Organic Chemistry from an Inorganic Perspective: The Serendipitous Discovery of New Chemistry by Attempting the Impossible

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To Mum and Dad

Abstract

Serendipity, a term commonly used to rationalise unexpected observations of unintentional merit, categorises discoveries at the interface of chance and sagacity. Some of the most profound chemical discoveries recorded owe serendipity for their occurrence. The discovery and development of penicillin by Fleming, Chain and Florey, the synthesis of polyethene by von Pechmann and Imperial Chemical Industries, the first electrically conducting polymer by Shirakawa, Heeger and MacDiarmid, and finally, the discovery of ferrocene independently and accidentally by three separate research groups highlight a few such examples. Remarkably, many of these discoveries have been the focus of Nobel Prizes and the subject of many high-impact research works. In this context, herein is described an examination of a reported N-Heterocyclic carbene (NHC)-halogen bonding interaction, a powerful Ag(I)/$PhICl_2$ chlorinating system, and an investigation into the Lewis base activation of $PhICl_2$. This thesis provides a combined synthetic and theoretical investigation into these serendipitous discoveries.

The attempted synthesis of an extraordinarily weak NHC supported carbon-carbon double bond was explored *via* several synthetic strategies. Carbon-carbon cross-coupling reactions, olefin metathesis and ligand displacement methodologies using an appropriate precursor were employed. Although unsuccessful for the isolation of the targeted species, the latter strategy presented a reported NHC-halogen bonding interaction. Efforts to synthesise and isolate a highly reactive phenyliodonium dication, $[PhI]^{2+}$, using $[Ag]_2[B_{12}Cl_{12}]$ mediated chloride abstraction from $PhICl_2$ provided a powerful new chlorinating agent *via* catalytic activation of $PhICl_2$. Whilst exploring related systems, the purported pyridine activation of $PhICl_2$ *via* a phenyliodonium monocation, $[PhICl]^+$ was examined. Attempts to observe or isolate $[PhICl]^+$ were unsuccessful, however, it was determined that pyridine forms a weak complex with $PhICl_2$ *via* a halogen bonding interaction. An investigation into this system unambiguously disproves formation of $[PhICl]^+$. Examination of the true activation of $PhICl_2$ by Lewis bases is presented, suggesting chloride is the species responsible in these interactions.

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I would like to thank our collaborators at La Trobe University. Dr David Wilson and his laboratory were responsible for undertaking some of the theoretical calculations presented in this work. I would also like to thank Dr Sevan Houston who helped perform some of the synthetic work described. A special thanks to Dr Mohammad Al Bayer and Prof. Robert Brownlee who jointly maintained and serviced the NMR spectrometers, without which, I would not have finished my Ph.D. in such a timely manner.

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List of Abbreviations

Δ	heat
δ	chemical shift
v/v	volume to volume
w/v	weight to volume
°C	degrees Celsius
μM	micromolar
Å	Angstrom
Ac	acetyl/acetate
Ar	aryl
aq.	aqueous
Bn	benzyl
Boc	*tert*-butyoxycarbonyl
br	broad
Celite®	diatomaceous earth
CH_2Cl_2	dichloromethane
d	doublet
DMF	*N*,*N*'-dimethylformamide
DMSO	dimethyl sulfoxide
ESI	electrospray ionisation
Et	ethyl
g	grams
h	hours
Hz	hertz
*i*Pr	isopropyl
m	multiplet
m.p.	melting point
M	moles per liter
m/z	mass to charge
Me	methyl
mg	milligrams
mins	minutes
mL	milliliters

mM	millimoles
NMR	nuclear magnetic resonance
o	*ortho*
OTf	trifluoromethanesulphonate; triflate
p	*para*
pH	potential hydrogen
Ph	phenyl
PPA	polyphosphoric acid
ppm	parts per million
Py	pyridine
R	organic group
r.t.	room temperature
s	singlet
t	triplet
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

Statement of Authorship

Except where reference is made in the text of the thesis, this thesis contains no material published elsewhere or extracted in whole or in part from a thesis accepted for the award of any other degree or diploma. No other person's work has been used without due acknowledgment in the main text of the thesis. This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution.

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Tiffany Poynder, April 30th, 2021

Preface to Thesis

The work presented in this thesis is of several disparate research projects broadly associated with a unifying theme. Each of these projects is confined to its respective section. As such, there will be no concluding chapter for the work presented. Rather, each individual chapter has its own concluding remarks.

Further, presented here is some jointly authored work. Reference to such has been made at the start of each chapter and is outlined below each chapter title where relevant.

Chapter 1. Coordination Chemistry at Carbon

1.01 General Introduction

The p-block houses a disparate assortment of elements; metals, metalloids and non-metals form the main group and thus a large variation in chemical properties is the result. Main group elements display a wide range of oxidation states and valencies, a trend that becomes increasingly exaggerated moving down a group.[1] The heavier p-block elements differ greatly from their lighter congeners and often mirror behaviour closer to that of the transition metals rather than their first-row counterparts.[2] As a consequence, the p-block elements display a plethora of diverse structures, properties and reactivity.[1] Modern main group chemistry aims to exploit the diversity of the p-block elements to challenge these ever changing notions of reactivity.

1.02 Coordination Chemistry in the Main Group

Ligand stabilised main group fragments (E_n) in the formal zero oxidation state are currently an area of significant interest in both synthetic and theoretical chemistry. The development of novel bonding motifs and unique structure and reactivity fuels interest in this field. Main group zero oxidation state complexes exist as small molecular fragments stabilised by coordination from neutral ligands (L), generally in the form EL_2, E_2L_2, or E_3L_3.[3] Such complexes may be considered molecular allotropes as the central atom(s) are in the formal zero oxidation state.[4] However, this idea is met with some contention suggesting species must be considered case-by-case and be subject to analysis before being deemed coordination complexes.[5] Main group coordination chemistry has been particularly fruitful for isolation of highly reactive species that cannot be achieved as free molecules,[6,7] which offers potential for new and interesting chemistry.

Aside from allotropes, the zero oxidation state is typically reserved for ligand stabilised transition metals and is considered rare in non-metal complexes.[4] Thus, zero oxidation state main group complexes are considered atypical. Neutral ligands

(*e.g.* carbenes or phosphines) are employed to coordinate to the central main group fragment, thereby filling the valence shell – a strong preference for main group elements. The central fragment is often observed to retain valence electrons in the form of lone pair(s). As a result, such complexes are very electron rich, exhibit unique properties, and consequently are of great interest from a research perspective.[8]

1.03 Carbodiphosphoranes: The Gateway to Main Group Coordination Chemistry

The study of zero oxidation state main group complexes is a relatively new area of interest, with the bulk of work performed in the last three decades.[9] The origin of which may be attributed to one of many seminal studies depending on what point "origin" is defined. This work will consider the origin of zero oxidation state main group chemistry as work pertaining to the carbodiphosphorane (CDP), $C(PPh_3)_2$.

Although $C(PPh_3)_2$ was discovered in 1961,[10] it was not until 2005 when CDPs became relevant to main group coordination chemistry. It was demonstrated that CDPs were able to act as double Lewis bases *via* coordination to CS_2, CO_2, and later platinum centres.[11,12] These results were particularly unusual as double Lewis bases were unknown at the time and thus prompted investigation into these complexes and CDPs.[11] Ultimately, it was determined that CDPs were able to simultaneously act as σ- and π-donors. Inspired by these results, Frenking and Tonner published an in-depth theoretical and experimental study analysing the nature of CDPs.[13] CDPs have unusual electronic properties about the central carbon atom. The phosphorus-carbon bonding adheres to a donor-acceptor interaction (P→C) rather than an electron-sharing interaction (P-C). That is, CDPs should be considered two phosphine ligands coordinating to a central carbon(0) atom with two lone pairs retained about the carbon atom. This is in direct contrast to earlier suggested bonding motifs where the species was hypothesised to have diylidic character pertaining to a more traditional Lewis structure depiction (Figure 1.01).[10]

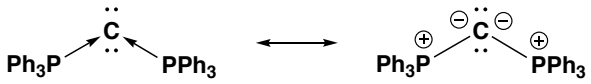


Figure 1.01. *Bonding description of $C(PPh_3)_2$ following a dative bonding model (left) and the more traditional Lewis structure (right).*

More recent studies have likened the electronic nature of CDPs to that of N-heterocyclic carbenes (NHCs),[14] as both species have divalent carbon atoms and a propensity to behave as donor ligands. However, the carbenic similarities of CDPs fail to provide a wholistic explanation of all observed properties of these species. If CDPs were truly akin to carbenes, it would follow that the central carbon shares covalent bonds with the adjacent phosphorus atoms and is a carbon(II) centre. Further, CDPs do not emulate the reactivity of carbenes entirely, as demonstrated by some peculiar experimental observations (*e.g.* the ability to coordinate twice from the central carbon atom). A dative bonding depiction of CDPs rationalises these unexplained observations that comparison to carbenes or a covalent bonding theory cannot. The dative bonding theory dictates that all four valence electrons of carbon remain as two lone pairs, and thus, justifies the observed properties.[13]

To explore the bonding theory for CDPs, Frenking *et al*. used theoretical and experimental methods to investigate the nature of $C(PPh_3)_2$. Molecular orbital (MO) and natural bond orbital calculations indicated that the highest occupied molecular orbital (HOMO) and the HOMO-1 can be assigned as lone pair containing MOs of π- and σ- symmetry, respectively (Figure 1.02). These MOs are both localised over the central carbon atom.

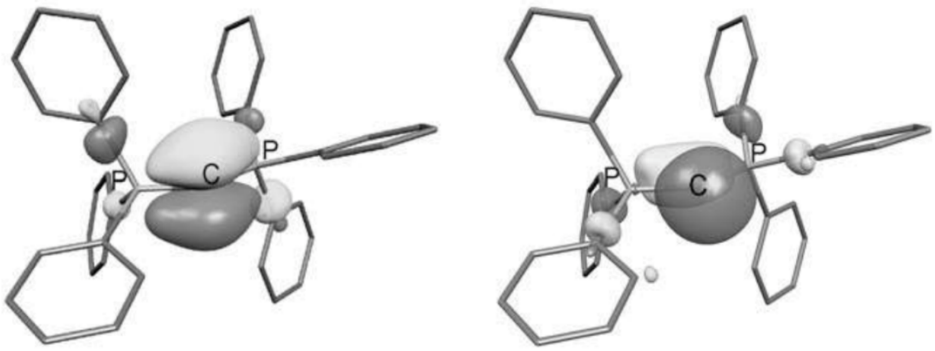


Figure 1.02. *Calculated HOMO (left) and HOMO-1 (right) of $C(PPh_3)_2$.*[13]

Further, the interaction of $C(PPh_3)_2$ and Lewis acids was probed. The first and second proton affinities for $C(PPh_3)_2$ were found to be very high. The HOMO and HOMO-1 were shown to coordinate to Lewis acids twice, corroborating the existence of two lone pairs at the central carbon atom. Finally, CDPs were demonstrated to doubly coordinate to a silver centre by the central carbon atom of the CDP moiety – this structure was confirmed by solid-state X-ray crystallography. Thus, experimental evidence supported the presence of two lone pairs about the central carbon atom by illustrating the ability of CDPs to behave as four-electron donors. These results suggest it most appropriate to deem CDPs as a carbon(0) atom ligated by two phosphine units.[13] This seminal analysis of $C(PPh_3)_2$ was pivotal as it signifies the first confirmed instance of coordination chemistry at carbon, a phenomenon once reserved for the transition metals.

1.04 Bonding Theory of Ligand Stabilised Main Group Fragments

Arguably, the most important feature of main group coordination complexes is the dative bonding interaction theorised between the ligand and central element (L→E).[13] This notion is in direct contrast with the traditionally accepted covalent model. The dative bonding model is a helpful consideration when trying to understand experimental observations of ligand stabilised low-oxidation state complexes.[3]

The use of coordination chemistry methodologies has enabled the synthesis of a large number of main group coordination complexes of which form the basis for a number of comprehensive reviews.[3,15,16] Bonding arrangements of zero oxidation state complexes reported generally adhere to the form E_xL_y.[17] A range of compounds of this nature have been successfully isolated, with E_x reported for C_1,[10,18] Si_1,[19,20] Ge_1,[20,21] B_2,[7] Si_2,[6] Ge_2,[22] Sn_2,[23] N_2,[24] P_2,[25] As_2,[26] Si_3,[27] and P_4,[28] to highlight a few. Of importance is an NHC stabilised B_2 complex exhibiting a boron-boron triple bond and an NHC stabilised Si_2 compound which yields a species with

Si=Si bond,[7,6] as achieving main group homonuclear multiple bonding is a feat in its own right (Figure 1.03).[9]

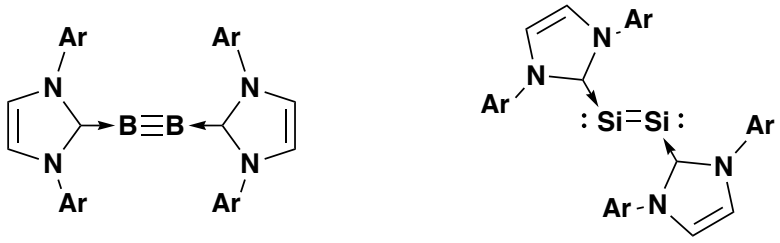


Figure 1.03. *NHC stabilised B_2 (left) and NHC stabilised Si_2 (right); Ar = 2,6-diisopropylphenyl.*

1.05 Applications of Main Group Coordination Complexes

The synthetic utility and application of main group coordination compounds aims to mirror that of the transition metals, whilst having the advantage of their precursor materials generally being less costly, less toxic and more abundant than their heavy metal congeners. Main group coordination complexes have demonstrated application in small-molecule activation,[29] with the first species reported being a digermanium complex able to activate dihydrogen.[30] Oxidative addition and reductive elimination processes are now commonplace in main group complexes.[31]

1.06 Synthetic Strategies to Access Main Group Coordination Complexes

With regard to the synthesis of highly reactive complexes, selection of the most appropriate ligand is critical. Importantly, the use of neutral donor ligands is essential to achieve low valent main group complexes.[15] It is this condition of carbenes that renders them excellent candidates in this context. Commonly, N-heterocyclic carbenes (NHCs) and cyclic alkylaminocarbenes (cAACs) are important ligands in this field, with the bulk of examples using NHCs.[17]

NHCs, discovered in 1991,[32] are extensively used in synthetic chemistry owing to their strong donor capacity and ease of preparation. NHCs have had an unmistakeable impact in the fields of organometallic chemistry and catalysis. NHCs

are excellent ligands for stabilising reactive species due to their strong σ-donating and weak π-accepting nature.[33] It is this specific character that is fundamental for the NHC-main group element interaction and explains their ubiquity in main group coordination chemistry.[34] There has also been reports of cyclic alkylaminocarbenes ligands being used in this field. cAACs offer slightly stronger σ-donating and π-accepting capacities (attributed to the number of cyclic nitrogen atoms) when compared with NHCs,[35] however, there is still preference for NHCs, owing to availability and ease of synthesis.

With the correct ligand in hand, there are several strategies employed for the isolation of stabilised main group fragments. Most commonly, routes involve the reduction of halogenated (X) precursors (carbene-E-X), deprotonation of cationic precursors, or (specifically for phosphorus complexes) activation of P_4 by carbenes.[16,28]

1.07 Ligand Stabilised Carbon Fragments in the Zero Oxidation State

Although there is interest in a variety of zero oxidation state main group fragments, the remainder of this work will focus on ligand stabilised carbon(0) fragments. Ligand stabilised carbon(0) complexes exhibit σ-donation from the ligands to the central carbon, and π-back donation from the lone pairs on carbon (Figure 1.04). This type of interaction is typically seen in transition metals, thus relating the chemistry of carbon to that of metal chemistry under particular circumstances and highlighting the significance of exploring carbon(0) complexes.[36]

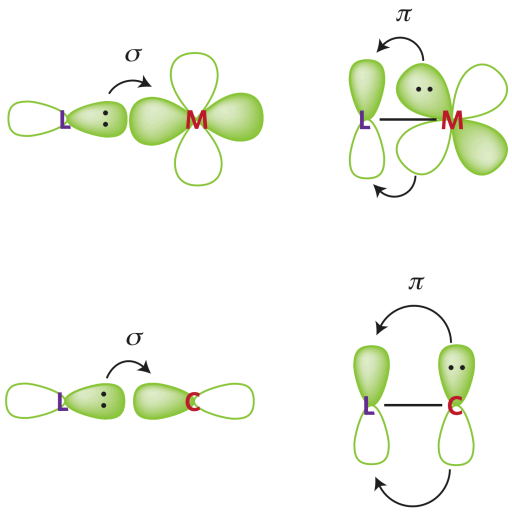
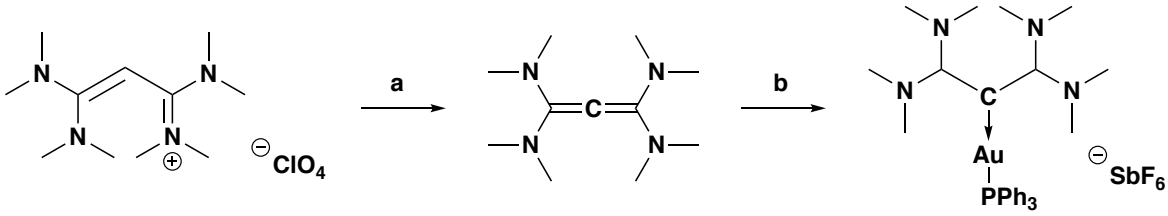


Figure 1.04. *Carbon (C) – ligand (L) interaction compared with metal (M) – ligand (L) interaction. σ-donation (left) and π-back donation (right).*[36]

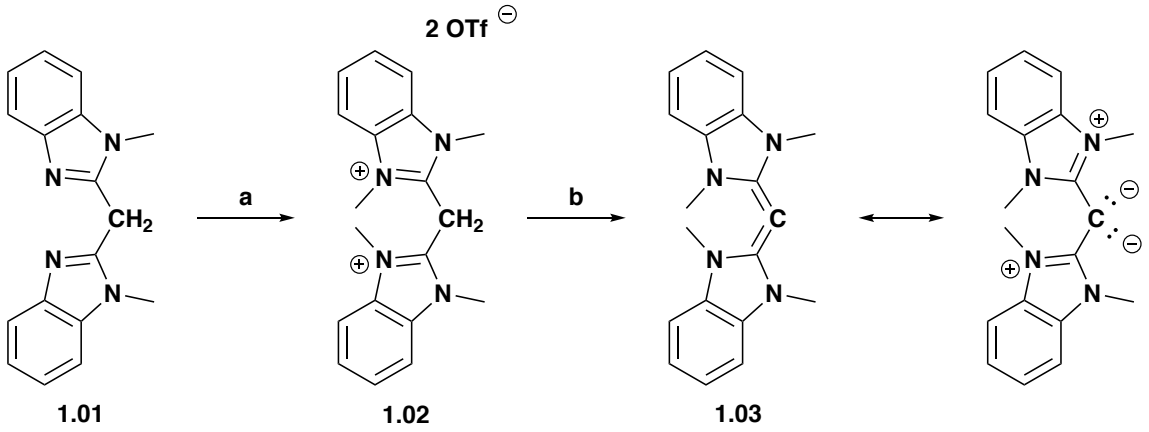
As aforementioned, the first identified carbon(0) (and main group centre) complex was the carbodiphosphorane, $C(PPh_3)_2$. As carbenes are generally the ligand of choice for main group coordination, it would follow that the substitution of the phosphine ligands to carbene ligands in CDPs would be a logical route of exploration. The use of carbenes to stabilise monoatomic carbon(0) has been extensively considered. Carbodicarbenes (CDCs), or CDPs where the phosphine ligands have been substituted with NHCs, were amongst the first investigated carbon(0) complexes.[37] Frenking *et al.* rationalised the apparent accessibility and interesting properties of CDCs using theoretical methods. It was hypothesised that the central carbon atom would retain its valence electrons as two lone pairs and would have a bent structure about the central C-C-C moiety. This 2007 study ends with a direct challenge to chemists to synthesise CDCs, thus provoking further research into ligand stabilised carbon(0) chemistry.[38]

A year following the Frenking challenge, two independent groups successfully synthesised monocarbon (C_1) carbodicarbene species. Fürstner *et al.* synthesised a carbodicarbene species *via* deprotonation of an iminium precursor using n-butyllithium (*n*-BuLi), from which it was subsequently confirmed as a donor ligand towards a gold centre (Scheme 1.01).[39]



Scheme 1.01. *Reagents and conditions: (a) n-BuLi, THF, 25 ºC; (b) AuCl(PPh$_3$). NaSbF$_6$, THF, 25 ºC. Carbodicarbene synthesised by Fürstner et al.*

Bertrand *et al.* synthesised a carbodicarbene through exploring the boundaries of allene (R-C=C=C-R) chemistry.[18] Allene, **1.03**, was synthesised in two steps from the known bis(N-methylbenzimidazolyl)methane, **1.01**.[40] Bismethylation using methyl trifluoromethanesulphonate (MeOTf) provided a dicationic precursor, **1.02**. Finally, bis-deprotonation using potassium hexamethyldisilazane (KHMDS) afforded **1.03** (Scheme 1.02).[18]



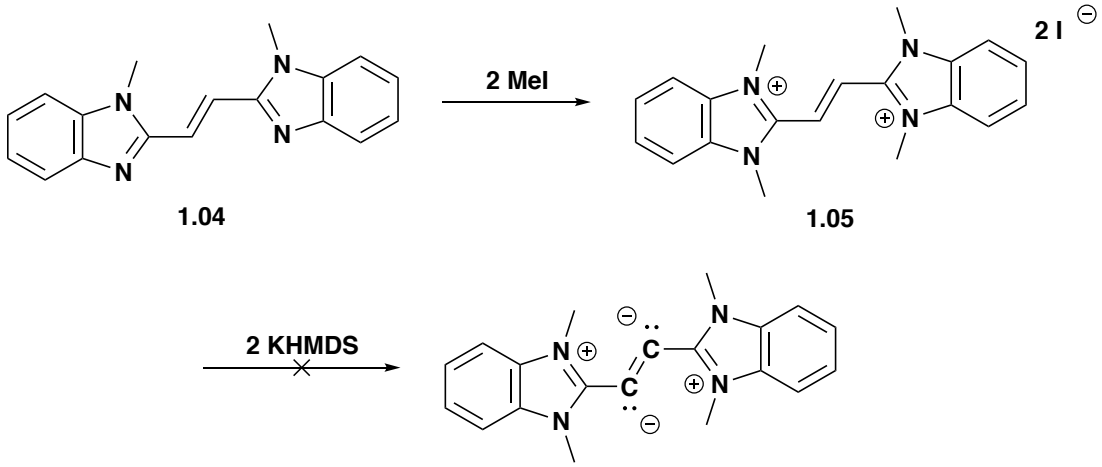
Scheme 1.02. *Reagents and conditions: (a) MeOTf, CH$_3$CN, 25 ºC; (b) KHMDS, C$_6$H$_6$, 25 ºC. Carbodicarbene synthesised by Bertrand et al.*[18]

Experimental work following the synthesis of **1.03** corroborated theoretical predictions made by Frenking. Single crystal X-ray analysis indicated a bond angle of 135º (*cf*. 132º predicted by Frenking).[38] It was further evidenced that **1.03** was able to coordinate to a rhodium centre *via* an η^1 coordination mode (rather than the η^2 coordination mode expected for 'regular' allenes), suggesting **1.03** is not a 'regular' allene and is more appropriately described as a carbon(0) complex (NHC → C ← NHC) with two lone pairs situated about the central carbon atom. Signficantly, analysis of the stretching frequencies of a rhodium-NHC species versus the corresponding rhodium-CDC species suggested that CDCs are stronger σ-donors than stable singlet carbenes.[18]

1.08 Attempted Synthesis of Ligand Stabilised Dicarbon

In 2012, our group proposed that an NHC stabilised two-centre carbon (C_2) fragment (NHC → C_2 ← NHC) would be an interesting synthetic target.[41] This particular target was inspired in part by the phosphine stabilised C_2 derivative (Ph_3P → C_2 ← PPh_3), which was observed by Stang *et al.* in 1991, and by Bertrand's aforementioned NHC → C ← NHC species.[18,42] Synthesis of Ph_3P → C_2 ← PPh_3 was achieved *via* deprotonation of a dicationic precursor using *n*-BuLi, however was only stable below - 40 °C.[42] Further, as there had been reports of other group 14 two-centre fragments (NHC_2Si_2 and NHC_2Ge_2),[6,22] the lighter NHC_2C_2 analogue reasoned to be an interesting target.

As the bonding in NHC → C_2 ← NHC was predicted to be much stronger than in Ph_3P → C_2 ← PPh_3,[43] isolation of this structure was a deemed a realistic goal and became a focal point of research in our group. The route employed mirrored that of Bertrand's synthesis whereby an analogous (to **1.02**) benzannulated dicationic precursor (**1.05**) was targeted, and then bis-deprotonation to yield the target NHC → C_2 ← NHC was attempted (Scheme 1.03).

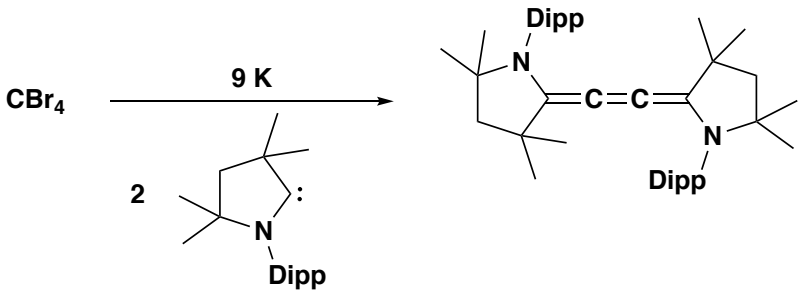


Scheme 1.03. *Attempted synthesis of NHC → C_2 ← NHC.*

Ultimately, synthesis of NHC → C_2 ← NHC was not successful.[17] In later reports, the NHC-stabilised dicarbon was determined to be a non-viable species. Similar results were also obtained with respect to isolation of the NHC-stabilised C_4 derivative, thus suggesting NHCs are not viable ligands to stabilise C_2 and C_4

fragments.[8] These observations were in accordance with an earlier proposal by Bestman that two donor ligands are unable to support C_n fragments when *n* is an even integer.[44,45]

Following our attempts to achieve NHC → C_2 ← NHC, there have since been reports of ligand stabilised C_2 fragments. In 2014, the successful synthesis of a cAAC stabilised dicarbon fragment was reported as generated from CBr_4, free cAAC and potassium metal (Scheme 1.04).[46]



Scheme 1.04. *Synthesis of the cAAC stabilised C_2 by Roesky et al.; Dipp = 2,6-diisopropylphenyl).*[46]

The cAAC stabilised C_2 demonstrated a cumulene ground-state structure and surprising stability.[46,47] The cAAC ligand is both more nucleophilic and electrophilic when compared with NHCs,[48] which can have a significant impact on the nature of a given species and provided an explanation as to why cAAC was successful in stabilisation of dicarbon when NHCs were not. Theoretical studies confirmed the cAAC-stabilised dicarbon to have significantly higher stability owing to a larger HOMO-LUMO gap when compared with its NHC counterpart.[17]

1.09 Later Developments of Carbon(0) Complexes and Synthetic Utility

Currently, carbon(0) complexes are no longer the elusive and mysterious species they were once considered. Since their initial discovery there has been several reported syntheses of carbodiphosphoranes and carbodicarbenes. Subsequent work has shifted from fundamental theory and discovery to potential applications and structural modifications of these electron rich and synthetically useful species.

CDCs are commonly compared to NHCs as there is well-defined similarities regarding their σ-donating capacity, with each having advantages or disadvantages when compared with the other. NHCs are easily synthesised and highly modular, however, are lacking in their π-accepting capacity.[49] Whereas, CDCs are stronger σ-donors and show unexpectedly strong π-accepting capacity owing to the empty p orbital of the central carbon of the NHC moiety.[50] It is these conditions that enable CDCs to find utility where NHCs are lacking, and gives importance to further development of this research field.

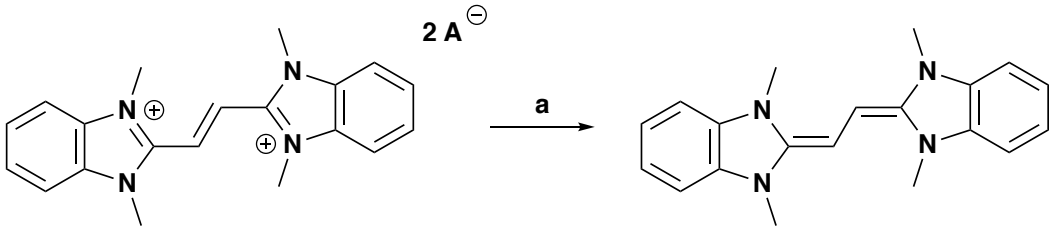
Carbon(0) complexes, although considered coordination compounds in their own right, have shown extensive application as strong donor ligands to isolate reactive transition metal complexes. Early in their discovery, one of the most common diagnostic tools used to identify carbon(0) species was their coordination to transition metal centres. Thus, one of the most common applications for carbon(0) species is coordination to metal centres. This includes geminal diauration and a double dative bond between carbon and uranium - a highly unusual bonding arrangement.[18,38,39,51–55]

Further, there has been significant application of carbon(0) complexes in main-group chemistry. Carbodicarbenes have been used as ligands toward boron centres, thus giving uncommon boron complexes.[56–58] E-H (E = B, C, Si) activation has been demonstrated *via* the 1,2-addition of E-H bonds over a carbodicarbene centre.[50] It has further been verified that CDCs can be used as competent organocatalysts for the methylation of amines using CO_2 as the substrate.[58] Finally, there has been work on expanding the structural diversity of this class of compounds with the report of asymmetrical synthesis of CDCs.[58]

1.10 The Serendipitous Synthesis of Compound 1.06

The attempted synthesis of an NHC stabilised C_2 fragment as reported in *Section 1.08* and observed in *Scheme 1.03*, although not successful, provided an interesting outcome. When dication **1.05** was subject to strong base, rather than a

deprotonation, a reduction was observed (Scheme 1.05). Although the target was not successfully isolated, the reduced species, **1.06**, displayed interesting properties, and as such became a focal point of work in our group.[8,17,59]



Scheme 1.05. *Reagents and conditions: (a) KHMDS or n-BuLi or $(CH_3)_3COK$ or $CoCp_2$, C_6H_6, 25 ºC. Reduction of **1.05** to **1.06** via strong base or reducing agent.*

The exocyclic carbon-carbon double bonds in **1.06** are unusually weak and as a result display unusual reactivity. This has been demonstrated *via* facile cleavage of these double bonds induced by triplet O_2, Ag_2O or tetrahydrothiophene-AuCl and will be further discussed in *Chapter Two*.

1.11 Scope of Thesis

It is evident that coordination chemistry at carbon is a new and flourishing field which challenges traditional paradigms of bonding at carbon. As per the above discussion, this thesis aims to further develop the field of ligand stabilised carbon fragments in low oxidation states, and chemistry related to these complexes. The study of carbon(0) complexes is currently a prosperous field of chemistry, and thus there is great merit in pushing the limits of these unusual species.

