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# Catalytic Activation of Nitriles Towards Nucleophilic Addition

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Thesis submitted to the University of Nottingham for the degree Doctor of Philosophy by:


Roy P. Lester

School of Chemistry, University of Nottingham

Supervisor - Dr Jason E. Camp

# Declaration

The material contained within this thesis has not previously been submitted for a degree at the University of Nottingham or any other University. The research reported within this thesis has been conducted by the author unless otherwise indicated.

Roy P. Lester

# Abstract

The work presented in this thesis is focused on the development of a multifaceted approach to the catalytic activation of nitriles. To develop a versatile method for catalytic nitrile activation two probes were utilised; i) the development of a direct synthesis of allylic amides from the corresponding allylic alcohol and nitrile using a commercial platinum salt, together with a detailed mechanistic investigation into the process, ii) the direct synthesis of 2-bezoxazole from the corresponding 2-aminophenol and nitrile with the aid of a commercial platinum salt as well as the use of alcoholic solvents. In addition to nitrile activation a preliminary study on the application and further functionisation of 2-trichlorobenzoxazoles was undertaken.

i) A novel multifaceted approach to the direct synthesis of allylic amides via the catalytic activation of di- and trichloroacetonitrile will be discussed. This one-pot methodology relies on the same platinum catalyst to activate a nitrile towards nucleophilic attack of allylic alcohol as well as activate the newly formed allylic imidate towards a [3,3]-sigmatropic rearrangement, which produced a number of allylic amides. In addition to the development of the one-pot allylic amide methodology a number of mechanistic studies including $^{1}H$, $^{13}C\{^{1}H\}$ and gas chromatography were under taken to better understand the process.

ii) The second probe used to identify the versatility of this multifaceted catalyst approach to nitrile activation was the direct synthesis of 2-benzoxazoles. Within this study it was discovered that protic solvents were able to activate di- and trichloroacetonitrile efficiently towards

nucleophilic attack of the nitrogen nucleophile. From this discovery a mild and effective synthesis of a variety of di- and trichlorobenzoxazoles was developed in which the solvent was acting as the activating agent towards nucleophilic attack.

iii) Preliminary results will also be reported on the novel manipulation of the trichloromethyl moiety of benzoxazoles. Within this study two efficient methodologies for the selective synthesis of 2-(pyrrolidin-1-yl)benzo[*d*]oxazole and benzo[*d*]oxazol-2-yl(pyrrolidin-1-yl)methanone were developed from a single starting material. These results show a positive direction for the study into diversity oriented synthesis to form a number of different small molecules from a single starting material by altering the conditions of the reaction.

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# Abbreviations

| | |
|---|---|
| **$1^{\circ}$** | primary |
| **$2^{\circ}$** | secondary |
| **Ac** | acetyl |
| **$add^{N}$** | nucleophilic addition |
| **aq** | aqueous |
| **Ar** | aromatic ring |
| **BINAP** | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| **Boc** | *tert*-butyloxycarbonyl |
| **Cat.** | catalytic/catalyst |
| **δ** | chemical shift in parts per million |
| **DABCO** | 1,4-diaxabicyclo[2.2.2]octane |
| **DBU** | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| **DIBAL-H** | diisobutylaluminium hydride |
| **DMAP** | 4-dimethylaminopyridine |
| **DMF** | *N*, *N*-dimethylformamide |
| **DMSO** | dimethyl sulfoxide |
| **dppe** | 1,2-bis(diphenylphosphino)ethane |
| **$E^{+}$/E** | electrophile |
| **equiv.** | equivalents |
| **$Et_2O$** | diethylether |
| **EtOH** | ethanol |
| **eV** | electron volts |
| **EWG** | electron withdrawing group |
| **GC** | gas chromatography |
| **h** | hours |
| **HOMO** | highest occupied molecular orbital |

| | |
|---|---|
| **HPLC** | high performance liquid chromatography |
| **HRMS** | high resolution mass spectrometry |
| **HWE** | horner-Wadsworth Emmons |
| **Hz** | hertz |
| **IR** | infrared spectrometry |
| ***J*** | NMR coupling constant |
| **$L/L_n$** | ligand/ligands |
| **LA** | lewis acid |
| **lit.** | literature |
| **LUMO** | lowest unoccupied molecular orbital |
| **M** | molar |
| **[M]/M** | metal complex |
| ***m*** | meta |
| **MeOH** | methanol |
| **MeCN** | acetonitrile |
| **MFC** | multifaceted catalysis |
| **min** | minutes |
| **MHz** | megahertz |
| **mol** | mole(s) |
| **m.p.** | melting point |
| **MS** | mass spectrometry |
| **MOM** | methyloxymethyl ether |
| **MW** | microwave |
| **m/z** | mass over charge ratio |
| **$NEt_3$** | triethyl amine |
| **NMR** | nuclear magnetic resonance |
| **$Nu/Nu^-$** | nucleophile |

| | |
|---|---|
| ***o*** | ortho |
| **OLED** | organic light emitting diode |
| **$^{-}$OH** | hydroxide ion |
| ***p*** | para |
| **PBO** | polybenzoxazole |
| **ppm** | parts per million |
| **$PPh_3$** | triphenylphosphine |
| **Pr/$^{i}$Pr/$^{n}$Pr** | propyl/*iso*-propyl/*normal*-propyl |
| **PT** | proton transfer |
| **R** | general group |
| **RCM** | ring closing metathesis |
| **r.t.** | room temperature |
| **SM** | starting material |
| **$S_N$** | nucleophilic substitution |
| **$S_NAr$** | nucleophilic aromatic substitution |
| **Tf** | trifluoromethanesulfonate |
| **THF** | tetrahydrofuran |
| **THP** | tetrahydropyran |
| **TLC** | thin layer chromatography |
| **TMS** | trimethyl silyl |
| **UV** | ultraviolet light |

# Chapter 1: Introduction

## 1a) Nitriles in synthesis

Nitriles are invaluable in the synthesis of acyclic, cyclic and heterocyclic compounds due to their electrophilic carbon centre. One of the most common ways that nitriles **1** are utilised is via nucleophilic addition. A number of useful synthetic transformations take advantage of the electrophilic nature of nitriles **1** including: i) reduction to the corresponding 1º/2º amine **2** and **3**,[1, 2] or aldehyde **4** via the Stephen aldehyde synthesis,[3] ii) Reformatsky type reaction where nitrile **1** is coupled to give ketone **5**,[4] iii) the syntheses of heterocycles **6**,[5] iv) alkylation to the corresponding ketone **7**,[6, 7] v) nitrile hydrolysis in which either a carboxylic acid **8** or amide **9** is formed [8, 9] and vi) activated nitriles can also be transformed to the corresponding allylic imidate **10** followed by a rearrangement to form allylic amides **11 (**Figure 1.1). [10]

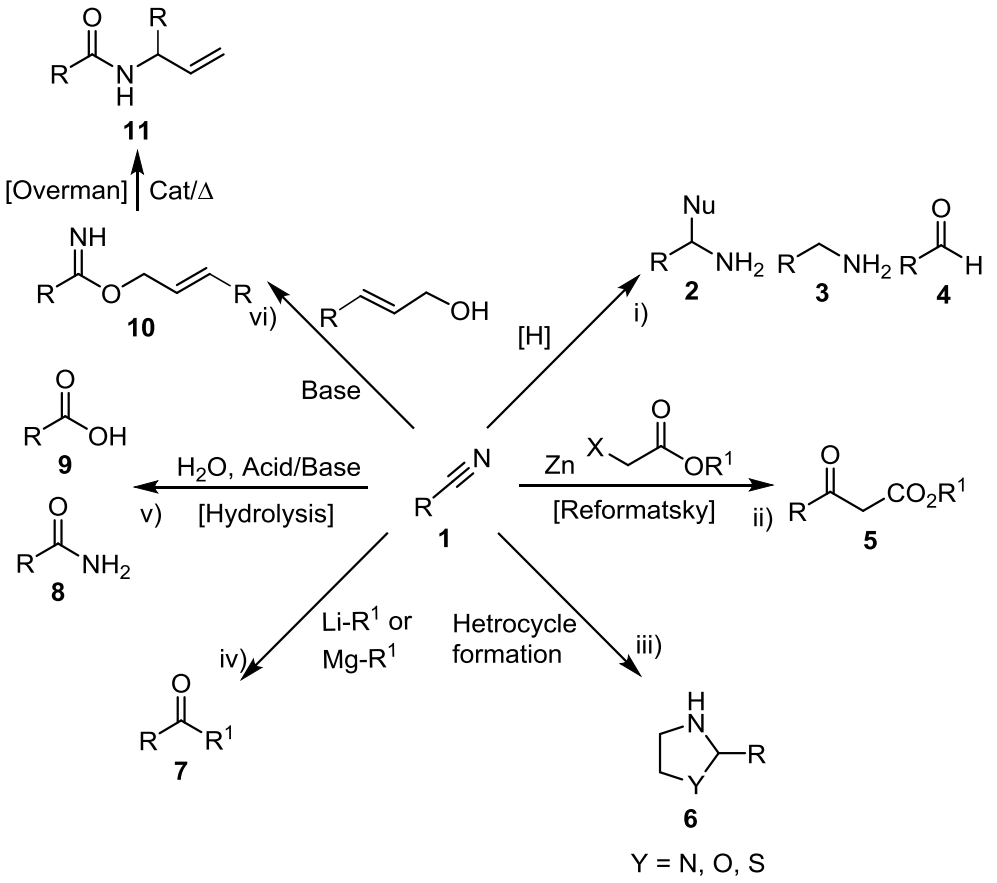
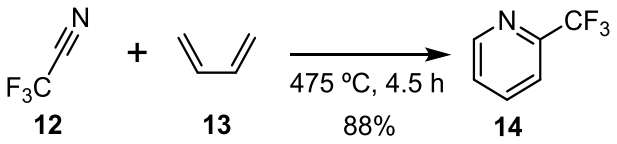



*Figure 1.1: Addition of nucleophiles into nitriles.*

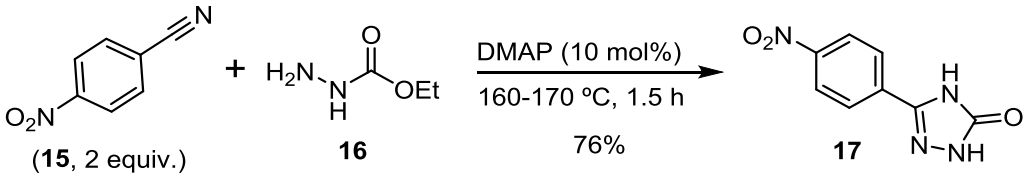
Many of the above processes require forcing conditions, including: strong bases, high temperatures and stoichiometric reagents. Most of the reactions shown above would therefore benefit from the addition of a catalytic activating agent. The activating agent could work by withdrawing electrons from the central carbon either inductively or by resonance, resulting in a facile addition of a nucleophile. Mild catalytic methods for the activation of nitriles are highly desirable in both industry and academia.[11] There are two main methods for activating nitriles towards the addition of a nucleophile. The first is by the inclusion of an electron withdrawing group (EWG) within the nitrile. A trihalogenated methyl group is commonly used as an EWG. For example, reaction of trifluoroacetonitrile (**12)** with 1,3-butdiene **(13)** proceeded via a

hetero Diels-Alder reaction to form trifluoropyridine **14** in 88% yield (Scheme 1.1).[12]




*Scheme 1.1: Hetero Diels-Alder.*

Alternatively, a conjugated EWG can be used. Behmadi et al. demonstrated that 1H-1,2,4-triazol-5(4H)-one **17** was formed in a high yield in one step by having a nitro moiety in conjugation with the nitrile. Reaction of 4-nitrobenzonitrile **(15)** with ethylhydrazine carboxylate **(16)** in the presence of DMAP (a nucleophilic catalyst) formed triazolone **17** (Scheme 1.2).[13]




*Scheme 1.2: Synthesis of 1H-1,2,4-triazole-5(4H)-one.*

A second method of nitrile activation is by the use of a Brønsted or Lewis acid. Brønsted acids can activate the carbon of nitriles towards nucleophilic addition by bonding to the lone pair of the nitrogen. The lone pair of the nitrogen attacks a Brønsted acid, to form nitrilium **18**. The newly formed nitrogen-proton bond results in a positive charge on the nitrogen atom, which causes the electron density to be withdrawn from the nitrile-carbon triple bond. The

overall effect makes the carbon of the nitrile more susceptible to nucleophilic attack **19**, resulting in the addition product **20 (**Figure 1.2).

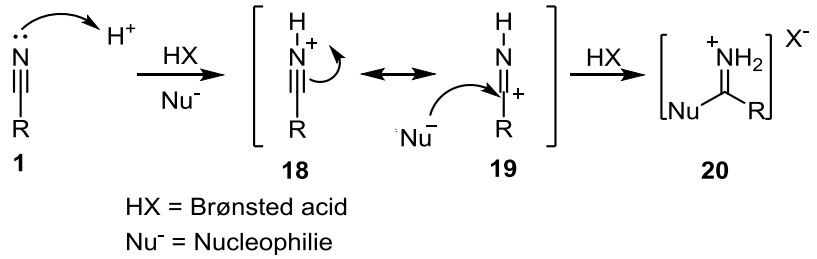
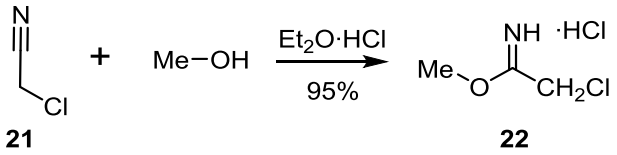



*Figure 1.2: Acid activation of nitriles towards nucleophilic attack.*

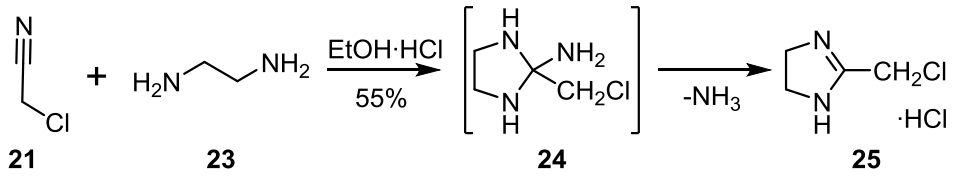
A common reaction that utilises this activation mode is known as the Pinner reaction. The Pinner reaction uses a Brønsted acid to activate a nitrile towards the nucleophilic addition of an alcohol. An example of this is the reaction of methanol with nitrile **21**, which was activated by the Brønsted acid hydrochloric acid to form imidate salt **22** in a good yield (Scheme 1.3).[14]




*Scheme 1.3: Pinner reaction of chloroacetonitrile.*

Zhao et al. showed that chloroacetonitrile **(21)** in the presence of hydrochloric acid underwent nucleophilic addition with 1,2-diaminoethane **(22)**, to form dihydroimidazole **25** via tetrahedral intermediate **24**. This reaction starts by a nucleophilic addition of an amino moiety from 1,2-diaminoethane **(22)**, followed by the addition of the second amino moiety to form the 2-

(chloromethyl)imidazolidin-2-amine intermediate **(24)**. Elimination of ammonia gave 2-(chloromethyl)-4,5-dihydro-1H-imidazole hydrochloric salt **(25)** in a moderate yield (Scheme 1.4).[15]




*Scheme 1.4: Synthesis of 2-(chloromethyl)-4,5-dihydro-1H-imidazole hydrochloric salt.*

The main advantage to using Brønsted acids is that they are generally inexpensive. There are three major disadvantages of using a Brønsted acid as an activator of nitriles towards nucleophilic addition. The first is that the acid is commonly used in stoichiometric quantities. The second is that the product formed after the reaction is the acid salt, which in many cases needs to be neutralised prior to isolation (*cf.* Schemes 1.3 and 1.4). The third is that by using a Brønsted acid the reactions that can be used are limited due to the harsh conditions causing undesirable side reactions that Brønsted acids can promote. For example, the undesirable deprotection of a silyl ether protecting group or with acetals or ketals present in the molecule.[16, 17]

In addition to Brønsted acids, Lewis acids have been shown to be very effective at the activation of nitriles. Similar to Brønsted acids, Lewis acids activate the nitrile by forming a bond between the metal centre of the Lewis acid and the nitrogen of the nitrile creating a partial positive charge, complex **26.** The activated carbon of the nitrile in the complex can undergo nucleophilic attack forming the addition product that is bound to the Lewis acid **27**. Many

transition metals can activate nitriles towards the attack of a nucleophile. Using a Lewis acid allows for an increase in functional group tolerance. To date, the majority of research in the area of metal activation of nitriles was aimed at the formation of metal addition adduct **27**, followed by the liberation of metal species **29** by displacement with a better ligand (L) such as triphenylphosphine ($PPh_3$), pyridine, or 1,2-bis-(diphenylphosphino)ethane (dppe) to produce the free addition adduct **28** (Figure 1.3).[18]

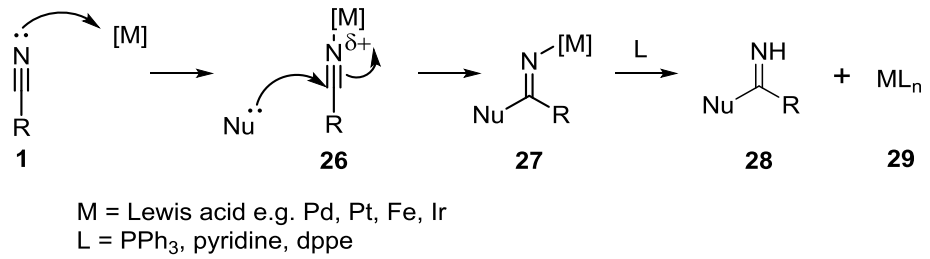



*Figure 1.3: Nitrile activation via Lewis acid catalysis.*

In a nucleophilic addition reaction to nitriles, the nucleophile adds into the lowest unoccupied molecular orbital (LUMO) of the nitrile triple bond. Therefore the LUMO controls the reactivity of the nitrile. The reason for the activation of nitriles towards nucleophilic addition upon coordination to a metal centre is that the metal lowers the energy of the LUMO of the nitrile triple bond, hence decreasing the gap between the highest occupied molecular orbital (HOMO) of the nucleophile and the LUMO of the nitrile, which facilitates the nucleophilic addition (Figure 1.4).[19]

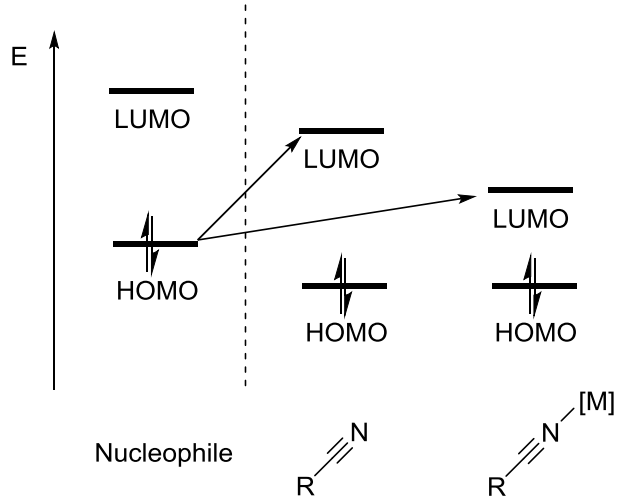
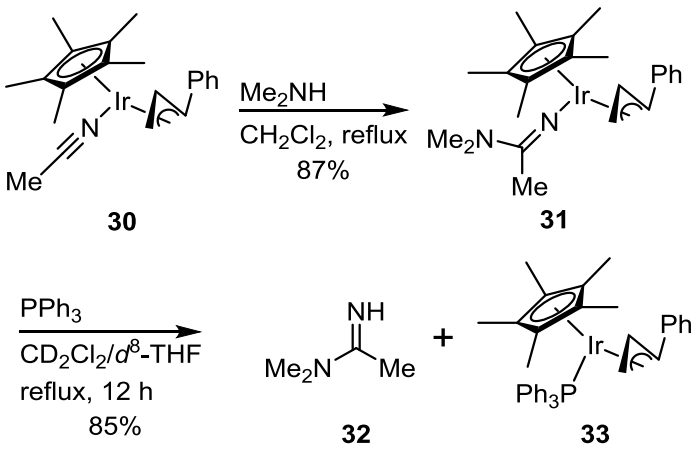


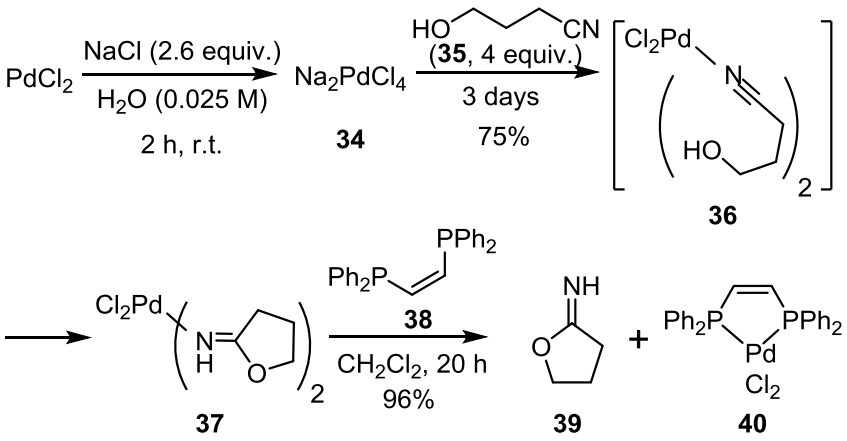

*Figure 1.4: Orbital energy profile diagram showing the LUMO lowering effect of a Lewis acid.*

Lewis acids are preferable compared to Brønsted acids due to the milder reaction conditions that can be employed. One of the limitations to using a Lewis acid for nitrile activation is that typically a nitrile-metal complex needs to be performed prior to addition of the nucleophile. Therefore stoichiometric quantities of Lewis acid are necessary to activate the nitrile. Park et al. demonstrated that a preformed alkyl nitrile iridium complex **30**, can be activated for addition of dimethyl amine to form iridium(III) bound amidine **31.** The Lewis acid then underwent ligand exchange with triphenylphosphine to give free amidine **32** and iridium(III) complex **33** in good overall yield (Scheme 1.5).[20]



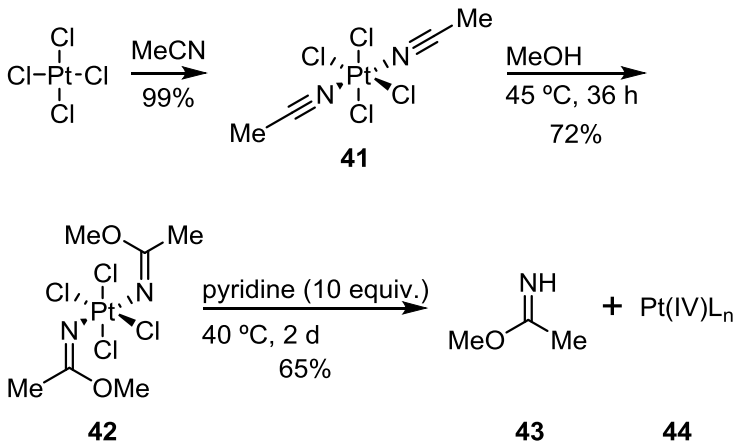

*Scheme 1.5: Iridium activation of acetonitrile towards nucleophilic addition.*

In another example, Michelin et al. showed that palladium(II) chloride was also a good metal for nitrile activation. However, sodium palladium tetrachloride **(34)** was required to be pre-formed before the addition of the nitrile by stirring palladium(II) chloride with sodium chloride in water at ambient temperature for 2 hours. Palladium salt **34** then underwent nucleophilic attack from nitrile **35** to form palladium nitrile complex **36**. Nitrile complex **36** then underwent intramolecular nucleophilic attack from the pendent alcohol moiety to produce palladium bonded imidate complex **37**. Imidate complex **37** was liberated with bisphosphine ligand **38** to form free cyclic imidate **39** in 96% yield and palladium complex **40** (Scheme 1.6).[21]




*Scheme 1.6: Synthesis of cyclic imidate via palladium(II) activation.*

Pombeiro et al. used platinum as a Lewis acid to activate acetonitrile towards nucleophilic addition. The reaction of preformed bisacetonitrile platinum tetrachloride **(41)** and methanol at 45 ºC gave platinum imidate **42** in a moderate yield. An excess of pyridine was used to facilitate ligand exchange with platinum species **42** and allowed for the isolation of free imidate **43** (Scheme 1.7).[18]




*Scheme 1.7: Nucleophilic addition into a Pt(IV)nitrile complex.*

Palladium(II) and platinum(II/IV) salts have been identified as excellent activators of nitriles due to the good overlap of their d-orbitals with the lone

pair on the nitrogen. [18, 22-24] Figures 1.5 and 1.6 show the HOMO and LUMO orbitals, which are involved when platinum(II/IV) chloride salts are bound in the bisnitrile complexes **45** and **41**. An in-depth theoretical study by Kuznetsov et al. showed that platinum(II/IV) chlorides significantly reduced the energy of the LUMO of the nitrile. The difference in energy between the HOMO of the nucleophile and the LUMO of the nitrile was calculated to be reduce by between 1.95 – 2.13 eV and the change of overall charge of the carbon in the nitrile from 0.29 e in the free nitrile to between 0.47 – 0.53 e in the complexes.[18, 22-24] The change in the energy difference and the overall charge on the carbon centre can increase the reaction rate of nucleophilic attack by a factor of 8.3 x $10^5$ – 2.4 x $10^{14}$ (Figure 1.7). [18, 22-24]

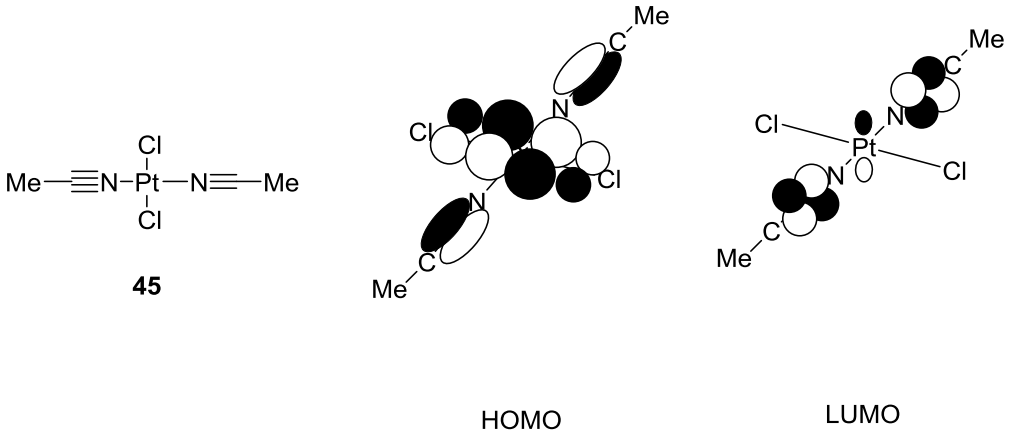



*Figure 1.5: Frontier molecular orbitals of platinum(II) nitrile complexes.*

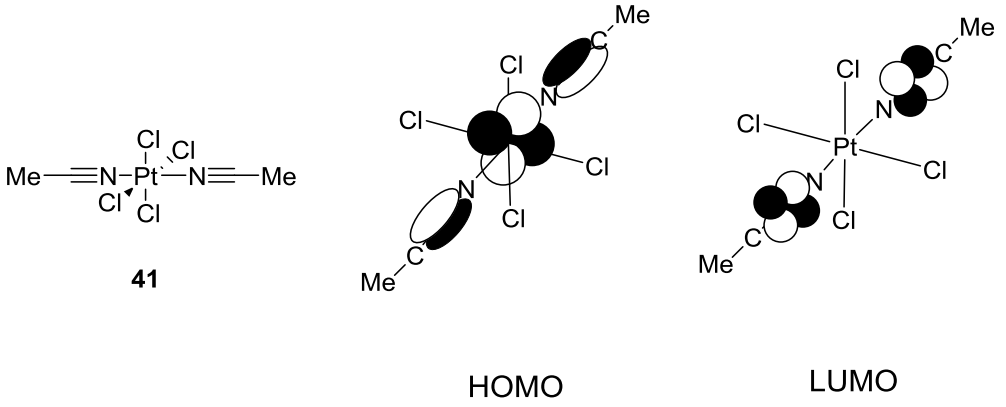



*Figure 1.6: Frontier molecular orbitals of platinum(IV) nitrile complexes.*

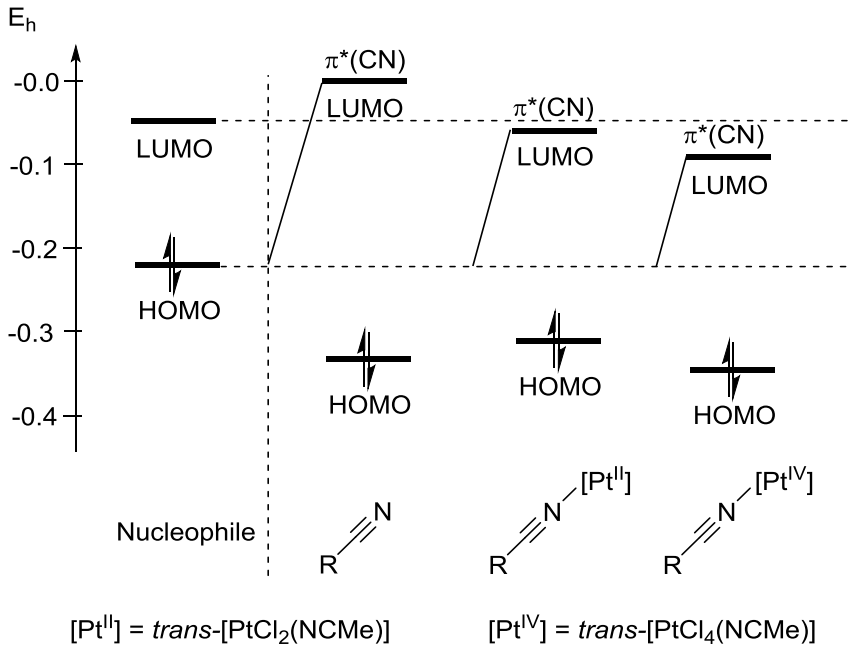
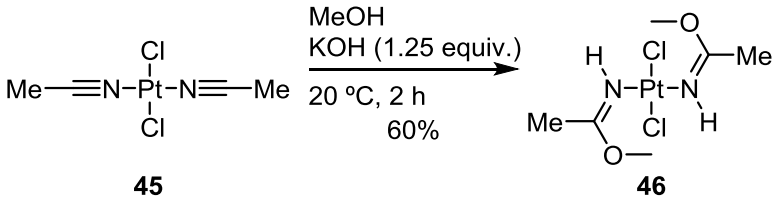



*Figure 1.7: Frontier molecular orbital energy diagram.*

Kuznetsov's theoretical research is supported by the direct comparison of oxidation states of platinum in the synthesis of platinum imidates. A comparison of the work by Pombeiro et al.[18] (*cf.* Scheme 1.7**)** and the research by Natile et al.[25] demonstrated the effects on the electrophilic nature of the nitrile bound to the platinum species (Scheme 1.8). Pombeiro et al. showed that the nucleophilic addition of methanol into the preformed platinum nitrile complex **41** occurred readily at 45 ºC. However, the investigation by Natile et al. showed that the nucleophilic addition reaction with *trans*-platinum(II) bisacetonitrile dichloride **(45)** and methanol to form *trans*-platinum *Z*-bis imino ester complex **46** required an excess of potassium hydroxide, which formed the more nucleophilic alkoxy species. Hence a decrease in activity at the nitrile centre with platinum(II) complex **45** compared to platinum(IV) complex **41** towards nucleophilic addition was observed. This reactivity trend can be explained by the fact that the metal centre of

platinum(IV) chloride is more electron poor due to the oxidation state of the platinum as a result of the increase in electron withdrawing effects of the extra two chlorine atoms




*Scheme 1.8: Nucleophilic addition into a Pt(II) nitrile complex.*

### 1b) Catalytic nitrile activation

As discussed above the addition adduct of a platinum complex, such as **46** is generally a stronger ligand than the nitrile starting material. Therefore the nitrile cannot displace the addition adduct from the metal to allow for a catalytic process (Figure 1.8).

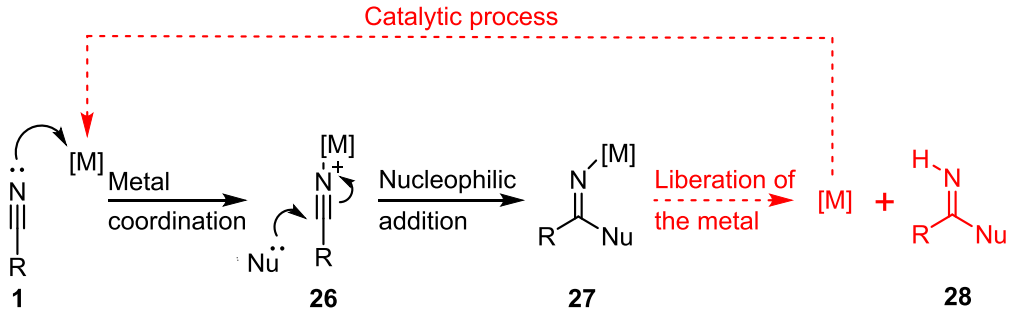
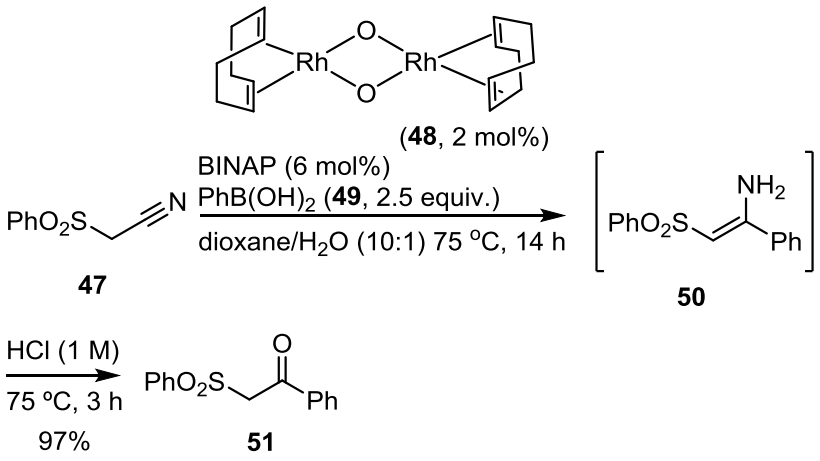



*Figure 1.8: Frontier molecular orbital energy diagram.*

One way to overcome the use of stoichiometric amounts of Lewis acid is the incorporation of an additional mechanistically distinct step to liberate the newly formed addition product. Lautens et al. used an oxo-bridged rhodium(I) dimer **48** to catalytically activate nitrile **47** for nucleophilic attack of

arylboronic acid **49** to form ketone **51** via vinyl amine intermediate **50** (Scheme 1.9).[26]




*Scheme 1.9: Rhodium-catalysed activation of nitriles.*

Lautens proposed that active rhodium complex **52** was formed from the reaction of boronic acid **49** and oxo-bridged rhodium catalyst **48**. Active rhodium complex **52** underwent nucleophilic attack from the lone pair of the nitrogen in nitrile **47**. The close proximity of the activated phenyl group allows for nucleophilic attack on the activated nitrile species **53** and **54** to give imine **55.** Imine **55** then underwent tautomerisation to give cyclic enamine **56.** Cyclic enamine complex **56** underwent ligand substitution with water to complete the catalytic cycle and produce free enamine **50** and rhodium complex **57**. Rhodium complex **57** can then be transformed to the active rhodium complex **52** by a reaction with boronic acid **49.** Hydrolysis of imine **50** with hydrochloric acid afforded alpha-sulfonic ketone **51**. The metal can be used catalytically because enamine **50** is a poor ligand, which can be easily displaced with water to allow for catalyst turn-over (Figure 1.9).[26]

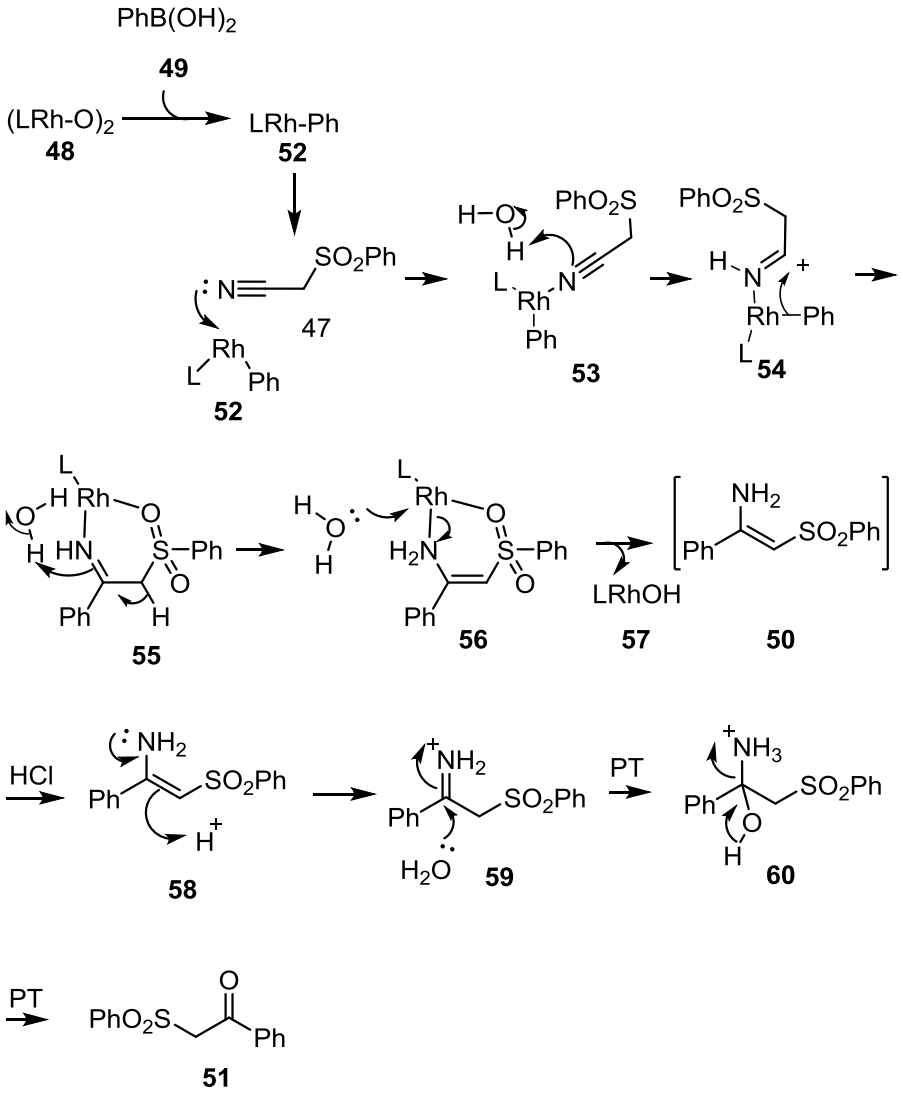
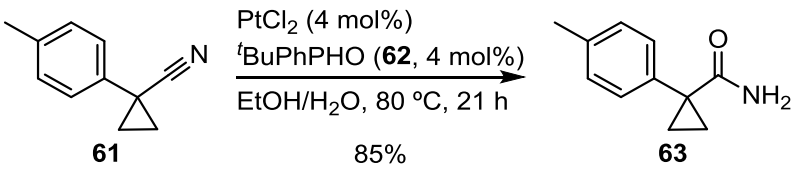



*Figure 1.9: Proposed mechanism of alpha-sulfonic ketone synthesis.*

Work by de Vries et al. also incorporated an additional hydrolysis step to liberate the metal from the addition adduct. In this redox neutral process, platinum(II) chloride and an equal amount of secondary phosphine oxide ligand **62** were used for the hydration of hindered nitrile **61** to form amide **63** in a good yield (Scheme 1.10).[27]




*Scheme 1.10: Hydrolysis of hindered nitriles.*

Parkins, who also did a large amount research on nitrile hydrolysis proposed that hydrolysis of hindered nitriles was achieved by activation of nitrile **61** by platinum species **64** followed by protonation of nitrile **65** to form charged imine **66**. The metal activates imine **66** towards the addition of the hydroxyl attached to one of the phosphorus ligands **62** to produce imidate **67**. Activated imidate **67** undergoes nucleophilic attack from water producing tetrahedral intermediate **68**. After a proton transfer**,** the secondary phosphine oxide ligand was reformed and amide **69** was produced. Amide **69** is a poorer ligand for the platinum metal centre compared to the starting nitrile, hence the catalyst is liberated by nitrile stating material **61** and is available to re-enter the catalytic cycle (Figure 1.10).[28] Thus one way to perform a catalytic process to activate nitriles is to incorporate a second mechanistic step to transform the addition product into a poorer ligand. Designing a process in which the final product is a poorer ligand than the original nitrile, allows the metal to undergo ligand substitution to liberate the product and turn-over the catalyst.

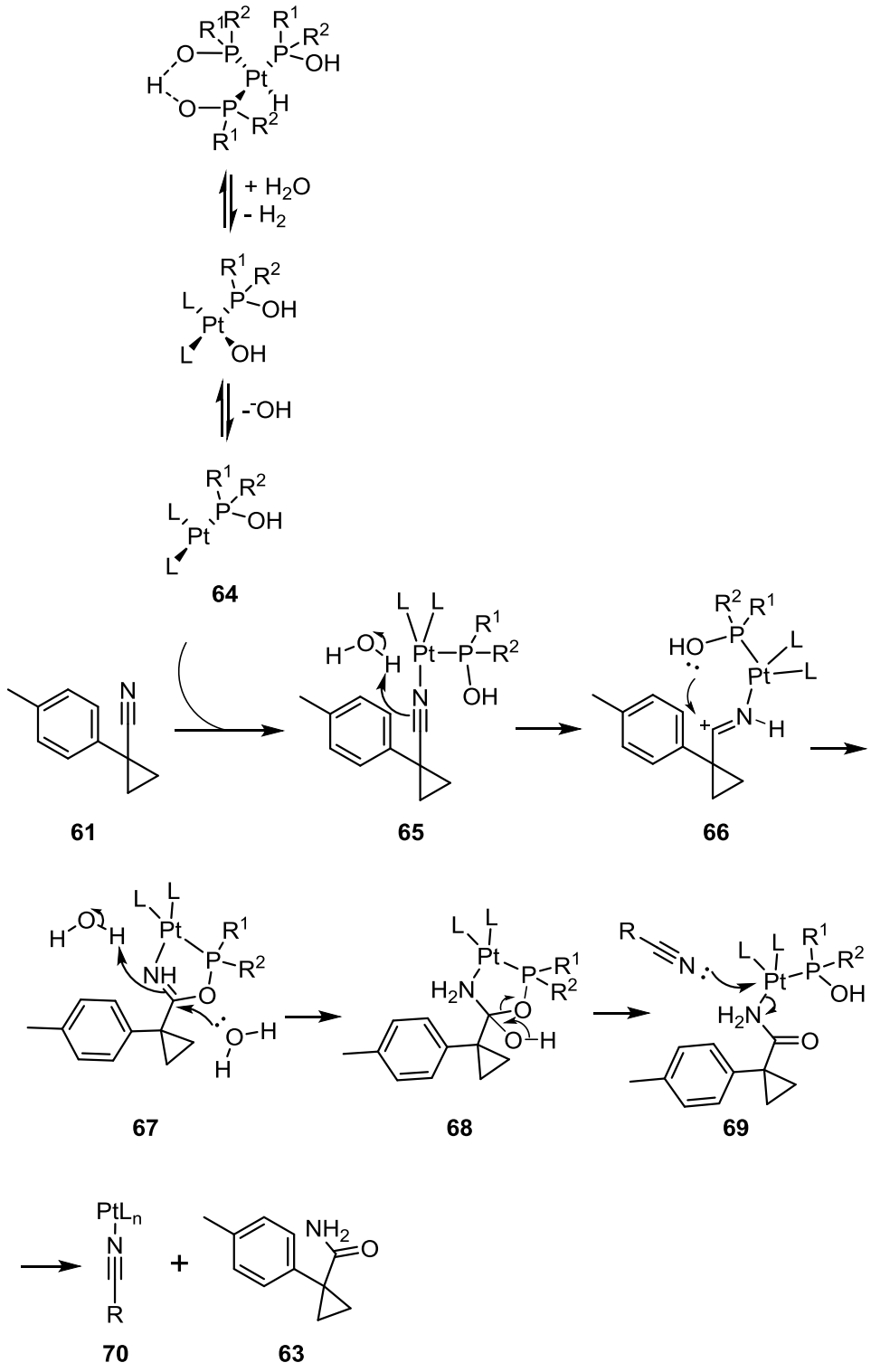
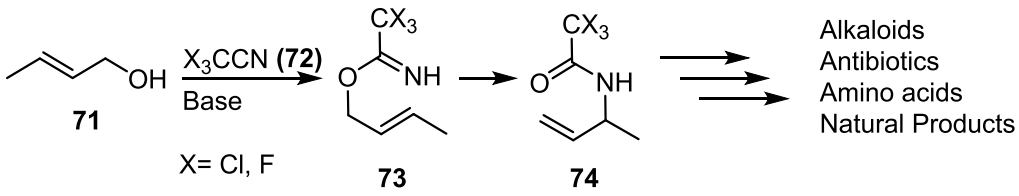



*Figure 1.10: Proposed mechanism for the hydrolysis of hindered nitriles.*

### 1c) Allylic amide uses and synthesis

An important synthetic sequence that results in nitrile activation towards nucleophilic addition followed by a second mechanistic step is the synthesis of allylic amide **74** from representative allylic alcohol **71** and nitrile via allylic imidate **73**. Allylic amides **74** are important synthetic intermediates that have been used in a number of applications including the formation of alkaloids,[29] antibiotics,[30] unnatural amino acids[31] and complex natural products (Scheme 1.11).[32]




*Scheme 1.11: Applications of allylic amides in synthesis.*

A common method to synthesise allylic amides **74** is to initially form allylic imidate **73** from nitrile **72** and allylic alcohol **71**. Allylic imidate **73** then can undergo a [3,3] sigmatropic aza-Claisen rearrangement, which is commonly known as the Overman rearrangement to form allylic amide **74**.[33] The [3,3]-sigmatropic rearrangement of allylic imidate **73** to the corresponding allylic amide **74** can be achieved both thermally or at room temperature with the aid of a soft Lewis acid catalyst.[34] Overman suggested that when the transformation is performed thermally the rearrangement is concerted and goes via a chair transition state **75**.[33] When a Lewis acid catalyst is used, the rearrangement is no longer concerted and proceeds by a cyclisation induced

rearrangement **76**.[35] Within the metal meditated reaction, the metal binds to the olefin to reduce the electron density in the π-bond, which lowers the energy of the LUMO of the electrophilic olefin. Coordination of the metal allows for the nucleophilic nitrogen to attack the carbon at the C-3 position to form cyclic intermediate **75**. The metal is then eliminated to neutralise the intermediate and complete the rearrangement. The metal additive lowers the activation energy which increases the rate of the reaction and allows the transformation to occur at lower temperatures (Figure 1.11).[35]

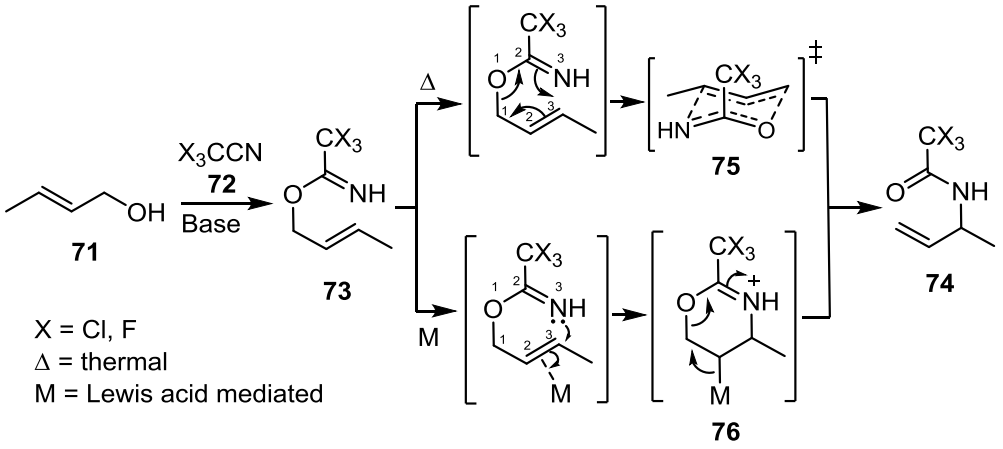
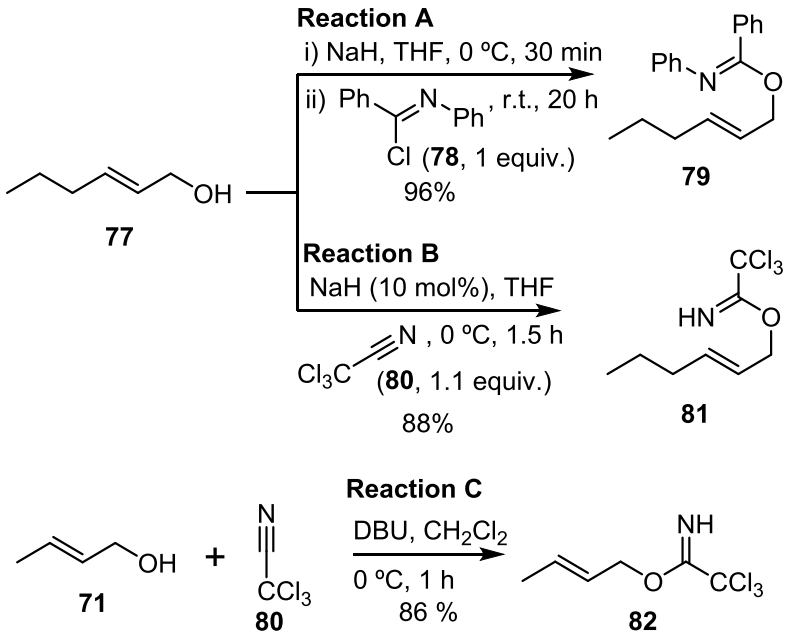



*Figure 1.11: Overman rearrangement under thermal and catalytic conditions.*

The precursor to the Overman rearrangement is an allylic imidate, such as imidate **79**, **81** and **82**. These complexes are generally formed under strong basic conditions with either imidoyl chloride **78** or trichloroacetonitrile **(80)** as the electrophile. The choice of coupling partner depends on the group located alpha to the imine moiety. If the group is not strongly electron withdrawing, either alkyl or an aromatic group, then imidoyl chloride **78** is required for the coupling.[36] If the group alpha to the imine function is strongly electron

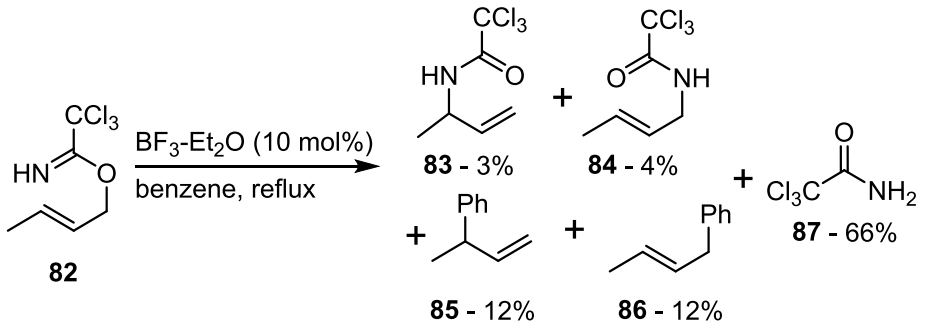
withdrawing, such as a trihalogenated methyl group, then imidate **81** can be formed by reacting allylic alcohol **77** with trichloroacetonitrile **(80)** under catalytic base conditions.[37] Traditionally a catalytic amount of strong base, either sodium/potassium hydride is used, however it has been shown that the weaker base DBU**,** which has a $pK_b$ of approximately 12 can also be used to form trichloro allylic imidate **82**. These reactions go efficiently and are usually completed in one hour at 0 ºC to produce the desired allylic imidate **82** (Scheme 1.12).




*Scheme 1.12: Methods for the synthesis of allylic imidates.*

The metal mediated [3,3] sigmatropic rearrangement of allylic imidates require a soft Lewis acid because when a Brønsted acid or a hard Lewis acid is used a combination of products are produced in addition to a small amount of the rearranged product.[38] For example, Cramer et al. showed that the rearrangement of allylic imidate **82** in the presence of a catalytic amount of

hard Lewis acid $BF_3$-$Et_2O$ gave 3% yield of the desired rearranged product **83** along with allylic amide **84,** Friedel-Crafts products **85**, **86** and trichloroacetamide **(87**, Scheme 1.13).[39]




*Scheme 1.13: Reaction of imidates with a hard Lewis acid.*

Cramer suggests that the way in which allylic amides **83** or **84** and Friedel-Crafts products **85** or **86** are formed was via an ionic process through ion pair intermediate **88**. The hard acid binds to the lone pair on the nitrogen in the imidate, which stabilises the anion and allows the ion to persist (Figure 1.12). This large product distribution illustrates why hard Lewis acids are undesirable for the transformation of an allylic imidate to the corresponding allylic amide.

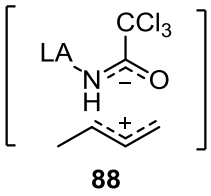
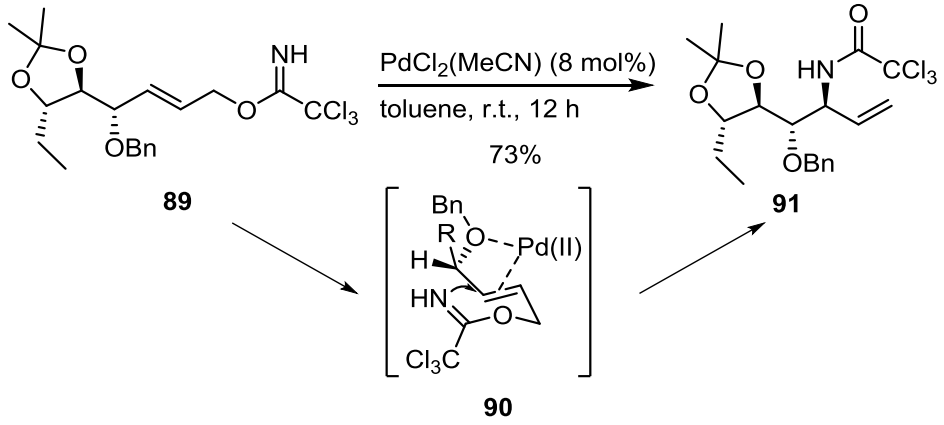



*Figure 1.12: Proposed ionic intermediate.*

Many studies have focused on identifying metal complexes that catalyse the Overman rearrangement. The majority of these reports have investigated palladium ($PdCl_2$/$PdCl_2(MeCN)_2$) or mercury ($Hg(O_2CCF_3)_2$/$Hg(OAc)_2$)

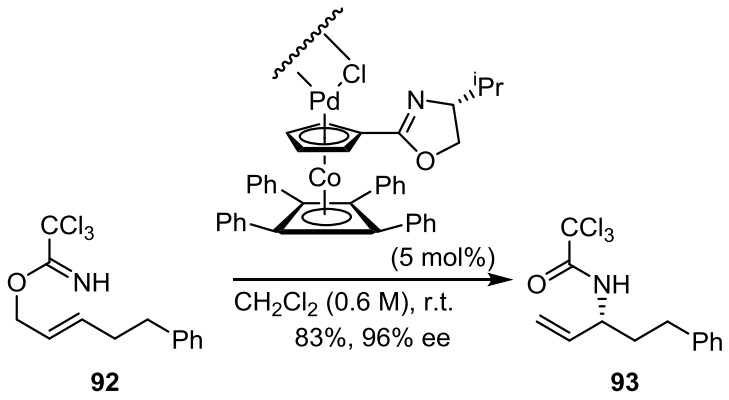
catalysts. Van Boom et al. showed that when palladium bisacetonitrile dichloride was used in the diastereoselective rearrangement of trichloroacetimidate **89** under ambient conditions that the corresponding allylic amide **91** was formed in 73% yield.[40] The diastereoselectivity was a result of both the steric bulk of the benzyl ether and the directing effects of the oxygen of the benzyl ether, which forced the attack of the nitrogen to one face of the alkene and formed the desired conformation via cyclic intermediate **90** (Scheme 1.14).[41]




*Scheme 1.14: Metal-catalysed Overman rearrangement.*

An enantioselective variant of the Overman rearrangement was investigated by Stevens and Richards, who used a COP-Cl catalyst to produce a high yield and high enantioselectivity of enantioenriched allylic amide **93** by reacting imidate **92** with a catalytic amount of COP-Cl in dichloromethane at ambient temperature.[33, 42, 43] The enantioselectivity was a direct result of the bulky isopropyl group on the oxazole ring. The metal centre is bound to the cyclopentadiene ring and the nitrogen on the oxazole. Once there is an interaction with the imidate the metal binds to the olefin and the nitrogen of the imidate. The isopropyl group on the oxazole moiety blocked one side of the

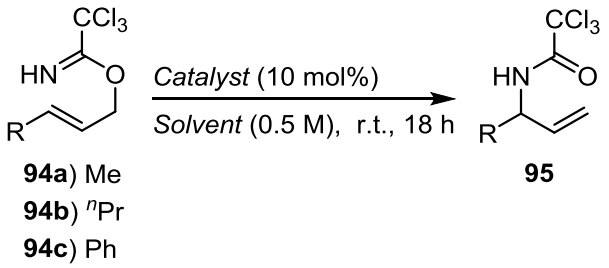
imidate, which allowed for a selective attack of the nitrogen and resulted in enantioenriched allylic amide **93** (Scheme 1.15).




