New Methods in Organophosphorus Chemistry: a Wide Reaching Tool Box for the Modern Chemist

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Declaration

I hereby declare that the work presented in this thesis was carried out at the University of Sussex under the supervision of Professor Mark C. Bagley between the dates of September 2012 and September 2016. The work presented in this thesis is my own, unless otherwise stated, and has not been submitted in whole or in part from the award of another degree.

David G. Neill-Hall

I would like to dedicate this thesis to my Father, William ‘Bill’ Neill-Hall, who sadly passed away on the 2nd of January 2015, whilst I was in the middle of completing this PhD.

A kind and generous man. A supporting and loving father. A friend who could always be relied upon when I needed him most with love and words of wisdom. Without him I would not be the man I am today.

I miss and love you Dad.

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Abstract

Phosphines have number useful properties most notably its nucleophilicity and high oxophilicity which allows it to be an effective activator and reducing agent of oxygen containing compounds such as alcohols and carbonyls. These properties allow phosphine to participate in a number of widely used reactions such as the Wittig, Appel, Mitsunobu and Staudinger reactions.[1–4] DMAP on the other hand has been used as an effective acylation catalyst and has been incorporated in to the widely utilised Steglich esterification. This thesis details the development of a new three component reagent system consisting of PPh_3, I_2 and DMAP. This new system takes advantage of both the initial activation properties of Ph_3P-I_2 adduct formed from the combination of phosphine and iodine, as well as the nucleophilic catalytic properties of DMAP.

This was initially developed as a new method for the direct coupling of carboxylic acids with alcohols and amines. For this purpose the new reagent system was highly successful resulting in good-excellent yields of both esters and amides in an extremely rapid reaction. The mechanism of this acylation process consists of two distinct stages; the first involves initial activation of the carboxylic acid the second a DMAP catalytic cycle. This led to the development of a catalytic system in terms of the DMAP but still offered significantly faster reaction times compared to other common mild reaction condition methods. The reagent system was also applied to the activation and further reactivity of oximes with the intramolecular cyclisation of 2-hydroxy-benzaldehyde oximes resulting in rapid formation of the corresponding 1,2-benzisoxazoles. The activation of oximes also led to the formation of novel DMAP-hydrazones which could undergo further reactivity with methoxide anion to form imidates. Benzaldehyde oxime did not produce a stable DMAP-hydrazone and instead undergo elimination reaction straight to the benzonitrile. Finally, the reagent system was applied to the formation of phosphazenes. This produced a range of aryl-phosphazene in high yields and fast reaction times. A one-pot urea system was then developed producing both asymmetrical and symmetrical ureas in good yield and under mild reaction conditions.

List of Abbreviations

2,4,6-col	2,4,6- Collidine
3,5-DMP	3,5-Dimethylpyrazole
Ac	Acyl
Ac_2O	Actic anhydride
AcCl	Actyl cholride
ACHE	Acetlcholinestase
ADDP	1,1'-(Azodicarbonyl)dipiperidine
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
BP	Basepairs
Br_2	Dibromide
CBr_4	Carbon tetrabromide
$CBrCl_3$	Bromotrichloromethane
CCl_4	Carbon tetrachloride
CH_3CN	Acetonitrile
Cl_2	Dichoride
CS_2	Carbon disulphide
CsF	Caesium fluoride
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
CH_2Cl_2	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate

DHP	3,4 Dihydropyran
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	*N*,*N*'-Diisopropylethylamine
DMAP	Diemthyl amino pryidine
DMP	Dess-Martin periodinane
DNA	Deoxyribonucleic acid
ee	Enantiomeric excess
EI	Electron ionization
ESI	Electrospray ionisation
ETC	Electron chain transport
FAD	Flavin adenine dinucleotide
FDA	Food and Drug Administration
FLP	Frustrated Lewis Pair
FMA	Furfuryl methacylate
GBM	Glioblastoma multiforme
gem	Geminal
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, *N*-[(Dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
HBTU	*N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate, *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate

HMPA	Hexamethylphosphoramide
HoBT	*N*-Hydroxybenzotriazole
HW	Horner-Wittig reaction
HWE	Horner-Wasworth-Emmons olfination
I_2	Diiodide
KHMDS	Potassium bis(trimethylsilyl)amide
LiAlH	Lithium aluminium hydride
LiBr	Lithium bromide
MBH	Morita-Baylis-Hillman reaction
MEEEP	Poly[bis2(2(2methyloxyethoxy)ethoxy phosphazene
MMA	Methyl methacrylate
Na_2CO_3	Sodium carbonate
$Na_2S_2O_3$	Sodium thiosulphatre
NADH	nicotinamide adenine dinucleotide H^+
NaH	Sodium Hydride
NaOH	Sodium hydroxide
NaOMe	Sodium Methoxide
NBS	*N*-bromosuccinimide
NCCD	Nomenculture Committee on Cell Death
NCS	*N*-chlorosuccinimide
NEt3	Triethyl amine
NMP	*N*-methylpyrrolidone
NMR	Nuclear magnetic resonance
OPA	Oxaphosphetane
$P(o\text{-tolyl})_3$	Tri(*o*-tolyl)phosphine

PBu_3	Tributyl phosphine
PEO	Poly(ethlene)oxide
PET	Positron emission tomography
PPAR	Peroxisome proliferator-activated receptors
PPh_3	Triphenyl phosphine
PPTS	Pyridinium p-toluenesulfonate
PPY	4-Pyrrolidinopyridine
PS	Phosphatidylserine
p-TsCl	*para*-Toulenesulfonyl chloride
p-TsF	*para*-Toulenesulfonyl flouride
PyBOP	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
RDS/rds	Rate Determining step
RNA	Ribonucleic acid
ROMP	Ring-Opening Metathesis Polymerization
SmI_2	Samarium(II) iodide
TATU	*N*-[(dimethylamino)(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium tetrafluoroborate
TBAF	Tetra-*N* -butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl ether
TBTU	*N,N,N′,N′*-Tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate,
TCB-DMAP	2,4,6-Trichlorobenzoylchloride–4-dimethylaminopyridine
TdT	Terminal deoxynucleotidyl transferase

TFA	Trifluro acetic acid
THF	Tetrahydrofuran
TiCl	Titainium (III) chloride
TLC	Thin layer chromatography
TMRE	Tetramethylrhodamine, ethyl ester
TsCl	*p*-Toluenesulfonyl chloride
TsF	*p*-Toluenesulfonyl floride

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1 Introduction

Over the last 150 years organophosphorus chemistry has formed an integral part of organic, medicinal, organometallic and main group chemistry. It provides a wide reaching and useful toolbox of reagents and starting materials that the modern synthetic organic chemist can utilise for a range of processes. It is the hope of this introduction to review and highlight the properties that have made organophosphorus chemistry such a versatile tool to chemists and to explain how these compounds have become important in modern catalytic, bioorganic and synthetic strategies employed across the chemical and biochemical fields. The role that phosphorus containing compounds play in life exemplified by DNA and ATP, will be discussed in order to highlight that without phosphorus-compounds life as we know it not could not exist. However, the main focus of this introduction will be to discuss the use of a special class of organophosphorus compounds; the phosphines, and their range of uses including as ligands in organometallic complexes, the newly emerged field of frustrated Lewis pair chemistry and the organic transformations where they have established themselves as valuable reagents.

The second half of the introduction will then focus on a review of the use and properties of the nucleophilic base 4-dimethylaminopyridine (DMAP). Attention to its mode of action and why it has become a useful catalytic reagent for a variety of reactions including esterification, the Baylis-Hillman reaction and the Steglich rearrangement. This will be in anticipation for the results and discussion chapters, which will describe a new reagent system combining triphenylphosphine (PPh_3), DMAP and iodine (I_2), and its use for in a number of different transformations. This is of particular application in the formation of ester and amide bonds, but can also be used in a new method for the synthesis of phosphazenes and isoxazoles.

1.1 Phosphorus: 'Light Bringer'-a Brief History.[5]

Phosphorus was the 13th element to be discovered but the first to have a known and recorded origin of discovery. It is the 15th element in the periodic table sitting in group 15, row 3. It is the 11th most abundant element in the earth's crust and the 2nd most abundant element in the human body. It contains 15 protons, 15 electrons and 16 neutrons with an atomic weight of 30.97 with the most abundant isotope being ^{31}P which is an spin active integer in NMR spectroscopy. The name 'phosphorus' is derived from the Greek words meaning 'light bringer'. This is due to the bright light produced when elemental 'white' phosphorus is exposed to elemental oxygen, a marvel of the age when it was first discovered and widely attributed to the German Alchemist Hennin Brand in 1669. In his attempt to extract gold out of urine and sand, he instead isolated the element via the distillation of urine and collection of the vapour in cold water. Its ability to spontaneously combust in a bright flame when exposed to oxygen and glows when exposed to air, quickly became the wonder of European natural philosophy circles in the late 17th century once Sir Robert Boyle published the recipe in 1680. Elemental phosphorus occurs in two major forms known as white (or yellow) and red (which can have several allotropes).

White phosphorus (P_4) is a highly toxic waxy solid that contains a crystal structure of 4 atoms in a tetrahedral geometry. This arrangement of atoms results in a strained ring system and therefore P^4 is highly unstable and therefore highly reactive, combusting when it comes into contact with air and coloured yellow in the present of sunlight. Red phosphorus on the other hand has an amorphous structure, meaning that it consists of chains of P atoms with no long range crystal structure. It is therefore much more stable than that of P^4 and will not spontaneously combust under 240^{o}C. However, friction heating can rapidly crystallise it back to white phosphorus which vaporises and it is this property that is exploited to light safety matches by striking the head against a friction surface on the side on the match box. Red phosphorus is formed form white phosphorus either by heating to 250-300^{o}C in an inert atmosphere or by exposure to sunlight.

1.2 From Light Bringer to Life Bringer

"*Life can multiply until all the phosphorus has gone and then there is an inexorable halt which nothing can prevent*", Isaac Azimov.[6]

As the quote above by Isaac Asimov indicates; phosphorus is critical for life in all its forms, from single cell organisms such as bacteria to complex multicellular plant and aminals. It is a vital element in the growth of crops and is an important component of fertilisers needed for mass food production. Phosphorus is the 2nd most abundant element in the human body and 6th in life of all kind. It is present in every cell as phosphonate, in the form of phosphodiester bonds linking together the deoxyribose sugars in DNA or ribose sugars in RNA, phospholipids that make up cell membranes to the role of phosphonates in the energy delivery system of the body using adenosine triphosphate (ATP) show how this element is essential for life.[7]

1.2.1 DNA and RNA

Phosphates (PO_4^{3-}) are inorganic salts of phosphoric acid. However, when in an organic setting, phosphoric esters and are an integral part of life as we know it. They are key components within nature as they form useful, stable linkages between molecules and therefore are essential component of DNA and RNA, which every living organism relies upon for the passing on of that organism's genetic information. Phosphodiesters form part of the backbone of the structure as the link between different nucleotides in DNA and RNA. This backbone is comprised of alternating sugar and phosphate groups which define both the directionality and shape of the polymer and thus helping to determine DNA's famous double helical shape.

The nucleotides of the DNA are held together via phosphodiester bonds that form between the sugar units of one nucleotide to the phosphate group of the next nucleotide. The phosphonate is attached to the carbon at position 5' of the sugar though an OH group whilst forming the phosphoester linkage to the adjacent nucleotide sugar via the OH group at position 3' on the ring. The DNA molecule is prepared biosynthetically in the 5' to 3' direction.

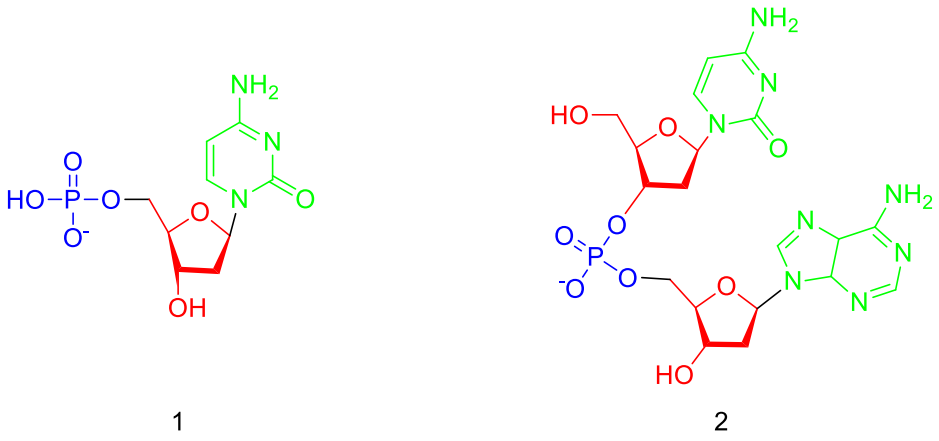


Figure 1.1: 1; DNA monomer nucleotide containing cytosine. **2**; shows how phosphate group acts as the link between two nucleotides cytosine and adenine by forming a phosphodiester.

Figure 1.1 shows a monomer nucleotide containing cytosine (**1)** and the phosphate di ester bonded dinucleotide between cytosine and adenine (**2)**. The nucleotide is made up of 3 distinct sections: the first, highlighted in blue, is the phosphate group that acts as the link between the nucleotide monomers. The pKa of phosphate group is between 1 and 2 and at physiological pH of 7.4 the phosphate will be deprotonated to its negatively charged state. This feature of the phosphate sugar backbone is one of the major driving forces for stabilizing the distinctive double helix shape of double stranded DNA that was postulated by Crick and Watson in 1953.[8] The second part of the nucleotide is the 5 membered sugar ring unit (highlighted in red). This sugar can either be deoxyribose (as in **1** and **2**) in DNA nucleotides or ribose in RNA which is similar but features an additional OH group at the 2' position of the sugar ring. The sugar forms an important part of the backbone of the DNA polymer as it is here where the phosphate group forms the phosphoester bond to the next nucleotide. Finally the section in green is the organic nucleotide base part of DNA or RNA. These bases are the part of the molecule that allows base pairing in DNA to form the double strand system where the genetic information is contained and stored. In DNA there are four such bases: cytosine, thymine, adenine and guanine. RNA bases contain the same bases apart from uracil which is used instead of thymine.

The genius of Crick and Watson was to realise that the basic sub-structure of DNA i.e. phosphate-sugar-base was ideal for the formation three dimensional coil. The negative charge of the phosphate groups along with the sugar molecules are the hydrophilic part of the DNA structure allowing DNA to dissolve in water therefore forming the outside of the polynucleotide. The heterocyclic bases are hydrophobic and therefore conjugate

in the centre of the helix, stacking themselves together in complimentary pairs (adenine and thymine; guanine and cytosine). Perhaps the two most important driving factors for the adopting a helical shape come from the balance between the repulsive forces of the highly charged phosphate groups and the attractive forces of the base stacking which actually disfavour the helicity.[9] Multitude of other interactions also play a role in the determination of the helical shape such as counterions of the various charges, which can act to reduce the charge of the phosphate and the water/ion balance can have a significant effect on DNA interactions.[10]

1.2.2 Adenosine Triphosphate (ATP)

Whilst phosphates provide stable linkages between molecules, such as the sugars of DNA, they can also be built up in such a way to form highly reactive molecules used in biological systems as a source of energy. Adenosine triphosphate (ATP) was first discovered by Karl Lohmann in 1929 and is central to the primary metabolic pathways used by the body.[11] It is often referred to as the energy currency of the cell or nature's energy storage system. Any energy intake by an organism e.g. food metabolism or photosynthesis, must first be converted to a form that the organism can handle/use for its cellular processes and that form is ATP.

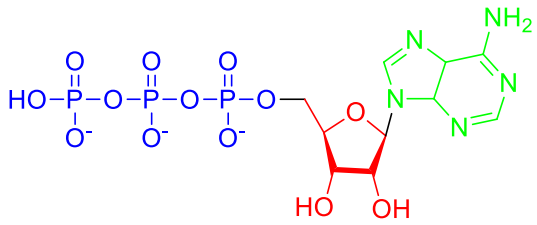


Figure 1.2: Structure of adenosine triphosphate (ATP)

Like DNA, ATP consists of three distinct parts; the central sugar this time is a ribose, so has an OH at the 2'-position, the base adenosine and finally a chain of three phosphate groups. It is these phosphate groups that makes ATP highly reactive and gives the ability to store and transport energy with in the cellular environment. When an enzyme instructs the hydrolysis of the terminal phospho anhydride bonds from ATP energy is released, under physiological conditions the Gibbs free energy of ATP hydrolysis has been estimated to be 50-70 kJ/mol. However, this value very much depends on the situation i.e. the type of cell/organism, due to the differing energy levels required for

cellular processes. ATP is used by the cell for hundreds of different processes from DNA replication to muscle contraction to signalling events, among many others.[12–14] It is in constant use and therefore has to be continually remade; it has been estimated that the human body contains around 100-250 grams of ATP at any one time. However, on a normal day of relatively little activity the individuals own body weight of ATP will be hydrolysed for the energy demands of the body.[15] This is a huge turnover and requires the recycling of each molecule of ATP between 500 to 750 times. The hydrolysis process converts ATP back to its primary components ADP and a phosphate group. There are several routes to achieve this constant recycling of ATP. In the human body this consists of three major pathways:

1.*Glycolysis*, provides the breakdown of glucose into pyruvate via a series of 10 enzyme mediated reactions. This mechanism does not require oxygen, is therefore anaerobic and is common to all organisms. The net yield of ATP for this pathway is 2 ATP units per molecule of glucose. However, two molecules of nicotinamide adenine dinucleotide H^+ (NADH) are also produced, each of which can be further converted to 2 molecules of ATP via electron transport chain thus giving an overall net ATP gain of 6.[16]

2. *The citric acid or Kerbs cycle* is the next stage of metabolism and converts the pyruvate into acetyl coenzyme A, which is then used to fuel the Kerbs cycle. The Kerbs cycle is coupled to a process known as the electron transport chain (ETC) which is the true powerhouse of aerobic ATP production. In its most basic form the ETC is a proton gradient system that drives the production of ATP. The combined ATP production of the Kerbs cycle and ETC is 30 molecules of ATP; Thus the total production of ATP from one molecule of glucose is 36 molecules.[17]

l.3. *The β oxidation pathway*. This is the catabolic process by which fatty acids are broken down by the mitochondria to generate acetyl coenzyme A, NADH and flavin adenine dinucleotide (FAD) which is a redox factor and plays a role is several reactions of metabolism including in the ETC. There are several different mechanisms due to the variety of different fatty acids available to the body. The yield for each oxidation cycle is on average around 14 ATP molecules; therefore for a fatty acid such as palmitate, which has a 16 carbon chain, has a net total of 129 ATP molecules are produced per

fatty acid molecule. This shows how efficient an energy storage system fats are and why hibernating animals can survive a winter on fat reserves alone.[18]

In summary; without ATP life could not exist. It is a molecule that seems perfectly-designed of the purpose for energy transfer and serves a critical role in providing the energy requirements for many classes of metabolic reactions that occur in all forms of life. Even viruses rely on the same ATP molecule to that used in humans. The ATP energy system is quick, highly efficient, produces a rapid turnover of ATP, and can rapidly respond to energy demand changes. This once again shows the importance of phosphorus to the life cycle and why sources of phosphorus, usually in the form of phosphate, are vital or all organisms.

1.2.3 Phospholipids

The final phosphorus-containing compounds of biological importance to be discussed are that of phospholipids. Phospholipids along with DNA and ATP can be seen as some of the most important molecules in biochemistry. They are indispensable for life and are abundant in humans. In 1884 Dr J.L.W Thudicum described Phospholipids thus "*Phospholipids are the centre, life and chemical soul of all bioplasm whatsoever, that of plants as well as animals*". This statement shows that even over 130 years ago the importance of these key molecules was appreciated. In the human body phospholipids are required to perform a variety of roles that are vital in maintaining homeostasis and therefore the health of the body over a sustained period of time. These roles vary from structural, biochemical and functional for both animals and plants. Phospholipids are amphipathic molecules that contain a hydrophobic tail consisting of one or two fatty acid chains on either a glycerol or sphingosine backbone. Phospholipids based on glycerol are known as phosphoglycerides and are by far the most common substituent of cell membranes. These consist of a hydrophobic tail of fatty acid ester (R_2 and R_3) attached to two of the alcohol groups of the glycerol at the sn1 (primary alcohol position) and sn2 position (secondary alcohol position). The sn3 position of the glycerol forms the hydrophilic head of a phosphonate ester, which is attached to one of several alcoholic moieties' including the amino acid ethanolamine, choline, serine, glycerol, or inositol (R_1) (Figure 1.3).

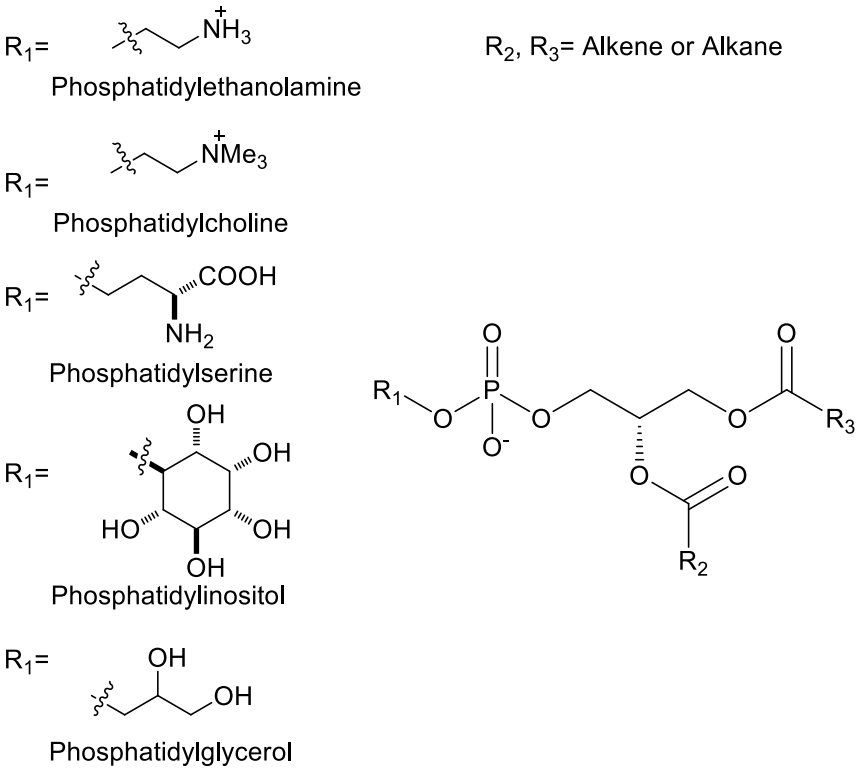


Figure 1.3: Common forms of phosphoglycerides found in cell membranes.

The amphipathic nature of phospholipids such as phosphatidylcholine means that they can self-assemble via the hydrophobic effect into a variety of different shapes governed by the type of phospholipid. In most complex life forms this takes the shape of a lipid bilayer that forms the cell membrane of all cells. In aqueous media such as that in the body, the hydrophobic tails of both layers face each other and *cis* unsaturation in the fatty acid tails causes a kink in one of the fatty acids. The variety in length of the fatty acid chain, affects how the lipids pack against one another, which in turn affects the fluidity and shape of the membrane, and therefore the cell itself. The hydrophilic phosphonate head groups assemble on the outside of the bilayer and favourably solvate in the aqueous media on both the exterior and interior of the cell. This self-assembly property allows the formation of the bilayer into the most energetically favourable structure, which also has the ability to self-repair making it ideal as a structure for cell membranes.[19,20] The lipid bilayer acts as a barrier that keeps ions (e.g. Na^+), proteins and other molecules localised and prevents them from diffusing into the extracellular space. Lipid bilayers are ideally suited to this role as they are impermeable to most water-soluble molecules. They are particularly impermeable to ions, therefore

allowing a cell to regulate salt concentrations and *pH* of the cell interior by transporting ions across their membranes using proteins called ion pumps.

Sphingomyelin (Figure 1.4) is an example of a phospholipid that is found in membranes but is not derived from glycerol.[21] The backbone of sphingomyelin is sphingosine, an amino alcohol that contains a long, unsaturated hydrocarbon chain. In sphingomyelin, the amino group of the sphingosine backbone is linked to a fatty acid by an amide bond rather than an ester bonds. In addition, the primary hydroxyl group of sphingosine is esterified to give a phosphorylcholine, phosphoethanolamine or phosphoserine. Sphingomyelin phospholipids share many of the same features as their glycerol based counterparts and typically make up 10-15% of human cell membrane. However, they have been found to be present the membrane of the myelin sheath that surrounds some nerve cell axons in much higher proportions.[22] Recently evidence has been growing that these phospholipids play a specific roles in many biochemical processes, from apoptosis to cellular senescence as well as being vital in many cell signalling pathways.[23–25]

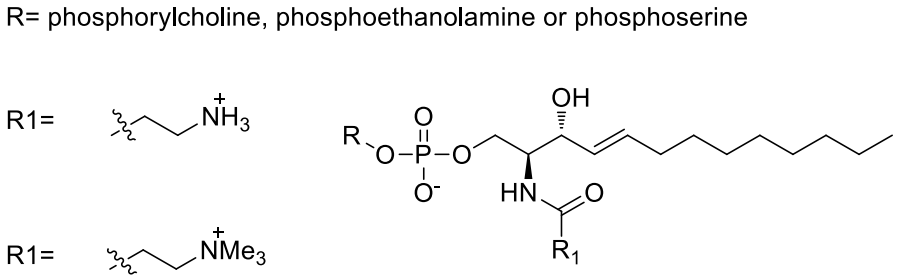


Figure 1.4: The structure and different head groups of sphingomyelin phospholipids

In summary, phospholipids again help demonstrate the vital role that phosphorus and especially the phosphate group plays in nature. They provide a well-regulated environment for a cell to carry out its functions. The self-repair mechanism of the hydrophobic effect means that not only does the cell membrane act a barrier to maintain the correct conditions for the internal workings of the cell but it also adds resistance to the cell to certain levels of damage and stress. These molecules also play a role in many other vital biochemical processes for living organisms. What has not been discussed in this brief overview of phospholipids is the new ways that scientists are devising to use phospholipids. These versatile molecules are currently being investigated for their

potential in lipid nanotechnology, either as novel drug delivery systems or nano-photonic systems.[26,27]

1.3 Organophosphines

The definition of organophosphorus compounds can be quite ambiguous due to different classifications as to what such compounds should contain. These classifications depend on which branch of chemistry is under discussion. In industrial and environmental chemistry an organophosphorus compound need only contain a phosphorus bound to an organic molecule; this can therefore means that there does not necessarily have to be a phosphorus–carbon bond and thus can include compounds such as phosphates in this definition. One of the most versatile and widely utilised organophosphorus compounds known are the phosphines. They have found wide spread use as ligands in metal complexes allowing many organometallic catalysed reactions to occur by functioning as labile ligands. The use of organophosphorus in synthetic organic chemistry and the role these reagents play in a number of named reactions will be discussed. Triphenyl phosphine (PPh_3) is perhaps the most useful in the sense of being a ligand but also as a reagent for a number of different classical organic named reactions.

1.3.1 General Properties of Phosphines

Phosphines or phosphanes are trivalent molecules with the general formula PR_3 (R=H, alkyl or aryl groups). The simplest phosphine is PH_3 which is an inorganic compound due to the lack of carbons and is a highly reactive and difficult to handle. This section will describe the organophosphine derivatives in which R= alkyl and aryl groups. The phosphorus atom of phosphine has a formal oxidation state of 3; due to this oxidation sate, the structure of these molecules and the position of phosphorus in the periodic table (one below, but the same group as nitrogen) phosphines are can be viewed as analogous to amines. They have the same pyrimidyl shape though have smaller bond angles, which depend on the R group but are rarely larger than 109.7^o (P^tBu_3). The smaller bond angles are due to the difference in valencies compared to say the analogous nitrogen equivalents due to access to 3d orbitals. Therefore, the phosphorus

orbitals contain less hybridisation compared to the sp^3 orbitals of the amine equivalent if there is no hybridisation the bond angle would be 90^o. This is exemplified by the differing bond angle of P-H in PH_3 (93.3^o) and NH_3 (107.0^o). They have shown to be weaker bases then their equivalent amines apart from when an aromatic group such as a phenyl group, as the lone pair of the nitrogen is able to partially delocalise into the ring while the lone pair on the phosphorus does not. This is shown by the pKa of the quaternary phosphonium ion of PPh_3 ($pKa\text{-}H = 2.23$) compared to triphenyl ammonium ($pKa\text{-}H = -5$).[28]

The comparison to amines continues in the reaction profile of phosphines. Their chemistry is dominated by their strong nucleophilicity such as the formation of quaternary salts with alky halides. Another important feature that governs much of their reactivity is their high oxophilicity. Phosphorus likes to form strong bonds to oxygen, and thus much of the chemistry of phosphines is dominated by them acting as reducing agents. They can stabilise ylides as well as make good leaving groups, allowing them to behave as effective reducing reagents. Some of these reactions will be described in detail later in this thesis. The other main use is as ligands for organometallic complexes acting as catalysts. The most widely utilised example of a phosphine is that of triphenyl phosphine (PPh_3), consisting of three phenyl rings attached to the phosphorus atom. This particular derivative plays a role in a wide variety of useful reactions and its use forms the basis of majority of the new work that is presented and discussed in later chapters.

1.3.2 Transition-Metal Phosphine Complexes

Ligands in organometallic complexes are ions or molecules that bind to a metal centre to form a metal coordination complex. Ligands are seen as Lewis bases as a metal-ligand bond involves a donation of electrons to the metal centre. There are two main types of Lewis basic electron donation; either one electron (X type ligand) or two (L type ligand), this donation can also be either covalent or ionic in nature. Phosphines as ligands have been known since Hofmann's first preparation of triethylphosphine, arsine platinum and gold complexes in 1857. The coordination of phosphines is dominated by the donation of the lone pair of electrons forming strong sigma covalent bonds to metal

centres and as such are ideal candidates for ligands for metal complexes that can be tuned to perform some useful chemistry such as small molecule activation.

Phosphines since their early introduction as coordination ligands have become some of the most widely utilised ligands, with hundreds of different phosphine ligands being developed in order to meet the needs of researchers. The majority of the bestselling homogenous catalysts reported to date contain a phosphine ligand. This is because they make the metal complex more lipophilic and thus dissolve better in organic solvents; they also are compatible with a wide range of transition metals and a wide range of oxidation states on those metals. It is for these reasons that the metal phosphine combination has been utilised repeatedly in homogeneous catalysis.[29] It is relatively simple to tune the metal centre's electronic and steric properties by changing the phosphine ligand in a systematic and predictable way. They vary a lot in their steric bulk and electronic character, and are well studied. This variability in properties of phosphines can be seen between the alkyl phosphines such as trimethyl phosphine (PMe_3) and aryl phosphines such as PPh_3. Both PMe_3 and PPh_3 donate electrons to the metal centre in a dative sigma fashion by donating a lone pair of electrons to an empty *d-orbital* of the metal centre (L type ligand). However the electronics properties can differ according to the electronegativity of the R groups of the phosphine.

Generally phosphines make poor π acids but the electronic nature of the R groups can have some effect on the phosphines ability to allow π-backbonding from the metal to the phosphine through the P-C antibonding (σ*) orbital. It was originally thought that the π-backbonding occurred from the metal to the phosphorus's empty *3-d* orbitals, but it has since been accepted that these orbitals are too high in energy.[30] A study by Orpen and Connelly has shown that phosphines with more electron withdrawing R groups (such as aromatic groups) have increased backbonding due to increased phosphorus *p*-orbital character in the σ* antibonding orbital of the P-C bond of the R group.[31] Therefore, the σ* antibonding orbital is more stable and lower in energy, which makes it a better acceptor of electrons. This increase in backbonding is shown by a lengthening of the of the P-C bond of the phosphine and the aryl group. This suggests that the backbonding of metals to phosphines is a sigma bond weakening donation. However, this effect is often hidden by shortening of the P-C bond due to the sigma donation from

the P lone pair to the metal, and the consequent decrease in P(lone pair)–R(bonding pair) repulsions.

The R groups also affect the steric bulk of the phosphine and thus the coordination sphere around the metal centre. The number of phosphine ligands that a metal can accommodate is restricted due to the steric bulk of phosphines ligands such as PPh_3. This means metal complexes with phosphine can break the 18 electron rule as no space for further ligands is present. The steric bulk of a ligand can measured by a parameter called ligand cone angle, first introduced by Chadwick A. Tolman and often referred to as Tolman cone angles (ɵ) as they are often used to describe phosphine ligands.[32] This parameter of steric measurement was originally proposed to help categorise the effects of the steric bulk of phosphorus ligands such as the phosphines. Phosphines with wider cone angles have increased steric bulk and are often vital in oxidative addition steps of many catalytic cycles; also the bulkier the phosphine are the more likely it is to be involved in dissociation events. Phosphine ligands have been employed with success in many cross-coupling reactions such as in the Heck reaction and the Buchwald–Hartwig amination.[33,34]

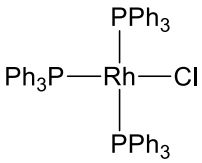
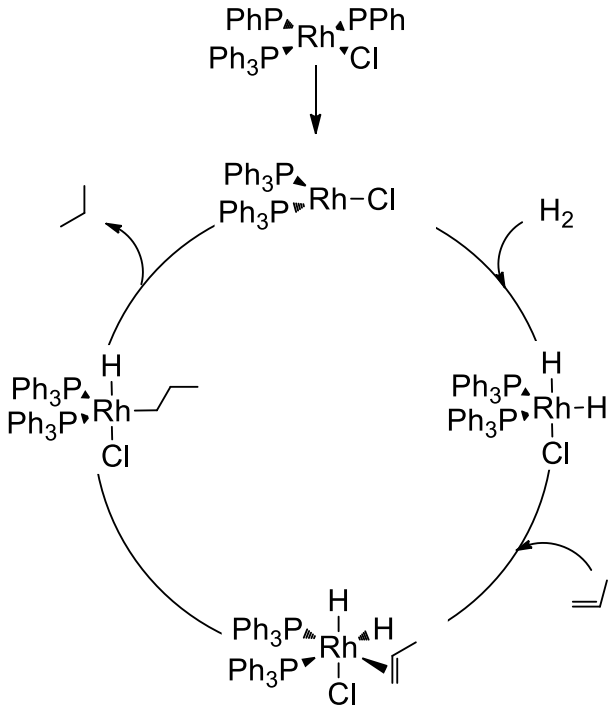


Figure 1.5: Wilkinson's catalyst

More often than not phosphines can be seen as spectator ligands even though they impart their electronic and steric character on the metal centre they rarely participate in the reactions of the metal complexes other than by dissociation. A classical coordination complex of phosphine and one of the first homogeneous catalysts to be discovered is that of $[RhCl(PPh_3)_3]$ better known as 'Wilkinson's catalyst' (Figure 1.5).[35] This complex is a square planar, 16 electron structure and can be synthesised from the reaction of rhodium (III) chloride with an excess PPh_3 in refluxing ethanol. The PPh_3 helps to stabilise the Rh(I) metal centre as a 16 electron complex rather than 18 electron complex. Wilkinson's catalyst was the first hydrogenation catalyst and is a well-studied

system. Under the conditions of 1 bar pressure of H_2 and a temperature of 298 K it can carry out hydrogenation of a multitude of different alkenes.

When the complex is dissolved in an organic solvent such as ethanol or benzene and under 1 atmosphere of H_2 one of the PPh_3 groups is replaced by a molecule of H_2. In this oxidative addition step, the H–H bond brakes forming a five-coordinate complex with two hydrides coordinating the rhodium atom acting as X type ligands. The complex now has a coordination site free in which an alkene can bind to form a 6-coordinate 18 electron complex. Rearrangement can then occur, in which the one of the hydrides inserts in to the alkene bond in a migratory insertion step. Finally the other hydride migrates to the alkane, which immediately gets eliminated in a reductive elimination step to give the release of the alkane so that the cycle can then start over (Scheme 1.1). Asymmetric hydrogenation can be performed with a modified Wilkinson's catalyst in which a chiral phosphine or chiral bidentate phosphine can be employed.[36]

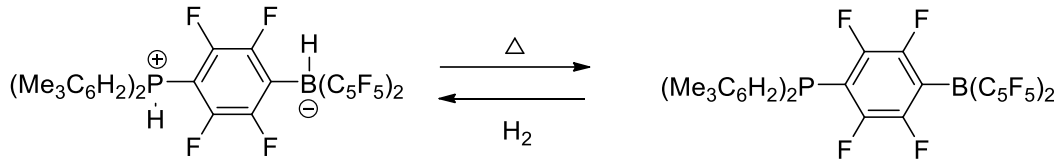


Scheme 1.1: Catalytic cycle for the hydrogenation of alkenes by Wilkinson's catalyst.

1.3.3 Frustrated Lewis Pair Chemistry.

The formation of Lewis acid base pairs is a classical concept that underpins much of the reactivity of main group chemistry including both stoichiometric and catalytic organic transformations, as well as forming the basis of coordination chemistry in the binding of ligands to transition metal centres. The observed chemistry can be explained and predicted via the interaction of Lewis basic and Lewis acidic sites in a donor-acceptor fashion. Frustrated Lewis Pair (FLP) chemistry is a strategy that has emerged in the last 10 years as a powerful and intriguing concept that allows for the activation of small molecules such as H_2, alkynes and CO_2. The concept of FLP chemistry relies on the use of main group compounds which contain Lewis basic and acidic properties but are so sterically encumbered it prevents the formation of Lewis acid/base adducts. The Lewis acid and base components work in unison to activate small molecules such as H_2. The concept behind FLP's was actually envisioned in the late 1960's as this quote by Halpern alludes to whist discussing the activation of H_2 by transition metal ions and complexes; '*To be effective, the two functional groups must be so disposed that they can interact simultaneously with a hydrogen molecule, but at the same time are prevented from interacting with (neutralizing) each other'*.[37]

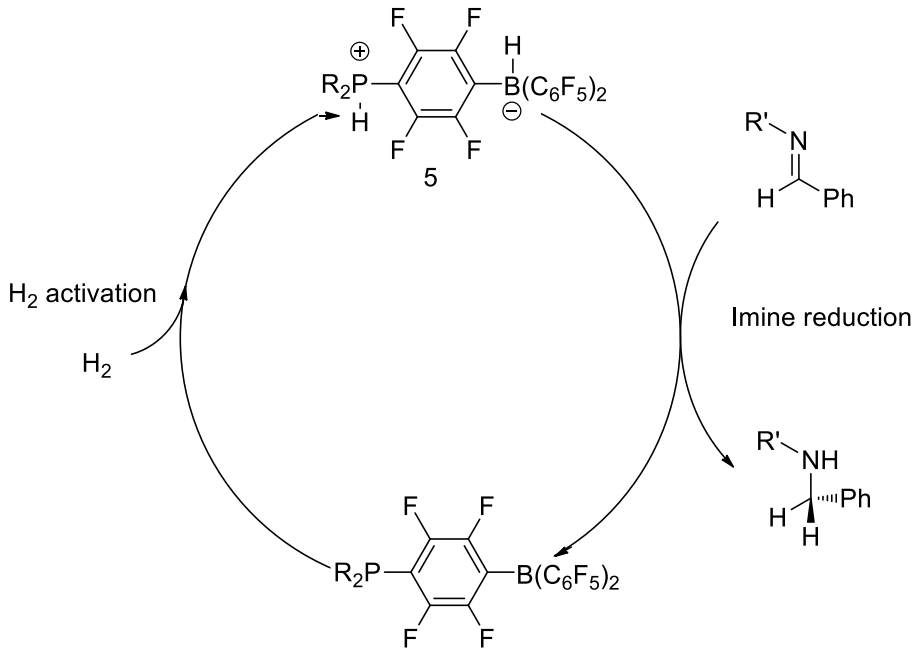
It was not until Pioneering work from Douglas W. Stephan's *et al.* in 2006 and 2007 that this concept became a reality. The results of these works have been summarised in a 2008 review,[38–40] paved the way for a flurry of research activity that lead to Stephan's original 2006 paper entitled revisable metal free hydrogen activation to be cited over 800 times in 10 years. In Stephan's pioneering work it was shown that the thermal liberation of H_2 was possible when complexes of phosphonium borane salt **3** were heated to temperatures above 100 ^{o}C H_2 was released to give complex **4**, upon cooling back to 25 ^{o}C in an atmosphere of H_2 the phosphonium-borane salt **3** was reformed (Scheme 1.2).[41] In these complexes the lone pair of the phosphine acts as the Lewis base and the empty *p*-orbital of the borane acts as the Lewis acid component.



3 4

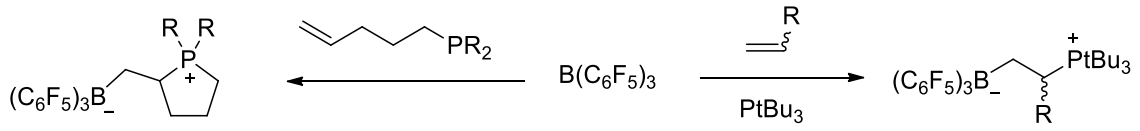
Scheme 1.2: Stephan *et al's* first example of FLP activation of H_2.[39]

The same body of work also tried to speculate on the mechanism of such a process via use of deuterium labeling studies. Although results were deemed to be inconclusive it was suggested that the most likely mechanism for such a process for the heterolytic cleavage of H_2 first involves initial interaction of H_2 with the boron atom followed by proton migration to the phosphorus atom. In a follow up paper which Stephan and Welch released the following year it was demonstrated that H_2 activation could be achieved via the use of separate phosphine and borane complexes and it wasn't required that both Lewis basic and acidic parts needed to be part of the same compound.[42] Toluene solutions of stoichiometric mixtures of R_3P (R= ^{t}Bu or $C_6H_2Me_3$) with $B(C_6F_5)_3$ were shown not to form the classic Lewis pair adducts due to the bulkiness of the phosphine. Upon exposure to one atmosphere of H_2, the frustrated Lewis pair adduct formed with the hydrogen split between the phosphine and the boran. However, this system would not release the H_2 again even upon heating to over 150 ^oC, as in the intramolecular adduct **3** described above. The combination of the two papers described above demonstrated that a relatively simple, facile, mild and metal-free system could be used in the heterolytic cleavage of H_2.



Scheme 1.3: Catalytic cycle for the reduction of imine using Stephan's *et al.* frustrated Lewis pair strategy.[38]

Whilst the concept of being able to reversibly release hydrogen with such complexes is an interesting one, it is the potential applications such as metal free hydrogenation reactions that have received the most amount of attention. Stephan *et al.* first employed such systems for the metal-free hydrogenation of a number of different function groups.[38] The reduction of imines and nitriles is a common method to access amines and is used throughout the pharmaceutical and chemical industries. It was demonstrated that intramolecular phosphonium borate salts of general formula $(R_2PH)(C_6F_4)BH(C_6F_5)_2$ (**5)**, where R=2,4,6-MeC_6H_2 or *t*-Butyl, are both air and moisture stable. It was shown that these compounds could successfully hydrogenate carbon-nitrogen multiple bonds, in high yields at relatively mild temperatures (80-140 ^oC) (Scheme 1.3).[39,42] A common requirement, for the success of these reactions was the inclusion of a large group on the nitrogen, as reduction of a less hindered imine afforded an amine that bound tightly to the borane centre of the phosphino–borane, precluding further H_2 activation. This problem of catalyst deactivation in systems where the imine was not sufficiently bulky could be prevented via coordination of the nitrogen to a strong Lewis acid such as $B(C_6F_5)_3$.



Scheme 1.4: Activation, both intramolecular and intermolecular activation, of olefins by frustrated Lewis pairs of phosphines and boranes.[43]

Stephan *et al.* also showed that sterically hindered Lewis acid-base pairs of phosphines and the borane $B(C_6F_5)_3$ exhibited unprecedented reactivity with alkenes, and undergo both intermolecular additions as well as intramolecular cyclisation (Scheme 1.4).[43] They demonstrated that sterically demanding phosphines and boranes react with olefins to give alkanediyl-linked phosphonium borates. These three-component reactions were surprising given that neither tertiary phosphines nor tertiary boranes are known to react with olefins. Since the initial paper, there have been a number of studies investigating the activation and hydrogenation of small molecules utilising Frustrated Lewis Pair chemistry in particular hydrogenation of alkenes in a catalytic manner.

Stephan *et al.* demonstrated that the use of frustrated Lewis pair systems that at first indicated little or no activation of H_2 at room temperature could in fact be used as an effective method for the hydrogenation of alkenes. By carrying out the NMR spectroscopic studies at reduced temperatures, they showed H_2 activation at -80 ^oC, whilst at room temperature H_2 was released. This system was then exploited to catalytically hydrogenate alkenes at 25-70 ^oC (Figure 1.6).[41] This example provided the lowest energy barrier for hydrogen activation that was known at the time for metal free H_2 activation. The low temperature loss of H_2, in part due to the increased Brønsted acidity of the cation formed at the phosphorus centre, led to the hydrogenation of olefins. It was demonstrated that mixtures of $(C_6F_5)Ph_2P$ and $B(C_6F_5)_3$ in 0.2 molar equivalents are capable of hydrogenate 1,1-diphenylethene (**6**) to compound **7** at room temperature in quantitative yield within 24 hours. A number of other electronic-deficient sterically hindered Lewis basic phosphines were also investigated along with the hydrogenation of a variety of different alkenes, finding that in general the system worked well though careful tuning of the electronic properties of the phosphine could be important in determining success. The success of the process is due to the FLP activating and then releasing hydrogen in an equilibrium process at such a fast rate at room temperature that it looks as if no reaction is happening on the NMR time scale. Addition of the alkene intercepts this process, thus allowing hydrogenation to proceed.

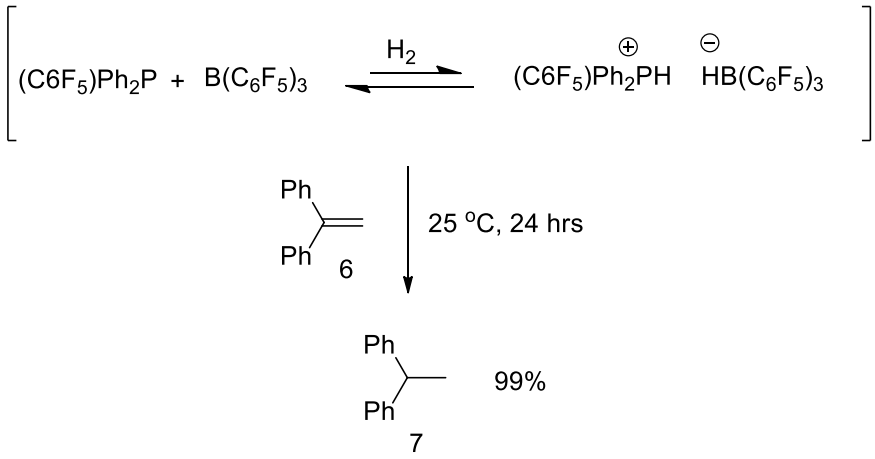


Figure 1.6: Hydrogenation of alkenes using low temperature FLP.

In summary; this brief review of just a few aspects of FLP chemistry demonstrates that it offers considerable potential in the field of metal-free activation of small molecule with in which further and more complete reviews can be found.[40,44,45] Phosphines have played a significant role in the development of this new and exciting chemistry and once again show the versatility of these remarkable reagents, but there are more classical chemistries that phosphine reagents offer to the synthetic chemist.

1.4 Phosphine Mediated Organic Synthetic Reactions.

Much of the field of organophosphorus chemistry is dominated by the reactions of tertiary phosphines. These reagents have gained much attention in the synthetic organic chemistry as versatile chemical reagents for functional group transformations and in their ability to mediate the formation of carbon-carbon and carbon-heteroatom bonds. A tribute to their success can be seen in a number of classic named reactions that have been in continuous use since their discovery. As alluded to at the beginning of section **1.3.1** the chemistry of phosphines is dominated by several properties: strong nucleophilicity but low Brønsted basicity, a polarisable lone pair of electrons, high oxophilicty and the ability to stabilize ylides. These properties mean that they can be used in a number of contexts.

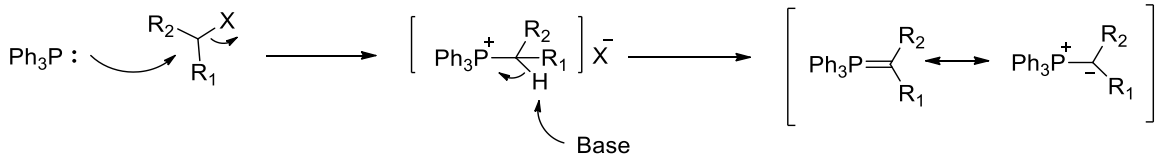
1.4.1 The Wittig Reaction: a Phosphine-Mediated Olefination.[1,46,47]

The Wittig reaction was first presented by Georg Wittig in 1954 who was subsequently awarded the Noble prize in Chemistry in 1979 for "*his development of the use of phosphorus containing compounds*".[1,47,48] Classically the reaction is a carbon-carbon alkene-forming reaction between an aldehyde or ketone (**9**) and a phosphine derived ylide (**8)** resulting in alkene product (**10**) and phosphine oxide (Scheme 1.5). Wittig first discovered this reaction when he was investigating the chemistry of pentavalent phosphorus, describing the reaction between methylenetriphenylphosphorane ($Ph_3P{=}CH_2$) and benzophenone. With the formation of $O{=}PPh_3$ and diphenylethene Wittig realised the significance of the reaction and consequently performed a systematic study on a number of different phosphoranes and carbonyl compounds.[49,50] The formation of double bonds using this method has since become known as the Wittig reaction and is now a widely used and effective method for the synthesis of alkenes.

8 9 10

Scheme 1.5: Classic Wittig reaction between a phosphine ylide and aldehyde or ketones.

The active species in the Wittig reaction is the phosphorus ylide/phosphorane, otherwise known as a Wittig reagent. Wittig reagents are usually prepared through reaction of a triaryl/trialkyl phosphine reacting with an alky halide in which the phosphine lone pair of electrons attacks the electrophilic alkyl halide forming a quaternary salt **(11)** in a S_N2 process. The mechanism of this first step means that less sterically hindered alkyl halides react more favourably. Strong bases such as butyl lithium are usually required to deprotonate the proton at the alpha position in order to form the ylide. A phosphorus ylide can be considered to be a combination of two resonance structures (**12)**, one contains a double bond to the phosphorus, otherwise known as a phosphorane, and a zwitterion complex in which the phosphorus is positively charged and the α-carbon is negatively charged (Scheme 1.6).

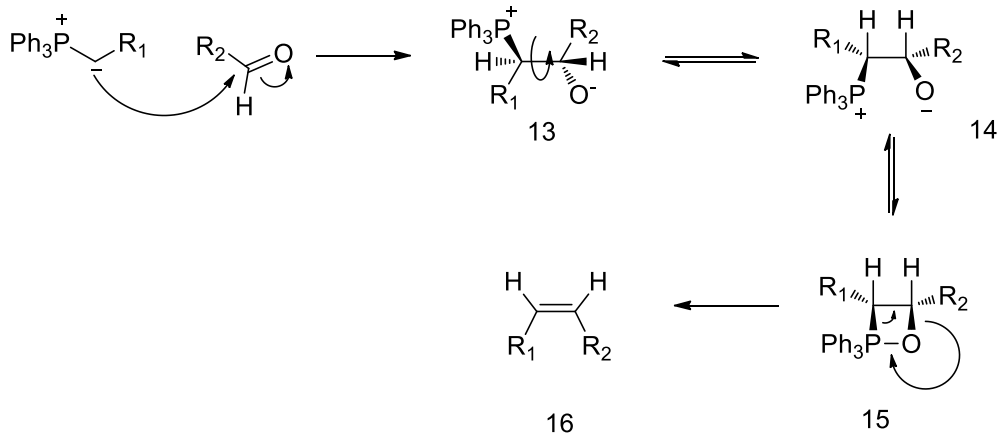


Scheme 1.6: The general synthesis and resonance structures of phosphorus ylides.

Ylides are water and oxygen sensitive and react preferentially with aldehydes over ketones. Phosphine ylides can be found in three different varieties which depend on the R^1 and R^2 groups. Stabilised ylides have a group at the R^1 or R^2 position that can stabilise the negative charge i.e. a strongly electron-withdrawing group such as esters; election-withdrawing aryl groups on the phosphine can also help in this regard. Semi-stabilised ylides have at least one of the R^1 or R^2 groups as an aryl or alky group which imparts a less stabilising effect of the negative charge and finally non-stabilised ylides which have only alkyl groups which don't stabilise the negative charge at all. The different types of ylides can affect the *E/Z* stereoselectivity of the reaction. Stabilised ylides, when performed under salt free conditions in dipolar aprotic solvents, result predominantly in *E*-alkenes. Non-stabilised ylides under the same conditions give predominantly in *Z*-alkenes. Semi-stabilised ylides under the same conditions result in mixtures of *E* and *Z*-alkenes.

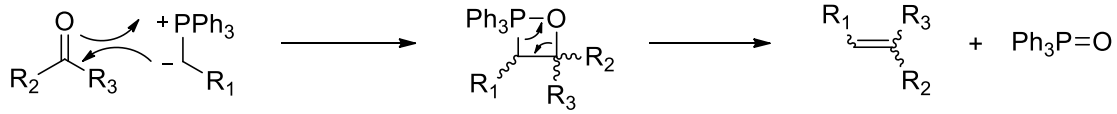
There have been a large number of proposed mechanisms for the Wittig reaction with the exact mechanism still under some debate. Classically the steric bulk of the ylide influences the stereochemical outcome of nucleophilic attack of the negatively charged ylide with the carbonyl group of the aldehyde or ketone. The resulting betaine (**13**) has the negatively charged oxygen and the positively charged phosphorous *anti* to one another. The same can be said for the two R groups. The next stage involves carbon-carbon bond rotation resulting in the phosphorus and oxygen ions being in the same plane (**14**) resulting in the formation of a strong oxygen phosphorus bond in a oxaphosphatane (OPA) (**15**). This then collapses to form the *Z*-alkene (**16**) and phosphine oxide (Scheme 1.7). For Wittig reagents which are relatively simple and non-stabilised the RDS is the bond rotation. If however, the ylide is stabilised the rate determining step is the initial step or the nucleophilic addition of the ylide to the

carbonyl group. This therefore, reduces the rate of alkene formation, leading to a higher proportion of *E*-isomer being formed.



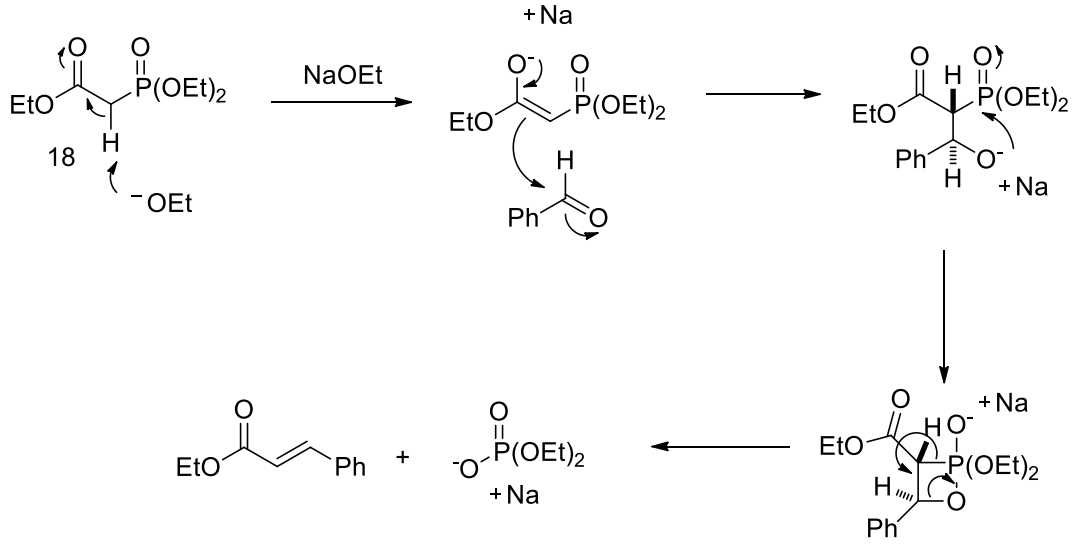
Scheme 1.7: Classic interpretation for the formation of *Z* alkenes via the Wittig reaction mechanism.

The modern interpretation of the mechanism as presented by Byrne and Gilheany in a Chemical Society Review presents substantial evidence that there are two major mechanistic pathways; the Li salt free mechanism (well known) and the Li salt mechanism (still little understood).[51] The lithium salt free mechanism is currently better understood: the formation of the alkenes proceeds in a 2 step mechanism, with the first step involves the formation the OPA **17** and this process is under kinetic control. Therefore, the stereochemistry is defined upon the formation of the C-C bond forming step. The OPA formation is believed to be a (2+2) cycloaddition between the double bond of the carbonyl group and the ylide, this forms the OPA directly and thus the stereochemistry is formed during the C-C bond formation of the (2+2) cycloaddition, rather than through the betaine and bond rotation suggested in the classical mechanism (Scheme 1.7). The second step is formation the alkene via decomposition of the OPA in a stereospecific manor. The varying shapes of the (2+2) cycloaddition transition states are responsible for the resulting stereoselectivity of the alkenes. The higher *E*-isomer selectivity of stabilised and semi-stabilised ylides is determined by a preference to form the *trans*-OPA which then goes on to decompose to form the *E*-alkene.



Scheme 1.8: Modern interpretation of Wittig reaction: 2 step mechanism; 1. 2+2 cycloaddition to form OPA followed by decomposition to form alkene and phosphine oxide.

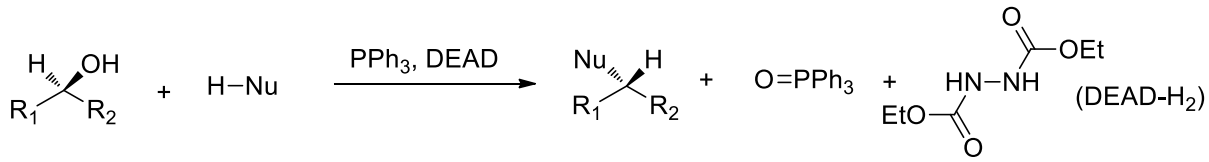
Since the discovery of the Wittig reaction it has become the method of choice for the formation of alkenes. There have been a number of important modifications that have allowed a greater degree of control over product stereochemistry. The Horner-Wittig reaction (HW),[52,53] describes the use of phosphine oxides in the Wittig reaction and allows the removal of the phosphorus as a water soluble side product. The use of lithium base salts allows for the formation of stable β-hydroxyphosphine which can be isolated and transformed into the alkene in subsequent steps. The Horner-Wadsworth-Emmons olefination (HWE) involves phosphonate stabilized carbon anions with an α electron withdrawing groups such as **18** (Scheme 1.9).[51] These modifications offer several advantages over the traditional Wittig olefination in that the preparation of the stating alkyl phosphonate is easier and cheaper than that of the phosphonium salts. The reaction is thought to be milder than the Wittig reaction due to the higher nucleophilicity of the phosphonate carbanion compared to the ylide of the classical Wittig reaction.



Scheme 1.9: Synthesis of *E*-isomer of ethyl cinnamate using the HWE reaction.

The stereoselectivity of the HWE and HW reactions generally favour *E*-alkenes, though the product outcome is largely substrate dependent. The larger the R group on the carbonyl with a weakly dissociating bases results increased *E* isomer, whilst the use of small R groups and strongly dissociating bases results in increase formation of the *Z* isomer. The reason for this is still under debate but it seems the most likely explanation is the extra stability of the phosphonate starting reagent results in the reaction in the formation of the OPA being revisable and is not the rate determining step but instead the formation of the phosphorus oxygen bond is. This results in a mechanism by which the OPA diastereoisomer can interconvert between the *syn* and *anti*-transition states. Therefore, the reaction is no longer under kinetic control but thermodynamic. If the rate of the interconversion is faster than the rate of formation of the alkene the stereospecific step will no longer reflect the kinetic ratio of the of the oxaphosphetane diastereoisomers. It seems that the formation of the *trans*-OPA is faster than that of the *cis*-OPA, and so the *E*-alkene is the major product.

1.4.2 The Mitsunobu Reaction[3,46,55]



Scheme 1.10: General reaction scheme for the Mitsunobu reaction.

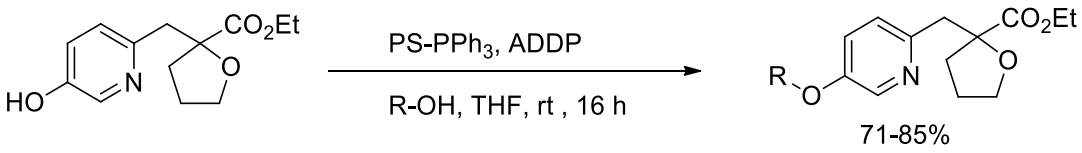
The Mitsunobu reaction (Scheme 1.10) is an important and widely used reaction, in which phosphine plays a central role. It is a versatile reaction, which is utilised for the dehydrative coupling of alcohols with acids or an acidic pro-nucleophile (pKa < 15) via the combination of an azodicarboxylate oxidising agent such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and phosphine which acts as a reducing agent. The Mitsunobu coupling reaction was first reported by Mitsunobu *et al* in 1967 detailing the reaction of benzoic acid with alcohols in the presence of PPh_3 and DEAD giving the corresponding ester in excellent yield.[56] Later it was found that the procedure was general, versatile and could be used with a wide variety of different pro-nucleophiles, offering a route for the substitution of alcohols in an efficient manner.[3] The Mitsunobu reaction is a procedure that has enjoyed great

success over the years being utilised in many synthetic methods; the original paper has since been cited over 500 times (*web of science*) in over 180000 reactions (REAXYS).[57] It has been employed in general organic synthesis and medicinal chemistry; as such there have been a number of detailed reviews.[3,55] The method offers wide substrate scope, stereospecificity and mild reaction conditions for a multitude of different functionalities. One of its biggest advantages is that when chiral secondary alcohols are used as substrates, this results in complete inversion of stereochemistry,[58] unless sterically constrained; this property has been widely applied and often consists a key step in the formation of medicinal and natural product targets.