Chapter Two will discuss the reactivity of **1.06** with electrophiles and small molecules *via* attempting to mirror reactivity akin to that of N-heterocyclic olefins and thus inducing rupture of the exocyclic carbon double bonds. It will be demonstrated that the electronic nature of this double bond is not conducive to this reactivity and subsequent work will focus on the alteration of this bond.

In *Chapter Three* a combined experimental and theoretical study on the discovery of the first NHC halogen bonding interaction is investigated. Exploration of this system as a protection method of carbon-carbon multiple bonds is detailed. The successful protection/deprotection of diphenylacetylene using NHC halogen bonding interactions is reported. However, it will be shown that this method is ultimately inefficient to be synthetically useful when applied to other systems.

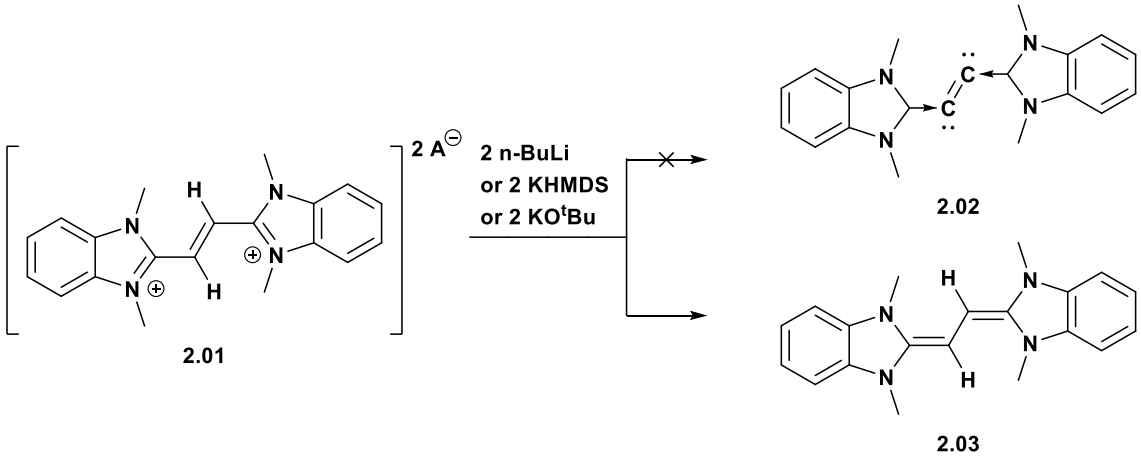
Chapter Four will discuss the attempted synthesis of a highly reactive phenyliodonium dication, $[PhI]^{2+}$, from $PhICl_2$ using $[Ag]_2[B_{12}Cl_{12}]$ mediated chloride abstraction. Although unsuccessful, a powerful new chlorinating agent *via* catalytic activation of $PhICl_2$ by $[Ag]_2[B_{12}Cl_{12}]$ was discovered. Following, an investigation of the scope of this system was investigated and electrophilic aromatic chlorination of a wide range of aryl species was achieved. This system was also demonstrated to be an effective chlorination method for carbon-carbon multiple bonds by acting as a stoichiometric source of activated Cl_2.

Finally, *Chapter Five* addresses the purported pyridine activation of $PhICl_2$ *via* a phenyliodonium monocation, $[PhI(Cl)]^+$. Attempts to observe or isolate $[PhI(Cl)]^+$ were unsuccessful, however, it was determined that pyridine forms a weak complex with $PhICl_2$ *via* a halogen bonding interaction. An investigation into this system unambiguously disproves formation of $[PhI(Cl)]^+$. Examination of the true activation of $PhICl_2$ by Lewis bases is presented, suggesting chloride is the species responsible in these interactions.

Chapter 2. The Weakest Organic Carbon-Carbon Double Bond

2.01 Introduction

During the attempted synthesis of the first N-heterocyclic carbene (NHC) stabilised dicarbon fragment (**2.02**), in 2015, our group had the serendipitous discovery of **2.03**. Initial efforts sought to deprotonate the central C_2 fragment, yielding the target NHC stabilised dicarbon compound, **2.02**, using a similar strategy reported for the synthesis of the analogous NHC stabilized C_1 fragment.[18] Treatment of **2.01** with two equivalents of strong base (*n*-BuLi or KHMDS or KO^{t}Bu) was employed. However, rather than the expected deprotonation, a reduction was observed (Scheme 2.01).[17]



Scheme 2.01. *Reduction of **2.01** to give reduced species **2.03**.*

Although not the intended target, **2.03** presented interesting structure and reactivity and became a focal point of work for this project. **2.03** showed asymmetry in the ^{1}H NMR spectrum, owing to prohibited rotation about the exocyclic carbon-carbon double bonds. This bonding situation deems it appropriate to consider **2.03** as a tetraamino-substituted 1,3-butadiene, or what has been coined as an N-heterocyclic olefin (NHO) dimer.

2.02 N-Heterocyclic Olefins

NHOs are a class of compounds that feature an alkylidene ($RN_2C=R$) moiety covalently bonded to an NHC scaffold and have the general structure, $NHC=CR_2$.

This bonding arrangement gives a highly polarised carbon-carbon double bond and simultaneous nucleophilic character at the exocyclic carbon atom. This can be rationalised by considering the resonance structures of an NHO (Figure 2.01).[60]

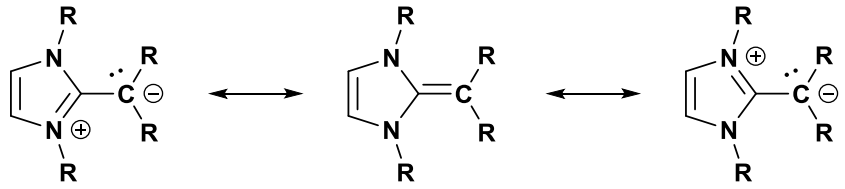
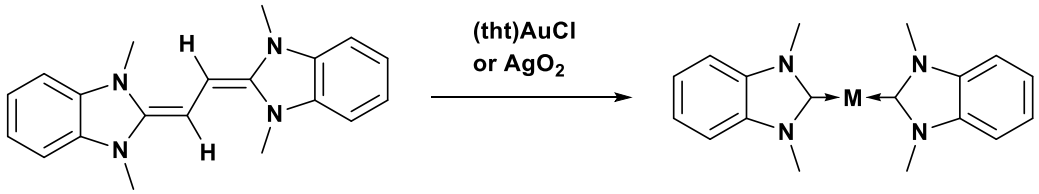


Figure 2.01. *Resonance structures of N-Heterocyclic Olefins (NHOs) indicating the polarized electronics of the exocyclic carbon-carbon double bond.*

The first NHO was synthesised (but not named as such) in 1993 by Kuhn *via* the deprotonation of a pentamethylimidazolium precursor.[61] These species were subsequently coined N-Heterocyclic Olefins (NHOs) in a later study exploring their capacity to stabilise low valent main group hydrides.[62] NHOs have displayed exceptional merit as ligands and have been used to isolate reactive species that were not accessible *via* more traditional ligands.[60] As **2.03** may be considered two NHO units tethered by an exocyclic carbon-carbon bond, we attempted to apply NHO chemistry to **2.03**. NHOs have been demonstrated to coordinate to metal centres, and subsequently have had useful application as catalysts.[63,64] We hypothesised that **2.03** may act as a bifunctional species that could coordinate to metal species or be used as an organocatalyst and further expand on NHO chemistry.

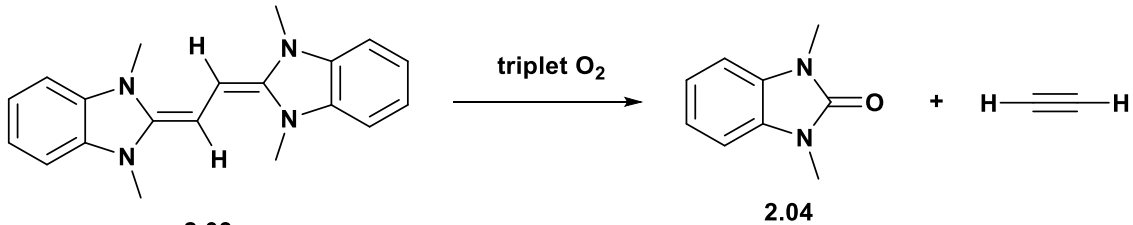
Upon reaction of **2.03** with chloro(tetrahydrothiophene)gold(I) ((tht)AuCl), the cationic bis-NHC-Au complex arising from the cleavage of the exocyclic carbon-carbon double bond was observed. Similar results were obtained upon reaction of **2.03** with silver oxide (Ag_2O) (Scheme 2.02).[59] This reactivity was not expected of **2.03** if the species was adhering to NHO-type chemistry. The expectation was that the exocyclic carbon atoms would behave as nucleophiles and coordinate to the metal centres giving a (**2.03**)AuCl (or the related silver) complex. Cleavage of the exocyclic carbon-carbon bond suggested an unusual electronic nature of this bond in compound **2.03**.



2.03

Scheme 2.02. *Reaction of* ***2.03*** *with (tht)AuCl or Ag_2O to give bis-NHC-metal(M) complexes; M = Ag or Au.*

Unusually, it was observed that **2.03** reacted with atmospheric oxygen at room temperature to give the urea, O=NHC, **2.04**, and acetylene gas. It is extremely rare for carbon-carbon double bonds to react with triplet O_2. Although this was not the first example of a carbon double bond reacting with O_2, all previous examples use activated singlet oxygen sources or catalysis to affect the reaction.[65,66] Whereas **2.03** undergoes reaction under mild conditions, uncatalysed and with an unactivated O_2 source (Scheme 2.03).



2.03 2.04

Scheme 2.03. *Reaction of* ***2.03*** *with triplet O_2 to give urea,* ***2.04****, and acetylene gas.*

This unprecedented reactivity observed for a carbon-carbon double bond prompted an examination of the nature of this species and its bonding situation *via* theoretical methods. The bond dissociation energy (D_e) for the exocyclic carbon-carbon bond was found to be 407.5 kJ mol^{-1} which is uncharacteristically weak (*cf.* 728.4 kJ mol^{-1} for the C=C bond in ethene).[67] Further, energy decomposition analysis and natural orbital for chemical valence (EDA-NOCV) calculations were performed. These calculations indicated the central C_2H_2 fragment carries a large negative charge and thus, the most appropriate description of the bonding in **2.03** is most appropriately described as dative in nature (*i.e.* NHC → (C_2H_2) ← NHC).[59]

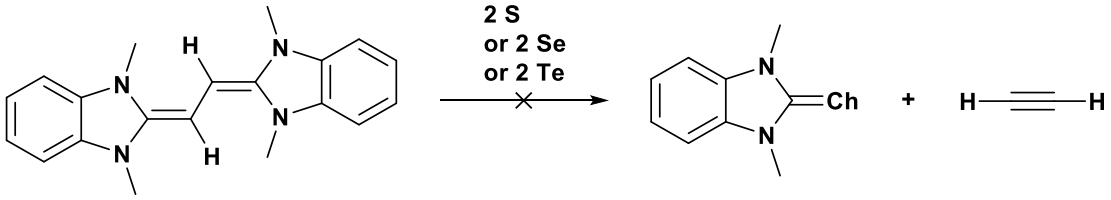
The facile cleavage to form bis-NHC-metal complexes and the surprising reactivity with singlet O_2 in conjunction with the theoretical investigation suggests that this bond is unusually weak and has no reported organic rival. Of course, tetrafluoroethene hosts a weaker carbon-carbon double bond, however, this unusual phenomenon can be explained by the stability of the two CF_2 groups as separate moietys.[68] An investigation into exploiting this electronic nature to deliver novel reactivity or synthetic species was performed. Initial work involved attempting cleavage of the exocyclic carbon bond to furnish species of the type NHC=R.

2.03 The Reaction of the Reduced Species with Elemental Chalcogens

As the reaction of **2.03** and O_2 induced cleavage of the exocyclic carbon-carbon bond to give the urea, **2.04**, reactivity of **2.03** with other group 16 elements (Ch) was explored. It would be advantageous to have access to NHC=Ch type species as this bonding motif is uncommon.[69] **2.03** was reacted with the other chalcogens (S, Se, Te) in elemental form. It was hypothesised that the reaction with S, Se and Te would induce cleavage of the exocyclic carbon-carbon double bond and give the corresponding chalcogen-urea analogues, Ch=NHC (Ch = S, Se, Te).

One stoichiometric equivalent of **2.03** and two equivalents of the elemental chalcogen were combined in benzene at room temperature. Reactions were rapidly stirred for one hour and subsequently analysed by NMR. The reaction of **2.03** and sulphur gave a complex mixture of unidentifiable products as determined *via* ^{1}H NMR spectroscopy. The reaction was repeated at cold temperatures (-78 ºC) in PhMe to the same fate. Following, the reaction was repeated with selenium and tellurium. For each, the reaction at room temperature indicated no change to starting material as determined by ^{1}H NMR and ^{77}Se or ^{125}Te NMR, respectively. In the case of selenium and tellurium, the reaction was repeated in a pressure flask and heated to 100 ºC in attempt for elevated temperatures and an increase in pressure to promote this transformation. Unfortunately, there was no reaction between **2.03** and selenium or tellurium (Scheme 2.04). The reason for the

inactivity was not clear. Presumably, the insolubility of elemental selenium and tellurium was a contributing factor.

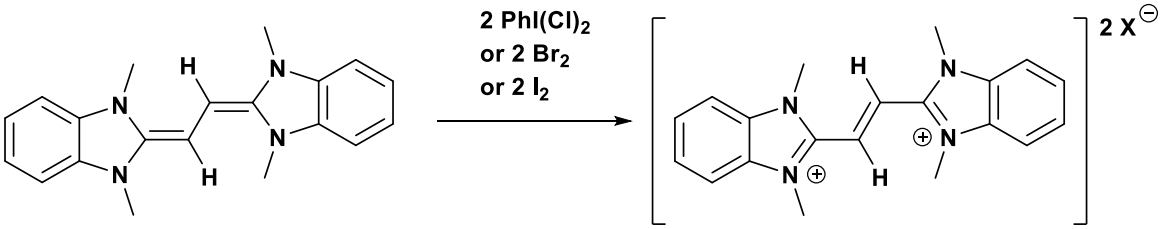


2.03

Scheme 2.04. *Attempted synthesis of Ch=NHC from* ***2.03*** *and elemental Ch (Ch = S, Se, Te).*

2.04 Further Reactions of the Reduced Species

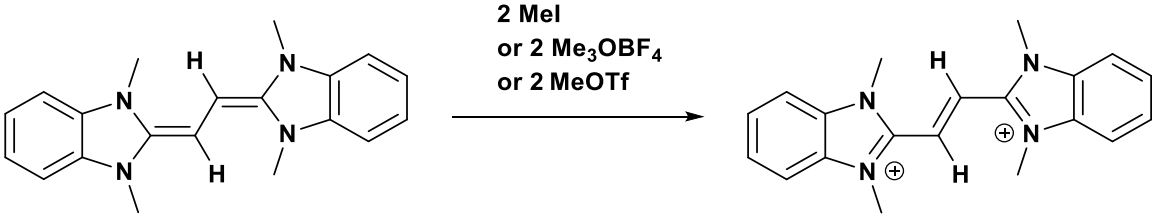
The next series of reactions explored was the reaction of **2.03** with halogens, X (X = Cl, Br, I). It was hypothesised that either addition of the halogen over the exocyclic carbon-carbon double bond, or formation of a 2-halobenzimidazolium salt and acetylene were possible outcomes. One stoichiometric equivalent of **2.03** and two equivalents of the given elemental halogen (Br_2, I_2) were combined in benzene at room temperature. As molecular chlorine is difficult to handle, iodobenzene dichloride ($PhICl_2$) was used as it represents an easy-to-handle source of Cl_2. Upon addition of the halogen source, in each case, an immediate formation of a yellow precipitate was observed. Isolation of this precipitate and subsequent dissolution in CD_3CN and ^1H NMR analysis indicated formation of dication **2.01** in quantitative yield. In all cases, oxidation from **2.03** to dication **2.01** was observed (Scheme 2.05). This observation was not particularly surprising as previous electrochemical studies performed show the facile redox reversibility between **2.03** and **2.01,** and the halogens are known oxidizing agents.[17]



2.03 2.01

Scheme 2.05. *Oxidation of* ***2.03*** *to* ***2.01*** *as induced by either $PhICl_2$, Br_2 or I_2.*

The next series of reactivity studies performed was the reaction of **2.03** with electrophilic methylating agents. Iodomethane (MeI), trimethyloxonium tetrafluoroborate (Me_3OBF_4), and methyl trifluoromethanesulfonate (MeOTf) were the selected methylating agents. The reaction was performed using one stoichiometric equivalent of **2.03** and two equivalents of the given methylating agent. As with the reaction with halogens, oxidation from **2.03** to dication **2.01** was observed.



2.03 **2.01**

Scheme 2.06. *Oxidation of **2.03** to **2.01** as induced by either MeI, Me_3OBF_4 or MeOTf.*

Attempts to induce reactivity of the exocyclic carbon-carbon double bond of **2.03** were unsuccessful. Upon reaction of **2.03** with chalcogens to emulate reactivity as observed with O_2, either decomposition (S) of starting material, or no reaction (Se, Te) was observed. The reaction of **2.03** with halogen or halogen substitutes afforded dication **2.01**, the product of an oxidation reaction as facilitated by the halogen species. Similarly, the reaction of **2.03** and electrophilic methylating reagents furnished dication **2.01**. The surprising stability of the exocyclic carbon-carbon double bond as demonstrated through these attempted reactions prompted investigation into a method in which this bond could be made weaker to affect these reactions.

2.05 Weakening the Weakest Carbon-Carbon Double Bond

Currently, **2.03** can be considered the one of the weakest organic carbon-carbon double bonds. This claim is substantiated by the unusual reactivity demonstrated at this site and further supported by theoretical analysis.[59] A dative bonding description between the NHC moiety and the central C_2H_2 fragment is an explanation for the weakness attributed to this carbon-double bond (Figure 2.02).[59]

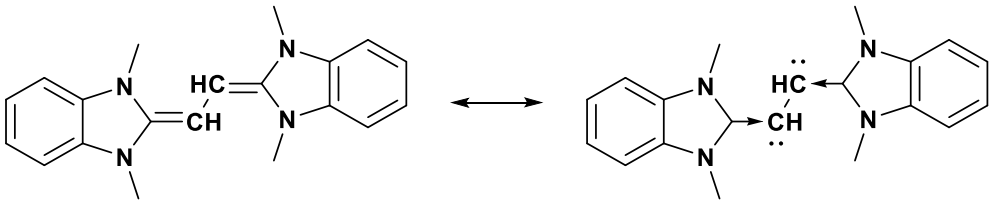


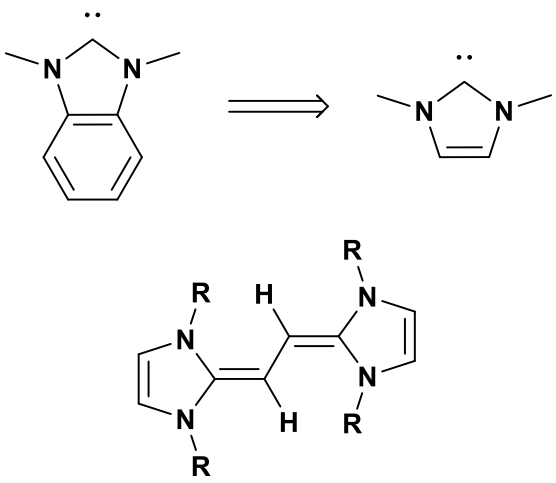
Figure 2.02. *Resonance depiction of* ***2.03*** *showing dative contribution.*

As demonstrated from the reactions with chalcogens, halogens and methylating agents, cleavage of this carbon-carbon was not induced by any of the aforementioned reagents. Thus, the primary focus of this project shifted towards further weakening the carbon-carbon double bond. As the bond is considered to have some dative nature, a method for tuning the electronics of this species would be to change the supporting NHC ligand to one with different electronic properties.

NHC ligands are highly modular and versatile as there are many possibilities for functional variation. The heterocyclic backbone and nitrogen sites both enable a wide range of chemical diversity. This variation directly impacts important properties of the ligand, and in turn, the species it is bonded to. Structural changes alter the σ- and π-donating, and π-accepting capacity of the ligand. Further, the steric bulk of the ligand is altered by changes in structure, which in turn, has an overall effect on the electronic properties of the ligand as a whole.[33] To alter the electronic nature of an NHC, two important factors must be considered: inductive effects and mesomeric effects. Inductive effects relate to the electron-withdrawing or -donating nature of atoms or functional groups, and mesomeric effects concern an atom or functional group's ability to withdraw or donate a lone pair of electrons. It follows that atoms/groups that give positive inductive or mesomeric effects

increase the electron density and thus donating capacity at the carbenic carbon. The reverse holds true; atoms or functional groups that have negative inductive or mesomeric effects decrease the donating capacity of the ligand.[33] In the case of NHCs, these effects explain their nucleophilicity. The lone pair from either of the cyclic nitrogen atoms interacts with the empty p orbital of the sp^2 hybridised carbene, thus increasing the electron density about the carbenic carbon.[70]

For this project, a ligand that had a weaker π-accepting capacity to the original benzimidazole based NHC (^{Me}BzIm) ligand was targeted. Changing ^{Me}BzIm to a ligand that had a weaker π-accepting capacity to support the central C_2H_2 fragment should have led to a decrease in strength of the exocyclic carbon-carbon bond, and consequently, increased the reactivity at this site. To support this hypothesis, the use of ^{77}Se NMR spectroscopy to quantify the π-accepting nature of NHCs has been demonstrated to provide a reliable comparison between NHC species. A report by Ganter *et al*. shows comparison between two NHCs that resemble ^{Me}BzIm and a de-benzylated imidazole (^{Me}Im) NHC. A decrease in the π-accepting capacity for the latter was demonstrated.[71] Therefore, the initial strategy involved alteration to the NHC backbone. It was hypothesised that the removal of both the π-system and functionality in general from the backbone of the NHC would decrease the accepting capacity of the ligand. A change from ^{Me}BzIm to ^{Me}Im was the first point of inquiry, to give the targeted **2.04** as hosting the new weakest organic carbon-carbon double bond (Figure 2.02).



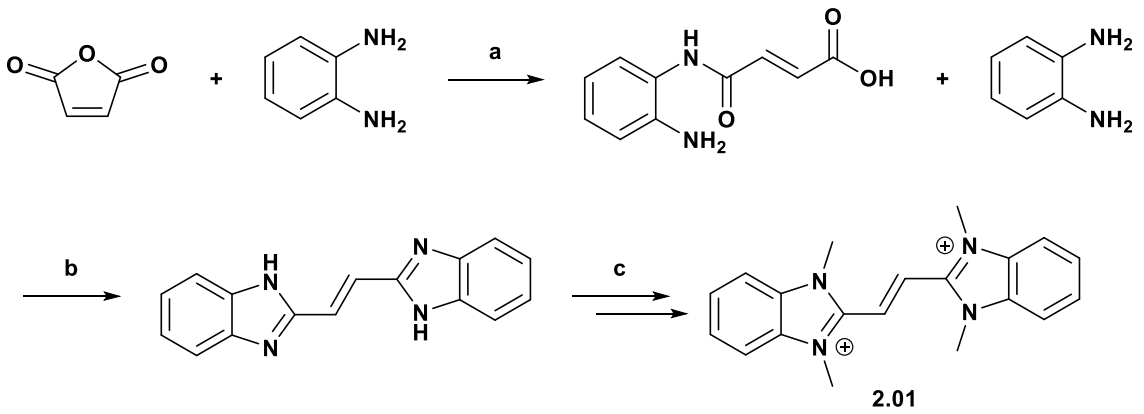
2.04

Figure 2.03. *Change of ^{Me}BzIm to ^{Me}Im in order to decrease the donicity of the NHC (above). Compound* ***2.04****, the new weakest carbon-carbon double bond; R = alkyl groups (below).*

2.06 Synthesis of Compound 2.04 as Supporting the New Weakest Carbon-Carbon Double Bond

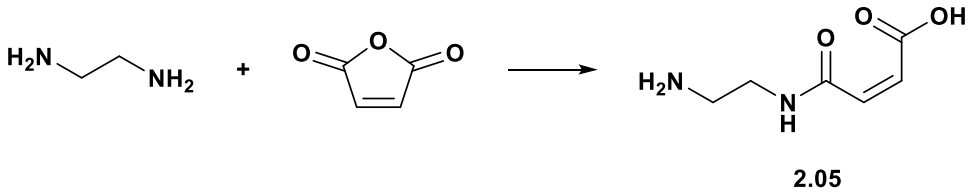
The general route to access **2.04** was to first synthesise the corresponding dicationic precursor. As with the previously reported method, reduction of the dication should afford the target molecule. A literature search for the debenzylated scaffold and similar structured species was performed. There had been one report in a 2008 patent of such a species,[72] however, attempts to replicate this chemistry were not successful. Therefore, a method was developed without direct literature precedent, starting with exploring the previously employed synthesis of **2.01**.

As previously depicted in *Scheme 2.01*, the original synthesis of **2.03** is from the advanced starting material, dicationic **2.01**. The synthetic route employed to **2.01** is from 1,2-diaminobenzene and maleic anhydride.[17,73] The synthesis involves the formation of an amide *via* attack of the amino group onto the carbonyl of maleic anhydride. Subsequent nucleophilic attack of a second amino group followed by polyphosphoric acid (PPA) cyclisation gives the required C_2 bis(benzimidazole) core. Finally, methylation of the nitrogen atoms in two steps yields the target dication, **2.01** (Scheme 2.07).



Scheme 2.07. *Reagents and conditions: (a) Et_2O, 25 ºC, 30 m; (b) PPA, 220 ºC, 3 h; (c) THF, KOH, MeI, ∆, 6 h; (c) MeCN, MeI, ∆, 8 h. Synthesis of* ***2.01*** *from 1,2-diaminobenene and maleic anhydride.*

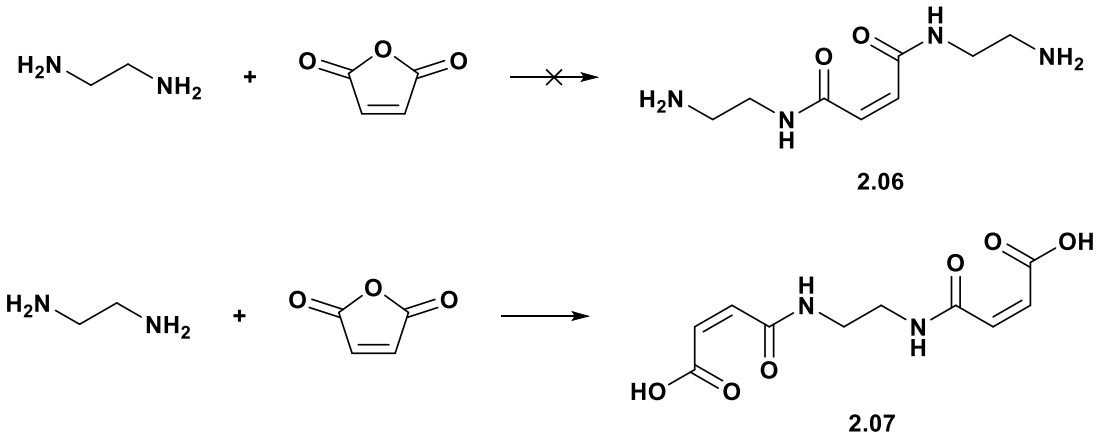
Although this synthesis worked well for generation of **2.01**, it inevitably incorporates the phenyl moiety onto the NHC backbone. Therefore, initial work attempted a similar reaction pathway using ethylenediamine and maleic anhydride in attempt to obtain the analogous amide intermediate, **2.05** (Scheme 2.08).



Scheme 2.08. *Reaction between ethylene diamine and maleic anhydride to give the monosubstituted* ***2.05****.*

It was planned that with **2.05** in hand, a second condensation with ethylene diamine to give the diamino-maleic acid product (**2.06**), followed by PPA induced cyclisation would give the bis(imidazole) core advanced starting material targeted for this project. There have been no reports of **2.05** in the literature, however, the reaction between ethylenediamine and maleic anhydride to give the diamino-maleic acid, **2.06**, had been reported.[74] Upon further investigation there was no mention of **2.06** in the report, but rather, a bis(maleic acid) substituted ethylene diamine species, **2.07**, was the product reported, suggesting an error in the CAS database. Regardless, the reaction between ethylene diamine and maleic anhydride was attempted according to the reports protocol. A solution of maleic anhydride in acetonitrile was added dropwise to an equimolar solution of ethylene diamine in acetonitrile. A white precipitate formed and was isolated. Characterisation of this

white solid determined **2.07** to be the sole product, and no evidence of generation of **2.06** was observed (Scheme 2.09).



Scheme 2.09. *Literature report of the reaction between ethylene diamine and maleic anhydride to give* ***2.06*** *or* ***2.07****.*

There had been other reports of **2.06** in the literature. However, these reports do not characterize the species and use it as an intermediate to obtain disubstituted diaminoethane products.[74–76] Nonetheless, the reaction between ethylene diamine and maleic anhydride was pursued. Referring to the original synthesis of **2.01**, the reaction was repeated using conditions analogous to that pathway. One equivalent of maleic anhydride was dissolved in Et_2O and was added dropwise to an equimolar solution of ethylene diamine in Et_2O. A white precipitate formed upon addition and was isolated. ^{1}H NMR spectroscopy and mass spectrometry indicated exclusive formation of **2.07**, and no formation of **2.06** or **2.05** was evident. As the product produced from these reactions was the bis-maleic acid substituted product, it was hypothesised that increasing the relative ratio of ethylene diamine to maleic anhydride would prevent formation of **2.07** and promote formation of **2.05** or **2.06**. The reaction was attempted in neat ethylene diamine to encourage formation of the monosubstituted or disubstituted amide target material. Regardless, **2.07** was the only obtained product.

The combination of ethylene diamine and maleic anhydride features heavily in polymer chemistry.[75,77–79] Suggesting that synthesis of monosubstituted products were unfavourable *via* this reaction pathway and by using these reagents, polymer type reactions were occurring preferentially. It was determined that this route was

not viable for the synthesis of compound **2.04**. Therefore, other routes to **2.04** were explored, with a focus on using materials with the imidazole ring pre-formed as imidazole products are commercially available and inexpensive.

2.07 Carbon Coupling Reactions

Using imidazole as a starting material, it was evident that a carbon-carbon bond forming reaction would be necessary along the synthesis, thus, carbon coupling reactions were explored. If the target is considered retrosynthetically, *Figure 2.04* shows the sequence of disconnections most appropriate for this method.