*Scheme 1.15: Overman rearrangement catalysed by COP-Cl.*

A number of researchers have recently examined alternative metals capable of catalysing the Overman rearrangement. Jirgensons et al. screened a range of metal complexes including: $Ti(OEt)_4$, $Al(O^iPr)_3$, $CeCl_3$, $FeCl_3$, $MgBr_2$, $Cu(OAc)_2$, $Rh(OAc)_2$, $NiCl_2$, $PtCl_2$, $PtCl_4$, AuCl and $AuCl_3$ at 10 mol% with successful catalysts exclusively from the noble metals platinum and gold (Scheme 1.16). Isolated yields using gold and platinum chlorides in dichloromethane and tetrahydrofuran are shown in table 1.1. It was shown that for imidate **94a**, platinum(II) chloride in dichloromethane produced the corresponding amide **95a** in the highest yield of 89% (Entry 1, table 1.1). The yield was similar under a variety of conditions, with the exception of platinum(IV) chloride in dichloromethane, in which amide **95a** was obtained in 30% yield (Entry 1, table 1.1). When the rearrangement was attempted on the more challenging *n*-propyl substrate **94b**, platinum(II) chloride in dichloromethane again gave the highest yield of 81% (Entry 2, table 1.1).

When attempting the rearrangement of *n*-propyl substrate **94b**, the difference in yield varied considerably when comparing the different conditions, but followed the basic trend of decreasing yield as complexity increases (Entry 2, table 1.1). The difference was even more evident with substrate **94c,** in which gold(I) chloride and platinum(IV) chloride produced amide **95c** in only 34% yield (Entry 3, table 1.1). Overall platinum(II) chloride in dichloromethane gave the highest yield of allylic amide **95a-c**. It is important to note that when platinum(IV) chloride was used in dichloromethane the yield is reduced considerably with allylic imidate (Entry 1, table 1.1). When attempting more hindered substrates **94b, 94c** platinum(IV) chloride was a poor catalyst in tetrahydrofuran. The lower oxidation state metals (platinum(II) and gold(I)) gave the highest yield when comparing oxidation states of the same metal. It was proposed that the increase in activity could be due to the softer nature of Lewis acids at lower oxidation states.[44]

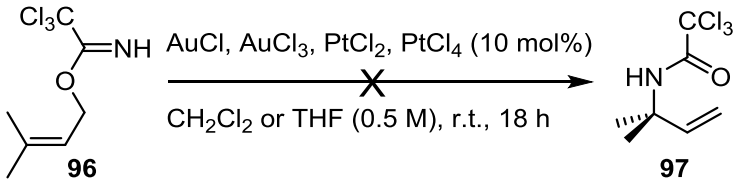



*Scheme 1.16: Jirgensons' conditions for the precious metal-catalysed Overman rearrangement.*

| Entry | R | AuCl | $AuCl_3$ | $PtCl_2$ | | $PtCl_4$ | |
|---|---|---|---|---|---|---|---|
| | | $CH_2Cl_2$ | $CH_2Cl_2$ | $CH_2Cl_2$ | THF | $CH_2Cl_2$ | THF |
| **1** | Me | 82% | 80% | 89% | 83% | 30% | 75% |
| **2** | *n*-Pr | 74% | 71% | 81% | n/a | n/a | 56% |
| **3** | Ph | 52% | 34% | 61% | n/a | n/a | 34% |

*Table 1.1: Jirgensons' study on the Overman rearrangement.*

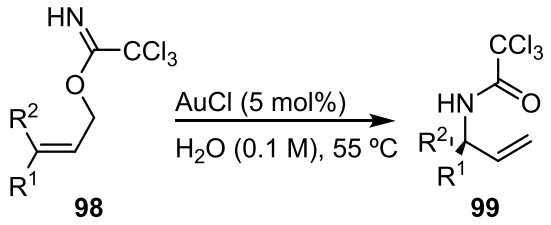
It is important to note that the reaction of allylic imidate **96** to give allylic amide **97**, which contained a quaternary carbon centre, did not give an isolated amide **97** (Scheme 1.17).




*Scheme 1.17: Unsuccessful rearrangement of 3-methylbut-2-en-1-yl 2,2,2-trichloroacetimidate using precious metals.*

A further study on the use of gold to catalyse the Overman rearrangement by Yang et al. successfully transformed a number of allylic imidates **98** to the corresponding allylic amides **99** by using gold(I) chloride in water (Scheme 1.18). The results showed excellent yields of 96% and 90% for the methyl (Entry 1, table 1.2) and $CH_2Bn$ (Entry 2, table 1.2) substituents after 2 hours of stirring at 50 ºC. The yield decreased slightly when imidate **98** containing a THP protected alcohol substituent was attempted (Entry 3, table 1.2). The application of these conditions on the methyl ester substituent took three times as long to get a yield of 71% (Entry 4, table 1.2). In contrast to Jirgensons' results subjection of phenyl substituent allylic imidate **98** to the aqueous gold conditions did not afford any of the desired product (Entry 5, table 1.2). The aqueous gold conditions were also unable to produce allylic amide **99** with a quaternary carbon centre (Entry 6, table 1.2). Overall the conditions used in Yang's study were a slight improvement on Jirgensons' work due to the decrease in catalyst loading, reaction times, the use of water as a sustainable

solvent and a slight increase in the yield of comparable substrate (Entry 1, table 1.2).




*Scheme 1.18: Gold-catalysed Overman rearrangement in water.*

| Entry | $R^1$ | $R^2$ | Time (h) | Yield (%) |
|---|---|---|---|---|
| **1** | Me | H | 2 | 96 |
| **2** | $CH_2Bn$ | H | 2 | 90 |
| **3** | $CH_2OTHP$ | H | 2 | 79 |
| **4** | $(CH_2)_2CO_2Me$ | H | 6 | 71 |
| **5** | Ph | H | 3 | 0 |
| **6** | Me | Me | 3 | 0 |

*Table 1.2: Gold(I) chloride-catalysed Overman rearrangement.*

Overman reported a significant limitation of the metal-catalysed allylic imidate rearrangement process. The reaction of allylic imidate **100**, which contains a terminal alkene, preferred to undergo an alternative transformation to form oxazolidine **102**. The transformation occurs when the nitrogen lone pair attacks at the C-2 position of the metal activated alkene rather than at the C-3 position. This alternative transformation forms oxazolidine ring **102** after protodemetalation of intermediate **101**.[34] To date there have not been any successful reports of metal-catalysed Overman rearrangements of an alcohol with a terminal alkene (Figure 1.13).[33]

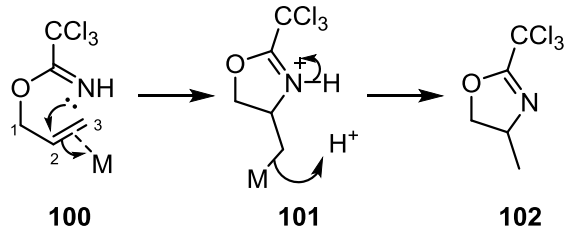
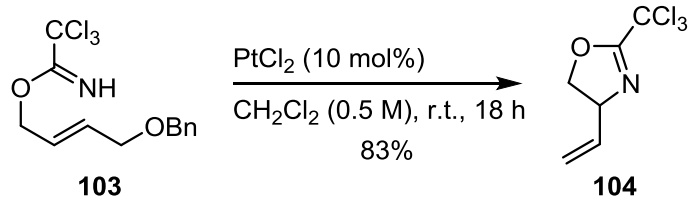



*Figure 1.13: undesirable oxazoline formation.*

Another alternative transformation occurs in the presents of a metal catalyst when a leaving group is present alpha to the olefin to form vinyl oxazolidine **104**. The synthesis of oxazolidine ring **104** from allylic imidate **103** shows how a leaving group can also affect the position in which the nitrogen nucleophile attacks (Scheme 1.19).[44]




*Scheme 1.19: undesirable oxazoline formation with OBn substrate.*

In the above reaction by Jirgensons et al. the metal binds to the olefin to form the activated olefin complex **105**. The metal then forms a π-allyl bond with the substrate after expulsion of the benzyl ether leaving group. This oxidative addition forms a $\eta^3$-bond preferentially over a $\eta^1$-bond due to the increase in the binding. The nitrogen then attacks at the C-2 position of **106** to form oxazolidine ring **104** after decomplexation of the metal catalyst in complex **107** **(**Figure 1.14).[45]

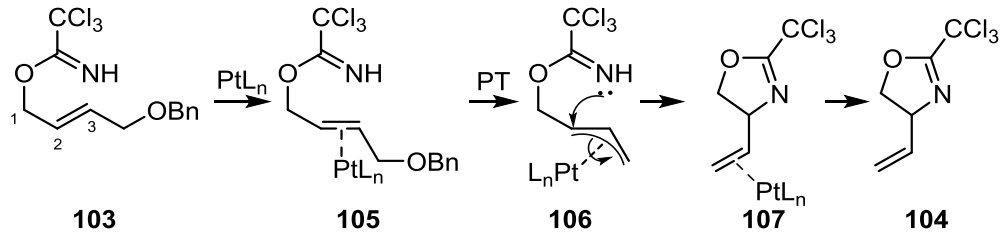



*Figure 1.14: Metal meditated loss of benzyl alcohol.*

An alternative mechanism to form oxazolidine ring **104** from allyl imidate **103** is also possible. Oxazolidine ring **104** could be formed via an $S_N2'$ reaction involving intermediate **108** that does not involve metal binding to the olefin (Figure 1.15).

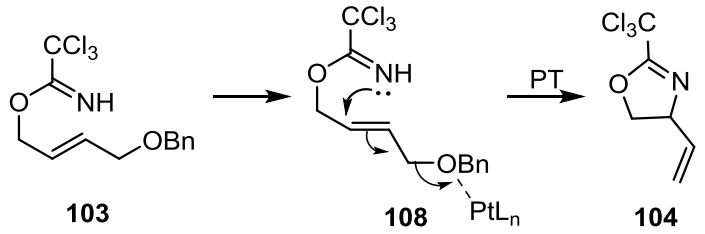
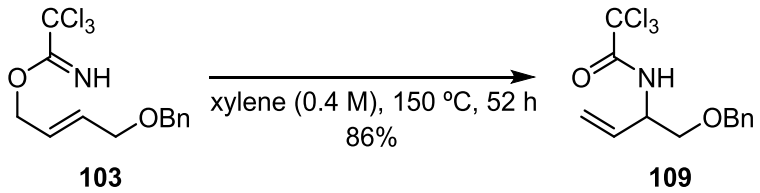


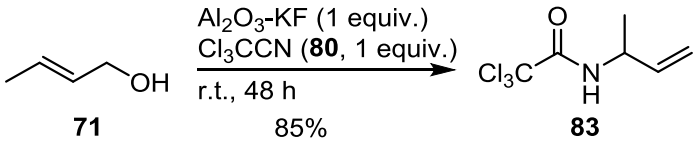

*Figure 1.15: $S_N2$ reaction resulting in a loss of benzyl alcohol.*

Ubukata et al. provided evidence that the $S_N2'$ mechanism is unlikely due to the successful rearrangement when the process was conducted under thermal conditions of allyl imidate **103** to form allyl amide **109** in a 86% yield (Scheme 1.20).[46]




*Scheme 1.20: Rearrangement of OBn substituted imidate*

Although the method of allylic imidate synthesis followed by the Overman rearrangement is an excellent and efficient method of synthesising allylic amides, there are a number of limitations to the technique. Firstly, the addition of an alcohol or alkoxide to a nitrile only works with activated trihalogenated acetonitriles, as less activated nitriles are insufficiently electrophilic for the nucleophilic addition reaction to occur. The second limitation is the basic conditions required for the nucleophilic addition reaction. The third limitation is the requirement to preform and isolate the imidate intermediate. Whilst there has been precedent for a one-pot synthesis of allylic amide **83** from allylic alcohol **71** and trichloroacetonitrile **(80)** by pre-absorbing alcohol **71** on to potassium fluoride on alumina, the current methods have not been demonstrated on a large substrate library and the conditions are not viable for wide scale use due to the pre-absorbing requirements (Scheme 1.21).[47]




*Scheme 1.21: One-pot allylic amide synthesis with $Al_2O_3$*

### 1d) Applications of trihalogenated allylic amides

Trihalogenated allylic amides are primarily synthesised as masked amines. The trihalomethyl group within the amide moiety is a strong EWG, which creates a highly electrophilic carbon centre. The electrophilic carbon centre allows for facile attack of hydroxide or water to form tetrahedral intermediate **111.** The

amine then acts as a leaving group to produce amine **112** and trihalogenated acetic acid **113 (**Figure 1.16).

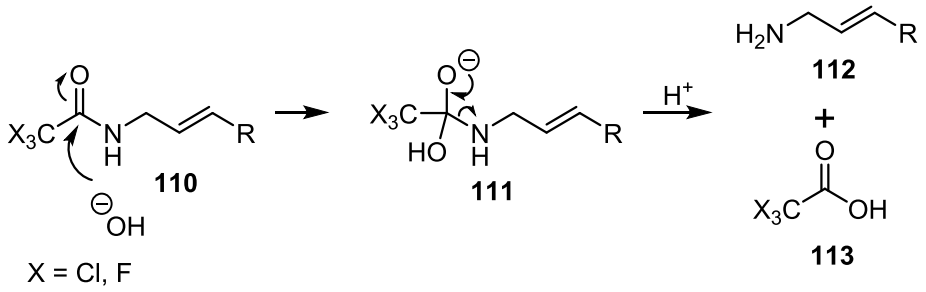
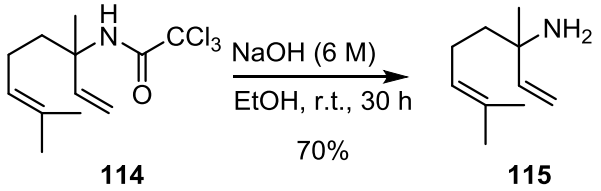



*Figure 1.16: Mechanism for the hydrolysis of trihalogenated allylic amides.*

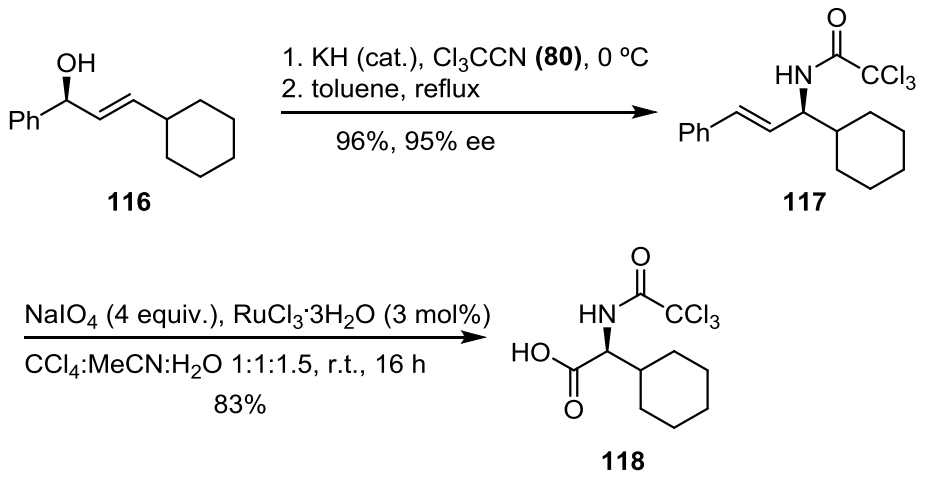
Overman et al. has shown that hydrolysis of trihalogenated amide **114** occurs in the presence of sodium hydroxide at ambient temperature to obtain hydrolysis product **115** in a good yield (Scheme 1.22).[10]




*Scheme 1.22: An example of hydrolysis of trichloro allylic amide.*

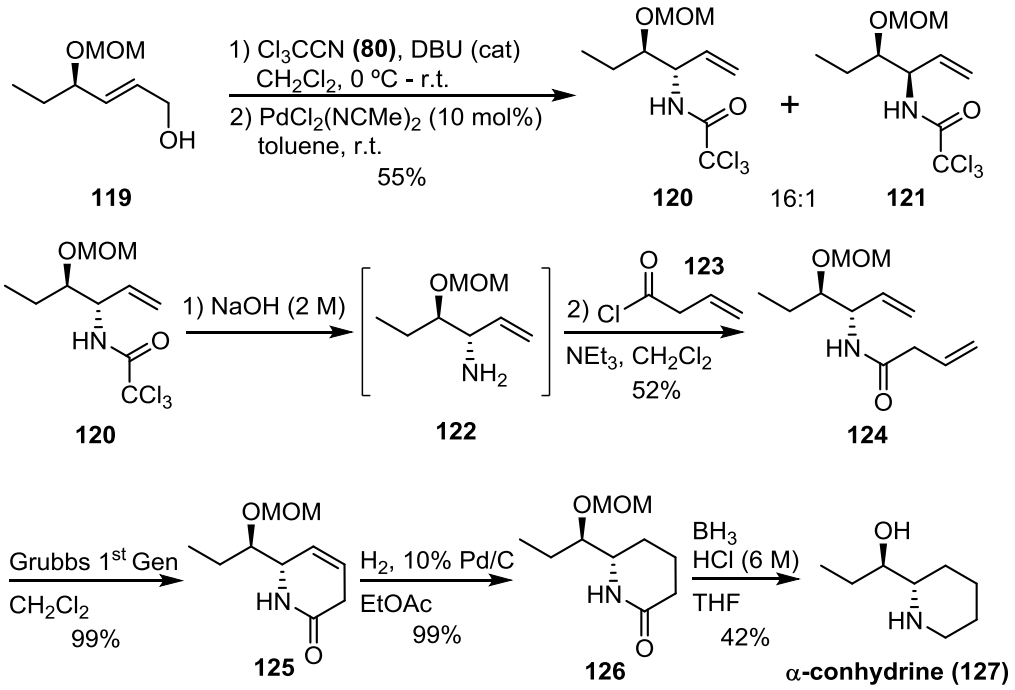
The Overman rearrangement combined with facile hydrolysis is a useful technique in the enantioselective synthesis of unnatural amino acids. Walsh et al. showed that a variety of protected amino acids can be synthesised stereospecifically in three steps from enantiopure alcohols.[48] A number of amino acids were synthesised by using the Overman rearrangement followed by an oxidative cleavage to form the carboxylic acid moiety. For example, enantioenriched amino acid **118** was synthesised by subjecting enantioenriched

allylic alcohol **116** to catalytic potassium hydride and trichloroacetonitrile **(80)**, which afforded the corresponding allylic imidate**.** Subjection of the allylic imidate to a thermal Overman rearrangement gave allylic amide **117**. Allylic amide **117** was then oxidatively cleaved to give the corresponding protected amino acid **118**, which can easily be deprotected to give the amino acid (Scheme 1.23).




*Scheme 1.23: Example of oxidative cleavage.*

In addition to oxidative cleavage of the double bond, the free amine can be used to form lactams. Sutherland et al. used free amine **122** in the stereospecific total synthesis of α-conhydrine **127**.[49] Allylic amide **120** was generated diastereoselectivity from the corresponding allylic imidate. Allylic amide **120** was hydrolysed to the amine **122** and then converted into allylic amide **124** via a reaction with acid chloride **123**. The newly formed amide was subjected to Grubbs ring closing metathesis conditions, which gave lactam **125** in an almost quantitative yield. Reduction of both the double bond and amide, followed by deprotection gave the natural product α-conhydrine (**127**) in a 42% yield (Scheme 1.24).




*Scheme 1.24: Total synthesis of α-conhydrine.*

### 1e) Benzoxazole uses, synthesis and functionisation

Another synthetic process that results in overall nitrile activation followed by a second mechanistic step is the synthesis of 2-substituted benzoxazoles from the corresponding 2-aminophenol and a nitrile. Benzoxazoles are a very useful scaffold in synthesis, they are found in many drug compounds and natural products. For example, the drugs Ontazolast **(128)** and Suvorexant **(129)** contain a benzoxazole core (Figure 1.17). Further to their occurrence in drug molecules benzoxazoles are used extensively as ligands for metals. Zinc complex **130** is a tetrahedral zinc species which has two benzoxazole ligands *trans* to each other. Zinc complex **130** is commercially available and is commonly found in organic light emitting diodes (OLED's) due to its good

luminescence ability (Figure 1.17).[50] As well as being good laminators, the benzoxazole core was found to be a good ligand for the formation of iridium nano-particles. Iridium complex **131** is a di-iridium species containing two benzoxazole ligands on each metal centre that is bridged by chlorine atoms. It is used for the oxidation of water (Figure 1.17).[51] Benzoxazoles are also used in the synthesis of complex polymers. Ishinda et al. showed that benzoxazole polymer **132** was easy to synthesise and had excellent thermal capabilities (Figure 1.18).[52] Polybenzoxazole **132** (PBOs) are desirable because they have a high flame retardance, heat resistant threshold and glass transition temperature. In addition, Lee et al. has shown that pentafluoro PBO **133** has an increase in permeability and selectivity for $H_2/CO_2$ compared to other high free volume polymers (Figure 1.18).[53] Therefore methods for synthesising these heterocycles under mild conditions are very desirable.[54-58]

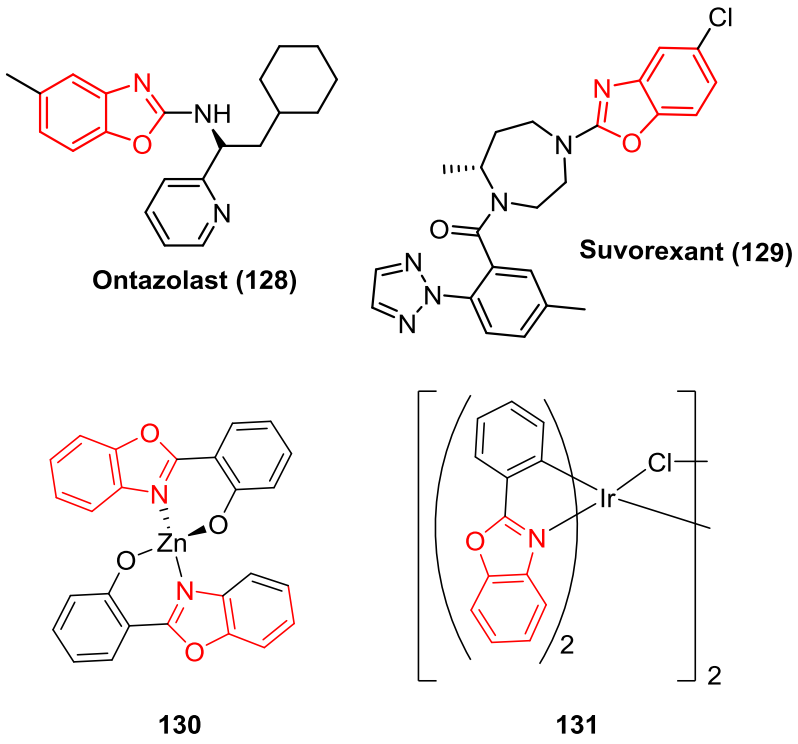
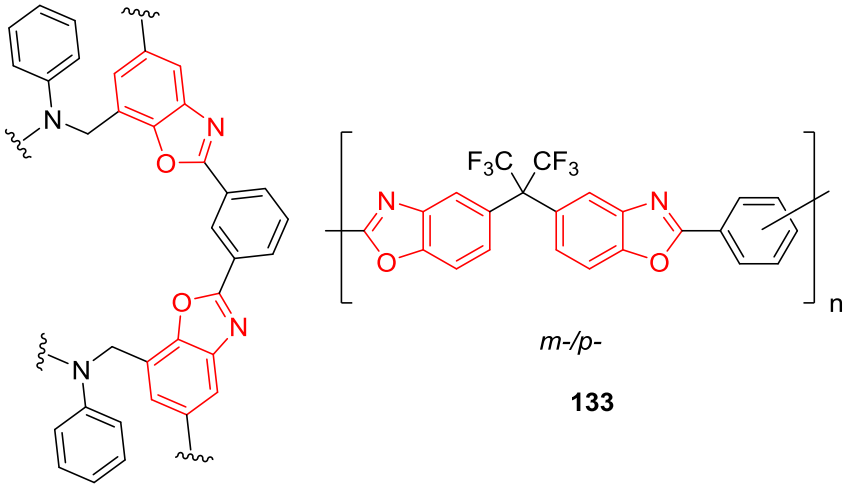



*Figure 1.17: Useful compounds containing a benzoxazole core*

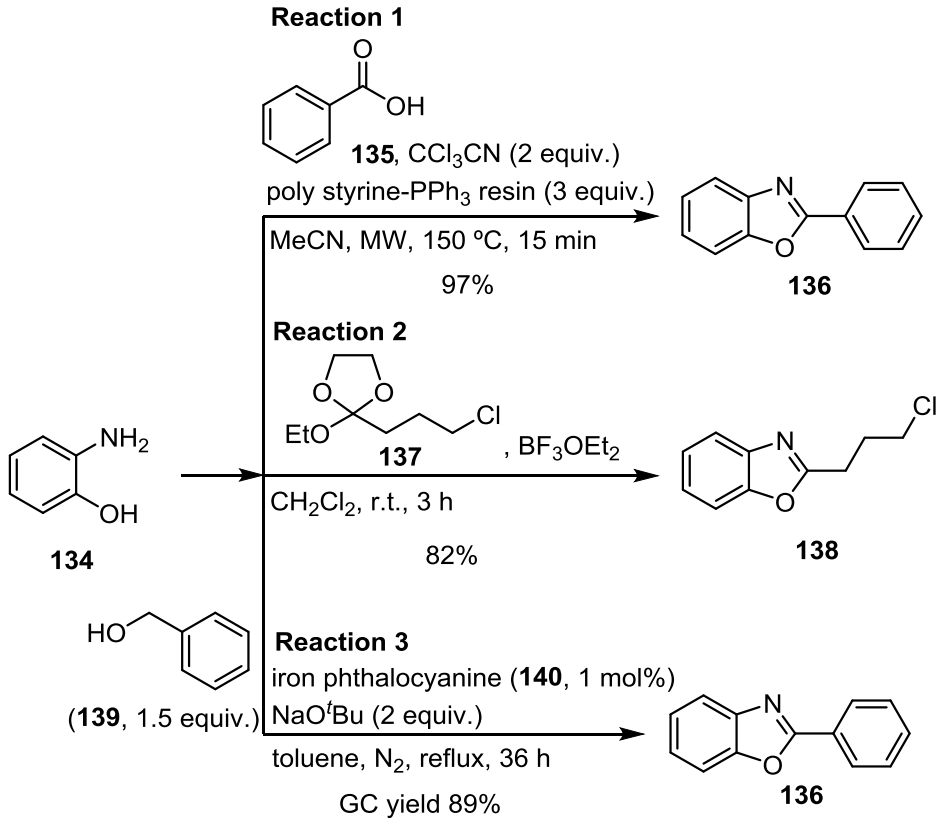



**132** **133**

*Figure 1.18: Useful polymers containing a benzoxazole core.*

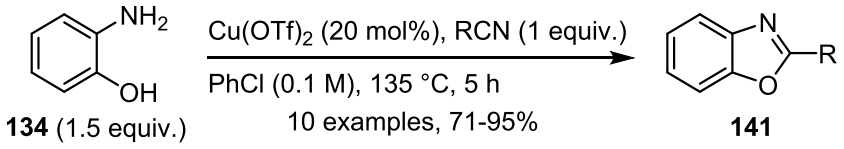
There are two major methods of synthesising 2-functionalised benzoxazoles. The first method involves a homologation/oxycyclisation process from the 2-aminophenol **(134)**. For example, Djuric et al. developed a method for forming aryl substituted benzoxazoles **136**, in which 2-aminophenol **(134)** was reacted with carboxylic acid **135** in the presence of trichloroacetonitrile **(80)** and a polystyrene resin at high temperatures (Reaction 1, scheme 1.25).[59] The trichloroacetonitrile **(80)** was added to the reaction to activate carboxylic acid **135** for coupling via an in situ formation of an acetic 2,2,2-trichloroacetimidic anhydride. In addition, Marko et al. developed a method for the synthesis of 2-benzoxazole **138** from 2-aminophenol **(134)** and the corresponding acetal orthoformate **137** (Reaction 2, scheme 1.25). In this approach a strong Lewis acid (boron trifluoro etherate) was used to activate orthoformate **137** and aid in the condensation.[60] Furthermore, Singh et al. used a tandem oxidation process to produce the desired 2-benzoxazole **136** from 2-aminophenol **134** and benzyl alcohol **(139)**. The method employed an iron catalyst **140** that oxidised benzyl

alcohol **(139)** to benzaldehyde, followed by a condensation with the amine moiety to produce a Schiff base. The Schiff base then underwent a nucleophilic attack from the pendent phenol moiety creating a 2,3-dihydroxy benzoxazole. Further oxidation by the iron catalyst afforded the desired benzoxazole **136** (Reaction 3, scheme 1.25).[61] All these reactions are an efficient way to synthesise a variety of molecules that contain a benzoxazole core.



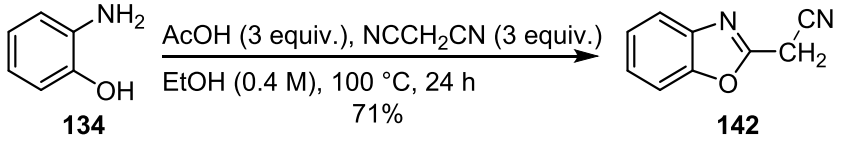

*Scheme 1.25: Synthesis of 2-benzoxazoles via carbonyl derivatives.*

There are many ways to synthesise the benzoxazole core from 2-aminophenols **134**. Recently Pan et al. demonstrated a one-pot process with a number of aromatic nitriles in refluxing chlorobenzene with catalytic copper(II) triflate to produce benzoxazoles **141** in a good to excellent yields (Scheme 1.26).



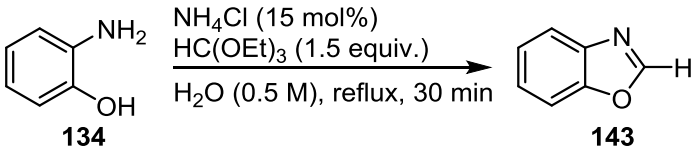

*Scheme 1.26: Benzoxazole synthesis with Cu(OTf)2 from nitriles.*

A similar method for forming the benzoxazole core from the activation of nitriles is the work by Tamura et al. in which glacial acetic acid is used to activate the malonitrile, to form benzoxazole **142** after 24 hours at 100 ºC (Scheme 1.27). Interestingly, neither the hydrolysis or dimerisation of the bis-nitrile were major products of the reaction[62]



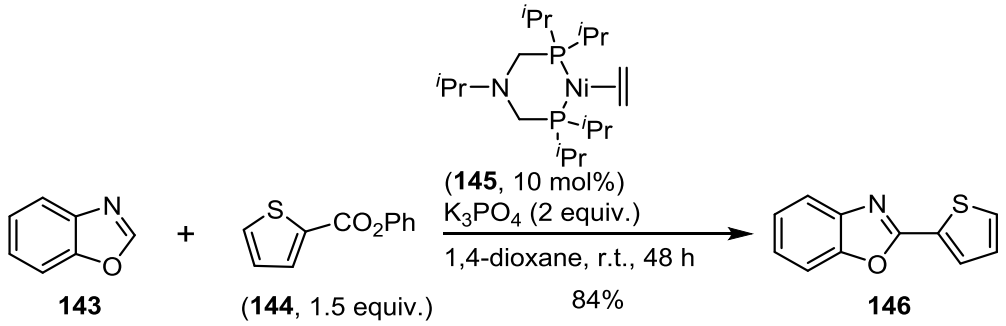

*Scheme 1.27: Brønsted acid activated benzoxazole synthesis from nitriles.*

The second main method of forming 2-functionalised benzoxazoles is by starting from the parent benzoxazole and further functionalising by either C-H activation using a metal catalyst or by displacement of a leaving group. The parent benzoxazole compound **143** can be synthesised from orthoformate. Chelsea et al. developed conditions to form benzoxazole **143** in 30 minutes, by refluxing 2-aminophenol **134** with ethyl orthoformate in the presence of a catalytic amount of a weak acid in water (Scheme 1.28).[63]




*Scheme 1.28: Direct synthesis of 2H-benzoxazole.*

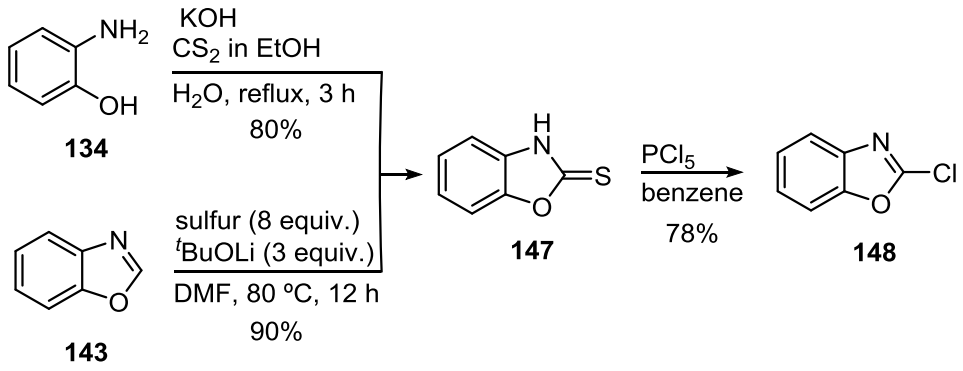
From the parent benzoxazole, C-H activation has been used as a versatile method to functionalise at the C-2 position. Gade et al. has shown that benzoxazole **143** reacts with ester **144** in the presence of nickel catalyst **145** to form the desired substituted benzoxazole **146** via a decarboxylation carbon-carbon bond forming process (Scheme 1.29).[64]




*Scheme 1.29: C-H activation of 2H-benzoxazole for the coupling of aromatic compounds.*

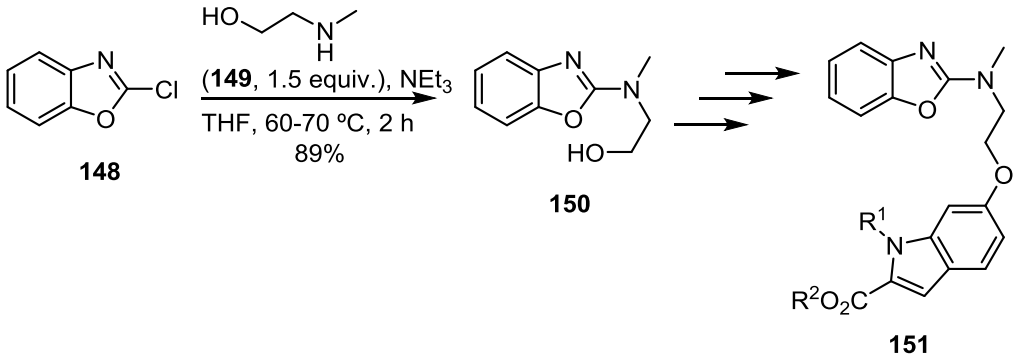
If the desired benzoxazole contains a heteroatom at the C-2 position, the traditional method of synthesis is via a step-wise introduction of a leaving group. For example Shinde et al. showed that the reaction of 2-aminophenol **(134)** with carbon disulfide afforded benzoxazol-2-(3*H*) thione **(147)** in a good yield.[65] Alternatively, Daugulis et al. reported that the same product can be obtained by reacting benzoxazole **(143**) with a large excess of elemental sulfur in the presence of $^{t}$BuOLi.[66] Benzoxazol-2-(3*H*) thiones **(147)** can

subsequently be converted to 2-chlorobenzoxazole **(148)** by reacting with phosphorus pentachloride (Scheme 1.30).[67]




*Scheme 1.30: Syntheses of 2-chlorobenzoxazole.*

2-Chlorobenzoxazoles **148** can be further transformed to the desired 2-functional benzoxazoles by nucleophilic aromatic substitution under mild conditions. Jeon et al. showed that 2-chlorobenzoxazole **148** can be useful in the synthesis of drug analogues. The reaction of 2-chlorobenzoxazole **148** under basic conditions in the presence of amino alcohol **149** gave substituted benzoxazole **150** in an 89% yield. After further manipulation drug compound **151** was formed. This method allowed with access to a variety of valuable analogues (Scheme 1.31).[68]

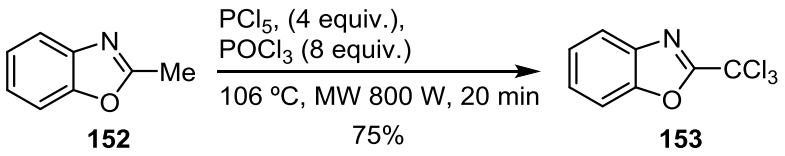



$R^1$ = Me, Et, Bn, CO2Me, CO2H, 4- fluorobenzyl
$R^2$ = H, Me,

*Scheme 1.31: The use of 2-chlorobenzoxazole for the synthesis of analogues.*

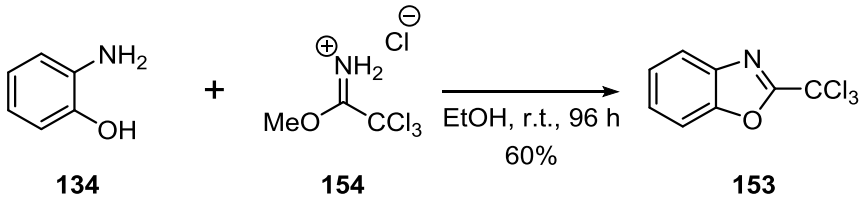
### 1f) Trichlorobenzoxazole synthesis and manipulation

Another potentially useful functional group at the C-2 position of a benzoxazole is a trichloromethyl moiety. One method for synthesising a trichloromethyl benzoxazole **153** is by chlorination of a 2-methyl benzoxazole **(152)**. Vanelle et al. reported that the reaction of 2-methyl benzoxazole **152** with phosphorus pentachloride in phosphorus oxychloride produced 2-trichlorobenzoxazole **152** in a 75% yield after heating in a microwave at 106 ºC for 20 min (Scheme 1.32).[69]




*Scheme 1.32: Synthesis of 2-trichloromethyl benzoxazole from 2-methyl benzoxazole.*

Holan et al. demonstrated a more direct synthesis for the formation of 2-trichlorobenzoxazole **153**. Reaction of 2-aminophenol **(134)** in the presents of trichloromethoxy imidate **154** gave trichlorobenzoxazole **153** in a moderate yield after 96 hours at ambient temperature.[70] Unfortunately, trichlorobenzoxazole **153** was the only substrate synthesised and no further derivatisations were attempted (Scheme 1.33).




*Scheme 1.33: Holan's synthesis of 2-trichloromethyl benzoxazole.*

This reaction was possible because the carbon centre of imidate **154** is activated towards nucleophilic addition from the amine moiety of 2-aminophenol **(134)** to form amidate intermediate **155**. The intermediate amidate **155** underwent a proton transfer to form **156** before the pendent phenol moiety attacks the central carbon to form tetrahedral intermediate **157**. Once the compound was neutralised, it underwent a further proton transfer and subsequent loss of ammonia **158** to produce trichlorobenzoxazole **153** (Figure 1.19).

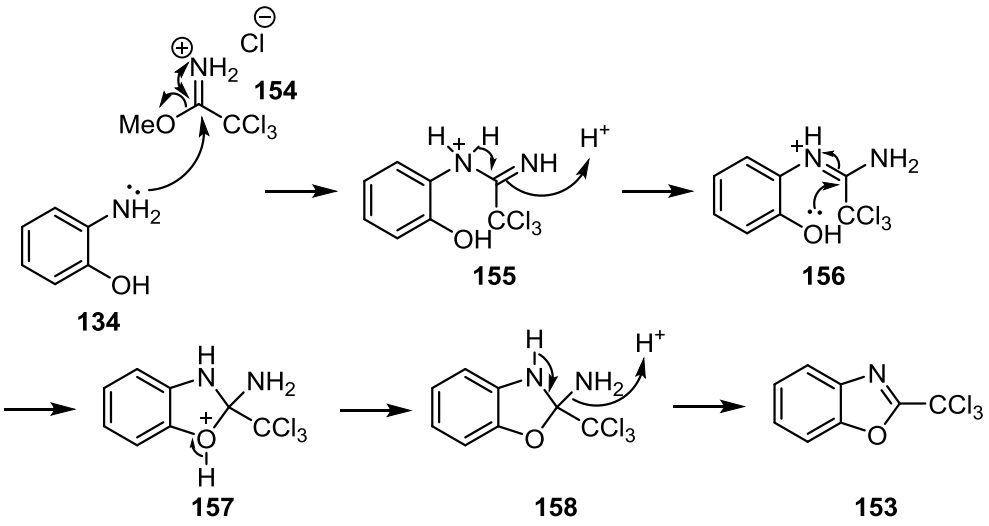
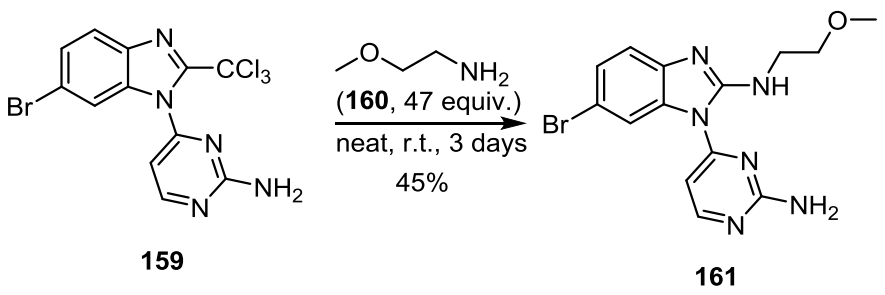


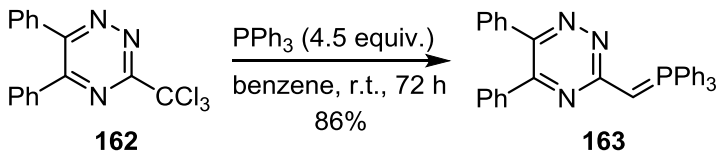

*Figure 1.19: Mechanism for Holan's synthesis of 2-trichloromethyl benzoxazole.*

Whilst the chemical reactivity of a 2-trichloromethyl moiety on a benzoxazole has not been explored, there are a number of transformations that utilise the aryl trichloromethyl moiety as a handle for further functionisation. Research by Stoben et al. utilised the trichloromethyl moiety as a leaving group to install amino ether **160** on to the 2 position of benzimidazole **159**, which gave aminobenzimidazole **161** in three days at ambient temperature (Scheme 1.34).[71]




*Scheme 1.34: Nucleophilic displacement of the trichloromethyl moiety of a benzimidazole with an amine.*

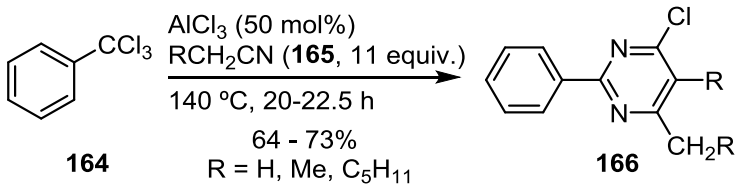
In addition to using the trichloromethyl moiety as a leaving group in a nucleophilic substitution reaction, the chlorine atoms can also be utilised to give useful and interesting precursors. An example of this was the work by Yamanaka et al. in which the reaction of trichloro-1,2,4 triazine substrate **162** and triphenylphosphine over 72 hours at ambiant temperature gave Wittig reagent **163** in a good yield (Sheme 1.35).[72] This Wittig reagent can undergo a series of olefination reaction with carbonyl substrates to form an analogue libary. This transformation is expected as there is an insitu reduction without a reducing agent being present one possible explination is the formation of radicals in from trichloromethyl moieties reported by Crozet et al.[73]




*Scheme 1.35: Conversion of the trichloromethyl moiety to a Wittig reagent.*

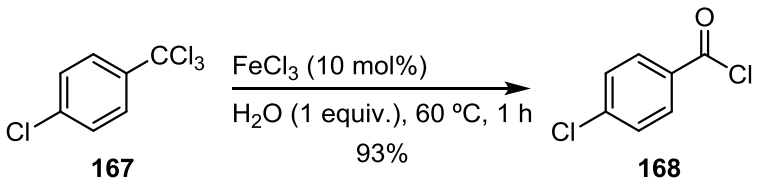
Nucleophilic substitution reaction on the trichloromethyl moiety can also be utilised to form highly substituted heterocyclic rings. Research by Shvo et al.

discovered that a reaction of trichlorotoluene **164** with an excess of nucleophilic nitrile **165** in the precents of aluminum(III) chloride at elevated temperatures resulted in the formation of pyrimidine **166** in a good yield (Scheme 1.36).[74]



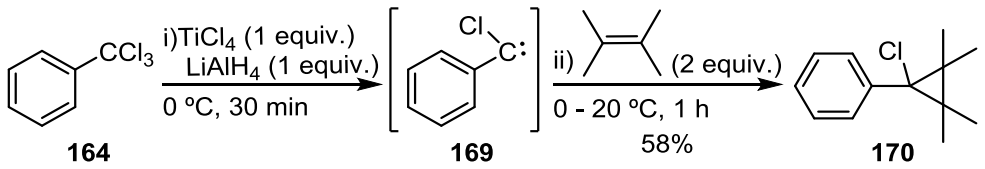

*Scheme 1.36: Synthesis of substituted pyrimidines from trichloromethyl benzene.*

An additional transformation of the trichloromethyl moiety is the formation of an acid chloride via hydrolysis. Van den Akker et al. designed an efficient synthesis of acid chloride **168** by reacting trichloromethyl substrate **167** with water in the presence of iron(III) chloride at 60 ºC to afford acid chloride **168** in 1 hour (Scheme 1.37).[75]




*Scheme 1.37: Synthesis of an acid chloride from trichloromethyl benzene.*

The trichloromethyl moiety has also been utilised as a precursor to a carbene. Work by Burkholder et al. reacted trichlorotoluene **164** with an in situ formed titanium zero reagent to form chloro carbene **169**, which then reacted with 2,3-dimethyl-2-butene to give highly substituted chlorocyclopropane **170** (Scheme 1.38).[76]




*Scheme 1.38: Synthesis of chloro cyclopropane from trichloromethyl benzene.*

### 1g) Introduction to MFC

A multifaceted catalyst (MFC) approach to synthesis has been defined as a catalytic process in which one species catalyses two or more mechanistically distinct steps in a reaction sequence.[77] For example, a simple starting material underwent a process to form an intermediate, which can undergo a second mechanistically distinct process. Both of these processes are catalysed by the same catalyst to produce an added value compound (Figure 1.20). The advantages to using this approach are: a) minimised operational complexity, which means no additional experimental procedures once the reaction is running, b) an increase in catalyst efficiency as the catalyst for multiple processes in the same system, c) an increase in step, atom and pot economy, d) a decrease in the overall cost and waste of a reaction.[77]

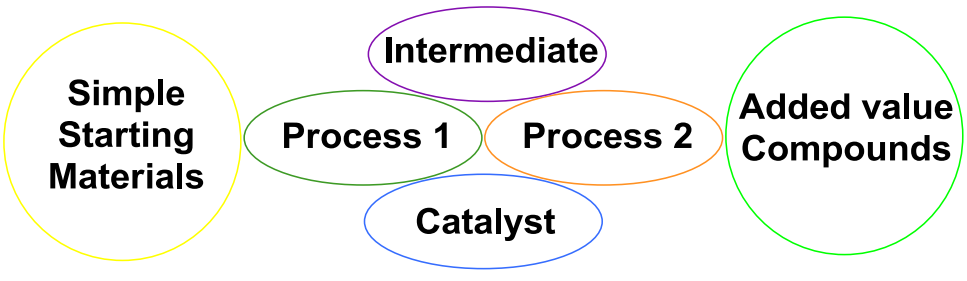
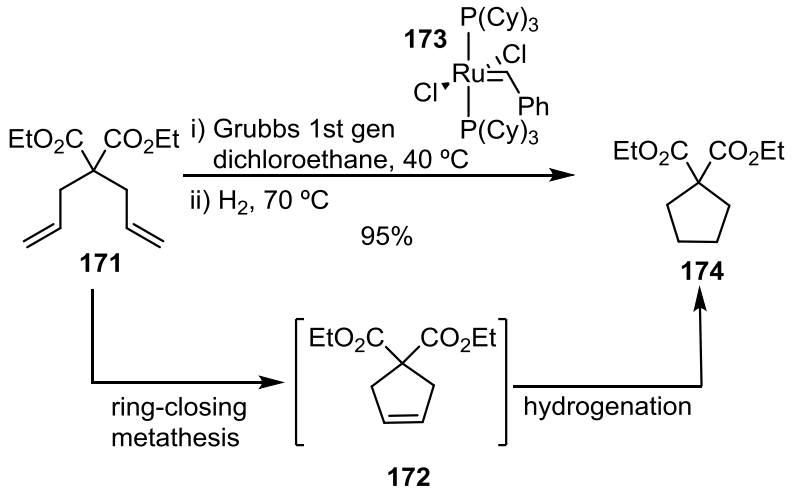


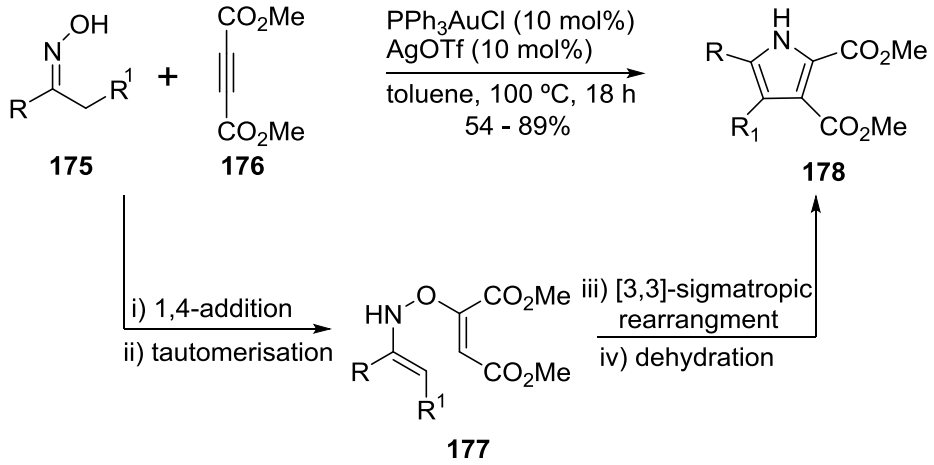

*Figure 1.20: Multifaceted catalysis approach to synthesis*

An early example of a MFC approach was reported by Grubbs *et al.*, in which a ring closing metathesis (RCM) and reduction of an olefin were catalysed by a ruthenium catalyst. Firstly, a RCM on symmetrical substituted diene **171** catalysed by the ruthenium catalyst **173** formed substituted cyclopentene intermediate **172**. The RCM was followed by a reduction of cyclopentene intermediate **172** with hydrogen gas, which was catalysed by the same complex to produce substituted cyclopentane **174** (Scheme 1.39).[78]




*Scheme 1.39: Example of MFC approach by Grubbs.*

Research in the Camp group has shown that highly substituted pyrroles **178** can be formed from the corresponding alkyne **176** and oxime **175** via a MFC approach. In this reaction a gold(I) catalyst binds to alkyne **176** to activate it toward 1,4-addition of oxime **175,** which forms enamine **177** after tautomerisation. Then enamine **177** was activated by the same gold catalyst towards a [3,3]-sigmatropic rearrangement, which followed by a dehydration, produced the desired pyrrole **178** in moderate to good yields (Scheme 1.40).[79]




*Scheme 1.40: Example of MFC approach by Camp.*

### 1h) Applying MFC to nitrile activation

Using a MFC approach to nitrile activation allows the second step to produce an added value compound. This compound needs to be a poorer ligand so that it can be displaced by the nitrile to allow for catalyst turn-over. substituting in nitrile activation towards nucleophilic addition into the MFC model shows clearly that the catalyst activates the nitrile towards nucleophilic addition to form the addition adduct (in purple). The addition adduct then undergoes a second mechanistically distinct step which is catalysed by the same catalyst to produce the added value compound and allows for turn-over of the catalyst (Figure 1.21).

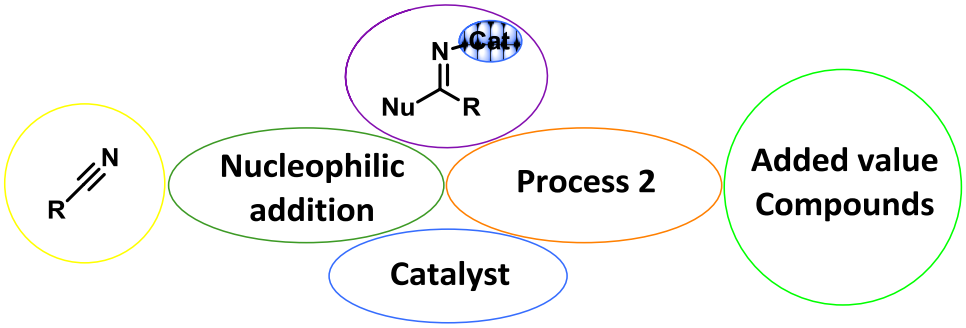



*Figure 1.21: Multifaceted catalysis approach towards nitrile activation*

Two reaction manifolds were investigated to access the feasibility of a MFC approach to nitrile activation. Firstly, the synthesis of allylic amides **181** from the corresponding allylic alcohol **182** and nitrile **1** was examined. The proposed reaction involves nucleophilic addition of allylic alcohol **182** to a Lewis acid activated nitrile, which would form metal bound allylic imidate intermediate **179**. This would be followed by a [3,3]-sigmatropic rearrangement **180** to form the desired allylic amide **181** (Reaction A, figure 1.22). The second process that was investigated was the synthesis of benzoxazole **185** from the corresponding aminophenol **186** and nitrile **1**. The proposed reaction involves nucleophilic addition of aminophenol **186** to Lewis acid activated nitrile**,** which would form metal bound amidine intermediate **183**. Nucleophilic attack on the carbon centre from the pendant phenol would form heterocyclic tetrahedral intermediate **184**. After the loss of ammonia, benzoxazole **185** would be formed (Reaction B, figure 1.22).

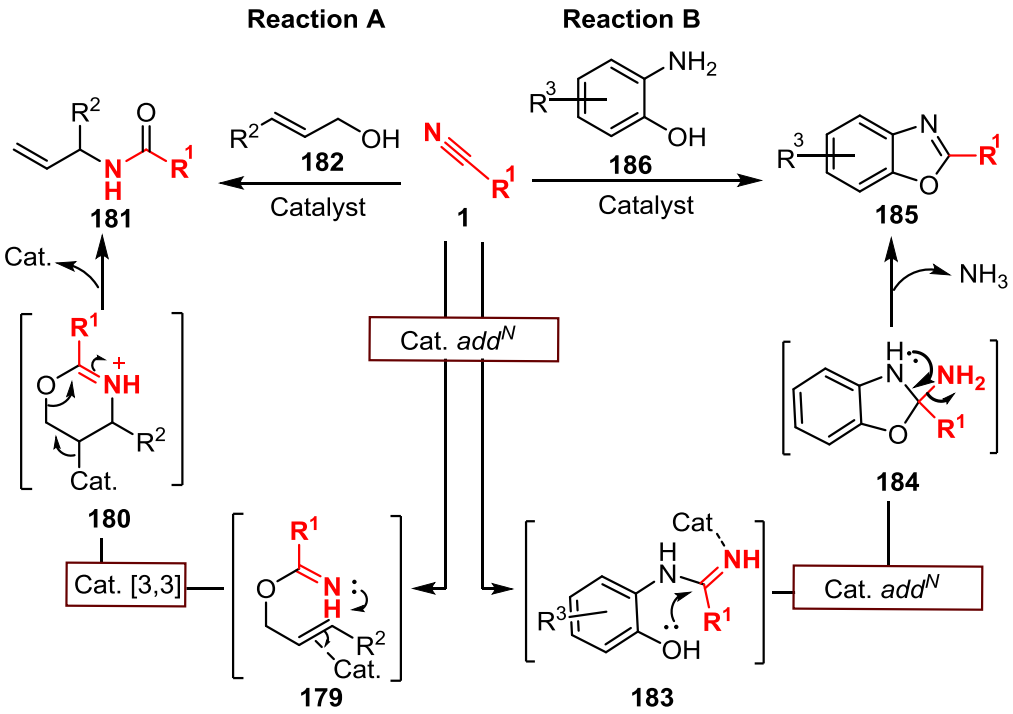


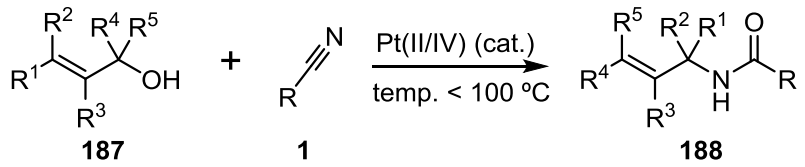

*Figure 1.22: Application of MFC approach to nitrile activation.*

### 1i) Project aims and objectives

The research disclosed herein concerns the design and development of an efficient and versatile method to catalytically activate nitriles towards the addition of nucleophiles in a single operation. To develop the methodology suitable systems have been selected that involve a second mechanistically distinct step. Thus applying a MFC approach to a) the synthesis of allylic amides and b) the synthesis of benzoxazoles as well as c) the chemistry of 2-trichlorobenzoxazoles was investigated.

