Studies in Palladium Catalyzed Carbohalogenation Chemistry

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Chemistry
University of Toronto

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Abstract

Since recognizing the significance of reversible oxidative addition of palladium into aryl halides in the synthesis of 2-bromo-indoles, the Lautens group has focused on unusual carbon-halogen reductive eliminations. These efforts led to the discovery of the novel palladium-catalyzed inter- and intramolecular carbohalogenation reaction – the formal addition of an sp² carbon–iodide bond across an alkene. One current research direction is utilizing a range of aryl halides and pseudohalides as starting materials for carbohalogenation chemistry. This thesis describes complementary research, focusing on the expansion of functional group scope. Carbohalogenation has been developed to synthesize novel products including heteroaromatic compounds and 7-membered rings. Polyunsaturated aryl iodide substrates were investigated with the goal of performing domino carbohalogenation. Ultimately, the successful halogen exchange process was combined with domino carbohalogenation in an efficient halogen-exchange domino reaction. Additionally, preliminary studies on enantioselective carbohalogenation, and functionalization of the neopentyl iodide products are also discussed.
Acknowledgments

I would like to take this opportunity to acknowledge the people who allowed this thesis to be possible. First and foremost, I would like to thank Professor Mark Lautens for the opportunity to work in his research group, for his insightful suggestions, and his encouragement. I am also grateful that he supported me in pursuing my passion for teaching and learning by allowing me to attend conferences and take on various Teaching Assistantship positions.

I am also indebted to my Team Carbohalogenation collaborators; Stephen Newman and Dr. Norman Nicolaus. In particular, I must thank Stephen for initiating carbohalogenation chemistry within the Lautens group, and for helping me find my way during my first semester at the University of Toronto. I truly appreciate all of the excellent discussion (research and otherwise), and I thoroughly enjoyed being your cubicle buddy. I would also like to thank Dr. Nicolaus for his awesome attitude and significant contributions to domino carbohalogenation chemistry.

I am so grateful for the entire Lautens group who provided me with an excellent environment to grow as a chemist. Whether it was teaching me new concepts and reactions, or showing me around the department, U of T campus and Toronto you were always there to help. Thank you for your continuous support and pushing me to pursue my dreams. I will never forget the great times from this lab!

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Abbreviations

All element abbreviations are in accordance with IUPAC standards.

Å angstrom
Ac acetate
acac acetylacetone
ACN acetonitrile
Ad adamantyl
Ar aryl
B base
Bn benzyl
Bu butyl
CP carbopalladation
Cy cyclohexyl
dba dibenzylideneacetone
DCC N,N’-dicyclohexylcarbodiimide
DCM dichloromethane
DIAD diisopropyl azodicarboxylate
DMAP 4-dimethylaminopyridine
DMF dimethylformamide
dppe 1,2-bis(diphenylphosphino)ethane
dppf 1,1’-bis(diphenylphosphino)ferrocene
E ester or entgegen
Equiv equivalent
Et ethyl
Fc ferrocene
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>L</td>
<td>generic 2e⁻ donating ligand</td>
</tr>
<tr>
<td>M</td>
<td>generic metal</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
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<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>mesylate</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>OTf</td>
<td>triflate</td>
</tr>
<tr>
<td>o-tol</td>
<td>ortho-tolyl</td>
</tr>
<tr>
<td>PEG</td>
<td>polyethylene glycol</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl ether</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>Q-Phos</td>
<td>1,2,3,4,5-pentaphenyl-1’-(di-tert-butylphosphino)ferrocene</td>
</tr>
<tr>
<td>R</td>
<td>generic organic group</td>
</tr>
<tr>
<td>R’</td>
<td>generic organic group different from R</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>SFC</td>
<td>supercritical fluid chromatography</td>
</tr>
<tr>
<td>T</td>
<td>generic temperature</td>
</tr>
<tr>
<td>TBAB</td>
<td>tetrabutylammonium bromide</td>
</tr>
<tr>
<td>TBAC</td>
<td>tetrabutylammonium chloride</td>
</tr>
<tr>
<td>TEAC</td>
<td>tetraethylammonium chloride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>TFP</td>
<td>tri(2-furyl)phosphine</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>Ts</td>
<td>tosylate</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>X</td>
<td>generic halide/heteroatom</td>
</tr>
<tr>
<td>Y</td>
<td>generic halide/heteroatom</td>
</tr>
<tr>
<td>Z</td>
<td>zusammen</td>
</tr>
</tbody>
</table>
Chapter 1

1 Introduction

1.1 Palladium Coupling Reactions

1.1.1 Background

Palladium catalyzed cross-coupling reactions are an invaluable tool in synthetic organic chemistry and earned the 2010 Nobel Prize for researchers Richard F. Heck, Ei-ichi Negishi and Akira Suzuki. Palladium is able to catalyze numerous cross-coupling reactions, as it possesses privileged electronics that are favourable for oxidative addition, carbopalladation, transmetallation, β-hydride elimination and reductive elimination under a broad range of reaction conditions.¹ These processes are most commonly realized between the Pd(0) and Pd(II) oxidation states, however in the past two decades, Pd(IV) has been suggested as a viable oxidation state in palladium catalysis.²

Palladium coupling reactions originated in the late 1960s, when Heck and co-workers demonstrated the coupling of organomercury compounds with alkenes in the presence of stoichiometric Pd(II) salts to give unsaturated species.³ Analogous catalytic processes followed shortly by Mizoroki in 1971, and by Heck in 1972, where the palladium catalyzed coupling of aryl halides was demonstrated in excellent yields (Figure 1); both reactions proceeded under similar conditions, with high temperatures and basic additives. Mizoroki’s work utilized PdCl₂ as the catalyst of choice, and was able to generate a 9:1 mixture of alkene regioisomers (1.1 and 1.2) in a yield of 90%.⁴ Heck employed Pd(OAc)₂ as a catalyst, and generated the alkenylation product with excellent regioselectivity of > 20:1 in favour of the trans alkene, albeit in a lower yield.⁵ To date, the Heck reaction (also known as the Mizoroki-Heck reaction) is one of the most widely used coupling reactions, and has been thoroughly reviewed.⁶
Kumada and Corriu also demonstrated early examples of metal catalyzed cross coupling reactions in 1972, by coupling sp² carbon-halides with a Grignard reagents using nickel phosphine complexes (Figure 2). In 1975, Murahashi extended this process, now known as Kumada coupling, to palladium catalysis using Pd(PPh₃)₄.

Another early example of palladium-catalyzed cross-coupling came from Cassar, Heck and Sonogashira in 1975, when they concurrently reported the coupling of terminal alkynes with aryl halides in the presence of a base (Table 1). Cassar utilized stoichiometric amounts of NaOMe to generate a sodium acetylide intermediate, while both Heck and Sonogashira preferred amine bases to deprotonate the alkyne. Sonogashira found that the addition of catalytic copper iodide could increase yields significantly over similar conditions utilized by Heck.
Table 1.1. Seminal work in Sonogashira coupling

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cassar</strong></td>
<td>95</td>
</tr>
<tr>
<td><strong>Heck</strong></td>
<td>73</td>
</tr>
<tr>
<td><strong>Sonogashira</strong></td>
<td>90</td>
</tr>
</tbody>
</table>

The aforementioned reports by Mizoroki, Heck, Kumada, Corriu, Murahashi, Cassar and Sonogashira were among the many groundbreaking accomplishments in transition metal catalyzed coupling reactions of the 1970s. These reactions allowed for the facile synthesis of sp and/or sp\(^2\) hybridized carbon–carbon bonds, which up until this time were non-trivial to generate.

1.1.2 Types of Palladium-Catalyzed Cross-Coupling Reactions

Since the 1970s, the field of palladium-catalyzed cross-coupling chemistry has produced a diverse range of tools that form the cornerstone of modern synthetic chemistry, allowing for the coupling of a wide variety of substrates (Table 2). The high yields and diverse range of commercially available boronic acids make the Suzuki reaction extremely popular with synthetic chemists.\(^{11}\) Conversely, the Heck reaction eliminates the need for pre-functionalization of one coupling partner thereby generating less waste than the other methods of cross-coupling, making it widely used in the synthesis of complex natural products.\(^{12}\)
Table 1.2. Common palladium catalyzed cross-coupling reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Coupling Partner A</th>
<th>Coupling Partner B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchwald-Hartwig</td>
<td>sp²</td>
<td>amine</td>
</tr>
<tr>
<td>Fukuyama</td>
<td>sp²</td>
<td>thioester</td>
</tr>
<tr>
<td>Heck</td>
<td>sp²</td>
<td>alkene</td>
</tr>
<tr>
<td>Hiyama</td>
<td>sp²</td>
<td>organosilane</td>
</tr>
<tr>
<td>Kumada</td>
<td>sp² or sp³</td>
<td>organomagnesium halide</td>
</tr>
<tr>
<td>Negishi</td>
<td>sp, sp² or sp³</td>
<td>organozinc</td>
</tr>
<tr>
<td>Sonogasahira</td>
<td>sp</td>
<td>terminal alkyne</td>
</tr>
<tr>
<td>Stille</td>
<td>sp, sp² or sp³</td>
<td>organotin</td>
</tr>
<tr>
<td>Suzuki</td>
<td>sp²</td>
<td>organoboron</td>
</tr>
</tbody>
</table>

1.2 The Heck Reaction

1.2.1 Heck Reaction Mechanism

In a general case of the Heck reaction, an sp² C–X bond is added across an alkene group. The double bond is regenerated by a β-hydride elimination, giving the formal generation of a single sp²–sp² carbon bond (Figure 3).

After the pre-catalyst undergoes ligand dissociation to generate an active catalyst (1.3), the Heck substrate (1.4) enters the catalytic cycle and undergoes oxidative addition. The alkene coordinates to palladium, and subsequent carbopalladation generates an alkyl-palladium intermediate (1.5). β-Hydride elimination occurs, which releases the Heck product, and a Pd(II) species (1.6), which undergoes a base-induced reductive elimination regenerating the active catalyst (1.3). This turns over the catalytic cycle allowing reaction of another substrate molecule. Each step of the catalytic cycle has its own unique considerations that will be discussed.
1.2.2 Elementary Steps of the Heck Reaction

1.2.2.1 Oxidative Addition

The formal process of oxidative addition is cleavage of a σ-bond X–Y with the formation of a Pd–X and a Pd–Y bond. This transformation involves an increase in the oxidation state of the M center by +2. Oxidative addition is favourable in a system possessing an electron rich metal center, electron donating ligands and/or a coordinatively unsaturated metal. Palladium has been shown to oxidatively add into H–H, C–H, M–H, aryl–halide, vinyl–halide, acyl–halide and alkyl–halide bonds depending on the system and reaction conditions.\textsuperscript{1b} Oxidative addition has been widely considered an irreversible step in palladium catalytic cycles, and must be followed by either transmetallation, carbopalladation or another productive transformation, otherwise the catalyst terminates at a Pd(II) intermediate incapable of regenerating a Pd(0) species.
In the Heck reaction, oxidative addition occurs at either a carbon–halide or a carbon–pseudohalide bond, where the carbon is typically sp\(^2\)-hybridized. The identity of the halide has a critical influence on reactivity, where the rate of addition into halides and pseudohalides is as follows: I \(>\) OTf \(>\) Br \(>>\) Cl \(>>>\) F.\(^{1b}\) Traditionally, oxidative addition was only feasible for bromides, iodides and triflates, however, the use of new types of ligands have allowed for much higher reactivity of chlorides, even at lower temperatures.\(^{13}\)

1.2.2.2 Coordination

When palladium possesses labile ligands, it is possible for other electron rich functionalities in solution to coordinate to the metal center. In the Heck reaction, this is typically an inter- or intramolecular alkene (or other unsaturated species). This coordination arranges the alkene with ideal geometry for carbopalladation to occur.

1.2.2.3 Carbopalladation

Carbopalladation is the addition of a C–Pd bond across an alkene or unsaturated species. The process occurs through a syn-migratory insertion and this regiospecificity can be utilized in rigid systems to introduce stereochemistry. For example, Grigg has shown that carbopalladation of an alkyne will produce a regiospecific palladium intermediate, which terminates with a Negishi coupling to give a single olefin regioisomer in good yield (Figure 4).\(^{14}\)

![Figure 4. Regiospecific carbopalladation is exploited to form single alkene isomer](image)

The intramolecular Heck reaction is a highly versatile method for cyclization, especially for the formation of 5, 6 and 7 membered rings.\(^{15}\) Additionally, 3-membered ring formation proceeds rapidly in Heck systems, and can be used to form cyclopropane units as shown by Negishi with 2 sequential carbopalladations (Figure 5).\(^{16}\) Formation of the product is dependent on the fact that
there is no possibility for the intermediate (1.7) to undergo β-hydride elimination, as there are no β-hydrogens present. Only a second carbopalladation (1.8) allows for β-hydride elimination and reductive elimination to occur.

![Figure 5. Double carbopalladation forming fused cyclopropane via Heck reaction](image)

Medium sized rings (8 ≤ n ≤ 12) are quite difficult to form by carbopalladation, but the Heck reaction has been extended to the synthesis of macrocycles with good results under dilute conditions. Ma and coworkers reported the formation of both 13- and 21-membered rings utilizing an intramolecular Heck reaction (Figure 6). It is noteworthy that these carbopalladations occur with endo cyclization, while smaller ring sizes are formed via an exo pathway.

