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Acyl Phosphates from Low Oxidation State Phosphorus for the Synthesis of Amides, Ketones and Heterocycles

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Abstract

Chapter I described the use of diethyl phosphite to activate carboxylic acids *via* acyl phosphate formation, using an aerobic copper-catalysed system. The acyl phosphates were used to synthesise a variety of amides in good yields (35-78 %), using 10 mol % catalyst. Simple methods of purification such as precipitating the amide from the reaction mixture produced amides in high purity. Initial insight into a potential mechanism suggests the reaction proceeds *via* the copper (II) oxidation state and that the halide counter anion can participate in the reaction.

Chapter II further explored other nucleophilic additions to acyl phosphates by reacting with Grignard reagents to generate ketones. Acyl phosphates were generated in good to excellent yields (48 to 88 %) from carboxylic acids and triethyl phosphite in the presence of iodine (Arbuzov-type reaction). Reacting Grignard reagents with acyl phosphates produced almost exclusively ketone at low temperature, with good to excellent isolated yields (68-90 %). ReactIR showed that acyl phosphates are 60-70 times more reactive towards Grignard reagents than acid chlorides, therefore, selectivity towards ketone formation was achieved by short reaction times and performing the reaction at low temperature.

In chapter III acyl phosphates were reacted with esters to give β-ketoesters (23-73 %). The Arbuzov-type reaction used to generate the acyl phosphates was telescoped allowing the β-ketoesters to be prepared from the carboxylic acid without isolation of the acyl phosphate. In some cases, the telescoped reaction was higher yielding than when the pure acyl phosphate was used. Some of the prepared β-ketoesters were subsequently converted to the corresponding 5-membered heterocycles by condensing with hydroxyl amine or hydrazine.

Accessing heterocycles from 1,3-dicarbonyls is not the only method for available, the final part of this thesis applied the 1,3-dipolar cycloaddition reaction to diazophosphonates and alkynes to give N-P pyrazoles *via* a [1,5]-sigmatropic shift of the phosphonate group. The N-P pyrazoles were subsequently hydrolysed to N-H pyrazoles (16-83 %).

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Abbreviations

Abbreviation	Name
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
CDI	1'-Carbonyldiimidazole
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*'-Dicyclohexylcarbodiimide
DCDMH	1,3-Dichloro-5,5-dimethylhydantoin
DCM	Dichloromethane
DECP	Diethyl chlorophosphate
DEPC	Diethyl phosphoryl cyanide
DIC	*N,N*'-Diisopropylcarbodiimide
DIPEA	*N,N*-Diisopropylethylamine
DPPA	Diphenylphosphoryl azide
DMC	Dimethylcarbonate
DMSO	Dimethyl sulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HATU	1-[Bis(dimethylamino)methylene]-*1H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate
HBTU	3-[Bis(dimethylamino)methyliumyl]-3*H*-benzotriazol-1-oxide hexafluorophosphate
HMDS	Hexamethyldisilazide
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
T3P	Tripropyl phosphonic anhydride
TAME	*Tert*-Amylmethyl ether
TCCA	1,3,5-Trichloroisocyanuric acid
TEPP	Tetraethyl pyrophosphate

Chapter I- Copper-Catalysed Synthesis of Amides

1.1. Phosphorus Chemistry and the advantages of dialkyl phosphites

Organophosphorus compounds are important within today's chemical industry, they are used in materials (flame retardants), medicinal chemistry (anti-cancer and HIV) and agriculture (insecticides) to name just a few examples.[1–6] Organophosphorus reagents are also very useful at promoting chemical reactions, for example, phosphines are effective ligands in metal catalysis.[7,8]

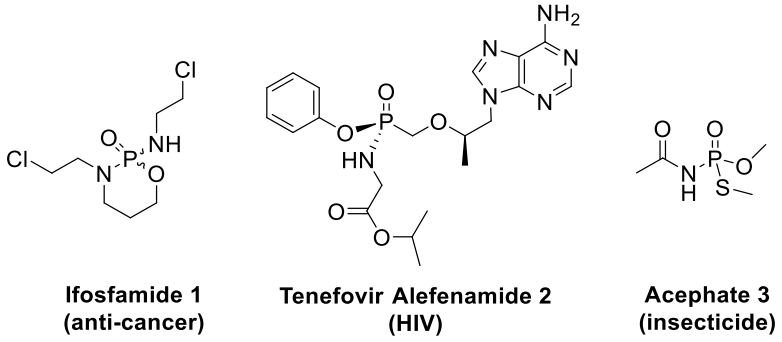


Fig 1. *Commercial phosphorus containing compounds; A) Ifosfamide **1** (anti-cancer),[9] B) Tenefovir Alefenamide **2** (HIV),[2] C) Acephate **3** (insecticide).[10]*

Organophosphorus reagents also play a pivotal role in the activation of organic molecules, with one important example being the activation of carboxylic acids for amide formation. One of the main advantages of using phosphorus-based coupling (activating) reagents in amide formation is due to the formation of water-soluble by-products, that can easily be removed by aqueous washing.

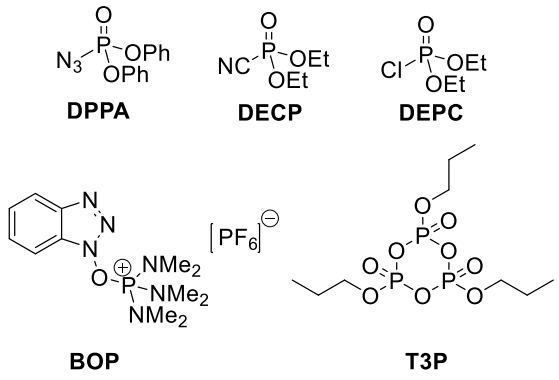


Fig 2. *Common P(V) coupling reagents.*

Phosphorus(V) containing compounds are commonly accessed from halogenated phosphorus reagents, such as, PCl_5, $P(O)Cl_3$ or the oxidation of PCl_3. These

compounds are highly toxic and moisture sensitive. Similarly, phosphorus(V) coupling reagents (such as; DEPC, DECP and DPPA (Fig 2.)) are also toxic and moisture sensitive.

Dialkyl phosphites(III) $(RO)_2P(O)H$ are relatively non-toxic, low molecular weight and odourless. Therefore, dialkyl phosphites are a promising alternative to the toxic phosphorus P(V) coupling reagents (DECP, DEPC, DPPA) and high molecular weight reagents (BOP and T3P) shown in Fig 2.

In addition, dialkyl phosphites can be synthesised from phosphinates. Phosphinates are produced on an industrial scale from the alkaline hydrolysis of P_4 (Fig 3).[1] Producing phosphorus compounds from alkaline hydrolysis is advantageous over using chlorine gas because it is safer and less energy intensive. However, it should be noted that most organophosphorus compounds are still produced from PCl_3 (Fig 3, red) but the 'phosphinate pathway' (Fig 3, green) provides a safer alternative.

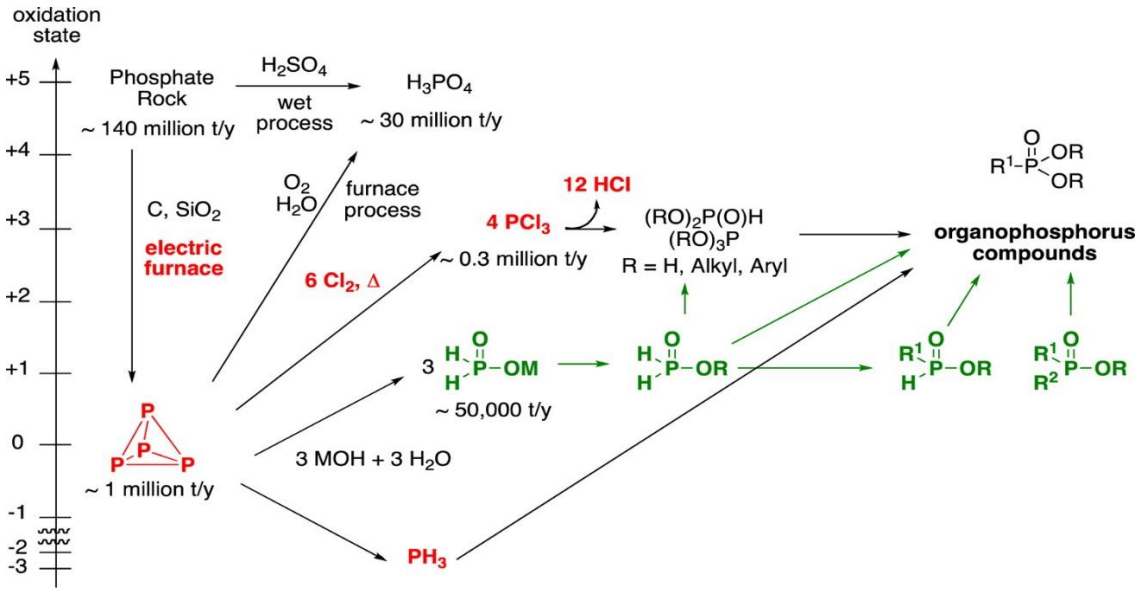


Fig 3. *Overview of industrial phosphorus chemistry.*[1]

1.2. Methods towards phosphorus-heteroatom bond formation from P(O)H compounds

1.2.1. Dialkyl phosphites and P(O)H compounds

In order to synthesise phosphorus-heteroatom bonds from dialkyl phosphites (*H*-phosphonates), the dialkyl phosphite first needs to be oxidised. Contained within this report are different *in situ* oxidations that have been used to couple P(O)H compounds with nucleophiles.

