\
\text{H}_3
\end{array}
\]

Synthesised according to general procedure A. Pale yellow oil, 216 mg, 64%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.56 (d, $J = 5.1$ Hz, 1H), 7.99 – 7.77 (m, 2H), 7.55 (s, 1H), 7.49 – 7.45 (m, 2H), 7.42 – 7.38 (m, 1H), 7.06 (d, $J = 4.8$ Hz, 1H), 2.42 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.5, 149.6, 147.9, 139.7, 128.9, 128.8, 127.1, 123.3, 121.7, 21.4.

13i, 5-methyl-2-phenylpyridine$^{170}$

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{C} \\
\text{H}_3
\end{array}
\]

Synthesised according to general procedure A. Yellow oil, 293 mg, 88%;

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.54 – 8.50 (m, 1H), 8.01 – 7.95 (m, 2H), 7.62 – 7.57 (dd, $J = 8.1$, 0.9 Hz, 1H), 7.56 (ddd, $J = 8.1$, 2.3, 0.9 Hz, 1H) 7.49 – 7.44 (m, 2H), 7.42 – 7.36 (m, 1H), 2.34 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 154.7, 150.0, 139.3, 137.3, 131.6, 128.7, 128.6, 126.7, 120.0, 18.1.
13k, 2-(o-tolyl)pyridine\textsuperscript{171}

\[ \begin{array}{c}
\text{Py}
\end{array} \]

Synthesised according to general procedure A. Yellow oil, 97.4 mg, 29%;

\(^1\text{H NMR (400 MHz, CDCl}_3\): } \delta 8.67 (\text{ddd, } J = 5.0, 1.9, 1.0 \text{ Hz, 1H}), 7.71 (\text{app td, } J = 7.7, 1.8 \text{ Hz, 1H}), 7.40 - 7.34 (\text{m, 2H}), 7.30 - 7.18 (\text{m, 4H}), 2.34 (\text{s, 3H}); \quad ^{13}\text{C NMR (100 MHz, CDCl}_3\): } \delta 13C \text{ NMR (101 MHz, CDCl}_3\) \delta 160.2, 149.4, 140.6, 136.2, 135.9, 130.9, 129.8, 128.4, 126.0, 124.2, 121.7, 20.2.

13l, 2-(m-tolyl)pyridine\textsuperscript{171}

\[ \begin{array}{c}
\text{Py}
\end{array} \]

Synthesised according to general procedure A. Yellow oil, 352 mg, 93%;

\(^1\text{H NMR (400 MHz, CDCl}_3\): } \delta 8.69 (\text{ddd, } J = 4.8, 1.4, 1.4 \text{ Hz, 1H}), 7.84 (\text{d, } J = 2.2 \text{ Hz, 1H}), 7.78 - 7.69 (\text{m, 3H}), 7.37 (\text{app t, } J = 7.6 \text{ Hz, 1H}), 7.26 - 7.19 (\text{m, 2H}), 2.44 (\text{s, 3H}); \quad ^{13}\text{C NMR (100 MHz, CDCl}_3\): } \delta 157.8, 149.7, 139.5, 138.6, 136.9, 129.9, 128.8, 127.8, 124.1, 122.2, 120.8, 21.7.

13m, 3-methyl-2-phenylpyridine\textsuperscript{169}

\[ \begin{array}{c}
\text{Py}
\end{array} \]

Synthesised according to general procedure A. Yellow oil, 152 mg, 45%;
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.53 (m, 1H), 7.58 (dd, $J = 7.7$, 1.7 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.41 – 7.37 (m, 3H), 7.18 (dd, $J = 7.7$, 4.8 Hz, 1H), 2.36 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.8, 147.1, 140.8, 138.6, 130.9, 129.1, 128.3, 128.0, 122.2, 20.2.

13n, 2-(4-methoxyphenyl)pyridine$^{166}$

![Image](image_url)

Synthesised according to general procedure A. Off white solid, 263 mg, 71%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.64 (ddd, $J = 4.8$, 1.7, 1.0 Hz, 1H), 7.97 – 7.92 (m, 2H), 7.69 – 7.61 (m, 2H), 7.13 (ddd, $J = 6.7$, 4.8, 1.7 Hz, 1H), 7.00 – 6.96 (m, 2H), 3.82 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 160.4, 157.1, 149.5, 136.7, 132.0, 128.2, 121.5, 119.8, 114.1, 55.3.

13o, 2-(2-methoxyphenyl)pyridine$^{169}$

![Image](image_url)

Synthesised according to general procedure A. Yellow oil, 189 mg, 55%;

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.72 – 8.68 (m, 1H), 7.81 (app dt, $J = 8.0$, 1.1 Hz, 1H), 7.76 (dd, $J = 7.7$, 1.8 Hz, 1H), 7.70 (app td, $J = 7.7$, 1.9 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.22 – 7.17 (m, 1H), 7.08 (app td, $J = 7.5$, 1.0 Hz, 1H), 7.01 (dd, $J = 8.3$, 1.0 Hz, 1H), 3.86 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.4, 156.6, 149.9, 136.1, 131.6, 130.4, 129.6, 125.6, 122.1, 121.5, 111.8, 56.1.
13p, 2-(3-methoxyphenyl)pyridine$^{171}$

Synthesised according to general procedure A. Yellow oil, 352 mg, 95%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.69 (d, $J = 4.8$ Hz, 1H), 7.77 – 7.71 (m, 2H), 7.60 – 7.58 (m, 1H), 7.55 (d, $J = 7.9$ Hz, 1H), 7.38 (app t, $J = 7.9$ Hz, 1H), 7.25 – 7.22 (m, 1H), 6.99 – 6.96 (m, 1H), 3.90 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 160.2, 157.4, 149.8, 141.0, 136.9, 129.9, 122.4, 120.9, 119.5, 115.2, 112.1, 55.5.

13q, 2-(3,4-dimethoxyphenyl)pyridine$^{172}$

Synthesised according to general procedure A. Light brown oil, 231 mg, 54%.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.65 (ddd, $J = 4.8$, 1.8, 1.1 Hz, 1H), 7.76 – 7.63 (m, 3H), 7.51 (dd, $J = 8.4$, 2.1 Hz, 1H), 7.18 (ddd, $J = 6.7$, 4.8, 1.8 Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.2, 150.1, 149.6, 149.4, 136.8, 132.4, 121.7, 120.1, 119.5, 111.1, 110.0, 56.1, 56.1.
13r, 2-(naphthalen-1-yl)pyridine\textsuperscript{168}

\begin{center}
\includegraphics[width=0.2\textwidth]{naphthalen-1-ylpyridine.png}
\end{center}

Synthesised according to general procedure A. Brown oil, 216 mg, 53%;

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): $\delta$ 8.81 (ddd, $J = 5.0$, 1.9, 0.9 Hz, 1H), 8.11 – 8.09 (m, 1H), 7.94 – 7.89 (m, 2H), 7.82 ($app$ td, $J = 7.7$, 1.8 Hz, 1H), 7.64 – 7.54 (m, 5H), 7.53 – 7.45 (m, 2H), 7.33 (ddd, $J = 7.5$, 4.9, 1.1 Hz, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): $\delta$ 159.3, 149.6, 138.6, 136.5, 134.0, 131.2, 129.0, 128.4, 127.6, 126.6, 126.0, 125.7, 125.4, 125.2, 122.1.

13s, 2-(4-(trifluoromethyl)phenyl)pyridine\textsuperscript{167}

\begin{center}
\includegraphics[width=0.2\textwidth]{trifluoromethyl-phenylpyridine.png}
\end{center}

Synthesised according to general procedure A. White solid, 175 mg, 39%;

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): $\delta$ 8.73 – 8.71 (m, 1H), 8.11 (d, $J = 8.1$ Hz, 2H), 7.78 (ddd, $J = 7.6$, 7.1, 1.8 Hz, 1H), 7.76 – 7.70 (m, 3H), 7.28 (ddd, $J = 6.7$, 4.8, 1.5 Hz, 1H); \textsuperscript{19}F NMR (471 MHz, CDCl\textsubscript{3}): $\delta$ -62.6; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): $\delta$ 156.0, 150.1, 142.8, 137.1, 130.9 (q, $J_{C,F} = 32.4$ Hz), 127.3, 125.8 (q, $J_{C,F} = 3.8$ Hz), 124.3 (q, $J_{C,F} = 272.0$ Hz), 123.1, 120.9.
13t, 4-(pyridin-2-yl)benzonitrile\textsuperscript{173}

\begin{center}
\includegraphics[width=0.1\textwidth]{13t.png}
\end{center}

Synthesised according to general procedure A. White solid, 138 mg, 38%;

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 8.74 – 8.73 (m, 1H), 8.13 – 8.11 (m, 2H), 7.83 – 7.75 (m, 4H), 7.33 – 7.31 (m, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 150.2, 143.6, 137.2, 133.0, 132.7, 128.1, 127.6, 123.5, 121.1, 112.6.

13u, 1-(4-(pyridin-2-yl)phenyl)ethan-1-one\textsuperscript{173}

\begin{center}
\includegraphics[width=0.1\textwidth]{13u.png}
\end{center}

Synthesised according to general procedure A. White solid, 149 mg, 38%;

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 8.73 – 8.71 (m, 1H), 8.11 – 8.07 (m, 2H), 8.06 – 8.03 (m, 2H), 7.79 – 7.74 (m, 2H), 7.29 – 7.26 (m, 1H), 2.64 (s, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 197.9, 156.2, 150.0, 143.7, 137.2, 137.0, 128.9, 127.1, 123.0, 121.1, 26.9.
13v, 2-(3-fluorophenyl)pyridine

\[
\begin{align*}
\text{Synthesised according to general procedure A. Yellow oil, 189.7 mg, 55\%;} \\
^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 8.70 (\text{ddd, } J = 4.9, 1.3, 1.3 \text{ Hz, 1H}), 7.82 – 7.66 (\text{m, 4H}), 7.43 (\text{app td, } J = 8.0, 5.9 \text{ Hz, 1H}), 7.30 – 7.23 (\text{m, 1H}), 7.11 (\text{app tdd, } J = 8.4, 2.5, 1.1 \text{ Hz, 1H}); \\
^19\text{F NMR (100 MHz, CDCl}_3\text{): } \delta -112.9; \\
^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta 163.4 (\text{d, } J_{\text{C-F}} = 245.2 \text{ Hz}), 156.2, 149.9, 141.8 (\text{d, } J_{\text{C-F}} = 7.5 \text{ Hz}), 137.0, 130.4 (\text{d, } J_{\text{C-F}} = 8.1 \text{ Hz}), 122.8, 122.5 (\text{d, } J_{\text{C-F}} = 2.8 \text{ Hz}), 120.7, 115.9 (\text{d, } J_{\text{C-F}} = 21.4 \text{ Hz}), 114.0 (\text{d, } J_{\text{C-F}} = 22.8 \text{ Hz}).
\end{align*}
\]

13w, 2-(naphthalen-2-yl)pyridine

\[
\begin{align*}
\text{Synthesised according to general procedure A on a 1 mmol scale. Off white solid, 86.5 mg, 42\%;} \\
^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 8.76 (\text{m, 1H}), 8.49 (\text{m, 1H}), 8.14 (\text{dd, } J = 8.6, 1.8 \text{ Hz, 1H}), 7.97 – 7.94 (\text{m, 2H}), 7.90 – 7.86 (\text{m, 2H}), 7.79 (\text{app td, } J = 7.8, 1.8 \text{ Hz, 1H}), 7.54 – 7.49 (\text{m, 2H}), 7.27 (\text{m, 1H}); \\
^{13}\text{C NMR (125 MHz, CDCl}_3\text{): } \delta 157.3, 149.8, 136.8, 136.7, 133.7, 133.5, 128.7, 128.5, 127.7, 126.5, 126.3, 126.3, 124.6, 122.2, 120.9.
\end{align*}
\]
151d, 2-phenylpyrazine\textsuperscript{175}

![2-phenylpyrazine](image)

Synthesised according to general procedure A using 2-chloropyrazine and phenylboronic acid as coupling partners. Off-white solid, 248 mg, 79%;

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 9.04 (d, \(J = 1.6\) Hz, 1H), 8.64 (dd, \(J = 2.5, 1.6\) Hz, 1H), 8.51 (d, \(J = 2.5\) Hz, 1H), 8.08 – 7.95 (m, 2H), 7.61 – 7.43 (m, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 153.0, 144.3, 143.1, 142.4, 136.5, 130.1, 129.2, 127.1.