![Figure 6. Ma’s Heck reaction used to form macrocycles](image)

1.2.2.4 β-Hydride Elimination

When a palladium-carbon bond is syn to a hydrogen at the β-position, the system can undergo β-hydride elimination. It is thought to proceed through a concerted 4-membered ring transition-state, which necessitates the need for the syn-relationship. Palladium forms a new bond with the hydrogen, and the C–Pd bond is broken, forming a new π-bond between the α and β carbons. The newly formed H–Pd(II)–X species can undergo subsequent reductive elimination (see Section 1.2.2.5). If the system has free rotation about the C–C bond as well as two β-hydrides, a mixture of E and Z alkenes can be formed (Figure 7).
If there are two adjacent \( \beta \)-hydrogens on different carbons that can both exist in a syn-relationship to palladium, then multiple alkene regioisomers can be formed. This was seen in work by Grigg who showed that a suitable Heck substrate (1.9) formed multiple alkene products (1.10 and 1.11, Figure 8).\(^{18}\) Employing the iodophilic additives AgNO\(_3\) and Tl\(_2\)CO\(_3\) allowed for moderate olefin selectivity, which the author suggested as selective \( \beta \)-hydride elimination and/or the suppression of double bond isomerization of the generated product. These additives likely generate cationic palladium catalysts where the difference in anions (NO\(_3\)\(^-\) vs. CO\(_3\)\(^{2-}\)) was responsible for the observed selectivity.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{\( \beta \)-hydride elimination can form multiple alkene isomers}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Grigg's Heck reaction generating 2 alkene regioisomers}
\end{figure}

### 1.2.2.5 Reductive Elimination

Reductive elimination is the coupling of two species coordinated to a palladium center ie. Y–Pd(n)–X forming one new sigma bond, X–Y, and a formally reduced palladium Pd(n-2). In the Heck reaction, the bis-ligated H–Pd(II)–X species formed from \( \beta \)-hydride elimination can undergo reductive elimination generating H–X and the active Pd(0) catalyst (Figure 9). Typical Heck conditions utilize a basic additive in order to promote reductive elimination and sequester
the acid byproduct. These bases are commonly trialkylamines, or inorganic salts such as potassium carbonate or acetate. More recently, cesium carbonate has emerged a commonly employed base in catalytic transition metal chemistry, potentially due to its higher solubility in non-polar reaction solvents compared to potassium salts.\textsuperscript{1b}

\[
\text{L}_2\text{Pd}^{(\text{II})}\text{HX} \xrightarrow{B \text{ or } B\text{H}^+\text{X}^-} \text{Pd}^{(0)}\text{L}_2
\]

**Figure 9.** Reductive elimination of palladium (II) hydrogen halide promoted by base

1.2.3 Catalyst Choice

Precatalysts used for the Heck reaction can be Pd(0)L\textsubscript{n} complexes (where L = phosphine-type ligand), such as the commercially available palladium tetrakistriphenylphosphine Pd(PPh\textsubscript{3})\textsubscript{4}. With this type of catalyst, ligands can dissociate creating a coordinatively unsaturated species, which is poised for oxidative addition. Alternatively, the catalyst can be generated in-situ from a Pd(II) species such as Pd(OAc)\textsubscript{2}. This transformation requires initial reduction to Pd(0) before entering the catalytic cycle.\textsuperscript{19} Heck reactions have also been performed in the absence of phosphine ligand, instead utilizing stoichiometric amounts of tetraalkylammonium salts. This modification is known as Jeffrey conditions, where it is postulated that colloidal Pd(0) acts as the catalytically active species (**Figure 10**).\textsuperscript{20,21}

\[
\text{Me}_2\text{O}_2\text{C} + \text{MeO}_2\text{C} \xrightarrow{\text{Pd}(\text{OAc})_2, \text{TEAC}} \text{MeO}_2\text{C} \xrightarrow{72\%} \text{MeO}_2\text{C} \text{Br}
\]

**Figure 10.** Ligandless Heck reaction under Jeffrey conditions

In recent years, preformed Pd(0)L\textsubscript{2} complexes have become commercially available. Catalysts that have found widespread use in research are Pd(tBu\textsubscript{3}P)\textsubscript{2} and Pd(Q-Phos)\textsubscript{2} (**Figure 11**). These complexes show excellent activity in the coupling of aryl chlorides at low temperature, which has been attributed to their unique electronic and steric profiles.\textsuperscript{13}
1.2.3.1 The Origin of Q-Phos

Hartwig and co-workers first synthesized the ligand Q-Phos, which is highly active in a number of palladium-catalyzed transformations including the amination, etherification and carbon-carbon coupling reactions of aryl chlorides and bromides. Its fortuitous discovery occurred when bis-tert-butyl-ferrocenylphosphine (1.12, Figure 12) was being explored for the etherification of aryl bromides. Excellent conversion was observed, however consumption of the aryl halide did not match the yield of aromatic ether product. Through further experimentation it was shown that the ligand (1.12) was being converted in-situ to the extremely active phosphine ligand Q-Phos by per-phenylation of the unsubstituted cyclopentadienyl ring; the cause for this increased activity has not been determined.

Domino Heck Reactions

In the instance where an aryl halide contains multiple alkenes or alkene analogues, multiple carbopalladations can occur. This type of sequential migratory insertion is often coined “domino” reactivity, as each successive intermediate allows for an additional reaction that was not previously feasible. Domino carbopalladation can only occur if the cyclization forms a
favourable ring size where the product is not highly strained and if cyclization is faster than any other possible terminating event (such as β-hydride elimination or intermolecular coupling). There are many examples of domino Heck reactions in the literature, which allow for the synthesis of multiple rings in a single step, reducing the resources required per bond formation. Negishi and coworkers reported one highlight of domino Heck chemistry where four carbon–carbon bonds were formed in a single reaction, (Figure 13).\textsuperscript{25} Domino chemistry is one of the many ways chemists are improving atom economy while lowering the environmental impact of their syntheses.

\textbf{Figure 13.} Negishi’s domino Heck reaction forming four carbon–carbon bonds

\section*{1.2.5 Palladium (II/IV) Heck Reaction}

There have been a number of reports in the literature that suggest particularly electron rich Pd(II) complexes may be able to undergo oxidative addition, generating productive Pd(II)/Pd(IV) catalytic cycles.\textsuperscript{26} The reports are mostly limited to reactions utilizing strong oxidants, and complexes with multidentate pincer-type ligands, which are less susceptible to oxidation.\textsuperscript{27} Aydin and coworkers reported a Pd(II)/Pd(IV) Heck-type coupling of allylic acetates with diaryliodonium salts, proceeding in good yield with a variety of substrates (Figure 14).\textsuperscript{28}
The Heck reaction is very functional group tolerant, and can easily couple complex substrates. As such, it has transformed the strategy for total synthesis of natural products by allowing for convergent synthetic pathways. Flessner and coworkers utilized a Heck reaction under Jeffery conditions to form a bis-steroid on the way to marine-like products (Figure 15). This reaction proceeded in good yield in the presence of various stereocenters, and a second alkene functionality. More importantly, it allowed each piece to be constructed independently, in a convergent synthesis.
1.3 Variations on the Heck Reaction

After oxidative addition and carbopalladation, some substrates do not have the ability to undergo β-hydride elimination. This could result from a lack of hydrogens at the β-position or none that can adopt the necessary syn-orientation. In these cases, the catalyst is rendered inactive unless other terminating events, such as anion capture, transmetallation followed by reductive elimination, or C–H activation / direct arylation, are utilized to turn over the catalytic cycle.

1.3.1 Anion Capture

Anionic capture of Pd(II) intermediates can occur inter- or intramolecularly, where common trapping agents include hydrides, acetates, malonates, carboxylates and sulfonates; nucleophiles such as alcohols and amines can also be implemented.\textsuperscript{1b} Figure 16 shows cyclization with a hydride source used for anion capture.\textsuperscript{30} In the intermediate 1.13 there are no β-hydrides present; anion capture by hydride is used to generate the isoindolinone product in moderate yield.

![Figure 16. Carbopalladation followed by intermolecular anion capture with hydride](image)

Alternatively, in Figure 17 Balme showed carbopalladation followed by trapping with a malonate anion.\textsuperscript{31} Initial oxidative addition was followed by carbopalladation to give intermediate organopalladium species 1.14. However, as carbopalladation is a syn addition, the only β-hydrogen was generated anti to the newly formed carbon-palladium bond and as such it did not have the correct orientation to undergo β-hydride elimination. Without an external nucleophile or coupling reagent, this catalytic cycle could not turn over. The malonate anion was generated in-situ by addition of stoichiometric potassium hydride, and this anion reacts intramolecularly to form the product. While the cyclization proceeded with good regioselectivity, a small amount of double bond isomerization was observed under the reaction conditions.
1.3.2 Transmetallation and Reductive Elimination

The palladium intermediate from carbopalladation is also capable of undergoing transmetallation with a variety of metal species including boronic acids, stannanes and zinicates. This transmetallation step generates a Pd intermediate capable of undergoing reductive elimination, which forms a new C–C bond and turns over the catalytic cycle.

In Figure 18 intermolecular carbopalladation of norbornadiene generates a Pd(II) intermediate. Due to the geometric constraints of the molecule, no syn-β-hydrogens are available to undergo elimination. In the absence of an additional reagent, no productive reaction is possible. However, with the addition of a boronic acid, transmetallation can occur in a formal Suzuki coupling to generate product and turn over the catalytic cycle.$^{32}$

Similarly, in Figure 19, the secondary palladium iodide intermediate cannot undergo β-hydride elimination. Use of a vinyl stannane transmetallates the palladium in a Stille-type coupling to furnish the product in good yield.$^{33}$
1.3.3 Direct Arylation

Under appropriate conditions, Pd(II) can perform direct arylation via C–H activation. Ruck and coworkers showed carbopalladation leading to intermediate 1.15, which was unable to perform β-hydride elimination (Figure 20). However, palladium participated in C–H activation at the ortho-position of the intramolecular tolyl group, forming a cyclic palladium species 1.16. The palladacycle intermediate then underwent reductive elimination to generate the spirocyclic product in excellent yield. 34

1.4 Reductive Elimination of Carbon–Halide Bonds

In palladium catalysis, oxidative addition into an aryl halide is rapid whereas the microscopic reverse, reductive elimination, to re-form a C–X bond is rare. The palladium-complex must generally undergo one or more transformations (as seen in Section 1.3) before the Pd(0) can be regenerated. However, literature examples where reductive elimination of C–X bonds has been observed stoichiometrically suggest it can be a feasible step in a palladium-catalyzed mechanism.
1.4.1 Hartwig’s Stoichiometric Studies

Hartwig and co-workers discovered that with the correct choice of ligand, aryl–halide reductive elimination could be a feasible elementary step in palladium catalysis.\textsuperscript{35} Studies were pursued in which stoichiometric palladium complexes of aryl halides 1.17 were generated through oxidative addition, and these dimeric species were stabilized by the electron rich tri-ortho-tolylphosphine ligand. With the addition of certain electron-rich, bulky phosphine ligands, reductive elimination could be observed to 1.18 (Table 1.3). The transformation was successful with tri-\textit{tert}-butylphosphine \textbf{L1}, cyclohexyl-di-\textit{tert}-butylphosphine \textbf{L2}, 1-adamantyl-di-\textit{tert}-butylphosphine \textbf{L3} and Q-Phos \textbf{L4}. Surprisingly, with the analogous non-phenylated analogue of Q-Phos, ferrocenyl-di-\textit{tert}-butylphosphine \textbf{L5}, the reaction did not proceed to any measurable extent. This was also true for JohnPhos \textbf{L6}, and the \textit{N}-heterocyclic carbene ligand IPr \textbf{L7}. The yields of reductive elimination were slightly higher for the aryl bromide as compared with the aryl chloride. Additional studies were performed on the kinetics of this stoichiometric transformation, but no catalytic processes were reported.\textsuperscript{36}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield X (%)</th>
<th>(X = \text{Br})</th>
<th>(X = \text{Cl})</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>(\text{P}^3\text{Bu}_3)</td>
<td>70</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>(\text{PCy}^3\text{Bu}_2)</td>
<td>15</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>L3</td>
<td>1-\text{AdP}^3\text{Bu}_2)</td>
<td>89</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>L4</td>
<td>Q-Phos</td>
<td>52</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>L5</td>
<td>(\text{FeP}^3\text{Bu}_2)</td>
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<td>&lt; 5</td>
<td></td>
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<tr>
<td>L6</td>
<td>JohnPhos</td>
<td>&lt; 5</td>
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<td></td>
</tr>
<tr>
<td>L7</td>
<td>IPr</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td></td>
</tr>
</tbody>
</table>
1.4.2 Buchwald’s Halide Interconversion

The Buchwald group developed three distinct methods for the interconversion of aryl halides and pseudohalides involving reductive elimination to form sp\(^2\) carbon–halide bonds. First, in 2002, they discovered an aromatic Finkelstein reaction in which aryl bromides could be converted into aryl iodides under copper catalysis in the presence of sodium iodide (Figure 21-A).\(^{37}\)

**Figure 21. Buchwald’s aryl halide interconversion chemistry**
Later, Buchwald also showed that aryl triflates could be converted into aryl fluorides in the presence of cesium fluoride and a palladium catalyst (Figure 21-B). Finally, in the presence of halide additives and a phase transfer catalyst conversion of aryl triflates to bromides and chlorides could be achieved (Figure 21-C). All three of these processes are metal catalyzed, and the mechanisms are postulated to involve oxidative addition, a halide exchange process, and terminate with the reductive elimination of a carbon–halide bond to generate the final aryl halide species.

1.4.3 Lautens’ Indole Synthesis from Gem-Dibromo-Olefins

The Lautens group observed reversible oxidative addition into sp² carbon–halide bonds in the synthesis of functionalized indoles from gem-dibromo-olefins. The proposed catalytic cycle of the reaction was palladium oxidative addition into a vinyl bromide, followed by Buchwald-Hartwig type C–N coupling to form the 5-membered indole ring (Figure 22). In addition to being a novel methodology, this process demonstrates the first synthetic application of reversible oxidative addition into aryl halides. A competition experiment showed that the product bromo-indole is much more susceptible to oxidative addition than the starting material. Without reductive elimination of the product C–Br bond, the palladium catalyst would be sequestered after the first catalytic turnover, and no measurable conversion would be achieved.
More impressive still was one particular substrate 1.19, possessing 3 reactive halogens in the starting material and 2 in the product 1.20, resulting in 5 halogens capable of undergoing oxidative addition, only one of which would lead to a productive coupling (Figure 23). Additionally, aryl iodides are known to be much more susceptible to oxidative addition than the aryl or vinyl bromides. However, cyclization to 1.20 was achieved in 68% yield, reaffirming that the oxidative addition into non-productive aryl halide bonds must be reversible.

![Diagram](image.png)

*Figure 23. Aryl iodide substrate possesses 4 sites of non-productive oxidative addition*

These literature examples suggest that reductive elimination from a carbon–palladium–halide intermediate can be a feasible step in a palladium-catalyzed mechanism.

### 1.4.4 Intra- and Intermolecular Carboiodonation

Carbohalogenation can be defined as the formal addition of a C–X σ-bond across a degree of unsaturation. This process often requires the uncommon reductive elimination of a carbon–halide bond as its key step.

Since observing reversible oxidative addition into aryl halides in the synthesis of indoles from gem-dibromo-olefins, the Lautens group has continued to study unusual carbon halogen...
reductive eliminations and subsequently discovered the carbohalogenation transformation. The developed reaction exploits catalytic reductive elimination of carbon–iodide bonds in the presence of electron rich, bulky phosphine ligands Q-Phos or tri-tert-butylphosphine (Figure 24).\textsuperscript{41} Oxidative addition is followed by inter- or intramolecular carbopalladation, and finally reductive elimination to give an alkyl iodide functionality.