The nucleophilic reactivity of dialkyl phosphites can be explained with the aid of the figure below (Fig 4.). The proton can tautomerise between the phosphonylidine P(O)-H and phosphite form P(OH). The same tautomerisation is known to occur with *H*-phosphinates and secondary phosphine oxides.[11]

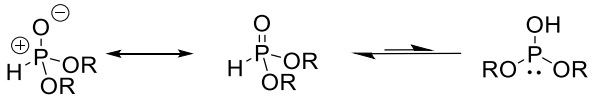
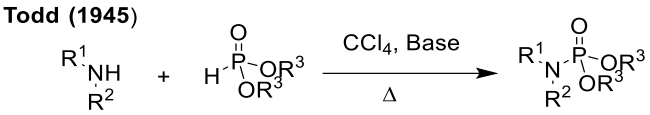


Fig 4. *Tautomeric equilibrium that exists between the phosphonylidine and phosphite form.*

1.2.2. Stoichiometric oxidative couplings from P(O)H compounds

One of the earliest *in situ* oxidation of dialkyl phosphites is the Atherton-Todd reaction developed in 1945 (Scheme 1).[12] This oxidation uses highly toxic carbon tetrachloride as a stoichiometric chemical oxidant to form chlorophosphate (V).[13] The Atherton-Todd reaction has since been applied to produce a variety of substituted P(O)X compounds (X: amine, alcohol, thiol etc…).[14,15]

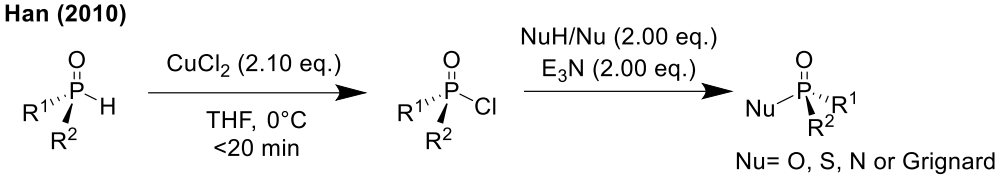


Scheme 1. *The Atherton-Todd reaction phosphoramidates.*

In addition to the Atherton-Todd reaction, a variety of other methods that require the use of stoichiometric halogenating agents to produce dialkyl halophosphates have been reported. Around the same time that the Atherton-Todd reaction was developed, Saunders reported using Cl_2 to produce diethyl chlorophosphite from dialkyl phosphites. Todd reported using sulfuryl chloride in 1948, to produce diethyl chlorophosphite from dialkyl phosphites. In 1955, Saunders showed *N*-

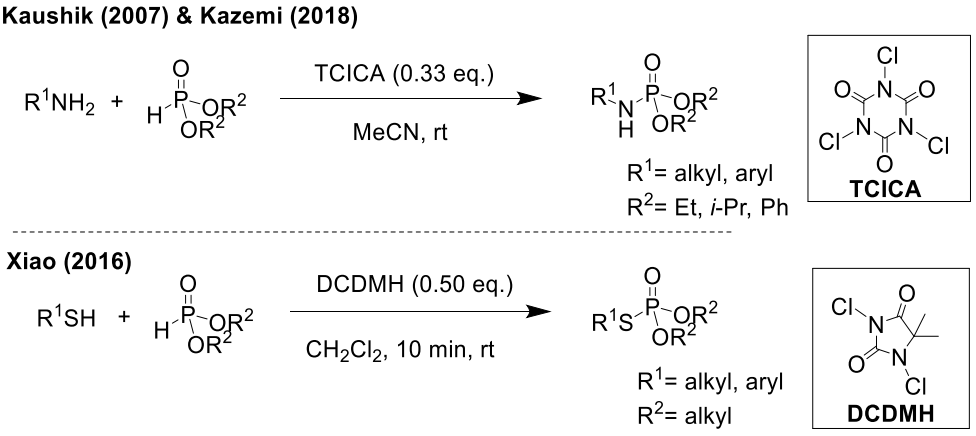
chlorosuccinimide and *N*-bromosuccinimide could produce the corresponding halophosphate from dialkyl phosphites.

In 1962, stoichiometric $CuCl_2$ was used to produce dialkyl chlorophosphates.[16] Han *et al*. recently applied this method to the synthesis of P-C, P-S, P-O and P-N bonds, producing a variety of P-stereogenic compounds.[14,17]



Scheme 2. *Halogenation of P(O)H compounds and stereospecific nucleophilic substitution.*[17]

The use of chlorinating reagents such as trichloroisocyanuric acid (TCICA) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) have proven to be effective at coupling nucleophiles to dialkyl phosphites.[18,19,20] Using N-X (X=halogen) reagents as halogen surrogates is advantageous compared to using halogenating reagents, such as, chlorine gas and tetrachloromethane because they are safer to handle. In 2007, Kaushik first used TCICA to generate phosphoramidates and phosphates in the presence of base.[18] More recently (2018), Kazemi used the same method to synthesise phosphoramidates under base free conditions.



Scheme 3. *The use of N-X compounds to couple oxygen, nitrogen or sulphur nucleophiles to dialkyl phosphites.*

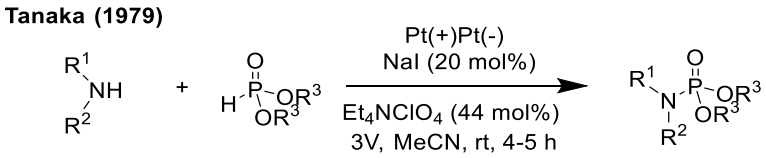
Despite the efficiency and selectivity of these reactions, using stoichiometric halogenating reagents is not the most effective method of using atoms in the reaction (in terms of mass input). This is because at least one molar equivalent of

halogenating reagent is required per substitution reaction. By principle, using sub-stoichiometric reagents (such as, catalysts) should provide a cleaner more atom economic approach for the oxidative coupling of dialkyl phosphites.

1.2.3. Sub-stoichiometric oxidative couplings from P(O)H compounds

In 1979, Tanaka *et al*. utilised the electrochemical generation of halogens from the equivalent halide salts to produce both P-S and P-N bonds.[21,22] The reported synthesis is efficient and uses sub-stoichiometric amounts of halide salts. The authors also coupled diphenyl phosphite to benzyldisulphide achieving 68% yield. Diaryl phoshites are notably more difficult substrates (compared to dialkyl phosphites) as they can degrade to produce triaryl phosphites under basic conditions.[23] Perhaps this degradation pathway is the reason there are very few successful oxidative cross-dehydrogenative couplings that use diaryl phosphites.

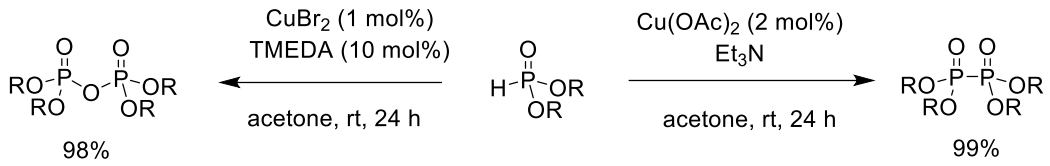
The electrochemical method is limited by the use of platinum (rare metal) as the electrode, however, the platinum electrode can easily be recycled by simply cleaning and polishing the electrode surface.



Scheme 4. *Electrochemical route towards phosphoramidate formation.[22]*

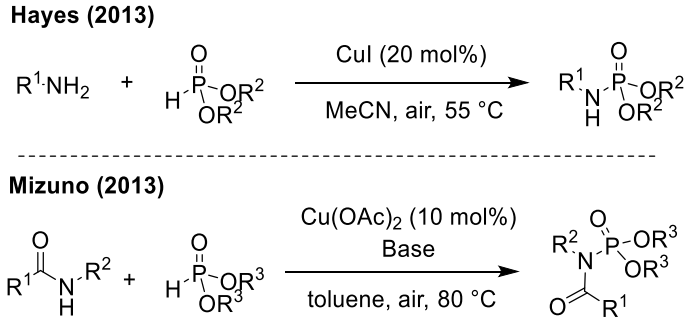
The use of first row transition metal catalysts is an attractive concept for coupling dialkyl phosphites to heteroatoms, due to their natural abundance and catalytic ability.

In 2010, Han reported a copper catalysed aerobic oxidation that selectively produced hypophosphate and pyrophosphate dimers. Using copper acetate and Et_3N selectively produced hypophosphate. Whereas, using $CuBr_2$ or any copper halide produced pyrophosphate. Adjusting the base/ligand to TMEDA enabled complete selectivity to pyrophosphate (Scheme 5.).[24] Han found that Et_3N favoured hypophosphates, whereas TMEDA favoured pyrophosphates.