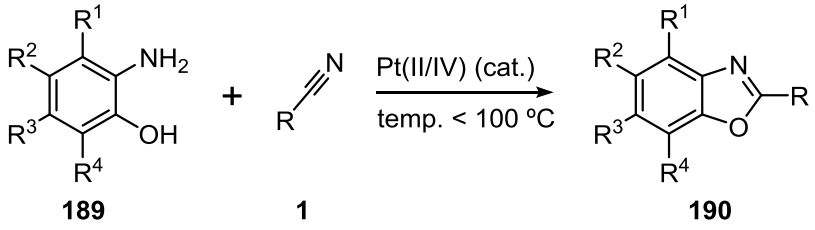
The synthesis of allylic amides **188** directly from the corresponding allylic alcohols **187** and nitriles **1** with the aid of a platinum catalyst is an ideal probe for the proposed MFC approach to catalytically activate nitriles. This process involves the required nucleophilic addition into nitriles followed by a [3,3]-sigmatropic rearrangement to turn-over the catalyst. Classically this process

has been solely used with trihalogenated nitriles with the purpose to hydrolyse the amide to the amine product (*cf.* Scheme 1.22). By the use of a catalytic activator a wide variety of nitriles could be utilised to synthesis allylic amides as the final product (Scheme 1.41).




*Scheme 1.41: Proposed MFC approach to allylic amide synthesis via nitrile activation.*

By applying the developed MFC approach to nitrile activation to the process in which 2-functionalised benzoxazoles **190** are synthesised from the corresponding 2-aminophenol **189** and nitrile **1**, the versatility of the method was explored. This process involves the required nucleophilic addition into a nitrile which is followed by a second nucleophilic addition and the loss of ammonia to allow turn-over of the catalyst. Although benzoxazole synthesis has been well studied the methods for the synthesis of 2-benzoxazoles are not versatile and require a range of conditions dependent on the functionality at the C-2 position (Scheme 1.42).




*Scheme 1.42: Proposed MFC approach to benzoxazole synthesis via nitrile activation.*

In addition, the most practised method for the synthesis of benzoxazole in which a heteroatom is present in the C-2 position is the undesirable chemistry with sulfur containing molecules which involves multiple steps and unwanted foul-smelling compounds (*cf.* Scheme 1.30). By using trichloroacetonitrile **(80)** to synthesise 2-trichlorobenzoxazoles **153** a number of transformation can be utilised to make a large compound library from a single starting compound, diversity orientated synthesis.[80] The trichloromethyl moiety can be utilised as a leaving group for a nucleophilic aromatic substitution reaction with a range of nucleophiles to form substituted benzoxazole **191** or the trichloromethyl moiety can undergo nucleophilic substitution reactions using the chlorine atoms as leaving groups to form benzoxazole **192** (Figure 1.23).

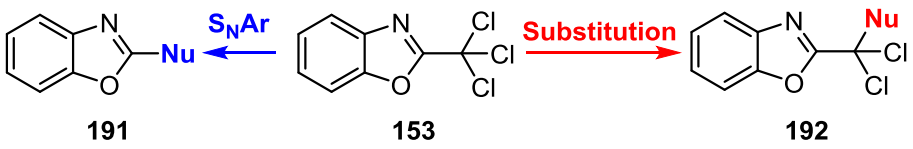



*Figure 1.23: Functional group manipulation of 2-trichloromethyl benzoxazoles.*

# Chapter 2: Results and discussion – Synthesis of allylic amides

## 2a) Proposed synthesis of allylic amides

Initially, a MFC approach towards catalytic activation of nitriles **1** was investigated on the one-pot synthesis of allylic amide **95** from the corresponding allylic alcohol **182** and nitrile **1** via allylic imidate intermediate **193.** This process is initiated via activation of nitrile **1** towards nucleophilic addition from the Lewis acid catalyst to form imidate intermediate **193**. Imidate intermediate **193** is activated by the same Lewis acid catalysts towards a [3,3]-sigmatropic rearrangement to form allylic amide **95**, which allows for turn-over the catalyst (Figure 2.1). To develop this methodology identification of an appropriate Lewis acid was crucial. Due to its known ability to activate nitriles towards nucleophilic addition of oxygen nucleophiles (*cf.* Scheme 1.10) and to activate allylic imidates towards a [3,3]-sigmatropic rearrangement (*cf.* Scheme 1.16) , our initial focus was on the use of simple platinum salts.

The advantages to our proposed method in comparison to traditional methods for the synthesis of trichloro allylic amides are the elimination of base within the nucleophilic addition step and the decrease in waste due to not isolating imidate **193**. This research also aims to overcome the limitation of using nitriles with a strong EWG incorporated. Using a wider range of nitriles will provide the opportunity to form a variety of allylic amides, this was accomplished by the inclusion of a Lewis acid to aid in the nucleophilic addition of allylic alcohol **182** within the reaction. The elimination of base is

an important advantage when changing the nitrile substrate because a proton alpha to the nitrile moiety is acidic. By using base in the nucleophilic step undesirable deprotonation at the alpha position can occur, resulting in side reactions and a decrease in overall yield.

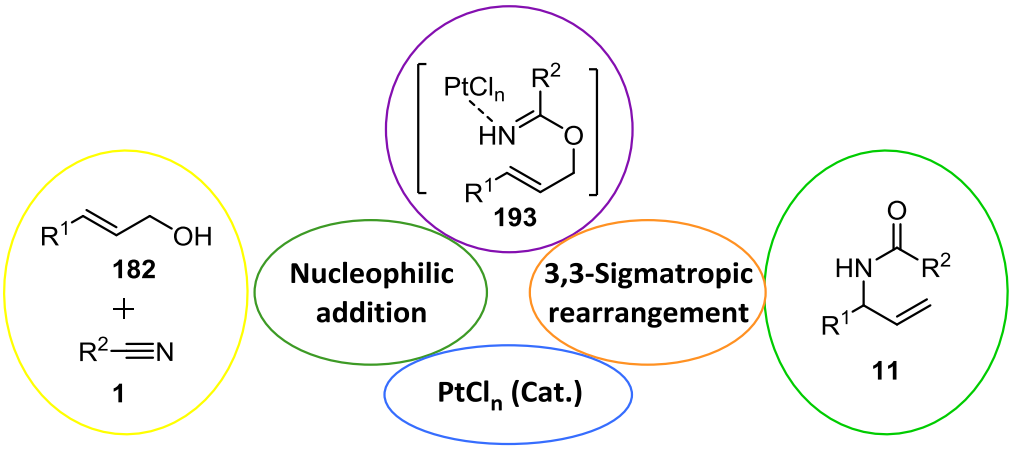


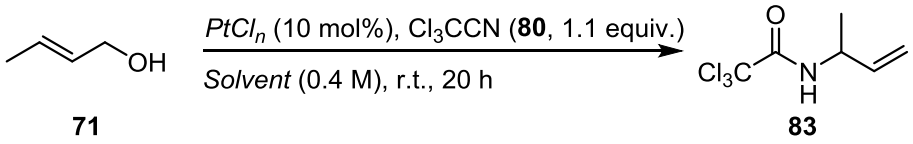

*Figure 2.1: MFC model of allylic amide synthesis.*

### 2b) Identifying highest yielding Lewis acid and solvent conditions

For the optimisation study (*E*)-2-buten-1-ol **(71)** was chosen as the allylic alcohol component due to its superior [3,3]-sigmatropic rearrangement abilities.[33] In addition, trichloroacetonitrile **(80)** was employed as the nitrile substrate because there is precedence for the [3,3]-sigmatropic platinum-catalysed rearrangement of trichloro allylic imidates**.** Trichloroacetonitrile **(80)** already contains a very electrophilic centre, on account of the inductive electron withdrawing effects of the trichloromethyl moiety, which will make it an ideal nitrile to probe the nucleophilic addition step. The activated electrophilic centre will become more electrophilic with the addition of a Lewis acid catalyst affording a sufficiently activated carbon for nucleophilic addition.[33]

To begin the investigation influence of solvents on the Pt-MFC process was investigated by accessing the ability of two platinum salts to catalyse the process. To accomplish the assessment the reaction of allylic alcohol **71** with trichloroacetonitrile **(80)** in the presence of $PtCl_2$ or $PtCl_4$ under a variety of solvent conditions was used (Scheme 2.1). The solvents were chosen due to their versatile properties including polarities ranging from non-polar, *n*-hexane, (Entry 1, table 2.1) to polar deuterium oxide (Entry 10, table 2.1).[81] The results from the solvent examination showed that the highest yield was obtain using $PtCl_2$ in dichloromethane (Entry 4 table 2.1) and the optimal solvent for $PtCl_4$ from the solvents that were screened was toluene (Entry 2, table 2.1). The more polar solvents (Entries 6-10, table 2.1) produced either very poor yields of the desired allylic amide **83** or no identifiable products. An anomaly within this investigation was the use of $PtCl_4$ in dichloromethane (Entry 4, table 2.1), in which the reaction did not produce the desired product. It is believed that non-polar solvents such as *n*-hexane and toluene are favourable due to their inability to interact with platinum's vacant coordination sites. Therefore the solvent does not compete with the binding of trichloroacetonitrile **(80)** to the metal centre. The result of using acetonitrile as the solvent with both Lewis acid catalysts (Entry 6, table 2.1) is understandable if the consideration of competing nitriles for the Lewis acid is acknowledged. Acetonitrile is much more nucleophilic towards the metal centre than trichloroacetonitrile **(80)** and there are far more acetonitrile molecules in the reaction than trichloroacetonitrile **(80)**. Therefore it would be expected that trichloroacetonitrile **(80)** would not be able to displace the acetonitrile ligand and hence acetonitrile would deactivate the Lewis acid. Overall the yields

using $PtCl_2$ are higher than $PtCl_4$ with the largest difference between the two catalysts observed in dichloromethane (Entry 4, table 2.1). Although this result cannot be explained without further investigation the result does agree with research undertaken by Jirgensons et al. (*cf.* table 1.1),[44] which showed $PtCl_4$ in dichloromethane does not work for the allylic imidate rearrangement. To conclude, the optimal solvents for an MFC approach to the synthesis of allylic amide **83** are toluene with $PtCl_4$ (Entry 2, table 2.1) and dichloromethane with $PtCl_2$ (Entry 4 table 2.1). The difference in yields between the two catalysts reveals that $PtCl_2$ is the optimal catalyst for the direct catalytic synthesis of allylic amide **83** from allyl alcohol **71** and trichloroacetonitrile **(80)**.



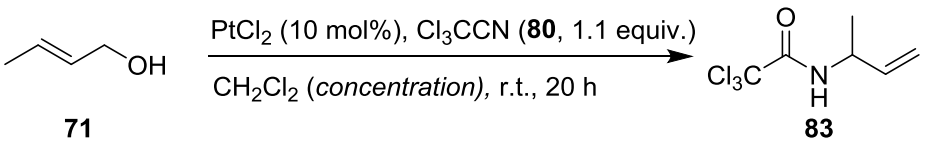

*Scheme 2.1: Screening of Lewis acids and solvents.*

| Entry | Solvent | Catalyst | Yield (%) | Catalyst | Yield (%) |
|---|---|---|---|---|---|
| **1** | *n*-hexane | $PtCl_2$ | 41 | $PtCl_4$ | 34 |
| **2** | toluene | $PtCl_2$ | 48 | $PtCl_4$ | 41 |
| **3** | diethyl ether | $PtCl_2$ | 35 | $PtCl_4$ | 18 |
| **4** | dichloromethane | $PtCl_2$ | 53 | $PtCl_4$ | 0 |
| **5** | tetrahydrofuran | $PtCl_2$ | 30 | $PtCl_4$ | 22 |
| **6** | acetonitrile | $PtCl_2$ | 0 | $PtCl_4$ | 0 |
| **7** | methanol | $PtCl_2$ | 0 | $PtCl_4$ | 0 |
| **8** | dimethylacetamide | $PtCl_2$ | 5 | $PtCl_4$ | 15 |
| **9** | dimethyl sulfoxide | $PtCl_2$ | 0 | $PtCl_4$ | 0 |
| **10** | water-$d_2$ | $PtCl_2$ | 0 | $PtCl_4$ | 0 |
| **11** | dichloromethane | No cat. | 0 | | |

*Table 2.1: Screening of Lewis acids and solvents.*

**2c) Examination of concentration in the MFC approach to the synthesis of allylic amides**

Concentration is an important variable of the reaction conditions to be investigated because concentration can have a large effect on the reaction pathway.[82] To probe the concentration effects of the MFC reaction, allylic alcohol **71** was reacted with trichloroacetonitrile **(80)** in dichloromethane with varying molarities in relation to allylic alcohol **71** to form allylic amide **83** (Scheme 2.2). The results showed that at 0.1 M the reaction gave allylic amide **83** in 13% yield (Entry 1, table 2.2). From 0.5-2 M there was very little difference in yield (Entries 2-4, table 2.2). Once the concentration is increased above 0.5 M, the concentration does not have a dramatic effect on the reaction yield (Entries 3-4, table 2.2). In summary, the concentration selected to proceed with the one-pot synthesis of allylic amide **83** was 1 M due to the optimal yield obtained (Entry 3, table 2.2).




**71** **83**

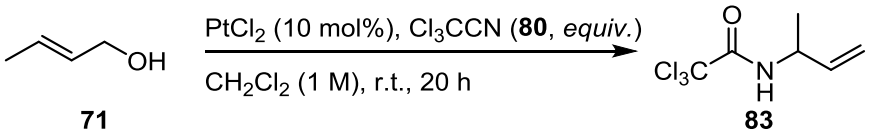
*Scheme 2.2: Concentration effect on the Pt-catalysed allyl amide synthesis.*

| Entry | Concentration (M) | Yield (%) |
|---|---|---|
| **1** | 0.1 | 13 |
| **2** | 0.5 | 53 |
| **3** | 1 | 56 |
| **4** | 2 | 53 |

*Table 2.2: Concentration effect on the Pt-catalysed allyl amide synthesis.*

### 2d) Examination of stoichiometry of trichloroacetonitrile in the catalytic synthesis of allylic amides

The next variable that was investigated was the concentration of trichloroacetonitrile **(80)** in relation to allylic alcohol **71**. Previously, this reaction was run with 1.1 equivalents of trichloroacetonitrile **(80)** to 1 equiv. of allylic alcohol. The reaction of allylic alcohol **71** in dichloromethane was reacted with a range of 0.5-5 equivalents of trichloroacetonitrile **(80)** in relation to allylic alcohol **71** to investigate the importance of stoichiometry on the reaction (Scheme 2.3). It was found that having the nitrile as the limiting reagent afforded a 66% yield in relation to the number of moles of the nitrile (Entry 1, table 2.3). Increasing the stoichiometry to 2.2 equivalents resulted in an 80% yield, (Entry 3, table 2.3). Further increasing the amount of nitrile to 5 equivalents did not lead to an increase in the yield (Entry 4, table 2.3). The results indicate that trichloroacetonitrile **(80)** should be employed in excess to alcohol **71** to obtain good yields.




*Scheme 2.3: Nitrile stoichiometry effect on the Pt-catalysed allyl amide synthesis.*

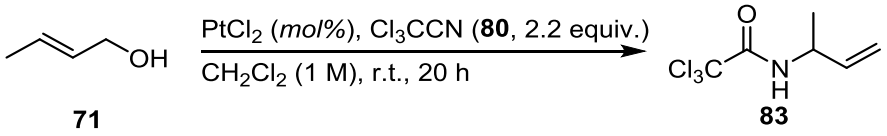
| Entry | Equivalents of nitrile (80) | Equivalents of alcohol (71) | Yield (%) |
|---|---|---|---|
| **1** | 1 | 2 | 66 |
| **2** | 1.1 | 1 | 56 |
| **3** | 2.2 | 1 | 80 |
| **4** | 5 | 1 | 80 |

*Table 2.3: Nitrile stoichiometry effect on the Pt-catalysed allyl amide synthesis.*

**2e) Examination of catalysis loading in the MFC approach to the synthesis of allylic amides**

An investigation of the catalysis loading in the reaction was undertaken in an effort to minimising the overall cost of the process. It has also been shown that in certain reactions a lower catalyst loading can lead to higher yields.[83] An experiment was designed to study the catalyst loading by altering the quantity of platinum(II) chloride in the reaction of allylic alcohol **71** with trichloroacetonitrile **(80)** in dichloromethane under the standard conditions. The results showed that decreasing the catalyst loading from 10 mo1% to 1 mol% decreased the yield of desired product **83** considerably from 80% to 12% (Entry 2-4, table 2.4). Alternatively, increasing the quantity of the catalyst from 10 to 20% did not increase the yield of the reaction (Entry 1, table 2.4).

Of the catalyst loading that was investigated, 10 mol% was found to give the highest yield for the one-pot synthesis of allylic amide **83** (Scheme 2.4).




*Scheme 2.4: Catalyst loading effect on the Pt-catalysed allyl amide synthesis.*

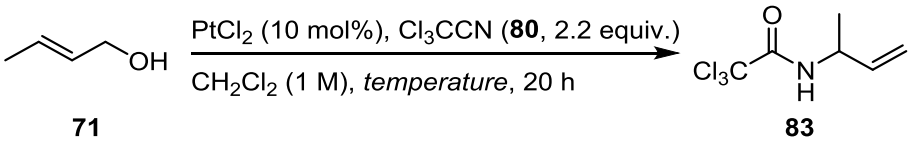
| Entry | Pt mol (%) | Yield (%) |
|---|---|---|
| **1** | 20 | 73 |
| **2** | 10 | 80 |
| **3** | 5 | 34 |
| **4** | 1 | 12 |

*Table 2.4: Catalyst loading effect on the Pt-catalysed allyl amide synthesis.*

**2f) Examination of the temperature of the reaction in the MFC approach to the synthesis of allylic amides**

An investigation of the reaction temperature was conducted in which allylic alcohol **71** was reacted with 2.2 equiv. of trichloroacetonitrile **(80)** in dichloromethane at a range of temperatures from ambient temperature to 100 ºC in 20 ºC increments. The results showed that at 40 ºC there was no difference in yield from the reaction at ambient temperature (Entries 2, table 2.5). An increase to 80 ºC increased the yield by only 10% (Entries 3-4, table 2.5). The highest temperature tested was 100 ºC, which afforded quantitative yields (Entry 5, table 2.5). The disadvantages of extra cost and potential hazards as a result of the high temperatures with dichloromethane as the solvent outweigh the advantage of an extra 10-19% yield, therefore the ideal

reaction conditions would be at ambient temperature. In addition, one of the advantages of this methodology is the elimination of high temperatures. Therefore, as the reaction yield at ambient temperature is an acceptable 80% this is the temperature the following optimisation experiments will be carried out at. It is important to note there was a limit to the temperatures that could be tested due to the possibility of an undesirable thermal rearrangement. The imidate made from allylic alcohol **71** can rearrange thermally at 140 ºC. Our test at 100 ºC, 40 ºC lower than the thermal rearrangement temperature, should be adequate to ensure that the temperature is not facilitating the thermal rearrangement.[18] To ensure this was true, the corresponding allylic imidate was synthesised under basic conditions. The imidate was then subjected to the classical rearrangement conditions at 100 ºC, which resulted in none of allylic amide **83**.




**71** **83**

*Scheme 2.5: Temperature effect on the Pt-catalysed allyl amide synthesis.*

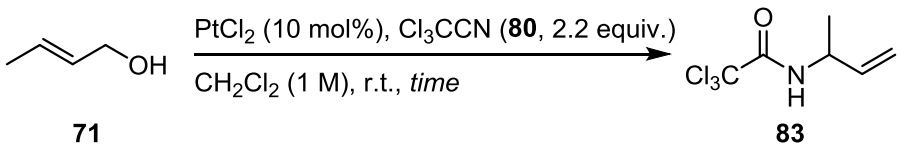
| Entry | Temperature (°C) | Yield (%) |
|---|---|---|
| **1** | Ambient temperature | 80 |
| **2** | 40 | 80 |
| **3** | 60 | 86 |
| **4** | 80 | 90 |
| **5** | 100 | 99 |
| **6**[a] | 100 | No reaction |

*a. No catalyst added*

*Table 2.5: Temperature effect on the Pt-catalysed allyl amide synthesis.*

### 2g) Examination of reaction time in the catalytic synthesis of allylic amides

The final variable that required investigation was the time the reaction takes to go to completion at ambient temperature. Isolated yields of allylic amide **83** by a reaction of allylic alcohol **71** with 2.2 equivalents of trichloroacetonitrile **(80)** in dichloromethane at 1 M at ambient temperature over 20 – 40 hours were used to identify completion of the reaction. It was shown that quantitative yields were obtained after 40 hours at room temperature (Entry 3, table 2.6). However, similar to the temperature investigation the disadvantages of the extra 20 hours reaction time outweighs the advantage of the extra 19% yield, hence a reaction time of 20 hours was employed for the substrate scope investigation of the one-pot MFC approach to the synthesis of allylic amides **83** (Scheme 2.6). Importantly, this study showed that the reactivity of the catalyst was not decreasing significantly under the reaction conditions.




*Scheme 2.6: Reaction time effect on the Pt-catalysed allyl amide synthesis.*

| Entry | Time (h) | Yield (%) |
|---|---|---|
| **1** | 20 | 80 |
| **2** | 30 | 91 |
| **3** | 40 | 99 |

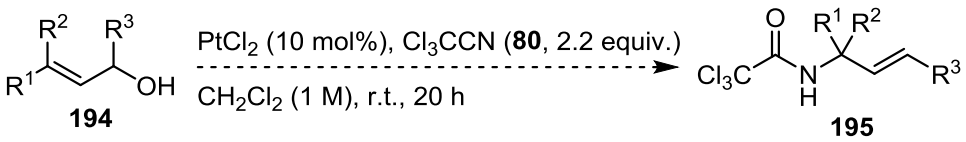
*Table 2.6: Reaction time effect on the Pt-catalysed allyl amide synthesis.*

### 2h) Optimisation conclusion

Insights gained from these studies into a one-pot MFC approach to the direct synthesis of allylic amide **83** from the corresponding allylic alcohol **71** and trichloroacetonitrile **(80)** were:

- Platinum(II) chloride in dichloromethane produced the highest yield for the synthesis.
- Concentration of the reaction did not have a huge effect on overall yield once the concentration was above 0.5 M with 1 M giving the highest yield.
- To gain the highest yields an excess of at least 2.2 equiv. of trichloroacetonitrile **(80)** was required.
- Catalyst loading at 10 mol% was optimal for the synthesis.
- Although an increase in temperature did increase yields by approximately 0.3%/ºC, this value was too small for the increase in temperature to be justified.
- Leaving the reaction to run for 40 hours resulted in a quantitative yield; however, the yield after 20 hours was adequate enough to investigate the substrate scope.

Ideal conditions for the substrate scope investigation were identified (Scheme 2.7).



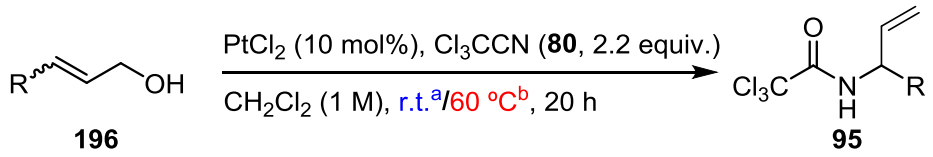

*Scheme 2.7: Optimised conditions.*

### 2i) Substrate scope – Investigating chain length of alkyl allylic alcohols

A variety of allylic alcohols **196** were examined to probe the substrate scope of the catalytic synthesis of allylic amides **196**. These experiments were conducted under optimised conditions of; trichloroacetonitrile (**80**, 2.2 equiv.), $PtCl_2$ (10 mol %), dichloromethane (1 M) at ambient temperature and pressure for 20 hours (Scheme 2.8). As a starting point, a series of acyclic homologues allylic alcohols **196** were reacted under the optimised conditions to produce allylic amides **95**. The alcohols were chosen to investigate how the chain length affects the reaction yield. The results from this study showed that extending the chain length produced allylic amides **83** and **197 - 201** in one carbon increments lead to a decreased overall yield from 85% to 36%. This follows the trend that thermally allylic imidate formed from alcohol of the 7 mebered chain length will not rearrange.[84]

When more complex allylic alcohols were attempted an increase in temperature to 60 ºC was required to obtain allylic amides **95** in acceptable yields. In consideration of the increase in temperature, the homologous series run at ambient temperature was also run at 60 ºC to understand the affect of temperature on a wider range of substrates. Reaction of allylic alcohols **196** under the conditions of 2.2 equivalents of trichloroacetonitrile **(80)**, 10 mol% of $PtCl_2$, dichloromethane (1 M) at 60 ºC for 20 hours was explored. The results of increasing temperature showed it had a small influence on the shorter chained allylic alcohols, which had an increase of the yield of 4-10% **197** and **198**. As the length of the alkyl chain was increased the yield difference increased to a maximum of 20% with allylic amide **199**. The increased difference in the yield for longer chain allylic alcohols **199** to **201** supports, the

hypothesis that the yield decreases as length increases because of the increased energy required to access the transition state.




*Scheme 2.8: Alkyl allylic alcohol substrate scope at ambient temperature and 60 °C.*

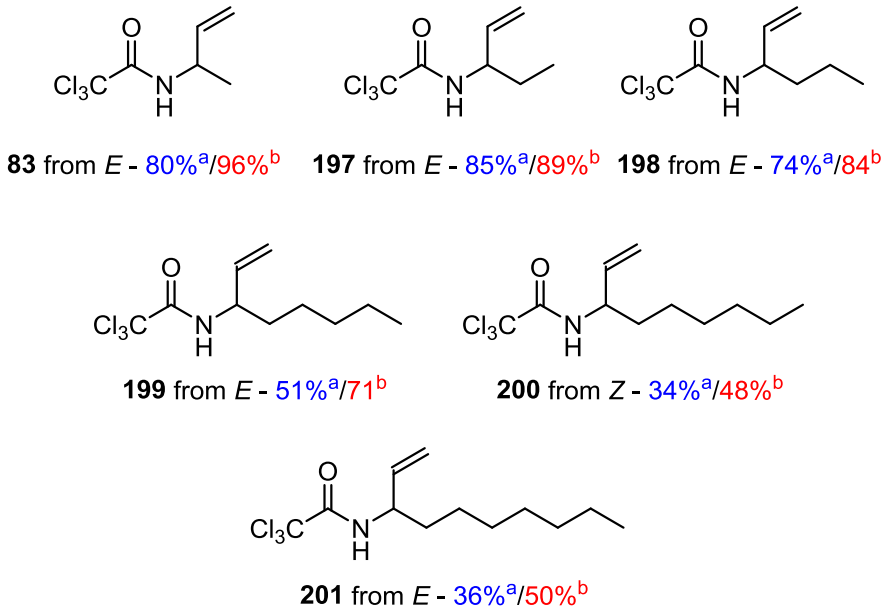
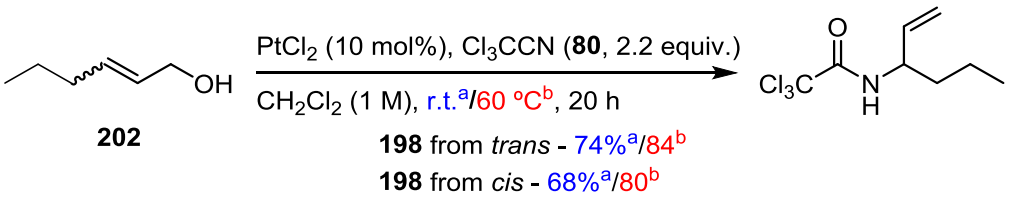



*Figure 2.2: Alkyl allylic alcohol substrate scope at ambient temperature and 60 °C.*

Another variable assessed within this series of experiments was the importance of the configuration of the olefin on the process. Comparison of the isolated yield of allylic amide **198** from the corresponding *cis* or *trans* isomer of allylic alcohol **202** showed a yield of 74% from the *trans* isomer and 68% yield from the *cis* isomer at ambient temperature and a yield of 84% from the *trans* isomer and 80% from the *cis* isomer at 60 ºC (Scheme 2.1). Although there is not a

large difference in the yield there is a decrease. The slight reduction in yield for the *cis* isomer was previously reported by Tanner et al. and is believed to be a result of the undesirable interactions in the transition state of the [3,3]-sigmatropic rearrangement.[85] An undesirable interaction in the transition state of the *cis* isomer of trichloro allylic imidate **203** between the alkyl group on the olefin and the trichloromethyl group is proposed. As a consequence the required conformation for the transition state from the *cis*- trichloro allylic imidate is more difficult to adopt. In contrast to the *trans* isomer in which this undesirable interaction is not present **204** (Figure 2.3).[85]




*Scheme 2.9: Olefin geometry effect on the Pt-catalysed allyl amide synthesis.*

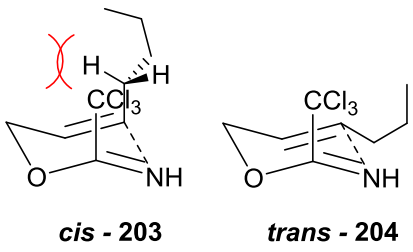
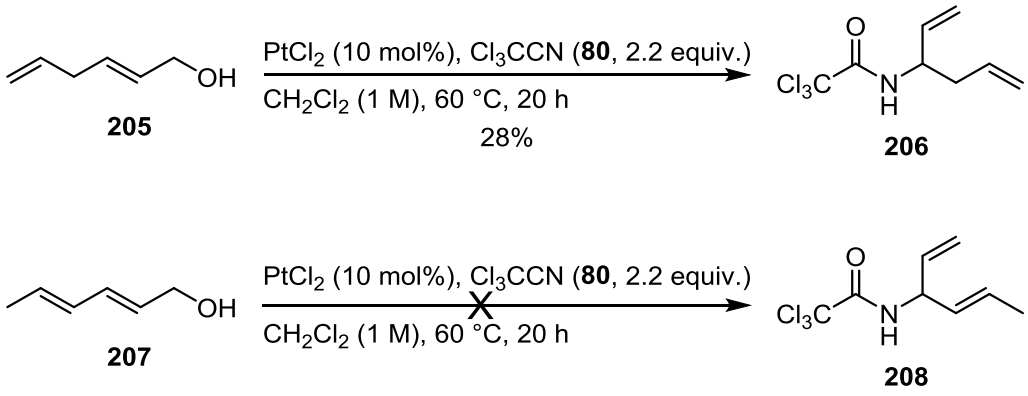



*Figure 2.3: Transition state of cis and trans imidate.*

### 2j) Substrate scope - Investigation into diene substrates

In addition to the acyclic series of allylic alcohols **196**, more complex allylic alcohols that contain a diene moiety were investigated. Allylic amide **206** was formed in 28% yield from allylic alcohol **205** when subjected to the 60 ºC conditions. In contrast, conjugated diene allylic alcohol **207** did not produce any of the desired allylic amide **208**.




*Scheme 2.10: conjugation effect on the Pt-catalysed allyl amide synthesis.*

One theory behind the lack of rearranged product formed when using diene alcohol **207** is that the nitrogen of imidate **210** will preferentially attack at the C-2 position to form oxazoline **211** after deactivation. Hydrolysis of oxazoline **211** to amino alcohol **212** can occur**,** which can undergo further nucleophilic addition reactions producing a range of by-products **213** and **214**. This mechanism is unable to occur with the unconjugated diene and therefore produces desired allylic amide **206** (Figure 2.4).

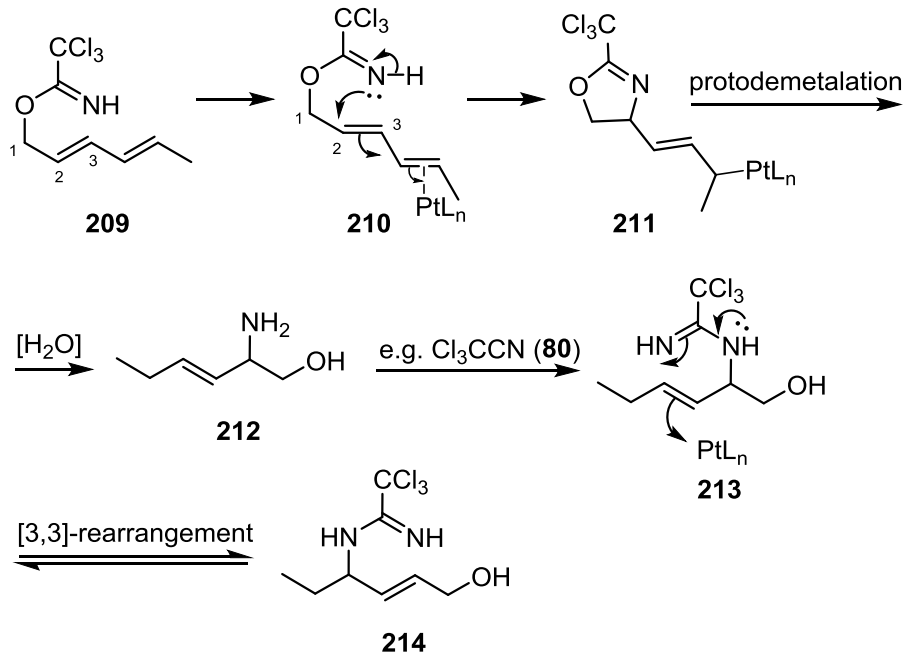
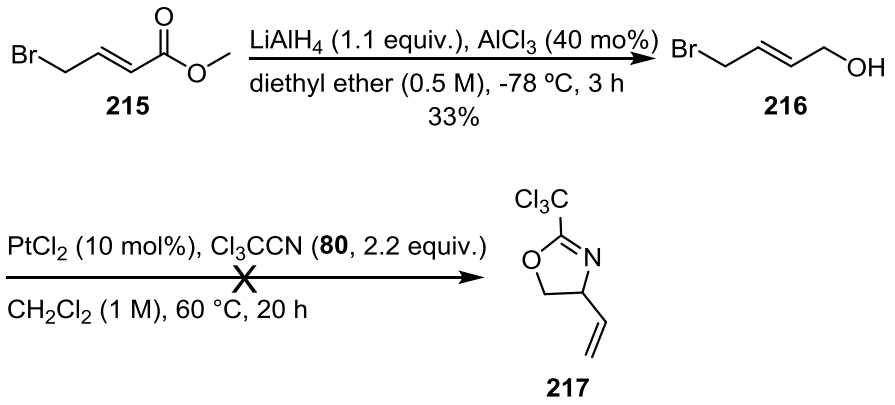



*Figure 2.4: Proposed mechanism for the reaction of the conjugated diene allylic alcohol.*

### 2k) Substrate scope - Substrates with a leaving group allyl to olefin

To further investigate the one-pot process a study on the attack of the nitrogen at the C-2 position of an allylic imidate containing a leaving group was undertaken. Bromo allylic alcohol **216** was used as the allylic alcohol substrate. Bromo allylic alcohol **216** was chosen due to the excellent leaving abilities of halide ions, as shown by the pKa = 0.9 for HBr in DMSO.[86] It was hoped that oxazoline **217** would form from bromo allylic alcohol **216**, hence providing evidence for the mechanism (*cf.* Figure 2.4). Bromo allylic alcohol **216** was synthesised by reducing commercially available methylester derivative **215**. Bromo allylic alcohol **216** was subject ed to the standard conditions at 60 ºC. Unfortunately, this reaction did not produce any identifiable products with no recovered starting material. It is likely that 2-

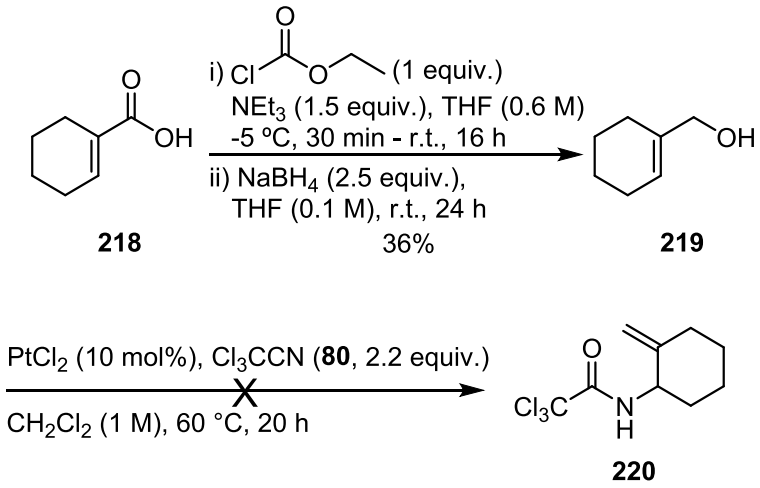
trichloro oxazolines **217** are not stable under the reaction conditions (Scheme 2.11).




*Scheme 2.11: Attempted bromo allylic alcohol substrate.*

### 2l) Substrate scope – Investigation into cyclic allylic alcohols

To explore the scope of the methodology, the synthesis of cyclic allylic amides were also attempted. First, cyclohex-1-en-1-ylmethanol **219** was synthesised from the reduction of commercially available carboxylic acid derivative **218** via reaction of ethyl chloroformate and sodium borohydride. When cyclic allylic alcohol **219** was subjected to the standard conditions of the one-pot allylic amide synthesis, none of the desired rearranged product **220** was observed.




*Scheme 2.12: Unsuccessful rearrangement of cyclic allylic alcohol.*

The inability of this substrate to rearrange could be due to a number of reasons; either the strain caused by the cyclic nature on the allylic alcohol, the extra steric hindrance around the platinum binding site in relation to the cyclisation induced rearrangement or the selectivity of the attack of the nitrogen. The most probable cause for the failure of the reaction is the extra steric hindrance around the olefin causing difficulties with binding of the metal catalyst. With the allylic imidate **82** the platinum catalyst can bind easily to the olefin because there is little steric hindrance **221**, however, with cyclic imidate **222** the ring is blocking the position for the platinum to bind to the olefin **223** causing no activation (Figure 2.5). This theory is reinforced by the rearrangement of similar substrates only being achieved via a thermal rearrangement at temperatures of 140 ºC.[87] This study showed that cyclic allylic alcohol **218** and similar substrates are not viable for the one-pot allylic amide synthesis.

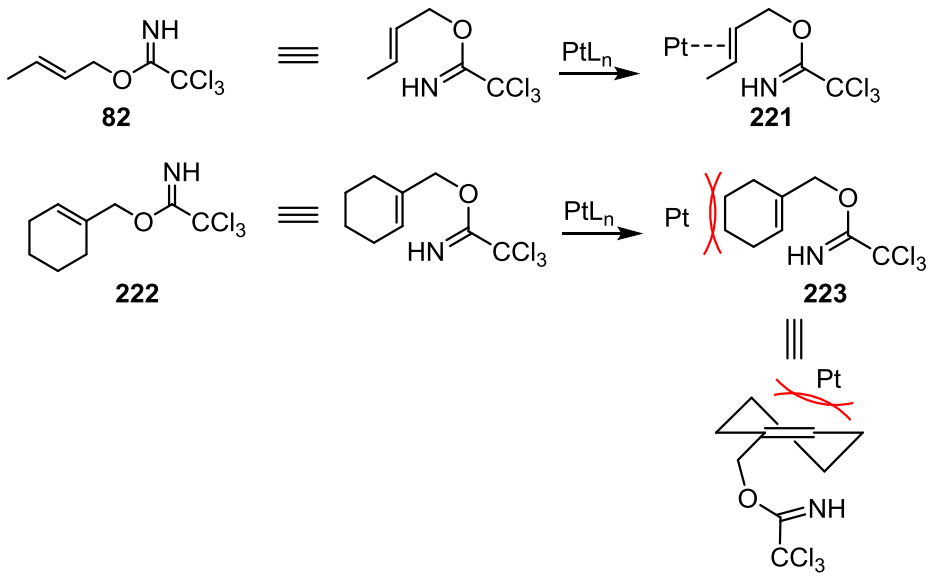
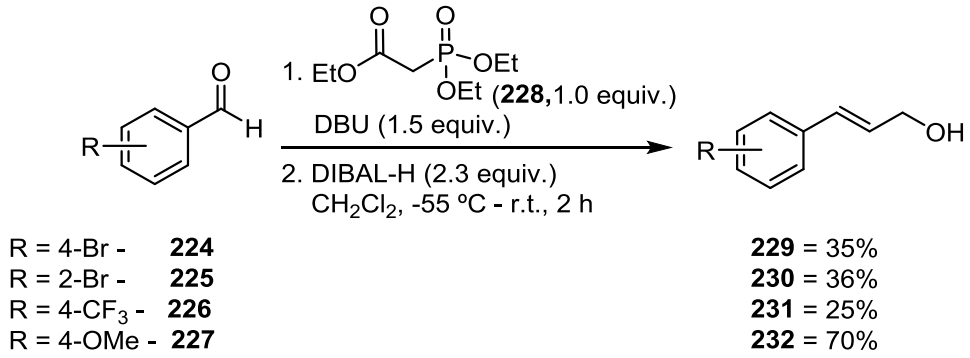



*Figure 2.5: Proposed reason for no allylic amide observed with cyclic allylic alcohol.*

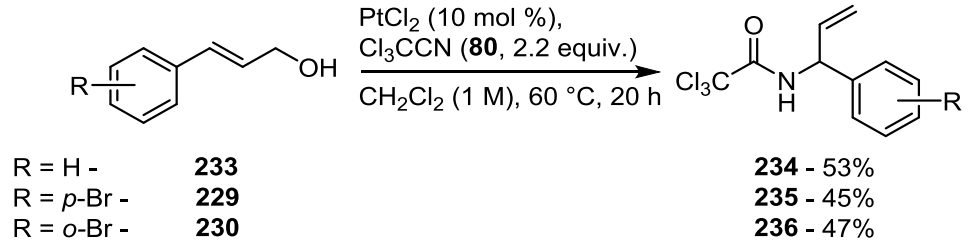
### 2m) Substrate scope - Investigation into the electronics of the olefin

Next the electronics of the olefin in the allylic alcohol were studied. It has been shown that the electronics of the system significantly affect the [3,3]-sigmatropic rearrangement.[88] To accomplish this investigation into the effects of the electronics of the system of the process a number of cinnamyl alcohols were synthesised with varying functional groups attached to the aromatic ring. The cinnamyl alcohol substrates were synthesised via a Horner-Wadsworth-Emmons olefination of the corresponding aromatic aldehyde **224** to **227** using phosphate ester **228** under basic conditions.[89] The newly formed allylic esters were reduced in situ with DIBAL-H to give cinnamyl alcohols **229** to **232** in 25% to 70% yield (Scheme 2.13).[88] Although moderate yields were obtained, enough of the allylic alcohol products were produced to start the investigation into the electronic effects of the olefin.



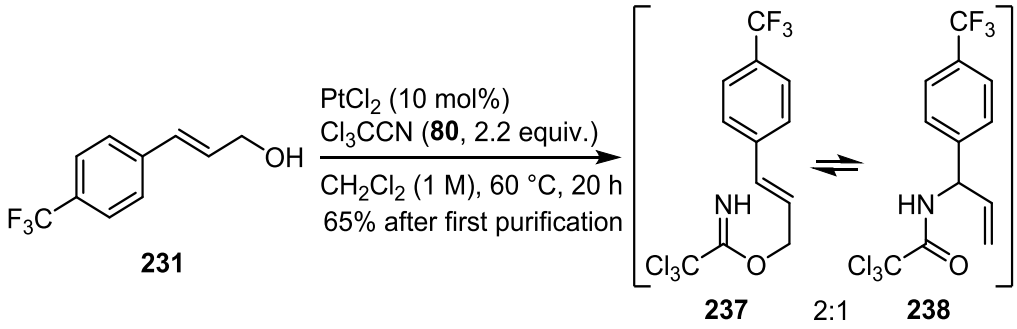

*Scheme 2.13: Synthesis of cinnamyl alcohol substrates.*

The cinnamyl alcohol substrates were subjected to the conditions identified for the primary alkyl allylic alcohols at 60 ºC (Scheme 2.14). Cinnamyl alcohol **233** was the highest yielding of the aromatic substrates that were tested and produced allylic amide **234** in a 53% yield. Other successful cinnamyl alcohols were the *p*- and *o*-bromo substrates, which produced allylic amides **235** and **236** in 45% and 47% respectively. If the yield of allylic amide **234** from cinnamyl alcohol is considered as the midpoint of the investigation, being neither electron rich or electron deficient, then by comparing the yields of the *ortho*-bromo substrates it can be deduced that making the olefin more electron deficient decreases the reactivity of the olefin and the overall reaction. Additionally, changing the position of the bromo substituent did not decrease the yield significantly suggesting the position of the group has little effect on the one-pot synthesis.



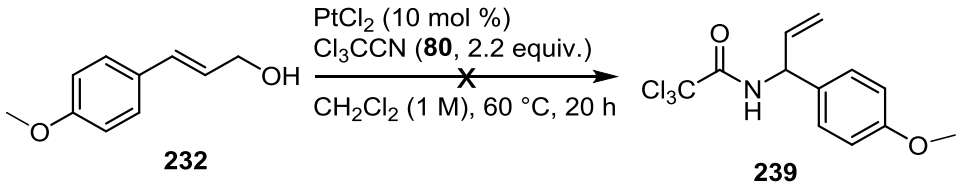

*Scheme 2.14: Reaction of cinnamyl substrates under the standard conditions.*

Interestingly, Subjection of trifluoro cinnamyl alcohol **231** to the standard reaction conditions resulted in a mixture of imidate **237** and allylic amide **238** in a 2:1 ratio with a 65% mass recovery (Scheme 2.15). This mixture was purified by flash column chromatography on silica gel, which resulted in a lower yield of the 2:1 mixture of imidate to amide. This mixture was purified further however the same result was observed. This observation suggests that the imidate **237** and amide **238** are in equilibrium with each other at ambient temperature and separation of the two compounds is not possible. By using bond dissociation constants, the enthalpy barier between the two products can be calculated as -233 in the forward direction. This is a small energy barrier that **238** needs to overcome to produce 237 and vice versa.



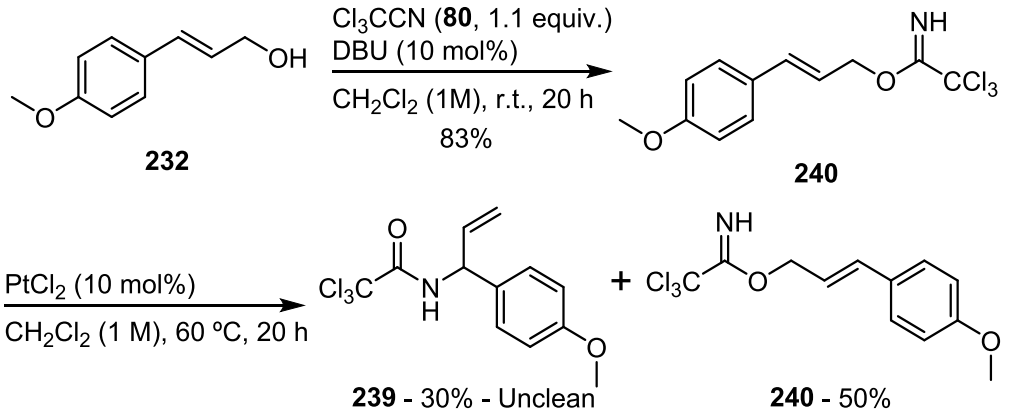

*Scheme 2.15: One-pot allylic amide synthesis of $CF_3$ substrate of cinnamyl alcohols.*

From the results above it would be expected that a strong electron donating group, such as a methoxy, would produce a higher yield of allylic amide **139** However, methoxy cinnamyl alcohol **232** did not produce any amide **239** with recovered starting alcohol accounting for 80% of the mass recovery. The large amount of recovered cinnamyl alcohol **232** suggests it is the nucleophilic addition step that is affected by the electron donating group.




*Scheme 2.16: One-pot unsuccessful methoxy cinnamyl substrate.*

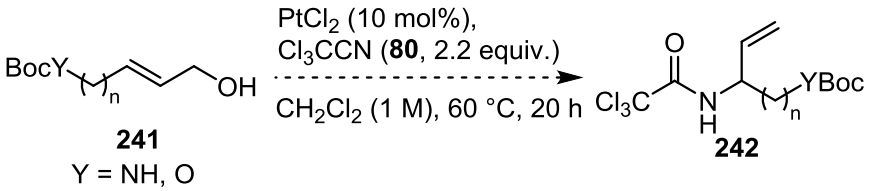
To investigate this theory imidate **240** was formed under catalytic basic conditions in 83% yield and used without further purification. Cinnamyl imidate **240** was subjected to rearrangement conditions with $PtCl_2$ at 60 ºC to identify if the rearrangement was achievable with this substrate. The rearrangement experiments resulted in a maximum of 30% recovery of amide **239** with an inseparable unidentified impurity and 50% recovered imidate **240** (Scheme 2.17). The poor rearrangement yield combined with the large amount of recovered starting material suggests that this substrate is not viable for the one-pot allylic amide synthesis.




*Scheme 2.17: Step-wise allylic amide synthesis of cinnamyl methoxy substrate.*

## 2n) Substrate scope - Investigation into thermally labile protecting groups

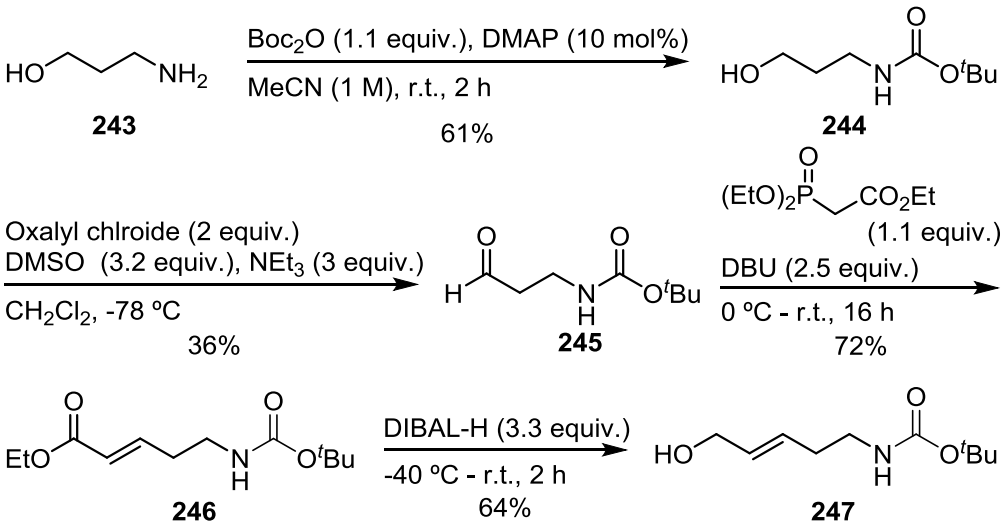
Traditionally the Overman rearrangement has been promoted under thermal conditions. Therefore attempts to use allylic alcohols **241** that contained a thermally labile moiety, which would not survive the thermal Overman protocol, in the MFC protocol were undertaken. To examine the stability of thermally labile protecting groups under the one-pot allylic amide synthesis conditions, substrates were made that contained a Boc group. The Boc protecting group was chosen because it can be removed under thermal conditions[90] and it was believed that it will not interact with the platinum catalyst (Scheme 2.18).




*Scheme 2.18: Proposed synthesis of Boc protected allylic amides.*

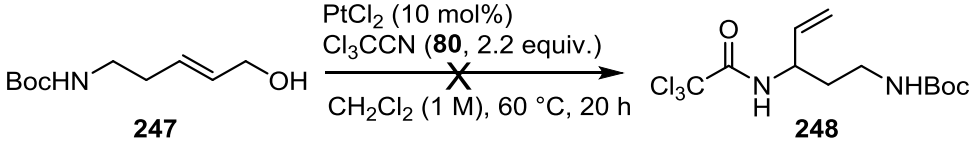
The first allylic alcohol that was targeted for synthesis was *(E)-tert*-butyl (5-hydroxypent-3-en-1-yl)carbamate **(247)**. This allylic alcohol was chosen due to its quick, straightforward and inexpensive synthesis by Deslongchamps et al.[91] To begin the synthesis of allylic alcohol **247**, 3-aminopropanol **(243)** was protected using the conditions previously developed by Appella et al.[92] to form alcohol **244** in 61% yield. Alcohol **244** was then reacted with oxalyl chloride and dimethyl sulfoxide under Swern oxidation conditions to produce aldehyde

**245**.[93] Aldehyde **245** underwent a HWE reaction to produce *trans*-α,β–unsaturated ester **246** in 72% yield.[94] Ester **246** was selectively reduced with DIBAL-H to give the desired allylic alcohol **247** in 64% (Scheme 2.19).[91]



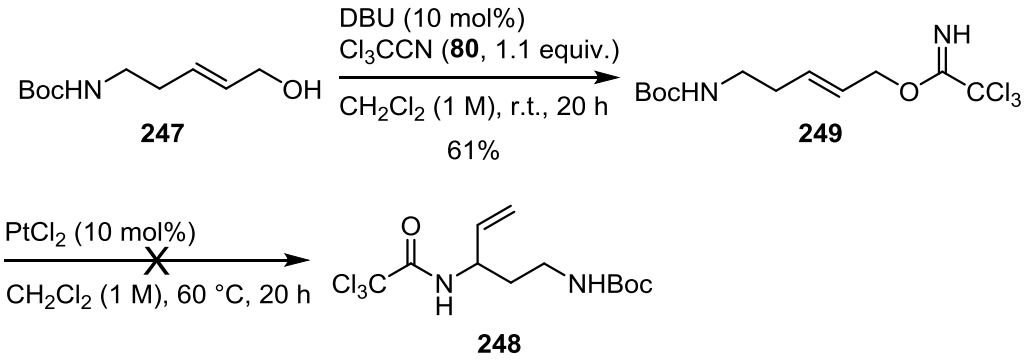

*Scheme 2.19: Synthesis of amino protected allylic alcohol.*

To probe the viability of the one-pot process on a substrate containing a thermally labile protecting group, *(E)-tert*-butyl (5-hydroxypent-3-en-1-yl)carbamate **(247)** was subjected to the standard one-pot allylic amide conditions. Unfortunately, none of the desired rearranged product **248** was isolated with recovered starting material accounting for 87% of the mass balance (Scheme 2.20).