151f, (E)-\(\text{N},1\)-diphenylethan-1-imine\textsuperscript{176}

![diphenylethan-1-imine](image)

A solution of acetophenone (2.92 ml, 2.5 mmol, 1.0 eq), aniline (2.73 ml, 3.0 mmol, 1.2 eq) and 4Å molecular sieves were dissolved in toluene (15 ml) and the reaction mixture refluxed for 28 hours. The reaction was cooled before filtering and concentrating to give the product as a yellow solid (3.28 g, 67%).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 8.04 – 7.97 (m, 2H), 7.50 – 7.44 (m, 3H), 7.37 (app t, \(J = 7.7\) Hz, 2H), 7.11 (t, \(J = 7.5\) Hz, 1H), 6.83 (d, \(J = 7.7\) Hz, 2H), 2.24 (s, 3H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 165.0, 151.5, 139.1, 130.2, 128.9, 128.3, 127.0, 123.0, 119.1, 17.0.
According to the literature procedure, a schlenk tube was charged with CuI (20 mg, 0.10 mmol, 5 mol%), 2-picolinic acid (50 mg, 0.40 mmol, 8 mol%), K₃PO₄ (848 mg, 4.0 mmol, 2.0 eq), and phenol (188 mg, 2.4 mmol, 1.2 eq). The tube was evacuated and backfilled with nitrogen three times before 2-bromopyridine (192 µl, 2.0 mmol, 1.0 eq) and DMSO (4 ml) were added. The reaction mixture was heated to the 110 °C for 24 hours. After cooling to room temperature, the mixture was diluted with ethyl acetate before being passed through a short pad of celite. The residue was then purified by column chromatography on silica gel to give the product as an off-white solid (335 mg, 98%).

¹H NMR (500 MHz, CDCl₃): δ 8.21 (ddd, J = 5.1, 2.0, 0.8 Hz, 1H), 7.68 (ddd, J = 8.2, 7.2, 2.0 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.23 – 7.18 (m, 1H), 7.17 – 7.12 (m, 2H), 6.99 (ddd, J = 7.2, 5.1, 0.8 Hz, 1H), 6.91 (dt, J = 8.2, 0.9 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 163.9, 154.3, 147.9, 139.5, 129.8, 124.8, 121.3, 118.6, 111.6.

¹⁵i, N-phenylpyrimidin-2-amine

A microwave vial was charged with 2-chloropyrimidine (228 mg, 2.0 mmol, 1.0 eq), Pd₂dba₃ (36.7 mg, 0.08 mmol, 4 mol%), Xantphos (69.4 mg, 0.24 mmol, 12 mol%) and Cs₂CO₃ (912 mg, 2.8 mmol, 1.4 eq). Degassed 1,4 dioxane (1.8 ml) and aniline (0.22 ml, 2.4 mmol, 1.2 eq) were added and the reaction mixture heated in the microwave at 140 °C for 30 minutes. The reaction was diluted with water, extracted with EtOAc (x2) and the combined organic layers dried over MgSO₄ before being
concentrated in vacuo. After column chromatography, the product was collected as a yellow oil (171.2 mg, 59%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.43 (d, $J = 4.8$ Hz, 2H), 7.65 – 7.58 (m, 2H), 7.47 (br s, 1H), 7.39 – 7.31 (m, 2H), 7.06 (tt, $J = 7.6$, 1.1 Hz, 1H), 6.72 (t, $J = 4.8$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 160.3, 158.1, 139.4, 129.1, 122.9, 119.7, 119.7, 112.7.

151o, *N*-quinolin-8-yl)benzamide$^{179}$

![Chemical Structure]

8-Quinolinamine (3.0 g, 21.0 mmol, 1.05 eq), trimethylamine (3.3 ml, 24.0 mmol, 1.2 eq) and DMAP (80 mg, 0.65 mmol, 3 mol%) were dissolved in dichloromethane (30 ml). The reaction was cooled to 0 °C before benzoyl chloride (2.3 ml, 20.0 mmol, 1.0 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and left to stir overnight. Water was added and the layers separated. The aqueous layer was further extracted with dichloromethane before the combined aqueous layers were dried over MgSO$_4$ and concentrated. Recrystallisation from toluene gave the product as a light brown solid (2.63 g, 53%).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 10.75 (s, 1H), 8.95 (dd, $J = 7.6$, 1.4 Hz, 1H), 8.85 (dd, $J = 4.2$, 1.7 Hz, 1H), 8.19 (dd, $J = 8.3$, 1.7 Hz, 1H), 8.14 – 8.04 (m, 2H), 7.63 – 7.53 (m, 5H), 7.48 (dd, $J = 8.2$, 4.2 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 165.6, 148.4, 138.9, 136.5, 135.3, 134.7, 132.0, 128.9, 128.1, 127.6, 127.4, 121.8, 116.6.
220b, 2-(2-bromophenyl)pyridine\textsuperscript{180}

\[ \text{\includegraphics[width=0.2\textwidth]{image}} \]

A microwave vial was charged with Pd(OAc)$_2$ (67.4 mg, 0.3 mmol, 10 mol%) and \(N\)-bromosuccinimide (587 mg, 3.3 mmol, 1.1 eq) before acetonitrile (5 ml) and 2-phenylpyridine (430 \(\mu\)l, 3.0 mmol, 1.0 eq) were added. The vial was sealed and heated to 100 °C for 24 hours before being diluted, the solvent evacuated and then purified by column chromatography giving the product as a yellow oil (360 mg, 51%).

\(^1H\) NMR (400 MHz, CDCl$_3$): \(\delta\) 8.72 (ddd, \(J = 4.9, 1.8, 1.0\) Hz, 1H), 7.77 (app td, \(J = 7.6, 1.8\) Hz, 1H), 7.68 (dd, \(J = 8.0, 1.2\) Hz, 1H), 7.61 (app dt, \(J = 8.0, 1.1\) Hz, 1H), 7.54 (dd, \(J = 7.6, 1.8\) Hz, 1H), 7.41 (td, \(J = 7.6, 1.2\) Hz, 1H), 7.31 (ddd, \(J = 7.6, 4.9, 1.2\) Hz, 1H), 7.26 (m, 1H); \(^{13}C\) NMR (100 MHz, CDCl$_3$): \(\delta\) 158.4, 149.5, 141.3, 136.0, 133.4, 131.5, 129.9, 127.7, 124.9, 122.6, 121.9.

13aa, 2-(phenyl-2-\textit{d})pyridine\textsuperscript{148}

\[ \text{\includegraphics[width=0.2\textwidth]{image}} \]

A solution of 2-(2-bromophenyl)pyridine (339 mg, 1.45 mmol, 1.0 eq) in THF (20 ml) was cooled to -40 °C before \(n\)-butyl lithium (1.81 ml, 1.6 M solution in hexanes, 2.0 eq) was added dropwise. After stirring for 30 minutes at this temperature, D$_2$O was added dropwise and the reaction mixture was allowed to warm to room temperature over the course of 45 minutes. Ethyl acetate (25 ml) was added and the mixture was transferred to a separating funnel. After addition of brine (25 ml), the layers were separated; the organic layer was dried over anhydrous MgSO$_4$ and
concentrated. Purification by column chromatography gave the product as a yellow oil (78.2 mg, 35%).

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\): \delta 8.70 (m, 1H), 8.00 (dd, J = 8.3, 1.4 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.53 – 7.45 (m, 2H), 7.46 – 7.39 (m, 1H), 7.23 (ddd, J = 6.2, 4.9, 2.3 Hz, 1H); \[^1\text{C} \text{NMR (100 MHz, CDCl}_3\): \delta 157.5, 149.8, 139.4, 136.9, 129.0, 128.9, 128.7, 127.0, 126.7 (t, J = 24.5 Hz), 122.2, 120.7.\]

**239, pivaloyl-L-valine**

\[
\begin{align*}
\text{O} & \quad \text{N} \\
& \quad \text{CO}_2\text{H}
\end{align*}
\]

Sodium hydroxide (4.0 g, 100 mmol, 2.9 eq) was dissolved in distilled water (100 ml) and cooled to 0 °C. L-valine (4.1 g, 35 mmol, 1.0 eq) was added before a solution of pivaloyl chloride (5.6 ml, 45.5 mmol, 1.3 eq) in 1,4 dioxane (40 ml) was added dropwise. After stirring overnight at room temperature, the solution was extracted with diethyl ether (3 x 50 ml) and the organic layers discarded. The aqueous layer was cooled once again to 0 °C and concentrated HCl was added dropwise until the pH had reached 2. Extraction with diethyl ether (3 x 100 ml) and subsequent drying of the combined organic layers over MgSO\(_4\) was followed by concentration *in vacuo*. After drying under high vacuum for six hours, the product was obtained as a white solid (6.49 g, 91%).

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\): \delta 9.40 (s, 1H), 6.23 (d, J = 8.4 Hz, 1H), 4.56 (dd, J = 8.5, 4.7 Hz, 1H), 2.24 (m, 1H), 1.23 (s, 9H), 0.97 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); \[^1\text{C} \text{NMR (100 MHz, CDCl}_3\): \delta 179.3, 176.0, 57.0, 39.1, 31.2, 27.6, 19.1, 17.8.\]
To a schlenk tube charged with [RuCl$_2$(p-cymene)$_2$] (919 mg, 1.5 mmol, 1.0 eq) and potassium acetate (442 mg, 4.5 mmol, 3.0 eq) was added acetonitrile (12 ml) followed by 2-phenylpyridine (430 µl, 3.0 mmol, 2.0 eq). The reaction was stirred at room temperature for 24 hours before being purified through neutral alumina (50:50 to 0:100, hexane/ethyl acetate). After solvent removal, the ruthenacycle was obtained as red-orange solid (868 mg, 68%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.23 (ddd, $J = 5.7, 1.5, 0.8$ Hz, 1H), 8.16 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.71 (ddd, $J = 8.3, 1.6, 0.8$ Hz, 1H), 7.69 – 7.63 (m, 1H), 7.61 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.18 (app td, $J = 7.4, 1.4$ Hz, 1H), 7.08 – 7.00 (m, 2H), 5.58 (dd, $J = 5.9, 1.2$ Hz, 1H), 5.56 (dd, $J = 5.9, 1.2$ Hz, 1H), 5.17 (dd, $J = 5.9, 1.2$ Hz, 1H), 4.99 (dd, $J = 5.9, 1.2$ Hz, 1H), 2.43 (hept, $J = 6.9$ Hz, 1H), 2.04 (s, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 181.5 (C$q_{Ar}$), 165.4 (C$q_{Ar}$), 154.7 (CH$_{Ar}$), 143.4 (C$q_{Ar}$), 139.7 (CH$_{Ar}$), 136.7 (CH$_{Ar}$), 129.6 (CH$_{Ar}$), 124.0 (CH$_{Ar}$), 122.6 (CH$_{Ar}$), 121.5 (CH$_{Ar}$), 118.9 (CH$_{Ar}$), 100.7 (C$q_{6^-Ar}$), 100.6 (C$q_{6^-Ar}$), 90.8 (CH$_{q6^-Ar}$), 89.7 (CH$_{q6^-Ar}$), 84.2 (CH$_{q6^-Ar}$), 82.3 (CH$_{q6^-Ar}$), 30.9 (CH), 22.7 (CH$_3$), 21.8 (CH$_3$), 18.9 (CH$_3$).

Iodine monochloride was weighed into a flask before dichloromethane was added. This was added dropwise to an equimolar amount of 1,4-dioxane in the same amount of dichloromethane. After stirring at room temperature, most of the solvent was blown off using nitrogen yielding a bright orange solid which was further dried under
vacuum. Elemental analysis confirmed that the sample was a 2:1 mixture of ICl to 1,4 dioxane: Elemental calculated C 11.64, H 1.95, Cl 17.17, I 61.48; found C 11.76, H 2.04, Cl approx. 17, I approx. 57 (halides are difficult to separate hence the approximate values given).
4.3 Products from ruthenium catalysed reactions

**General procedure B**

A schlenk tube was charged with [RuCl₂(p-cymene)]₂ (15.3 mg, 0.025 mmol, 5 mol%), potassium carbonate (138 mg, 1.0 mmol, 2.0 eq), MesCO₂H (24.6 mg, 0.15 mmol, 0.3 eq) and TBATB (723 mg, 1.5 mmol, 3.0 eq) before being evacuated and then back-filled with nitrogen three times. Dry 1,4-dioxane (2 ml) was added and then 2-phenylpyridine (72 μl, 0.5 mmol, 1.0 eq) in dioxane (1 ml) before the flask was sealed and the reaction mixture heated to 110 ºC for 20 hours. After cooling, sodium thiosulphate (~20 ml, 10 wt%) was added before extracting the aqueous layer with EtOAc (x3). The combined organic layers were washed with brine and then dried over MgSO₄. After concentration *in vacuo*, the crude reaction mixture was purified by flash column chromatography (typically ethyl acetate:hexane (2:98 to 10:90) although dichloromethane:hexane mixtures were used in some cases where separation from starting material was much clearer).