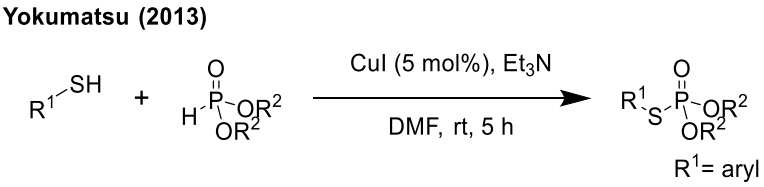
Scheme 5. *Selective P-P and P-O-P dimerisations reported by Han.*

Both Hayes and Mizuno independently developed copper catalysed methods for coupling nitrogen compounds with dialkyl phosphites (Scheme 6.).[25,26] Hayes published an approach for coupling a variety of primary and secondary amines to produce phosphoramidates. The conditions developed by Mizuno were applied to the synthesis of *N*-acyl phosphoramidates. Interestingly, Hayes *et al.* showed that CuI was the most efficient catalyst for coupling amines to dialkyl phosphites, whereas Mizuno found that $Cu(OAc)_2$ was the most efficient catalyst for coupling amides to dialkyl phosphites.



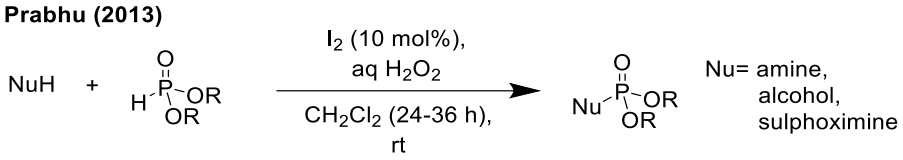
Scheme 6. *Copper catalysed synthesis of phosphoramidates and N-acylphosphoramidates.*[25,26]

Yokomatsu reported using a copper catalysed approach to the synthesis of thiophosphates (Scheme 7.). The authors attempted to use diphenyl phosphite to produce the desired diphenyl thiophosphate, however, no desired product was isolated. The authors did report the formation of diphenyl pyrophosphate, when 4-fluorobenzothiol was used as a substrate, suggesting that diphenyl phosphites are still prone to oxidation.[27]



Scheme 7. *Copper catalysed thiophosphate synthesis.*[27]

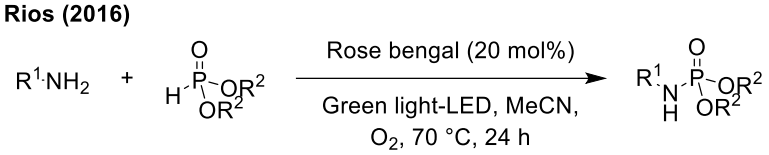
The use of catalytic iodine in the presence of peroxide has also been reported as a transition metal free approach to coupling amines, alcohols and sulphoximines to dialkyl phosphites (Scheme 9.).[28] This reaction is limited by excessive use of potentially explosive peroxides. The authors suggest the *in-situ* generation of hypoiodous acid (HOI) serves as the active oxidant.



Scheme 9. *Iodine mediated cross-dehydogenative coupling between nucleophiles and dialkyl phosphites.[28]*

Photochemical and electrochemical oxidations are widely considered to be 'greener' alternatives compared to transition metal and stoichiometric oxidations.[29,30] This is because both methods avoid the use of potentially hazardous oxidants, either by utilising air (oxygen) or an electrode surface the terminal oxidant. Therefore, more recent publications have revisited the electrochemical method or developed photo-redox catalysed procedures.

Rios reported that organic dyes can produce phosphoramidates from amines by using air (oxygen) as the terminal oxidant and light to promote the reaction (Scheme 10.).

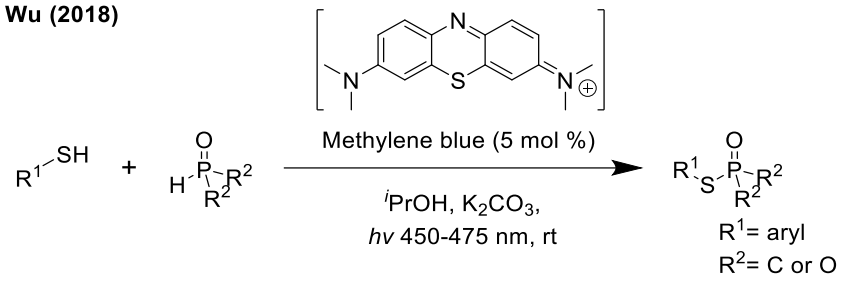


Scheme 10. *Photo-redox approach to phosphoramidates.[31]*

The authors consider this reaction (Scheme 10) to be clean, specifically promoting the fact that no chromatography was used.[31] However, it was evident that the authors failed to remove the dye from the final compounds. This was easily recognised because the phosphoramidates were red/black in colour even though these compounds are usually colourless/brown oils. Some of the carbon NMR data presented also omitted the aromatic regions where you would expect to see signals corresponding to Rose Bengal (the catalyst used in the synthesis).

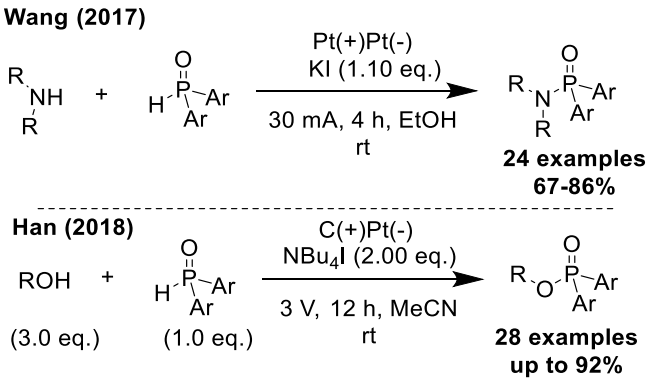
However, the reaction itself does appear to be selective as no dimeric phosphorus species were reported. The reaction is not very efficient as heating to 70 °C was required and the reaction takes 1-2 days.[31]

Wu *et al*. used methylene blue as the photocatalyst consequently overcoming the water solubility issue that presides when using Rose Bengal. This method was applied to the synthesis of thiophosphate and thiophosphine oxides (Scheme 11.).[32]



Scheme 11. *Photo-redox catalysed synthesis of thiophosphates using methylene blue.*[32]

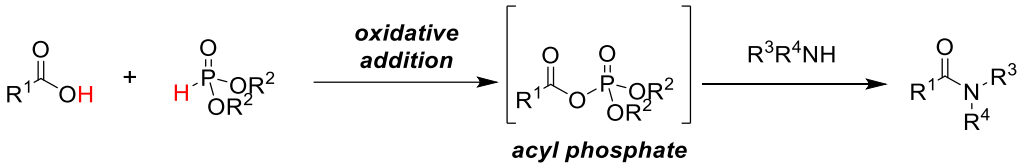
Recently, Wang and Han utilised electrochemistry to couple secondary phosphine oxides as coupling partners to secondary amines and primary alcohols.[33,34] Both methods avoid the use of additional supporting electrolytes such as perchlorates by using the iodide source as the both electrolyte and mediator. This does mean that more halide source is required to maintain current. Wang reported unsuccessful attempts using benzylic amines, postulating that this may be a result of other oxidation reactions occurring. However, Tanaka (1979) reported a successful coupling with benzylamine and diethylphosphite (Scheme 12.).[22,33]



Scheme 12. *Electrochemical methods for the synthesis of phosphinic amides (above) and phosphine oxides (below).*[33,34]

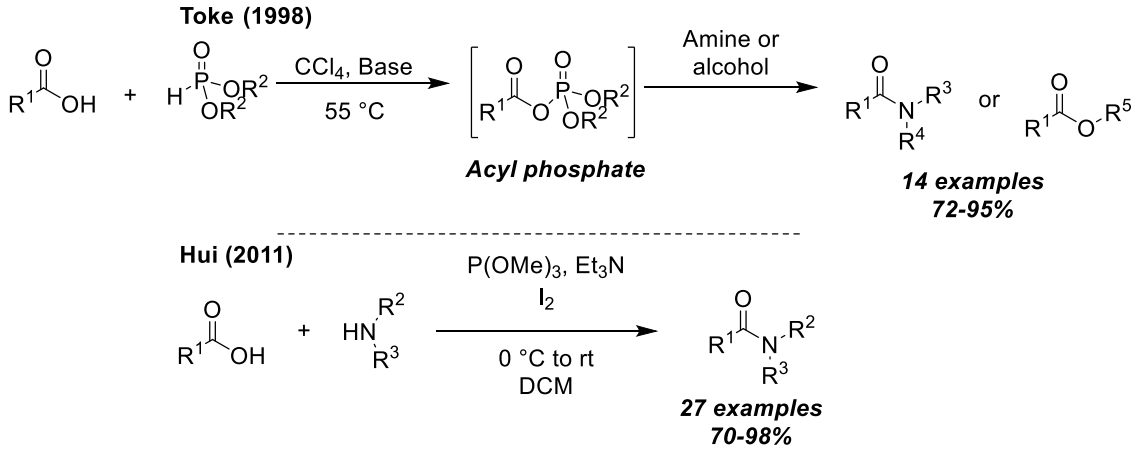
1.3. Synthesis of acyl phosphates from P(III) compounds

As previously explained (Section 1.1.), common P(V) coupling reagents are disadvantageous due to issues with toxicity and moisture sensitivity. Using safer P(III) compounds, such as dialkyl phosphites, is a potential solution to this problem. The dehydrogenative coupling of carboxylic acids with dialkyl phosphites will produce acyl phosphates (activated carboxylic acids). The most common use of coupling reagents is amide bond formation, therefore, this will be the initial focus of this work.[35]



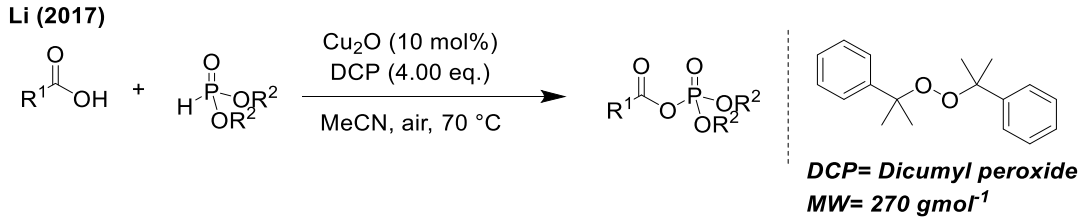
Scheme 13*. Proposed synthesis of acyl phosphates from dialkyl phosphites and subsequent nucleophilic attack to generate amides.*

The current literature precedent for synthesising acyl phosphates from P(III) compounds is described from hereon. In 1998, Toke utilised the Atherton-Todd reaction for the synthesis of esters and amides (Scheme 14.).[36] In addition, the Arbuzov reaction (using molecular iodine as the electrophile) has been applied to the synthesis of amides both methods reported excellent yields.[37,38,39] However, trimethyl phosphite is disadvantageous compared to dialkyl phosphites because it is a stench compound and can only be produced from PCl_3.