*Scheme 2.20: Attempted one-pot allylic amide synthesis of amino protected allylic alcohol.*

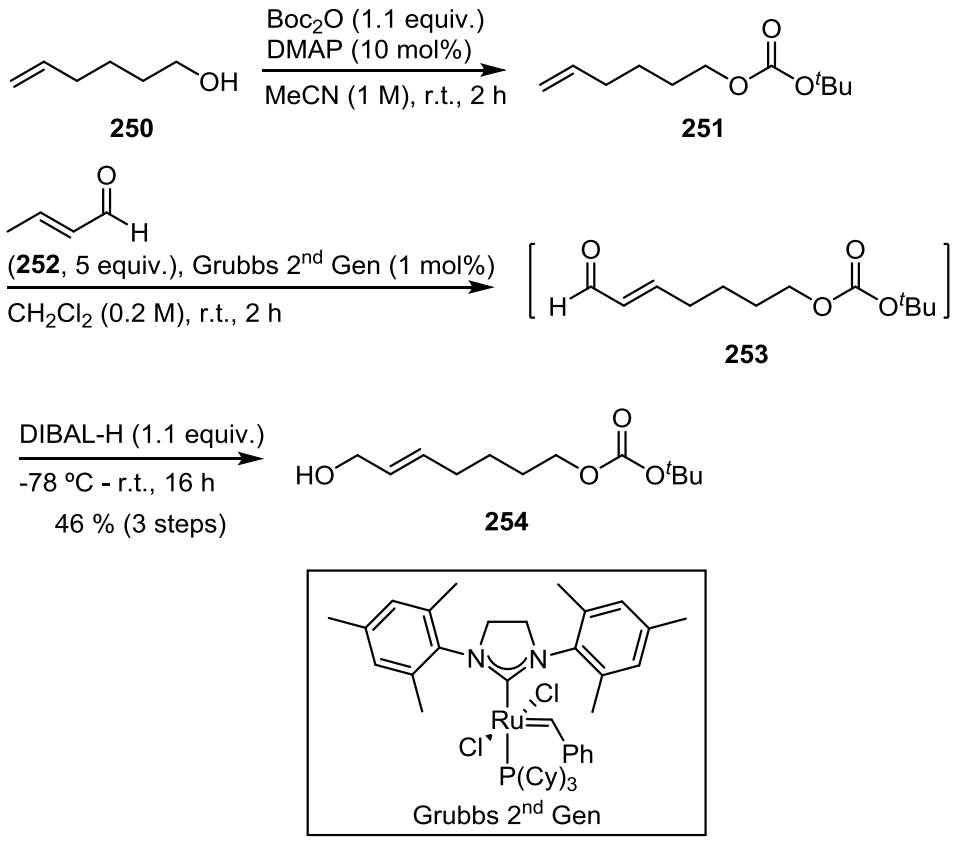
To understand which step was problematic in the one-pot synthesis, the corresponding allylic imidate **249** was formed via the classical conditions with catalytic DBU from allylic alcohol **247**. Subjection of allylic imidate **249** to the rearrangement conditions with platinum(II) chloride only gave trace amount of amide **248** when the crude residue was subjected to NMR analysis (Scheme 2.21).




*Scheme 2.21: Attempted rearrangement of amino protected allylic imidate.*

The unsuccessful rearrangement of allylic imidate **249** suggested that a different substrate was required for the investigation into thermally labile protecting groups. Two variables that will be altered for the new substrate that could have been the cause of the unsuccessful reactions are i) the free NH that could be interacting in the rearrangement or deactivating the catalyst by forming a ligand with the aid of the Boc group and ii) the distance between the Boc group and the olefin, as it has been shown that functionality close to the olefin has a great effect on the one-pot synthesis (Scheme 2.11). The new compound identified as a viable one-pot allylic amide substrate was *(E)-tert*-butyl (7-hydroxyhept-5-en-1-yl) carbonate **(254)**. The difference between the two substrates is the heteroatom that is protected is an oxygen atom, eliminating the NH that could bind to the metal centre. Also the distance

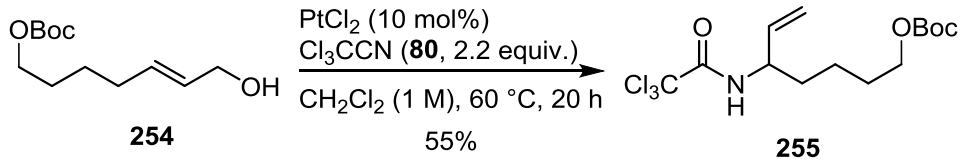
between the olefin and the heteroatom has doubled from a two to a four carbons. To synthesise the desired substrate, hex-5-en-1-ol **(250)** was protected with a Boc group and then subjected to cross metathesis conditions with crotonaldehyde **(252)** to afford aldehyde **253**. The crude reaction mixture was reduced with DIBAL-H, to give the desired protected allylic alcohol **254** in 46% overall yield from hex-5-en-1-ol **(250**, Scheme 2.22).




*Scheme 2.22: Synthesis of alcohol protected allylic alcohol.*

Protected allylic alcohol **254** was subjected to the one-pot allylic amide synthesis at 60 ºC to produce the desired Boc protected allylic amide **255** in 55% yield (Scheme 2.23). This provides evidence that the Boc group attached

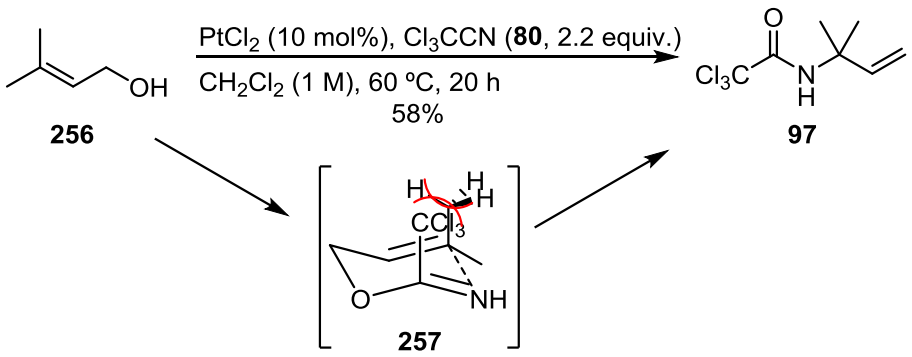
to an oxygen atom is stable under the one-pot allylic amide synthesis conditions.




*Scheme 2.23: Rearrangement of Boc protected allylic alcohol.*

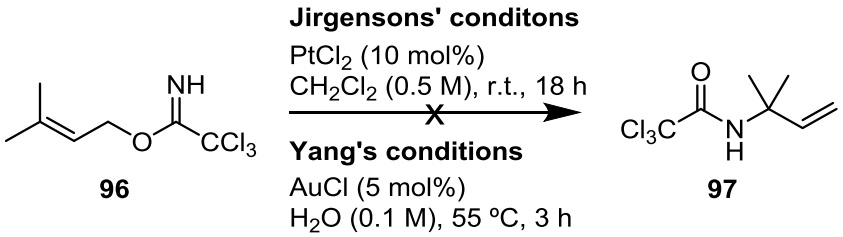
**2o) Substrate Scope - Investigation into forming quaternary carbon centres**

To further investigate the versatility of the method a difficult substrate was selected that previous noble metal rearrangements could not rearrange.[44, 95] Allylic imidate **257** is a challenging substrate to rearrange via a metal catalysed rearrangement because of the steric hindrance of the two methyl groups. Pleasingly, subjection of allylic alcohol **256** to the one-pot conditions at 60 ºC afforded allylic amide **97** in 58% isolated yield (Scheme 2.24).



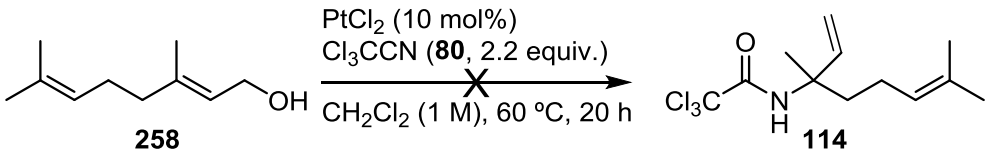

*Scheme 2.24: Rearrangement of 3-methylbut-2-en-1-ol.*

This is a significant improvement in comparison to Jirgensons' and Yang's conditions in which trace amounts of rearranged product **97** was obtained with platinum(II) chloride and gold(I) chloride (Scheme 2.25).[44, 95] Additionally, base has been eliminated from the process and the number of steps has been decrease.




*Scheme 2.25: Previously reported unsuccessful rearrangement conditions.*

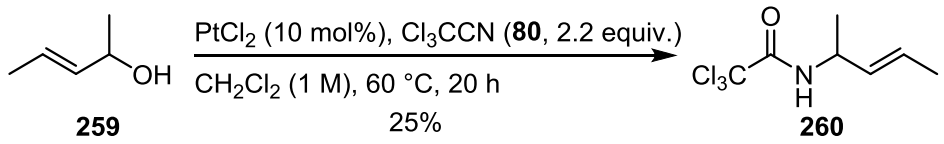
Due to the successful rearrangement of 3-methylbut-2-en-1-ol, geraniol **(258),** was subjected to the same conditions. Unfortunately, geraniol (**258)** did not produce any of the desired allylic amide **114**, showing that this substrate is not viable for the one-pot allylic amide synthesis (Scheme 2.26). This is most likely due to the ability for the allylic alcohol to bind to the metal complex from the positions of the olefins causing deactivation of the catalyst (*cf.* Figure 2.2).




*Scheme 2.26: Attempted rearrangement of geraniol.*

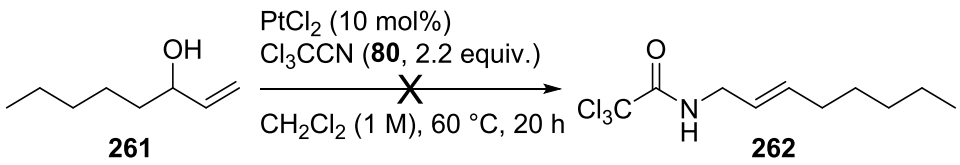
### 2p) Substrate scope - Investigation into secondary allylic alcohols

To further the substrate scope, a number of secondary allylic alcohols were attempted under the standard conditions. (*E*)-Pent-3-en-2-ol **(259)** was found to give the desired allylic amide **260** in a moderate 25% yield (Scheme 2.27). The decrease in yield could be a result of increased steric interaction caused by the secondary nature of the alcohol during the nucleophilic addition step. However, as this is one of the few examples of a metal mediated rearrangement of a secondary allylic alcohol it is more likely that the rearrangement step is the cause of the decrease in yield.



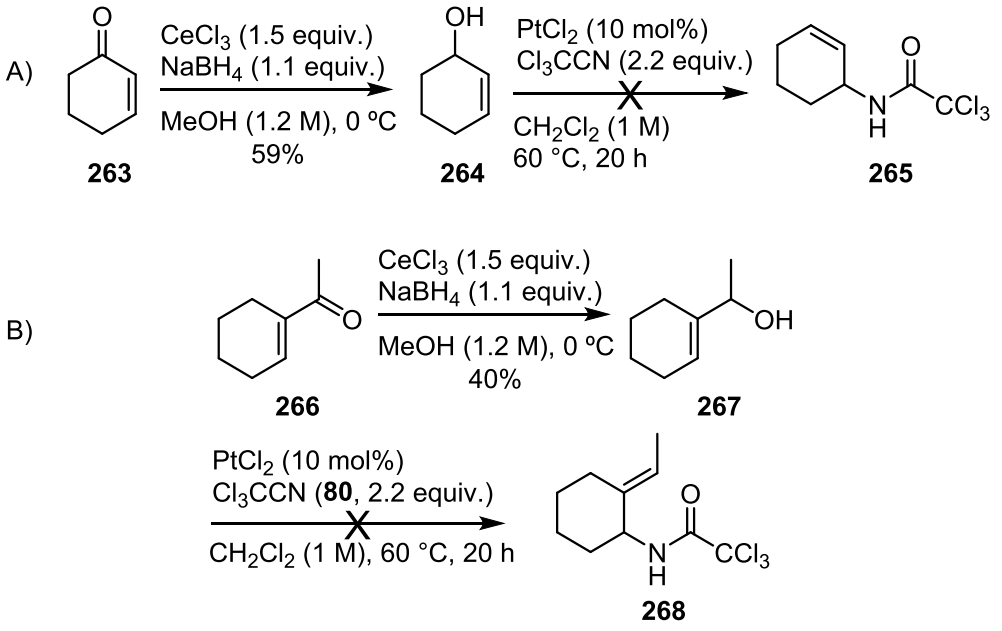

*Scheme 2.27: Successful one-pot of allylic amide synthesis of a secondary allylic alcohol.*

Upon attempting a longer chained secondary allylic alcohol, octen-2-ol **(261)**, product **262** was not observed (Scheme 2.28). This lack of success of the reaction could be due to the extra sterics, however, it is more likely that the failure is due to the terminal olefin in this substrate causing undesirable side reactions (*cf.* Figure 1.13).[34]




*Scheme 2.28: Attempted rearrangement of octen-2-ol.*

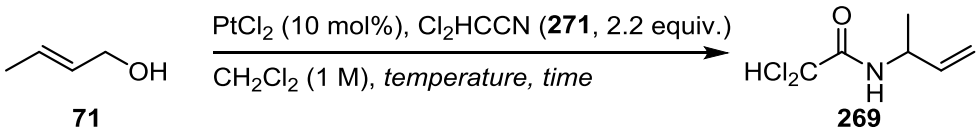
In addition to acyclic secondary allylic alcohol, two cyclic allylic alcohols, **264** and **267,** were subjected to the standard conditions. Cyclic allylic alcohol **264** and **267** were synthesised by reducing the commercially available corresponding cyclic ketone **263** and **266** with cerium(III) chloride and sodium borohydride under Luche reduction conditions.[96] These mild conditions are required due to the competing conjugate reduction pathway, which removes the olefin. Subjecting the cyclic secondary allylic alcohols **264** and **267** to the standard conditions produced none of the amides **265** and **268** (Scheme 2.29). This result is not unexpected as cyclic primary allylic alcohol **219** did not work and a decrease in yield was observed for secondary allylic alcohols (*cf*. Scheme 2.12).




*Scheme 2.29: Cyclic secondary allylic alcohol synthesis and attempts.*

### 2q) Substrate scope - Investigation into less activated nitriles

As discussed previously the overall aim of this work was to develop a method for the conversion of nitriles to allylic amides. With this in mind, the less activated nitrile dichloroacetonitrile **(271)** was reacted with (*E)*-2-buten-1-ol **(71**, Scheme 2.30). It would be expected that this nitrile has a decrease in reactivity due to the lesser inductive withdrawing effects of the dichloromethyl moiety compared to the trichloromethyl moiety. The reaction was run at a variety of temperatures to probe the feasibility of the process. Running the reaction at ambient temperature after 20 hours or 40 hours resulted in only 10% yield (Entries 1 and 2, table 2.7). This suggested that the catalyst was deactivated after the first cycle. The temperature of the reaction was subsequently elevated to 60 ºC and the reaction was run for 20 hours, which increased the yield to 20% (Entry 3, table 2.7). Increasing the temperature further to 80 ºC gave an increased yield of 25% (Entry 4, table 2.7). If the temperature was increased further multiple products were formed which were inseparable and unidentifiable (Entry 5, table 2.7).



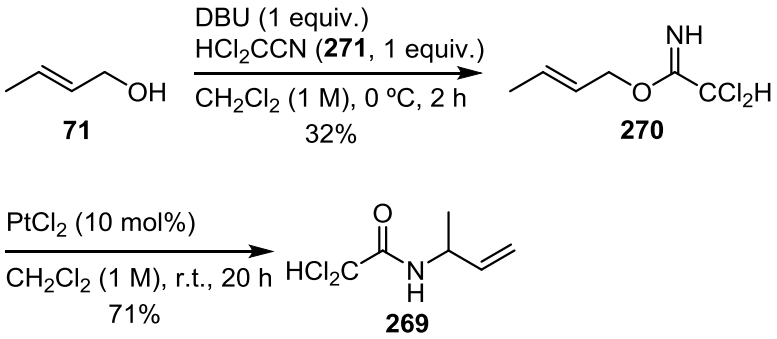

**71** **269**

*Scheme 2.30: One-pot dichloro allylic amide synthesis.*

| Entry | Temp (ºC) | Time (h) | Yield (%) |
|---|---|---|---|
| **1** | r.t. | 20 | 10 |
| **2** | r.t. | 40 | 10 |
| **3** | 60 | 20 | 20 |
| **4** | 80 | 20 | 25 |
| **5** | 100 | 20 | Unidentifiable products |

*Table 2.7: Optimisation of the one-pot dichloro allylic amide synthesis.*

To investigate which step of the process was leading to a decrease in yield, dichloro allylic imidate **270** was synthesised and rearranged under classical conditions with stoichiometric base producing the desired allylic imidate **270** in 32% yield. Subsequently rearrangement with $PtCl_2$ at ambient temperature produced dichloro allylic amide **269** in 71% yield (Scheme 2.31). Thus, the initial nucleophilic addition step seemed to limit the overall process. The successful rearrangement also showed that the catalyst does not get deactivated in this step. The moderate yield of the one-pot process is comparable to the uncatalysed two-step approach.




*Scheme 2.31: Two-step synthesis of dichloro allylic amide.*

The decrease in yield in the formation of dichloro allylic imidate **270** is believed to be because of the decrease in activity of the nitrile and the acidic nature of the alpha proton. The acidic nature of the alpha proton is a factor because once the proton in dichloroacetonitrile **(271)** is removed by a base, a ketenimine **273** can be formed. The intermediate can participate in a number of possible side reactions decreasing the overall yield of the formation of the desired dichloro allylic imidate **270** (Figure 2.6). The one-pot method

eliminates the need for base and allows for the synthesis of dichloro allylic amides **269**

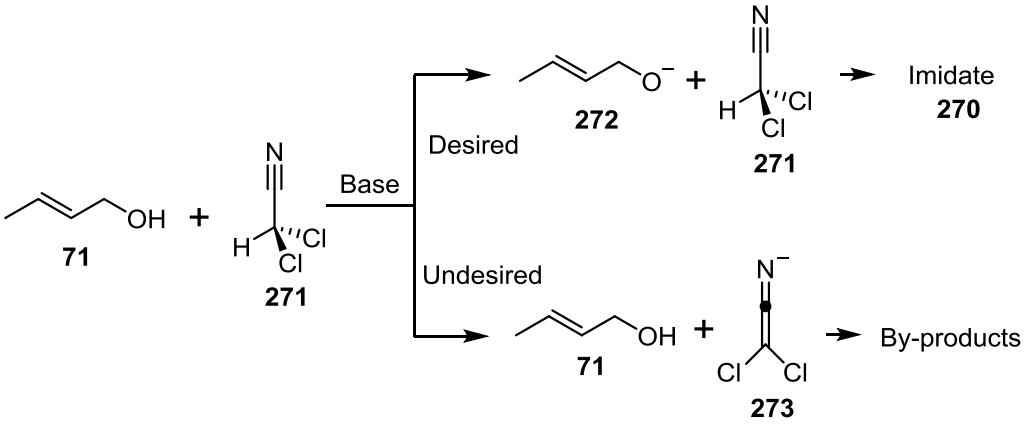



*Figure 2.6: Undesirable deprotonation of dichloroacetonitrile **(271)***

## 2r) Mechanistic studies

In order to further develop a MFC approach to nitrile activation a mechanistic study was undertaken. The proposed mechanism for the MFC approach to allylic amide synthesis from the corresponding allylic alcohol and nitrile is believed to involve two separate mechanistically distinct steps. The first part of the catalytic cycle is based on the literature precedent for the formation of platinum bound imidates (Figure 2.7).[18] The process starts with the activation of trichloroacetonitrile **(80)** by platinum(II) chloride to form activated nitrile complex **274**. Activated nitrile **274** is susceptible to nucleophilic attack from allylic alcohol **182** followed by a proton transfer to produce platinum imidate **275**. The second part of the cycle is based on literature precedent for the formation of allylic amides from the corresponding allylic imidate with a metal catalyst.[35] A platinum(II) complex binds to olefin **276** to activate it for a cyclisation induced [3,3]-sigmatropic rearrangement to form cyclic oxonium

**278**. Once the cycle is formed the platinum species is liberated by the nucleophilic attack of another trichloroacetonitrile molecule **(80)**, which neutralises cyclic intermediate **278** forming the desired allylic amide **95** and platinum(II) complex **274**. The main question that arises from combining the two known reaction mechanisms is whether the same platinum species is used to activate the nitrile for nucleophilic addition as well as activating the olefin for the rearrangement in intermediate **276**. Transition state **277** in which a platinum complex is bound to nitrogen and the olefin of the allylic imidate simultaneously could be envisaged (Figure 2.7).

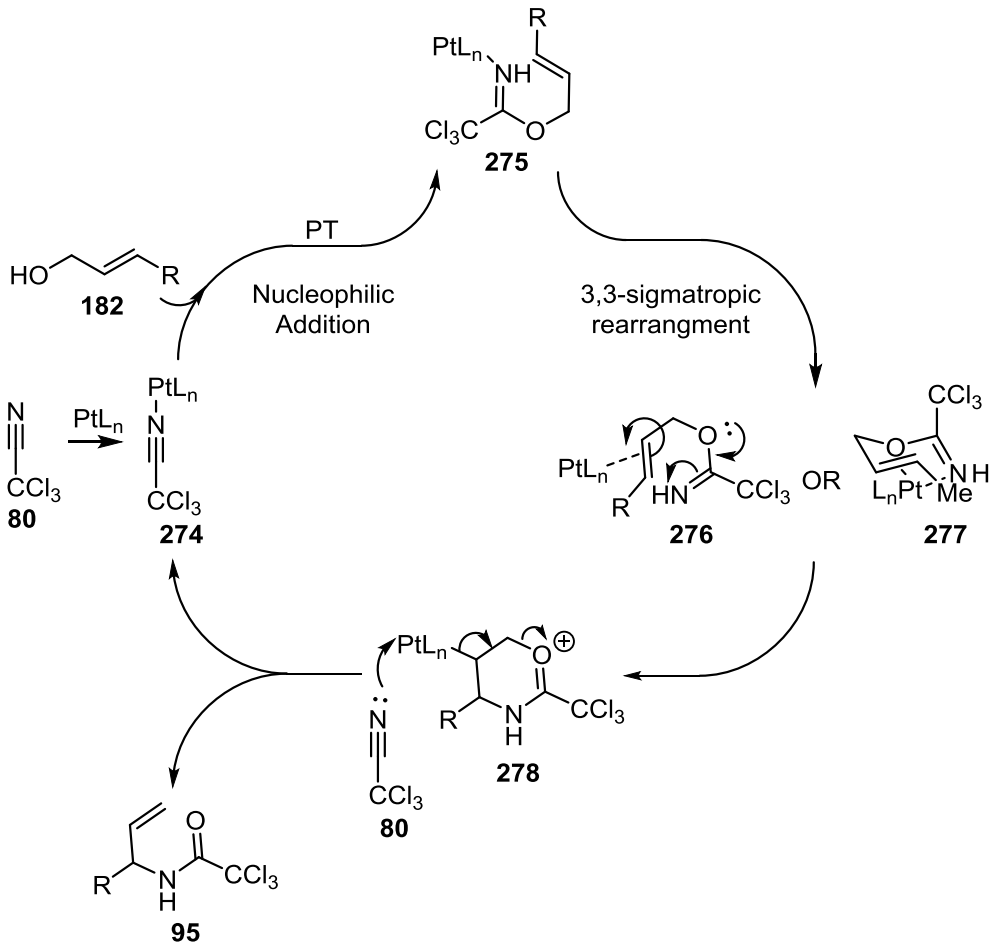



*Figure 2.7: Proposed catalytic cycle.*

A number of experiments were designed to investigate the mechanism of the one-pot synthesis of allylic amides. The first experiment was designed to look at each step within the reaction and try and observe any intermediates within the process. Thus, the reaction of (*E)*-2-buten-1-ol **(71)** with trichloroacetonitrile **(80)** was monitored hourly by $^{1}H$ and $^{13}C\{1H\}$ NMR. For the experiment, a reaction of (*E)*-2-buten-1-ol (**71,** 1 equiv.), trichloroacetonitrile (**80**, 2.2 equiv.) and platinum(II) chloride (10 mol%) in deuterated dichloromethane was placed in an NMR machine. The reaction was monitored by $^{1}H$ and $^{13}C\{^{1}H\}$ NMR hourly for 19 hours at ambient temperature to try and identify any intermediates (Figure 2.8). The overlay of the $^{1}H$ NMR spectra shows clearly that as allylic alcohol **71** decreases in concentration, allylic amide **83** increases (Figure 2.9). The peaks that clearly show this trend are 2, 3, 15 and 17. Whilst there are a number of possible intermediates which we hoped to observe, **82, 279** to **281**, we were unable to unambiguously assign any of the novel $^{1}H$ peaks to them.

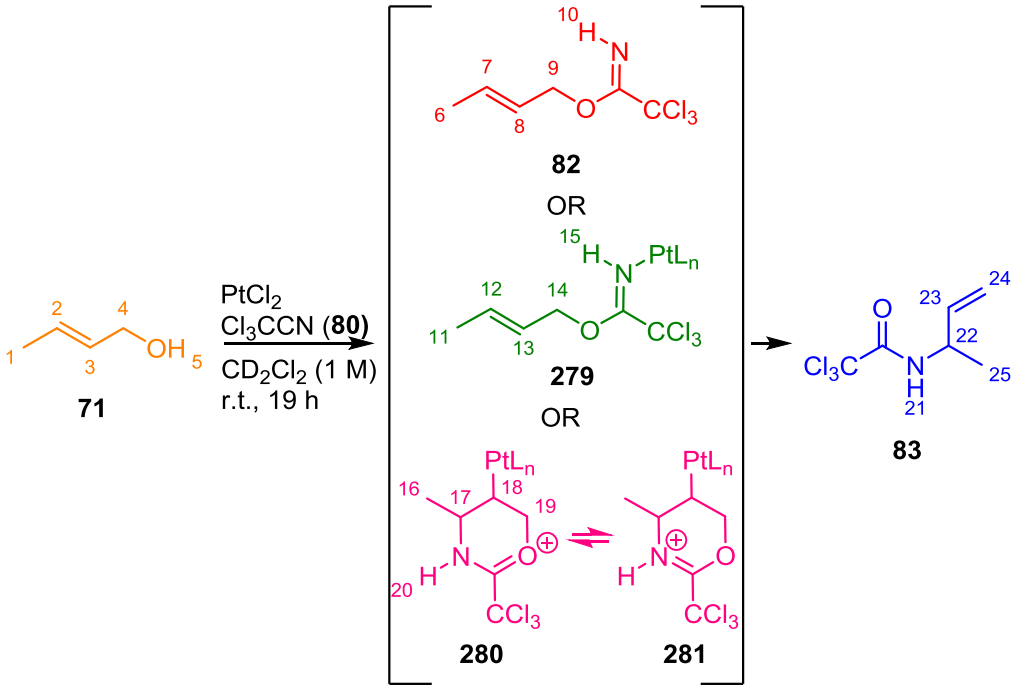



*Figure 2.8: Assigned structures for $^{1}H$ NMR analysis*

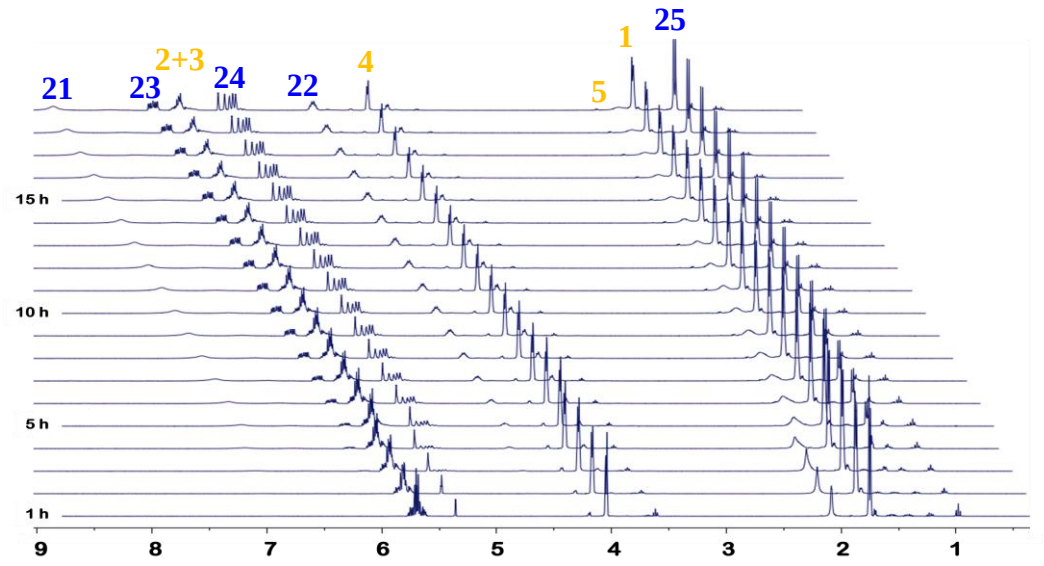
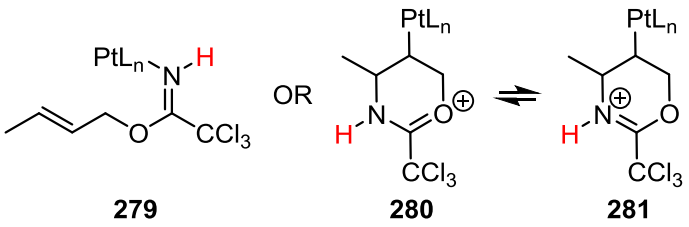



*Figure 2.9: layered $^{1}H$ spectra for the monitored experiment*

As the extra peaks observed in the $^{1}$H NMR spectra do not correspond to any known isolable compound, all the peaks corresponding to alcohol **71,** amide **83** and the solvent were removed from the spectra after the reaction had run for 19 hours. This alteration of the spectra allowed the low intensity peaks of the unidentifiable intermediates to be visible (Figure 2.11). The low intensity of the peaks suggests that intermediates are present in the reaction mixture however, without forming the intermediates and analysing these separately it is difficult to say for sure what structures the peaks correspond to. There are some deductions that can be made, which suggest what intermediate the peaks correspond to. For example, the broad singlet at 6.3 ppm suggests that the peak corresponds to a proton directly attached to a nitrogen atom. This could correspond to the platinum bound imidate **279** or the N-H within the charged cyclised intermediate **280** or **281** (Figure 2.10). Further predictions are difficult as the multiplets are not clear due to the low intensity of these intermediate and the resolution of the machine.




**279** **280** **281**

*Figure 2.10: Cyclic intermediates*

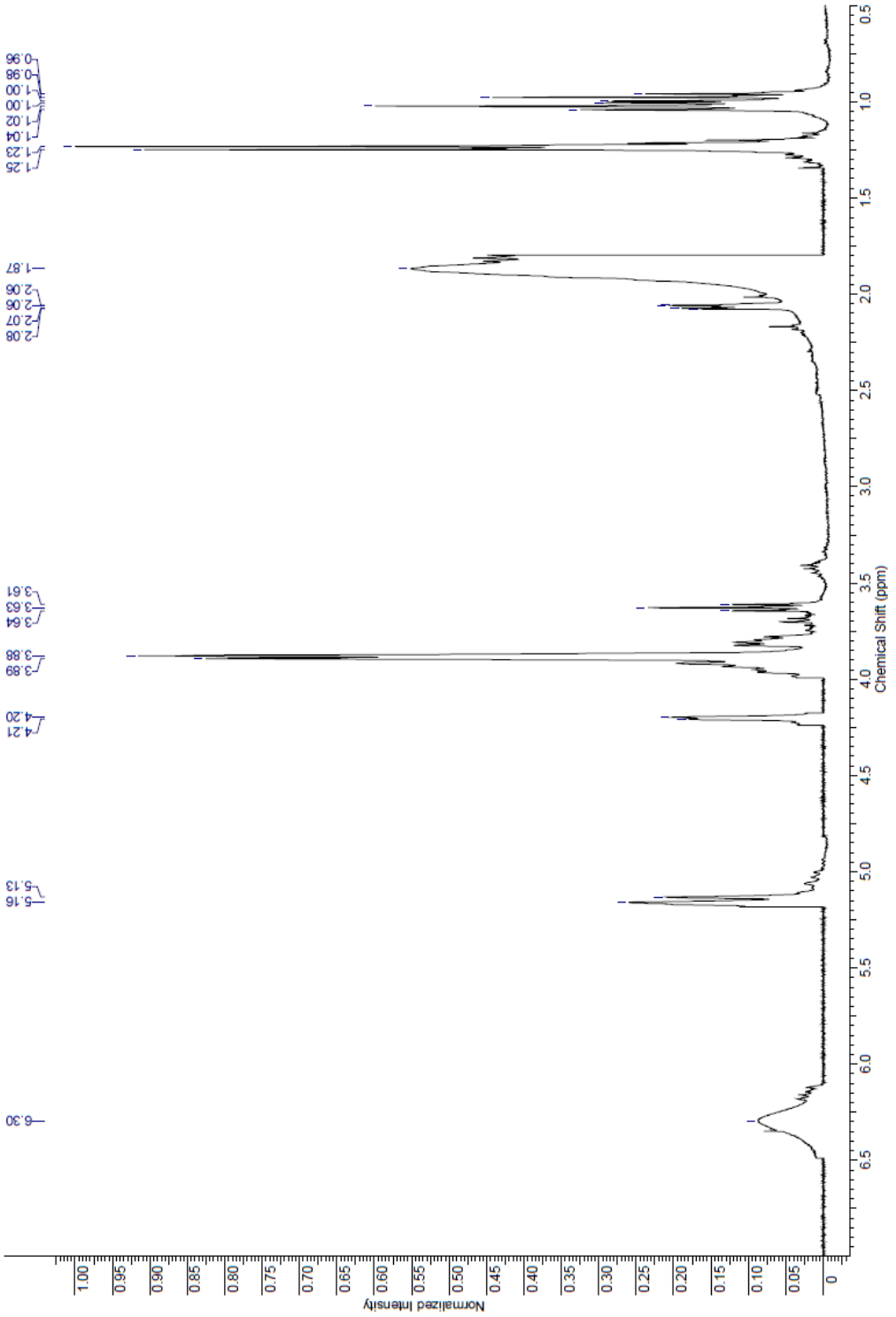



*Figure 2.11: $^{1}H$ spectra after 19 hours with known compounds removed*

To further investigate the process $^{13}C\{^{1}H\}$ NMR spectra was taken at 1 hour intervals for 19 hours. $^{13}C\{^{1}H\}$ NMR should give a clearer view of any platinum bound intermediates because a direct comparison can be made

between free nitriles and imidates and the platinum bound compounds. Similarly, to the $^{1}$H NMR spectra the overlay of the $^{13}$C{$^{1}$H} NMR spectra of the same experiment showed clearly that as allylic alcohol **71** decreases in concentration, allylic amide **83** increases (Figure 2.13). The peaks that show this clearly are 2, 3, 15 and 17. Unfortunately, it was not possible to unambigusly assign any peaks that correlate to the intermediates **82**, **279** to **281**. The identifiable peaks in the $^{13}$C study are firstly allylic alcohol **71** and nitrile **80** starting material. The only other identifiable compound within the spectra is allylic amide **83**

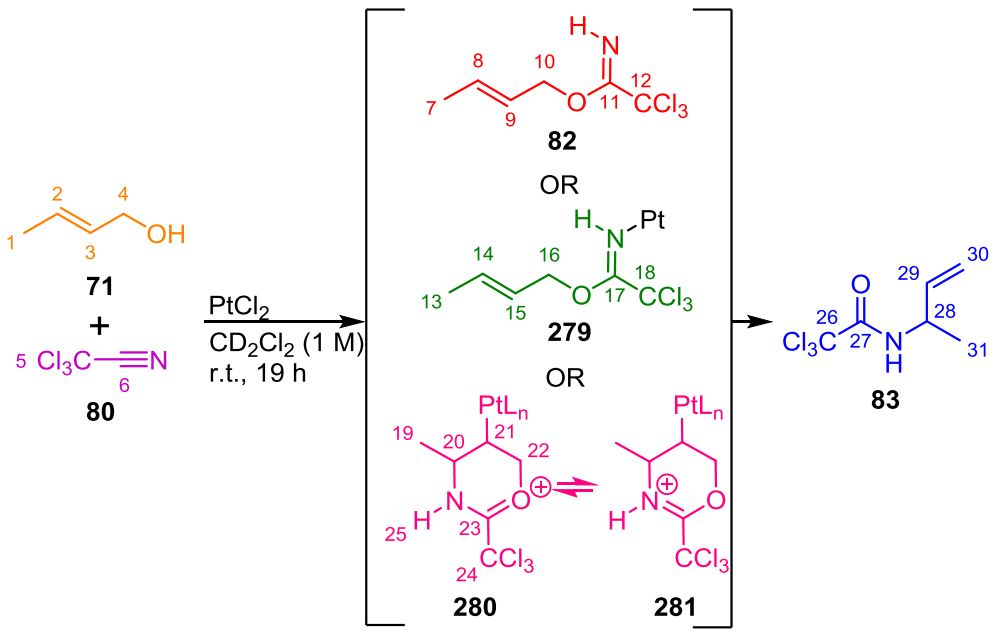



*Figure 2.12: Assigned structures for $^{13}$C NMR analysis*

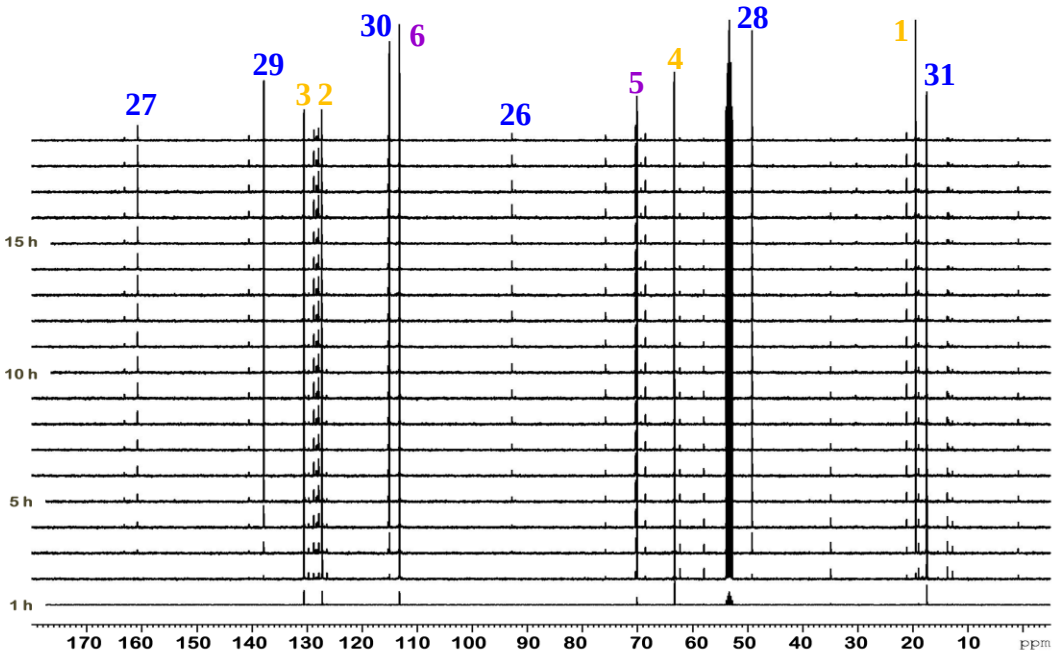



*Figure 2.13: layered $^{13}C$ spectra for the monitored experiment*

To identify any intermediates, the identifiable peaks were removed from the spectra taken after a reaction time of 19 hours (Figure 2.14). This was more effective than $^{1}H$ NMR as the regions of a $^{13}C$ NMR are more specific. The specificity of carbon regions should help identify interesting intermediate carbon peaks when they are compared to known platinum nitrile and platinum imidate complexes (*vide infra).* The spectra below shows a number of extra carbon peaks that do not correspond to the starting materials **71** or **80** or allylic amide **83** (*cf.* Figure 2.12).

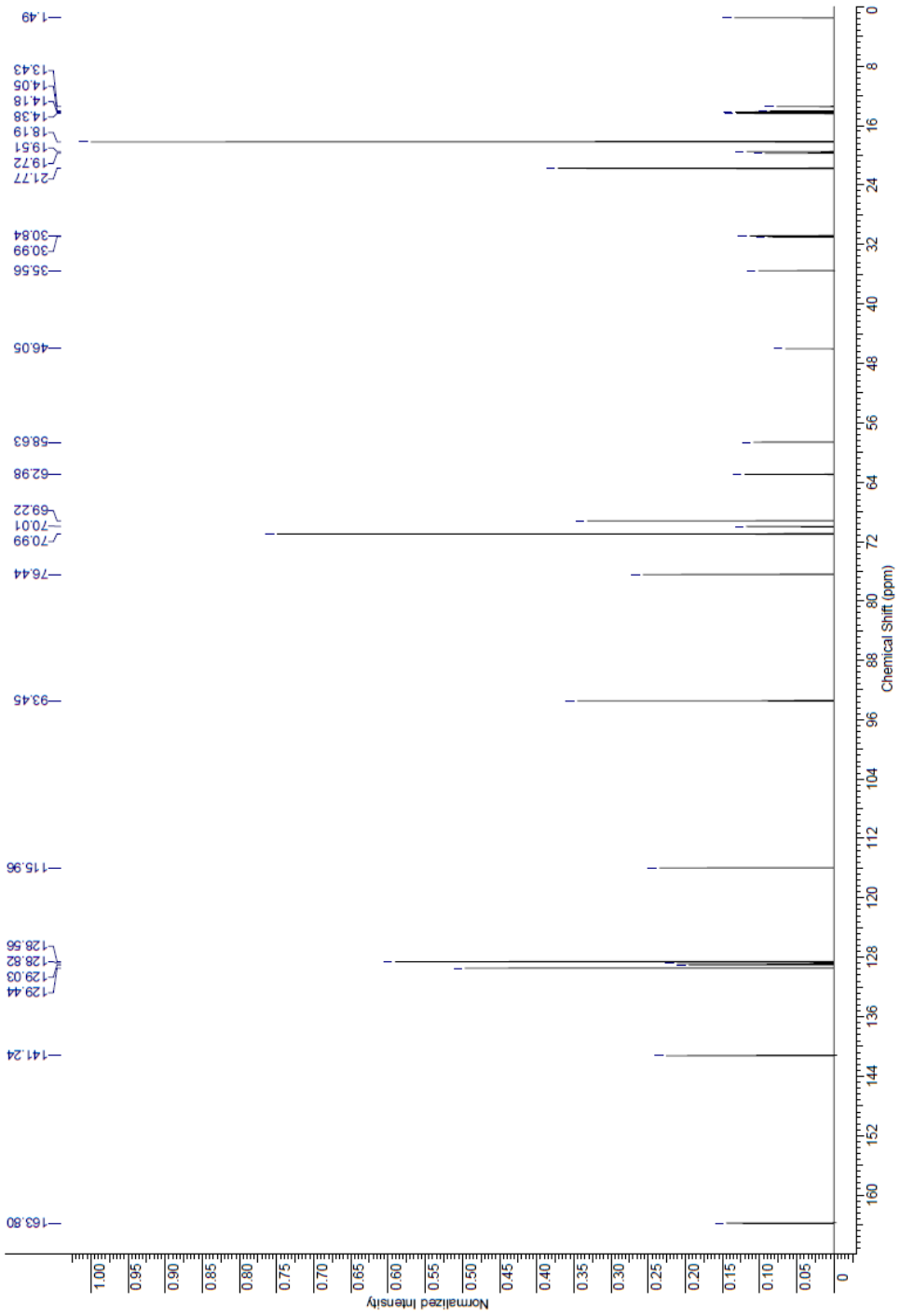



*Figure 2.14: Unidentifiable intermediate $^{13}C$ peaks*

A variety of chemical shift data for free nitriles and the platinum bound nitriles are available in the literature for comparison to our system. Substitution of benzyl versions were chosen to probe how the electronics affect the chemical

shifts (Table 2.8).[97, 98] Comparison of the chemical shift of the carbon of the nitrile showed that the platinum bound version changes the chemical shift by 0.5 ppm upfield. This suggested that the predicted chemical shift for trichloroacetonitrile **(80)** is approximately 112.8 ppm (Entry 4, table 2.8). The difference is more evident when comparing the chemical shift of the carbon alpha to the nitrile. The comparison shows the biggest difference with the 4-methyl substituent **283** (Entry 2, table 2.8) in which the chemical shift changes by 3.8 ppm downfield. However, the methoxy substituent **282** and the fluorine substituent **284** have the smallest change (Entries 1 and 3, table 2.8). What is clear from this analysis is that the platinum(II) metal centre shifts the peak of the $^{13}C$ NMR of the nitrile carbon upfield and the carbon alpha to the nitrile moiety downfield.

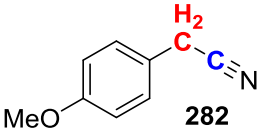
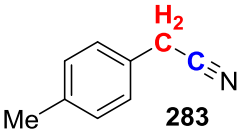
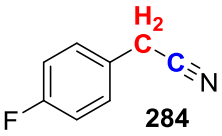
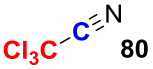
| Entry | Nitrile | δ of RCN | | δ of $R_3CCN$ | |
|---|---|---|---|---|---|
| | | Free nitrile[97] | $PtCl_2$ bound[98] | Free nitrile[97] | $PtCl_2$ bound[98] |
| **1** |  **282** | 118.1 | 117.6 | 22.8 | 24.6 |
| **2** |  **283** | 118.0 | 117.5 | 21.1 | 24.9 |
| **3** |  **284** | 117.6 | 117.1 | 23.0 | 24.7 |
| **4** |  **80** | 113.3 | Predicted 112.8 | 70.1 | Predicted 71.8 - 73.9 |

*Table 2.8: Comparison of nitrile to platinum bound nitrile*

In addition to the nitriles, it is important to identify any trends in the change in chemical shift when imidates are bound to platinum(II). The data in table 2.9 shows how the central carbon of the imidate moiety shifts upfield when coordinated to platinum(II) chloride.[18, 99, 100] The peak corresponding to the imidate shifts to a greater extent than in the nitrile system. This increase in shift when comparing platinum imidates to platinum nitrile complexes could be due to the stronger bond between the nitrogen of the imidate and the metal centre. The stronger bond is caused by the greater overlap of the p-orbitals of the imidate bond and the d-orbitals of platinum metal centre, creating a greater effect on the shielding on the carbon of the imidate. Contrary to the nitrile investigation there is not a clear trend with the carbon alpha to the imidate moiety, the chemical shift of the carbon can go either up- or downfield depending on the nature of the imidate (Table 2.9).

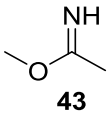
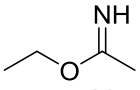
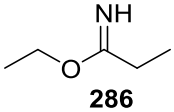
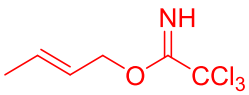
| Entry | Imidates | δ of NH=*C*(CR$_3$)OR | | δ of NH=C(*C*R$_3$)OR | |
|---|---|---|---|---|---|
| | | **Free imidate** | **PtCl$_2$ bound** | **Free imidate** | **PtCl$_2$ bound** |
| **1** |  **43** | 176.8[100] salt | 171.2[18] | 18.4[100] salt | 21.4[18] |
| **2** |  **285** 18 | 175.7 | 170.6 | 23.8 | 21.7 |
| **3** |  **286** 99 | 175.3 | 171.2 | 26.2 | 28.8 |
| **4** |  **82** | 162.7 | Predicted 157 -158.6 | 91.6 | Predicted 88.6 – 94.6 |

*Table 2.9: Comparison of imidate to platinum bound imidate*

When comparing the literature data against the spectra of free imidate **82** the only peak that matches is the peak at 18.2 ppm, which correlates to the carbon of C-8 of imidate **82**. As this is the only peak and it is the carbon furthest away from the functionality of the imidate it is unlikely that the reaction mixture contains the free imidate.

There are though a number of interesting peaks of note. Firstly, the peaks that are closely related to free trichloroacetonitrile (**80**, 116.0 and 76.4 ppm) suggest a species very similar to the free trichloroacetonitrile **(80)**. The peak at 116.0 ppm is in the nitrile region, this peak has a difference of 2.7 ppm downfield of the free nitrile (C-6), which is found at 113.3 ppm. The peak at 76.4 is in the region of the trichloromethyl moiety of the free nitrile at 70.1 (C-5). Both have been moved downfield, suggesting the nitrile intermediate observed will be less shielded in comparison to the free nitrile. It is predicted that the carbon in the nitrile of the platinum bound nitrile peaks should be shifted upfield suggesting the intermediate observed is not the platinum bound nitrile.

The second interesting intermediate peaks are at 163.8 and 93.5 ppm. The peak at 163.8 is in the region of C-11 or C-27 of the free imidate **82** and amide **83**. The peak has shifted downfield of both the isolated imidate **82** and amide **83**, which have peaks at 162.9 and 161.0 ppm. This trend is also found in the peak at 93.5 ppm, which corresponds to the C-12 or C-26 the trichloromethyl moiety of the free imidate **82** or amide **83** at 92.2 and 92.7 ppm. These peaks suggest one of the intermediates observed will have a similar character to these compounds; however, the intermediate will have a decrease of shielding around these carbon atoms. This observation does not agree with the predicted

platinum bound imidate suggesting that the intermediate is not the platinum bound imidate.[18, 99, 100] However, the predictions are only a guide and the systems are far from ideal to compare.

Although, analysis has been obtained on the intermediates within the reaction mixture, the complete structure of an intermediate cannot be confirmed due to the uncertainty of the trends when platinum is bound to intermediate structures. The ideal method for the identification of intermediates is by the direct comparison of isolated intermediate complexes. The direct comparison is not possible due to the instability of these intermediates. In addition to the intermediates discussed, a number of non-productive intermediates could be present in the reaction mixture, which account for the multiple unidentifiable peaks in both NMR techniques (Figure 2.15). Double addition intermediate **287** could be present as a result of the nitrogen in imidate intermediate **82** attacking an activated nitrile.[99] However, once double addition intermediate **287** is formed it is unlikely this could further react so it decomposes into imidate intermediate **82**. The second possible reversible intermediate **288** is formed from the addition of a second molecule of allylic alcohol **71** into the imidate **279** or **82** forming tetrahedral intermediate **288**.[101] Intermediate **288** has been identified by high resolution mass spectroscopy, but was not isolated or detected by any other techniques, suggesting this intermediate is present in very low quantities.

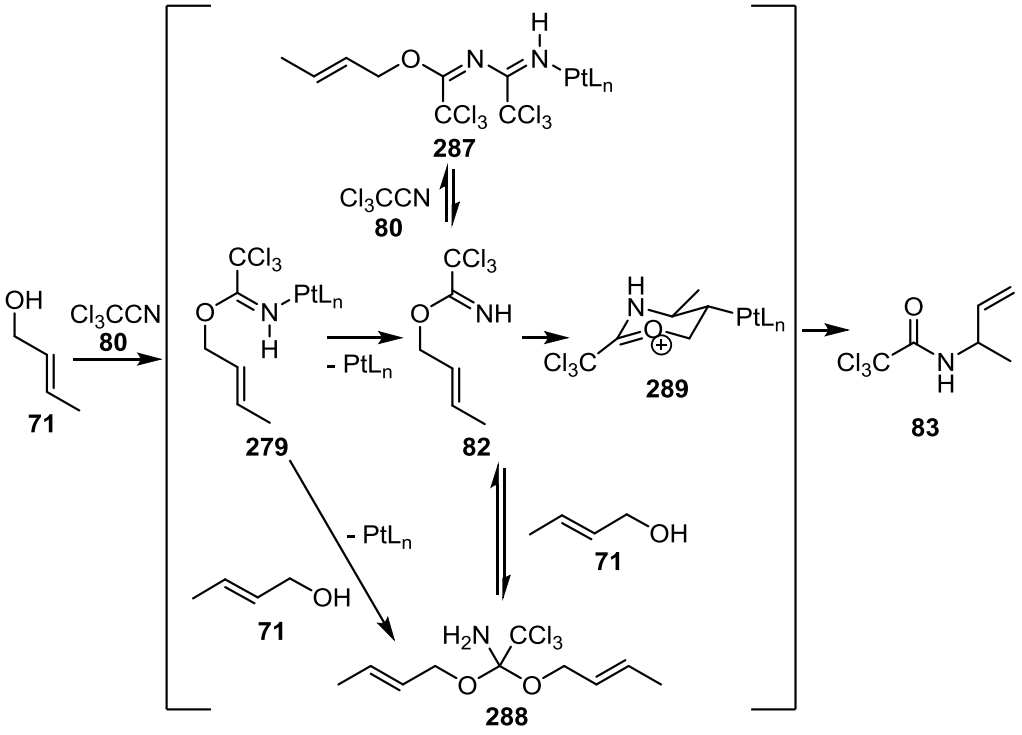
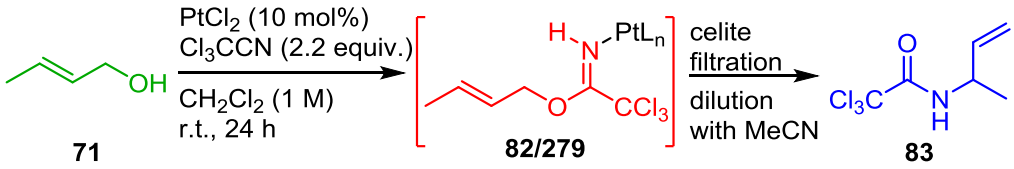



*Figure 2.15: Other possible intermediates off the cycle.*

A further study to help understand the mechanism of the one-pot allylic amide synthesis was undertaken using gas chromatography (GC) analysis. GC analysis will aid in identifying the number of intermediates observed within the reaction. For the experiment, which was conducted in collaboration with Dr Jay Dunsford, the reaction of (*E*)-2-buten-1-ol (1 equiv.), trichloroacetonitrile (**80**, 2.2 equiv.) and platinum(II) chloride (10 mol%) in dichloromethane was run for 24 hours and aliquots of the reaction mixture were extracted at 1 hour intervals. The aliquots were filtered through Celite to remove the platinum and prevent further reaction before diluting with acetonitrile and running on a GC analysis machine with decane as an internal standard (Scheme 2.32).




*Scheme 2.32: Experimental conditions for GC analysis study.*

The overlay of representative GC spectra shows that as allylic alcohol **71** decreases in concentration, allylic amide **83** increases. An important observation to note is that the peak corresponding to the free imidate is present at a very low, but constant, intensity throughout the reaction. This shows that the quantity of imidate is not building up in the reaction. Two possible explanations are i) the platinum imidate is present within the reaction mixture, although a new peak is not seen it is believed that the platinum is displaced upon filtration or ii) The imidate is rearranged readily under the conditions so that only a small amount is present at any point in the reaction.