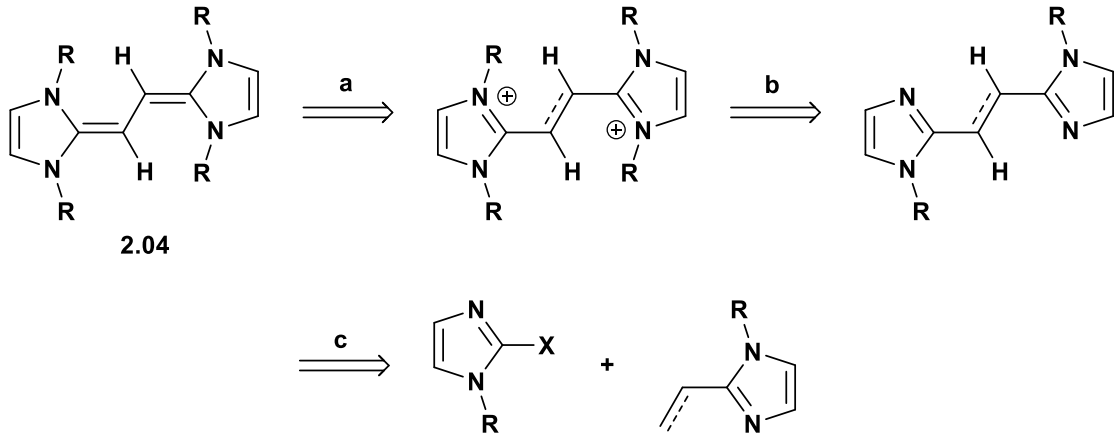


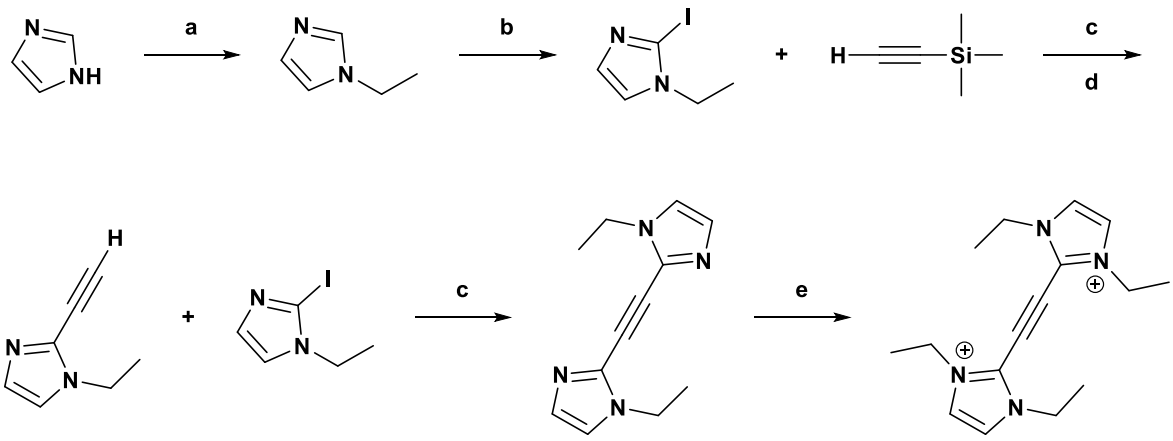
Figure 2.04. *Retrosynthetic analysis of target material* ***2.04****.*

Disconnection **a** is a two-electron reduction. Previous methods using two equivalents of strong base or cobaltocene used to generate **2.03** from **2.01** were highly effective, this strategy was expected to work efficiently for this analogous transformation. Disconnection **b** is a di-alkylation. As this type of reaction is very common and highly effective, this sequence was expected to work well. Formation of the dicationic salt was considered to be a straightforward transformation and the expected stability of this salt product is beneficial (*cf.* stability of dication **2.01** has been found to be stable >5 years in under ambient conditions). This can be affected using an alkylhalide (*e.g.* iodomethane or methyltriflate) in conjunction with base and forcing conditions. Finally, **c** could be achieved through a cross coupling reaction from a 2-haloimidazole and a 2-vinyl- or 2-ethynylimidazole. The particular cross coupling reactions that best fit these criteria are the Heck coupling and Sonogashira coupling reactions.

In 2017, we reported the synthesis of a ^{Me}BzIm C_4 derivative. Two successive Sonogashira coupling reactions were employed.[8] Initially, procedures attempted to

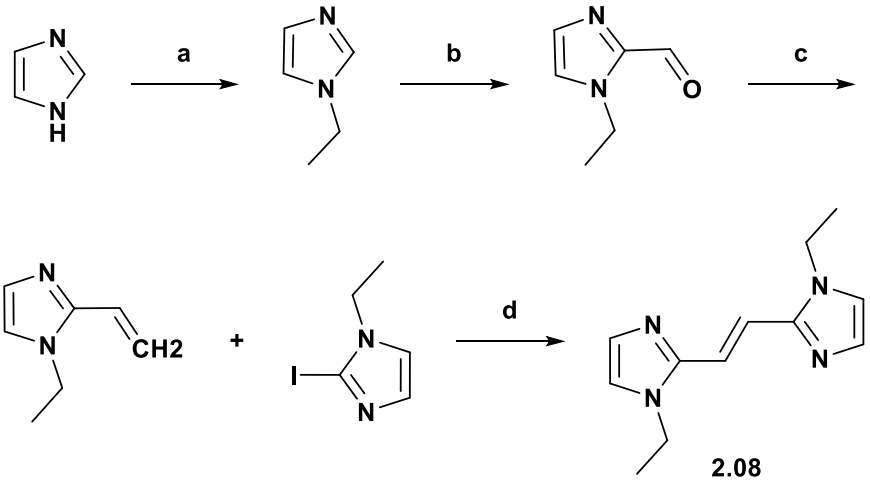
adopt this previously used method to install a carbon-carbon triple bond at the 2-position of an imidazole unit, and then subsequently couple it to another 2-haloimdazole unit. Following that, reduction of the triple bond could yield the core structure of the targeted **2.04**.

Starting from imidazole, an alkylation using bromoethane (EtBr) was performed. This reaction was well documented and gave N-ethylimidazole.[80] Following, lithiation/iodination using n-butyllithium (n-BuLi) and molecular iodine was performed to give 2-iodo-N-ethylimidazole.[81] To install the alkynyl functionality at the 2- position, 2-iodo-N-ethylimidazole was dissolved in anhydrous tetrahydrofuran (THF) and degassed. 1 mol % $Pd(PPh_3)_2Cl_2$ and 0.5 mol % CuI were added following with the addition of two stoichiometric equivalents of trimethylsilane (TMS) acetylene. The solution was refluxed for 5 hours.[82] Installation of the TMS acetylene functionality at the 2- position was achieved as confirmed by ^{1}H NMR spectroscopy *via* the clear indication of the TMS moiety present integrating to 9 relative to two new imidazole backbone protons. Although the 2-alkynyl-N-ethylimidazole was observed, extremely poor yields were obtained with < 1% crude total yield (based on imidazole). The poor yield was attributed both to the volatility and instability of these species. Decomposition of 2-iodo-N-ethylimidazole and 2-alkynyl-N-ethylimidazole was indicated through ^{1}H NMR analysis of samples being left in NMR tubes under ambient conditions at times less than 24 hours. This synthetic route was determined to be too inefficient to pursue as less than halfway through the total synthesis yield prohibited continuation. Therefore, other carbon coupling based synthetic routes to **2.04** were considered (Scheme 2.10).



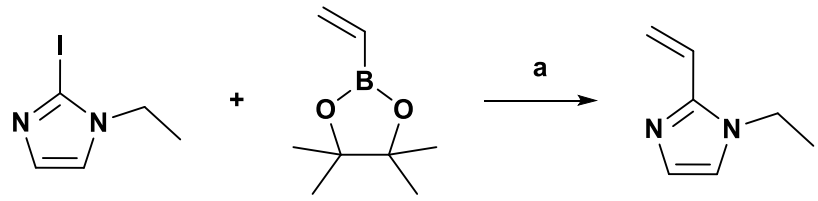
Scheme 2.10. *Reagents and conditions: (a) $(CH_3)_2CO$, EtBr, K_2CO_3, Δ, 12 h; (b) THF, n-BuLi, I_2, -78 ºC to 25 ºC, 12 h; (c) THF, NEt_3, $Pd(PPh_3)_2Cl_2$, CuI, TMS acetylene, 25 ºC to Δ, 5 h; (d) CH_3OH, K_2CO_3, 25 ºC, 30 m. Proposed Sonogashira coupling method attempted to achieve compound* ***2.04*** *from imidazole.*

Established chemistry on 2- substituted imidazoles in the literature was limited, presumably due to the previously described instability. Owing to the lack of diversity of 2-substituted imidazoles, there was a limited scope of cross coupling reactions possible for this system. The Heck reaction was the most promising candidate as N-ethyl-2-iodoimidazole had previously been synthesised and installation of a vinyl group at the 2- position on N-methylimidazole had been reported.[83] Synthesis of N-ethyl-2-vinylimidazole was targeted, and subsequently the Heck reaction by coupling with N-ethyl-2-iodoimidazole, to give **2.08.** Starting from imidazole, alkylation using bromoethane was performed as previously described, yielding N-ethylimidazole.[80] Following, formylation at the 2- position was performed using n-BuLi and dimethylformamide (DMF).[84] A Wittig reaction was used to transform the formyl functionality to a vinyl group *via* the use of n-BuLi and methyl triphenylphosphonium bromide ($MePPh_3Br$).[83] Synthesis of N-ethyl-2-vinylimidazole using the Wittig reagent, $MePPh_3Br$, was challenging and did not give reliable or reproducible results. The reaction worked sporadically and in poor yields. Therefore, an alternative route to install the vinyl group at the 2- position of the imidazole ring was investigated (Scheme 2.11).



Scheme 2.11. *Reactions and conditions: (a) $(CH_3)_2CO$, EtBr, K_2CO_3, ∆, 12 h; (b) Et_2O, n-BuLi, DMF, -78 ºC to 25 ºC, 24 hr(c) THF, n-BuLi, $CH_3(PPh_3)Br$, 0 ºC to 25 ºC, 24 h (d) DMF, K_2CO_3, $Pd(PPh_3)_2Cl_2$, ∆, 24 h. Heck coupling method to give* ***2.08****.*

As there were only two reports of 2-vinyl imidazole species in the literature, the other method described was explored. In a 2009 study, Dubois *et al.* reported the successful installation of a vinyl group at the 2- position of N-methylimidazole ring starting from N-methyl-2-iodoimidazole. The reaction employs a Suzuki cross-coupling reaction between N-methyl-2-iodoimidazole and vinylboronic acid pinacol ester.[85] This reaction was applied to our system in attempt to obtain a reliable synthesis of N-ethyl-2-vinylimidazole (Scheme 2.12).



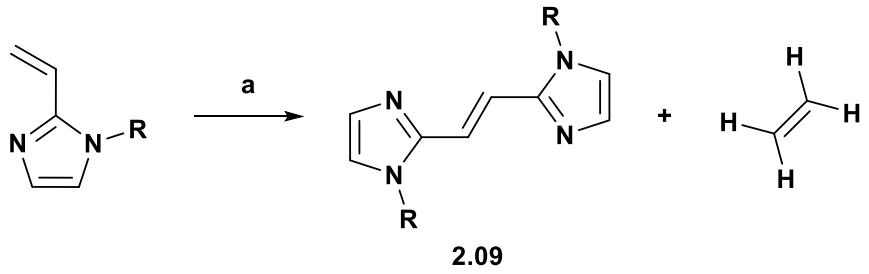
Scheme 2.12. *Reagents and conditions: (a) DMF, Na_2CO_3, $Pd(PPh_3)_4$, 135 ºC, 3.5 h. Suzuki coupling of 1-ethyl-2-iodoimidazole and vinylboronic acid pinacol ester.*

This reaction was unsuccessful. In this particular case, after several repeats, N-ethyl-2-vinylimidazole was not observed in the crude reaction mixture. We troubleshooted issues with this reaction to attempt to find a working synthesis. Both N-ethyl-2-iodoimidazole and vinylboronic acid pinacol ester (commercially purchased) were checked by NMR spectroscopy to ensure no decomposition or

unexpected materials were present. $Pd(PPh)_4$ was freshly generated for this reaction and had been successfully used for other transformations unrelated to this project. Finally, the reaction was attempted in dry DMF, as indicated in the paper,[85] and in wet DMF as is more commonly practiced in Suzuki cross-coupling reactions. All of these attempted optimisations were unsuccessful, suggesting this method was not suitable for the synthesis of compound **2.04**.

2.08 Olefin Metathesis Reactions

While our focus was devoted to installing the vinyl group at the 2- position of an imidazole ring, it was hypothesised that olefin metathesis could be used in order to synthesise the target compound from an N-alkyl-2-vinylimidazole, giving the target scaffold (**2.09**) and ethylene gas (Scheme 2.13).



2.09

Scheme 2.13. *Reagents and conditions: (a) CH_2Cl_2, 1% Ru cat., 40 ºC, 24 h. Synthesis of **2.09** using olefin metathesis conditions from N-alkyl-2-vinylimidazole; R = alkyl/protecting group.*

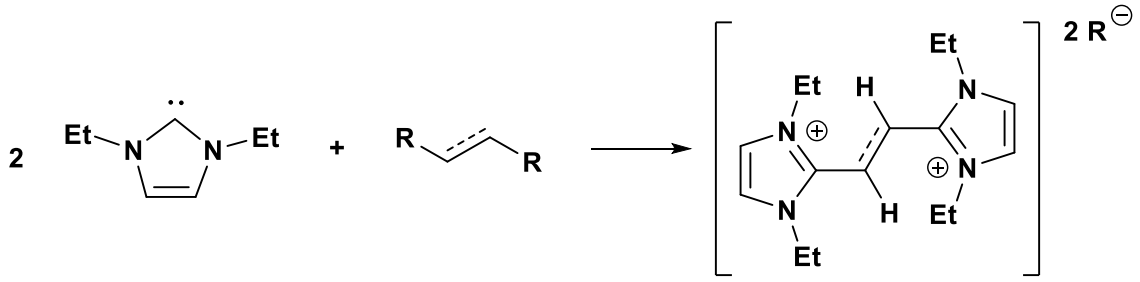
The olefin metathesis route to **2.09** was expected to be relatively straightforward and was expected to work well on the basis that an N-alkyl-2-vinylimidazole could be readily synthesised. As discussed previously, it was evident that N- methyl/ethyl imidazole species were not amenable to reproducible installation of a vinyl group at the 2- position of the imidazole ring. As this route seemed promising, great effort was pursued in order to achieve this. Rather than the use of alkyl groups, protecting groups were explored hoping that the bulkiness of these groups would enable stability of the imidazole species enough to support and enable installation of the vinyl group at the 2- position, and then could subsequently be removed and replaced with alkyl groups at a later stage of the synthesis.

The first N-protected imidazole species explored was the tert-butoxycarbonyl (Boc) protected species. N-Boc-imidazole was synthesised using standard conditions for this type of transformation. Following, installation of the vinyl group at the 2-position of N-Boc-imidazole was attempted. Initially, the initial Wittig reaction method was attempted, however, it was determined that the Boc group was not tolerant of the nucleophilicity of n-BuLi. In these attempts, cleavage of the Boc group was observed and the crude reaction mixture showed the fate of the imidazole moiety as free imidazole.

Following, 2-iodo-N-Boc-imidazole was synthesised following a literature procedure,[86] in hope that 2-iodo-N-Boc-imidazole could be employed in a Suzuki reaction with vinylboronic acid pinacol ester as described in *Scheme 2.12*. Unfortunately, this pursuit was unsuccessful, and no formation of 2-vinyl-N-Boc-imidazole was observed in the crude ^{1}H NMR spectrum. As these cross-coupling reactions were unsuccessful, we hypothesised that having a vinyl group at the 2-position of the imidazole species was not amenable for gram scale synthesis and isolation, thus rendering this method unfeasible for generation of **2.04**. Our attention was diverted to other potential methods that avoid the stepwise formation, but rather, installed the central C_2 fragment flanked by imidazole rings in one step.

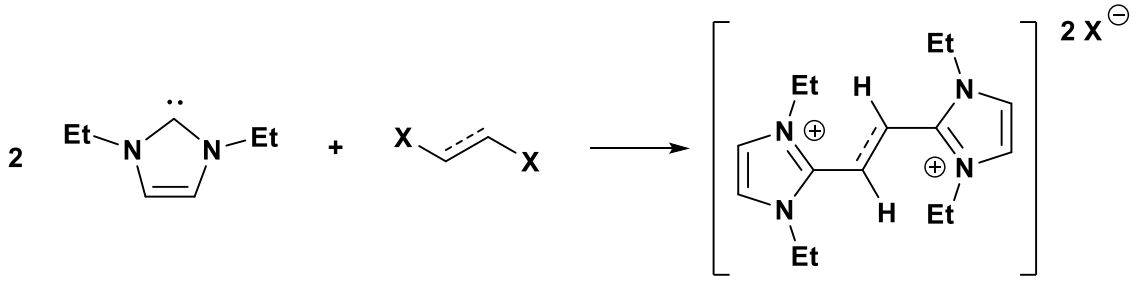
2.09 Substitution Reactions – Alkylhalides and Pseudoalkylhalides

Due to the challenges outlined using carbon coupling reactions, a different synthetic route to the dicationic precursor **2.04** was targeted. It was hypothesised that the strong nucleophilicity of free carbenes (*e.g.* ^{Et}Im) could be exploited in an S_N2 reaction with an appropriate electrophilic C_2 substrate to furnish the dicationic target material in one step (Scheme 2.14).



Scheme 2.14. *General nucleophilic substitution reaction of ^{Et}Im and an electrophilic C_2 species (R = leaving group).*

1,2-Dihaloalkanes were the first investigated C_2 sources as typically, halogens make good leaving groups and counter anions. Further, 1,2-dihaloalkanes are inexpensive and readily available reagents (Scheme 2.15).



Scheme 2.15. *General nucleophilic substitution reaction of ^{Et}Im and a haloalkane C_2 species (X = Cl, Br, I).*

Initially, the reaction was attempted with 1,2-dichloroethane. A solution of two equivalents of ^{Et}Im in benzene was added to 1,2-dichloroethane. Immediately, a yellow precipitate crashed out of solution and was analysed by ^{1}H NMR spectroscopy. NMR analysis indicated a complex mixture of products from the reaction. Rather than the intended dication, the major products were determined to be 2-chloro-N,N-diethylimidazolium chloride, N,N-diethylimidazolium chloride, and vinyl chloride. These results were consistent with observations reported by Kuhn.[87] Following, the reaction was repeated with 1,2-dibromoethane. Similarly, the target dication was not achieved *via* this reaction. As with the reaction with 1,2-dichloroethane, the major products identified from this reaction were 2-bromo-N,N-diethylimidazolium bromide, N,N-diethylimidazolium bromide, and vinyl bromide. This result was in conjunction with results obtained by Jones and Junk.[88]

Following, the reaction was explored using 1,2-diiodoethane with hope that the greater leaving group capacity of iodide would help deliver the target dication.

Unfortunately, the reaction did not proceed as expected. Neither the target dication, nor results in conjunction with the 1,2-dichloro- or 1,2-dibromoethane reactions were obtained. Rather, the clean generation of N,N-diethyl-2-iodoimidazolium iodide and ethylene were observed. This unexpected result led us to perform a detailed theoretical study as to the possible mechanism in which the transformation was occurring, which will be explored in greater detail in *Chapter Three*.

Further S_N2 reactions within the class of alkyl halides was explored. The reaction was performed with 1,1,2-tribromoethane and 1,2-dichloroethene. These reactions displayed similar observations with the related 1,2-dichloro- or 1,2-dibromoethane. Finally, 1,2-dipseudohalide C_2 sources were prepared as potential electrophilic reactants for this transformation. Namely, tosylate (Ts), mesylate (OMs), and acetate (OAc) in the 1,2- positions on the C_2 scaffold (XCH_2CH_2X; X = Ts, OMes, OAc) were synthesised. Synthesis of these compounds was performed from literature procedures.[89–91]

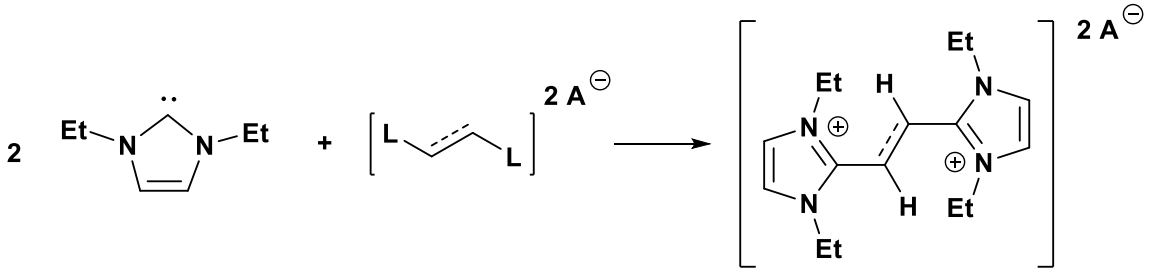
The 1,2-dipseudohalide C_2 source was suspended in benzene and treated with two equivalents of ^{Et}Im. In the case of 1,2-ditosyl- and 1,2-dimesyl-ethane, the reaction rapidly changed colour to a deep brown solution. ^{1}H NMR spectroscopic analysis indicated a complex mixture of unidentifiable products. Upon analysis it was determined that neither starting material nor the expected ^{Et}Im-C_2-^{Et}Im dication was obtained. When the reaction was attempted with 1,2-diacetylethane, no visible change had occurred. Following 24 h, ^{1}H NMR indicated no change to starting materials.

The S_N2 reaction pathway was explored to achieve the target ^{Et}Im-C_2-^{Et}Im dication. A range of 'ideal' C_2 sources were selected and reacted with free carbene, ^{Et}Im. Initial work used 1,2-dihaloalkanes and 1,2-dihaloalkenes owing to their accessibility. The results of these reactions did not yield the target ^{Et}Im-C_2-^{Et}Im dication, but rather a range of imidazolium salts and vinyl halides. Following, 1,2-dipseudohalides were explored as a possible alternative. For these reactions, addition of ^{Et}Im to the 1,2-dipseudohalide either induced total decomposition of starting materials or provided no reaction. It was determined that substitution

reactions *via* use of 1,2-alkylhalides and 1,2-alkyldipseudohalide C_2 sources were not viable to access the ^{Et}Im-C_2-^{Et}Im dication.

2.10 Substitution Reactions – Dicationic Species

Following the unsuccessful use of 1,2-alkylhalides and 1,2-alkyldipseudohalide C_2 sources, other C_2 species were considered. A series of C_2 dications in the form L-C_2H_x-L (L = PPh_3, Py, 4-DMAP, PyCN, $N(Me)_3$; X = 2, 4) were synthesised. It was hypothesised that the C-L bond could be manipulated by ligand exchange reactions with ^{Et}Im to furnish the target material (Scheme 2.16).



Scheme 2.16. *General reaction scheme for ligand exchange reaction between L-C_2H_x-L dications and ^{Et}Im.*

A range of C_2 species supported by ligands with a weaker donating capacity than NHCs were explored. It has been determined that NHCs are "better" ligands than phosphines as NHCs provide stronger σ-donation compared to phosphines.[43] Therefore, triphenylphosphine (PPh_3) was the first ligand selected for this series of reactions. It was hypothesised that a stronger bonding interaction between the NHC and the central C_2 fragment would facilitate ligand substitution (*i.e.* $PPh_3 \rightarrow C_2H_x \leftarrow PPh_3$ to NHC $\rightarrow C_2H_x \leftarrow$ NHC) to give the ^{Et}Im-C_2-^{Et}Im dication and liberate free triphenylphosphine.

[PPh_3-C_2H_4-PPh_3][Br]$_2$ was synthesised according to a literature proceedure.[92] A suspension of [PPh_3-C_2H_4-PPh_3][Br]$_2$ in benzene was prepared. To this, two equivalents of ^{Et}Im were added. The reaction mixture rapidly changed colour from white/colourless to black. Although a signal of -5.50 ppm in the ^{31}P NMR spectrum indicated free triphenylphosphine as the sole fate of the PPh_3 moiety, ^{1}H NMR analysis indicated ethene gas alongside a complex mixture of unidentifiable

products. Importantly, resonances from the expected imidazolium backbone or the central methylene fragment were not present. Further, mass spectrometry did not give any evidence of the targeted dicationic material. The reaction was repeated with commercially available $[PPh_3\text{-}C_2H_2\text{-}PPh_3][Br]_2$ to the same fate.

Following, a series of pyridyl ligands were explored based on their comparatively low σ-donating and π-accepting capacity. Pyridine (Py) and its derivatives, 4-(dimethylamino)pyridine ($PyN(Me_2)$), and 4-cyanopyridine (PyCN) were used to synthesise dications in the form $PyX\text{-}C_2H_{2,4}\text{-}PyX$ (X = H, $N(Me_2)$, CN). Synthesis of the 2-fluoropyridine analog was attempted, however, the fluorine atom was found to be too withdrawing to allow the initial substitution reaction necessary. Also, within this class was synthesised the trimethylamine derivative ($NMe_3\text{-}C_2H_4\text{-}NMe_3$).[93]

$PyX\text{-}C_2H_4\text{-}PyX$ (X = H, $N(Me_2)$, CN) was synthesised by dissolving 1,2-dibromoethane in acetonitrile. To this solution was added two equivalents of the appropriately substituted pyridine. The reaction was heated to 70 ºC for 24 h.[94] Additionally, unsaturated $PyX\text{-}C_2H_2\text{-}PyX$ species were explored. A literature search indicated synthesis of the pyridine derivative had been reported. This reaction was performed by reacting 1,1,2-tribromoethane with pyridine and heating to 70 ºC for 24 h.[95] These conditions were used in attempt to obtain the $PyN(Me_2)$ and PyCN derivatives, however, these species were unable to be synthesised. The $PyN(Me_2)$ reaction gave quantitive formation of an unknown (and unwanted) product. And the PyCN route gave no change to starting materials, even at elevated temperatures for prolonged periods.

Finally, the pyridyl (and NEt_3 based) C_2 dications were reacted with ^{Et}Im in effort to induce ligand substitution reactions to give the target $^{Et}Im\text{-}C_2\text{-}^{Et}Im$ dication. To a suspension of the given pyridyl (or NEt_3 based) C_2 dication in benzene was added two equivalents of freshly generated ^{Et}Im. Reactions were subsequently monitored *via* ^1H NMR. Results are summarised in *Table 2.01.*

Table 2.01. *Conditions and results of attempted ligand exchange reactions with PPh_3 and pyridyl C_2 dications.*

Ligand	C_2	Conditions	Result
PPh_3	Saturated	Benzene, r.t., 30 m	Decomposition
PPh_3	Unsaturated	Benzene, r.t., 30 m	Decomposition
Pyridine	Unsaturated	Benzene, r.t., 30 m	Decomposition
4-DMAP	Saturated	Benzene, r.t., 30 m	Decomposition
4-PyCN	Saturated	Benzene, r.t, 72 h	No reaction
$N(Me)_3$	Saturated	Benzene, r.t, 72 h	No reaction

As highlighted in *Table 2.01* the ligand exchange reactions between pyridyl C_2 sources and ^{Et}Im were unsuccessful. In all cases either unreacted starting material or a total decomposition of starting material was evident. It was determined that these C_2 sources were not feasible for ligand substitution reactions to achieve the target ^{Et}Im-C_2-^{Et}Im dication.

A ligand exchange pathway was explored to achieve the target ^{Et}Im-C_2-^{Et}Im dication. A range of 'ligand stabilised' C_2 sources were synthesised. Initial work started with phosphine ligands based on their decreased capacity as donor ligands. When unsuccessful, pyridyl ligands were used as an alternative. For these reactions, addition of free ^{Et}Im to the L-C_2H_x-L source either induced total decomposition of starting materials or provided no change to starting materials, even after prolonged reaction times and elevated temperatures. It was determined that ligand substitution reactions *via* use of phosphine or pyridyl supported C_2 sources were not viable to access the ^{Et}Im-C_2-^{Et}Im dication.

2.11 Concluding Remarks

Following the serendipitous discovery of **2.03**, unusual reactivity about the exocyclic carbon-carbon double bonds was discovered. The unusual reactivity indicated this carbon-carbon double bond as the weakest known organic carbon-carbon double bond. Attempts to push this peculiar reactivity to extremes were met with inactivity. Therefore, it became the focal point of this project to synthesise a

related species with a weaker carbon-carbon double bond. It was hypothesised that by decreasing the σ-donating and π-accepting capacity of the flanking NHC ligands, the exocyclic carbon-carbon double bond in question would be weakened and thus permit reactivity unknown at carbon-carbon double bonds.

Strategies initially attempted to follow the same synthetic route as was employed to synthesise **2.03**. However, it was determined that the highly specific pathway used starting from 1,2-diaminobenzene and maleic anhydride did not translate when using the de-benzylated ethylenediamine.

Following, carbon coupling reactions were explored using 2-substituted imidazoles to install the central C_2 unit. The Sonogashira cross-coupling method was explored as this pathway had been successful in the synthesis of the related ^{Me}BzIm C_4 species. Synthesis of 2-ethynylimidazole was consistently poor yielding and it was determined unfeasible to pursue this pathway. Following, a Heck reaction pathway was considered. However, 2-vinylimidazole was volatile and onerous to work with. This pathway was also considered ineffective. Finally, it was thought that olefin metathesis was a possible route to the target ^{Et}Im C_2 species. 2-vinylimidazole could be coupled with itself to yield the target scaffold and ethene gas. However, as previously described, a reliable and reasonable yielding synthesis of 2-vinylimidazole was the limiting factor for this route. Stability of the 2-substituted imidazoles, even with protecting groups employed, was poor and prohibited a reliable or reproducible synthesis for the target ^{Et}Im supported C_2 species, therefore an alternative method was explored.

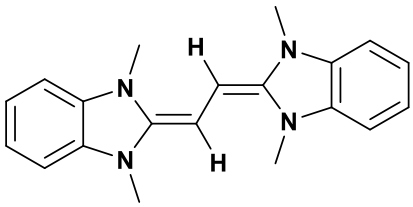
It was hypothesised that the strong nucleophilicity of ^{Et}Im could be exploited to induce substitution reactions at an electrophilic C_2 source. Initially, work focused on using 1,2-dihaloalkanes and 1,2-dipseudohalolkanes. For the 1,2-dichloro and 1,2-dibromoalkyl species, mixtures of 2-haloimidazolium salts, imidazolium salts and vinyl halides were generated. In the case of 1,2-diiodoethane, an unusual result was obtained, which will be explored in greater detail later in this work. The reactions of ^{Et}Im and 1,2-dipseudohalolkanes resulted in either rapid decomposition of starting material or no reactivity at all. Following, it was thought

that 1,2-substituted dicationic C_2 sources could be used to affect ligand substitution at the 1,2-position of the C_2 species. A series of phosphine and pyridyl dications were synthesised and reacted with ^{Et}Im. In a similar fashion to 1,2-dihaloalkanes and 1,2-dipseudohalolkanes, either rapid decomposition or no reaction was observed. Therefore, the substitution reaction method to obtain the target ^{Et}Im C_2 species was also deemed non-viable.

The pursuit to access the weakest carbon-carbon double *via* reduction of a ^{Et}Im-C_2-^{Et}Im dication was planned. Carbon coupling reactions, olefin metathesis, and ligand substitution reactions were explored to synthetically access the appropriate precursor. The 2-substituted imidazoles necessary for carbon coupling reactions were challenging to work with and limited these pathways. The S_N2 and ligand substitution methods resulted in either unwanted reaction pathways, decomposition, or total inactivity. For the reaction between ^{Et}Im and 1,2-diiodoethane, an unusual and unreported result was obtained which prompted us to further investigate this system. This investigation will be explored in greater detail in *Chapter Three*.