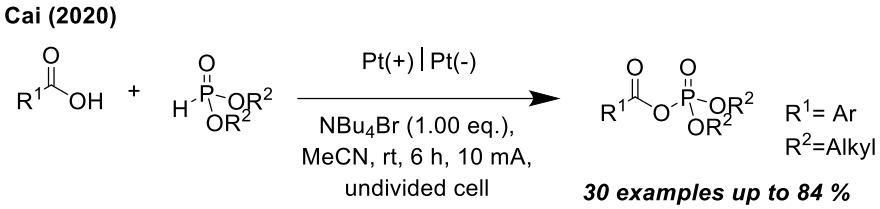
Scheme 15. *Stoichiometric approaches to acyl phosphate intermediates to produce esters and amides.*

The literature precedent for the synthesis of acyl phosphates from P(III) reagents was limited to Arbuzov-type chemistry and the Atherton-Todd reaction until recently, when Li reported a copper catalysed approach from dialkyl phosphites and carboxylic acids (Scheme 16). The authors managed to isolate these species in moderate to good yields but reported no further studies with the isolated acyl phosphates. The described procedure is limited by an excess of external oxidant (4 equivalents of dicumyl peroxide) and long reaction times.[40]



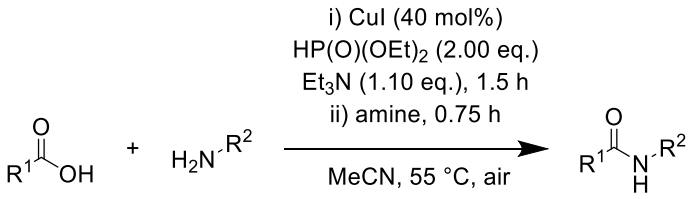
Scheme 16. *Generation of acyl phosphates through a copper catalysed oxidative addition reaction.*[40]

More recently, electrochemistry was applied to the synthesis of acyl phosphates. The reaction proceeds at room temperature under galvanostatic conditions, whereby NBu_4Br is used as the electrolyte. Essentially the reaction proceeds *via* the oxidation of bromide at the anode. This route was applicable to dialkyl phosphites but did not work with diphenyl phosphite. In addition, only aromatic acids were reported. The product acyl phosphates were also reactive with primary and secondary amines over two steps, without the addition of base (Scheme 17).[41]



Scheme 17. *Electrochemical route to acyl phosphates.*[41]

In 2013, J. Fraser and C. J. Hayes were investigating a copper-catalysed approach to phosphoramidates; during optimisation carboxylic acid containing catalysts such as CuTc and $Cu(OAc)_2$ resulted in the formation of amides from the carboxylate ligands. It was found that these amides were formed from acyl phosphate intermediates. Ensuing this investigation a set of conditions were developed that produced amides from carboxylic acids in the presence of a copper-catalyst (Scheme 18).[42] The use of copper as a catalyst, in this instance, has a significant advantage over the previously reported copper-catalysed route by Li (Scheme 16) because the reaction proceeds by using oxygen from the air as the terminal oxidant rather than stoichiometric chemical oxidants.[40] In addition, no specialist equipment is required, as is required for electrochemical methods.[41]



Scheme 18. *Initial results from Hayes et al. for copper catalysed carboxylic acid activation.*[42]

The initial results show good substrate scope (31 examples) with moderate to excellent yields (up to 80 %), however, the current procedure is limited by high catalyst loadings (40 mol %).

1.4. Carboxylic acids for amide formation

1.4.1. Stoichiometric coupling reagents

The first area of study in this thesis uses diethyl phosphite as a coupling reagent for amide formation. Herein, is a summary of commonly used carboxylic acid coupling reagents.

The majority of amides are currently synthesised from the condensation reaction between a carboxylic acid and an amine. A recent study by Sheppard evaluated ~450,000 amide formation reactions reported in Reaxys (2017-2018). The coupling reagents shown below (Fig 4) accounted for around 65 % of all amide formations within this period. The most common solvents used were DCM and DMF, both have obvious environmental and health concerns associated.[35]

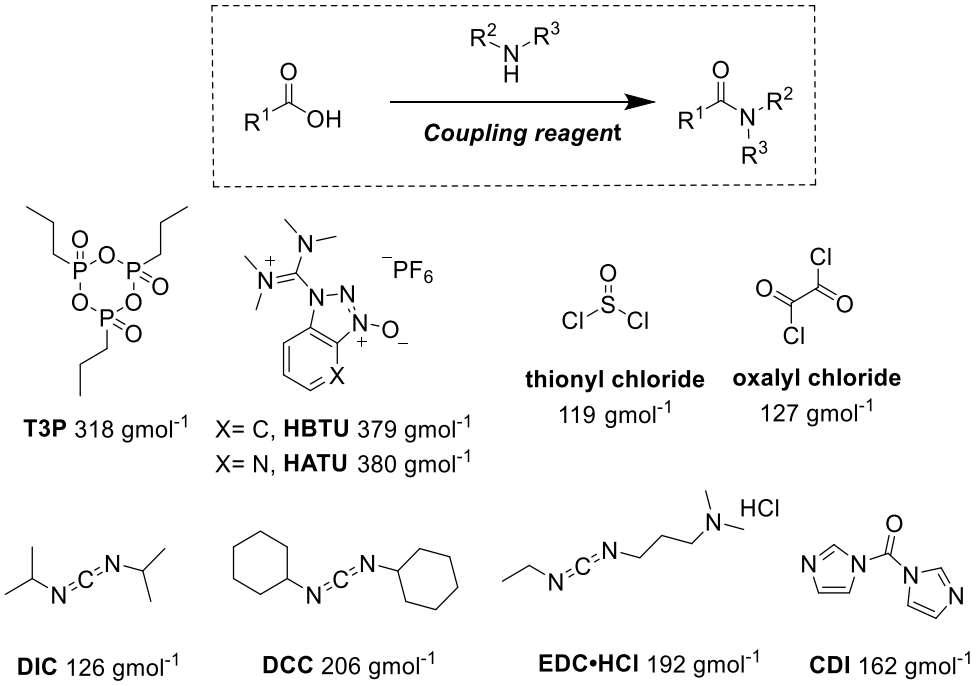


Fig 4. *Commonly used coupling reagents and molecular weight.*[35]

For efficient couplings, lower molecular weight coupling reagents produce less waste than high molecular weight coupling reagents, such as, HATU (379 $gmol^{-1}$ or T3P (318 $gmol^{-1}$). However, despite their low molecular weight acylating reagents such as, thionyl chloride (119 $gmol^{-1}$ or oxalyl chloride (127 $gmol^{-1}$), suffer from toxicity and moisture sensitivity. In addition, the product amides may not be resistant to epimerisation. HATU and HBTU on the other hand, are effective reagents at suppressing epimerisation. T3P in the presence of pyridine is also known to suppress epimerisation.[43]

Carbodiimides, such as, DCC (206 $gmol^{-1}$) and DIC (126 $gmol^{-1}$) are of relatively low molecular weight compared to T3P (318 $gmol^{-1}$), however, using carbodiimides results in urea as a by-product that can be difficult to remove.