Tertiary alcohols in general don't react under Mitsunobu conditions but there has been at least one example in which a tertiary alcohol has been reported by Shi *et al*.[59] In this report chiral tertiary alcohols with observed to couple with phenols where complete inversion of the (*S)*-alcohol to the (*R*)-ether. Forcing conditions of 100 ^{o}C in toluene were required resulting in 56% of the ether. Nucleophiles that can be used in this substitution reaction, a whole array of different examples have been demonstrated since its discovery. The only limiting factor in choice of nucleophile or pro-nucleophile is that they must contain either an OH, NH or SH group that has a pKa $\leq$ 15, best results however, are achieved when the pKa < 11. Common nucleophiles include carboxylic acids, phenols, thiols, thiocarboxylic acids and hydroxamates.[60–62] The reaction can be also can be performed in a number of different solvents, however by far the most commonly used is tetrahydrofuran (THF) or toluene.[63]

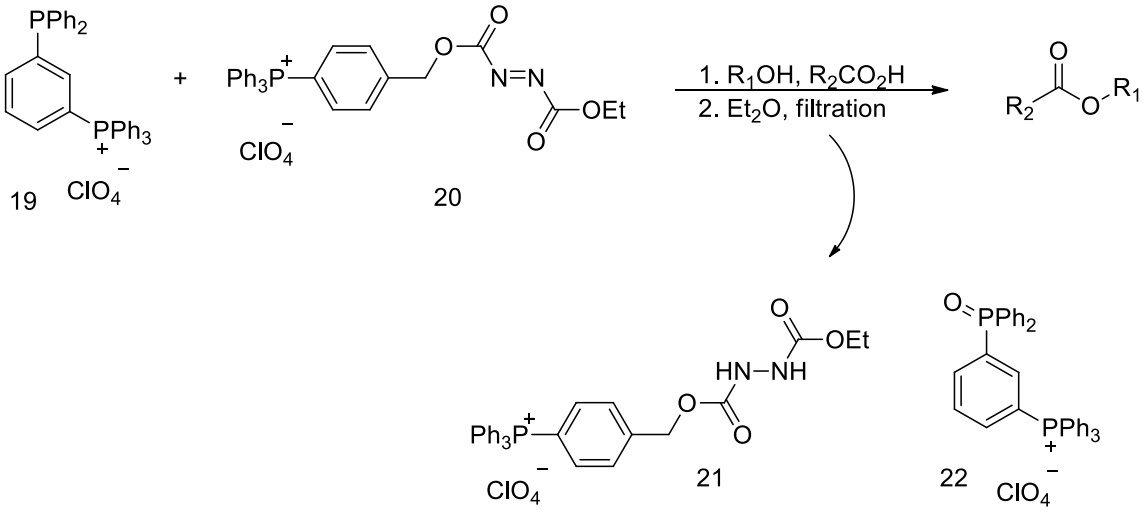
A variety of different phosphines can be employed for this reaction but the most common are PPh_3 and PBu_3. Both of these phosphines are cheap and commerically available. One of the biggest limitations of the Mitsunobu reaction is formation of the phosphine oxide as by-product (as in the Wittig reaction) which can be difficult to remove requiring silica chromatography. However, the Mitsunobu products can often have similar chromatographic behaviour as the oxide and so can be difficult to isolate. The use of solid-phase-resin bound PPh_3 has been shown to be an, effective alternative to PPh_3 and PBu_3. The use of a solid-supported reagent avoids the homogenous formation of phosphine oxide in solution. The immobilised phosphine oxide by-product is simply removed by filtration allowing simple a work up of the resulting solution. Humphries *et al* employed resin bound PPh_3 along with an a alternative azo reagent 1,1'-

(azodicarbonyl)dipiperidine (ADDP) to efficiently couple a series of pyridine-ether PPAR agonists in good to excellent yields, most > +70% of which proved unattainable to synthesise using conventional Mitsunobu procedures (Scheme 1.11).[64]



Scheme 1.11: Humphries *et al* synthesis of pyridine-ether PPAR agonists using solid phase PPh_3 and ADDP.[64]

Alternatively, the use of phosphonium salts has been shown to aid control of by product solubility, thus facilitating product purification and isolation. Tetra-aryl phosphonium perchlorate and hexa-fluorophosphate salts for example, tend to be insoluble in diethyl ether; this allows them to be precipitated from reaction mixtures. Poupon *et al.* demonstrated the use of phosphine reagents containing phosphonium salts in their structure (**19**) can provide comparable yields to those offered by both PPh_3 and solid supported-PPh_3 reagents. With the added advantage of the resulting phosphonium-phosphine oxide salt (**22)** precipitating out upon addition of diethyl ether giving phosphorus free products, as determined by ^{31}P NMR spectroscopic analysis (Scheme 1.12).[65]



Scheme 1.12: Mitsunobu reaction using phosphine and DEAD reagents containing a phosphonium salt allowing solubility controlled removal of hydrazine **21** and oxide **22** by-products.[65]

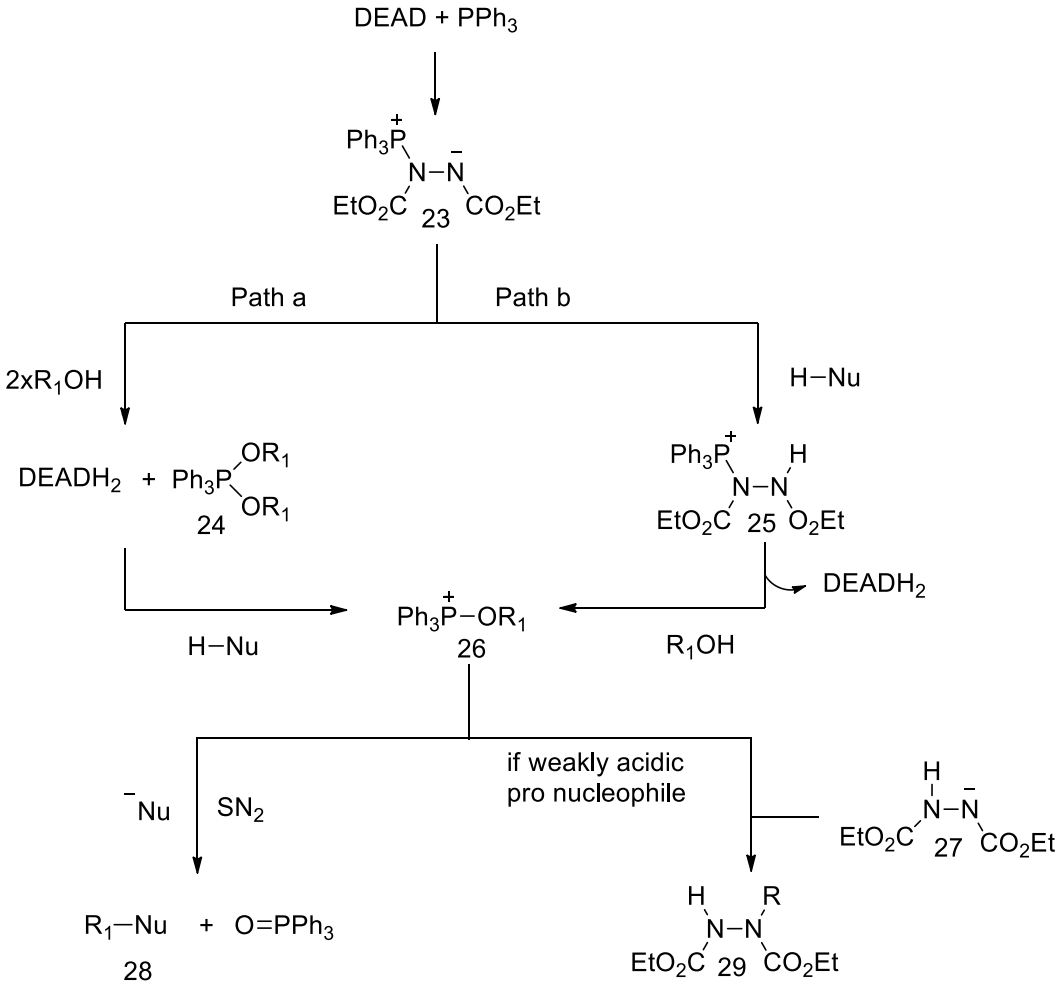
The most common azo-derivatives used in the Mitsunobu reaction are DEAD and DIAD they and often can be used interchangeably as both are commercially available. Another by-product of the Mitsunobu reaction is the hydrazines derived from the

azocarboxylates; again, like the phosphine oxides, these can often contaminate the Mitsunobu product owing to similar chromatographic behaviour. Due to this problem, there has been some interest in the last couple of decades on the development of new DEAD analogues to facilitate purification of the reaction mixture. As part of the same study; Poupon *et al.* developed a phosphonium supported DEAD reagent (**20**) in an attempt to once again precipitate and remove the resulting hydrazine by-product (**21**). The combination of both phosphine analogue **19** and the DEAD analogue **20** led to the complete removal of both unwanted by-products of the Mitsunobu esterification, achieving the Mitsunobu ester product between 2-octanol with 4-nitrobenzoic acid in 89% yield. There are other alternatives to DEAD and DIAD; for instance ADDP as demonstrated by Humphries *et al.* in combination with the solid supported-phosphine (Scheme 1.11) contains strong electron donating piperidine groups in place of -OEt groups of DEAD.[64] This increases the basicity of the resulting anion from the azo moiety allows the use of pro-nucleophiles which have a larger pKa (up to pKa= ~15).

In the generally accepted mechanism as presented by the Kumar *et al.* review.[55] The first step in the Mitsunobu reaction consist of the nucleophilic addition of PPh_3 to DEAD to form the Morrison–Brunn–Huisgen betaine **23** via attack of the phosphine across the N=N.[66] This zwitterionic intermediate **23** contains a positively charged phosphorus and a negatively charged nitrogen. From this intermediate there are then 2 pathways that reactions can proceed by *Path A* involves the reactive intermediate **23** reacting with two molecules of the alcohol to produce dialkoxy-phosphonium species **24** and DEAD-H_2. In presence of the pro-nucleophile species one of the hydroxy groups can dissociate and become protonated, and hence phosphonium salt **26** forms.

In *Path B* the negatively charged nitrogen acts as base to deprotonate the acidic pro-nucleophile resulting in the phosphonium salt **25** and the newly formed anionic nucleophile. The alcohol reagent then attacks the positively charged phosphorus in an S_N2 fashion, displacing the carbamate anion resulting in DEAD-H_2 and alkoxyphosphonium salt **26**. The alcohol group is then activated towards nucleophilic attack; if the pro nucleophile is acidic enough (i.e. pKa < 11) the oxyphosphonium salt **26** undergoes S_N2 attack from the anionic nucleophile resulting in the formation of a strong P=O double bond (which is the driving force for this reaction) and the Mitsunobu reaction product **28** (Scheme 1.13).[3]

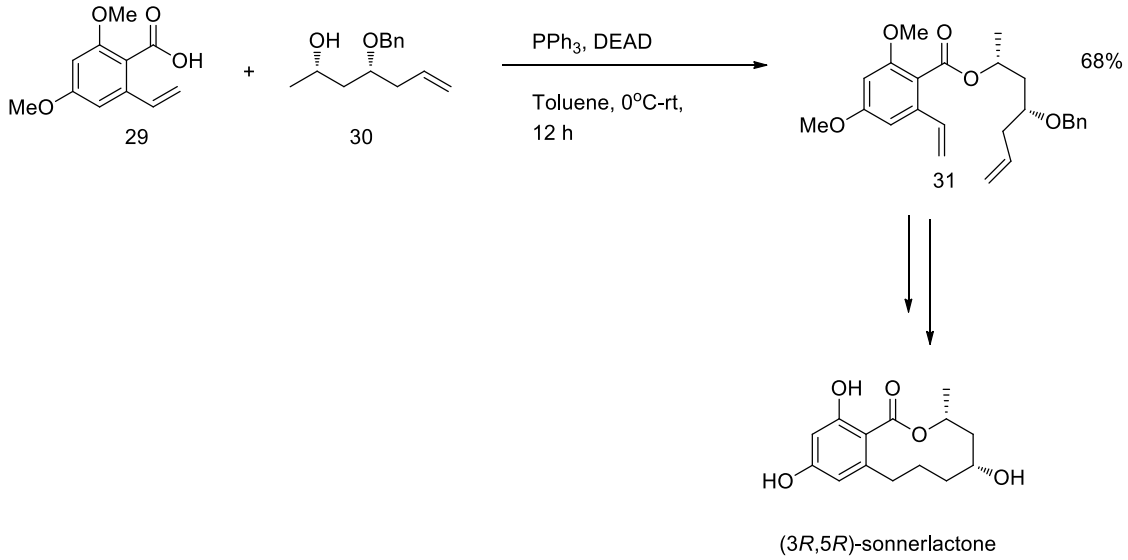
However, if the pro-nucleophile is weakly acidic then a side reaction can occur in which the conjugate base of the azodicarboxylate (**27)** is too weak a base to deprotonate, the pro-nucleophile and instead attacks **26** to form species **29** (Scheme 1.13)**.** To overcome these limitations alternatives to the azodicarboxylate reagent s such as azodicarboxyamides derivatives have been employed e.g. ADDP. The use of ADDP has shown to be effective for pro-nucleophiles in which pKa<15. These modifications to this component of the Mitsunobu reaction, however, can have a detrimental effect on the Michael acceptor abilities of the process and as such often require a phosphine that is more nucleophilic, such as PBu_3.[67]



Scheme 1.13: generally accepted mechanism for the Mitsunobu reaction.

In regards to synthetic applications, there are a multitude of different examples of the use of the Mitsunobu reaction in the total synthesis of natural products and

pharmaceuticals. One such recent example is that of the total synthesis of the macrolactones; (3*R*,5*R*)-sonnerlactone and (3*R*,5*S*)-sonnerlactone which are originally derived from the marine fungus Zh6-B1 found in the bark of *Sonneratia apetala*.[68] these macrolactones show interesting biological activity including anti-bacterial, anti-fungi and anti-cancer properties and therefore have been the focus of a number of total synthesis. Sanabonia *et al.* reported the total synthesis of these two macrocycles with one of the key steps being the stereoselective esterification between acid **29** and secondary alcohol **30** in a 68% yield. The second key step was the ring closing metathesis of the resulting Mitsunobu product **31,** via the use of the 2nd generation Grubbs catalyst.[69]

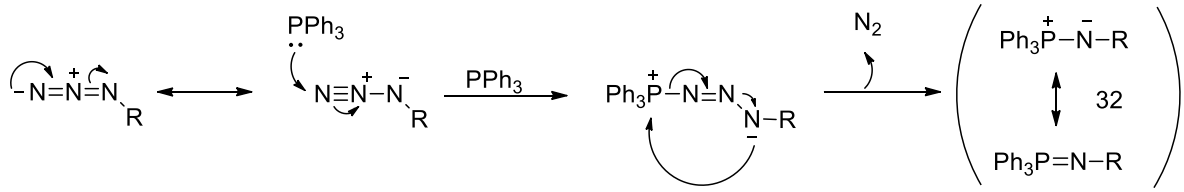


Scheme 1.14: The key Mitsunobu esterification step of Sanabonia *et al.* synthesis of (3*R*,5*R*)-sonnerlactone and (3*R*,5*S*)-sonnerlactones.

1.4.3 The Staudinger Reaction.[4,46]

The Staudinger reaction is an organic redox reaction much like the other phosphine-mediated reactions that have been described so far. The Staudinger reaction converts organic azides to a multitude of functional groups via an intermediate known as an aza-Wittig reagent or phosphazene. The reaction was first reported by H. Staudinger and J. Meyer in 1919 with a follow up paper in 1921.[4,70] The original paper written in 1919, has since been cited 1233 times (Web of Science),[57] giving an indication as to the importance and applicability of this reaction. Classically the Staudinger reaction

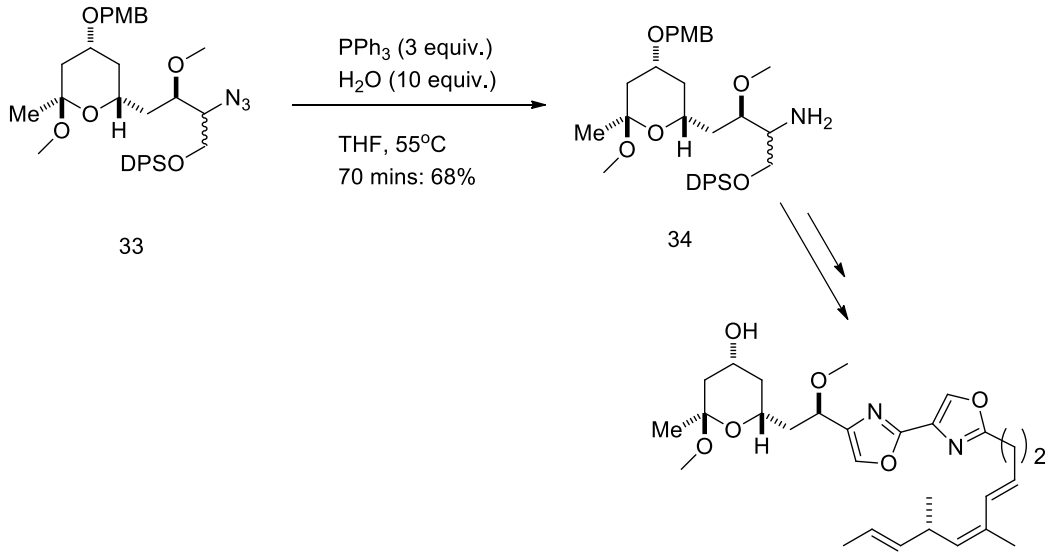
involves the electrophilic addition of an organic azide to an electron rich phosphine with the most commonly used phosphine being PPh_3. This is followed by rearrangement to release dinitrogen gas and form the N=P intermediate (**32**), with the loss of N_2 as the driving force for the formation of the phosphazene (scheme 1.15). The phosphazene that is produced is known as an aza-Wittig reagent due to it structural analogy with a phosphorus carbo-ylide utilised in the Wittig reaction. The process for the formation of the aza-ylide is generally very fast and takes place in almost quantitative yield. It has also been shown that virtually any tri-alkyl or tri-aryl phosphine will undergo the process to form the corresponding phosphazene and the structure of the azide component can also be widely varied. Thus, the resulting phosphazene products provide access to a wide range of versatile synthetic intermediates. Reactions of phosphazenes will be further discussed in chapter 4. For this reason only a brief discussion of the types of aza-Wittig chemistry that can be performed with the products of the Staudinger reaction will be covered here.



Scheme 1.15: Mechanism for the formation of phosphazene intermediate **32** via Staudinger reaction.

The phosphazene intermediate can react in a number of ways. The simplest reaction that aza-Wittig reagents can undergo is with water in a hydrolysis reaction which leads to the formation of the amine. The addition of water can be carried out at the beginning of the Staudinger reaction as it will not affect the formation of the phosphazene intermediate. The Staudinger reaction system has been utilised in a large number of synthetic procedures, in order to install a primary amine within a molecule. The Staudinger reaction for the formation of amines from azides was demonstrated by F. Yokokawa *et al.* in their total synthesis of the antiviral marine natural product (–)-hennoxazole A.[71] In this synthesis the Staudinger reaction was used to convert a secondary alkyl azide **33** to the primary amine **34** by reacting PPh_3 in a THF/H_2O mixture at an evaluated temperature of 55^oC. Primary amine **34** was synthesised in good

yields (68%) and was then acylated in a further reactions to form an oxazole rings present in the natural product (Scheme 1.16).



33 34

Scheme 1.16: Use of azide reduction in the Staudinger reaction for the synthesis of (–)-hennoxazole A.[71]

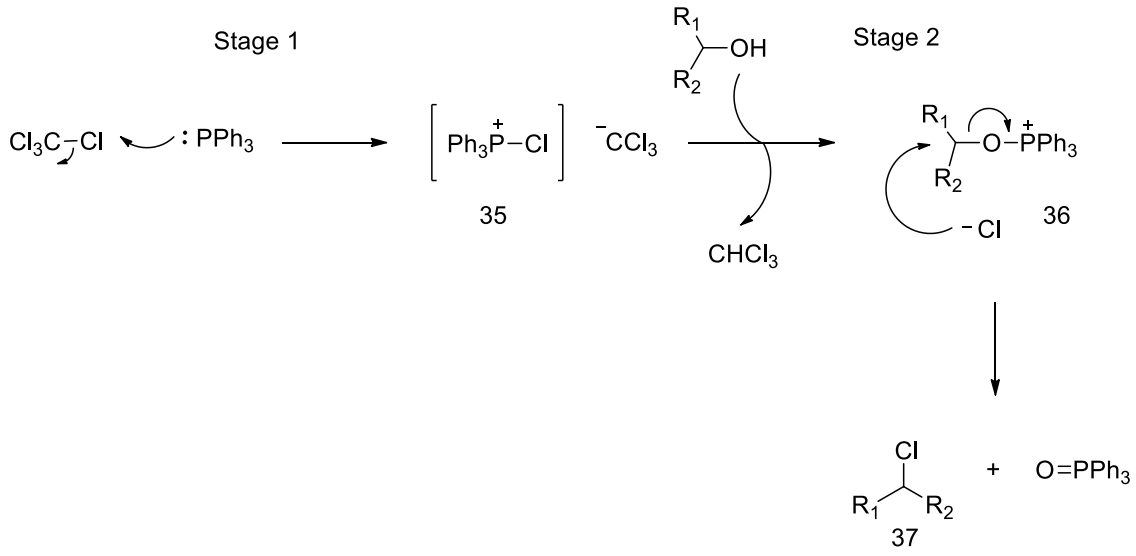
Aza-Wittig reagents formed from the Staudinger reaction can also react with a number of other functionalities allowing access to different products. Perhaps the most widely utilised subsequent reaction, aside from hydrolysis, is that with carbonyl groups such as ketones or aldehydes in order to produce imines. The imines can be reduced to form secondary or tertiary amines using sodium borohydride. This is known as the aza-Wittig reaction from which the phosphazene products get their name (aza-Wittig reagents). Whilst the reduction of the phosphazene with water was observed as early as 1919 by Staudinger and Meyer, the aza-Wittig reaction was not discovered until Wittig's pioneering work on the formation of olefins during the 1950's.[47] Phosphazenes can also react with other diverse functionalities, including epoxides, isocyanates, CO_2 and SO_2 all of which will be discussed in detail in chapter 4.

1.4.4 The Appel Reaction

The Appel reaction is another example of an important reaction in which phosphine plays a central mediating role. The reaction was first reported in detail by Rauf Appel in 1974 with Appel releasing a review on the process a year later which summarised the formation of the key phosphonium salt and its reaction with both alcohols and thiols.[2,72] This process was, however, reported before this time though not in any great detail and

understanding of the underlying principles. The Appel reaction and its modifications have now become a classic and widely utilised method that allows the efficient conversion of alcohols to alkyl halides using the combination of a phosphine and carbon tetra halides. It provides an elegant and simple method for the preparation of alkyl halides which are often key intermediates in many reactions. In terms of chlorination the classic reagent for the Appel reaction is carbon tetrachloride, whilst for bromination reactions carbon tetrabromide or bromine can be used. Iodination using this method require iodine (I_2) to be used as halide donor with imidazole as the base.

The mechanism of the Appel reaction is simple to understand and can be spilt into two distinct steps; first the formation of the intermediate phosphonium salt with a negatively charged carbon tri-halide counterion such as **35** via the combination of triaryl or alkyl phosphines and carbon tetra-halide (CCl_4 or CBr_4). The second stage of the reaction involves the deprotonation of the alcohol or thiol by the CX_3 anion. The resulting oxyanion can participate in an S_N2 attack of the phosphonium intermediate **35** forming an O-P bond and resulting tin the formation the intermediate **36**. The halide counter anion can then participate in a S_N2 substitution, to form the halide product **37** and the strong P=O bond which acts as the driving force for the reaction (Scheme 1.17).



Scheme 1.17: General reaction mechanism for the Appel reaction.

There are two major drawbacks to this reaction; firstly again, the formation of phosphine oxide as a by-product, which can as in the Mitsunobu and Wittig reactions

cause problems with the isolation of the product. This can be addressed by the use of solid phase resin bound phosphines; an example of such a system was shown by Arstad *et al.* in their work on the scope of a newly synthesised polymer-derived resin prepared by ring opening metathesis, ROMP-gel supported PPh_3.[73] After synthesis of the ROMP-gel-PPh_3 in 67% yield over 3 steps, they tested its use in a number of phosphine-mediated reactions including the conversion of alcohols to halides via the Appel reaction. A small library of alcohols was converted into halides by heating a mixture of ROMP-gel-PPh_3 and substrate in a mixture of CH_2Cl_2 using CCl_4, CBr_4 or I_2 as halide source. Chlorides where obtained in excellent yields (89-100%), whereas synthesis of the corresponding bromides and iodides was slightly less efficient (71-74%).

Ley *et al.'s* innovative use of monolith (single continuous piece of uniformly porous material) supported PPh_3 for the conversion of alcohols to bromides offers another alternative in this case using flow micro-reactor technology.[74] Flow chemistry technology is fast becoming a new and exciting tool receiving high levels of investment and development in industry.[75,76] Flow chemistry techniques offer serval advantages over traditional batch chemistry. Often when reactions are scaled up, issues such as exothermic run away and overheating of reactions can occur but this is not so much of a problem in smaller scale. Flow chemistry permits small volumes of the reactants to mix at any one time therefore reducing the risk of exotherm and making the process much safer and easier to scale up whilst still producing large quantities of the product.[77]

Toxic reagents too can be handling in small volumes at any one time, thereby reducing any risks of exposure. Exothermic and endothermic runaways are unlikely due to only small amounts of reactants combing at any one time combined with rapid heat transfer due to large area to volume ratio allowing the controlled heating or cooling of reactions. Mixing of reagents can be achieved far quicker than in batch processes and reactions can be performed at temperatures far above the boiling point of the reaction solvent, reducing reaction times dramatically. Flow chemistry can also allow for multiple step synthesis to be performed by machines with modular designs and modular purification and analysis units. Specific and careful design can lead to the continuous production of target product.

Ley *et al.* used flow chemistry reactor technology for the Appel reaction by first the monolith immobilised phosphine to the active bromine-phosphonium salt via cycling of CBr_4 in CH_2Cl_2 through a tube of the monolith-supported phosphine over a period of 16 hours resulting in a colour change of the colourless phosphine to a light brown. A 0.1 M solution of alcohol in CH_2Cl_2 could then be flowed through the activated phosphine reagent at a flow rate of 0.5 ml/min. For benzyl and sterically unhindered alcohols, it was found that complete conversion to the corresponding bromide was achieved by a single pass through the monolith phosphine with just solvent removal required to give a high yield of the pure brominated product. Less reactive alcohols required a decrease in flow rate and a recycle of the flow system to achieve full conversion. It was also found that a single monolith could be used for many different alcohols with no cross contamination according to ^1H NMR spectroscopic analysis. This method provided improved yields than analogous reactions with polymer-supported triphenylphosphine beads, loaded and reacted in an identical way, which only gave 26% conversion to halogenated material.[74]

The second drawback of the Appel reaction and a feature that has reduced the use of this reaction is the high carcinogenicity and environmental impact of carbon tetrabromide, which is highly toxic for marine life.[78,79] These compounds have become restricted, and the use of these solvents and reagents has gone out of fashion and alternatives have been sought. An example of alternative chlorinating reagents includes the use of bromotrichloromethane ($CBrCl_3$) as used by Lautens *et al.*[80] In their report, it was shown that $CBrCl_3$ can act as an effective alternative to the CCl_4 giving good to excellent yields for both the conversion of benzyl alcohols to chlorides and aldehydes into *gem*-dicholoralkenes. Magid *et al.* used hexachloroacetone (a common pesticide and herbicide) in their mild regioselective and stereospecific chlorinations of allylic alcohols.[81] Whilst hexachloroacetone was also used by Deslongchamps *et al.* in their total synthesis of (+)-maritimol producing the chloride from the alcohol in a yield of 94%.[82]

Denton *et al.* showed that a catalytic version of the classical Appel halogenation reaction is possible via the use of oxalyl chloride as a consumable stoichiometric reagent to generate a phosphonium-chloride salt responsible for halogenation from catalytic phosphine oxides.[83] This catalytic form of the Appel reaction occurs at

room temperature and can be applied to both the chlorination and bromination of alcohols in a highly efficient and atom economical alternative to the traditional Appel reaction. The addition of the halide salt lithium bromide (LiBr) to the reaction mixture ensures the bromination of the alcohol substrate over chlorination (Figure 1.7). A similar approach was also shown to be effective for catalytic Apple reactions by Delft *et al*.[84] 5-Phenyldibenzophosphole was shown to undergo reduction by diphenylsilane and, with the inclusion of the bromination donor diethyl bromo-malonate, bromination of alcohols could be achieved elevated temperatures (82-100 ^{o}C) in good yield.

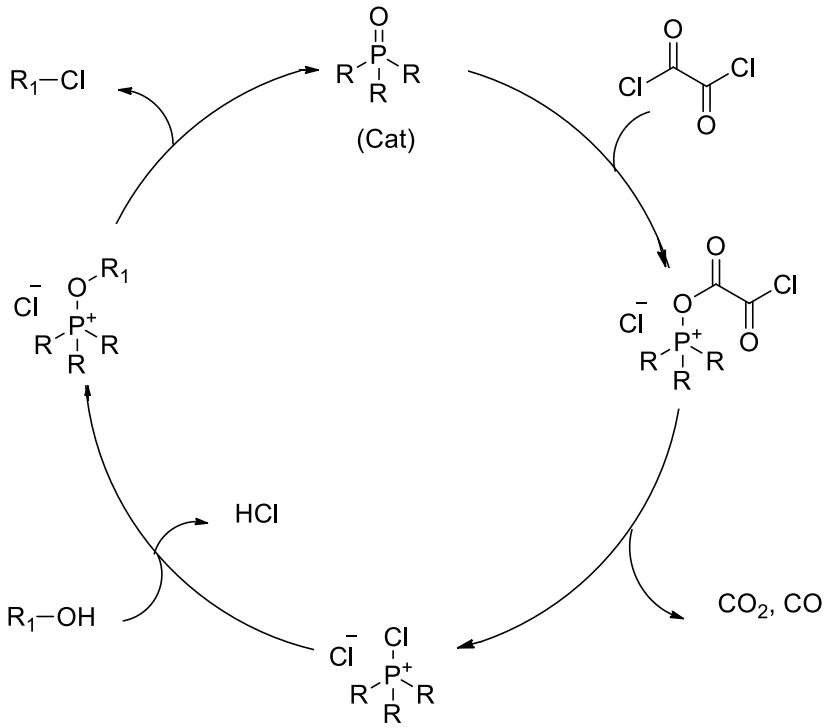
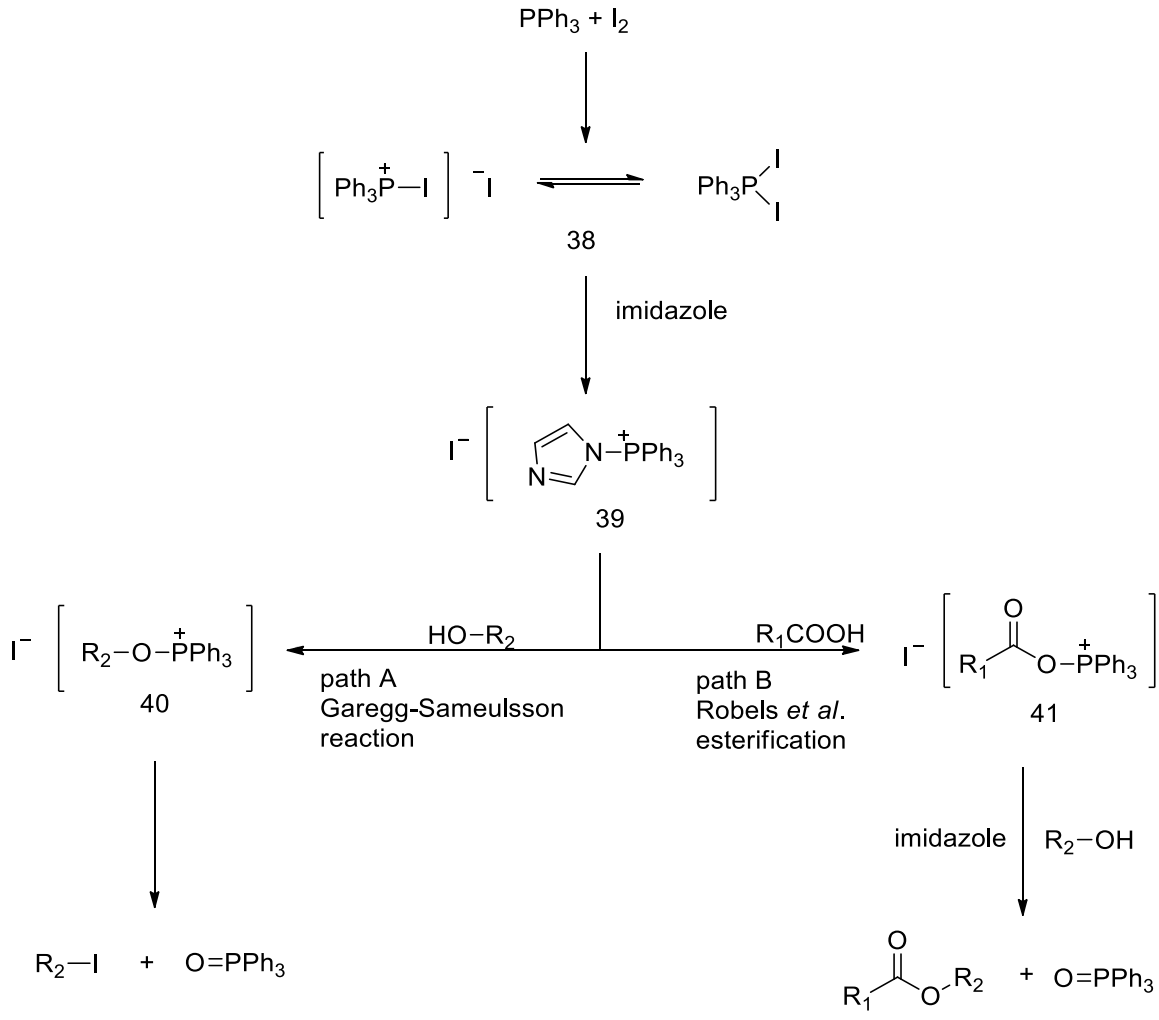


Figure 1.7: Catalytic cycle for the regeneration of the Appel reagent in the halogenation of alcohols as proposed by Deton *et al*.[83]

For the conversion of alcohols to iodides, modifications to original Appel reaction procedure are required. Iodine (I_2) can be used as the iodide source, however the iodide counter anion, unlike the carbanion of the standard Appel reagents, is not a strong enough base to deprotonate the incoming alcohol. Therefore, the addition of a base is required. Imidazole has been shown to be effective for this process, with the system first reported by Garegg and Samuelsson in 1979.[85–88] Addition of PPh_3 and I_2 leads to iodo-phosphonium intermediate **38**. Imidazole then displaces the iodide forming a phosphonium imidazole intermediate **39** as shown by ^{31}P studies. The alcohol reagent

can then displace the imidazole forming the alkoxy phosphonium **40** in which the iodide counterion can displace the oxygen in much the same way as the previously mentioned Appel mechanism (Scheme 1.18, path A).



Scheme 1.18. Path B; Garegg-Samuelsson reaction, Path B; Robles *et al* phosphine/iodine/imidazole mediated acylation reaction..

This method described above is known as the Garegg-Samuelsson reaction and has also been shown to be effective for the transformation of vicinal diols into olefins in a carbohydrate ring, providing alternatives for modification of carbohydrate to other biologically relevant molecules. The method was elaborated further by Kita *et al.* using a solid-supported phosphine, providing an effective and rapid method for the iodination of a variety of different alcohols.[89] When the method was applied to primary alcohols it was found that the reaction was complete within 15 minutes at room temperature; the use of solid-supported phosphine meant that only filtration of the resin followed by

aqueous work up was required for purification avoiding the need for chromatographic techniques. However, secondary alcohols proved to be more sluggish in their conversion and chromatography was required in the purification of the iodinated product. Scale up of the process also proved to be successful though care was needed as the reaction was slightly exothermic. The procedure has since been shown to be useful for reactions other than halogenation of alcohols.

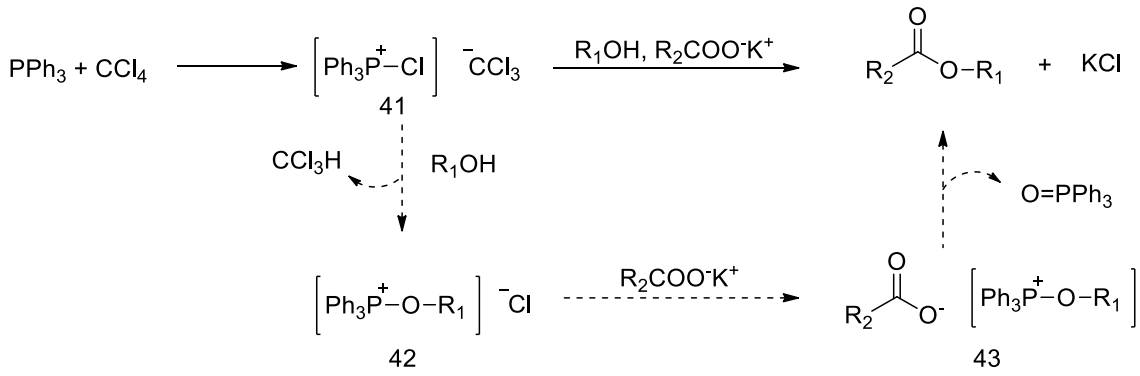
1.4.4.1 Acylations Reactions Using Appel like Conditions

In 2012 Robles *et al.* developed a mild and efficient system based around the *in situ* activation of a carboxylic acid via the formation of an acyloxy phosphonium intermediate.[90] Robels *et al*. reasoned that if an alcohol could be activated towards nucleophilic attack of an iodide as in the Garegg-Samuelsson then a carboxylic acid could also be activated. The presence of better nucleophile then iodide anion would result in coupling of the carboxylic acid and the nucleophile.[90] Scheme 1.18 shows the difference between the Garegg-Samuelsson reaction (Path A) and the Robles *et al.* acylation method (path B). Both pathways start with the formation of the phosphonium iodo intermediate **38,** which upon addition of imidazole forms the intermediate **39**. This is the point at which the Robel *et al.* acylation method and Garegg-Samuelsson reaction diverge. Addition of carboxylic acid leads to activation of the acid via formation of acyloxyphosphonium salt **41**. Addition of the alcohol or amine results in mild and selective acylations with a range of alcohols and amines in good to excellent yields. Esterification reactions with secondary alcohols produce poor yields and tertiary alcohols gave no ester product.

The use of a more sterically hindered phosphine such as tris(*o*-tolyl)phosphine resulted in lower esterification yields when using hindered alcohols as demonstrated by a drop in yield for the esterification of isopropanol from of 37% for PPh_3 to 20% for P(*o*-tolyl)$_3$. This suggests that the use of more hindered phosphines results in the chemoselective esterification of primary alcohols in the presence of secondary and tertiary alcohols. The success of this process was shown by performing the reaction with the model acid here in the presence of a primary (ethanol) and a secondary alcohol (*i*-PrOH) using P(o-tolyl)$_3$. This resulted in 99% chemoselectivity towards esterification of the primary

alcohol over the secondary. This selectivity for the primary alcohol was also shown to be the case when the reaction was performed on the 1,5 hexanediol resulting in complete regioselectivity on the primary alcohol.

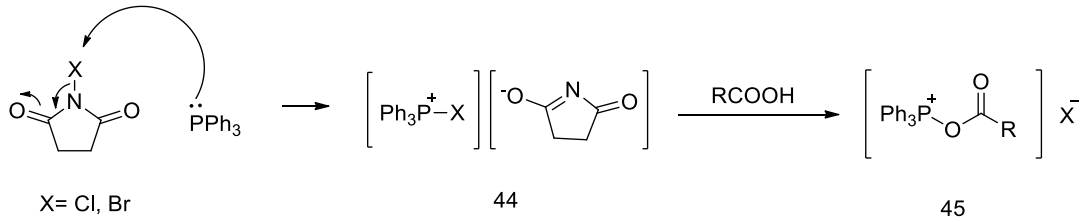
Other procedures have also been developed for the acylation of alcohols and amines using Appel like salts as activation agents for carboxylic acids. Phosphonium halide salts such as **42** were first reported to react with carboxylic acids by Lee in 1966.[91] Lee demonstrated that addition of a number of different carboxylic acids to PPh_3 and CCl_4 produced acetyl chloride and $O{=}PPh_3$ in good yields. 20 years later, Ramaiah released a paper in 1985 describing the use of metal carboxylate salts in combination with PPh_3 and CCl_4 for both ester and amide bond formation.[94] Ramaiah reasoned that if a carboxylate anion nucleophile was introduced in the Appel reaction, then the halide ion that usually substitutes the alcohol group would be removed from the reaction as an insoluble metal halide (KCl). The oxyphosphonium salt would then have the carboxylate anion which can then partake in nucleophilic attack resulting in the ester product, $O{=}PPh_3$ and metal chloride salt (Scheme 1.19). Good to excellent yields were reported using this method for esters from a range of aromatic, heteroaromatic, unsaturated and saturated acids under mild reactions conditions.



Scheme 1.19: Ramaiah's proposed mechanism for the esterifications of alcohols using metal carboxylate salts.

Frøyen also developed a system using similar chemistry to that of Appel, releasing a series of papers in the mid 1990's describing the formation of acyloxy-triphenylphosphonium salts via reaction of PPh_3, carboxylic acids and *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS).[93–97] Frøyen demonstrated that

this reagent system allowed for the rapid formation of the key acyloxyphosphonium intermediate **45**, which can undergo coupling reactions with a number of different nucleophiles such as azides, alcohols and amines. Fröyden's use of *N*-halosuccinimide for the formation of the key acyloxy-triphenylphosphonium salt **45** was inspired as it meant a base was not required, as the deprotonation of the acid the addition would be performed by the succinimide anion in salt **44**. Salt **44** is relatively stable and can be stored under inert atmosphere (argon or nitrogen), but are however, highly reactive to S_N2 attack by nucleophiles giving efficient and rapid conversion to esters and amides in the presence of a base such as pyridine as an auxiliary base.



Scheme 1.20: Frøyen's formation of the key acyloxy triphenylphosphonium salt intermediate **45**.

1.5 Dimethylaminopyridine (DMAP)

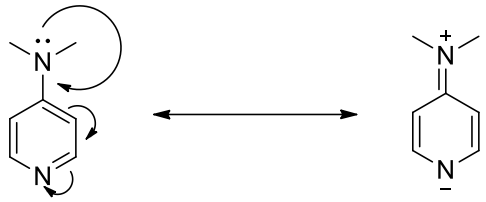


Figure 1.8: The resonance structures of DMAP.

Dimethylaminopyridine (DMAP) and its derivatives such as 4-pyrrolidinopyridine (PPY) are electron rich derivatives of pyridine. They are better bases than pyridine with a pKa-H of 9.2 (cf. pyridines pKa-H of 5) and also better nucleophils.[98] DMAP is highly toxic and corrosive but an easy to handle solid that has become an important reagent, common in synthetic laboratories since the discovery of its ability to act as a highly efficient catalyst for a wide variety of group transfer reactions, such as acylations. These reactions are some of the most crucial and widely used reactions in organic synthesis industries including the fragrance,[99] polymer,[100] and pharmaceutical.[101,102] The reaction between anhydrides e.g. acetic anhydride and

hydroxy or amine compounds are one of the most effective ways to produce esters or amides. The addition of pyridine to a mixture of an anhydride and hydroxy compound had provided a reliable and general synthetic route to the corresponding ester for over 70 years after the procedure was first developed by Verley and Bölsing in 1901.[103]

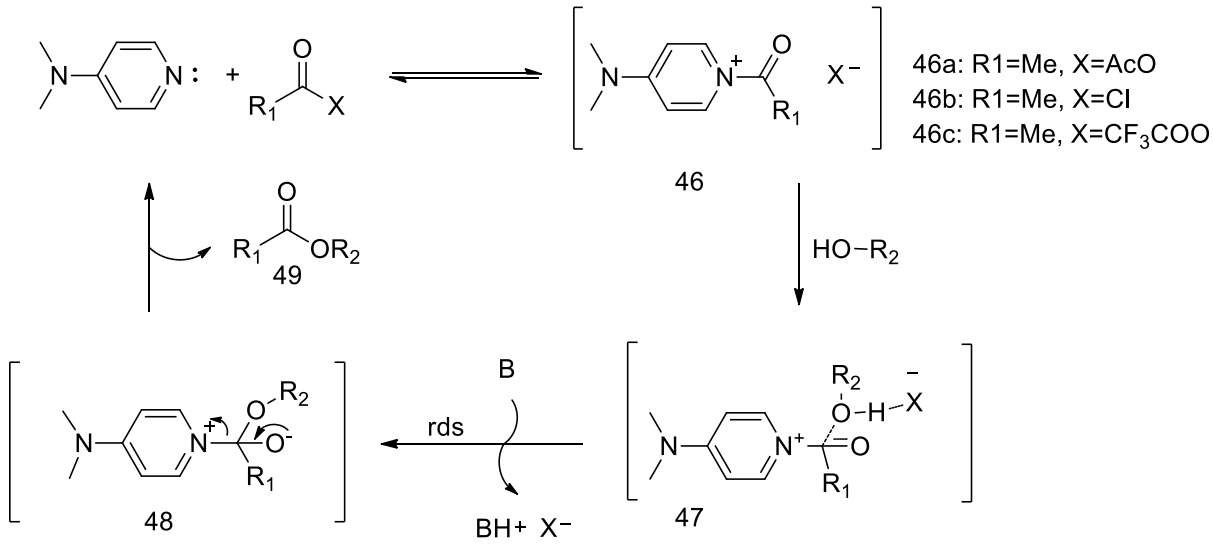
DMAP and other electron donating pyridine derivatives have since proved to be many times more effective than pyridine. The effectiveness of DMAP as acylation catalyst was first described by Litvinenko and Kirichenko in 1967 as part of a course of kinetic studies: the addition of DMAP in place of pyridine resulted in a rate increase of 10^4 in the benzoylation of *m*-chloroaniline.[104] However, this work went relatively unnoticed. It was work performed independently by Steglich and Höfle, that demonstrated the strong catalytic effect of DMAP and 4-pyrrolidinopyridine (PPY) as part of their investigation into the reactions of substituted pyridines.[105] Steglich and Höfle described the effectiveness of DMAP, both in stoichiometric quantities and in a catalytic sense when used in combination with an auxiliary base such a tertiary amine. They demonstrated that even tertiary alcohols, *tert*-butyl alcohol and 1-methyl-1-cyclohexanol, which failed to acylate in the presence of pyridine, could be acylated using an equivalent amount of DMAP and acetic anhydride. Steglich also demonstrated that the reaction could made catalytic in terms of DMAP via the addition of the auxiliary base which has higher basicity such as NEt_3 providing high yields of acetates in comparison to the use of pyridine.

1.5.1 Mechanism of DMAP Catalysed Acylation Reactions.

DMAP acts to activate the carboxylic component of the ester or amine before attack of the alcohol or amine. Despite this, little was known about the underlying mechanism of even simple DMAP catalysed reactions. Until researchers started to take more interest in the mechanism due to the development of enantiomerically pure chiral derivatives for use kinetic resolution of alcohols. Spivey's 2005 review gathered data on a wide variety of factors that affect the efficiency of this mechanism. A successful acylation using DMAP and its analogues relies on interplay of several factors including: catalyst structure, solvent, acylating agent and auxiliary base.

The currently accepted mechanism for the DMAP catalysed acylation of alcohols with acyl donors such acetic anhydrides or acetyl chlorides can be viewed as a nucleophilic catalytic mechanism, rather than a general base catalysed mechanism. One reason for this is the pronounced drop in rate of the reaction if the DMAP catalyst has substitution at the 2 and 6 positons relative to the internal N of the ring. Also basicity seems to have little correlation catalytic activity e.g. DMAP and NEt_3 both have similar pKa (9.7 and 11) but very different catalytic activities. The reaction first involves the pre-equilibrium formation of an *N*-acylpyridinium species **46** as an ion pair, through the reaction of DMAP and an acyl donor.

This is supported by H^1-NMR spectroscopy with the detection of **46a** at low temperatures upon mixing of Ac_2O and DMAP in $CDCl_3$.[106] Whilst **46b** is formed quantitatively upon mixture of DMAP and AcCl.[107] The alcohol then reacts with this acylated catalyst (**46**) to give transition sate **47**, the alcohol is deprotonated by the counterion $\mathbf{X}^-$ in the rate determining step. The auxiliary base acts as to stop DMAP from becoming inactive via pronation of the catalyst and therefore it is important to have a base that has higher basicity then the DMAP itself thus NEt_3 which is slightly more basic then the DMAP is ideal as an auxiliary base. This leads to the transition state **48** in which the DMAP is then regenerated by the formation of the ester product **49.** The *rds* is determined by the deprotonation of the alcohol shown by a mechanistic studies by Zipse *et al.* based on kinetic studies, DMAP nor auxiliary base are involved in the rate determining step deprotonation step. This leaves the counter anion contained in the acyl-pyridinium ion pair as the most likely base.[108]



Scheme 1.21: Nucleophilic catalytic mechanism of DMAP mediated acylation of alcohols with an acyl donor.

The importance of the role counter ion has been known for some time with Steglich *et al.* establishing that acyl anhydrides are more effective acyl donors then acyl chloride, with acylation of 1-ethinylcyclohexanol Ac_2O up to 3x faster than with AcCl.[109] This was also supported by evidence presented by Kattnig and Albert,[110] who found that nature of the counterion of the catalytic DMAP-acetyl complex influences the outcome of the reaction, indicating that the deprotonation of the transition state is controlling the rate of the reaction. They also found that the Ac_2O acylation of secondary alcohols was 10x faster than acylation with AcCl when combination of DMAP and insoluble carbonate auxiliary base.

Schreiner *et al.* investigated both the formation and structures of N-acetylated 4-(dimethylamino)pyridine (DMAP) salts (**46**) and the effect of structure on the ability to participate in acylation reactions with alcohol.[111] In this study several DMAP salts containing different counterions were investigated. These included DMAP acyl salts with acetate (**46a)**, chloride (**46b**), and trifluoroacetate counterions (**46c**), respectively. X-ray structures of these salts indicated weak bonding interactions between the C2 position of the pyridine ring and the anions of the counterion. Whilst it seems that the acetate anion is either too basic or nucleophilic to form an isolatable salt of **46a**, trifluoroacetate anion of **46c** was shown to have an interaction with a bond length of 2.80 Å. The Chloride anion of **46b** on the other hand is longer and can't be considered a

tight ion pair with solvent molecules associated with the chloride anion. Based on their X-Ray results as well as a number of calculations and both IR and NMR data they concluded that the counterion in was a crucial determinant the rate determining step of the reaction mechanism.

1.5.2 The Quest for More Potent Acylation Catalysts

DMAP has many analogues which can also act as acylation catalysts. 4-pyrrolidinopyridine (PPY) is classic example and has been showed to be more potent than DMAP, reducing by half the time of acylation reactions compared to DMAP.[112] Steglich *et al.* also demonstrated that DMAP analogue **51**, in which the 4 amino group is conformationally restricted via alkyl groups connected to the *meta*-positions of the pyridinium ring, is to be up 6 times more effective acylation catalyst than DMAP. Steglich *et al.* reasoned that catalytic activity depends on the stabilisation of the N-acyl pyridinium cation via donation from the lone pair of electrons of the 4-amino group nitrogen. An increase in this stabilisation would therefore increase the catalytic ability of the DMAP derivative.[112]

Studies on 4,4′-bis(dialkylamino)benzhydryl cations demonstrated an increase in stabilization of the cation when the nitrogen atom donor was part of a conformationally fixed ring system.[113] This is due to fixation of the nitrogen lone pair orbital parallel to that of the π orbitals of the pyridine ring in **51** Therefore the combination of conformational restriction and the inductive electron-donating effect of an alkyl group in the *meta*-position might have a similar effect on the corresponding (4-dialkylamino)pyridines and cause an increase in electron density at the pyridine nitrogen atom, thus resulting in stabilisation of the a catalytic active *N*-acyl pyridinium cation. Steglich demonstrated that this was the case by comparing the catalytic efficiencies of DMAP analogues **50** and **51** via half-life times for the acylation reactions. The conformational restricted nitrogen donor of **51** was shown to be the most effective catalyst (Figure 1.9).[112]

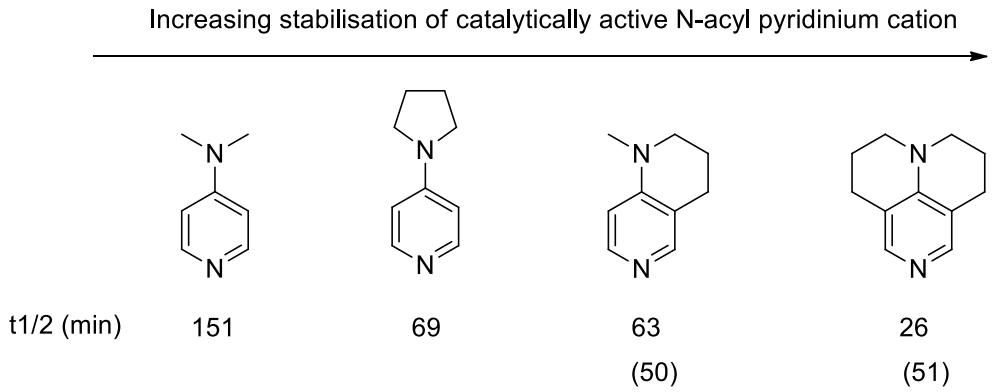
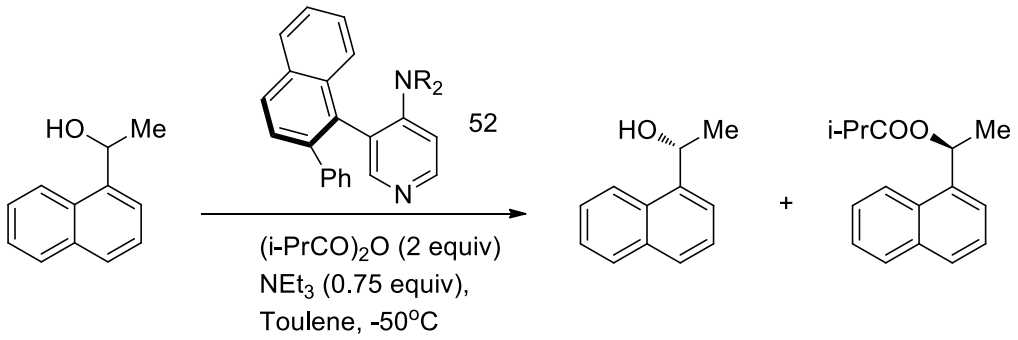


Figure 1.9: The increasing potency of DMAP analogues during acylation reactions, which correlates with the increasing stability of *N*-acylpryidinium cation of catalytically active action species.[112]

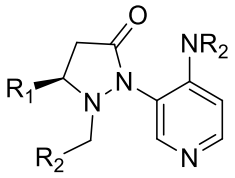
1.5.2.1 Kinetic Resolution of Secondary Alcohols.

In the last 15 to 20 years the most there has been much attention on the development of enantiomerically pure chiral 4-(dialkylamino)-pyridines for use in kinetic resolution of alcohols. Kinetic resolution allows for the formation of enantiopure products from racemic starting materials which tend to be cheaper than their enantiopure starting materials. Some of the best known examples where introduced by Spivey, with the introduction of a novel family of chiral DMAP-based nucleophilic catalysts as early as 1998. These chiral DMAP derivatives can have comparable reactivity to DMAP for the esterification of 1-methylcyclohexanol with acetic anhydride.[114] Since the introduction of the first such chiral 4-aminopyridine derivatives, a multitude of different chiral derivatives have been synthesised. Spivey's catalyst **52**, as shown in Scheme 1.22, is a good example giving a selectivity factor of 36 when the *N*-substituent R=*n*-Bu in the kinetic resolution.[115] This is compared to a selectivity factor of 3.5 when R=pyrrolidino. The reason why the R groups have such an effect on the selectivity is as yet unclear. Selectivity of a kinetic resolution is related to the rate constants of the reaction of R and S enantiomers, k_R and k_S respectively ($s=k_R/k_S$ for when $k_R > k_S$).



Scheme 1.22: Kinetic resolution of (±)-1-(1-naphthyl)ethanol by Spivey *et al.*[115]

Further examples of chiral 4-aminopyridine derivatives include the addition of chiral pyrazolidinone as a chirality element as reported by Sibi *et al* (Figure 1.10).[116] An advantage of Sibi *et al.* chiral catalyst **53** is that fluxional substituents pattern whose size can readily be varied as a blocking group. Conceptually, the R^1 group dictates the orientation of the CH_2R^2 group, which in turn both influences the orientation of the DMAP group and provides steric discrimination during acylation. The 4-(*N,N*-dialkylamino)-pyridine is connected to the chiral pyrazolidinone at the *meta* position. Additionally, the nucleophilicity of the pyridine can be tuned by varying the dialkylamino substituent. The optimised resolution systems offer selectivity factors of up to 37. The kinetic resolution of a racemic mixture of the secondary alcohol 1-(2-naphthyl) ethanol was attempted at -50 ^oC when the sterically demanding isobutyric anhydride is used over a 48 hour period.

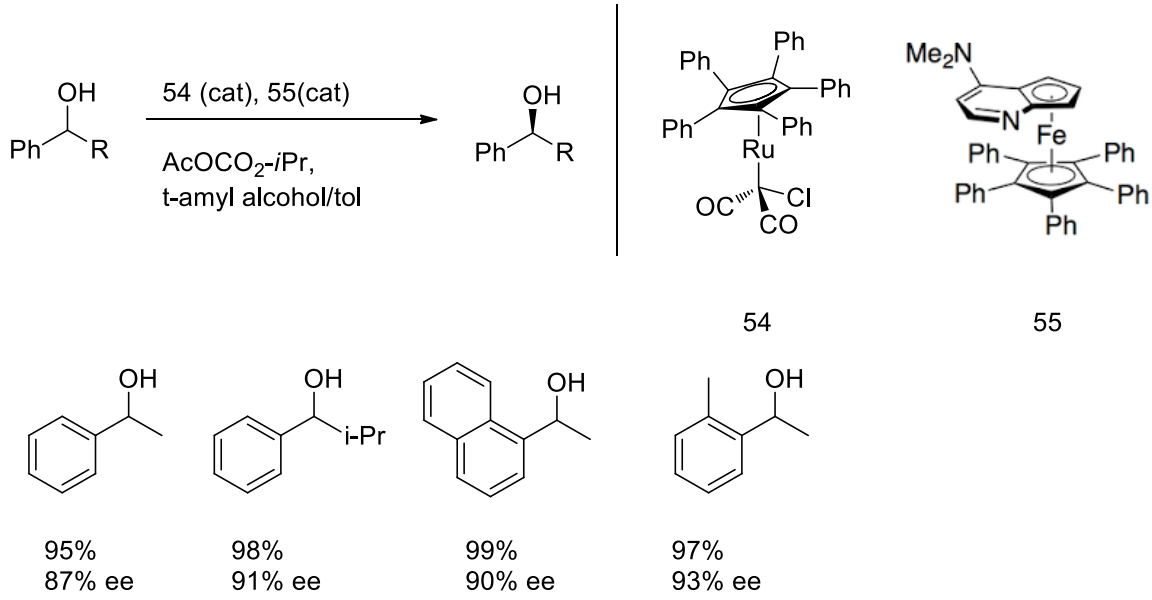


53

Figure 1.10: Chiral 4-aminopyridine derivative **53** containing chiral pyrazolidinone as a chirality element.[116]

Perhaps the most effective chiral DMAP derivative in the kinetic resolution of racemic mixtures of secondary alcohols is the example of a planar DMAP catalyst (**55**) which is contains a ferrocene unit in combination with a ruthenium racemization catalyst (**54)** of Fu *et al*. Use of the two catalysts in combination with each other resulted in yields the ester products >95% with an enantiomeric excess >90%.[117] This work is an extension of their original development of the ferrocene containing 4-amino pyridine catalyst, which

showed a very good resolution of racemic mixtures of alcohols reagents.[118] This example of dynamic kinetic resolution (DKR) is a powerful strategy in asymmetric synthesis, allowing the stereoconvergent transformation of both enantiomers of a racemic substrate into a single enantiomer of a target molecule. The initial studies of bicyclic 4-aminopyridine containing a ferrocene without use of a ruthenium co-catalyst, gave selectivity factors ranging from 19-52 with the *ee*'s of the recovered alcohol of up to 99% when *t*-amyl alcohol was used as the solvent.[119]



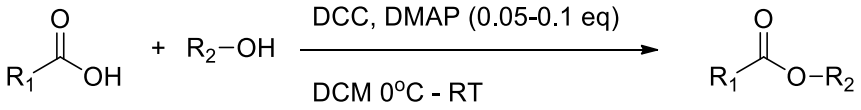
Scheme 1.23: kinetic resolution of racemic mixture of alcohols using combination of a DMAP-ferrocene and Ruthenium catalyst by Fu *et al*.'s.[117]

1.5.3 The Steglich Esterification.

Steglich and co-workers originally demonstrated DMAP and PPY to be highly effective acylation catalysts, when used in combination with active carboxylic acid derivatives such as anhydrides or acyl halides and an auxiliary base. While this offers an effective method for the capping of alcohols with an acetate group, it is not always practical to use anhydrides and acyl chlorides. One reason for this is that the carboxylic acid element of any ester or amide formation reaction (especially in the case of total synthesis of natural products) is often precious. Therefore, the anhydride or acyl halide derivative must be synthesised before any acylation reaction can occur. This can adds further steps to the synthetic route thus lowering overall yields. Methods that involve the direct coupling of a carboxylic acid and alcohols are therefore attractive for the

synthetic organic chemist. Such methods require an *in situ* activation of the carboxylic acid followed by nucleophilic attack of the alcohol or amine reagent. One of the most widely used methods for the direct formation of esters from carboxylic acids and alcohols is the Steglich reaction.

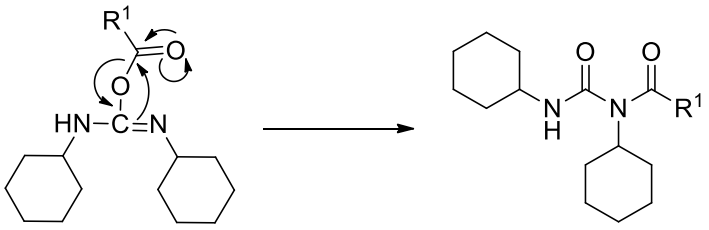
The Steglich reaction was first reported by Steglich in 1978 (Scheme 1.24).[115] It is an adapted form of an older method used in the formation of amides via the use of dicyclohexylcarbodiimide (DDC) and 1-hydroxybenzotriazole (HOBT).[116] This method proved to be effective in the formation of amides via the activation of the carboxylic acids by DCC. However, when it came to the formation of esters and thioesters the method gave variable yields and the formation of side products such as *N*-acyl ureas. The modification introduced by Steglich applies to the use of a catalytic amount of DMAP; this accelerates the rate of esterification between the carboxylic acid component activated via the formation of an adduct with DCC and the alcohol by displacing the DCC and forming the same acyl DMAP species (**46)** observed in Steglich's studies of 4-aminopyridine derivatives (DMAP and PPY) using acyl anhydrides and acyl chlorides. The Steglich reaction generally allows for mild reaction conditions, e.g. room temperature, the solvent most commonly being CH_2Cl_2. The mild reaction temperatures make it is possible to form esters using acids that can't be obtained with using other methods because of their sensitive nature. A good example of this is the esterification of *t*-butyl alcohol, due to the tendency of such tertiary alcohols to form carbocations under the conditions employed in classic esterification methods such as the Fischer esterification (acid and heat).[122]



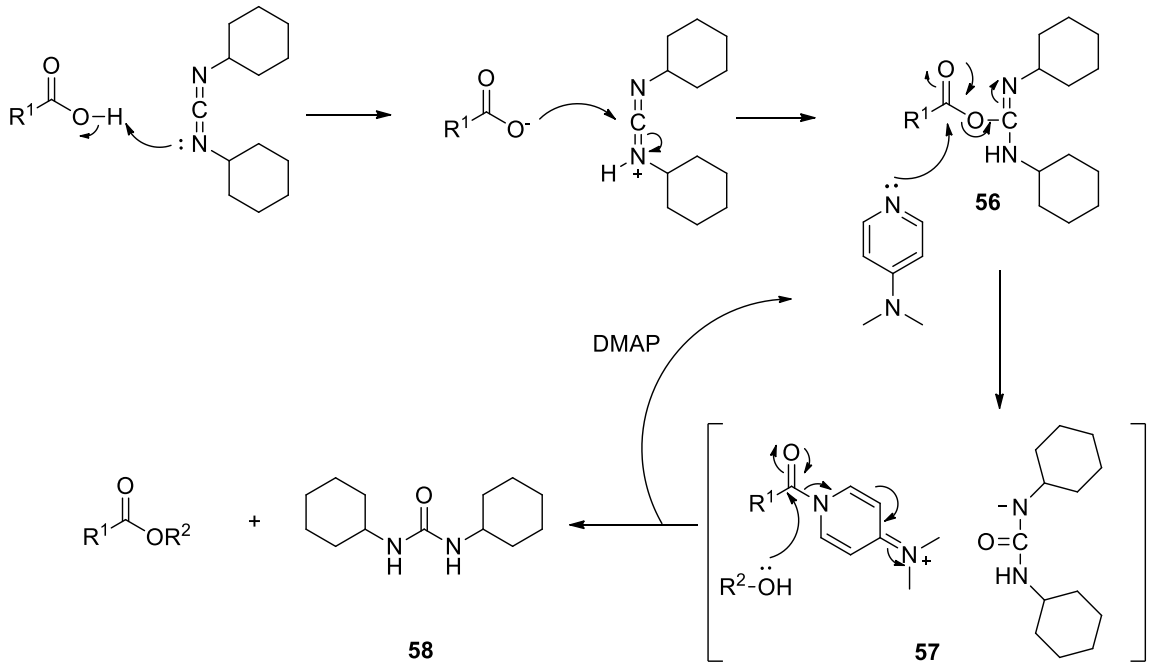
Scheme 1.24: General reaction scheme for the Steglich esterification.[120]

Mechanistically the reaction starts with an initial deprotonation of the carboxylic acid by either the DMAP or the DCC. This is followed by formation of an intermediate species between DCC and the carboxylate anion. This *O*-acyl isourea intermediate formed has similar reactivity to acyl anhydrides. The nucleophile can now attack **56** but while amines can react with this intermediate to produce amides easily, reaction with

alcohols are slower which can lead to an unwanted side reaction of *N*-acyl migration to form *N*-acyl urea **55** (Scheme 1.25). In the absence of any nucleophile the *N*-acyl urea **55** can be isolated in almost quantitative yields. The addition of the strong nucleophilic DMAP reacts faster than both the alcohol and *N*-acyl migration, thus forming the catalytically active *N*-acylpyridinium species (**57**) that is the hallmark of DMAP chemistry. **57** can then not form the side products and reacts far more readily with the alcohol. The deprotonation of the alcohol is achieved by the now negatively charged nitrogen of the urea counterion forming the stable dicyclohexylurea (**58)** which can be removed via a combination of filtration and column chromatography (Scheme 1.26).