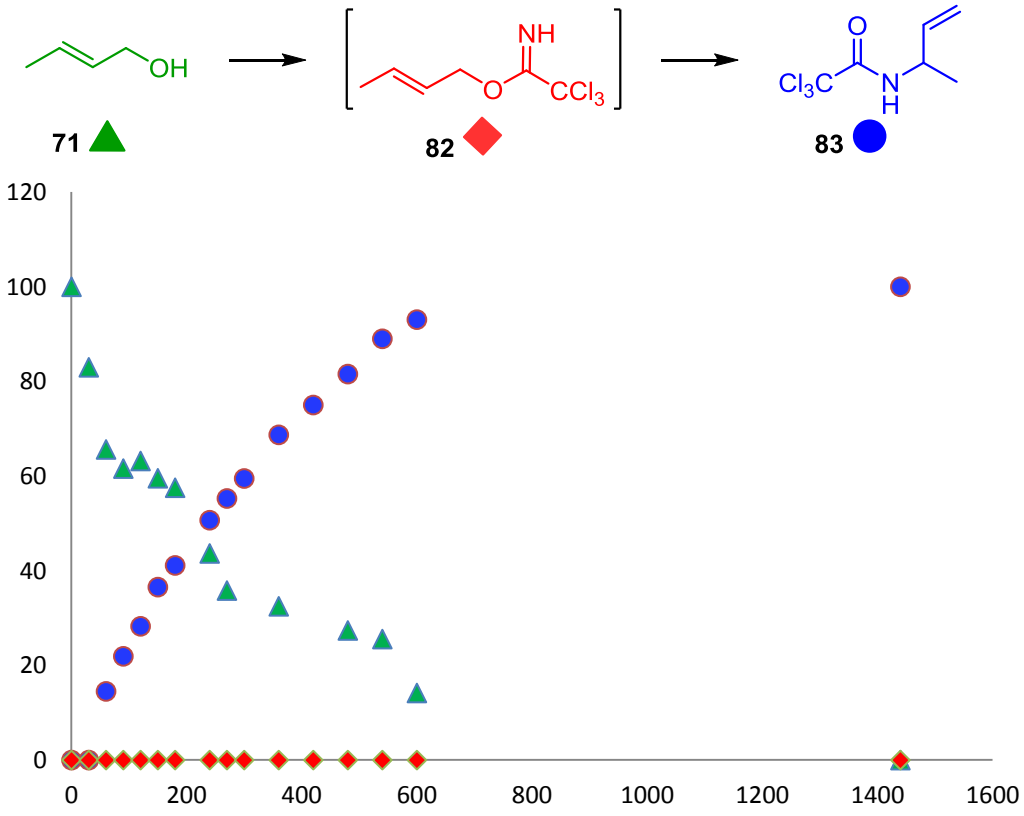



*Figure 2.16: Graph of the results from the GC investigation*

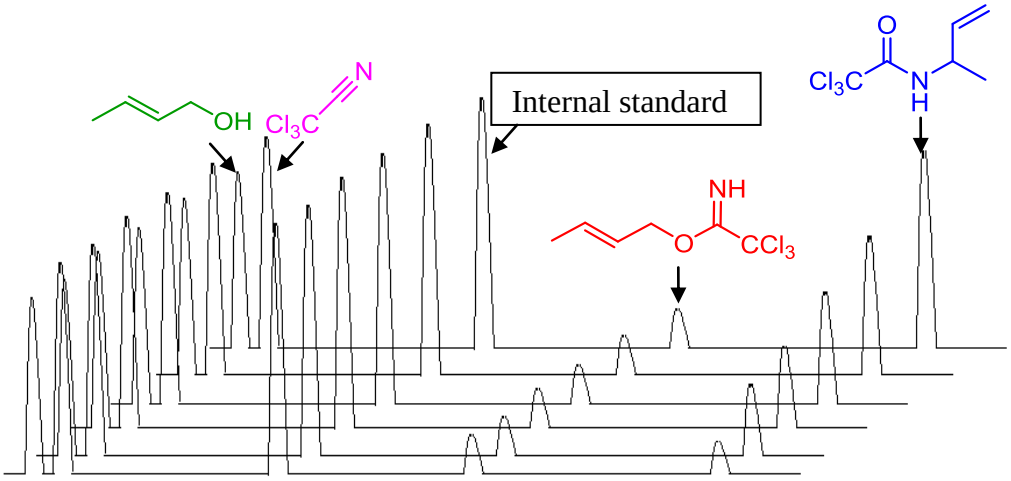
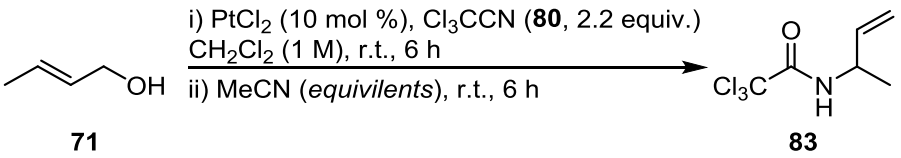



*Figure 2.17: representation of GC spectra for the monitored experiment*

To further investigate the reaction mechanism, a number of experiments were designed to identify if deactivation of the catalyst was achievable by adding a better ligand into the reaction mixture. The ligand that was chosen was acetonitrile as it is known to bond with platinum(II) chloride. It was expected that trichloroacetonitrile **(80)** will be displaced by acetonitrile, which would result in the inactive platinum bisacetonitrile complex. It was also hoped that the imidate intermediate could be isolated. For this investigation a reaction of (*E*)-2-buten-1-ol **(71**, 1 equiv.) with trichloroacetonitrile (**80**, 2.2 equiv.) in the presence of platinum(II) chloride (10 mol%) in dichloromethane was conducted at ambient temperature. Acetonitrile (0.1, 0.3, 5 equivalents in relation to allylic alcohol) was added to the reaction mixture after 6 hours of stirring at room temperature (Scheme 2.33). The isolated yields were compared to the two controls at 6 and 12 hours in which acetonitrile was not added (Entries 1 and 5, table 2.10). An isolated yield of 54% was obtained from the control after 12 hours of stirring the reaction at ambient temperature (Entry 1, table 2.10). The yield decreased from 49% to 38% after the addition of

increasing equivalents of acetonitrile after 6 hours (Entries 2 to 4, table 2.10). The second control of isolating the yield after 6 hours resulted in 30% product (Entry 5, table 2.10). Once an excess of 5 equivalents (50 times the amount of platinum catalyst) was added to the reaction it almost completely shut down and produced the product in almost the same amount of yield as the 6 hours reaction (Entries 4 and 5, table 2.10). However, after the addition of equal quantities of acetonitrile (10 mol%) compared to the platinum catalyst (10 mol%) the reaction proceeded although at a slower rate, producing a decreased yield of 5%. This result is most likely due to the two vacant sites on the platinum catalyst as the acetonitrile added can only deactivate half of the active sites.[25]




*Scheme 2.33: Deactivation investigation.*

| Entry | MeCN added (equiv.) | Yield (%) |
|---|---|---|
| **1** | 0 (run for 12 h) | 54 |
| **2** | 0.1 (added after 6 h) | 49 |
| **3** | 0.3 (added after 6 h) | 41 |
| **4** | 5 (added after 6 h) | 38 |
| **5** | 0 (run for 6 h) | 30 |

*Table 2.10: Deactivation investigation*

The $^{1}H$ and $^{13}C$ NMR, GC and deactivation studies have given an insight into the mechanism of the MFC approach to allylic amide synthesis. Although, the

proposed mechanism has not been completely confirmed, mechanistically, the one-pot process is believed to work via a platinum imidate species. The imidate species is in quantities stoichiometric to the amount of platinum catalyst added and does not produce an excess of free imidate **82.** Further to the nucleophilic addition step there is no evidence to suggest the rearrangement does not go via the proven cyclisation induced rearrangement.[33]

### 2s) Conclusion

To summarise, a simple commerically available platinum chloride salt was used to catalytically activate halogenated nitriles towards nucleophilic addition. This has been achieved by developing a MFC approach to the synthesis of trichloro allylic amides. During the investigation it was discovered that:

- Configuration of the olefin involved in the rearrangement had little effect on the overall yield of the reaction.
- Electronics of the allylic alcohol have a significant impact on the overall process with electron rich or electron poor systems decreasing the overall yield.
- Sterically hindered 3-methylbut-2-en-1-ol **(256)** was successfully rearranged to form a quaternary carbon centre, in contrast to existing metal-catalysed methods.
- The thermally labile Boc group is stable under the MFC reaction conditions.

- One key limitation to this process is cyclic allylic alcohols. It is believed that the cyclic nature of the alcohols cause a hindrance to the platinum catalyst.
- An important limitation of this process is the decreased ability to synthesise less activated allylic amides e.g. dichloro. Although moderate yields were obtained, a classical approach also gave low yields due to problems in the formation/isolation of allylic imidate **270**.
- Within the mechanistic studies it was revealed by $^{1}H$ and $^{13}C$ NMR that free imidate **82** was not forming in significant amounts. This observation was confirmed by GC studies in which free imidate **82** was present in constant trace amounts throughout the reaction over 24 hours.
- Lack of conclusive evidence of platinum bound complex within the NMR studies suggested that the intermediates are short lived.
- Excess acetonitrile poisons the catalyst and shuts down the reaction stopping any further activation shown via the deactivation experiments.

# Chapter 3: Results and discussion - synthesis of halogenated benzoxazoles

## 3a) The proposed MFC one-pot synthesis of 2-trichlorobenzoxazoles

The second probe that was used to explore the viability of a MFC approach towards catalytic activation of nitriles **1** was the one-pot synthesis of 2-benzoxazoles **291**. Benzoxazoles **291**, in which the C-2 position is functionalised, were synthesised from the corresponding 2-aminophenol **134** and nitrile **289** via amidine intermediate **290.** This process is initiated via activation of nitrile **289** towards nucleophilic addition from the Lewis acid catalyst to form amidine intermediate **290**. The amidine intermediate **290** is activated by the same Lewis acid catalysts towards a second nucleophilic addition from the pendant phenol moiety and after a tautomerisation and the loss of ammonia 2-benzoxazoles **291** are formed, which allows for turnover of the platinum catalyst (Figure 3.1). The successful synthesis of 2-benzoxazoles **291** will further demonstrate the activity of a MFC approach to nitrile activation. The advantages to our method in comparison to traditional methods for the synthesis of 2-benzoxazoles are firstly, the mild reaction conditions, with temperatures well below the 100 ºC previously reported (*cf.* Scheme 1.26 and 1.27). The second advantage is the ability to manipulate di- and trichloromethyl moieties into interesting and useful added value compounds. The adaptability of this method could be largely beneficial to medicinal chemistry when undertaking fragment screening.

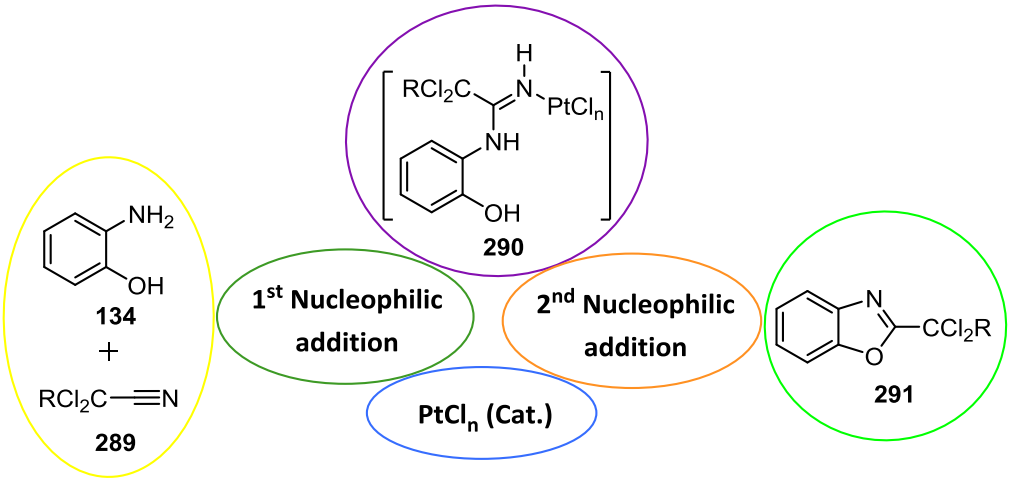
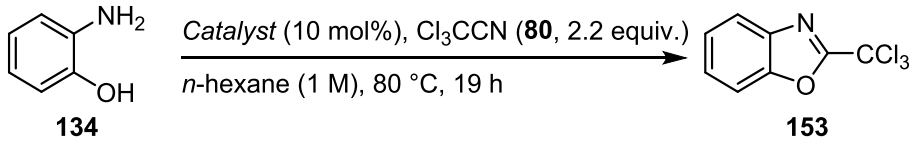



*Figure 3.1: Multifaceted catalyst approach to benzoxazole synthesis.*

### 3b) Catalyst in *n*-hexane for the synthesis of trichlorobenzoxazoles

With the knowledge gained from the previous study into allylic amide synthesis, platinum(II/IV) chlorides (10 mol%) were used in *n*-hexane at 80 ºC for 19 hours to catalyse the reaction of 2-aminophenol **(134)** and trichloroacetonitrile (**80**, 2.2 equiv.) to form 2-trichlorobenzoxazole **153** (Scheme 3.1, table 3.1). The results from this investigation showed, firstly, the reaction does not proceed without the catalyst (Entry 1, table 3.1) and secondly that platinum(IV) chloride was better for this one-pot process than platinum(II) chloride in *n*-hexane (Entries 2, 3, table 3.1). The observation that platinum(IV) chloride is the better catalyst is contrary to the results of the allylic amide synthesis. This could be due to the superior nitrile activation properties of $PtCl_4$ and the difference in overall mechanism (*cf.* Scheme 1.7 and 1.8).



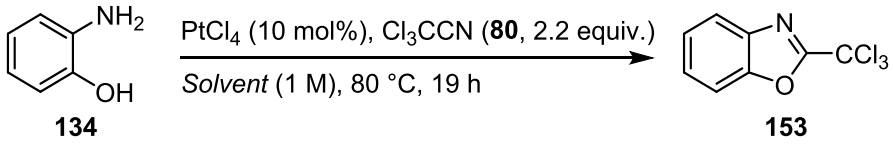

134 153

*Scheme 3.1: Identification of catalyst in n-hexane.*

| Entry | Solvent | Catalyst | Yield (%) |
|---|---|---|---|
| **1** | *n*-hexane | No catalyst | 0 |
| **2** | *n*-hexane | $PtCl_2$ | 60 |
| **3** | *n*-hexane | $PtCl_4$ | 82 |

*Table 3.1: Identifying the catalysts for the synthesis of benzoxazoles.*

Once platinum(IV) chloride was identified as a good catalyst for the MFC approach to benzoxazole synthesis, a range of solvents were screened. The solvent screen involved a number of different solvents with varying polarities and protic/aprotic properties. The table below shows that *n*-hexane with platinum(IV) chloride was the optimal conditions for the benzoxazole synthesis giving a yield of 82% of desired benzoxazole **153** (Entry 1, table 3.2). This was followed closely by ethanol which gave a yield of 64% (Entry 7, table 3.2).



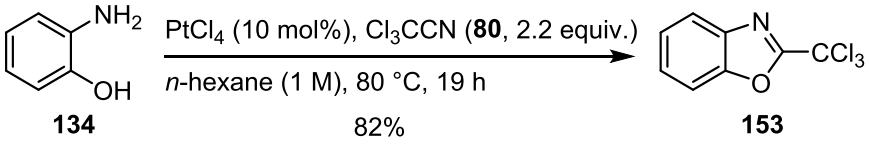

**134** **153**

*Scheme 3.2: Solvent screen for the synthesis of trichlorobenzoxazole.*

| Entry | Solvent | Yield (%) |
|---|---|---|
| **1** | *n*-hexane | 82 |
| **2** | $d^8$-toluene | 47 |
| **3** | *d-chloroform* | 53 |
| **4** | acetone | 27 |
| **5** | tetrahydrofuran/water (1:1) | 0 |
| **6** | dimethylacetamide | 27 |
| **7** | ethanol | 64 |
| **8** | *tert*-butanol | 22 |

*Table 3.2: Solvent screen for the synthesis of trichlorobenzoxazole.*

After additional optimisation reactions of nitrile equivalents, concentration and temperature the optimal conditions that were used for subsequent substrate scope investigation were identified (Scheme 3.3).

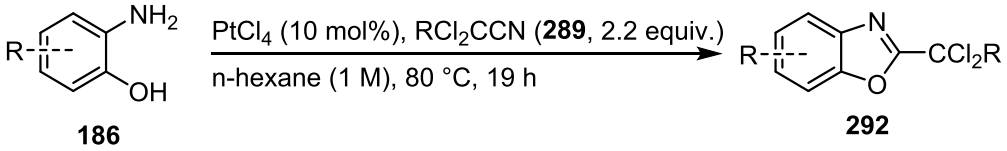



**134** **153**

*Scheme 3.3: Optimised conditions.*

### 3c) Platinum catalysed synthesis of 2-di and 2-trichlorobenzoxazoles

Next, the substrate scope of the process was investigated. Aminophenols **186** were reacted with trichloroacetonitrile (**80**, 2.2 equiv.) in the presence of $PtCl_4$ in *n*-hexane at 80 ºC for 19 h to produce di- and trichlorobenzoxazoles **292**. Interestingly, there was a significant decrease in yield for the electron rich substrates **293 – 295** in comparison to the parent compound **153**. In addition, the slightly electron poor substrate **296** and **304** had a slight decrease in yield form the parent. These two trends show that the electronics of the aromatic ring have a large affect on the overall reaction. The investigation also showed a potential for using less activated nitriles (dichloroacetonitrile) by forming 2-dichlorobenzoxazole **297** in a 33% yield. This decrease in yield by changing the nitrile is similar to that observed in the one-pot allylic amide synthesis (*cf.* Table 2.7).




*Scheme 3.4: Substrate scope for the one-pot MFC synthesis of benzoxazoles.*

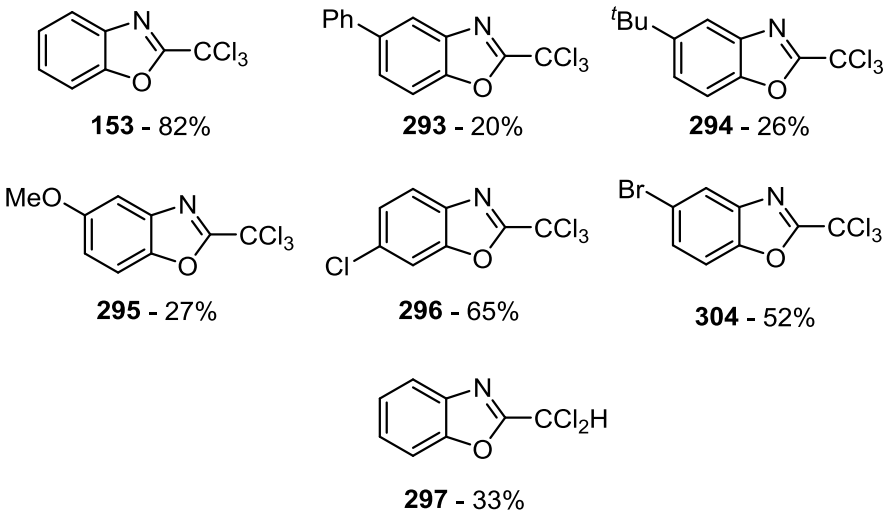
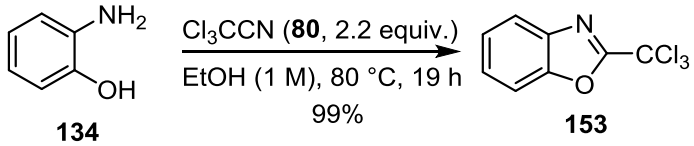



*Figure 3.2: Substrate scope for the catalytic synthesis of trichlorobenzoxazoles.*

### 3d) Further solvent study

The majority of yields obtained were average (below 35%) when subjecting 2-aminophenol substrates to the optimised conditions of $PtCl_4$ in *n*-hexane. These yields were deemed insufficient for a viable, widely used method. Further examination of the solvent studies uncovered an anomaly. The second best solvent screened was ethanol, which produced the desired product in 64% (*cf.* Entry 7, table 3.2). This is unexpected as ethanol has very different chemical properties to *n*-hexane. *n*-Hexane is nonpolar and aprotic, therefore is not miscible with water, however, ethanol is polar and protic and is miscible with water. In an attempt to better understand this disparity between the differing solvents an experiment was disghned. A control reaction in ethanol was undertaken to identify if the platinum was catalysing the reaction in the presence of excess ethanol. Unexpectedly, this reaction produced the desired benzoxazole **153** in a near quantitative yield (Scheme 3.5). This is an improvement on any yields obtained so far, suggesting that the platinum within the reaction is inhibiting the reaction not catalysing it when under ethanol conditions.

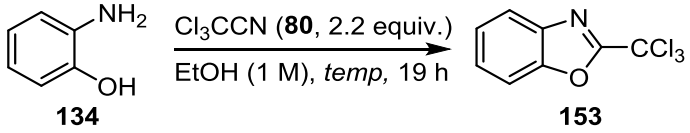



**134** **153**

*Scheme 3.5: Control reaction for the synthesis of trichlorobenzoxazole.*

### 3e) Examination of the temperature in the metal free synthesis of trichlorobenzoxazole

As near quantitative yields were obtained from the use of ethanol as the solvent, the intention of the optimisation study was not to increase the yield but to improve the conditions of the synthesis while maintaining the high efficiency of the reaction. Temperature is the most costly variable and will affect the sustainability of the process significantly. The 80 ºC temperature used for the solvent study was chosen due to previous similar condensation reactions.[102] Therefore an investigation into the reaction temperature was undertaken (Scheme 3.6). During the study it was discovered that near quantitative yields were obtained down to 40 ºC and a high 84% yield was produced at room temperature of 2–trichlorobenzoxazole **153** (Table 3.3). A temperature of 40 ºC was chosen to go forward with the optimisation because it was the lowest temperature that produced almost quantitative yield.



**134** **153**

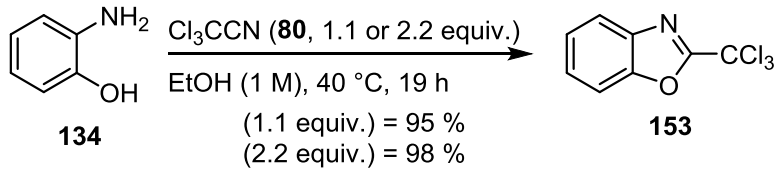
*Scheme 3.6: Temperature effect on the metal free trichlorobenzoxazole synthesis.*

| Entry | Temperature (°C) | Yield (%) |
|---|---|---|
| **1** | 80 | 99 |
| **2** | 60 | 99 |
| **3** | 40 | 98 |
| **4** | Ambient temperature | 84 |

*Table 3.3: Temperature effect on the metal free trichlorobenzoxazole synthesis.*

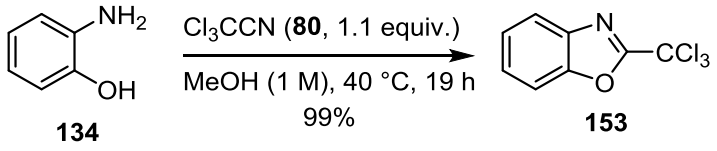
### 3f) Examination of the nitrile equiv. and solvents in the metal free synthesis of trichlorobenzoxazole

The second highest cost of this method was the excess of the nitrile reagent. Decreasing the stoichiometry of trichloroacetonitrile **(80)** down to a slight excess of 1.1 equiv. produced a pleasing result of 95% yield (Scheme 3.7).




*Scheme 3.7: Nitrile stoichiometry effect on the metal free trichlorobenzoxazole synthesis.*

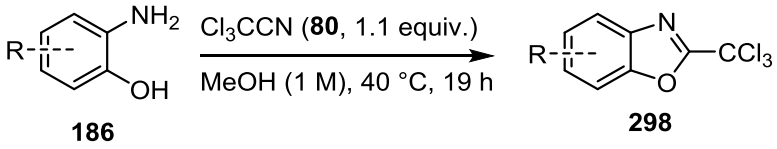
To further improve the conditions, methanol was also attempted as the solvent because it is a greener solvent. Methanol is a more sustainable solvent due to the better carbon and mass efficacy.[100, 101] The reaction in the presence of methanol produced quantitative yields, demonstrating the optimised conditions that will be used to probe the versatility of this methodology.[103, 104]




*Scheme 3.8: Solvent effect on the metal free trichlorobenzoxazole synthesis.*

### 3g) Substrate scope - Metal free trichlorobenzoxazole synthesis

Once the optimised conditions were identified, the reaction of substituted 2-aminophenols **186** with trichloroacetonitrile (**80**, 1.1 equiv.) in methanol at 40 ºC for 19 hours was investigated (Scheme 3.9). A number of trichlorobenzoxazoles were successfully synthesised in good to excellent yields via the standard alcoholic conditions. The substrates ranged from increasing the aromaticity **299** and **293**, addition of alkyl substituents **294**, **300** to **302**, addition of a strong electron donating group (OMe) **295** and addition of electron withdrawing halogen groups **296**, **303** to **304**.




*Scheme 3.9: Substrate scope of metal free trichlorobenzoxazole synthesis.*

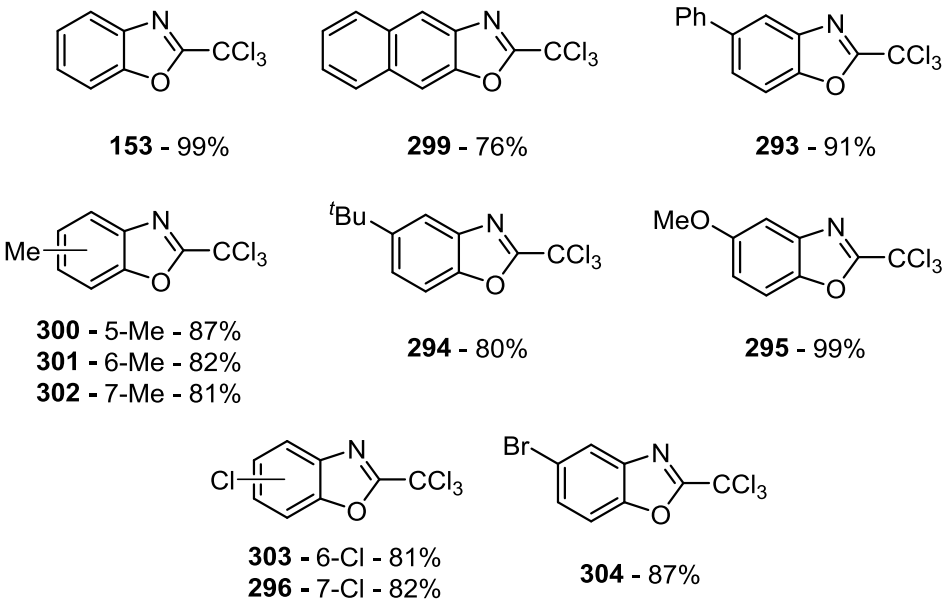
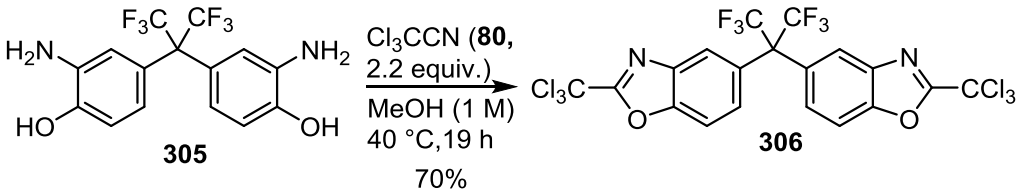


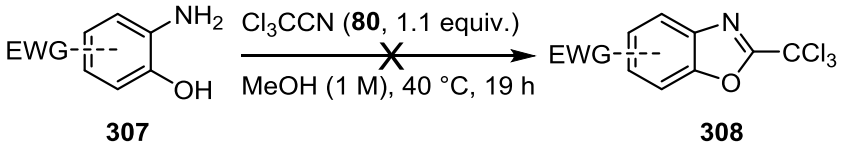

*Figure 3.3: Substrate scope of metal free trichlorobenzoxazole synthesis.*

A potentially useful substrate that was identified is the bis-aminophenol **305**. Benzoxazole **306** formed from a reaction with bis aminophenol **305** is highly desirable within organo polymer chemistry. There are a number of research papers forming products similar to bis-benzoxazole **306**, due to the excellent chemical and physical properties of the associated polymers. Reaction of bis-aminophenol **305** under the standard conditions with 2.2 equivalents of nitrile afforded bis-benzoxazole **306** in 70% yield (Scheme 3.10).



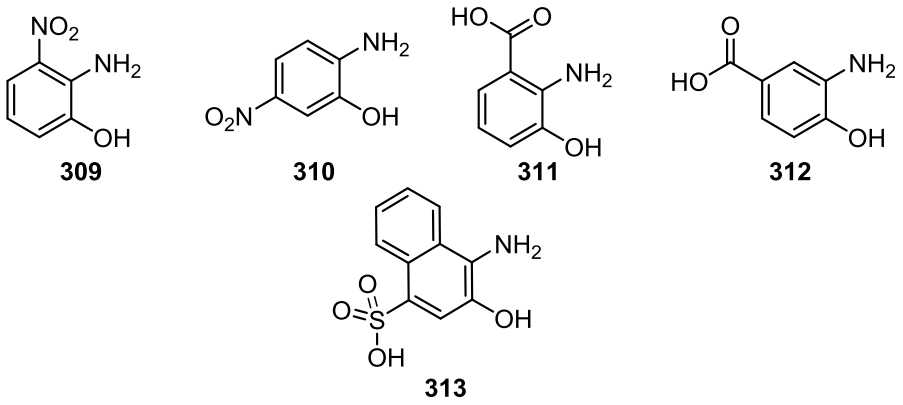

*Scheme 3.10: Synthesis of bis-trichlorobenzoxazole.*

A number of 2-aminophenol substrates **307** with nitro, acetic and sulfonic acid group at different positions were also attempted. Unfortunately, strong electron withdrawing groups were not compatible with the alcoholic conditions and no desired products **308** were observed (Scheme 3.11, figure 3.4).




**307** **308**

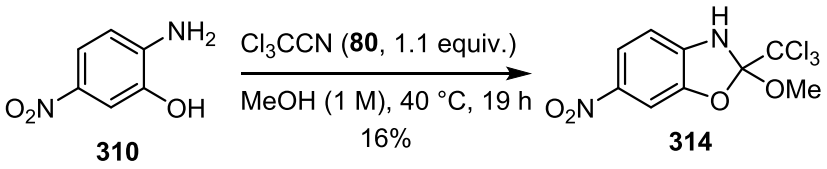
*Scheme 3.11: attempted 2-aminophols containing a strong electron withdrawing group.*




**309** **310** **311** **312** **313**

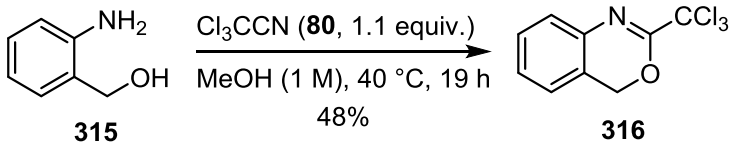
*Figure 3.4: Attempted 2-aminopheol substrates (electron withdrawing)*

One explanation for the unsuccessful reactions with electron withdrawing 2-aminophenols **309** to **313** is that the electron withdrawing character is reducing the nucleophilic ability of the amino and phenol moieties. Another explanation for this observation is that the strong electron withdrawing group is increasing the electrophilicity of the C-2 position of the benzoxazole product. Nucleophiles will then attack and form a variety of products. This theory is reinforced by the formation of a small amount of methoxy addition product **314** when 2-amino-5-nitrophenol **(310)** and trichloroacetonitrile **(80)** were reacted in methanol.



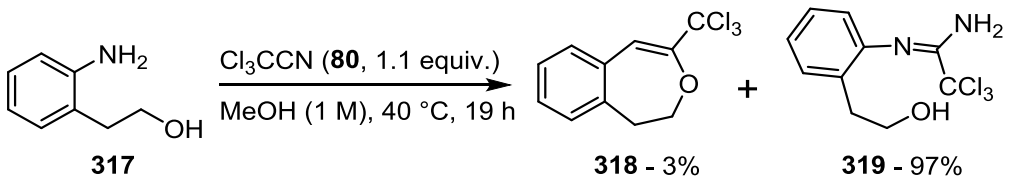

*Scheme 3.12: nitro addition product*

In addition to the formation of benzoxazoles, the synthesis of benzoxazine **316** and dihydrobenzoxazepine **318** were attempted under the standard conditions. Benzoxazine **316** was synthesised via reaction of aniline alcohol **315** with trichloroacetonitrile **(80)** under standard conditions to obtain a moderate 48% yield (Scheme 3.13). The decrease in yield in relation to the parent benzoxazole could be due to the fact that this system no longer has the added driving force of aromatisation.




*Scheme 3.13: Synthesis of trichlorobenzoxazine **316***

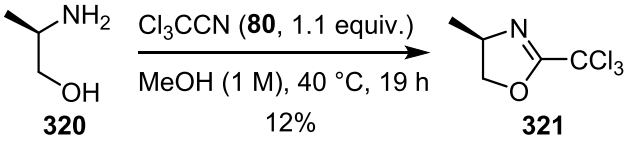
Formation of dihydrobenzoxazepine **318** was more challenging due to the formation of a strained seven-membered ring. The reaction of aniline alcohol **317** under the standard conditions produced the desired product **318** in a poor 3% yield. However, the remaining mass balance is made up of ring opened amidine derivative **319** (Scheme 3.14). This result shows that although this is not a viable route towards the benzoxapine core, it is an excellent alternative to amidine synthesis.[105]




**317** **318** - 3% **319** - 97%

*Scheme 3.14: Synthesis of 4,5-dihydrobenzo[d][1,3]oxazepine*

One way to utilise the full potential of the methodology of the base free synthesis of the benzoxazole core is by the formation of chiral oxazolines. For example oxazoline **321** is base sensitive and racemises in the presence of a base. For this reaction, 2-amino alcohol **320** was subjected to the standard conditions to produce oxazoline **321**. Although the yield was low this result shows the potential of the method for the direct formation of oxazolines.

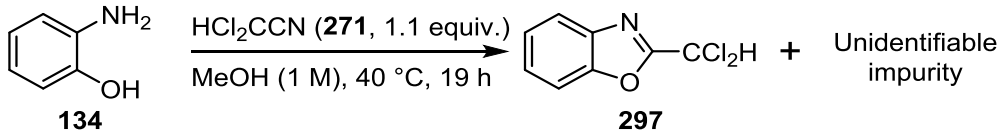



**320** **321**

*Scheme 3.15: Synthesis of oxazole **321***

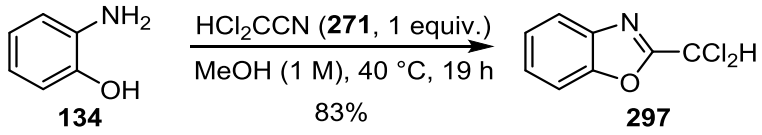
### 3h) Substrate scope - Metal free dichlorobenzoxazole synthesis

The next stage was to vary the nitrile involved in the synthesis of the benzoxazole. Dichloroacetonitrile **(271)** was used because it is slightly less activated than trichloroacetonitrile **(80)** and could be used for some interesting further transformations (*cf.* Figure 1.23). Reaction of 2-aminophenol **134** under the standard conditions with dichloroacetonitrile (**271**, 1.1 equiv.) gave product **297** plus an inseparable unidentifiable impurity, which contained the distinctive $CCl_2H$ by NMR analysis (Scheme 3.16).



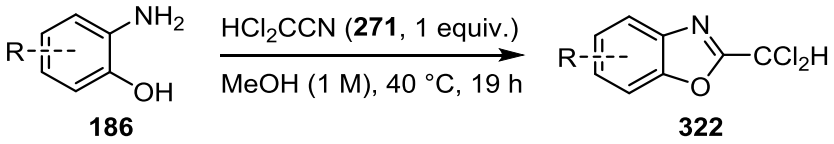

*Scheme 3.16: Attempt of using the standard conditions with dichloroacetonitrile **(271)**.*

To overcome the separation and obtain pure dichlorobenzoxazole the nitrile was added in stoichiometric quantities. This alteration inhibited the formation of the impurity producing dichlorobenzoxazole **297** in an 83% yield (Scheme 3.17).



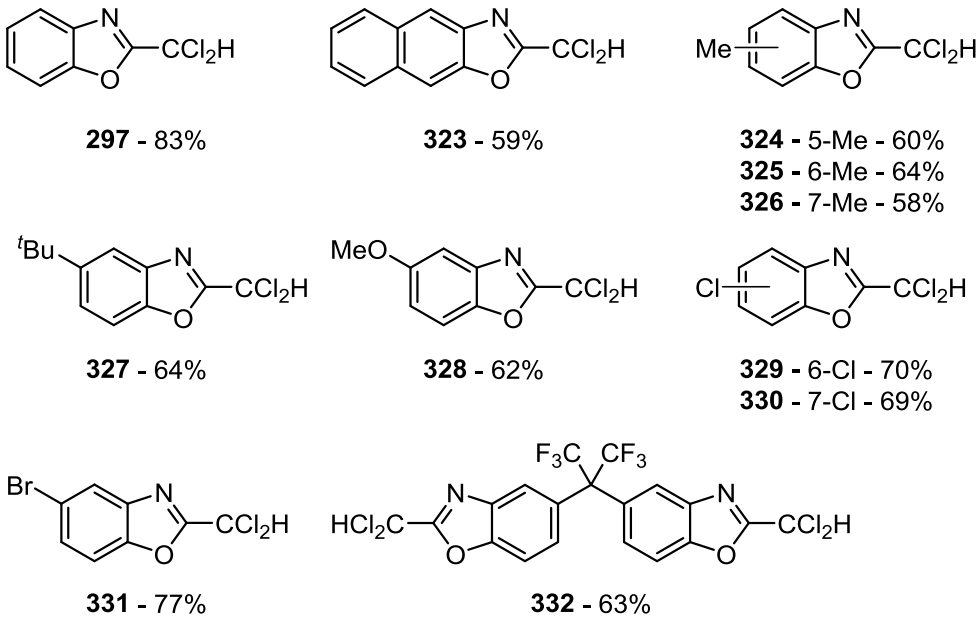

*Scheme 3.17: Alteration of conditions for dichlorobenzoxazole.*

After successfully altering the conditions, a number of 2-aminophenols **186** were subjected to the new conditions to produce dichlorobenzoxazoles **322** in moderate to good yields (Scheme 3.18). The overall trend in the isolated yield of the dichloro substrates was an approximately 20% decrease in yield compared to the trichloro derivatives (Figure 3.5). The decrease in yield could be because of two aspects of the reaction. Firstly the nitrile is less activated so it would be expected that the nitrile is less efficient at the nucleophilic addition step. The second possible reason for the lower yield could be due altering the stoichiometry of the nitrile within the reaction. It is possible that to get optimal yields of the desired benzoxazole a slight excess of the nitrite starting material is required.




**186** **322**

*Scheme 3.18: Substrate scope for metal free synthesis of dichlorobenzoxazoles.*




**297** - 83% **323** - 59% **324** - 5-Me - 60%
**325** - 6-Me - 64%
**326** - 7-Me - 58%

**327** - 64% **328** - 62% **329** - 6-Cl - 70%
**330** - 7-Cl - 69%

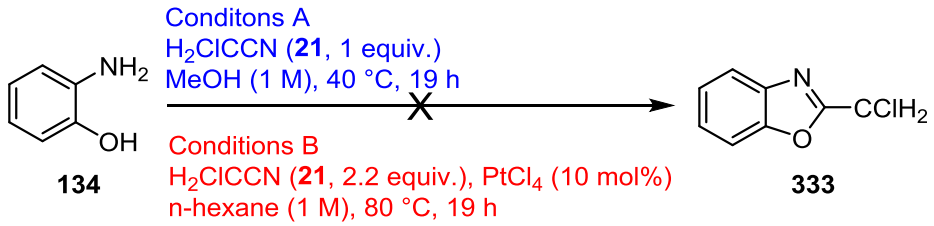
**331** - 77% **332** - 63%

*Figure 3.5: Substrate scope for metal free synthesis of dichlorobenzoxazoles.*

### 3i) Substrate scope – metal free chlorobenzoxazole synthesis

To further expand the versatility of this method, an investigation was undertaken to determine if benzoxazoles could be produced under the uncatalysed conditions with less activated chloroacetonitrile. After the reaction under the uncatalysed conditions (Conditions A, scheme 3.19) none of the desired chlorobenzoxazole **333** was observed. To identify if this nitrile substrate required further activation by the use of a Lewis acid, the reaction was run under the catalysed conditions (Conditions B, scheme 3.19), however,

both reactions produced a mixture of products, none of which were the desired benzoxazole product **333** (Scheme 3.19).




*Scheme 3.19: Attempted chlorobenzoxazole synthesis.*

### 3j) Mechanistic study – di- and trichlorobenzoxazole

A mechanistic investigation was undertaken to better understand the synthesis of 2-trichloro and 2-dichlorobenzoxazoles in alcoholic solvents. One theory behind the successful reaction in alcoholic solvents is the in situ formation of imidate intermediate **334**. It was shown by Holan et al. that the hydrochloric salt of imidate **154** would react to form benzoxazole without any additional activation (*cf.* Scheme 1.33).[70] The imidate intermediate could be formed from a reversible reaction involving a nucleophilic attack of the alcohol into nitrile **289**. This type of activation is known as nucleophilic catalysis, because the nucleophilic activating agent is used catalytically.

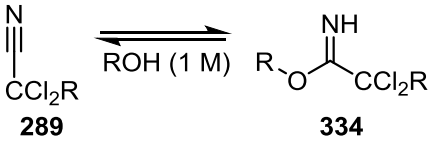



*Figure 3.6: Reversible nucleophilic addition into nitrile **289**.*

It is believed that the imidate intermediate **334** is a better electrophile because it allows for a less hindered attack of the approaching nucleophile. Addition into the di- and trichloroacetonitrile **289** has steric hindrance of the large di- and trichloromethyl group when considering the Bürgi–Dunitz angle of attack

**335**.[106] However, when the electrophile is imidate **336** the di- and trichloromethyl group is moved out of the path of the nucleophile (Figure 3.7).

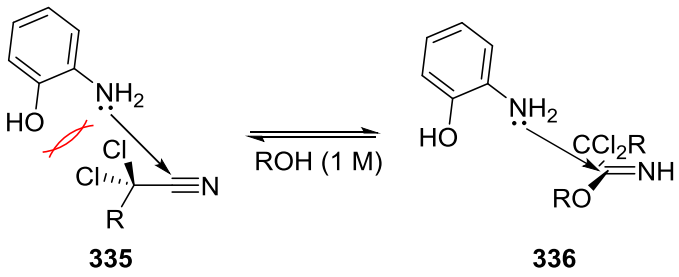



*Figure 3.7: Comparing steric effects nitrile vs. Imidate*

.

The proposed mechanism for the synthesis of trichlorobenzoxazole via in situ formation of imidate **337** is based on the work by Holan et al.[70] The reaction is initiated by the nucleophilic attack of methanol into di- and trichloroacetonitrile forming di- and trichloro imidate **337**. Imidate **337** then underwent nucleophilic attack from the amino moiety from 2-aminophenol **(134)** to form amidine **338**. Amidine **338** undergoes a further nucleophilic attack from the pendent phenol moiety to close the ring and form tetrahedral intermediate **339** and after the loss of ammonia produces benzoxazole **291** (Figure 3.8).

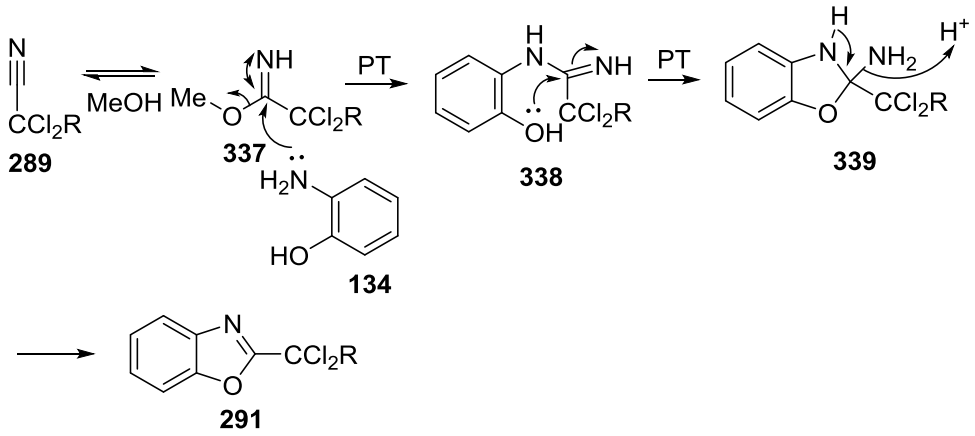
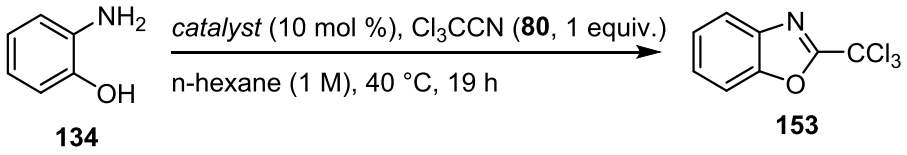



*Figure 3.8: Proposed nucleophile catalysed benzoxazole mechanism*

To investigate the nucleophilic catalysis hypothesis, a number of experiments were designed with the addition of known nucleophilic catalysts at 10 mol% in *n*-hexane at 40 ºC over 19 hours (Scheme 3.2). These experiments were used to identify if a nucleophilic catalyst is the reason for high yields for the synthesis of benzoxazoles in an alcoholic solvents. A yield of 39% was obtained using ethanol in catalytic amounts in *n*-hexane (Entry 1, table 3.4). When the same reaction was run using better nucleophilic catalysts, the yield increased to a maximum of 46% (Entry 4, table 3.4). These results show that a nucleophilic catalyst is beneficial for this process, though this does not fully explain the high yield observed in alcoholic solvents. One explanation is that the nucleophilic catalysts attempted were poor catalysts in *n*-hexane with a low turn-over. As the alcohol is in a large excess when it is the solvent, running the reaction at 1 equivalent of the alcohol rather than 10 mol% should identify if this theory is likely. Reaction of 2-aminophenol **(134)** with trichloroacetonitrile (**80**, 1.1 equiv.) and methanol (1 equiv.) in *n*-hexane at 40 ºC for 19 hours resulted in a 60% yield (Entry 5, table 3.4). The yield is increased significantly when stoichiometric alcohol is used, although the 60% yield obtained is still below the reproduced quantity when methanol is used as the solvent. An explanation of this result is that the protic nature of the alcohol is activating the nitrile moiety similarly to a Lewis acid by forming a hydrogen bond. One way to confirm this theory is by running the same reaction in a non-nucleophilic protic solvent. This was achieved by using the much less nucleophilic alcohol *tert*-butanol. It is less nucleophilic due to the extra steric hindrance caused by the three methyl groups. Reaction of 2-aminophenol **(134)** with trichloroacetonitrile (**80**, 1.1 equiv.) and methanol (1 equiv.) in *tert*-butanol at

40 ºC for 19 hours was run (Entry 6, table 3.4). Benzoxazole **153** was isolated in 90% yield, which confirmed that the protic nature of the solvent does have a large impact on the overall reaction.




*Scheme 3.20: Nucleophilic catalyst effect on the metal free trichlorobenzoxazole synthesis.*

| Entry | Catalyst | Catalyst loading | Solvent | Yield (%) |
|---|---|---|---|---|
| **1** | No cat. | - | *n*-hexane | 0 |
| **2** | methanol | 10 mol% | *n*-hexane | 39 |
| **3** | $PPh_3$ | 10 mol% | *n*-hexane | 37 |
| **4** | DABCO | 10 mol% | *n*-hexane | 46 |
| **5** | methanol | 1 equiv. | *n*-hexane | 60 |
| **6** | methanol | 1 equiv. | $^t$BuOH | 90 |

*Table 3.4: Nucleophilic catalyst effect on the metal free trichlorobenzoxazole synthesis.*

Based on these experiments the revised mechanism for the metal free synthesis of 2-benzoxazoles starts by the activation of nitrile **289** via hydrogen bonding with the protic alcohol. The newly formed hydrogen bond allows for nucleophilic addition of a molecule of methanol **340** to form imidate intermediate **341**. Imidate intermediate **341** then undergoes nucleophilic attack from 2-amino phenol and follows the mechanism previously stated to form benzoxazole **291** (Figure 3.9)**.** Another example of nitrile activation via

hydrogen bonding is the work by Fleming et al. in which he shows a number of drug like compounds binding to receptors via nitrile hydrogen bonds.[107]

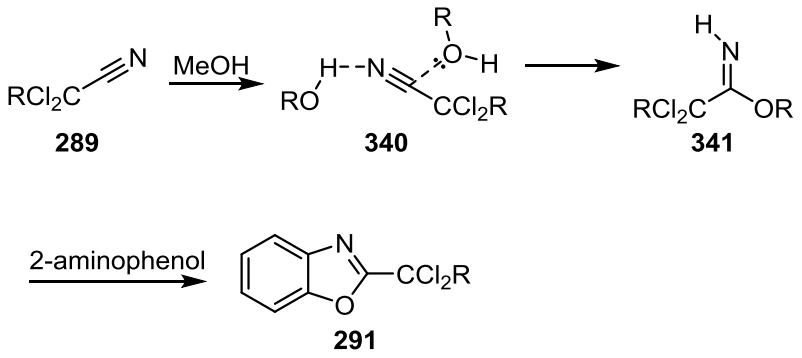



*Figure 3.9: Proposed mechanism for the uncatalysed synthesis of benzoxazole* **291**

### 3k) Conclusion

To conclude a platinum-catalysed method for the synthesis of benzoxazoles was developed in the solvent *n*-hexane. This method produced the desired benzoxazole in good to reduced yields. Further analysis of the solvent study presented an anomaly that protic alcoholic solvents produced the desired benzoxazole in excellent yields without the aid of a Lewis acid catalyst. Further development of a metal free method showed that a decrease in the stoichiometry of the nitrile was achievable without a reduction in the yield. Further to this, a temperature decrease of 40 ºC was also achievable without a decrease in the yield producing trichlorobenzoxazole in almost a quantitative yield. Increasing the substrate versatility by using less activated dichloroacetonitrile **(271)** within this methodology is viable with a decrease in yield of approximately 20% when 1 equiv. of the nitrile was used.

# Chapter 4: Results and discussion - functionalisation of halogenated methyl moieties

## 4a) Introduction

The majority of the benzoxazoles that were synthesised in the previous project are novel compounds. As a result, there has been little investigation into the reactivity of di- and trichlorobenzoxazoles. We felt that the functionality at the C-2 position would be useful for diversity orientated synthesis. Diversity orientated synthesis is the synthesis of many different compounds from a single starting material by altering the conditions of the reaction.[80] This approach is commonly found in industry for synthesising large libraries of compounds to test for biological activity.

Trichlorobenzoxazoles **153** have an excellent potential for further functionalisation, as they can be manipulated in a multitude of ways. One important reaction is nucleophilic substitution of the chlorine atoms on the trichloromethyl moiety **191** (Reaction A, figure 4.1). The second advantageous reaction is nucleophilic aromatic substitution at the C-2 position of the benzoxazole with the trichloromethyl group acting as a leaving group **192** (Reaction B, figure 4.1). If a successful selective nucleophilic displacement reaction can be achieved on trichlorobenzoxazoles the sulfur chemistry outlined earlier (*cf.* Scheme 1.30) would be avoided as well as novel chemistry on the benzoxazole core.

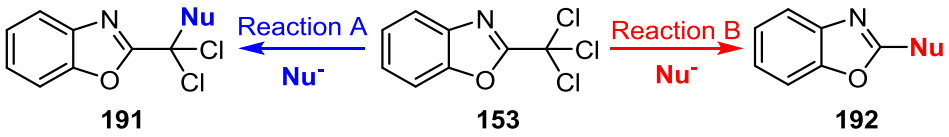



*Figure 4.1: Manipulation of the trichloromethyl moiety attached to benzoxazole.*

Dichlorobenzoxazole substrate **322** can also be manipulated into useful compounds that contain the benzoxazole core. There are two main approaches to the functionalisation of dichlorobenzoxazole. The first method is via a deprotonation of the alpha chloro proton to form anion **342**, followed by the addition of an electrophile to form the addition adduct **343** (Reaction A, figure 4.2). The second method is the loss of a chlorine cation to form carbene **344**.[108] The carbene reactive intermediate can then undergo further transformations, for example cyclopropanation with olefins to form tricycle **345** (Reaction B, figure 4.2).

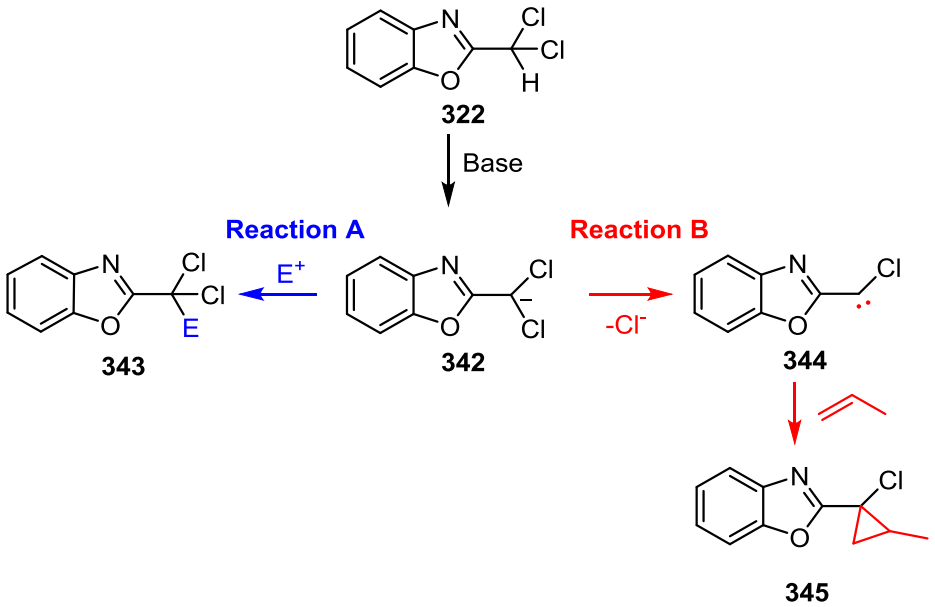
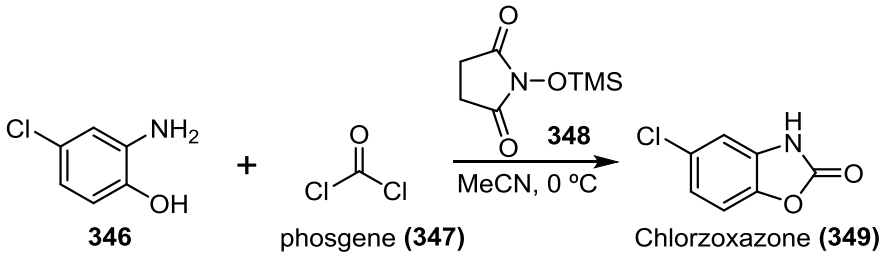



*Figure 4.2: Manipulation of the dichloromethyl moiety attached to benzoxazole.*

### 4b) Hydrolysis of trichlorobenzoxazoles

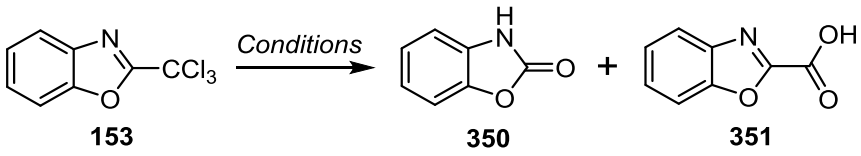
One of the simplest $S_NAr$ reactions on 2-trichlorobenzoxazole **153** would be to use water as the nucleophile to form a benzoxazolone. Benzoxazolones are important added-value compounds for their use in medicinal chemistry. For example chlorzoxazone **(349)** was shown to be an active muscle relaxant. It is also currently a prescribed pain killer for muscle spasms that has significant activity in cystic fibrosis patients.[109] It is synthesised commercially by reacting 2-amino-4-chlorophenol **(346)** with phosgene **(347)** in the presence of OTMS succinamide **348**.[75] Phosgene **347** is highly poisonous;[110] ideally industry would like to avoid this compound so a selective hydrolysis of trichlorobenzoxazoles is an attractive alternative (Scheme 4.1).




*Scheme 4.1: Industrial synthesis of chlorzoxazone **(349)***

The hydrolysis of trichlorobenzoxazole could form two major products, namely benzoxazolone **350** and carboxylic acid derivative **351**. Therefore selectivity is important for a viable process (Scheme 4.2). To develop a selective hydrolysis reaction a number of conditions were screened. Two reactions from the screening gave the desired product selectively with the highest yielding being the reaction of trichlorobenzoxazole in a mixture of 1:1

water and methanol at 150 ºC for 2 hours to form benzoxazone **350** in 65% yield (Entry 7, table 4.1). The second reaction that produced benzoxazone **350** was the reaction of trichlorobenzoxazole **153** in neat sulfuric acid at 60 ºC for 20 hours, followed by increasing the temperature to 120 ºC for 4 hours (Entry 9, table 4.1). In all the conditions attempted none of carboxylic acid **351** was observed, suggesting that nucleophilic attack of the aromatic ring is more facile than hydrolysis of the trichloromethyl moiety, under these conditions.




**153** **350** **351**

*Scheme 4.2: Development of the conditions for the hydrolysis of trichlorobenzoxazoles.*

| Entry | Conditions | Yield (%) |
|---|---|---|
| **1** | NaOH, MeCN, 60 ºC, 24 h | 0 |
| **2** | $D_2O$, 150 ºC, MW, 10 min | 0 |
| **3** | $D_2O$, r.t., 17 h | RSM |
| **4** | $D_2O$, 50 ºC, 17 h | RSM |
| **5** | $D_2O$, 100 ºC, 17 h | 0 |
| **6** | $H_2O$/MeOH, 120 ºC MW, 5 min | 0 |
| **7** | $H_2O$/MeOH, 150 ºC, 2 h | 69% of **350** |
| **8** | $H_2O$/MeOH, 150 ºC, 24 h | 0 |
| **9** | $H_2SO_4$, 120 ºC, 20 h | 54% of **350** |

*Table 4.1: Development of the conditions for the hydrolysis of trichlorobenzoxazoles.*

### 4c) Preliminary results for nucleophilic aromatic substitution reaction

In addition to using water as a nucleophile to displace the trichloromethyl moiety, amino and alcohol nucleophiles were investigated. The nucleophilic aromatic substitution reaction would functionalise the C-2 position with a heteroatom. This method could be a useful method for coupling a heteroatom on to the benzoxazole core. Conceptually the process would start with a nucleophilic addition into the electrophilic carbon centre of **352** forming tetrahedral intermediate **353**. The lone pair of the nitrogen would come down and releases the trichloromethyl group to form iminium **354**. Loss of the proton on the nitrogen neutralises the compound and completes the nucleophilic aromatic substitution via a $S_NAr$ process to form the newly substituted benzoxazole **191** and chloroform (**355**, Figure 4.3).