Phosphorus containing coupling reagents, such as T3P possess a significant advantage here due to the formation of water soluble by-products.[44]

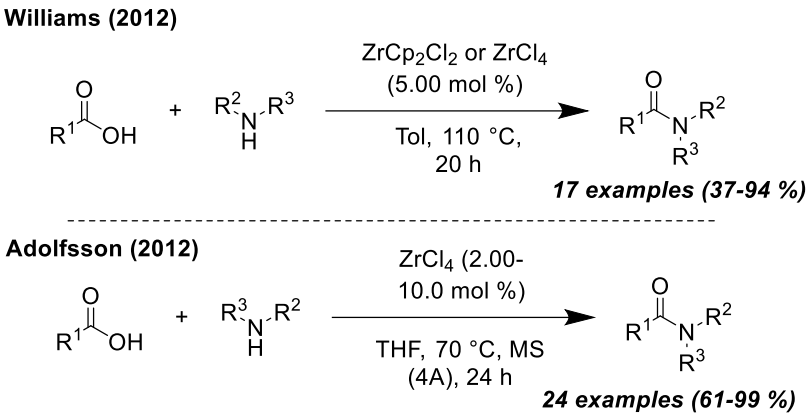
EDC-HCl was developed to ease the removal of the urea by-product by incorporating a tertiary amide into the structure, so that the urea can be removed *via* acidic work up. Although EDC-HCl has a significant advantage over its carbodiimide counterparts its advantages are restricted, because it is commonly used with HOBt or Oxyma which cannot be removed by aqueous work up. In addition, HOBt and Oxyma possess potential safety concerns, HOBt is explosive whereas Oxyma can react with carbodiimides to produce hydrogen cyanide under mild conditions.[45]

1.4.2. Recent advances in catalytic amide formation - group (IV) metals

In 2007, the ACS pharmaceutical round table published a list of key research areas. One area that required improvement was amide formation and the need to avoid using poor atom economy reagents.[46] The direct thermal coupling of carboxylic acids would be the most atom economic method. However, this approach has found very little synthetic utility due to the very high temperatures (>180 °C) required to overcome ammonium carboxylate salt formation.[47]

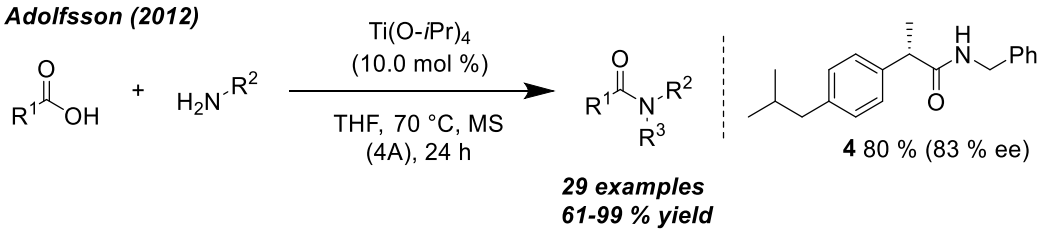
To answer the call by the pharmaceutical round table, a number of research groups have focused their efforts on catalytic amide formation. Group IV metals (Zr and Ti) have been the most successful metals at lowering the energy requirements associated with the direct condensation of carboxylic acids and amines.[35]

Williams and Adolfsson independently investigated [Zr] catalysts for amide formation (Scheme 19).[47,48] Williams found the reaction to proceed at 110 °C but the reaction was more sluggish when anilines were used.[47] Adolfsson's procedure incorporated molecular sieves which resulted in a lower temperature coupling because of the removal of water. However, only primary and secondary amines were reported.[48]



Scheme 19. *Zirconium catalysed direct amidation reactions.*[47,48]

Around the same time, Adolfsson also showed Ti(O-*i*Pr)$_4$ efficiently catalyses amide formation (Scheme 20).[49] However, despite the high yields, only primary and secondary amines were reported. In addition, epimerisation had occurred when (*S*)-ibuprofen was reacted with benzyl amine to give the product amide **4** in 83 % ee (Scheme 20).[49]



Scheme 20. *Titanium catalysed direct amidation.*[49]

Although group IV metals have better atom economy, when compared to stoichiometric coupling reagents. It is unclear whether [Zr] and [Ti] catalysts are suitable for coupling less nucleophilic amines, such as heterocycles and anilines, with carboxylic acids.

1.4.3. Recent advances in catalytic amide formation – Boron catalysts

In recent years boron-based catalysis has gained considerable interest for use in amide couplings.[50] In 1996, Yamamoto showed electon deficient benzene boronic acids were efficient at catalysing amide formation in non-polar solvents.[51] Since then, a number of boronic acid derivatives have been used as catalysts in amide formation (Fig 5).[52,53,54,55] Notably, only boric acid has been used in large scale applications.[35]

Similarly to Group IV metal catalysts the removal of water is key for increasing reactivity of boronic acid amidations, with all examples either requiring the azeotropic removal of water and/or the incorporation of molecular sieves.

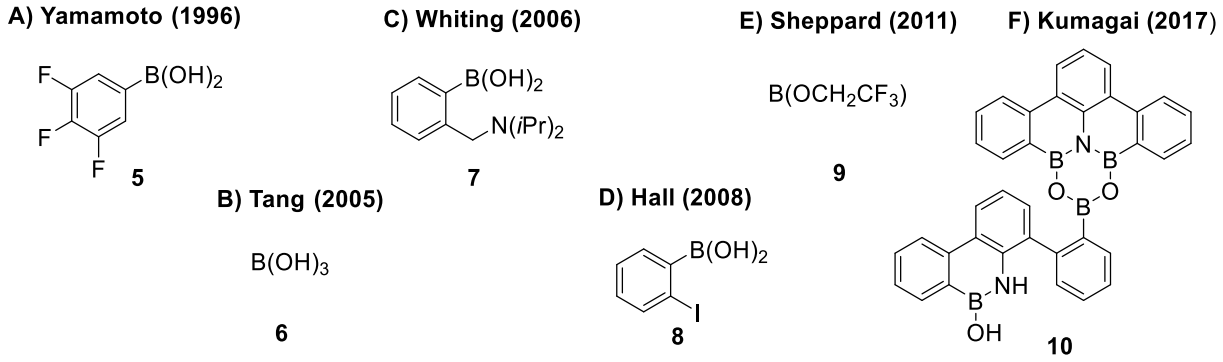


Fig 5. *Boronic acid derivatives used as catalysts for amide formation. A) Yamamoto,[56] B) Tang,[35] C) Whiting,[52] D) Hall,[53] E) Sheppard,[54] F) Kumagai.[55]*

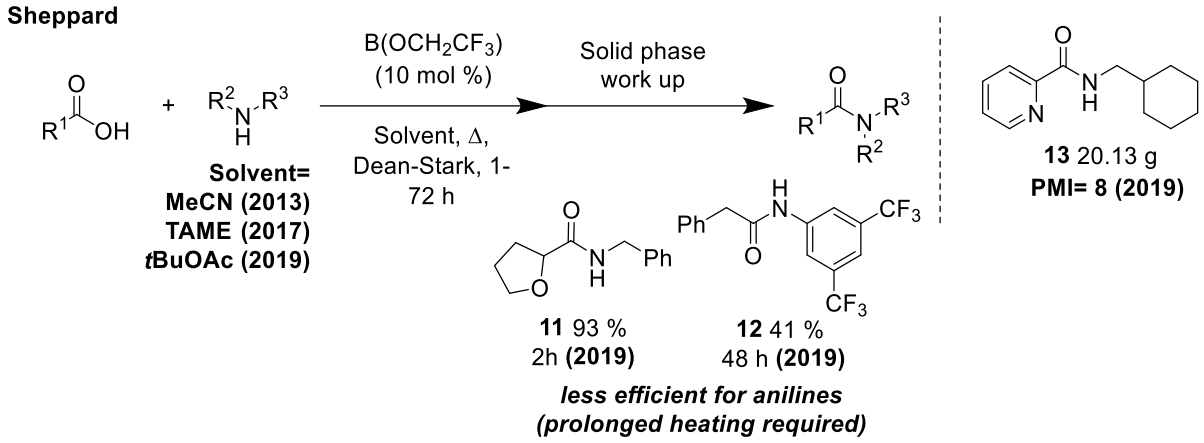
Sheppard's catalyst is of particular interest because multiple papers have been published by the group since 2011, that address the problems put forward by the pharmaceutical round table in 2007.[57,58,59,46] Problems addressed include, the use of an atom economic reagent ($B(OCH_2CF_3$ catalyst) and simplified purification. A brief summary of Sheppard's amidation follows.

Initially, $B(OCH_2CF_3)$ amidations were performed in a microwave at 100 °C.[54] However, more recent developments have incorporated a Dean-Stark trap to remove water from the reaction mixture (Scheme 21).[57,58,59]

Sheppard's catalyst has the propensity to work in polar solvents, whereas the other aryl-boron catalysts (Fig 5) perform best in non-polar solvents.[57,59] The ability to perform in polar solvents means that more pharmaceutically relevant amides can be prepared. Sheppard has demonstrated the procedure can tolerate a wide range of acids and amines (including anilines and heterocycles). It should be noted, less nucleophilic amines, such as electron deficient anilines, did require longer reaction times (up to 48 h) therefore, the application of this method is somewhat dependant on the reactivity of the starting materials (Scheme 21).[59]

Sheppard has incorporated the use of ion-exchange resins to simplify purification, ultimately leading to excellent PMI values (Scheme 21).[57,58,59] PMI (process mass intensity) is a widely used metric because it calculates the total

input of all reagents and solvents (Kg) vs total mass of product (Kg). PMI =total mass input (Kg)/total mass product (Kg).