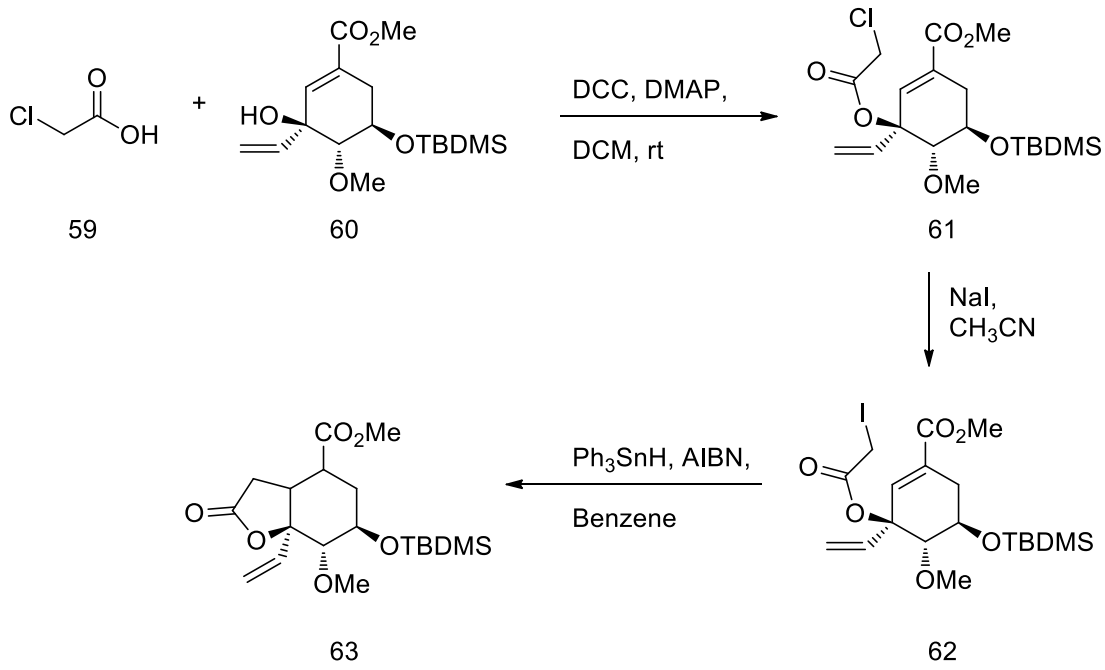
Scheme 1.25: *N*-acyl migration to form *N*-acyl urea the major unwanted side reaction in the Steglich reaction with alcohol, if DMAP is not used.



Scheme 1.26: Mechanism of the Steglich reaction using DCC and DMAP the direct coupling of carboxylic acids and alcohols to form esters.

This procedure has since become one of the most successful methods for direct coupling of a carboxylic acid and an alcohol. It has been used in many synthetic routes over the last 35 years due to the mild reaction conditions and cheap commerically available reagents. Low temperature control offers some degree of regioselectivity; for example the synthesis of mixed fatty acid phospholipids often requires the select esterification of a primary alcohol in the presence of a secondary alcohol. Martin *et al.' s* development of a general method for the synthesis of phospholipid derivatives of 1,2-*O*-diacyl-glycerols showed that low temperature control of the Steglich reaction with DCC and DMAP allowed for the selective acylation of the primary alcohol could be achieved.[123] Performing the Steglich reaction at 0 ^{o}C allowed for the formation of 1-*O*-acyl-3-*O*-benzyl-*sn*-gycerol that is an essential part of glycerol-derived phospholipids. They found that slow addition of DCC (over 45 mins) to a solution of 3-benzyl glycerol, fatty acid and DMAP in dry CH_2Cl_2 at 0 ^{o}C and stirring at this temperature for an hour followed by warming to room temperature and a further 12 hours of stirring resulted in selective acylation of the primary alcohol in good yields (69-79%). This is compared to the method in which anhydrides, e.g. palmitic anhydride, was used which offered yields of 67% but over a period of 48 hours stirring at 0 ^{o}C.[124]

Another good example of the selectivity and mild reaction conditions that the Steglich reaction can offer is demonstrated by Hanessian *et al.'s* total synthesis of (-)-reserpine.[125] This alkaloid, which shows antipsychotic and antihypertensive properties, has found use as a drug for the treatment of these symptoms. A key step in the synthesis is the intramolecular free-radical cyclisation of α-iodoacetate **62** to give the corresponding lactone **63**. The required α-halo acetate was prepared by esterification of the ring bound alcohol with chloroacetic acid using the Steglich reaction. Chloroacetic acid contains chlorine on the alpha carbon; therefore the conditions for the esterification procedures are required to be mild. The use of the mild and efficient Steglich reaction allowed esterification between **59** and **60** resulting in **61** in an excellent yield of 86%. This was followed by conversion of the **61** to the iodide **62** via the Finkelstein reaction thus allowing the radical cyclisation too takes place. This use of the Steglich procedure demonstrates how useful a mild esterification method can be when using highly sensitive acids.



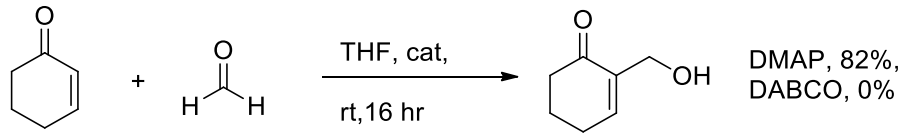
59 60 61 62 63

Scheme 1.27: Hanessian *et al.'s* use of Steglich esterification for the acylation of chloroacetic acid followed by Finkelstein reaction and radical cyclisation.

1.5.4 The Morita-Baylis-Hillman Reaction

DMAP has also found use as an effective base catalyst in the Morita-Baylis-Hillman reaction. The Morita-Baylis-Hillman reaction was first reported by Mortita in 1968, followed by a German patent application by Balyis and Hillman in 1972.[125,126] it provides a method for the formation of carbon-carbon bonds between the α-position of an activated electron poor alkene and an aldehyde or ketone, or more generally an electrophilic carbon. A nucleophilic catalyst such as tertiary amine or phosphine allows the synthesis of highly functionalised products in an atom economical coupling under mild conditions without the use of a metal catalyst. The most common catalytic base used is DABCO (1,4-diazabicyclo[2.2.2]octane). However, Rezgui *et al*. described the use of DMAP as a replacement for DABCO as the nucleophilic catalyst to this process. The use of DABCO was shown to be ineffective for the Mortia-Baylis-Hillman hydroxy-methylation of cyclohexenone; DMAP on the other hand gave an excellent yield of 82% (Scheme 1.28).[127] In other work it was also found that DMAP was highly effective for the for Morita-Baylis-Hillamn reaction between aromatic aldehydes such as nitrobenzaldehyde with methyl acrylate in a solvent free reaction compared to

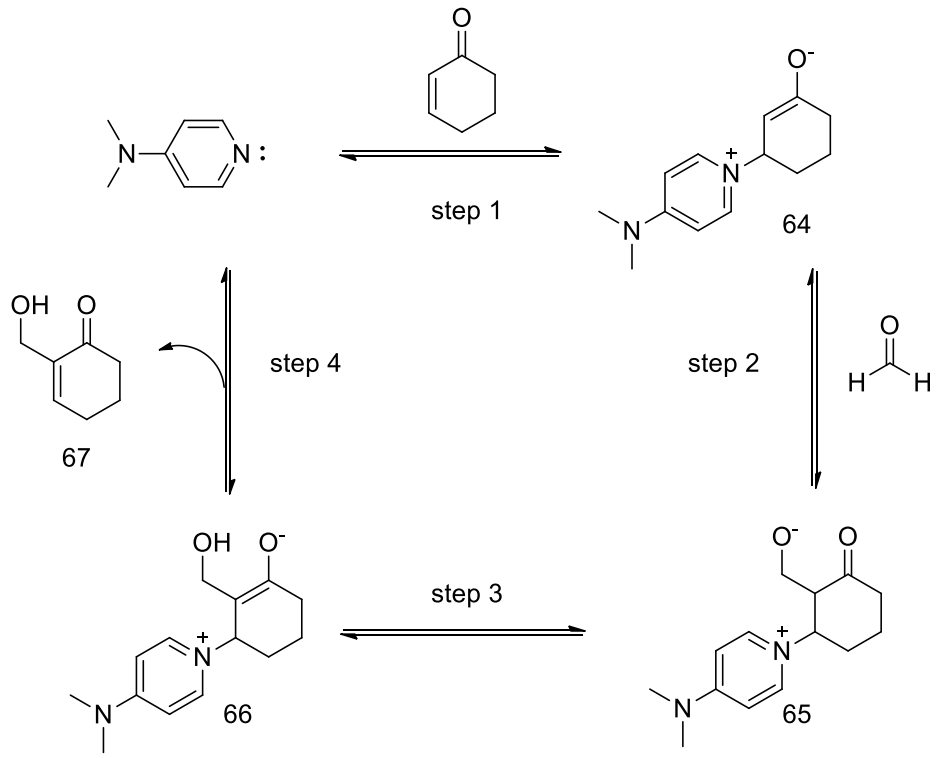
DABCO, producing high yields in a matter of hours with conventional heating and within 15 minutes using microwave heating.[128]



Scheme 1.28: Mortia-Baylis-Hillman reaction showing the of DMAP over DABCO in the hydroxymethylation of cyclohexenone.[127]

The contrast in reactivity of DMAP and DABCO was investigated in a 2007 paper and it was shown that in some cases DMAP was superior whilst in other cases DABCO is preferred.[129] Both nucleophilic and basic properties of the two organocatalysts were investigated, using laser flash techniques to determine the nucleophilicity and a comparison of the results from both this and the basicity, it was determined that DABCO was a both superior nucleophile determined by the difference in the equilibrium rate consent for the reactions of the DABCO and DMAP with benzhydrylium ions Ar_2CH^+ (by a factor of 10^3) their reverse reaction (disrupted by laser flash techniques). It was also possible to calculate the equilibrium constant of the reverse reaction i.e. their nucleofuge ability (by a factor of 10^5).

DMAP which has already been determined as a good nucleophilic catalyst has slightly superior Brønsted basicity with a pKa of 9.6 compared to DABCO pKa of 8.8. The differences between the two can be then be utilised depending on how the reactivity is controlled in the Morita Baylis Hillman reaction. DMAP which has higher carbon basicity compared to DABCO will therefore generally be superior to DABCO; if reactivity depends on the concentrations of the intermediate ions produced in steps 1 (**64**). However, if the reactivity is controlled by the rate of the nucleophilic attack of the organo catalyst to the Michael acceptor (step 1) or nucleofuge ability i.e. the elimination of the amine component in step 4, then DABCO catalysed reaction will be superior. The Baylis–Hillman reactions with cycloalkanones and acrylates are better catalyzed by DMAP than by the standard catalyst DABCO possibly because of the need for higher concentrations of the zwitterionic intermediates in these cases.

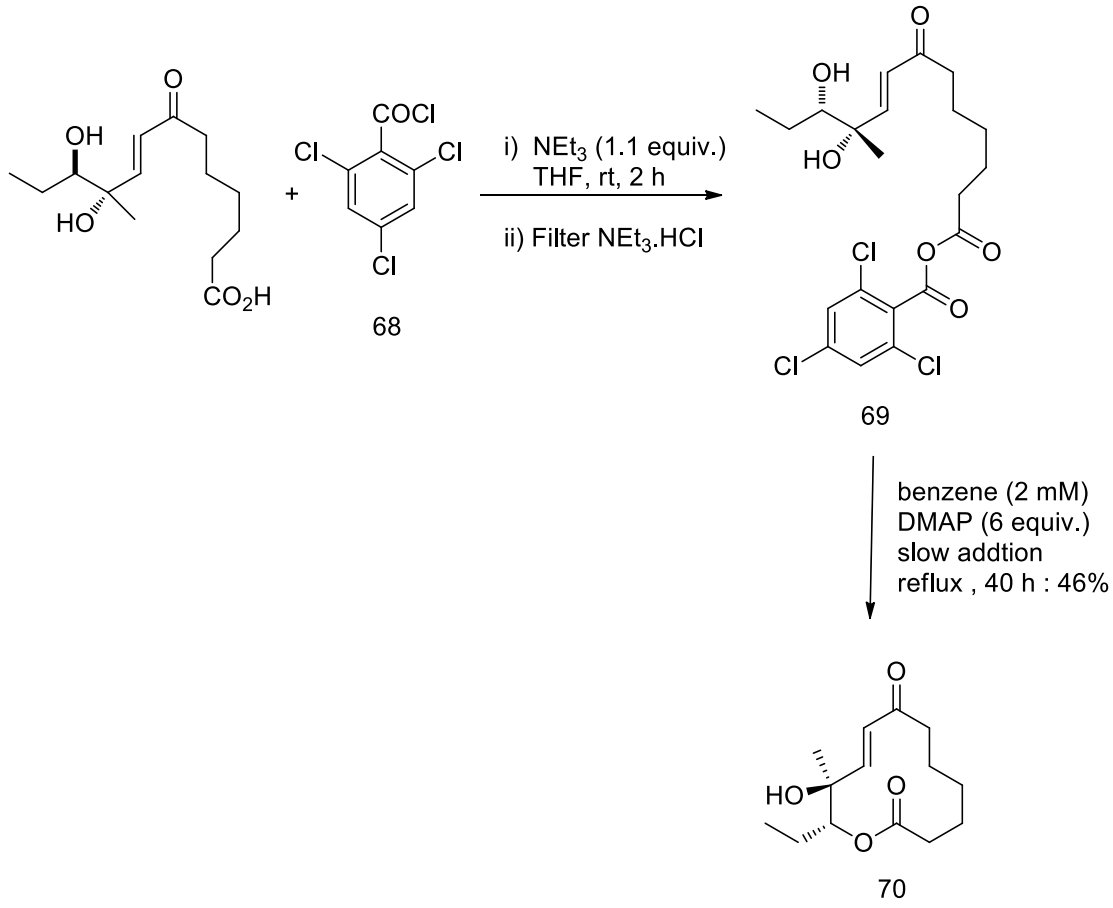


Scheme 1.29: generally accepted mechanism the Morita-Baylis-Hillman reaction using DMAP is acting as nucleophilic catalyst in the hydroxy-methylation of cyclohexenone.

The mechanism` can be seen as three separate steps; Michael addition, aldol reaction, and β-elimination (Scheme 1.29).[130] The Michael addition of the nucleophilic organocatalyst, in this case DMAP, to the electron poor alkene to produce intermediate **64** which is in equilibrium with the starting Michael acceptor and nucleophile. The zwitterion **64** can be intercepted with the electrophile reagent such as an aldehyde via nucleophilic attack of the enolate (**64**) to the electrophile such as an aldehyde in a aldol condensation as part of the second step producing zwitterion **65** (step 2)**.** A proton shift from the α-carbon atom to the β-alkoxide anion of the resulting aldol condensation (step 3) produces enolate (**66**), this is followed by β elimination affords then the MBH product **67** and regeneration of the nucleophilic catalyst (step 4). The aldol reaction of step 2 generates two stereogenic centres and has for a long time been considered as the rate-determining step (*rds*). However, mechanistic studies by Aggarwal *et al.* suggested that the rate determining step in a system with no added protic species involves the proton transfer process of step 3. This however changes as the concentrations of the product increases. The proton transfer reaction becomes increasing efficient and the *rds* becomes the interception of the Michael reaction product (**64**) with electrophile in step 2.

1.5.5 Yamaguchi Esterification.

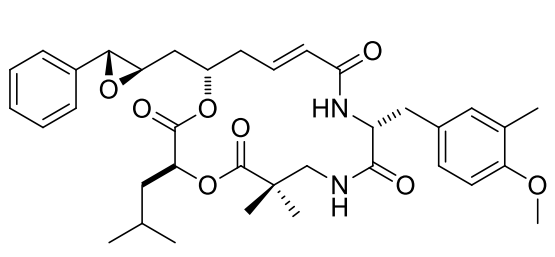
The final DMAP-mediated named reaction to be discussed is the Yamaguchi esterification and is another example of DMAP acting in an acylation reaction. The reaction was first described by Masaru Yamaguchi in 1979 as part of his investigation in the synthesis of large ring lactones from the corresponding long chain hydroxy acids (Scheme 1.30).[131,132] The Yamaguchi esterification offers a mild method for the esterification of highly functionalised acids. It has since become a particularly well-used method for synthesis of large macrolactones. The reaction involves first the formation of a mixed anhydride via the reaction of the carboxylic acid or hydroxy acid precursor and 2,4,6-trichlorobenzoyl chloride (Yamaguchi reagent) **68**. Addition of a stoichiometric amount of DMAP then forms the highly activated acylation reagent from the reaction of anhydride (**70**) and DMAP. This allows rapid attack of the alcohol, whether an intramolecular alcohol as in the case of a large chain hydroxy acid or an intermolecular alcohol.



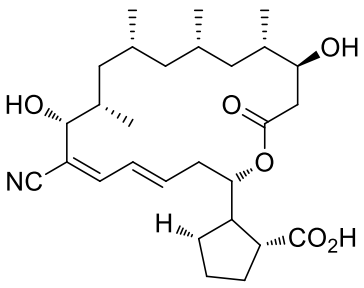
Scheme 1.30: Yamaguchi's original procedure for the synthesis of the macrolactone (±)-2,4,6-tridemethyl-3-deoxymethynolide (**70**).

The macrolactonization of this sort of hydroxy acids that Yamgucihi *et al.* where investigating as part of their original studies in the late 70's and early 80's, are acid sensitive substrates, that are known to rapidly decompose on contact with catalytic amounts of hydrochloric acid. The Yamaguchi esterification procedure avoids the need for an acid catalyst system. The original conditions put forward by Yamaguchi consisted of two steps (Scheme 1.30). The first step involved the formation of the mixed anhydride using a carboxylic acid substrate and trichlorobenzoyl chloride in the presence of NEt_3 in THF. The mixed anhydride can then be isolated via filtration of the resulting precipitate of hydrochloric salt of the NEt_3 after concentration of the reaction mixture. The isolated reaction mixture is then diluted with either benzene or toluene to a concentration of 2 mM. The high dilution factor is important as a dilute solution means that intermolecular coupling reactions are avoided. This mixture is then slowly added to a solution of DMAP which is in stoichiometric amounts, often in serval fold excess. The reaction can be run at room temperature or at reflux which offers a faster reaction rates.

An example of the use of the Yamaguchi reaction in synthesis is Gosh and Swanson's total synthesis of the potent antitumor agent (+)-cryptophycin 52 (Figure 1.11).[133] Yamaguchi esterification was used in a key step to couple two highly functionalised substrates. Another example of the use of Yamaguchi esterification in the synthesis of a complex macrocycle is that that of borrelidin, an 18-membered cycle the synthesis of which was reported by Ōmura *et al.* Yamaguchi esterification was used due to the sensitive and highly functionalised nature of the carboxylic acid component (Figure 1.11).[134]



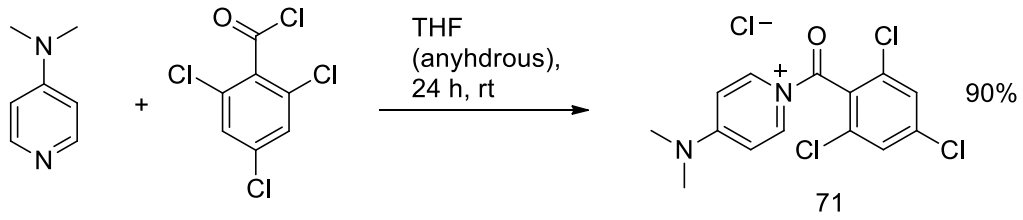
Cryptophycin 52



Borrelidin

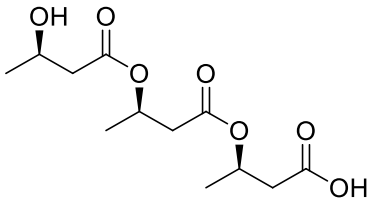
Figure 1.11: Two examples of complex macrocycles prepared using Yamaguchi esterification as a key steps in the synthesis due to high sensitive functionality.

A modification of the Yamaguchi esterification was recently introduced by Okuno *et al.*[135] As part of this study they investigated the use of a modified Yamaguchi reagent (2,4,6-trichlorobenzoylchloride–4-dimethylaminopyridine) (TCB-DMAP) in order to avoid the use of the acid chlorides and also to make the Yamaguchi esterification a one pot procedure rather than two as in the original method. The method also allowed DMAP to be used stoichiometrically instead of in vast excess. As part of the investigation they also managed to determine a mechanism for the reaction via the use of infrared spectroscopy, supported by a density functional theory calculation. They first produced the TBC-DMAP chloride salt by stirring of trichlorobenzoyl chloride and DMAP in THF over a period of 24 hours. The resulting precipitate was then collected via filtration and recrystallised to produce the modified Yamaguchi reagent **71** in 90% yields (Scheme 1.31). The resulting crystals were stable when in the absence of humidity and could be stored under dry conditions for a long time with no change in reactivity.



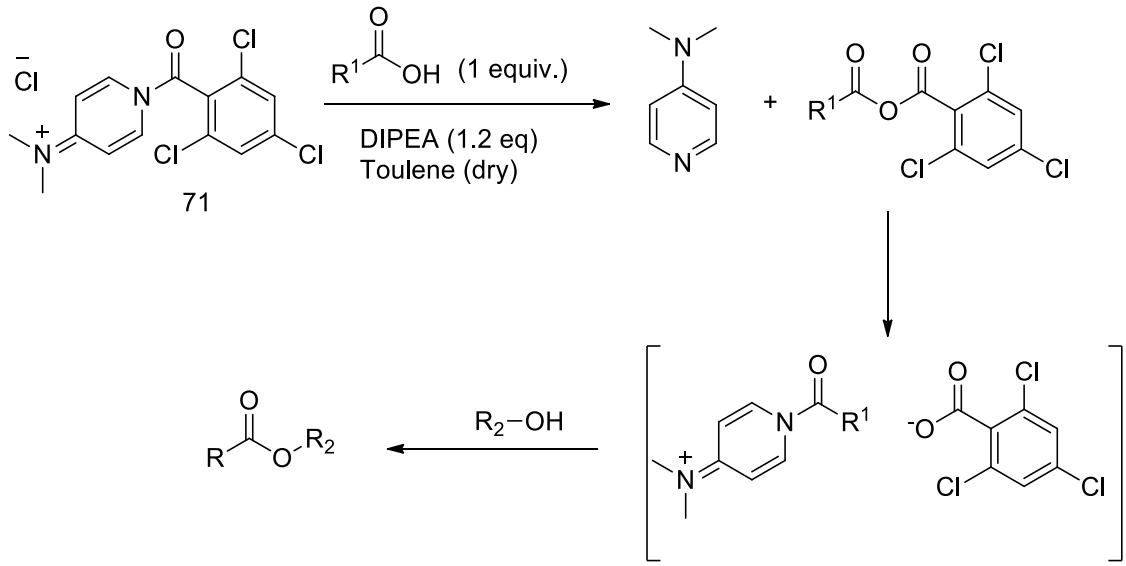
Scheme 1.31: Formation of modified Yamaguchi reagent TCB-DMAP as described by Okuno *et al.*[135]

Salt **71** can then be used in a simple esterification procedure in which 1.2 equiv. is added to a mixture of carboxylic acid (1 equiv.) and DIPEA base (1.2 equiv.) in toluene. This mixture was then allowed to stir for a minute before the alcohol was added and reacted for 24 h. They found that the esterification of a benzyl and aryl carboxylic acids with a variety of alcohols resulted in good to excellent yields under mild reaction conditions. In addition the method was also applied successfully to the synthesis of the natural product Linyphia triangularis pheromone (**72)** (Figure 1.12) achieving a 99% yield for each of the esterification steps. Through both the infrared studies and DFT calculations it was also shown that the reaction mechanism proceed through a the same pathway of mixed anhydrides and N-pyridinium acyl salts as observed for the classical Yamaguchi reaction, thus supporting the DMAP catalysed acylation transfer mechanism as observed in other DMAP acylation mediated reactions.



72

Figure 1.12: Linyphia triangularis pheromone (**72**)



Scheme 1.32: General mechanism for the modified Yamaguchi reagent mediated esterification reaction.

1.6 Need for New Acylation Reactions

Esters are some of the most important products in nature as well as the chemical, food and pharmaceutical industries. In nature, esters form the chemical basis of fats which in general consist of triglyceride esters of long-chain fatty acids in humans, animals and plants. Esters are also very common in many other biological molecules and compounds. They are often volatile, sweet-smelling liquids and as such are responsible for many of the aromas of fruits, flowers and sweets such as apples, bananas, pineapples, strawberries and pear drops.[136] The fragrance industry is built upon ester chemistry and is projected to be worth globally a staggering $38.8 billion by 2017.[99] The plastic industry also relies on esters; for example, polyesters contain ester bonds as the link between monomer units. The global forecast for the market of just unsaturated polyesters is thought to be in the region of $9.97 billion.[100] Within the pharmaceutical

industry it has been calculated that 25% of all chemical operations involve carboxylic acid derivatisation e.g. ester and amide bond formation.[101,102] These figures demonstrated the importance of esterification and amidation reactions. As a consequence, different methods to these important bond forming reactions have been developed and new routes are always sought. Three of the most widely used methods for esterification include the classic Fischer esterification,[137] the Steglich reaction,[122] and the Mitsunobu reaction.[56]

1.7 Goals and Aims

The goal of this thesis is to investigate a variety of different reactions potentially mediated by the combination of a phosphine and DMAP. Phosphines are useful redox reagents and have found use mainly in for the activation of oxygen containing function groups. DMAP is a known acyl transfer catalyst and has become one of the most well utilised catalysts for this purpose. It is the plan of this thesis to investigate how the combination of phosphine and DMAP could reduce reaction times of common phosphine mediated reactions. The plan was to start the investigation by making phosphine mediated reactions more efficient by the introduction of DMAP as a base and nucleophilic catalyst. Once a suitable system for the esterification and amidation directly from carboxylic acid had been established, it was planned to then utilise the same reagent system in a number of other transformations. These include ring closing reactions of 2 hydroxy benzyloxime, and the formation of phosphazenes.

2 A New Mild and Rapid Route for the Esterification and Amidation of Carboxylic Acids Mediated by Phosphine, Iodine and DMAP.

The work now described details the development of a new system that offers a method which complements the work of Robles *et al.*,[90] Frøyen,[94,95] and Steglich.[109,122] At the start of this PhD, the combination of both phosphine and DMAP in the synthesis of esters and amides had not been investigated. It is the aim of this chapter to describe the development of a new efficient and rapid method for the acylation of alcohols and amines. In order to meet the criteria of a useful addition to the synthetic toolbox of esterification reactions available, it was decided that a new method was required to meet certain criteria in order to compete with other available esterification methods:

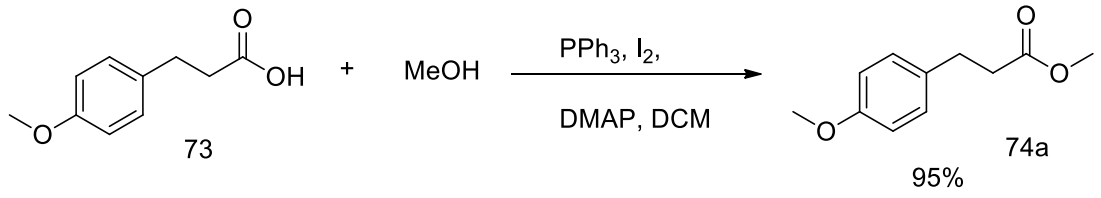
1. The method must be conducted under mild reaction conditions so that the use of sensitive reagents such as sensitive acid and alcohol starting materials which decompose under more forcing conditions could be utilised.
2. Use of inexpensive starting materials which are widely available in most synthetic laboratory's, so as to make the use of such a reaction more attractive to the end user.
3. Make the reaction procedure as simple as possible to perform and require little specialist equipment whilst also avoiding the need inert atmosphere techniques.
4. Decrease the reaction time of the acylation from 12-24 hours.

2.1 A New Esterification Method Mediated by Phosphine, I_2 and DMAP.

The method developed by Robles *et al.* seemed an attractive place to start the investigation due to a number of reasons:[90] The method uses inexpensive phosphine and iodine, which are commonly available in most synthetic laboratories and thus meet criteria 2. It also provides mild reaction conditions and a simple reaction procedure performed at atmospheric conditions thus meeting criteria 1 and 3. Also attractive was the ability for control of the regioselectivity of the acylation reaction on substrates which contain both secondary and primary alcohol positions. Robles *et al.*'s method

however, requires long reaction times of 12-24 hours and it was reasoned that changing the base from imidazole to DMAP could have a positive effect on the reaction rate due to its ability to catalyse acylation reactions as demonstrated by Steglich.[105] As part of Robles *et al* report paper a base screen was reported in which the bases; pyridine, 3,5-dimethylpyrazole (3,5-DMP), and 2,4,6- collidine (2,4,6-col) were tested but imidazole was found to be the most effective base. Surprisingly DMAP was not screened as a potential base in these reaction systems.

DMAP as a base was tested using the same model reaction system as Robles, in order to get a comparison with the use of imidazole base (Scheme 2.1). The reaction conditions were kept as close as possible to that of the original method developed by Robles *at al*. To a stirring mixture of 1.5 equivalents of the PPh_3 and I_2 in anhydrous CH_2Cl_2, were added 3 equivalents of DMAP. Subsequently, 1 equivalent of the carboxylic acid; 3-(4-methoxyphenyl) propanoic acid (**73**) was added to the reaction mixture leading to a formation of yellow precipitate. After 5 minutes of stirring, 1.5 equivalents of MeOH was added which resulted in the dissolving of the precipitate. Thin layered chromatography (TLC) was used to determine when the reaction was complete and no carboxylic acid was present after 20 minutes. Purification by flash chromatography on silica gave an excellent yield of methyl ester **74a** (95%) in a fraction of the time required when imidazole is used as the base (12-24 h). It should be noted that an inert atmosphere was not required although the use of anhydrous CH_2Cl_2 gave the best results.



Scheme 2.1. Test reaction for the PPh_3, I_2, and DMAP mediated acylation of acid **73**.

2.1.1 Scope for the Esterification of Carboxylic Acids.

After the initial success, the scope of the PPh_3-I_2-DMAP reagent system was tested by applying the reaction system to a variety of acids and alcohols (Figure 2.1). Many of the

reactions performed were replicas of reactions carried out by Robles,[90] so as to provide good comparison with the results of the imidazole system. In some cases, the use of a bulkier phosphine P(*o*-tolyl)$_3$ was compared to the standard PPh_3 to scrutinise if the process could be selective for primary over secondary alcohols as demonstrated by Robles. The method works very well for the formation of relatively simple esters. Good to excellent yields (71-98%) were obtained with a range of acids and alcohols including primary and secondary alcohols and phenols, as well as alkyl and aryl carboxylic acids. The only negative result was for the acylation of a tertiary alcohol *t*-butanol in which no ester was formed: this was not entirely surprising as tertiary alcohols are notoriously difficult to acylate due to their increased steric bulk.

The yields for the synthesis of esters **74d** and **74e** were much improved over Robles imidazole-mediated method, which gave poor yields for the acylation of secondary alcohols. The comparison was most profound for ester **74d** which gave an excellent isolated yield of 87%, when PPh_3 was used, and 63%, when the bulkier phosphine P(*o*-tolyl)$_3$ was used, both after 2 hours of reaction. The Robles imidazole-method, achieved a maximum yield for ester **74d** of 37% and 20% using PPh_3 and P(*o*-tolyl)$_3$ respectively after 12-24 h reaction time. The significant differences in these yields for the acylation of secondary alcohols suggest that the DMAP-mediated reaction and the imidazole-mediated precede by significantly different reaction pathways (to be discussed later). Where comparisons could be made to the Robles imidazole-mediated method, PPh_3-I_2-DMAP mediated method gave similar or better isolated yields of products and the reaction was completed in a fraction of the time (no longer than 2 h). One result that stood out as being superior was the synthesis of ester **74i** in which acid **73** was coupled with phenol; the DMAP-mediated gave an excellent yield of 94% compared to that of yield of 71% for the imidazole mediated method.

A number of other phenols where subjected to DMAP-mediated acylation using acid **73** in order to investigate how the electronics of the phenol ring system affected the efficiency of the process. Both electron rich and electron poor systems coupled efficiently, although slightly lower yields where observed for the more electron poor ring systems this suggested that the addition of the alcohol could be the rate determining step of the reaction mechanism. The effect of different electronic requirements in the benzoic acid was also investigated as shown by the coupling of MeOH with *para*-

substituted benzoic acids giving esters **74m-q**. Both electron rich (**74q**, *p*-OMe) and electron poor (**74n**, *p*-NO_2) benzoate esters where achieved in very good yield (98% and 91%, respectively), although ester **74p** (*p*-Cl) did form in a lower yield than expected (79%), which could be a due the possible side reaction of DMAP displacement of the chloride of the ring. This suggests that the electronics of the carboxylate precursor didn't have a significant effect of the overall kinetics. Finally the esterification of fatty acids palmitic acid and dodecanoic acid with MeOH was attempted, resulting in excellent yields of the corresponding esters **74r** and **74s.**

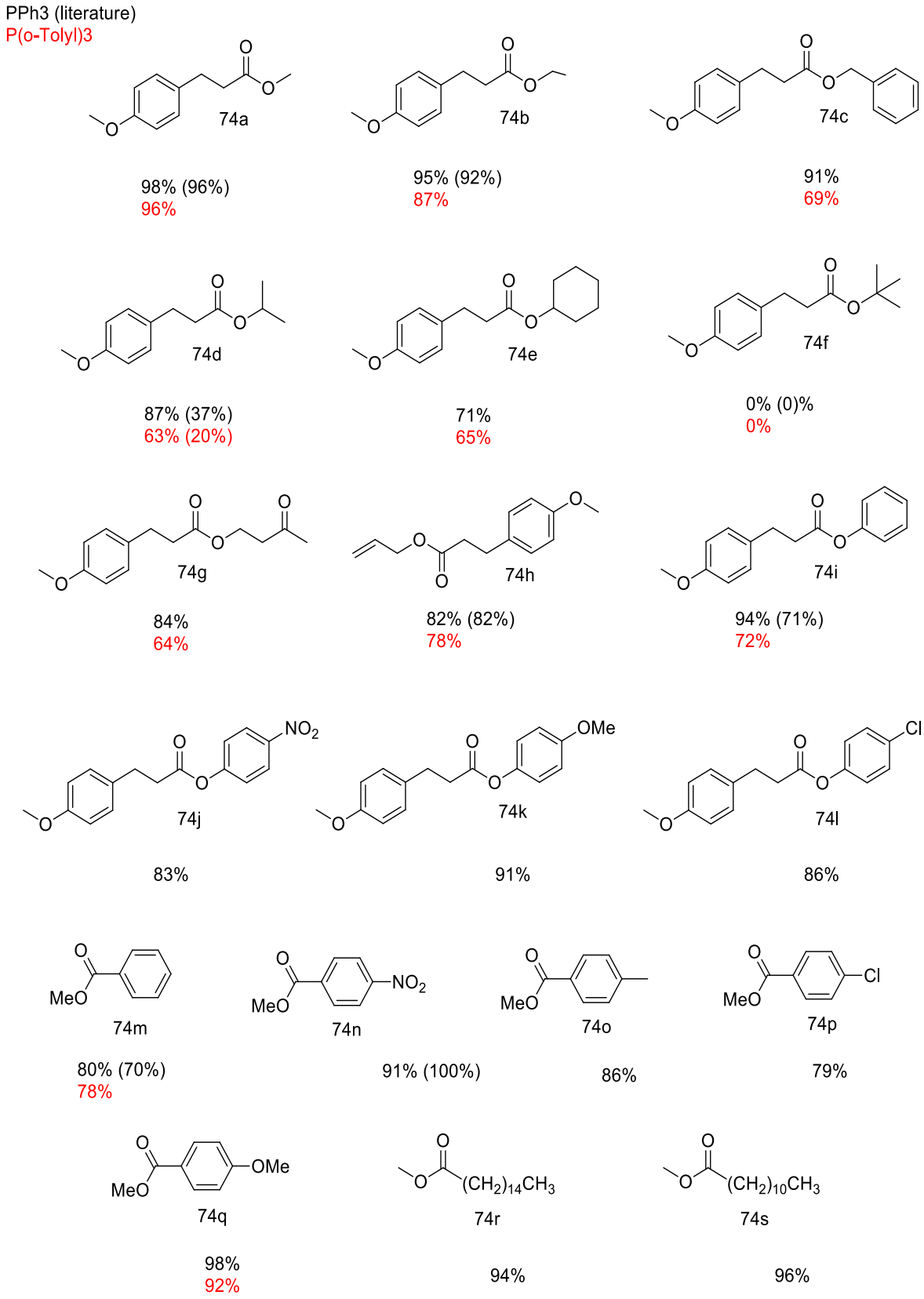


Figure 2.1. Isolated yields from esterification reactions using PPh_3/I_2/DMAP or P(*o*-Tolyl)$_3$ reagent system**.** Yields in parentheses represent literature findings using the Robles imidazoles mediated method.[90]

Now that good scope had been demonstrated by the phosphine-I_2-DMAP mediated system for the synthesis of esters, the next stage was to investigate the coupling of carboxylic acids with amines. The amines where chosen according to their ready availability, including primary and secondary aryl, alkyl and benzyl derivatives. All the amines showed good to excellent isolated yields in excess of 80% yields. However, where comparison ware possible, the yields appeared to be lower than the Robles imidazole-mediated method. For example the synthesis of amide **75b** using octyl amine gave a 20% lower isolated yield (79%) then the Robles study (99%).[90] The yields, although reasonably good were generally lower than the synthesis of the esters using this method which regularly achieved yields in excess of 90%. This initially came as a surprise: amines generally are better nucleophiles then their alcohol equivalents. Interestingly the use of aniline which is generally seen as a poor nucleophile or Lewis base because of the aromatic ring compared to the other amines used for this reaction gave good yields in rapid formation of the corresponding amide **75c** (87%).

One reason for the lower yields could be the rapid formation of phosphazenes species, a process which was found to occur rapidly in the presence of PPh_3, I_2 and DMAP (as presented in Chapter 4). The formation of phosphazenes might occur extremely rapidly when addition of the amine to a phosphine-I_2-DMAP mixture. A recent study by Phakhodee *et al.* (released after the start of this work):[138] their investigation into how the order of addition of reagents, for a phosphine and iodine mediated amidation reaction, is important could also shed some light on this problem. They demonstrated through ^{31}P NMR spectroscopic studies that, when NEt_3 was used as base, the order of addition of reagents was vital to the outcome of the amidation reactions mediated by PPh_3 and I_2. When amines were added first, followed by NEt_3 rapid formation of (benzylamino) triphenylphosphonium iodide occurred as determined by the ^{31}P NMR chemical shift value of ~35 ppm. This salt could be seen as a precursor to the formation of phosphazenes. Upon addition of the carboxylic acid to the (benzylamino) triphenylphosphonium iodide salt, no reaction occurred. Addition of NEt_3 post addition of both the acid and amine, led to the rapid formation of an amide. Despite this limitation, the PPh_3-I_2-DMAP reagent system was a rapid and reliable method for the coupling of amine and carboxylic acid, giving the corresponding amide in reasonably good yield.

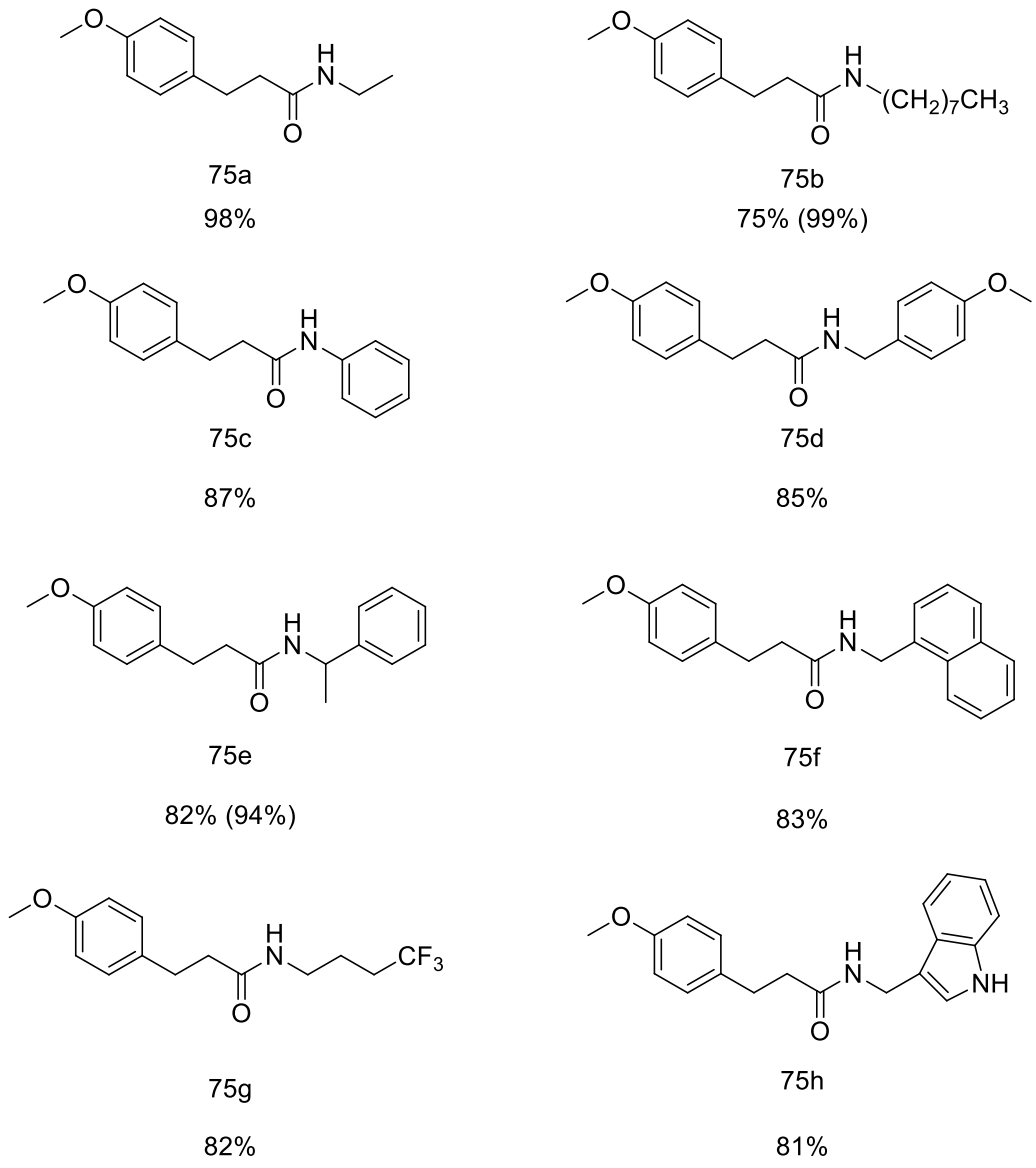


Figure 2.2: Isolated yields in the formation of amides using PPh_3-I_2-DMAP. Yields in parentheses represent literature findings using the Robles imidazoles mediated method.[90] All reactions carried out for no longer than two hours.

2.1.2 Phosphine, I_2 and DMAP for the Formation of Anhydrides.

The method so far has been shown to be both rapid and reliable for synthesis of both esters and amides. In order to probe the mechanism of the process and see if this reaction could be used for the synthesis of anhydrides the reaction was repeated in the absence of an alcohol or amine nucleophile. Carboxylic acids have been shown to be effective nucleophiles in their own right, for example the Mitsunobu reaction allows for the efficient formation esters via use of carboxylic acid pro-nucleophiles in good to excellent yield. There are a number of different synthetic procedures that can be used

for the synthesis of anhydrides, depending upon the acid moiety in question. Symmetrical anhydrides can be made via the reaction between the corresponding acid and phosphorus pentoxide.[139] Other popular methods include the reaction between acid chlorides such as the Yamaguchi reagent (**68**) and carboxylic acids in the presence of a base such as in the first part of the Yamaguchi esterification, where a mixed anhydride is formed to activate the acid toward nucleophilic attack.[131]

Anhydride formation was seen as an unwanted side product by Robles and thus the stoichiometry of PPh_3 and I_2 were optimised in the phosphine-imidazole system to try and ensure no anhydride is formed as all the carboxylic acid was converted to the acyloxyphosphonium intermediate. The competitive formation of anhydride is a problem accounted regularly in phosphine mediated system for amidation or esterifications and forced Robles *et al* to up the equivalents of phosphine and I_2 to counteract the formation of anhydrides. Anhydrides where also formed during Phakhodee *et al.* investigation into the significance of the order of addition of reagents in the PPh_3-I_2-NEt_3 mediated synthesis synthesis.[138] They described the rapid formation benzoic anhydride upon addition of NEt_3 (2 equiv.) to the reaction mixture containing PPh_3 (1.2 equiv.), I_2 (1.2 equiv.) and benzoic acid (1 equiv.) in CH_2Cl_2. It was therefore decided to investigate whether the method could be adapted for the formation of anhydrides to complement the formation of esters and amides, already discussed.

Figure 2.3 shows the results for the formation of symmetrical anhydrides using the PPh_3-I_2-DMAP system. The procedure used was similar to the esterification and amidation procedure described above. To a mixture of PPh_3 (1.5 equiv.) and I_2 (1.5 equiv.) and DMAP (3 equiv.) in anhydrous CH_2Cl_2 was added of the carboxylic acid (2 equiv.). This was then left to react for 2 hours before isolation purification via flash column chromatography on silica. The yields varied considerably for the different acids with no real pattern. Good yields where achieved for the synthesis of anhydrides **76b** (75%), **76d** (75%) and **76e** (70%) all anhydrides from derivatives of benzoic acid whereas benzoic acid itself only gave anhydride **76a** yield of 48%. reasonable yields were achieved for anhydrides **76f** (46%), **76g** (53%) and **76h** (54%) which are derived from alkyl carboxylic acids. By far the worst result was that for anhydride **76c** which only gave a yield of 10%. The reason for the low yield of **76h** is likely due to the steric

congestion imparted by the methyl groups at the *ortho* position of the trimethylbenzoic acid.

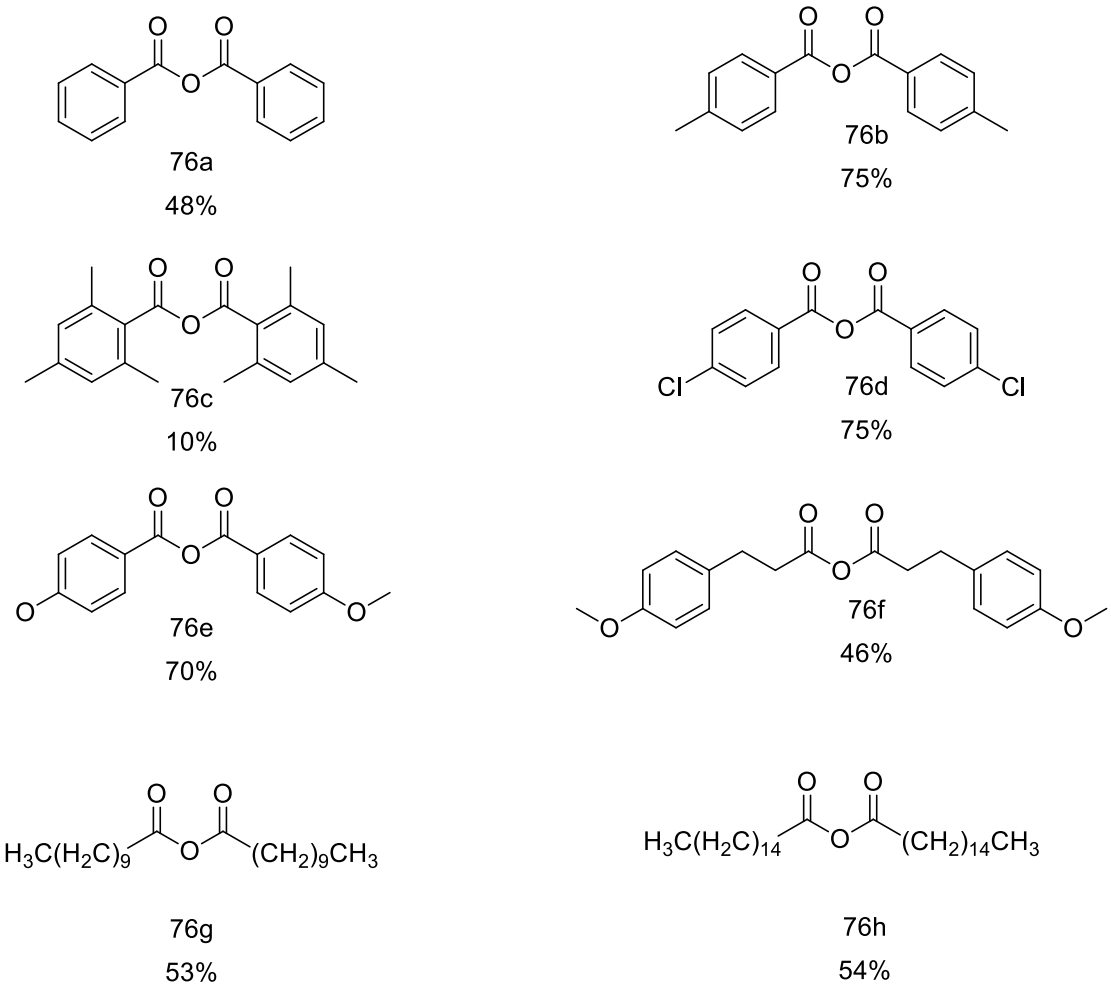
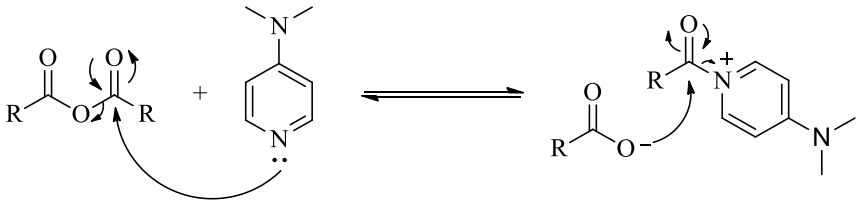


Figure 2.3. Isolated yields for symmetrical anhydride formation mediated by PPh_3/I_2/DMAP. All reactions where left for 2 hours in anhydrous CH_2Cl_2.

The yield of anhydride **74a** was low compared to Phakhodee's investigation on reagent sequence addition, where they achieved a 98% yield of benzoic anhydride.[138] In their investigation they found that if NEt_3 was added to the PPh_3 and I_2 mixture before addition of the acid and amine then rapid formation of anhydride was achieved, with attack the carboxylate anion nucleophile on the acyloxyphosphonium intermediate formed by the reaction of one equiv. of acid with the PPh_3-I_2 complex. Another possible problem with the formation of anhydrides with this system could be the use of DMAP as a base. DMAP is known to catalyse esterification reactions including the use acid anhydrides and acid chlorides as activated carboxylic acid donors.[108] Nucleophilic attack of DMAP on the activated acid component (anhydride) gives the intermediate acyl-DMAP cation with an acyl counter anion salt. This intermediate the known

reactive species and act as the acyl donor. This competing side reaction could lead to the lower yields that are observed due to the presence of active DMAP, where it is likely that some of the anhydride is in equilibrium with the acyl DMAP salt. This process could be in equilibrium as although DMAP is an excellent nucleophile it also makes for a reactive nucleofuge when there is no alternative nucleophile the acyl anion could attack the acyl DMAP species to reform the anhydride. It could be that the reaction simply needs longer reaction times then the two hours given for each of the anhydride experiments.



Scheme 2.2: Equilibrium between DMAP and Acyl-DMAP salt that could contribute responsible for potential poor yields achieved.

2.1.3 Mono-Acylation of Primary Alcohol in the Presence of Secondary Alcohol of 3-Benzyl-Glycerol.

As part of an ongoing project, the group was investigating a new general synthetic route towards asymmetrical phospholipids. A key step in the synthesis of asymmetrical phospholipids is the formation of the glyceride backbone which requires selective acylation of the 3-benzyloxy-1,2-propanediol (**77**) with a fatty acid at the primary alcohol position. Due to the need for the chemoselectively of the primary alcohol in the presence of the secondary alcohol on the α-carbon the Robles *et al.* P(*o*-tolyl)$_3$ and imidazole mediated method seemed like the ideal reaction. Robles *et al* found that the addition of the bulky phosphine allowed for increased chemoselectivity for the acylation of primary alcohols in the presence of secondary alcohols. Unfortunately, the Robles method produced disappointing results, with long reaction times, unreliable yields and poor selectivity. When the selective coupling of 3-(benzyloxy)propane-1,2-diol (**66)** and stearic acid was attempted using the Robles system mediated by PPh_3 and imidazole it was found that after 24 hours of reacting at room temperature only 30% yield of the ester was obtained in a 1:1 mixture of primary and secondary alcohol acylated product. When the same reaction was attempted with P(*o*-toly)$_3$) low yields where again

observed. As part of a wider project involving the synthesis of phospholipids with the selective esterification of 1,2 diols, rapid access to the primary acylated benzyl glycerol's was desired, in yields that could compete with the Steglich esterification, carried out at 0 ^{o}C to room temperature over a period of 12-24 hours.[123]

In order to compete with the Steglich reaction, the new DMAP and phosphine mediated system needs to satisfy several different parameters: it must offer comparable yields, a reduction in reaction time and provide chemoselectivity that is not dependent on temperature control. It has already been determined that the DMAP mediated method gave much improved yields in the acylation of secondary alcohols compared to Robles imidazole method (e.g. ester **74d)**. However, due the reduced reaction times the reaction was the acylation of glycerol **77** attempted using the DMAP method. The synthesis for the primary acylated 3-(benzyloxy)-2-hydroxypropyl stearate (**78a**) is 65%,[140] and palmitate (**78b**) in 78% using the Steglich esterification reaction.[141] The glycerol derivative **77** was chosen due to it being commercial availability as the racemate or in it enantiomerically pure forms. It is also regularly used in triglyceride and phospholipid synthesis.[140,141]

The DMAP-phosphine-I_2 mediated acylation reactions of the glycerol derivative **77** resulted reasonable yields of the ester products **78a**, **78b** and **78c** (Table 2.1). The synthesis of each of the esters was attempted with both PPh_3 and P(*o*-tolyl)$_3$, as well running the reaction with microwave heating with P(*o*-tolyl)$_3$ at 100 ^{o}C for 10 minutes. The ester **78a** was obtained in a 55% yield when the reaction conditions when PPh_3 was used (entry 1), the isolated yield was increased slightly when P(*o*-tolyl)$_3$ was used to give an isolated yield of 58% (entry 2). The best yield obtained for the synthesis of **78a** was with the microwave heating method in which an isolated yield in a 61% isolated yield (entry 3). Although these results although not do not produce as good yields as the Steglich esterification, the process is favourable in terms of reactions times: the room temperature reactions where run for a total to two hours whilst the microwave reaction only required ten minutes. Ester **78b** was obtained in an isolated yield of 61% when PPh_3 was used (entry 4), unlike the ester **78a** the results didn't improve for ester **78b** when either P(*o*-tolyl)$_3$ (54%, entry 5) or when microwave conditions where used (57%, entry 6). The ester **78c** was obtained in a 55% yield when PPh_3 was used (entry 7). The

use of P(*o*-tolyl)$_3$ again didn't improve the isolated yield (52%, entry 8). However microwave heating did improve the isolated yield (64%, entry 9).

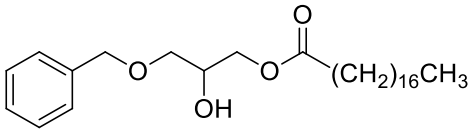
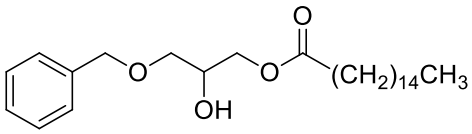
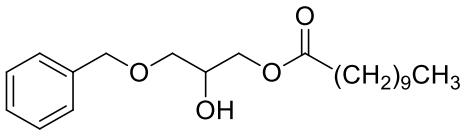
Entry	*Mono acylated product*	*Yield %*	*Literature yield (%)*
1 2 3	 78a	55[a] 58[b] 61[c]	65[140]
4 5 6	 78b	61[a] 54[b] 57[c]	78[141]
7 8 9	 78c	55[a] 52[b] 64[c]	N/A

Table 2.1: Selective acylation of primary alcohol of glycerol **77**. [a]PPh_3, room temperature 2h. [b] P(*o*-tolyl)$_3$, room temperature. [c] P(*o*-tolyl)$_3$, MW 100^{o}C 10 min.

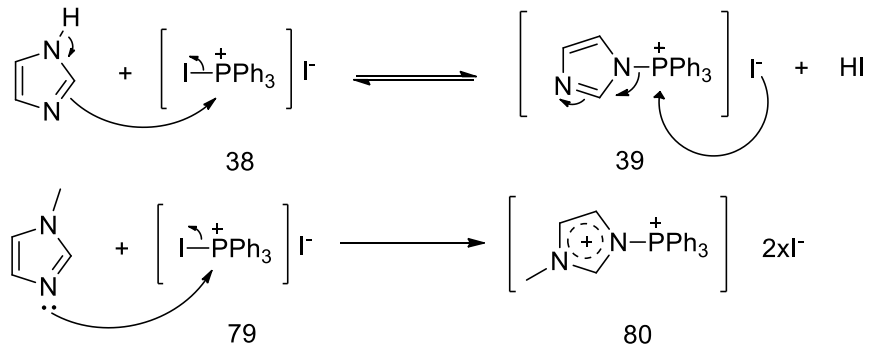
Although the yields reported for esters **78a** and **78b** are comparable lower to those achieved using the Steglich reaction. The DMAP-PPh_3-I_2 mediated method does however offers significantly improved reaction times compared to that of other acylation methods such as the Steglich esterification. The microwave method allows for an even quicker reaction time with similar yields as the room temperature methods. Comparable to the results from Figure 2.1 the bulkiness of the phosphine didn't seem to make much difference in yield when either PPh_3 or P(*o*-toly)$_3$ were used. This suggested that selectivity between primary and secondary alcohols doesn't for the PPh_3-I_2-DMAP mediated acylation doesn't rely on the bulkiness of the phosphine like in the Robles *et al.* which blocks the approach of the incoming alcohol. This then suggest that the

alcohol nucleophile doesn't attack the acyloxyphosphonium intermediate as part of the acylation mechanism, instead attacking an acyl DMAP derivative.

2.1.4 Mechanistic Studies: DMAP's Active Role in Acylation Reactions Using the PPh_3-I_2-DMAP System.

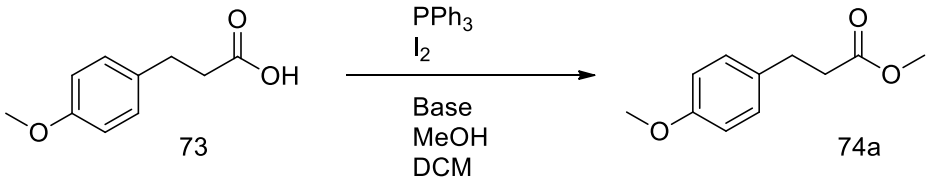
Once the effectiveness of DMAP as a nucleophilic base in acylation reaction systems had been established, it was clear that DMAP was playing a different role to that observed by Robles *et al.* for a similar reaction with imidazole as the base.[90] To further investigate how DMAP differed in function, the synthesis of ester 74a **was attempted using different bases including, triethylamine (NEt_3), imidazole, *N*-methylimidazole, and pyridine (Scheme 2.4,**

Table 2.2). The reactions were stirred for 2 hours at room temperature upon addition of the alcohol. The DMAP reaction gave ester **74a** in a 95% isolated yield. Under comparable conditions the use of imidazole gave ester **74a** in a yield of 53% whereas *N*-methyl imidazoles gave no detectable yield of ester **74a** but did produce a small amount of anhydride **78f** in a yield of 21%. This difference between imidazole and *N*-methyl imidazole can be explained by the ability for imidazole to tautomerize, whist *N*-methyl imidazole cannot. As part of their ^{31}P NMR spectroscopic mechanistic study Roble *et al*. proposed the formation of intermediate **39** between imidazole and the phosphonium diiodide **38** which is characterised by the ^{31}P NMR chemical shift 49.7 ppm (Scheme 2.3). This process is an equilibrium and the imidazole moiety can be displaced because of its ability to tautomerize, and then be displaced by the incoming carboxylate anion to form acyloxyphosphonium intermediate. *N*-Methylimidazole on the other hand, whilst it can act as a nucleophile its lack of tautomerization means that this is not a reversible process so the *N*-methylimidazole cannot behave as a leaving group. This property that has been utilised in the formation of ionic liquid solvents via alkylation of *N*-methylimidazole with alkyl halides.[142]. This observation indicates that imidazole like DMAP plays a significant role in increasing reaction rates for this process.



Scheme 2.3: the difference for imidazole and *N*-methylimidazole to act as a leaving in the esterification or amidation reactions of carboxylic acids.

Pyridine gave ester **74a** in 40% yield; the use of pyridine in this process already has been shown be a less effective than imidazole as demonstrated in Roble's study. NEt_3 gave a low yield ester **74a** (3%), this result can be explained by the observations made by Phakhodeeas. The addition of NEt_3 at the same time as the acid, lead to the rapid formation of the anhydride, the formation of anhydride **76f** was not characterised.[138] Another interesting observation was that the pKa-H of the base did not seem to have doesn't seem to have a direct correlation with the yields of the ester product. NEt_3 (pKa-H=10.75) has the highest basicity of the selected bases but resulted in a very poor yield of the ester product (3%). This can be compared to pyridine (pKa-H=5.21) results in a much higher yield of ester **74a** (40%). It therefore was apparent that that it was the ability for the base to act as a nucleophile and nucleofuge that was an important aspect for the success of the acylation reaction, with the stability of the acylated derivative proposed as the most important factor.



Scheme 2.4: Base screen for esterification of test acid 3-(4-methoxyphenyl) propanoic acid (1). *All reactions left for 2 h at room temperature open to air. Mole eq. based on moles of acid 1.*

Base (Molar equiv.)	*Isolated yield (%)*
NEt_3 (3)	3
Imidazole (3)	53
Pyridine (3)	40
N Methyl imidazole (3)	0
DMAP (3)	95

Table 2.2. Scope of different bases for the esterification of acid 1

The results in the Table clary show that DMAP is the most effective base for this phosphine mediated coupling and that it is the acyl transfer properties of DMAP which are important in the success of this process. Further evidence for the active role of DMAP plays in this acylation system was observed by isolation of an intermediate that can be collected through the course of the reaction. Upon the addition of carboxylic acid **73**, to the stirred solution of PPh_3, I_2 and DMAP in anhydrous CH_2Cl_2, after 5-10 minutes a pale yellow precipitate was formed. This precipitate then dissolved upon addition of the alcohol in this case MeOH. This yellow solid precipitate can be collected by vacuum filtration and upon analysis, was found to be the Ac-DMAP$^+$I$^-$ salt **81** in a 66% yield. The reaction was then repeated with acetic acid and the corresponding Ac-DMAP$^+$I$^-$ salt **82** was collected as a pale yellow solid in a 71% yield (Figure 2.4). The characterisation of the Ac-DMAP$^+$I$^-$ salts **81** and **82** was determined by ^{1}H and ^{13}C-NMR spectroscopy, and electrospray ionization mass spectrometry (ESI-MS). Both the ^{1}H-NMR spectrums showed the correct integration of the proton environment expected for **81** and **82,** whilst the ^{13}C-NMR spectra of **81** showed a carbon resonance at 173.80 ppm which can be attributed to amide carbon. The ^{13}C-NMR spectra of **82** showed a carbon resonance of 171.95 ppm which can again be attributed to the carbon of the amide bond. The mass spectrum of **81** showed an *m/z* peak of 285.15 which can be assigned to the cation of the Ac-DMAP$^+$ whilst there was also an *m/z* peak of 697.23 which can be attributed to the dimer of the cation along with I$^-$ indicating that the counter anion in this species is I$^-$. The mass spectrum of **82** showed an *m/z* peak at 165.10 which can be attributed to Ac-DMAP$^+$ cation whilst the *m/z* peak of 457.11 which again can be attributed to dimer of the cation along with an I$^-$ anion.