### 77a, 2-(3-bromophenyl)pyridine

![Structure](image)

Synthesised according to general procedure B. Yellow oil, average of three yields: 76%.

**¹H NMR** (400 MHz, CDCl₃): δ 8.72 (d, J = 4.8 Hz, 1H), 8.20 (app t, J = 1.5 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.79 (app td, J = 7.5, 1.5 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.36 (app t, J = 8.0 Hz, 1H), 7.30 – 7.26 (m, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 156.0 (C₉Ar), 149.9 (CH₉Ar), 141.5 (C₇Ar), 137.0 (CH₇Ar), 132.0 (CH₇Ar), 130.4 (CH₉Ar), 130.2 (CH₇Ar), 125.5 (CH₇Ar), 123.2 (C₉Ar), 122.8 (CH₉Ar), 120.7 (CH₇Ar);

**LRMS (EI):** 235 (C₁₁H₈N⁸⁺Br; 86%), 233 (C₁₁H₈N⁷⁺Br; 88%), 154 (C₁₁H₈N; 100%); **HRMS (EI):** calculated for C₁₁H₈N⁷⁺Br, theoretical 232.9835, measured 232.9831.
77b, 2-(3-bromo-4-methylphenyl)pyridine

\[
\begin{align*}
&\text{Synthesised according to general procedure B. Yellow oil, average of two yields: 86%;} \\
&\text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): } \delta 8.68 (d, J = 4.7 \text{ Hz}, 1\text{H}), 8.20 (d, J = 1.4 \text{ Hz}, 1\text{H}), 7.83 (dd, J = 7.9, 1.4 \text{ Hz}, 1\text{H}), 7.76 - 7.72 (m, 1\text{H}), 7.68 (d, J = 7.9 \text{ Hz}, 1\text{H}), 7.32 (d, J = 8.0 \text{ Hz}, 1\text{H}), 7.25 - 7.22 (m, 1\text{H}), 2.45 (s, 3\text{H}); \\
&\text{\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): } \delta 156.0 (C\textsubscript{q}Ar), 149.8 (CH\textsubscript{Ar}), 138.9 (C\textsubscript{q}Ar), 138.8 (C\textsubscript{q}Ar), 137.0 (CH\textsubscript{Ar}), 131.2 (CH\textsubscript{Ar}), 130.8 (CH\textsubscript{Ar}), 125.7 (CH\textsubscript{Ar}), 125.6 (C\textsubscript{q}Ar), 122.5 (CH\textsubscript{Ar}), 120.4 (CH\textsubscript{Ar}), 22.9 (CH\textsubscript{3}); \\
&\text{LRMS (EI): } 249 (C\textsubscript{12}H\textsubscript{10}N\textsuperscript{81}Br; 97\%), 247 (C\textsubscript{12}H\textsubscript{10}N\textsuperscript{79}Br; 100\%), 168 (C\textsubscript{12}H\textsubscript{10}N; 86\%); HRMS (EI): calculated for C\textsubscript{12}H\textsubscript{10}N\textsuperscript{79}Br, theoretical 246.9991, measured 246.9993.
\end{align*}
\]

77c, N-(2-bromo-4-(pyridin-2-yl)phenyl)acetamide

\[
\begin{align*}
&\text{Synthesised according to general procedure B. Off-white solid, 143.1 mg, 98%;} \\
&\text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): } \delta 8.67 (m, 1\text{H}), 8.48 (d, J = 8.6 \text{ Hz}, 1\text{H}), 8.30 (d, J = 2.1 \text{ Hz}, 1\text{H}), 7.90 (dd, J = 8.6, 2.1 \text{ Hz}, 1\text{H}), 7.74 (m, 1\text{H}), 7.72 (br s, 1\text{H}), 7.69 (m, 1\text{H}), 7.74 (m, 1\text{H}), 2.27 (s, 3\text{H}); \\
&\text{\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): } 168.4 (C=O), 155.3 (C\textsubscript{q}Ar), 149.8 (CH\textsubscript{Ar}), 137.0 (CH\textsubscript{Ar}), 136.3 (C\textsubscript{q}Ar), 136.2 (C\textsubscript{q}Ar), 130.7 (CH\textsubscript{Ar}), 126.7 (CH\textsubscript{Ar}), 122.5 (CH\textsubscript{Ar}), 121.6 (CH\textsubscript{Ar}), 120.3 (CH\textsubscript{Ar}), 113.7 (C\textsubscript{q}Ar), 25.1 (CH\textsubscript{3}).
\end{align*}
\]
LRMS (EI): 292 (C_{13}H_{11}^{81}BrN_{2}O; 25%), 290 (C_{13}H_{11}^{79}BrN_{2}O; 25%), 249 (C_{11}H_{8}^{81}BrN_{2}; 100%), 247 (C_{11}H_{8}^{79}BrN_{2}; 100%), 211 (C_{13}H_{11}N_{2}O); 75%; HRMS (EI): calculated for C_{13}H_{11}^{79}BrN_{2}O, theoretical 290.0049, measured 290.0047;

m.p. 132 – 135 °C.

**77d, 2-(3-bromo-4-(tert-butyl)phenyl)pyridine**

![Chemical structure of 77d](image)

Synthesised according to general procedure B. Yellow oil, 47.0 mg, 32%;

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.71 – 8.69 (m, 1H), 7.75 (app td, J = 7.7, 1.8 Hz, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.61 (app dt, J = 7.9, 1.0 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.42 (dd, J = 8.1, 1.8 Hz, 1H), 7.29 – 7.26 (m, 1H), 1.34 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 158.4 (C$_{q\text{Ar}}$), 153.5 (C$_{q\text{Ar}}$), 149.4 (CH$_{\text{Ar}}$), 138.3 (C$_{q\text{Ar}}$), 135.9 (CH$_{\text{Ar}}$), 131.2 (CH$_{\text{Ar}}$), 130.4 (CH$_{\text{Ar}}$), 124.9 (CH$_{\text{Ar}}$), 124.9 (CH$_{\text{Ar}}$), 122.4 (CH$_{\text{Ar}}$), 121.7 (C$_{q\text{Ar}}$), 34.9 (C(CH$_3$)$_3$), 31.3(C(CH$_3$)$_3$);

LRMS (EI): 291 (C$_{15}$H$_{16}$N$^{81}$Br, 93%), 289 (C$_{15}$H$_{16}$N$^{79}$Br, 100%); HRMS (EI): calculated for C$_{15}$H$_{16}$N$^{79}$Br, theoretical 289.0461, measured 289.0451.

**77e, 2-(3-bromo-4-fluorophenyl)pyridine**

![Chemical structure of 77e](image)

Synthesised according to general procedure B. White solid, 102.0 mg, 81%;
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.68 (d, $J = 4.4$ Hz, 1H), 8.24 (dd, $J = 6.7$, 2.1 Hz, 1H), 7.92 – 7.88 (m, 1H), 7.78 – 7.74 (m, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.27 – 7.24 (m, 1H), 7.21 (app t, $J = 8.4$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.8 (d, $J_{C-F} = 249.6$ Hz, C$_{qAr}$), 155.1 (C$_{qAr}$), 149.9 (CH$_{Ar}$), 137.1 (CH$_{Ar}$), 137.0 (d, $J_{C-F} = 3.7$ Hz, C$_{qAr}$), 132.3 (CH$_{Ar}$), 127.5 (d, $J_{C-F} = 7.6$ Hz, CH$_{Ar}$), 122.7 (CH$_{Ar}$), 120.4 (CH$_{Ar}$), 116.8 (d, $J = 22.5$ Hz, CH$_{Ar}$), 109.7 (d, $J = 21.3$ Hz, C$_{qAr}$); $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -104.22 – -110.57 (m);

LRMS (EI): 251 (C$_{11}$H$_7$N$_7$9BrF, 90%), 249 (C$_{11}$H$_7$N$_7$9BrF, 100%); HRMS (APCI+): calculated for C$_{11}$H$_8$N$^{79}$BrF (M + H$^+$), theoretical 251.9824, measured 251.9835;

m.p. 47 – 49 ºC.

77f, 2-bromo-4-(pyridin-2-yl)benzaldehyde

\[
\begin{align*}
\text{Synthesised according to general procedure B. Off-white solid, 36.7 mg, 28%;} \\

^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.41 (s, 1H), 8.76 – 8.70 (m, 1H), 8.37 (d, $J = 1.4$ Hz, 1H), 8.07 – 7.97 (m, 2H), 7.86 – 7.73 (m, 2H), 7.34 (ddd, $J = 6.7$, 4.8, 1.7 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 191.8 (CHO), 154.5 (C$_{qAr}$), 150.3 (CH$_{Ar}$), 146.0 (C$_{qAr}$), 137.3 (CH$_{Ar}$), 133.4 (C$_{qAr}$), 132.4 (CH$_{Ar}$), 130.3 (CH$_{Ar}$), 127.8 (C$_{qAr}$), 126.2 (CH$_{Ar}$), 123.8 (CH$_{Ar}$), 121.4 (CH$_{Ar}$);

LRMS (APCI+): 264 (C$_{12}$H$_9$NO$^{81}$Br, 100%), 262 (C$_{12}$H$_9$NO$^{79}$Br, 100%); HRMS (APCI+): calculated for C$_{12}$H$_9$NO$^{79}$Br (M + H$^+$), theoretical 261.9868, measured 261.9863;

m.p. 95 – 97 ºC.
77g, 2-(3-bromo-4-chlorophenyl)pyridine

Synthesised according to general procedure B. Off-white solid, 79.0 mg, 59%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.69 (d, $J = 4.3$ Hz, 1H), 8.29 (d, $J = 2.1$ Hz, 1H), 7.87 (dd, $J = 8.3$, 2.1 Hz, 1H), 7.79 – 7.74 (m, 1H), 7.69 – 7.67 (m, 1H), 7.53 (d, $J = 8.3$ Hz, 1H), 7.28 – 7.25 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.9 (C$_{q}$Ar), 150.0 (CH$_{Ar}$), 139.4 (C$_{q}$Ar), 137.2 (CH$_{Ar}$), 135.2 (C$_{q}$Ar), 132.2 (CH$_{Ar}$), 130.6 (CH$_{Ar}$), 126.8 (CH$_{Ar}$), 123.1 (C$_{q}$Ar), 123.0 (CH$_{Ar}$), 120.5 (CH$_{Ar}$); LRMS (EI): 270.9 (C$_{11}$H$_7^{78}$Cl$_{81}$BrN; 24%), 268.9 (C$_{11}$H$_7^{75}$Cl$_{81}$BrN + C$_{11}$H$_7^{78}$Cl$_{79}$BrN; 96%), 266.9 (C$_{11}$H$_7^{75}$Cl$_{79}$BrN; 74%), 190.0 (C$_{11}$H$_7^{77}$ClN; 32%), 188.0 (C$_{11}$H$_7^{75}$ClN; 32%); HRMS (EI): calculated for C$_{11}$H$_7^{75}$Cl$_{79}$BrN, theoretical 266.9445, measured 266.9455; m.p. 60 – 62 ºC.

77h, 2-(3-bromophenyl)-4-methylpyridine

Synthesised according to general procedure B. Yellow oil, 98.0 mg, 79%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.54 (dd, $J = 5.0$, 0.8 Hz, 1H), 8.15 (app t, $J = 1.9$ Hz, 1H), 7.88 (app dt, $J = 7.9$, 1.4 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.33 (app t, $J = 7.9$ Hz, 1H), 7.12 – 7.06 (m, 1H), 2.42 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.8
(CqAr), 149.6 (CHAr), 148.1 (CqAr), 141.6 (CqAr), 131.8 (CHAr), 130.3 (CHAr), 130.1 (CHAr), 125.5 (CHAr), 123.8 (CHAr), 123.1 (CqAr), 121.7 (CHAr), 21.4 (CH3);

LRMS (APCI+): 250 (C12H11N79Br; 94%), 248 (C12H11N79Br; 100%); HRMS (APCI+): calculated for C12H11N79Br (M + H+), theoretical 248.0075, measured 248.0083.

77i, 2-(3-bromophenyl)-5-methylpyridine

![Chemical structure of 2-(3-bromophenyl)-5-methylpyridine]

Synthesised according to general procedure B. Yellow oil, 90.6 mg, 73%;

1H NMR (400 MHz, CDCl3): δ 8.52 (m, 1H), 8.14 (app t, J = 1.8 Hz, 1H), 7.88 (m, 1H), 7.60 (dd, J = 8.1, 1.0 Hz, 1H), 7.56 (m, 1H), 7.51 (m, 1H), 7.32 (app t, J = 8.0 Hz, 1H), 2.38 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 153.3 (CqAr), 150.4 (CHAr), 141.6 (CqAr), 137.6 (CHAr), 132.5 (CqAr), 131.6 (CHAr), 130.3 (CHAr), 129.9 (CHAr), 125.3 (CHAr), 123.2 (CqAr), 120.2 (CHAr), 18.4 (CH3);

LRMS (EI): 249 (C12H10N81Br; 97%), 247 (C12H10N79Br; 100%), 168 (C12H10N, 86%); HRMS (EI): calculated for C12H10N79Br, theoretical 246.9991, measured 246.9986.