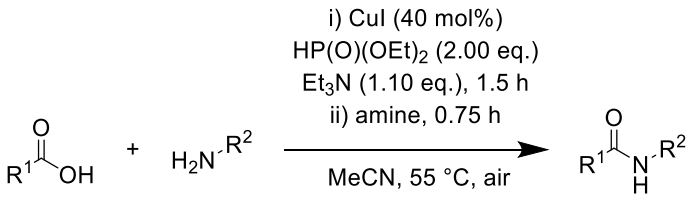


Scheme 21. *Sheppard's amidation; illustrating different solvents, substrate reactivity and process mass intensity (PMI).*[57,58,59]

Despite addressing some of the challenges associated with amide formation, there are concerns because of the potential reproductive toxicity of boric acid. This is because the decomposition of $B(OCH_2CF_3)$ would ultimately lead to boric acid and trifluoroethanol.[35]

1.5. Aims and objectives

Using diethyl phosphite as a coupling reagent for amide formation has significant advantages over commonly used stoichiometric coupling reagents because of its low toxicity and molecular weight. The formation of water soluble by-products will also allow for ease of purification. Due to the advantages of diethyl phosphites, this thesis will further develop the amidation procedure from J. Fraser's thesis.[42]



Scheme 22. *Original amidation developed by J. Fraser.*[42]

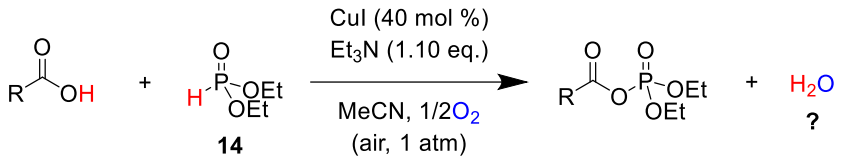
The reaction is currently limited by high catalyst loading. Therefore, a wider range of catalysts and bases will be explored, with the goal of reducing the

catalyst loading to a more practical level (e.g. <10 mol %). Once an optimal set of conditions has been achieved attempts will be made to scale the reaction. Different methods of purification will be investigated, and metric analysis carried out to provide comparison between commonly used amide coupling reagents and boron catalysts. Attempts will be made to gain insight into the mechanism, specifically focusing on the role of the counter anion.

2. Copper-catalysed amide synthesis

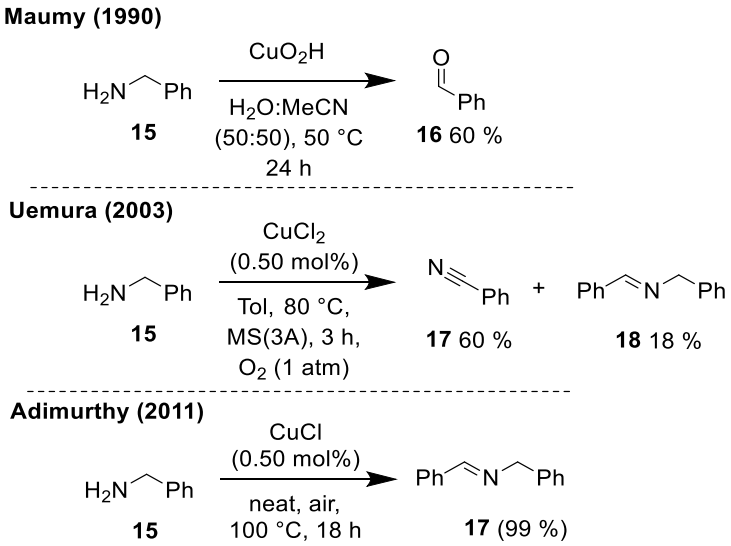
2.1. Optimisation

The copper-catalysed approach to amides developed by J. Fraser used base and oxygen (from the air) as the oxidant. Diethyl phosphite was used to mediate the reaction by producing an acyl phosphate intermediate (Scheme 22).[42]



Scheme 22. *Representation of the copper-catalysed oxidation of diethylphosphite to give acyl phosphate and theoretical water by-product.*

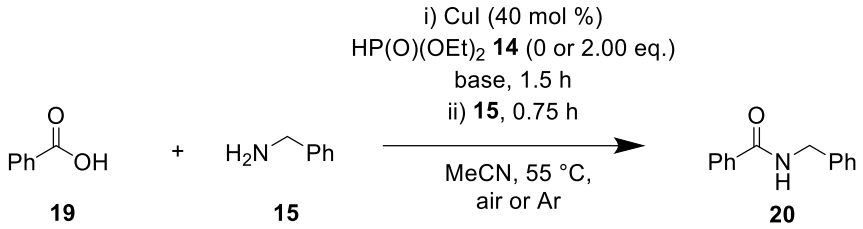
Benzyl amine **15** can oxidise the presence of copper to give benzaldehyde **16**, benzonitrile **17** and *N*-benzylidenebenzylamine **18** (Scheme 23).[60–62] Benzyl amine was used during optimisation. This was to ensure reaction conditions can tolerate amines that are susceptible to oxidation.



Scheme 23*. Examples of copper-catalysed oxidation of benzyl amine **15**.*

To confirm that each of the additives (base, oxygen and diethyl phosphite) in the copper-catalysed synthesis of amides were essential for the reaction to proceed, a series of control experiments were performed by reacting benzoic acid **19** with benzyl amine **15** to give *N*-benzylbenzamide **20** (Table 1). The control experiments illustrated that [Cu], oxygen, dialkyl phosphite and base are

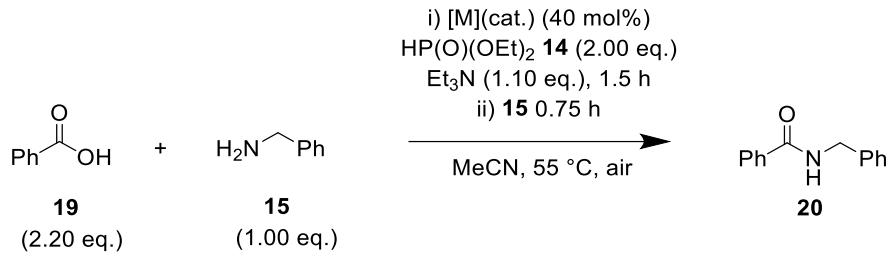
essential for the generation of **20** (Table 1.). When diethyl phosphite **14** was not added, a complex mixture of oxidation products from **15** were detected after aqueous washing.



Entry	Base	$HP(O)(OEt)_2$ (eq.)	Atmosphere	Yield
1	Et_3N (1.1 eq.)	2.00	air	68[a]
2	--	2.00	air	24
3	Et_3N (1.1 eq.)	0	air	0[b]
4	Et_3N (1.1 eq.)	2.00	Ar	0

Table 1. *Control experiments. [a]Trace amounts of benzaldehyde **16** in crude. [b]A mixture of oxidation products were detected.*

Initially, a series of Cu(I) and Cu(II) catalysts were screened using 40 mol % catalyst. Changing the initial oxidation state of the copper appeared to have little effect on the reaction as CuI (I) and $CuCl_2$ (II) produced the best results 68 % yield (Table 2, entries 1 and 9). The catalyst screen indicated that the nature of the counter anion has a greater influence on the reaction than changing the initial oxidation state of the metal. Catalysts containing halides as the counter anions produced the best yields. Other examples such as Cu_2O and $Cu(OMe)_2$ (entries 5 and 6) resulted in poor yields. Attempts to use other metal halide salts; $FeCl_3$, $NiCl_2$ and $CoCl_2$ (entries 10-12) were unsuccessful.

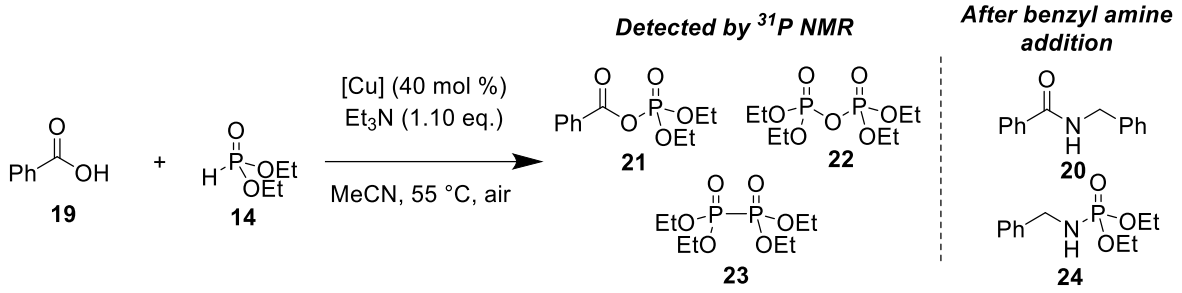


19 (2.20 eq.) + **15** (1.00 eq.) → **20**

Entry	Catalyst	Yield %
1	**CuI**	**68**
2	CuCl	50
3	CuBr	48
4	$Cu(MeCN)_4BF_4$	55
5	Cu_2O	9
6	$Cu(OMe)_2$	10
7	$Cu(NO_3)_23H_2O$	41
8	$CuBr_2$	55
9	**$CuCl_2$**	**68**
10	$FeCl_3$	0
11	$NiCl_2$	0
12	$CoCl_2$	0

Table 2. *Screening using 40 mol % catalyst loading.*

^{31}P NMR was used to identify by-products and reactants when copper loading was 40 mol % (Table 3). Assignments were obtained from literature values.[25,63] Copper salts containing halides (Table 3, entries 1-3) contained a mixture of acyl phosphate **21**, pyrophosphate **22** and hypophosphate **23**, whereas non-halide copper salts (entries 4 and 5) only contained pyrophosphate **22**. The formation of pyrophosphate **22** is perhaps formed from a halophosphate intermediate (see section no.). $CuCl_2$ and $CuBr_2$ (entries 2 and 3) both contained diethyl phosphite **14** and as a result, a mixture of amide **20** and phosphoramidate **24** were present in the ^1H NMR spectrum after work up. The amount of acyl phosphate **21** observed by ^{31}P NMR was not representative of isolated yield because of the formation of benzoic acid anhydride **25**.