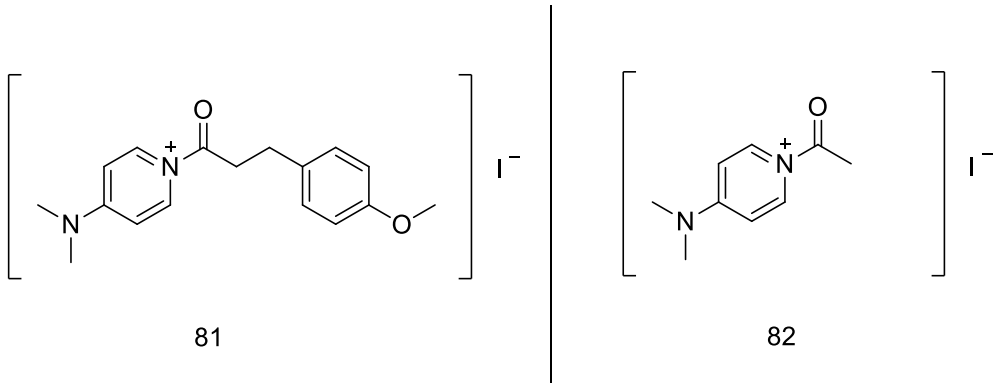
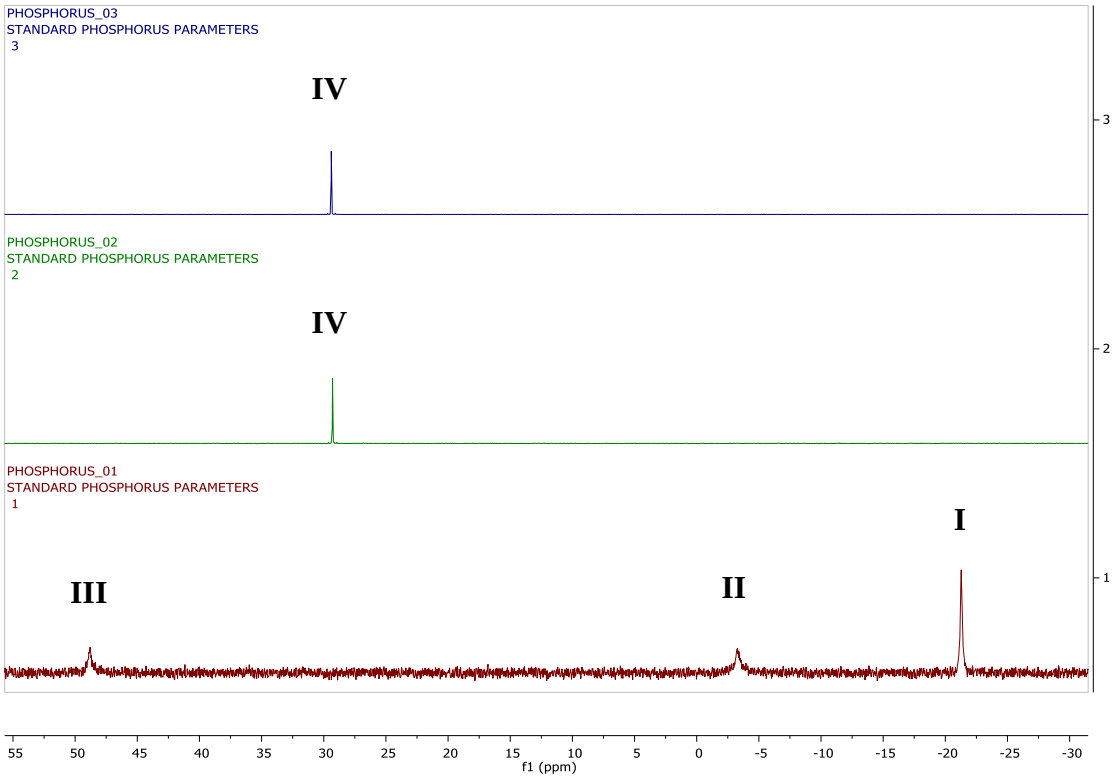


Figure 2.4: Structures of Ac-DMAP^{+}I^{-} species **81** and **82**

This isolation of these acyl-DMAP salts showed that DMAP was playing a different role to that of the other bases. The Acyl-DMAP^{+}I^{-} salts are highly reactive acyl-donor species which allow for the rapid formation of the esters, amides and anhydrides. They is similar to the reactive species suggested in the mechanisms of other DMAP catalysed acylations reactions such as the Steglich esterification, only with a differing counterion in the form of I^{-}.[108,109,111] This was further supported by the Ac-DMAP^{+}I^{-} salt precipitate disappeared following addition of the alcohol or amine nucleophile. The speed that the precipitate disappeared once MeOH was added, demonstrates that the Ac-DMAP^{+}I^{-} salts are highly reactive towards alcohols and could be used a good indication of when the reaction was nearing completion. Simple alcohols such as MeOH result in rapid disappearance of the precipitate and thus fast reaction times (10-20 minutes). More structurally complicated alcohols slowed the disappearance of the precipitate, resulting in slower reaction times. It should be noted however that not all acids tested produced precipitates, depending upon the solubility of the corresponding Ac-DMAP^{+}I^{-} salt intermediates in CH_2Cl_2.



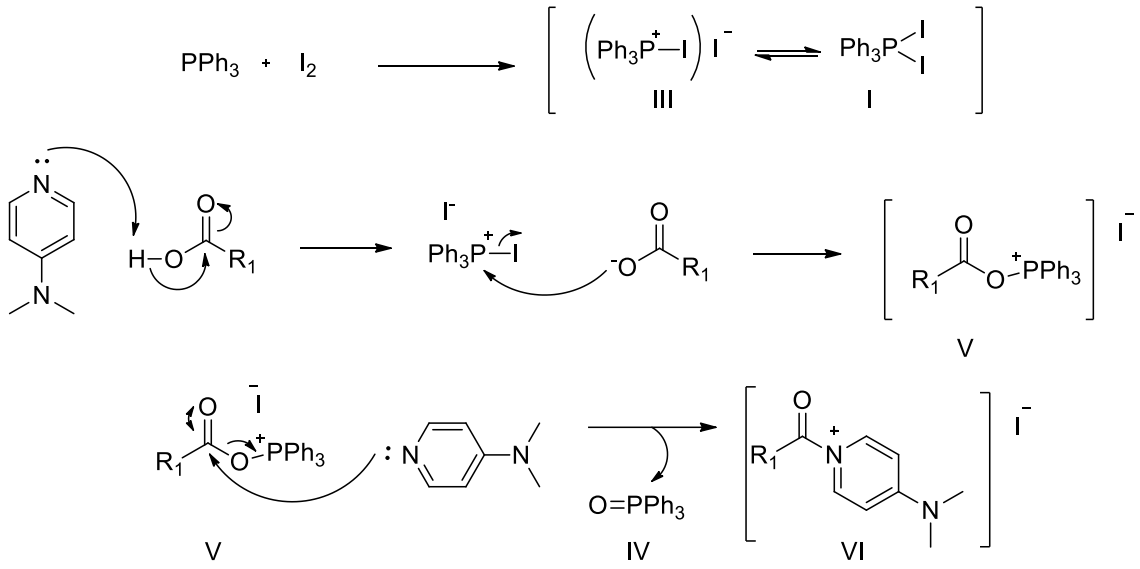
Peak number	Chemical shift (ppm)	Assignment of phosphorus species	Literature (ppm)[138]
I	-21.30	$Ph_3P\begin{matrix}I\\I\end{matrix}$	~ -17.00
II	-3.28	PPh_3	-5.30
III	48.85	$\left[Ph_3P^{+}-I \right] I^{-}$	~ 45.00
IV	29.30	$O=PPh_3$	29.44

Figure 2.5: ^{31}P NMR spectrum study of acylation reaction mediated by PPh_3-I_2-DMAP. Red shows iodine phosphine mixture. Green shows reaction mixture post additional of DMAP and acid **1**. Green shows reaction mixture post addition of MeOH.

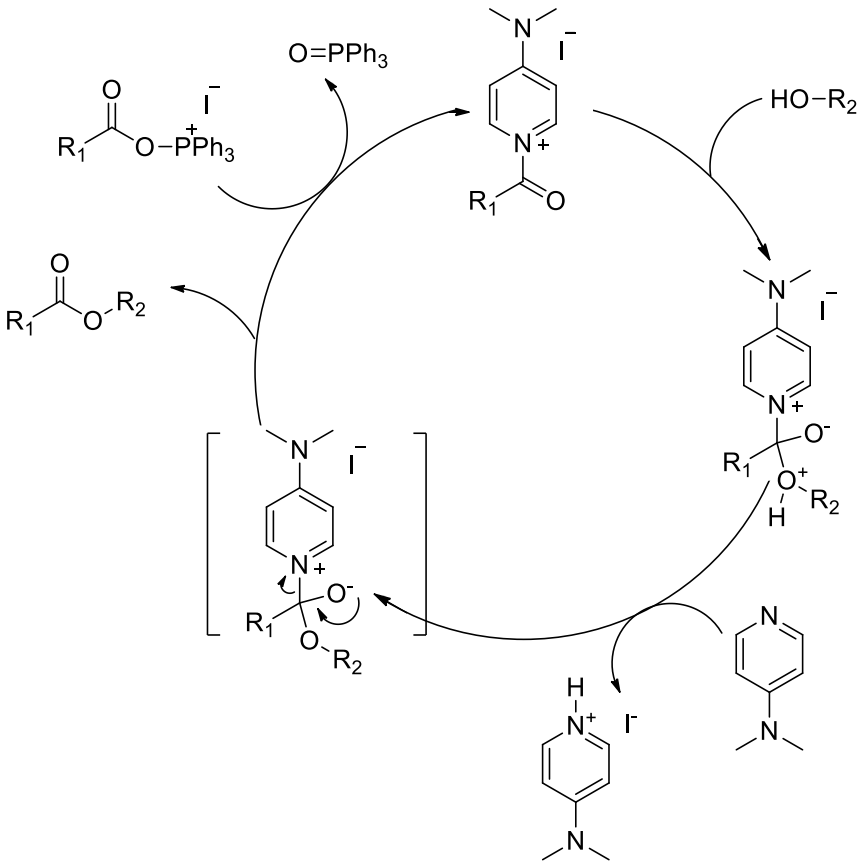
In order to further probe the mechanism as series of ^{31}P NMR spectroscopy experiments were performed. The acylation reaction was carried out in $CDCl_3$ and a sample of the reaction mixture was taken at each stage of the reaction (Figure 2.5). The first ^{31}P NMR spectra show the equilibrium between species **I** and **III**, upon mixing of PPh_3 and I_2. The next ^{31}P NMR spectra show that upon addition of DMAP and acid **73** the only

phosphorus species is that of phosphine oxide (**IV**). This indicates that the carboxylic acid **1** is now no longer associated with the phosphorus and as in now in the form of Ac-DMAP^{+}I^{-} salt **81**. Addition of MeOH to the reaction mixture then produces no difference in ^{31}P NMR spectra. The results of the ^{31}P NMR study (Figure 2.5) and the observation of rapid formation of O=PPh$_3$ (**IV**) leads to the conclusion that the mechanism of the reaction can be seen as having two distinct stages.

The first stage of the reaction (Scheme 2.5) involves the activation of the carboxylic acid via an attack of carboxylate anion species to the phosphonium iodo equilibrium, between **I** (major peak) and **III** (minor broad peak). Upon addition of the carboxylic acid to the reaction mixture of PPh$_3$, I$_2$ and DMAP, the acid becomes deprotonated by one equivalent of the DMAP (thus acting in a specific bases catalyst). S$_N$2 attack of the carboxylate anion to disrupt the phosphonium-iodo equilibrium (**I** and **III**), affords the activated acyloxyphosphonium iodide species that is proposed as a key intermediate by Robles and Froyden.[90,96] DMAP then can attack the acyloxyphosphonium species to form the Ac-DMAP^{+}I^{-} intermediate (**VI**) that is observed as a precipitate, whilst the irreversible formation of O=PPh$_3$ drives the reaction forward. This first stage of the reaction appears to be an extremely rapid process as observed by the rapid formation of O=PPh$_3$ by ^{31}P NMR spectroscopic analysis. The next stage of the reaction proceeds through the classic mechanism of a DMAP catalysed esterification (Scheme 2.6). The activated carbonyl group of **VI** is attacked by the alcohol or amine followed by proton transfer of from the nucleophile to the final equivalent of DMAP (which could be acting as a general base catalyst as well as a nucleophilic base). This allows for the departure of the DMAP leaving group, resulting in in the ester or amide product and regeneration of the DMAP catalyst.



Scheme 2.5: Proposed 1st stage of acylation reaction mediated by PPh_3/I_2/DMAP to form N-Acyl-DMAP species **VI**.

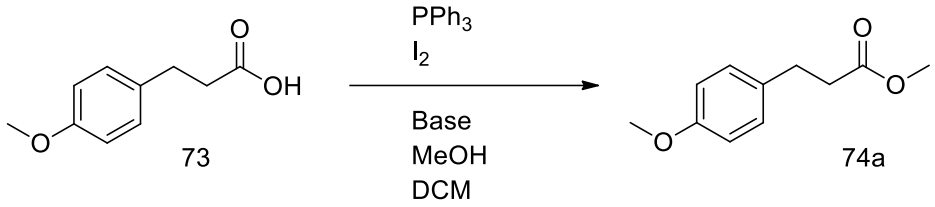


Scheme 2.6: Proposed 2nd stage of reaction mechanism, formation of ester product via classic catalytic DMAP mechanism**.**

2.2 Catalytic DMAP Studies

The result of the ^{31}P NMR spectroscopic studies led to the proposition that if the *N*-acyl DMAP species described above was the active intermediate for transforming the alcohol or amine to the ester or amide product, then it would share features of the mechanism at this stage of the reaction with other DMAP catalysed acylation reactions (Steglich and Yamaguchi reactions). Therefore, there should be an opportunity to make this reaction catalytic in DMAP, thus reducing cost and any risks via the use of an auxiliary base. According to the mechanisms described above two of the three equivalents of DMAP become protonated and do not take further part in the reaction. This would then suggest that only a small proportion of DMAP is be required to act as the catalyst, as the DMAP would be getting recycled as the reaction proceeds. If this was the case then the amount of DMAP required could be reduced in molar quantities and replaced with an auxiliary base providing the pKa of the conjugant acid is higher than that of DMAP (pKa-H 9.2).[98] NEt_3 (pKa-H of 10.75) looked to be one good option as an auxiliary base due to its relatively low cost and common use as base in ester and amide bond formation.[98]

In order to determine how the reduction in DMAP would affect the reaction. The procedure was carried out under the same reaction conditions as before; the base or mixture of bases were added to a stirred solution PPh_3 (1.5 equiv.) and I_2 (1.5 equiv.) in anhydrous CH_2Cl_2. This was followed addition of acid **73** (1 equiv.), the mixture was allowed to stir for 10 minutes before MeOH (1.5 equiv.) was added after the reaction was stirred at room temperature for 2 hours, followed by purification by flash column chromatography on silica resulted in ester **74a** (Table 2.3). The use DMAP (three equiv.) alone gave isolated ester **74a** in 95% isolated yield (entry 1). However, reducing the stoichiometry of DMAP to two equivalents dramatically reduces the isolated yield of ester **74a** to 16% (entry 2). The same was true when only one molar equivalent of DMAP was used resulting in an isolated yield of 16% (entry 3) whereas when no base was present used no product was isolated (entry 4). These results can be explained by the mechanism described previously, which indicate that at least two equivalents of base are needed as for complete reaction leaving no DMAP available to take part in the catalytic cycle (Scheme 2.6).



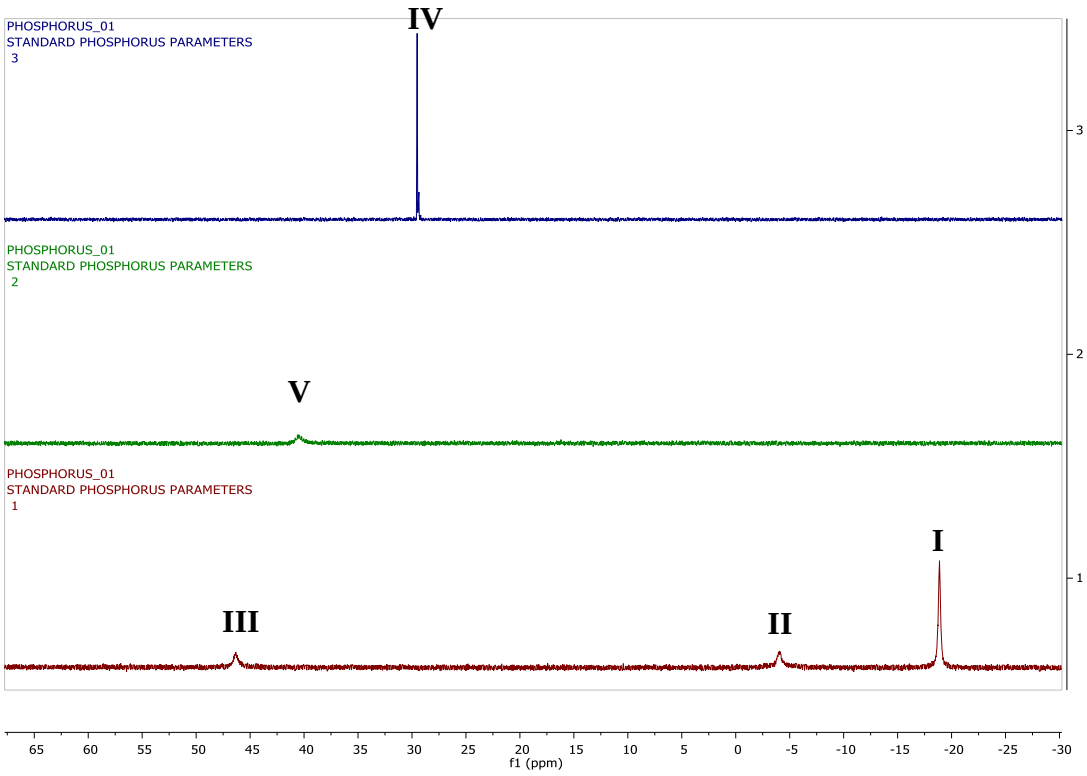
Entry	Base (Molar equiv.)	Auxiliary base (Molar equiv.)	Isolated yield (%)
1	DMAP (3)	NEt_3 (0)	95
2	DMAP (2)	NEt_3 (0)	16
3	DMAP (1)	NEt_3 (0)	16
4	DMAP (0)	NEt_3 (0)	0
5	DMAP (0)	NEt_3 (3)	3
6	DMAP (1)	NEt_3 (2)	89
7	DMAP (0.5)	NEt_3 (2)	82
8	DMAP (0.1)	NEt_3 (2)	68
9	DMAP (0.1)	NEt_3 (3)	63

Table 2.3: A base study to determine the molar equivalents of DMAP and auxiliary base required for esterification reaction between acid 1 and MeOH. All reaction where carried out in anhydrous CH_2Cl_2 and reacted for two hours.

Introducing NEt_3 as an auxiliary base demonstrates that it is indeed possible for the reaction to be made catalytic with respect to DMAP. When 1 equivalent of DMAP and 2 equivalents of NEt_3 were used a very good isolated yield (89%) was obtained (entry 6). This was a promising result which showed that good yields could be achieved in a short period of time with reduced amounts of DMAP. When the quantity of DMAP was reduced to 0.5 equivalents and 2 equivalent of NEt_3 (entry 7) a good isolated yield was achieved (82%). When the DMAP equivalents where further dropped to 0.1 equivalents with 2 equivalent of NEt_3 (entry 8, 68%) and 3 equivalents of NEt_3 (entry 9, 63%), good yields where achieved though the yield did drop down quite significantly. The reason for this lowering in yield is most likely due to the reduced concentrations of the key acyl-DMAP species. Increased reaction times could help with improve yield, but these

results are still offer kinetic improvements over other common acylation methods. The reaction time was kept to 2 hours so that direct comparison could be made. In conclusion the results from show that this acylation process can precede in high efficiency catalytic in DMAP therefore reduce the cost and risk by using an auxiliary base such as NEt_3 as long as that base has a higher pKa-H than DMAP.

A second ^{31}P NMR spectroscopic study was performed in order to determine if there was any difference in the formation of phosphorus species in the presence of NEt_3 as an auxiliary base (Figure 2.6) compared to the reaction performed using DMAP system (Figure 2.5). For these ^{31}P NMR experiments, the reaction was again performed in deuterated chloroform ($CDCl_3$). The red spectrum shows the ^{31}P NMR spectra for the phosphine iodine mixture which results in the phosphorus species **I**, **II**, and **III** as observed in the previous study. The green spectrum shows the reaction mixture after simultaneous addition of NEt_3 and carboxylic acid **1** this gives a new peak at chemical shift of δ 40.49 ppm which is labelled as **V** and has been assigned speculatively as the intermediate acyloxyphosphonium salt. To date there has been little NMR evidence of such a species in the literature. However, a study by Cruz-Almanza *et al.* suggested a similar species as part of a P^{31} NMR study assigned at δ 46.9 ppm and attributed to the phosphorus nucleus of the benzoic acid adduct as a benzyloxyphosphonium salt with bromide ion as the counter ion, synthesised from the reaction PPh_3, NBS and benzoic acid.[143] The peak at δ 40.49 ppm also closely matches that of other 4 coordinate phosphonium species; for instance the assignment of **III** which has a chemical shift of around δ 45 ppm according to literature.[88,90] However, the formation of a NEt_3 phosphonium adduct can be ruled out as there is no literature evidence. Finally the blue spectrum following the addition of 1 equivalent of DMAP; once again it showed almost instantaneous formation of **IV** ($O=PPh_3$). The rapid formation of **IV** following the addition once the DMAP to the reaction mixture also suggests that the peak at δ 40.49 ppm is likely to be the acyloxyphosphonium intermediate.



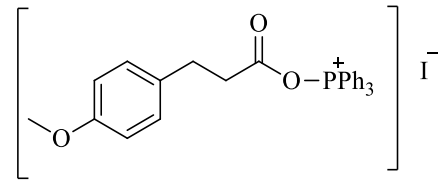
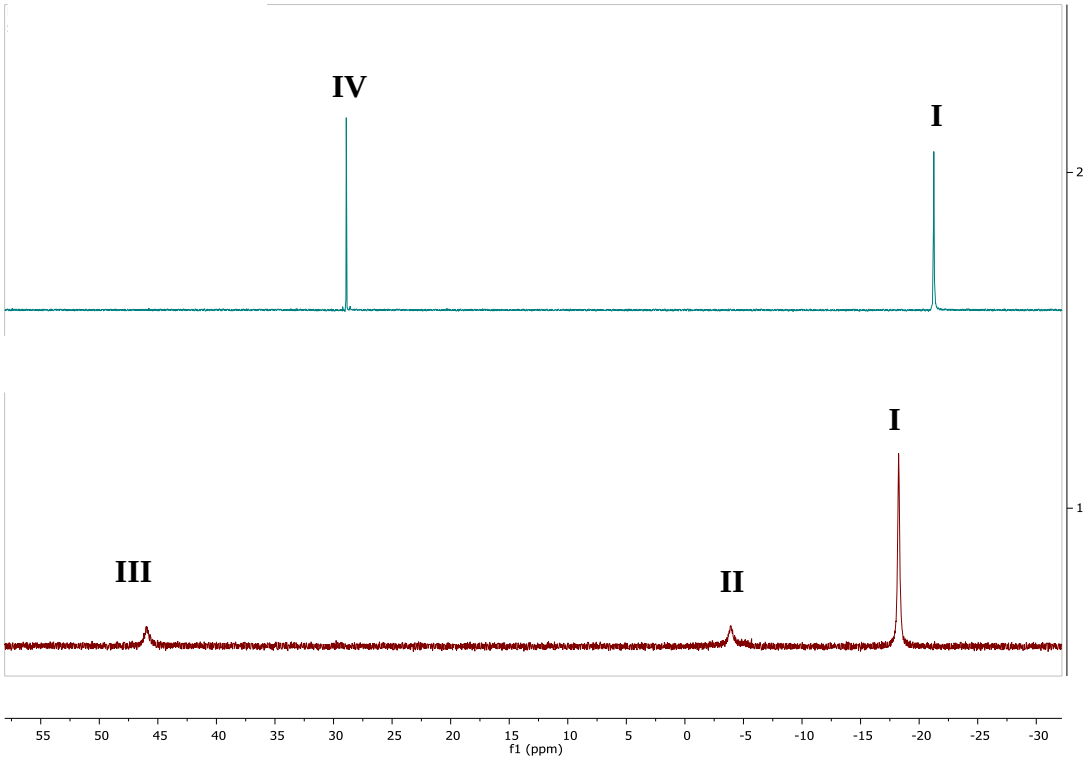
Peak number	Chemical shift/ ppm	Assignment of Phosphorus species	Literature values[138,143] /ppm
I	-18.88	$Ph_3P(I)_2$	~ -17.00
II	-3.99	PPh_3	-5.30
III	46.31	$[Ph_3P^+-I]\ I^-$	~ 45.00
IV	29.52	$O=PPh_3$	29.44
V*	40.49		46.9[*143] (similar salt)

Figure 2.6: P^{31} NMR study of reaction catalytic in DMAP with NEt_3 as auxiliary base. Red shows iodine -phosphine mixture. Green shows reaction mixture post-additional of NEt_3 and acid **1**. Blue shows reaction mixture post addition of 1 equiv. of DMAP. *Speculative assignment; similar salt assigned in literature.

In order to further qualify the assignment of peak **V**, an additional ^{31}P NMR experiment was performed (Figure 2.7). The addition of NEt_3 to phosphine-iodine mixture in $CDCl_3$ led to the formation of peaks at δ -21.25 and at δ 28.91ppm. The peak at δ 28.91 ppm suggested the formation of $O=PPh_3$ (**IV**). The peak at δ -21.25 suggested the presence of species **I** as seen in our previous P^{31} NMR studies (Figure 2.5, Figure 2.6), the slight change of chemical shift attributed to an altered solvation sphere in the presence of NEt_3. There is no indication of a peak around δ 40 ppm seen in previous study Figure 2.6. This suggested that species **V** was not the NEt_3-PPh_3 adduct. Addition of acid **73** to the reaction mixture before the addition of any base gave similar results to the reaction between PPh_3 and I_2 with peaks at δ 46.03, -3.88 and -18.25 ppm, indicating that deprotonation of the carboxylic acid is important in the initial formation of the active acyloxyphosphonium species **V**. Both these studies give further evidence that the peak assigned **V** was most likely to be the acyloxyphosphonium intermediate suggested above.



Peak number	Chemical shift (ppm)	Assignment of Phosphorus atom	Literature values[138] (ppm)
I	-18.25[a], -21.25[b]	$Ph_3P\begin{matrix}I\\I\end{matrix}$	~ -17.00
II	-3.88	PPh_3	-5.30
III	46.03	$\left[Ph_3P^{+}-I \right] I^{-}$	~ 45.00
IV	28.91	$O=PPh_3$	29.44

Figure 2.7: ^{31}P NMR study to support the assignment of V. Red shows mixture of acid **1**, PPh_3 and I_2. Blue study shows NEt_3 added to mixture of PPh_3 and I_2. [a] Red, [b] Blue

2.2.1 Scope of Catalytic System.

In order to determine the scope of the catalytic DMAP system a small study was performed to test its effectiveness in the formation of esters. The synthesis of six different products, already prepared using three equivalents of DMAP, was investigated so that the results could be compared. The procedure again followed the original method in with reaction times of two hours at room temperature, the only difference being the use of 0.5 equivalents of DMAP and two equivalents of NEt_3 as the auxiliary base. This base system was chosen as although it didn't produce the best results in terms of yields it still gave high yields within the 2 hours whilst also giving significantly reduced quantities of DMAP (Figure 2.8). The isolated yields for esters **74a** (89%) and **74i** (92%) were only slightly lower than that achieved with DMAP alone. Ester **74d** (78%) however resulted in a 9% lower yield then that for DMAP alone. It was noticed that a precipitate formed after addition of alcohol which persisted form about 30 minutes, whereas no precipitate was seen for the synthesis of ester **74a** and **74i**. This precipitate was not collected for isolation. Amides **75c** (83%) and **75d** (79%) again gave slightly lower yields than those achieved with the DMAP only system. Ester **75n** (93%) gave and gave an improved yield compared to that of DMAP only system showing that the catalytic system works very well for acid that are electron poor.

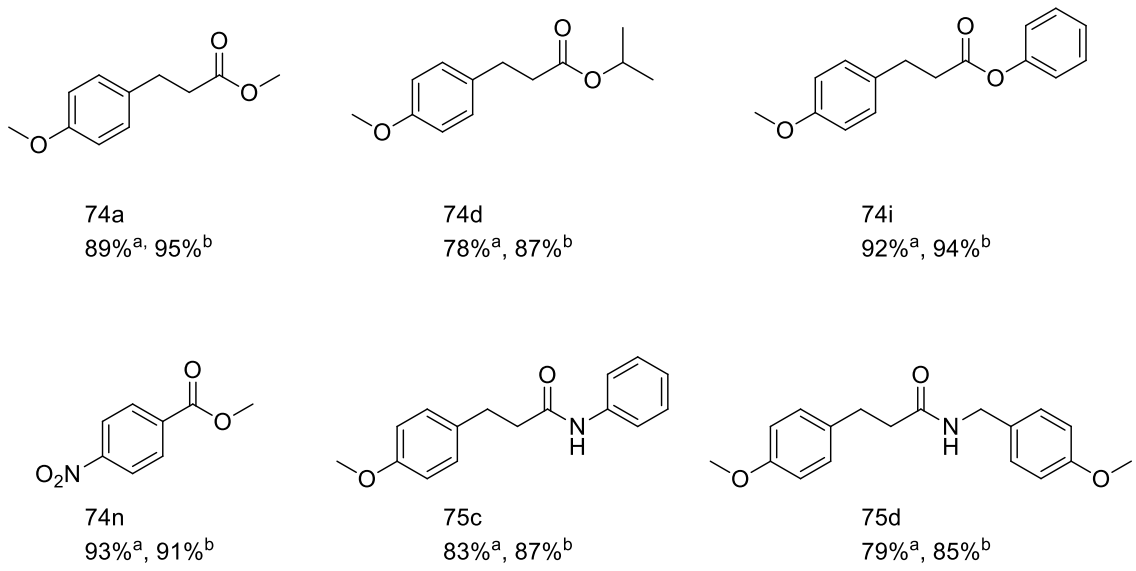


Figure 2.8: scope of catalytic procedure; all reactions were performed for 2 h in anhydrous CH_2Cl_2 with 2 equiv. of NEt_3 and 0.5 equiv. of DMAP. [a]Catalytic yield, [b]DMAP only yield.

2.3 Conclusion

In conclusion the work carried out and discussed in this chapter has described the development of a new reagent system for the direct coupling of carboxylic acids with alcohols and amines. The new PPh_3-I_2-DMAP reagent system developed matches the criteria set at the start of the chapter;

1. The method is mild and performed at room temperature therefore allowing the use of sensitive acids and nucleophiles as demonstrated by the board range of functionalities producing good to excellent yields for all esters and amides tried. Secondary alcohols where synthesised in high yields compared with the imidazole method even when the bulkier P(*o*-(tolyl)$_3$) was used in place of PPh_3. Apart from the formation of ester formation with *t*-butyl alcohol. The method has also been shown to be able to form anhydrides.
2. The new system is based around PPh_3, I_2 and DMAP all of which are relatively cheap commerically available reagents and are readily available in many organic chemistry laboratories.
3. The method is simple to perform requiring no specialist equipment just the simple mixing of the reagents. An inert atmosphere is not required and purification by flash chromatography makes the procedure easy to perform.
4. Many of the esters and amides were synthesised in less than 30 minutes with the reaction taking no longer than 2 hours. This compares favourably with other common esterification methods such as the Steglich reaction. The use of microwave chemistry can again cut this reaction time down further to 10 minutes.

Even though the method was not shown to be as selective towards primary alcohols as Roble's imidazole method, the application of the DMAP reagent system to the formation of primary alcohol, acylated glycerol's produced results that were comparable to more the commonly used Steglich reaction. Furthermore a mechanism has been proposed and is supported by a series of ^{31}P NMR spectroscopic studies and isolation of *N*-acyl-DMAP salts. The mechanism has two distinct parts. In the first part the *N*-acyl-DMAP salt is formed via initial activation of the carboxylic acid with phosphine followed by further activation via nucleophilic attack of DMAP. The second part

follows the classic catalytic cycle of DMAP acylations as postulated by Steglich and others. The catalytic system was shown to produce similar results to that produced when an excess of DMAP was used but still in short reaction times, meeting criteria 4 of the aims stated at the start of the chapter.

2.4 Experimental and Characterisation

General Methods

Commercially available reagents were used without further purification;. Solvents where dired using. Unless otherwise stated reaction where carried out in air at roomtemperature. Microwave irradiation experiments were performed in a sealed Pyrex tube using a self-tunable CEM Explorer focused monomodal microwave synthesizer at the given temperature using the instrument's in-built IR temperature measuring device, by varying the irradiation power. Flash chromatography was carried out using a Teledyne ISCO Combiflash Rf instrument and Biotage SNAP KP-Sil cartridges packed with 50 μm silica particles. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck TLC Silica gel 60 F_{254} that were visualized under UV light (at λ 254 and/or 360 nm).

Fully characterized compounds were chromatographically homogeneous. Melting points were determined using tanford Research Systems Optimelt and are uncorrected. NMR spectra were recorded using a Varian VNMRS instrument operating at 500 MHz for ^{1}H spectra and 125 MHz for ^{13}C spectra; *J* values were recorded in Hertz (Hz) and multiplicities were expressed by the usual conventions. Low resolution mass spectra were determined using a Fisons VG autospec instrument using atmospheric pressure chemical ionization (APcI). High resolution mass spectra were determined using a Bruker Daltronics Apex III instrument by electrospray ionization (ESI).

General Procedure for Esterification/Amidation of Carboxylic Acids with Phosphine/I_2/DMAP System.

Room temperature method

To a well stirred solution of I_2 (1.5 equiv.) in anhydrous CH_2Cl_2 (15 mL), PPH_3 (1.5 equiv.), DMAP (3.0 equiv.) was added carboxylic acid (1.0 equiv.). The reaction was allowed to stir for 5 min before the alcohol or amine (1.5 equiv.) was added and the reaction mixture was stirred for a maximum of 2 h. The progress of reaction was monitored by the TLC (Hexane/EtOAc). After the completion of the reaction, Celite® was added to the reaction mixture and the solvent removed *in vacuo* resulting in a fine dry powder. The resulting solid was purified via solid loading flash column chromatography on silica (Hexane/EtOAc) providing ester or amide in good to excellent yields.

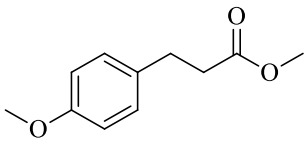
Microwave method

To a well stirred solution of I_2 (1.5 equiv.) in anhydrous CH_2Cl_2 (10-15 mL), PPh_3 (1.5 equiv.), DMAP (3.0 equiv.) was added carboxylic acid (1.0 equiv.). After stirring for 5 min, the alcohol or amine (1.5 equiv.) was added and the solution was heated under microwave conditions of 100^{o}C for 10 minutes. After the completion of the reaction, Celite® was added to the reaction mixture, the solvent removed *in vacuo* resulting in a fine dry powder. The solid was purified via solid loading flash column chromatography on silica (Hexane/EtOAc) providing ester or amide in good to excellent yields.

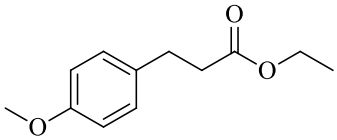
Catalytic method

To a well stirred solution of I_2 (1.5 equiv.) in anhydrous CH_2Cl_2 (10-15 mL), Phosphine (1.5 equiv.), DMAP (0.5 equiv.), NEt_3 (2 equiv.) was added the carboxylic acid (1.0 equiv.). The reaction mixture was allowed to stir for 5 minutes before the alcohol or amine (1.5equiv.) was added and the reaction was further stirred at room temperature for 2 hours. After the completion of the reaction, Celite® was added to the reaction mixture and the solvent removed *in vacuo* resulting in a fine dry powder. The solid was purified via solid loading flash column chromatography on silica (Hexane/EtOAc) providing ester products in good to excellent yields.

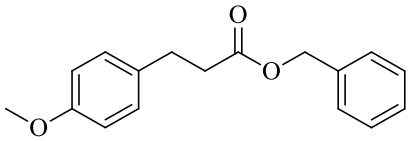
Characterisation of Esterification Products



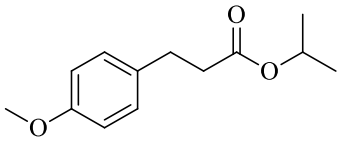
Methyl 3-(4-methoxyphenyl)propanoate (74a), room temperature yield 95% (PPh_3), 87% (P(*o*-tolyl)$_3$), microwave yield 93% (P(*o*-tolyl)$_3$), catalytic yield 89%, white low melting point solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.5 Hz, 2H, ArH), 6.84 (d, *J* = 8.5 Hz, 2 ArH), 3.79 (s, 3H, CH_3), 3.67 (s, 3H), 2.91 (t, *J* = 7.8 Hz, 2H), 2.61 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.34 (C=O), 158.09 (C), 132.58 (C), 129.19 (CH), 113.92 (CH), 55.21 (CH_3), 51.51 (CH_3), 35.98 (CH_2), 30.10 (CH_2). ESI-MS (*m/z*) 195.1016 (M^{+H}). Known compound, spectra matches.[144]



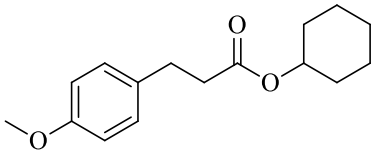
Ethyl 3-(4-methoxyphenyl)propanoate (74b), room temperature yield 98% (PPh_3), 96% (P(*o*-tolyl)$_3$), microwave yield 93% (P(*o*-tolyl)$_3$), yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 2.90 (t, *J* = 8.0 Hz, 2H), 2.59 (t, *J* = 8.0 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.93 (C=O), 158.06 (C), 132.66 (C), 129.21 (CH), 113.88 (CH), 60.32 (CH_3), 55.23 (CH_2), 36.24 (CH_2), 30.13 (CH_2), 14.20 (CH_3). ESI-MS (*m/z*) 209.1172 (M^{+H}). Known compound, spectra matches.[145]



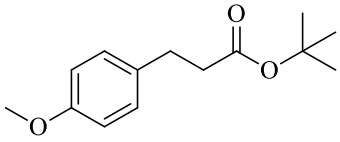
Benzyl 3-(4-methoxyphenyl) propanoate (74c), room temperature yield 91% (PPH_3) 69%, (P(*o*-tolyl)$_3$), microwave yield 89% (P(*o*-tolyl)$_3$), yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.12 (s, 2H), 3.79 (s, 3H), 2.93 (t, *J* = 8.0 Hz, 2H), 2.67 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.73 (C=O), 158.09 (C), 135.97 (C), 132.47 (C), 129.23 (CH), 128.50 (CH), 128.17 (CH), 113.91 (CH), 66.20 (CH_2), 55.24 (CH_3), 36.20 (CH_2), 30.12 (CH_2). ESI-MS (*m/z*) 293.1149 ($M^{+\ Na}$). Known compound, spectra matches.[146]



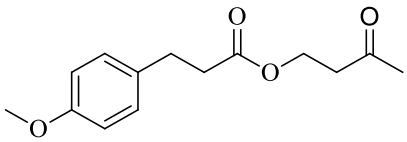
Isopropyl 3-(4-methoxyphenyl)propanoate (74d), room temperature yield 87% (PPh_3), 63% (P(*o*-tolyl)$_3$), microwave yield 77% (P(*o*-tolyl)$_3$), catalytic yield 78%, yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.01 (hept, *J* = 6.5 Hz, 1H), 3.79 (s, 3H), 2.89 (t, *J* = 8.0 Hz, 2H), 2.56 (t, *J* = 8.0 Hz, 2H), 1.21 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.46 (C=O), 158.04 (C), 132.70 (C), 129.22 (CH), 113.85 (CH), 67.59 (CH), 55.24 (CH_3), 36.53 (CH_2), 30.19 (CH_2), 21.80 (CH_3). ESI-MS (*m/z*) 223.1327 (M^{+H}). Known compound, spectra matches.[90]



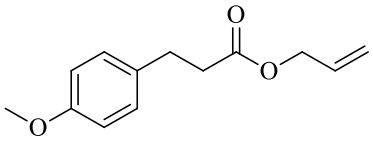
Cyclohexyl 3-(4-methoxyphenyl)propanoate (74e), room temperature yield 71% (PPh_3) 65% (P(*o*-tolyl)$_3$), microwave yield 76% (P(*o*-tolyl)$_3$), yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.76 (tt, *J* = 8.0, 4.0 Hz, 1H), 3.79 (s, 3H), 2.90 (t, *J* = 8.0 Hz, 2H), 2.58 (t, *J* = 8.0 Hz, 2H), 1.81 (s, 2H), 1.71 (m, 2H), 1.53 (m, 1H), 1.37 (m, 4H), 1.26 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.40 (C=O), 158.03 (C), 132.73 (C), 129.21 (CH), 113.85 (CH), 72.57 (CH), 55.24 (CH_3), 36.55 (CH_2), 31.61 (CH_2), 30.23 (CH_2), 25.38 (CH_2), 23.73 (CH_2). EI-MS (*m/z*) 262 ($M^{\cdot+}$).



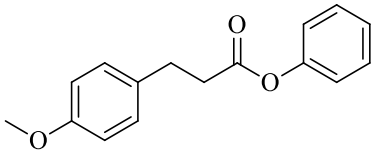
Tert-butyl 3-(4-methoxyphenyl)propanoate (74f), *yield 0%*



3-Oxobutyl 3-(4-methoxyphenyl)propanoate (74g), room temperature yield 80% (PPh_3) 64% (P(*o*-tolyl)$_3$), microwave yield 62 % (P(*o*-tolyl)$_3$), clear oil. IR (cm^{-1}): *v* = 1728 (s, br), 1513 (s), 1244 (s), 1032 (s), 826.16 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 4.33 (t, *J* = 6.5 Hz, 2H), 3.79 (s, 3H), 2.88 (t, *J* = 8.0 Hz, 3H), 2.71 (t, *J* = 6.5 Hz, 2H), 2.58 (t, *J* = 8.0 Hz, 2H), 2.16 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.45 (C=O), 172.73 (C=O), 158.10 (C), 132.42 (C), 129.20 (CH), 113.90 (CH), 59.20 (CH_2), 55.23 (CH_3), 42.25 (CH_2), 36.00 (CH_2), 30.15 (CH_2), 30.03(CH_3). ESI-MS (*m/z*) 273.1093 (M^{+Na})

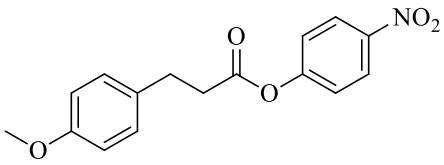


Allyl 3-(4-methoxyphenyl)propanoate (74h), room temperature yield 82% (PPh_3), 78% (P(*o*-tolyl)$_3$), microwave yield 91% (P(*o*-Tolyl)$_3$), yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.91 (m, 1H), 5.34 – 5.20 (m, 2H), 4.59 (d, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 2.92 (t, *J* = 8.0 Hz, 2H), 2.64 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.54 (C=O), 158.10 (C), 132.53 (C), 132.20 (CH), 129.22 (CH), 118.14 (CH_2), 113.91 (CH), 65.07 (CH_2), 55.23 (CH_3), 36.14 (CH_2), 30.09 (CH_2). EI-MS (*m/z*) 220 ($M^{\cdot +}$). Known compound, matches spectra.[90]

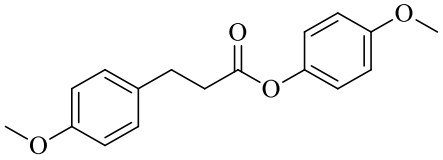


Phenyl 3-(4-methoxyphenyl)propanoate (74i), room temperature yield 94% (PPh_3), 72% (P(*o*-tolyl)$_3$), microwave yield 90% (P(*o*-tolyl)$_3$), catalytic yield 92%, yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.0 Hz, 2H), 7.24 (m, 3H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 3.83 (s, 3H), 3.06 (t, *J* = 7.5 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.41 (C=O), 158.27 (C), 150.74 (C), 132.23 (C), 129.39 (CH), 129.38 (CH), 125.77 (CH), 121.56 (CH), 114.04 (CH), 55.27 (CH_3),

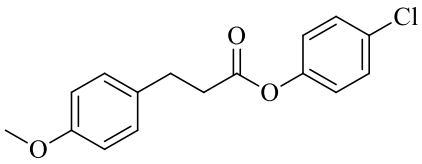
36.31 (CH_2), 30.16 (CH_2). EI-MS (*m/z*) 256 ($M^{\cdot +}$). Know compound, matches spectra.[147]



4-Nitrophenyl 3-(4-methoxyphenyl)propanoate (74j), room temperature yield 83% (PPh_3), colourless solid- mp 105.1-106.5°C. IR (cm^{-1}) *v*= 1746 (m), 1515 (s), 1350 (s), 1240 (m), 1205 (m), 1121 (s), 860 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.5 Hz, 2H), 7.19 (m, 4H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.81 (s, 3H), 3.03 (t, *J* = 7.5 Hz, 2H), 2.90 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.72 (C=O), 158.23 (C), 157.22 (C), 144.21 (C), 132.25 (C), 129.31 (CH), 122.22 (CH), 114.42 (CH), 113.99 (CH), 55.55 (CH_3), 36.21 (CH_2), 30.14 (CH_2). ESI-MS (*m/z*) 324.0846 ($M^{+ Na}$)

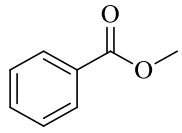


4-Methoxyphenyl 3-(4-methoxyphenyl)propanoate (74k), room temperature yield 91% (PPh_3), colourless solid, mp 86.1-88.3°C, IR (cm^{-1}) *v*= 1748.52 (m), 1504.92 (m), 1466.95 (m), 1237.86 (m), 1131.36 (s), 1099.33 (s), 1031.36 (s), 851.54 (s), 813.37 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.88 – 6.85 (m, 4H), 3.80 (s, 3H), 3.79 (s, 3H) 3.01 (t, *J* = 7.6 Hz, 2H), 2.83 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.72 (C=O), 158.23 (C_{ar}), 157.22 (C_{ar}), 144.21 (C_{ar}), 132.25 (C_{ar}), 129.31 (C_{ar}), 122.22 (C_{ar}), 114.42 (C_{ar}), 113.99 (C_{ar}), 55.55 (OCH_3), 55.25 (OCH_3), 36.21 (CH_2), 30.14 (CH_2). ESI-MS (*m/z*) 309.1099 ($M^{+ Na}$)

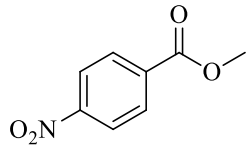


4-Chlorophenyl 3-(4-methoxyphenyl)propanoate (74l), room temperature yield 91% (PPh_3),white solid, mp 69.5-70.9°C. IR (cm^{-1}) *v*= 1751 (m), 1513 (m), 1489 (m), 1203 (s), 1122 (s), 1035 (m), 816 (m, br); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, 8.5 Hz, 2H),

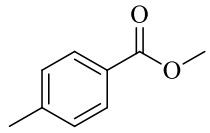
7.18 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.81 (s, 3H), 3.01 (t, *J* = 7.5 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.11 (C=O), 158.29 (C), 149.14 (C), 132.00 (C), 131.11 (C), 129.38 (CH), 122.86 (CH), 114.03 (C_{ar}), 55.25 (CH_3), 36.17 (CH_2), 30.05 (CH_2). ESI-MS (*m/z*) 313.0603 ($M^{+\,Na}$)



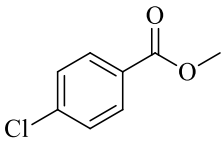
Methyl benzoate (74m), room temperature yield 80% (PPh_3), colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$):δ 8.07 – 8.03 (2H, m), 7.56 (1H, m), 7.47 – 7.42 (2H, m), 3.93 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.05 (C=O), 132.83 (CH), 130.22 (C), 129.54 (CH), 128.31 (CH), 52.00 (*C*H_3); EI-MS (*m/z*): 136 ($M^{\cdot+}$). Known compound, spectra matches.[148]



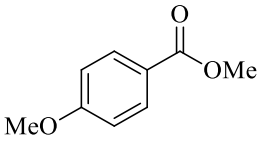
Methyl 4-nitrobenzoate (74n), room temperature yield 91% (PPh_3), cataytic yield 93%, pale yellow solid, mp 94.7-95.6 ^{o}C, (lit[149] mp 95-96 ^{o}C) ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (2H, d, J= 9.0 Hz), 8.22 (2H, d, J= 9.0 Hz), 3.99 (3H, s, O-CH_3).^{13}C NMR (126 MHz, $CDCl_3$) δ 165.12 (C=O), 150.58 (C), 135.50 (CH), 130.67 (CH), 123.49 (CH), 52.75 (O-CH_3); EI-MS (*m/z*): 181 ($M^{\cdot+}$). Known compound, spectra matches.[149]



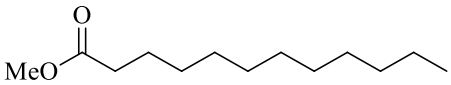
Methyl 4 methlybenzoate (74o), room temperature yeild 86% (PPh_3), low melting point solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J*= 8.0 Hz, 2H), 7.24 (d, *J*= 8.0 Hz, 2H), 3.90 (3H, s), 2.41 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.11 (C=O), 143.46 (C), 129.57 (CH), 129.01 (CH), 127.49 (CH), 51.83 (O-*C*H_3), 21.56 (*C*H_3); EI-MS (m/z): 150 ($M^{\cdot+}$). Known compound, spectra matches.[149]



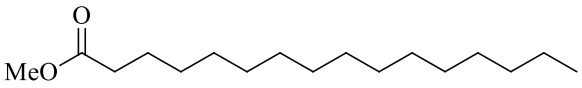
Methyl 4-chlorobenzoate (74p), room temperature yield 79% (PPh_3), colourless oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 – 7.94 (d, *J* = 9.0 Hz, 2H), 7.45 – 7.38 (d, *J* = 9.0 Hz, 2H), 3.92 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.15 (C=O), 139.34 (C_{ar}), 130.93 (C_{ar}), 128.67 (CH), 128.64 (CH), 52.17 (CH_3); EI-MS (*m/z*): 170 ($M^{\cdot+}$). Known compound, spectra matches.[148]



Methyl 4 methoxybenzoate (74q), room temperature yield 98% (PPh_3), colourless solid MP 48.6-49.3 ^{o}C (*lit*[148] 49-51^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 9.0, 2H), 6.90 (d, *J* = 9.0, 2H), 3.88 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.80 (C=O), 163.33 (C_{ar}), 131.55 (C_{ar}), 122.67 (C_{ar}), 113.59 (C_{ar}), 55.36 (OCH_3), 51.76 (CO_2CH_3); EI-MS (*m/z*): 166 ($M^{\cdot+}$). Known compound, spectra matches.[148]



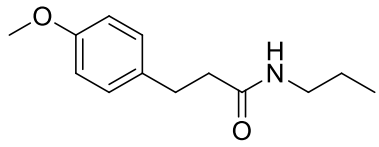
Methyl dodecanoate (74r), roomtemperature yield 96% (PPh_3), colourless oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.68 (s, OCH_3, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.62 (q, *J* = 7.5 Hz, 2H), 1.28 (14H, m), 0.89 (3H, t, J= 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.19 (C=O), 51.30 (OCH_3), 34.08 (CH_2), 31.86 (CH_2), 29.65 (CH_2), 29.61 (CH_2), 29.55 (CH_2), 29.40 (CH_2), 29.27 (CH_2), 29.21 (CH_2), 24.79 (CH_2), 22.62 (CH_2), 14.01 (CH_3); EI-MS (*m/z*): 215 (M^{+H}). Known compound, spectra matches.[150]



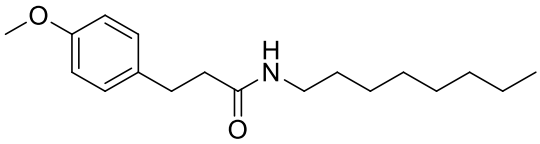
Methyl palmitate (74s), room temperature yield 94% (PPh_3), colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.64 (q, *J* = 7.5 Hz, 2H), 1.27 (m, 24H), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 174.22 (C=O), 51.32 (OCH_3), 34.09 (CH_2), 31.89 (CH_2), 29.65 (CH_2), 29.64 (CH_2), 29.63 (CH_2), 29.61 (CH_2), 29.60 (CH_2), 29.55 (CH_2), 29.41 (CH_2), 29.31 (CH_2), 29.21 (CH_2), 29.13 (CH_2),

24.94 (CH_2), 22.64 (CH_2), 14.03 (CH_3); EI-MS (*m/z*): 270 ($M^{\cdot+}$). Known compound, spectra matches.[150]

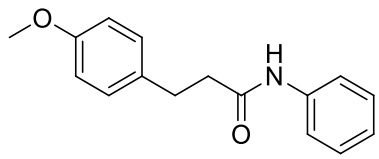
Classification of Amides Products



3-(4-Methoxyphenyl)-N-propylpropanamide (75a), room temperature yield 98% (PPh_3), colourless solid, mp 87.2-88.1 ^oC (*lit*[151] 90-91 ^oC); ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 5.38 (s, NH), 3.78 (s, 3H), 3.17 (q, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.45 (*app* h, *J*=6.5, 2H), 0.86 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.06 (C=O), 158.05 (C_{ar}), 132.98 (C_{ar}), 129.26 (C_{ar}), 113.92 (C_{ar}), 55.25 (CH_3), 41.19 (CH_2), 38.86 (CH_2), 30.93 (CH_2), 22.80 (CH_2), 11.26 (CH_3). ESI-MS (*m/z*) ; 222.1486 (M^{+H}). Known compound, spectra matches.[151]

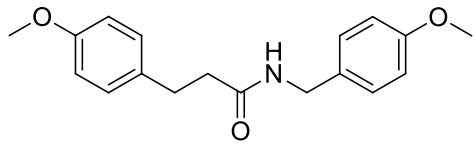


3-(4-Methoxyphenyl)-N-octyl propanamide (75b), room temperature yield 75% (PPh_3), colourless solid, mp 79.9-80.4 ^oC (*no lit*); ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 5.50 (s, NH), 3.77 (s, 3H), 3.18 (*app* q, *J* = 6.5 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 1.44 – 1.37 (m, 2H), 1.25 (s, 10H), 0.88 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.04 (C=O), 158.03 (C_{ar}), 132.98 (C_{ar}), 129.24 (C_{ar}), 113.88 (C_{ar}), 55.20 (CH_3), 39.51 (CH_2), 38.79 (CH_2), 31.77 (CH_2), 30.93 (CH_2), 29.57 (CH_2), 29.24 (CH_2), 29.16 (CH_2), 26.86 (CH_2), 22.60 (CH_2), 14.04 (CH_3). EI-MS (*m/z*) 291 ($M^{\cdot+}$). Known compound, spectra matches.[151]

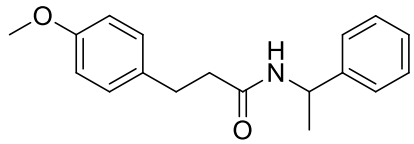


3-(4-methoxyphenyl)-N-phenylpropanamide (75c), room temperature yield 87% (PPh_3), catalytic yield 83%, colourless solid, mp 127.6-128.3^oC; IR (cm^{-1}): *v* = 3319 (w,

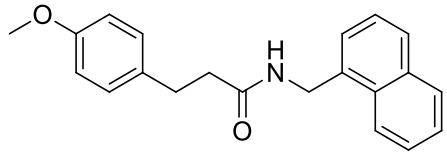
br), 1650 (s), 1528 (s), 1440 (s), 1035 (m), 750 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.06 (s, HN), 6.85 (d, *J* = 8.0 Hz, 2H), 3.80 (s, 3H), 3.01 (t, *J* = 7.5 Hz, 2H), 2.63 (t, *J* = 7.5 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 170.35 (C=O), 158.21 (C), 132.64 (C), 129.33(CH), 128.93 (CH), 124.24 (CH), 119.88 (CH), 114.08 (CH), 55.26 (O*C*H_3), 39.76 (CH_2), 30.70 (CH_2); ESI-MS (m/z): 278.1143 (M^{+Na}).



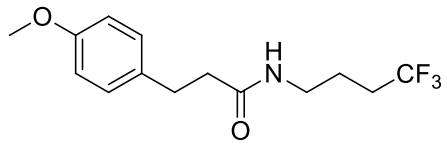
N-(4-methoxybenzyl)-3-(4-methoxyphenyl)propanamide (75d), room temperature yield 85% (PPh_3), catalytic yield 79%, colourless solid, MP 104.3-104.9 ^{o}C; IR (cm^{-1}) *v*= 3299 (m, br), 1637 (s), 1611 (m), 1548 (m), 1510 (s), 1222 (s, br), 1174 (s), 1031 (s), 831 (s). ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.10 (m, 4H), 6.82 (m, 4H), 5.55 (s, NH), 4.33 (*app* d, *J* = 5.6 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.47 (t, *J* = 7.5 Hz, 2H). 13C NMR (126 MHz, $CDCl_3$) δ 171.80 (C=O), 158.98 (C), 158.07 (C), 132.80 (C), 130.28 (C), 129.33 (CH), 129.09 (CH), 113.93 (CH), 55.28 (CH_3), 55.23 (CH_3), 43.03 (CH_2), 38.82 (CH_2), 30.87 (CH_2). ESI-MS (m/z): 322.1428 (M+Na).



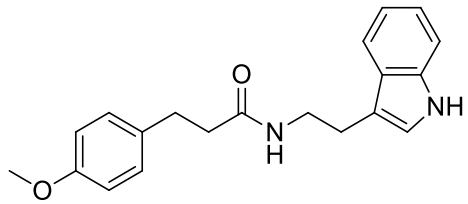
3-(4-methoxyphenyl)-N-(1-phenylethyl)propanamide (75e); room temperature yield 82% (PPh_3), colourless solid, MP 62.8-74.9 ^{o}C. IR (cm^{-1}) *v*= 3319 (w), 1653 (m) 1535 (s), 1514 (s), 1444 (s), 1240 (s), 1035 (m), 826 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.5 Hz, 2H), 7.24 (m, 1H), 7.20 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.50 (s, NH), 5.11 (p, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.45 (m, 2H), 1.42 (d, *J* = 7.0 Hz, 2H).^{13}C-NMR (126 MHz, $CDCl_3$): δ 171.06 (C=O), 158.1 (C), 143.07 (C), 132.82 (C), 129.32 (CH), 128.56 (CH), 127.25 (CH), 126.12 (CH), 113.96 (CH), 55.24 (OCH_3), 48.5 (NH-CH-), 38.89 (CH_2), 30.86 (CH_2), 21.57 (*C*H_3); ESI-MS (m/z): 306.1476 (M^{+Na}).



3-(4-Methoxyphenyl)-N-(naphthalen-1-ylmethyl)propanamide (75f), room temperature yield 82% (PPh_3), pale yellow solid, MP 125-126 ^oC; IR (cm^1) *v*= 3317 (m), 1650 (s), 1599 (m), 1528 (s), 1510 (s), 1140 (s), 1240 (s), 1033 (s), 827 (m), 814 (m), 750 (s). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.94–7.90 (m, 1H), 7.89 – 7.85 (m, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.54–7.49 (m, 2H), 7.41 – 7.37 (m, 1H), 7.31 (*app*-d, *J* = 7.0 Hz, 1H), 7.08 (2H, d, *J* = 8.5 Hz), 6.76 (d, *J* = 8.5 Hz, 2H), 5.64 (bs, NH), 4.85 (d, *J* = 5.3 Hz, 1H), 3.77 (s, 3H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.47 (2H, t, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.72 (C=O), 158.06 (C), 133.85 (C), 133.51 (C), 132.76 (C), 129.26 (CH), 128.69 (CH), 128.52 (CH), 126.63 (CH), 126.57 (CH), 125.93 (CH), 123.48 (CH), 113.92 (CH), 55.19 (OCH_3), 41.70 ($NHCH_2$), 38.69 (CH_2), 30.84 (CH_2); EI-MS (*m/z*): 342.1481 (M^{+Na}).



3-(4-Methoxyphenyl)-N-(4,4,4-trifluorobutyl)propanamide (75g), room temperature 83% (PPh_3), colourless solid, MP 62.8-64.9 ^oC; IR (cm^{-1}): *v* = 3317 (w, br), 1643 (m), 1542 (m), 1230 (m), 1138 (s), 1027 (s), 829 (m) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.38 (s, NH), 3.78 (s, 3H), 3.27 (q, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.05 – 1.92 (m, 2H), 1.69 (q, *J* = 7.3 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 172.30 (C=O), 158.20 (C), 132.61 (C), 129.24 (CH), 113.99 (CH), 109.98 (CH), 55.18 (OCH_3), 38.70 (CH_2), 38.12 (CH_2), 31.24 (CH_2), 30.81 (CH_2), 22.39 (CH_2); EI-MS (m/z): 290.1359 (M^{+H}).



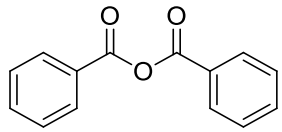
N-*(2-(1H-Indol-3-yl)ethyl)-3-(4-methoxyphenyl)propanamide (75h)*, room temperature 81% (PPH_3), brown solid, MP 62.8-74.9 ^oC; ^{1}H-NMR (500 MHz, $CDCl_3$):

δ 8.12 (bs, NH), 7.57 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.42 (bs, NH), 3.79 (s, 3H), 3.58 (q, *J* = 6.5 Hz, 2H), 2.92 (t, *J* = 6.5 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.06 (C=O), 158.07 (C_{ar}), 136.42 (C_{ar}), 133.00 (C_{ar}), 129.29 (C_{ar}), 127.36 (C_{ar}), 122.18 (C_{ar}), 121.94 (C_{ar}), 119.47 (C_{ar}), 118.65 (C_{ar}), 113.01 (C_{ar}), 111.20 (C_{ar}), 55.28 (OCH_3), 39.63 (CH_2), 38.81 (CH_2), 30.82 (CH_2), 25.23 (CH_2); ESI-MS (m/z): 323.1767 (M^{+H}).

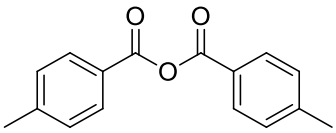
General Procedure for Formation of Anhydrides with the Phosphine/I_2/DMAP System.

To a well stirred solution of I_2 (1.5 equiv.) in anhydrous CH_2Cl_2, PPh_3 (1.5 equiv.), DMAP (3.0 equiv.) and then carboxylic acid (2.0 equiv.) were added sequentially. The reaction mixture was stirred for a further 2 hours and the progress of reaction was monitored by the TLC (hexane/EtOAc) analysis. After the reaction was complete, Celite® was added and reaction mixture was dried in vacuo. The resulting solid was purified via solid loading flash column chromatography on silica (Hexane/EtOAc) providing the anhydride in good yields.

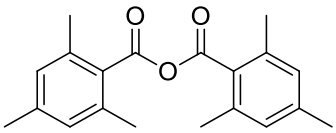
Characterisation of Anhydride Products



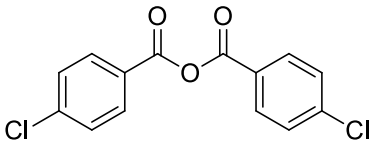
Benzoic anhydride (76a); 48%, colourless oil, ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.30–8.10 (d, *J*= 8.0 Hz, 4H), 7.82–7.63 (t, *J* = 7.5 Hz, 2H), 7.59-7.44 (t, *J*= 8.0 Hz, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 162.34 (C=O), 134.46 (CH), 130.53 (CH), 128.93 (C), 128.85 (CH); EI-MS (*m/z*): 226 ($M^{\cdot+}$). Known compound, spectra matches.[152]



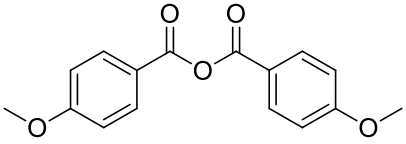
4-Methylbenzoic anhydride (76b); 75% (PPh_3), colourless solid, MP 95.3-97.6^{o}C,(*lit*[152] 95-96 ^{o}C); H-NMR (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.0 Hz, 4H), 7.33 (d, *J* = 7.9 Hz, 4H), 2.47 (s, 6H,); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 162.52 (C=O), 145.47 (C), 130.60 (C), 129.52 (CH), 126.29 (C), 21.77 (*C*H_3); EI-MS: (*m/z*) 255 ($M^{\cdot+}$). Known compound, spectra matches.[152]



2,4,6-Trimethylbenzoic anhydride (76c); room temperature yield 10%, colourless solid; MP 101.7-103.4^{o}C, (*lit*[153] 102-104 ^{o}C). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.88 (s, 4H), 2.41 (s 12H), 2.30 (s, 6H,); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 178.09 (C=O), 140.71 (C), 136.27 (C), 128.80 (CH), 21.19 (CH_3), 19.98 (*C*H_3); EI-MS (*m/z*): 310 ($M^{\cdot+}$). Known compound, spectra matches.[153]

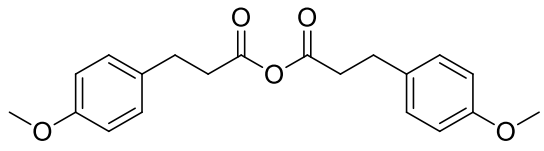


4-Chloro-benzoic anhydride (76d); room temperature yield 75%, white solid MP; 185.2-187.1 ^{o}C, (*lit*[153] 184-185 ^{o}C). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J*= 8.5 Hz, 4H), 7.52 (d, *J* = 8.5 Hz, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 161.27 (C=O), 141.39 (C), 131.83 (C), 129.34 (CH), 127.13 (C); EI-MS (*m/z*): 295 ($M^{\cdot+}$). Known compound, spectra matches.[153]

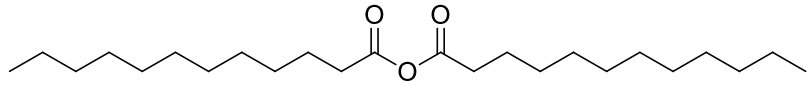


4-Methoxybenzoic-anhydride (76e); room temperature 70%, white solid, MP 87.9-90.8^{o}C, (*lit*[153] 88-93 ^{o}C), ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.8 Hz, 4H), 7.02–

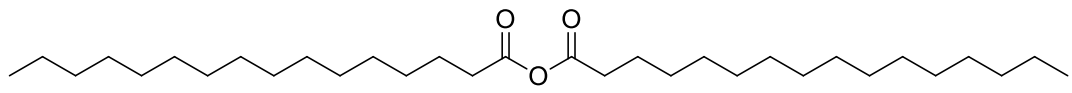
6.92 (s, *J*= 9.0 Hz 4H,), 3.91 (s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 164.57 (C=O), 162.25 (C=O), 142.44 (C), 132.79 (CH), 121.36 (C), 114.13 (CH), 55.55 (CH_3); EI-MS (m/z): 286 ($M^{\cdot+}$). Known compound, spectra matches.[153]



3(4-Methoxyphenyl) propionic anhydride (76f)*;* room temperature 46%, brown solid, MP 55.8-57.6^{o}C, (*lit*[154] ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.6 Hz, 4H), 6.84 (d, *J* = 8.6 Hz, 4H), 3.79 (s, 6H), 2.91 (t, *J* = 7.6 Hz, 4H), 2.71 (t, *J* = 7.6 Hz, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 178.78 (C=O), 158.13 (C), 132.22 (C), 129.21 (CH), 113.96 (CH), 55.25 (*C*H_3), 35.84 (*C*H_2), 29.75 (CH_2); EI-MS (*m/z*): 342 ($M^{\cdot+}$).