2.12 Experimental

2.03



2.03 was synthesised according to a literature procedure.[59] **2.03** was freshly generated for all subsequent manipulations.

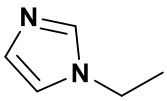
^{1}H NMR (C_6D_6, 400MHz) δ (ppm): (q, J= 4Hz, 4H), 6.41-6.39 (d, J= 8Hz, 2H), 6.29-6.26 (d, J= 8Hz, 2H), 4.32 (s, 2H), 3.24 (s, 6H) 2.60 (s, 6H).
^{13}C NMR (C_6D_6, 100MHz) δ (ppm): 144.1, 138.5, 137.1, 120.0, 118.8, 104.5, 103.0, 66.5, 33.2, 28.7.

General Procedure A: Reaction of 2.03 with elemental chalcogens
To a freshly prepared solution of **2.03** (50 mg, 0.16 mmol, 1.0 eq.) stirring in C_6D_6 (2 mL) was added the relevant elemental chalcogen (0.32 mmol, 2.0 eq.). The reaction was left to stir at room temperature and monitored by ^{1}H NMR and heteronuclear (where possible) spectroscopy.

General Procedure B: Reaction of 2.03 with $PhI(Cl)_2$ or elemental halogens
To a freshly prepared solution of **2.03** (50 mg, 0.16 mmol, 1.0 eq.) stirring in C_6D_6 (2 mL) was added $PhI(Cl)_2$ or the relevant elemental halogen (0.32 mmol, 2.0 eq.). The reaction was left to stir at room temperature and monitored by ^{1}H NMR spectroscopy.

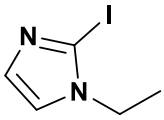
General Procedure C: Reaction of 2.03 with MeI, Me_3OBF_4 or MeOTf
To a freshly prepared solution of **2.03** (50 mg, 0.16 mmol, 1.0 eq.) stirring in C_6D_6 (2 mL) was added the relevant methylating agent (0.32 mmol, 2.0 eq.). The reaction was left to stir at room temperature and monitored by ^{1}H NMR spectroscopy.

1-Ethylimidazole



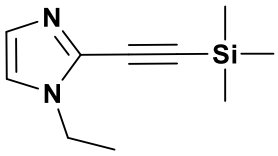
1-Ethylimidazole was synthesised according to a literature procedure.[80]

2-Iodo-N-ethylimidazole



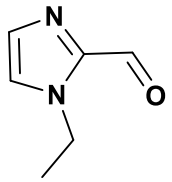
2-Iodo-N-ethylimidazole was synthesised according to a literature procedure.[81]

2.07



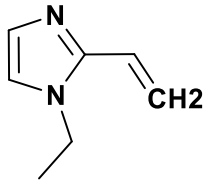
2.07 was synthesised *via* a modified literature procedure.[82] Using standard Schlenk techniques, 2-Iodo-N-ethylimidazole (500 mg, 2.25 mmol) was dissolved in 20 mL of triethylamine. The solution was sparged for 20 minutes. $Pd(PPh_3)_4$ (5 mol%) and CuI (5 mol%) were added under positive N_2 pressure. To the solution was added trimethylsilyl acetylene (1.1 eq, 2.48 mmol) *via* syringe. The reaction was stirred at r.t. for 1 hr and then heated to 70 ºC for 5 hr. Following, the reaction was cooled to r.t. and the triethylamine removed *in vacuo.* The reside was dissolved in 20 mL of $CHCl_3$ and washed with 30 mL portions of NH_4Cl solution, H_2O and NaCl brine. The organic layer was collected, dried over $MgSO_4$, filtered and then the solvent was removed *in vacuo*. The crude reside was analysed by ^1H NMR spectroscopy and assumed to contain traces of the title compound. The quantity was too small to characterise.

1-Ethyl-2-formylimidazole



1-Ethyl-2-formylimidazole was synthesised *via* a modified literature procedure.[96] Using standard Schlenk techniques, 1-ethylimidazole (1.0 eq.) was dissolved in 20 mL of THF and cooled to -78 ºC. *n*-BuLi (1.2 eq.) was added dropwise over 30minand then left to stir at -78 ºC for 1.5 hr. Dimethylformamide (3.0 eq.) in 10 mL of THF was added dropwise and the solution was stirred at -78 ºC for 2 hr. Following, the cooling bath was removed, and the reaction was stirred at r.t. overnight. The reaction was quenched with the addition of 20 mL of H_2O and extracted with $CHCl_3$ (3 × 50 mL). The organic layers were combined and washed with H_2O (6 × 50 mL) and the $CHCl_3$ was removed *in vacuo*. The residue was purified *via* flash column chromatography (PET spirit/EtOAc).

1-Ethyl-2-vinylimidazole



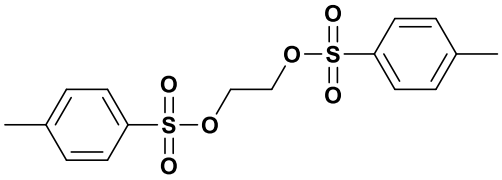
1-Ethyl-2-vinylimidazole was synthesised *via* a modified literature procedure.[83] Using standard Schlenk techniques, *n*-BuLi (1.2 eq.) was added dropwise to a suspension of methytriphenylphosphonium bromide (1.0 eq.) in 15 mL of THF at 0 ºC with stirring. The reaction was warmed to r.t. and stirred for 40 min. A solution of 1-ethyl-2-formylimidazole in 15 mL of THF was added dropwise and the reaction was left to stir for 24 hr. The reaction mixture was subsequently filtered, and the filter cake washed with Et_2O (3 × 15 mL).

General Procedure D: Generation of free carbenes

In a nitrogen filled glove box, the appropriate N,N-dialkylimidazolium salt (1.00 eq.) was suspended in a solution of C_6H_6. A solution of KHMDS (1.05 eq.) in C_6H_6 was added in one portion and the reaction was left to stir for 1 hr. Following the solids

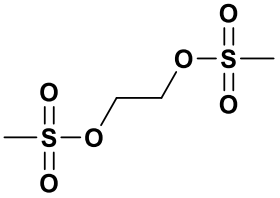
were removed *via* centrifugation. Free carbene was collected in the supernatant and used immediately.

Ethylene di(*p*-tolunesulfonate)



Ethylene di(*p*-tolunesulfonate) was synthesised according to a literature procedure.[97]

Ethylene di(mesylate)

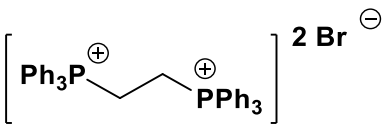


Ethylene di(mesylate) was synthesised according to a literature procedure.[90]

General Procedure E: Reaction of 1,2-alkylhalides/pseudohalides with free carbene

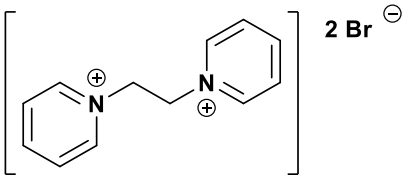
In a nitrogen filled glove box, the appropriate 1,2-alkylhalide/pseudohalide (1.0 eq.) was dissolved in C_6D_6. To this was added freshly generated carbene (as per General Procedure D) and the reaction was left to stir. The reaction was monitored *via* ^{1}H NMR for consumption of free carbene.

Ethylene bis(triphenylphosphonium) dibromide



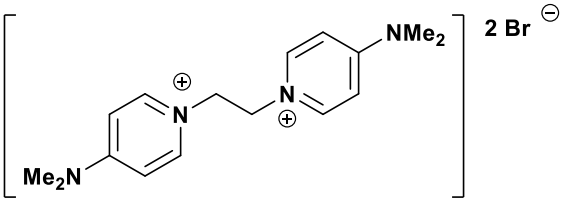
Ethylene bis(triphenylphosphonium) dibromide was synthesised according to a literature procedure.[92]

Ethylene bis(pyridinium) dibromide



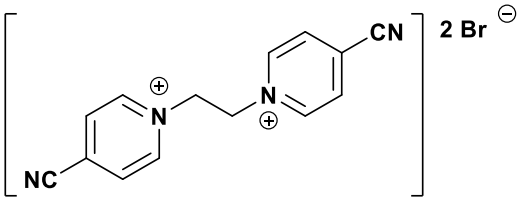
Ethylene bis(pyridinium) dibromide was synthesised according to a literature procedure.[94]

Ethylene bis(4-DMAP) dibromide



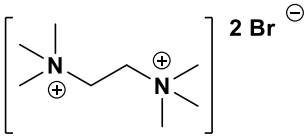
Ethylene bis(4-DMAP) dibromide was synthesised according to a literature procedure.[94]

Ethylene bis(4-cyanopyridine) dibromide



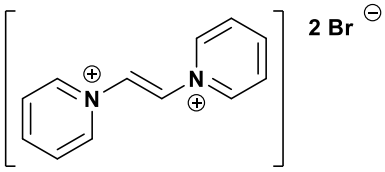
Ethylene bis(4-cyanopyridine) dibromide was synthesised according to a literature procedure.[98]

N,N,N,N',N',N'-hexamethyl-1,2-diaminoethane diiodide



N,N,N,N',N',N'-hexamethyl-1,2-diaminoethane diiodide was synthesised according to a literature procedure.[93]

Ethene bis(pyridinium) dibromide



Ethene bis(pyridinium) dibromide was synthesised according to a literature procedure.[95]

General procedure F: Reaction of 1,2-phosphonium/pyridyl dications with free carbene

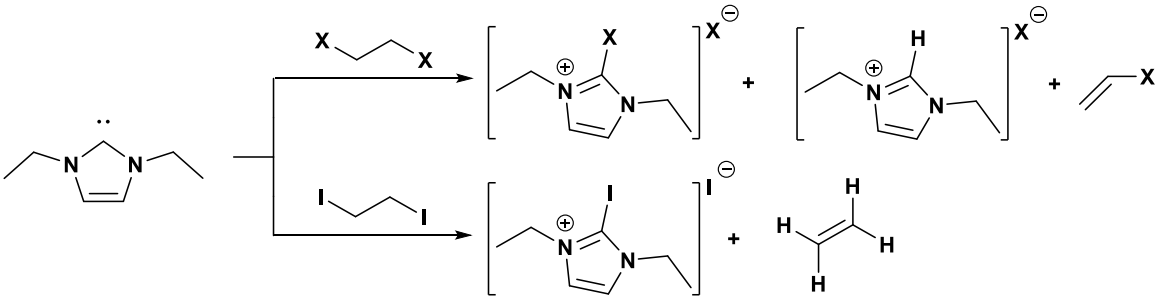
In a nitrogen filled glove box, the appropriate 1,2-phosphonium/pyridyl (1.0 eq.) was suspended in C_6D_6. To this was added freshly generated carbene (as per General Procedure D) and the reaction was left to stir. The reaction was monitored *via* ^{1}H NMR for consumption of free carbene.

Chapter 3. Elimination of Ethene from 1,2-Diiodoethane Induced by N-Heterocyclic Carbene Halogen Bonding‡

‡This chapter contains work that is published: Poynder, T. B.; Savaliya, D. P.; Molino, A.; Wilson, D. J. D.; Dutton, J. L. Aust. J. Chem. 2019, 72 (8), 614–619. Savaliya, D. P. performed the initial reaction between 1,2-diiodo ethane and ^{Et}Im under the guidance of Poynder, T. B. All subsequent synthetic work was performed by Poynder, T. B. Theoretical calculations presented in section *3.05* were performed by Wilson, D. J. D. and Molino, A.

3.01 Introduction

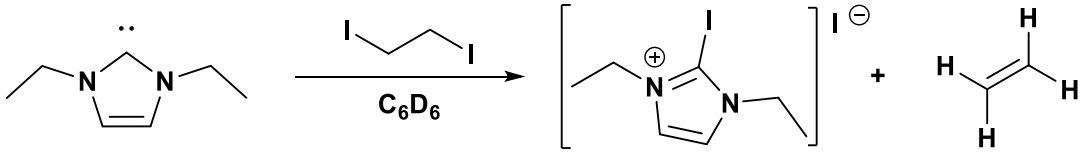
As discussed in *Chapter Two*, the synthesis of an extremely weak carbon-carbon double bond was attempted. One method explored was the use of an S_N2 pathway by reacting free carbene with an appropriate electrophilic C_2 source in hope that the carbene would displace leaving groups at the C_2 source and furnish the target compound, [^{Et}Im-C_2-^{Et}Im][X]$_2$. Initially, 1,2-dihaloalkane C_2 sources were explored due to their accessibility and the good leaving group capacity of the halogens. The reactions between the NHC, ^{Et}Im, and 1,2-dichloro- or 1,2-dibromoethane did not undergo the planned S_N2 pathway. Rather, a mixture of imidazolium salts and vinyl halides were obtained. Subsequently, the use of 1,2-diiodoethane was explored in hope that the better leaving group capacity of iodide (compared to Cl^- and Br^-) would yield the target scaffold, [^{Et}Im-C_2-^{Et}Im][I]$_2$. Neither formation of [^{Et}Im-C_2-^{Et}Im][I]$_2$ or analogous reactivity to that of 1,2-dichloro- or 1,2-dibromoethane was observed. Rather, near quantitative formation of 2-iodo-N,N-diethylimidazolium iodide and liberation of ethene gas was observed (Scheme 3.01). This Chapter investigates this peculiar outcome and explores the mechanism by which this transformation was occurring.



Scheme 3.01. *The reaction of ^{Et}Im and 1,2-dichloroethane or 1,2-dibromoethane or 1,2-diiodoethane. (X = Cl, Br).*

3.02 The Reaction Between ^{Et}Im and 1,2-Diiodoethane

To a stirred solution of 1,2-diiodoethane in deuterated benzene (C_6D_6) was added two equivalents of ^{Et}Im. Immediately, evolution of gas and precipitation of an orange solid was observed. ^{1}H NMR analysis of the reaction mixture indicated a clean spectrum with signals corresponding to unreacted ^{Et}Im and a sharp singlet at 5.26 ppm. As the formation of gas was apparent, it was suspected that this signal was from ethene gas. The ^{13}C NMR indicated a resonance at 122.96 ppm. This, in conjunction with the ^{1}H NMR data confirmed the presence of ethene gas.[99] The orange precipitate, which was insoluble in C_6D_6, was isolated and subsequently dissolved in $CDCl_3$ for which the ^{1}H NMR spectrum indicated a single, symmetric, NHC-containing compound missing the proton at the 2-position of the imidazolium ring. ESI mass spectrometry gave signals at *m/z* 251.0 and *m/z* 127.1 in positive and negative ion mode, respectively. Suggesting formation of an iodinated imidazolium species. It was hypothesised that formation of N,N-diethyl-2-iodoimidazolium iodide was the product of this reaction, however, there had been no spectral reports of N,N-diethyl-2-iodoimidazolium in the literature for comparison. To circumvent this, N,N-diethyl-2-iodoimidazolium was separely generated from the reaction of ^{Et}Im and molecular iodine for comparison. Spectral data obtained from each of these reactions matched, thus, it was determined that the products from the reaction of ^{Et}Im and 1,2-diiodoethane were N,N-diethyl-2-iodoimidazolium and ethene gas (Scheme 3.02).



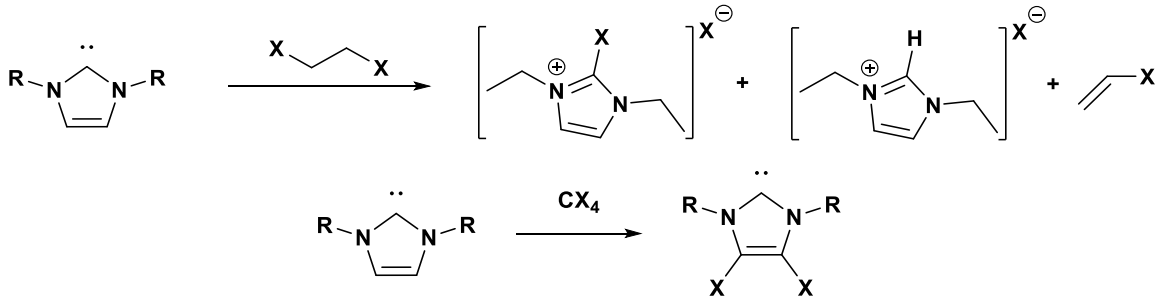
Scheme 3.02. *The reaction of ^{Et}Im and 1,2-diiodoethane to give N,N-diethyl-2-iodoimidazolium and ethene gas.*

As it was observed that there was residual free carbene in the *in-situ* NMR spectrum obtained from the reaction of ^{Et}Im and a half equivalent of 1,2-diiodoethane. The reaction was repeated to determine the correct stoichiometry, as it was believed that only one equivalent of carbene was reacting with 1,2-diiodoethane. Following, the reaction of ^{Et}Im to an equimolar amount of

1,2-diiodoethane was performed. In this scenario, N,N-diethyl-2-iodoimidazolium iodide was isolated in 87% yield. These results indicated N,N-diethyl-2-iodoimidazolium iodide and ethene gas are the primary products from this reaction and the reaction was occurring at a one-to-one ratio.

3.03 Other Reactions Between NHCs and Alkyl Halides

Scheme 3.01 indicates the different reaction outcomes from the reaction between ^{Et}Im and 1,2-dichloroethane or 1,2-dibromoethane or 1,2-diiodoethane. In the case of 1,2-dichloroethane or 1,2-dibromoethane, generation of N,N-diethylimidazolium, 2-halo-N,N-diethylimidazolium salts, vinyl halide and a complex mixture of other unidentifiable products were achieved. A literature investigation was performed to identify any similar transformations between NHCs and haloalkanes. Denk and co-workers had described the reduction of alkyl halides with folates and imidazolidine derivatives, but not with free carbenes. Jones and Junk have reported reactions between NHCs and 1,2-dibromoethane to give a mixture of protonated NHC, 2-bromoimidazolium bromide salts, and vinyl bromide.[88] Reactions of NHCs with 1,2-dichloroethane as reported by Kuhn gives 2-chloroimidazolium chloride, however, Jones and Junk indicate in their study that the reaction gives a substantial fraction of protonated carbene and vinyl chloride from an elimination pathway.[87,88] Early reports from Arduengo after the isolation of the first N-heterocyclic carbene involving CCl_4 indicate that the reactions with NHCs primarily result in halogenation of the NHC backbone,[100] with the same observation by Jones and Junk for the reaction of NHC and CBr_4.[88] These previous accounts are summarised in *Scheme 3.03*.



Scheme 3.03. *Previously reported reactions between alkyl halides and NHCs. (X = Cl, Br.)*

What was evident was that there was a clear lack of reported reactivity between alkyl iodides and NHCs in the literature. Presumably owing to the assumption that the same reactivity would be observed, and also as 1,2-diiodoethane is a far less common reagent than the chloro- and bromo- analogues. Interestingly, the reaction between ^{Et}Im and 1,2-diiodoethane cleanly generated N,N-diethyl-2-iodoimidazolium iodide and ethylene gas. The mechanism by which this transformation occurred piqued our interest as it did not provide target product nor products *via* expected alternate pathways (as described in Scheme 3.03). A substitution pathway would have generated either the target [^{Et}Im-C_2-^{Et}Im][I]$_2$ or the monosubstituted [^{Et}Im-C_2-I][I]. An elimination pathway would have generated N,N-diethylimidazolium iodide and iodoethene. As the facile production of N,N-diethyl-2-iodoimidazolium iodide and ethylene gas was unique to previous reports and not an expected product, a theoretical investigation was performed to understand the true nature of this transformation. It was hypothesised that direct attack of the NHC onto an iodine atom *via* a halogen bonding mechanism was the cause.

3.04 Halogen Bonding and N-Heterocyclic Carbenes

Halogen bonding refers to the net electrostatic interaction between the electrophilic region of a halogen atom and the nucleophilic region of another moiety. An electron rich species (halogen bond acceptor) donates electron density to a halogen atom (halogen bond donor). As the halogens are commonly regarded as species of high electron density, this notion appears counterintuitive.[101] However, a halogen atom may display sites of electrophilicity owing to the polarisability of the atom induced by neighbouring atoms it is bonded to. This electrophilic site is referred to as a sigma-hole.[102] As the sigma-hole arises from the polarisability of an atom, it follows that the strength of the halogen bond adheres to the trend I > Br > Cl > F as polarisability is correlated to an increase in atomic radius.[103]

The strength of a halogen bond is determined by a few major factors. The first relates to the electrophilicity of the sigma-hole. Accordingly, the nucleophilicity of the halogen bond acceptor is also indicative of the strength of the halogen bond, with an increase in nucleophilicity generally correlating to an increase in halogen

bond strength. Additionally, the molecular orbital interactions play a crucial role in determining the viability and strength of a halogen bond. There is an important interaction between the lone pair containing HOMO of the halogen bond acceptor and the σ* antibonding LUMO of the halogen bond donor.[104] Further, the accessibility and shape of the σ* antibonding LUMO is an essential consideration when determining the strength of a halogen bond.[101]

NHCs are good candidates as halogen bond acceptors as they have high electron density owing to the lone pair of electrons at the carbenic carbon. The symmetry of the lone pair containing orbital is also conducive to halogen bond accepting.[105] Iodine species are fantastic halogen bond donors as iodine is readily polarizable due to its size, and thus, formation of the sigma-hole is facile.[106] Consequently, the proposal that ^{Et}Im is acting as a halogen bond acceptor and 1,2-diiodoethane is participating as a halogen bond donor seemed like a plausible hypothesis. To probe this suspicion, an in-depth theoretical analysis was performed on this system.

3.05 Theoretical Analysis of the Elimination of Ethene Gas from 1,2-Diiodoethane

Initially, it was anticipated that the reaction between ^{Et}Im and 1,2-diiodoethane should have followed a substitution pathway to give the NHC unit bonded to the C_2 fragment of 1,2-diiodoethane. A possible alternative was to observe reactivity parallel to the chloro- and bromo- analogous species *via* an elimination pathway. Therefore, the energy profiles of these two pathways alongside the hypothesised halogen bonding pathway were modelled at the B3LYP-D3(BJ)/def2-TZVP (SMD,MeCN)//DSDPBEP86/def2-TZVPP (SMD, MeCN) level of theory, using an N-Me substituted NHC as a model system. *Figure 3.01* shows the reaction profile calculated.

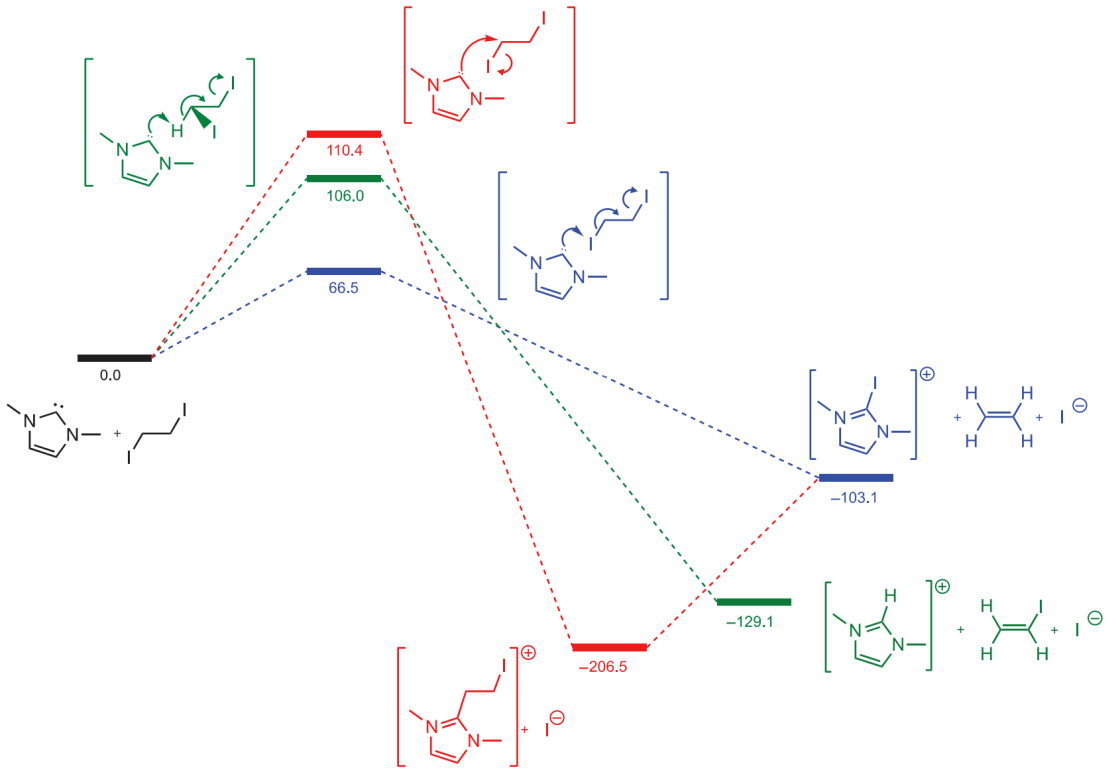


Figure 3.01. *Reaction profile for S_N2 (red), elimination (green), and nucleophilic attack via halogen bonding (blue) for the reaction between Me_2NHC and 1,2-diiodoethane. All values are calculated relative free energies (kJ mol^{-1}).*

For the S_N2 pathway, the initial transition state barrier was calculated to be 110.4 kJ mol^{-1}, with the products -206.5 kJ mol^{-1} below the reactants. To reach the final observed products, attack on the 2-carbon by iodide is required to induce rupture of the C-C bond. This second step is calculated to be endothermic by 103.4 kJ mol^{-1}. This suggests the reaction should stop after formation of the cation arising from displacement of iodide if one equivalent of NHC is used. The elimination pathway gives a similarly high value of 106.0 kJ mol^{-1} for the initial transition state barrier. For the halogen bonding pathway, direct attack of the NHC on the iodine atom breaking the C-I bonds and forming ethene gas has a much lower transition state barrier of 66.5 kJ mol^{-1}. This is consistent with the observation of the rapid room temperature reaction and supports the NHC halogen bonding pathway as the basis for this transformation. To further investigate, an examination of the lowest unoccupied molecular orbital (LUMO) of 1,2-diiodoethane was performed (figure 3.02).

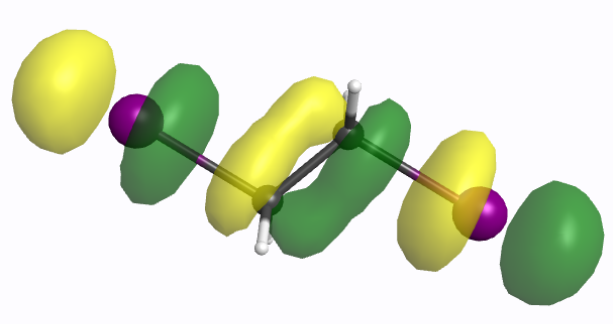


Figure 3.02. *Calculated LUMO of 1,2-diiodoethane.*

It can be observed that the LUMO is of sigma-antibonding character with respect to the C-I bonds and pi-bonding with respect to the C-C bond. The symmetry of the LUMO is amenable to population from a lone pair of electrons as the sigma-antibonding character situated about the periphery of 1,2-diiodethane and is accessible. Population of the LUMO of 1,2-diiodoethane by the lone pair of electrons from the NHC would then promote the observed transformation involving the rupture of the C-I bonds and subsequent formation of the carbon-carbon pi bond.

The analogous reaction between 1,2-dibromoethane and ^{Et}Im was modelled and the barrier for the halogen bonding pathway was determined to be 123.0 kJ mol^{-1}. This value much higher than that of 1,2-diiodoethane and ^{Et}Im (cf. 66.5 kJ mol^{-1}). Further, the LUMO of 1,2-dibromoethane was calculated to be 0.4 eV higher in energy when compared to that of 1,2-diiodoethane, suggesting that population of this orbital by the lone pair of electrons from the NHC would come at a greater energy cost and therefore was less likely to transpire. These observations lend credence to the notion that the halogen bonding interaction between ^{Et}Im and 1,2-diiodooethane occurs readily but does not occur between ^{Et}Im and 1,2-dibromoethane (Figure 3.03).[107]

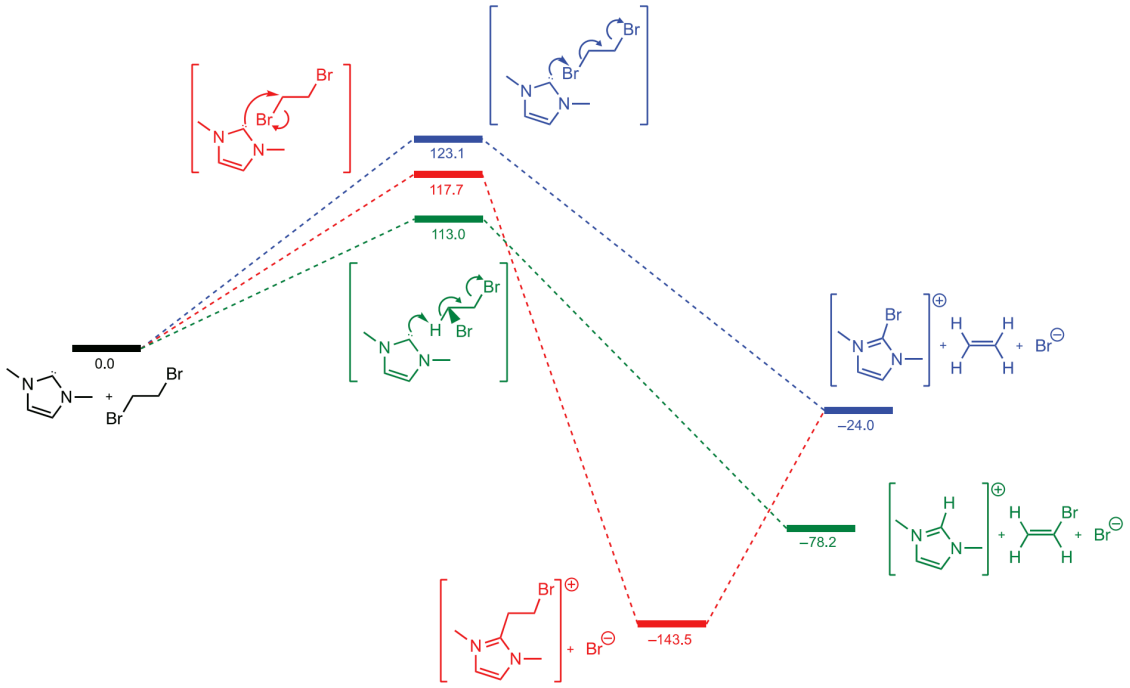


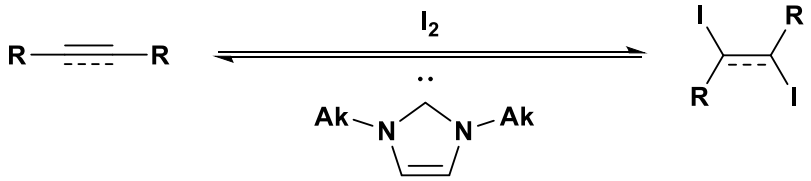
Figure 3.03. *Reaction profile for S_N2 (red), elimination (green), and nucleophilic attack via halogen bonding (blue) for the reaction between Me_2NHC and 1,2-dibromoethane. All values are calculated relative free energies (kJ mol^{-1}).*

Theoretical analysis was performed on this system in order to determine the true nature of the transformation occurring between ^{Et}Im and 1,2-diiodooethane. Through mapping the reaction profile of S_N2, elimination and halogen bonding pathways, alongside investigation of the molecular orbitals of 1,2-diiodoethane and 1,2-dibromoethane, it was determined that the halogen bonding pathway was the cause of this reaction. Significantly, this was a case of halogen bonding being invoked as the key interaction in a reaction with NHCs. Further, the importance of the halogen bonding capacity between NHCs and iodine compared with other halogens was highlighted. Following will be a discussion on attempts to develop a synthetically useful application of this novel interaction.