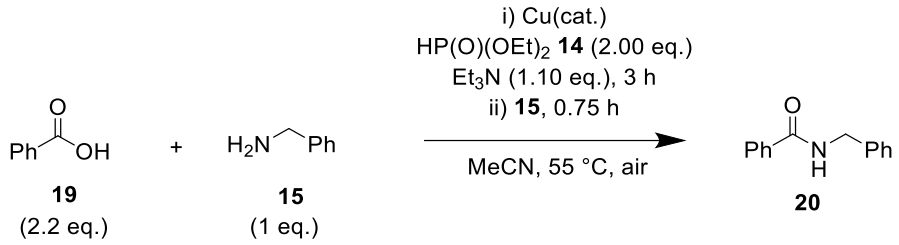
		Integration of products by ^{31}P NMR[a]				Ratio of amine derivatives by ^{1}H NMR[b]		
Entry	**Catalyst**	**14**	**21**	**22**	**23**	**20**	**24**	**Yield (20) %[c]**
1	CuI	0	1.00	0.82	0.81	1.00	0	68
2	$CuCl_2$	4	1.00	2.70	0.35	0.80	0.20	68
3	$CuBr_2$	16.32	1.00	2.43	0.13	0.78	0.22	55
4	$Cu(MeCN)_4BF_4$	0	1.00	0	1.00	1.00	0	55
5	$Cu(OMe)_2$	0	0	0	1.00	1.00	0	10

Table 3. *Distribution of products when different copper salts were used. [a]Phosphorus containing compounds in detected in reaction mixture. [b]Amide **20** and phosphoramidate **24** present after work up. [c]Isolated yield of **20**.*

After screening catalysts at 40 mol % attempts were then made to reduce the catalyst loading (Table 4). The reaction time at lower catalyst loadings was extended to 3 hours because reaction monitoring by ^{31}P NMR (using CuI 10 mol %) showed full consumption of diethyl phosphite. At 10 mol %, CuI retained its catalytic activity (entry 1). However, $CuCl_2$ and CuCl (entries 2 and 3) showed a reduction in catalytic activity and gave diminished yields of **20** in 26 and 28% respectfully.

Interestingly, using a mixture of $CuCl_2$:CuCl (entry 5) increased the yield of **20** to 64%. This indicates the formation of a dicopper complex in solution, which may act as a two-electron oxidant. The mixture of Cu(I) and Cu(II) may promote the formation of the active catalyst and/or increase the redox cycling of the catalyst. This will be discussed in further detail in Section 2.5.

Further reducing the loading of CuI resulted in diminished yields (entries 6 and 7). CuI was the most effective catalyst at lower catalyst loadings; therefore, further experiments were carried out using CuI (10 mol %).

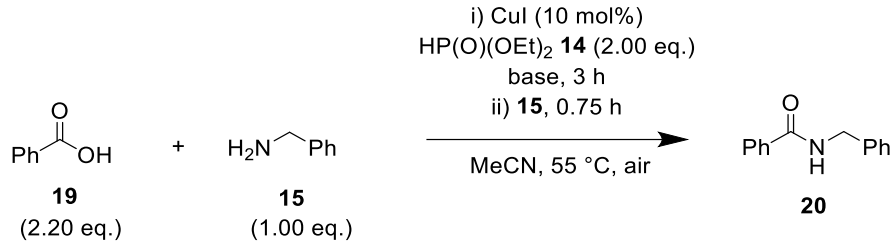


Entry	Catalyst (mol %)	Yield
1	CuI (10)	68
2	$CuCl_2$ (10)	26
3	CuCl (10)	28
4	CuBr (10)	38
5	$CuCl_2$:CuCl (5:5)	64
6	CuI (5)	43
7	CuI (5)	0

Table 4. *Screening using 10 mol % catalyst loading.*

In other reported copper reactions changing base has been known to alter the selectivity between pyrophosphate **22** and hypophosphate **23**, as described earlier TMEDA favoured pyrophosphate **22** formation and Et_3N favoured **23**.[24] However, in this case, changing the base failed to achieve better selectivity towards the desired acyl phosphate **21** (Table 5). Alkyl amine bases (entries 1-5) such as DBU or Et_3N were more effective than pyridine or DMAP (entries 6 and 7).

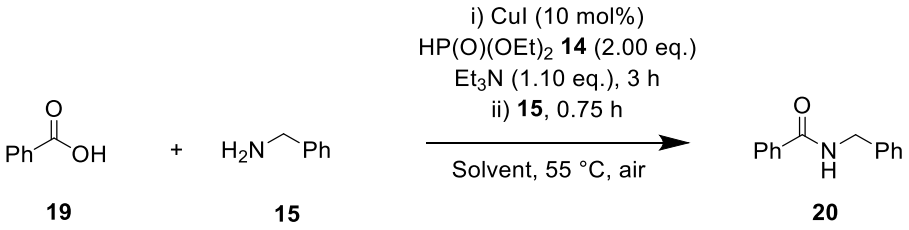
Using higher equivalents of Et_3N (entry 2) resulted in diminished yields due to hydrolyses of **14** and greater selectivity to hypophosphate **23**. The hydrolysis could be observed by the formation of a small quantity of tetraethylammonium benzoate. Inorganic bases (entries 9 and 10.) resulted in an intractable solid that was discarded from any future investigation.



Entry	Base	Yield
1	Et_3N (0.5 eq.)	35
2	Et_3N (2.2 eq.)	26
3	DBU (0.5 eq.)	48
4	DBU (1.1 eq.)	66
5	DIPEA (1.1 eq.)	61
6	Pyridine (1.1 eq.)	20
7	DMAP (1.1 eq.)	35
8	TMEDA (1.1 eq.)	0
9	Trisodium phosphate (1.1 eq.)	0
10	Na_2CO_3 (1.1 eq.)	0

Table 5. *Screening of different bases.*

A small solvent screen was performed as an attempt to use a 'greener' solvent system in the reaction medium. From the solvents tested, polar aprotic solvents such as DMC or MeCN proved most effective (Table 6).



Solvent	Yield
MeCN	68
EtOAc	23
DMC	68
EtOH	8
Isopropanol	23

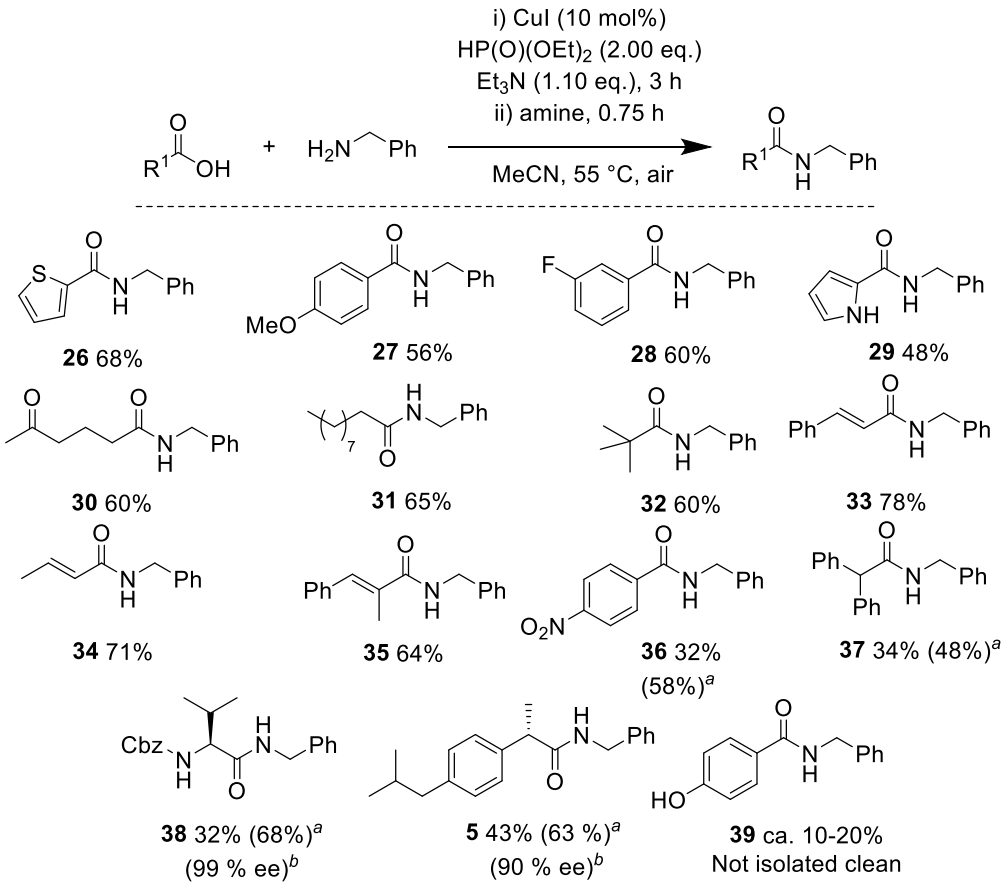
Table 6. *Solvent screen using CuI (10 mol%).*

It was a possibility that the presence of moisture could hinder the formation of *N*-benzylbenzamide **20** by reacting with acyl phosphate **21** to give benzoic acid **19**. As a result, attempts were made to remove adventitious water by using powdered molecular sieves and dry acetonitrile, however, this failed to improve the yield.

2.2. Substrate scope and limitations

2.2.1. Scope of carboxylic acids

Following optimisation of the reaction a new set of conditions were derived (Scheme 24). Initial studies focused on varying the acid and using benzyl amine **15** as a coupling partner.