![Diagram](attachment:image.png)

\textbf{Figure 24.} Lautens’ intra- and intermolecular carbohalogenation

The intramolecular method is both high-yielding, and can be used to synthesize a wide variety of backbones including both 5- and 6-membered rings, dihydroindoles, dihydrobenzofurans and dihydroisoquinolinones. The intermolecular variant is also promising, although the yields are lower. Additional work to identify the potential applications and the limitations of this methodology would increase its desirability as a synthetic tool.
Chapter 2

2 Experimental Results

2.1 Proposed Directions in Carbohalogenation Chemistry

Reflecting on the existing status of carboiodonation chemistry (Section 1.4.4), numerous modifications to expand the scope of this methodology could be proposed (Figure 25). Additional functionalization of the aromatic portion of the intramolecular substrate needed attention (i). In the initial report, only five- and six-membered ring formation was reported, however the reaction may be amenable to form larger or smaller ring sizes (ii). It is established that β-hydrogens are detrimental to the formation of carbohalogenated products, however only alkyl substituents were reported at the β-position. The introduction of heteroatoms could generate a broad range of substrates difficult to access by alternative methods (iii). Another possibility is the use of other aryl halides such as chlorides or bromides, and pseudo halides such as triflates to access a less expensive and larger pool of commercially available coupling partners (iv). Finally, the complexity of the products could be greatly increased, and the introduction of stereocenters could be realized by the use of polyunsaturated compounds to perform the first examples of domino-carbohalogenation chemistry (v).

For intermolecular carbohalogenation, only three examples were presented, and as such further experimentation to broaden the scope of this reaction is needed (vi). Additionally, the only unsaturated coupling partner used in the intermolecular variant was norbornene. For this reaction to be synthetically useful, a broader scope is required – many alkene equivalents could be imagined for coupling partners including simple substituted alkenes, alkyne moieties, strained cyclopropenes and allenes (vii). Finally, the use of additional aryl halides and pseudohalides would greatly improve the desirability of the intermolecular reaction (viii). Both the intra- and intermolecular variants would benefit from extension to enantioselective methods using chiral ligands.
2.2 Functional Group Modifications

2.2.1 Heteroatom Substitution at β-Position

Initial studies in carbohalogenation had limited substrates to those bearing either methyl or phenyl groups to prevent competitive Heck reactions (Figure 26). It would be highly desirable to utilize alternative functional groups at this position, which could generate novel compounds.

Maintaining the backbone of the initial intramolecular substrate poised for a 5-exo-trig cyclization, substrates could be generated by alkylation of 2-iodophenol using an allylic chloride, or a Mitsunobu reaction using the allylic alcohol. The literature was searched to find terminal
allylic chlorides or alcohols with 1,1-substitution, one group being a heteroatom (Figure 27). Three such compounds were selected utilizing chlorine, silicon and oxygen groups.

**Figure 27.** Allylic chlorides or alcohols can be utilized to generate carbohalogenation substrates

2.2.1.1 Vinyl Chloride Analogue

Allylic chloride 2.1 is commercially available, and was used in a standard alkylation with 2-iodophenol. This generated the novel compound 2.2 in 52% yield (Figure 28). In addition to containing a non-carbon functionality to block β-hydride elimination, this is the first example of a carbohalogenation substrate containing a vinyl halide.

**Figure 28.** Synthesis of vinyl chloride carbohalogenation substrate 2.2

2.2.1.2 Vinyl Silane Analogue

Previously Menozzi and coworkers have synthesized allylic alcohol 2.3 in one step from commercially available starting materials (Figure 29). It then underwent a Mitsunobu reaction
with 2-iodophenol in 81% yield to generate the novel substrate 2.4. This is the first example of a carbohalogenation substrate containing a silyl group.

### 2.2.1.3 Ether Analogue

Finally, a vinyl ether substrate was desired, and literature known THP-protected allylic chloride 2.5 was generated in 2 steps. With 2.5 in hand, alkylation to 2-iodophenol proceeded under standard conditions to give novel substrate 2.6 in 76% yield (Figure 30).

![Figure 30. Synthesis of vinyl ether carbohalogenation substrate 2.6](image)

### 2.2.1.4 \(\beta\)-Heteroatom Substituted Cyclization Attempts

With compounds 2.2, 2.4 and 2.6 in hand, carbohalogenation was attempted. Standard reaction conditions of Pd(Q-Phos)\(_2\) (5 mol\%) in toluene at 100 °C were tested, but no desired reactivity was observed in all three cases (Figure 31). Vinyl chloride 2.2 and vinyl silane 2.4 showed no conversion, and vinyl ether 2.6 showed small amounts of decomposition under reaction conditions. Modifications to the standard conditions for all substrates were unsuccessful.

![Figure 31. Unsuccessful carbohalogenation attempts of \(\beta\)-heteroatom substrates 2.2, 2.4, 2.6](image)
2.2.2 Tri-substituted Alkenes

Carboiodonation of a tri-substituted alkene for form a spirocycle was also attempted. The starting material was synthesized in accordance with Grigg’s literature procedure in 2 steps. The benzyl imine of 3,3,5,5-tetramethylcyclohexanone was formed, and without further purification subjected to 2-iodobenzoyl chloride to give 2.7 in 40% yield (Figure 32). Unfortunately, numerous cyclization attempts of 2.7 did not yield any desired product (Table 4); variables such as ligand, additive, temperature and solvent were explored.

![Figure 32. Synthesis of pro-spirocycle carbohalogenation substrate 2.7](image)

**Table 2.1 – Conditions for attempted carbohalogenation of substrate 2.7**

<table>
<thead>
<tr>
<th>Attempt</th>
<th>Catalyst (5 mol%)</th>
<th>Additive</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(Q-Phos)₂</td>
<td>-</td>
<td>100</td>
<td>PhMe</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Pd(Q-Phos)₂</td>
<td>1 equiv Et₃N</td>
<td>100</td>
<td>PhMe</td>
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</tr>
<tr>
<td>3</td>
<td>Pd(Q-Phos)₂</td>
<td>3 equiv Et₃N</td>
<td>100</td>
<td>PhMe</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>Pd(Q-Phos)₂</td>
<td>-</td>
<td>120</td>
<td>PhMe</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>Pd(P₃Bu₃)₂</td>
<td>-</td>
<td>100</td>
<td>PhMe</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Pd(Q-Phos)₂</td>
<td>2 equiv TBAC</td>
<td>100</td>
<td>ACN</td>
<td>NR</td>
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<td>2 equiv K₂CO₃</td>
<td>100</td>
<td>ACN</td>
<td>NR</td>
</tr>
</tbody>
</table>
2.2.3 Alkyl Halide

As our carbohalogenation method forms alkyl halides, the presence of an additional alkyl halide was explored. N-tosyl-2-iodoaniline was alkylated with 2.8 in 76% yield to give literature known allylic chloride 2.9 (Figure 33). Unfortunately, upon treatment of 2.9 with the standard carbohalogenation conditions, no reaction was observed. Although no experimental confirmation has been obtained, it is possible that palladium could undergo oxidative addition into the alkyl chloride bond, thereby sequestering the catalyst. Reductive elimination to form an alkyl chloride is unprecedented.

Figure 33. Synthesis and unsuccessful carbohalogenation of alkyl chloride substrate 2.9

2.2.4 Heteroaromatics

While pursuing a range of novel substrates, the halogenated hydroxyquinoline family of compounds was discovered. Commercially available clioquinol 2.10 contains the desired 1-hydroxy-2-iodo motif utilized in carbohalogenation chemistry. Also available is its diiodo-analogue 2.11; both are inexpensive due to their use as HPLC internal standards. Alkylation with methallylchloride gave the novel chloro-analogue 2.12 and iodo-analogue 2.13 in good yields of 90% and 80% respectively (Figure 34). With these substrates in hand, standard carbohalogenation reactions were attempted.

Figure 34. Synthesis of halo-quinoline carbohalogenation substrates 2.12 and 2.13
Under standard reaction conditions, the chloro-analogue 2.12 appeared to be proceeding efficiently by crude $^1$H-NMR analysis, showing exclusively product formation, however multiple attempts at isolation proved ineffective. It was discovered that purification by neutral alumina was necessary; otherwise decomposition of the product would occur. With this purification method, compound 2.14 could be isolated in 89% yield (Figure 35). Preparation of this compound demonstrates an expansion in functional group tolerance, being the first example of an aromatic nitrogen-containing heterocycle undergoing carbohalogenation. Additionally, 2.14 possesses both an aryl chloride and an alkyl iodide, which could allow for selective functionalization of this heterocycle.

![Figure 35. Successful carbohalogenation of chloroquinoline substrate 2.12](image)

In the analogous iodinated compound 2.13 cyclization attempts were unproductive, giving 5-15% conversion, but no isolable product (Figure 36, Reaction A). It has been postulated that the second iodide can undergo non-productive oxidative addition, which does not reductively eliminate. Attempts at performing the cyclization in the presence of boronic acid to prevent sequestering of the catalyst were unsuccessful showing unreacted starting material, and decomposition (Figure 36, Reaction B).

![Figure 36. Unsuccessful carbohalogenation attempt of diodoquinoline substrate 2.13](image)
2.2.5 7-Membered Rings

Another possibility for expanding the scope of carbohalogenation chemistry is for the formation of additional ring sizes, primarily seven-membered rings. The desired carbohalogenation starting material was achieved through a Mitsunobu reaction to give novel compound 2.15 in 62% yield (Figure 37).

![Figure 37. Synthesis of pro-7-membered ring carbohalogenation substrate 2.15](image)

With substrate 2.15 in hand, the key carbohalogenation reaction could be tested. In general, carbopalladation of a seven-membered ring is a slower process than that of a 5- or 6-membered ring. This is due to the increase in chain length, which can exist in multiple unproductive conformations for cyclization. Under standard reaction conditions no cyclization occurred, and 95% of the starting material could be observed by $^1$H-NMR with internal standard after 16 h at 100 °C. Due to the slow nature of the 7-membered ring cyclization, competitive intermolecular reactions could result in small amounts of intermolecular Heck-type products, which result in the catalytically inactive H–Pd–X species, shutting down the catalytic cycle. It was postulated that addition of base might inhibit this potential side reaction. One equivalent of Et$_3$N was added to the reaction and 85% conversion to the desired product was observed by $^1$H-NMR. An optimization showed that only 0.2 equivalents of base were necessary to achieve the desired carbohalogenation product 2.16 in 88% isolated yield (Figure 38). This is the first example that shows carbohalogenation is amenable to the formation of 7 membered rings.

![Figure 38. Successful carbohalogenation of pro-7-membered ring substrate 2.15](image)
2.3 Domino Carbohalogenation

Domino processes would be a major advancement in carbohalogenation chemistry by increasing complexity of the generated products. Reactions of polyunsaturated substrates could be used to form polycyclic alkyl iodides containing multiple stereogenic centers. To this end, a study was undertaken to extend carbohalogenation to domino reactivity.

2.3.1 5,5-Fused Amide

2.3.1.1 Synthesis

The first diene synthesized was literature known compound 2.17, in 65% yield (Figure 39). While distillation of the intermediate imine was suggested for purification, this compound required only subjection to high vacuum under mild heating (50 °C) to remove the volatile starting materials (boiling points 78 °C and 202 °C respectively).

![Figure 39. Synthesis of 5,5-fused amide domino carbohalogenation substrate 2.17](image)

2.3.1.2 Considerations for Domino Carbohalogenation

With the first polyunsaturated substrate 2.17 in hand, there were numerous considerations for the extension of carbohalogenation to domino processes. In the carboxpalladation/anion trapping reactions shown by Grigg and Balme (Figure 16 & Figure 17, Section 1.3.1), intramolecular
carbopalladation has been shown to occur on a faster time scale than both inter- and intramolecular anion capture respectively. This allows for the successive carbopalladations to proceed uninhibited. However, the time scale of intramolecular carbon–halide reductive elimination compared with the intramolecular carbopalladation is unprecedented.

Based on precedence, reversible oxidative addition into the aryl iodide of substrate 2.17 should proceed with appropriate ligand (Q-Phos or P^Bu_3) to intermediate 2.18 (Figure 40). Additionally, carbopalladation should occur to give 2.19, which has 2 possible pathways: reductive elimination to the alkyl halide 2.20 or a second carbopalladation can occur to intermediate 2.21, followed by reductive elimination to 2.22. As a result, upon cyclization of substrate 2.17 there are three possibilities: solely mono-cyclization product 2.20, only domino carbohalogenation product 2.22 or a mixture of 2.20 and 2.22.

![Figure 40. Possible carbohalogenation products of 5,5-fused amide domino carbohalogenation substrate 2.17](image)

2.3.1.3 Cyclization

The substrate 2.17 was reacted under standard carbohalogenation conditions (Figure 41) producing only the domino cyclization product 2.22, with none of the mono-cyclization product 2.20 observed. The isolated yield was 91% as a 5:1 mixture of diastereomers 2.22a and 2.22b.

The diastereomeric ratio could be unambiguously determined by crude ^1H-NMR as the methylene protons adjacent to the amide nitrogen have distinct chemical shifts in the major and
minor isomers. Although difficult to separate by column chromatography, recrystallization was used to obtain crystals of the major product 2.22a. The stereochemistry of this product was confirmed by single X-ray crystallography to be the syn isomer with the iodomethylene and phenyl group on the same face of the molecule (Figure 42).

2.3.1.4 Ligand Screen

One important question in domino carbohalogenation chemistry is the effect of ligand choice. Using domino substrate 2.17, a variety of ligands were screened (Table 5). It can be seen that Q-Phos and tri-tert-butylphosphine were by far the highest yielding ligands tested for this domino carbohalogenation. Both gave excellent yields and high diastereoselectivities of 5:1, however in subsequent screens P(P^tBu)_3 gave inconsistent results.

Some ligands under standard carbohalogenation conditions demonstrated evidence of reactivity, albeit in poor yields of 30% or less with equally poor diastereoselectivities of <3:1. These included ^1Bu- and AdbippyPHOS, JohnPhos, CataXcium P^tBu_3 and Ad_2PBu (Figure 43). Although its reactivity and selectivity were substantially lower than Q-Phos, Ad_2PBu had the
opposite diastereoselectivity to Q-Phos. By increasing catalyst loading and reaction time, 89% yield and 1:2 d.r. in favour of isomer 2.22b was achieved (see Entry 7, Table 5).

A variety of ligands proved inefficient for this carboiodonation including tBuBrettPhos, tBu₂PMe, XANTPhos and SPhos. Therefore, the use of Q-Phos was preferred for all subsequent reactions of domino substrates.