77j, 7-bromobenzo[h]quinolone

![Chemical structure of 7-bromobenzo[h]quinolone]

Synthesised according to general procedure B. Off-white solid, 67.4 mg, 52%;
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.34 – 9.30 (m, 1H), 9.02 (dd, \(J = 4.3, 1.8\) Hz, 1H), 8.24 (d, \(J = 9.1\) Hz, 1H), 8.18 (dd, \(J = 8.0, 1.8\) Hz, 1H), 7.97 (dd, \(J = 7.5, 1.2\) Hz, 1H), 7.76 (d, \(J = 9.1\) Hz, 1H), 7.60 – 7.52 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 149.5 (CH\(_{Ar}\)), 146.1 (C\(_{qAr}\)), 136.1 (CH\(_{Ar}\)), 133.3 (C\(_{qAr}\)), 132.4 (CH\(_{Ar}\)), 132.2 (C\(_{qAr}\)), 127.6 (CH\(_{Ar}\)), 126.9 (CH\(_{Ar}\)), 126.3 (CH\(_{Ar}\)), 126.2 (C\(_{qAr}\)), 124.3 (CH\(_{Ar}\)), 122.9 (C\(_{qAr}\)), 122.5 (CH\(_{Ar}\));

LRMS (EI): 259 (C\(_{13}\)H\(_8\)N\(_{81}\)Br; 93%), 257 (C\(_{13}\)H\(_8\)N\(_{79}\)Br; 94%), 178 (C\(_{13}\)H\(_8\)N; 100%);
HRMS (EI): calculated for C\(_{13}\)H\(_8\)N\(_{79}\)Br, theoretical 256.9835, measured 256.9830;

m.p. 84 – 86 °C.

**77w, 2,4-dibromo-6-(pyridin-2-yl)phenol**

\[
\begin{array}{c}
\text{Br} \\
\text{Br}
\end{array}
\]

Synthesised according to general procedure B with 2-(2-methoxyphenyl)pyridine as starting material. Bright yellow solid, 82.4 mg, 50%.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 15.58 (s, 1H), 8.50 (\text{app dt}, \(J = 5.3, 1.3\) Hz, 1H), 7.93 – 7.85 (m, 2H), 7.84 (d, \(J = 2.3\) Hz, 1H), 7.67 (d, \(J = 2.3\) Hz, 1H), 7.33 (ddd, \(J = 6.7, 5.0, 1.9\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 156.2 (C\(_{qAr}\)), 155.6 (C\(_{qAr}\)), 145.7 (CH\(_{Ar}\)), 138.5 (CH\(_{Ar}\)), 136.7 (CH\(_{Ar}\)), 128.0 (CH\(_{Ar}\)), 122.8 (CH\(_{Ar}\)), 120.8 (C\(_{qAr}\)), 119.5 (CH\(_{Ar}\)), 113.5 (C\(_{qAr}\)), 110.2 (C\(_{qAr}\)).

LRMS (EI): 331 (C\(_{11}\)H\(_7\)NO\(_{81}\)Br\(_2\); 48%), 329 (C\(_{11}\)H\(_7\)NO\(_{81}\)Br\(_{79}\)Br; 100%), 327 (C\(_{11}\)H\(_7\)NO\(_{79}\)Br\(_2\); 52%); HRMS (APCI+): calculated for C\(_{11}\)H\(_8\)N\(_{79}\)Br\(_2\) (M + H\(^+\)), theoretical 327.8967, measured 327.8963.

m.p. 119 – 121 °C.
One-pot bromination-Suzuki-Miuara reactions: general procedure C

A schlenk tube was charged with [RuCl₂(p-cymene)]₂ (15.3 mg, 0.025 mmol, 5 mol%), potassium carbonate (276 mg, 2.0 mmol, 4.0 eq), MesCO₂H (24.6 mg, 0.15 mmol, 0.3 eq) and TBATB (723 mg, 1.5 mmol, 3.0 eq) before being evacuated and then back-filled with nitrogen three times. Dry 1,4-dioxane (2 ml) was added and then 2-phenylpyridine (71.5 μl, 0.5 mmol, 1.0 eq) in dioxane (1 ml) before the flask was sealed and the reaction mixture heated to 110 ºC for 20 hours. After cooling, water (1 ml), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 3 mol%), PPh₃ (7.9 mg, 0.03 mmol, 6 mol%) and the boronic acid (1.5 mmol, 3.0 eq) were added under a stream of nitrogen. After resealing the vial and heating at 110 ºC for 15 hours, the reaction mixture was allowed to cool and sodium thiosulphate (~20 ml, 10 wt%) was added. The reaction mixture was then extracted with EtOAc (x3). The combined organic layers were washed with brine and then dried over MgSO₄. After concentration in vacuo, the crude reaction mixture was purified by flash column chromatography (typically ethyl acetate:hexane (4:96 to 20:80)).

154a, 2-(4'-methoxy-[1,1'-biphenyl]-3-yl)pyridine

![Structural formula of 154a](image)

Synthesised according to general procedure C. Yellow solid, 75.5 mg, 58%;

¹H NMR (400 MHz, CDCl₃): 8.75 – 8.70 (m, 1H), 8.21 (app t, J = 1.9 Hz, 1H), 7.92 (dd, J = 7.6, 1.8, 1.2 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.65 – 7.59 (m, 3H), 7.53 (app t, J = 7.7 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.03 – 6.96 (m, 2H), 3.86 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 159.4 (C₁₃Ar), 157.7 (C₂₁Ar), 149.8 (C₂₃Ar), 141.5 (C₂₄Ar), 140.0 (C₁₁Ar), 136.9 (CH₁₃), 133.7 (C₁₂Ar), 129.3 (CH₁₃Ar), 128.4 (CH₂₄Ar), 127.5 (CH₂₃Ar), 125.6 (CH₁₄Ar), 125.4 (CH₁₃Ar), 122.3 (CH₁₂Ar), 120.9 (CH₁₄Ar), 114.3 (CH₁₃Ar), 55.5 (CH₃);
HRMS (APCI+) calculated for C$_{18}$H$_{16}$NO (M + H$^+$), theoretical 262.1232, measured 262.1237;

m.p. 65 – 67 °C.

154b, 2-((4'-chloro-[1,1'-biphenyl]-3-yl)pyridine

Synthesised according to general procedure C. Yellow oil, 91.2 mg, 69%;

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.76 – 8.69 (m, 1H), 8.21 (app t, J = 1.7 Hz, 1H), 7.96 (dd, J = 7.7, 1.5 Hz, 1H), 7.79 (d, J = 4.1 Hz, 2H), 7.63 – 7.58 (m, 3H), 7.55 (app t, J = 7.7 Hz, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.29 – 7.24 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 157.2 (C$_q$Ar), 149.8 (CH$_q$Ar), 140.6 (C$_q$Ar), 140.1 (C$_q$Ar), 139.5 (C$_q$Ar), 136.9 (CH$_q$Ar), 133.6 (C$_q$Ar), 129.4 (CH$_q$Ar), 129.0 (CH$_q$Ar), 128.6 (CH$_q$Ar), 127.6 (CH$_q$Ar), 126.2 (CH$_q$Ar), 125.7 (CH$_q$Ar), 122.5 (CH$_q$Ar), 120.8 (CH$_q$Ar);

HRMS (APCI+): calculated for C$_{17}$H$_{13}$NCl (M + H$^+$), theoretical 266.0737, measured 266.0736.

154c, 2-((1,1'-biphenyl)-3-yl)pyridine$^{184}$

Synthesised according to general procedure C. Yellow oil, 68.7 mg, 59%;
$^1$H NMR (500 MHz, CDCl$_3$): δ 8.75 – 8.70 (m, 1H), 8.25 (app t, $J = 1.7$ Hz, 1H), 7.99 – 7.95 (m, 1H), 7.81 – 7.75 (m, 2H), 7.71 – 7.68 (m, 2H), 7.67 – 7.64 (m, 1H), 7.56 (app t, $J = 7.7$ Hz, 1H), 7.47 (app t, $J = 7.7$ Hz, 2H), 7.38 (tt, $J = 7.2$, 1.4 Hz, 1H), 7.27 – 7.23 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 157.5 (C$q_{Ar}$), 149.8 (CH$_{Ar}$), 141.9 (C$q_{Ar}$), 141.2 (C$q_{Ar}$), 140.0 (C$q_{Ar}$), 136.9 (CH$_{Ar}$), 129.3 (CH$_{Ar}$), 128.9 (CH$_{Ar}$), 127.9 (CH$_{Ar}$), 127.5 (CH$_{Ar}$), 127.4 (CH$_{Ar}$), 126.0 (CH$_{Ar}$), 126.0 (CH$_{Ar}$), 122.4 (CH$_{Ar}$), 120.8 (CH$_{Ar}$);

HRMS (APCI+), calculated for C$_{17}$H$_{14}$N (M + H$^+$), theoretical 232.1126, measured 232.1120.

154d, 2-(2'-methyl-[1,1'-biphenyl]-3-yl)pyridine

![Pyridine structure]

Synthesised according to general procedure C. Yellow oil, 84.1 mg, 69%;

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.73 – 8.68 (m, 1H), 7.99 (ddd, $J = 7.8$, 1.9, 1.2 Hz, 1H), 7.95 (app t, $J = 1.7$ Hz, 1H), 7.78 – 7.72 (m, 2H), 7.53 (app t, $J = 7.7$ Hz, 1H), 7.39 (app dt, $J = 7.6$, 1.4 Hz, 1H), 7.31 – 7.22 (m, 5H), 2.29 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 157.5, 149.8 (CH$_{Ar}$), 142.5 (C$q_{Ar}$), 141.8 (C$q_{Ar}$), 139.4 (C$q_{Ar}$), 136.9 (CH$_{Ar}$), 135.5 (C$q_{Ar}$), 130.4 (CH$_{Ar}$), 129.9 (CH$_{Ar}$), 129.9 (CH$_{Ar}$), 128.6 (CH$_{Ar}$), 127.9 (CH$_{Ar}$), 127.5 (CH$_{Ar}$), 125.9 (CH$_{Ar}$), 125.5 (CH$_{Ar}$), 122.3 (CH$_{Ar}$), 120.8 (CH$_{Ar}$), 20.7 (CH);

HRMS (APCI+): calculated for C$_{18}$H$_{16}$N (M + H$^+$), theoretical 246.1283, measured 246.1278.
154e, 2-(3′-methyl-[1,1′-biphenyl]-3-yl)pyridine

Synthesised according to general procedure C. Yellow oil, 50.8 mg, 41%;

$^1$H NMR (500 MHz, CDCl$_3$): 8.77 – 8.69 (m, 1H), 8.22 (app t, $J = 1.8$ Hz, 1H), 8.02 – 7.88 (m, 1H), 7.82 – 7.75 (m, 2H), 7.68 – 7.62 (m, 1H), 7.55 (app t, $J = 7.7$ Hz, 1H), 7.52 – 7.46 (m, 2H), 7.36 (app t, $J = 7.6$ Hz, 1H), 7.28 – 7.24 (m, 1H), 7.21 – 7.17 (m, 1H), 2.44 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 157.6 (C$_{Ar}$), 149.8 (CH$_{Ar}$), 142.0 (C$_{Ar}$), 141.2 (C$_{Ar}$), 140.0 (C$_{Ar}$), 138.5 (C$_{Ar}$), 137.0 (CH), 129.3 (CH$_{Ar}$), 128.8 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 128.2 (CH$_{Ar}$), 127.9 (CH$_{Ar}$), 126.0 (CH$_{Ar}$), 125.9 (CH$_{Ar}$), 124.5 (CH$_{Ar}$), 122.4 (CH$_{Ar}$), 120.9 (CH$_{Ar}$), 21.7 (CH$_3$);

HRMS (APCI+) calculated for C$_{18}$H$_{15}$N (M + H$^+$), theoretical 246.1283, measured 246.1271.