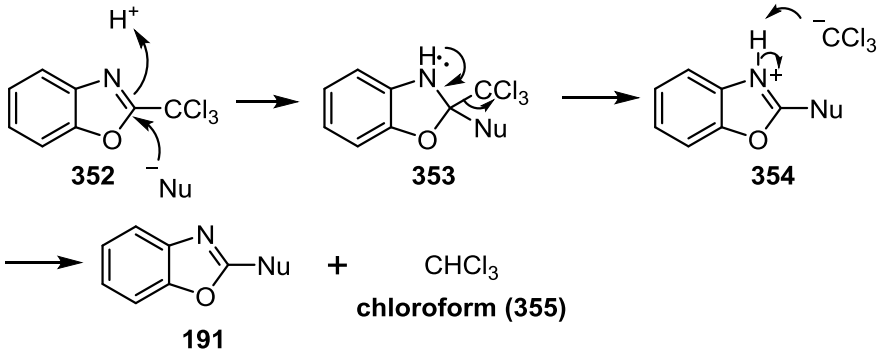



*Figure 4.3: Proposed mechanism for $S_NAr$ reaction of trichlorobenzoxazole.*

It would be expected that from tetrahedral intermediate **353** the elimination of the group is dependent on the pKa of the leaving group. It would be expected that dependent on the nucleophile the pendant phenol moiety will be the most likely leaving group as it has a typical pKa 10, compared to chloroform that

has a pKa 15. However, both the removal of the nucleophile and the ring opening is a reversible reaction, which can form tetrahedral intermediate **353** again. Importantly, the $S_NAr$ is possible due to a chloroform degradation pathway to give carbon dioxide. The elimination of chloroform and is subsequent degradation is irreversible and therefore proceeds to form the $S_NAr$ product **191** (Figure 4.4).

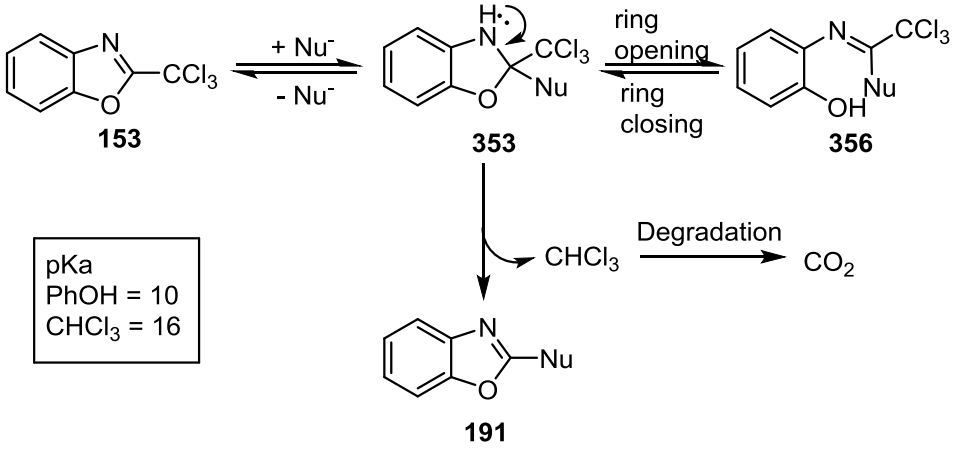
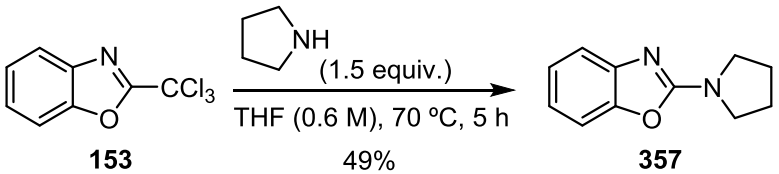


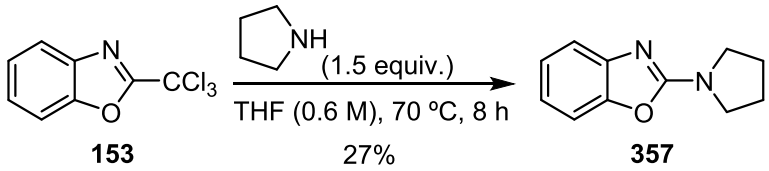

*Figure 4.4: Proposed reasoning for the successful $S_NAr$ of 2-trichlorobenzoxazoles.*

To develop a $S_NAr$ reaction with nitrogen nucleophiles, pyrrolidine was chosen because of its excellent nucleophilic abilities. Preliminary results of a reaction based on the conditions developed by Jeon et al. in which trichlorobenzoxazole **153** was reacted with pyrolidine (1.5 equiv.) in refluxing THF for 5 hours resulted in a yield of 49% of the desired nucleophilic substitution product **357** (Scheme 4.4).[68]



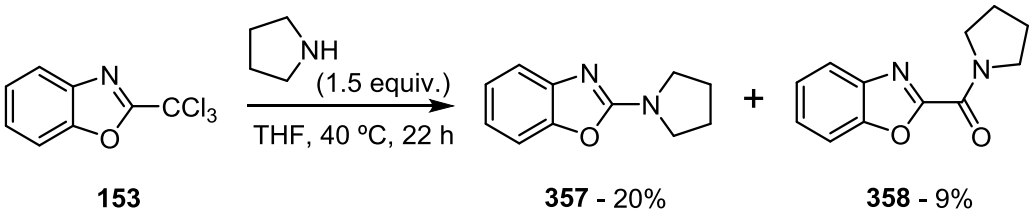

*Scheme 4.3: Preliminary synthesis of pyrolidine benzoxazole derivative **357**.*

To try to increase the yield the reaction was left to stir for an increased time of 8 h, however, this produced a poorer yield of 27% of substituted benzoxazole **357**. This poor result suggests, once the product is formed it degrades into other products at this temperature (Scheme 4.5).




*Scheme 4.4: Increasing the reaction time of the synthesis of pyrolidine benzoxazole derivative **357**.*

To identify if the temperature was reducing the overall yield, a lower temperature of 40 ºC was used. By monitoring the reaction by TLC it was possible to stop the reaction once all of the starting material had been transformed. Within this investigation the starting material was not used up after a 22 hour period and produced a maximum yield of 20% of pyrrolidine substituted benzoxazole **357** was obtained. In addition to the desired amino benzoxazole **357**, another major product was identified as the amido benzoxazole **358** (Scheme 4.6).




*Scheme 4.5: Identification of amido benzoxazole derivative **358**.*

It is believed that the amido benzoxazole **358** is formed from firstly, nucleophilic attack of a chloroine atom forming a stabalised carbon anion **359**, this is followed by a nucleophilic attack of the chloro pyrrolidine, which then forms dichlorobenzoxazole **360**. The lone pair on the nitrogen of the substituted benzoxazole **360** comes down to kick off a chloride anion to form iminium **361**. Upon work up, water attacks the very electrophilic iminium **362** to eventually give 2-amido benzoxazole **358** (Figure 4.5).

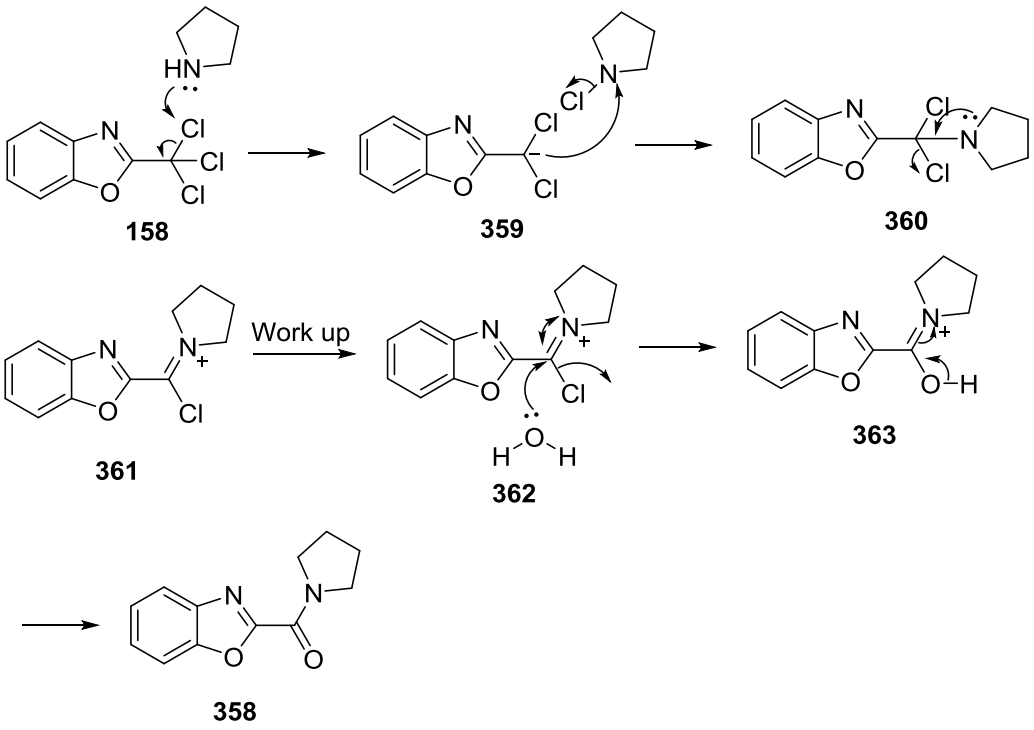
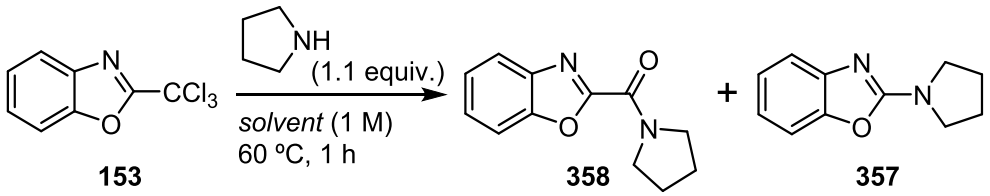



*Figure 4.5: Proposed mechanism for the synthesis of amido benzoxazole **358**.*

### 4d) Development of a selective amino/amido transformation

Building upon the preliminary investigation, we set out to develop the selective formation of 2-amino or 2-amido benzoxazole **357** and **358** from trichlorobenzoxazole **153** and pyrrolidine. HPLC analysis was used to analyse

a large number of reactions in a short period of time. Although this method does not give quantitative results it is a good indicator for identifying the optimal reaction conditions. The first variable to be investigated was the solvent used for this reaction. A variety of solvents were screened including industry alternatives to common solvents e.g. 2-methyl tetrahydrofuran instead of tetrahydrofuran (Scheme 4.7). The optimal solvent for the selective synthesis of 2-aminobenzoxazole **357** was acetonitrile, which selectively formed the amine with 32% starting material remaining after 1 hour (Entry 7, table 4.2).




*Scheme 4.6: Solvent effects on the selectivity of the $S_NAr$ of trichlorobenzoxazoles.*

| Entry | Solvent | % of SM[a] | % of amide[a] | % of amine[a] |
|---|---|---|---|---|
| **1** | MeOH | 76 | 10 | 13 |
| **2** | EtAc | 59 | 10 | 28 |
| **3** | $^t$BuOMe | 68 | 10 | 20 |
| **4** | 2-MeTHF | 61 | 13 | 23 |
| **5** | $H_2O$ | 52 | 20 | 5 |
| **6** | MeCN/$H_2O$ | 58 | 33 | 3 |
| **7** | MeCN | 32 | 7 | 61 |

*a.* Conersions determined by relative areas under the curve of a HPLC trace after 2 h

*Table 4.2: Solvent effects on the selectivity of the $S_NAr$ of trichlorobenzoxazoles.*

One way to force selectivity towards the formation of the amino benzoxazole **357** is to use a Lewis acid to activate the electrophilic carbon further. This would happen by the Lewis acid binding to the nitrogen lone pair **364**, forming

a bond which would pull electron density from the carbon centre resulting in an increase of electrophilicity at the C-2 position. Following the nucleophilic addition into **365** the loss of trichloromethyl group **366** results in the $S_NAr$ product **191** (Figure 4.6). The choice of Lewis acid is important as a Lewis acid could also aid in the removal of a chlorine cation **367** to **368** to form dichloro carbocation **359,** which would eventually give 2-amidobenzoxazole **369**.[111]

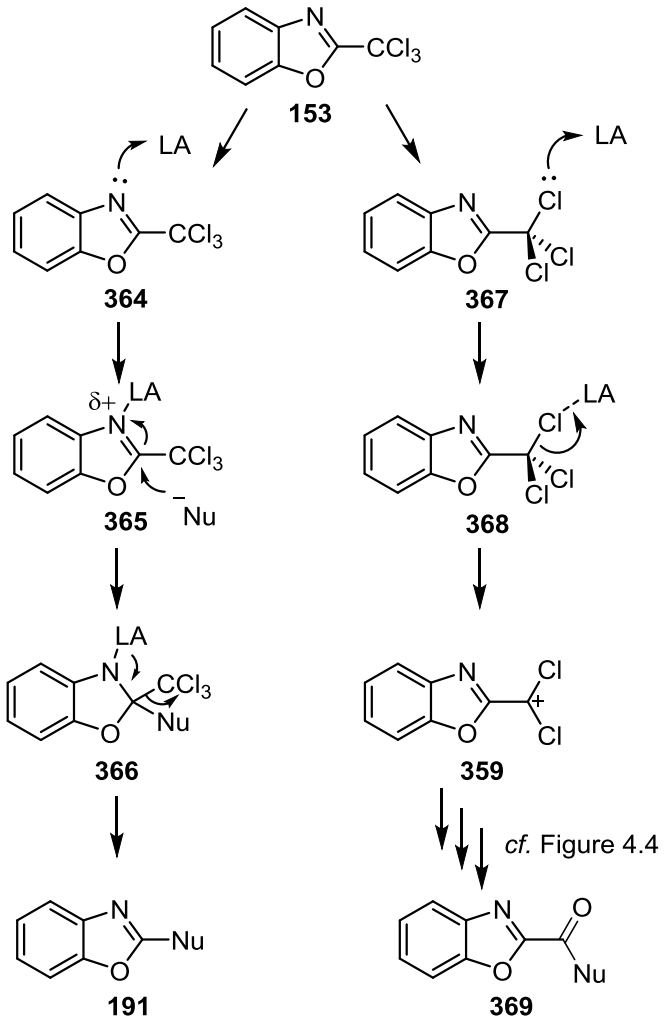
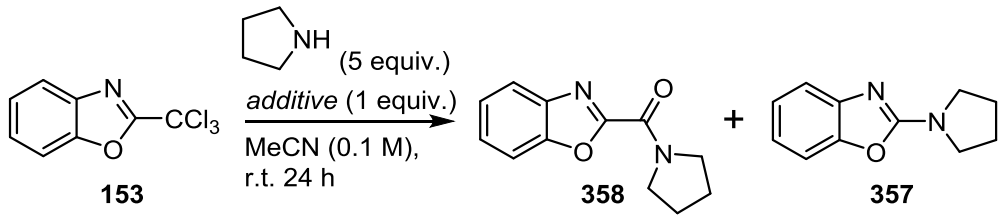



*Figure 4.6: Two possible Lewis acid activation pathways for trichlorobenzoxazoles.*

A number of Lewis acids were screened using pyrrolidine as the nucleophile at ambient temperature to identify selective reaction conditions (Scheme 4.8). Adding a Lewis acid additive produced the amido benzoxazole as the major product for all the examples (Table 4.3). After running the control reaction in which the additive was excluded from the reaction, amidobenzoxazole **358** was still the major product (Entry 10, table 4.3). Further investigation into the parameters that control selectivity of this reaction was required.



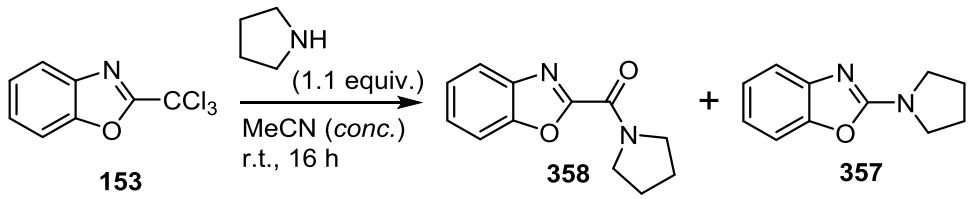

*Scheme 4.7: Additive effects on the selectivity of the $S_NAr$ of trichlorobenzoxazoles.*

| Entry | Additive | % of SM[a] | % of amide[a] | % of amine[a] |
|---|---|---|---|---|
| **1** | $ZnCl_2$ | 27 | 63 | 10 |
| **2** | $AlCl_3$ | 73 | 23 | 4 |
| **3** | $BF_3(OEt_2)$ | 13 | 67 | 20 |
| **4** | $FeCl_2$ | 7 | 81 | 13 |
| **5** | $FeCl_3$ | 24 | 75 | 0 |
| **6** | $Ti(O^iPr)_3$ | 14 | 56 | 29 |
| **7** | YbOTf | 70 | 15 | 15 |
| **8** | $PtCl_2$ | 39 | 55 | 6 |
| **9** | AgOTf | 11 | 49 | 40 |
| **10** | None | 0 | 75 | 25 |

a. *Yields determined by relative areas under the curve of a HPLC trace after 2 h*

*Table 4.3: Additive effects on the selectivity of the $S_NAr$ of trichlorobenzoxazoles.*

To further investigate and identify the variable(s) that changed the selectivity, a reaction at ambient temperature was run with varied concentrations from 0.05 M up to 5.0 M (Scheme 4.9). These experiments showed that the concentration was vital in controlling the selectivity of the reaction. The selectivity of amido benzoxazole **358** compared to amino benzoxazole **357** varied from 81:19 to 6:93 when the concentration was changed from 0.05 M to 1 M (Entries 1 to 4, table 4.4). Increasing the concentration further slightly improved the selectivity of the reaction in favour of aminobenzoxazole **357**, but these conditions also reduced the overall conversion of the stating material (Entry 5 to 6, table 4.4).



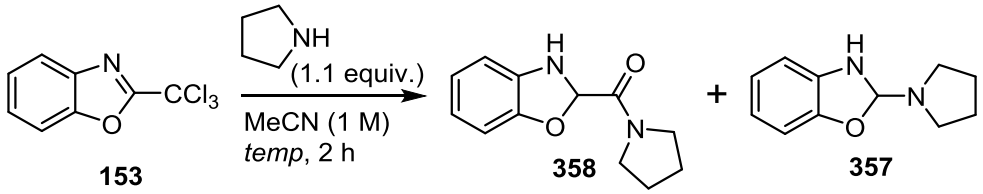

*Scheme 4.8: Concentration effects on the selectivity of the $S_NAr$ of trichlorobenzoxazoles.*

| Entry | Conc. (M) | % of SM[a] | % of amide[a] | % of amine[a] |
|---|---|---|---|---|
| **1** | 0.05 | 2 | 81 | 17 |
| **2** | 0.1 | 51 | 45 | 4 |
| **3** | 0.5 | 41 | 1 | 49 |
| **4** | 1 | 1 | 6 | 93 |
| **5** | 2 | 9 | 5 | 86 |
| **6** | 5 | 19 | 4 | 77 |

*a. Yields determined by relative areas under the curve of a HPLC trace after 2 h*

*Table 4.4: Concentration effects on the selectivity of the $S_NAr$ of trichlorobenzoxazoles.*

Now that the selectivity was better understood, the next variable that was explored was the temperature. A sample was taken after a reaction time of 2 hours at varying temperatures, ambient to 100 ºC (Scheme 4.10). The results confirm that the selectivity trend was a result of the concentration and the temperature had little effect on the selectivity (Entries 1 to 5, table 4.5).




*Scheme 4.9: Temperature effects on the selectivity of the $S_NAr$ of trichlorobenzoxazoles.*

| Entry | Temp | % of SM[a] | % of amide[a] | % of amine[a] |
|---|---|---|---|---|
| **1** | ambient | 16 | 5 | 79 |
| **2** | 40 ºC | 15 | 5 | 80 |
| **3** | 60 ºC | 2 | 6 | 90 |
| **4** | 80 ºC | 0 | 7 | 93 |
| **5** | 100 ºC | 0 | 6 | 94 |

*a. Yields determined by relative areas under the curve of a HPLC trace after 2 h*

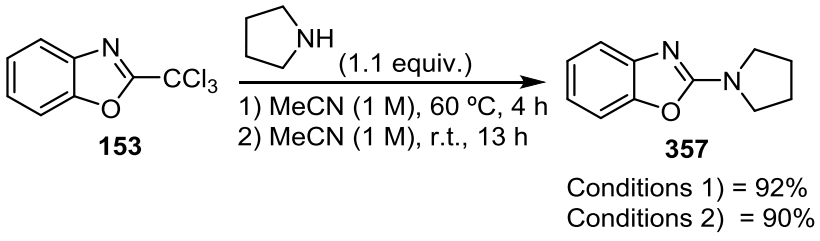
*Table 4.5: Temperature effects on the selectivity of the $S_NAr$ of trichlorobenzoxazoles.*

After running each of the above reactions to completion it was found that the reaction at ambient temperature required over night stirring before all of the starting material had been used up (Entry 1, table 4.6). In contrast, the reaction at 60 ºC was complete in 4 h (Entry 3, table 4.6).

| Entry | Temp | Completion time |
|---|---|---|
| **1** | ambient | o/n |
| **2** | 40 ºC | 7 h |
| **3** | 60 ºC | 4 h |
| **4** | 80 ºC | 2 h |
| **5** | 100 ºC | 1 h |

*Table 4.6: Temperature effects on the reaction time of $S_NAr$ of trichlorobenzoxazoles.*

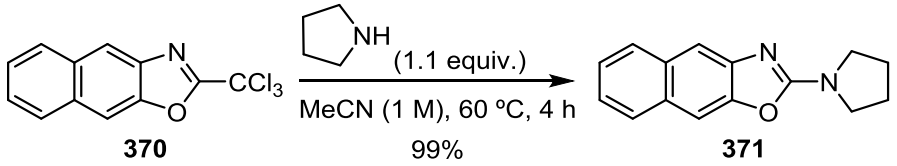
To summarise the optimisation studies, the conditions developed for the selective synthesis of the nucleophilic aromatic substitution of trichlorobenzoxazoles with pyrrolidine is: trichlorobenzoxazole **153** (1 equiv.) with pyrrolidine (1.1 equiv.) in acetonitrile (1 M) at 60 ºC for 4 hours (Scheme 4.11). These conditions produced the desired amino benzoxazole **357** in a 92% isolated yield. The isolated yield shows a strong correlation to the HPLC analysis results. In addition to the optimised conditions it was also shown that the reaction proceeds readily at ambient temperature with the same reagents in approximately the same yield, although with an increased reaction time (Scheme 4.11).




*Scheme 4.10: Optimal conditions for the $S_NAr$ reaction of trichlorobenzoxazole*

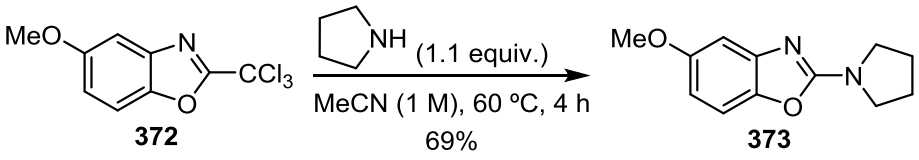
### 4e) Substrate scope for nucleophilic aromatic substitution

The substrate scope of the nucleophilic aromatic substitution process was undertaken using the optimised reaction conditions with a number of trichlorobenzoxazoles. The first substrate that was initially attempted was the naphthol derivative **370** in which the aromaticity of the substrate has been increased. Under the standard conditions the desired amino benzoxazole **371** was produced selectively in a 92% yield (Scheme 4.11).




*Scheme 4.11: Substrate scope – naphthol derivative*

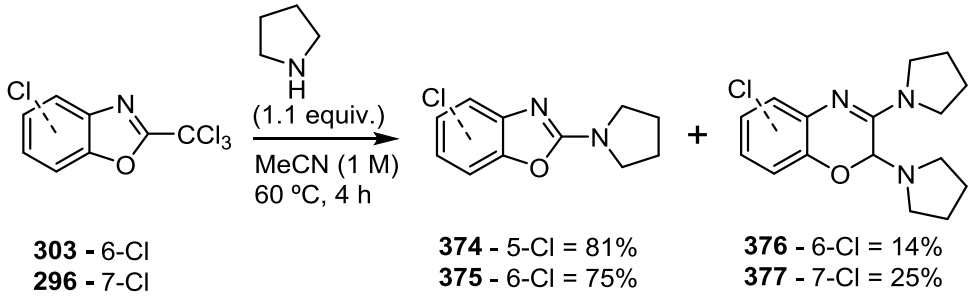
In addition, an electron rich substrate, methoxy trichlorobenzoxazole **372,** produced the desired amino benzoxazole **373** in a reduced yield of 69% (Scheme 4.13). This reduction in yield was expected because the electron donating effects of the methoxy moiety reduces the electrophilicity of the carbon that underwent substitution.




*Scheme 4.12: Substrate scope – electron donating substituent*

Substitution with an electron withdrawing chlorine substituent on the trichlorobenzoxazole also successfully formed amino benzoxazole **374** and **375** in moderate yields of 75-81% depending on the position of the chlorine atom.

Additionally, small quantities of benzoxazin **376** and **377** were formed (Scheme 4.14). The structures were confirmed by x-ray crystallography. The presence of the aminal and amidine moiety is clearly visible in benzoxazine's crystal structure. The formation of benzoxazines **376** and **377** are interesting by-products because during the reaction an overall reduction must have taken place.




*Scheme 4.13: Substrate scope – chloro derivatives*

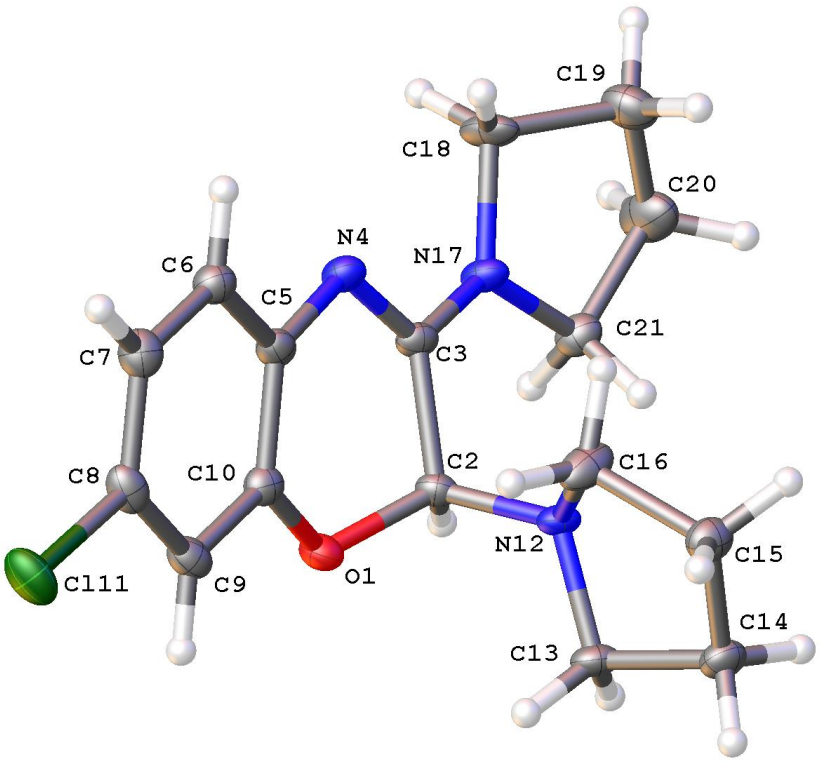



*Figure 4.7: Crystal structure of benzoxazine **377***

A possible mechanism for the formation of generic benzoxazine **384** is proposed to start via a same method as seen in Figure 4.5 to form stabalised carbon anion, which instead of attacking the newly formed chloro pyrrolidine as seen with the formation of the amide it attacks a proton from pyrrolidine forming dichloro benzoxazole **322**. **322** undergoes an $S_NAr$ type mechanism to iniciate a ring opening process to form amidine **379**. The negative oxygen ion attacks the trichloromethyl group via an $S_N1$ type process, via **380**, to form benzoxazine **381**. The lone pair of the oxygen atom then comes down to displace a chloride **381** atom forming oxonium **382**. A molecule of pyrrolidine then attacks the electrophilic carbon forming the aminol of benzoxazine **383**. If R is a chloride in benzoxazine **383** (Figure 4.8). A related mechanism was proposed by Heitzer et al. in which dichlorobenzoxazole was reacted with a similar nucleophile to produce the observed benzoxazine **383**.[112]

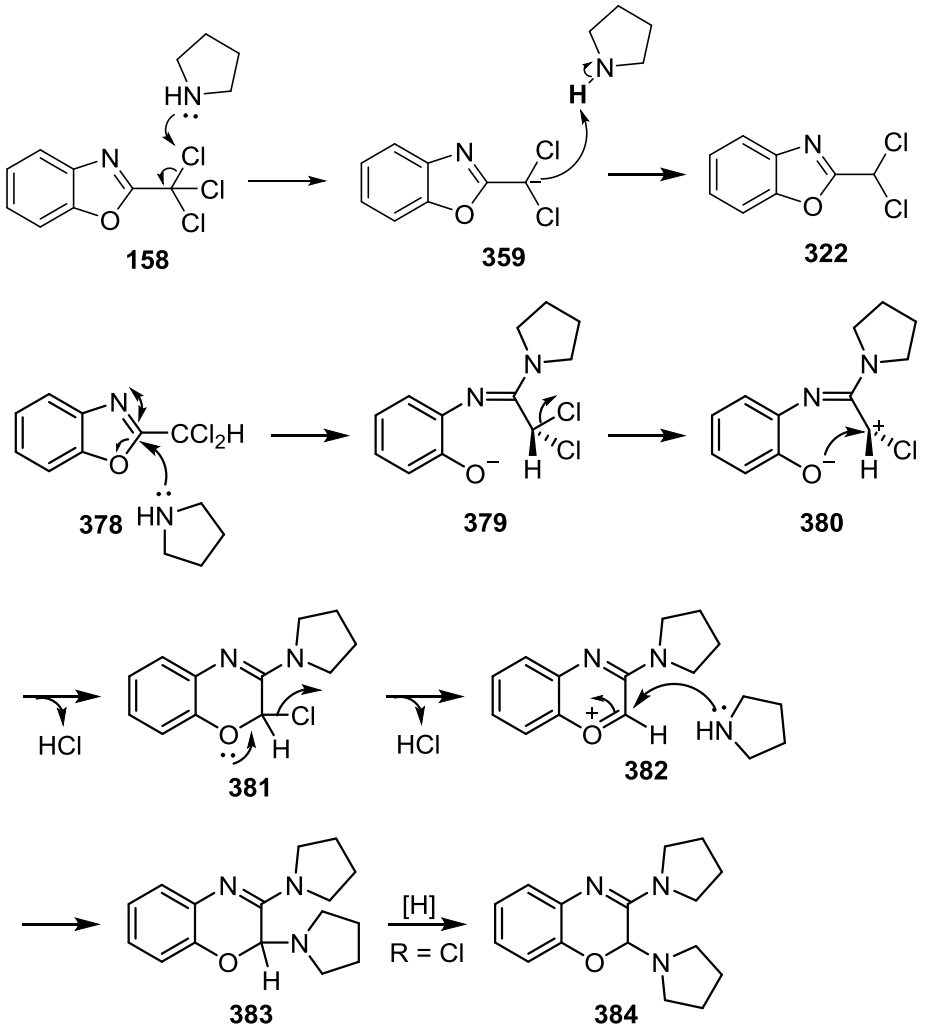



*Figure 4.8: Proposed mechanism of by-product with the chloro derivatives*

Heitzer et al. research suggested that rather than a reduction occurring once benzoxazoline **383** is formed the reduction takes place on the parent trichlorobenzoxazole **153** to form dichlorobenzoxazole **297** followed by the nucleophilic mechanism above where R = H. Trichlorobenzoxazole **153** is transformed into dichlorobenzoxazole **297** by initial insertion of a metal between the carbon and the chlorine atom. Complex **385** then underwent an elimination reaction forming dichloro enamine **386**, which underwent a re-aromatisation process to form dichlorobenzoxazole **297** (Figure 4.9).

Reduction of parent trichlorobenzoxazole **153** is believed to be more likely because of three reasons. Firstly, if the first mechanism is correct you would expect to see a small amount of the chloro derivative of benzoxazoline **383** that has not been reduced. Secondly, starting from the dichlorobenzoxazole is more likely to undergo the nucleophilic addition reaction shown in figure 4.8 rather than a nucleophilic aromatic substitution reaction due to the poorer leaving abilities of the dichloromethyl group. Finally, the nucleophilic substitution reaction of the phenol moiety, to close the ring within the first mechanism (*cf.* Figure 4.8) is much more likely with the dichloro rather than the trichloro substrate due to the extra steric hindrance of quaternary carbon centre.

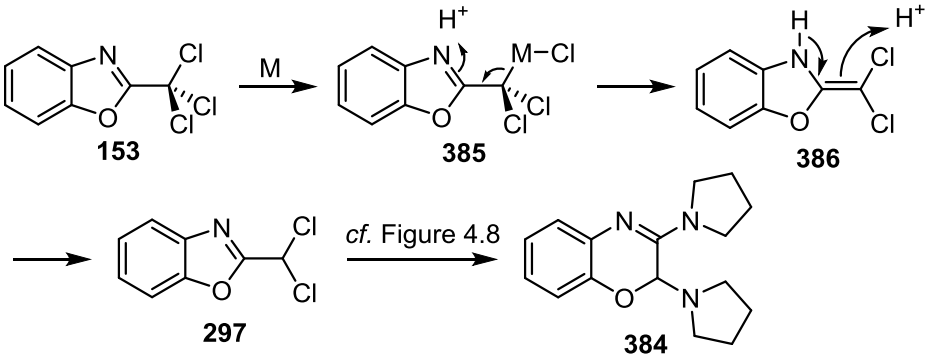
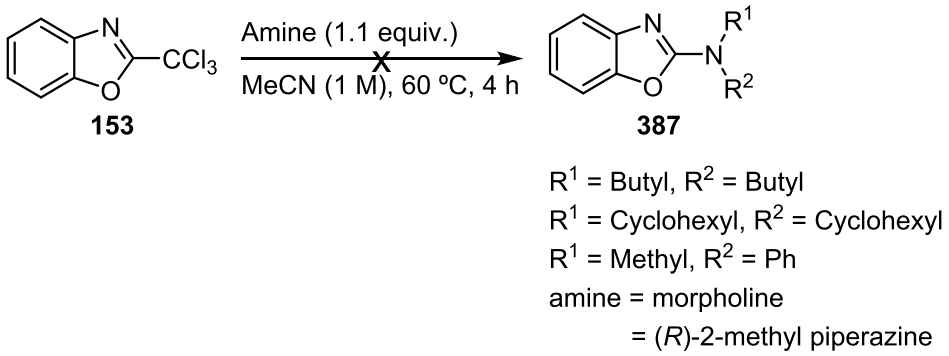



*Figure 4.9: Second proposed mechanism for the reduction of chloro derivative by-product*

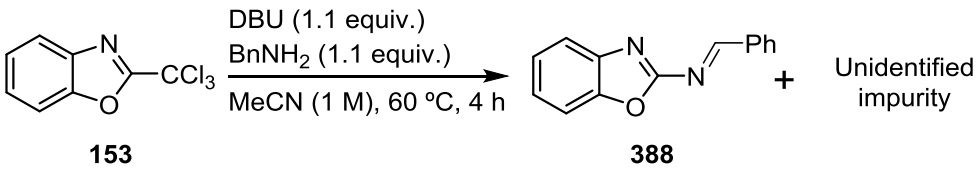
In addition to pyrrolidine, other amine/alcohol nucleophiles were attempted on trichlorobenzoxazole **153**. Firstly, a number of different secondary amines including: dibutylamine, dicyclohexylamine, methylaniline, morpholine and (*R*)-methylpiperazine were attempted under the optimised conditions (Scheme 4.15). All of the secondary amines resulted in recovered starting material. One possible explanation for these results is that the sterics of the amine is reducing its nucleophilicity. This is a very important factor because the rate limiting step within an $S_NAr$ reaction is the formation of the tetrahedral intermediate, the

loss of the leaving group is generally facile due to the re-aromatisation of the ring.[113]



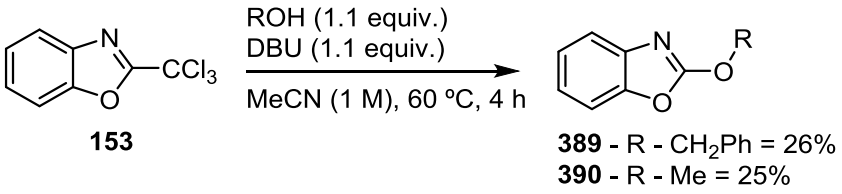

*Scheme 4.14: Attempted amines in $S_NAr$ reaction of trichlorobenzoxazole*

To remove the sterics found with secondary amines, two primary amines, aniline and benzylamine were subjected to the standard conditions. However, these reactions only gave recovered starting material. One way to increase the nucleophilicity of the amine is to use a base to deprotonate the nitrogen once the nucleophilic addition step has taken place, ensuring that the trichloromethyl group is a better leaving group. Aniline and benzylamine were. subjected to the optimised conditions with the addition of a non-nucleophilic weak base (DBU) (Scheme 4.16). Preliminary results show that when attempting the basic conditions with aniline none of the desired product was observed. Under the same conditions with benzylamine, a mixture of imine **388** and an additional impurity were isolated. Further analysis is required to confirm these results.




*Scheme 4.15: Formation of aldehyde derivative from trichlorobenzoxazole*

To identify if it was only amines that could undergo the $S_NAr$ reaction two alcohols were attempted under the basic conditions. These produced the desired benzoxazole derivative **389** and **390** in 26% and 25% yield by using benzyl alcohol and methanol respectively (Scheme 4.17).




*Scheme 4.16: $S_NAr$ reaction with alcohols as nucleophiles*

### 4f) Selective synthesis of benzoxazoles containing a 2-amido moiety

Next, we turned our attention to the selective formation of 2-amido benzoxazoles. It is important to note that within the additives investigation (*cf.* table 4.3), iron(III) chloride produced amido benzoxazole **358** with the greatest selectivity producing none of amino benzoxazole product **357.** Akker et al. showed that catalytic quantities of iron(III) chloride can be used to hydrolyse 4-chloro trichloromethylbenzene **(167)** at 60 ºC with 1 equivalent of water. [73, 108] The proposed mechanism for the catalytic hydrolysis of trichloromethylbenzene **(167)** with iron(III) chloride works by the close proximity of the iron complex to a chlorine atom weakening the C-Cl bond **391**. The newly formed carbocation **392** is much more susceptible to nucleophilic attack of water, which reduces the probability of the $S_NAr$ reaction pathway. Dichloro alcohol **393** forms 4-chlorobenzoylchloride **(168**) after the elimination of a hydrogen chloride (Figure 4.10).

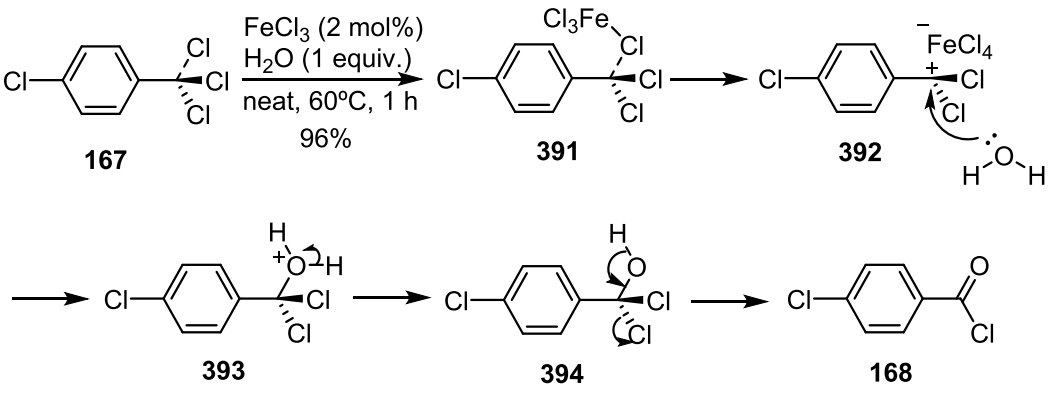
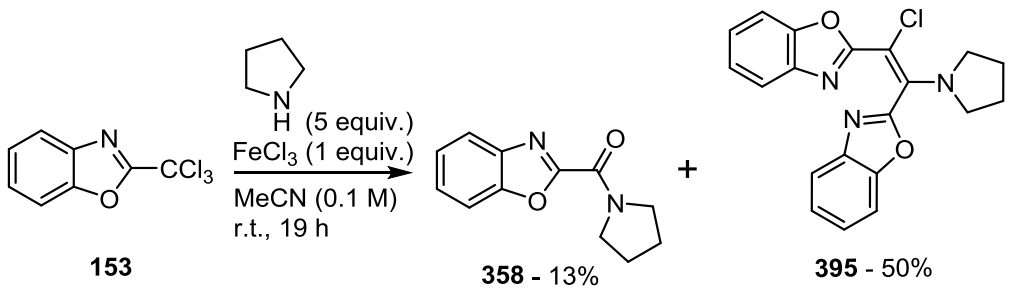



*Figure 4.10: The mechanisms for the iron -catalysed hydration of trichloromethylbenzene*

When the HPLC reaction was repeated on a slightly increased scale from 0.1 mmol to 0.6 mmol, the desired amido benzoxazole **358** was formed in 13% isolated yield. Interestingly, an additional compound bis-benzoxazole **395** formed a moderate 53% yield (Scheme 4.18). The dimerised product's structure was confirmed by x-ray crystallography. The crystallography analysis showed that the two nitrogen's were positioned facing one another and that the olefin geometry was *cis* (Figure 4.11).




*Scheme 4.17: Conditions for the synthesis of amido benzoxazole **358***

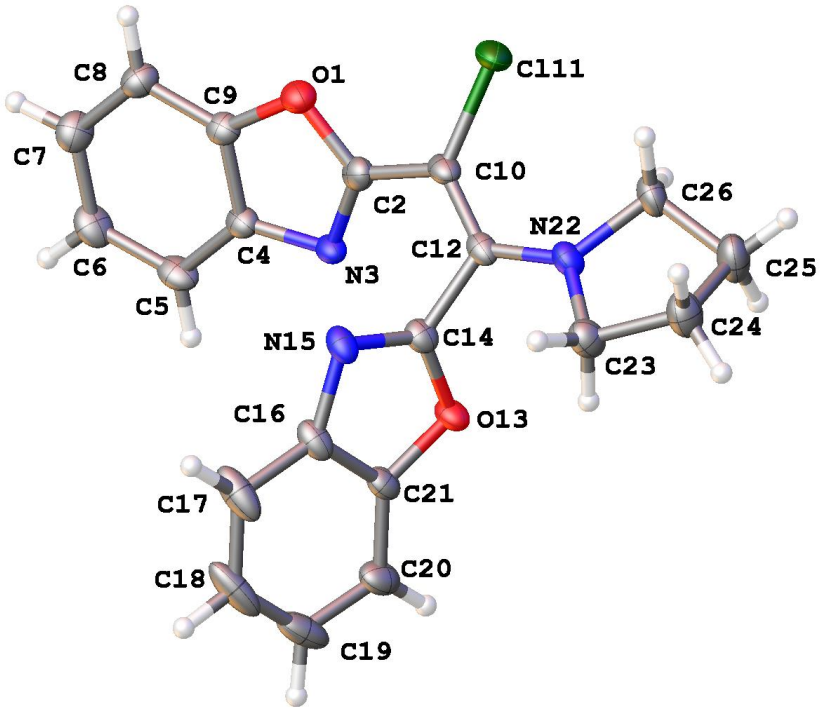
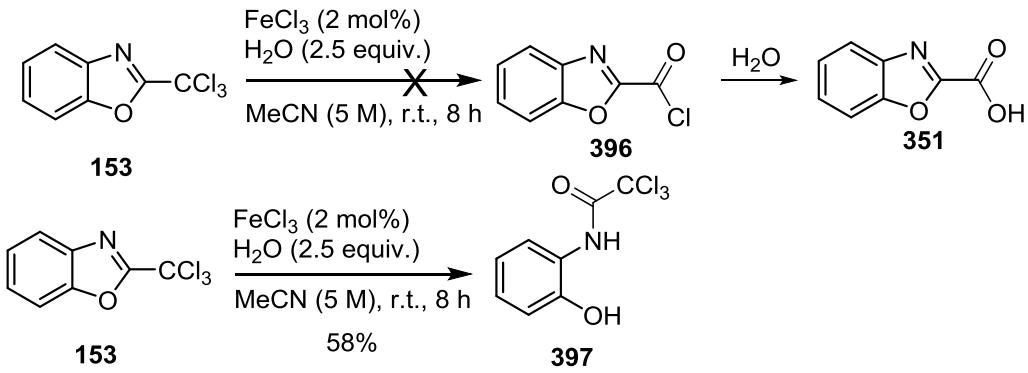



*Figure 4.11: Crystal structure of bis-benzoxazole **395***

To probe the formation of this interesting compound, an attempt to directly form acid chloride **396** followed by hydrolysis with water was undertaken. Reaction of trichlorobenzoxazole **153** in the presence of iron(III) chloride and water did not produce the discussed carboxylic acid, but instead formed the ring opened trichloro acetamide **397**. The structure of trichloro acetamide **397** was confirmed by x-ray crystallography. The crystal structure showed evidence of hydrogen bonding between the hydrogen on the nitrogen of the amide and the oxygen from the pendant phenol.




*Scheme 4.18: attempted hydrolysis of trichlorobenzoxazole*

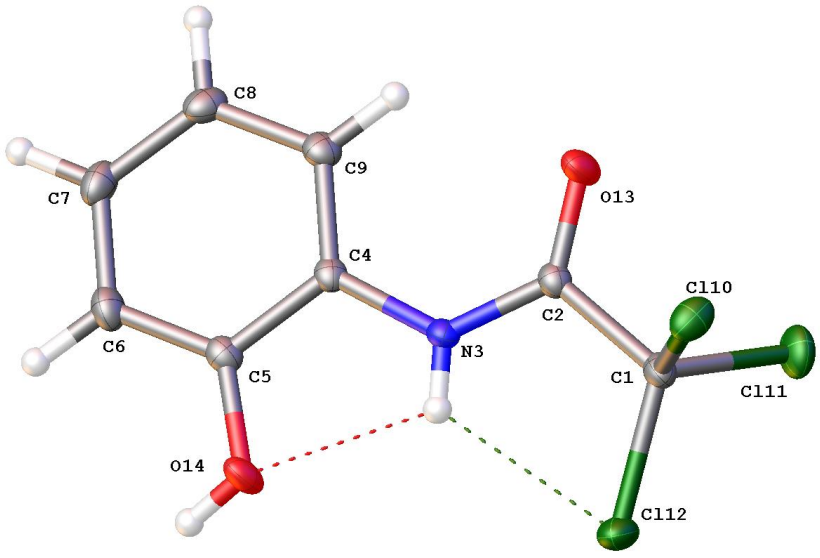


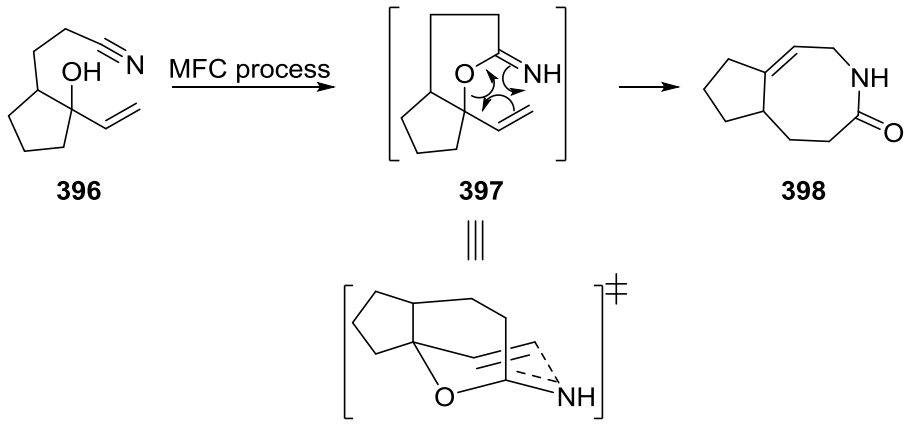

*Figure 4.12: x-ray crystal structure of ring opened **397***

## 4g) Conclusion

In summary a number of transformations have been successfully achieved on trichlorobenzoxazole **153**. These include: i) the formation of benzoxazolone **350** via a hydrolysis reaction, ii) a base free selective nucleophilic aromatic substitution of pyrrolidine, iii) nucleophilic aromatic substitution with primary alcohols with the addition of a weak base, iv) a selective amido benzoxazole synthesis was developed, although further investigation is required to eliminate the observed bis-benzoxazole **395** which is interesting in its own right.

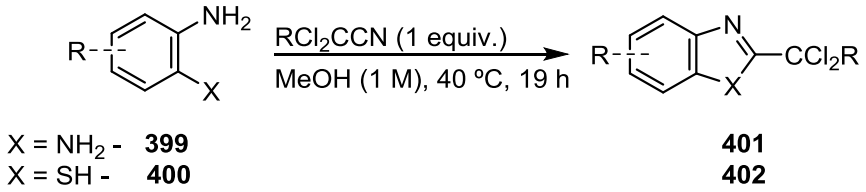
# Chapter 5: Future work

In relation to the MFC approach to a one-pot synthesis of allylic amides, future work would focus on successfully achieving a rearrangement with less activated and unactivated nitriles. Activation could be accomplished by either using different metal catalysts or by manipulating the electronics of the platinum chlorides salts. An important extension of this work will be to develop the methodology for an unprecedented intramolecular allylic amide synthesis via a [3,3]-sigmatropic rearrangement. An intramolecular system will be useful in the total synthesis of natural product and biologically active compounds. For example allylic alcohol **396** that has a pendent nitrile could be transformed in to the corresponding lactam **398** (Scheme 5.1). This proposed synthesis has never been achieved due to the limitations of using trihalogenated acetonitrile.



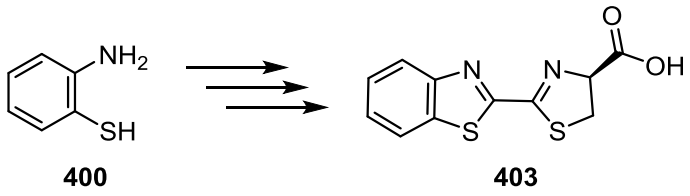

*Scheme 5.1: Intramolecular lactam synthesis via a [3,3]-sigmatropic rearrangement*

An important expansion of the metal free synthesis of benzoxazoles is the increase of the substrate scope to involve 2-aminoanilines **399** and 2-mercaptophenol(s) **400**. The work described in this thesis provides a strong basis for the expansion of the substrate scope (Scheme 5.2).




*Scheme 5.2: Proposed synthesis of benzothiazoles and benzoimidazole*

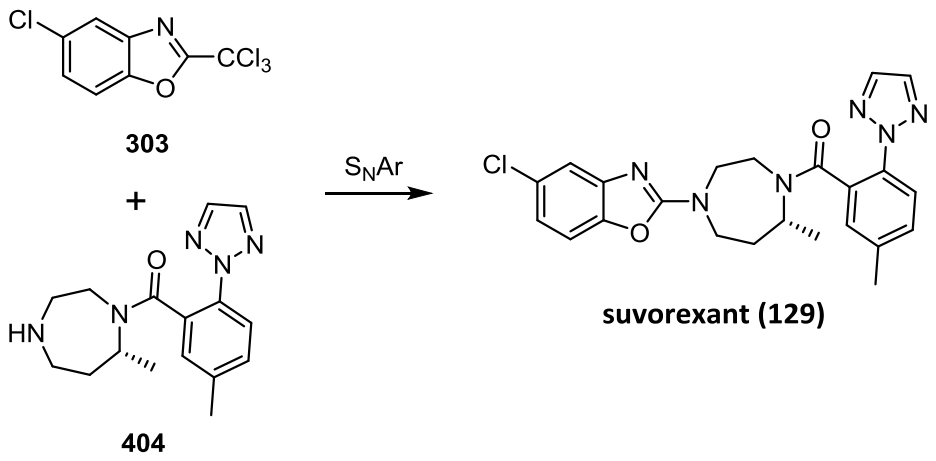
Once 2-mercaptophenol **400** has been incorporated into the metal free methodology, it will be used in the total synthesis of Luciferin **403**. From the methodology developed an efficient synthesis of Luciferin **403** and its analogues could be achieved (Scheme 5.3).




*Scheme 5.3: Proposed efficient synthesis of Luciferin*

Further research into the development of the manipulation of the trichloromethyl moiety is an exciting area to pursue due to the vast possibilities of diversity oriented synthesis. Following the work so far it is plausible to propose that after further development of the conditions for the nucleophilic aromatic substitution reaction a number of different nucleophiles could be employed to form a variety of small molecules that contain the benzoxazole

core. One example where this method could be useful in synthesis is in the formation of suvorexant **(129)** developed by Merck for the treatment of insomnia. This drug could be formed by coupling the amine compound **404** and benzoxazole **303** (Scheme 5.4).




*Scheme 5.4: Proposed synthesis of suvorexant via a $S_NAr$.*

In addition, to the manipulations of the trichloromethyl moiety demonstrated in this research a large quantity of possible and interesting transformations have not been explored. For example; i) nucleophilic aromatic substitution to form **406**, ii) amidation to form **407**, iii) esterification/saponification to form **408**, iv) azidation to form **409**, v) electrophilic addition to form **410**, vi) cyclopropanation via carbene synthesis to form **411**, vii) Wittig reagent formation to form **412** and viii) heterocyclic formation to form **413**.

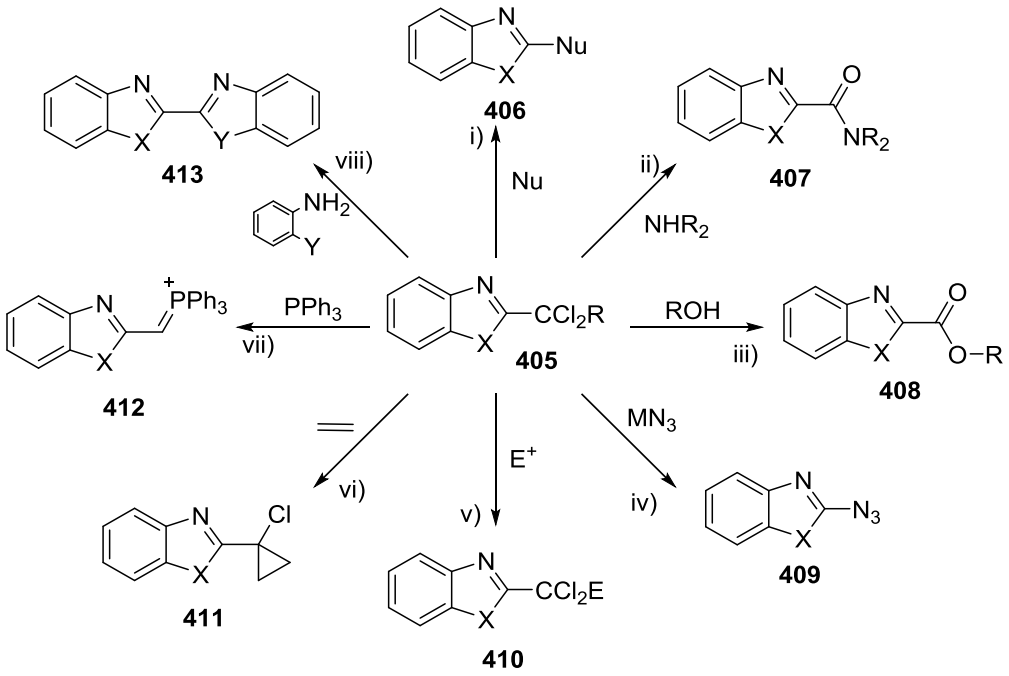



*Figure 5.1: possible transformations of benzoxazoles*

# Chapter 6: Experimental (allylic amide synthesis)

## 6a) General experimental

Unless otherwise indicated, all commercially available reagents and solvents were used directly from the supplier without further purification. Analytical grade dichloromethane was dried over calcium hydride and purified by distillation prior to use. Solvents for column chromatography were of technical grade and used without further purification. Flash column chromatography was performed on silica gel mesh (60-120) mesh. Visualisation was accomplished with UV light and/or potassium permanganate solution. $^{1}H$, $^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra were obtained on Bruker DPX300, Bruker AV3400 or Bruker DPX400 spectrometers at ambient temperature. The chemical shifts are reported as dimensionless δ values and are frequency referenced relative to the solvent peaks (chloroform =7.27 ppm) for $^{1}H$ and (chloroform =77.1 ppm) for $^{13}C\{^{1}H\}$. Coupling constants, *J*, are reported to the nearest 0.1 Hz and as positive values regardless of their real individual signs. The multiplicity of the signals is indicated as “s”, “d”, “t” “q” “quint” or “m” for singlet, doublet, triplet, quartet, quintet or multiplet, respectively or a combination there of. IR spectra were recorded on a Perkin Elmer 1600 series FTIR-spectrophotometer. Mass spectra were recorded on a Bruker MicroTOF spectrometer ionised by electrospray ionisation (ESI), unless otherwise stated all calculated masses are based on $Cl^{35}$ and $Br^{79}$. Melting points were measured on a Koflerr Hot-Stage or Bibby$^{TM}$ Stuart Scientific SMP3 melting point apparatus. The melting points are reported as a range to the nearest ºC and are uncorrected. Gas chromatographic data was obtained on a Hewlett Packard HP4890A gas chromatograph equipped

with a Hewlett Packard HP3395 integrator system, employing a HP-5 (crosslinked 5% PH ME siloxane) column of dimensions 15 m × 0.53 mm × 1.5 μm.