Table 2.2 – Ligand screen for domino carbohalogenation reaction of 2.17

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield(^a) (%))</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Q-Phos</td>
<td>94</td>
<td>5:1</td>
</tr>
<tr>
<td>2</td>
<td>P(^t)Bu(_3)</td>
<td>95(^b)</td>
<td>5:1</td>
</tr>
<tr>
<td>3</td>
<td>tBu-bippyPhos</td>
<td>30</td>
<td>3:1</td>
</tr>
<tr>
<td>4</td>
<td>Ad(_2)bippyPhos</td>
<td>30</td>
<td>3:1</td>
</tr>
<tr>
<td>5</td>
<td>CataXCium P(^t)Bu</td>
<td>30</td>
<td>5:1</td>
</tr>
<tr>
<td>6</td>
<td>JohnPhos</td>
<td>25</td>
<td>2:1</td>
</tr>
<tr>
<td>7(^c)</td>
<td>Ad(_2)PBu</td>
<td>89</td>
<td>1:2</td>
</tr>
<tr>
<td>8</td>
<td>tBu₂PMe</td>
<td>&lt; 5</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>tBuBrettPhos</td>
<td>&lt; 5</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>tBudp(_f)</td>
<td>&lt; 5</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>tBuXANTPhos</td>
<td>&lt; 5</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>SPhos</td>
<td>&lt; 5</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>dppf</td>
<td>&lt; 5</td>
<td>-</td>
</tr>
</tbody>
</table>

(a) yields measured by internal standard 1,3,5-trimethoxybenzene (b) inconsistent yields (c) 72 h reaction time, 10 mol% catalyst loading
2.3.2 6,5-Fused Ether

2.3.2.1 Synthesis

An ether-containing domino substrate was imagined in which a chiral racemic alcohol could be used to alkylate iodobenzyl chloride. This known alcohol was synthesized through Grignard addition of to methacrolein generating \( \text{2.23} \) in 83% yield (Figure 44).\(^{45} \) This compound was then alkylated with iodobenzyl chloride to give the literature known compound \( \text{2.24} \) in 75% yield.\(^{44} \)

![Figure 44. Synthesis of 6,5-fused ether domino carbohalogenation substrate 2.24](image-url)
2.3.2.2 Cyclization

With the domino substrate 2.24 in hand, it was subjected to carbohalogenation conditions (Figure 45). In all cases, the reaction proceeded smoothly but full conversion could never be obtained by increasing reaction time or temperature. Regardless of incomplete conversion,

![Image of cyclization reaction](image)

*Figure 45. Successful carbohalogenation of 6,5-fused ether domino substrate 2.24*

domino product 2.25 containing three stereogenic centers could be isolated in 68% yield as a single diastereomer, with no minor diastereomer observed by $^1$H-NMR analysis of the crude reaction mixture. The relative stereochemistry was established by nuclear Overhauser effect (nOe) analysis; correlation of the methyl group, syn protons and iodomethylene group were observed.

2.3.3 7,5-Fused Ester

2.3.3.1 Synthesis

Another scaffold of interest involved utilizing the successful seven-membered ring cyclization observed in Figure 38, and pairing it with a second cyclization for domino reactivity. The desired substrate could be easily formed from alcohol 2.23 in a coupling reaction with 2-(2-iodophenyl)acetic acid. A Steglich type coupling with DCC and DMAP was used, and the reaction proceeded with good yield to give novel compound 2.26 in 86% yield (Figure 46).
2.3.3.2 Cyclization

Standard reaction conditions for the domino carboiodonation of compound 2.26 were tested, but none of the cyclization product was observed. Additional conditions including elevated temperature and basic additives did not show signs of the desired cyclization. It was postulated that the ester linkage might be too rigid to adapt the necessary \textit{cis}-confirmation for cyclization to occur, as compared with the ether linkage used in 2.16. Another possibility is that after oxidative addition palladium could coordinate to the carbonyl oxygen in a stable species that does not undergo further reactions (Figure 47).

\textbf{Figure 46.} Synthesis of 7,5-fused ester domino carbohalogenation substrate 2.26

\textbf{Figure 47.} Unsuccessful carbohalogenation attempt of 7,5-fused ester carbohalogenation substrate 2.26
2.3.4  5,5-Branched Alkyne Relay

2.3.4.1  Synthesis

Another idea for domino reactivity was to use an alkyne relay moiety as a carbo palladation source. The starting material was synthesized in 3 steps from but-3-yne-1,4-diol. First, using a literature procedure, mono-mesylation of but-2-yne-1,4-diol was achieved by using a huge excess of diol as compared with mesyl chloride; this allowed for 51% of the mesylate to be isolated.\(^{47}\) Substitution using 2-iodophenolate under standard conditions generated the novel propargyl alcohol \(2.27\) in 85% yield (Figure 48). Finally, a standard alkylation with methallyl chloride was performed to give the desired starting material \(2.28\) in 36% yield.

![Figure 48. Synthesis of 5,5-branched alkyne relay carbohalogenation substrate 2.28](image)

2.3.4.2  Cyclization

Although the yield was low, enough of ene-yne \(2.28\) was generated to test for carbohalogenation reactivity. Figure 49 shows two possible products that were postulated. Two successive carbo palladations, followed by reductive elimination would generate the desired neopentyl halide product. However, another possibility is a third carbo palladation of the tetrasubstituted alkene intermediate to give a cyclopropane. This would leave an \(\text{sp}^3\) hybridized palladium-halide species with an available proton for \(\beta\)-hydride elimination to the Heck product.\(^{48}\) This conversion would require stoichiometric amounts to promote \(\beta\)-hydride elimination.

With substrate \(2.28\) in hand, carbohalogenation was attempted under both standard conditions, and with the addition of \(\text{Et}_3\text{N}\). In both instances decomposition of the starting material and no evidence of desired product was observed.
2.3.5 5,6-Spirocyclic Malonates\(^i\)

2.3.5.1 Synthesis

Another type of domino substrate could be imagined in which a 1,1-substituted alkene under carbohalogenation conditions could form spirocyclic products (Figure 50). There are numerous possibilities for the linkages, providing many potential domino substrates.

![Figure 50. Proposed structure of spirocyclic carbohalogenation substrates](image)

A spirocyclic precursor was generated by subsequent alkylations of 2-iodophenol, first with 3-chloro-2-(chloromethyl)prop-1-ene 2.8 to give the known compound 2.29 in 70% yield, and then with dimethyl 2-(2-methylallyl)malonate 2.30 to give 2.31 in 60% yield (Figure 51).\(^4^9\) The second alkylation partner 2.30 could be synthesized by a literature procedure in 74% yield.\(^4^9\)

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\(^i\) Collaboration with Dr. N. Nicolaus
This method proved useful, however the final product 2.31 was difficult to separate from unreacted 2.29.

![Diagram of synthesis process]

**Figure 51.** Synthesis of 5,6-spiroyclic malonate carbohalogenation substrate 2.31

To minimize this separation problem, an alternate synthetic route was devised. For the synthesis of the chloroquinoline analogue, the side chain alkenyl chloride was generated first to give intermediate 2.32 in 94% yield (Figure 52). It was then used to alkylate 2.10 generating substrate 2.33 in 64% yield. All substrates were easily separable from their starting materials making this the favourable synthetic pathway for spirocyclic domino substrates.

![Diagram of synthesis process]

**Figure 52.** Synthesis of chloroquinoline 5,6-spiroyclic malonate carbohalogenation substrate 2.33

### 2.3.5.2 Cyclization

Carboiodonation of the pro-spirocycles were attempted using standard conditions. First 2.31 gave spirocycle 2.34 in 92% yield and 3:1 d.r. The major product was determined by nOe analysis (Figure 53). Quinoline 2.33 provided spirocycle 2.35 in 90% yield and 2:1 d.r., and the stereochemistry was confirmed by single-crystal X-ray analysis. In both cases the chiral centers on each product have the same relative configuration.
2.3.6 5,6-Spirocyclic Malonitrile

An additional spirocycle derivative was generated using a malonitrile linkage in place of the malonate. The synthesis proceeded efficiently with alkylation of aryl iodide 2.29 using malonitrile 2.36 to give polyunsaturated aryl iodide 2.37 in a yield of 77% (Figure 54). However, upon subjecting the substrate to standard and modified reactions conditions, no reactivity was observed. It is postulated that the electron rich nitrile groups have the ability to coordinate to the palladium catalyst, and render it inactive.

Collaboration with Dr. N. Nicolaus
2.3.7 5,6-Spirocyclic Ether

In the successful carbohalogenation reactions with substrates 2.17, 2.24, 2.31, and 2.33, only the domino cyclization products were ever observed. It was hypothesized that if carbopalladation of the monocyclized intermediate could be slowed, the reductive elimination to the mono-unsaturated product might be possible. Thus, we proposed to make ether 2.38, which lacks the Thorpe-Ingold effect found in the malonate spirocycle substrates 2.31 and 2.33. This was achieved alkylating 2.29 with methallylalcohol generating desired substrate 2.38 was synthesized in 50% yield (Figure 55).

![Figure 55. Synthesis of vinyl chloride carbohalogenation substrate 2.38](image)

As was predicted, when compound 2.38 was subjected to the reaction conditions it provided monocyclized product 2.39 in 60% yield (Figure 56). No evidence of domino cyclization arising from a second carbopalladation was observed. While further studies are necessary to make definitive conclusions, this experiment gives insight into potential synthetic applications of this methodology.

![Figure 56. Successful cyclization of the bis-ether domino substrate yielding only the monocyclized product](image)

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iii Collaboration with Dr. N. Nicolaus
2.4 Halogen Exchange\textsuperscript{iv}

2.4.1 Initial Studies in Halogen Exchange

One drawback to Lautens’ original methodology is that only carbohalogenation of iodides was reported. Although aryl iodides are the most reactive aryl halides toward oxidative addition, they are the least desirable from the standpoint of availability. Additionally, aryl iodides are the most expensive of the aryl halides, as demonstrated in Figure 57.\textsuperscript{51}

\[
\begin{align*}
X = \text{Cl} & : 0.26 \text{ $/g} \\
X = \text{Br} & : 4.99 \text{ $/g} \\
X = \text{I} & : 7.06 \text{ $/g}
\end{align*}
\]

*Sigma Aldrich* 2-halophenols - 98% purity

**Figure 57.** Cost per gram of 2-halophenols (98% purity) from Sigma Aldrich

In the hopes of extending carbohalogenation chemistry to different halides and pseudohalides substrates, chloro-, bromo- and triflate analogues of compound 2.40 were screened (Figure 58).\textsuperscript{52} Despite a broad range of conditions, none of the desired carbohalogenation products 2.41 were obtained.

![Image of failed attempts to extend carbohalogenation to other halides](image)

**Figure 58.** Failed attempts to extend carbohalogenation to other halides

Although the analogous processes to carboiodonation were not realized, inspiration was taken from Buchwald and coworkers halide interconversion chemistry (\textbf{Section 1.4.2}). The hope was to utilize a more affordable and readily available halide starting material in the presence of an iodide source to perform a carbohalogenation with halogen exchange. Indeed, after optimization it was found that treatment of an aryl bromide with catalytic Pd(Q-Phos)\textsubscript{2} and 2 equivalents of potassium iodide, at a dilution of 0.05 M, gave the corresponding cyclized alkyl iodide (Figure

\textsuperscript{iv} Studies performed by Dr. N. Nicolaus and S. G. Newman
The scope of the bromide to iodide exchange included a number of useful functionalized dihydrobenzofurans, indolines and an isochroman. This is a noteworthy achievement in scope expansion for the Lautens’ carbohalogenation method.

![Diagram](image)

**Figure 59.** Lautens carbohalogenation with halogen exchange

The mechanism for this reaction has not been thoroughly studied, but it is presumed that first the aryl bromide undergoes oxidative addition with the Pd(0) catalyst. There are then two possible pathways for the reaction to follow. Utilizing the standard substrate 2.42, which generates 2.43 in 89% yield, halide exchange of the bromide for an iodide in solution could occur, followed by carboxpalladation and reductive elimination (Figure 60, Path A). Alternatively, after oxidative addition, carboxpalladation could occur first, followed by halide exchange (Figure 60, Path B). Additional experiments need to be performed to elucidate the order of events in the halogen exchange process.

![Diagram](image)

**Figure 60.** Possible mechanisms for carbohalogenation with halide exchange
2.4.2 Domino Carbohalogenation with Halogen Exchange\textsuperscript{v}

The domino carbohalogenation process could ultimately be combined with the work on halogen exchange in an efficient halogen-exchange domino reaction. The bromide analogue of 2.17, was sought utilizing a modified literature procedure.\textsuperscript{44} Novel compound 2.44 was successfully generated in 74% yield (Figure 61).

![Figure 61. Synthesis of aryl bromide domino carbohalogenation substrate 2.44](image)

Utilizing standard halogen exchange conditions, cyclization of 2.44 was performed in 89% isolated yield and 3:1 d.r. of 2.22\textsubscript{a} and 2.22\textsubscript{b} (Figure 62). Thus, carbohalogenation with halogen exchange and domino carbohalogenation chemistry have been successfully merged into a one-pot transformation.

![Figure 62. Successful carbohalogenation with halogen exchange of domino substrate 2.44](image)

2.5 Enantioselective Carbohalogenation\textsuperscript{vi}

Another interesting aspect of carbohalogenation chemistry was the development of an enantioselective process. With this in mind, over 30 chiral ligands were screened for the standard

\textsuperscript{v} Collaboration with S. G Newman

\textsuperscript{vi} Studies performed by S. G. Newman
bromo-substrate 2.42. It was found that in the presence of Josiphos a 14% yield of 2.43 could be obtained with a 94% ee (Figure 63). The standard domino substrate 2.17 was also reacted in the presence of the chiral ligand Walphos and it was found to undergo carbohalogenation in 65% yield with a 2:1 d.r. and 40% ee. The absolute configuration of the major enantiomers (2.43 and 2.22a) in these reactions has not yet been determined. It is noteworthy that the use of Josiphos on substrate 2.17 and the use of Walphos on substrate 2.42 proved ineffective at generating desired product. This is not surprising as the ligand screen (Section 2.3.1.4) showed that carbohalogenation is a very ligand specific process. Further studies are being performed to find optimal ligands to increase % ee and yield of the domino and halogen exchange carbohalogenation reactions.