154f, 2-(3-(1H-pyrrol-2-yl)phenyl)pyridine

Synthesised according to general procedure C. Brown oil, 70.6 mg, 64%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.93 (br s, 1H), 8.76 – 8.64 (m, 1H), 8.14 (app t, $J = 1.8$ Hz, 1H), 7.79 – 7.71 (m, 3H), 7.55 (app dt, $J = 8.0$, 1.4 Hz, 1H), 7.44 (app t, $J = 7.7$ Hz, 1H), 7.29 – 7.23 (m, 1H), 6.88 – 6.84 (m, 1H), 6.63 – 6.58 (m, 1H), 6.34 – 6.30 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.4 (C$_{Ar}$), 149.7 (CH$_{Ar}$), 139.9 (C$_{Ar}$), 137.1 (CH$_{Ar}$), 133.4 (C$_{Ar}$), 132.0 (C$_{Ar}$), 129.4 (CH$_{Ar}$), 124.8 (CH$_{Ar}$), 124.7
(CH₃), 122.5 (CH₃), 122.3 (CH₃), 120.9 (CH₂), 119.2 (CH₂), 110.1 (CH₂), 106.4 (CH₂);

HRMS (APCI+): calculated for C₁₅H₁₅N₂ (M + H⁺), theoretical 221.1079, measured 221.1077.

**One-pot bromination-Heck reactions: general procedure D**

A schlenk tube was charged with [RuCl₂(p-cymene)]₂ (15.3 mg, 0.025 mmol, 5 mol%), potassium carbonate (276 mg, 2.0 mmol, 4.0 eq), MesCO₂H (24.6 mg, 0.15 mmol, 0.3 eq) and TBATB (723 mg, 1.5 mmol, 3.0 eq) before being evacuated and then back-filled with nitrogen three times. Dry 1,4-dioxane (2 ml) was added and then 2-phenylpyridine (71.5 μl, 0.5 mmol, 1.0 eq) in dioxane (1 ml) before the flask was sealed and the reaction mixture heated to 110 ºC for 20 hours. After cooling, Pd(OAc)₂ (3.4 mg, 0.015 mmol, 3 mol%) and the olefin (1.5 mmol, 3.0 eq) were added under a stream of nitrogen. After resealing the vial and heating at 110 ºC for 15 hours, the reaction mixture was allowed to cool and sodium thiosulphate (~20 ml, 10 wt%) was added. The reaction mixture was then extracted with EtOAc (x3). The combined organic layers were washed with brine and then dried over MgSO₄. After concentration *in vacuo*, the crude reaction mixture was purified by flash column chromatography (typically ethyl acetate:hexane (4:96 to 20:80))

**155a, ethyl (E)-3-(3-(pyridin-2-yl)phenyl)acrylate**

Synthesised according to general procedure D with ethyl acrylate as the olefin. Compounds **155a** and **155aa** were both isolated.

![Chemical Structure](image)

Yellow solid, 71.4 mg, 56%;
$^1$H NMR (400 MHz, CDCl$_3$): δ 8.74 – 8.67 (m, 1H), 8.18 (app t, $J = 1.8$ Hz, 1H), 8.00 – 7.97 (m, 1H), 7.80 – 7.71 (m, 3H), 7.57 (app dt, $J = 7.8$, 1.5 Hz, 1H), 7.49 (app t, $J = 7.7$ Hz, 1H), 7.28 – 7.24 (m, 1H), 6.55 (d, $J = 16.0$ Hz, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 1.34 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 167.0 (C=O), 156.6 (C$q_{Ar}$), 149.8 (CH$_{Ar}$), 144.4 (CH), 140.1 (C$q_{Ar}$), 136.9 (CH$_{Ar}$), 135.0 (C$q_{Ar}$), 129.3 (CH$_{Ar}$), 128.6 (C$q_{Ar}$), 128.5 (CH$_{Ar}$), 126.7 (CH$_{Ar}$), 122.6 (CH$_{Ar}$), 120.6 (CH$_{Ar}$), 118.8 (CH), 60.6 (CH$_2$), 14.4 (CH$_3$); HRMS (EI): calculated for C$_{16}$H$_{15}$NO$_2$, theoretical 253.1097, measured 253.1101;

m.p. 63 – 65 °C.

155aa, ethyl (E)-3-(4-(3-ethoxy-3-oxopropyl)-3-(pyridin-2-yl)phenyl)acrylate

Yellow oil, 30.8 mg, 17%;

$^1$H NMR (400 MHz, CDCl$_3$): 8.71 – 8.66 (m, 1H), 7.79 (app td, $J = 7.7$, 1.8 Hz, 1H), 7.69 (d, $J = 16.0$ Hz, 1H), 7.54 – 7.47 (m, 2H), 7.41 (app dt, $J = 7.8$, 1.0 Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.29 (ddd, $J = 7.6$, 4.9, 1.1 Hz, 1H), 6.44 (d, $J = 16.0$ Hz, 1H), 4.25 (q, $J = 7.1$ Hz, 2H), 4.06 (q, $J = 7.1$ Hz, 2H), 3.08 – 3.01 (m, 2H), 2.55 – 2.49 (m, 2H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.19 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 172.9 (CO$_2$Et), 167.1 (CO$_2$Et), 159.2 (C$q_{Ar}$), 149.4 (CH$_{Ar}$), 144.1 (CH), 141.3 (C$q_{Ar}$), 141.1 (C$q_{Ar}$), 136.7 (CH$_{Ar}$), 132.9 (C$q_{Ar}$), 130.5 (CH$_{Ar}$), 129.8 (CH$_{Ar}$), 128.1 (CH$_{Ar}$), 124.0 (CH$_{Ar}$), 122.3 (CH$_{Ar}$), 118.3 (CH), 60.6 (CH$_2$), 60.5 (CH$_2$), 35.5 (CH$_2$), 28.5 (CH$_2$), 14.4 (CH$_3$), 14.3 (CH$_3$).

HRMS (APCI+): calculated for C$_{21}$H$_{24}$NO$_4$ (M + H$^+$), theoretical 354.1700, measured 354.1694.
155b, 4-(3-(pyridin-2-yl)phenyl)butan-2-one

Synthesised according to general procedure D. Yellow oil, 61.7 mg, 55%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.70 (dd, $J = 4.7$, 1.5 Hz, 1H), 7.86 (app t, $J = 1.8$ Hz, 1H), 7.81 – 7.68 (m, 3H), 7.39 (app t, $J = 7.7$ Hz, 1H), 7.29 – 7.21 (m, 2H), 2.99 (t, $J = 7.6$ Hz, 2H), 2.83 (t, $J = 7.6$ Hz, 2H), 2.16 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 208.1 (C=O), 157.5 (C$_{qAr}$), 149.7 (CH$_{Ar}$), 141.7 (C$_{qAr}$), 139.7 (C$_{qAr}$), 137.0 (CH$_{Ar}$), 129.2 (CH$_{Ar}$), 129.1 (CH$_{Ar}$), 127.0 (CH$_{Ar}$), 124.9 (CH$_{Ar}$), 122.3 (CH$_{Ar}$), 120.9 (CH$_{Ar}$), 45.4 (CH$_2$), 30.3 (CH$_3$), 29.9 (CH$_2$);

HRMS (APCI+): calculated for C$_{15}$H$_{16}$NO (M + H$^+$), theoretical 226.1232, measured 226.1225.

155c, (E)-2-(3-styrylphenyl)pyridine

Synthesised according to general procedure D. Yellow solid, 63.0 mg, 49%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.75 – 8.70 (m, 1H), 8.18 (app t, $J = 1.8$ Hz, 1H), 7.89 – 7.82 (m, 1H), 7.81 – 7.76 (m, 2H), 7.60 – 7.57 (m, 1H), 7.56 – 7.54 (m, 2H), 7.48 (app t, $J = 7.7$ Hz, 1H), 7.40 – 7.35 (m, 2H), 7.30 – 7.25 (m, 2H), 7.22 (d, $J = 2.6$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.4 (C$_{qAr}$), 149.8 (CH), 139.9 (C$_{qAr}$), 138.0 (C$_{qAr}$), 137.4 (C$_{qAr}$), 137.0 (CH$_{Ar}$), 129.2 (CH$_{Ar}$), 129.2 (CH$_{Ar}$), 128.8 (CH),
128.6 (CH$_3$Ar), 127.8 (CH$_3$Ar), 127.2 (CH$_3$Ar), 126.7 (CH), 126.2 (CH$_3$Ar), 125.2 (CH$_3$Ar), 122.4 (CH$_3$Ar), 120.8 (CH$_3$Ar);

HRMS (APCI+): calculated for C$_{19}$H$_{16}$N (M + H$^+$), theoretical 258.1289, measured 258.1275;

m.p. 98 – 100 °C.

155d, (E)-2-(3-(2-(phenylsulfonyl)vinyl)phenyl)pyridine

\[
\text{Synthesised according to general procedure D. Brown oil, 26.5 mg, 16%;}
\]

$^1$H NMR (400 MHz, CDCl$_3$): 8.69 (m, 1H), 8.17 (app t, $J$ = 1.8 Hz, 1H), 7.99 (app dt, $J$ = 7.0, 2.0 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.82 – 7.70 (m, 3H), 7.65 – 7.59 (m, 1H), 7.58 – 7.50 (m, 4H), 7.30 – 7.26 (m, 1H), 6.98 (d, $J$ = 15.3 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.2 (C$_q$Ar), 149.9 (CH$_3$Ar), 142.3 (CH$_3$Ar), 140.6 (C$_q$Ar), 140.4 (C$_q$Ar), 137.1 (CH$_3$Ar), 133.6 (CH$_3$Ar), 133.0 (C$_q$Ar), 129.6 (CH$_3$Ar), 129.6 (CH$_3$Ar), 129.5 (CH), 129.3 (CH$_3$Ar), 127.9 (CH$_3$Ar), 127.8 (CH), 127.0 (CH$_3$Ar), 122.9 (CH$_3$Ar), 120.7 (CH$_3$Ar).

HRMS (APCI+): calculated for C$_{19}$H$_{16}$O$_2$NS (M + H$^+$), theoretical 322.0896, measured 322.0892.
156a, 2-(3-bromophenyl)piperidine

A solution of 0.1M SmI\(_2\) in THF (15 ml, 0.75 mmol, 3.0 eq) was added to 2-(3-bromophenyl)pyridine (58.5 mg, 0.25 mmol, 1.0 eq) under argon. To this, degassed water was added (0.25 ml, 56 mmol, 14 eq) and the reaction was stirred at room temperature for 45 minutes until the colour changed from blue to yellow. 10% aqueous HCl was added to the reaction and it was further stirred for 10 mins. The reaction mixture was then extracted three times with diethyl ether before the aqueous layer was then basified with 10% aqueous NaOH. This was saturated with NaCl and then extracted three times with diethyl ether. After drying the second set of combined organic layers over MgSO\(_4\) and concentration in vacuo, the crude product was purified by preparative TLC (90% EtOAc: 10% MeOH). The compound was collected as a pale yellow oil (31.2 mg, 52%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.54\) (app t, \(J = 1.8\) Hz, 1H), 7.36 (m, 1H), 7.28 (m, 1H), 7.17 (app t, \(J = 7.8\) Hz, 1H), 3.58 – 3.54 (m, 1H), 3.18 (app dt, \(J = 11.7, 2.0\) Hz, 1H), 2.77 (app td, \(J = 11.7, 2.9\) Hz, 1H), 2.12 (br s, 1H), 1.89 (m, 1H), 1.77 (m, 1H), 1.65 (ddd, \(J = 12.0, 4.3, 2.1\) Hz, 1H), 1.59 – 1.43 (m, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 147.8\) (C\(_{q}\)), 130.3 (CH\(_{Ar}\)), 130.1 (CH\(_{Ar}\)), 129.9 (CH\(_{Ar}\)), 125.5 (CH\(_{Ar}\)), 122.6 (C\(_{q}\)), 61.9 (CH), 47.7 (CH\(_2\)), 35.0 (CH\(_2\)), 25.8 (CH\(_2\)), 25.4 (CH\(_2\));

LRMS (EI): 241 (C\(_{11}H_{14}N^{81}\)Br; 88%), 239 (C\(_{11}H_{14}N^{79}\)Br; 100%); HRMS (EI): calculated for C\(_{11}H_{14}N^{79}\)Br, theoretical 239.0304, measured 239.0294.
167a, 3-(pyridin-2-yl)benzaldehyde

A schlenk tube was charged with \([\text{RuCl}_2(p\text{-cymene})]_2\) (15.3 mg, 0.025 mmol, 5 mol%), potassium carbonate (138 mg, 1.0 mmol, 2.0 eq) and Piv-Val-OH (30.2 mg, 0.15 mmol, 0.3 eq) before being evacuated and then back-filled with nitrogen three times. Dry 1,4-dioxane (2 ml) and degassed CHCl\(_3\) (1 ml) were added and then 2-phenylpyridine (72 μl, 0.50 mmol, 1.0 eq) before the flask was sealed and the reaction mixture heated to 110 ºC for 20 hours. After cooling, the reaction mixture was concentrated in vacuo, and purified by flash column chromatography to give the product as a yellow oil (19.1 mg, 21%).