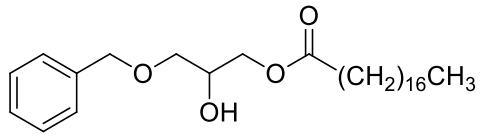


Dodecanoic anhydride (76g); room temperature 53%, white solid MP 41.7-43.4^{o}C, (*lit*[155] 40-42 ^{o}C), ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.45 (t, *J* = 7.5 Hz, 4H), 1.67 (p, *J* = 7.5 Hz, 4H), 1.40–1.25 (m, 32H), 0.89 (t, *J* = 7.0 Hz, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 169.56 (C=O), 35.29 (*C*H_2), 31.86 (*C*H_2), 29.55 (*C*H_2), 29.53 (*C*H_2), 29.36 (*C*H_2), 29.27 (*C*H_2), 29.15 (*C*H_2), 28.85 (*C*H_2), 24.24 (*C*H_2), 22.63 (*C*H_2), 14.03 (*C*H_3); EI-MS (m/z): 382 ($M^{\cdot+}$). Known compound, spectra matches.[155]

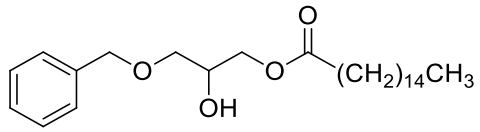


Palmitic-anhydride (76h); room temperature 54%, white solid, MP 62.5-64.3 ^{o}C, (*Lit*[156] 62-64 ^{o}C), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.45 (t, *J* = 7.5 Hz, 4H), 1.67 (p, *J* = 7.5 Hz, 4H), 1.27 (m, 48H), 0.89 (t, *J* = 7.0 Hz, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 169.56 (*C*=O), 35.29 (*C*H_2), 31.89 (*C*H_2), 29.66 (*C*H_2), 29.64 (*C*H_2), 29.63 (*C*H_2), 29.62 (*C*H_2), 29.60 (*C*H_2), 29.53 (*C*H_2), 29.36 (*C*H_2), 29.31 (*C*H_2), 29.16 (*C*H_2), 28.86 (*C*H_2), 24.24 (*C*H_2), 22.65 (*C*H_2), 14.04 (*C*H_3); EI-MS (m/z): 494 ($M^{\cdot+}$). Known compound spectra matches.[156]

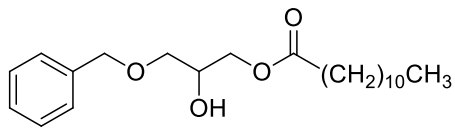
Mono-Acylation of Glycerol Derivative



3-(Benzyloxy)-2-hydroxypropyl stearate (78a), room temperature yield 55% (PPh_3), 58% (P(*o*-Tolyl)$_3$), microwave yield 61% (P(*o*-Tolyl)$_3$), white waxy solid, MP 37.0-37.4^{o}C, (*Lit*[157] 41-43 ^{o}C), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.57 (s, 2H), 4.18 (2H, qd, *J* = 11.5, 5.5 Hz), 4.04 (p, *J* = 5.5 Hz, 1H), 3.59 – 3.48 (m, 2H), 2.33 (2H, t, *J* = 7.5 Hz), 1.62 (2H, p, *J* = 7.5 Hz), 1.27 (bs, 28H), 0.89 (3H, t, *J* = 6.9 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.90 (C=O), 137.68 (C), 128.46 (CH), 127.85 (CH), 127.72 (CH), 73.52 (CH_2), 70.89 (CH_2), 68.97 (CH), 65.35 (CH_2), 34.16 (CH_2), 31.91 (CH_2), 29.68 (CH_2), 29.66 (CH_2), 29.64 (CH_2), 29.59 (CH_2), 29.44 (CH_2), 29.34 (CH_2), 29.24 (CH_2), 29.12 (CH_2), 24.91 (CH_2), 22.67 (CH_2), 14.08 (CH_3). ESI-MS (*m/z*) 471.3445 (M^{+Na}). Known compound, spectra matches.[140]



3-(Benzyloxy)-2-hydroxypropyl palmitate (78b), room temperature yield 61% (PPh_3), 54% (P(*o*-Tolyl)$_3$), microwave yield 57% (P(*o*-Tolyl)$_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 4.57 (s, 1H), 4.18 (2H qd, J = 11.5, 5.5 Hz), 4.09 – 3.97 (m, 1H), 3.61 – 3.45 (m, 2H), 2.33 (2H, t, J = 7.5 Hz), 1.63 (2H, m), 1.27 (24H, bs), 0.90 (3H, t, J = 6.8 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.90(C=O), 137.69 (C), 128.46 (CH), 127.85 (CH), 127.72 (CH), 73.52 (CH_2), 70.91 (CH_2), 68.96 (CH), 65.35(CH_2), 34.16 (CH_2), 31.91 (CH_2), 29.68 (CH_2), 29.66 (CH_2), 29.64 (CH_2), 29.59 (CH_2), 29.45 (CH_2), 29.34 (CH_2), 29.24 (CH_2), 29.12 (CH_2), 24.91 (CH_2), 22.67 (CH_2), 14.09 (CH_3). ESI-MS (m/z) 443.3112 (M^{+Na}). Known compound, spectra matches.[141]



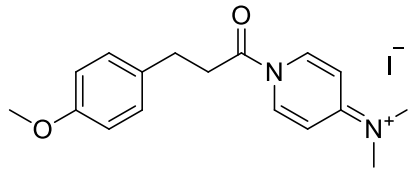
3-(Benzyloxy)-2-hydroxypropyl dodecanoate (78c), room temperature yield, 55% (PPh_3), 52% (P(*o*-Tolyl)$_3$, microwave yield 64% (P(*o*-Tolyl)$_3$, colourless oil; IR (cm^{-1}).

v= 2923 (m, br), 2854 (m), 1746 (s), 1100 (s, br). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.57 (s, 2H), 4.17 (qd, *J* = 11.5, 5.5 Hz, 2H), 4.04 (p, *J* = 6.0 Hz, 1H), 3.59 – 3.47 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.61 (m, 2H), 1.27 (m, 14H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.91 (C=O), 137.68 (C), 128.46 (CH), 127.85 (CH), 127.72 (CH), 73.51 (CH_2), 70.90 (CH_2), 68.96 (CH), 65.34 (CH_2), 34.15 (CH_2), 31.89 (CH_2), 29.58 (CH_2), 29.44 (CH_2), 29.31 (CH_2), 29.23 (CH_2), 29.12 (CH_2), 24.91 (CH_2), 22.66 (CH_2), 14.08 (CH_3). ESI-MS (*m/z*) 387.2489 (M^{+Na}).

General Procedure for Collection of N-acyl-DMAP Iodide Salts

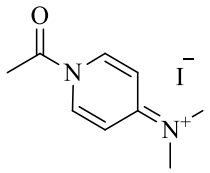
To a well stirred solution of I_2 (1.5 equiv.) in anhydrous CH_2Cl_2 (10-15 mL), PPh_3 (1.5 equiv.), DMAP (3.0 equiv.) was added the carboxylic acid (1 equiv.). After 5-10 minutes of stirring at room temperature a fine yellow precipitate drop out of solution. This was collected via vacuum filtration and the resulting solid was washed with cold CH_2Cl_2 and dried under vacuum.

Characterisation of N-acyl DMAP Salts



N-*(1-(3-(4-methoxyphenyl)propanoyl)pyridin-4(1H)-ylidene)-N-methylmethanaminium iodide (80),*

yield 66%, pale yellow solid; ^{1}H NMR (500 MHz,CD_3OD) δ 8.12 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 3.75 (s, 3H), 3.26 (s, 6H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, cd_3od) δ 173.80 (C=O), 158.28 (C), 157.78 (C), 138.55 (CH), 132.56 (C), 128.80 (CH), 113.58 (CH), 106.94 (CH), 54.36 (OCH_3), 38.96 (CH_3), 35.49(CH_2), 29.70 (CH_2). ESI-MS (m/z) 285.1596 (M-I$^-$), ESI-MS (*m/z*) 697.2251 (M+[M-I$^-$]).



N-*(1-acetylpyridin-4(1*H*)-ylidene)*-N-*methylmethanaminium iodide (81),* yield 71%, pale yellow solid; ^{1}H NMR (500 MHz, CD_3OD) δ 8.12 (d, *J* = 7.7 Hz, 2H), 7.14 – 6.94 (m, 2H), 3.27 (s, 6H), 2.03 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 171.95 (C=O), 157.77 (C), 138.64 (CH), 106.93 (CH), 38.93 (CH_3), 19.04 (CH_3). ESI-MS (*m/z*) 165.1023 (M-I$^-$), ESI-MS (*m/z*) 457.1100 (M+[M+I$^-$]).

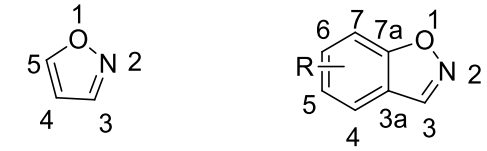
3 Synthesis of Benzisoxazoles and Novel DMAP-Hydrazones

3.1 Introduction

Chapter 2 detailed the development, optimisation and scope of a new reagent system combining PPh_3-I_2-DMAP. This reagent system was shown to be effective for rapid and efficient formation of esters and amides. It was also demonstrated that that the process could be carried out using catalytic amounts of DMAP when in the prescene of another stronger base. The simple change from imidazole to the nucleophilic base DMAP could dramatically change the reactivity. Using this system the reaction time was reduced from 12-24 hours to a maximum of two hours, often with the reaction going to completion within 10-30 minutes. This chapter describes follow up work, involving the development of some novel and interesting chemistry that offers a glimpse into the versatility and potential for this three-component reagent system.

Work presented in this Chapter includes the reaction between reagent system of DMAP, PPh_3 and I_2 with simple 2-hydroxarylaldoximes to form 1,2- benzisoxazole via an intramolecular ring closing reaction and the formation an oxygen-nitrogen bond. Also detailed is the formation of novel *N*-pyridinium functionalised imine intermediates. These novel compounds can undergo further reactivity with the hard nucleophile sodium methoxide (NaOMe) to form imidates via a rearrangement mechanism that is analogous to that of the Beckman rearrangement resulting in similar products. Finally, the discovery that the system can provide a new pathway for the rapid synthesis of aza-Wittig reagents, otherwise known as phosphazenes is described. This new variant of the Kirsanov reaction underpins the work described in the result and discussion of chapter 4.

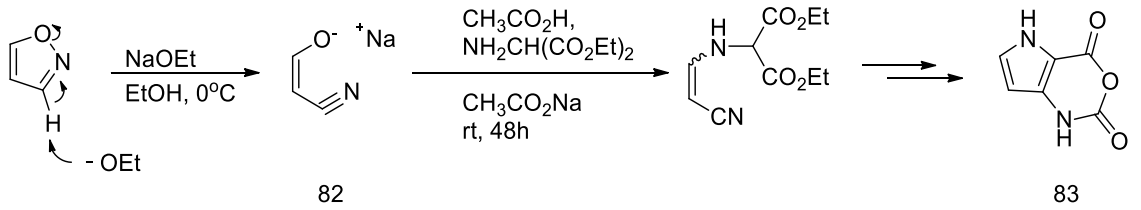
3.2 1,2 Benzisoxazoles



1,2 isoxazole 1, 2 benzisoxazole

Figure 3.1: Structures of 1, 2 isoxazole and 1, 2 benzisoxazole**.**

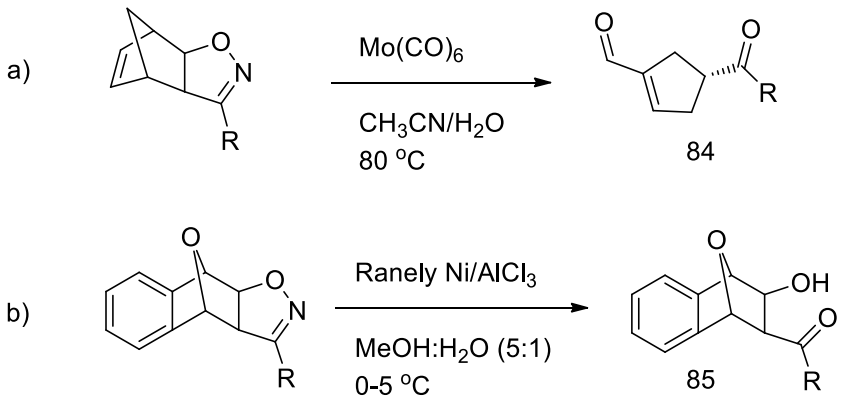
Structurally, isoxazoles and their benzene fused analogues share characteristics with most electron-rich ring aromatic systems. They undergo similar chemistry when reacting with electrophiles such as Br_2 e.g. functionalise at the 4-position. The rate of reaction is fast compared to benzene due to the mesomeric electron donating effect of the oxygen. However, due to the electron withdrawing effect of the nitrogen atom, they are far less reactive towards electrophilic substitution reactions than furans and pyrroles. Unlike other 1,2-azole derivatives such as *N*-substituted pyrazoles and isothiazoles, they cannot be deprotonated with strong bases such as alkyl lithium reagents, and then functionalised with an electrophile (e.g. MeI) at the C3 position. This is due to the instability of the nitrogen-oxygen bond leading to ring opening with an oxy anion leaving group. The resultant enolate salts can then be condensed with various reagents. An example of this can be seen in synthesis of 3,4-dihydro[1,4]diazepine-2,5-dione (**83)** by Lisowski *et al.,* in which the 1,2 isoxazole ring was opened using sodium ethanoate at 0 ^{o}C.[158] This enolate (**82**) was then condensed with diethyl aminomalonate in presence of acetic acid and sodium acetate. Subsequent steps eventually resulted in the target compound pyrrolo[3,2-*d*][1,3]oxazine-2,4-dione **83** (Scheme 3.1). A similar reactivity profile is observed with benzisoxazoles following deprotonation at the C3 position.



Scheme 3.1: Lisowski's synthesis of 3,4-dihydro[1,4]diazepine-2,5-dione **83** starting from 1,2 isoxazole

The instability of the isoxazole N-O bond has been used to the advantage of a number of researchers. They are considered important latent synthons, offering routes to natural products and pharmaceutical motifs. Benzisoxazole and isoxazoles can act as latent masked functionalities for a number of different functional groups, including various carbonyl compounds such as β-hydroxyketones and β-aminoketones. These functional groups can be readily attained through ring cleavage of 1.2-isoxazolines using suitable reagents.[159] The most common methods for cleavage of the N-O bond is via the use of metal catalysed based reduction, such as hydrogenolysis using Raney nickel,[160]

reduction by $LiAlH_4$,[161] $TiCl_3$,[162] SmI_2,[163] Zn in acetic acid,[164] or by treatment with molybdenum hexacarbonyl ($Mo(CO)_6$).[159]



Scheme 3.2: Tam and Tellers different approaches to N-O bond cleavage in tri or tetracyclic isoxazoline systems**.**

Simoni *et al.* showed that efficient cleavage of the N-O bond could be used for the preparation of β-hydroxy ketones by the reaction of 2-isoxazolines and molybdenum hexacarbonyl in wet acetonitrile (a Scheme 3.2).[159] This investigation was followed some years by later by Tam and Tranmer's study into the tandem N-O cleavage and retro-aldol reactions of isoxazolines.[160] In order to give access to novel stereospecific synthesis of cyclopentene, cyclopentane with attached ring systems. Additional work by Tam and Tranmer has gone to show that N–O bond cleavage reactions of heterobicycloalkene-fused 3-methyl-2-isoxazolines were inefficient with the $Mo(CO)_6$ system.[165] They instead employed and developed a dual cleavage system via the use of Raney nickel/$AlCl_3$ in aqueous methanol (b Scheme 3.2). The reaction provided a diverse collection of novel heterobicycle-fused β-hydroxy ketones (**85**) with good to excellent yields.

3.2.1 Isoxazoles and Benzisoxazoles: Potent Psychoactive, Antipsychotic and Antibiotic drugs.

Isoxazoline ring systems are important oxygen and nitrogen containing heterocycles that offer a great range of diverse precursors to useful structural motifs. These structures can be found in naturally many occurring alkaloids, pharmaceutical drugs and agrochemicals e.g. ibotenic acid and ibotenate. These compounds are derived from *Amanita muscaria* and other species of mushroom and act as a psychoactive

drugs, powerful neurotoxins and a brain-lesioning agents as demonstrated by neurological studies in rats.[166] Isoxazoles and their benzisoxazole derivatives also form key structural motifs in multiple pharmaceuticals including a number of different antipsychotic and anticonvulsant drugs such as; iloperidone, risperidone and Zonisamide, as well as the potent antibiotic cycloserine (Figure 3.2).

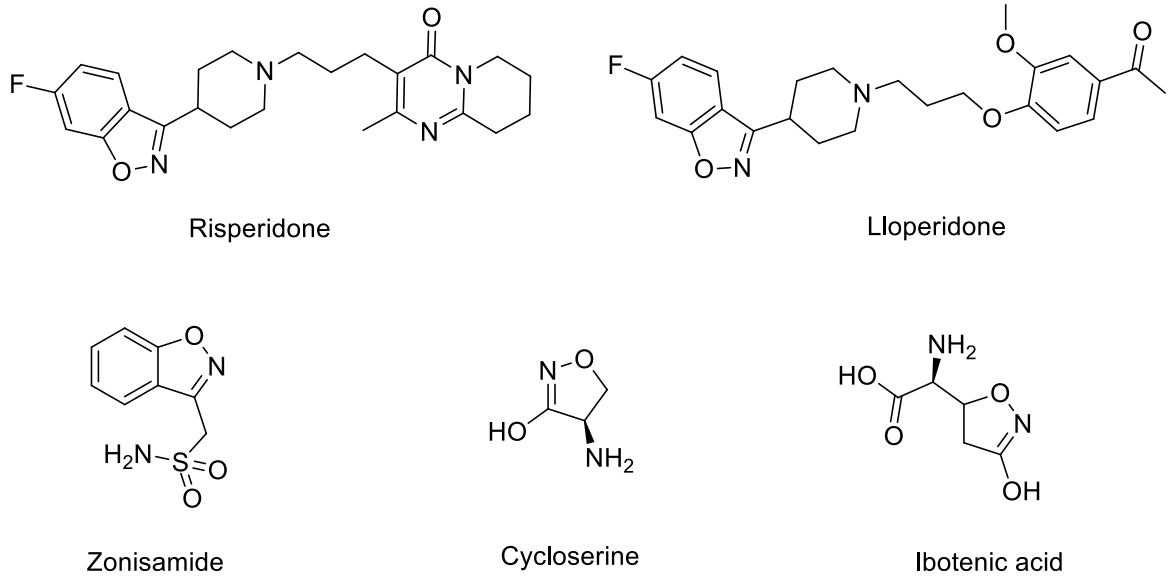


Figure 3.2: Various drugs and natural products that include the isoxazole or benzisoxazole moiety.

Iloperidone, is an atypical antipsychotic for the treatment of schizophrenia that was approved for use by the FDA in 2009,[167] It acts as an agonist for multiple dopamine and serotonin receptor subtypes. It contains a benzisoxazole moiety and is seen as a 2nd generation 'atypical' antipsychotic agent due to its interaction with serotonin receptors. Risperidone is similar to Iloperudone both structurally and functionally in that it is an employed as antipsychotic medication.[168] It is mainly used to treat disorders such as schizophrenia, bipolar disorder, and irritability in people with autism. Zonisamide has a relatively simple structure containing a benzisoxazole with a sulphonamide attached to a methyl group spacer.[169] This anticonvulsant drug has seen use in tackling a number of different disorders such as epilepsy and Parkinson's disease. It has also been claimed as a potential weight loss drug and is currently in several clinical trials for this purpose.[170]

The isoxazole structure can also be found in the unusual naturally occurring amino acid derivative cycloserine. This naturally occurring structure is produced by bacteria through cyclisation of serine, oxidatively forming a nitrogen-oxygen bond to produce the dihydroisoxazole motif. Since its first isolation from a family of *Streptomyces* bacteria,[171] and subsequent synthesis,[172] it has become one of the most important antibiotics in medicine. It shows high activity against tuberculosis and is considered a 2nd line drug (i.e. one that is used when 1st line drugs fail) due to its remarkable potency. This means that it is only used for the treatment of multiple drug-resistant and extensively drug-resistant strains of *Mycobacterium* tuberculosis. Another reason for the restricted use is due to increased side-effects, potentially having a negative effect on the nervous system leading to unwanted side effects such as headaches, drowsiness, and even seizures in the case of an overdose.

3.2.2 Synthetic Methods for the Formation of Benzisoxazoles.

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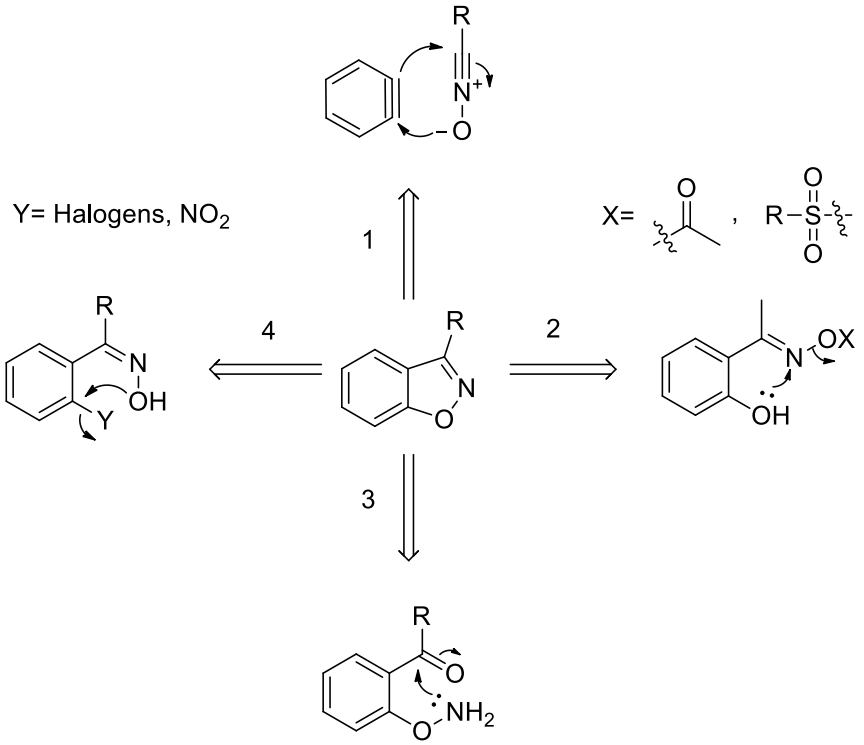
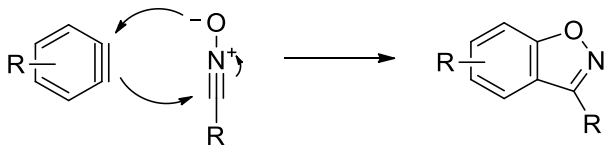


Scheme 3.3: Synthetic strategies for synthesis of 1, 2 benzisoxazoles

Due to the prevalence and importance of benzisoxazoles moieties in both natural products and their role in new antipsychotic, anticonvulsant and antibiotic drugs a number of different synthetic strategies have been developed. The synthesis of

benzisoxazoles can, in general, be split into four distinct strategies (Scheme 3.3), each having its own advantages and limitations.

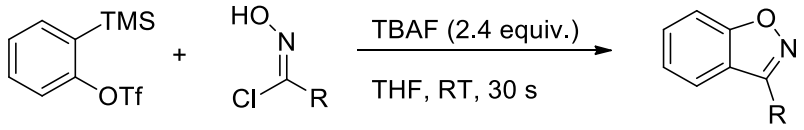
3.2.3 Strategy 1; 1,3-Dipolar Cycloaddition



Scheme 3.4: Mechanism for the 1,3-dipolar cycloaddition in the formation of 1,2 benzisoxazoles.

Strategy 1 involves the 1,3-dipolar cycloaddition between a benzyne group or masked benzyne group and a nitrile oxide component. 1,3-cycloadditions were pioneered by Huisgen in the 1960's and have since become one of the most widely used methods to form 5-membered ring systems.[173] This methodology is attractive due to its convergent nature and low number of synthetic steps. However, there are only a handful of examples of this method being used for the synthesis of benzisoxazoles. One of the first uses of such a reaction in the formation benzisoxazoles were performed in the 1969 by Sasaki and Yoshioka as part of their investigations in hetero aromaticity.[174] They describe the formation 3-(5-nitro-2-furyl) benzisoxazole via a thermal 1,3-dipolar cycloaddition between benzyne and 5-nitrofuronitrile oxide or *3*-Nitrobenzonitrile. The nitrile oxides used where masked with chloride, with the nitrile being formed *in situ*. They successfully showed that 1,3-dipolar cycloaddition can be used to form isoxazoles. However, low yields of 10% where observed for each of the reactions attempted.

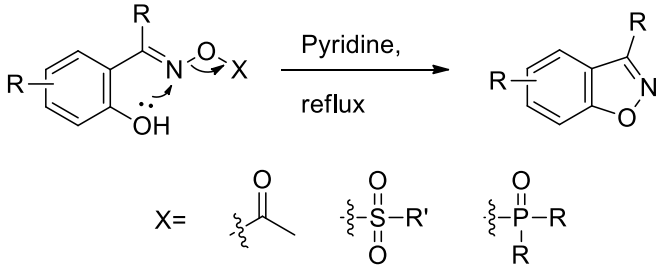
More recently, similar strategies have been developed where the nitrile oxide and benzyne groups were both masked with other functionalities Moses *et al.,* developed a TBAF-mediated 1,3-dipolar cycloaddition of nitrile oxides and benzynes (Scheme 3.5).[175] Using this method they successfully synthesised a range of 1,2-benzisoxazole in a simple and rapid procedure. A furoxane derivative was the only side product to be produced, and was easily removed via standard chromatographic techniques. These reactions went to completion within 30 seconds and achieved good to excellent yields. The benzyne derivative was formed *in situ* via a fluoride promoted ortho-elimination of *O*-(trimethylsilyl)aryltriflates which is a common method for the formation of aryne derivatives.



Scheme 3.5: The use of masked arynes and nitrile oxides mediated by dual purpose reagent of TBAF Moses *et al's*.[175]

The nitrile is thought to be formed via base induced dehalogenation of hydroximoyl chlorides. It was found that premixing the masked nitrile oxide and benzyne derivatives followed by the addition of the TBAF was required in order for the reaction to go to completion. It was also found that more than one equivalent of TBAF was needed for the reaction to form the isoxazole suggesting that that TBAF was exclusively inducing dehydrohalogenation, requiring higher quantities of fluoride. Other groups have developed very similar reaction conditions with different fluoride sources. For example, Larock and Dubrovsky used caesium fluoride (CsF) in acetonitrile which also led to a simple and effective procedure.[176] The reaction tolerates a variety of functional groups and provides an alternative route to potentially important benzisoxazoles bearing aryl, alkyl, alkenyl and heterocyclic substituents at the 3-position of the benzisoxazole.

3.2.3.1 Strategy 2; Cyclisation of O-hydroxy-Benzyloxime Sulfonates, Acetates and Phosphonates.

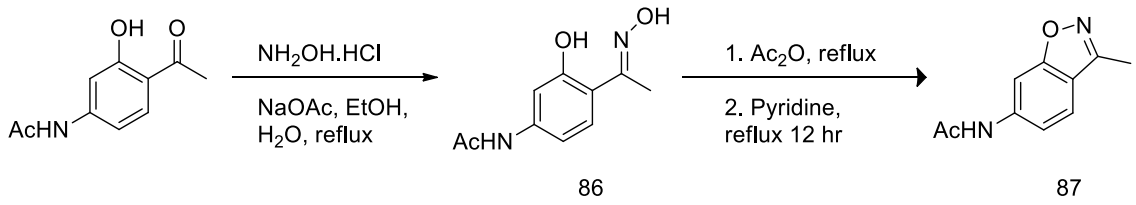


Scheme 3.6: The intramolecular cyclisation of activated oximes to form 1,2-isoxazoles.

Strategy 2 requires the activation of the hydroxy component of an oxime followed by cyclisation *via* attack of the hydroxy group *ortho* to the oxime on the ring, leading to displacement of the leaving group (Scheme 3.6). This approach was pioneered by Blatt and Russel in the 1930's as part of their investigation in to the action of an alkali on acylated ketoximes.[177] In their study they discovered that the use of a hard alkali such as NaOH led to conversion of the acetates of *o*-hydroxybenzophenone oximes back to their

original oximes via hydrolysis of the acetyl group. However, use of a soft non-nucleophilic base such as Na_2CO_3 provided different reactivity. They described a Beckman-like rearrangement occurring in the acetate group which led to formation of the 1,2-benzoxazoles.[178] They also found that the oxime diastereoisomer had a large effect on the reaction with the *E* isomer predominantly resulting in the 1,2 benzisoxazole whereas the *Z* isomer produces a mixture of products from which the 1,2-benzisoxazole could be isolated but in much lower yield.

60 years later Villalobos *et al.* used a similar method as part of their synthesis of a number of novel benzisoxazole derivatives, which behaved as potent and selective inhibitors of enzyme acetylcholinesterase (ACHE).[179] This enzyme is thought to play a role in the breakdown of acetylcholine and of some other choline esters that function as neurotransmitters. Therefore, if this enzyme is over active it can lead to a number of neurological problems. It is also the target for many organophosphorus based nerve reagents and pesticides as irreversible inhibition of this enzyme can lead to muscular paralysis, convulsions, and death by asphyxiation. Reversible inhibitors however, are used in medical settings as a means of treating a wide range of range of central nervous system diseases such as Alzheimer's disease. Villalobos *et al.*'s synthesis of the 1,2-benzisoxazole **87** moiety proceeded by first forming oxime **86** via reaction with hydroxyamine followed by treatment with acetic anhydride (Scheme 3.7).[179] The cyclisation reaction was facilitated by heating at reflux in pyridine for 12 hours to give the 1,2-benzisoxazole **87** in yields of up to 62% for the cyclisation step.



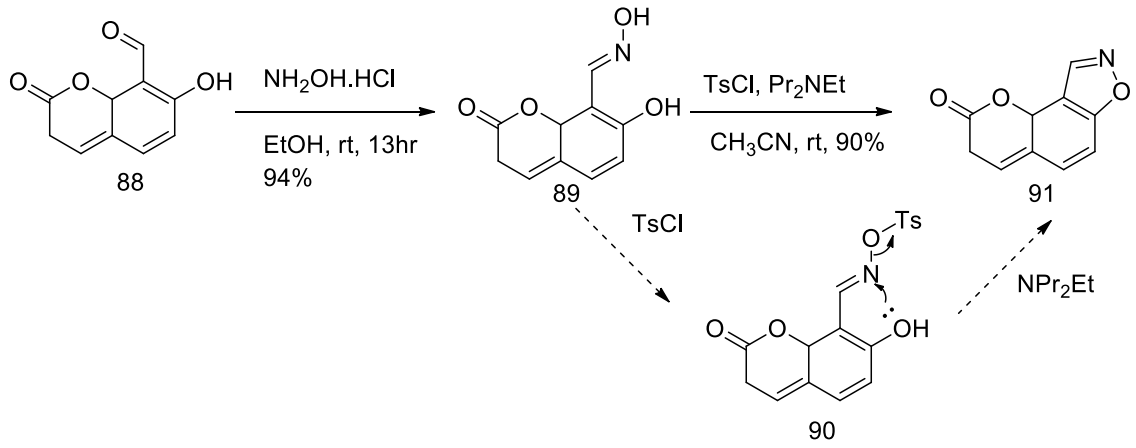
86 87

Scheme 3.7: synthesis of the core benzisoxazole for their potent inhibitors of ACHE by Villalobos *et al.*[179]

Alternatives to the acetate leaving group such as sulfonyl-substituted oximes can also be used. As part of an investigation in to the reactivity of oximes, Dale *et al.* released a paper describing the mild and efficient synthesis of 1,2-benzisoxazole.[180] The reaction between *o*-hydroxyaryl oximes and *p*-toluenesulfonyl chloride (*p*-TsCl) in the presence of a tertiary amine such as DIPEA, resulted in complete conversion to the benzisoxazole

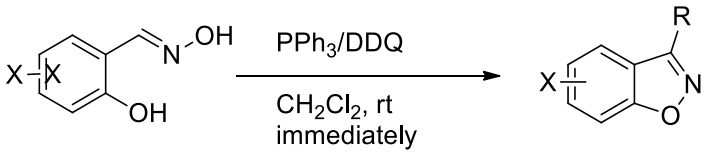
within 5-30 minutes. They also found that the polarity of the solvent could greatly affect the rate of cyclisation. The relative polarity of different solvents was compared to the rate of completion of the reaction and it was found that polar solvents increased the rate of reaction with acetonitrile (CH_3CN) providing the best results, proceeding 6300 times faster than when carried out in THF.

Dale *et al.* started by investigating the conversion of 2-hydroxy-naphthalene-1-carbaldehyde oxime to 1,2-naphthisoxazole, via the commercially available 2-hydroxy-1-naphthaldehyde. Optimisation of the reaction conditions led to yields of 74% for the cyclisation step. The rate determining step for this reaction was determined by monitoring the change in wave length absorption of the UV spectra between the oxime and the 1,2-benzisoxazole, showing that the reaction proceeded cleanly through the isosbestic point (specific wavelength, wavenumber or frequency at which the total absorbance of a sample does not change during a chemical reaction), indicating that the initial tosylation reaction was the rate-limiting step in the reaction. Additional evidence for this was supplied by the fact that the reaction rate was dependent on the concentration of the TsCl. The rate was aslo reduced if a weaker electrophile was used (i.e. TsF). This mild and efficient method for cyclisation of *o*-hydroxyaryl oximes has potential for synthesis of useful intermediates and compounds e.g. novel fluorophores such as coumarin oxazole **91** and pyrene oxazole. The synthesis of coumarin oxazole starting from commerically available 7-hydroxycoumarin **88** gave a 90% yield in the 1,2-benzisoxazole forming step, with a reaction time of less than 5 minutes (Scheme 3.8). First the hydroxy group of the oxime **89** is activated via formation of tosylate intermediate **90**. This is then followed by nucleophilic attack of the hydroxy group on to the nitrogen of the displacing the TsOH leaving group.



Scheme 3.8: Synthesis of novel fluorophore oxazole coumarin **91** using the cyclisation method developed by Dale *et al.*[180]

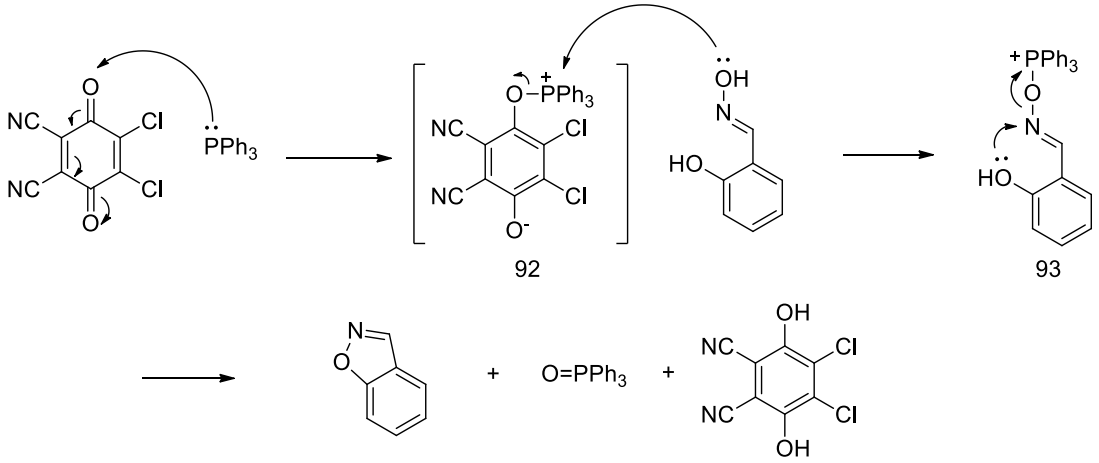
Another example for this type of cyclisation includes the use 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and PPh_3. This procedure was developed by Iranpoor *et al.* (Scheme 3.9).[181] Previous work by the same group had already shown that the combination of DDQ and PPh_3 offered a useful method for the conversion of alcohols, thiols and selenols to halides.[182] It was also shown, that the system could be employed as a facile method for the preparation of diethyl α-bromo, α-iodo and α-azidophosphonates from α-hydroxyphosphonates.[183] DDQ is a known oxidising agent whilst PPh_3 is a useful and versatile reducing agent. For the purpose of the cyclisation of *o*-hydroxyaryl oximes addition of the oxime to a mixture of DDQ and of PPh_3 in CH_2Cl_2 gave the corresponding 1,2-benzisoxazoles ware formed immediately from the starting oxime. Yields of 90-95% were obtained for a wide range of isoxazoles including both aldehyde and ketone derivatives.



Scheme 3.9: The rapid and efficient synthesis of 1, 2-isoxazole using PPh_3/DDQ.

The proposed mechanism proceeds by initial formation of a DDQ-PPh_3 adduct **92** by donation of the phosphine lone pairs to the ketone oxygen of the DDQ. This positively charged phosphonium species then undergoes nucleophilic attack from the oxygen of

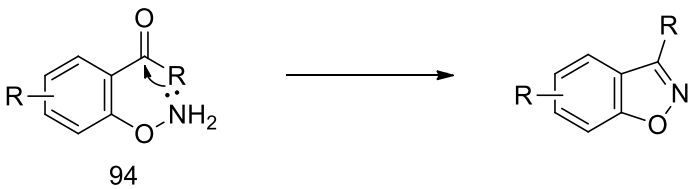
the oxime. The resulting intermediate **93** then rapidly cyclises via attack at the nitrogen by the *o*-hydroxy group with triphenylphosphine oxide as the leaving group, giving the 1,2-benzisoxazole in high yields (Scheme 3.10).



Scheme 3.10: Mechanism for the rapid and efficient formation of 1,2-benzisoxazoles mediated by PPh_3/DDQ.

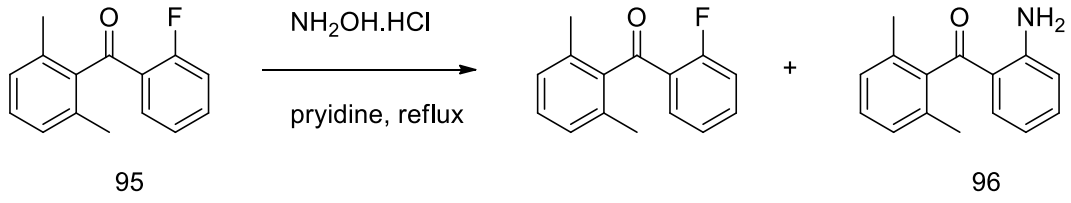
This strategy for the formation of benzisoxazoles described above has since proven to one of the most effective way to produce diverse libraries of natural products and pharmaceutically relevant molecules. It has seen major development in the last 10-12 years and is so effective electron-poor carbocyclic rings can be accommodated with ease and within minutes in a mild three component system. Villalobos *et al* showed that the use of acetyl leaving groups provides access to an impressive range of molecules with the potential for diversification on the ring systems, proving routes to complex molecules that have been shown to have potent biological activity.[179] The use of tosylate-based leaving group championed by Dale *et al.* offers alternative rapid and efficient method for the synthesis of the 1,2 oxazole ring system.[180]

3.2.3.2 Strategy 3: Intramolecular Condensation of Sterically Hindered Carbonyl Compounds with Aminoxyl Functionality.



Scheme 3.11: General scheme for the cyclocondensation of aminoxyphenone **94** to form 1,2-benzoisoxazoles .

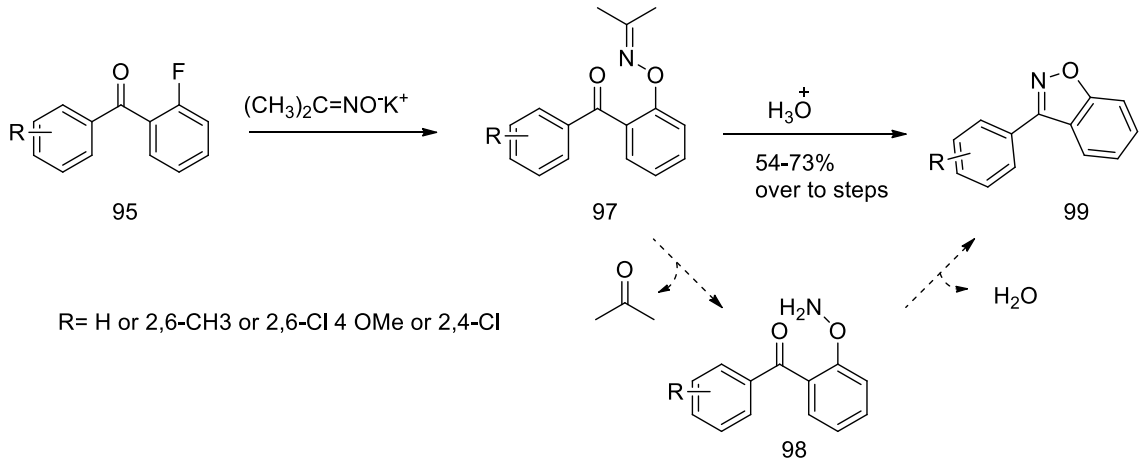
Strategy 3 for 1,2-benzisoxazole synthesis involves an intramolecular cyclisation *via* condensation of a carbonyl group with an aminooxy group. This strategy shown to be an effective method for the synthesis of sterically constrained 3-arly-1,2-benzisoxazoles by Shutske in the mid 1980.[184] Before this example, there was no known method to form sterically encumbered 3-aryl-1,2-benzisoxazoles with substituents at both *ortho* positions of the phenyl ring at position 3. Shutske initially attempted to use the classical method (strategy 4) for the formation of 3-aryl-1,2-benzisoxazoles by first converting aryl-2'-fluorobenzophenone to the corresponding oximes by reaction with hydroxylamine, and then to facilitate cyclisation under basic conditions through a S_nAr displacement. Shutske found that the conversion of the ketones to the corresponding oxime was unsuccessful when derivatives of ortho-functionalised 2'-fluorobenzophenone's such as **95.** When subjected to refluxing conditions in a pyridine solution, only retrieval of the starting ketone **95** and formation of **96** were achieved. It was concluded that the reason oxime formation failed was due to the sterically-congested environment around the carbonyl group. However, S_nAr of the aryl-fluoride was still possible for these substrates giving keto amine **96** (Scheme 3.12). Shutske reasoned that this was most likely due to initial formation of a hydroxyamino benzophenone, which was then reduced in the presence of excess hydroxy amine. In a reaction that has is analogy to that of the synthesis of 2,4,6-trinitroaniline from picryl chloride and excess hydroxylamine hydrochloride as shown by Borsche.[185]



Scheme 3.12: Failed attempt to form an oxime from a sterically hindered ketone by Shutske.[184]

It was reasoned that the fluoride is far less influenced by the steric environment than the carbonyl group, and therefore the hydroxy group anion of a suitable *N*-functionalised oxime could displace the fluoride in a S_nAr reaction to yield the *O*-arylated oxime. Upon treatment with catalytic acid the newly formed oxime can undergo hydrolysis followed by cyclocondensation leading to the 3-aryl-1,2-benzisoxazole. Upon treatment of 2-fluorobenzophenones **95** with the potassium anion of acetone oxime in refluxing THF gave 2-(isopropy1ideneamino)-oxylbenzophenone intermediate **97**. **97** then

underwent acid catalysed transoximation (transfer of oxime to a carbonyl compound) via treatment of aqueous ethanolic hydrochloric acid under reflux. First the amine is amino group is reduced to the oxyamine functionality (**98**) followed by cyclisation by imine formation producing 1,2-benzioxazoles **99** in yields varied from 54-73% (Scheme 3.13).



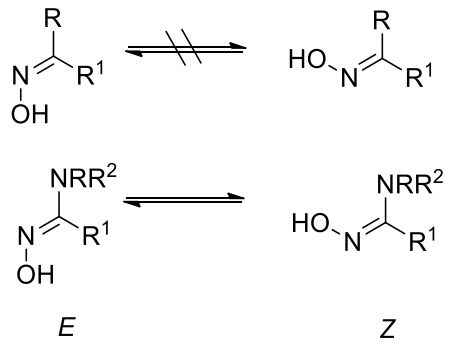
Scheme 3.13; Use of intramolecular condensation of sterically hindered ketones with aminooxyl functionality for the synthesis of 3-phenyl-1, 2-benziosoxazoles.

3.2.3.3 Strategy 4: Cyclisation of *o*-Halo or *o*-Nitrobenzyloximes.

Scheme 3.14: General strategy 4 for the synthesis of 1,2 benzisoxazoles via S_nAr displacement of halide**.**

Strategy 4 involves the S_nAr substitution of a halide by the hydroxy group of the oxime and represents one of the simplest ways to synthesis simple benzisoxazoles. The process commonly involves formation of the oxime via condensation of hydroxyamine hydrochloride with an aryl ketone or aldehyde containing an *ortho* halide. This is then followed by nucleophilic aromatic substitution, via heating the oxime in the presence of a base, with it possible for both these steps can be combined in to a one-pot, two-step process. An example of this can be seen by the use of such a one pot system in the early 1930's by in a study by Kohler and Bruce.[186] This one pot procedure involves the

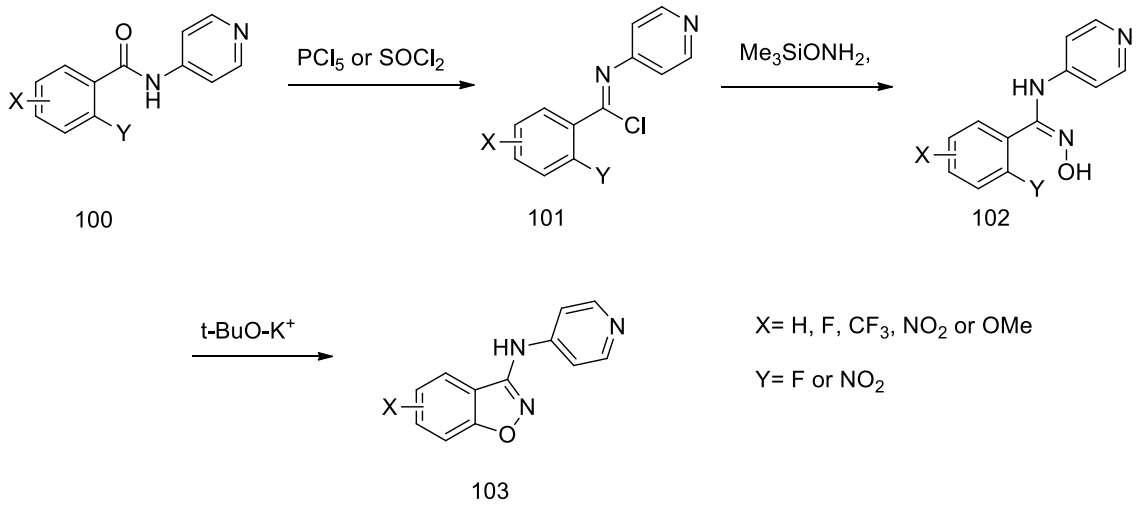
reaction of hydroxylamine hydrochloride and *o*-chloro-benzophenone in a water/ethanol mixture in the presence of sodium hydroxide. This is then followed by heating in aqueous potassium hydroxide, resulting in a 77% yield of 3-phenyl-1,2-benzisoxazole. The major drawback of this type of cyclisation is that only the *Z*-isomer will undergo cyclisation. Therefore, a high yields relies upon the possibility for equilibration between oxime diastereoisomers. This was exemplified by Fink and Kury in their synthesis of 3-(4-pyridylamino-1,2-benzisoxazoles).[187] At the time, there were no known examples of the synthesis of 3-aminobenxioxazoles by amidoxime cyclisation. Amidoxime cyclisation was an interesting proposition as, unlike their ketoxime counterparts, they are usually configurationally labile. Therefore, isomerisation from *E* to *Z* can be achieved in solution (Scheme 3.15). This is important as it means that amidoxime, generated form the corresponding amide, can undergo cyclisation by isomerization *Z* isomer.[188].



Scheme 3.15: scheme showing the ready equilibration of (*Z*)-amidoximes.

Fink and Kurys studied this reaction and developed a new route to 3-arylaminobenzisoxazole through a 3 step process (Scheme 3.16).[187] Treatment of 2-Fluro-3-*N*-4-pyridinylbenzamide derivatives (**100**) with either phosphorus pentachloride or thionyl chloride in refluxing THF or DMF led to formation of imidoyl chloride **101**. Following work up, the crude imidoyl chloride **101** was reacted with *O*-trimethylsilylhydroxylamine, which formed the corresponding O-trimethylsilyl amidoximes. Further stirring for 20 hours in THF and work-up under basic conditions, resulted in protodesilylation to give the free amido-oxime **102**. Treatment of **102** with base forms the hydroxy anion intermediate that undergo cyclisation to give the corresponding 1,2-benzisoxazole **103**. It was found that incorporation of an electron withdrawing group in the phenyl ring allowed the cyclisation to proceed at room

temperature.[187] Whilst, incorporation of strong electron donating groups on the phenyl ring, particularly in the *para* position to the leaving group, led to no desired benzisoxazole product being formed. This was due to increased strength of the carbon-leaving group bond, thus reducing the rate of S_NAr substitution. However, the use hasher reaction conditions and polar aprotic solvents e.g. heating to 60 ^oC in DMF, or 100 ^oC in *N*-methylpyrrolidone (NMP) for particularly electron-rich cases, led to respectable yields (50-86%). Overall, this method gave impressive results giving generally good yields after simple work up and purification by recrystallization.

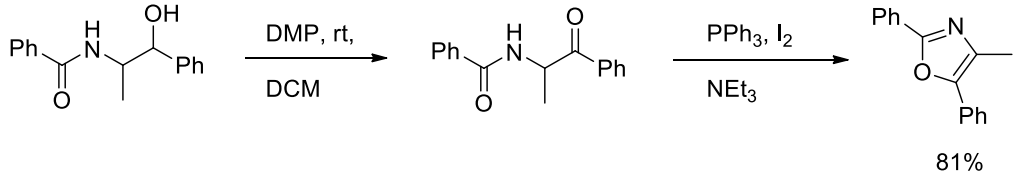


Scheme 3.16: Fink and Kury's 3 step process for the synthesis of 3-(4-pyrindylamino-1,2-benzioxazoles) **103**.[187]

3.3 Use of PPh_3 Systems for the Formation of Isoxazoles and Benzisoxazole

The synthesis of benzisoxazoles was identified as a reaction that the PPh_3-I_2-DMAP system could be used to promote. A similar strategy has been described by Iranpoor *et al.* who used a DDQ/PPh_3 method for the synthesis of 1,2-benzisoxazoles.[181] The use of PPh_3 in the activation of the hydroxy group of an oxime via the formation of phosphine oxide leaving group seemed to be analogues to the activation of other oxygen functionalities such as in the Appel reaction. Wipf and Miller,[189] had used a related reagent system in the Robinson–Gabriel type synthesis,[190] of highly functionalised oxazoles via first the oxidation of serine side chains with Dess-Martin Periodinane (DMP) followed by the use of a PPh_3-I_2-NEt_3 system for a cyclodehydration of the

resulting β-keto amide (Scheme 3.17). Using this method good yields where achieved for the synthesis of oxazole building blocks as part of their efforts to synthesise antiviral tantazoles. They found the mild reaction conditions permitted the use of epimerisable substrates without loss of stereochemical integrity but also allowed wide tolerance of functional groups (amide, carbamate, ester, silyl ether).



Scheme 3.17: The synthesis of oxazoles via Dess-Martin periodinane oxidation, followed by cyclodehydration with PPh_3-I_2-NEt_3. [189]

3.4 Results and Discussion:

Presented now is a new synthetic route towards a small library of 1,2-benzisoxazoles *via* a strategy 2 like approach. It has been developed as an extension of the conditions that were developed in chapter 2 for the synthesis of esters and amides. Following the discussion of the results for the formation of aldehyde derived benzisoxazoles, the formation of novel *N*-pyridinium functionalised imines and their reactions with strong nucleophiles will be discussed. Finally work leading up to a new rapid synthesis of phosphazenes which will further described in chapter 4.

3.4.1 Synthesis of 1,2-Benzisoxazoles.

Initial experiments were carried out to investigate the effectiveness of the PPh_3-I_2-DMAP reagent system for the intramolecular cyclisation of 2-hydroxy-benzaldehyde oximes to 1,2-benzisoxazoles. Studies began with a test cyclisation of the commerically available salicylaldoxime (2-hydroxybenzaldehyde oxime) to 1,2-benzisoxazole in order to determining whether the PPh_3-I_2-DMAP reaction system was suitable for the formation of these useful heterocycles. The reaction procedure mirrored the procedure used for formation of ester amide described in chapter 2. PPh_3, I_2 and DMAP (1.25:1.25:2.5 equivalent ratio) were stirred together in anhydrous CH_2Cl_2 at room temperature. To this stirring mixture, one equivalent of salicylaldoxime was added.

TLC indicated that the reaction had gone to completion within 5 minutes, giving 1,2-benzisoxazole (**104a)** in an 85% yield. In comparison, Iranpoor *et al*.'s use of DDQ/PPh_3 also achieved **104a** in excellent yields of 95% within minutes. Whilst, the results from this test reaction showed that although the yield is not as good as that achieved with PPh_3 and DDQ, it did show that the use of PPh_3-I_2-DMAP system is suitable for the cyclisation of 2-hydroxy benzaldehyde oximes.

A small series of 2-hydroxybenzaldehyde oximes **104a**-**104e** and one *o*-hydroxy ketoxime were screened to try and ascertain the effects of different substituents on cyclisation. Different 2-hydroxy-benzaldehydes where chosen according to their availability and different electronic properties. They were first converted to their corresponding oximes by heating at reflux in ethanol, in the presence of an excess of hydroxyamine hydrochloride and pyridine. The oximes were then subjected to the reactions conditions described above to give aldehyde derived 1,2-benzioxazoles in good to excellent yields and inconclusive results for the ketone derived 1,2-benzisoxazoles (Figure 3.3).

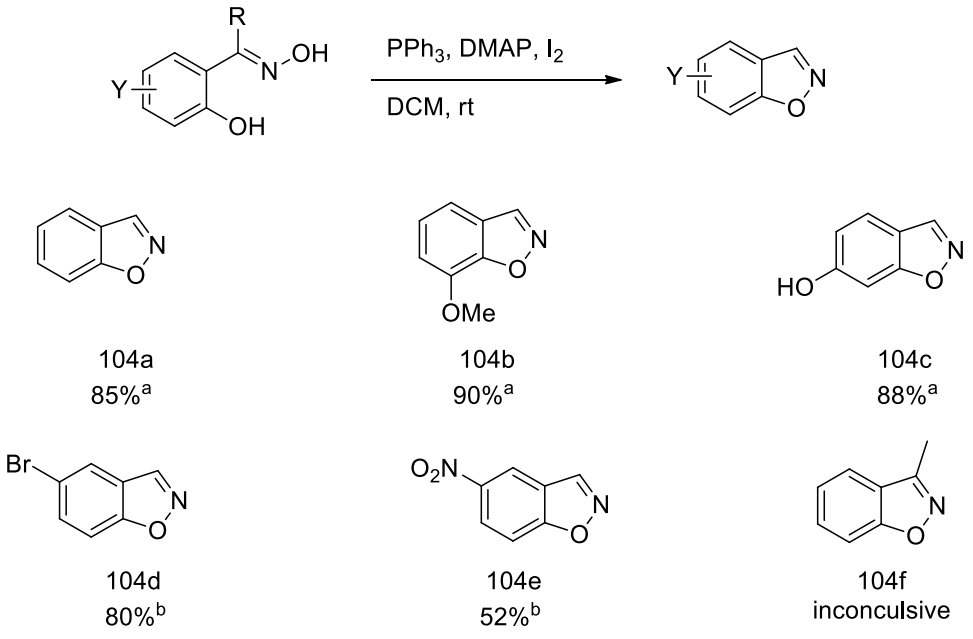
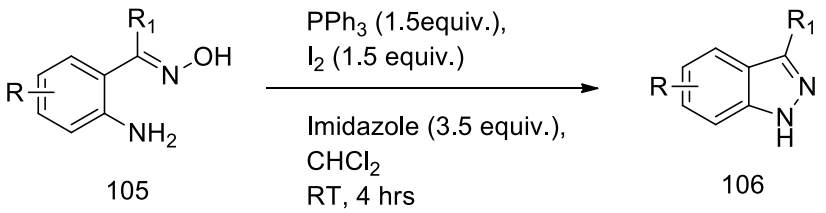


Figure 3.3: Results for the intramolecular cyclisation of 2-hyrdoxy-benzaldehyde oximes. a) Reaction time 10-20 mins b) Reaction time 2 hours.

The results demonstrate the effect that different substituents can have on the reactivity of the cyclisation. Electron-donating groups on the ring system cause the reaction to

proceed quickly and efficiently to the corresponding product in 10-20 mins, with benzisoxazole **104b** and **104c** produced in excellent yields (90% and 88% respectively). In comparison, examples with an electron-withdrawing group on the ring (**104d)** gave the product in a lower yield (80%) and required extended reaction times. The synthesis of **104e** was halted after 2 hours due to a slower rate of reaction, resulting in a 52% yield. The observation that electron-withdrawing groups resulted in poorer yields, suggests that the reaction proceeds by the phenol acting nucleophile. Inclusion of an electron-withdrawing group in the *para* position to the hydroxyl group reduced its nucleophilicity, slowing the rate of substitution at the oxime nitrogen. When the cyclisation of 1-(2-hydroxyphenyl)ethanone oxime to form benzisoxazole **104f** was attempted, the reaction resulted in a mixture of different products that proved to be difficult to isolate via chromatographic techniques. This suggested that this procedure was not compatible for the synthesis of 3-substituted benzisoxazoles from 2-hydroxy benzyl ketone oximes i.e. 1,2-benzioxazoles derived from ketoximes.

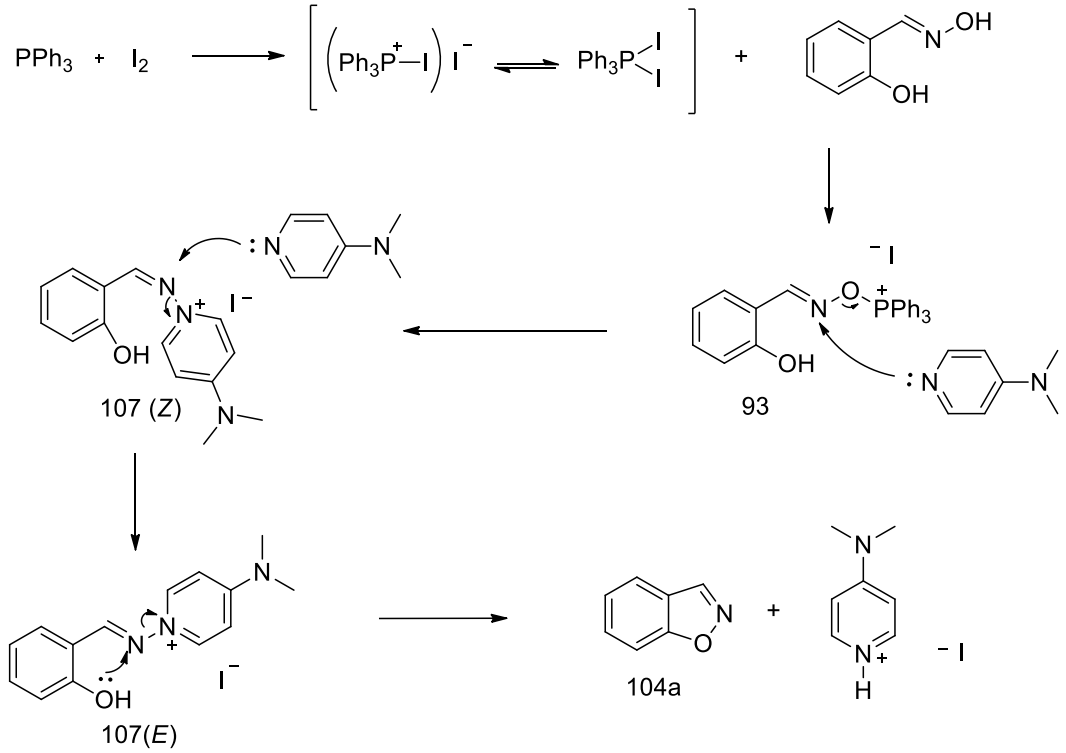
Paul, Panda and Manna showed that the substituents on the aryl ring could also have a significant effect on the nucleophilicity of an aniline in the synthesis of inidazole.[191] 1*H*-Benzindazoles (**106**) were formed from *o*-aminobenzoximes (**106**) via N–N bond formation using PPh_3, I_2, and imidazole (Scheme 3.18). In this same body of work Manna *et al.* also showed that the electrophilicity of the activating oxime could be tuned in order to increase the susceptibility towards attack form the nucleophilic amino group of the ring. For example, the inclusion of an electron-withdrawing group at C-6 of the 2-aminobenzaldhyde oxime increased the yield of benzylhydrazone formation, increasing the overall yield of indazole formation. Interestingly, in the same paper as part of their optimisation process, they investigated the use of DMAP base and found that it didn't work for the purpose of N-N bond formation.



Scheme 3.18: General scheme Manna *et al's* formation of intramolecular formation of 1H-Imdiazoles using PPh_3/I_2/imidazole methodology.

If the mechanism of the formation of the 1-2-benzisoxazole follows a similar path as that for the activation of the carboxylic acid described in chapter 2 then we would expect one of the equivalents of DMAP to displace oxyphosphonium intermediate formed upon the nucleophilic attack of the oxime hydroxy group to the phosphonium iodide. This would then form N-N bond between the DMAP and the nitrogen of the oxime. The DMAP has already been shown to a strong enough nucleophile in order to rapidly facilitate the formation of $O{=}PPh_3$ to produce the acyl-DMAP salts such as **81** and **82** in a matter of minutes and thus, catalyse the formation of ester, amide and anhydrides. It is therefore reasonable to suggest that a similar effect is occurring with the activation of the oxime in order to catalyse the formation of the 1,2-benzisoxazole as observed in Figure 3.3.

Scheme 3.19 proposes a mechanism in how DMAP could activate the oxime towards nucleophilic attack of the 2-hydroxyl group if the activation follows a similar path as overserved in chapter 2. First, the phosphonium iodide equilibrium is formed upon mixing of PPh_3 and I_2. This is followed by the nucleophilic attack of the hydroxy group of the oxime in order to form the same intermediate (**93**) as suggested by Iranpoor *et al.* using their DDQ and PPh_3 system (Scheme 3.10).[181] It is suggested that **93** in the presence of DDQ, is highly activated, producing extremely rapid intramolecular cyclisation. Intermediates such as **93** are known to cyclise rapidly. Therefore it could be that the DMAP is simply acting as base thus increasing the nucleophilicity of the phenol by deprotonating and facilitating the attack and cyclisation. However, DMAP would also be able act as a nucleophile thus, displacing the phosphorus oxygen bond forming $O{=}PPh_3$ and intermediate **107.** Initially intermediate **107** would presumably in the *Z* configuration due to the starting oxime being in the most stable *E* configuration in intermediate **93**. Another DMAP molecule would then be able to displace the DMAP in a further step to produce the more stable *E* configuration allowing intramolecular cyclisation to occur displacing the DMAP resulting in the formation the 1,2-benzisoxazole product (**104a**) and protonated DMAP.