Figure 63. Preliminary enantioselective results for carbohalogenation chemistry

2.6 \textit{S}_2\textit{N}2 Reactions of Carbohalogenation Products

In all successful carbohalogenation reactions explored, the generated functional group is a neopentyl iodide. Neopentyl halides are thought to be unreactive, making the carbohalogenation products not useful in synthetic applications. To test the usefulness of the neopentyl iodide, functionalization using \textit{S}_2\textit{N}2 chemistry was explored. Substrate 2.46 was chosen which could be synthesized in 3 steps through functional group conversion, alkylation and carbohalogenation (Figure 64).\textsuperscript{54} The key carbohalogenation of 2.45 proceeded to give 94% yield of 2.46. Functionalization using nucleophilic substitution of the neopentyl iodide proved effective with a
variety of nucleophiles in high yield including thiophenolate giving 2.47 (90%), cyanide generating 2.48 (98%) and azide to synthesize 2.49 (86%). Using oxygen as a nucleophile was more challenging, but in the presence of silver nitrate water could substitute the iodide generating 2.50 in 45% yield. One possible hypothesis for the successful substitution of these neopentyl halides could be as a result of the rigid aromatic group reducing steric bulk around the iodide allowing for facile approach of the nucleophile in substrate 2.46. It is also noteworthy that the alkyl-iodide is homo-benzylic, and the aromatic ring could be stabilizing formation of positive charge in the nucleophilic substitution.

\[
\begin{align*}
\text{Cl} & \text{Me} \quad \text{Cl} & \text{Me} \\
\text{OH} & \quad \text{OH} & \quad \text{I} \\
\text{Cl} & \text{Me} \text{SPh} \\
\text{2.47} & \quad \text{2.48} & \quad \text{2.49} & \quad \text{2.50}
\end{align*}
\]

Figure 64. Functionalization of neopentyl iodide products using an Sn2 reaction
Chapter 3

3 Concurrent Literature Examples of Carbohalogenation

Examples of formal carbohalogenation as a synthetic tool have been reported in the literature concurrently with the Lautens group research in this area.

3.1 Carbobromination and Carbochlorination of Alkenes

Sanford and coworkers have recently reported the palladium-catalyzed arylhalogenation of alkenes with an organotin species and an electrophilic halogenating reagent (Figure 65). Modification from a strong oxidant (PhICl$_2$) to a weak oxidant (CuCl$_2$) changed the selectivity from favouring 1,2-arylhalogenation to the 1,1- substituted product. These reactions proceed in excellent yield, but have not been shown to be functional group tolerant. The proposed mechanism to form the 1,2-substituted product involves a transmetallation of palladium with the stannane, carbopalladation to the Mizoroki-Heck intermediate, and trapping with the strong oxidative halogenating reagent. When using copper chloride, this weak oxidant allows for β-hydride elimination to the Heck product, and a second carbopalladation to the more stable 1,1-substituted intermediate, and finally trapping with chloride. The palladium in this catalytic cycle is proposed to be high oxidation state, multimeric palladium complexes, although there has been no strong mechanistic proof provided.

Figure 65. Sanford’s intermolecular oxidative arylchlorination of terminal alkenes
3.2 Carbobromination of Alkynes and Norbornene

The group of Jiang has demonstrated carbohalogenation of alkynes and norbornenes using ligand free palladium catalysis (Figure 66). The proposed mechanism also involves a Pd(II)/Pd(IV) catalytic cycle with oxidative addition into the halo-alkyne, syn-carbopalladation of the degree of unsaturation, and reductive elimination to generate the desired product.

![Figure 66. Jiang intermolecular carbobromination of alkynes and norbornene](image)

This reaction is highly desirable as it occurs under extremely mild conditions, and is suitable for the formation of both sp² and sp³ carbon-halide bonds. However, the reaction scope was limited to alcohol and ketone functional groups, making it a far more limited methodology. It should be noted that in the case of the norbornene substrates, a skeletal rearrangement occurs, leading to the alkyne and bromide on non-adjacent carbons.

3.3 Cycloisomerization of Vinyl Iodides

Tong and coworkers reported the cycloisomerization of vinyl iodides, which is the formal intramolecular carbohalogenation of vinyl-iodide starting materials. The proposed mechanism involves oxidative addition, carbopalladation and reductive elimination to an alkyl iodide similar to the carbohalogenation reported by Lautens (Figure 67).

This reaction utilizes a higher catalyst loading of 10 mol% Pd(OAc)₂, with a 3:1 excess of the bidentate phosphine ligand dppf. They provided 10 examples in moderate to good yield, however the scope was limited to cis-alkenes, 1,1-dialkyl substituted alkenes, and formation of only 6-
membered rings. Attempts to apply Tong’s conditions to the Lautens carbohalogenation substrates have not produced synthetically useful results

![Figure 67. Tong’s intramolecular carboiodonation of vinyl iodides](image-url)
Chapter 4

4 Conclusion

4.1 Summary

In conclusion, carbohalogenation chemistry has been extended to numerous new substrates. While substitution of heteroatoms at the β-position proved unsuccessful, carbohalogenation to form heteroaromatics and 7-membered rings was observed. Polyunsaturated aryl iodide substrates were shown to be amenable to domino carbohalogenation reactions yielding complex bicyclic alkyl iodides with multiple stereogenic centers. With decreased sterics, selective monocyclization of a poly-unsaturated substrate was achieved. Carbohalogenation of aryl bromides in the presence of an iodide source to generate alkyl iodide products was demonstrated. Domino reactivity and halogen exchange were merged to allow polyunsaturated aryl bromide substrates to participate in domino chemistry, generating bicyclic alkyl iodide products from aryl bromide starting materials. Preliminary studies of asymmetric carboiodination have given promising results. Finally, functionalization of the neopentyl iodide group has been achieved by a range of S_N2 reactions in excellent yields. These modifications significantly broaden the range of substrates that can be utilized for carbohalogenation chemistry.

4.2 Future Work

Research on carbohalogenation continues within the Lautens group towards a variety of goals. Enantioselective carbohalogenation is a primary focus, with many promising leads on reactive ligands. Additionally, examples of diastereoselective carbohalogenation would demonstrate the potential selectivity of this methodology. Extension of carbohalogenation to substrates with β-hydrogens would vastly improve the scope and utility of this transformation. However, for this to be achieved the rate of reductive elimination with respect to β-hydride elimination must be increased. Use of carbohalogenation chemistry in the synthesis of biologically important or pharmaceutically relevant targets is also under exploration.
Chapter 5

5  Supporting Information

5.1  Experimental Procedures

Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware equipped with magnetic stirring. Solvents and solutions were transferred by syringe or cannula. When required, solvents were degassed by bubbling of argon through a needle. Organic solutions were concentrated by rotary evaporation at reduced pressure (15 – 30 torr, house vacuum) at 25-50 °C. Analytical Thin Layer Chromatography (TLC) was performed using EM Separations pre-coated silica gel 0.2 mm layer UV 254 fluorescent sheets, and visualization was accomplished with 250 nm UV light followed by immersion in solid iodine powder, KMnO₄ solution or ceric ammonium molybdate (CAM) solution. Column chromatography was performed using Ultra Pure 230-400 mesh silica gel purchased from Silicycle.

Materials. Toluene was distilled under nitrogen from Na/benzophenone immediately prior to use. DMF was purchased from Sigma-Aldrich (>99.8%) and used as received. All reagents, metal catalysts, and ligands were purchased from Sigma-Aldrich, VWR International, Alfa Aesar, or Strem Chemical Company and used as received. Palladium catalysts were supplied by Johnson Matthey and are commercially available from Alfa Aesar. CataCXium ligands and were supplied by Solvias AG and are commercially available from Strem. Pd(Q-Phos)₂ and Pd(P'Bu₃)₂ were kept in an argon-filled glovebox for long term storage. Small quantities were removed from the glovebox in a vial so that reactions could be weighed out in air. The vials were stored in the freezer under argon between uses, and were found to stay active for up to 3 months. Potassium iodide (>99.0%) was obtained from ACP Chemicals Inc. and was ground with a mortar and pestle and stored in a desiccator. Starting materials 2.3¹², 2.5¹³, 2.7¹⁴, 2.9¹⁴, 2.17¹⁴, 2.23¹⁶, 2.24¹⁴, 2.29⁴⁹, 2.30⁴⁰, 2.36⁵⁸, 2.42⁵⁴ and 2.43⁵⁴ were prepared according to literature procedures. Reagents 2.1, 2.8, 2.10 and 2.11 are commercially available.
**Instrumentation.** Melting points were taken on a Fisher-Johns melting point apparatus. IR spectra were obtained using a Shimadzu FTIR-8400S FT-IR spectrometer on NaCl plates. High-resolution mass spectra were obtained by electron impact ionization (EI) using a VG 70-250S (double focusing) mass spectrometer at 70eV or electrospray ionization (ESI) using an ABI/Sciex Qstar mass spectrometer. $^1$H and $^{13}$C NMR spectra were obtained using either a Bruker Avance III 400 MHz or Varian Mercury 400 MHz, spectrometer. Single crystal X-ray diffraction was performed at the University of Toronto X-ray Laboratory using a Nonius Kappa-CCD System. Enantiomeric excess was determined on either an Agilent 1100 series HPLC or an Agilent 1200 Series SFC. $^1$H NMR spectra were internally referenced to tetramethylsilane (TMS, 0 ppm). $^{13}$C NMR spectra were internally referenced to the carbon resonances of the solvent (CDCl$_3$: 77.0). Spectral features are tabulated in the following order: chemical shift (, ppm); multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad); coupling constant (J, Hz); number of protons.

5.1.1 General Experimental Procedures

**ALKYLATION**

A suspension of phenol, alkyl chloride and base in DMF was prepared in a round bottom flask equipped with a magnetic stir bar and condenser. The reaction was stirred for 16 h at 80 °C, and then diluted with ethyl acetate and quenched with water. The organic phase was separated and successively washed 5x with a 1:1 mixture of brine:water to remove all traces of DMF. The organic layer was dried over MgSO$_4$ and concentrated to dryness; column chromatography was used to obtain pure product.
CARBOHALOGENATION

In a 0.5-2 mL Biotage microwave vial equipped with a magnetic stir bar the aryl iodide (0.10 mmol, 1.0 equiv), Pd(Q-Phos)\(_2\) (7.6 mg, 5.0 mol%) and toluene (1.0 mL, 0.10 M) were combined and purged with argon. The reaction was sealed with a Teflon coated septa, placed in a preheated 100 °C oil bath, and stirred overnight. The crude reaction was loaded directly onto silica gel and purified by column chromatography.

LIGAND SCREEN

In a 0.5-2 mL Biotage microwave vial equipped with a magnetic stir bar, aryl iodide 2.17 (40. mg, 0.10 mmol, 1.0 equiv), tris(dibenzylideneacetone)dipalladium(0) (2.3 mg, 2.5 mol%), ligand (10. mol%) and toluene (1.0 mL, 0.10 M) were combined and purged with argon. The reaction was sealed with a Teflon septa, placed in a preheated 100 °C oil bath, and stirred overnight. Internal standard solution of 1,3,5-trimethoxybenzene (1.0 mL, 0.033 M in THF) was added, and the reaction was filtered over a plug of silica with ethyl acetate. The filtrate was concentrated under reduced pressure, and conversion and diastereoselective ratio of 2.22a:2.22b were measured by \(^1\)H-NMR.
NUCLEOPHILIC SUBSTITUTION

In a 2 dram screw cap vial equipped with a magnetic stir bar the neopentyl iodide 2.46 (31 mg, 0.10 mmol, 1.0 equiv), nucleophile (0.50 mmol, 5.0 equiv) and DMF (2.0 mL, 0.050 M) were combined and purged with argon. The reaction was sealed with a Teflon coated screwcap, placed in a preheated 80 °C oil bath, and stirred overnight. The reaction was diluted with ethyl acetate (2 mL) and water (1 mL) was added. The organic layer was separated and successively washed 5x with a 1:1 mixture of brine:water to remove all traces of DMF. The organic layer was dried over MgSO₄ and concentrated to dryness; if necessary column chromatography was used to obtain pure product.

5.2 Compound Data

Note: compounds failing to undergo the key carbohalogenation step may not have complete characterization.

1-((2-Chloroallyl)oxy)-2-iodobenzene (2.2)

General procedure ALKYLATION was followed starting from 2-iodophenol (660 mg, 3.0 mmol, 1.0 equiv), 2,3-dichloroprop-1-ene (250 µL, 2.7 mmol, 0.90 equiv) and potassium carbonate (498 mg, 3.6 mmol, 1.2 equiv) in DMF (20. mL, 0.20 M). The product was filtered over a short silica pad with hexanes to provide 2.2 as a colourless oil (417 mg, 52%). IR (cm⁻¹, neat) 3061, 2926, 2863, 1641, 1582, 1571, 1571, 1471, 1439, 1277, 1249, 1226, 1057, 1018, 894, 747. IH NMR (CDCl₃, 400 MHz): δ 7.79 (d, J = 7.7 Hz, 1H), 7.29 (dd, J = 8.5, 7.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.75 (t, J = 7.6 Hz, 1H), 5.74 (s, 1H), 5.48 (s, 1H), 4.61 (s, 2H). 13C NMR (CDCl₃, 100 MHz): δ 156.4, 139.7, 135.2, 129.5, 123.4, 113.7, 112.6, 86.4, 70.6.
(3-(2-Iodophenoxy)prop-1-en-2-yl)triphenylsilane (2.4)

A solution of DIAD (75 µL, 0.36 mmol, 1.2 equiv) in dichloromethane (2.0 mL) was cooled to 0 °C. To it was added a solution of 2-iodophenol (66 mg, 0.30 mmol, 1.0 equiv), 2-(triphenylsilyl)prop-2-en-1-ol (95 mg, 0.30 mmol, 1.0 equiv), and triphenylphosphine (94 mg, 0.36 mmol, 1.2 equiv) in dichloromethane (10 mL, 0.35 M) dropwise, rinsing with dichloromethane (2.0 mL). The reaction was stirred at 0 °C for 4 h, and warmed to RT where it was stirred for 2 h until consumption of 2-iodophenol was observed by TLC. The reaction was quenched with brine, and extracted with dichloromethane (3x) and concentrated to dryness. Hexanes (50 mL) was added and the solution was cooled to -20 °C overnight to precipitate out the triphenylphosphine oxide, which was filtered off. The product was purified by column chromatography on silica gel eluting with 5% diethyl ether in pentane to provide 2.4 as a colourless oil (125 mg, 81%). IR (cm⁻¹, neat) 3068, 3051, 3009, 2998, 2921, 2858, 1581, 1469, 1429, 1276, 1241, 1232, 1189, 1110, 1049, 1017, 951, 747, 741, 728, 699. ¹H NMR (CDCl₃, 400 MHz): δ 7.73 (dd, J = 7.8, 1.6 Hz, 1H), 7.62–7.58 (m, 6H), 7.47–7.35 (m, 9H), 7.18 (dd, J = 8.2, 7.4 Hz, 1H), 6.66 (t, J = 7.6 Hz, 1H), 6.59–6.52 (m, 2H), 5.78 (d, J = 1.9 Hz, 1H), 4.69 (t, J = 1.9 Hz, 2H). ¹³C NMR (CDCl₃, 100 MHz): δ 156.9, 140.6, 139.4, 136.2, 132.9, 131.5, 129.8, 129.2, 128.0, 122.4, 112.2, 86.3, 71.6.