3.06 Molecular Iodine as a Protecting Group for Alkenes and Alkynes

The propensity of NHCs to halogen bond with iodo-based substrates prompted exploration of possible applications of this novel system. It was hypothesised that NHCs could be used as 1,2-diiodo- abstraction reagents. Thus, it followed that if

the 1,2-diiodo- abstraction was efficient, the addition of I_2 to double or triple bonds and then subsequent removal with NHCs could be used as a facile protecting method for carbon-carbon multiple bonds. This notion can be visualised with the exemplar system shown in *Scheme 3.04*.

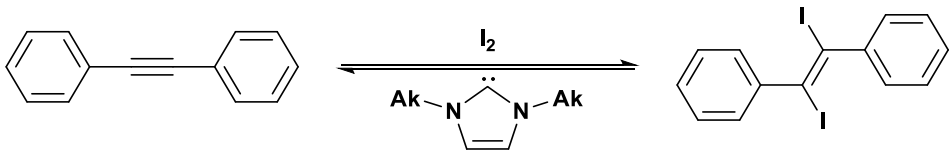


Scheme 3.04. *General scheme for 1,2-diiodination and NHC induced abstraction of 1,2-diiodoalkanes and 1,2-diiodoalkenes.*

The 1,2-addition of molecular halides (or hydrogen halides) to double and triple bonds is one of the most well-known reactions in chemistry. It is usually the first exposure undergraduate chemistry students have to addition reactions, and forms the basis of which addition reactions are taught.[108] The chemistry of these transformations is well known and consequently highly established. Dehalogenation is similarly a well-established class of reactions in synthetic chemistry. There are two types of dehalogenation reactions, reductive dehalogenation (removal of a halide) and dehydrohalogenation (base catalysed removal of H-X). In both cases, cleavage of a carbon-halogen bond occurs. Methods for reductive dehalogenation often use highly reactive alkali metal species or transition metal complexes to affect the reaction.[109] Most commonly, the use of metal species or harsh conditions are required. Moreover, there are few methods for the protection of carbon-carbon double bonds, for example, the use of epoxides or transition metal complexes.[110,111] However, existing literature regarding protection of carbon-carbon triple bonds focuses solely on protection of the acetylenic hydrogen,[112] but none actively protect the carbon-carbon triple bond itself. It would benefit to develop a methodology for reductive dehalogenation, that can be applied to a range of systems, that does not necessitate the use of these undesirable and highly specific conditions in conjunction with the selective protection and deprotection of carbon-carbon multiple bonds.

3.07 Synthesis of 1,2-Diiodo Species and Attempted 1,2-Diiodo- Abstraction

To investigate this hypothesis, a model system was developed such that this method could be explored as a possible technique for the protection and subsequent deprotection of carbon-carbon multiple bonds. Initial work targeted the synthesis of 1,2-diiodoalkenes from the related alkyne. As a proof of concept, initial work focused on the 1,2-diiodination of diphenylacetylene and subsequent diiodo-abstraction (Scheme 3.05). This was targeted as a symmetrical alkyne was needed for simplicity, further, the solid-state of these species enabled ease of handling.



Scheme 3.05. *Iodination of diphenylacetylene to 1,2-diiodo-1,2-diphenylethene and NHC induced abstraction to diphenylacetylene.*

Synthesis of 1,2-diiodo-1,2-diphenylethene from 1,2-diphenylacetylene had been previously reported in the literature with limited procedures available. Synthetic routes involving common or at-hand reagents were either extraordinarily long, not well documented, or gave inseparable 1,2-diiodo-1,2-diphenylethane as a byproduct.[113–115] Initial attempts involved the reaction of 1,2-diphenylacetylene and one equivalent of molecular iodine in acetic acid (AcOH) at room temperature.[115] Meanwhile, the same reaction was set up and heated to 90 ºC in attempt to affect the reaction more quickly as literature reported a 40 day timespan required for this transformation. These reactions were monitored *via* TLC and ^{1}H NMR spectroscopy, however, after 10 days neither reaction showed formation of new products.

Separately, the reaction was attempted using 1,2-diphenylacetylene, molecular iodine and hydrogen peroxide at room temperature. The use of hydrogen peroxide is to generate iodine pentoxide *via* iodic acid, as an electrophilic iodinating reagent. Literature specified no reaction time other than “monitored *via* TLC”. This reaction was monitored *via* TLC and ^{1}H NMR spectroscopy for the consumption of starting

material. Following 10 days, there was no change to the reaction mixture. The most likely error with this reaction was the temperature was likely too low to allow for the formation of iodine pentoxide from iodic acid, despite the paper reporting success at room temperature.[116]

It was thought that microwave synthesis may be a good counter to the exceptionally long reaction times and observed inactivity. Initial conditions for microwave synthesis were an equimolar quantity of 1,2-diphenylacetylene and molecular iodine in AcOH. Initially, the reaction was heated to 90 ºC for 1 hr. Following these conditions, no formation of new products was observed *via* TLC or ^{1}H NMR spectroscopy. The reaction was repeated, heating the reaction vessel to 150 ºC for 4 hr. Similarly, there was no evidence of formation of the desired 1,2-diiodo-1,2-diphenylethene from 1,2-diphenylacetylene. Finally, it was discovered that after leaving 1,2-diphenylacetylene stirring in AcOH with a very large excess of I_2 for 10 days, 1,2-diiodo-1,2-diphenylethene was obtained in mediocre yield following work-up. With 1,2-diiodo-1,2-diphenylethene available, attempts to use NHC halogen bonding interactions in order to abstract the iodine atoms were trialled.

^{Et}Im was prepared *via* previously reported methods. The NHC solution was added in one portion to a vial with an equimolar quantity of 1,2-diiodo-1,2-diphenylethene. Immediately, the reaction formed an orange precipitate. The reaction mixture was analysed *via* ^{1}H NMR and ^{13}C NMR spectroscopy, which indicated the formation of 1,2-diphenylacetylene and N,N-diethyl-2-iodoimidazolium iodide. The orange solid was isolated *via* filtration and washed with diethyl ether. The orange solid was subsequently analysed via ^{1}H NMR spectroscopy in deuterated acetonitrile, which confirmed the generation of N,N-diethyl-2-iodoimidazolium iodide by comparison with previously acquired spectra. Following flash chromatography, a yield of 74% of diphenylacetylene was obtained. This result was particularly promising as the hypothesis that molecular iodine could be added and subsequently removed to and from carbon-carbon multiple bonds appeared to be a realistic endeavour. That is, this particular methodology could be used as a facile method for alkyne protection. Further, a yield of 74%, without any optimisation, was encouraging as

protection/deprotection reactions require high yield.[112] The major limitation of this method was the difficulty in synthesising 1,2-diiodo-1,2-diphenylacetylene. Most concerning was the difficulty in iodinating such a simple system. It would stand to reason that 1,2-diiodination in more complicated systems with more diverse functionality would likely prove troublesome. Thus, the necessity to 1,2-diiodinate became a foreseeable limitation of this project.

1,2-Diiodo- species were initially targeted as directed by the reaction of 1,2-diiodoethane and ^{Et}Im, as this allowed the observation of the first NHC-halogen bonding induced reaction. Other 1,2-dihalo- species did not follow a halogen bonding pathway as the elimination products outcompete the formation of the 2-haloimidazolium halide salt. However, if the 1,2-dihalo- functionality is flanked by an atom other than hydrogen, the elimination product becomes unviable, preventing the pathway altogether. This suggested that 1,2-dibromo- species could be used for the protection of carbon-carbon triple bonds so long as the atoms adjacent to both of the bromo-bonded carbons were not hydrogen atoms. The major benefit of this revelation was the abolition of the lengthy amount of time and difficulty required for the 1,2-diiodination reaction. The iodination of 1,2-diphenylacetylene required a minimum of 10 days, whereas reports of 1,2-dibromination of diphenylacetylene occur in 30 minutes.[111]

1,2-dibromo-1,2-diphenylethene was synthesised following a literature procedure. A solution of diphenylacetylene in dichloromethane was cooled to 0 ºC. Following, a slight excess of molecular bromine in dichloromethane was added dropwise to the solution. After stirring for 30 minutes and upon work-up 1,2-dibromo-1,2-diphenylethene was obtained.[111] 1,2-dibromo-1,2-diphenylethene was then subject to previously used reaction conditions in attempt to dehalogenate to 1,2-diphenylacetylene. A solution of ^{Et}Im was prepared *via* previously reported methods and isolated to a solution of deuterated benzene. The NHC solution was then added to an equimolar quantity of 1,2-dibromo-1,2-diphenylethene in deuterated benzene. ^{1}H NMR spectroscopy indicated formation of 1,2-diphenylacetylene. However, 1,2-diphenylethene was also identified in the reaction mixture alongside a complex mixture of unidentifiable products. Following flash

chromatography, an isolated yield of 40% of 1,2-diphenylacetylene was obtained. These results indicated the successful, but unclean generation of the target material. It was concluded that bromination of carbon-carbon triple bonds was not selectively reversible enough for this method to be feasible as a protection/deprotection methodology.

Following, the reaction between 1,2-diiodo-1,2-diphenylethene and triphenylphosphine (PPh_3) was explored in order to observe whether PPh_3 could be used to affect this reaction instead of ^{Et}Im. The benefit of using PPh_3 over an NHC species was the ability to perform these reactions without the use of air-free techniques. Further, the cost of PPh_3 is negligible in comparison to the synthesis of and generation of free carbene. To 1,2-diiodo-1,2-diphenylethene in deuterated benzene was added an equimolar solution of PPh_3. The reaction was monitored *via* ^1H and ^{31}P NMR spectroscopy. ^{31}P NMR indicated consumption of free PPh_3 after 2 hours. Two signals at -12 ppm and -40 ppm were the major fate of the phosphorus containing species. This was believed to be attributed to formation of PPh_3/I_2 species. ^1H NMR spectroscopy identified the formation of a mixture of products. TLC of the crude reaction mixture indicated four species had been generated. Following flash chromatography, 1,2-diphenylacetylene was obtained in 25% yield. Although PPh_3 induced 1,2-diiodo- abstraction from 1,2-diiodo-1,2-diphenylethene, this reaction did not proceed efficiently, with multiple side reactions occurring and unreacted 1,2-diiodo-1,2-diphenylethene recovered. The poor yield of this reaction deemed it unfeasible for quantitative protection/deprotection of carbon-carbon multiple bonds.

Finally, the reaction was performed between 1,2-dibromo-1,2-diphenylethene and PPh_3. An equimolar quantity of 1,2-dibromo-1,2-diphenylethene and PPh_3 were combined in deuterated benzene. The reaction was monitored *via* ^1H and ^{31}P NMR spectroscopy. After 24 hr at room temperature there was no change to starting materials. The reaction was heated at reflux for 24 hr and then analysed *via* NMR spectroscopy. There was no change to starting materials. It was determined that PPh_3 was unable to abstract the bromine atoms from 1,2-dibromo-1,2-

diphenylethene, and thus, not useful for this project. These reactions can be summarised in *Table 3.01*.

Table 3.01. *The reaction of 1,2-dihalo-1,2-diphenylethene and ^{Et}Im or PPh_3.*

Halide Species	Halide Abstractor	Yield[a] (%)
1,2-diiodo-1,2-diphenylethene	^{Et}Im	74
1,2-dibromo-1,2-diphenylethene	^{Et}Im	40
1,2-diiodo-1,2-diphenylethene	PPh_3	25
1,2-dibromo-1,2-diphenylethene	PPh_3	0

[a] *Yield refers to isolated yield of diphenylacetylene.*

To gain further understanding of these observed interactions, theoretical analysis was performed on these systems with a focus on investigating the molecular orbitals of each of the 1,2-dihalo-1,2-diphenyl species.

3.08 Theoretical Analysis on 1,2-Dihalo-1,2-diphenylethene Species

A theoretical investigation was performed in order to compare 1,2-dibromo-1,2-diphenylethene and 1,2-diiodo-1,2-diphenylethene to rationalise the observed differences in reactivity. Molecular orbital calculations were performed at the B3LYP level of theory. The LUMO for each of 1,2-diiodo-1,2-diphenylethene and 1,2-dibromo-1,2-diphenylethene were generated and can be observed in *Figure 3.04.*

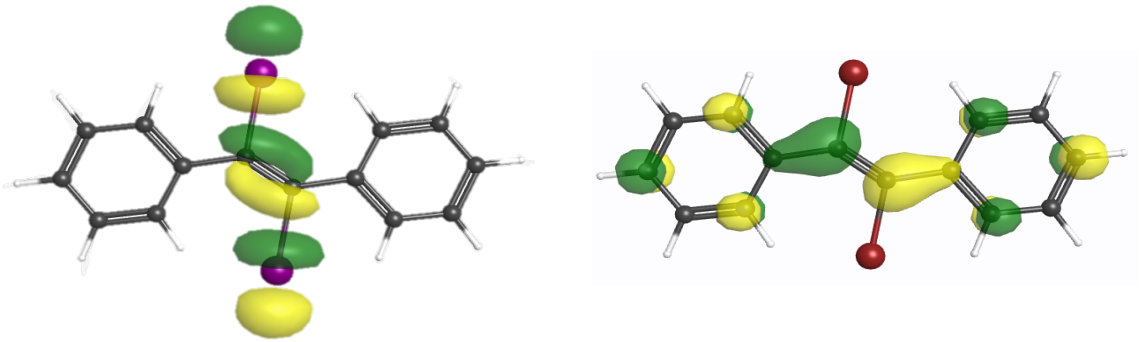


Figure 3.04. *Calculated LUMO of 1,2-diiodo-1,2-diphenylethene (left) and 1,2-dibromo-1,2-diphenylethene (right).*

Figure 3.04 shows the LUMO of 1,2-diiodo-1,2-diphenylethene is of sigma-antibonding character with respect to the C-I bonds and shows resemblance to the LUMO of 1,2-diiodoethane (Figure 3.02). This molecular orbital arrangement is necessary for the NHC-halogen bonding interaction to occur. As the LUMO is of sigma-antibonding character, population of the LUMO by the lone pair of electrons from ^{Et}Im and subsequent rupturing of the C-I bonds is possible. This supports the observed abstraction of the iodine atoms from 1,2-diiodo-1,2-diphenylethene by ^{Et}Im and subsequent formation of N,N-diethyl-2-iodoimidazolium iodide. In direct contrast, the LUMO of 1,2-dibromo-1,2-diphenylethene is not situated about the bromine atoms, but rather localised to the central carbon-carbon bonds and the phenyl rings. This supports the observation that the NHC-halogen bonding interaction does not occur as efficiently in 1,2-dibromo-1,2-diphenylethene as it does with 1,2-diiodo-1,2-diphenylethene. However, experimental results did indicate some formation of the NHC-halogen bonding products, N,N-diethyl-2-bromoimidazolium bromide and diphenylacetylene. This suggested that a halogen bonding interaction was occurring, albeit, to a much lesser degree. To investigate this observation, the LUMO-1 of 1,2-dibromo-1,2-diphenylethene was considered (Figure 3.04). *Figure 3.04* shows the LUMO-1 of 1,2-dibromo-1,2-diphenylethene. It is apparent that the LUMO-1 is of σ^* character with respect to the C-Br bonds and thus explains the minor formation of the NHC-halogen bonding product as this molecular orbital is prime to population from the lone pair of electrons of the NHC, which explains why a mixture of products was observed.

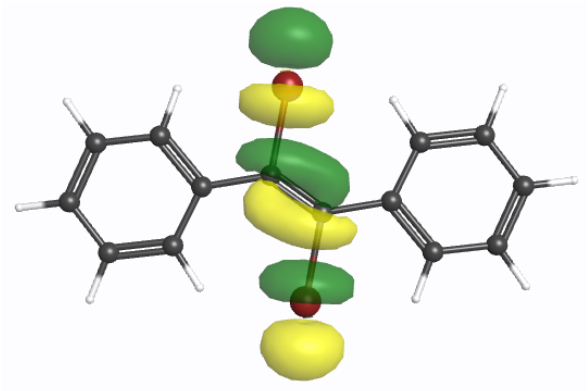


Figure 3.05. *Calculated LUMO-1 of 1,2-dibromo-1,2-diphenylethene.*

The inefficiency of phosphines as halogen bond acceptors has long been established, as such, rare examples of this interaction qualify as discoveries in their own right.[117] The reason for this is due to phosphines and intermolecular halides are more likely to form P-X covalent bonds rather than P···X halogen bonds, due to the strongly polarising nature of the phosphorus atom.[118] As such, it was determined unnecessary to model any PPh_3 induced halide abstraction data for this project.

3.09 Concluding Remarks

During the pursuit to synthesise a [NHC-C_2-NHC][X]$_2$ type species to facilitate formation of an unusually weak carbon-carbon double bond, an example of NHC induced halogen bonding was discovered. It was observed that upon reaction of ^{Et}Im and 1,2-diiodoethane, generation of N,N-diethyl-2-iodoimidazolium iodide occurred rather than the targeted [^{Et}Im-C_2-^{Et}Im][I]$_2$ or products that NHCs and alkyl halides are known to form. The peculiar interaction observed prompted a theoretical investigation into this system as well as comparison to related alkyl halide/NHC systems. The reaction pathways possible for the reaction of ^{Et}Im and 1,2-diiodoethane were all modelled at the B3LYP-D3(BJ)/def2-TZVP (SMD,MeCN)//DSDPBEP86/def2-TZVPP (SMD, MeCN) level of theory. It was determined that the most energetically favourable pathway was *via* a halogen bonding mechanism as this pathway had a much lower transition state barrier compared to the elimination and S_N2 pathways. This is consistent with the observation of the rapid room temperature reaction and supported the NHC

halogen bonding pathway as the basis for this transformation. These analyses also highlighted the importance of iodine as a halogen bond donor compared with other halogens, and further confirmed that N-heterocyclic carbenes make excellent halogen bond acceptors.

Subsequently, this chapter outlined potential application of the NHC induced halogen bonding interactions discovered. The protection of carbon-carbon multiple bonds using molecular halides, followed by subsequent deprotection using NHC halogen bonding interactions was hypothesised to be a valuable application of this system. Initial work focused on iodinating diphenylacetylene to give the corresponding 1,2-diiodo-1,2-diphenylethene. Synthesis of 1,2-diiodo-1,2-diphenylethne was challenging and was a major limitation. Despite these challenges, 1,2-diiodo-1,2-diphenylethene was successfully synthesised. NHC induced bis-iodide abstraction was facile and occurred in reasonably good yield (*cf.* 74% diphenylacetylene obtained without optimisation). This result was promising and encouraged further exploration as it was apparent that this could be used as a protection/deprotection method for carbon-carbon multiple bonds. The significant hurdle to overcome was the synthesis of 1,2-diiodo- species. It was hypothesised that formation of 1,2-dibromo- species would be effective for this method as the previous limitations using alkyl bromides where elimination pathways dominated over the halogen bonding pathway were nullified if the brominated carbon-carbon bond did not have a hydrogen directly bonded to it. Further, the synthesis of 1,2-alkyldibromides is well documented and occurs more rapidly than iodine-based analogues. Upon attempts to abstract the bromide atoms, although successful, the reaction was less selective and the yield of diphenylacetylene obtained prohibited this route as a protection/deprotection methodology.

Following, the reaction was attempted with 1,2-diiodo-1,2-diphenylethene and PPh_3 in order to determine whether PPh_3 could affect this reaction. The merit of which was improved ease of handling and a substantial decrease in cost, thereby justifying a poorer yield. Although PPh_3 successfully generated diphenylacetylene from 1,2-diiodo-1,2-diphenylethene, a substantially poorer yield of 25% was

achieved. Finally, the reaction was performed with 1,2-dibromo-1,2-diphenylethene and PPh_3. For this reaction, there was no observed change to starting materials.

Theoretical investigation compared the molecular orbitals of 1,2-dibromo-1,2-diphenylethene and 1,2-diiodo-1,2-diphenylethene to gain more understanding of these systems. The LUMO for each was calculated. The LUMO of 1,2-diiodo-1,2-diphenylethene resembled that of 1,2-diiodoethane, whereby it displayed sigma-antibonding character with respect to the C-I bonds and π-bonding with respect to the C-C bond. This comparable molecular orbital depiction explains why 1,2-diiodo abstraction from 1,2-diiodo-1,2-diphenylethene occurred in a facile manner, as the halogen bonding pathway is conceivable with this species. The calculated LUMO of 1,2-dibromo-1,2-diphenylethene was localised to the central carbon-carbon bonds and the phenyl rings. A LUMO of this description is not conducive for a halogen bonding pathway to occur and explains the inefficiency observed for this reaction. The LUMO-1 of 1,2-dibromo-1,2-diphenylethene displayed sigma-antibonding character with respect to the C-Br bonds and π-bonding with respect to the C-C bond and explains why there was some formation of diphenylethylene observed.

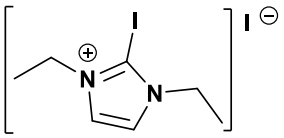
This chapter gave an unusual example of halogen bonding with NHCs being invoked as the key interaction in a reaction. It was attempted to employ this interaction as a method for the protection and subsequent deprotection of carbon-carbon multiple bonds. Ultimately, it was determined that the use of NHC halogen bonding interactions as a protection method for carbon-carbon multiple bonds was not viable as the poor yields obtained prohibited use.

3.10 Experimental

General Procedure A: Generation of free carbenes

In a nitrogen filled glove box, the appropriate 1,3-dialkylimidazolium salt (1.00 eq.) was suspended in a solution of C_6H_6. A solution of KHMDS (1.05eq.) in C_6H_6 was added in one portion and the reaction was left to stir for 1 hr. Following the solids were removed *via* centrifugation. Free carbene was collected in the supernatant and used immediately.

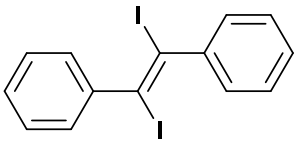
1,3-Diethyl-2-iodoimidazolium iodide



In a nitrogen filled glove box, 1,2-diiodoethane (102 mg, 0.36 mmol, 1.0 eq.) was dissolved in 1 mL of C_6D_6 with stirring. A solution of 1,3-diethylimidazolylidine (45 mg, 0.36 mmol, 1.0 eq.) in 1 mL of C_6D_6 was added to the 1,2-diiodoethane solution in one portion. Immediately, evolution of gas and formation of an orange precipitate was observed. The reaction was stirred for 5 min. NMR analysis was performed on the crude reaction mixture. The solid was then filtered, washed with Et_2O (3 × 10 mL) and dried under vacuum giving the title compound (119 mg, 87%).

^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm): (s, 2H), 7.34 (q, 4H) 4.28, (t, 6H) 1.54.
m/z (ESI): 251.0 $[M]^+$
m/z (ESI): 127.1 $[M]^-$

1,2-Diiodo-1,2-diphenylethene

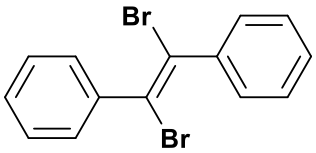


To a stirred solution of diphenylacetylene (283 mg, 1.59 mmol, 1.00 eq.) in 10 mL of acetic acid was added molecular iodine (2.02 g, 7.95 mmol, 5.00 eq.). The reaction was left to stir at room temperature for 10 d. Following 10 d the reaction mixture turned orange and a white precipitate formed. The precipitate was filtered

off and recrystallised from $CHCl_3$. 1,2-diiodo-1,2-diphenylethene was obtained as a white crystalline solid (306 mg, 45%).

^1H NMR (C_6D_6, 400MHz) δ (ppm): (m), 7.39-7.21.

1,2-dibromo-1,2-diphenylethene



1,2-dibromo-1,2-diphenylethene was synthesised according to a literature procedure.[111]

General Procedure B: the reaction of free carbene and 1,2-dihalo-1,2-diphenylethene

In a nitrogen filled glove box was made solution of 1,2-dihalo-1,2-diphenylethene (1.00 eq.) in C_6D_6. Subsequently, freshly generated carbene (1.00 eq.), as per General Procedure A, was added to the solution. The reaction was monitored *via* ^1H NMR spectroscopy.

General Procedure C: the reaction of PPh_3 and 1,2-dihalo-1,2-diphenylethene

In a nitrogen filled glovebox was made solution of 1,2-dihalo-1,2-diphenylethene (1.00 eq.) in C_6D_6. Subsequently, PPh_3 (1.00 eq.) in C_6D_6 was added to the solution in one portion. In the case of 1,2-dibromo-1,2-diphenylethene, the mixture was transferred to a sealed flask and was heated to reflux for a period of 24 hr. The reaction was monitored *via* ^1H NMR and ^{31}P NMR spectroscopy.

Chapter 4. Supercharging $PhICl_2$: $[Ag]_2[B_{12}Cl_{12}]$ as a Catalyst in $PhICl_2$ Mediated Chlorination‡

‡This chapter contains work that has been accepted for publication, DOI: 10.1002/ejoc.202100447. Houston, S. D. assisted in performing some of the large-scale synthesis presented in section *4.06.* Tania optimised the synthesis of 3-chloro-4-dimethylaminopyridine under the mentorship of Poynder, T. B.

4.01 Introduction

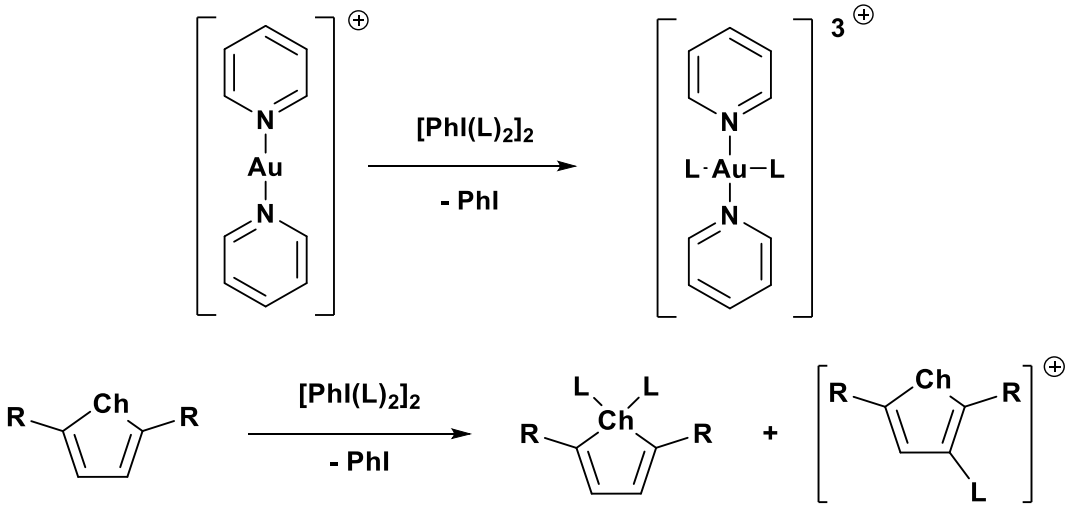
Iodine, located in group seventeen and period five of the Periodic Table, is the heaviest non-radioactive element and is commonly classified as a nonmetal.[119] Owing to its large atomic radius, and consistent with trends moving down groups in the Periodic Table, the bonding situation in iodine compounds do not mirror lighter main-group congeners.[120] Rather, the reactivity displayed by iodine more closely resembles that of the transition metals.[121] Characteristic of iodine is a linear 3-centre-4-electron-bond (L-I-L; L = ligand) which is formed by the 5p orbital of iodine and the appropriate orbitals of the two ligands. This bond is commonly referred to as "hypervalent" and offers explanation as to why reactivity of hypervalent iodine compounds more closely adheres to transition metal reactivity than lighter main-group compounds. As such, much of the chemistry of hypervalent iodine reagents consists of transformations involving oxidative addition, reductive elimination, ligand exchange, and ligand coupling.[122]

Most commonly, hypervalent iodine reagents are either trivalent, I(III), or pentavalent, I(V), at the iodine centre. Our group is interested in hypervalent I(III) reagents for the oxidation of metal and main group centres, and the fundamentally interesting properties that arise when exploring their synthesis and reactivity. As such, this work will focus on iodine(III) reagents.

4.02 Hypervalent Iodine(III) Reagents in our Group

The chemistry surrounding hypervalent iodine(III) reagents in our group can be broadly categorised into two distinct interests: I(III) mediated oxidation of main group and transition metal centres, and fundamental investigations regarding novel synthesis, structure and reactivity of these reagents. The oxidation of main group

and metal centres to form new coordination complexes is an area of prominent research in our group. Methods for which we explore these systems is generally *via* the use of hypervalent iodine(III) reagents and relies on the reductive elimination of iodobenzene (PhI) for effective reactivity. These transformations commonly demonstrate oxidation and ligand delivery using Weiss' reagents ($[PhI(pyridine)_2]^{2+}$) and derivatives of diacetoxyiodobenzene (*e.g.* $PhI(OAc)(OTf)$).[123–131] Of particular note is the formation of gold(III) cations *via* simultaneous oxidation and ligands delivery from $[PhI(pyridine)_2]^{2+}$,[124] and the oxidation and diverse reactivity of thiophenes, selenophenes and tellurophenes with $PhI(L)_2$ reagents (Scheme 4.01).[125]

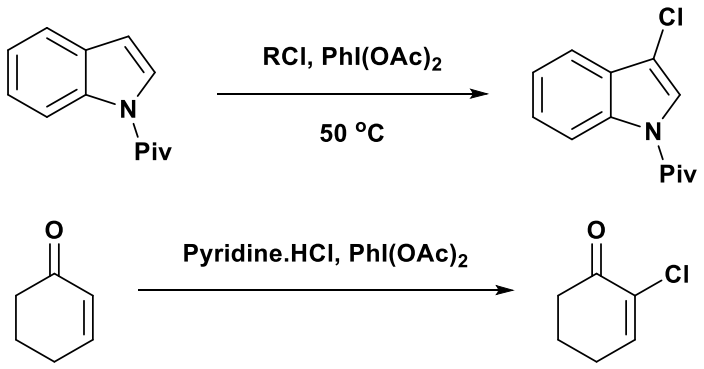


Scheme 4.01. *Formation of gold(III) cations and oxidation of chalcogen heterocycles/formation of chalcogen heterocyclic cations via I(III) reagents.*

Also, as part of our research we have explored chemical reactivity of iodine(IIII) reagents from a more fundamental perspective. For example, the discovery of a 2,2′-bipyridine coordination complex of $[ICl_2]^+$, which demonstrated oxidative chlorination of gold(I)-N-Heterocyclic species.[132] The use of a $PhI(OAc)_2$/TMS-OTf system which enabled formation of coordination complexes at iodine or oxidative ligand coupling reactions.[133] Followed by a related synthetic and theoretical study which went on to disprove the existence of the long-reported and widely used I(III) reagent, $PhI(OTf)_2$.[134] This work will detail our focus on the trivalent iodine (I(III)) reagent, iodobenzene dichloride ($PhICl_2$).