\(^1\text{H NMR (400 MHz, CDCl}_3\): \(\delta 10.13\) (s, 1H), \(8.73\) (app dt, \(J = 5.0, 1.4\) Hz, 1H), \(8.51\) (app t, \(J = 1.8\) Hz, 1H), \(8.30\) (ddd, \(J = 7.8, 1.9, 1.2\) Hz, 1H), \(7.95\) (app dt, \(J = 7.6, 1.4\) Hz, 1H), \(7.83 - 7.78\) (m, 2H), \(7.66\) (app t, \(J = 7.7\) Hz, 1H), \(7.33 - 7.28\) (m, 1H);

\(^{13}\text{C NMR (100 MHz, CDCl}_3\): \(\delta 192.4\) (CHO), \(156.1\) (Cq\(\text{Ar}\)), \(150.0\) (CH\(\text{Ar}\)), \(140.5\) (Cq\(\text{Ar}\)), \(137.2\) (CH\(\text{Ar}\)), \(137.1\) (Cq\(\text{Ar}\)), \(132.9\) (CH\(\text{Ar}\)), \(129.9\) (CH\(\text{Ar}\)), \(129.7\) (CH\(\text{Ar}\)), \(128.6\) (CH\(\text{Ar}\)), \(123.0\) (CH\(\text{Ar}\)), \(120.8\) (CH\(\text{Ar}\)).

HRMS (ESI+): calculated for C\(_{12}\)H\(_{10}\)ON (M + H\(^+\)), theoretical 184.0757, measured 184.0753.

203a, 2-(2-iodophenyl)pyridine

A schlenk tube was charged with [Ru\(_3\)(CO)\(_{12}\)] (9.6 mg, 0.015 mmol, 3 mol%), 1-phenylisoquinoline (103 mg, 0.50 mmol, 1.0 eq) and a 2:1 complex of ICl/1,4-
dioxane (206 mg, 0.50 mmol, 1.0 eq) before being evacuated and then back-filled with nitrogen three times. Dry 1,4-dioxane (3 ml) was added before the flask was sealed and the reaction mixture heated to 90 °C for 20 hours. After cooling, sodium thiosulphate (~20 ml, 10 wt%) was added before extracting the aqueous layer with EtOAc (×3). The combined organic layers were washed with brine and then dried over MgSO₄. After concentration in vacuo, the crude reaction mixture was purified by column chromatography. The product 203a was isolated as a yellow oil (99.7 mg, 71%).

¹H NMR (400 MHz, CDCl₃): δ 8.72 – 8.69 (m, 1H), 7.96 (dd, J = 8.0, 1.1 Hz, 1H), 7.77 (app td, J = 7.7, 1.8 Hz, 1H), 7.50 (app dt, J = 7.8, 1.1 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.33 – 7.27 (m, 1H), 7.08 (ddd, J = 7.9, 6.7, 2.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 160.8, 149.3, 145.0, 139.8, 136.0, 130.3, 129.8, 128.3, 124.4, 122.6, 96.7.

**Chlorination procedure**

A schlenk tube was charged with [RuCl₂(PPh₃)₃] (12.0 mg, 0.0125 mmol, 2.5 mol%), a 2:1 complex of ICl/1,4-dioxane (206 mg, 0.50 mmol, 1.0 eq) and PPh₃ (39.3 mg, 0.15 mmol, 30 mol%). Dry 1,4-dioxane (3 ml) was added followed by 2-phenylpyridine (72 µl, 0.5 mmol, 1.0 eq) before the flask was sealed under air atmosphere and the reaction mixture heated to 110 °C for 20 hours. After cooling, sodium thiosulphate (~20 ml, 10 wt%) was added before extracting the aqueous layer with EtOAc (×3). The combined organic layers were washed with brine and then dried over MgSO₄. After concentration in vacuo, the crude reaction mixture was purified by column chromatography to give products 165a as a pale yellow oil (58.7 mg, 62%) and 166a as a pale yellow oil (13.5 mg, 12%).

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165a, 2-(2-chlorophenyl)pyridine$^{185}$

![Structure of 2-(2-chlorophenyl)pyridine](image)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.72 (ddd, $J = 4.9$, 1.8, 1.0 Hz, 1H), 7.76 (app td, $J = 7.7$, 1.8 Hz, 1H), 7.65 (app dt, $J = 7.9$, 1.1 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.50 – 7.45 (m, 1H), 7.35 (app td, $J = 7.1$, 1.9 Hz, 2H), 7.29 (ddd, $J = 7.5$, 4.9, 1.2 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.0, 149.7, 139.3, 135.9, 132.2, 131.6, 130.2, 129.7, 127.1, 125.0, 122.5.

166a, 2-(2,6-dichlorophenyl)pyridine$^{185}$

![Structure of 2-(2,6-dichlorophenyl)pyridine](image)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.76 (ddd, $J = 4.8$, 1.8, 1.2 Hz, 1H), 7.82 (app td, $J = 7.7$, 1.8 Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 2H), 7.34 (d, $J = 7.7$ Hz, 2H), 7.28 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.6, 149.8, 138.6, 136.5, 134.8, 130.0, 128.3, 125.2, 123.1.

207n, 1-(2-iodophenyl)isoquinoline$^{185}$

![Structure of 1-(2-iodophenyl)isoquinoline](image)

A schlenk tube was charged with [Ru$_3$(CO)$_{12}$] (9.6 mg, 0.015 mmol, 3 mol%), 1-phenylisoquinoline (102.6 mg, 0.5 mmol, 1.0 eq) and a 2:1 complex of ICl/1,4-dioxane (206 mg, 0.5 mmol, 1.0 eq) before being evacuated and then back-filled with nitrogen three times. Dry 1,4-dioxane (3 ml) was added before the flask was sealed.
and the reaction mixture heated to 110 °C for 20 hours. After cooling, sodium thiosulphate (~20 ml, 10 wt%) was added before extracting the aqueous layer with EtOAc (×3). The combined organic layers were washed with brine and then dried over MgSO₄. After concentration in vacuo, the crude reaction mixture was purified by column chromatography to give the product as an off-white solid (66.9 mg, 40%).

¹H NMR (400 MHz, CDCl₃): 8.64 (d, J = 5.7 Hz, 1H), 8.01 (dd, J = 8.0, 1.1 Hz, 1H), 7.91 (app dt, J = 8.4, 0.9 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.62 – 7.58 (m, 1H), 7.54 – 7.48 (m, 2H), 7.41 (dd, J = 7.6, 1.7 Hz, 1H), 7.19 (ddd, J = 8.0, 7.4, 1.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 161.3, 143.0, 141.0, 138.2, 135.4, 129.3, 128.9, 127.0, 126.3, 126.3, 125.9, 125.7, 119.6, 96.8.

208n, 1-(2-chlorophenyl)isoquinoline¹⁸⁵

A schlenk tube was charged with [RuCl₂(PPh₃)₃] (12.0 mg, 0.0125 mmol, 2.5 mol%), 1-phenylisoquinoline (102.6 mg, 0.5 mmol, 1.0 eq), a 2:1 complex of ICl/1,4-dioxane (206 mg, 0.5 mmol, 1.0 eq) and PPh₃ (39.4 mg, 0.15 mmol, 30 mol%). Dry 1,4-dioxane (3 ml) was added before the flask was sealed under air atmosphere and the reaction mixture heated to 110 °C for 20 hours. After cooling, sodium thiosulphate (~20 ml, 10 wt%) was added before extracting the aqueous layer with EtOAc (×3). The combined organic layers were washed with brine and then dried over MgSO₄. After concentration in vacuo, the crude reaction mixture was purified by column chromatography to give the product as an off-white solid (93.2 mg, 78%).

¹H NMR (400 MHz, CDCl₃): δ 8.64 (d, J = 5.7 Hz, 1H), 7.89 (dt, J = 8.3, 1.0 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.66 – 7.63 (m, 1H), 7.56 – 7.49 (m, 2H), 7.48 – 7.41 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 158.9, 142.3, 138.4, 136.4, 133.4, 131.4, 130.3, 129.9, 129.8, 127.5, 127.3, 127.3, 127.0, 126.9, 120.7.
4.4 Copper project products

Benzylation reaction: general procedure E

To a 10 mL reaction tube, equipped with a magnetic stirrer bar, was added the electron rich arene (0.25 mmol, 1.0 eq), copper(II) bromide (112 mg, 0.5 mmol, 2.0 eq) and the toluene component (between 5 and 35 eq). The reaction vessel was then purged with N₂ and luperox 101 (320 µL, 1.1 mmol, 2.25 eq) was added and the reaction vessel was immediately sealed under an N₂ atmosphere with a crimp cap seal and placed directly into a preheated oil bath at 110 ºC. The reaction was heated for 18 hours, after which time the reaction was allowed to cool, diluted with dichloromethane (ca. 10 mL), analysed by thin layer chromatography and filtered through a cotton wool plug. The reaction mixture was then adsorbed onto the minimum amount of silica gel and purified by silica gel chromatography (ethyl acetate:hexane 2:98 to 3.5:96.5 to 5:95).

223a, 2-bromo-1,3,5-trimethoxy-4-(4-methylbenzyl)benzene

\[
\begin{align*}
\text{Br} & \quad \text{OMe} \\
\text{MeO} & \quad \text{I} \\
\end{align*}
\]

Synthesised according to general procedure E. Off-white solid, 44.4 mg, 51%;

\(^1\)H NMR (400 MHz, CDCl₃): δ 7.09 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.34 (s, 1H), 3.96 (s, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 2.28 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl₃): δ 158.4 (CqAr), 157.0 (CqAr), 155.9 (CqAr), 138.4 (CqAr), 135.1 (CqAr), 128.9 (CHAr), 128.3 (CHAr), 117.3 (CqAr), 98.3 (CqAr), 93.0 (CHAr), 61.2 (OCH₃), 56.6 (OCH₃), 56.0 (OCH₃), 29.3 (CH₃), 21.1 (CH₃);

HRMS (EI): calculated for C₁₇H₁₉O₃Br (M⁺), theoretical 350.0512, found 350.0518;

m.p. 110 – 112 ºC.
225c, 1-(3-bromo-2,4,6-trimethoxyphenyl)-2,3-dihydro-1H-indene

Synthesised according to general procedure E. Yellow solid, 19.3 mg, 21%;

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.24 (d, $J = 7.4$ Hz, 1H), 7.11 (app t, $J = 7.4$ Hz, 1H), 7.04 (app t, $J = 7.4$ Hz, 1H), 6.83 (d, $J = 7.4$ Hz, 1H), 6.32 (s, 1H), 4.89 (app t, $J = 8.1$ Hz, 1H), 3.90 (s, 3H), 3.56 (br s, 6H), 3.15 – 3.11 (m, 1H), 3.04 – 2.97 (m, 1H), 2.41 – 2.29 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 159.0 (C$_{qAr}$), 157.5 (C$_{qAr}$), 155.9 (C$_{qAr}$), 147.5 (C$_{qAr}$), 143.7 (C$_{qAr}$), 125.9 (CH$_{Ar}$), 125.8 (CH$_{Ar}$), 124.2 (CH$_{Ar}$), 123.2 (CH$_{Ar}$), 120.9 (C$_{qAr}$), 98.6 (C$_{qAr}$), 94.0 (CH$_{Ar}$), 56.5 (2x OCH$_3$), 56.1 (OCH$_3$), 41.8 (CH), 32.4 (CH$_2$), 31.8 (CH$_2$);

HRMS (EI): calculated for C$_{18}$H$_{19}$O$_3$Br ($M^+$), theoretical 362.0518, found 362.0508;

m.p. 110 – 112 ºC.

225d, 9-(2,4,6-trimethoxyphenyl)-9H-fluorene

Synthesised according to general procedure E but with fluorene (15 eq) in degassed benzene (1 ml). Yellow solid, 17.8 mg, 21%;

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.79 (d, $J = 7.5$ Hz, 2H), 7.34 – 7.29 (m, 2H), 7.24 – 7.17 (m, 4H), 6.31 (d, $J = 2.3$ Hz, 1H), 5.95 (d, $J = 2.3$ Hz, 1H), 5.61 (s, 1H), 3.98 (s, 3H), 3.80 (s, 3H), 2.97 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 160.2 (C$_{qAr}$), 159.9 (C$_{qAr}$), 159.8 (C$_{qAr}$), 148.9 (C$_{qAr}$), 141.2 (C$_{qAr}$), 126.6 (CH$_{Ar}$), 126.2 (CH$_{Ar}$), 123.7
(CH$_\text{Ar}$), 119.5 (CH$_\text{Ar}$), 110.7 (Cq$_\text{Ar}$), 92.7 (CH$_\text{Ar}$), 91.1 (CH$_\text{Ar}$), 56.4 (CH$_3$), 55.9 (CH$_3$), 55.4 (CH$_3$), 43.8 (CH);

HRMS (APCI+): calculated for C$_{22}$H$_{21}$O$_3$ (M + H$^+$), theoretical 333.1485, found 333.1470.

m.p. 98 – 100 ºC.