2-((3-(2-Iodophenoxy)prop-1-en-2-yl)oxy)tetrahydro-2H-pyran (2.6)

2-((3-(2-Iodophenoxy)prop-1-en-2-yl)oxy)tetrahydro-2H-pyran (2.6)

General procedure ALKYLATION was followed starting from 2-iodophenol (340 mg, 1.6 mmol, 1.2 equiv), 2.5 (230 mg, 1.3 mmol, 1.0 equiv) and potassium carbonate (360 mg, 2.6 mmol, 2.0 equiv) in DMF (6.5 mL, 0.20 M). The product was purified by column chromatography on silica gel eluting with pentane to provide 2.6 as a yellow oil (360 mg, 76%). ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, J = 7.8 Hz, 1H), 7.34–7.24 (m, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.72 (t, J = 7.6 Hz, 1H), 5.30 (t, J = 3.2 Hz, 1H), 4.60–4.54 (m, 2H), 4.52 (s, 2H), 3.92–3.82 (m, 1H), 3.63–3.53 (m, 1H), 1.98–1.81 (m, 1H), 1.81–1.72 (m, 2H), 1.66–1.52 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 157.1, 154.8, 139.5, 129.3, 122.8, 112.7, 95.8, 88.3, 86.7, 69.0, 62.0, 30.1, 25.2, 18.7.
5-Chloro-7-iodo-8-((2-methylallyl)oxy)quinoline (2.12)

General procedure ALKYLATION was followed starting from 5-chloro-7-iodo-8-quinolinol 2.10 (1.5 g, 5.0 mmol, 1.0 equiv), methallylchloride (0.73 mL, 7.5 mmol, 1.2 equiv) and potassium carbonate (1.4 g, 10. mmol, 2.0 equiv) in DMF (25 mL, 0.20 M). The product was purified by column chromatography on silica gel eluting from 10% to 20% diethyl ether in pentane to provide 2.12 as a yellow solid (1.6 g, 90%). mp = 52-54 °C, IR (cm$^{-1}$, neat) 3076, 2972, 2916, 1599, 1572, 1482, 1443, 1436, 1344, 1205, 1088, 940, 902, 787. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.95 (d, $J$ = 4.1 Hz, 1H), 8.51 (d, $J$ = 8.5 Hz, 1H), 7.97 (s, 1H), 7.54 (dd, $J$ = 8.5, 4.1 Hz, 1H), 5.28 (s, 1H), 5.04 (s, 1H), 4.83 (s, 2H), 2.02 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 155.1, 150.3, 142.4, 141.3, 135.1, 133.4, 127.4, 126.3, 122.2, 113.5, 90.1, 78.4, 20.2. HRMS (ESI): Calcd for C$_{13}$H$_{12}$ClINO$^+$ 359.9652, found 359.9650

5,7-Diiodo-8-((2-methylallyl)oxy)quinoline (2.13)

General procedure ALKYLATION was followed starting from 5,7-diiodo-8-quinolinol 2.11 (2.0 g, 5.0 mmol, 1.0 equiv), methallylchloride (0.70 mL, 7.5 mmol, 1.5 equiv) and potassium carbonate (1.4 g, 10. mmol, 2.0 equiv) in DMF (25 mL, 0.20 M). The product was purified by column chromatography on silica gel eluting with 10 % diethyl ether in pentane to provide 2.13 as a yellow solid (1.8 g, 80%). mp = 60-62 °C, IR (cm$^{-1}$, neat) 3075, 3059, 2970, 2943, 1596, 1560, 1476, 1436, 1338, 1213, 1089, 987, 906, 785. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.87 (d, $J$ = 4.2 Hz, 1H), 8.45 (s, 1H), 8.32 (d, $J$ = 8.6 Hz, 1H), 7.49 (dd, $J$ = 8.6, 4.2 Hz, 1H), 5.27 (s, 1H), 5.04 (s, 1H), 4.85 (s, 2H), 2.01 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 156.7, 150.3, 145.2, 142.8, 141.3, 140.7, 131.3, 123.1, 113.6, 92.0, 91.8, 78.4, 20.2.
5-Chloro-3-(iodomethyl)-3-methyl-2,3-dihydrofuro[3,2-h]quinoline (2.14)

General procedure CYCLIZATION was followed starting from 2.12 (36 mg, 0.10 mmol) using toluene (1.0 mL, 0.1 M). The product was purified by column chromatography on alumina eluting with 50% diethyl ether in pentane to provide 2.14 as an off-white solid (32 mg, 89%). mp = 126-127 °C, IR (cm⁻¹, neat) 2964, 2925, 2889, 1588, 1505, 1454, 1398, 1346, 1187, 1082, 987, 941. ¹H NMR (CDCl₃, 400 MHz): δ 8.92 (dd, J = 4.1, 1.7 Hz, 1H), 8.52 (dd, J = 8.7, 1.6 Hz, 1H), 7.51 (dd, J = 8.7, 4.2 Hz, 1H), 7.42 (s, 1H), 4.79 (d, J = 9.4 Hz, 1H), 4.50 (d, J = 9.4 Hz, 1H), 3.47 (s, 2H), 1.64 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 154.3, 150.5, 136.7, 133.2, 129.4, 127.0, 122.5, 122.2, 121.2, 84.3, 47.2, 25.7, 16.7. HRMS (ESI): Calc’d for C₁₃H₁₂ClINO⁺ 359.9652, found 359.9645

1-Iodo-2-((4-methylpent-4-en-1-yl)oxy)benzene (2.15)

A solution of DIAD (690 µL, 3.5 mmol, 2.0 equiv) in dichloromethane (2 mL) was cooled to 0 °C and a solution of 2-iodophenol (390 mg, 1.8 mmol, 1.0 equiv), 4-methylpent-4-en-1-ol (850 mg, 3.5 mmol, 2.0 equiv), and triphenylphosphine (920 mg, 3.5 mmol, 2.0 equiv) in dichloromethane (10 mL, 0.35 M) was added dropwise, followed by rinsing with dichloromethane (2 mL). The reaction was stirred at 0 °C for 4 h, and warmed to RT where it was stirred for 2 h until consumption of 2-iodophenol was observed by TLC. The reaction was quenched with brine, and extracted with dichloromethane (3x) and concentrated to dryness. Hexanes (50 mL) was added and the solution was cooled to -20°C overnight to precipitate out the triphenylphosphine oxide, which was removed by filtration to provide 2.15 as a colourless oil (320 mg, 62%). IR (cm⁻¹, neat) 3070, 2935, 2875, 1648, 1582, 1464, 1439, 1276, 1247, 1050, 1017, 890, 747. ¹H NMR (CDCl₃, 400 MHz): δ 7.76 (d, J = 7.8 Hz, 1H), 7.30–7.24 (m, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.69 (t, J = 7.6 Hz, 1H), 4.77–4.73 (m, 2H), 4.01 (t, J = 6.3 Hz, 2H), 2.30–2.24 (m, 2H), 2.02–1.94 (m, 2H), 1.77 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 157.5, 144.9, 139.4, 129.4, 122.3, 112.1, 110.5, 86.7, 68.5, 34.1, 27.1, 22.5. HRMS (ESI): Calc’d for C₁₂H₁₆O⁺ 303.0246; found 303.0244.
5-(Iodomethyl)-5-methyl-2,3,4,5-tetrahydrobenzo[b] (2.16)

General procedure CARBOHALOGENATION was followed starting from 2.15 (30. mg, 0.10 mmol) with the addition of triethylamine (2.8 µL, 0.020 mmol, 0.20 equiv). The product was purified by column chromatography on silica gel eluting from 0 to 3% diethyl ether in pentane to provide 2.16 as a pale yellow oil (27 mg, 88%). IR (cm⁻¹, neat) 3062, 3027, 2968, 2935, 2847, 1599, 1482, 1440, 1375, 1282, 1225, 1196, 1012, 784, 763, 751. ¹H NMR (CDCl₃, 400 MHz): δ 7.31 (d, J = 7.9 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 4.34 (dt, J = 11.8, 3.6 Hz, 1H), 3.96 (d, J = 9.8 Hz, 1H), 3.54 (td, J = 11.8, 2.1 Hz, 1H), 3.42 (d, J = 9.8 Hz, 1H), 2.28 (dddt, J = 15.9, 12.5, 7.4, 3.7 Hz, 1H), 1.97 (dt, J = 14.1, 4.0 Hz, 1H), 1.77 (m, 1H), 1.66 (td, J = 13.5, 3.5 Hz, 1H), 1.51 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 160.0, 136.4, 128.5, 127.5, 124.1, 122.9, 122.3, 75.6, 52.9, 49.5, 48.8, 29.1, 19.5. HRMS (ESI): Calc’d for C₁₂H₁₉INO⁺ 320.0511, found: 320.0514.

(±) (2R,9bR)-2-(Iodomethyl)-2-methyl-9b-phenyl-2,3-dihydro-1H-pyrrolo
[2,1-a]isoindol-5(9bH)-one (2.22)

General procedure CARBOHALOGENATION was followed starting from 2.17 (40. mg, 0.10 mmol) using toluene (1.0 mL, 0.10 M). The product was purified by column chromatography on silica gel eluting with 50% diethyl ether in pentane to provide 2.22 as an off-white solid (37 mg, 91%, d.r. 5:1). The major diastereomer 2.22a could be separated by recrystallization from hot isopropanol. Characterization of Major Isomer: mp = 197-198 °C, IR (cm⁻¹, neat) 2973, 2929, 1667, 1629, 1511, 1246, 1080. ¹H NMR (CDCl₃, 400 MHz): δ = 7.78 (d, J = 7.4 Hz, 1H), 7.54 (m, 2H), 7.27–7.50 (m, 6H), 4.06 (d, J = 12.3 Hz, 1H), 3.26 (d, J = 12.4 Hz, 1H), 3.06 (d, J = 9.9 Hz, 1H), 2.99 (d, J = 9.9 Hz, 1H), 2.93 (d, J = 13.3 Hz, 1H), 1.98 (d, J = 13.4 Hz, 1H), 1.23 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 171.7, 151.7, 141.5, 132.4, 130.3, 129.2, 128.3, 128.0, 124.7, 124.4, 122.3, 75.6, 52.9, 49.5, 48.8, 29.1, 19.5. HRMS (ESI): Calc’d for C₁₀H₁₈INO, 403.0433; found, 403.0443.
Alternatively, in a 0.5-2 mL Biotage microwave vial equipped with a magnetic stir bar was added the aryl bromide 2.44 (36 mg, 0.10 mmol, 1.0 equiv). The vial was purged with argon for 5 minutes, after which Pd(Q-Phos)$_2$ (7.6 mg, 5.0 mol%), potassium iodide (33 mg, 0.20 mmol, 2.0 equiv), and toluene (2.0 mL, 0.05 M) were added. The vial was capped and added to an oil bath pre-heated to 100 °C. After stirring for 16 hours, the vial was cooled and the contents filtered over a pad of silica gel, washing with ether. The crude material was purified by column chromatography on silica gel.

(±)(2R,3aS,9bS)-2-(Iodomethyl)-2,9b-dimethyl-1,2,3,3a,5,9b-hexahydrocyclopenta-[c]isochromene (2.25)

General procedure CARBOHALOGENATION was followed starting from 2.24 (34 mg, 0.1 mmol) using 1 mL of toluene (0.1 M). The product was purified by column chromatography on silica gel eluting with 2.5% diethyl ether in pentane to provide 2.25 as a pale yellow oil (23 mg, 68%). IR (cm$^{-1}$, neat) 2956, 2863, 1489, 1458, 1445, 1397, 1204, 1099. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 7.26–7.20 (m, 2H), 7.13 (td, $J$ = 7.2, 1.9 Hz, 1H), 6.98 (d, $J$ = 7.5 Hz, 1H), 4.73 (d, $J$ = 14.6 Hz, 1H), 4.64 (d, $J$ = 14.6 Hz, 1H), 3.91 (d, $J$ = 5.3 Hz, 1H), 3.35 (m, 2H), 2.23 (dd, $J$ = 14.5, 5.4 Hz, 1H), 2.09 (d, $J$ = 13.8 Hz, 1H), 2.00 (d, $J$ = 13.7 Hz, 1H), 1.88 (d, $J$ = 14.5 Hz, 1H), 1.34 (s, 3H), 1.25 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 142.5, 132.8, 127.2, 126.6, 125.5, 124.2, 87.3, 67.5, 53.4, 45.3, 44.8, 42.7, 30.9, 28.0, 26.1 HRMS (ESI): Calc’d for C$_{15}$H$_{20}$IO, 343.0559; found, 343.0561.
2,5-Dimethylhexa-1,5-dien-3-yl 2-(2-iodophenyl)acetate (2.26)

Alcohol 2.23 was dissolved in dichloromethane (15 mL, 0.10 M) and 2-iodophenylacetic acid (390 mg, 1.5 mmol, 1.0 equiv) and DMAP (150 mg, 1.2 mmol, 0.80 equiv) were added. The solution was cooled to 0 °C, and DCC (340 mg, 1.7 mmol, 1.1 equiv) was added dropwise to maintain the temperature. The solution was warmed to room temperature and stirred for 3 h, then filtered over Celite and washed twice with 0.5 M HCl and twice with saturated sodium bicarbonate solution. The organic phase was concentrated in vacuo and purified by column chromatography on silica gel eluting with 30% diethyl ether in pentane to provide 2.26 as a colourless oil (480 mg, 86%). ¹H NMR (300 MHz, CDCl₃) δ 7.84 (d, J = 7.3 Hz, 2H), 7.36–7.21 (m, 2H), 6.95 (ddd, J = 7.9, 6.5, 2.7 Hz, 1H), 5.38 (dd, J = 8.4, 5.3 Hz, 1H), 4.95 (s, 1H), 4.87 (s, 1H), 4.76 (s, 1H), 4.69 (s, 1H), 3.80 (s, 2H), 2.45–2.19 (m, 2H), 1.71 (t, J = 2.5 Hz, 6H).