### 6b) General procedures

*General Procedure 1a:* A flame dried 5 mL microwave vial was charged with $PtCl_2$ (10 mol%) under nitrogen and the reaction vessel was evacuated under vacuum for *ca.* 10 minutes prior to the addition of dichloromethane (1 M solution). The vial was flushed with nitrogen and to the resulting suspension was added trichloroacetonitrile (**80**, 2.2 equiv.) and allylic alcohol (1 equiv.). The reaction vessel was sealed and the mixture was allowed to stir at ambient temperature for 20 hours. The reaction mixture was filtered through Celite® (dichloromethane) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, with 1% triethylamine) to afford allylic amides.

*General procedure 1b:* A flame dried 5 mL microwave vial was charged with $PtCl_2$ (10 mol%) under nitrogen and the reaction vessel was evacuated under vacuum for *ca.* 10 minutes prior to the addition of dichloromethane (1 M solution). The vial was flushed with nitrogen and to the resulting suspension was added trichloroacetonitrile (**80**, 2.2 equiv.) and allylic alcohol (1 equiv.). The reaction vessel was sealed and the mixture allowed to stir at 60 ºC for 20 hours. The reaction mixture was filtered through Celite® (dichloromethane) and the solvent was removed *in vacuo*. The residue was purified by flash column

chromatography on silica gel (ethyl acetate/petroleum ether, with 1% triethylamine) to afford allylic amide.

*General Procedure 2:* A mixture of the corresponding substituted benzaldehyde (1.1 equiv.) and triethyl phosphonoacetate (1 equiv.) was stirred at 0 °C and DBU (1.5 equiv.) was added drop-wise. The resulting solution was stirred at ambient temperature for 1-2 hours. The reaction mixture was diluted with ethyl acetate, washed with water, brine and the organic phase was removed *in vacuo*. The residue was dissolved in dichloromethane (0.3 M) and cooled to below -55 °C. DIBAL-H (2.3 equiv., 1 M in *n*-hexane) was added drop-wise. The solution was allowed to warm to -40 °C and stirred for 1 hour. Aqueous potassium sodium tartrate and diethyl ether was added. The mixture was washed with water, brine, dried over magnesium sulfate and removed *in vacuo*. The residue was purified either by column chromatography with ethyl acetate/petroleum ether or re-crystallised from *n*-hexane to afford substituted aromatic allylic alcohols.

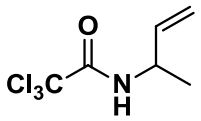
*General procedure 3a*: To a stirred suspension of $PtCl_4$ (10 mol%) and 2-aminophenols (1 equiv.) in *n*-hexane (1 M) at ambient temperature was added trichloroacetonitrile (**80**, 2.2 equiv.). The resultant mixture was stirred at 80 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford benzoxazoles.

*General procedure 3b*: To a solution of 2-aminophenols (1 equiv.) in methanol (1 M) at ambient temperature was added trichloroacetonitrile (**80**, 1.1 equiv.). The resultant mixture was stirred at 40 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford trichlorobenzoxazoles.

*General procedure 4*: To a solution of 2-aminophenol (1. equiv.) in methanol (1 M) at ambient temperature was added dichloroacetonitrile (**271**, 1 equiv.). The resultant mixture was stirred at 40 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford the dichlorobenzoxazoles.

*General procedure 5*: To a stirred solution of trichlorobenzoxazole (1 equiv.) in acetonitrile (1 M) at ambient temperature was added amine (1.1 equiv.). The resultant solution was stirred at 60 °C for 4 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford substituted benzoxazole.

***N*-(But-3-en-2-yl)-2,2,2-trichloroacetamide[84] (83)**

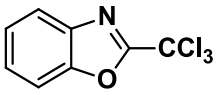


*General Procedure 1a:* $PtCl_2$ (11 mg, 0.041 mmol), dichloromethane (0.4 mL), (*E*)-2-buten-1-ol (**71**, 35 µL, 0.41 mmol) and trichloroacetonitrile (**80**, 90 µL, 0.90 mmol) were stirred at ambient temperature for 20 hours. Purification by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(but-3-en-2-yl)-2,2,2-trichloroacetamide (**83**, 71 mg, 80%) as a clear oil that had spectra identical to the literature.[84]

*General Procedure 1b:* $PtCl_2$ (12 mg, 0.04 mmol), dichloromethane (0.4 mL), (*E*)-2-buten-1-ol (**71**, 37 µL, 0.43 mmol) and trichloroacetonitrile (**80**, 94 µL, 0.94 mmol) were stirred at 60 ºC for 20 hours. Purification by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(but-3-en-2-yl)-2,2,2-trichloroacetamide (**83**, 90 mg, 96%) as a clear oil that had spectra identical to the literature.[84]

IR ($CHCl_3$) $\nu(cm^{-1})$ 3428, 3028, 1714, 1510; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 6.55 (1H, br.s), 5.88 (1H, ddd, *J* = 17.2, 10.5, 5.1 Hz), 5.26 (1H, ddd, *J* = 17.2, 1.6, 0.8 Hz), 5.20 (1H, ddd, *J* = 10.5, 1.6, 0.8 Hz), 4.61 - 4.48 (1H, m), 1.36 (3H, d, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 161.0, 137.6, 115.6, 92.7, 49.1, 19.7; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_6H_8Cl_3NONa^+$, 237.9564, found: 237.9558.

**2-(Trichloromethyl)benzo[*d*]oxazole[69] (153)**

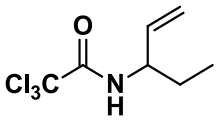



*General procedure 3a*: The reaction of $PtCl_4$ (18 mg, 0.05 mmol), 2-aminophenol (**134**, 58 mg, 0.5 mmol) and trichloroacetonitrile (**80**, 117 μL, 1.2 mmol) in *n*-hexane (0.5 mL) afforded after work up and purification 2-(trichloromethyl)benzo[*d*]oxazole (**153**, 103 mg, 82% yield) as a white solid that had spectra identical to the literature.[69]

*General procedure 3b*: The reaction of 2-aminophenol (**134**, 233 mg, 2.1 mmol) and trichloroacetonitrile (**80**, 236 μL, 2.4 mmol) in methanol (2.1 mL) afforded after work up and purification 2-(trichloromethyl)benzo[*d*]oxazole (**153**, 499 mg, 99% yield) as a white solid that had spectra identical to the literature.[69]

m.p. 60 – 62 ºC (lit 61 ºC); IR ($CHCl_3$) $\nu$($cm^{-1}$) 3011, 1617, 1556; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.89 - 7.86 (1H, m), 7.67 - 7.64 (1H, m), 7.55 - 7.44 (2H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 160.1, 151.5, 139.9, 127.5, 125.7, 121.8, 111.5, 86.0; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_8H_5Cl_3NO^+$, 235.9432 found: 235.9430.

***N*-(Pent-3-en-2-yl)-2,2,2-trichloroacetamide[95] (197)**

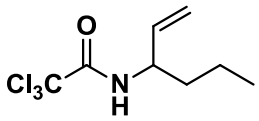


*General Procedure 1a:* $PtCl_2$ (10 mg, 0.040 mmol), dichloromethane (0.4 mL), (*Z*)-2-penten-1-ol (38 µL, 0.37 mmol) and trichloroacetonitrile (**80**, 84 µL, 0.84 mmol) were stirred at ambient temperature for 20 hours. Purification by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(pent-3-en-2-yl)-2,2,2-trichloroacetamide (**197**, 73 mg, 85%) as a clear oil that had spectra identical to the literature.[95]

*General Procedure 1b:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*Z*)-2-penten-1-ol (38 µL, 0.37 mmol) and trichloroacetonitrile (**80**, 84 µL, 0.84 mmol) were stirred at 60 ºC for 20 hours. Purification by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(pent-3-en-2-yl)-2,2,2-trichloroacetamide (**197**, 77 mg, 89%) as a clear oil that had spectra identical to the literature.[95]

IR ($CHCl_3$) ν($cm^{-1}$) 3427, 3028, 1714, 1510; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 6.52 (1H, br.s), 5.81 (1H, ddd, *J* = 15.4, 8.6, 5.6 Hz), 5.26 (1H, dt, *J* = 15.4, 1.1 Hz), 5.21 (1H, dt, *J* = 8.6, 1.1 Hz), 4.42 - 4.32 (1H, m), 1.81 - 1.57 (2H, m), 0.98 (3H, t, *J* = 7.4 Hz); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 161.3, 136.4, 116.2, 92.9, 54.8, 27.5 10.0; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_7H_{10}Cl_3NONa^+$, 251.9721, found: 251.9718.

***N*-(Hex-3-en-2-yl)-2,2,2-trichloroacetamide[95] (198)**



*General Procedure 1a:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*E*)-2-hexen-1-ol (45 µL, 0.38 mmol) and trichloroacetonitrile (**80**, 84 µL, 0.84 mmol) were stirred at ambient temperature for 20 hours. Purification by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(hex-3-en-2-yl)-2,2,2-trichloroacetamide (**198**, 69 mg, 74%) as a clear oil that had spectra identical to the literature.[95]

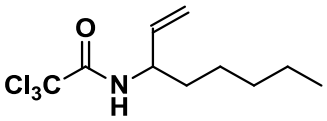
*General Procedure 1a:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*Z*)-2-hexen-1-ol (45 µL, 0.38 mmol) and trichloroacetonitrile (**80**, 84 µL, 0.84 mmol) were stirred at ambient temperature for 20 hours. Purification by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(hex-3-en-2-yl)-2,2,2-trichloroacetamide (**198**, 63 mg, 68%) as a clear oil that had spectra identical to the literature.[95]

*General Procedure 1b:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*E*)-2-hexen-1-ol (45 µL, 0.38 mmol) and trichloroacetonitrile (**80**, 84 µL, 0.84 mmol) were stirred at 60 ºC for 20 hours. Purification by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(hex-3-en-2-yl)-2,2,2-trichloroacetamide (**198**, 78 mg, 84%) as a clear oil that had spectra identical to the literature.[95]

*General Procedure 1b:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*Z*)-2-hexen-1-ol (45 µL, 0.38 mmol) and trichloroacetonitrile (**80**, 84 µL, 0.84 mmol) were stirred at 60 ºC for 20 hours. Purification by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(hex-3-en-2-yl)-2,2,2-trichloroacetamide (**198**, 75 mg, 80%) as a clear oil that had spectra identical to the literature.[95]

IR ($CHCl_3$) $\nu(cm^{-1})$ 3425, 2963, 2254, 1795, 1510; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 6.54 (1H, br.s), 5.80 (1H, ddd, *J* = 17.2, 10.5, 5.7 Hz), 5.25 (1H, dt, *J* = 17.2, 1.0 Hz), 5.20 (1H, dt, *J* = 10.5, 1.0 Hz), 4.49 - 4.39 (1H, m), 1.73 - 1.53 (2H, m), 1.48 - 1.33 (2H, m), 0.97 (3H, t, *J* = 7.3 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 161.1, 136.7, 115.9, 92.8, 53.3, 36.5, 18.8, 13.7; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_8H_{13}Cl_3NO^+$, 244.0058, found: 244.0065.

***N*-(Oct-3-en-2-yl)-2,2,2-trichloroacetamide (199)**

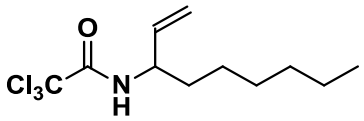


*General Procedure 1a:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*E*)-2-octen-1-ol (60 µL, 0.40 mmol) and trichloroacetonitrile (**80**, 88 µL, 0.88 mmol) were stirred at ambient temperature for 20 hours. Purification by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(oct-3-en-2-yl)-2,2,2-trichloroacetamide (**199**, 55 mg, 51%) as a clear oil.

*General Procedure 1b:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*E*)-2-octen-1-ol (60 µL, 0.40 mmol) and trichloroacetonitrile (**80**, 88 µL, 0.88 mmol) were stirred at 60 ºC for 20 hours. Purification by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(oct-3-en-2-yl)-2,2,2-trichloroacetamide (**199**, 76 mg, 71%) as a clear oil.

IR ($CHCl_3$) $\nu$($cm^{-1}$) 3425, 2933, 2861, 1715, 1510; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 6.52 (1H br.s), 5.82 (1H, ddd, $J$ = 17.2, 10.5, 5.7 Hz), 5.29 - 5.19 (2H, m), 4.48 - 4.36 (1H, m), 1.75 - 1.52 (2H, m), 1.45 - 1.24 (6H, m), 0.89 (3H, t, $J$ = 6.5 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 161.2, 136.7, 116.0, 92.9, 53.5, 34.4, 31.4, 25.2, 22.5, 13.9; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{10}H_{16}Cl_3NONa^+$, 294.0190, found: 294.0187.

***N*-(Non-3-en-2-yl)-2,2,2-trichloroacetamide (200)**

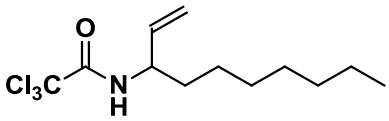


*General Procedure 1a:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*Z*)-2-nonen-1-ol (64 µL, 0.38 mmol) and trichloroacetonitrile (**80**, 84 µL, 0.84 mmol) were stirred at ambient temperature for 20 hours. Purification by column chromatography (1% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(non-3-en-2-yl)-2,2,2-trichloroacetamide (**200**, 37 mg, 34%) as a clear oil.

*General Procedure 1b:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*Z*)-2-nonen-1-ol (64 µL, 0.38 mmol) and trichloroacetonitrile (**80**, 84 µL, 0.84 mmol) were stirred at 60 ºC for 20 hours. Purification by column chromatography (1% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(non-3-en-2-yl)-2,2,2-trichloroacetamide (**200**, 52 mg, 48%) as a clear oil.

IR ($CHCl_3$) $\nu(cm^{-1})$ 3425, 2931, 1715, 1510; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 6.58 (1H br.s), 5.65 (1H, ddd, $J$ = 17.2, 10.4, 5.7 Hz), 5.33 - 5.26 (2H, m), 4.38 - 4.48 (1H, m), 1.75 - 1.51 (2H, m), 1.46 - 1.22 (8H, m), 0.98 - 0.83 (3H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 161.2, 136.7, 116.0, 92.9, 53.6, 34.4, 31.4, 28.9, 25.5, 22.5, 14.0; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{11}H_{18}Cl_3NONa^+$, 308.0347, found: 308.0334.

***N*-(Dec-3-en-2-yl)-2,2,2-trichloroacetamide (201)**

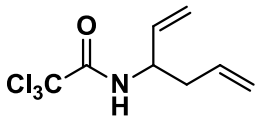


*General Procedure 1a:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*E*)-2-decen-1-ol (73 µL, 0.39 mmol) and trichloroacetonitrile (**80**, 84 µL, 0.84 mmol) were stirred at ambient temperature for 20 hours. Purification by column chromatography (5% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(dec-3-en-2-yl)-2,2,2-trichloroacetamide (**201**, 43 mg, 36%) as a clear oil.

*General Procedure 1b:* $PtCl_2$ (10 mg, 0.04 mmol), dichloromethane (0.4 mL), (*E*)-2-decen-1-ol (73 µL, 0.39 mmol) and trichloroacetonitrile (**80**, 84 µL, 0.84 mmol) were stirred at 60 ºC for 20 hours. Purification by column chromatography (5% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(dec-3-en-2-yl)-2,2,2-trichloroacetamide (**201**, 59 mg, 50%) as a clear oil.

IR ($CHCl_3$) $\nu(cm^{-1})$ 3424, 2929, 1711, 1503; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 6.53 (1H br.d, *J* = *7*.5 Hz), 5.82 (1H, ddd, *J* = 17.2, 10.4, 5.7 Hz), 5.33 - 5.17 (2H, m), 4.48 - 4.38 (1H, m), 1.75 - 1.51 (2H, m), 1.46 - 1.22 (10H, m), 0.88 (3H, t, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 161.2, 136.7, 116.0, 92.9, 53.6, 34.4, 31.4, 29.2, 29.1, 25.6, 22.6, 14.1; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{12}H_{20}Cl_3NONa^+$, 322.0503, found: 322.0506.

***N*-(Hexa-1,5-dien-3-yl)-2,2,2-trichloroacetamide[114] (206)**

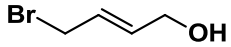


*General Procedure 1b:* $PtCl_2$ (12 mg, 0.04 mmol), dichloromethane (0.4 mL), (*E*)-2,5-hexadien-1-ol (**205**, 44 mg, 0.45 mmol) and trichloroacetonitrile (**80**, 88 µL, 0.88 mmol) were stirred at 60 ºC for 20 hours. Purification by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(hexa-1,5-dien-3-yl)-2,2,2-trichloroacetamide (**206**, 30 mg, 28%) as a clear oil that had spectra identical to the literature.[114]

IR ($CHCl_3$) ν($cm^{-1}$) 3423, 2985, 1715, 1508; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 6.65 (1H, br.s), 5.98 - 5.69 (2H, m), 5.38 - 5.04 (4H, m), 4.61 - 4.46 (1H, m), 2.58 - 2.29 (2H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 161.1, 135.9, 132.6, 119.5, 116.2, 92.8, 52.2, 38.5; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_8H_{10}Cl_3NONa^+$, 263.9721, found: 263.9716.

### 6c) Synthesis of bromo allylic alcohol

**(*E*)-4-Bromobut-2-en-1-ol (216)**

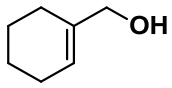



A suspension of lithium aluminium hydride (710 mg, 18.71 mmol, 1.1 equiv.) and aluminium chloride (997 mg, 7.48 mmol, 40 mol%) in diethyl ether (11.6 mL 1.5 M) was stirred for 40 minutes at -78 ºC. A solution of methyl-4-bromocrotonate (**215**, 2 mL, 17 mmol) in diethyl ether (23.8 mL, 0.7 M) was added and the resultant solution was stirred at -78 ºC for 3 hours. Water (2.8 mL) and 15% w/w sodium hydroxide solution (0.7 mL) was added. The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (12% ethyl acetate in petroleum ether) to afford (*E*)-4-bromobut-2-en-1-ol (**216**, 840 mg, 33%) as a clear oil.

$^{1}$H NMR (300 MHz $CDCl_3$, 298 K) $\delta_H$ 5.89 – 5.83 (2H, m), 4.10 (2H, d, $J$ = 3.6 Hz), 3.93 (2H, d, $J$ = 5.7 Hz), 3.48 (1H, br.s); $^{13}C\{^{1}H\}$ NMR (75 MHz $CDCl_3$, 298 K) $\delta_C$ 134.0, 126.8, 61.8, 32.1; HRMS (ESI) m/z: calculated for $[M+Na]^+$, $C_4H_7BrONa^+$, 172.9573, found: 172.9572.

### 6d) Synthesis of primary cyclic allylic alcohol

**Cyclohex-1-en-1-ylmethanol[115] (219)**

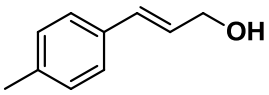



A solution of 1-cyclohexen-1-carboxylic acid (**218**, 200 mg, 1.59 mmol) and triethylamine (335 µL, 2.4 mmol, 1.5 equiv.) in tetrahydrofuran (0.5 mL, 3.5 M) was cooled to -5 ºC before ethyl chloroformate (151 µL, 1.58 mmol, 1 equiv.) in tetrahydrofuran (2.7 mL, 0.6 M) was added over 15 minutes. The reaction mixture was stirred at -5 ºC for 30 minutes then warmed to ambient temperature and stirred for 16 hours. The reaction mixture was filtered through cotton wool and the residue was washed with tetrahydrofuran (15 mL). The combined organic layer was added drop-wise to sodium borohydride (150 mg, 4.0 mmol, 2.5 equiv.) at 5 ºC over 30 minutes. The reaction mixture was allowed to warm to ambient temperature and continued to stir for 24 hours. 1 M hydrochloric acid was added until the solution was at pH 4-5. Diethyl ether (30 mL) and 10% w/w sodium hydroxide (20 mL) was added. The organic layer was dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether) to afford cyclohex-1-en-1-ylmethanol (**219**, 64 mg, 36%) as a clear yellow oil that had spectra identical to that reported in the literature.[115]

$^{1}$H NMR (300 MHz $CDCl_3$, 298 K) $\delta_H$ 5.65 (1H, s), 3.94 (2H, s), 2.03 – 1.98 (4H, m), 1.72 (1H, br.s), 1.66 – 1.53 (4H, m); $^{13}C\{^{1}H\}$ NMR (75 MHz $CDCl_3$, 298 K) $\delta_C$ 137.5, 122.8, 67.4, 25.5, 24.8, 22.5, 22.4; HRMS (ESI) m/z: calculated for $[M+Na]^+$, $C_7H_{12}ONa^+$, 135.0781, found: 135.0780.

### 6e) Synthesis of aromatic allylic alcohols

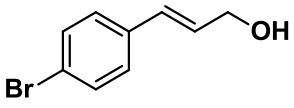
**(*E*)-3-(*p*-Tolyl)prop-2-en-1-ol[116] (228)**




*General procedure 2*: 4-methylbenzaldehyde (1.0 mL, 8.48 mmol), triethyl phosphonoacetate (1.54 mL, 7.71 mmol), DBU (1.73 mL, 11.57 mmol) was stirred at ambient temperature for 1 h and dichloromethane (15 mL) was added and cooled to -55 ºC before DIBAL-H (7.71 mL, 7.71 mmol) was added. The resultant mixture was stirred at -40 ºC of 1 hour. After work up the residue was purified by flash column chromatography on silica gel (33% ethyl acetate in petroleum ether) to afford (*E*)-3-(4-bromophenyl)prop-2-en-1-ol (**228**, 716 mg, 57%) as a yellow oil that had spectra identical to that reported in the literature.[116]

$^{1}$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.30 (2H, d, *J* = 8.0 Hz), 7.14 (2H, d, *J* = 8.0 Hz), 6.60 (1H, d, *J* = 15.8 Hz), 6.33 (1H, dt, *J* = 15.8, 5.3 Hz), 4.33 (2H, d, *J* = 5.3 Hz), 2.35 (3H, s), 1.46 (1H, br.s); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 137.6, 133.9, 131.2, 129.3 (2C), 127.4, 126.4 (2C), 63.9, 21.2; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{10}H_{12}ONa^+$, 171.0781, found: 171.0785.

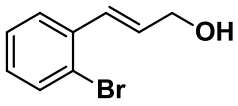
**(*E*)-3-(4-Bromophenyl)prop-2-en-1-ol[116] (229)**




*General procedure 2*: 4-bromobenzaldehyde (1.0 g, 5.5 mmol), triethyl phosphonoacetate (990 µL, 5.0 mmol), DBU (1.1 mL, 7.4 mmol) was stirred at ambient temperature for 1 h and dichloromethane (15 mL) was added and cooled to -55 ºC before DIBAL-H (5.0 mL, 5.0 mmol) was added. The resultant mixture was stirred at -40 ºC of 1 hour. After work up the residue was purified by recrystallization from boiling *n*-hexane to afford (*E*)-3-(4-bromophenyl)prop-2-en-1-ol (**229**, 412 mg, 35%) as white crystals, which had spectra identical to that reported in the literature.[116]

m.p. 62 - 64 ºC, lit: 60 - 63 ºC; IR ($CHCl_3$) ν($cm^{-1}$) 3611, 3462, 3007, 2933, 2873, 1710; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.39 (2H, d, *J* = 8.5 Hz), 7.16 (2H, d, *J* = 8.5 Hz), 6.49 (1H, d, *J* = 15.9 Hz), 6.29 (1H, dt, *J* = 15.9, 5.5 Hz), 4.26 (2H, dd, *J* = 5.5, 1.4 Hz), 3.05 (1H, br.s); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 135.5, 131.5 (2C), 131.5, 129.3 (2C), 127.8, 121.1, 63.0; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_9H_9BrONa^+$, 234.9729, found: 234.9719.

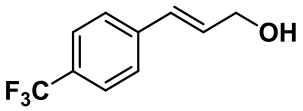
**(*E*)-3-(2-Bromophenyl)prop-2-en-1-ol[117] (230)**




*General procedure 2*: 2-bromobenzaldehyde (1.0 mL, 8.6 mmol), triethyl phosphonoacetate (1.6 mL, 7.9 mmol), DBU (1.8 mL, 11.8 mmol) was stirred at ambient temperature for 1 h and dichloromethane (30 mL) was added and cooled to -55 ºC before DIBAL-H (20.4 mL, 20.4 mmol) was added. The resultant mixture was stirred at -40 ºC of 1 hour. After work up the residue was purified by flash column chromatography on silica gel (50% ethyl acetate in petroleum ether) to afford (*E*)-3-(2-bromophenyl)prop-2-en-1-ol (**230**, 654 mg, 36%) as a clear oil which had spectra identical to that reported in the literature.[117]

IR ($CHCl_3$) $\nu$($cm^{-1}$) 3608, 3449, 3062, 3007, 2931, 2874, 1724, 1683; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.54 (2H, td, *J* = 8.1, 1.6 Hz), 7.28 (1H, td, *J* = 7.7, 0.7 Hz), 7.11 (1H, td, *J* = 7.7, 1.6 Hz), 6.97 (1H, d, *J* = 15.9 Hz), 6.32 (1H, dt, *J* = 15.9, 5.3 Hz), 4.37 (2H, d, *J* = 5.3 Hz), 1.68 (1H, s); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 136.7, 132.9, 131.6, 129.7, 128.9, 127.5, 127.1, 123.6, 63.5; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_9H_9BrONa^+$, 234.9729, found: 234.9719.

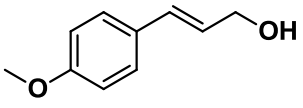
**(*E*)-3-(4-(Trifluoromethyl)phenyl)prop-2-en-1-ol[116] (231)**




*General procedure 2*: 4-triflоromethyl benzaldehyde (1.5 mL, 11.0 mmol), triethyl phosphonoacetate (2.2 mL, 10.0 mmol), DBU (2.2 mL, 15.0 mmol) was stirred at ambient temperature for 1 h and dichloromethane (38 mL) was added and cooled to -55 ºC before DIBAL-H (26.0 mL, 26.0 mmol) was added. The resultant mixture was stirred at -40 ºC of 1 hour. After work up the residue was purified by flash column chromatography on silica gel (33% ethyl acetate in petroleum ether) to afford (*E*)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (**230**, 549 mg, 25%) as dark orange crystals, which had spectra identical to that reported in the literature.[116]

m.p. 65 – 67 ºC, (lit: 63 – 65 ºC); IR ($CHCl_3$) $\nu(cm^{-1})$ 3614, 3461, 3008, 2930, 2873, 1616; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.58 (2H, d, $J$ = 8.3 Hz), 7.48 (2H, d, $J$ = 8.3 Hz), 6.68 (1H, d, $J$ = 16.1 Hz), 6.47 (1H, dt, $J$ = 16.1, 5.1 Hz), 4.38 (2H, d, $J$ = 5.1 Hz), 1.6 (1H, br.s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 140.1, 131.2, 129.3, 129.1 (2C), 126.5, 125.4 (2C), 124.1, 63.1; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{10}H_9F_3ONa^+$, 225.0498, found: 225.0502.

**(*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol[118] (232)**

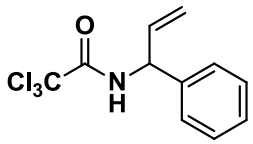



*General procedure 2*: 4-methoxybenzaldehyde (1.0 mL, 8.2 mmol), triethyl phosphonoacetate (1.5 mL, 7.48 mmol), DBU (1.6 mL, 11.2 mmol) was stirred at ambient temperature for 1 h and dichloromethane (25 mL) was added and cooled to -55 ºC before DIBAL-H (17.2 mL, 17.2 mmol) was added. The resultant mixture was stirred at -40 ºC of 1 hour. After work up the residue was purified by recrystallization from boiling *n*-hexane to afford (*E*)-3-(4-bromophenyl)prop-2-en-1-ol (**232**, 946 mg, 70%) as white crystals, which had spectra identical to that reported in the literature. [118]

$^{1}$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.33 (2H, d, *J* = 8.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 6.56 (1H, d, *J* = 15.9 Hz), 6.24 (1H, dt, *J* = 15.9, 5.9 Hz), 4.33 – 4.27 (2H, m), 3.82 (3H, t, *J* = 5.0 Hz) 1.73 (1H, br.s); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 131.0, 129.4, 128.6, 127.7 (2C), 126.3 (2C), 114.0, 63.9, 55.3; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{10}H_{12}O_2Na^+$, 187.0730, found: 187.0732.

## 6f) Synthesis of aromatic allylic amides

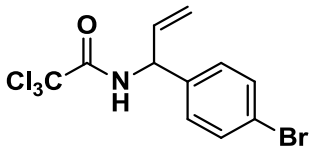
### 2,2,2-Trichloro-*N*-(1-phenylallyl)acetamide[10] (234)




*General Procedure 1b:* $PtCl_2$ (8 mg, 0.03 mmol), dichloromethane (0.3 mL), (*E*)-cinnamyl alcohol (**233**, 41 mg, 0.31 mmol) and trichloroacetonitrile (**80**, 66 µL, 0.66 mmol) were stirred at 60 ºC for 20 hours. Purification by flash column chromatography on silica gel (1% ethyl acetate in petroleum ether with 1% triethylamine) afforded 2,2,2-trichloro-*N*-(1-phenylallyl)acetamide (**234**, 45 mg, 53%) as a clear oil, which had spectra identical to that reported in the literature.[10]

IR ($CHCl_3$) ν($cm^{-1}$) 3426, 3033, 3015, 2928, 1716, 1506; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.43 - 7.34 (5H, m), 6.91 (1H, br.s), 6.07 (1H, ddd, *J* = 17.1, 10.5, 5.5 Hz), 5.59 (1H, dd, *J* = 7.7, 5.5 Hz), 5.41 - 5.30 (2H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 160.9, 138.8, 135.5, 129.1, 128.4 (2C), 127.7 (2C), 117.2, 92.6, 57.1; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{11}H_{10}Cl_3NONa^+$, 299.9721, found: 299.9719.

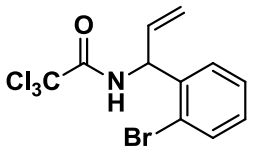
***N*-(1-(4-Bromophenyl)allyl)-2,2,2-trichloroacetamide[6] (235)**




*General Procedure 1b:* $PtCl_2$ (8 mg, 0.03 mmol), dichloromethane (0.3 mL), (*E*)-3-(4-bromophenyl)-2-propen-1-ol (**229**, 64 mg, 0.30 mmol) and trichloroacetonitrile (**80**, 66 µL, 0.66 mmol) were stirred at 60 ºC for 20 hours. Purification by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(1-(4-bromophenyl)allyl)-2,2,2-trichloroacetamide (**235**, 48 mg, 45%) as a clear oil, which had spectra identical to that reported in the literature.[6]

IR ($CHCl_3$) ν($cm^{-1}$) 3425, 2929, 1716, 1490; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.53 (2H, d, *J* = 8.4 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 6.90 (1H, d, *J* = 6.8 Hz), 6.05 (1H, ddd, *J* = 17.1, 10.4, 5.6 Hz), 5.55 (1H, dd, 6.8, 5.6 Hz), 5.40 (1H, dd, *J* = 10.4, 1.1 Hz), 5.33 (1H, dd, *J* = 17.1, 1.1 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 161.0, 137.8, 135.1, 132.2 (2C), 128.8 (2C), 122.4, 117.9, 92.5, 56.5; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{11}H_9Cl_3BrNONa^+$, 377.8826, found: 377.8826.

***N*-(1-(2-Bromophenyl)allyl)-2,2,2-trichloroacetamide[119] (236)**

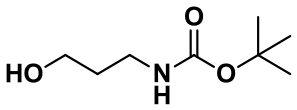



*General Procedure 1b:* $PtCl_2$ (14 mg, 0.05 mmol), dichloromethane (0.5 mL), (*E*)-3-(2-bromophenyl)-2-propen-1-ol (**230**, 115 mg, 0.5 mmol) and trichloroacetonitrile (**80**, 118 µL, 1.2 mmol) were stirred at 60 ºC for 20 hours. Purification by flash column chromatography on silica gel (1% ethyl acetate in petroleum ether with 1% triethylamine) afforded *N*-(1-(2-bromophenyl)allyl)-2,2,2-trichloroacetamide (**236**, 91 mg, 47%) as a clear oil, which had spectra identical to that reported in the literature.[119]

IR ($CHCl_3$) ν($cm^{-1}$) 3427, 2927, 1717, 1498; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.62 (1H, d, *J* = 7.9 Hz), 7.35 (2H, d, *J* = 4.1 Hz), 7.24 - 7.19 (1H, m), 7.12 (1H, br.d, *J* = 6.2 Hz), 6.07 (1H, ddd, *J* = 17.2, 10.4, 4.8 Hz), 5.91 - 5.83 (1H, m), 5.38 (1H, dd, *J* = 10.4, 1.4 Hz), 5.29 (1H, dd, *J* = 17.2, 1.4 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 160.8, 137.7, 134.5, 133.8, 129.9, 129.1, 128.0, 123.8, 117.6, 92.5, 57.0; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{11}H_9Cl_3BrNONa^+$, 377.8826, found: 377.8811.

## 6g) Synthesis of *N*-Boc protected allylic alcohol

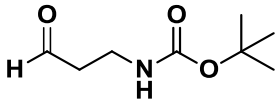
### *tert*-Butyl (3-hydroxypropyl)carbamate[120] (244)




To a stirred solution of 3-aminopropanol (**243**, 7.68 mL, 100 mmol) in acetonitrile (100 mL, 1 M) at ambient temperature were added di-*tert*-butyl dicarbonate (25.3 mL, 110 mmol, 1.1 equiv.) and dimethyl aminopyridine (1.2 g, 10 mol%) and the resultant mixture was stirred at ambient temperature for 2 hours. The solvent was removed *in vacuo* and ethyl acetate (100 mL) was added. To the resultant solution was added 1 M sulfuric acid (2 x 60 mL) and brine (1 x 60 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% ethyl acetate in petroleum ether) to afford *tert*-butyl (3-hydroxypropyl)carbamate (**244**, 10.7 g, 61%) as a yellow oil that had spectra identical to that reported in the literature.[120]

$^{1}$H NMR (300 MHz $CDCl_3$, 298 K) $\delta_H$ 5.01 (1H, br.s), 3.61 (2H, q, $J$ = 6.1 Hz), 3.43 (1H, br.s), 3.23 (2H, q, $J$ = 6.1 Hz), 1.63 (2H, quint, $J$ = 6.1 Hz), 1.40 (9H, s); $^{13}$C{$^{1}$H} NMR (75 MHz $CDCl_3$, 298 K) $\delta_C$ 157.0, 79.4, 59.2, 36.9, 32.6, 28.3 (3C); HRMS (ESI) m/z: calculated for $[M+Na]^+$, $C_8H_{17}NO_3Na^+$, 198.1101, found: 198.1098.

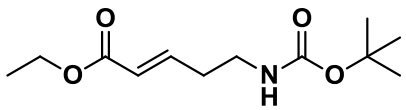
***tert*-Butyl (3-oxopropyl)carbamate[121] (245)**



Dichloromethane (57 mL, 0.2 M) was cooled to -78 ºC before oxalyl chloride (1 mL, 11.4 mmol, 2 equiv.) and dimethyl sulfoxide (1.3 mL, 18 mmol, 3.2 equiv.) were added and the resultant solution was stirred at -78 ºC for 10 minutes. A solution of *tert*-butyl (3-hydroxypropyl)carbamate (**244**, 1.0 g, 5.7 mmol) in dichloromethane (1 mL, 0.5 M) was added followed by triethylamine (2.5 mL, 3 equiv.). The reaction mixture was allowed to warm to ambient temperature over 16 hours. Ethyl acetate (10 mL) was added and the resultant solution was washed with brine (2 x 20 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in petroleum ether) to afford *tert*-butyl (3-oxopropyl)carbamate (**245**, 358 mg, 36%) as a clear oil that had spectra identical to that reported in the literature.[121]

$^{1}$H NMR (300 MHz $CDCl_3$, 298 K) $\delta_H$ 9.78 (1H, s), 4.94 (1H, br.s), 3.40 (2H, q, $J$ = 6.0 Hz), 2.68 (2H, t, $J$ = 6.0 Hz), 1.40 (9H, s); $^{13}C\{^{1}H\}$ NMR (75 MHz $CDCl_3$, 298 K) $\delta_C$ 201.4, 155.8, 79.4, 44.3, 34.0, 28.3 (3C); HRMS (ESI) m/z: calculated for $[M+Na]^+$, $C_8H_{15}NO_3Na^+$, 196.0945, found: 196.0950.

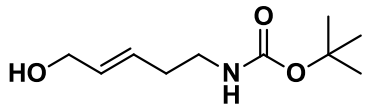
**(*E*)-Ethyl-5-((*tert*-butoxycarbonyl)amino)pent-2-enoate[122] (246)**



To a stirred solution of *tert*-butyl (3-oxopropyl)carbamate (**245**, 987 mg, 5.7 mmol) at 0 ºC were added triethyl phosphonoacetate (1.3 mL, 6.3 mmol, 1.1 equiv.) and DBU (2.1 mL, 14.3 mmol, 2.5 equiv.). The resultant solution was allowed to warm to ambient temperature over 16 hours. Water (50 mL) and ethyl acetate (2 x 50 mL) were added. The organic layer was washed with brine (30 mL), dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in petroleum ether) to afford (*E*)-ethyl-5-((*tert*-butoxycarbonyl)amino)pent-2-enoate (**246**, 1 g, 72%) as a clear oil that had spectra identical to that reported in the literature.[122]

$^{1}$H NMR (300 MHz $CDCl_3$, 298 K) $\delta_H$ 6.82 (1H, dt, *J* = 15.6, 7.1 Hz), 5.82 (1H, d, *J* = 15.6 Hz), 4.74 (1H, br.s) 4.13 (2H, q, *J* = 7.2 Hz) 3.21 (2H, q, *J* = 6.3 Hz) 2.36 (2H, q *J* = 6.3 Hz) 1.40 (9H, s) 1.23 (3H, t, *J* = 7.2 Hz); $^{13}$C{$^{1}$H} NMR (75 MHz $CDCl_3$, 298 K) $\delta_C$ 166.1, 155.7, 145.3, 123.2, 79.1, 60.2, 40.2, 32.6, 28.2, 14.09 (3C); HRMS (ESI) m/z: calculated for $[M+Na]^+$, $C_{12}H_{21}NO_4Na^+$, 266.1363, found: 266.1361.

***(E)-tert*-Butyl (5-hydroxypent-3-en-1-yl)carbamate[91] (247)**

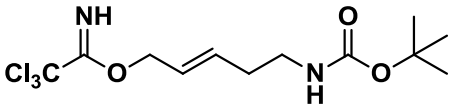



To a stirred solution of (*E*)-ethyl-5-((*tert*-butoxycarbonyl)amino)pent-2-enoate (**246** 680 mg, 2.8 mmol) in dichloromethane (9.3 mL, 0.3 M) at -40 ºC was added DIBAL-H (9.22 mL, 9.22 mmol, 3.3 equiv.) drop-wise and the resultant solution was allowed to warm to ambient temperature over 2 hours. A saturated solution of Rochelle's salt (10 mL) and diethyl ether (2 x 15 mL) were added. The organic layer was washed with brine (30 mL), dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% ethyl acetate in petroleum ether) to afford *(E)-tert*-butyl (5-hydroxypent-3-en-1-yl)carbamate (**247**, 359 mg, 64%) as a clear oil that had spectra identical to that reported in the literature.[91]

$^{1}$H NMR (300 MHz $CDCl_3$, 298 K) $\delta_H$ 5.75 – 5.58 (2H, m), 4.66 (1H, br.s) 4.09 (2H, t, *J* = 5.0 Hz), 3.17 (2H, q, *J* = 6.3 Hz) 2.22 (2H, q, *J* = 6.3 Hz) 2.02 (1H, s) 1.41 (9H, s); $^{13}$C{$^{1}$H} NMR (75 MHz $CDCl_3$, 298 K) $\delta_C$ 155.9, 131.6, 129.0, 79.2, 63.3, 39.9, 32.8, 28.4 (3C); HRMS (ESI) m/z: calculated for $[M+Na]^+$, $C_{10}H_{19}NO_3Na^+$, 224.1258, found: 224.1259.

### 6h) Synthesis of *N*-Boc protected allylic imidate

**(*E*)-5-((*tert*-butoxycarbonyl)amino)pent-2-en-1-yl 2,2,2-trichloroacetimidate (249)**

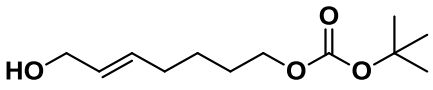



To a stirred solution of *(E)-tert*-butyl (5-hydroxypent-3-en-1-yl)carbamate (**247**, 148 mg, 0.74 mmol) in dichloromethane (4 mL, 0.2 M) at 0 ºC were added DBU (22 µL, 0.2 mmol, 30 mol%) and trichloroacetonitrile (**80**, 111 µL, 1.11 mmol, 1.5 equiv.). The resultant mixture was allowed to warm to ambient temperature and stirred for 1 hour. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether) to afford (*E*)-5-((*tert*-butoxycarbonyl)amino)pent-2-en-1-yl 2,2,2-trichloroacetimidate (**249**, 156 mg, 61%) as a clear oil.

$^1$H NMR (300 MHz $CDCl_3$, 298 K) $\delta_H$ 8.30 (1H, s), 5.87 – 5.70 (2H, m), 4.76 (2H, d, *J* = 4.9 Hz), 4.58 (1H, br.s), 3.20 (2H, q, *J* = 6.3 Hz), 2.28 (2H, q, *J* = 6.3 Hz), 1.43 (9H, s); HRMS (ESI) m/z: calculated for $[M+Na]^+$, $C_{12}H_{19}Cl_3N_2O_3Na^+$, 367.0354, found: 367.0347.

### 6i) Synthesis of *O*-Boc protected allylic alcohol

***(E)-tert*-Butyl (7-hydroxyhept-5-en-1-yl) carbonate (254)**




To a stirred solution of 5-hexen-1-ol (**250**, 10 mL, 83.27 mmol) in acetonitrile (83 mL, 1 M) at ambient temperature were added di-*tert*-butyl dicarbonate (38.3 mL, 166.5 mmol, 2 equiv.) and dimethyl aminopyridine (1 g, 10 mol%) and the resultant mixture was stirred at ambient temperature for 2 hours. The solvent was removed *in vacuo* and ethyl acetate (100 mL) was added. To the resultant solution was added 1 M sulfuric acid (2 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% ethyl acetate in petroleum ether) to afford *tert*-butyl hex-5-en-1-yl carbonate **(251),** which was used without further purification.

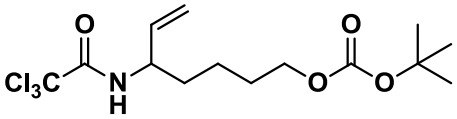
To a mixture of Grubbs 2$^{nd}$ generation (100 mg, 0.12 mmol, 1 mol%) in dichloromethane (30 mL, 0.4 M) at ambient temperature was cannulated a solution of *tert*-butyl hex-5-en-1-yl carbonate (**251**, 2.36 g, 11.8 mmol) and crotonaldehyde (4.82 mL, 58.9 mmol, 5 equiv.) in dichloromethane (30 mL, 0.4 M). The resultant mixture was stirred for 2 hours at ambient temperature, followed by cooling to -78 ºC. DIBAL-H (13 mL, 13 mmol, 1.1 equiv.) was added and the resultant mixture was allowed to warm to ambient temperature over 16 hours. A solution of saturated Rochelle's salt (25 mL) and dethyl ether

(40 mL) was added. The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (15% ethyl acetate in petroleum ether) to afford *(E)-tert*-butyl (7-hydroxyhept-5-en-1-yl) carbonate (**254**, 1.2 g, 46%) as a yellow oil.

IR ($CHCl_3$) $\nu$($cm^{-1}$) 3611, 3052, 2938, 2873, 1736; $^1H$ NMR (300 MHz $CDCl_3$, 298 K) $\delta_H$ 5.68 - 563 (2H, m), 4.07 – 4.02 (4H, m), 2.10 – 2.03 (2H, m), 1.74 – 1.61 (4H, m), 1.47 (9H, s); $^{13}C\{1H\}$ NMR (75 MHz $CDCl_3$, 298 K) $\delta_C$ 153.7, 132.4, 129.5, 81.9, 66.9, 63.6, 31.7, 28.1, 27.8, 25.2 (3C); HRMS (ESI) m/z: calculated for $[M+Na]^+$, $C_{12}H_{22}O_4Na^+$, 253.1411, found: 253.1395.

### 6j) Synthesis of *O*-Boc protected allylic amide

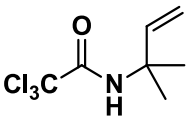
**_tert_-Butyl (5-(2,2,2-trichloroacetamido)hept-6-en-1-yl) carbonate (255)**



*General Procedure 1b:* $PtCl_2$ (5 mg, 0.02 mmol), dichloromethane (0.2 mL), (*E*)-*tert*-butyl (7-hydroxyhept-5-en-1-yl) carbonate (**254**, 39 mg, 0.2 mmol) and trichloroacetonitrile (**80**, 37 µL, 0.4 mmol) were stirred at 60 ºC for 20 hours. Purification by column chromatography (4% ethyl acetate in petroleum ether with 1% triethylamine) afforded *tert*-butyl (5-(2,2,2-trichloroacetamido)hept-6-en-1-yl) carbonate (**255**, 35 mg, 55%) as a clear oil.

IR ($CHCl_3$) $\nu$($cm^{-1}$) 3422, 3011, 2932, 2857, 1737, 1580, 1510; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 6.55 (1H, br.d, $J$ = 7.9 Hz), 5.80 (1H, ddd, $J$ = 17.1, 10.5, 5.7 Hz), 5.28 - 5.19 (2H, m), 4.47 - 4.37 (1H, m), 4.05 (2H, t, $J$ = 6.5), 1.77 - 1.60 (6H, m), 1.48 (9H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 161.2, 153.5, 136.3, 116.4, 92.7, 81.9, 66.5, 53.4, 34.0 28.3, 27.7, 21.9 (3C); HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{14}H_{22}Cl_3NO_4Na^+$, 396.0507, found: 396.0522.

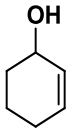
**_N_-(2-Methylbut-3-en-2-yl)-2,2,2-trichloroacetamide[123] (258)**



*General Procedure 1b:* $PtCl_2$ (12 mg, 0.04 mmol) dichloromethane (0.4 mL), (*E*)-3-methyl-2-buten-1-ol (**256**, 44 µL, 0.43 mmol) and trichloroacetonitrile (**80**, 95 µL, 0.95 mmol) were stirred at 60 ºC for 20 hours. Purification by flash column chromatography on silica gel (4% diethyl ether in petroleum ether with 1% triethylamine) afforded *N*-(2-methylbut-3-en-2-yl)-2,2,2-trichloroacetamide (**258**, 58 mg, 58%) as a clear oil that had spectra identical to that reported in the literature.[123]

IR ($CHCl_3$) ν($cm^{-1}$) 3428, 3028, 1714, 1510; $^1H$ NMR (300 MHz $CDCl_3$, 298 K) $\delta_H$ 6.61 (1H, br.s), 6.03 (1H, dd, *J* = 17.4, 10.7 Hz), 5.23 (1H, d, *J* = 17.4 Hz), 5.17 (1H, d, *J* = 10.7 Hz), 1.54 (6H, s); $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$, 298 K) $\delta_C$ 161.7, 137.6, 115.6, 98.5, 49.0, 19.7 (2C); HRMS (ESI) m/z: calculated for $[M+Na]^+$, $C_7H_{10}Cl_3NONa^+$, 251.9721, found: 251.9715.

**6k) Synthesis of secondary cyclic allylic alcohol cyclohex-2-enol[124] (264)**

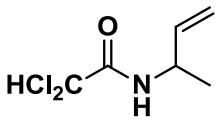



To a stirred solution of 2-cyclohexenone (**263**, 2.4 mL, 24.79 mmol) and cerium(III) chloride (9.3 g, 37.73 mmol, 1.5 equiv.) in methanol (20 mL, 1.2 M) at 0 ºC sodium borohydride (1 g, 26.43 mmol, 1.1 equiv.) was added portionwise and resultant mixture was stirred for 2 hours. 1 M hydrochloric acid (20 mL) was slowly added. Diethyl ether (3 x 25 mL) was added and the organic layer was dried over sodium sulfate and the solvent was removed *in vacuo* to afford cyclohex-2-enol (**264**, 1.43g, 59%) as a clear oil, which was used without further purification and had spectra identical to that reported in the literature.[124]

$^{1}$H NMR (300 MHz $CDCl_3$, 298 K) $\delta_H$ 5.82 – 5.73 (2H, m), 4.17 (1H, d, $J$ = 2.5 Hz), 2.08 – 1.50 (6H, m); $^{13}C\{^{1}H\}$ NMR (75 MHz $CDCl_3$, 298 K) $\delta_C$ 130.3, 129.9, 65.4, 31.8, 25.0, 18.9; HRMS (ESI) m/z: calculated for $[M+Na]^+$, $C_6H_{10}ONa^+$, 121.0624, found: 121.070.

## 6l) Syntheses of dichloro allylic imidate and amide

### *N*-(But-3-en-2-yl)-2,2-dichloroacetamide (269)



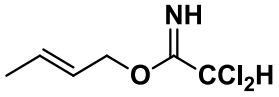

To a flame dried 5 mL microwave vial $PtCl_2$ (12 mg, 0.05 mmol, 10 mol%) was added under nitrogen and the reaction vessel was evacuated under vacuum for *ca.* 10 minutes prior to the addition of dichloromethane (0.4 mL, 1 M). The vial was flushed with nitrogen and to the resulting suspension were added dichloroacetonitrile (**271**, 78 µL, 0.78 mmol, 2.2 equiv.) and 2-buten-1-ol (**71**, 37 µL, 0.4 mmol, 1 equiv.). The reaction vessel was sealed and the mixture was allowed to stir at 80 ºC for 20 hours. The reaction mixture was filtered through Celite® (dichloromethane) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, with 1% triethylamine) to afford *N*-(but-3-en-2-yl)-2,2-dichloroacetamide (**269**, 20 mg, 25%) as a clear oil.

To A flame dried 5 mL microwave vial $PtCl_2$ (11 mg, 0.04 mmol, 10 mol%) was added under nitrogen and the reaction vessel was evacuated under vacuum for *ca.* 10 minutes prior to the addition of *d*-chloroform (0.4 mL, 1 M). (*E*)-But-3-en-2-yl-2,2-dichloroacetimidate (**270**, 80 mg, 0.4 mmol, 1 equiv.) was added and the resultant mixture was stirred at ambient temperature for 15 hours. The reaction mixture was filtered through Celite® (dichloromethane) and the solvent

was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (6% ethyl acetate in petroleum ether with 1% triethylamine) to afford *N*-(but-3-en-2-yl)-2,2-dichloroacetamide (**269**, 56 mg, 71%) as a clear oil.

IR ($CHCl_3$) $\nu(cm^{-1})$ 3419, 3089, 2986, 1696, 1538; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 6.64 (1H, br.s), 5.96 (1H, s), 5.83 (1H, ddd, $J$ =17.3, 10.5, 6.0 Hz), 5.23 – 5.12 (2H, m), 4.57 – 4.47 (1H, m), 1.30 (3H, d, $J$ = 6.0 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 163.4, 137.9, 115.0, 66.4, 47.8, 19.7; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_6H_9Cl_2NONa^+$, 203.9954, found: 203.9956.

**(*E*)-But-3-en-2-yl-2,2-dichloroacetimidate (270)**



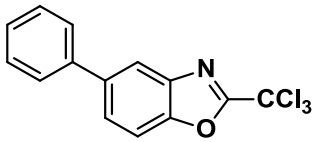

To a stirred solution of (*E*)-2-buten-1-ol (**71**, 425 µL, 5.0 mmol) in dry dichloromethane (5 mL, 1 M) at 0 ºC were added dichloroacetonitrile (**271**, 602 µL, 7.5 mmol, 1.5 equiv.) and DBU (37 µL, 0.5 mmol, 0.1 equiv.). The resultant mixture was stirred at ambient temperature for 16 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (5% ethyl acetate: petroleum ether) to afford (*E*)-but-3-en-2-yl-2,2-dichloroacetimidate (**270**, 290 mg, 32%) as an orange oil.

IR ($CHCl_3$) ν($cm^{-1}$) 3341, 3022, 1731, 1664; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 8.13 (1H, br.s), 5.94 (1H, s), 5.91 – 5.80 (1H, m), 5.72 – 5.62 (1H, m), 4.66 (2H, d, *J* = 6.2 Hz), 1.74 (3H, dd, *J* = 6.4, 1.3 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 165.2, 131.7, 124.6, 68.6, 65.7, 17.8; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_6H_9Cl_2NONa^+$, 203.9954, found: 203.9956.

# Experimental (benzoxazole synthesis)

## 6m) Synthesis of trichloro- benzoxazoles, benzoxazine, benzoxapine and oxazoline

**5-Phenyl-2-(trichloromethyl)benzo[*d*]oxazole (293)**

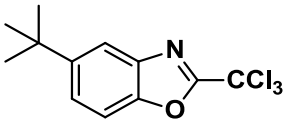



*General procedure 3a*: The reaction of $PtCl_4$ (20 mg, 0.06 mmol), 2-amino-4-phenylphenol (110 mg, 0.6 mmol) and trichloroacetonitrile (**80**, 130 μL, 1.3 mmol) in *n*-hexane (0.6 mL) afforded after work up and purification 5-phenyl-2-(trichloromethyl)benzo[*d*]oxazole (**293**, 36 mg, 20% yield) as a white solid.

*General procedure 3b*: The reaction of 2-amino-4-phenylphenol (104 mg, 0.6 mmol) and trichloroacetonitrile (**80**, 62 μL, 0.6 mmol) in methanol (0.6 mL) afforded after work up and purification 5-phenyl-2-(trichloromethyl)benzo[*d*]-oxazole (**293**, 159 mg, 91% yield) as a white solid.

m.p. 113 – 115 ºC; IR ($CHCl_3$) ν($cm^{-1}$) 3011, 1602, 1554; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 8.06 (1H, s), 7.76 - 7.38 (7H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 160.6, 151.0, 140.5, 140.3, 139.8, 129.0 (2C), 127.7, 127.5 (2C), 127.2, 120.0, 111.5, 86.0; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_{14}H_8Cl_3NONa^+$, 333.9564 found: 333.9570.

**5-(*tert*-Butyl)-2-(trichloromethyl)benzo[*d*]oxazole (294)**

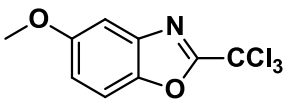



*General procedure 3a*: The reaction of $PtCl_4$ (27 mg, 0.08 mmol), 2-amino-4-*tert*-butylphenol (132 mg, 0.8 mmol) and trichloroacetonitrile (**80**, 176 μL, 1.8 mmol) in *n*-hexane (0.8 mL) afforded after work up and purification 5-(*tert*-butyl)-2-(trichloromethyl)benzo[*d*]oxazole (**294**, 60 mg, 26% yield) as a light brown solid.

*General procedure 3b*: The reaction of 2-amino-4-*tert*-butylphenol (123 mg, 0.8 mmol) and trichloroacetonitrile (**80**, 82 μL, 0.8 mmol) in methanol (0.8 mL) afforded after work up and purification 5-(*tert*-butyl)-2-(trichloromethyl) benzo[*d*]oxazole (**294**, 176 mg, 81% yield) as a light brown solid.

m.p. 39 – 41 ºC; IR ($CHCl_3$) $\nu$($cm^{-1}$) 3011, 2967, 2435, 1602, 1555; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.86 (1H, t, $J$ = 1.3 Hz), 7.56 - 7.52 (2H, m), 1.37 (9H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 160.1, 149.5, 149.4, 139.8, 125.4, 118.0, 110.6, 86.1, 35.1, 31.7 (3C); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{12}H_{13}Cl_3NO^+$, 292.0058 found: 292.0061.