**Mixture of 2-bromo-1,3,5-tris(methoxy-d$_3$)-4-(4-methylbenzyl)benzene, 226aa and 2-bromo-1,3,5-tris(methoxy-d$_3$)-4-(4-methylbenzyl)benzene-6-d, 226ab**

Synthesised according to general procedure E with the starting material as a 2:1 mixture of 2-bromo-1,3,5-tris(methoxy-d$_3$)benzene and 2-bromo-1,3,5-tris(methoxy-d$_3$)benzene-d as the starting material. Compounds 226aa and 226ab were obtained as a an inseparable mixture (white solid, 42.1 mg, 48%).

![Chemical structure](image)

$^1$H NMR (500 MHz, CDCl$_3$): 7.10 (d, J = 7.8 Hz, 2H), 7.04 (d, J = 7.8 Hz, 2H), 6.34 (s, 0.66H), 3.97 (s, 2H), 2.29 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 158.3, 158.3*, 156.9, 155.9, 155.8*, 138.4, 135.1, 128.9 (CH), 128.8* (CH), 128.2 (CH), 128.2* (CH), 117.3, 117.2*, 98.2, 98.1*, 92.8 (CH), 60.4 (OCD$_3$, m), 55.8 (OCD$_3$, m), 55.2 (OCD$_3$, m), 29.3 (CH$_2$), 21.1 (CH$_3$);

*Denotes carbon peaks on compound 226ab.

HRMS (EI): calculated for C$_{17}$H$_{10}$D$_6$O$_3$Br$^+$ (M$^+$), theoretical 359.1082, found 359.1072.
226b, 2-bromo-1,3,5-triethoxy-4-(4-methylbenzyl)benzene

![Chemical structure of 226b]

Synthesised according to general procedure E. Off-white solid, 32.9 mg, 33%;

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.12 (d, $J = 7.9$ Hz, 2H), 7.02 (d, $J = 7.9$ Hz, 2H), 6.29 (s, 1H), 4.06 (q, $J = 7.0$ Hz, 2H), 3.96 (q, $J = 7.0$ Hz, 2H), 3.94 (s, 2H), 3.86 (q, $J = 7.0$ Hz, 2H), 2.28 (s, 3H), 1.46 (t, $J = 7.0$ Hz, 3H), 1.40 (t, $J = 7.0$ Hz, 3H), 1.34 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 157.6 (C$_{qAr}$), 156.1 (C$_{qAr}$), 155.2 (C$_{qAr}$), 138.8 (C$_{qAr}$), 135.0 (C$_{qAr}$), 128.8 (CH$_{Ar}$), 128.5 (CH$_{Ar}$), 117.9 (C$_{qAr}$), 99.1 (C$_{qAr}$), 95.1 (CH$_{Ar}$), 69.5 (CH$_2$), 65.3 (CH$_2$), 64.3 (CH$_2$), 29.7 (CH$_2$), 21.1 (CH$_3$), 15.7 (CH$_3$), 14.9 (CH$_3$), 14.9 (CH$_3$);

HRMS (EI): calculated for C$_{20}$H$_{25}$O$_3$Br (M$^+$), theoretical 392.0982, found 392.0983;

m.p. 74 – 76 ºC.

226c, 2-bromo-4-(4-methylbenzyl)-1,3,5-tripropoxybenzene

![Chemical structure of 226c]

Synthesised according to general procedure E. Yellow oil, 32.4 mg, 30%;

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.09 (d, $J = 7.8$ Hz, 2H), 7.01 (d, $J = 7.8$ Hz, 2H), 6.28 (s, 1H), 3.97 – 3.94 (m, 4H), 3.85 (t, $J = 6.3$ Hz, 2H), 3.76 (t, $J = 6.6$ Hz, 2H), 2.27 (s, 3H), 1.93 – 1.77 (m, 6H), 1.08 (t, $J = 7.4$ Hz, 3H), 1.01 (t, $J = 7.4$, 3H), 0.94 (t, $J = 7.4$, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 157.8 (C$_{qAr}$), 156.1 (C$_{qAr}$), 155.4 (C$_{qAr}$), 138.9 (C$_{qAr}$), 135.0 (C$_{qAr}$), 128.9 (CH$_{Ar}$), 128.6 (CH$_{Ar}$), 117.6 (C$_{qAr}$), 99.1
(CqAr), 94.8 (CHAr), 75.3 (OCH2), 71.2 (OCH2), 70.2 (OCH2), 29.7 (ArCH2Ar), 23.6 (CH2), 22.9 (CH2), 22.9 (CH2), 21.2 (ArCH3), 10.9 (CH3), 10.9 (CH3), 10.8 (CH3).

HRMS (EI): calculated for C22H31O379Br (M+), theoretical 434.1451, found 434.1458.

226d, 2-bromo-1,3,5-triisopropoxy-4-(4-methylbenzyl)benzene

\[
\text{Synthesised according to general procedure E. Yellow oil, 22.3 mg, 20%;}
\]

\[^{1}H \text{ NMR (400 MHz, CDCl}_3): \delta 7.09 (d, J = 7.8 \text{ Hz, 2H}), 6.99 (d, J = 7.8 \text{ Hz, 2H}), 6.28 (s, 1H), 4.53 (quint, J = 6.2 \text{ Hz, 1H}), 4.45 (quint, J = 6.1 \text{ Hz, 1H}), 4.41 (quint, J = 6.0 \text{ Hz, 1H}), 3.93 (s, 2H), 2.27 (s, 3H), 1.36 (d, J = 6.1 \text{ Hz, 6H}), 1.30 (d, J = 6.2 \text{ Hz, 6H}), 1.18 (d, J = 6.0 \text{ Hz, 6H}); \]

\[^{13}C \text{ NMR (100 MHz, CDCl}_3): \delta 156.1 (CqAr), 154.8 (CqAr), 154.2 (CqAr), 138.8 (CqAr), 134.8 (CqAr), 128.6 (2x CHAr), 119.9 (CqAr), 101.1 (CqAr), 98.5 (CHAr), 76.1 (CH), 72.9 (CH), 70.2 (CH), 30.3 (CH2), 22.5 (CH3), 22.3 (CH3), 22.0 (CH3), 21.1 (CH3);\]

HRMS (EI): calculated for C22H31O379Br (M+), theoretical 434.1451, found 434.1447.

226e, 1-bromo-2,4-dimethoxy-5-(4-methylbenzyl)benzene

\[
\text{Synthesised according to general procedure E. Off-white solid, 34.8 mg, 43%;}
\]
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.20\) (s, 1H), 7.08 (s, 4H), 6.47 (s, 1H), 3.89 (s, 3H), 3.83 (s, 2H), 3.82 (s, 3H), 2.31 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 157.6\) (C\(_{qAr}\)), 155.2 (C\(_{qAr}\)), 137.7 (C\(_{qAr}\)), 135.5 (C\(_{qAr}\)), 134.0 (CH\(_{Ar}\)), 129.2 (CH\(_{Ar}\)), 128.8 (CH\(_{Ar}\)), 123.9 (C\(_{qAr}\)), 101.7 (C\(_{qAr}\)), 96.8 (CH\(_{Ar}\)), 56.6 (OCH\(_3\)), 55.9 (OCH\(_3\)), 34.6 (CH\(_2\)), 21.2 (CH\(_3\));

HRMS (EI): calculated for C\(_{16}\)H\(_{17}\)O\(_2\)\(^{79}\)Br (M\(^+\)), theoretical 320.0412, found 320.0400;

m.p. 81 – 83 °C.

**226f, 1-bromo-2,3,4-trimethoxy-6-methyl-5-(4-methylbenzyl)benzene**

![Chemical structure](image)

Synthesised according to general procedure E. Yellow oil, 11.0 mg, 12%;

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.06\) (d, \(J = 7.7\) Hz, 2H), 6.97 (d, \(J = 7.7\) Hz, 2H), 4.04 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.74 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 151.6\) (C\(_{qAr}\)), 149.6 (C\(_{qAr}\)), 145.2 (C\(_{qAr}\)), 137.3 (C\(_{qAr}\)), 135.4 (C\(_{qAr}\)), 132.9 (C\(_{qAr}\)), 129.6 (C\(_{qAr}\)), 129.2 (CH\(_{Ar}\)), 128.0 (CH\(_{Ar}\)), 115.7 (C\(_{qAr}\)), 61.2 (OCH\(_3\)), 61.1 (OCH\(_3\)), 61.0 (OCH\(_3\)), 32.8 (CH\(_2\)), 21.1 (CH\(_3\)), 19.9 (CH\(_3\));

HRMS (EI): calculated for C\(_{18}\)H\(_{21}\)O\(_3\)\(^{79}\)Br (M\(^+\)), theoretical 364.0674, found 364.0665.
226g, 1,3,5-trimethoxy-2-(4-methylbenzyl)-4-nitrobenzene

Synthesised according to general procedure E. Yellow solid, 60.0 mg, 76%;

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.05 (s, 4H), 6.32 (s, 1H), 3.93 (s, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.72 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): 160.2 (C$_{qA}$), 152.0 (C$_{qA}$), 151.5 (C$_{qA}$), 137.4 (C$_{qA}$), 135.4 (C$_{qA}$), 129.0 (CH$_A$), 128.1 (CH$_A$), 116.1 (C$_{qA}$), 91.7 (CH$_A$), 63.2 (OCH$_3$), 56.6 (OCH$_3$), 56.1 (OCH$_3$), 28.6 (CH$_2$), 21.1 (CH$_3$);

HRMS (APCI+): calculated for C$_{17}$H$_{19}$NO$_5$ (M$^+$), theoretical 317.1258, found 317.1246;

m.p. 104 – 106 ºC.

226h, 1,2,3-trimethoxy-4-(4-methylbenzyl)benzene

Synthesised according to general procedure E. Yellow oil, 19.7 mg, 29%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.08 (s, 4H), 6.78 (d, $J = 8.5$ Hz, 2H), 6.60 (d, $J = 8.5$ Hz, 2H), 3.88 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 152.4 (C$_{qA}$), 152.0 (C$_{qA}$), 142.5 (C$_{qA}$), 138.5 (C$_{qA}$), 135.4 (C$_{qA}$), 129.1 (CH$_A$), 128.8 (CH$_A$), 127.7 (C$_{qA}$), 124.6 (CH$_A$), 107.2 (CH$_A$), 60.9 (OCH$_3$), 60.9 (OCH$_3$), 56.1 (OCH$_3$), 35.3 (CH$_2$), 21.1 (CH$_3$);

HRMS (EI): calculated for C$_{17}$H$_{20}$O$_3$ (M$^+$), theoretical 272.1412, found 272.1408.
226i, 1,2,4,5-tetramethoxy-3-(4-methylbenzyl)benzene

![Chemical Structure]

Synthesised according to general procedure E. Off-white solid, 16.5 mg, 22%;

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.14 (d, $J$ = 7.6 Hz, 2H), 7.02 (d, $J$ = 7.60 Hz, 2H), 6.46 (s, 1H), 3.99 (s, 2H), 3.85 (s, 6H), 3.63 (s, 6H), 2.27 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): 149.1 (C$_{q\text{Ar}}$), 141.3 (C$_{q\text{Ar}}$), 138.5 (C$_{q\text{Ar}}$), 135.1 (C$_{q\text{Ar}}$), 129.6 (C$_{q\text{Ar}}$), 128.9 (CH$_{Ac}$), 128.6 (CH$_{Ar}$), 97.6 (CH$_{Ar}$), 60.9 (OCH$_3$), 56.4 (OCH$_3$), 29.9 (CH$_2$), 21.1 (CH$_3$);

HRMS (EI): calculated for C$_{18}$H$_{22}$O$_4$ (M$^+$), theoretical 302.1513, found 302.1512;

m.p. 57 – 59 ºC.

226ja, 2-fluoro-1,3,5-trimethoxy-4-(4-methylbenzyl)benzene

Synthesised according to general procedure E with 2-fluoro-1,3,5-trimethoxybenzene as the starting material. Compound 226ja was isolated as a white solid (12.8 mg, 18%), as well as 226jb and 226jc as an inseparable mixture (11.3 mg, 7% and 4%) as determined by GCMS and $^1$H NMR.