4.03 Introduction to $PhICl_2$ and Activation of I(III) Reagents

$PhICl_2$, the first reported hypervalent iodine(III) reagent,[135] is a versatile oxidant, primarily acting as a chlorinating agent representing a convenient substitute for the highly toxic and difficult to handle Cl_2. Conversely, $PhICl_2$ is an easily weighed solid which is readily accessible from PhI, HCl, and H_2O_2,[122] can be used without the need for rigorously anhydrous conditions. $PhICl_2$ offers broad reactivity and enables mild and environmentally benign reaction conditions,[136] and has been used widely in the oxidation and chlorination of organic and inorganic compounds.[137,138] Despite all its merits as a reagent, $PhICl_2$ is not without limitation. $PhICl_2$ is a weaker oxidising agent than the Cl_2 it replaces. As such, it is rendered unreactive towards many substrates. It is established that the reactivity of iodine(III) reagents can be enhanced upon the addition of acids, either Lewis or Brønsted.[139] Activation of $PhICl_2$ can be accomplished using Lewis acids, with a handful of reports over the years, including use of stoichiometric $AgBF_4$ or $SbCl_5$ in the chlorination of norbornene derivatives,[140] and by catalytic $AlCl_3$ for the replacement of diazo functional groups by chlorines. Lewis acids such as BF_3 have also been shown to increase the activity of the related oxidant $PhI(OAc)_2$.[141] A recent paper by Nagib described the activation of $PhI(OAc)_2$ using either HCl or acid chloride, or of $PhICl_2$ using acetic anhydride, in each case giving a mixed PhI(OAc)(Cl) species capable of chlorinating the C-H bonds of a variety of (hetero)arenes in a few hours at 50 °C.[142] Lupton employed the same concept a decade earlier using excess pyridinium chloride as the chloride source in concert with $PhI(OAc)_2$ to chlorinate α,β-unsaturated carbonyls and alkenes (Scheme 4.02).[143]



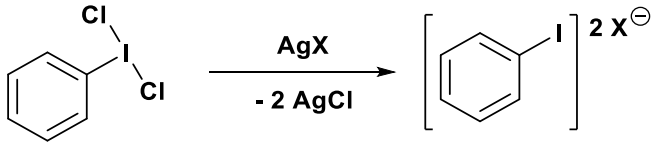
Scheme 4.02. *Chlorination examples using a mixed PhI(OAc)(Cl) intermediate.*

In this chapter, the serendipitous discovery that abstraction of chloride from $PhICl_2$ using catalytic amounts of silver salts of the weakly coordinating anion $[B_{12}Cl_{12}]^{2-}$ is outlined. This discovery is the result of the attempted synthesis of a phenyliodonium dication, $[PhI]^{2+}$. It was discovered that catalytic $[B_{12}Cl_{12}]^{2-}$ increases the activity of $PhICl_2$ such that substrates unreactive or poorly reactive to $PhICl_2$ can be rapidly chlorinated at room temperature.

4.04 Attempted Synthesis of the PhI^{2+} Dication: The Reaction of $PhICl_2$ and $Ag_2B_{12}Cl_{12}$

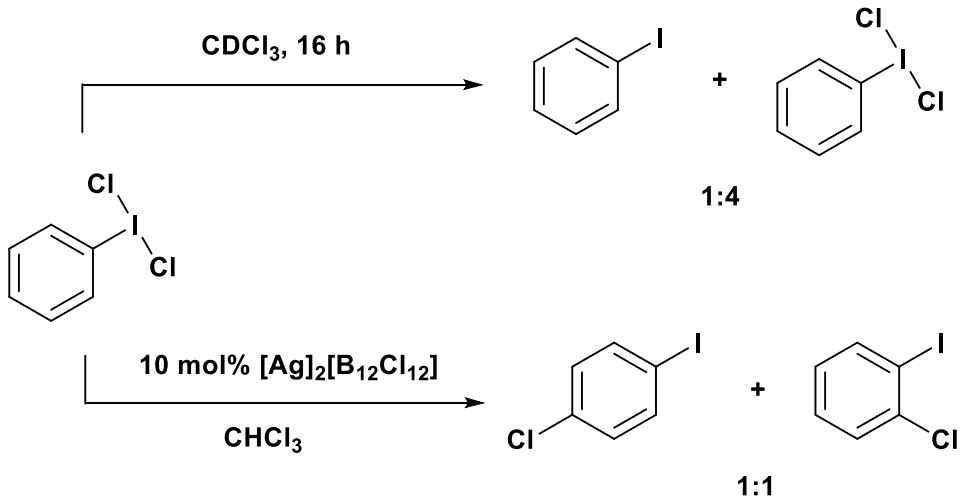
The synthesis of highly reactive main group cations as stabilised by weakly coordinating anions (WCAs) is currently a flourishing field of chemistry.[144] We have been interested in the synthesis and characterisation of some of these species, namely, the perfluorinated triphenylmethyl cation and a cyclopentadienyl cation.[145–147] With this backdrop in mind, and $PhICl_2$ in hand, it was hypothesised that $[PhI]^{2+}$ would be an attractive species to access under the theme of coordination chemistry at iodine. Specifically, we were interested in exploring reactions of the type: $[PhI]^{2+}$ + 2 L (where L = ligand), to access as yet unknown I(III) species.

One of the most common methods employed for the generation of reactive main group cations is halide abstraction as driven by salt elimination.[144] Starting with the precursor, $PhICl_2$, we sought potential chloride abstracting reagents to facilitate this transformation. Silver triflate induced metathesis *via* precipitation of AgCl would generally be the preferred method for such a transformation in our group. However, we recently demonstrated that phenyliodine(III) systems have a poor tolerance to triflate moieties at iodine.[134] In cases where triflate species are unviable, it has been demonstrated that carborane reagents are suitable alternatives where triflates are too nucleophilic.[148] Carborane reagents are widely employed in the synthesis of highly reactive main group cations owing to their low nucleophilicity, chemical inertness and weak coordination capacity.[149] We decided to attempt synthesis of $[PhI]^{2+}$ as stabilised by a weakly coordinating carborane-type anion (Scheme 4.03).



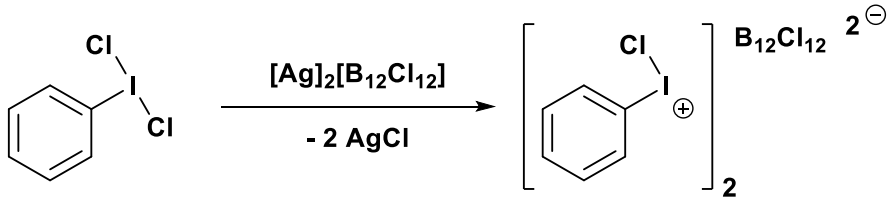
Scheme 4.03. *Targeted synthesis of $[PhI]^{2+}$ via silver induced chloride abstraction.*

To achieve this, we aimed to generate the $[PhI][B_{12}Cl_{12}]$ salt, using the weakly coordinating and highly robust nature of the $[B_{12}Cl_{12}]^{2-}$ dianion to allow for an isolable, or at least, observable species. $[B_{12}Cl_{12}]^{2-}$ was selected for its ease of synthesis relative to other related carborane reagents and derivatives, as this reagent can be generated from the common: $NaBH_4$, I_2 and SO_2Cl_2. To this end, $PhICl_2$ was reacted with stoichiometric $[Ag]_2[B_{12}Cl_{12}]$ in $CDCl_3$. A ^{1}H-NMR spectrum of the reaction mixture revealed total conversion of $PhICl_2$ to new species that were not consistent with generation of a singular PhI species, as well as residual iodobenzene. Notably, identical reactivity was observed in the presence of catalytic (10 mol%) $[Ag]_2[B_{12}Cl_{12}]$. Upon purification these signals were attributed to the formation of 4-chloro-iodobenzene and 2-chloro-iodobenzene in approximately a 1:1 ratio. Addition of NEt_3 to the mixture resulted in the immediate precipitation of $[HNEt_3][Cl]$, indicating that HCl was generated during the course of the reaction. It was noted that a solution of $PhICl_2$ in $CDCl_3$ left stirring in the absence of $[Ag]_2[B_{12}Cl_{12}]$ exhibited decomposition into PhI, with a PhI:$PhICl_2$ ratio of 1:4 after 16 h. Neither 4-chloro or 2-chloro-iodobenzene were observed in this experiment (Scheme 4.04).



Scheme 4.04. *Decomposition reaction of $PhICl_2$ (top) and reaction of $PhICl_2$ with 10 mol% $[Ag]_2[B_{12}Cl_{12}]$ (bottom).*

We have previously observed electrophilic aromatic substitution processes in reactions with electron poor iodine(III) species, and therefore surmised that residual PhI generated from the decomposition of $PhICl_2$ was undergoing electrophilic aromatic chlorination. $[Ag]_2[B_{12}Cl_{12}]$ was essential for the reaction to proceed, suggestive of an iodonium type mechanism, in which Ag(I) abstracts a chloride from $PhICl_2$ resulting in an activated $[PhICl]^+$ species, which is presumably stabilised by the weakly coordinating $[B_{12}Cl_{12}]^{2-}$ anion (Scheme 4.05).



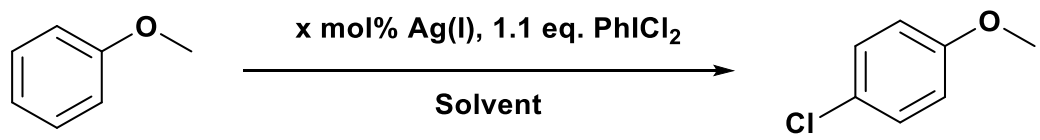
Scheme 4.05. *$[Ag]_2[B_{12}Cl_{12}]$ induced chloride abstraction from $PhICl_2$ to give active species, $[PhICl]^+$.*

4.05 Exploration of Electrophilic Aromatic Substitution Reactivity and Other Ag(I) Salts

Encouraged by this preliminary reactivity, we decided to explore the efficacy of a number of other Ag(I) sources as mediators of electrophilic aromatic chlorination with $PhICl_2$ using the electron rich arene, methoxybenzene, as an exemplar substrate. A range of in-house and commercial Ag(I) sources, and the Cs salt of

the $[B_{12}Cl_{12}]^{2-}$ were all explored as mediators for the electrophilic aromatic chlorination of methoxybenzene (Table 4.01).

Table 4.01. *Exploration of in-house and commercially available Ag(I) sources for the electrophilic aromatic chlorination of methoxybenzene.*



major product[a]

Entry	Catalyst	Loading (mol%)	Solvent	Conversion[b] (%)
1	none	n/a	$CDCl_3$	7
2	$[Ag]_2[B_{12}Cl_{12}]$	5	$CDCl_3$	55
3	$[Ag]_2[B_{12}Cl_{12}]$	10	$CDCl_3$	67
4	$[Ag]_2[B_{12}Cl_{12}]$	10	CD_3CN	42
5	$[Ag]_2[B_{12}H_{12}]$	10	$CDCl_3$	61
6	$[Cs]_2[B_{12}H_{12}]$	10	$CDCl_3$	25
7	AgCl	20	$CDCl_3$	4
8	AgOTf	25	$CDCl_3$	6
9	AgOTf	100	$CDCl_3$	59
10	$AgBF_4$	25	$CDCl_3$	8
11	$AgBF_4$	100	$CDCl_3$	56
12	$AgSbF_6$	25	$CDCl_3$	46
13	$AgSbF_6$	100	$CDCl_3$	62
14	$AgNO_3$	100	$CDCl_3$	2

[a]Major observed isomer. [b]Conversion as determined by ^{1}H-NMR. All reactions monitored after 20minat room temperature.

Some conversion was observed in all cases; however, activity on the whole was worse than $[Ag]_2[B_{12}Cl_{12}]$. Reactions with AgOTf, $AgBF_4$, and $AgSbF_6$ (traditionally considered weakly coordinating),[150] displayed similar levels of activity only when stoichiometric quantities of Ag(I) were used (entries 9, 11, & 13, respectively). Lower loadings resulted in activity comparable to the use of no Ag(I) at all. $AgNO_3$

was the worst activator investigated, resulting in only minimal conversion even when deployed stoichiometrically (entry 14). Only minor conversion to 4-chloromethoxybenzene was observed in the absence of any catalyst (entry 1). As expected, addition of 5 mol% $[Ag]_2[B_{12}Cl_{12}]$ resulted in substantially greater reactivity, which was further improved to a conversion of 67% upon doubling catalyst loading to 10 mol% (entries 2 & 3). Pleasingly, conversion was rapid (20 minutes) and occurred readily at room temperature. Changing solvent to acetonitrile (entry 4) or altering the nature of the counteranion and cation (entries 5 & 6) were all detrimental. AgCl, potentially generated in quantities up to 20 mol% during the catalytic cycle with $[Ag]_2[B_{12}Cl_{12}]$, was also investigated as a potential catalyst, and resulted little conversion at 20% loading (entry 7).

Following, the optimum conditions (*i.e.* entry 3) were then applied to a range of substituted arenes in order to investigate the scope of the system. For each substrate, a control reaction was also performed in the absence of $[Ag]_2[B_{12}Cl_{12}]$ to probe its innate reactivity with $PhICl_2$.

4.06 The Scope of the $PhICl_2$/$[Ag]_2[B_{12}Cl_{12}]$ System

Methoxybenzene translated well to scale, with 4-chloromethoxybenzene isolated as the sole isomer in 55% yield. 2,6-Dimethyl phenol was also isolated exclusively as the 4-chloro- isomer and performed much better in the presence of catalyst (*i.e*. 76% vs. 20%). Selectivity and yields were lower for unsubstituted phenol, with the 2,4-dichloro- isomer isolated in higher proportions in the presence of catalyst. Incorporation of an electron withdrawing group to the phenol ring was well tolerated, as demonstrated by ethyl salicylate, which was chlorinated in the 4-position relative to the hydroxyl group. Notably, this reaction did not proceed at all in the absence of catalyst. Napthalen-1-ol proved problematic, with a range of isomers isolated in either event, although the 4-chloro- isomer was the major in each case. Rerunning the reaction at 0 ºC gave similar results and did not afford any improvement in selectivity. Using a phenol in which the 4-position was blocked gave a mixture of 2-chloro isomers. Interestingly, moving to propiophenone, an electron deficient arene, resulted exclusively in chlorination alpha to the ketone,

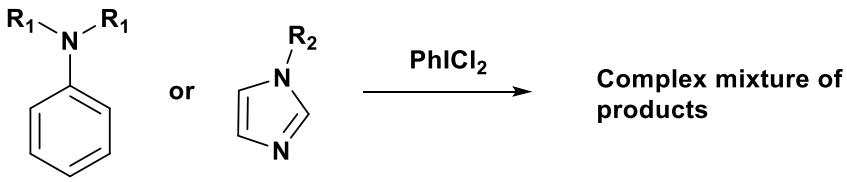
with the aromatic ring left untouched. Introduction of an electron donating substituent marked a complete reversal in chemoselectivity. Neither substrate showed reactivity in a control reaction. 3,4,5-Trimethoxybenzoic acid, the most electron rich arene in the series, was the only member to display superior reactivity in the absence of catalyst, giving the 4-chloro isomer in 84% yield in a control experiment, but only 64% in the presence of $[Ag]_2[B_{12}Cl_{12}]$. The reason for this remains unclear, but may be explained, in part, by the propensity of residual PhI (generated as a by-product) to undergo chlorination (as depicted in Scheme 4.04), thereby reducing the amount of $PhICl_2$ available for productive pathways. The conditions were also successful in delivering chlorinated oxazolidinone as a single isomer, as confirmed by HSQC and subsequently X-ray crystallography. This species is a structural analogue of the commercially available antibiotic Linezolid,[151] and highlights the utility of this approach in late stage chlorination, an attractive strategy in drug design.[152] Finally, a series of heteroarenes were investigated, and unfortunately proved to be a limitation.

4.07 Limitations with Heteroarenes

Unlike the model phenols and alkoxy aryl species which displayed predictable reactivity, heteroarenes and nitrogen containing species were diverse in their response to this system, and often were reactive to $PhICl_2$ prior to the addition of silver, thus, were not suitable substrates for this electrophilic aromatic chlorinating methodology.

Upon the addition of $PhICl_2$ to aryl amine derivatives (*e.g.* aniline), complicated mixtures of products which were unable to be identified and/or separated from each other formed. The crude ^1H NMR analysis indicated complicated mixtures of products, and total consumption of starting material. TLC analysis of reaction mixtures showed majority of species on the baseline regardless of the solvent system trailed, suggesting formation of salt species. Mass spectrometry confirmed presence of HCl salts of starting materials and other unidentifiable ions. Similarly, attempted chlorination of 5-membered N-heterocycles presented with comparable challenges. For example, the attempted chlorination of imidazole or indole

derivatives furnished complex mixtures of hydrochloride salts and other indeterminate species as intractable mixtures. Protection of the nitrogen atom of imidazole was attempted with both alkyl groups (methyl, ethyl) and with tert-butyloxycarbonyl (Boc) to no improved outcome (Scheme 4.06). In particular, Boc was not amenable to this system due to its inherent incompatibility with the HCl generated from this system. Owing to both reaction of the nitrogenous substrate with $PhICl_2$ prior to addition of silver, and the complicated reaction mixtures achieved, these substrates were not pursued further as substrates for this chlorination method.

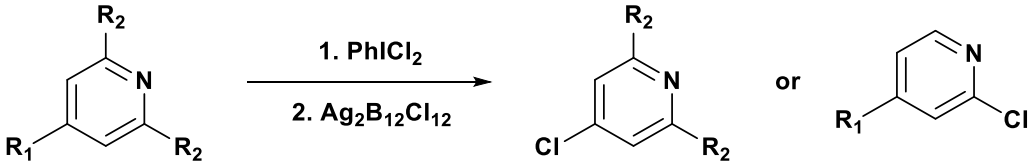


Scheme 4.06. *General reactivity of arylamines and imidazole derivatives with $PhICl_2$. R_1, R_2 = -H, -Alkyl, -Boc.*

Following, the next explored group of substrates was 6-membered N-heterocycles. Quinoline was screened as a substrate for chlorination, however, as previously described, this species reacted with $PhICl_2$ prior to the addition of silver and gave a complex mixture of unidentifiable products. 8-hydroxyquinoline was probed as it was thought that the phenol functionality would render this substrate more amenable to chlorination, however, this was unsuccessful. Interestingly, the series of reactions involving $PhICl_2$ and derivatives of pyridine provided alternate reactivity to that which is described in *Scheme 4.06*, and therefore, was explored in greater detail.

4.08 Attempted Chlorination of Pyridine and its Derivatives

The attempted $PhICl_2/[Ag]_2[B_{12}Cl_{12}]$ chlorination of pyridine and its derivatives aimed to target aryl chlorination of 6-membered N-heterocyclic rings, thereby increasing the scope and synthetic utility of the $PhICl_2/[Ag]_2[B_{12}Cl_{12}]$ chlorinating system (Scheme 4.07).



Scheme 4.07. *Targeted chlorination of pyridine derivatives. R_1 = -H, -NMe_2, Me; R_2 = H, Me.*

First explored in this class was the reaction of pyridine with $PhICl_2$. To determine if the species reacted prior to the addition of silver, a stoichiometric ratio of pyridine and $PhICl_2$ were combined in $CDCl_3$ and stirred. ^1H NMR analysis of the reaction mixture at 30 minutes showed no change in the chemical shift for either the pyridine or $PhICl_2$ moieties, however a slight broadening of signals was observed as compared to the separate species under the same conditions. As there was no spontaneous reaction observed between pyridine and $PhICl_2$, $[Ag]_2[B_{12}Cl_{12}]$ was added to the system in attempt to achieve aryl chlorination as previously described. To a freshly generated reaction mixture of stoichiometric pyridine and $PhICl_2$ was added 10% $[Ag]_2[B_{12}Cl_{12}]$ in $CDCl_3$. The reaction mixture was monitored *via* ^1H NMR spectroscopy. At six hours, there was no observed reaction between the two species, but rather, identical NMR spectra to those obtained at 30minand without silver were observed. As there was no spontaneous reaction of $PhICl_2$ and pyridine (as with other N- containing species), nor any observed chlorination upon the addition of $[Ag]_2[B_{12}Cl_{12}]$, this suggested some alternate interaction between $PhICl_2$ and pyridine was occurring.

To further investigate reactivity of this class of compounds, other 6-membered pyridine derivatives were explored as substrates. In the case of 2,6-dimethylpyridine and $PhICl_2$, no reaction or broadening of signals (as with pyridine) in the ^1H NMR spectrum was observed. Upon the addition of 10 mol% $[Ag]_2[B_{12}Cl_{12}]$, it was determined that decomposition of $PhICl_2$ to iodobenzene and subsequent protonation of 2,6-dimethylpyridine was occurring at a slow rate. 4-methylpyridine displayed analogous reactivity, where no reaction between the substrate and $PhICl_2$ was observed *via* ^1H NMR spectroscopy and following the addition of 10 mol% $[Ag]_2[B_{12}Cl_{12}]$, decomposition of $PhICl_2$ and protonation of 4-methylpyridine occurred (Scheme 4.08). Presumably, the slow decomposition of

$PhICl_2$ into PhI and Cl_2 (*cf.* $PhICl_2$ decomposes to PhI in a 4:1 ratio at t = 16 h) was inducing protonation of the pyridine derivative at a similar rate.

The reaction of 4-dimethylaminopyridine and $PhICl_2$ occurred spontaneously and without silver as evidenced by an immediate colour change upon addition of 4-dimethylaminopyridine to a solution containing one equivalent of $PhICl_2$ in $CDCl_3$. ^1H NMR analysis of this reaction mixture indicated total consumption of starting materials and formation of a new 4-dimethylaminopyridine species with ^1H splitting patterns consistent with a monosubstituted 4-dimethylaminopyridine ring, as well as protonated 4-dimethylaminopyridine. Mass spectrometry of the reaction mixture indicated two major signals at *m/z* 123.1 for protonated 4-dimethylaminopyridine, and *m/z* 157.1 in positive mode, with an isotope pattern consistent with one chlorine atom present. This suggested a monochlorinated 4-dimethylaminopyridine species was being formed from this reaction. Literature reports indicated that the species being generated was not 2-chloro-4-dimethylaminopyridine by comparison of ^1H NMR spectra.[153] We hypothesised that formation of 3-chloro-4-dimethylaminopyridine was occurring in this system, however there had been no reports of this species in the literature for comparison.

To investigate, the protonated 4-dimethylaminopyridine was precipitated from the system upon addition of dropwise Et_2O and removed *via* filtration. Subsequently, the dropwise addition of triflic acid in Et_2O to the resultant filtrate was performed to afford the suspected 3-chloro-4-dimethylaminopyridine as a triflate salt. A white precipitate formed upon addition of the triflic acid solution which was washed with Et_2O and collected *via* filtration. Single crystals were grown from a CH_3CN solution *via* vapour diffusion of Et_2O and X-ray diffraction analysis gave the pyridinium triflate salt of 3-chloro-4-dimethylaminopyridine (figure 4.01). These reactions can be summarised in *Scheme 4.08.*

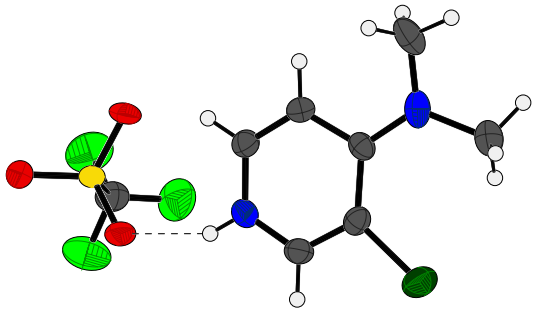
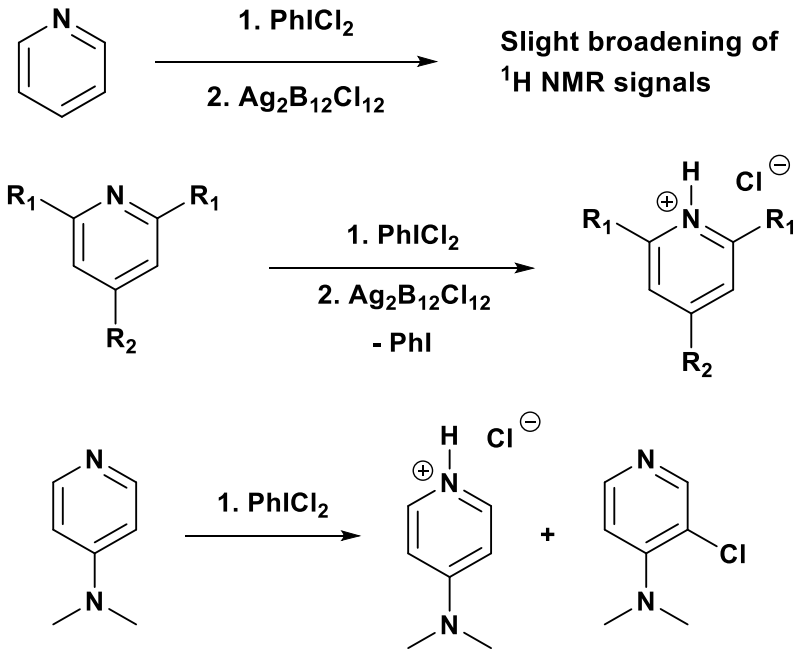


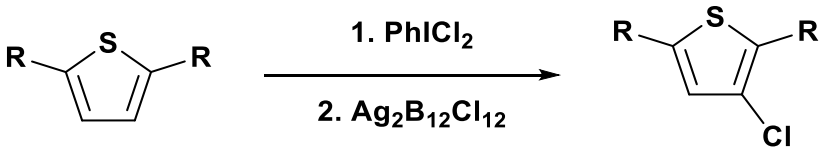
Figure 4.01. *Solid-state structure of the pyridinium triflate salt of 3-chloro-4-dimethylaminopyridine.*



Scheme 4.08. *Reactivity of 6 membered N-heterocycles with $PhICl_2$/Ag(I). R_1 = -H, -Me; R_2 = -H, -Me.*

The unusual observation of the interaction of pyridine and $PhICl_2$ piqued our interest as it demonstrated neither reactivity of other nitrogen species (spontaneous reaction and/or formation of hydrochloride salts), nor aryl chlorination upon the addition of $Ag_2B_{12}Cl_{12}$ as with the substrates explored in this chapter. Rather, broadening of signals in the ^1H NMR spectrum suggested that some interaction between pyridine and $PhICl_2$ was occurring that was prohibiting these pathways of reactivity. To further investigate, an in-depth analysis of this system and previously reported systems involving pyridine and $PhICl_2$ was performed and forms the basis of *Chapter 5*.

The $PhICl_2/[Ag]_2[B_{12}Cl_{12}]$ system was then applied to thiophenes in attempt to further expand the scope of this system. These species were subject to the optimum conditions previously described (entry 3, table 4.01). In the case of thiophene, addition of 10 mol% $[Ag]_2[B_{12}Cl_{12}]$ resulted in the precipitation of a black solid, which was insoluble in organic solvents and presumed to be polythiophene. ^{1}H-NMR analysis of the crude reaction mixture indicated trace formation of 3-chlorothiophene, however, it was clear the major fate of the thiophene was lost as polythiophene based on the mass recovered. The reaction of 2,5-dimethylthiophene and 10 mol% $[Ag]_2[B_{12}Cl_{12}]$ rapidly changed colour to deep red. ^{1}H-NMR analysis of the crude reaction mixture indicated formation of a new 2,5-dimethylthiophene species at a low conversion, relative to residual starting material. Repeating the reaction with stoichiometric $[Ag]_2[B_{12}Cl_{12}]$ increased formation of this species to approximately 50% conversion (based on ^{1}H-NMR integration). The ^{1}H-NMR suggested this species was 3-chloro-2,5-dimethylthiophene, as two new signals in the methyl region each integrating to three protons and one aromatic signal integrating to one was observed. Attempts to isolate this species were not pursued owing to the stoichiometric $[Ag]_2[B_{12}Cl_{12}]$ required, prohibiting this reactivity form being synthetically useful. In both cases, there was no observed reaction with $PhICl_2$ alone (Scheme 4.09).



Scheme 4.09. *Reactivity of thiophenes with $PhICl_2$/Ag(I). R = -H, -Me.*

4.09 Chlorination of Alkenes and Alkynes

Given related methods (*i.e.* Nagib and Lupton) have both capitalised on PhI(OAc)(Cl), an active intermediate capable of delivering a single chlorine atom, and recent reports of the enantioselective dichlorination of alkenes,[154] we speculated whether this methodology would be capable of activating $PhICl_2$ to formally deliver a unit of molecular Cl_2. To this end, the chlorination of several alkenes/alkynes was investigated. Gratifyingly, this approach proved fruitful.

Styrene delivered 1,2-dichloro-styrene, albeit in modest yield. Methyl cinnamate was also readily chlorinated, giving the corresponding dichlorides in a combined yield of 56% and a 2:1 d.r. in favour of the anti-isomer. Minor amounts of the elimination product, methyl β-chlorocinnamate, were also isolated. Diphenylacetylene gave the corresponding trans-dichloride. In all examples, the presence of $[Ag]_2[B_{12}Cl_{12}]$ was essential, and reactions were completely chemoselective for exocyclic π-bonds over arenes. The electron poor dimethyl acetylenedicarboxylate, was not tolerated under these conditions, under which no chlorinated adducts were observed.

4.10 Concluding Remarks

In summary, during the pursuit to isolate a phenyliodonium dication, $[PhI]^{2+}$, it was demonstrated that catalytic $[Ag]_2[B_{12}Cl_{12}]$ was able to activate $PhICl_2$ to act as a source of Cl^+ in the electrophilic aromatic substitution of arenes, and also to deliver a full equivalent of Cl_2 in the chlorination of alkenes and alkynes. The reactions discussed herein likely proceed through the intermediate, $[PhICl]^+$, *via* an iodonium mechanism, as opposed to a radical cation mechanism observed by others in related systems, and thereby present an attractive complimentary reactivity manifold. Further evidence for this comes from the fact that electron rich arenes outperformed their electron poor counterparts, and that chlorination was generally selective for positions on which the greatest delocalisation of partial negative charge would be expected. Whilst innate reactivity was observed with some arenes, in all but one substrate surveyed, $[Ag]_2[B_{12}Cl_{12}]$ resulted in enhanced reactivity. Presence of the Ag(I) salt was essential for the chlorination of alkenes and alkynes.