4-(2-Iodophenoxy)but-2-yn-1-ol (2.27)

General procedure ALKYLATION was followed starting from 2-iodophenol (220 mg, 1.0 mmol, 1.0 equiv), 4-hydroxybut-2-yn-1-yl methanesulphonate (180 mg, 1.1 mmol, 1.1 equiv) and potassium carbonate (410 mg, 3.0 mmol, 3.0 equiv) in DMF (10. mL, 0.10 M). The product was purified by column chromatography on silica gel eluting with 40% diethyl ether in pentane to provide 2.27 as a colourless oil (250 mg, 85%). IR (cm⁻¹, neat) 3358, 3061, 2917, 2864, 1582, 1569, 1464, 1436, 1372, 1278, 1222, 1129, 1050, 1017, 998, 749, 645. ¹H NMR (CDCl₃, 400 MHz): δ 7.79 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.76 (t, J = 7.6 Hz, 1H), 4.80 (br s, 2H), 4.31 (br s, 2H), 1.76–1.59 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ 156.3, 139.7, 129.4, 123.4, 113.0, 86.6, 86.1, 80.2, 57.2, 51.1.
**1-Iodo-2-((4-(2-methylallyloxy)but-2-yn-1-yl)oxy)benzene (2.28)**

General procedure **ALKYLATION** was followed starting from 4-(2-iodophenoxy)but-2-yn-1-ol 2.27 (240 mg, 0.82 mmol, 1.0 equiv), methallylchloride (0.10 mL, 0.98 mmol, 1.2 equiv) and sodium hydride (60% wt, 65 mg, 1.6 mmol, 2.0 equiv) in DMF (8.0 mL, 0.10 M). The product was purified by column chromatography on silica gel eluting with 20% diethyl ether in pentane to provide 2.28 as a colourless oil (100 mg, 36%). IR (cm⁻¹, neat) 3074, 2935, 2915, 2850, 1583, 1570, 1471, 1440, 1354, 1278, 1225, 1126, 1079, 1018, 902, 748. 

**¹H NMR (CDCl₃, 400 MHz):** δ 7.79 (d, *J* = 7.8 Hz, 1H), 7.30 (dd, *J* = 8.6, 7.4 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.75 (t, *J* = 7.6 Hz, 1H), 4.94 (s, 1H), 4.91 (s, 1H), 4.81 (t, *J* = 1.8 Hz, 2H), 4.16 (t, *J* = 1.8 Hz, 2H), 3.92 (s, 2H), 1.72 (s, 3H).

**¹³C NMR (CDCl₃, 100 MHz):** δ 156.4, 141.3, 139.7, 129.3, 123.3, 113.1, 113.1, 86.6, 84.1, 80.6, 73.7, 57.2, 57.1, 19.5.

**Dimethyl 2-(2-((iodophenoxy)methyl)allyl)-2-(2-methylallyl)malonate (2.31)**

Under argon atmosphere, 1-((2-(chloromethyl)allyl)oxy)-2-iodobenzene 2.29 (0.20 g, 0.65 mmol, 1.0 equiv) and 2.30 (0.15 g, 0.78 mmol, 1.2 equiv) were dissolved in acetone (1.0 mL). Tetrabutylammonium bromide (21 mg, 0.060 mmol, 10. mol%) and K₂CO₃ (130 mg, 0.97 mmol, 1.5 equiv) were added and the mixture was stirred at RT over night. The reaction mixture was quenched with water, diluted with ethyl acetate and transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3x), the combined organic phases were washed with brine, dried over MgSO₄ and filtered. After rotary evaporation, the crude product was purified by column chromatography on silica gel eluting with 10 % ethyl acetate in hexanes to provide 2.31 as a colourless oil (180 mg, 60%). IR (cm⁻¹, neat): 2950, 1733, 1581, 1470, 1438, 1277, 1208, 1181, 1017, 913, 749. 

**¹H NMR (CDCl₃, 400 MHz):** δ = 7.75 (d, *J* = 6.0 Hz, 1H), 7.27–7.23 (m, 1H), 6.72 (d, *J* = 6.0 Hz, 1H), 6.68 (t, *J* = 6.0 Hz, 1H), 5.41 (s, 1H), 5.05 (s, 1H), 4.85 (s, 1H), 4.72 (s, 1H), 4.42 (s, 2H), 3.65 (s, 6H), 2.87 (s, 2H), 2.78 (s, 2H), 1.66 (s, 3H). 

**¹³C NMR (CDCl₃, 100 MHz):** δ = 171.7, 157.0, 140.6, 139.6, 139.5, 129.4, 122.6, 116.6, 115.5,
112.2, 86.4, 71.5, 57.3, 52.4, 41.7, 36.7, 23.4. HRMS (ESI): Calc’d for C_{19}H_{24}I_{5}O^{+}, 459.0668; found, 459.0668.

**Dimethyl-2-(2-(chloromethyl)allyl)-2-(2-methylallyl)malonate (2.32)**

![Chemical structure](image)

Compound **2.30** (0.77 g, 4.1 mmol, 1.0 equiv), 3-chloro-2-(chloromethyl)prop-1-ene (1.5 g, 1.3 mL, 12 mmol, 2.8 equiv), K$_2$CO$_3$ (1.7 g, 12 mmol, 3.0 equiv) and KI (69 mg, 0.42 mmol, 10. mol%) were dissolved in 15 mL of acetone. The reaction mixture was heated to 50 °C overnight, quenched with NH$_4$Cl, diluted with dichloromethane and transferred to a separatory funnel. After extracting the aqueous phase with dichloromethane (4x), the combined organic phases were washed with brine, dried over MgSO$_4$ and filtered. After rotary evaporation the crude product was purified by column chromatography on silica gel eluting with 6% ethyl acetate in hexanes to afford **2.32** as a colourless liquid (1.1 g, 94%). IR (cm$^{-1}$, neat): 2953, 2358, 2331, 2323, 1735, 1700, 1437, 1244, 1202, 1181, 1076, 668. $^1$H NMR (CDCl$_3$, 400 MHz): δ = 5.28 (s, 1H), 5.01 (s, 1H), 4.88 (s, 1H), 4.74 (s, 1H), 4.00 (s, 2H), 3.72 (s, 6H), 2.88 (s, 2H), 2.75 (s, 2H), 1.68 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ = 171.6, 141.0, 140.4, 119.0, 115.9, 57.1, 52.4, 48.5, 46.1, 41.4, 36.1, 23.3. HRMS (ESI): Calc’d for C$_{13}$H$_{20}$ClO$_4$+, 275.1050; found, 275.1056.

**Dimethyl-2-((5-chloro-7-iodoquinolin-8-yl)oxy)allyl)-2-(2-methylallyl)-malonate (2.33)**

Under an argon atmosphere, 5-chloro-7-iodoquinolin-8-ol **2.10** (180 mg, 0.60 mmol, 1.0 equiv), **2.32** (200 mg, 0.72 mmol, 1.2 equiv) and tetrabutylammonium bromide (20. mg, 0.060 mmol, 10. mol%) were suspended in acetone (4.0 mL). After 20 min, K$_2$CO$_3$ (170 mg, 1.2 mmol, 2.0 equiv) was added resulting in a green suspension. The mixture was heated to 50 °C for 48 h, diluted with water and extracted with dichloromethane (4x). The combined organic phases were washed with brine, dried over MgSO$_4$ and filtered. After rotary evaporation the crude product was purified by column chromatography on silica gel eluting with 10% ethyl acetate in hexanes.
on basic alumina to afford compound 2.33 as a colourless oil (210 mg, 64%). IR (cm\(^{-1}\), neat): 3074, 2950, 1733, 1572, 1484, 1440, 1344, 1203, 1177, 1088, 943, 906. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 8.91\) (d, \(J = 3.3\) Hz, 1H), 8.48 (d, \(J = 6.4\) Hz, 1H), 7.94 (s, 1H), 7.51 (dd, \(J = 6.4, 3.3\) Hz, 1H), 5.58 (s, 1H), 5.08 (s, 1H), 4.82 (s, 1H), 4.80 (s, 2H), 4.74 (s, 1H), 3.67 (s, 6H), 2.97 (s, 2H), 2.81 (s, 2H), 1.66 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 171.8, 154.9, 150.1, 142.3, 140.8, 140.3, 135.2, 133.4, 127.4, 126.2, 122.2, 116.6, 115.4, 100.0, 90.0, 57.5, 52.4, 41.2, 36.7, 23.5. HRMS (ESI): Calc’d for C\(_{22}\)H\(_{24}\)ClINO\(_5\)\(^+\), 544.0388; found, 544.0399.

(\(\pm\))-\((1'R,5'R)\)-Dimethyl-\(5'\)-(iodomethyl)-\(5'\)-methyl-2H-spiro[benzofuran-3,1'\(\)'-cyclo-hexane]-3',3'-di-carboxylate (2.34)

General procedure CARBOHALOGENATION was followed starting from 2.31 (46 mg, 0.10 mmol scale) stirring for 16 hours. The product was purified by column chromatography on silica gel eluting with 5% ethyl acetate in hexanes to provide 2.34 as a mixture of diastereoisomers (colorless oil; 42 mg, 92%, 3:1 d.r.). The pure major diastereoisomer could partially be separated (colorless oil; 30 mg, 59%). IR (cm\(^{-1}\), neat): 2954, 2925, 1731, 1597, 1482, 1459, 1447, 1432, 1260, 1233, 1160, 1020, 971, 752, 732. \(^1\)H NMR (CDCl\(_3\), 400 MHz; major): \(\delta = 7.13\) (t, \(J = 6.0\) Hz, 1H), 7.04 (d, \(J = 5.7\) Hz, 1H), 6.87 (t, \(J = 6.0\) Hz, 1H), 6.80 (d, \(J = 5.7\) Hz, 1H), 4.76 (d, \(J = 6.9\) Hz, 1H), 4.28 (d, \(J = 6.9\) Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.15 (d, \(J = 7.8\) Hz, 1H), 3.05 (d, \(J = 7.8\) Hz, 1H), 2.67 (d, \(J = 12.3\) Hz, 1H), 2.53 (d, \(J = 11.1\) Hz, 1H), 2.10 (d, \(J = 11.1\) Hz, 1H), 2.05–2.02 (m, 1H), 1.75 (d, \(J = 10.8\) Hz, 1H), 1.67 (d, \(J = 11.1\) Hz, 1H), 1.14 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 172.6, 172.1, 158.8, 135.3, 128.8, 122.4, 120.7, 109.7, 80.0, 53.5, 53.2, 52.9, 45.1, 44.2, 38.6, 38.2, 34.2, 33.7, 19.9. HRMS (ESI): Calc’d for C\(_{19}\)H\(_{23}\)INO\(_5\)\(^+\), 476.0934; found, 476.0946.
(±)-(1R,5R)-Dimethyl-5'-chloro-5-(iodomethyl)-5-methyl-2'H-spiro[cyclohexane-1,3'-furo[3,2-h]quinoline]-3,3-dicarboxylate (2.35).

General procedure CARBOHALOGENATION was followed starting from 2.33 (54 mg, 0.10 mmol) stirring for 16 hours. The crude product was purified by column chromatography on neutral alumina eluting with 10% ethyl acetate in hexanes on basic alumina to provide diastereoisomer 2.35a (33 mg; colorless solid) and 2.35b (17 mg; colorless oil) (total yield: 50 mg, 90%, 2:1 d.r.). A single crystal of the major diastereoisomer for X-ray analysis could be obtained by crystallization from ethyl acetate/hexanes. Major diastereoisomer: mp: 195 °C, IR (cm⁻¹, neat): 3073, 2954, 1729, 1655, 1627, 1504, 1456, 1432, 1260, 1248, 1225, 1162, 1085. ¹H NMR (CDCl₃, 400 MHz): δ = 8.90 (d, J = 3.3 Hz, 1H), 8.48 (d, J = 6.4 Hz, 1H), 7.47 (dd, J = 6.4, 3.3 Hz, 1H), 7.35 (s, 1H), 5.07 (d, J = 6.9 Hz, 1H), 4.61 (d, J = 6.9 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.18 (d, J = 7.8 Hz, 1H), 3.07 (d, J = 8.1 Hz, 1H), 2.75 (d, J = 10.8 Hz, 1H), 2.56 (d, J = 9.0 Hz, 1H), 2.16–2.09 (m, 2H), 1.84 (d, J = 11.1 Hz, 1H), 1.73 (d, J = 11.1 Hz, 1H), 1.16 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 172.4, 171.9, 153.5, 150.4, 136.2, 133.2, 132.5, 126.7, 122.3, 122.1, 121.3, 81.4, 53.4, 53.3, 53.1, 46.5, 44.3, 38.6, 38.1, 34.2, 33.7, 19.5. HRMS (ESI): Calc’d for C₂₂H₂₄ClINO₅⁺, 544.0388; found, 544.0390.

In a round bottom flask, 2.29 (250 mg, 0.95 mmol, 1.0 equiv), 2.36 (140 mg, 1.1 mmol, 1.2 equiv), and TBAB (30. mg, 0.095 mmol, 10. mol%) were combined in THF (0.50 mL). After stirring for 30 minutes, potassium carbonate (200 mg, 1.4 mmol, 1.5 equiv) was added. The reaction was stirred overnight, quenched with water, diluted with ethyl acetate and transferred to a separatory funnel. The aqueous phase was extracted (3x) and the combined organic phases were washed with brine, dried over MgSO₄ and filtered. After rotary evaporation, the crude product was purified by column chromatography on silica gel eluting with 10% ethyl acetate in hexanes to provide compound 2.37 as a colourless oil (280 mg, 77%). ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 7.8 Hz, 1H), 7.30 (dd, J = 8.3, 7.4 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.75 (t, J = 7.6 Hz, 1H), 5.68 (s, 1H), 5.42 (s, 1H), 4.17–3.55 (m, 2H), 3.08–2.80 (m, 1H), 2.48–2.11 (m, 1H), 2.08–1.96 (m, 1H), 1.93–1.80 (m, 1H), 1.73–1.52 (m, 2H), 1.47–1.30 (m, 2H), 1.19–1.00 (m, 2H), 0.92–0.75 (m, 2H).
1H), 5.55 (s, 1H), 5.19 (s, 1H), 5.12 (s, 1H), 4.72 (s, 2H), 2.94 (s, 2H), 2.73 (s, 2H), 1.98 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.7, 139.8, 137.2, 136.7, 129.8, 123.5, 121.4, 119.4, 115.8, 112.8, 86.8, 71.3, 45.9, 40.7, 36.4, 23.4.