Scheme 3.19: proposed mechanism on how DMAP acts in the formation of 1,2-benzisoxazole**.**

3.4.2 Formation of Novel *N*-Pyridinium Functionalised Imines.

In order to investigate the role of DMAP in the cyclisation of the 2-hydroxy benzaldehydes oximes, studies were carried out to try to determine if the DMAP/PPh_3/I_2 system activates the 2-hyroxybenzaldehyde oximes towards cyclisation via the formation of intermediates **107** described in Scheme 3.19. Iranpoor *et al.*'s use of DDQ and PPh_3, suggest that that the oxime is activated via the formation of P-O bond which converting the hydroxy group of the oxime into a good leaving group.[181] However, it was determined in Chapter 2 that DMAP acts as a nucleophile to further activate carboxylic acids by displacing this initial P-O bond resulting in O=PPh_3 and the acyl-DMAP species. This acyl-DMAP species dramatically reduces reaction time for the formation of ester and amides. It was decided to carry out an investigation were no cyclisation of the activated oxime could take place. It was also hoped to gain an understanding into why the reagent system gave inconclusive mixture of products, when the formation of **104f** was attempted.

A reaction between the commerically available acetophenone oxime with the PPh_3-I_2-DMAP system was chosen, in order to observe the species formed during the procedure.

Acetophenone oxime (1 equiv.) was added to a stirring mixture of PPh_3 (1.5 equiv.), I_2 (1.5 equiv.) and DMAP (3 equiv.) in anhydrous CH_2Cl_2. The mixture was stirred for 10 minutes at room temperature until TLC analysis indicated complete consumption of acetophenone oxime. The solvent was then removed *in vacuo* and EtOAc was added to a precipitate a solid. Immediate precipitation of a light-yellow solid proceeded which was collected by filtration. ^{1}H NMR spectroscopic analysis of this solid indicated two distinct DMAP containing species (Figure 3.4).

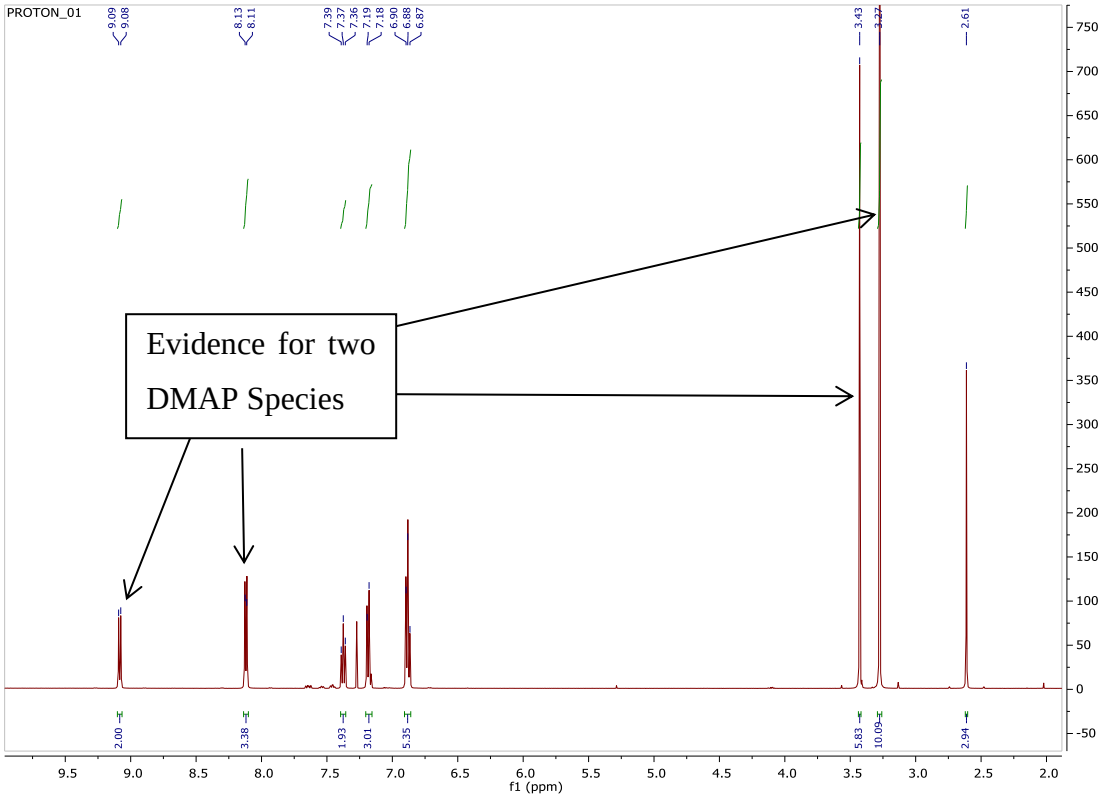


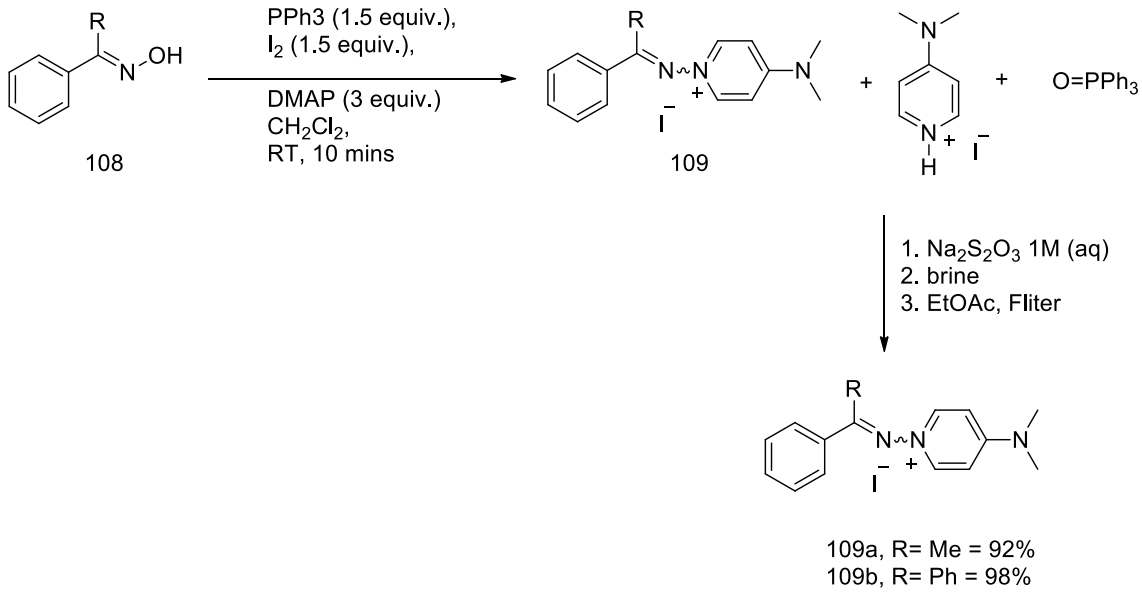
Figure 3.4: H[1] NMR spectra of precipitate containing two DMAP species.

One of the DMAP derivatives present in this mixture was proposed to be derived from protonated DMAP salt, with doublet resonance at δ 8.1 and δ 6.89 ppm, and singlet resonance at δ 3.27 ppm. A new DMAP derivative species was also present, with a deshielded aromatic doublet resonance at δ 9.08 ppm with accompanying doublet resonating at δ 6.84 ppm and a single resonance at δ 3.43 ppm. There were also further peaks at δ 7.35 ppm and δ 7.18–7.14 ppm, as well as a singlet at δ 2.58 ppm. This indicated unprecedented and, to the best of our knowledge, unseen reaction pathway for DMAP in forming N-N bond between the pyridine nitrogen of the DMAP and the

nitrogen acetophenone oxime. This indicates that DMAP has a dual role to play in the above formation of benzisoxazoles as both a base and a nucleophilic catalyst.

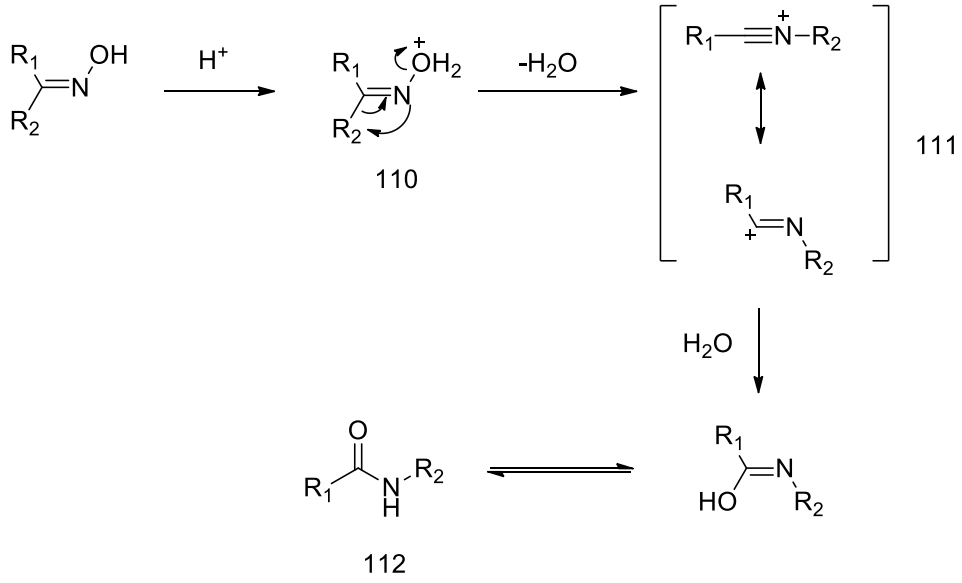
Efforts were then made to isolate and identify this new DMAP hydrazones species by separating it from the DMAP-H^+ salt and phosphine oxide by products. Purification on silica by column chromatography was impractical due to the highly polarity of the product. It was found that the DMAP-hydrazone salt was insoluble in both water and ethylacetate. This allowed for a simple work up procedure consisting of washing the reaction mixture with $Na_2S_2O_3$ (aq, 1 Molar) allowed for traces of iodine in the solution to be removed from the organic layer. This step also allowed the transference of protonated DMAP to the aqueous layer. The organic layer was then washed with brine against this lead to the transference of the protonated DMAP salt to the aqueous layer. The washed organic layer was then dried by passing through a phase separating column and the CH_2Cl_2 was evaporated *in-vacuo*. **109a** could be precipitated from the resulting residue by addition of ethyl acetate followed by filtration. This gave the novel DMAP-hydrazone **109a** in one diastereoisomer (as of yet undetermined) in 92% yield (Scheme 3.20). With the successful high yielding formation of DMAP-Hydrazone **109a** the reaction was repeated with benzophenone oxime. Using identical reaction procedure, the corresponding DMAP hydrazone **109b** was synthesised in an excellent yield of 98% (Scheme 3.20). Identification of both **109a** and **109b** was determined by ^1H and ^{13}NMR spectroscopy and mass spectrometry.

The formation of these stable DMAP-Hydrazones suggests that this intermediate could be involved in the cyclisation of aldehyde oximes to form 1,2-benzisoxazoles. DMAP has already been shown to act as a better leaving group then phosphine oxide and has been shown to be a key in the effectiveness in the esterification and amidation reactions presented in chapter 2, catalysing the attack of alcohol and amine nucleophiles. It therefore, could activate the electrophile towards attack by the *o*-hydroxy group in the cyclisation reaction. However, this might also mean that the oxime may be prone to other unwanted side reactions. This would help explain why the reaction of the ketoxime produces a range of different products when the cyclisation of the keto oximes to form 1,2-benzisoxazole **104f** was attempted. Why this might affect 2-hydroxy-benzketoximes and not the 2-hydroxy-benzaldehyde oximes are as yet unclear.



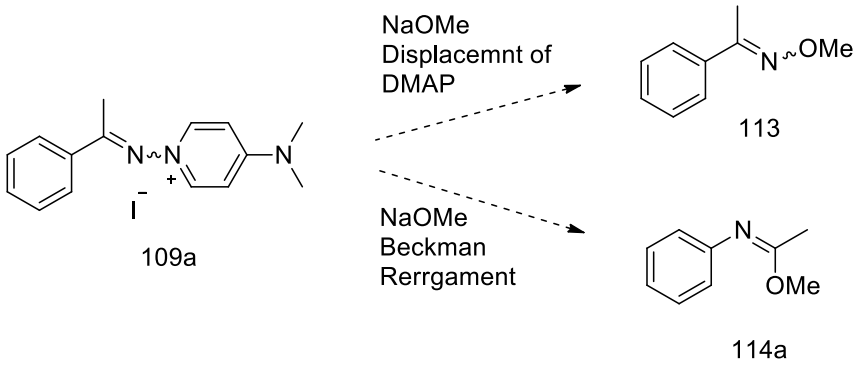
Scheme 3.20: Rapid and Efficient Synthesis of novel DMAP-hydrazones **109a** and **109b**

A reaction that oximes are known to precipitate in is the Beckman rearrangement.[178] Classically the Beckmann rearrangement in acid catalysed rearrangement of oximes to amides (ketone derived oximes) or nitriles (aldehyde derived oximes). The mechanism is commonly believed to consist of an 1,2-alkyl migration (in the case of keto oximes) or 1,2-hydride migration (in the case of aldehyde oximes) resulting in the expulsion of water to form a nitrilium group which then undergoes hydrolysis. Under acidic conditions the hydroxyl group of the oxime is first protonated forming a water leaving group (**110**). 1,2-Migration of the *trans* or '*anti*' R group leads to a positively charged nitrilium ion which can tautomerize to the carbocation ion (**111**). The carbocation intermediate can then undergoes hydrolysis ending in the amine product (**112**) (Scheme 3.21) such in the case of keto derived oximes or nitriles in the case of aldehyde derived oximes.[192] The key to the Beckmann rearrangement is transformation of the hydroxy group of the oxime to a good leaving group via protonation. The inclusion of a DMAP group in place of the hydroxyl group means that the compounds **109a** and **109b** have a good leaving group. Thus, Beckmann rearrangement can occur far more readily.



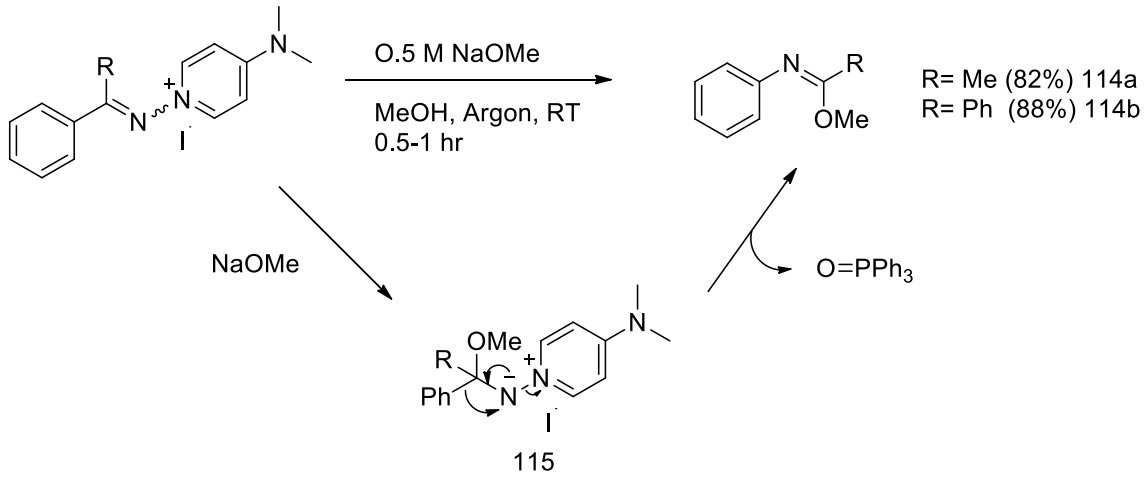
Scheme 3.21: Mechanism of Beckmann rearrangement under standard conditions.

In order to investigate the reactivity of *N*-pyridinium functionalised imines **109a** and **109b** and why this might cause the mixture of products observed for the attempted formation of **104f**, their reactivity profile was explored by studying their reaction with the hard nucleophile NaOMe. The outcome for this process could give rise to two possible outcomes: the nucleophilic substitution of the DAMP with OMe anion resulting in *O*-methyloxime **113** via or the Beckman rearrangement product in the form of an imidate. The outcome of which could provide further evidence of the stereochemistry of DMAP-hydrazones **109a** and **109b** (Scheme 3.22). This seemed a likely outcome due to the results already observed in the cyclisation reactions in which the hydroxy group attacks the activated oxime in the formation of the 1,2-benzioxazoles (Figure 3.3). The possible reaction outcome would be the Beckmann-type rearrangement but for the formation of imidate (**114a**) due to the inability for the oxygen tautomerize to the amide.[178]



Scheme 3.22: Possible products from reaction of the NaOMe with **109a.**

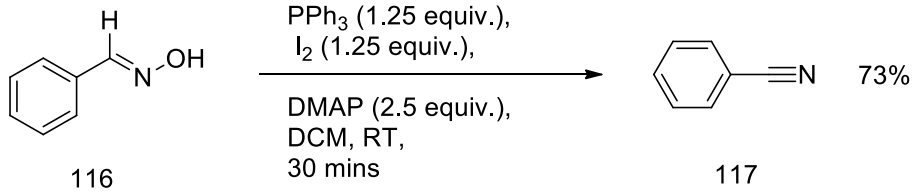
Both **109a** and **109b** were treated with a 0.5 M solution of NaOMe in anhydrous methanol (3 equiv.). The reaction mixture was stirred at room temperature under an atmosphere of argon (0.5-1 h) followed by purification by flash chromatography on silica. The resulting products were characterised as imidate's **114a** and **114b**, with the structure elucidation by the comparison of spectroscopic data with previously published results (**114a**,[193] and **114b**,[194] Scheme 3.23). This demonstrated that the reaction is preferentially undergoing a Beckman like rearrangement rather the direct nucleophilic substitution of the DMAP group. However, it should also be noted that when **109a** and **109b** were stirred in methanol resulted in no reaction occurred and both DMAP hydrazones where retrieved. This suggests that the reaction requires the presence of the anion of NaOMe for the reaction to occur, thus a classical Beckman rearrangement reaction mechanism for this process is unlikely. Instead initial nucleophilic attack of the methoxy anion to form intermediate **115** might be occurring**.** The rearrangement then takes place with the imine nitrogen bond reforming and the phenyl group migrating to the nitrogen displacing the DMAP leaving group forming imidate **114** (Scheme 3.23). These results may explain why a mixture of products results. The hydroxy group of the phenols have pKa values of around 10. The use of an election withdrawing group such as an oxime would result in a lower pKa of this phenol group therefore bring it into the range in which DMAP could act to deprotonate the phenol group and thus facilitate an similar rearrangement as shown in Scheme 3.23.



Scheme 3.23: proposed mechanism of imidate formation of novel DMAP-Hydrazones in the presence of NaOMe in methanol at room temperature**.**

3.4.3 Reaction of Acetophenone Oxime with PPh_3-I_2-DMAP.

The formation of the novel *N*-pyridinium functionalised imines **109a** and **109b** and their subsequent rearrangement to imidate's **114a** and **114b** was an exciting development. However, it was unclear if oximes derived from aldehydes such as benzaldehyde oxime could also form similar intermediates which were stable enough to isolate and undergo similar chemistry. Benzaldehyde oxime was synthesised from benzaldehyde in a 91% yield, using standard conditions. Benzaldehyde oxime (**116**) was submitted to similar reaction conditions as of PPh_3 (1.25 equiv.), I_2 (1.25 equiv.) and DMAP (2.5 equiv.) and stirred for 30 mins in anhydrous CH_2Cl_2 until TLC indicated the oxime had been consumed (Scheme 3.24). Unlike the previous experiments the precipitate that was generated upon addition of ethyl acetate was found to contain no *N*-pyridinium functionalised imine species by ^1H NMR spectroscopic analysis. However, upon purification of the filtrate via first washing with $Na_2S_2O_3$ (aq) and brine, followed by flash column chromatography afforded benzonitrile (**117**) as colourless sweet smelling oil in 73% yield. The formation of a Nitrile product is not surprising as Nagaiah *et al.*, demonstrated an efficient dehydration of oximes via of use of PPh_3 and I_2 in CH_2Cl_2 yielding nitriles in high yields and within reaction times of 3-5 hrs with a good tolerance for functional groups.[195]

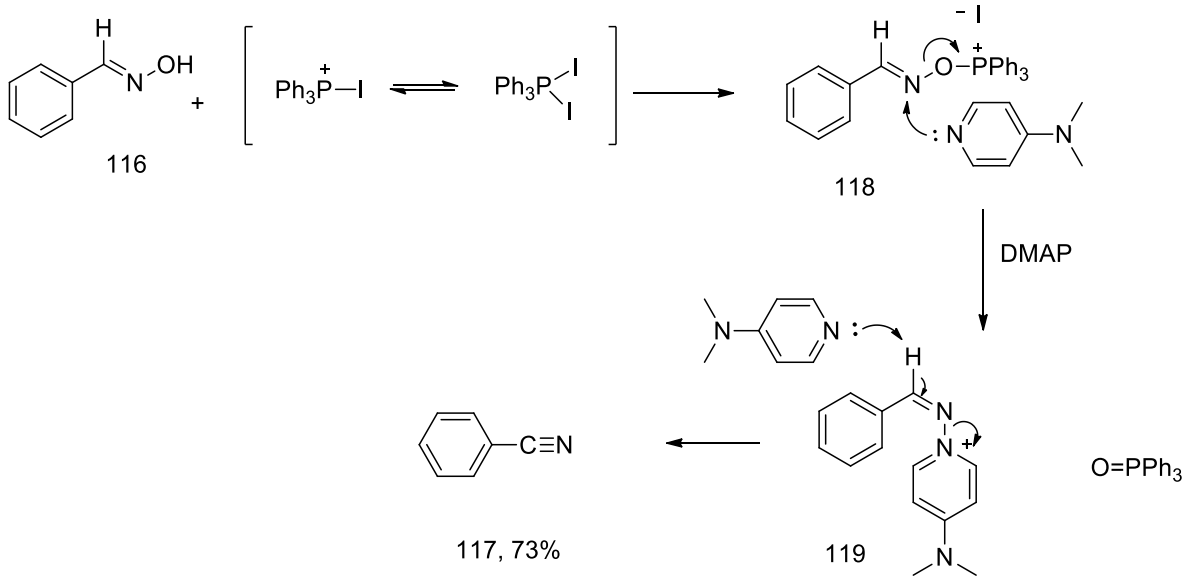


Scheme 3.24: Formation of benzonitrile in a Beckman rearrangement from acetophenone oxime in the presence of PPh_3-I_2-DMAP.

This suggested that the aldehyde oximes derivatives, upon addition of reagents, underwent spontaneous elimination to form to the corresponding nitrile, in either a synperiplanar elimination if the oxime intermediate is in the *E* configuration or in a antiperiplanar elimination if the intermediate is in a *Z* configuration. The preferred route for elimination of oxime ethers is the antiperiplanar E_2 elimination of the Z isomer as the electrons from the σ bonding C-H orbital can most easily reach the rear lobe of the C-leaving group σ^* antibonding orbital. Hegarty showed that this was the case through

comparative kinetic studies for the hydroxide catalysed elimination reactions of *E* and *Z* aromatic oxime ethers established that base driven oxime ethers eliminate in a *syn* fashion with the *Z* isomers eliminating up to 73 times faster than the *E* isomers.[196] Similar results were also reported by Ortiz-Marciales *et al.* in their synthesis of Nitriles from O-*t*-butyldimethylsilyl aldoximes.[197] This established mechanism suggests that DMAP must be playing a role in the formation of a reactive intermediate that is in a *Z* configuration in order to afford the rapid formation of **117**.

Scheme 3.25 offers a possible mechanism for the rapid formation of benzonitrile from **116** when subjected to the PPh_3-I_2-DMAP reagent system in anhydrous CH_2Cl_2. Initially the hydroxyl group of the benzaldehyde oxime (**116**) participates in nucleophilic attack of the phosphonium iodide equilibrium forming ***E*-118**. Based on the observation of the rapid formation of DMAP-hydrazone salts **109a** and **109b**, it is reasonable to assume that a similar DMAP-hydrazine **119** is formed as the *Z* isomer via the nucleophilic attack of DMAP at the nitrogen, displacing phosphine oxide. Base driven antiperiplanar E2 elimination then takes place by another equivalent of DMAP forming the triple bond of the nitrile **117** in a 73% yield. This proposed mechanism is based on the observation that air and moisture stable DMAP-hydrazone salts form within minutes form aryl-ketoximes. **109a** and **109b** were formed in +90% yields within 10 minutes, it seems reasonable to propose that the benzaldehyde oxime is reacting in a similar way.

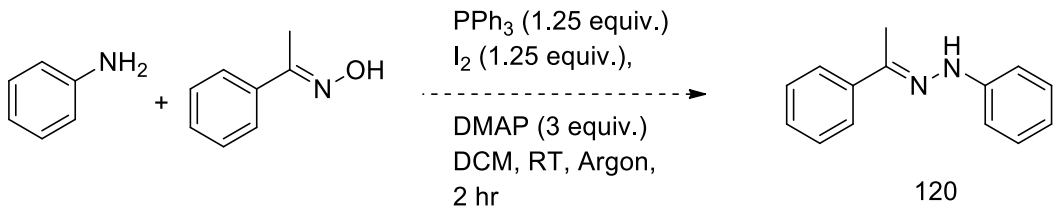


Scheme 3.25: Proposed reaction mechanism for the dehydration of benzaldehyde oxime mediated by PPh_3-I_2-DMAP.

The nitrile or cyano moiety is a highly important due to its synthetic versatility as a precursor to a variety of different functionalities e.g. carboxamides and amides.[198] Nitriles are also very useful is everyday life especially for a synthetic chemist in the form nitrile butadiene rubber a synthetic rubber which is used in disposable latex gloves as well as synthetic rubbers used in the automotive and aeronautical industries.[199] Nitriles appear in a number of highly successful medicinal drugs such as cimetidine, saxagliptin and anasatrazole to name just few.[200] For these reasons having a range of different nitrile formation methods are highly desirable. Some of the most widely used methods nitrile formation is the dehydration of aldoximes.

3.5 Rapid Formation of Phosphazene or Aza-Wittig Reagents via PPh_3-I_2-DMAP Reagent System.

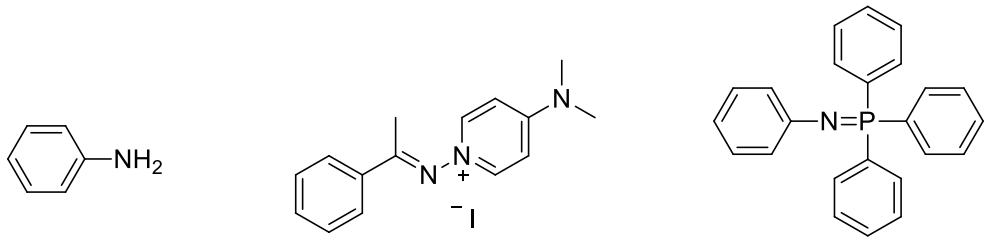
The final reaction that is described was part of the investigation to observe if the PPh_3-I_2-DMAP system would allow facile formation of intermolecular bonds between acetophenone oxime and amines. The initial aim of the experiment was to form a hydrazone between the oxime and aniline hydrazones. At the start of this investigation we believed that the formation of DMAP-hydrazone **109a** would allow us to couple an amine (aniline) to the oxime in order to form a hydrazone in much the same way as the PPh_3-I_2-imdadazole system allowed Manna *et al*. to form a variety of 1H-indazole and hydrazones to give **120** in a one pot reaction (Scheme 3.26).



Scheme 3.26: Proposed formation of hydrazone **120** mediated by PPh_3-I_2-DMAP.

In order to test whether formation hydrazone **120** using the PPh_3-I_2-DMAP system was feasible, acetophenone oxime **108** and aniline were added subsequently in to a stirring solution of PPh_3, I_2 and DMAP in anhydrous CH_2Cl_2. The reaction mixture was placed under an atmosphere of argon and left to stir at room temperature for 2 hours. TLC indicated that there was still both oxime and aniline in the reaction mixture but with an

appearance of a new product. The reaction was stopped by worked up by first washing the reaction mixture with an aqueous solution $Na_2S_2O_3$ (1M) and brine. The organic layer was then dried by passing it through phase separating column. Evaporation of the CH_2Cl_2 followed by taking up of the residue in ethyl acetate resulted in recovery of **107a** in a 52% yield (in relation to starting oxime). The filtrate was then subjected to flash column chromatography resulting in the isolation aniline (32%) and a new compound which was characterised as triphenylphosphoranylidene aniline (**119a**) in a 57% yield (in relation to starting aniline).



32% 52%, 109a 57%, 121a

Scheme 3.27: Structures and yields of the isolatable products from the reaction of acetophenone oxime and aniline with PPh_3-I_2-DMAP reagent system.

This mixture of products came as a surprise but can help explain why Manna *et al*. found that use of DMAP as base did not produced the desired indazole as part of their optimisation studies for the synthesis of 1*H*-indazoles through oxime-phosphonium ion intermediate.[201] Clearly the formation of the phosphazene **119a** was in competition with the formation of **109a** and is a facile process which forms at similar rates to the formation of the DMAP-hydrazone. The rapid formation of phosphazene shown in this reaction led to the project taking a new direction, and showed yet another use for the PPh_3-I_2-DMAP reagent system. Phosphazenes are versatile reagents and the key intermediates in the widely used Staudinger reaction. One of the major drawbacks of the Staudinger reaction is the use of organic azides which have to be handled with extreme care. Due to their explosive properties via the potential for rapid release of N_2 gas which is the driving force of the Staudinger formation of phosphazenes. The use of the DMAP/PPh_3/I_2 system for the formation of these versatile reagents offers a new route for mild and rapid formation of phosphazene directly from the amine whereas with the Staudinger reaction often requiring an addition step in order to form the starting azide via reaction of an alky halide and sodium azide (NaN_3).

3.6 Conclusions

The formation of 1,2 benzisoxazoles from benzaldehyde oxime derivatives works well, producing rapid results. Electron rich systems such as 1,2-benzioxazole **104b** gave the best yields, whilst electron poor ring systems gave significantly lower yields as with 1,2-benzioxazole **104e.** When it came to the synthesis of ketone derived 1,2-benzisoxazoles such as **104f** the results were inconclusive and gave a variety of different products. The difference in reactivity for the cyclisation of keto and aldehyde oximes was then studied via the reaction with keto and aldehyde derived oximes that are unable to cyclise. For ketoximes this led to the rapid and efficient formation of novel *N*-pyridinium functionalised imines; **109a** (92%) and **109b** (98%). Whilst, the reaction with aryl-aldehyde oxime resulted in the elimination to the corresponding nitrile **117** a 73% yield. The reactivity of **109a** and **109b** was then tested via the reaction with NaOMe. This resulted in imidate products **114a** (82%) and **114b** (88%) in good yields. Although this is a product expected of a Beckman rearrangement the observation that this reaction only occurs in the presence of NaOMe suggests that the rearrangement is different in mechanism. Finally the PPh_3-I_2-DMAP system was tested as a new route towards hydrazones with reaction between benzaldehyde oxime (**108**) and aniline; this resulted in the formation of phosphazene **121a** suggesting a new route towards a rapid synthesis of phosphazenes a without the use of azide as the starting material.

3.7 Experimental and Characterisation

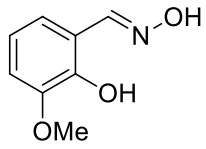
General Methods

Commercially available reagents were used without further purification;. Solvents where dired using. Unless other wise stated reaction where carried out in air at roomtemperature. Microwave irradiation experiments were performed in a sealed Pyrex tube using a self-tunable CEM Explorer focused monomodal microwave synthesizer at the given temperature using the instrument's in-built IR temperature measuring device, by varying the irradiation power. Flash chromatography was carried out using a Teledyne ISCO Combiflash Rf instrument and Biotage SNAP KP-Sil cartridges packed with 50 μm silica particles. Analytical thin layer chromatography was carried out using

aluminium-backed plates coated with Merck TLC Silica gel 60 F_{254} that were visualized under UV light (at λ 254 and/or 360 nm).

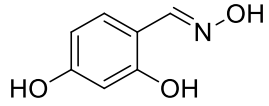
Fully characterized compounds were chromatographically homogeneous. Melting points were determined using tanford Research Systems Optimelt and are uncorrected. NMR spectra were recorded using a Varian VNMRS instrument operating at 500 MHz for ^{1}H spectra and 125 MHz for ^{13}C spectra; *J* values were recorded in Hertz (Hz) and multiplicities were expressed by the usual conventions. Low resolution mass spectra were determined using a Fisons VG autospec instrument using atmospheric pressure chemical ionization (APcI). High resolution mass spectra were determined using a Bruker Daltronics Apex III instrument by electrospray ionization (ESI).

Synthesis of Oximes.



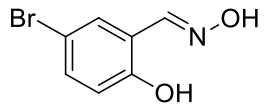
2-Hydroxy-3-methoxybenzaldehyde oxime

To a stirring solution of *o*-vanillin (0.554 g, 3.64 mmol) in 25 ml of EtOH was added $NH_2OH.HCl$ (1.292 g, 18.59 mmol) this was followed by addition of pyridine (0.6 ml, 7.3 mmol). The reaction mixture was then heated at reflux temperature until TLC indicated that the reaction had gone to completion (3h). The solvent was then evaporated under vacuo and the resulting residue was taken up in EtOAc and washed with 1M HCl (aq) (3x20 ml) and brine (3x 20 ml) and dried over $NaSO_4$. The Solvent was then evaporated affording 2-hydroxy-3-methoxybenzaldehyde oxime as a white solid with no need for further purification (0.560 g, 92%); MP 121.1-123.1^{o}C (*lit*[202] 120-121 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, -N-OH), 8.26 (s, 1H), 7.28 (s, OH), 6.95 – 6.84 (m, 3H), 3.93 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.69 (N=C), 148.18 (C-OH), 147.04 (C-OMe), 122.26 (CH), 119.45(CH), 113.50 (CH), 56.19 (CH_3). EI-MS (*m/z*) 167 (M^+). Known compound, spectra matches.[203]



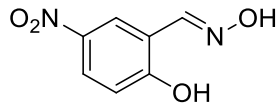
2,4-Dihydroxybenzaldehyde oxime

To a stirring solution of 2,4-dihydroxybenzaldehyde (0.329 g, 2.38 mmol) in 20 ml of EtOH was added $NH_2OH.HCl$ (0.829 g, 1.19 mmol) this was followed by addition of of pyridine (0.39 ml, 4.76 mmol). The reaction mixture was then heated at reflux temperature until TLC indicated that the reaction had gone to completion (3h). The solvent was then evaporated under vacuo and the resulting residue was taken up in EtOAc and washed with 1M HCl (aq) (3x20 ml) and brine (3x 20 ml) and dried over $NaSO_4$. The Solvent was then evaporated affording 2,4-hydroxybenzaldehyde oxime as an off white solid with no need for further purification (0.319 g, 88%); MP 194.5-195.9 ^oC (*lit*[204] 194-196 ^oC). ^1H NMR (500 MHz, CD_3OD) δ 8.11 (s, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.34 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.30 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 159.73 (C-OH), 158.69 (C-OH), 150.82 (N=C), 130.91 (C), 109.65 (CH), 107.04 (CH), 102.25 (C). ESI-MS (*m/z*) 154.0499 (M^{+H}). Know compound, spectra matches.[205]



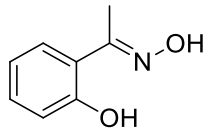
5-Bromo-2-hydroxybenzaldehyde oxime

To a stirring solution of 5-bromo-2-hydroxybenzaldehyde (0.939 g, 4.67 mmol) in 20 ml of EtOH was added of $NH_2OH.HCl$ (0.163 g, 23.40 mmol) this was followed by addition of pyridine (0.76 ml, 9.36 mmol). The reaction mixture was then heated at reflux temperature until TLC indicated that the reaction had gone to completion (2hours). The solvent was then evaporated under vacuo and the resulting residue was taken up in EtOAc and washed with 1M HCl (aq) (3x20 ml) and brine (3x 20 ml) and dried over $NaSO_4$. The Solvent was then evaporated affording 5-bromo-2-hydroxybenzaldehyde oxime as white solid with no need for further purification (0.950 g, 94%); MP 125.5-128.7^oC (*lit*[206]133-134.5 ^oC). ^1H NMR (500 MHz, CD_3OD) δ 8.21 (s, 1H), 7.46 (d, *J* = 2.5 Hz, 1H), 7.32 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 156.00 (C-Br), 148.97 (N=C), 132.63 (CH), 131.41 (CH), 119.48 (C), 117.74 (CH), 110.60 (C). EI-MS (*m/z*) 216 (M^+). Know Compound, spectra matches.[206]



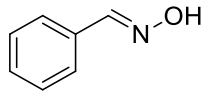
2-Hydroxy-5-nitrobenzaldehyde oxime

To a stirring solution of 2-hydroxy-5-nitrobenzaldehyde (0.747 g, 4.47 mmol) in 20 ml of EtOH was added $NH_2OH.HCl$ (1.551 g, 22.3 mmol) this was followed by addition of pyridine (0.73ml, 8.94 mmol). The reaction mixture was then heated at reflux temperature until TLC indicated that the reaction had gone to completion (2 hours). The solvent was then evaporated under vacuo and the resulting residue was taken up in EtOAc and washed with 1M HCl (aq) (3x20 ml) and brine (3x 20 ml) and dried over $NaSO_4$. The Solvent was then evaporated affording 2-hydroxy-5-nitrobenzaldehyde oxime as yellow solid with no need for further purification (0.786 g, 97%); MP 227.1-229.2^{o}C, (*lit*[207] 230-232 ^{o}C). ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.37 (s, 1H), 8.34 (d, J = 3.0 Hz, 1H), 8.14 (dd, J = 9.0, 3.0 Hz, 1H), 7.03 (d, J = 9.0 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 162.16 (HO-C), 148.23 (C=N), 140.56 (C-NO_2), 125.49 (CH), 124.92 (CH), 118.07 (C), 116.41 (CH). EI-MS (*m/z*) 182 (M^+). Known compound, spectra marches.[207]



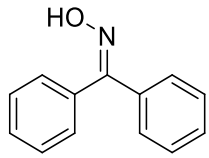
1-(2-Hydroxyphenyl)ethanone oxime

To a stirring solution of $NH_2OH.Cl$ (0.998 g, 14.37 mmol) and of KOH (1.597 g, 28.45 mmol) in 70% EtOH in H_2O was added of 1-(2-hydroxy phenyl)ethanone (0.968 g, 7.11 mmol) The mixture was then allowed to reflux overnight. The solvent mixture was then removed in vacuo the residue was taken up in EtOAc and washed with brine and dried over $NaSO_4$ to afford 1-(2-hydroxyphenyl)ethanone oxime as a white solid without the need for further purification (0.566 g, 53%); MP 213.5-215.7^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.73 (bs, -NOH), 8.31 (bs, OH), 7.46 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 2.38 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 159.46 (HO-C), 157.35 (C=N), 130.76 (CH), 127.61 (CH), 119.33 (CH), 118.66 (C), 117.24 (CH), 10.74 (CH_3). ESI-MS (*m/z*) 152.0708 (M^{+H}). Known compound, spectra matches.[208]



Benzaldehyde oxime

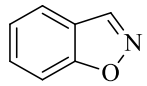
To a stirring solution of benzaldehyde (1.135 g, 1.07 mmol) in 20 ml of EtOH was added $NH_2OH.HCl$ (3.701 g, 5.80 mmol), this was followed by addition of pyridine (1.72 ml, 21.4 mmol). The reaction mixture was then heated at reflux temperature until TLC indicated that the reaction had gone to completion (2 hours). The solvent was then evaporated under vacuo and the resulting residue was taken up in EtOAc and washed with 1M HCl (aq) (3x20 ml) and brine (3x20 ml) and dried over $NaSO_4$ to afford benzaldehyde oxime as colourless oil without the need for further purification. (1.174 g, 91%). ^{1}H NMR (500 MHz,$CDCl_3$) δ 8.35 (bs, N-OH), 8.18 (s, 1H), 7.61 – 7.58 (m, 2H), 7.42 – 7.39 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.35 (C=N), 131.99 (C), 130.01 (CH), 128.75 (CH), 127.02 (CH). Known compound, matches spectra.[209]



Benzophenone oxime

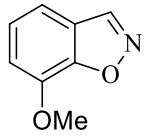
To a stirring solution of $NH_2OH.Cl$ (1.555 g, 22.2 mmol) and NaOH (1.597 g, 44.46 mmol) in 50% EtOH/H_2O, was added benzophenone (1.008 g, 5.53 mmol). The mixture was then allowed to reflux overnight. The solvent mixture was then removed in vacuo the residue was taken up in EtOAc and washed with brine (3x20 ml) and dried over $NaSO_4$ the resulting residue was then purified via flash column chromatography (0-10% EtOAc in CH_2Cl_2) to afford benzophenone oxime as a mixture of E and Z isomers white crystalline solid (0.981 g, 90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (bs, N-OH), 7.52 – 7.31 (m, 10H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.23 (C=N), 136.42 (C), 132.53 (C), 129.61 (CH), 129.39 (CH), 129.21 (CH), 128.47 (CH), 128.41 (CH), 128.37 (CH), 128.01 (C) ESI-MS (*m/z*) 198.0913 (M^{+H}). Know compound, spectra matches.[210]

Synthesis of 1, 2 Benzisoxazoles



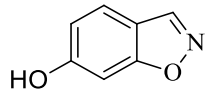
1, 2 Benzisoxazole (104a)

To a stirring solution of I_2 (0.351 g, 1.39 mmol) and PPh_3 (0.363 g, 1.38 mmol) in 15ml of anhydrous CH_2Cl_2 was added of DMAP (0.337 g, 2.76 mmol) along with 2-hydroxybenzaldehyde oxime (0.151 g, 1.10 mmol). After 15 minutes the reaction had gone completion by TLC analysis. The reaction mixture was the washed with 1M $Na_2S_2O_3$ (aq) solution 2x20 ml and brine (2x20 ml). The solvent was then dried by passing through a phase separating column and purified via flash chromatography on silica gel (EtOAc in hexane 10-30%) to afford **104a** as a colourless oil (0.112 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$ δ 8.72 (s, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.57 (t, *J* = 8.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (126 MHz,$CDCl_3$) δ 162.26 (C-O), 146.09 (C=N), 129.97 (CH), 123.69 (CH), 121.92 (CH), 121.30 (C), 109.72 (CH). EI-MS (*m/z*) 119 ($M^{\cdot+}$). Known compound, spectra matches.[211]



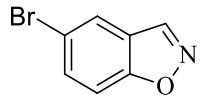
7-methoxy-1,2-benzisoxazole (104b)

To a stirring solution of I_2 (0.273 g, 1.08 mmol) and PPh_3 (0.280 g, 1.07 mmol) in 20ml of anhydrous CH_2Cl_2 was added DMAP (0.259 g, 2.09 mmol) along with 2-hydroxy-3-methoxy-benzaldehyde oxime (0.139 g, 0.82 mmol). After 10 minutes the reaction had deemed too have gone completion by TLC analysis via absence of any starting oxime. The reaction mixture was the washed with 1M $Na_2S_2O_3$ (aq) solution (2x20 ml) and brine (2x20 ml). The solvent was then dried by passing through a phase separating column and purified via flash chromatography on silica gel (EtOAc in hexanes 20-40%) to afford **104b** as a colourless oil (0.112 g, 90%). ^{1}H NMR (500 MHz,$CDCl_3$) δ 8.69 (s, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 4.06 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.97 (O-C_{ar}), 146.26 (-N=C-), 144.56 (MeO-C_{ar}), 124.86 (C_{ar}), 123.17(C_{ar}), 113.38 (C_{ar}), 111.23 (C_{ar}), 56.43 (O-Me). EI-MS (*m/z*) 149 (M^+). Known compound, spectra matches.[212]



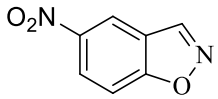
1,2-Benzisoxazol-6-ol (104c)

To a stirring solution of I_2 (0.258 g, 1.02 mmol) and PPh_3 (0.273 g, 1.08 mmol) in 20 ml of anhydrous CH_2Cl_2 was added of DMAP (0.249 g, 2.02 mmol) along with of 2,4-hydroxy-benzaldehyde oxime (0.123 g, 0.80 mmol). After 10 minutes the reaction had deemed too have gone completion by TLC analysis. The reaction mixture was the washed with 1M $Na_2S_2O_3$ (aq) solution (2x20 ml) and brine (2x20 ml). The solvent was then dried by passing through a phase separating column and purified via flash chromatography on silica gel (EtOAc in hexanes 40-60%) to afford **104c** as a colourless oil (0.095 g, 88%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.67 (s, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.0 Hz, 1H) 4.89 (s, OH). ^{13}C NMR (126 MHz,CD_3OD) δ 163.94 (O-C), 160.55 (C-OH), 145.77 ($N=C_{ar}$), 122.33 (CH), 114.20 (CH), 113.87 (C), 94.10 (CH). EI-MS (m/z) 135 (M^+). Known compound, spectra matches.[212]



5-bromo-1,2-benzisoxazole (104d)

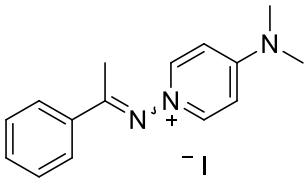
To a stirring solution of I_2 (0.213 g, 0.81 mmol) and PPh_3 (0.218 g, 0.81 mmol) in 20 ml of anhydrous CH_2Cl_2 was added DMAP (0.201 g, 1.63 mmol) along with of 5-bromo-2-hydroxy-benzaldehyde oxime (0.141 g, 0.651 mmol). After 10 minutes the reaction had deemed too have gone completion by TLC analysis. The reaction mixture was the washed with 1M $Na_2S_2O_3$ (aq) solution (2x20 ml) and brine (2x20 ml). The solvent was then dried by passing through a phase separating column and purified via flash chromatography on silica gel (EtOAc in hexanes 15-20%) to afford **104d** as a white solid (0.104 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.67 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.18 (O-C), 145.35 (N=C), 133.12 (C-Br), 124.42 (CH), 123.25 (C), 116.58 (CH), 111.20 (CH). EI-MS (*m/z*) 197 ($M^{\cdot+}(Br^{79})$), 199 ($M^{\cdot+}$ (Br^{81})). Known compound, spectra known.[211]



5-nitro-1,2-benzisoxazole (104f)

To a stirring solution of of I_2 (0.190 g, 0.748 mmol) and of PPh_3 (0.196 g, 0.748 mmol) in 15ml of anhydrous CH_2Cl_2 was added of DMAP (0.183 g, 1.48 mmol) along with 5-nitro-2-hydroxy-benzaldehyde oxime (0.108 g, 0.592 mmol). After 2 hours the reaction had still not deemed too have gone completion by TLC analysis. The reaction mixture was quenched and washed with 1M $Na_2S_2O_3$ (aq) solution (2x20 ml), followed by washes of the organic layer with brine (2x20 ml). The solvent was then dried by passing through a phase separating column and purified via flash chromatography on silica gel (EtOAc in hexanes 25-35%) to afford **104f** as a white solid (0.051 g, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.72 (d, *J* =2.0 Hz, 1H), 8.50 (dd, *J* = 9.0, 2. Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.35 (O-C), 146.97 (N=C), 144.81 (NO_2-C), 125.54 (CH), 121.85 (C), 119.15 (CH), 110.42 (CH). EI-MS (*m/z*) 164 ($M^{\cdot+}$). Known compound, spectra matches.[211]

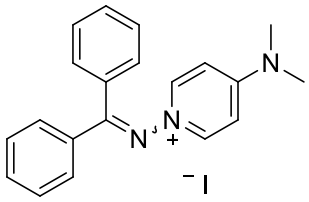
Formation of *N*-pyridinium functionalised imines salts and their reactions with NaOMe



4-(dimethylamino)-1-((1-phenylethylidene)amino)pyridin-1-ium iodide (109a)

To a stirring solution of PPh_3 (2.979 g, 11.36 mmol), I_2 (2.875 g, 11.33 mmol) and of DMAP (2.770 g, 7.56 mmol) in 40 ml of anhydrous CH_2Cl_2 was added acetophenone oxime (1.021 g, 7.56 mmol). The reaction mixture was allowed to stir for until the oxime had been consumed by TLC (10-15 minutes). The reaction mixture was then washed with 1M $Na_2S_2O_3$ (aq) (2x20 ml) and brine (3x20 ml). The organic layer was then passed through a phase separating column and the solvent removed in vacuo. The resulting residue was then taken backup in EtOAc and the resulting precipitate was collected via vacuum filtration to afford **109a** as a yellow solid (2.553 g, 92%), decomposition point 176.5-198.0 ^{o}C. IR (cm^{-1}).*v*= 1695 (w), 1636 (s), 1578 (s), 1401 (s), 1374 (s), 1185 (s, br), 1081 (s), 822 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ

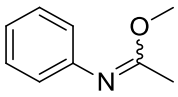
9.08 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.18 – 7.14 (m, 3H), 6.84 (d, *J* = 7.5 Hz, 2H), 3.37 (s, 6H), 2.58 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.81 (C=N), 152.33 (C), 146.09 (C), 137.92 (CH), 129.35 (CH), 125.25 (CH), 119.97 (CH), 108.25 (CH), 41.54 (CH_3), 16.69 (CH_3). ESI-MS (*m/z*) 240.1495 (M-I$^-$), ESI-MS (*m/z*) 607.2047 (M+(M-I$^-$).



4-(dimethylamino)-1-((diphenylmethylene)amino)pyridin-1-ium iodide.(109b)

To a stirring solution of PPh_3 (1.068 g, 4.06 mmol), I_2 (1.028 g. 4.06 mmol) and DMAP (0.990 g, 8.11 mmol) in 25 ml of anhydrous CH_2Cl_2 was added g acetophenone oxime (0.534 g, 2.71 mmol). The reaction mixture was allowed to stir for until all oxime had been consumed by TLC (10-15 minutes). The reaction mixture was then washed with 1M $Na_2S_2O_3$ (aq) (2x20 ml) and brine (3x20 ml). The organic layer was then passed through a phase separating column and the solvent removed in vacuo. The resulting residue was then taken backup in EtOAc and the resulting precipitate was collected via vacuum filtration to afford **109a** as a white solid (1.132 g, 98%), decomposition points =206.3-239.4 ^{o}C. IR: *v* = 1698 (w), 1638 (m, N=C), 1587 (w), 1260 (w), 1205 (s), 1116 (vs), 822 (m), 712 (s) cm^{-1}. ^{1}H NMR (500 MHz,$CDCl_3$) δ 8.45 (d, *J* = 8.0 Hz, 2H), 7.51 – 7.47 (m, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.25 (m, 4H), 7.20 (t, *J* = 8.0 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.77 – 6.73 (m, 2H), 3.50 (s, 6H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 158.15 (C=N), 152.90 (C), 145.84 (C), 138.19 (C), 132.00 (CH), 129.89 (CH), 129.59 (CH), 129.02 (CH), 127.13 (C), 125.36 (CH), 121.10 (CH), 108.70 (CH), 42.10 (CH_3). ESI-MS (*m/z*) 302.16 43 (M-I$^-$), ESI-MS (*m/z*) 731.2346 (M+(M-I$^-$).

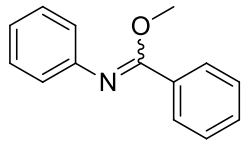
Imidate Formation



Methyl* N-*phenylacetimidate (114a)

6 ml of 0.5 Molar sodium methoxide in methanol was added to 4-(dimethylamino)-1-((1-phenylethylidene)amino)pyridin-1-ium iodide (0.310 g, 0.845 mmol) under an

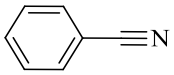
atmosphere of argon. The reaction mixture was then stirred for 1h until ^{1}H-NMR spectroscopy indicated the starting DMAP-Hydrazone salt was consumed. The mixture was then diluted with CH_2Cl_2 and dry loaded on to silica and purified via flash chromatography on silica 5-15% EtOAc in hexane to afford **114a** phenylacetimidate as a colourless oil (0.103 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 3.81 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.60 (C=N), 149.16 (C), 128.91 (CH), 122.83 (C), 121.12 (CH), 53.04 (OCH_3), 15.84 (CH_3). ESI-MS (*m/z*) 150.0909 (M^{+H}). Known compound, spectra matches.[193]



Methyl* N-*phenylbenzimidate (114b)

6 ml of 0.5 Molar sodium methoxide in methanol was added to of 4-(dimethylamino)-1-((diphenylmethylene)amino)pyridin-1-ium iodide (0.421 g, 0.981 mmol) under an atmosphere of argon. The reaction mixture was then stirred for 1 hour until NMR indicated the starting DMAP-Hydrazone salt was consumed. The mixture was then diluted with CH_2Cl_2 and dry loaded on to silica and purified via flash chromatography on silica 5-15% EtOAc in hexane to afford **114b** as a colourless oil (0.183 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.29 (m, 3H), 721 6.97 (m, 1H), 6.76–6.72 (m, 2H), 3.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.07 (C=N), 148.42 (C), 131.39 (C), 129.78 (CH), 129.24 (CH), 128.82 (CH), 127.87 (CH), 122.54 (CH), 121.62 (C_{ar}), 53.90 (OCH_3). ESI-MS (*m/z*) 212.1065 (M^{+H}). Known compound, spectra matches.[194]

Benzonitrile Formation Mediated by PPh_3-I_2-DMAP.



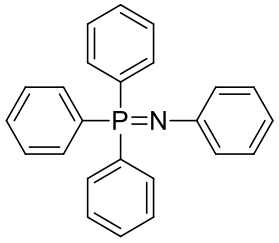
Benzonitrile (117)

To a stirring solution of PPh_3 (0.401 g, 1.51 mmol), I_2 (0.386 g, 151 mmol) and of DMAP (0.370 g, 3.03 mmol) in 10 ml of anhydrous CH_2Cl_2 was added benzaldehyde oxime (0.147 g, 1.21 mmol). The reaction mixture was allowed to stir for until the oxime had been consumed by TLC (30 mins).. The resulting precipitate was then

filtered and the filtrate was washed with 1M $Na_2S_2O_3$ (aq) (2 x 20 ml) and brine (3 x 20 ml). The organic layer was then dried with anhydrous $MgSO_4$. The solvent was then evaporated in vacuo and the residue was taken back up in EtOAc. The mixture was then purified on silica flash chromatography on silica 20% EtOAc in hexane to afford **117** as a colourless oil (0.091 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 132.74 (CH), 132.14 (CH), 129.10 (CH), 118.81 (C), 112.48 (C). EI-MS (*m/z*) 103. Known compound, spectra matches.[213]

4 A New Method for the Rapid and Efficient Synthesis of Aza-Wittig Reagents.

4.1 Introduction[214–216]



119a

Figure 4.1: The first example of an aza-Wittig reagent **119a** as synthesised by Staudinger and Mayer.[4,70]

Staudinger and Meyer first prepared the phosphazene **119a** in 1919 (Figure 4.1).[4] It was the first known nitrogen analogue of a phospho-carbon ylide otherwise known as a Wittig reagent and thus the first example of an aza-Wittig reagent. In terms of nomenclature aza-Wittig reagent is one of several terms that can be used to describe this functional group i.e. the nitrogen phosphorus double bond, others terms including; imino-phosphoranes, phosphine imines or phosphazenes. The Wittig reaction and its derivatives (HWE and HW reactions), react ketones or aldehydes with phosphorus carbon ylides in a C=C double bond forming reaction. They have since become widely used and efficient methods in the formation of carbon-carbon double bonds.[217]

Phosphorous-carbon ylides have been described as "*a substance in which a carbanion is attached directly to a heteroatom carrying a substantial degree of positive charge and in which the positive charge is created by the sigma bonding of substituents to the heteroatom*".[218] Similarly phosphazenes can act as useful and efficient reagents for the formation of imines under mild reaction conditions. Phosphazenes can be reacted with a number of other functional groups to form important intermediate products. Although phosphazenes were first prepared at the beginning of the 20th century it was not until Wittig's work that "aza-Wittig chemistry" became common practice.[1,47,49] Since Staudinger's and Wittig's initial studies, both Wittig and aza–Wittig chemistry have undergone much development and have become significantly utilised tools within organic chemistry that has found use in natural product and heterocycle synthesis.

The aza-Wittig reaction is a widely used method's for imine synthesis via the reaction of phosphazenes with the aldehydes or ketones. The reactivity of these compounds is a consequence of the polarity of the phosphorus-nitrogen bond. Taking the most extreme view of resonance the nitrogen can be seen as having a substantial negative charge while the phosphorus has a positive charge (Figure 4.2). This allows the nitrogen to attack the electrophilic carbon of a carbonyl group and the phosphorus to accept a bond with the oxygen atom. A major driving force for aza-Wittig reactions is the formation of very stable phosphorous oxygen double bond. This is often the only side product of an aza-Wittig reactions. However, phosphine oxide can prove problematic when it comes to isolation of the final due to similar retention times on silica during chromatography.

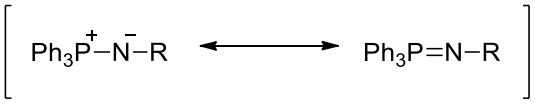


Figure 4.2: Resonance structures of aza-Wittig reagent.

4.1.1 Phosphazene 'Organic Super bases'

Another prominent feature of phosphazene reactivity is their basicity. A class of phosphazene in which the phosphorus atom is attached to three amino groups rather than three aryl or alkyl groups (as in the majority aza-Wittig reagents), have been found to have remarkable affinity for protons and have been demonstrated to be excellent examples of "organic superbases" (Figure 4.3).[219] The basic properties of phosphazenes of this class was first discovered by Schwesinger, who has since developed a number of different examples.[220–222] Phosphazenes bases like those exemplified in Figure 4.3 are extremely strong, non-ionic and metal free bases. They also exhibit low nucleophilicity and inertness towards electrophilic components can help form highly reactive carbon anions from precursors with weak hydrogen acidity enabling alkylation of otherwise unattainable by covenantal means. The more phosphazenes components there are the higher the basicity, as shown by the increasing pKa-H^+ shown in Figure 4.3.

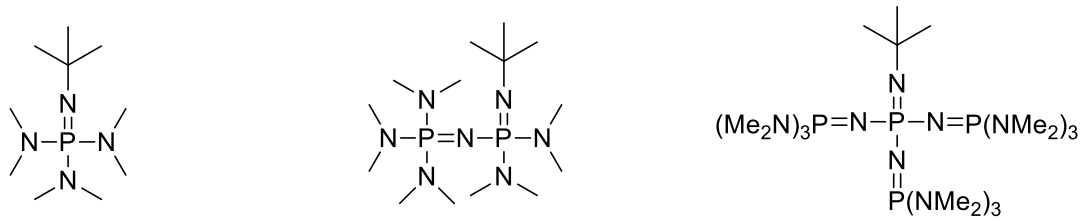
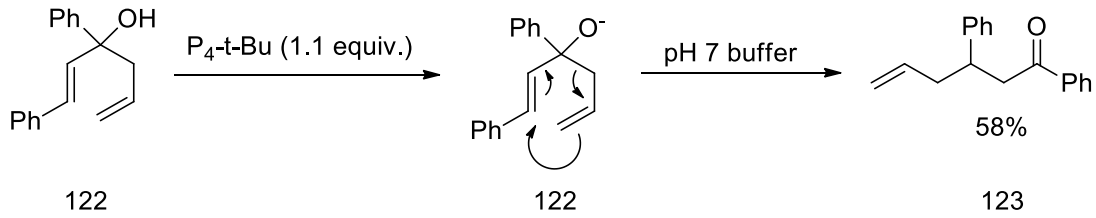


Figure 4.3: Comparison of phosphazene bases. pKa-H^+ of base increases as more phosphine nitrogen double bonds are added bond are added to the structure.

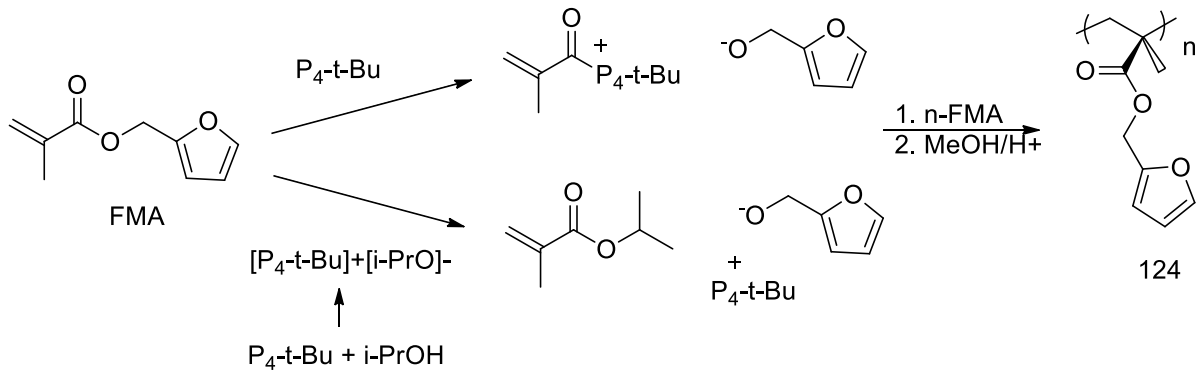
Reactions using phosphazene superbases include Hartley and Mamdani's anionic 3,3 sigmatropic Cope rearrangement in which 1,5-hexadien-3-ol such as **122** were subjected to phosphazene P_4-*t*-Bu or P_2-Et (Scheme 4.1).[223] The phosphazene super base acts to deprotonate the alcohol (**122**); once in anion form (**123**), the Oxy-Cope rearrangement occurs 10^7-10^9 times faster than the hydroxy group. Due to the use of phosphazene superbase the rearrangement also occurs at a much faster rate, due to the anion being naked *i.e.* not association with a the countercation.[224] Traditionally potassium salts have been used alongside crown ethers in polar aprotic solvents in order to reduce the association between the anion and cation. Hartley *et al*. demonstrated the first use of metal free bases (P_4-*t*-Bu) for the anionic cope rearrangement producing yields of 44-58%. Once deprotonation had taken place the base acts as a large soft cation that can delocalise its positive charge over a large volume, thus allowing sufficient naked anion character of the alkoxide for the rearrangement to occur.



Scheme 4.1: Hartley and Mamdni use of P_4-*t*-Bu for the sigmatropic oxy Cope rearrangement of 1,5-heaxdien-3-ol.

Phosphazene bases have also been used as effective organic initiators or catalysts in promotion of various types of polymerisation reactions especially anionic and group transfer polymerisations.[225] Chen *et al.* showed that P_4-*t*-Bu could be used for the

organocatalytic polymerisation of the biomass derived furfuryl methacrylate (FMA), which has the potential to replace/substitute the use of petroleum based methyl methacrylate (MMA) as a monomer unit used for speciality chemicals and material production.[226] P_4-*t*-Bu could be used by itself as an initiator however, in the presence of *i*-PrOH produced facilitating the rapid polymerisation of FMA at ambient temperature to give syndio-rich atactic poly furfuryl methacrylate (**124**, Scheme 4.2). The organocatalyst properties of the phosphazene where shown by initiation efficiencies of up to 370%, thus effectively proving a catalytic polymerisation system. The true initiation species was shown to be 2-furfurylmethoxide which is formed via the reaction of FMA with ^{t}Bu-P_4 or $[P_4$-*t*-BuH$]^{+}[i$-PrO$]^{-}$.



Scheme 4.2: Organocatalyzed initiation in the polymerization of FMA by the organic phosphazene superbase P_4-*t*-Bu.

4.1.2 Polyphosphazenes

Poly-phosphazenes are polymers that contain monomers of alternating phosphorus and nitrogen atoms with the chain containing a variety of different R groups attached to the phosphorus atom. The vast majority of the poly phosphazenes were first synthesised by the Allcock group at Pennsylvania State University.[227] These versatile polymers can be easily engineered by changing side groups to manipulate their properties and is a relatively simple process via simple adjustments to the R groups of the phosphorus proving high flexibility, radiation resistance, a high refractive index, ultraviolet/visible light transparency and fire resistance. Allowing the use of these polymers in a wide variety of applications including energy related research, biomedical polymers, photonic materials, aerospace materials and surface science.[228–233]

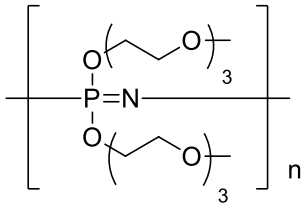
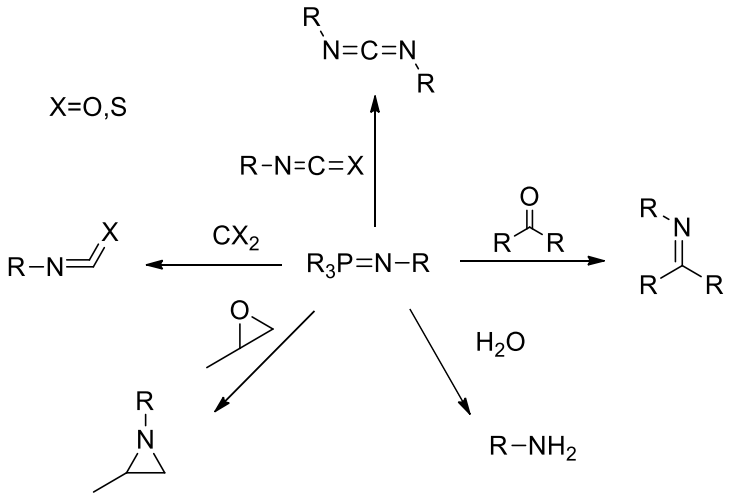


Figure 4.4: Poly [bis 2-(2-(2-methoxyethoxy) ethoxy) ethoxy phosphazene] or MEEEP.