During this investigation, it was determined that this system was not useful for the chlorination of heteroarenes and nitrogen containing species. Results varied for these compounds. Generally, amine-based substrates displayed innate reactivity to $PhICl_2$ prior to the addition of Ag(I) and formed complex mixtures of unidentifiable products. In the case of thiophenes, traces of chlorinated isomers were observed *via* ^{1}H-NMR spectroscopy, however, side reactions (thiophene) and the

stoichiometric $[Ag]_2[B_{12}Cl_{12}]$ required (2,5-dimethylthiophene) prohibited this pathway from being synthetically useful. Pyridine derivatives displayed diverse reactivity within their class. 4-dimethylaminopyridine formed 3-chloro-4-dimethylaminopyridine from $PhICl_2$ alone. 4-Methylpyridine and 2,5-dimethylpyridine furnished the corresponding hydrochloride salts after extended reaction times. Finally, in the case of pyridine, displayed no innate reactivity with $PhICl_2$, nor any reactivity when subjected to the optimised reaction conditions. A slight broadening of signals was observed as compared to the separate species under the same conditions. This observation suggested some interaction between pyridine and $PhICl_2$ was occurring and will be explored in greater detail in *Chapter 5*.

4.11 Experimental

$[NEt_3H]_2[B_{12}H_{12}]$

Following the procedure of Knapp *et al*,[155] iodine (41.7 g, 0.16 mol) was stirred vigorously in diglyme (70 mL) [Note: the diglyme was vacuum distilled over calcium hydride prior to use] in a flame dried round-bottom flask under an inert nitrogen atmosphere for 16hrto ensure full dissolution. Separately, a flame dried 250 mL 2-neck RBF equipped with a reflux condenser was charged with $NaBH_4$ (20.0 g, 053 mol) and diglyme (80 mL) under an inert nitrogen atmosphere and heated to 100 ºC. The iodine solution was transferred to a flame dried dropping funnel [Note: the end of the dropping funnel was not submerged in the reaction mixture as stated in the original procedure] and added dropwise to the 2-neck RBF over a period of 6 h, at which point the reaction mixture turned purple. Heating was continued at 100 ºC for a further 24 h, at which point the temperature was increased to 185 ºC for a further 16 h. The diglyme was then removed by vacuum distillation to leave a pink/purple paste. The residue was cooled in an ice bath before H_2O (120 mL), followed by HCl (32%, 56 mL), were cautiously added with vigorous stirring. The mixture was left in a fridge (+6 ºC) for 16hrthen the resulting crystals (boric acid) were removed by filtration. Triethylamine (80 mL) was cautiously added to filtrate and the resulting mixture was left to stir vigorously for 16 h. The colour changed multiple times during this period, ending with dark purple. The resulting precipitate was collected by filtration then dried under vacuum to give the title compound (5.0 g, 44%) as a white solid. ^{1}H- and ^{11}B-NMR data are consistent with those reported and did not show the presence of boric acid.

^{11}B-NMR (160 MHz, D_2O): δ (ppm) -15.36 (d, J = 126.9 Hz)
^{1}H-NMR (500 MHz, D_2O): δ (ppm) 3.22 (q, J = 7.3 Hz, 2H), 1.29 (t, J = 7.3 Hz, 3H).

$Cs_2[B_{12}H_{12}]$

Following the procedure of Knapp *et al*,[155] to a solution of $[NHEt_3][B_{12}Cl_{12}]$ (3.36 g, 9.70 mol) in H_2O (34 mL) was added CsOH (50% w/w H_2O, 3.56 mL, 20.37 mmol). The resulting mixture was heated to 100 ºC for 1 h, at which point the minor amount of residual precipitate was removed by hot filtration. The filtrate was left to cool to

rt, then further cooled in an ice bath. The resulting precipitate was collected by filtration then dried under vacuum to give the title compound (2.57 g, 65%) as a white solid.

$Cs_2[B_{12}Cl_{12}]$

Following the procedure of Gu and Ozerov,[156] a flame dried 100 mL 2-neck RBF equipped with a reflux condenser was charged with $Cs_2[B_{12}H_{12}]$ (925 mg, 2.25 mmol). The flask was evacuated then backflushed with nitrogen. MeCN (30 mL) was added [Note: the MeCN was taken from an Innovative Technologies Solvent Purification System directly prior to use], followed by the dropwise addition of SO_2Cl_2 (30 mL). The resulting mixture soon became clear and was heated to 70 ºC for 16 h. [Note: at this stage an aliquot was removed for ^{1}H-NMR analysis. The presence of NH_4^+ was not observed, so no additional steps were taken to ensure its removal as reported in the original procedure.] The reaction mixture was cooled to rt then concentrated *in vacuo*. H_2O (*c.a*. 12 mL) was added, and the resulting mixture was heated to reflux, at which point the minor amount of residual precipitate was removed by hot filtration. The filtrate was reduced in volume by approximately half then cooled in an ice bath. The resulting precipitate was collected by filtration, washed with a small amount of cold water, then dried under vacuum to give the title compound (1.191 g, 59%) as a white solid. ^{11}B-NMR data are consistent with those reported.

^{11}B-NMR (160 MHz, D_2O): δ (ppm) -12.96.

$[Ag_2][B_{12}Cl_{12}]$

Following the procedure of Gu and Ozerov,[156] $Cs_2[B_{12}Cl_{12}]$ was dissolved in H_2O (25 mL) and heated to 55 ºC to give a clear solution. $AgNO_3$ (840 mg, 4.94 mmol) was added in one portion, followed by the dropwise addition of MeCN (1 mL). The resulting precipitate was collected by filtration, washed with cold water, then dried under high vacuum at 80 ºC for 4hrto give the title compound (887 mg, 95%) as a white solid.

$PhICl_2$

Iodobenzene (2 mL, 17.87 mmol) was suspended in HCl (32%, 20 mL) in a conical flask and stirred vigorously then H_2O_2 (30% w/w H_2O, 8 mL) was quickly added. The flask was covered with foil then left to stir for 1 h. The resulting precipitate was collected by filtration, washed with H_2O (10 × 10 mL) then petroleum ether (10 × 10 mL), then air dried for 3hrusing a Büchner funnel to give the title compound (4.09 g, 83%) as a yellow solid. ^{1}H-NMR data are consistent with those reported previously.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 8.19 (dd, *J* = 8.5, 0.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 2H).

General Procedure A: Catalyst Screening

Methoxybenzene (0.073 mmol, 1.0 eq), $PhICl_2$ (1.0 eq) and n% of an Ag(I) salt were suspended in chloroform-*d* (1 mL), stirred in an RBF then sealed with a glass stopper. The flask was not covered in foil. After *c.a.* 30minthe reaction mixture was analysed by ^{1}H-NMR.

General Procedure B: Control Reaction

A control reaction, performed in the absence of $Ag_2[B_{12}Cl_{12}]$, was carried out for all substrates in the same manner as the above procedure. The outcomes of these reactions, either isolated % yield (unless specified otherwise) or n.r. (no reaction), are reported in brackets below the corresponding % yield recorded with $Ag_2[B_{12}Cl_{12}]$.

General Procedure C: Chlorination Reaction Using $[Ag_2][B_{12}Cl_{12}]$

Substrate (*c.a.* 0.75 mmol, 1 eq), $PhICl_2$ (1.1 eq) and $Ag_2[B_{12}Cl_{12}]$ (0.1 eq) were suspended in chloroform (10 mL) [Note: the chloroform was washed with H_2O (3 × volume) then distilled over CaH_2 prior to use in order to remove the ethanol stabiliser], stirred in an RBF then sealed with a glass stopper. The flask was not covered in foil. After *c.a.* 1hrthe reaction mixture was filtered through a pad of Celite®, washed with DCM (*c.a.* 10 mL), concentrated *in vacuo*, then purified by

column chromatography. Reaction progress was monitored by either TLC or ^{1}H-NMR and was usually complete within 30 min.

4-Chloromethoxybenzene

Methoxybenzene (150 mg, 1.39 mmol) was subjected to general procedure C. Purification by column chromatography (petroleum ether) gave the title compound (R_f 0.30, 110 mg, 55%) as a colourless liquid. **7% conversion as determined by ^{1}H-NMR*. ^{1}H-NMR data are consistent with those reported previously.[157]

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 3.79 (s, 3H).

4-Chloro-2,6-dimethylphenol

2,6-Dimethylphenol (100 mg, 0.82) was subjected to general procedure C. Purification by column chromatography (2-10% ethyl acetate/petroleum ether v/v) gave the title compound (Rf 0.35, 112 mg, 76%) as a white solid. m.p. 74–75 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.96 (s, 1H), 4.54 (br. s, 1H), 3.22 (s, 3H)
^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 150.9, 128.2, 124.8, 124.7, 16.0
Acquisition of HRMS-ESI was unsuccessful.

2- and 2,3-, 2,4-, and 4-Chloronaphthalen-1-ol

Naphthalen-1-ol (100 mg, 0.69 mmol) was subjected to general procedure C. Purification by column chromatography (5-10% ethyl acetate/petroleum ether v/v) gave the title compounds as white solids. 2-Chloro and 2,3-dichloronaphthalen-1-ol (R_f 0.59, 26 mg, 20%) were isolated as a 4:1 mixture that was inseparable under the conditions screened. ^{1}H-NMR data for 2-chloro-naphthalen-1-ol are consistent with those reported previously.[158]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 8.23–8.21 (m, 1H), 7.79–7.77 (m, 1H), 7.54–7.48 (m, 2H). 7.37 (s, 2H), 5.99 (br. s, 1H). Signals consistent with the previously reported 2,3-dichloronaphthalen-1-ol were also present.[159]

2,4-Dichloronaphthalen-1-ol (R_f 0.52, 13 mg, 9%). ^{1}H-NMR data are consistent with those reported previously,[158]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 8.25 (d, *J* = 9.0 Hz, 1H), 8.15 (d, *J* = 9.0 Hz, 1H), 7.64–7.57 (m, 2H), 7.50 (s, 1H), 5.97 (br. s, 1H).

4-Chloronaphthalen-1-ol (R_f 0.27, 62 mg, 50%). ^{1}H-NMR data are consistent with those reported previously,[158]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 8.21 (dd, *J* = 8.6, 3.3 Hz, 1H), 7.63 (dt, *J* = 8.3, 1.2 Hz, 1H), 7.56 (dt, *J* = 8.3, 1.2 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.26 (br. s, 1H).

Ethyl 5-chloro-2-hydroxybenzoate

Ethyl salicylate (100 mg, 0.60 mmol) was subjected to the general procedure. Purification by column chromatography (2-5% ethyl acetate/petroleum ether v/v) gave the title compound (R_f 0.65, 91 mg, 76%) as a colourless oil. ^{1}H-NMR data are consistent with those reported previously.[160]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 10.77 (s, 1H), 7.82 (d, *J* = 2.6 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

2- and 2,2-Dichloro-1-phenylpropan-1-one

Propiophenone was subjected to the general procedure *using DCM instead of $CHCl_3$*. Purification by column chromatography (0-5% ethyl acetate/petroleum ether v/v) gave the title compounds as colourless oils.

2,2-Dichloro-1-phenylpropan-1-one (R_f 0.68, 3 mg, 2%). ^{1}H-NMR data are consistent with those reported previously.[161]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 8.32 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.60 (dt, *J* = 7.4, 1.2 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 2.36 (s, 3H).

2-Chloro-1-phenylpropan-1-one (R_f 0.45, 24 mg, 19%) was initially isolated as a mixture with propiophenone, which was subsequently removed upon exposure to high vacuum for 16 h. ^{1}H-NMR data are consistent with those reported previously.[162]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 8.02 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.61 (dt, *J* = 7.4, 1.2 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 5.26 (q, *J* = 6.7 Hz, 1H), 1.75 (d, *J* = 6.7 Hz, 3H).

Methyl 2-chloro-3,4,5-trimethoxybenzoate and methyl 3,4,5-trimethoxybenzoate

3,4,5-Trimethoxybenzoic acid (100 mg, 0.47 mmol) was subjected to the general procedure. Separation of the resulting carboxylic acids was problematic, so the crude residue was suspended in methanol (30 mL), then H_2SO_4 (0.1 mL) was added, and the mixture was heated to reflux for 16 h. The solvent was removed *in vacuo* then the residue was taken up $NaHCO_3$ (10 mL) and extracted with DCM (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo*, then purified by column chromatography (5-20% ethyl acetate/petroleum ether v/v) gave the title compounds as a colourless oil and a white solid, respectively.

Methyl 2-chloro-3,4,5-trimethoxybenzoate (R_f 0.31, 78 mg, 64%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.18 (s, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 166.1, 151.7, 150.7, 146.6, 125.3, 121.3, 109.9, 61.4, 61.3, 56.4, 52.6.
HRMS-ESI calcd for $C_{11}H_{13}O_5ClNa$ ($[M+Na]^+$): 283.0344, found 283.0343.

Methyl 3,4,5-trimethoxybenzoate (R_f 0.24, 16 mg, 15%). ^{1}H-NMR data are consistent with those reported previously.[163]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.30 (s, 2H), 3.91 (s, 12H).

6-Chloro and 4-chloroindan-5-ol

5-Indanol (100 mg, 0.75 mmol) was subjected to the general procedure. Purification by column chromatography (5% ethyl acetate/petroleum ether v/v) gave the title compounds (R_f 0.30, 58 mg, 46%) as a 5:1 mixture that was inseparable under the conditions screened. ^{1}H and ^{13}C-NMR spectra indicated presence of title compounds. Acquisition of HRMS-ESI was unsuccessful.

2,4- and 4-Chlorophenol

Phenol (50 mg, 0.53 mmol) was subjected to the general procedure. Purification by column chromatography (2-10% ethyl acetate/petroleum ether v/v) gave the title compounds as a white solid, and an oil, respectively. Other phenols, including 2-chlorophenol and 2,6-dichlorophenol were observed as components of complex mixtures which could not be fully elucidated.

2,4-Dichlorophenol (R_f 0.31, 15 mg, 17%). ^{1}H-NMR data are consistent with those reported previously.[164]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.33 (d, *J* = 9.4 Hz, 1H), 7.15 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.95 (d, *J* = 9.4 Hz, 1H), 5.49 (br. s, 1H).

4-Chlorophenol (R_f 0.25, 5 mg, 7%). ^{1}H-NMR data are consistent with those reported previously.[165]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.19 (d, *J* = 8.9 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 4.77 (br. s, 1H).

3-(3-Chloro-5-fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one

3-(3-Fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one (100 mg, 0.34 mmol) was subjected to the general procedure. Purification by column chromatography (1-5% MeOH/DCM v/v) gave the title compound (R_f 0.60, 39 mg,

35%) as an off-white solid. **Attempts to recover starting material were unsuccessful*.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.36 (dd, *J* = 13.8, 2.6 Hz, 1H), 7.29–7.28 (m, 1H), 4.78–4.71 (m, 1H), 4.01–3.93 (m, 3H), 3.82–3.80 (m, 4H), 3.74 (dd, *J* = 12.7, 3.5 Hz, 1H), 3.17–3.07 (m, 4H), 2.33 (br. s, 1H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 160.6 (d, *J* = 249.9 Hz), 154.5, 135.5 (d, *J* = 12.5 Hz), 134.2 (d, *J* = 8.8 Hz), 132.2 (d, *J* = 13.7 Hz), 115.1 (d, *J* = 2.8 Hz), 106.0 (d, *J* = 27.5 Hz), 73.0, 67.8, 62.7, 51.2 (d, *J* = 4.3 Hz), 46.3.
^{19}F-NMR (375 MHz, $CDCl_3$): δ (ppm) -116.81 (d, *J* = 13.7 Hz).
HRMS-ESI calculated for $C_{14}H_{16}O_4N_2$ ClFNa ($[M+Na]^+$): 353.0675, found 353.0679.
m.p. 108–109 °C
Crystals suitable for X-ray diffraction were grown from a minimum amount of DCM.

1-(3-Chloro-4-methoxyphenyl)ethan-1-one

1-(4-methoxyphenyl)ethan-1-one (60 mg, 0.40 mmol) was subjected to general procedure C. Purification by column chromatography (20% ethyl acetate/petroleum ether v/v) gave the title compound (R_f 0.45, 11 mg, 15%) as a white solid. ^{1}H-NMR data are consistent with those reported previously.[166]

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.00 (d, *J* = 2.0 Hz, 1H), 7.87 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 3.97 (s, 3H), 2.55 (s, 3H).

(1,2-Dichloroethyl)benzene

Styrene (60 mg, 0.40 mmol) was subjected to general procedure C. Purification by column chromatography (petroleum ether) gave the title compound (R_f 0.45, 11 mg, 25%) as a yellow liquid. ^{1}H-NMR data are consistent with those reported previously.[167]

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41–7.37 (m, 5H), 5.00 (t, *J* = 7.2 Hz, 1H), 4.00 (dd, *J* = 11.3, 6.2 Hz, 1H), 3.93 (dd, *J* = 11.2, 7.8 Hz, 1H).

Methyl 2,3-dichloro-3-phenylpropanoates and methyl (*Z*)-2-chloro-3-phenylacrylate

Methyl trans-cinnamate (100 mg, 0.62 mmol) was subjected to the general procedure. Purification by column chromatography (2-5% ethyl acetate/petroleum ether v/v) gave the title compounds as a white solid and two colourless oils.

(*Anti*)-methyl 2,3-dichloro-3phenylpropanoate (R_f 0.43, 54 mg, 37%). ^{1}H-NMR data are consistent with those reported previously.[168]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.43–7.37 (m, 5H), 5.18 (d, *J* = 10.7 Hz, 1H), 4.62 (d, *J* = 10.7 Hz, 1H), 3.90 (s, 3H).

Methyl (*Z*)-2-chloro-3-phenylacrylate (R_f 0.40, 7 mg, 6%). ^{1}H-NMR data are consistent with those reported previously.[169]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.92 (s, 1H), 7.85–7.83 (m, 2H), 7.46–7.41 (m, 3H), 3.91 (s, 3H).

(*Syn*)-methyl 2,3-dichloro-3phenylpropanoate (R_f 0.36, 28 mg, 19%). ^{1}H-NMR data are consistent with those reported previously.[168]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.43–7.40 (m, 2H), 7.39–7.35 (m, 3H), 5.31 (d, *J* = 8.0 Hz, 1H), 4.67 (d, *J* = 8.0 Hz), 3.62 (s, 3H).

(*E*)-1,2-dichloro-1,2-diphenylethene and (*Z*)-(1-chloro-2-(4-iodophenyl)ethene-1,2-diyl)dibenzene

Diphenylacetylene (100 mg, 0.56 mmol) was subjected to the general procedure. Purification by column chromatography (petroleum ether) gave the title compounds (R_f 0.45, 11 mg, 15%) as white solids. (*E*)-1,2-dichloro-1,2-diphenylethene (R_f 0.40, 30 mg, 22%).

m.p. 92–94 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.62–7.61 (m, 4H), 7.46–7.43 (m, 4H), 7.40–7.38 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 137.7, 129.3, 129.2, 128.4, 127.9.

Acquisition of HRMS-ESI was unsuccessful.

Crystals suitable for X-ray diffraction were grown from a minimum amount of n-pentane/DCM.

(*Z*)-(1-Chloro-2-(4-iodophenyl)ethene-1,2-diyl)dibenzene (R_f 0.35, 9 mg, 4%).

m.p. 138–140 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.71–7.69 (m, 2H), 7.30–7.28 (m, 2H), 7.20–7.18 (m, 3H), 7.14–7.09 (m, 5H), 6.94–6.93 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 141.5, 140.7, 139.4, 139.2, 137.5, 131.9, 130.7, 130.1, 128.4, 128.2, 128.1, 127.4, 93.5 *(one resonance is believed to be incident; better resolution was not achieved using C_6D_6)*.

Acquisition of HRMS-ESI was unsuccessful.

Crystals suitable for X-ray diffraction were grown from a minimum amount of n-pentane/DCM.

Chapter 5. On the Interaction of Pyridine with $PhICl_2$[‡]

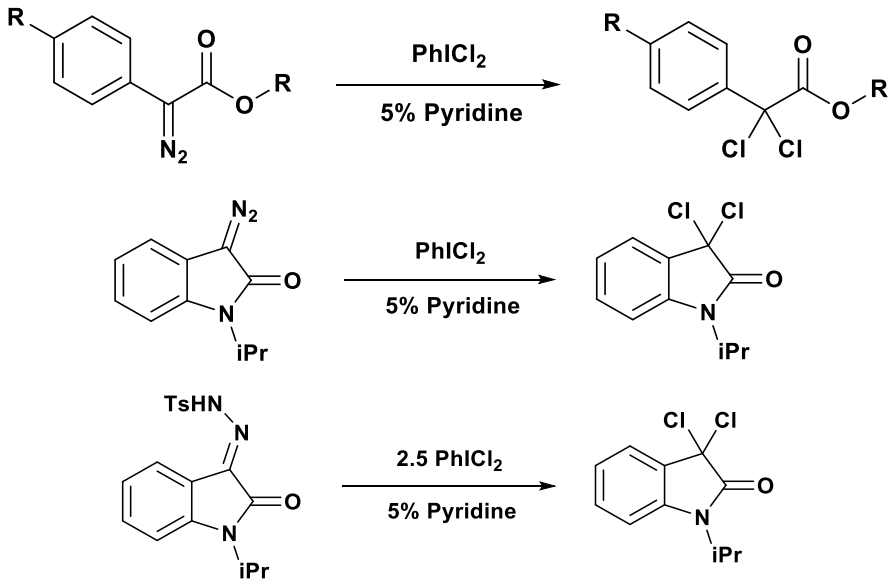
[‡]This chapter contains work that is published: Poynder, T. B.; Chamorro Orué, A. I.; Tania; Sharp-Bucknall, L.; Flynn, M. T.; Wilson, D. J. D.; Athukorala Arachchige, K. S.; Clegg, J. K.; Dutton, J. L. Chem. Commun. 2021. Theoretical work presented in section 5.05 was performed by Wilson, D. J. D. Solid-state X-ray crystallography was performed by Clegg, J. K.

5.01 Introduction

In the process of exploring the scope of the chlorinating system, $PhICl_2/Ag_2B_{12}Cl_{12}$, discussed in *Chapter 4,* it was observed that there was unusual reactivity between $PhICl_2$ and nitrogen containing species. The reaction of $PhICl_2$ and pyridine caught our attention as when combined with $PhICl_2$ there was no observation of a spontaneous reaction (as with other nitrogen heterocycles and amines), nor was there a reaction after the addition of catalytic or stoichiometric $Ag_2B_{12}Cl_{12}$. Rather, in both cases, there was a slight broadening of the signals of $PhICl_2$ as well as a slight shift in the NMR spectrum when compared with free $PhICl_2$ or pyridine under the same conditions. These observations suggested that there was some interaction occurring between $PhICl_2$ and pyridine. Owing to this peculiar observation, an investigation into the interaction of these two species was performed.

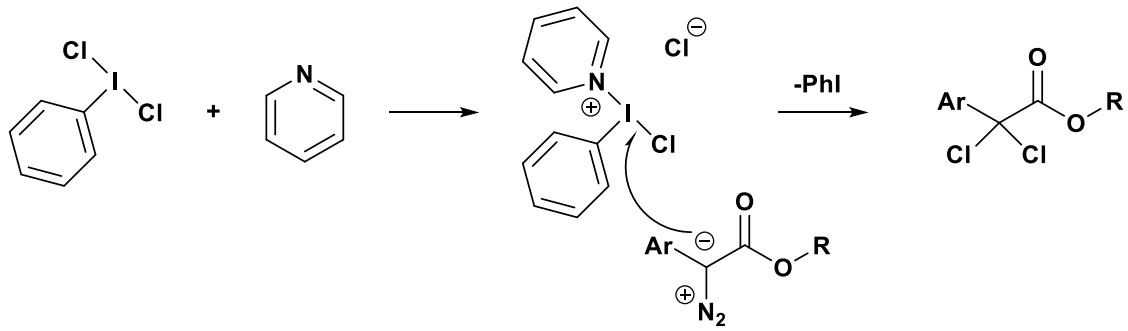
5.02 $PhICl_2$ and Pyridine in the Literature

The combination of $PhICl_2$ and pyridine has been previously reported in the literature. These studies use this system for chlorination or oxidation reactions and generally use an excess of pyridine acting as a base.[137,170–175] In addition to these systems, there have been several reports from Murphy indicating the use of catalytic pyridine to activate $PhICl_2$ for its use as an alpha dichlorinating agent of diazo and hydrozone species.[176–181] These reports can be broadly summarised in *scheme 5.01*.



Scheme 5.01. *Pyridine activation of $PhICl_2$ as reported by Murphy.*

These reports were of particular interest to us as activation of $PhICl_2$ is an ongoing theme of research in our group, and the suggestion of a catalytic (5 mol%) quantity of pyridine affecting this transformation was significant. The initial report of the $PhICl_2$/5% pyridine system proposes a mechanism for the formation of the gem-dichlorinated species. The first step of this process suggests pyridine displaces a chloride from $PhICl_2$ giving the activated cationic complex, [PhICl(pyridine)][Cl], which subsequently is susceptible to attack by the nucleophilic carbon of the diazo species (Scheme 5.02).[176]



Scheme 5.02. *Simplified mechanism presented by Murphy for the activation of $PhICl_2$ by pyridine as mediated by [PhICl(pyridine)][Cl].*

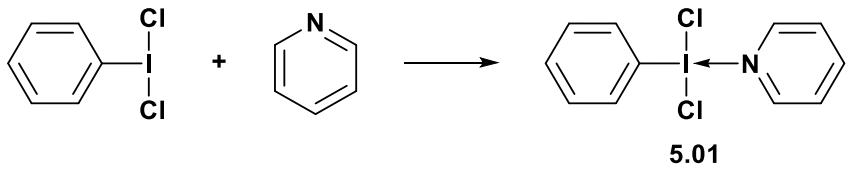
As part of our interest in the coordination chemistry of iodine(III) reagents with pyridyl ligands the proposed active cationic species, [PhICl(pyridine)][Cl], caught our attention as we have been attempting to isolate such a complex for some time.

5.03 The Investigation into [PhICl(pyridine)][Cl], a Masked $PhICl^+$

The observation and subsequent synthesis of [PhICl(pyridine)][Cl] was targeted. Initial methods to observe [PhICl(pyridine)][Cl] began with the reaction of one stoichiometric equivalent of pyridine to $PhICl_2$ in $CDCl_3$. As previously described, the ^1H NMR spectrum indicated a slight broadening of signals for each species as compared to separate species under the same conditions. It was expected that if [PhICl(pyridine)][Cl] was being formed, a substantial downfield shift of the proton *ortho*- to the nitrogen atom within the pyridine ring would be observed. This hypothesis is supported by comparison of the ^1H NMR spectra of free pyridine and Weiss' reagent, $[PhI(pyridine)_2]^{2+}$, where this proton has a shift of 8.57 ppm for free pyridine and 8.99 ppm in Weiss' reagent in CD_3CN.[99] It is expected that formation of the monosubstituted hypervalent iodine cation, [PhICl(pyridine)][Cl], would shift this proton somewhere between 8.57 and 8.99 ppm.

To further gain understanding on the interaction of pyridine on $PhICl_2$, solutions of various concentrations of pyridine relative to $PhICl_2$, in $CHCl_3$ (and one solution of $PhICl_2$ in neat pyridine) were generated and held at -30 °C overnight in attempt to induce crystallisation and enable solid-state X-ray analysis on this system. In the case of $PhICl_2$ in neat pyridine bright yellow block-like crystals formed, which were suitable for X-ray analysis. At lower concentrations of added pyridine, there was

crystallization of yellow needle-like material observed. In the case of the neat pyridine crystals, single crystal X-ray analysis gave a structure of $PhICl_2$ with a pyridine unit completing the square planar coordination sphere of the iodine atom opposite the I-C bond, giving the neutral complex $PhICl_2$.pyridine, **5.01** (Scheme 5.03). The needle-like crystals obtained from the other solutions were free $PhICl_2$.



5.01

Scheme 5.03. *Formation of $PhICl_2$.pyridine,* ***5.01****, from $PhICl_2$ and neat pyridine.*

The N-I bond distance was 2.75 Å and the C-I bond was 2.17 Å, elongated from 2.10 Å in a high-resolution structure of $PhICl_2$ that we obtained. The N-I bonds can be compared to 2.22 Å in Weiss' reagent, or 2.27 Å in the bipyridine adduct of $[ICl_2]^+$, both demonstrating a much stronger interaction.[133,182] The 4-coordinate pyridine adduct of iodine triacetate was recently reported with an N-I bond length of 2.41 Å.[183] The much stronger -*trans* influence of phenyl in **5.01** as compared to the ligands in these species is apparent from the significantly longer N-I bond length. The I-Cl bond of **5.01** are 2.49 Å and 2.51 Å, unchanged from that in $PhICl_2$ at 2.49 and 2.51 Å (Figure 5.01).

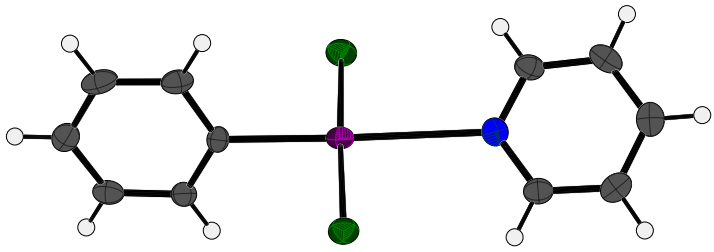


Figure 5.01. *Solid-state structure of complex* ***5.01.***

Considering the solid-state structure obtained, and the unchanged I-Cl bond lengths compared with $PhICl_2$, it is clear that pyridine does not displace a chloride from the iodine in $PhICl_2$ with either stoichiometric pyridine or when dissolved in neat pyridine. Following, theoretical analysis was performed to gain a more in-depth understanding of this system.

5.04 Theoretical Analysis of the Interaction of Pyridine and $PhICl_2$

The optimised geometry for **5.01** (B3LYP-D3(BJ)/def2-TZVPPD with acetonitrile solvation) gave a slightly elongated N-I bond and slightly shortened C-I bond at 2.83 Å and 2.12 Å, respectively, as compared to the experimental results (N-I bond distance was 2.75 Å and the C-I bond was 2.17 Å). The calculated ΔG for the addition of pyridine to $PhICl_2$ was +12.1 kJ/mol at the B3LYP-D3(BJ)/def2-QZVPPD(SMD,acetonitrile)//B3LYP-D3(BJ)/def2 TZVPPD(SMD,acetonitrile) level of theory. The small, positive ΔG is consistent with experimental observations with crystals of **5.01** only produced in neat pyridine that drives equilibrium towards formation of **5.01**, and low temperature was essential for crystallisation, minimising the effect of entropy.

The displacement of chloride by catalytic pyridine to give $[PhI(pyridine)Cl]^+$ as proposed by Murphy is calculated to be unfavourable, with a ΔG of +30.0 kJ/mol at the B3LYP-D3(BJ)/def2-QZVPPD(SMD,acetonitrile)//B3LYP-D3(BJ)/def2-TZVPPD(SMD,acetonitrile) level of theory.[176]

Different levels of theory and solvation were also modelled. At all levels of theory and solvents considered, the calculated ΔG is consistently more unfavourable for chloride displacement than for addition of pyridine to $PhICl_2$ to form **5.01**. As there was a weak interaction between $PhICl_2$ and pyridine evident, probing the interaction experimentally using NMR titration techniques to obtain an experimental binding constant value was pursued.