**5-Methoxy-2-(trichloromethyl)benzo[*d*]oxazole (295)**

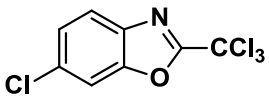



*General procedure 3a*: The reaction of $PtCl_4$ (23 mg, 0.07 mmol), 2-amino-4-methoxyphenol (95 mg, 0.7 mmol) and trichloroacetonitrile (**80**, 150 μL, 1.5 mmol) in *n*-hexane (0.7 mL) afforded after work up and purification 5-methoxy-2-(trichloromethyl)benzo[*d*]oxazole (**295**, 49 mg, 27% yield) as an orange solid.

*General procedure 3b*: The reaction of 2-amino-4-methoxyphenol (89 mg, 0.6 mmol) and trichloroacetonitrile (**80**, 71 μL, 0.7 mmol) in methanol (0.6 mL) afforded after work up and purification 5-methoxy-2-(trichloromethyl) benzo[*d*]oxazole (**295**, 169 mg, 99% yield) as an orange solid.

m.p. 52 – 54 ºC; IR ($CHCl_3$) ν($cm^{-1}$) 3011, 2962, 2838, 2435, 1733, 1614, 1581, 1551; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.51 (1H, d, $J$ = 9.0 Hz), 7.29 (1H, d, $J$ = 2.5 Hz), 7.09 (1H, dd, $J$ = 9.0, 2.5 Hz), 3.87 (3H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 160.6, 158.1, 146.1, 140.7, 116.8, 111.7, 103.7, 86.0, 56.0; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_9H_7Cl_3NO_2$, 265.9537 found: 265.9529.

**6-Chloro-2-(trichloromethyl)benzo[*d*]oxazole (296)**

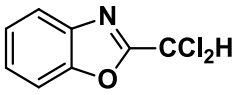



*General procedure 3a*: The reaction of $PtCl_4$ (21 mg, 0.06 mmol), 2-amino-5-chlorophenol (90 mg, 0.6 mmol) and trichloroacetonitrile (**80**, 137 μL, 1.4 mmol) in *n*-hexane (0.6 mL) afforded after work up and purification 6-chloro-2-(trichloromethyl)benzo[*d*]oxazole (**296**, 110 mg, 65% yield) as a brown/grey solid.

*General procedure 3b*: The reaction of 2-amino-5-chlorophenol (170 mg, 1.2 mmol) and trichloroacetonitrile (**80**, 130 μL, 1.3 mmol) in methanol (1.2 mL) afforded after work up and purification 6-chloro-2-(trichloromethyl) benzo[*d*]oxazole (**296**, 262 mg, 82% yield) as a brown/grey solid.

m.p. 78 – 80 ºC; IR ($CHCl_3$) ν($cm^{-1}$) 3011, 2435, 1606, 1556; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.74 (1H, d, *J* = 8.8 Hz), 7.62 (1H, d, *J* = 2.3 Hz), 7.40 (1H, dd, *J* = 8.8, 2.3 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 160.4, 151.5, 138.5, 133.2, 126.5, 122.2, 112.0, 85.6; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_8H_4Cl_4NO^+$, 271.9012 found: 271.9018.

**2-(Dichloromethyl)benzo[*d*]oxazole[112] (297)**

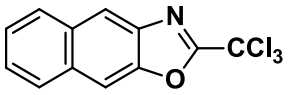



To a stirred suspension of $PtCl_4$ (22 mg, 0.07 mmol) and 2-aminophenol (**134**, 65 mg, 0.6 mmol) in *n*-hexane (0.6 mL, 1 M) at ambient temperature was added dichloroacetonitrile (**271**, 47 μL, 0.6 mmol). The resultant mixture was stirred at 80 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford (dichloromethyl)benzo[*d*]oxazole (**297**, 40 mg, 33% yield) as a white solid that had spectra identical to the literature.[112]

*General procedure 4*: The reaction of 2-aminophenol (**134**, 447 mg, 4.1 mmol), dichloroacetonitrile (**271**, 331 μL, 4.1 mmol) in methanol (4.1 mL) afforded after work up and purification 2-(dichloromethyl)benzo[*d*]oxazole (**297**, 690 mg, 83% yield) as a white solid that had spectra identical to the literature.[112]

m.p. 68 – 70 °C, (lit. m.p. 70 °C); IR ($CHCl_3$) ν($cm^{-1}$) 3011, 2436, 1613, 1568, 1522; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.81 - 7.75 (1H, m), 7.61 - 7.57 (1H, m), 7.46 - 7.35 (2H, m), 6.89 (1H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 159.5, 151.0, 140.0, 126.7, 125.2, 121.1, 111.2, 61.0; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_8H_6Cl_2NO^+$, 201.9821 found: 201.9839.

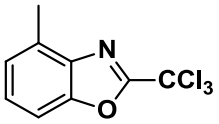
**2-(Trichloromethyl)naphtho[*2,3-d*]oxazole (299)**




*General procedure 3b*: The reaction of 3-amino-2-naphthol (108 mg, 0.7 mmol) and trichloroacetonitrile (**80**, 75 μL, 0.8 mmol) in methanol (0.7 mL) afforded after work up and purification 2-(trichloromethyl)naphtho[2,3-*d*]oxazole (**299**, 147 mg, 76% yield) as a cream coloured solid.

m.p. 148 – 150 °C; IR ($CHCl_3$) ν($cm^{-1}$) 3011, 2435, 1639, 1603, 1562, 1508; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 8.30 (1H, s), 8.06 - 7.92 (3H, m), 7.60 - 7.48 (2H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 161.7, 149.9, 139.2, 132.5, 131.54, 128.7, 127.9, 126.5, 125.3, 119.8, 107.4, 86.0; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{12}H_7Cl_3NO^+$, 285.9588 found: 285.9599

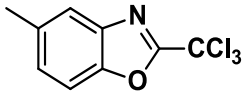
**4-Methyl-2-(trichloromethyl)benzo[*d*]oxazole[125] (300)**




*General procedure 3b*: The reaction of 2-amino-3-methylphenol (109 mg, 0.9 mmol) and trichloroacetonitrile (**80**, 97 μL, 1.0 mmol) in methanol (0.9 mL) afforded after work up and purification 4-methyl-2-(trichloromethyl) benzo[*d*]oxazole (**300**, 192 mg, 87% yield) as a white solid that had spectra identical to the literature.[125]

m.p. 63 – 64 °C (lit. m.p. 68 °C); IR ($CHCl_3$) $\nu$($cm^{-1}$) 3011, 2928, 1625, 1605, 1556, 1500; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.44 (1H, d, $J$ = 8.3 Hz), 7.37 (1H, dd, $J$ = 7.4, 8.3 Hz), 7.23 (1H, d, $J$ = 7.4 Hz), 2.68 (3H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 159.2, 151.3, 139.3, 132.5, 127.1, 126.0, 108.5, 86.2, 16.4; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_9H_7Cl_3NO^+$, 249.9588 found: 249.9589.

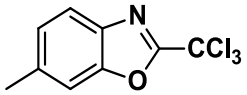
**5-Methyl-2-(trichloromethyl)benzo[*d*]oxazole[70] (301)**




*General procedure 3b*: The reaction of 2-amino-4-methylphenol (154 mg, 1.3 mmol) and trichloroacetonitrile (**80**, 138 μL, 1.4 mmol) in methanol (1.3 mL) afforded after work up and purification 5-methyl-2-(trichloromethyl) benzo[*d*]oxazole (**301**, 258 mg, 82% yield) as a white solid that had spectra identical to the literature.[70]

m.p. 55 – 56 °C (lit. m.p. 58 °C); IR ($CHCl_3$) $\nu$($cm^{-1}$) 3011, 2927, 2436, 1612, 1543; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.55 (1H, s), 7.41 (1H, d, $J$ = 8.5 Hz), 7.20 (1H, dd, $J$ = 8.5, 1.1 Hz), 2.43 (3H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 159.9, 149.6, 139.9, 135.6, 128.5, 121.2, 110.6, 86.0, 21.6; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_9H_7Cl_3NO^+$, 249.9588 found: 249.9589.

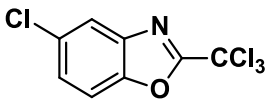
**6-Methyl-2-(trichloromethyl)benzo[*d*]oxazole[125] (302)**




*General procedure 3b*: The reaction of 2-amino-5-methylphenol (172 mg, 1.4 mmol) and trichloroacetonitrile (**80**, 154 μL, 1.5 mmol) in methanol (1.7 mL) afforded after work up and purification 6-methyl-2-(trichloromethyl) benzo[*d*]oxazole (**302**, 284 mg, 81% yield) as a white solid that had spectra identical to the literature.[125]

m.p. 64 – 66 °C (lit. m.p. 69 °C); IR ($CHCl_3$) $\nu$($cm^{-1}$) 3011, 2435, 1618, 1556; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.71 (1H, d, $J$ = 8.3 Hz), 7.44 – 7.42 (1H, m), 7.29 – 7.24 (1H, m), 2.53 (3H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 159.5, 151.8, 138.3, 137.7, 127.0, 121.0, 111.4, 86.1, 21.9; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_9H_7Cl_3NO^+$, 249.9588 found: 249.9589.

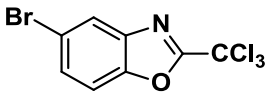
**5-Chloro-2-(trichloromethyl)benzo[*d*]oxazole[70] (303)**




*General procedure 3b*: The reaction of 2-amino-4-chlorophenol (163 mg, 1.1 mmol) and trichloroacetonitrile (**80**, 125 μL, 1.3 mmol) in methanol (1.1 mL) afforded after work up and purification 5-chloro-2-(trichloromethyl) benzo[*d*]oxazole (**303**, 250 mg, 81% yield) as a grey solid that had spectra identical to the literature.[70]

m.p. 82 – 84 °C (lit. m.p. 84 °C); IR ($CHCl_3$) $\nu(cm^{-1})$ 3011, 2436, 1739, 1605, 1555; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.77 (1H, d, $J$ = 2.0 Hz), 7.52 (1H, d, $J$ = 8.8 Hz), 7.40 (1H, dd, $J$ = 8.8, 2.0 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 161.0, 149.8, 140.7, 131.2, 127.8, 121.4, 112.1, 85.5; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_8H_4Cl_4NO^+$, 271.9012 found: 271.9023.

**5-Bromo-2-(trichloromethyl)benzo[*d*]oxazole (304)**

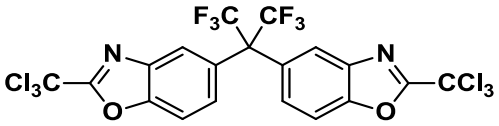



*General procedure 3a*: The reaction of $PtCl_4$ (20 mg, 0.06 mmol), 2-amino-4-bromophenol (111 mg, 0.6 mmol) and trichloroacetonitrile (**80**, 128 μL, 1.3 mmol) in *n*-hexane (0.6 mL) afforded after work up and purification 5-bromo-2-(trichloromethyl)benzo[*d*]oxazole (**304**, 96 mg, 52% yield) as a grey solid.

*General procedure 3b*: The reaction of 2-amino-4-bromophenol (157 mg, 0.8 mmol) and trichloroacetonitrile (**80**, 92 μL, 0.9 mmol) in methanol (0.8 mL) afforded after work up and purification 5-bromo-2-(trichloromethyl) benzo[*d*]oxazole (**304**, 229 mg, 87% yield) as a grey solid.

m.p. 72 – 74 °C; IR ($CHCl_3$) ν($cm^{-1}$) 3011, 1739, 1606, 1552; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 8.00 (1H, d, *J* = 1.8 Hz), 7.63 (1H, dd, *J* = 8.8, 1.8 Hz), 7.50 (1H, d, *J* = 8.8 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 161.1, 150.4, 141.3, 130.7, 124.7, 118.5, 112.8, 85.6; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_8H_4BrCl_3NO$, 313.8537 found: 313.8539.

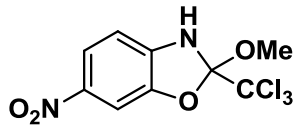
**5,5'-(Perfluoropropane-2,2-diyl)bis(2-(trichloromethyl)benzo[*d*]oxazole) (306)**




To a stirred solution of 2,2-*bis*(3-amino-4-hydroxyphenyl)hexafluoropropane (**305**, 79 mg, 0.2 mmol) in methanol (0.2 mL, 1 M) at ambient temperature was added trichloroacetonitrile (**80**, 48 μL, 0.5 mmol). The resultant mixture was stirred at 40 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford 5,5'-(perfluoropropane-2,2-diyl)*bis*(2-(trichloromethyl)benzo[*d*]oxazole) (**306**, 94 mg, 70% yield) as a brown solid.

m.p. 150 – 154 ºC; IR ($CHCl_3$) ν($cm^{-1}$) 3011, 2928, 1619, 1557; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 8.03 (2H, s), 7.66 (2H, d, *J* = 8.9 Hz), 7.50 (2H, d, *J* = 8.9 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 161.4 (2C), 151.5 (2C), 140.0 (2C), 131.3 (2C), 129.5 (2C), 124.2 (2C), 124.0 (2C, q, *J* = 287.0 Hz) , 111.5 (2C), 85.6 (2C), 64.8 (1C, q, *J* = 26.0 Hz); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) 63.7 (6F, s); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{19}H_7Cl_6F_6N_2O_2^+$, 620.8508 found: 620.8512.

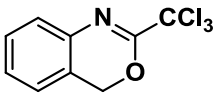
**2-Methoxy-6-nitro-2-(trichloromethyl)-2,3-dihydrobenzo[*d*]oxazole (314)**




To a solution of 2-amino-5-nitrophenol (**310**, 178 mg, 1.2 mmol) in methanol (1.2 mL, 1 M) at ambient temperature was added trichloroacetonitrile (**80**, 130 μL, 1.3 mmol). The resultant mixture was stirred at 40 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford 2-methoxy-6-nitro-2-(trichloromethyl)-2,3-dihydrobenzo[*d*]oxazole (**314**, 59 mg, 16% yield) as a yellow solid.

m.p. 124 – 126 ºC; IR ($CHCl_3$) ν($cm^{-1}$) 3443, 2950, 1733, 1615; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.97 (1H, dd, *J* = 8.5, 1.6 Hz), 7.79 (1H, d, *J* = 1.6 Hz), 6.79 (1H, d, *J* = 8.5 Hz) 5.75 (1H, br.s) 3.49 (3H, s); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 147.9, 140.8, 120.7, 119.0, 108.4, 105.7, 104.1, 99.7, 51.5; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_9H_7Cl_3N_2O_4Na^+$, 334.9364 found: 334.9362

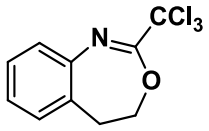
**2-(Trichloromethyl)-4H-benzo[*d*][1,3]oxazine (316)**




To a solution of (2-aminophenyl)methanol (**315**, 123 mg, 1.0 mmol) in methanol (1 mL, 1 M) at ambient temperature was added trichloroacetonitrile (**80**, 110 μL, 1.1 mmol). The resultant mixture was stirred at 40 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford 2-(trichloromethyl)-4H-benzo[*d*]oxazine (**316**, 119 mg, 48% yield) as a light pink solid.

m.p. 56 – 60 ºC; IR ($CHCl_3$) $\nu$($cm^{-1}$) 3079, 3002, 2928, 1763, 1644, 1606; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.36 – 7.27 (3H, m,), 7.04 (1H, d, $J$ = 7.1 Hz), 5.49 (2H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 155.2, 137.4, 129.4, 128.7, 126.0, 123.7, 121.4, 91.5, 68.7; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_9H_7Cl_3NO^+$, 249.9588 found: 249.9595.

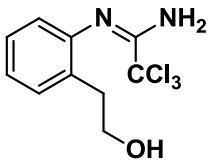
**2-(Trichloromethyl)-4,5-dihydrobenzo[*d*][1,3]oxazepine (318)**




To a solution of 2-(2-aminophenyl)ethanol (**317**, 131 μL, 1.0 mmol) in methanol (1 mL, 1 M) at ambient temperature was added trichloroacetonitrile (**80**, 110 μL, 1.1 mmol). The resultant mixture was stirred at 40 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford 2-(trichloromethyl)-4,5-dihydrobenzo[*d*][1,3]oxazepine (**318**, 7 mg, 3% yield) as a clear oil.

IR ($CHCl_3$) ν($cm^{-1}$) 2928, 2856, 1690, 1600; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.43 (1H, dd, *J* = 7.9, 1.1 Hz), 7.31 (1H, dd, *J* = 7.1, 1.8 Hz), 7.19 - 710 (2H, m), 4.68 – 4.63 (2H, m), 3.22 (2H, t, *J* = 4.4); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 149.1, 140.6, 135.3, 130.2, 128.8, 127.8, 126.8, 91.2, 73.3, 36.2; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{10}H_9Cl_3NO^+$, 263.9745 found: 263.9742.

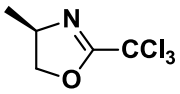
**(*E*)-2,2,2-Trichloro-N'-(2-(2-hydroxyethyl)phenyl) acetimidamide (319)**




To a solution of 2-(2-aminophenyl)ethanol (**317**, 131 μL, 1.0 mmol) in methanol (1 mL, 1 M) at ambient temperature was added trichloroacetonitrile (**80**, 110 μL, 1.1 mmol). The resultant mixture was stirred at 40 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford 2-(trichloromethyl)-4H-benzo[*d*]oxazine (**319**, 255 mg, 97% yield) as a yellow oil.

IR ($CHCl_3$) ν($cm^{-1}$) 3621, 3506, 3397, 3070, 3003, 2884, 1667, 1582; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.21 – 7.16 (2H, m), 7.06 – 7.01 (1H, m), 6.82 (1H, d, $J$ = 7.6) 5.27 (1H, s), 5.17 (2H, br.s), 3.69 (2H, t, $J$ = 6.2), 2.69 (2H, t, $J$ = 6.2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 152.7, 145.4, 131.4, 131.2, 127.6, 124.5, 119.9, 94.1, 63.0, 34.7; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{10}H_{12}Cl_3N_2O^+$, 281.0010 found: 281.0030.

**(*R*)-4-Methyl-2-(trichloromethyl)-4,5-dihydrooxazole (321)**

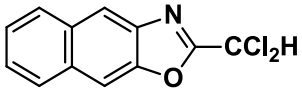



To a solution of (*R*)-2-aminopropan-1-ol (**320**, 78 μL, 1.0 mmol) in methanol (1 mL, 1 M) at ambient temperature was added trichloroacetonitrile (**80**, 110 μL, 1.1 mmol). The resultant mixture was stirred at 40 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford (*R*)-4-methyl-2-(trichloromethyl)-4,5-dihydrooxazole (**321**, 25 mg, 12% yield) as a yellow oil.

IR ($CHCl_3$) $\nu(cm^{-1})$ 3629, 3518, 3419. 2931, 1713, 1664, 1580, 1513; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 4.72 (1H, dd, , $J$ = 8.4, 8.1), 4.51 – 4.38 (1H, m), 4.17 (1H, t, $J$ = 8.1) 4.39 (3H, d, 6.7); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_C$ 162.2, 86.6, 62.5, 56.4, 20.5; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_5H_7Cl_3NO^+$, 201.9588 found: 201.9592.

## 6n) Synthesis of dichlorobenzoxazoles

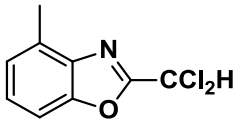
### 2-(Dichloromethyl)naphtho[2,3-*d*]oxazole (323)




*General procedure 4*: The reaction of 3-amino-2-napthol (143 mg, 0.9 mmol), dichloroacetonitrile (**271**, 81 μL, 1 mmol) in methanol (1 mL) afforded after work up and purification 2-(dichloromethyl)naphtho[2,3-*d*]oxazole. (**323**, 149 mg, 59% yield) as a colourless oil.

IR ($CHCl_3$) $\nu(cm^{-1})$ 3059, 3005, 1703, 1640, 1614, 1572, 1550, 1507; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 8.24 (1H, s,), 8.02 - 7.94 (3H, m), 7.58 – 7.48 (2H, m), 6.91 (1H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 161.6, 149.5, 139.7, 132.4, 131.6, 128.7, 128.0, 126.4, 125.2, 119.2, 107.3, 61.1; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{12}H_8Cl_2NO^+$, 251.9978, found: 251.9974.

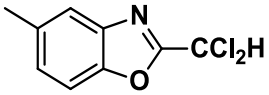
**4-Methyl-2-(dichloromethyl)benzo[*d*]oxazole (324)**




*General procedure 4*: The reaction of 3-Methyl-2-aminophenol (123 mg, 1 mmol), dichloroacetonitrile (**271**, 80 μL, 1 mmol) in methanol (1 mL) afforded after work up and purification 4-methyl-2-(dichloromethyl)benzo[*d*]oxazole (**324**, 128 mg, 60% yield) as a white solid.

m.p. 62 – 64 °C; IR ($CHCl_3$) ν($cm^{-1}$) 3004, 1608, 1569; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.45 (1H, d, *J* = 8.2 Hz), 7.33 (1H, dd, *J* = 8.2, 7.4 Hz), 7.21 (1H, dd, *J* = 7.4, 0.9 Hz), 6.88 (1H, s), 2.64 (3H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 158.8, 150.8, 139.4, 131.9, 126.6, 125.8, 108.5, 61.1, 16.4; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_9H_8Cl_2NO^+$, 215.9978, found: 215.9980.

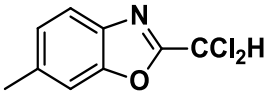
**5-Methyl-2-(dichloromethyl)benzo[*d*]oxazole[4] (325)**




*General procedure 4*: The reaction of 4-Methyl-2-aminophenol (123 mg, 1 mmol), dichloroacetonitrile (**271**, 80 μL, 1 mmol) in methanol (1 mL) afforded after work up and purification 5-methyl-2-(dichloromethyl)benzo[*d*]oxazole (**325**, 137 mg, 64% yield) as a white solid that had spectra identical to the literature.[4]

m.p. 42 – 44 °C, (lit. m.p. 45 °C); IR ($CHCl_3$) ν($cm^{-1}$) 3004, 2927, 1613, 1570; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.55 (1H, t, *J* = 1.0 Hz), 7.46 (1H, d, *J* = 8.5 Hz), 7.24 (1H, dd, *J* = 8.5, 1.0 Hz), 6.86 (1H, s), 2.47 (3H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 159.7, 149.3, 140.3, 135.4, 128.0, 120.9, 110.6, 61.1, 21.5; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_9H_8Cl_2NO^+$, 215.9978, found: 215.9984.

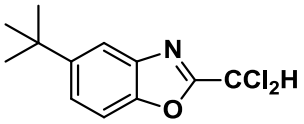
**6-Methyl-2-(dichloromethyl)benzo[*d*]oxazole (326)**




*General procedure 4*: The reaction of 5-Methyl-2-aminophenol (135 mg, 1. mmol), dichloroacetonitrile (**271**, 87 μL, 1.1 mmol) in methanol (1.1 mL) afforded after work up and purification 6-methyl-2-(dichloromethyl) benzo[*d*]oxazole (**326**, 136 mg, 58% yield) as a grey solid.

m.p. 62 – 64 °C; IR ($CHCl_3$) $\nu$($cm^{-1}$) 3011, 2434, 1609, 1567, 1520; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.64 (1H, d, $J$ = 8.3 Hz), 7.38 (1H, s), 7.20 (1H, d, $J$ = 8.3 Hz), 6.86 (1H, s), 2.50 (3H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 159.0, 151.3, 137.8, 137.6, 126.6, 120.5, 111.3, 61.1, 21.9; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_9H_8Cl_2NO^+$, 215.9978, found: 215.9998.

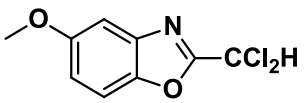
**5-(*tert*-Butyl)-2-(dichloromethyl)benzo[*d*]oxazole (327)**




*General procedure 4*: The reaction of 4-(*tert*-butyl)-2-aminophenol (165 mg, 1 mmol), dichloroacetonitrile (**271**, 80 μL, 1 mmol) in methanol (1 mL) afforded after work up and purification 5-(*tert*-butyl)-2-(dichloromethyl) benzo[*d*]oxazole (**327**, 165 mg, 64% yield) as a light yellow oil.

IR ($CHCl_3$) $\nu(cm^{-1})$ 2967, 1616; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.80 (1H, t, $J$ = 1.3 Hz), 7.52 - 7.51 (2H, m), 6.87 (1H, s), 1.37 (9H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 171.0, 159.7, 149.0, 140.0, 124.7, 117.5, 110.4, 61.1, 34.9, 31.6 (3C); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{12}H_{14}Cl_2NO^+$, 258.0447, found: 258.0443.

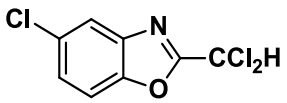
**5-Methoxy-2-(dichloromethyl)benzo[*d*]oxazole (328)**




*General procedure 4*: The reaction of 4-methoxy-2-aminophenol (140 mg, 1 mmol), dichloroacetonitrile (**271**, 81 μL, 1 mmol) in methanol (1 mL) afforded after work up and purification 5-methoxy-2-(dichloromethyl)benzo[*d*]oxazole (**328**, 145 mg, 62% yield) as a yellow oil.

IR ($CHCl_3$) $\nu(cm^{-1})$ 3006, 2962, 2838, 1615, 1567; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.46 (1H, d, $J$ = 9.0 Hz), 7.21 (1H, d, $J$ = 2.5 Hz), 7.02 (1H, dd, $J$ = 9.0, 2.5 Hz), 6.85 (1H, s), 3.84 (3H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 160.2, 157.8, 145.6, 140.9, 115.9, 111.5, 103.4, 61.1, 56.0; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_9H_8Cl_2NO_2^+$, 231.9927, found: 231.9931.

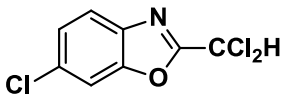
**5-Chloro-2-(dichloromethyl)benzo[*d*]oxazole[112] (329)**




*General procedure 4*: The reaction of 4-Chloro-2-aminophenol (115 mg, 0.8 mmol), dichloroacetonitrile (**271**, 63 μL, 0.8 mmol) in methanol (0.7 mL) afforded after work up and purification 5-chloro-2-(dichloromethyl)benzo[*d*]oxazole (**329**, 130 mg, 70% yield) as a white solid that had spectra identical to the literature.[4]

m.p. 68 – 70 °C, (lit. m.p. 70 °C); IR ($CHCl_3$) ν($cm^{-1}$) 3011, 2435, 1605, 1567; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.77 (1H, d, *J* = 2.0 Hz), 7.54 (1H, d, *J* = 8.8 Hz), 7.42 (1H, dd, *J* = 8.8, 2.0 Hz), 6.85 (1H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 160.9, 149.5, 141.1, 130.9, 127.3, 121.1, 112.1, 60.7; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_8H_5Cl_3NO^+$, 235.9432, found: 235.9450.

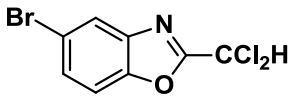
**6-Chloro-2-(dichloromethyl)benzo[*d*]oxazole (330)**




*General procedure 4*: The reaction of 5-Chloro-2-aminophenol (144 mg, 1 mmol), dichloroacetonitrile (**271**, 80 μL, 1 mmol) in methanol (1 mL) afforded after work up and purification 6-chloro-2-(dichloromethyl)benzo[*d*]oxazole (**330**, 162 mg, 69% yield) as a white solid.

m.p. 57 – 59 °C; IR ($CHCl_3$) ν($cm^{-1}$) 3006, 1610, 1568; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.7 (1H, d, *J* = 8.6 Hz), 7.63 (1H, d, *J* = 1.8 Hz), 7.40 (1H, dd, *J* = 8.6, 1.8 Hz), 6.86 (1H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 160.2, 151.1, 138.8, 132.7, 126.2, 121.7, 111.9, 60.7; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_8H_5Cl_3NO^+$, 235.9432, found: 235.9437.

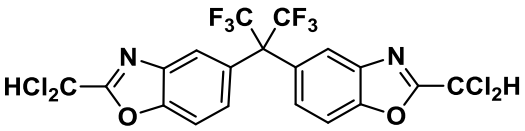
**5-Bromo-2-(dichloromethyl)benzo[*d*]oxazole (331)**




*General procedure 4*: The reaction of 4-Bromo-2-aminophenol (112 mg, 0.6 mmol), dichloroacetonitrile (**271**, 49 μL, 0.6 mmol) in methanol (0.5 mL) afforded after work up and purification 5-bromo-2-(dichloromethyl)benzo[*d*]oxazole (**331**, 130 mg, 77% yield) as a yellow solid.

m.p. 54 – 56 °C; IR ($CHCl_3$) $\nu$($cm^{-1}$) 3098, 3009, 1739, 1607, 1565; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.92 (1H, s), 7.58 - 7.47 (2H, m), 6.85 (1H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 160.6, 149.9, 141.5, 130.0, 124.1, 118.1, 112.5, 60.6; HRMS (ESI) *m/z:* calculated for $[M+Na]^+$, $C_8H_4BrCl_2NONa^+$, 301.8746, found: 301.8730.

**5,5'-(Perfluoropropane-2,2-diyl)*bis*(2-(dichloromethyl)benzo[*d*]oxazole) (332)**



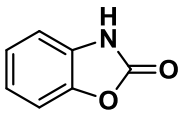

To a solution of 2,2-b*is*(3-amino-4-hydroxyphenyl)hexafluoropropane (**305**, 114 mg, 0.3 mmol) in methanol (0.3 mL, 1 M) at ambient temperature was added dichloroacetonitrile (**271**, 100 μL, 1.4 mmol, 4 equiv.). The resultant mixture was stirred at 40 °C for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford 5,5'-(perfluoropropane-2,2-diyl)*bis*(2-(dichloromethyl)benzo[*d*]oxazole) (**332**, 118 mg, 63% yield) as a brown solid.

m.p. 55 – 58 °C; IR ($CHCl_3$) ν($cm^{-1}$) 3008, 1751, 1621, 1573; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.95 (2H, s), 7.64 (2H, d, *J* = 9.0 Hz), 7.45 (2H, d, *J* = 9.0 Hz), 6.87 (2H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 161.0 (2C), 151.0 (2C), 140.2 (2C), 130.9 (2C), 129.0 (2C), 124.0 (2C, d, *J* = 287.5 Hz, CF), 123.7 (2C), 111.3 (2C), 60.7; $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$, 298 K) 63.7 (6F, s); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{19}H_9Cl_4F_6N_2O_2^+$, 552.9288, found: 552.9330.

# Experimental (benzoxazole transformations)

## 6o) Synthesis of benzoxazone

**Benzo[*d*]oxazol-2(*3H*)-one (350)[126]**

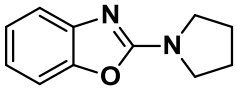


2-(Trichloromethyl)benzo[*d*]oxazole (**153**, 61 mg, 0.26 mmol) in $D_2O$ (1.0 mL, 5.55 mmol, 21 equiv.) was stirred at 150 ºC for 2 h. The solution was allowed to cool to ambient temperature a dichloromethane (10 ml) was added, the resultant solution was washed with water (3 x 5 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to afford benzo[d]oxazol-2(3H)-one (**350**, 24 mg, 69%) as a colourless oil that had spectra identical to the literature.[126]

$^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 8.99 (1H, br.s), 7.98 (1H, dd, *J* = 8.0, 1.51 Hz), 7.15 – 7.09 (1H, m), 7.04 - 6.94 (2H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 159.4, 150.0, 127.1, 123.8, 119.1, 115.6, 115.1; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_7H_6NO_2^+$, 136.0393, found: 136.0380.

## 6p) Synthesis of amino/amido benzoxazoles and by-products

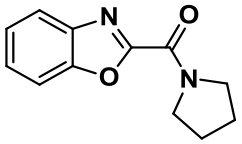
### 2-(Pyrrolidin-1-yl)benzo[*d*]oxazole[127] (357)



*General procedure 5*: The reaction of 2-(trichloromethyl)benzo[*d*]oxazole (**153**, 200 mg, 0.8 mmol) and pyrrolidine (79 μL, 0.9 mmol) in acetonitrile (0.8 mL) afforded after work up and purification 2-(pyrrolidin-1-yl) benzo[*d*]oxazole (**357**, 146 mg, 92% yield) as a yellow solid that had spectra identical to the literature.[127]

m.p. 133 – 135 °C (lit. m.p. 136 –137 °C); IR ($CHCl_3$) ν($cm^{-1}$) 3011, 2978, 2880, 1648; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.36 (1H, d, *J* = 7.8 Hz), 7.26 (1H, d, *J* = 7.8 Hz), 7.15 (1H, td, *J* = 7.7, 1.2 Hz), 6.99 (1H, td, *J* = 7.7, 1.2 Hz), 3.69 – 3.62 (4H, m), 2.07 – 2.01 (4H, m); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 160.9, 148.9, 143.5, 123.6, 119.9, 115.8, 108.4, 47.2 (2C), 25.4 (2C); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{11}H_{13}N_2O^+$, 189.1023, found: 189.1030.

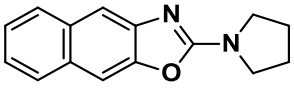
**Benzo[*d*]oxazol-2-yl(pyrrolidin-1-yl)methanone (358)**



To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**153**, 150 mg, 0.6 mmol, 1 equiv.) in acetonitrile (6 mL, 0.1 M) at ambient temperature were added iron(II) chloride (97 mg, 0.6 mmol, 1.0 equiv.) and pyrrolidine (260 μL, 3.17 mmol, 5.0 equiv.). The resultant solution was stirred at ambient temperature for 19 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in diethyl ether) to afford benzo[*d*]oxazol-2-yl(pyrrolidin-1-yl)methanone (**358**, 17 mg, 13%) as a yellow solid.

m.p. 126-128 ºC; IR ($CHCl_3$) ν($cm^{-1}$) 3006, 2886, 1640; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.83 (1H, d, *J* = 7.5 Hz) 7.66 (1H, d, *J* = 7.6 Hz) 7.48 (1H, td, *J* = 7.6, 1.4 Hz), 7.42 (1H, td, *J* = 7.5, 1.4 Hz), 4.14 (2H, t, *J* = 6.8 Hz), 3.76 (2H, t, *J* = 6.8 Hz), 2.11 – 1.93 (4H, m); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 155.8, 155.3, 150.1, 140.6, 127.2, 125.2, 121.4, 111.7, 49.3, 47.5, 26.5, 23.9; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{12}H_{13}N_2O_2^+$, 217.0972, found: 217.0970.

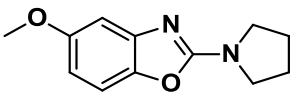
**2-(Pyrrolidin-1-yl)naphtho[2,3-*d*]oxazole (371)**



*General procedure 5*: The reaction of 2-(Trichloromethyl)naphtho[*2,3-d*]oxazole (**299**, 158 mg, 0.55 mmol), pyrrolidine (51μL, 0.6 mmol) in acetonitrile (0.6 mL) afforded after work up and purification 2-(pyrrolidin-1-yl)naphtho[2,3-*d*]oxazole (**371**, 130 mg, 99% yield) as a yellow oil.

IR ($CHCl_3$) ν($cm^{-1}$) 2969, 2881, 1656; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.86 – 7.80 (2H, m), 7.68 (1H, s), 7.58 (1H, s), 7.37 (2H, quind, $J$ = 6.9, 1.3 Hz), 3.66 (4H, t, $J$ = 6.7 Hz ), 2.05 – 1.97 (4H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 161.9, 149.3, 144.1, 131.9, 129.2, 127.6, 127.5, 124.2, 123.5, 111.4, 104.3, 47.5 (2C), 25.5 (2C); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{15}H_{15}N_2O^+$, 239.1179, found: 239.1189.

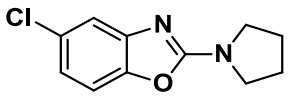
**5-Methoxy-2-(pyrrolidin-1-yl)benzo[*d*]oxazole[128] (373)**



*General procedure 5*: The reaction of 5-methoxy-2-(trichloromethyl) benzo[*d*]oxazole (**295**, 147 mg, 0.55 mmol), pyrrolidine (51 μL, 0.6 mmol) in acetonitrile (0.6 mL) afforded after work up and purification 5-methoxy-2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**373**, 83 mg, 69% yield) as a light brown crystals that had spectra identical to the literature.[128]

IR ($CHCl_3$) ν($cm^{-1}$) 2957, 2880, 1650; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.10 (1H, d, *J* = 8.6 Hz), 6.92 (1H, d, *J* = 2.5 Hz), 6.53 (1H, dd, *J* = 8.6, 2.5 Hz), 3.79 (3H, s), 3.64 – 3.60 (4H, m), 2.04 – 1.99 (4H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 161.8, 156.9, 144.7, 143.6, 108.3, 106.3, 101.2, 55.8, 47.3 (2C), 25.6 (2C); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{12}H_{15}N_2O_2^+$, 219.1129, found: 219.1134.

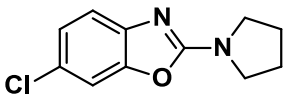
**5-Chloro-2-(pyrrolidin-1-yl)benzo[*d*]oxazole[128] (374)**




*General procedure 5*: The reaction of 5-Chloro-2-(trichloromethyl) benzo[*d*]oxazole (**303**, 150 mg, 0.55 mmol), pyrrolidine (51 μL, 0.6 mmol) in acetonitrile (0.6 mL) afforded after work up and purification 5-chloro-2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**374**, 100 mg, 81% yield) as a white solid that had spectra identical to the literature.[128]

m.p. 121 – 123 °C; IR ($CHCl_3$) ν($cm^{-1}$) 2979, 2882, 1650; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.28 (1H, d, *J* = 2.1 Hz), 7.10 (1H, d, *J* = 8.4 Hz), 6.90 (1H, dd, *J* = 8.4, 2.1 Hz), 3.60 (4H, t, *J* = 6.7 Hz), 2.05 – 1.96 (4H, m); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 161.6, 147.5, 145.0, 128.9, 119.6, 115.8, 108.9, 47.3 (2C), 25.4 (2C); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{11}H_{12}ClN_2O^+$, 223.0633, found: 223.0637.

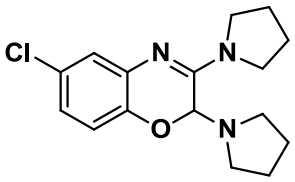
**6-Chloro-2-(pyrrolidin-1-yl)benzo[*d*]oxazole (375)**




*General procedure 5*: The reaction of 6-Chloro-2-(trichloromethyl) benzo[*d*]oxazole (**296**, 150 mg, 0.55 mmol), pyrrolidine (51 μL, 0.6 mmol) in acetonitrile (0.6 mL) afforded after work up and purification 6-chloro-2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**375**, 93 mg, 75% yield) as a white solid.

m.p. 126 – 128 °C; IR ($CHCl_3$) ν($cm^{-1}$) 2979, 2881, 1651; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.22 – 7.19 (2H, m), 7.08 (1H, dd, *J* = 8.3, 1.9 Hz), 3.62 – 3.58 (4H, m), 2.05 – 1.96 (4H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 161.2, 149.1, 142.6, 125.0, 124.0, 116.1, 109.3, 47.4 (2C), 25.5 (2C); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{11}H_{12}ClN_2O^+$, 223.0633, found: 223.0639.

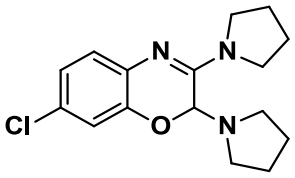
**6-Chloro-2,3-di(pyrrolidin-1-yl)-*2H*-benzo[*b*][1,4]oxazine (376)**




*General procedure 5*: The reaction of 5-Chloro-2-(trichloromethyl) benzo[*d*]oxazole (**303**, 150 mg, 0.55 mmol), pyrrolidine (51 μL, 0.6 mmol) in acetonitrile (0.6 mL) afforded after work up and purification 6-Chloro-2,3-di(pyrrolidin-1-yl)-*2H*-benzo[*b*][1,4]oxazine (**376**, 24 mg, 14% yield) as a yellow gummy solid.

IR ($CHCl_3$) ν($cm^{-1}$) 3690, 2929, 2876, 1610; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.08 (1H, d, $J$ = 2.1 Hz ), 6.80 – 6.72 (2H, m), 5.45 (1H, s), 3.65 (3H, br.s), 3.36 (1H, br.s) 2.96 – 2.89 (2H, m) 2.68 – 2.61 (2H, m) 1.97 (4H, br.s) 1.72 – 1.60 (4H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 152.3, 144.7, 136.0, 125.8, 123.3, 121.9, 115.0, 80.2, 46.7 (4C), 24.4 (4C); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{16}H_{21}ClN_3O^+$, 306.1368, found: 306.1373.

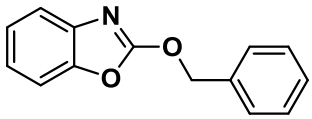
**7-Chloro-2,3-di(pyrrolidin-1-yl)-*2H*-benzo[*b*][1,4]oxazine (377)**




*General procedure 5*: The reaction of 6-Chloro-2-(trichloromethyl) benzo[*d*]oxazole (**296**, 150 mg, 0.55 mmol), pyrrolidine (51 μL, 0.6 mmol) in acetonitrile (0.6 mL) afforded after work up and purification 7-Chloro-2,3-di(pyrrolidin-1-yl)-*2H*-benzo[*b*][1,4]oxazine (**377**, 42 mg, 25% yield) as a yellow gummy solid.

IR ($CHCl_3$) ν($cm^{-1}$) 3667, 2974, 2876, 1607; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.01 (1H, dd, *J* = 7.9, 0.7 Hz ), 6.84 – 6.80 (2H, m), 5.46 (1H, s), 3.63 (3H, br.s), 3.37 (1H, br.s) 2.96 – 2.88 (2H, m) 2.68 – 261 (2H, m) 2.01 – 1.94 (4H, m) 1.69 – 1.60 (4H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 151.8, 146.5, 133.5, 126.6, 124.1, 121.3, 114.6, 80.2, 46.6 (4C), 24.4 (4C); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{16}H_{21}ClN_3O^+$, 306.1368, found: 306.1360.

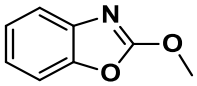
**2-(Benzyloxy)-2,3-dihydrobenzo[*d*]oxazole (389)**



To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**153**, 150 mg, 0.6 mmol, 1 equiv.) in acetonitrile (0.6 mL, 1 M) were added benzyl alcohol (73 μL, 0.7 mmol, 1.1 equiv.) and DBU (104 μL, 0.7 mmol, 1.1 equiv.). The resultant solution was stirred at 60 ºC for 16 hours and filtered through silica (dichloromethane). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on base washed silica gel (1% ethyl acetate in petroleum ether) to afford 2-(benzyloxy)-2,3-dihydrobenzo [*d*]oxazole (**389**, 37 mg, 26%) as a clear oil.

IR ($CHCl_3$) ν($cm^{-1}$) 3009, 2928, 2855, 1741, 1613, 1568; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.81 – 7.79 (2H, m) 7.64 – 7.62 (2H, m), 7.47 (2H, td, *J* = 7.7, 1.4 Hz ), 7.42 (2H, td, *J* = 7.5, 1.4 Hz ) 7.39 – 7.35 (1H, m), 6.87 (2H s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 159.6, 151.0, 140.1, 128.6, 128.3, 126.9 (2C), 125.3 (2C), 121.2 (2C), 119.4, 111.3, 61.0; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{14}H_{12}NO_2^+$, 226.0863, found: 226.0873.

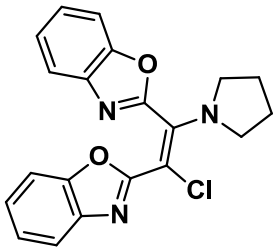
**2-Methoxybenzo[*d*]oxazole (390)**



To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**153**, 150 mg, 0.6 mmol, 1 equiv.) in acetonitrile (0.6 mL, 1 M) at ambient temperature were added methanol (28 μL, 0.7 mmol, 1.1 equiv.) and DBU (104 μL, 0.7 mmol, 1.1 equiv.). The resultant solution was stirred at 60ºC for 16 hours and filtered through silica (dichloromethane). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on base washed silica gel (3% ethyl acetate in petroleum ether) to afford 2-methoxybenzo[*d*]oxazole (**390**, 24 mg, 25%) as a clear oil.

IR ($CHCl_3$) ν($cm^{-1}$) 3156, 2927, 2254, 1792, 1747, 1552; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.90 (1H, d *J* = 7.9 Hz) 7.67 (1H, d *J* = 8.1 Hz), 7.56 – 7.44 (2H, m), 4.10 (3H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 156.9, 150.9, 140.5, 128.3, 125.9, 122.2, 111.8, 53.7; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_8H_8NO_2^+$, 150.0550, found: 150.0540.

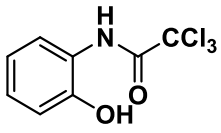
**(*Z*)-2,2'-(1-Chloro-2-(pyrrolidin-1-yl)ethene-1,2-diyl)bis(benzo[*d*]oxazole) (395)**




To a stirred suspension of 2-(trichloromethyl)benzo[*d*]oxazole (**153**, 150 mg, 0.6 mmol, 1.0 equiv.) and iron(III) chloride (97mg, 0.6 mmol, 1.0 equiv.) in acetonitrile (6 mL, 0.1 M) at ambient temperature was added pyrrolidine (260 μL, 3.17 mmol, 5.0 equiv.). The resultant mixture was stirred at ambient temperature for 19 hours and filtered through base washed silica. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% diethyl ether in petroleum ether) to afford (*Z*)-2,2'-(1-chloro-2-(pyrrolidin-1-yl)ethene-1,2-diyl)bis(benzo[*d*]oxazole) (**395**, 58 mg, 50%) as a yellow solid.

IR ($CHCl_3$) ν($cm^{-1}$) 2982, 2882, 1607, 1578, 1549; $^1H$ NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 7.80 – 7.77 (1H, m) 7.56 – 7.54 (1H, m) 7.44 – 7.39 (3H, m) 7.13 (1H, td, *J* = 7.7, 1.1 Hz ), 7.05 (1H, td, *J* = 7.8, 1.3 Hz ), 6.87 (1H, d, *J* = 7.8 Hz ) 3.66 – 3.62 (4H, m) 2.00 – 1.97 (4H, m); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 161.8, 158.1, 150.5, 150.4, 141.9, 141.2, 138.6, 126.1, 124.8, 124.1, 124.0, 120.9, 119.3, 111.1, 109.5, 94.7, 51.3 (2C), 25.6 (2C); HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_{20}H_{17}ClN_3O_2^+$, 366.1004, found: 366.1000.

**2,2,2-Trichloro-*N*-(2-hydroxyphenyl) acetamide (397)[129]**




To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**153**, 237mg, 1 mmol, 1 equiv.) and iron(III) chloride (3.0 mg, 0.02 mmol, 2 mol%) in acetonitrile (0.2 mL, 5 M) at ambient temperature was added water (18 μL, 1 mmol, 1.0 equiv.) after 5 minutes. The resultant mixture was stirred at ambient temperature for 5 hours and water (27 μL, 1.5 mmol, 1.5 equiv.) was added. The mixture was stirred at ambient temperature for 3 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2,2,2-trichloro-*N*-(2-hydroxyphenyl) acetamide (**397**, 148 mg, 58%) as a yellow solid that had spectra identical to the literature.[129]

m.p. 160 - 161 °C (lit. m.p. 160 °C); 159-160 ºCIR ($CHCl_3$) ν($cm^{-1}$) 3594, 3397, 1720, 1615; $^1$H NMR (300 MHz, $CDCl_3$, 298 K) $\delta_H$ 8.86 (1H, br.s) 7.95 (1H, d, *J* = 8.0 Hz ), 7.16 – 7.10 (1H, m), 7.04 – 6.94 (2H, m) 5.99 (1H br.s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) $\delta_c$ 172.0, 159.7, 146.1, 126.6, 124.5, 121.7, 121.2, 116.5; HRMS (ESI) *m/z:* calculated for $[M+H]^+$, $C_8H_7Cl_3NO_2^+$, 253.9537, found: 253.9534.

# Chapter 7: Bibliography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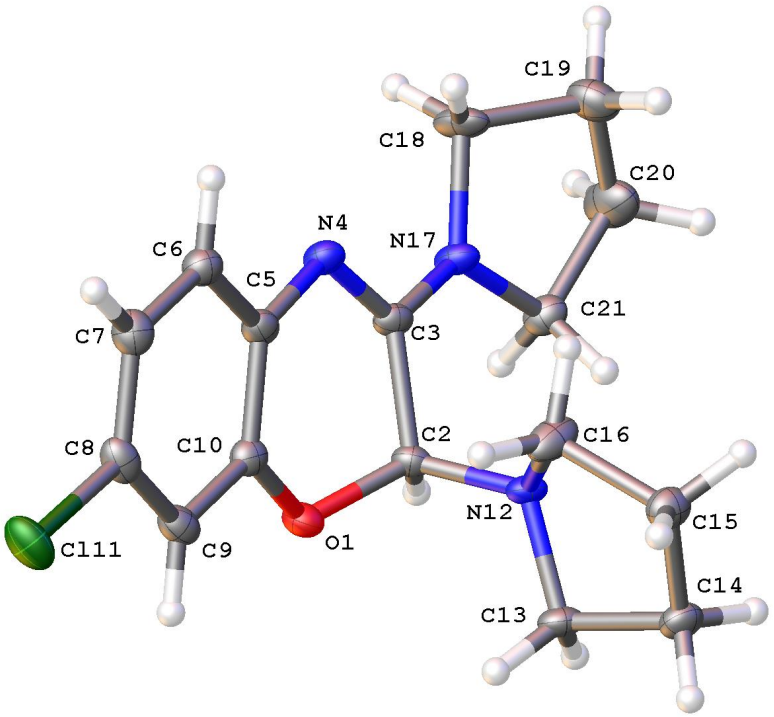
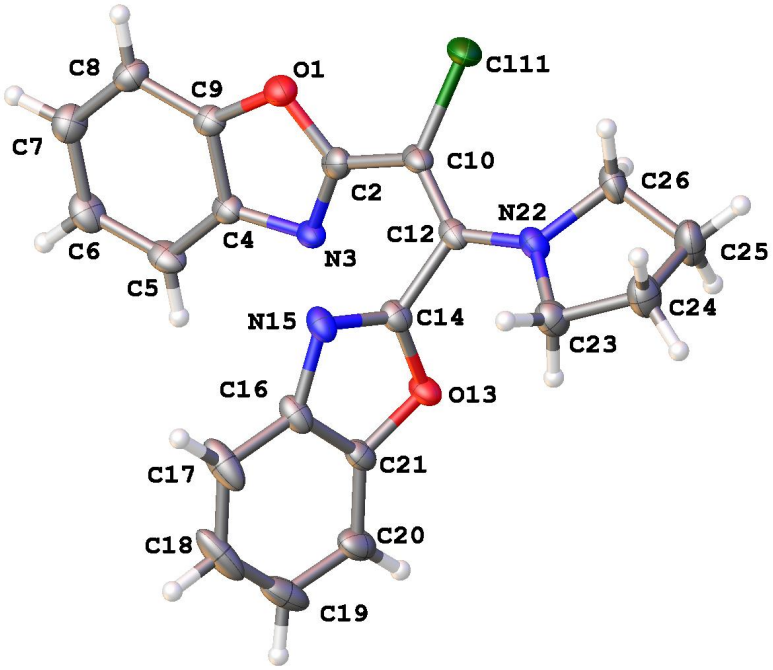
# Chapter 8: Appendices

**x-ray crystallography data for 7-Chloro-2,3-di(pyrrolidin-1-yl)-*2H*-benzo[*b*][1,4]oxazine (377)**



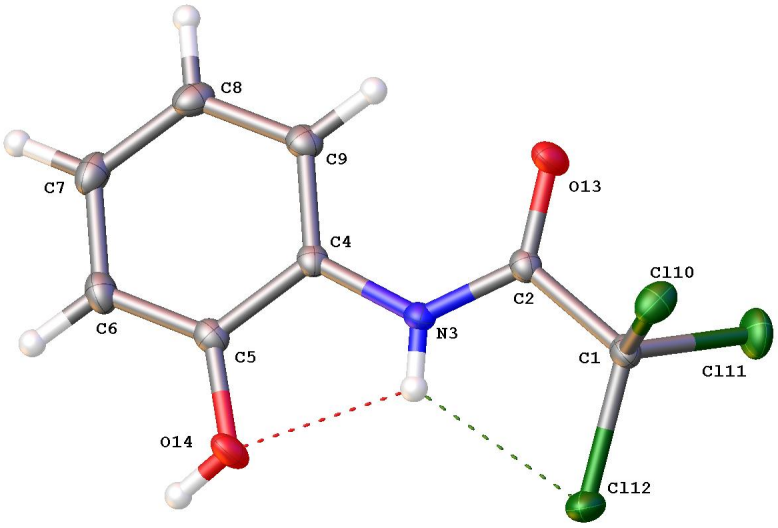

| | |
|---|---|
| Empirical formula | $C_{16}H_{20}N_3OCl$ |
| Formula weight | 305.80 |
| Crystal system | triclinic |
| Space group | P-1 |
| β/° | 107.455(14) |
| γ/° | 111.917(13) |
| Volume/Å$^3$ | 740.7(2) |
| Z | 2 |
| $\rho_{calc}$mg/mm$^3$ | 1.371 |
| m/mm$^{-1}$ | 2.299 |
| F(000) | 324.0 |
| Crystal size/mm$^3$ | 0.4734 × 0.2377 × 0.1971 |
| Radiation | CuKα (λ = 1.54184) |
| 2Θ range for data collection | 9.34 to 149.424° |
| Index ranges | $-9 \leq h \leq 11$, $-11 \leq k \leq 7$, $-12 \leq l \leq 12$ |
| Reflections collected | 4796 |
| Independent reflections | 2862 [$R_{int}$ = 0.0292, $R_{sigma}$ = 0.0345] |
| Goodness-of-fit on $F^2$ | 1.054 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0421, $wR_2$ = 0.1130 |
| Final R indexes [all data] | $R_1$ = 0.0451, $wR_2$ = 0.1161 |

x-ray crystallography data for (Z)-2,2'-(1-Chloro-2-(pyrrolidin-1-yl)ethene-1,2-diyl)bis(benzo[d]oxazole) (395)




| | |
|---|---|
| Empirical formula | $C_{20}H_{16}N_3O_2Cl$ |
| Formula weight | 365.82 |
| Crystal system | triclinic |
| Space group | P-1 |
| β/° | 107.168(8) |
| γ/° | 99.308(7) |
| Volume/Å$^3$ | 873.25(18) |
| Z | 2 |
| $\rho_{calc}$mg/mm$^3$ | 1.3912 |
| m/mm$^{-1}$ | 2.102 |
| F(000) | 381.8 |
| Crystal size/mm$^3$ | 0.1382 × 0.1038 × 0.0426 |
| Radiation | Cu Kα (λ = 1.54184) |
| 2Θ range for data collection | 9.52 to 148.72° |
| Index ranges | -11 ≤ h ≤ 9, -12 ≤ k ≤ 13, -13 ≤ l ≤ 12 |
| Reflections collected | 5242 |
| Independent reflections | 3357 [$R_{int}$ = 0.0505, $R_{sigma}$ = 0.0648] |
| Data/restraints/parameters | 3357/0/234 |
| Goodness-of-fit on F$^2$ | 1.051 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0538, w$R_2$ = 0.1372 |
| Final R indexes [all data] | $R_1$ = 0.0628, w$R_2$ = 0.1473 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.44/-0.58 |

**x-ray crystallography data for 2,2,2-Trichloro-*N*-(2-hydroxyphenyl) acetamide (397)**




| | |
|---|---|
| Empirical formula | $C_8H_6NO_2Cl_3$ |
| Formula weight | 254.49 |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| β/° | 97.5772(13) |
| γ/° | 90 |
| Volume/Å$^3$ | 1004.49(3) |
| Z | 4 |
| $\rho_{calc}$mg/mm$^3$ | 1.683 |
| m/mm$^{-1}$ | 8.054 |
| F(000) | 512.0 |
| Crystal size/mm$^3$ | 0.3282 × 0.174 × 0.1086 |
| Radiation | CuKα (λ = 1.54184) |
| 2Θ range for data collection | 10.746 to 148.178° |
| Index ranges | $-9 \leq h \leq 9$, $-15 \leq k \leq 14$, $-14 \leq l \leq 14$ |
| Reflections collected | 34200 |
| Independent reflections | 2035 [$R_{int}$ = 0.0491, $R_{sigma}$ = 0.0130] |
| Data/restraints/parameters | 2035/0/133 |
| Goodness-of-fit on $F^2$ | 1.098 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0245, $wR_2$ = 0.0654 |
| Final R indexes [all data] | $R_1$ = 0.0251, $wR_2$ = 0.0658 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.39/-0.23 |