One of the most interesting and promising uses of polyphosphazene polymers is in energy storage, as polyphosphazene-based salt-in-polymer electrolyte membranes for lithium ion batteries. There is a great need for a new generation of more efficient and safer lithium battery energy storage devices due to the ever increasing demand for portable electronic device and vehicles. Many common lithium ion batteries currently use liquid organic electrolytes, which have the drawback of being volatile and highly flammable. Other organic polymers have been investigated, including the use of poly(ethylene) oxide (PEO) swollen with liquid electrolytes like $LiPF_6$. However, PEO based batteries are often limited by low ionic conductivity, often in the range of 10^{-5} to 10^{-7} S cm^{-1}.[234,235] Polyphosphazenes such as poly [bis 2-(2-(2-methoxyethoxy) ethoxy) ethoxy phosphazene] or "MEEEP" (Figure 4.4) have shown promise due to their ability to solubilising lithium salts and facilitating ion pair separation via coordination with the cations, thus improving the conductivity and Li transport. Modern examples of these polymers have shown conductivity of up to 10^{-4} S cm^{-1}. The ability to cross link these polymers via UV-radiation has help to improve both the mechanical and electrochemical stability without losing conductivity.[228,229]

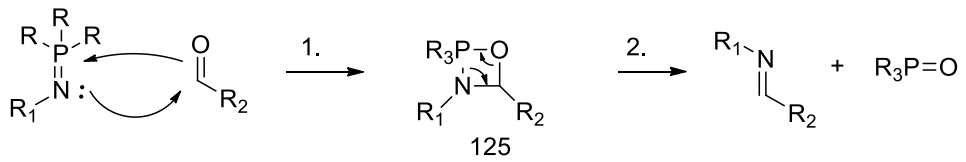
4.2 Aza-Wittig Chemistry.



Scheme 4.3: aza-Wittig reactions with CO_2, SO_2, isocyanates and carbonyl compounds.

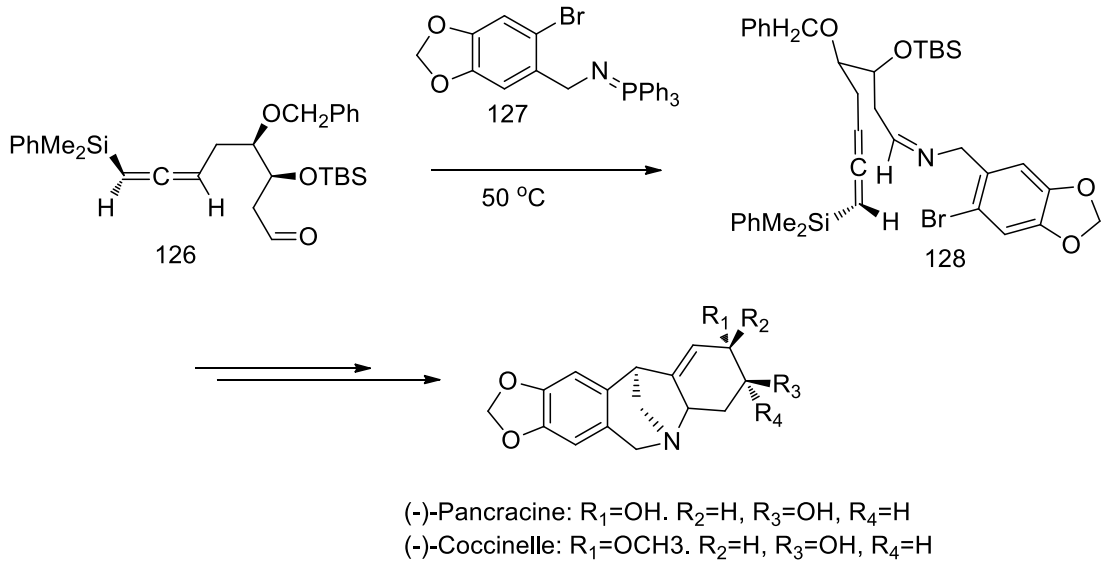
4.2.1 Aza-Wittig Chemistry with Ketones, Aldehydes and Acyl Halides.

The reaction of phosphazenes with ketones and aldehydes is a valuable tool in the synthesis and construction of imine bonds using the aza-Wittig reaction. This reaction offers one of the most efficient and mild ways to form imine bonds. Palacios *et al.* performed a mechanistic and stereoselective study of the aza-Wittig reaction between phosphazenes and aldehydes.[236] From the combined computational and theoretical study Palacios *et al.* determined that the aza-Wittig reaction between phosphazenes and aldehydes consists of a tandem [2+2]-cycloaddition-cycloreversion with 1,3,2-λ^5-oxazaphosphetidine (**125**) as the reactive intermediate (Scheme 4.4). They also determined that Both [2+2] cycloaddition and cycloreversion processes are associated with asynchronous thermally allowed supra-supra interactions involving lone pairs as well as the σ and π systems. Finally they predicted that almost exclusive formation of *E*-imines in the aza-Wittig reaction between N-alkyl and N-aryl phosphazenes and Aryl or Alky aldehydes and tested this prediction by experimental laboratory work.



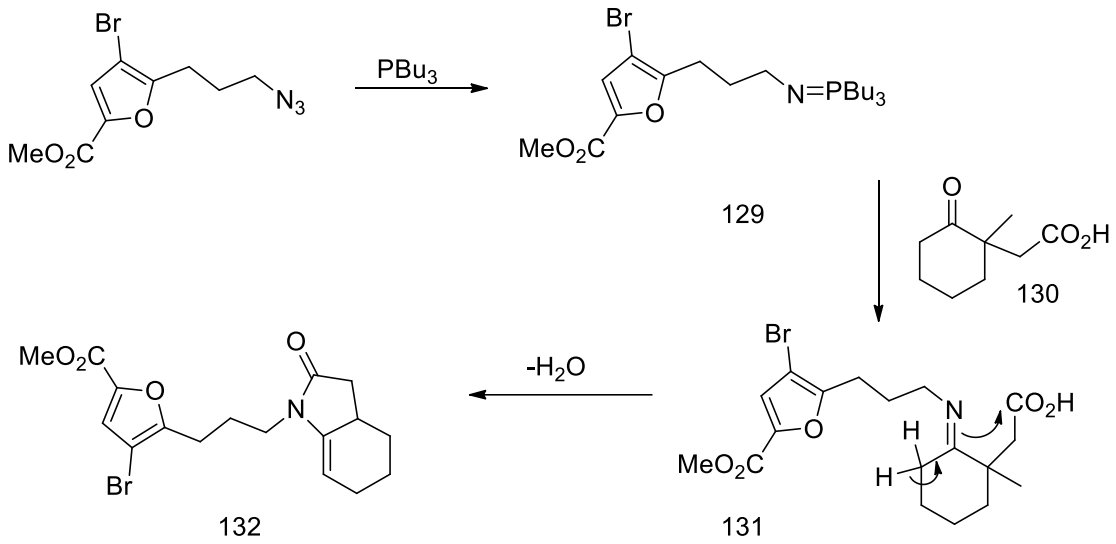
Scheme 4.4: Reaction mechanism of aza-Wittig reaction as determined by Palacios *et al.*[236]

An example of the reaction of phosphazenes with aldehydes for a meaningful synthesis was described in the synthesis of (-)-coccinine and (-)-pancracine by Weinreb *et al.* (Scheme 4.5).[237] The imines required in the important intermediate **128** for this synthesis of these complex natural products were prepared by reaction of *N*-Phenyl phosphazene **127** and a functionalised aldehyde **126**. The intermediate **128** then underwent a stereospecific cyclization upon heating in mesitylene at 162 ^{o}C followed by subsequent alkyne desilylation to afford amino acetylene. Subsequent transformations led to the formation of a pentacyclic framework, which could be reduced to (−)-pancracine with sodium triacetoxyborohydride or transformed into (−)–coccinine.



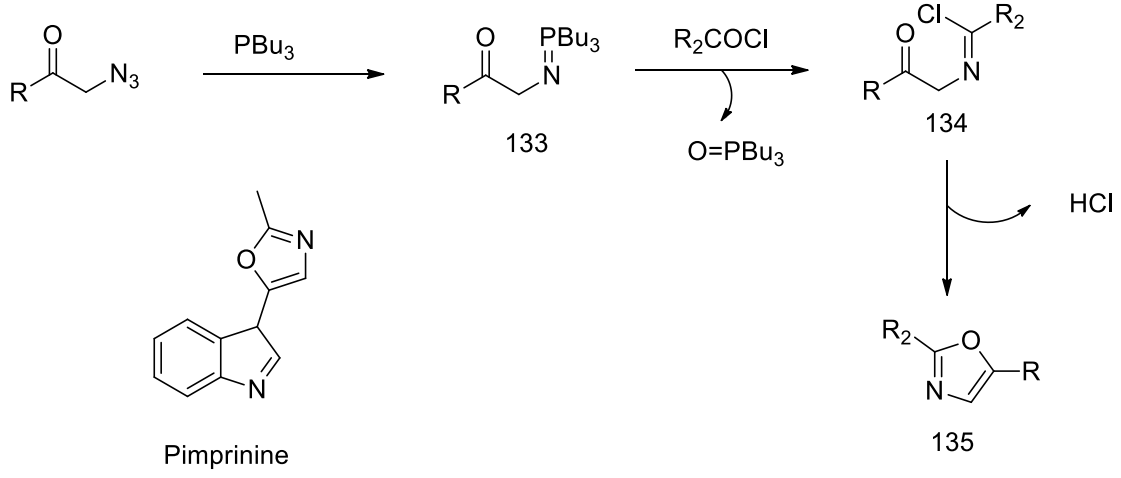
Scheme 4.5: Synthesis of (-)-coccinine and (-)-pancracine as described by Weinreb *et al.*[237]

The use of aza-Wittig reaction with ketones has been exemplified by the synthesis of the alkaloid (±)-selaginoidine, via synthesis of vinylogous amide (**132**) precursors (Scheme 4.6).[238] Out of a number of different methods the aza-Wittig reaction, in which phosphazene (**129**) was directly coupled with ketoacid (**130**) to give the key intermediate (**131**). This was followed by an intramolecular cyclisation between the acid and imine in conjunction with microwave heating. This innovative use of the aza Wittig chemistry proved the only method that to deliver the desired hexahydroindolinone (**132**) good yields.



Scheme 4.6: aza-Wittig reaction used in the formation of hexahydroindolinones intermediates.[238]

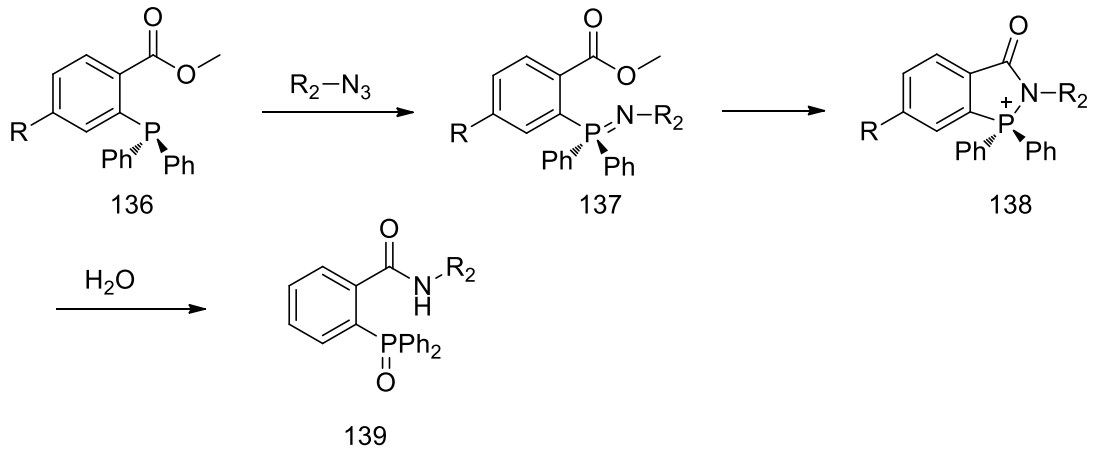
Phosphazenes can also undergo aza-Wittig reactions with carboxylic acid derivatives such as acid halides. The reaction between phosphazenes and acid halides offers a mild method for the synthesis of 2,5-disubstituted oxazoles.[239] Molina *et al*. used aza-Wittig chemistry in the formation of oxazole alkaloids including a number of different pimprinine analogues.[240] Two different approaches were developed, both methods first involving the formation of the aza–Wittig reagent **133** derived from 3-azidoacetyl-1-methylindole and PBu_3. The first method used the aza-Wittig reaction of phosphazene **133** and isocyanate to give carbodiimide which cyclised to give 2 amino functionalised oxazoles in good yields (80-90%). The second method involved an aza-Wittig reaction with an acyl chloride derivative eliminating phosphine oxide and generating amine **134** which cyclises to oxazole **135** in reasonable yields of 60-68% in a one pot reaction (Scheme 4.7).



Scheme 4.7 aza-Wittig chemistry with acyl chloride derivatives in the synthesis of pimprinine derivatives as demonstrated by Molina *et al*.[240]

4.2.2 The Staudinger Ligation

Saxon and Bertozzi demonstrated the aza-Wittig reaction could be used as an innovative method for engineering cell surfaces via a modified Staudinger reaction, known as the Staudinger ligation (Scheme 4.8).[241] Saxon and Bertozzi reported a relatively simple method for amide bond formation via the coupling of an azide and a specifically engineered triarylphosphine **136** which contains an intramolecular electrophilic trap. Phosphazene **137** then reacts with the ester group, which acts as an electrophilic trap cyclising to form intermediate **128.** The presence of water, leads to formation of the amide (**129**) with the driving force of the formation of phosphorus oxygen double bond. In order to be successful for cell surface modification, both the azide and the phosphine must be abiotic and chemically orthogonal with respect to existing cell surface components. The azide can first be installed to cell surface glycoconjugates via metabolism of synthetic azido sugar. The phosphine was then able to react in a highly selective manor with biotinylated aryl phosphine to produce labelled and stable cell surface adducts. Since Saxon and Bertozzi first introduced the method, the Staudinger ligation has become used to conjugate small molecules probes to biomolecules. Ranging from lipid labelling to DNA and protein labelling as shown in the review by Hest *et al.*[242]

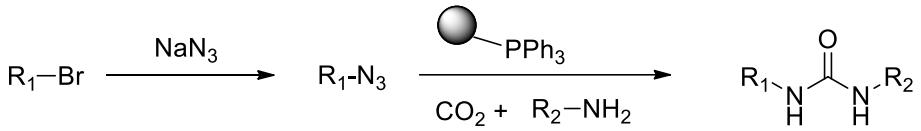


Scheme 4.8: The Staudinger ligation.

4.2.3 Aza-Wittig Chemistry: Formation of Isocyanates and Isothiocyanates.

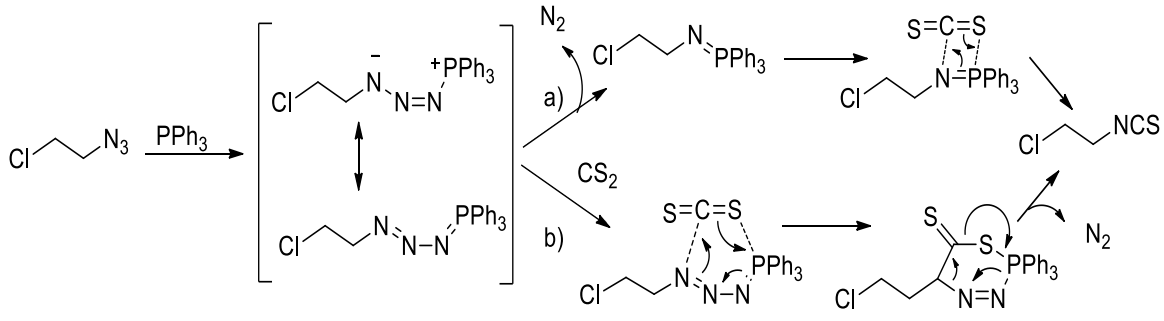
Not only are phosphazenes useful in the formation of imines from carbonyl compounds but Staudinger also demonstrated phosphazenes can react with a variety of small molecules such as carbon dioxide (CO_2) and carbon disulfide (CS_2).[4,70] Reactions of phosphazenes with CO_2 and SO_2 lead to the formation of isocyanates and isothiocyanates, respectively. Isocyanates are often useful intermediates for further reactions and commercial applications. A good example being Drewry's synthesis of trisubstituted guanidines [243,244] Alternative methods for the synthesis of isocyanates include the reaction between amines and phosgene in the presence of a base such as pyridine.[245] It is not however, a particularly attractive method, as phosgene is a highly toxic gas requiring careful handling. The use of phosphazenes is the synthesis of isocyanates, offers a one-pot process in which subsequent reaction of the isocyanate with various nucleophiles allow for access to species such as ureas.[246,247]

The synthesis of isocyanates using aza-Wittig reactions can be a simple process of conducting the Staudinger reaction in an atmosphere of carbon dioxide (Scheme 4.9). Once all the phosphazene has been consumed, a nucleophile such as an amine can be added without isolating the isocyanate. A nucleophilic attack on the highly electrophilic carbon to form the urea product.[248] In this fashion, the Cravotto group reported the formation of an isocyanate intermediate and *in-situ* formation of ureas under microwave irradation.[247] This method proved to be a reliable for the synthesis of a wide variety of *N*,*N*-disubstituted urea derivatives directly from alkyl halides, using reacted primary or secondary amines via tandem Staudinger and aza-Wittig reactions in the presence of solid-phase PPh_3 resin and under 14 bar of CO_2 pressure. Yields varied from 79-98% with commonly achieving yields in excess of 90%. The use of solid-phase PPh_3 offered a simple workup procedure, involving filtration of phosphine oxide, followed by treatment with Dowex ion exchange resin in MeOH to remove excess amine. Although the one-pot microwave assisted method presented by Cravotto *et al.* gave access to a wide variety of ureas in excellent yield, it did require forcing conditions. High reaction temperatures and long reaction times where needed considering it is a microwave reaction. It also required the use of azides to generate phosphazene, which although well-established does have a risks involved in that they have the potential to decompose explosively either thermally or on contact.[249]



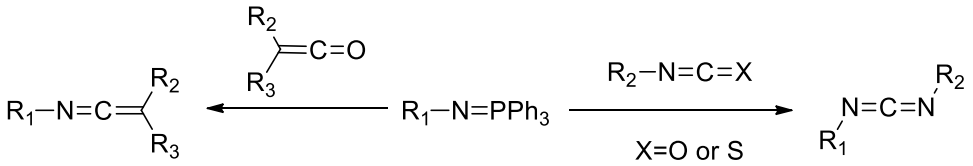
Scheme 4.9: One-pot microwave assisted synthesis of urea derivatives.

Replacement of CO_2 with carbon disulfide (CS_2) as a co-solvent leads to the formation of isothiocyanates. Tsuge *et al.* reported a procedure involving tandem Staudinger/aza-Wittig reactions in the presence of CS_2 solvent gave (trimethylsilyl) methyl isothiocyanate in a 94% yield.[250] Isoda *et al.* followed this publication with a paper describing similar reaction conditions,[41] as part of their investigation of a new route to 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine which is a useful moiety contained in the oral antibiotic L-084.[42] The process can run as a one-pot reaction, which includes the preparation of chloroethyl isothiocyanate followed by aza-Wittig reaction with CS_2 as a co-solvent (83%). This tandem one-pot synthesis achieves a much better yield of the key intermediate compared to that of a stepwise synthesis (16%). They reasoned that the difference in yield was due the instability of the resulting phosphazene intermediate. If the phosphazene is isolated as in pathway A in Scheme 4.10 than the aza-Wittig chemistry is performed in a separate step and this can lead to degradation of the phosphazene. The one-pot system allows a 4+2 cycloaddition to take place, followed by rearrangement to eliminate N_2 (pathway B), which was proposed as an alternative mechanistic pathway in order to explain the difference in yields. The need for formation of the unstable phosphazene is diminished and thus the yield is dramatically increased.



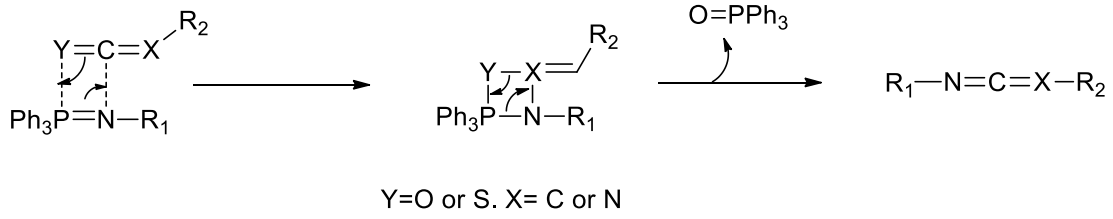
Scheme 4.10: Mechanistic pathways proposed by Isoda *et al.* for the formation of isothiocyanates. a) Classic Staudinger followed by aza-Wittig reaction in the presence of CS_2. b) Proposed one pot reaction in which a 4+2 cycloaddition followed by a rearrangement to afford the isothiocyanate.

4.2.4 Aza-Wittig Chemistry: Reactions with Isocyanates, Isothiocyanates and Ketenes.



Scheme 4.11: aza-Wittig reactions of phosphazenes with isocyanates, isothiocyanates and ketenes.

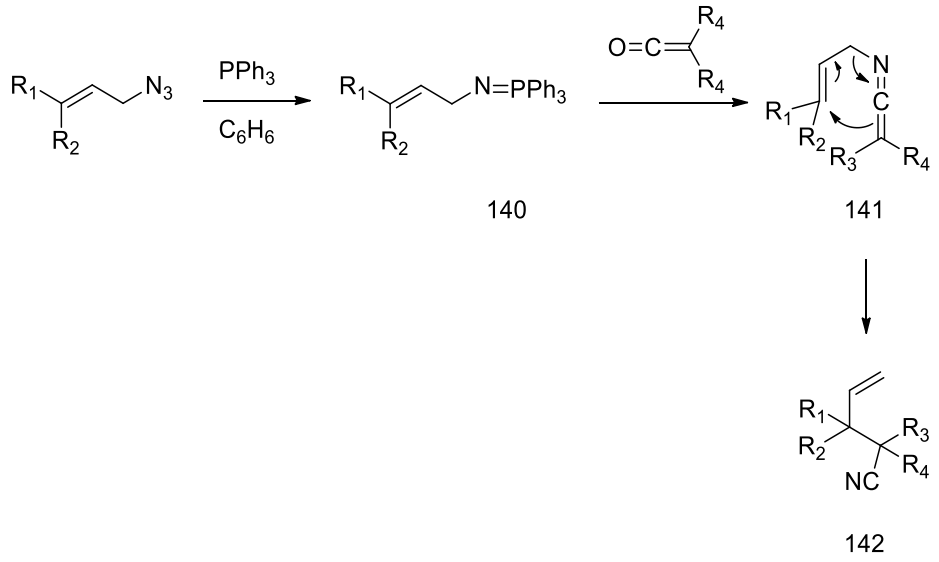
Phosphazenes are useful reagents for the synthesis of isocyanates and ureas using Staudinger and aza-Wittig reactions. However, these compounds are also of value for their reactions with isocyanates, isothiocyanates and ketenes to form carbodiimides and ketenimines.[253] The latter as useful intermediates for inter/intramolecular in cycloaddition reactions.[254] The reaction mechanism for the aza-Wittig reaction of a phosphazene, ketene and isocyanate or isothiocyanate follows a similar mechanism. The driving force for the reaction is the formation of the formation and loss of $O=PPh_3$ via a tandem 2+2 cycloaddition-cycloreversion (Scheme 4.12). This is similar to the way phosphazenes react with carbonyl compounds such as ketones and azides.



Scheme 4.12: Mechanism for the aza-Wittig reaction between phosphazene and isocyanate, isothiocyanate and ketene derivatives.

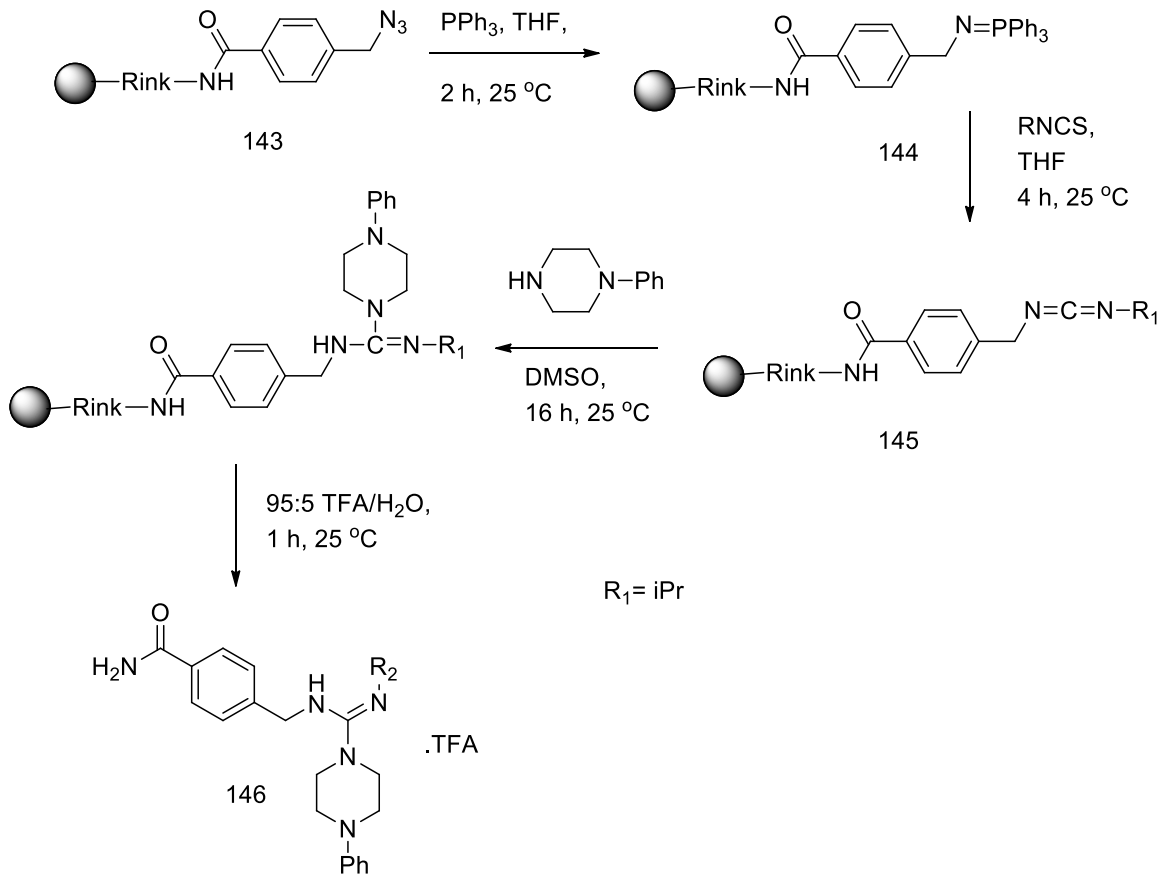
A novel use of the aza-Wittig reaction of phosphazene with ketene was performed by Molina *et al.* for the synthesis of 4-pentenenitriles via reaction of allyl phosphazenes (**140**) with ketenes or acyl chlorides.[255] It was proposed that when vinyl azides were subjected to Staudinger conditions, the resulting phosphazene could then be reacted with various ketenes to produce the corresponding ketenimines (**141**). However, upon carry out of the experiment it was found that this did not occur. Instead of forming the expected ketenimine they instead formed 4-pentenenitrile (**143**) in good to moderate yields. This observation was explained by on formation of the ketenimine **141**, can undergo 3-aza-claisen rearrangement to give **142** observed by Molina *et al*. Kinetic,

stereochemical and trapping experiments involving N-(arylmethyl)diphenylketenimines have shown that the [1,3]-nitrogen-carbon rearrangement proceeds via a free radical mechanismn.[256]



Scheme 4.13: Moline *et al.'s* reaction of ally azide in a tandem Staudinger and aza-Wittig reaction with ketenes to produce 4- pentenenitrile**.**

A good example of the aza-Wittig reaction between phosphazenes and isocyanates included the synthetic useful method developed by Drewry *et al*. in which the use of the solid-supported Azide resin to aid in the work up procedures. The Staudinger reaction of a resin bound azide to form a phosphazene intermediate followed by aza-Wittig reaction with isothiocyanate, for the synthesis of trisubstituted guanidines (Scheme 4.14).[244] Guanidines possess a wide range of biological properties; therefore new methods for their synthesis are of interest. Drewry's approach used resin bound solid-phase chemistry: first the Staudinger reaction between the solid-supported azide (**143**) and PPh_3 gave the solid supported phosphazene **144**. This is followed by treatment with phenyl isothiocyanate to give carbodiimide **145** which is then further reacted with *N*-phenylpiperazine to yield the solid supported guanidine (**146)**. Cleavage from the support with a mixture of TFA/H_2O gave **146** as the TFA salt in yields of 63-96%.



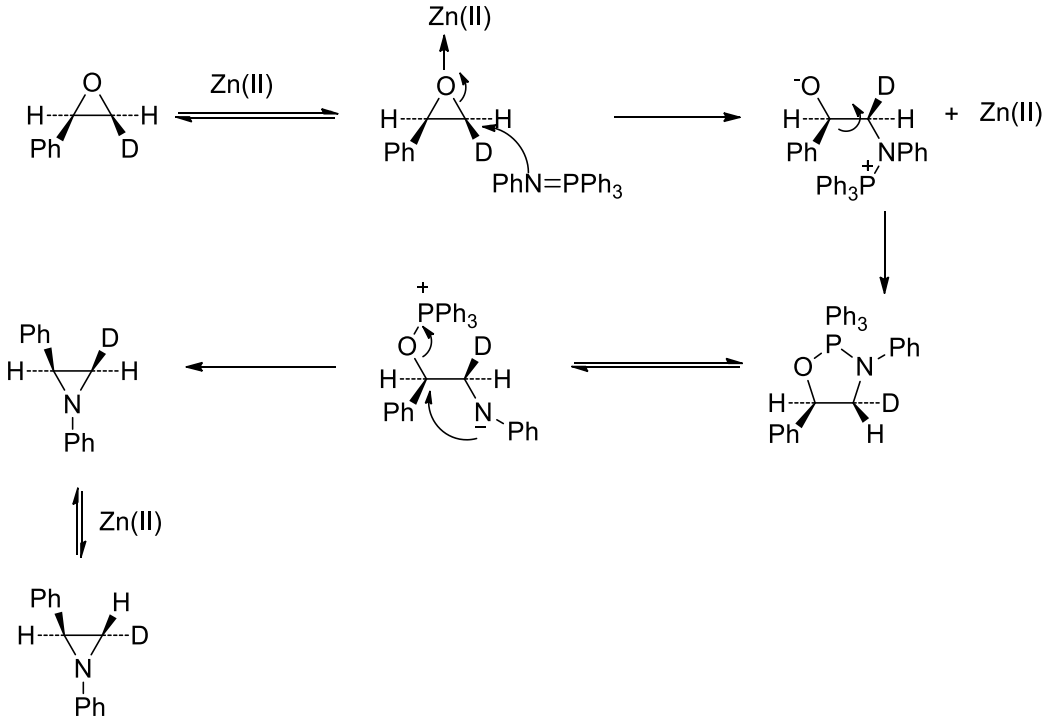
Scheme 4.14: Drewry's solid phase synthesis of trisubstituted guanidines.[244]

4.2.5 Aza-Wittig Chemistry of Epoxides

Phosphazenes can also act as nitrogen donors in the synthesis of aziridines directly from epoxides in the presence of a Lewis acid catalyst. Aziridines are the nitrogen equivalent of epoxides and are valuable intermediates. They undergo a number of useful reactions, including the stereospecific ring opening with a wide selection of nucleophiles. Aziridines also constitute the key motif in a number of different potent anticancer natural products e.g. azinomycin and mitomycin families.[257] Jørgensen *et al.* reported use of iminophosphoranes in the presence of Zn(II)-Lewis acids for the direct conversion of epoxides to aziridines under mild conditions.[258] A number of different Lewis acids were screened and it was found that Zn(II)-Lewis acid complexes had the best catalytic properties giving yields of 70% and over for the reaction of styrene oxide and a simple phosphazene, *N*-(triphenylphosphoranylidene)aniline (**121**). The transformation worked best for the conversion of terminal and cyclic epoxides as they

are more reactive then internal epoxides due to the decreased steric hindrance compared to internal epoxides.

The mechanism for this reaction was determined from the comparison of results from the reaction of different epoxides as well as from deuterium labeling studies (Scheme 4.15). The Zn(II) complex first coordinates to the oxygen of the epoxide, changing the epoxide's electronic character such that the phosphazene can attack the least sterically hindered carbon. This leads to ring opening and formation of a zwitterionic species; rotation of the carbon-carbon bond is then possible and leading to the formation of a 1,3,2-oxazaphospholane Intermediate. The nitrogen-phosphorus bond can then break leading to a new zwitterionic species in which the negatively charged nitrogen is able to attack the carbon bearing a phosphine oxide leaving group to form the aziridine. It was also found that the longer the reaction time the lower the enantiomeric excess with the mixture becoming nearly racemic after 2 hours of reaction. This study demonstrated that isomerisation of aziridines can occur under Lewis acidic conditions. Therefore, helping explain the observation that reaction time influenced the stereochemical outcome and the *cis/trans* ratio of the aziridine product when using this tranformation.[259]



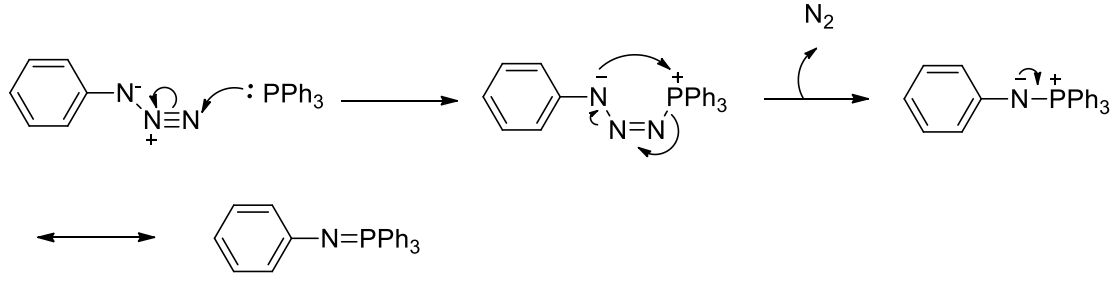
Scheme 4.15: Jørgensen *et al.'s* proposed mechanism for the conversion of epoxides to aziridines in the presence of Zn(II) Lewis acids.[258]

4.3 Synthesis of Phosphazenes.

4.3.1 Staudinger Reaction

Concerning the synthesis of phosphazene there are three major methods that are in use. The first method is the Staudinger reaction, first reported by Staudinger and Meyer in 1919.[4] This is by far the most common method for the synthesis of phosphazene reagents. It is especially attractive due to the ability to perform one pot reactions in aza-Wittig reaction. As a method, the process is relatively simple and often provides the most efficient route to aza-Wittig reagents. It has been shown to work extremely well for the purpose of synthesising simple phosphazenes often in a near quantitative yield. The Staudinger reaction involves a reaction between an organic azide and a phosphine. It is an efficient and atom economical reaction with the only side product being the release of nitrogen gas, which also acts as a driving force for the process. An aqueous work up produces the corresponding amine or the phosphazene can be isolated as the phosphazene in good to excellent yields.

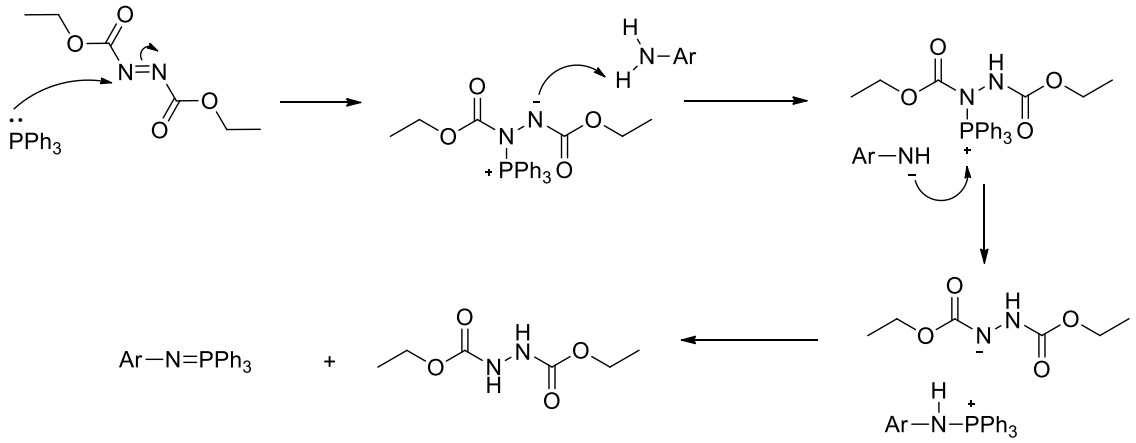
A quantitative yield of **121a** was been reported by Khatib *et al*. as part of their investigation into the reaction of *N*-phenyl iminophosphoranes and ozone.[260] The procedure requires slow addition of phenyl azide to a solution of PPh_3, under inert gas and at room temperature followed by 2 hours of stirring. In a similar fashion but with a slightly modified procedure Katritzky *et al*. produced a quantitative yield of the **121a** as part of their synthesis of 1,2,3-trisubstituted guanidines.[261] For their synthesis they heated a solution phenyl azide and PPh_3 in diethyl ether at reflux for two hours. This method is suitable for a number of different phosphines and not just PPh_3; PBu_3 and PMe_3 are often used where the reactivity of PPh_3 is not sufficient.



Scheme 4.16: Mechanism of the Staudinger reaction for the synthesis of a **121a**.

4.3.2 Mitsunobu-Type Conditions for the Synthesis of Phosphazenes.

The Mitsunobu reaction as described in chapter 1 is an extremely useful and well-studied process. Since its introduction it has found widespread use in many synthetic routes towards pharmaceutical compounds and natural products as a means to covert alcohols to a variety of functional groups. It offers stereospecific inversion and mild reaction conditions. Recently Adib *et al.* developed a method for the preparation of stable phosphazene ylides using Mitsunobu reaction conditions.[262] The Mitsunobu reaction offers significant advantages for the synthesis of phosphazenes. Phosphazenes can be prepared directly from amines, therefore avoiding the risk associated with azides such as their potential to spontaneously explode. Amines are also much more likely to be commerically available then the azide equivalent. The method has so far proven to provide excellent yields of the phosphazene products, along mild reaction conditions and short reaction times. Adib *et al.* observed the highly efficient reaction for a series of anilines by simply stirring them in a solution of PPh_3 with addition of DEAD over a period of 10 min. Post-addition the reaction mixture was left to stir for a period of 2 hours, by which time the reaction was complete giving the phosphazene in excellent isolated yields (85-98%). The use of a 1:1:1 mixture of reagents means there is little waste requiring only simple aqueous $NaHCO_3$ wash to remove the hydrazine waste product followed by evaporation of the solvent and recrystallization from a 1:1 mixture of hexane and ethyl acetate.

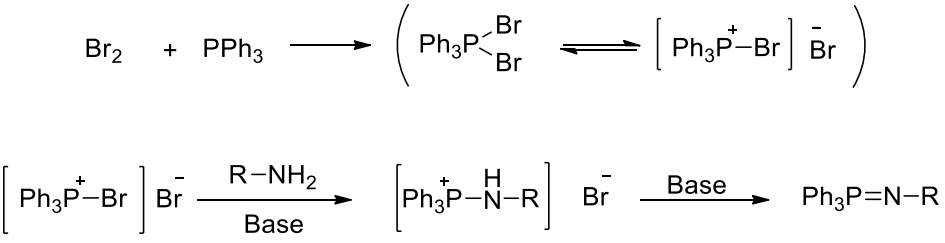


Scheme 4.17: Mechanism for Mitsunobu type reaction for the efficient synthesis of phosphazenes.[262]

4.3.3 The Kirsanov Reaction

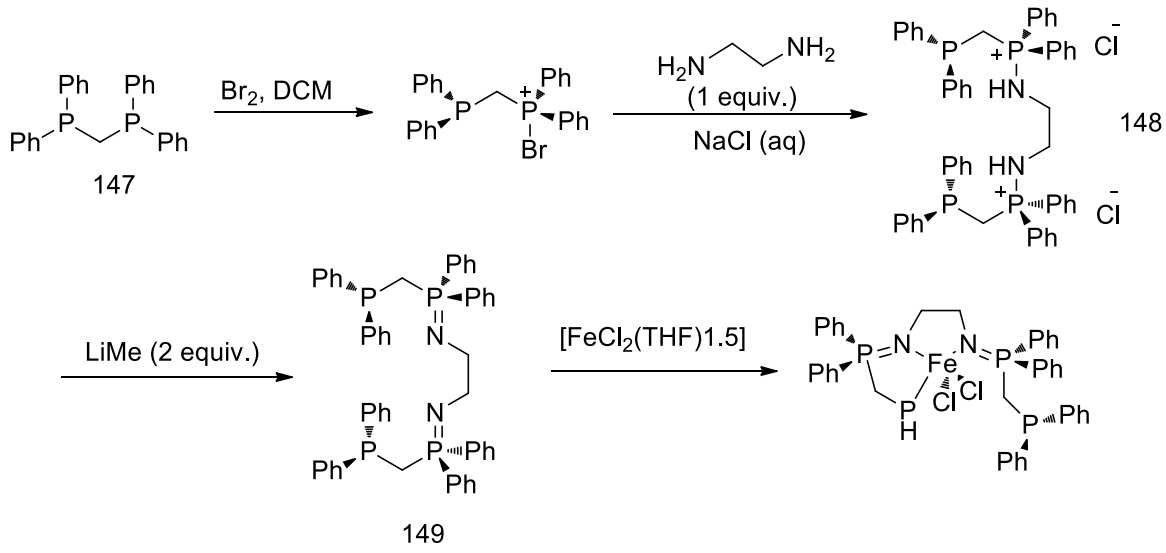
The Kirsanov reaction is generally used as an alternative method to the Staudinger reaction.[263] It is most often used when the Staudinger reaction is not suitable or the organic azide is not available or would require multiple additional steps in order to synthesise. For this reason it is most often used for the synthesis of phosphazenes from primary alkyl amines. The main advantage of this method over the Staudinger reaction is that the phosphazene can be made directly from the amine. Amines are safer to handle than their azide equivalents with many organic azides classed as highly explosive and toxic. As a result only a few azides are commerically available, thus the Staudinger reaction commonly necessitates the reaction of sodium azide (NaN_3) with an organic halide thus adding extra steps to the synthesis. The Kirsanov reaction enables the synthesis of wide variety of phosphazenes making it highly appropriate for the synthesis of phosphazene ligands. Another advantage of the Kirsanov reaction is the ability for the reaction products to be isolated as their protonated salts. This allows for better storage of the intermediates as phosphazenes can be sensitive to humidity and thus decompose easily.

A typical Kirsanov reaction first involves the formation of a phosphonium dibromide species in a similar fashion to the process described in chapter 2 (Scheme 4.18). Addition of the amine to the phosphonium dibromides intermediate along with one equivalent of base results in the formation of the protonated salt form of the phosphazene. This salt can easily be stored and used at later date. The addition of the amine and two equivalents of base, results in the phosphazene product. Typically NEt_3 is a strong enough base although organolithium bases e.g. LiMe have been shown to be effective when higher basicity is required.



Scheme 4.18: The formation of phosphazenes via a typical Kirsanov reaction conditions.

Le Frock *et al.* utilised this simple procedure for the synthesis of number of mixed tetradentate ligands, which when bound to ferric metal centres, could be employed in the catalytic transfer hydrogenation of ketones (Scheme 4.19).[264,265] Formation of the dicationic salt **148** via bromination of diphosphine species **147**, followed by reaction with ethylenediamine which acts as both nucleophile and base, gave salt **148** in a 72% yield. Deprotonation of this dication with 2 equivalents of LiMe led to the formation of the diphosphazene ligand **149** which coordinated formed *in situ* to the iron metal centre via addition of ferrous complex to give a number of different ferrous based catalysts for the hydrogenation of ketones.



Scheme 4.19: Le Frock's formation of tetradentate ligands using the Kirsanov reaction.[265]

Another example of the use of a Kirsanov reaction was shown by Stephan and Jiang, whilst investigating frustrated Lewis pairs chemistry and the interaction of different boron and phosphazene combinations.[266] The synthesise of a simple aryl phosphazene **121a** was in turn reacted with borane complex $B(C_6F_5)_3$ in order to investigate FLP properties and their ability to activate a variety of small molecules such as H_2, CO_2 and styrene. A simple Kirsanov reaction using phosphine dibromide via reaction of PPh_3 and Br_2 in CH_2Cl_2 followed by addition of aniline in the presence of two equivalents of NEt_3 gave phosphazene **121a** in a 75% yield.

4.4 Results and Discussion

Presented now is a modification to the Kirsanov method for the synthesis of phosphazenes. This new route to phosphazene was initially discovered during studies into possible alternative reaction profiles for the PPh_3, I_2 and DMAP system, described in chapter 3. This new method offers direct and rapid route to a variety of simple aryl phosphazenes, under mild conditions using relatively cheap and readily available laboratory reagents avoiding the use of azide starting materials. As part of our studies into the reaction of aniline with PPh_3-I_2-DMAP, in the search for a method for hydrazone synthesis (chapter 3), it was discovered that this reagent combination led to the rapid formation of phosphazene. Given the value of the Kirsanov reaction and it phosphazene product, it was decided to further explore and optimise this procedure.

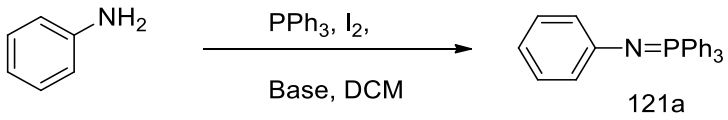
4.4.1 Optimisation of Reaction Conditions.

As a first, the same conditions were investigated as employed in the esterification process. To a stirred mixture of PPh_3 (1.5 equiv.) and I_2 (1.5 equiv.) in anhydrous CH_2Cl_2, DMAP (3 equiv.) and aniline (1 equiv.) was added. The aniline was found to be fully consumed within 10 minutes, indicated by the disappearance of aniline by TLC suggesting the reaction has gone to completion. The solvent was removed in vacuo and the addition of ethyl acetate resulted immediate formation of a precipitate (protonated DMAP salt) which was filtered off and the resulting filtrate was purified on silica via flash chromatography to afford **121a** as a yellow crystalline solid in 90% yield.

The yield and the speed by which phosphazene **121a** was formed was very encouraging: this mild and efficient method appeared quicker than other methods e.g. the Staudinger reaction and the Kirsanov reaction. However, to reduce the quantity of waste, the stoichiometry of the phosphine and iodine were reduced (1.25 equiv. of PPh_3 and I_2) which proved to make no difference to the yield or reaction time length (Table 4.1, entry 1). Reducing the equivalent of DMAP (entry 2, 2.5 equiv.) led to complete consumption of aniline within 10 minutes, affording phosphazene **121a** in 92% yield. When 2 equiv. of DMAP was used (entry 3) the reaction did not go to completion after 2 h and yields of 44% were obtained. The poor yield came as a surprise as initially these reaction conditions bear similarity to that of the Kirsanov reaction, using phosphine and

bromine are used in conjunction with a base. Should a simple Kirsanov process be operating, 2 equiv. of base would have been adequate, assuming that the DMAP was acting as a base rather than also in some roles as a nucleophilic catalyst. Indeed this could be one possible pathway for the formation of phosphazenes mediated by DMAP. However, it was clear that an excess of the DMAP was required for this reaction to go to completion.

Now that a procedure which gave rapid formation of the phosphazene had been established, a base study was performed in order to compare how different organic bases affected the process. In the study of different bases, all of the reactions were left to react overnight. However, according to TLC analysis they did not go to completion (Table 4.1, entries 4-7). In all the cases the alternative bases gave not only lower yields but also slower reaction times. Pyridine gave no indication of phosphazene formation (entry 4) whilst, imidazole gave the phosphazene in poor yields poor yield (17%, entry 5). These results were not that surprising due to the fact that the pKa-H^+ of the conjugants acids for both pyridine (pKa-H^+=5.21) and imidazole (pKa-H^+=7.05) compared to that of aniline (pKa-H^+=4.6). NEt_3 (pKa-H^+=10.75) on the other hand gave a moderate yield of 54% (entry 6). As part of an investigation frustrated Lewis pair chemistry Jiang and Stephan reported yields of 75% in their synthesis of phosphazene **121a**, their synthesis did require heating at reflux conditions in toluene for 4 h.[266] By far the best yield achieved by the use of any alternative base was found for DIPEA (pKa-H^+ = 10.75) which gave a yield of 68% (entry 7). As the pKa-H^+ of the bases increased the yield of **121a** seemed to also increase. If these bases mediated phosphazene formation via the Kirsanov reaction mechanism it might be expected that the stronger bases could well increase the reaction rate. However, the slow kinetic suggest that the formation of some other quaternary ammonium species, perhaps through reaction at phosphorus must be retarding the rate.



Entry	Base (pKa of conjugate acid in H_2O)	Equivalents	Yield of Phosphazene 53 (%)	Time
1	DMAP (9.6)	3.0	90	10 mins
2	DMAP (9.6)	2.5	92	10 mins
3	DMAP (9.6)	2.0	44	2 hrs
4	Pyridine (5.21)	2.5	0	20 hrs
5	Imidazole (7.05)	2.5	17	20 hrs
6	NEt_3 (10.75)	2.5	54	20 hrs
7	DIPEA (10.75)	2.5	68	20 hrs

Table 4.1: % yield for the formation of phosphazene (**121a**) with a series of different bases.

4.4.2 The Scope of PPh_3, I_2 and DMAP Mediated Phosphazene Synthesis.

Now that DMAP was determined to be the most effective base giving far superior results to that of any other base investigated, a scope of different amines was studied. A range of different aryl amines was tested, the results of which are shown in

Figure 4.5. The reactions were run until all of the amine was consumed according to TLC analysis. The results of this study show that this method could tolerate a range of functional groups within the aniline structure. All the reactions were quick to perform with the vast majority showing complete consumption of aniline derivative within 10-30 minutes. Again the speed at which these reactions were complete was remarkable, considering the reaction time required for bases such as NEt_3. Even the Staudinger method which has a driving force of the release of N_2 gas often requires heating in order for the reaction to go to completion.

The yields achieved show that, as a method, the procedure was highly successful for the synthesis of aryl phosphazenes, giving excellent yields of 75-99% (

Figure 4.5). One reason for the lower yield in the case of phosphazene **121l** could be due to the presence of a ketone functionalised group, giving the possibilty of imine formation through reaction with the phosphazene via the aza-Wittig reaction. This however, is unlikely as imine formation from phosphazenes usually requires prolonged

heating. Upon further investigation, 15% of the starting amine was recovered. The rest of the results compared favourably to the classical Staudinger method used by Katritzky *et al*. for the synthesis of phosphazene **121a**.[261] Their synthesis was achieved **121a** quantitative yield but required heating at refluxing for two hours whereas, the method presented was complete in 10 min at room temperature in CH_2Cl_2. This method also allows direct phosphazene synthesis from the amine rather than via an azide

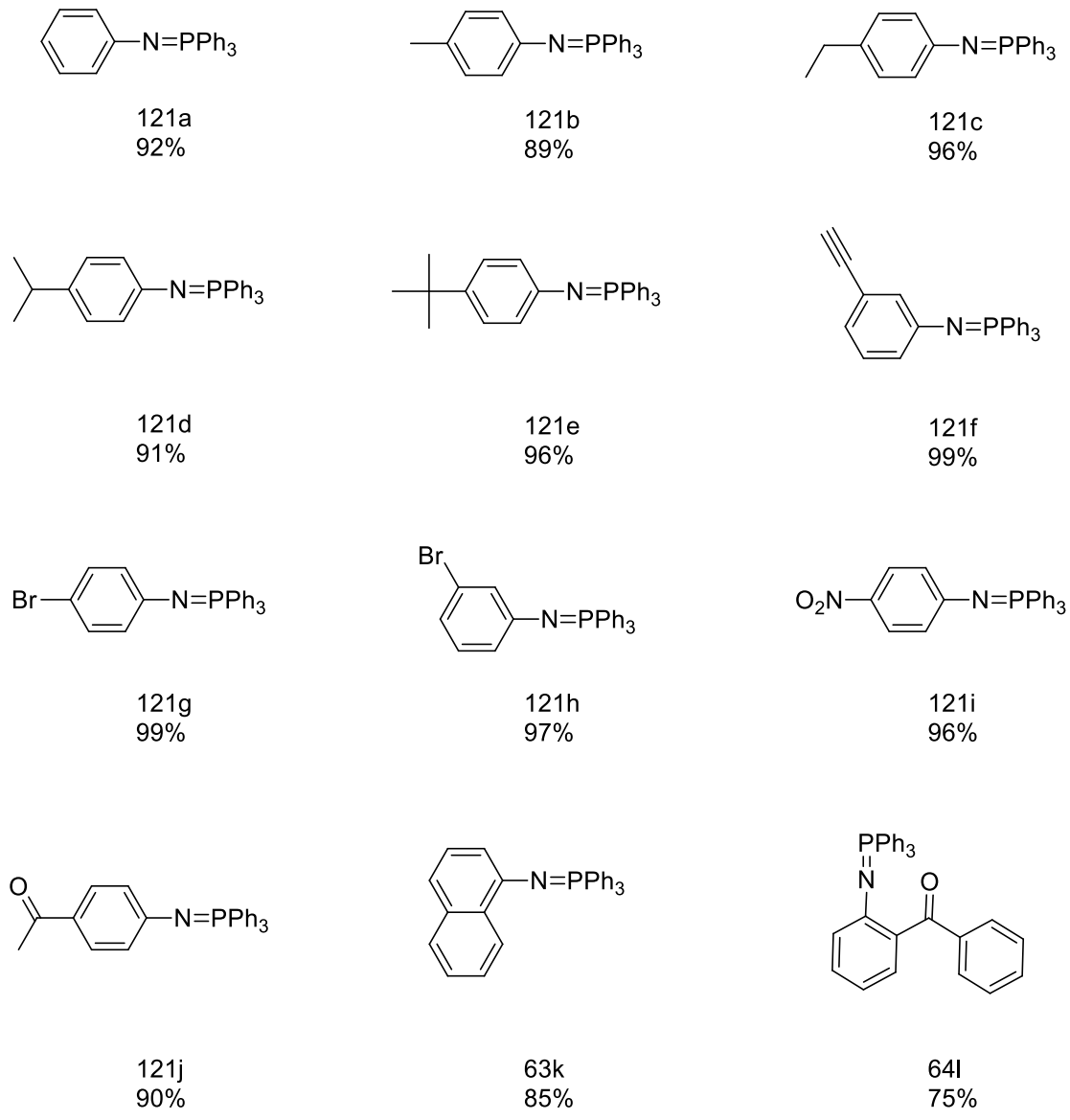


Figure 4.5: DMAP-mediated phosphazene synthesis. Reactions all performed with the aniline derivative as the limiting reagent with 1.25 equiv. of PPh_3-I_2 and 2.5 equiv. DMAP.

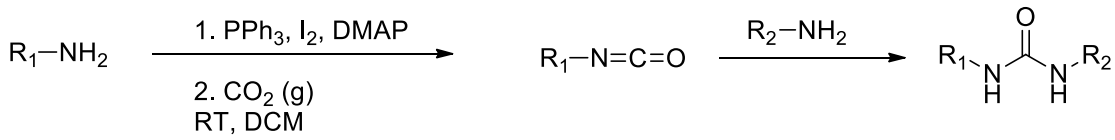
4.4.3 One-Pot Synthesis of Ureas

The synthesis of an alkyl phosphazene *N*-(triphenylphosphoranylidene)octan-1-amine was attempted using the PPh_3, DMAP and I_2 mediated system. However, the isolation of the alkyl phosphazenes proved difficult, even though ^{1}H-NMR spectroscopic analysis of the crude reaction mixture indicated that the reaction had gone to completion. Purification of the polar alkyl phosphazene via flash chromatography on silica, eluting with 5-10% MeOH in CH_2Cl_2 resulted in co-elution of the product with unwanted waste product of phosphine oxide. It was also not possible to recrystallize the alky phosphazene product due to the product being oil it was therefore an isolated yield could not be recovered.

Although disappointing that alkyl phosphazenes could not be isolated easily there was still the possibilty of using the PPh_3/I_2/DMAP reagent system with alkyl amines in the synthesis of ureas through modification of the experimental procedure was investigated. A similar method was employed by Cravotto *et al.* as shown in Scheme 4.9.[247] Their approach was used in the formation of ureas starting from alkyl and aryl halides, proceeding via reaction of alkyl and aryl halides with sodium azide followed by a tandem Staudinger/aza-Wittig reaction in the presence of polymer-bound diphenylphosphine under 14 bar of CO_2 (g). A further step in which additional amine was added which proceed to nucleophilic attack of the isocyanate intermediate resulted in the urea product in good to excellent yields. Cravotto *et al's*. protocol was optimized under microwave irradiation to provide a process that took a total of 7.5 hours from start to finish. Although Cravotto's method gave impressive results it did require a microwave reactor fitted with a gas insertion unit in order to provide the required temperatures and pressure of CO_2. This makes the reaction impractical for laboratory's that do not contain this equipment.

The success of the regent system in the synthesis of phosphazenes indicated that a one-pot, PPh_3, I_2 and DMAP mediated reaction could be investigated (Scheme 4.20). An aryl or alkyl amine was added to a stirred solution of PPh_3, I_2 and DMAP in anhydrous CH_2Cl_2. This mixture is then stirred under an atmosphere of argon at room temperature until TLC analysis indicates all amine has been consumed (10-30 min). At that point an atmosphere of CO_2 (g) was introduced via a direct line from a pressurised canister using

needle. As the CO_2 was bubbled through the solution a further 1.5 equiv. of amine was added, either at the same amine for symmetrical ureas or a different amine for asymmetrical ureas. The CO_2 was then allowed to build a slight positive pressure before the needle was removed. The reaction mixture was then stirred for a further 3 hours at room temperature. Residual iodine and amine were then removed by washes with $Na_2S_2O_4$ (aq) and acid, respectively along with any DMAP-H^+ salt. Finally the solvent was died by passing through a phase separator column. Isolation of the urea products was achieved via flash chromatography on silica in ethyl acetate and hexane resulting in ureas compounds in good to excellent yields.



Scheme 4.20: Reaction scheme for one pot, room temperature formation of symmetrical and asymmetrical ureas.

Results for the one pot method for the synthesis of ureas can be seen in Figure 4.6. In general good to excellent yields were achieved using this method. **150a** (41%) and **150e** (46%) in which aniline acted as the secondary nucleophile i.e. the amine that was added post formation of the phosphazene resulted in lower yields, when compared to alkyl amines where used as the secondary nucleophile. It was clear that the synthesis of phosphazenes from aniline derivatives was a rapid and reliable process with isolated yields in excess of 90%, but it would seem that aniline is simply not a strong enough nucleophile in order to attack the isocyanate as it is formed under these conditions. This is most likely due to electron withdrawing effects of the aromatic ring, therefore making the aniline a poorer nucleophile. However, others methods such as Tian *et al.'s* use of a novel Selenium based catalysts in ionic liquids gave diphenyl urea **150a** in a 99% yield.[267] Ureas **150b-g** was obtained in moderate yields, especially considering that the reaction was run at room temperature and under much lower pressures of CO_2 compared to the microwave method of by Cravotto *et al.*[247] The best results were achieved for urea **150b-g** in which alkyl amines such as, benzyl amines or octyl amine was used as the secondary nucleophile in the formation of the these urea products. The results also indicated that the process was suitable for the formation of phosphazenes from alkyl

amines. However isolation of the phosphazene derived from alkyl amines proved to be difficult due to their high polarity.

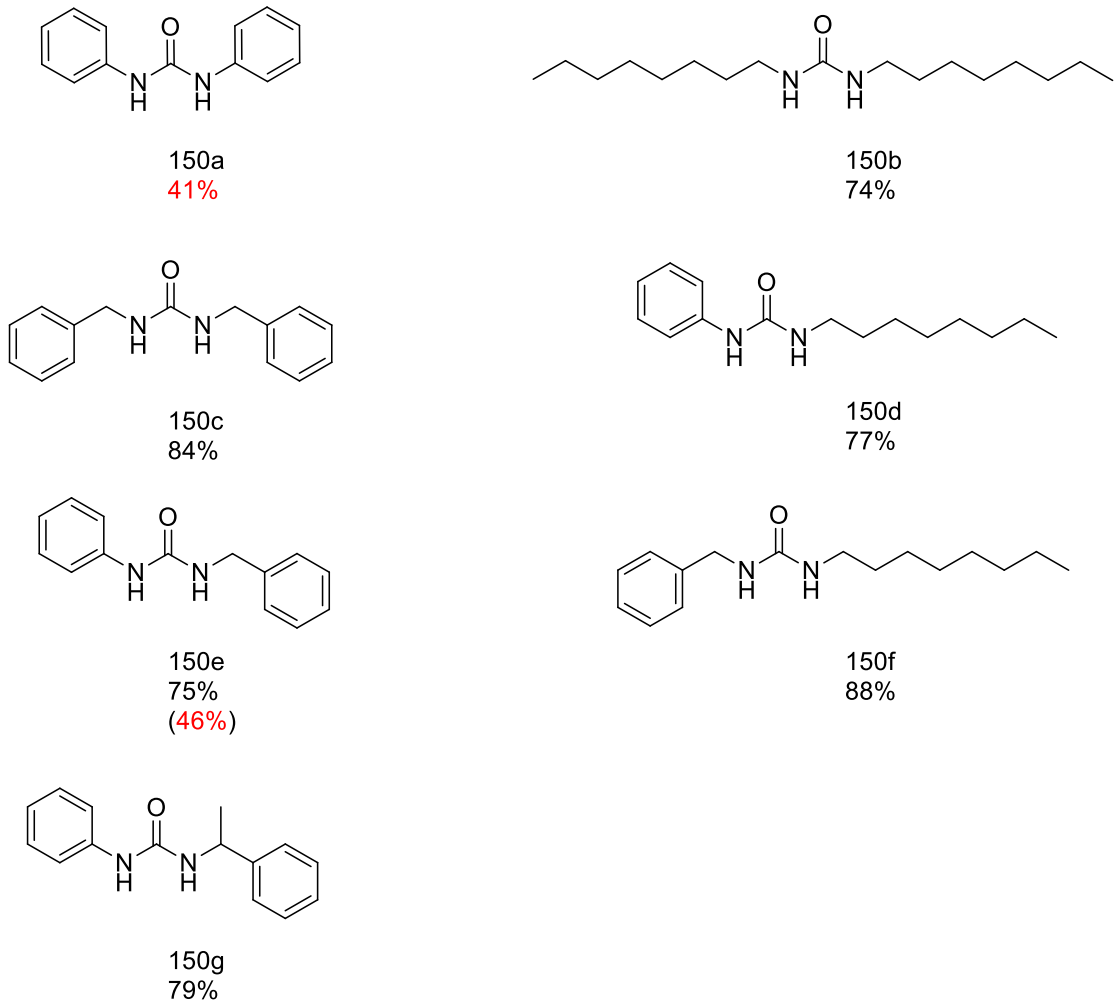
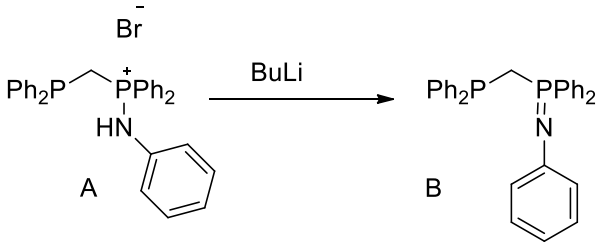


Figure 4.6: The scope of urea formation using a one-pot system mediated by PPh_3, I_2 and DMAP. All reactions where run for a maximum of 5 hours at room temperature. Results in red indicate aniline as secondary nucleophile in second stage of the procedure.

4.5 ^{31}P NMR Spectroscopic Studies to Determine Possible Mechanistic Pathway for the Formation of Phosphazenes Using DMAP.

It was clear from these results that DMAP was playing a role in accelerating the formation of phosphazenes compared to the use of other bases such as NEt_3. It was considered that DMAP was playing an catalytic role, thus speeding up the formation of the phosphazene over other conventional bases in a mechanistic pathway distinct from the Kirsanov reaction. In order to try and understand the difference in reactivity

observed using DMAP over conventional bases a number of ^{31}P NMR spectroscopic experiments where performed. These experiments are also supported by a review of the literature to establish whether any pervious ^{31}P NMR spectroscopic studies could help to identify potential phosphorus species involved in the Kirsanov reaction conditions.