5.05 NMR Titration Experiments on $PhICl_2$ and Pyridine

In order to further probe the interaction of $PhICl_2$ and pyridine, NMR titration experiments were employed to determine a binding constant using BindFit.[184,185] A known concentration solution of $PhICl_2$ in $CDCl_3$ was added to six separate NMR tubes. Following, pyridine (1, 2, 3, 4, 5 and 10 equivalents) was added and immediately taken for ^1H NMR analysis. Using BindFit analysis, a binding constant

of 0.7 M^{-1} (+0.9 kJ mol^{-1}) was obtained, which is reasonably consistent with the calculated ΔG of +12.1 kJ/mol.

Analysis of the obtained ^{1}H NMR spectrum was performed for each sample. In each case, a slight downfield shift of the $PhICl_2$ signals was observed (calibrated to an internal standard), which was more exaggerated with the greater proportion of pyridine added. Although not a huge distortion, the trend is clear that pyridine is interacting with $PhICl_2$ and that a greater concentration is inducing a greater effect. This effect is shown in *Figure 5.02* by observing the proton *ortho*- with respect to the iodine.

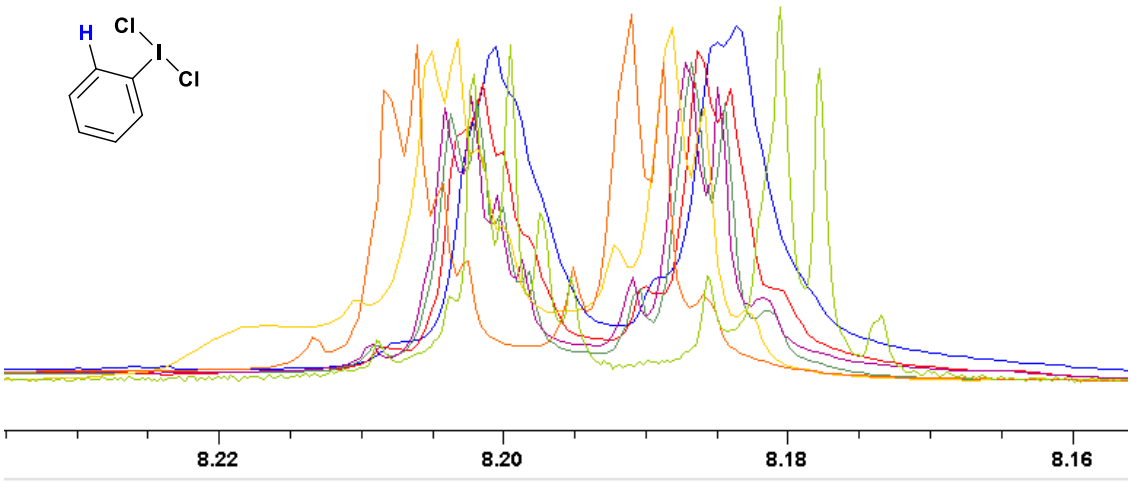


Figure 5.02. *NMR spectra overlayed for the ortho proton of $PhICl_2$ with 0 (lime green), 1 (blue), 2 (red), 3 (green), 4 (purple), 5 (yellow) and 10 (orange) equivalents of pyridine.*

5.06 On the Activation of $PhICl_2$ by Pyridine

We also considered alternative pathways to produce the hypothesised $[PhI(Pyr)Cl]^{+}$ intermediate with B3LYP-D3(BJ)/def2-QZVPPD(SMD,acetonitrile). Loss of Cl^{-} from $PhICl_2$ is unfavourable by +94.9 kJ/mol (ΔG), while loss of Cl^{-} from $PhICl_2$.pyridine to yield $[PhI(Pyr)Cl]^{+}$ is unfavourable by +17.9 kJ/mol. In combination with the results from the synthetic studies described above it is concluded that displacement of a chloride by pyridine is not the mechanism by which $PhICl_2$ is activated. Calculated CM5 and NPA atomic charges (B3LYP-

D3(BJ)/def2-TZVPPD(SMD,acetonitrile)) indicate that the atomic charges on C_{Ph} (bonded to I), I, and Cl, vary by less than 0.04 e between **5.01** and $PhICl_2$. The optimised I-C and I-Cl bond distances are also similar in $PhICl_2$ and **5.01**, with I-C bond distances of 2.11 Å and 2.12 Å, and I-Cl bond distances of 2.54 Å and 2.55 Å, respectively. The similar atomic charges and bond distances indicate that the electronic environment in $PhICl_2$ is not significantly impacted by coordination of pyridine in **5.01**.

It is possible that pyridine might also transiently interact with chlorine along the I-Cl bond axis, however, attempts at optimising a geometry from a starting point with the pyridine interacting with a chlorine atom resulted in the pyridine dissociating. Molecular orbitals (MOs) of $PhICl_2$ were calculated at the B3LYP-D3(BJ)/def2-TZVPPD(SMD,acetonitrile) level of theory. The lowest unoccupied MO (LUMO) for $PhICl_2$ is a sigma-symmetric antibonding orbital orientated along the Cl-I-Cl bond axes. The LUMO+1 is found 1.46 eV higher in energy than the LUMO and is also a sigma-symmetric antibonding orbital although it is orientated along the I-C bond axis, which is the orbital the lone pair of the pyridine attacks, despite being higher in energy than the Cl-I-Cl based LUMO (Figure 5.03).

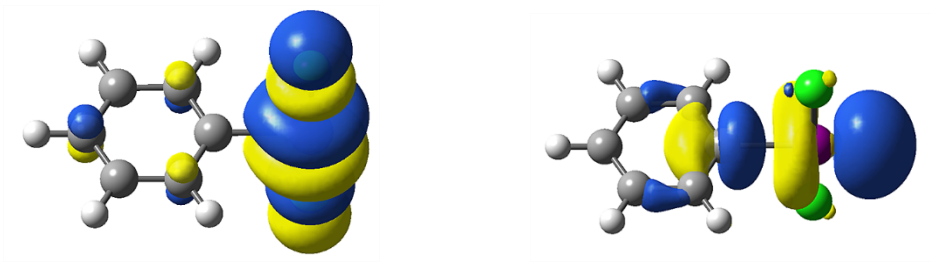
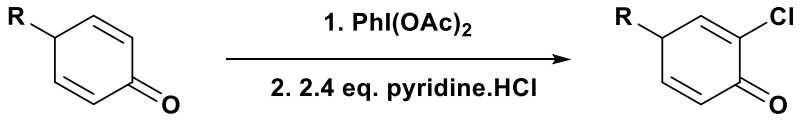


Figure 5.03. *Plots of the LUMO (left) and LUMO +1 (right) of* $PhICl_2$.

The theoretical work performed unambiguously suggests that the mechanism by which pyridine activates $PhICl_2$ and subsequently promotes the transformations reported in the literature is not by the proposed cationic species, [PhICl(pyridine)][Cl]. The remainder of this work will discuss attempts to determine by what species and mechanism $PhICl_2$ is activated.

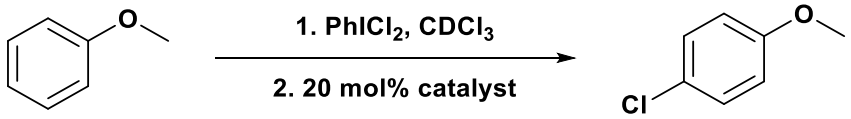
5.07 $PhICl_2$ Activation by Pyridine and Related Species

There have been reports of pyridinium salts for the activation of hypervalent iodine reagents. Namely, in 2009 Lupton evidenced α-halogenation of α,β-unsaturated carbonyl species and alkenes using a bis(acetoxy)iodobenzene/pyridinium chloride or bromide system. These transformations occur after 6 hours, and require superstoichiometric amounts of the pyridinium salt (Scheme 5.04).[186] Similar work has also been demonstrated in a 2019 report by Nagib.[142] Importantly, both of these reports propose PhI(OAc)Cl as the active intermediate for the transformations reported. Considering these two reports, and that hydrogen chloride (HCl) is generated as a by-product when $PhICl_2$ is reacted, it was hypothesised that pyridinium salts were the species responsible for the activation of $PhICl_2$.



Scheme 5.04. *α-chlorination of α,β-unsaturated carbonyl species using bis(acetoxy)iodobenzene and pyridinium chloride.*

To investigate the catalytic activating capacity of various species on $PhICl_2$, a model system that could enable an accurate and comparable results of potential catalysts screened was developed. Owing to the reasons outlined in *Chapter 4*, the system used to explore this was the conversion of methoxybenzene to 4-chloromethoxybenzene in $CHCl_3$/$CDCl_3$ (Scheme 5.05).



Scheme 5.05. *Model system used to probe the catalytic effects of pyridine and a range of related reagents.*

As pyridinium salts were shown to activate $PhI(OAc)_2$ and Murphy has reported the use of pyridine to activate $PhICl_2$, the first catalysts screened were pyridine and its salts. To an equimolar solution of $PhICl_2$ and methoxybenzene in $CDCl_3$ (Note: the $CDCl_3$/$CHCl_3$ used in these reactions was distilled from CaH_2 prior to use) was

added 20 mol% pyridine. After one hour, it was observed that conversion of methoxybenzene to 4-chloromethoxybezene occurred to 88% (*cf.* 7% conversion with no additive) as determined by analysis of the ^{1}H NMR spectrum. The use of pyridine and concurrent generation of HCl suggested that it was not possible for pyridine to be the active species in these transformations when employed sub-stoichiometrically, but more likely the corresponding pyridinium chloride (as formed from the free HCl generated) salt was affecting these transformations. To explore this possibility, pyridinium chloride (pyridine.HCl) was synthesised separately *via* the reaction of pyridine and ethereal hydrogen chloride solution to determine if this species was an effective catalyst for the transformation of methoxybenzene to 4-chloromethoxybenzene. Following, to a stoichiometric solution of $PhICl_2$ and methoxybenzene was added 20 mol% pyridinium chloride. The reaction was stirred for 1 hour. It was observed that conversion of methoxybenzene to 4-chloromethoxybezene occurred in 96% yield as determined by ^{1}H NMR spectroscopy. These preliminary results suggested that pyridinium chloride was responsible for the catalytic aryl chlorination. Following, a range of neutral, chloride salt, and triflate salt catalysts were investigated and compared in order to gain understanding of the active species and mechanism by which these transformations were occurring. These results are summarised in *Table 5.01*.

Table 5.01. *Pyridinium and ammonium salt catalyst loadings and conversion rates.*

Entry	Catalyst	Loading (mol %)	Conversion (%)
1	None	0	7
2	Pyridine	20	88
3	Pyridine.HCl	20	96
4	Pyridine.HOTf	20	37
5	Pyridine.HOTf	50	37
6	NEt_3.HCl	20	78
7	NBu_4Cl	20	97
8	HCl.Et_2O	20	79
9	NBu_4OTf	20	7
10	4-DMAP	20	85
11	4-DMAP.HCl	20	88
12	4-DMAP.HOTf	20	50
13	3-Cl-4-DMAP	20	72
14	3-Cl-4-DMAP.HCl	20	86
15	TMSCl	20	5
16	KCl	20	0
17	KCl/18-crown-6	20	0
18	CsCl	20	2
19	TsCl	20	6
20	NBu_4Cl	5	72

Initially, we examined if the presence of the chloride counter ion of pyridine.HCl in these reactions was integral to these transformations. It was thought that switching the counter ion to a triflate instead of the chloride was the best method to probe this. Synthesis of pyridinium triflate from pyridine and triflic acid (HOTf) was performed to afford pyridinium triflate (pyridine.HOTf). Following, 20 mol% pyridine.HOTf was subject to the general procedure as described in *Scheme 5.08*. The reaction was stirred for 1 hour, after which ^{1}H NMR analysis indicated a conversion of methoxybenzene to 4-chloromethoxybenzene of 37% (Entry 4, Table

5.01). The decreased conversion suggested that presence of the chloride counter ion with the pyridinium salt was important for this transformation, but not the sole contributor (*cf.* 7% conversion of methoxybenzene to 4-chloromethoxybenzene with no catalytic additive). The chlorination of methoxybenzene to 4-chloromethoxybenzene using an increased loading of 50 mol% of pyridinium triflate was explored to determine if this transformation was occurring stoichiometrically, however, after increasing the loading to 50 mol%, the conversion rate remained at 37% (Entry 5, Table 5.01).

Other chloride salts were explored to determine the propensity of chloride to affect this transformation. Initial work began with commercially available and at-hand reagents. Triethylamine hydrochloride (NEt_3.HCl) was the first explored to probe the importance of the pyridine moiety within the system. To a stoichiometric solution of $PhICl_2$ and methoxybenzene was added 20 mol% NEt_3.HCl. The reaction was stirred for one hour and then subsequently analysed by ^{1}H NMR spectroscopy. It was determined that methoxybenzene was converted to 4-chloromethoxybenzene at 78% (Entry 6, Table 5.01). Also screened *via* the general procedure was tetrabutylammonium chloride (NBu_4Cl). The conversion of methoxybenzene to 4-methoxybenzene was 97% as per ^{1}H NMR analysis (Entry 7, Table 5.01). At this point, evidence strongly suggested that chloride salts were facilitating this transformation and providing superior conversion rates compared with the corresponding uncharged species and their triflate analogs.

To identify or eliminate whether hydrogen chloride was the sole species responsible for these transformations, hydrogen chloride etherate ($HCl.Et_2O$) was screened to observe its catalytic effects on this system. This reaction was performed on a larger scale and in $CHCl_3$ and worked up to determine conversion rate as the molecular weight of $HCl.Et_2O$ was too small to work on a viable NMR scale. To a stoichiometric solution of $PhICl_2$ and methoxybenzene in $CHCl_3$ was added 20 mol% $HCl.Et_2O$. The reaction was stirred for one hour and then volatiles were removed *in vacuo* at room temperature. An aliquot of the colourless liquid reside was dissolved in $CDCl_3$, and the mixture was taken for ^{1}H NMR analysis. It

was determined that the conversion of methoxybenzene to 4-chloromethoxybenzene was 79% (Entry 8, Table 5.01).

The Murphy papers investigate use of a 5% 4-dimethylaminopyridine (4-DMAP)/$PhICl_2$ system. In these reports, it was demonstrated that this system activates $PhICl_2$, however, less effectively that 5% pyridine.[176] Owing to this, 4-DMAP, 4-DMAP.HCl and 4-DMAP.HOTf were screened under this system (Entries 10, 11 and 12, Table 5.01). In line with the results obtained for pyridine, pyridine.HCl and pyridine.HOTf (Entries 2, 3 and 4, Table 5.01), the trend is consistent in that chloride salts perform better than the corresponding neutral species which out performs the corresponding triflate salt for both of these systems. This trend is consistent with the hypothesis that the chloride salts are the most effective catalysts for this transformation. Further, pyridine and pyridine.HCl outperform 4-DMAP and 4-DMAP.HCl. This may be rationalised as the formation of 3-chloro-4-dimethylaminopyridine is occurring concurrently, as discussed in *Chapter 4*. We tested the efficacy of 3-chloro-4-dimethylaminopyridine (3-Cl-4-DMAP) and its corresponding salts (Entries 13 and 14, Table 5.01) as catalysts for this transformation. It was observed that both 3-Cl-4-DMAP and 3-Cl-4-DMAP.HCl converted methoxybenznene to 4-chloromethoxybenzene at a conversion rate of 72% and 86%, respectively. This justifies why 4-DMAP and related species do not perform as well pyridine species as the competing formation of 3-Cl-4-DMAP and 3-Cl-4-DMAP.HCl renders 4-DMAP a less effective catalyst. Finally, a range of other chloride salts and chloride containing reagents were screened under these conditions (Entries 15-19, Table 5.01). KCl and CsCl were found to be totally ineffective for this transformation, most likely owing to their insolubility in organic solvents. KCl was used in conjunction with 18-crown-6 to facilitate solubility, however, this did not promote chlorination of anisole. Finally, the catalytic chlorination of methoxybenzene to 4-chloromethoxybenzene was attempted with 5% NBu_4Cl in attempt to gauge if a lower catalyst loading will enable this transformation. Under identical reaction conditions, 5% NBu_4Cl was added to an equimolar solution of $PhICl_2$ and methoxybenzene in $CDCl_3$. After one hour, the reaction was analysed by ^1H NMR spectroscopy. It was determined that there was a conversion of methoxybenzene to 4-chloromethoxybenzene of 72% (Entry 20,

Table 5.01). Albeit this value is less than the conversion obtained for 20 mol% loading (*cf.* 97%), it was promising to obtain a moderate conversion using 5% of an inexpensive, commercially available chloride salt.

As NBu_4Cl was identified as the most powerful catalyst for these transformations, an investigation into the interaction of NBu_4Cl and $PhICl_2$ was performed. To quantitatively probe the strength of this interaction and compare with the pyridine/$PhICl_2$ system, NMR titration and BindFit analysis was performed. This interaction was also performed on a NBu_4OTf/$PhICl_2$ system.

5.08 NMR Titration experiments on $PhICl_2$ and Tetrabutylammonium Salts

A known concentration solution of $PhICl_2$ in $CDCl_3$ was added to six separate NMR tubes. Following, NBu_4Cl (1, 2, 3, 4, 5 and 10 equivalents) was added and immediately taken for ^1H NMR analysis. Analysis of the obtained ^1H NMR spectrum was performed for each sample. In each case, a slight upfield shift of the $PhICl_2$ signals was observed (calibrated to an internal standard), which was more exaggerated with a greater proportion of NBu_4Cl added, with a significant shift observed for the addition of ten equivalents of NBu_4Cl. The trend observed indicated a greater shift of the $PhICl_2$ protons when compared with the corresponding pyridine experiment. This effect is shown in *Figure 5.04* using the proton *ortho*- with respect to the iodine.

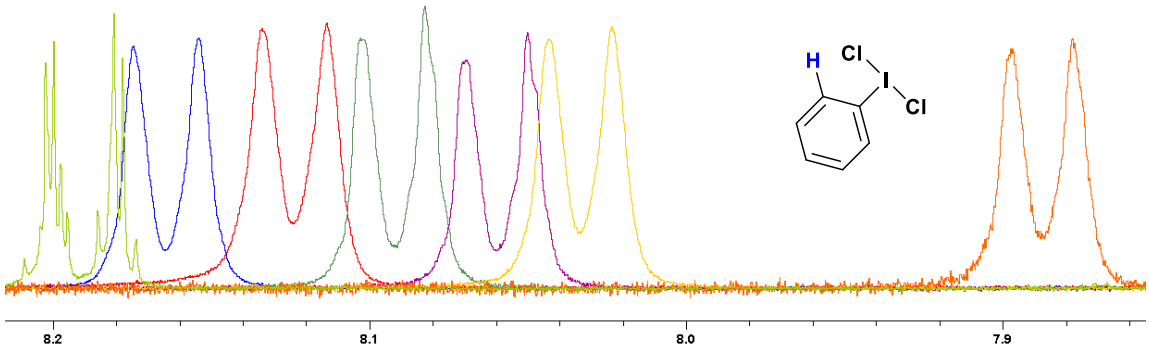


Figure 5.04. *NMR spectra overlayed for the ortho- proton of $PhICl_2$ with 0 (lime green), 1 (blue), 2 (red), 3 (green), 4 (purple), 5 (yellow) and 10 (orange) equivalents of NBu_4Cl.*

Following, the experiment was repeated with NBu_4OTf using the same procedure. There was a slight shift in the $PhICl_2$ signals, but less than observed for NBu_4Cl (Figure 5.05).

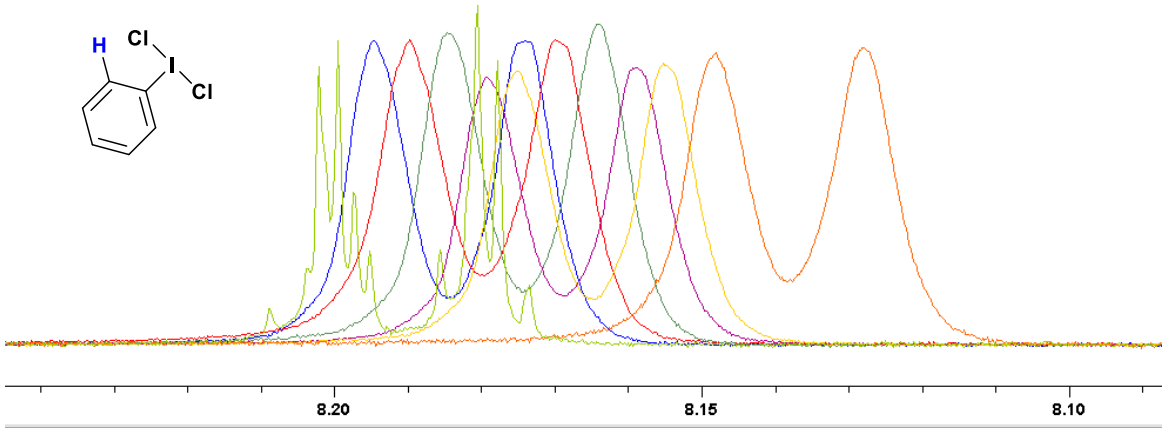


Figure 5.05. *NMR spectra overlayed for the ortho- proton of $PhICl_2$ with 0 (lime green), 1 (blue), 2 (red), 3 (green), 4 (purple), 5 (yellow) and 10 (orange) equivalents of NBu_4OTf.*

Each dataset was analysed using BindFit in order to obtain a binding constant for the interaction of $PhICl_2$ and NBu_4Cl or NBu_4OTf, giving values of 3.36 M^{-1} and 6.55E-10 M^{-1}, respectively. When comparing this data with the binding constant for the interaction of $PhICl_2$ and pyridine, it is evident that there is a stronger interaction between $PhICl_2$ and NBu_4Cl. The bigger binding constant obtained from the

interaction of NBu_4Cl as compared to NBu_4OTf and pyridine suggests that NBu_4Cl is interacting more strongly with $PhICl_2$ and as a consequence activating it to a greater capacity which in turn facilities the catalytic chlorination capacity.

5.09 Concluding Remarks and Future work

Following the experimental work presented, we hypothesise that chloride salts are responsible for the activation of $PhICl_2$. Specifically, when exploring the pyridine/$PhICl_2$ system, evidence suggested that pyridine.HCl is in effect, and not the proposed cationic complex, [PhICl(pyridine)][Cl]. To support this notion, a range of pyridine and alkylamine reagents and their corresponding chloride or triflate salts were screened for their catalytic chlorinating capacity on the model substrate, methoxybenzene. In the case of pyridine, 20 mol% catalyst loading affords the target material in 88% conversion. Supporting our hypothesis, if the pyridinium salt is used, and not generated *in situ*, the conversion increased to 96% using the same catalyst loading. Pyridine outperforms 4-DMAP and its derivates which is rationalised by the screening 3-Cl-4-DMAP and its HCl salt, which is invariably made when 4-DMAP and $PhICl_2$ are in the same system. 3-Cl-4-DMAP and its HCl salt gave reduced conversions of 72% And 86%, respectively, accounting for the lower conversion from 4-DMAP when compared with pyridine. Upon exploring other chloride salts and related species that could affect this transformation, NBu_4Cl was screened and was found to provide the highest conversion of 97% at 20 mol% loading. It was also demonstrated that 5 mol% loading of NBu_4Cl afforded 72% conversion.

To determine the strength of interaction between $PhICl_2$ and NBu_4Cl or NBu_4OTf, NMR titration experiments were performed so as to compare to the activating capacity of pyridine. It was observed that NBu_4Cl perturbs the chemical shift of $PhICl_2$ significantly as compared with both pyridine and NBu_4OTf. All of this data was highly promising as the inexpensive, and commercially available NBu_4Cl was shown to activate $PhICl_2$ most effectively. Significantly, this activation was observed to be greater than pyridine, 4-DMAP and $[Ag_2][B_{12}Cl_{12}]$. Following work

for this project will involve exploring and expanding the scope of chlorination reactions using the $PhICl_2/NBu_4Cl$ system reported here.

5.10 Experimental

General procedure A: Probing the interaction of $PhICl_2$ and Pyridine Derivatives

Iodobenzene dichloride (25.0 mg, 0.0909 mmol) was dissolved in $CDCl_3$ (0.6 mL) and rapidly stirred to give a pale-yellow solution. To this, a given pyridine derivative (0.0909 mmol) was added in one portion and the reaction was left to stir. At t = 15 m, the reaction mixture was transferred to an NMR tube and taken for analysis.

5.01

Iodobenzene dichloride (100 mg, 0.364 mmol) was dissolved in a minimum amount of pyridine (approximately 0.5 mL) in a scintillation vial. The reaction mixture was held at -30 °C overnight, after which yellow block like crystals had formed. The crystals were prone to decomposition once removed from the pyridine solution. Owing to decomposition, NMR data was not collected. The structure was confirmed *via* solid-state X-ray crystallography.

3-Chloro-4-dimethylaminopyridine

Iodobenzene dichloride (200 mg, 0.728 mmol) was dissolved in $CHCl_3$ (6 mL) in a reaction flask. 4-Dimethylaminopyridine (178 mg, 1.46 mmol) dissolved in $CHCl_3$ (0.5 mL) was added to the flask. The mixture was stirred for 15 minutes. Subsequently, hexane was added to reaction mixture and a white solid precipitated. The precipitate was removed *via* centrifugation and identified as 4-dimethylaminopyridine.HCl by ^1H NMR via comparison with a genuine sample. The supernatant was collected, and volatiles were removed *in vacuo* to give a colourless liquid. The liquid was dissolved in $CHCl_3$ (1 mL), and triflic acid (64 µL, 0.728 mmol) was added dropwise as a $CHCl_3$ solution, with stirring. Diethyl ether (5 mL) was added to yield a white precipitate which was collected *via* centrifugation (m/z = 157.13). The solid was dissolved in H_2O (1 mL) and basified with 1M NaOH (approx. 1 mL) until pH 14. The aqueous solution was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined and washed with H_2O (3 × 10 mL) and subsequently dried over $MgSO_4$ and filtered. Volatiles were removed *in vacuo* to give the title compound as a colourless liquid (70 mg, 61%).

^{1}H NMR, ppm ($CDCl_3$, 400 MHz): δ 8.32 (1H, s), 8.22-8.20 (1H, d), 6.75-6.74 (1H, d), 2.99 (6H, s).
^{13}C NMR, ppm ($CDCl_3$): δ 155.50, 150.24, 147.68, 121.66, 112.82, 42.32.

Pyridine activation of $PhICl_2$ for chlorination of methoxybenzene

Iodobenzene dichloride (75.0 mg, 0.273 mmol) was dissolved in $CDCl_3$ (2.00 mL). To this was added methoxybenzene (29.7 μL, 0.273 mmol) and the solution was stirred. After 5 m, pyridine (4.4 μL, 0.0546 mmol) was added in one portion, and the mixture was left to stir for 1 hr. Following, the reaction mixture was transferred to an NMR tube and subsequently analysed *via* ^{1}H NMR spectroscopy.

General Procedure B: Synthesis of amine hydrochloride salts

In a 15 mL conical tube, the appropriate amine (2.00 mmol) was dissolved in Et_2O (2.0 mL) and rapidly stirred. 2M HCl.Et_2O (1.1 eq., 2.20 mmol) was added dropwise to the solution. Formation of a white precipitate was observed. The white solid was washed with Et_2O (3 × 5 mL) *via* centrifugation and subsequently dried *in vacuo* to give the title compound as a colourless solid.

General Procedure C: Synthesis of amine hydrotriflate salts

In a 15 mL conical tube, the appropriate amine (2.00 mmol) was dissolved in Et_2O (2.0 mL) and rapidly stirred. Trifluoromethanesulphonic acid (1.1 eq., 2.20 mmol) in Et_2O was added dropwise to the solution. Formation of a white precipitate was observed. The white solid was washed with Et_2O (3 × 5 mL) *via* centrifugation and subsequently dried *in vacuo* to give the title compound as a colourless solid.

General Procedure D: Alkyl amine/salt mediated chlorination of methoxybenzene *via* activation of $PhICl_2$

Iodobenzene dichloride (25.0 mg, 0.0909 mmol) was dissolved in $CDCl_3$ (1.00 mL). To this was added methoxybenzene (9.9 μL, 0.0909 mmol) and the solution was stirred. After 5 m, the appropriate alkyl amine/salt (20%, 0.0182 mmol) was added in one portion, and the mixture was left to stir for 1 hr. Following, the reaction mixture was transferred to an NMR tube and subsequently analysed *via* ^{1}H NMR spectroscopy.

BindFit Experimental Data

Note: These manipulations were performed in a N_2 filled glovebox and all solvents and reagents were free from water and oxygen.

Iodobenzene dichloride (120 mg, 0.437 mmol) was dissolved in $CDCl_3$ (4.00 mL) to give a stock solution of $PhICl_2$ in $CDCl_3$ (4.00 mL, 0.109 M). Aliquots (400 μL) of this stock solution were added to six separate NMR tubes, followed by the addition of pyridine (1-5 and 10 equivalents). Each of the NMR tubes were made up to a total volume of 550 μL with $CDCl_3$, and then taken for NMR analysis. This can be summarised in *Table 5.02*.

Table 5.02. *Amounts and volumes of each NMR tube used for BindFit experiment for the interaction of $PhICl_2$ and pyridine.*

NMR Tube (#)	$PhICl_2$ (equivalents)	Pyridine (equivalents)	Pyridine (μL)	$CDCl_3$ (μL)	Total Volume (μL)
1	1	1	3.50	546.5	550.0
2	1	2	7.00	543.0	550.0
3	1	3	10.5	539.5	550.0
4	1	4	14.0	536.0	550.0
5	1	5	17.6	532.4	550.0
6	1	10	35.1	514.9	550.0

Table 5.03. *Excel data used for BindFit experiment for the interaction of $PhICl_2$ and pyridine.*

Host concentration / M	Guest concentration / M	Proton 1	Proton 2	Proton 3
0.0792	0.0792	8.1919	7.5986	7.48
0.0792	0.158	8.1933	7.5942	7.4763
0.0792	0.238	8.1938	7.5912	7.4747
0.0792	0.317	8.1949	7.5897	7.4729
0.0792	0.396	8.1954	7.5859	7.4706

0.0792	0.792	8.1983	7.575	7.4616

Table 5.04. *Amounts and volumes of each NMR tube used for BindFit experiment for the interaction of $PhICl_2$ and NBu_4Cl.*

NMR Tube (#)	$PhICl_2$ (equivalents)	NBu_4Cl (equivalents)	NBu_4Cl (mg)	Total Volume (µL)
1	1	1	5.30	600.0
2	1	2	10.6	600.0
3	1	3	15.9	600.0
4	1	4	21.2	600.0
5	1	5	16.5	600.0
6	1	10	53.0	600.0

Table 5.05. *Excel data used for BindFit experiment for the interaction of $PhICl_2$ and NBu_4Cl.*

Host concentration / M	Guest concentration / M	Proton 1	Proton 2	Proton 3
0.0272	0.0272	8.184	7.600	7.479
0.0272	0.0454	8.180	7.599	7.477
0.0272	0.0681	8.174	7.596	7.474
0.0272	0.0908	8.169	7.594	7.471
0.0272	0.1135	8.165	7.592	7.469
0.0272	0.227	8.138	7.576	7.451

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