![Chemical Structure]

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.10 (d, $J$ = 7.9 Hz, 2H), 7.03 (d, $J$ = 7.9 Hz, 2H), 6.29 (d, $J$ = 6.5 Hz, 1H), 3.90 (s, 2H), 3.88 (s, 3H), 3.81 (d, $J$ = 1.9 Hz, 3H), 3.77 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 153.3 (d, $J$ = 2.6 Hz, C$_{q\text{Ar}}$), 147.1 (d, $J$ = 17 Hz, C$_{q\text{Ar}}$), 147.0 (d, $J$ = 17 Hz, C$_{q\text{Ar}}$), 141.3 (d, $J$ = 240 Hz, C$_{q\text{Ar}}$), 138.6 (C$_{q\text{Ar}}$), 135.1 (C$_{q\text{Ar}}$), 128.9 (CH$_{Ac}$), 128.4 (CH$_{Ar}$), 115.9 (C$_{q\text{Ar}}$), 93.2 (CH$_{Ar}$), 61.4
(OCH₃, d, \( J = 6.5 \) Hz), 56.9 (OCH₃), 56.3 (OCH₃), 28.6 (d, \( J = 1.5 \) Hz, CH₂), 21.1 (CH₃);

HRMS (EI): calculated for C₁₇H₁₉O₃F (M⁺), theoretical 290.1318, found 290.1317;

m.p. 46 – 48 °C.

**Mixture of 226ja, 1-bromo-3-fluoro-2,4,6-trimethoxy-5-(4-methylbenzyl) benzene, and 226jc, 4,4’-((5-fluoro-2,4,6-trimethoxy-1,3-phenylene)bis (methylene))bis(methyl-benzene)**

![](image)

(H is dibenzyl, H* is bromobenzyl; 1:1.7)

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 7.11 – 7.08 (m, 4H + 2H*), 7.06 – 7.03 (m, 4H + 2H*), 3.97 (s, 2H*), 3.96 (s, 4H), 3.94 (d, \( J = 1.1 \) Hz, 3H*), 3.78 (d, \( J = 2.0 \) Hz, 3H*), 3.74 (d, \( J = 1.6 \) Hz, 6H), 3.69 (s, 3H*), 3.48 (s, 3H), 2.29 (s, 6H + 3H*).

**226k, 2,4,6-trimethoxy-3-(4-methylbenzyl)benzaldehyde**

![](image)

Synthesised according to general procedure E. Colourless oil, 14.9 mg, 20%;

\(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 10.33 (s, 1H), 7.09 (d, \( J = 7.9 \) Hz, 2H), 7.03 (d, \( J = 7.9 \) Hz, 2H), 6.27 (s, 1H), 3.92 (s, 3H), 3.91 (s, 2H), 3.88 (s, 3H), 3.71 (s, 3H), 2.28 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 188.1 (CHO), 164.3 (C\(_{Ar}\)), 163.0 (C\(_{Ar}\)), 162.2 (C\(_{Ar}\)), 138.2 (C\(_{Ar}\)), 135.2 (C\(_{Ar}\)), 129.0 (CH\(_{Ar}\)), 128.3 (CH\(_{Ar}\)), 116.3 (C\(_{Ar}\)), 112.4 (C\(_{Ar}\)), 91.1 (CH\(_{Ar}\)), 63.3 (OCH₃), 56.2 (OCH₃), 55.9 (OCH₃), 28.1 (CH₂), 21.1 (CH₃);
HRMS (APCI+): calculated for C_{18}H_{21}O_{4} (M + H^{+}), theoretical 301.1434, found 301.1422.

226l, 1,4-dimethoxy-2-(4-methylbenzyl)benzene^{186}

![Structure](image)

Synthesised according to general procedure E. Off-white solid, 12.6 mg, 21%;

^1H NMR (400 MHz, CDCl_{3}): δ 7.10 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 6.79 (d, J = 8.8 Hz, 1H), 6.70 (dd, J = 8.8, 3.1 Hz, 1H), 6.65 (d, J = 3.1 Hz, 1H), 3.90 (s, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 2.30 (s, 3H); ^13C NMR (100 MHz, CDCl_{3}): δ 153.6 (C_{q}Ar), 151.8 (C_{q}Ar), 137.7 (C_{q}Ar), 135.4 (C_{q}Ar), 131.3 (C_{q}Ar), 129.1 (CH_{Ar}), 128.9 (CH_{Ar}), 116.9 (CH_{Ar}), 111.5 (CH_{Ar}), 111.2 (CH_{Ar}), 56.2 (OCH_{3}), 55.8 (OCH_{3}), 35.6 (CH_{2}), 21.2 (CH_{3});

HRMS (EI): calculated for C_{16}H_{18}O_{2} (M^{+}), theoretical 242.1301, found 242.1313.

223m, penta-methyl vidalol A^{157}

![Structure](image)

To a 10 mL reaction tube, equipped with a magnetic stirrer bar, was added 1,3,5-trimethoxybenzene (55.0 mg, 0.327 mmol, 1.0 eq), copper(II) bromide (147 mg, 0.5 mmol, 2.0 eq) and 2,3-dibromo-4,5-dimethoxy-1-methylbenzene (507 mg, 1.64 mmol, 5.0 eq) in degassed benzene (1 ml). The reaction vessel was then purged with N\textsubscript{2} and luperox 101 (244 µl, 0.838 mmol, 2.25 eq) was added and the reaction vessel was immediately sealed under an N\textsubscript{2} atmosphere with a crimp cap seal and placed directly into a preheated oil bath at 110 °C. The reaction was heated for 18 hours,
after which time the reaction was allowed to cool, diluted with dichloromethane (ca. 10 mL), analysed by thin layer chromatography and filtered through a cotton wool plug. The reaction mixture was then purified by automated column chromatography to give the product as a yellow oil (38.4 mg, 19%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 6.37 (s, 1H), 6.31 (s, 1H), 4.05 (s, 2H), 3.94 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H), 3.61 (s, 3H);\) \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 158.5 (C_{qAr}), 157.3 (C_{qAr}), 156.5 (C_{qAr}), 152.4 (C_{qAr}), 145.7 (C_{qAr}), 137.9 (C_{qAr}), 121.6 (C_{qAr}), 117.5 (C_{qAr}), 114.9 (C_{qAr}), 111.9 (C_{qAr}), 98.2 (C_{qAr}), 92.5 (CH_{Ar}), 61.3 (OCH\(_3\)), 60.6 (OCH\(_3\)), 56.6 (OCH\(_3\)), 56.2 (OCH\(_3\)), 56.1 (OCH\(_3\)), 32.0 (CH\(_2\));\)

HRMS (ESI+): calculated for C\(_{18}\)H\(_{20}\)O\(_5\)\(^79\)Br\(_3\) (M + H)\(^+\), theoretical 552.8855, measured 552.8857.

227, vidalol A\(^{156}\)

A solution of pentamethyl vidalol A (18 mg, 0.32 mmol, 1.0 eq) in dichloromethane (1 ml) was cooled to 0 °C and a 1 M solution of BBr\(_3\) in DCM (0.32 ml, 0.32 mmol, 10.0 eq) was added slowly. The reaction was allowed to warm to room temperature and stir overnight. The reaction mixture was then cooled to 0 °C once again and MeOH (1 ml) was added. After stirring at room temperature for six hours, the reaction solvent was evaporated and after dissolving in (CD\(_3\))\(_2\)CO, NMR data was collected. The sample was not sufficiently clean to obtain a yield and various attempts to purify the compound including column chromatography were unsuccessful. The peaks assigned to the natural product were seen to disappear over time even for samples stored under inert atmosphere in the freezer.

\(^1\)H NMR (500 MHz, (CD\(_3\))\(_2\)CO): \(\delta 8.63 (s, 1H, OH), 8.60 (s, 1H, OH), 8.40 (s, 1H, OH), 8.01 (s, 1H, OH), 7.53 (s, 1H, OH), 6.33 (s, 1H, CH), 6.32 (s, 1H, CH), 3.96 (s, 2H, ArCH\(_2\)Ar);\) \(^{13}\)C NMR (100 MHz, (CD\(_3\))\(_2\)CO): \(\delta 156.8, 154.3, 154.1, 145.2, 143.0, 133.5, 116.2, 114.7, 113.3, 106.1, 96.3, 90.2, 31.6.\)
HRMS (ESI-) calculated for C₁₃H₈O₅Br₃ (M - H), theoretical 480.7927, measured 480.7945.

**233a, 4,4’-((2,4,6-trimethoxy-1,3-phenylene)bis(methylene))bis(methylbenzene)**

To a 10 mL reaction tube, equipped with a magnetic stirrer bar, was added the electron rich arene (0.25 mmol, 1.0 eq), copper(II) bromide (112 mg, 0.5 mmol, 2.0 eq) and the toluene component (between 5 and 35 eq). The reaction vessel was then purged with N₂ and di-tert-butylperoxide (207 µL, 1.1 mmol, 4.5 eq) was added and the reaction vessel was immediately sealed under an N₂ atmosphere with a crimp cap seal and placed directly into a preheated oil bath at 110 °C. The reaction was heated for 24 hours, after which time the reaction was allowed to cool. The vessel was then opened and CuBr (71.7 mg, 0.25 mmol, 1.0 eq) was added. The reaction was then re-sealed and heated at 110 °C for a further 24 h. before once again being opened and diluted with dichloromethane (*ca.* 10 mL). The mixture was then filtered through a cotton wool plug before being adsorbed onto the minimum amount of silica gel and purified by silica gel chromatography (ethyl acetate:hexane 2:98 to 3.5:96.5 to 5:95). Compounds 233a (36.4 mg, 27%) and 223a (36.4 mg, 41%) were isolated.

**¹H NMR (400 MHz, CDCl₃):** δ 7.08 (d, J = 8.1 Hz, 4H), 7.02 (d, J = 8.1 Hz, 4H), 6.35 (s, 1H), 3.95 (s, 4H), 3.78 (s, 6H), 3.46 (s, 3H), 2.28 (s, 6H); **¹³C NMR (100 MHz, CDCl₃):** δ 158.5 (C₉Ar), 157.7 (C₉Ar), 139.1 (C₉Ar), 134.8 (C₉Ar), 128.9 (CH₉), 128.2 (CH₉), 115.1 (C₉Ar), 92.1 (CH₉), 62.0 (OCH₃), 55.9 (OCH₃), 29.0 (CH₂), 21.1 (CH₃);

HRMS (EI): calculated for C₂₅H₂₉O₃ (M⁺), theoretical 376.2038, found 376.2036;

m.p. 112 – 114 °C.
Mixture of 235a, 2-chloro-1,3,5-trimethoxy-4-(4-methylbenzyl)benzene and 223a, 2-bromo-1,3,5-trimethoxy-4-(4-methylbenzyl)benzene

Synthesised according to general procedure E with 2-chloro-1,3,5-trimethoxybenzene, as the starting material. Compounds 235a and 223a were obtained as an inseparable mixture (27.8 mg, 26% and 9% respectively).

H are protons from compound 235a, H* refers to protons from compound 223a.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.09 (d, $J = 8.0$ Hz, 2H + 2H*), 7.03 (d, $J = 8.0$ Hz, 2H + 2H*), 6.35 (s, 1H), 6.34 (s, 1H*), 3.96 (s, 2H), 3.94 (s, 2H*), 3.90 (s, 3H + 3H*), 3.80 (s, 3H + 3H*), 3.71 (s, 3H*), 3.70 (s, 3H), 2.28 (s, 3H + 3H*);

Compound 235a (Cl):
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 157.3 (C$_{Ar}$), 156.0 (C$_{Ar}$), 155.0 (C$_{Ar}$), 138.4 (C$_{Ar}$), 135.1 (C$_{Ar}$), 129.0 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 117.1 (C$_{Ar}$), 108.6 (C$_{Ar}$), 93.0 (CH$_{Ar}$), 61.2 (OCH$_3$), 56.6 (OCH$_3$), 56.0 (OCH$_3$), 29.1 (CH$_2$), 21.1 (CH$_3$)

Compound 223a (Br):
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 158.4 (C$_{Ar}$), 157.0 (C$_{Ar}$), 155.9 (C$_{Ar}$), 138.4 (C$_{Ar}$), 135.1 (C$_{Ar}$), 128.9 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 117.3 (C$_{Ar}$), 98.3 (C$_{Ar}$), 92.9 (CH$_{Ar}$), 61.1 (OCH$_3$), 56.6 (OCH$_3$), 56.0 (OCH$_3$), 29.3 (CH$_2$), 21.1 (CH$_3$).
5. References


Tyman, J. H. P. Synthetic and Natural Phenols; Elsevier: 1996.


Private correspondence from Dr Scott Cockroft to Professor Michael Greaney and Christopher Teskey.