1-Iodo-2-(((2-methylallyloxy)methyl)allyloxy)benzene (2.38)

Under argon atmosphere of sodium hydride (71 mg, 60% suspension in mineral oil, 1.8 mmol, 1.5 equiv) and KI (20. mg, 0.12 mmol, 0.10 equiv) were suspended in dry THF (3.0 mL). After cooling the mixture to 0 °C, 2-methylprop-2-en-1-ol (100 mg, 1.5 mmol, 1.2 equiv) was slowly added by syringe. The mixture was stirred for 15 min and 2.29 (360 mg, 1.2 mmol, 1.0 equiv) dissolved in THF (2 mL). The reaction was warmed to RT and stirred overnight, quenched with water, diluted with ethyl acetate and transferred to a separatory funnel. The aqueous phase was extracted (3x) and the combined organic phases were washed with brine, dried over MgSO$_4$ and filtered. After rotary evaporation, the crude product was purified by column chromatography on silica gel eluting with 7% ethyl acetate in hexanes to provide compound 2.38 as a colourless oil (200 mg, 50%). IR (cm$^{-1}$, neat): 2915, 2853, 2363, 2336, 1657, 1581, 1474, 1470, 1438, 1275, 1247, 1100, 1057, 1017, 909, 747. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 7.78 (d, $J$ = 5.7 Hz, 1H), 7.29 (t, $J$ = 6.0 Hz, 1H), 6.83 (d, $J$ = 6.2 Hz, 1H), 6.72 (t, $J$ = 5.7 Hz, 1H), 5.45 (s, 1H), 5.32 (s, 1H), 4.99 (s, 1H), 4.91 (s, 1H), 4.62 (s, 2H), 4.12 (s, 2H), 3.93 (s, 2H), 1.75 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 157.1, 142.0, 140.9, 139.4, 129.4, 122.6, 114.9, 112.3, 86.5, 74.2, 70.7, 69.5, 19.5. HRMS (EI): Calc’d for C$_{14}$H$_{17}$O$_2$I, 344.0273; found, 344.0275.

3-(Iodomethyl)-3-(((2-methylallyloxy)methyl)-2,3-dihydrobenzofuran (2.39)

General procedure CARBOHALOGENATION was followed starting from 2.38 (34 mg, 0.1 mmol) stirring for 16 hours. The product was purified by column chromatography on silica gel eluting with 10% ethyl acetate in hexanes to provide 2.39 as a colorless oil (21 mg, 60%). IR (cm$^{-1}$, neat): 2884, 2853, 1594, 1479, 1459, 1225, 1196, 1112, 1096, 988, 903, 751. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 7.27 (d,
J = 6.0 Hz, 1H), 7.18 (t, J = 6.0 Hz, 1H), 7.87 (t, J = 6.0 Hz, 1H), 6.77 (d, J = 6.0 Hz, 1H), 4.93 (s, 1H), 4.88 (s, 1H), 4.40 (d, J = 9.0 Hz, 1H), 4.30 (d, J = 9.0 Hz, 1H), 3.90 (s, 2H), 3.71 (d, J = 9.0 Hz, 1H), 3.64 (d, J = 6.0 Hz, 1H), 1.71 (s, 3H).

13C NMR (CDCl3, 100 MHz): δ = 160.1, 141.9, 129.5, 129.2, 124.7, 120.5, 112.5, 110.1, 79.4, 75.6, 73.8, 50.1, 19.5, 13.9. HRMS (EI): Calc’d for C14H17O2I, 344.0273; found, 344.0273.

2-Bromo-N-(2-methylallyl)-N-(1-phenylvinyl)benzamide (2.44)

To a solution of 2-bromobenzoic acid (200 mg, 1.0 mmol, 1.0 equiv), and oxalyl chloride (190 µL, 2.2 mmol, 2.0 equiv) in dichloromethane (10. mL, 0.10 M) was added a drop of DMF. The reaction was stirred at room temperature until the evolution of gas had stopped (~1 h), and concentrated to dryness to give an acyl chloride intermediate, which was dissolved in dichloromethane (2 mL) and added to a separate solution of the methallyl imine of benzophenone (190 mg, 1.1 mmol, 1.1 equiv) and Et3N (150 µL, 1.1 mmol, 1.1 equiv) in dichloromethane (10 mL). The solution was stirred overnight at RT, quenched with water, extracted with diethyl ether (3x), and concentrated to dryness. The product was purified by column chromatography on silica gel eluting with 50% diethyl ether in pentane to provide 2.44 as a yellow solid (270 mg, 74%). mp = 83–84 °C, IR (cm–1, neat): 3058, 2921, 1656, 1645, 1387, 1303. 1H NMR (CDCl3, 400 MHz): δ = 7.46–7.50 (m, 1H), 7.32–7.38 (m, 5H), 7.03–7.16 (m, 3H), 5.30 (s, 1H), 5.23 (s, 1H), 4.89 (s, 1H), 4.79 (s, 1H), 4.30 (br s, 2H), 1.88 (s, 3H). 13C NMR (CDCl3, 100 MHz): δ = 169.0, 145.7, 140.5, 138.7, 135.9, 132.8, 129.8, 128.8, 128.7, 126.7, 126.6, 126.1, 120.6, 113.9, 113.8, 51.9, 20.6. HRMS (ESI): Calc’d for C19H18BrNO+, 356.0650; found 356.0651.

4-Chloro-2-iodo-1-((2-methylallyl)oxy)benzene (2.45)

General procedure ALKYLATION was followed starting from 4-chloro-2-iodophenol (760 mg, 3 mmol, 1 equiv), methallylchloride (0.35 mL, 3.6 mmol, 1.2 equiv) and potassium carbonate (0.80 g, 6.0 mmol, 2.0 equiv) in DMF (12 mL, 0.25 M). The product was purified by column chromatography on silica gel
eluting with pentane to provide **2.45** as a yellow oil (720 mg, 78%). IR (cm⁻¹, neat) 3079, 2975, 2915, 2859, 1580, 1562, 1450, 1380, 1262, 1245, 1228, 1056, 1037, 905, 801, 709. ¹H NMR (CDCl₃, 400 MHz): δ 7.75 (d, J = 2.5 Hz, 1H), 7.24 (dd, J = 8.8, 2.5 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.17 (s, 1H), 5.02 (s, 1H), 4.45 (s, 2H), 1.86 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 156.0, 139.8, 138.6, 129.1, 126.4, 113.2, 112.7, 86.7, 72.9, 19.4. HRMS (ESI): Calc’d for C₁₀H₁₀ClIO⁺ 307.9465, found 307.9472.

**5-Chloro-3-(iodomethyl)-3-methyl-2,3-dihydrobenzofuran (2.46)**

![Chemical Structure]

General procedure **CARBOHALOGENATION** was followed starting from **2.45** (31 mg, 0.10 mmol). The product was purified by column chromatography on silica gel eluting with pentane to provide **2.46** as a yellow oil (29 mg, 92%). IR (cm⁻¹, neat) 2966, 2883, 1603, 1480, 1456, 1417, 1379, 1267, 1211, 1159, 1089, 983, 875, 813, 684. ¹H NMR (CDCl₃, 400 MHz): δ 7.13 (dd, J = 8.5, 2.3 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.72 (d, J = 8.5 Hz, 1H), 4.50 (d, J = 9.2 Hz, 1H), 4.18 (d, J = 9.2 Hz, 1H), 3.36 (s, 2H), 1.50 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 158.2, 133.6, 129.1, 125.4, 123.0, 111.3, 83.4, 46.1, 25.3, 17.2. HRMS (ESI): Calc’d for C₁₀H₁₁ClIO⁺ 308.9543, found 308.9555.

**5-Chloro-3-methyl-3-((phenylthio)methyl)-2,3-dihydrobenzofuran (2.47)**

![Chemical Structure]

General procedure **NUCLEOPHILIC ADDITION** was followed using NaSPh as the nucleophile generated from 60 % NaH (20. mg, 0.50 mmol, 5.0 equiv) and PhSH (51 mL, 0.50 mmol, 5.0 equiv). The crude product was purified by column chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford compound **2.47** as a colourless oil (26 mg, 90% yield). IR (cm⁻¹, neat): 3059, 2963, 2926, 2884, 1583, 1479, 1455, 1439, 973, 812, 739. ¹H NMR (400 MHz, CDCl₃): δ 7.34–7.11 (m, 5H), 7.13–7.03 (m, 2H), 6.71 (d, J = 8.3 Hz, 1H), 4.58 (d, J = 9.1 Hz, 1H), 4.19 (d, J = 9.1 Hz, 1H), 3.19 (s, 2H), 1.44 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 158.1, 136.6, 135.6, 129.8, 129.0, 128.6, 126.4, 125.3, 123.4, 110.9, 82.2, 47.0, 45.0, 24.5. HRMS (ESI): Calc’d for C₁₆H₁₆ClOS⁺, 291.0610; found 291.0613.
2-(5-Chloro-3-methyl-2,3-dihydrobenzofuran-3-yl)acetonitrile (2.48)

General procedure **NUCLEOPHILIC SUBSTITUTION** was followed using NaCN as the nucleophile (25 mg, 0.50 mmol, 5.0 equiv). The crude product was filtered over a pad of silica using ethyl acetate to give **2.48** as a colourless oil (20. mg, 98% yield). IR (cm⁻¹, neat): 2965, 2929, 2888, 2249, 1480, 1464, 1456, 1089, 979, 815, 683. ¹H NMR (400 MHz, CDCl₃): δ 7.17 (m, 2H), 6.77 (d, J = 8.2 Hz, 1H), 4.46 (d, J = 9.4 Hz, 1H), 4.27 (d, J = 9.4 Hz, 1H), 2.61 (s, 2H), 1.56 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 157.8, 133.5, 129.5, 126.0, 123.1, 116.9, 111.5, 82.1, 44.1, 29.2, 23.6. HRMS (ESI): Calc’d for C₁₁H₁₀ClNO⁻, 207.0451; found, 207.0456.

3-(Azidomethyl)-5-chloro-3-methyl-2,3-dihydrobenzofuran (2.49)

General procedure **NUCLEOPHILIC SUBSTITUTION** was followed using NaN₃ as the nucleophile (33 mg, 0.50 mmol, 5.0 equiv). This reaction afforded compound **2.49** as a pale yellow oil (19 mg, 86% yield) without the need for further purification. IR (cm⁻¹, neat): 2965, 2927, 2888, 2323, 2101, 1480, 1456, 1261, 1089, 978, 811. ¹H NMR (400 MHz, CDCl₃): δ 7.13 (dd, J = 8.4, 2.3 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 4.48 (d, J = 9.1 Hz, 1H), 4.17 (d, J = 9.1 Hz, 1H), 3.46 (d, J = 12.0 Hz, 1H), 3.39 (d, J = 12.1 Hz, 1H), 1.40 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 158.5, 133.7, 129.0, 125.5, 123.5, 111.1, 80.9, 59.3, 46.8, 22.6. HRMS (ESI): Calc’d for C₁₀H₁₄ClN₄O⁺, 241.0856; found, 241.0847.

(5-Chloro-3-methyl-2,3-dihydrobenzofuran-3-yl)methanol (2.50)

In a 2 dram screw cap vial equipped with a magnetic stir bar neopentyl iodide **2.46** (31 mg, 0.10 mmol, 1 equiv), AgNO₃ (20 mg, 0.12 mmol, 1.2 equiv), acetone (2.0 mL) and water (0.50 mL) were combined and purged with argon. The reaction was sealed stirred at room temperature overnight. The reaction was diluted with ethyl acetate (2 mL) and extracted with ethyl acetate (3x). The organic layer was dried over MgSO₄ and concentrated to dryness in vacuo. The crude product was purified by column
chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford compound 2.50 as a colourless oil (9.0 mg, 45% yield). IR (cm$^{-1}$, neat): 3336, 2973, 2929, 2881, 1486, 1249, 1180, 1121, 1037, 815 $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.08 (dd, J = 8.6, 2.5 Hz, 1H), 7.04–6.99 (m, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.94 (dd, J = 11.0, 2.3 Hz, 1H), 3.82 (d, J = 11.0 Hz, 1H), 2.86 (d, J = 16.7 Hz, 1H), 2.75 (d, J = 16.7 Hz, 1H), 2.07 (s, 1H), 1.36 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 152.0, 130.1, 127.9, 126.1, 122.0, 118.2, 74.0, 65.9, 39.3, 25.0. HRMS (ESI): Calcd for C$_{10}$H$_{15}$ClNO$_2^-$, 216.0791; found 216.0785.
5.3 $^1$H and $^{13}$C NMR Spectra

$^1$H-NMR

$^{13}$C-NMR
\[ ^{1}\text{H-NMR} \]

\[ ^{13}\text{C-NMR} \]
$^1$H-NMR

$^{13}$C-NMR
$^{1}H$-NMR

$^{13}C$-NMR
**1H-NMR**

![1H-NMR Spectrum](image)

**13C-NMR**

![13C-NMR Spectrum](image)
$^{1}H$-NMR

$^{13}C$-NMR
$^1$H-NMR

$^{13}$C-NMR
$^1$H-NMR

$^{13}$C-NMR
$^{1}H$-NMR

$^{13}$C-NMR
$^1$H-NMR

$^{13}$C-NMR
$^1$H-NMR

$^{13}$C-NMR
\[ ^1H\text{-NMR} \]

\[ ^{13}C\text{-NMR} \]
\textbf{\(^1\)H-NMR}

\textbf{\(^{13}\)C-NMR}
$^{1}H$-NMR

$^{13}C$-NMR
$^{1}$H-NMR

$^{13}$C-NMR
\(^1\text{H-NMR}\)

\(^{13}\text{C-NMR}\)
$^{1}H$-NMR

$^{13}C$-NMR
$^{1}$H-NMR

$^{13}$C-NMR
$^{1}H$-NMR

![H-NMR spectrum]

$^{13}C$-NMR

![C-NMR spectrum]
$\text{H-NMR}$

$\text{C-NMR}$
1H-NMR

13C-NMR
$^1$H-NMR

$^{13}$C-NMR
$^1$H-NMR

$^{13}$C-NMR
$^1$H-NMR

$^{13}$C-NMR
$^{1}H$-NMR

$^{13}C$-NMR
$^1$H-NMR

$^{13}$C-NMR
$^1$H-NMR

$^{13}$C-NMR
References


8 Corriu, R. J. P.; Masse, J. P. *Chem. Commun.* 1972, 144.


51 www.sigmaaldrich.com

52 Unpublished results, Stephen G. Newman and Dr. Norman Nicolaus, University of Toronto