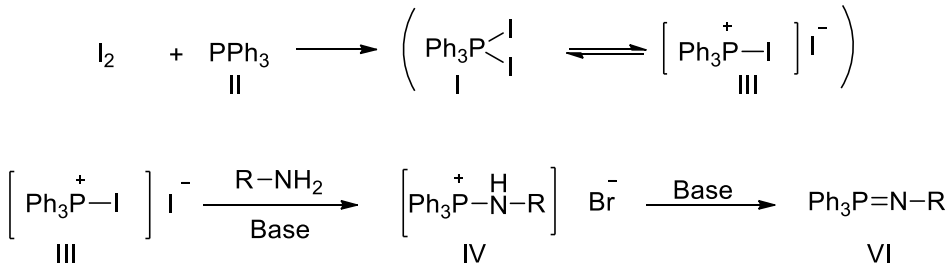


Scheme 4.21: Le Floch *et al.'s* formation of mixed phosphine/phosphorane ligand

As part of Le Floch *et al's.* reported synthesis of mixed phosphine/iminophosphorane bidentate ligands for coordinating to group 10 metal centres. A comprehensive ^{31}P NMR spectroscopic study of the phosphine species involved was presented, providing analysis and characterisation of the chemical shifts of the different phosphorus species formed throughout the poroducdure.[268] Scheme 4.21 shows the synthesis of the iminophosphorane from the bromide salt **A** via the Kirsanov reaction. ^{31}P NMR spectroscopic study of these molecules showed that for the salt of **A** provides two ^{31}P resonances and assigned the phosphine species as doublet resonance with a chemical shift of δ -30.8 ppm whilst the aza-phosphorane salt phosphorus was assigned as doublet resonance with at a chemical shift of δ 34.5 ppm. ^{31}P NMR spectroscopic study of the phosphazene species **B** again produced two resonances with the assignment of the phosphine as a doublet resonance with a chemical shift of δ -27.2 ppm. The phosphazene phosphorus on the other hand was assigned as a doublet with a chemical shift of δ 0.4 ppm. These chemical shifts provided by Le Flock's study are useful as the provide good reference points for the possible chemical shifts for the different phosphorus species for use in our own ^{31}P NMR spectroscopic investigation.

A series of ^{31}P NMR spectroscopic experiments all the reactions were performed in deuterated chloroform ($CDCl_3$) to simplify the analysis procedure. To begin, a study of the phosphorus species present at each stage of the Kirsanov reaction was carried out (Figure 4.7, Table 4.2). Spectra 1 (red) shows phosphorus environments when PPh_3 and I_2 were dissolved in $CDCl_3$: this resulted in 3 peaks: a resonance at δ -21.40ppm (**I**) was

assigned to the formation of 5 coordinate phosphine diiodide. The second peak appeared at δ -3.25 ppm (**II**) was assigned to PPh_3. The final peak appeared at δ 48.85 ppm (**III**) was assigned as the phosphonium diiodo salt. Upon addition of aniline (spectra 2, green) to the reaction mixture and after 10 min stirring, another sample was taken and subjected to P^{31} NMR spectroscopic analysis. Two phosphorus environments were observed, a peak at δ 33.31 ppm (**IV**) assigned to aza-phosphonium salt and a peak at δ -21.39 ppm (**I**). Spectra 3 (blue) indicate the phosphorous environments when NEt_3 was added before addition of aniline in order to get a good comparison when the order of reagent addition was changed. Two peaks resulted: a peak at δ 29.24 ppm (**V**) which was indicative of phosphine oxide and a peak at δ -20.65 (**I**). Spectra 4 (purple) indicate the phosphorus environments upon addition of NEt_3 to the mixture of aniline, PPh_3 and I_2. Peak at δ 29.24 (**V**) indicate phosphine oxide and a peak at δ -19.57 (**I**) indicate the presence of phosphine diiodide finally a newly emerged peak at δ 4.14 ppm (**VI**) was assigned to the formation of phosphazene **121a**. This suggested the mechanism of reaction proceeded through a standard base type mechanism in which the aniline salt was first formed followed by deprotonation to form the phosphorus nitrogen double bond (Scheme 4.22).



Scheme 4.22: Mechanism for base driven Kirsanov Reaction

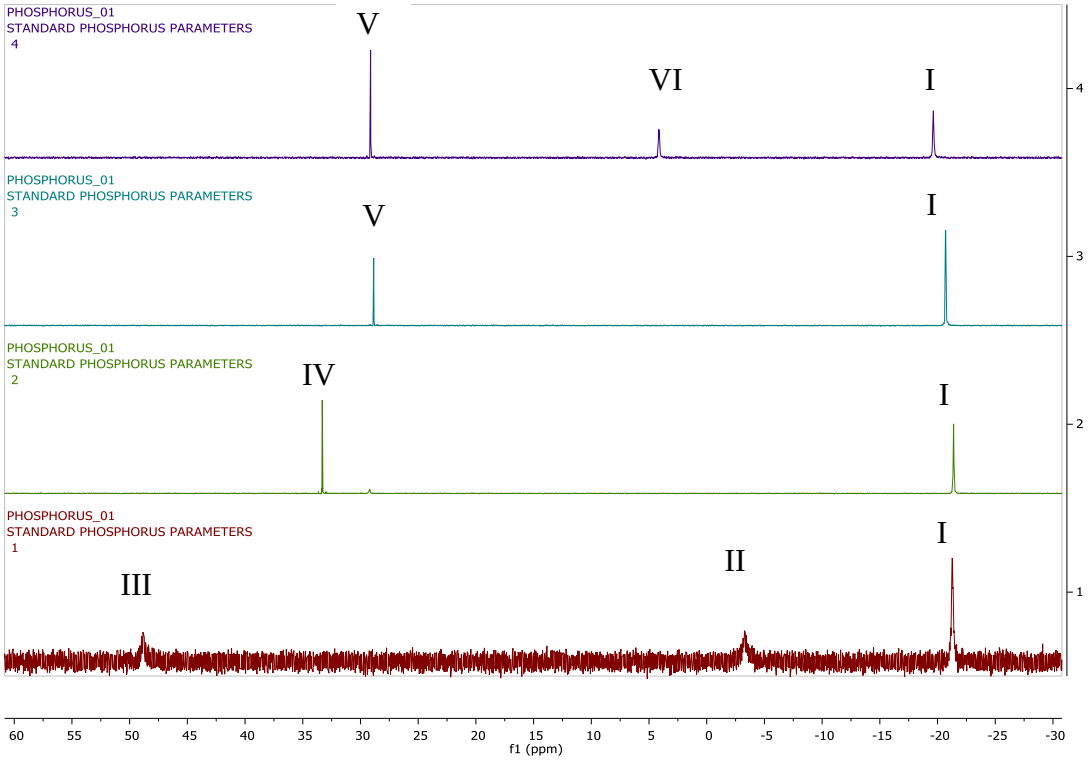


Figure 4.7: ^{31}P spectroscopic studies performed in order to determine the presence of different phosphorus species during phosphazene formation mediated by NEt_3. Spectra 1 (red); PPh_3, I_2. Spectra 2 (green); aniline, PPh_3, I_2. Spectra 3 (blue); NEt_3, PPh_3, I_2. Spectra 4 (purple); PPh_3, I_2, NEt_3 followed by addition of aniline.

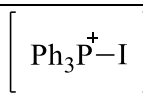
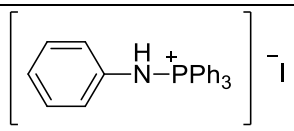
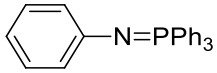
Peak number	Chemical shift	Assignment of Phosphorus atom	Literature values[138]
I	-21.28, -21.40, -20.65, -19.57		~ -17.00 [138]
II	-3.28	PPh_3	-5.30 [138]
III	48.85		~ 45.00 [138]
IV	33.31		34.50 [268]
V	29.30, 29.24	$O=PPh_3$	29.44 [138]
VI (53)	5.63		-1.3 (C_6D_6)[266]

Table 4.2: Table to show the assignment of ^{31}P NMR peaks.

A similar study was then carried out in which DMAP was used as in place of NEt_3 as the base (Figure 4.8, Table 4.3). Spectra 1 (red) once again indicate the phosphorus environments generated simple mixture of PPh_3 and I_2. Upon addition of the aniline (spectra 2, yellow), a resonance was observed at δ 33.31 ppm (**IV**) assigned to the formation of the complex of aza phosphonium iodo salt (as seen previously) and in line with assignments made by Le Flock *et al.* (Scheme 4.21, compound **A**),[265] as well as a resonance at δ -21.39 ppm (**I**). Upon addition of DMAP (spectra 3, green) a resonance at δ 33.31 **(IV)** disappeared and a new resonance at 21.29 ppm (**VII**) was observed as well as at δ 29.59 ppm (**V**). The emergence of this new peak was intriguing, because as already discussed when the NEt_3 is added (Figure 4.7) no such peak was observed and instead the phosphazene is formed. This suggested that this phosphorus species was new and important intermediate in the effectiveness of DMAP over bases conventionally used in the Kirsanov reaction (Table 4.1). Spectra 4 (Blue) indicate the addition of aniline to a reaction mixture of PPh_3, I_2 and DMAP mixture, a resonance at δ 23.85 ppm (**VII**) appeared which again seemed to correspond to the new intermediate. A peak at δ 29.69 ppm (**V**) was also observed, but no peak at δ -20 ppm (**I**) was present suggesting that the reaction had gone to completion.

Assignment of the new peak attributed to species VII has proved to be a challenge. In an attempt to try and isolate this species a work up of the reaction mixture was attempted; evaporation of the $CDCl_3$ solvent followed by residue and addition of ethyl acetate resulted in precipitation of DMAP-H^+ I^- salt. This solid was removed by filtration and the ethyl acetate was evaporated. Another ^{31}P NMR spectroscopic study was performed on the resulting residue; this resulted in the observation of resonance for phosphine oxide **V** and disappearance of the resonance at δ ~22 ppm **IV** and emergence of a resonance at δ 5.63 ppm (**VI**) assigned to phosphazene **121a.** This led to the problem that the assignment of what was clearly an important intermediate could therefore only be speculative.

When the DMAP-H^+ I^- salt was removed from the reaction mixture via precipitation, the phosphazene was formed whilst when free base DMAP is added is added back the new species was not reformed. This therefore led to the question, how does evaporation of the solvent and removal of protonated DMAP salt lead to the formation of the phosphazene. The appearances of peak at δ 21.29 ppm (**VII**) once aniline is added to the

PPh_3-I_2-DMAP system suggested that this could well be a phosphorus species containing both DMAP and aniline. It also seemed that this intermediate was not stable under reduced pressure or in the absence of solvent, eliminating the DMAP-H^+ I^- salt which is insoluble in ethyl acetate and thus removed via filtration.

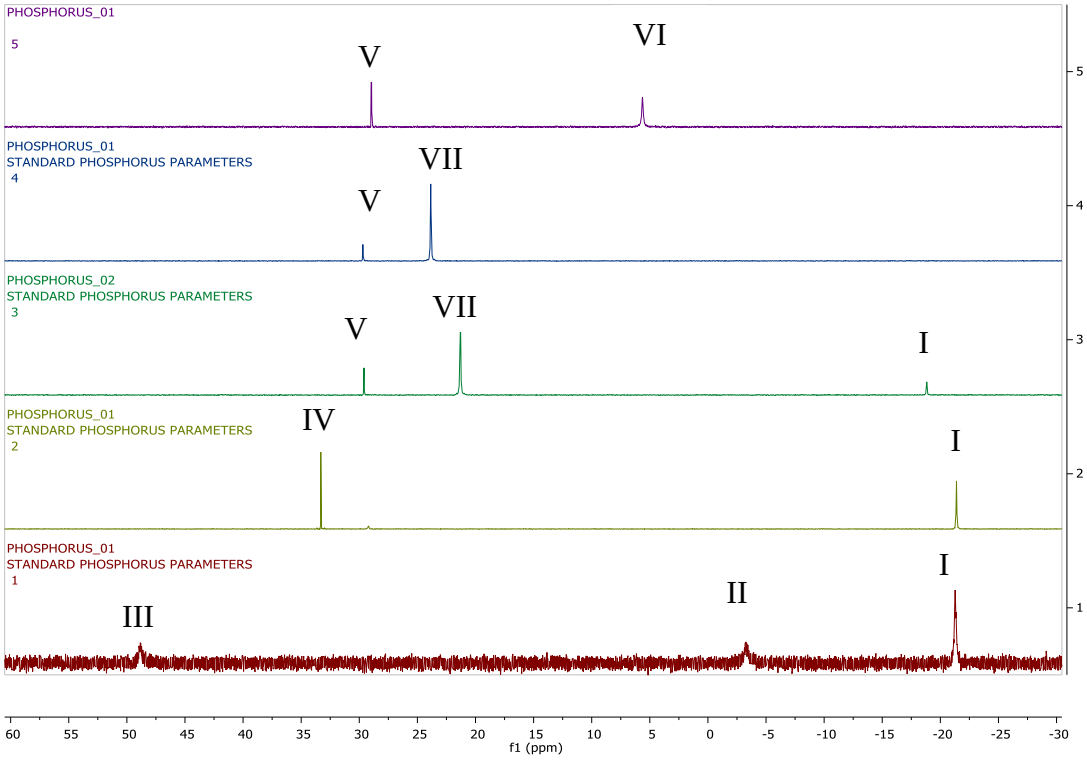


Figure 4.8: ^{31}P NMR spectroscopic studies performed in order to determine the presence of different phosphorus species during phosphazene formation mediated by DMAP. Spectrum 1 (red); PPh_3, I_2. Spectrum 2 (yellow); aniline, PPh_3, I_2. Spectrum 3 (green); aniline, PPh_3, I_2 followed by DMAP addition. Spectrum 4 (blue); PPh_3, I_2, DMAP followed by addition of aniline. Spectrum 5 (purple); post evaporation of solvent and ethyl acetate workup.

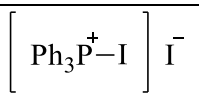
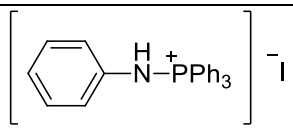
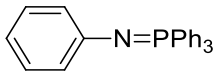
Peak number	Chemical shift	Assignment of Phosphorus atom	Literature values[138]
I	-21.30, -21.39, -18.89		~ -17.00 [138]
II	-3.28	PPh_3	-5.30 [138]
III	48.85		~ 45.00 [138]
IV	33.31		34.50 [268]
V	29.30, 29.24, 29.59	$O{=}PPh_3$	29.44 [138]
VI	5.63		-1.3 (C_6D_6)[266]
VII	21.29, 23.85	Speculative assignment of compound **151**	N/A

Table 4.3: Table to show the assignment of ^{31}P NMR peaks as shown from DMAP mediated studies.

This theory was tested by running an experiment in which phosphazene **121a** was synthesised in the standard way by mixing aniline, PPh_3, I_2, and DMAP. The solvent was evaporated and ethyl acetate was added; the resulting precipitate was filtered and the ethyl acetate was removed. The resulting residue was then dissolved in $CDCl_3$ and analysed by ^{31}P NMR spectroscopy. The resulting spectrum showed resonances at δ 28.94 ppm (**V**) and δ 5.84 ppm (**VI**) showing that the phosphazene had been formed and residual phosphine oxide was present in solution. The DMAP-H^+I^- salt obtained from the reaction was then added back to the NMR solution. Resonances at δ 29.54 ppm (**V**) and δ 22.86 ppm (**VII**) were observed with no sign of a peak between 0-5 ppm (Figure 4.9). This experiment suggested that the presence of the DMAP salt was important in the formation of this intermediate species. To further test this, the purified phosphazene **121a** was added to DMAP in order to see whether it was indeed the protonated form that was important in the formation of species **VII.** On addition of DMAP to the purified phosphazene the spectra gave one peak at δ 2.64 ppm thus showing that Species **VII** is only formed in the presence of DMAP-H^+I^- salt.

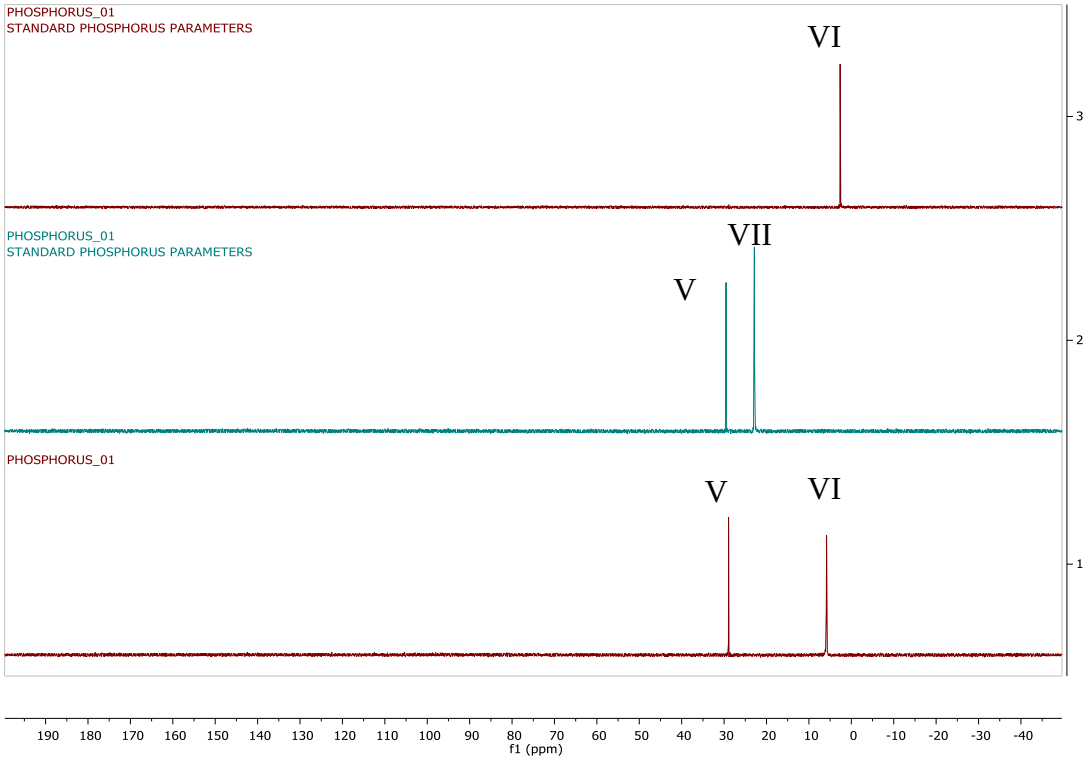


Figure 4.9: ^{31}P NMR spectroscopic study showed that upon evaporation and removal of DMAP-H^{+}I^{-} salt phosphazene is formed whilst in solution in the presence of DMAP-H^{+} iodo salt in chlorinated solvents intermediate **VII** is formed. Spectrum 1 (red) residue with DMAP-H^{+} iodo salt removed. Spectrum 2 (blue) DMAP-H^{+} iodo salt added back into solution. Spectrum 3 (red) DMAP added to purified phosphazene 1.

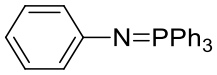
Peak number	Chemical shift (ppm)	Assignment of Phosphorus atom	Literature values[138] (ppm)
V	29.30, 29.24, 29.59	$O{=}PPh_3$	29.44 [138]
VI	5.63, 2.64		-1.3 (C_6D_6)[266]
VII	21.29, 23.85	Speculative assignment of compound **151**	N/A

Table 4.4: Table to show the assignment of P^{31} NMR peaks from figure 1.10.

As already discussed phosphazenes can act as effective bases e.g. the potent organic superbase P$_4$-*t*-Bu. It therefore goes to reason that the pKa-H^{+} of phosphazene might well be higher than that of DMAP. If we take the assumption that DMAP is not a strong enough base to fully deprotonated aniline phosphonium species then addition of protonated DMAP to a solution of phosphazene and transfer of a proton to the nitrogen

of the phosphorus nitrogen double bond is feasible. It is also reasonable to suggest that DMAP could then act as a nucleophile and attack the resulting positively charge phosphorus to form a 5 coordinate phosphorus species. Figure 4.10 offers a speculative assignment for the intermediate species **VII** seen in the ^{31}P NMR spectroscopic studies (Figure 4.8 and Figure 4.9.) Froyden suggested that a 5-coordinate phosphorus species was the active intermediate in PPh_3, I_2 and NBS mediated acylations in which the amine component and acyl component of the ester were attached to the phosphine and quickly collapse to form a resulting amide.[95] These species however, have not previously been isolated, possibly due to their instability in the solid phase; thus upon evaporation of solvent, species **VII** could collapse to give phosphazene and protonated DMAP salt.

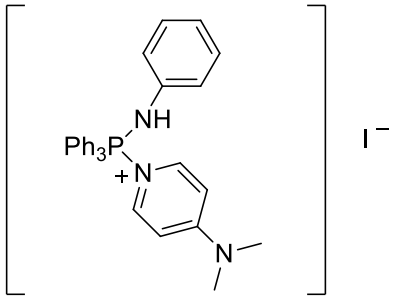
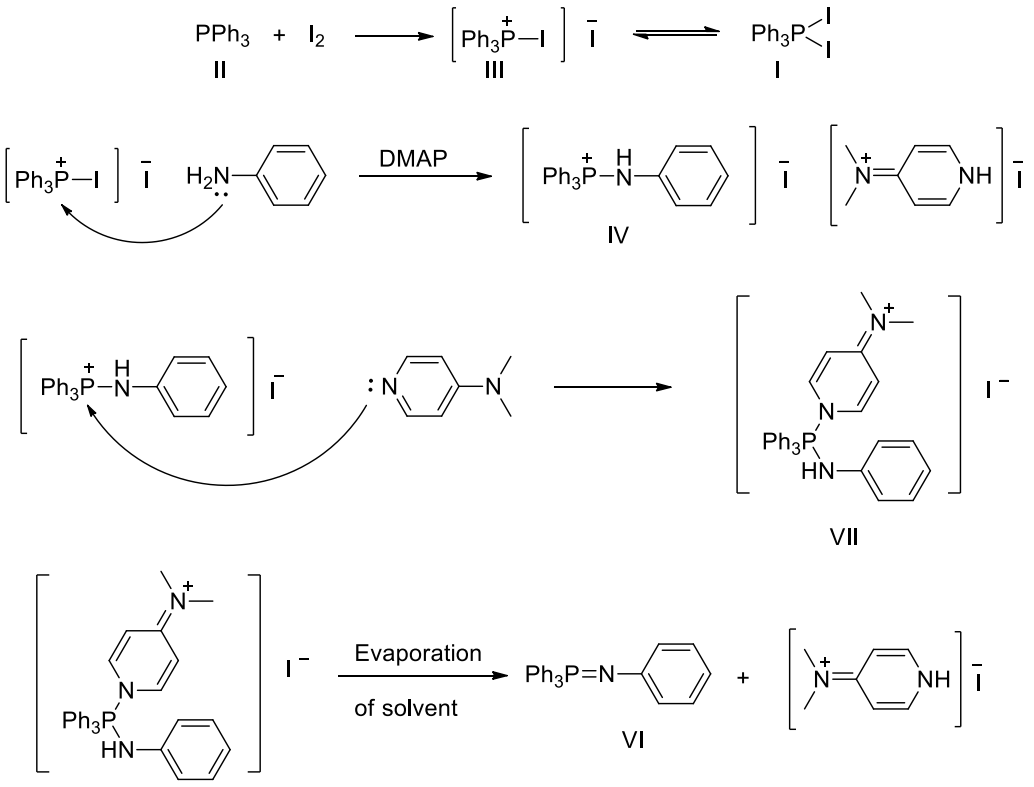


Figure 4.10: Speculative assignment of intermediate **IV** as compound **151.**

Scheme 4.23 shows a proposed mechanism for the formation of phosphazenes mediated by DMAP, consistent with the suggested 5-coordinate phosphorus species **151** tentatively assigned for species **VII** (δ ~22ppm). Upon mixing PPh_3 and I_2 equilibrium between phosphonium diiodo species **I** and **III** is established, as observed in previous PPh_3-I_2 mediated reactions**.** Addition of DMAP and aniline leads to the rapid formation of compound **151**. It is known that phosphonium amine adducts can form, as observed in previous ^{31}P NMR spectroscopic studies most notably in the studies performed by Phakhodee *et al.*[138] The amine, in this case aniline, can act as a nucleophile to attack one of the equilibrium species, displacing the coordinated iodide as observed in the ^{31}P NMR spectroscopic study shown in Figure 4.7. Nucleophilic attack of the DMAP to the positively charged phosphorus atom leads to formation of the 5-coordinate phosphorus compound **151**, which upon evaporation of the solvent collapses to form the phosphorus-nitrogen double bond and DMAP-H^+I^- salt. Removal of this salt via taking precipitation and filtration of the resulting precipitate provides phosphazene **121a**.

A possible alternative in the formation of compound **151** could be that the DMAP first attacks the phosphonium diiodide to form a phosphonium-DMAP adduct. The DMAP could then act as an effective leaving group and be displaced via nucleophilic attack of the aniline thus catalysing the formation of species **IV**. Formation of DMAP phosphine adducts would allow for increased rate of attack of aniline in the formation of intermediate species **IV** due to nucleofuge properties of DMAP. However, there is no direct evidence of DMAP adduct formation by ^{31}P NMR spectroscopy. Only the formation of phosphine oxide is observed upon addition to the PPh_3-I_2 mixture in $CDCl_3$. It therefore, seems that DMAP catalyses the formation of phosphine oxide offering some indication that an interaction between the DMAP and phosphine iodide is likely but any adduct is so reactive that moisture in the air can react. Any DMAP adduct is likely to be highly reactive and would be rapidly displaced any nucleophile such as aniline or any moisture in the system which would explain the formation of phosphine oxide.



Scheme 4.23: Proposed mechanism for the formation of Phosphazenes when mediated by DMAP as base and nucleophilic catalyst.

Manners *et al.* produced a series of cationic phosphoranimines bearing chloro, methyl, phenyl, and trifluoroethoxy substituents, which were stabilised by the electron donor

properties of DMAP.[269,270] The reaction between DMAP and $Cl_3P{=}NSiMe_3$ led to a new adduct $(DMAPCl_2P{=}NSiMe_3)^+Cl^-$. Interestingly it was then found that in the solid state this slowly reverted back to DMAP and $Cl_3P{=}NSiMe_3$ over a period of two weeks at ambient temperature. Conversion back to the DMAP-stabilized adduct occurred rapidly upon re-dissolving in CH_2Cl_2. Another DMAP adduct containing methyl groups in place of two chlorine substitutes on the phosphorus atom and bromide ion as the counter ion gave no reversion back to staring phosphazene and DMAP constituents thus suggesting that the dialkyl substituted cations are more stable to retro-conversion.

An alternative proposal for the identity of ^{31}P NMR spectroscopy resonance **VII** was the formation of dimers or trimers of the phosphazene so that an alternating phosphorus nitrogen heterocycle was formed whilst in solution in the presence of protonated DMAP salt. Why this might be the case was unknown but phosphazene heterocycles are known, for example hexachlorophosphazene is an inorganic compound with the formula $(NPCl_2)_3$. In order to try and test this idea a classic crossover experiment was attempted. To 1 equiv. of DMAP-H^+I^- salt in $CDCl_3$ was added 0.5 equiv. of phosphazene **121a** and 0.5 equiv. of phosphazene **121b**. The resulting ^{31}P NMR spectrum gave resonances at δ 23.33 ppm and δ 16.30 ppm (Figure 4.11). The fact that there were only two distinct peaks tells us that a dimer or trimer is unlikely as if it was a dimer it would be expected that there would be at least three distinct possibilities for the combination of the two phosphazenes, one in which **121a** was paired with **121a**, another where **121a** was paired with **121b** and finally where **121b** was paired with **121b.** If a trimer formed then the pattern would be even more complicated with a possibilty of four different combinations of phosphazene **121a** and **121b**. The fact that there were only two peaks (as well as a small one for $O{=}PPh_3$) indicated that there are only two distinct phosphorus containing species were in the solution which also suggests that a dimer and trimer are not forming when phosphazenes were in the presence of protonated DMAP salts.

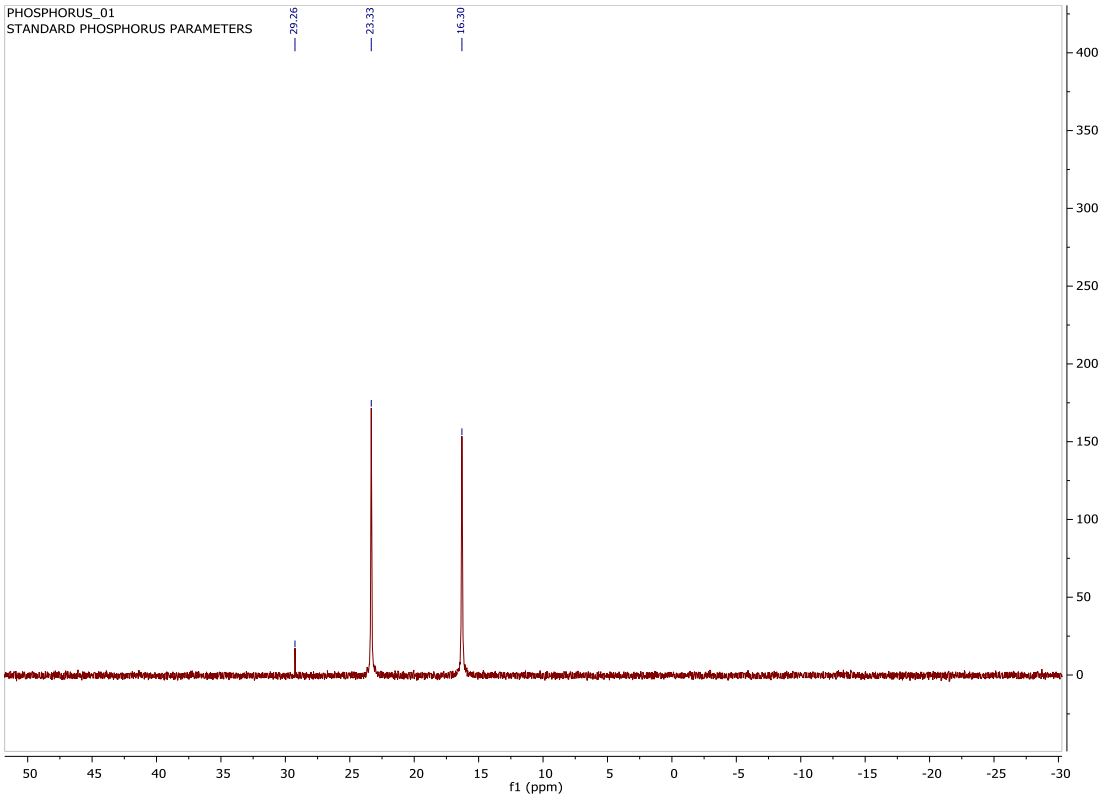


Figure 4.11: ^{31}P NMR spectrum of crossover experiment in which 0.5 equiv. each of phosphazenes 1 and 2 where mixed with 1 eq of DMAP-H^+I^- salt in $CDCl_3$

The results from the ^{31}P spectroscopic experiments were inconclusive in offering clear evidence of the mechanism for the rapid formation of phosphazenes might. The ^{31}P NMR spectrum resonances observed at ~22 ppm indicated the presence to an important intermediate for the rapid formation of phosphazenes. A likely candidate for this intermediate is the 5-coordinate compound **151** presented in Figure 4.10. Phosphazenes are known to be strong and effective bases which suggest that DMAP would not be a strong enough base to deprotonate the intermediate phosphonium anilide salt **IV**. The formation of the intermediate only seems to occur in the presence of protonated DMAP and not in the presence of protonated NEt_3. It seems likely that this formation is reliant on the transfer of a proton to the phosphazene species followed by interaction with the now free nucleophilic DMAP. This is constituent with the lack of any observed phosphorus species with a ^{31}P NMR peak at δ ~22 ppm when DMAP free base was added to a solution of isolated phosphazene. Although this is only a speculative proposal for the mechanism by which the PPh_3, I_2 and DMAP mediated formation of phosphazenes proceeds it is clear that DMAP is playing an alternative role to that of a simple base due to the rapid formation of phosphazenes in this system compared to the

other bases investigated such as NEt_3 and DIPEA. This method offers an efficient process for the formation of phosphazenes directly from amines. Even though the exact mechanism for the rapid formation of phosphazene can't be described with any certainty it is also clear that the PPh_3-I_2-DMAP mediated route to phosphazenes has a lot to offer synthetic organic chemists as a rapid and efficient route to aryl phosphazenes.

4.6 Conclusion

In conclusion, the results from this chapter have again shown the versatility of the PPh_3, I_2 and DMAP system. Addition of amines to this versatile reagent system allows for the rapid formation of synthetically useful phosphazenes. Isolated yields of in excess of 90% for aniline derived phosphazenes are achievable within reaction times of 10 min to 2 h at room temperature. The focus of the study was the formation of phosphazenes derived from aryl amines (anilines) due to their ease of isolation compared to alkyl amine-derived phosphazenes. The procedure used again is very similar to that used for both the formation of esters and amide's as described in chapter 2 and for the formation of 1,2-isoxazoles. Due to the rapid nature of the formation of the phosphazene it was decided to develop a mild method using the aza-Wittig chemistry of the phosphazenes. In a small study it was shown that ureas could be produced in a one pot process. By performing the reaction in a slight positive pressure atmosphere of CO_2 the corresponding isocyanate was formed further addition of an 2^{nd} equivalent of amine led to the formation of the corresponding urea. This simple method for the formation of ureas allows good yields to be obtained at room temperature upon addition of alkyl amine (e.g. octyl urea) to the phosphazene/CO_2 mixture but gave poor yields when aniline was used. It is a milder and simpler method and avoids the need for azides and the extra steps required for the formation of the azide from the corresponding halide then alternative procedures such as the microwave method developed by Cravotto *et al*.[247]

In terms of mechanism, the optimisation studies clearly showed that DMAP was by far the most effective base for this transformation. A series of ^{31}P-NMR spectroscopic experiments was performed in order to gain an understanding to why DMAP enhanced

the rate of phosphazene synthesis compared to bases with similar or better basicities. It was discovered that the rapid formation of a new phosphorus containing species with a chemical shift of δ ~22 ppm indicated the formation of unknown intermediate. This species seemly is unstable at low pressure or in the absence of solvent and collapses into phosphazene upon evaporation of CH_2Cl_2 or $CDCl_3$ solvent. Removal of protonated DMAP salt via it insolubility in ethyl acetate led to formation of the phosphazene **121a** resulting in phosphazene with a P^{31} NMR spectroscopic resonance of between δ 0-5 ppm. As a result of these NMR spectroscopic experiments the resonance at δ ~22 ppm was tentatively assigned to 5-coordinate phosphonium species **151** as likely candidate of this intermediate. However, there is no direct evidence of this structure as it cannot be isolated.

4.7 Phosphazenes Experimental and Characterisation

General Methods

Commercially available reagents were used without further purification;. Solvents where dired using. Unless otherwise stated reaction where carried out in air at roomtemperature. Microwave irradiation experiments were performed in a sealed Pyrex tube using a self-tunable CEM Explorer focused monomodal microwave synthesizer at the given temperature using the instrument's in-built IR temperature measuring device, by varying the irradiation power. Flash chromatography was carried out using a Teledyne ISCO Combiflash Rf instrument and Biotage SNAP KP-Sil cartridges packed with 50 μm silica particles. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck TLC Silica gel 60 F_{254} that were visualized under UV light (at λ 254 and/or 360 nm).

Fully characterized compounds were chromatographically homogeneous. Melting points were determined using tanford Research Systems Optimelt and are uncorrected. NMR spectra were recorded using a Varian VNMRS instrument operating at 500 MHz for ^{1}H spectra and 125 MHz for ^{13}C spectra; *J* values were recorded in Hertz (Hz) and multiplicities were expressed by the usual conventions. Low resolution mass spectra were determined using a Fisons VG autospec instrument using atmospheric pressure chemical ionization (APcI). High resolution mass spectra were determined using a Bruker Daltronics Apex III instrument by electrospray ionization (ESI).

Procedure for the formation of 121a with NEt_3 as the base

To a well stirred solution of I_2 (0.396 g, 1.56 mmol) in 10 ml of dry CH_2Cl_2, triphenylphosphine (0.414 g, 1.58 mmol) and NEt_3 (0.37 ml, 2.65 mmol) were added sequentially. A few of minutes later, the aniline (0.098 g, 1.05 mmol) in 1 ml of dry CH_2Cl_2 was added and the solution was stirred at room temperature for a total of 20 hours. Once complete the solvent was evaporated and the residue taken up in EtOAc. The solvent was removed via evaporation and the resulting residue was purified via flash column chromatography on silica (40-50% EtOAc in hexanes) to provide **53** as a yellow solid (0.201 g, 54%).

Procedure for the formation of 121a with pyridine as the base

To a well stirred solution of I_2 (0.325 g, 1.28 mmol) in 10 ml dry CH_2Cl_2 was added PPh_3 (0.338 g, 1.29 mmol) and pyridine (0.20 ml, 2.58 mmol) sequentially. A few of minutes later, aniline (0.0944 g) in 1 ml of dry CH_2Cl_2 was added and the solution was stirred at room temperature for a total of 20 hrs. NMR indicated that the reaction had not undergone any sort of transformation with in the allotted time frame so reaction was stopped and abandoned.

Procedure for the formation of 121a with imidazole as the base

To a well stirred solution of I_2 (0.376 g, 1.48 mmol) in 10ml dry CH_2Cl_2 was added PPh_3 (0.387 g, 1.48 mmol) and imidazole (0.201 g, 2.96 mmol) sequentially. A few minutes later, aniline (0.110 g, 1.18 mmol) in 1ml of dry CH_2Cl_2 was added and the solution was stirred at room temperature for a total of 20 hours. Once complete the solvent was evaporated and the residue taken up in Ethylacetate. The solvent was removed via evaporation and the resulting residue was purified via flash column chromatography on silica 40-50% ethyl acetate in hexanes to provide (0.073 g, 17%) of phosphazene **54** as a yellow solid.

Procedure for the formation of 121a with DIPEA as the base

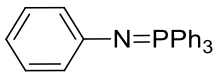
To a well stirred solution of I_2 (0.282 g, 1.11 mmol) in 10 ml of dry CH_2Cl_2 was added PPh_3 (0.292 g, 1.11 mmol) and DPIEA (0.333 g, 2.58 mmol) were added sequentially. A few minutes later, aniline (0.101 g, 1.08 mmol) in 1 ml of dry CH_2Cl_2 was added the solution was stirred at room temperature for a total of 20 hrs. Once complete the solvent was evaporated and the residue taken up in Ethylacetate. The solvent was removed via evaporation and the resulting residue was purified via flash column chromatography on silica (40-50% EtOAc in hexanes) to provide (0.240 g, 68%) of phosphazene **53** as a yellow solid.

General procedure for formation of phosphazenes mediated by DMAP and I_2

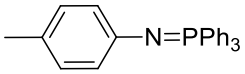
To a well stirred solution of I_2 (1.25 eq) in 10ml dry CH_2Cl_2 was added PPh_3 (1.25 equiv.) and DMAP (2.5 equiv.) sequentially. A few minutes later, the aniline (1 equiv.) in 1 ml of dry CH_2Cl_2 was added the solution was stirred at room temperature until complete consumption the of starting aniline was observed by TLC (Hexane/EtOAc) (10-120 mins). Once complete the solvent was evaporated and the residue taken up in

Ethylacetate. The resulting white precipitate was removed by filtration and the resulting filtrate was concentrated, the resulting residue was purified via flash column chromatography on silica (Hexane/EtOAc) providing phosphazenes **53-64** in good to excellent isolated yields.

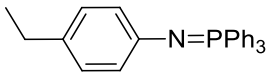
Characterisation of phosphazene products



N-*(Triphenylphosphoranylidene) aniline (121a),* yellow solid, mp 132.7-135.4^{o}C, (hexane/ethylacetate) (*lit*[262] 132-133 ^{o}C), yield: 0.413 g, 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 6H), 7.53 (t, *J* = 7.5 Hz, 3H), 7.49 – 7.43 (m, 7H), 7.02 (t, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 7.5 Hz, 2H), 6.66 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.16 (d, J_{PC} = 2.5 Hz, C-N-P), 132.64 (d, J_{PC} = 9.5 Hz, CH), 131.58 (d, J_{PC} = 3.0 Hz, CH), 131.33 (d, J_{PC} = 99.0 Hz, CH), 128.58 (CH), 128.55 (d, J_{PC} = 11.9 Hz, CH), 123.52 (d, J_{PC} = 17.5 Hz, CH), 117.35 (CH). ^{31}P NMR (162 MHz, $CDCl_3$) δ 2.60. ESI-MS (*m/z*) 354.1392 (M^{+H}). Known compound, spectra matches.[262]

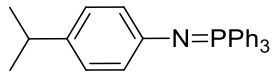


4-Methyl*-N-*(triphenylphosphoranylidene)aniline-(121b), colourless solid, mp 136.7-137.9^{o}C (hexane/ethylacetate) (*lit*[262] 138 ^{o}C), yield 0.436 g, 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 6H), 7.52 (t, *J* = 7.5 Hz, 3H), 7.45 (m, 6H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 2.20 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.30 (C-N=P), 132.64 (d, J_{PC} = 9.5 Hz, CH), 131.49 (d, J_{PC} = 2.5 Hz, CH), 131.41 (d, J_{PC} = 98.0 Hz, C-P) 129.2 (CH), 128.50 (d, J_{PC} = 12.0 Hz), 126.28 (C), 123.21 (d, J_{PC} = 17.5 Hz, CH), 20.49 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 2.33. ESI-MS (*m/z*) 368.1560 (M^{+H}). Known compound, spectra matches.[262]

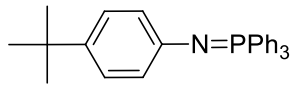


4-Ethyl*-N-*(triphenylphosphoranylidene) aniline-(121c), brown solid, MP 103.1-104.3^{o}C (hexane/ethylacetate), yield: 0.4233 g, 96%. IR (cm^{-1}).*v* = 1601 (w), 1504 (m), 1437 (m), 1323 (br), 1178, 1118, 720 (s), 693 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.75 (m, 6H), 7.55 – 7.50 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 6H), 6.87 (d, *J* =

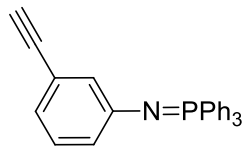
8.0 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 2.52 (q, *J* = 7.5 Hz, 2H), 1.17 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$). δ 148.51 (C-N=P), 132.81 (CH), 132.65 (d, J_{PC} = 9.5 Hz, CH), 131.52 (d, J_{PC} = 98.0 Hz, C-P), 131.46 (d, J_{PC} = 3.0 Hz, CH), 123.17 (d, J_{PC} = 17.5 Hz, CH), 27.93 (CH_2), 15.57 (CH_3).^{31}P NMR (162 MHz, $CDCl_3$) δ 2.01. ESI-MS (*m/z*) 382.1703 (M^{+H}).



4-Isopropyl*-N-*(triphenylphosphoranylidene)aniline-(121d), colourless solid, MP 125.4-128.4^{o}C (hexane/ethylacetate), yield 0.3318 g, 91%. IR (cm^{-1}).*v* = 1637 (s), 1578 (m), 1187 (s, br), 823, 692. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 6H), 7.55 – 7.50 (m, 3H), 7.48 – 7.43 (m, 6H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 2H), 2.78 (hept, 7.0 Hz, 1H), 1.20 (d, J = 7.0 Hz, 6H). 13C NMR (126 MHz, CDCl3) δ 148.57 (d, J_{PC} = 2.5 Hz, C-N=P), 137.49 (CH), 132.67 (d, J_{PC} = 9.5 Hz, CH), 31.61 (d, J_{PC} = 98.5 Hz, C-P), 131.47 (d, *J* = 3.0 Hz, CH), 128.50 (d, J_{PC} = 11.9 Hz, CH), 126.46 (C), 123.08 (d, J_{PC} = 17.24, CH), 33.10 (CH), 24.20 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.62. ESI-MS (*m/z*) 396.1866 (M^{+H}).

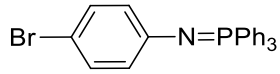


4-(Tert-butyl)*-N-*(triphenylphosphoranylidene)aniline-(121e), colourless solid, mp 168.0-169.9^{o}C (hexane/ethylacetate), yield 0.3097 g, 95%. IR (cm^{-1}).*v* = 1637 (m), 1578, 1187 (s), 824, 692 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 6H), 7.55 – 7.50 (m, 3H), 7.46 (m, 6H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.21 (d, *J* = 2.5 Hz), 139.79 (C), 132.68 (d, *J* = 9.5 Hz), 131.64 (d, *J* = 99.5 Hz), 131.48 (d, *J* = 2.8 Hz), 128.50 (d, *J* = 12.0 Hz), 125.38 (d, *J* = 1.3 Hz), 125.46 – 125.24 (m), 122.75 (d, *J* = 17.5 Hz), 33.81 (C), 31.63 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.39. ESI-MS (*m/z*) 410.2031 (M^{+H}).

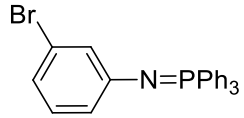


3-Ethynyl*-N-*(triphenylphosphoranylidene)aniline-(121f), brown solid, MP 101.4-103.5^{o}C (hexane/ ethylacetate), yield 0.4188 g, 99%. IR (cm^{-1}).*v* = 1578 (m), 1471

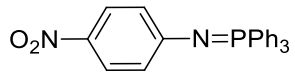
(m), 1404 (m), 1331 (s), 1300 (m), 1105 (s), 1042, 782, 690 (s) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 7H), 7.57 – 7.52 (m, 4H), 7.47 (td, *J* = 7.5, 3.0 Hz, 7H), 6.96 (s, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.0 Hz, 1H), 2.90 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.10 (C-N=P), 132.57 (d, J_{PC} = 9.6 Hz, CH), 131.70 (d, J_{PC} = 3.0 Hz), 130.96 (d, J_{PC} = 99.5 Hz, C-P), 128.60 (d, J_{PC} = 12.0 Hz, CH), 128.46 (CH), 127.07 (d, J_{PC} = 18.0 Hz, CH), 124.36 (d, J_{PC} = 16.5 Hz, CH), 121.97 (C), 121.35 (CH), 84.87 (C), 75.22 (CH). ^{31}P NMR (162 MHz, $CDCl_3$) δ 3.23. ESI-MS (*m/z*) 378.1401 (M^{+H}).



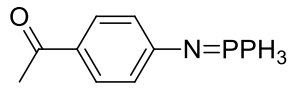
4-Bromo*-N-*(triphenylphosphoranylidene)aniline-(121g), colourless solid, MP 124.2-125.4^{o}C (hexane/ethylacetate), *(lit*[262] 126-127 ^{o}C), yield 0.4234 g, 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 6H), 7.54 (td, *J* = 7.5, 1.5 Hz, 3H), 7.46 (td, *J* = 7.5, J_{PC} = 3.0 Hz, 6H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.43 (d, J_{PC} = 2.0 Hz), 132.57 (d, J_{PC} = 9.5 Hz), 131.81 (d, *J* = 3.0 Hz), 131.34 (CH), 128.67 (d, J_{PC}= 12.0 Hz), 125.03 (d, *J* = 17.5 Hz), 109.42 (CBr). ^{31}P NMR (162 MHz, $CDCl_3$) δ 3.92. ESI-MS (*m/z*) 434.0516 ($M^{+H}{}_{Br}{}^{81}$) ESI-MS (*m/z*) 432.0511 ($M^{+H}{}_{Br}{}^{79}$). Know compound, matches spectra.[262]



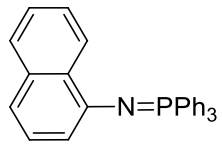
3-Bromo*-N-*(triphenylphosphoranylidene)aniline-(121h), yellow solid, MP 117.8-119.4^{o}C (hexane/ethylacetate) yield 0.4369 g, 97%. IR (cm^{-1}).*v* = 1577, (m), 1470 (m), 1437 (m), 1404 (m), 1331 (s), 1300, 1104 (s), 782, 690 (s, br). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (ddt, *J* = 12.2, 7.1, 1.4 Hz, 6H), 7.59 – 7.52 (m, 3H), 7.51 – 7.44 (m, 6H), 6.98 (t, *J* = 1.9 Hz, 1H), 6.84 (t, *J* = 7.9 Hz, 1H), 6.80 – 6.74 (m, 1H), 6.68 – 6.63 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.93 (C-N=P), 132.57 (d, J_{PC}= 9.5 Hz), 131.82 (d, J_{PC} = 3.0 Hz), 130.65 (d, J_{PC} = 99.5 Hz), 129.54, 128.67 (d, J_{PC} = 12.0 Hz), 126.43 (d, J_{PC} = 19.0 Hz), 122.40 (C), 121.76 (d, J_{PC} = 16.5 Hz, CH), 120.17 (CH).^{31}P NMR (162 MHz, $CDCl_3$) δ 3.79. ESI-MS (*m/z*) 434.0151 ($M^{+H}{}_{Br}{}^{81}$) 432.0516 ($M^{+H}{}_{Br}{}^{79}$)



4-Nitro-N-(triphenylphosphoranylidene)aniline-(121i), yellow solid, MP 161.6-162.9^{o}C (hexane/ethylacetate) yield, (*lit*[232] 156-158 ^{o}C) 0.3707 g, 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.78 – 7.72 (m, 6H), 7.63 – 7.58 (m, 3H), 7.51 (td, *J* = 7.5, 3.0 Hz, 6H), 6.69 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.87 (d, J_{PC} = 2.0 Hz, C-N=P), 138.15 (C), 132.50 (d, *J* = 10.0 Hz), 132.34 (d, *J* = 3.0 Hz), 129.79, 128.94 (d, J_{PC} = 12.5 Hz, CH), 125.43 (CH), 122.25 (d, *J* = 19.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.03. ESI-MS (m/z) 399.1256 (M^{+H}). Known compound, spectra matches.[262]

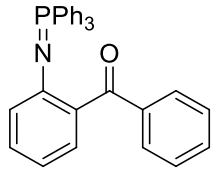


N-*(4-Acetylphenyl)triphenyliminophosphorane-(121j)*, yellow solid, MP 132.6-135.4^{o}C (hexane/ethylacetate), (*lit*[262]130-131 ^{o}C) yield 0.3496 g, 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.72 (m, 6H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.59 – 7.54 (m, 3H), 7.51 – 7.46 (m, 6H), 6.77 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.50 (C=O), 157.55 (C-N=P), 132.55 (d, J_{PC} = 10.0 Hz, CH), 132.02 (d, J_{PC} = 3.0 Hz), 130.13 (d, J_{PC} = 99.5 Hz, C-P), 129.92 (CH), 128.78 (d, J_{PC} = 12.0 Hz, CH), 122.62 (d, $J_{PC\,z}$= 18.5 Hz), 25.9. ^{31}P NMR (162 MHz, $CDCl_3$) δ 5.60. ESI-MS 396.1499 (M^{+H}). Known compound, spectra matches.[262]



N-(triphenylphosphoranylidene)naphthalen-1-amine-(121k), colourless solid, MP 105.3-109.2^{o}C (hexane/ethyl acetate), (*lit*[262] 112 ^{o}C), yield 0.2438 g, 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, *J* = 8.0d Hz, 1H), 7.91 – 7.84 (m, 6H), 7.73 (d, *J* = 7.5, 1H), 7.58 – 7.52 (m, 3H), 7.50 – 7.40 (m, 8H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 7.5) Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.99 (C-N=P), 135.07 (C), 132.65 (d, J_{PC} = 9.5 Hz, CH), 132.00 (d, J_{PC} = 22.7 Hz, C), 131.62 (d, *J* = 2.8 Hz), 131.29 (d, J_{PC} = 99.5 Hz, C-P), 128.57 (d, J_{PC} = 12.0 Hz, CH), 127.37 (CH), 126.19 (CH), 125.43 f(d, *J* = 7.1 Hz), 123.69, 116.70, 114.17 (d, *J* = 11.0 Hz). ^{31}P NMR

(162 MHz, $CDCl_3$) δ 2.91. ESI-MS (*m/z*) 404.1545 (M^{+H}), Known compound, spectra matches.[262]

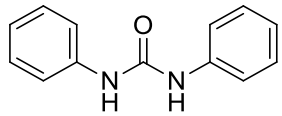


Phenyl(2-((triphenylphosphoranylidene)amino)phenyl)methanone (121l), yellow solid, MP 192.3-194.3°C (hexane/ethylacetate), yield 0.3352 g , 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (m, 2H), 7.54 – 7.28 (m, 20H), 7.02 (td, *J* = 7.5, 1.5 Hz, 1H), 6.75 (t, *J* = 7.0 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.58 (C=O), 149.95 (C-N=P), 139.25 (C), 135.00 (d, J_{PC} = 23.5 Hz, C), 132.40 (d, J_{PC} = 10.0 Hz, C), 131.57 (d, *J* = 16.4 Hz), 130.75 (d, J_{PC} = 100.5 Hz, C-P) 130.66 (CH), 129.98 (CH), 129.56 (d, J_{PC} = 2.5 Hz), 128.40 (d, *J* = 12.0 Hz, CH), 127.77, 121.83 (d, *J* = 10.4 Hz), 117.05 (CH). ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.35. ESI-MS (*m/z*) 458.1651 (M^{+H}). Known compound, spectra matches.[271]

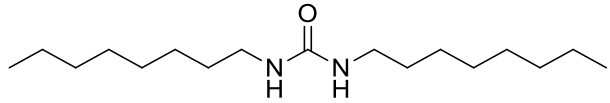
General method for the synthesis of Ureas.

To a well stirred solution of I_2 (1.1 equiv.) PPh_3 (1.1 equiv.), DMAP (2.5 equiv.) in 20 ml of anhydrous CH_2Cl_2 was added the amine (1 equiv.) in 1 ml of anhydrous CH_2Cl_2. The solution was stirred at room temperature until complete consumption of the starting amine was observed by TLC (10-120 mins). Once complete CO_2 gas was bubbled through the solution and the secondary amine (1.5 equiv.) in 1 ml of CH_2Cl_2 was added. CO_2 was bubbled through the reaction mixture for 10 minutes and then the reaction mixture was put under positive pressure of CO_2. Once the reaction had gone to completion (3-5h), the reaction mixture was diluted with CH_2Cl_2 and washed with 2x 15 ml 1M $Na_2S_2O_3$ (aq), 3x 15 ml 1M HCl (aq) and dried via passing through phase separator column. The organic layer was then concentrated and purified via flash column chromatography on silica 5-30% EtOAc in CH_2Cl_2.

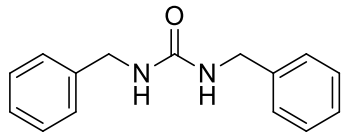
Characterisation of Urea Products



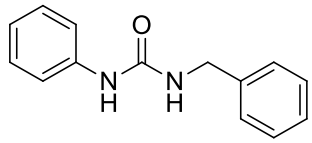
1,3 Diphenylurea (150a), colourless solid, mp 235.3-237.8 ^{o}C, (*lit*[272] 235-239 ^{o}C) yield 0.074 g, 41%. ^{1}H NMR (500 MHz, CD_3OD) δ 8.60 (s, 2NH) 7.41 (d, *J* = 8.0 Hz, 4H), 7.28 (t, *J* = 8.0 Hz, 4H), 7.01 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 154.05 (CO), 139.06 (C-N), 128.42 (CH), 122.45 (CH), 119.05 (CH). ESI-MS 235.0838 (M^{+Na}). Known compound, spectra matches.[272]



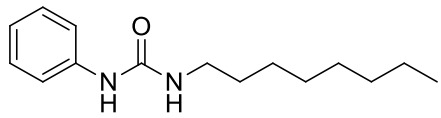
1,3-Dioctylurea (150b), colourless solid, MP 89.9-91.3^{o}C, (*lit*[273] 89-90 ^{o}C) yield 0.200 g, 74%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (s, 2NH), 3.15 (q, *J* = 7.0 Hz, 4H), 1.49 (p, *J* = 7.0 Hz, 4H), 1.29 (m, 24H), 0.88 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.22 (CO), 40.69 (CH_2), 31.76 (CH_2), 30.23 (CH_2), 29.27 (CH_2), 29.18 (CH_2), 26.88 (CH_2), 22.58 CH_2), 14.00 (CH_3). ESI-MS 285.2895 (M^{+H}). Known compound, spectra matches.[273]



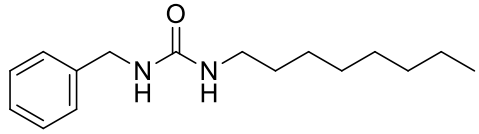
1,3-Dibenzylurea (150c), colourless solid, mp 171.3-172 ^{o}C, (*lit*[273] 170-171 ^{o}C), yield 0.231 g, 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 10H), 4.70 (s, 2NH), 4.37 (d, *J* = 5.8 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.86 (CO), 139.02 (C), 128.62 (CH), 127.42 (CH), 127.33 (CH), 44.68 (CH_2). ESI-MS (*m/z*) 263.1151 (M^{+Na}). Known compound, spectra matches.[273]



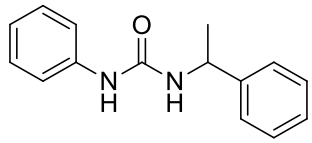
1-Phenyl-3-benzylurea (150d), white solid, mp 170.6-172.6^{o}C, (*lit*[274] 173-174 ^{o}C) yield 0.197 g, 75%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1NH), 7.40 – 7.18 (m, 9H), 6.91 – 6.84 (m, 1H), 6.56 (t, *J* = 6.0 Hz, 1H), 4.28 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.14 (CO), 140.38 (C_{ar}), 140.26 (C_{ar}), 128.55 (C_{ar}), 128.21 (C_{ar}), 127.04 (C_{ar}), 126.63 (C_{ar}), 121.01 (C_{ar}), 117.64 (C_{ar}), 42.69 (CH_2). ESI-MS 249.0994 (M^{+Na}). Known compound, spectra matches.[275]



1-Phenyl-3-octylurea (150e), colourless solid, mp 75.8-77.3 ^{o}C, (*lit*[276] 72-74 ^{o}C) yield 0.200 g, 77%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (s, NH), 7.35 (d, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 2H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.05 (t, *J* = 5.5 Hz, NH), 3.04 (q, *J* = 7.0 Hz, 2H), 1.44 – 1.36 (m, 2H), 1.25 (s, 10H), 0.88 – 0.82 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.62 (C=O), 141.05 (C_{ar}), 129.01 (C_{ar}), 121.29 (C_{ar}), 118.00 (C_{ar}), 31.68 (CH_2), 30.20 (CH_2), 29.13 (CH_2), 26.83 (CH_2), 22.51 (CH_2), 14.37 (CH_3). ESI-MS (*m/z*) 271.1779 (M^{+Na}). Known compound, spectra matches.[247]



1-Benzyl-3-octylurea (150f), colourless solid, mp 86.7-88.0^{o}C, yields 0.289 g, 88%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31 – 7.16 (m, 5H), 6.21 (t, *J* = 6.0 Hz, 1NH), 5.84 (t, *J* = 5.5 Hz, 1NH), 4.17 (d, *J* = 6.0 Hz, 2H), 2.97 (q, *J*= 6.5, 2H), 1.33 (m, 2H), 1.23 (s, 10H), 0.84 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.49 (C=O), 141.48 (C), 128.58 (CH), 127.41 (CH), 126.91 (CH), 43.35 (CH_2), 31.67 (CH_2), 30.47 (CH_2), 29.20 (CH_2), 29.13 (CH_2), 26.82 (CH_2), 22.52 (CH_2), 14.37 (CH_3). EI-MS (*m/z*) 263 (M^{+Na}). Known compound, spectra matches.[247]



1-Phenyl-3-(1-phenylethyl)urea (150g), cream solid, yield 0.201 g, 79%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 (s, NH), 7.36 – 7.31 (m, 5H), 7.23 – 7.16 (m, 3H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 8.O Hz, 1H), 4.80 (p, *J* = 7.0 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.82 (C=O), 145.62 (C), 140.82 (C), 129.07 (CH), 128.75 (CH), 127.07 (CH), 126.25 (CH), 121.49 (CH), 118.00 (C), 49.02 (CH), 23.49 (CH_3). ESI-MS (*m/z*) 263.1158. (M^{+Na}). Known compound, spectra matches.[247]

5 Conclusions and Future Work

5.1 Conclusion

This thesis has covered the development and application of a new three component of PPh_3, I_2 and 4-DMAP. The initial aim of this thesis was to develop a new and efficient acylation method and this work is detailed in chapter 2. The method developed is a continuation of previously published method Robles method and involves the replacement of imidazole with 4-DMAP. This simple change offered comparably high yields, especially for the formation with significantly improved reaction times compared to other commonly used esterification methods. Amines where also formed in relatively high yields again with short reaction times. The formation and subsequent isolation of acyl pyridinium salt intermediates, as well as NMR spectroscopic studies lead to the conclusion that the reaction had two distinct stages. This finding then led to the development of a system that was catalytic in 4-DMAP whilst in the presence of the auxiliary base NEt_3. Both the short reaction times and high yields where retained with this catalytic method.

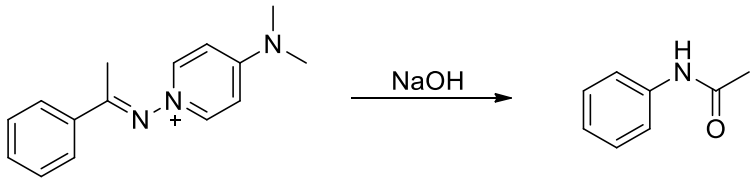
Chapter 3 describes the application of the PPh_3/I_2/4DMAP reagent system to the synthesis of 1,2-benzisoxazoles from 2 hydroxybenz aldoximes. The method again proved to be efficient reaction, resulting in high yields and short reaction times especially when electron donating groups where para to the hydroxy group on the ring system. However, the reagent system proved to provided inconclusive results when applied to the cyclisation of 2-hydroxyketoxime. Further investigation into the difference in reactivity of ketone derived oximes led to the formation of novel and interesting *N*-pyridinium functionalised imines. These novel imines are remarkable stable and be stored for long periods. They also show further reactivity when in the presence of a hard nucleophile such as sodium methoxide resulting in a Beckman like rearrangement to produce imidates. When the reagent system is applied to aldehyde derived oximes a 1,2 hydride shift resulted to produce benzonitrile.

The final application of the PPh_3/I_2/4-DAMP system was to affect a variant of the Kirsanov reaction which is a method used for the synthesis of phosphazenes. The regent system proved to be extremely effective producing high yields again in substantially

shorter reaction times then other commonly used methods such as the Staudinger reaction. As a method for the formation of simple phosphazenes this method is even more successful than the more commonly used Staudinger reaction. Not only are much shorter reaction times are required compared to the Staudinger reaction, the method also avoids the use of potentially explosive azides. The method was also incorporated into a one pot system for the synthesis of ureas under mild conditions which resulting in moderate to good yields relatively short reaction times. Although yields are not as impressive as other one pot urea examples, the mild reactions it does offer a viable alternative to conditions that are forcing

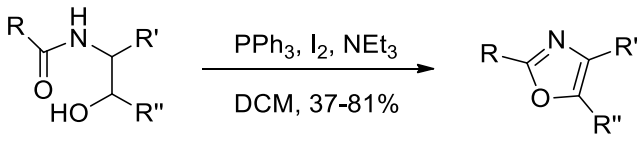
5.2 Future Work

This thesis has led to a number to a number of areas were further work can be done. The work conducted in Chapter 3 requires further investigation the unprecedented chemistry of DMAP in the formation of DMAP-hydrazones. Only two example of these DMAP hydrazone where synthesised and therefore a wider scope of would be useful in order to determine the effect both electron rich and electron poor examples. Also the reaction with various other nucleophiles would be interesting. Reactions with hydroxide anion would possible lead to the formation of amides.



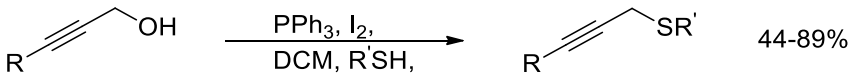
Scheme 5.1: reaction of DMAP-hydrazone with NaOH to from amides.

PPH_3-I_2-NEt_3 system has previously been applied to the synthesis of oxazoles in a cyclodehydration of β hydroxy amides.[277] We have demonstrated that the PPh_3-I_2-DMAP rapidly increases the rates of similar reactions, so it goes to reason that the system could increase the rate of such a dehydration process.



Scheme 5.2: Cyclodehydration β hydroxy amides to oxazoles.[277]

There are also a number of other PPh_3-I_2-imdazole mediated reactions in which the PPh_3-I_2-DMAP reagent system could be applied too. Common uses of such system included the conversion of primary alcohols to various nucleophiles via the *in-situ* generation of alkly and vinyl iodides. Such method was used in the preparation of novel propargylic aryl and heteroaryl sulfides and sulfones.[278]



Scheme 0.1: PPh_3-I_2-DMAP mediated reparation of Novel Propargylic Aryl and Heteroaryl Sulfides and Sulfones.[278]

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