Scheme 24. *Acid scope; [a]Reaction performed using 40 mol% catalyst.* [b]ee- enantiomeric excess *determined by chiral HPLC.*

A variety of carboxylic acids were tested, most resulted in moderate to good yields of 43-78%. Aliphatic acids produced **30** and **31** in 60 and 65 % yield respectively. Using more hindered pivalic acid also gave **32** in 60 % yield. (*E*)-Cinnamic acid gave the highest yield **33** (78 %), other α-β-unsaturated acids also gave amides in good yield with crotonic acid producing **34** in 71 % yield and α-methyl cinnamic acid producing **35** in 64 % yield.

4-Nitrobenzoic acid, diphenyl acetic acid and CBz-valine all gave poor yields of amide when CuI (10 mol %) was used. The yield of these substrates improved when the catalyst loading was increased to 40 mol %.

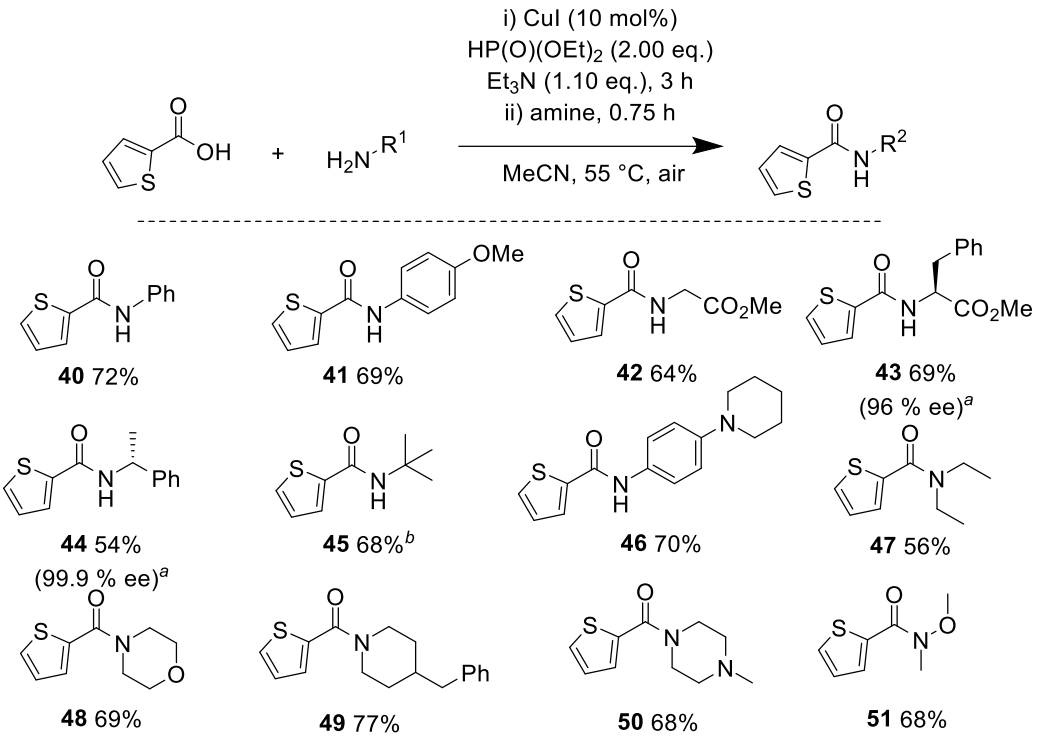
Ibuprofen is known to epimerise under basic conditions.[64] HPLC analysis determined compound **5** had undergone partial epimerisation (90 % ee) because the starting enantiomeric excess (ee) of (*S*)-Ibuprofen was >98 % ee. CBz-Valine showed no signs of epimerisation.

Using 4-hydroxybenzoic acid did not give complete selectivity to the amide **39**. The reaction resulted in a mixture of products that were difficult to separate from the amide. 90 minutes into the reaction a signal at -0.44 ppm (^{31}P NMR) was detected, which disappeared after the addition of the benzyl amine **15**. Presumably, the peak at -0.44 ppm is an unstable phosphate ester (from the phenolic hydroxyl group).

2.2.2. Scope of amines

Good yields were obtained (between 50-77%) when different amines were coupled with thiophene-2-carboxylic acid (Scheme 25). Thiophene-2-carboxylic acid was used because this allowed for direct comparison with the initial studies by Jamie Fraser, to which similar results were obtained using 40 mol % catalyst.[42]

As with *N*-benzylbenzamide **15**, anilines are also susceptible to oxidation, however, no oxidised anilines were observed during the synthesis of **40** and **41**. Aminoester derivatives such as, glycine and phenyl alanine were tolerated. Chiral amines **43** and **44** showed little sign of epimerisation. Secondary amines gave similar yields to primary amines (Scheme 25).



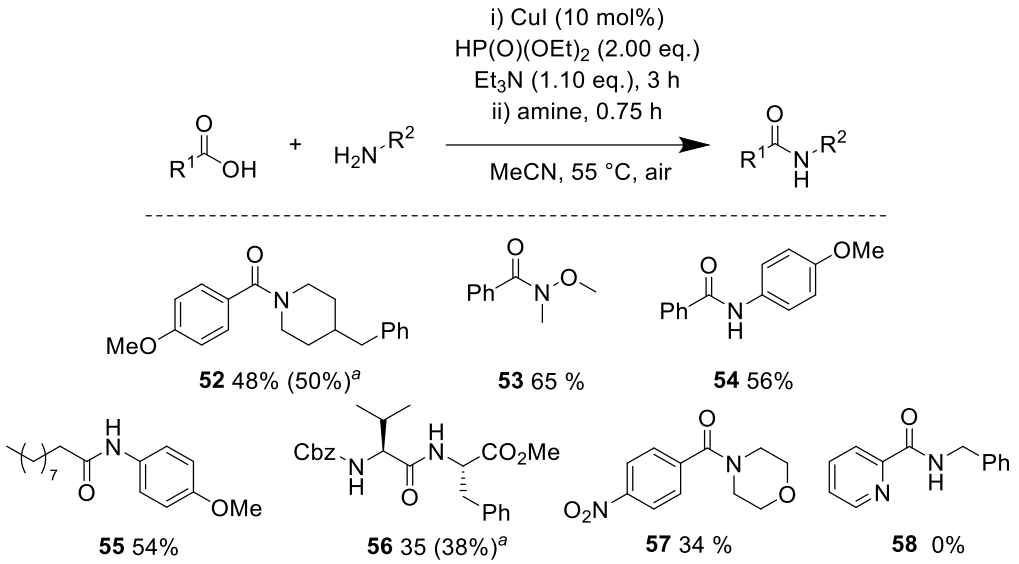
Scheme 25. *Amine scope.* [a]ee- enantiomeric excess determined by chiral HPLC. [b]*Reaction required 16 hours after amine addition*.

2.2.3. Additional substrates

At this juncture, a mixture of acids and amines were coupled together (Scheme 26). No oxidation was observed when 2-thiophene carboxylic acid or benzoic acid were coupled with 4-methoxyaniline. However, when 4-methoxyaniline and decanoic acid were coupled to give **55**, some oxidisation of aniline occurred. This was evident by the presence of about 5 mgs of bright yellow oil that contained additional signals in the aromatic region of the ^{1}H NMR spectrum.

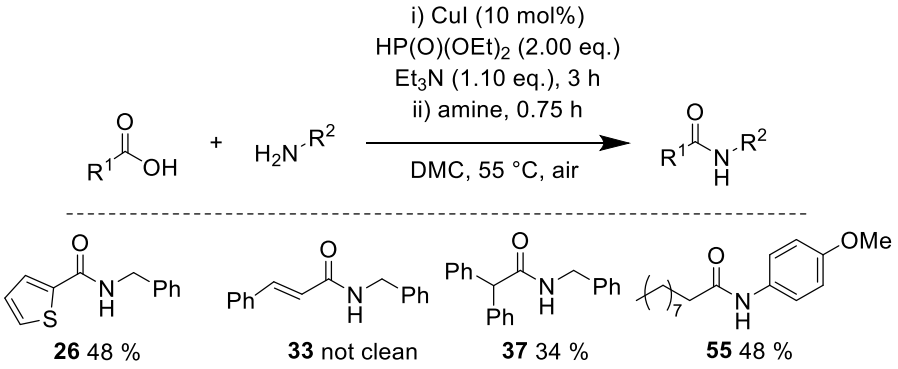
Reacting CBz-valine with phenylalanine gave **56** as a single diastereomer but in a low yield, even at 40 % catalyst loading. It was considered that the lower yield of **56** was due to the steric hinderance associated with valine and phenyl alanine. Attempts were made to react 'less bulky' glycine ethyl ester and glycine methyl ester with each other; however, the desired amide was not isolated clean, indicating that steric hinderance does not govern the lower yields observed from coupling amino acids together.

4-Nitrobenzoic acid also reacted poorly with morpholine using 10 mol % catalyst giving **57** in 34 % yield. No reaction was observed when picolinic acid was reacted with **15** because of the strong coordination between pyridine and copper.



Scheme 26. *Mix and match. [a]Reaction performed using CuI (40 mol%).*

During the earlier solvent screen DMC showed promise as an alternative solvent to MeCN and gave **20** in 68 % yield. However, when DMC was tested on other substrates the yields were slightly poorer than when MeCN was used (Scheme 27). In addition, **33** was isolated with an unknown impurity.

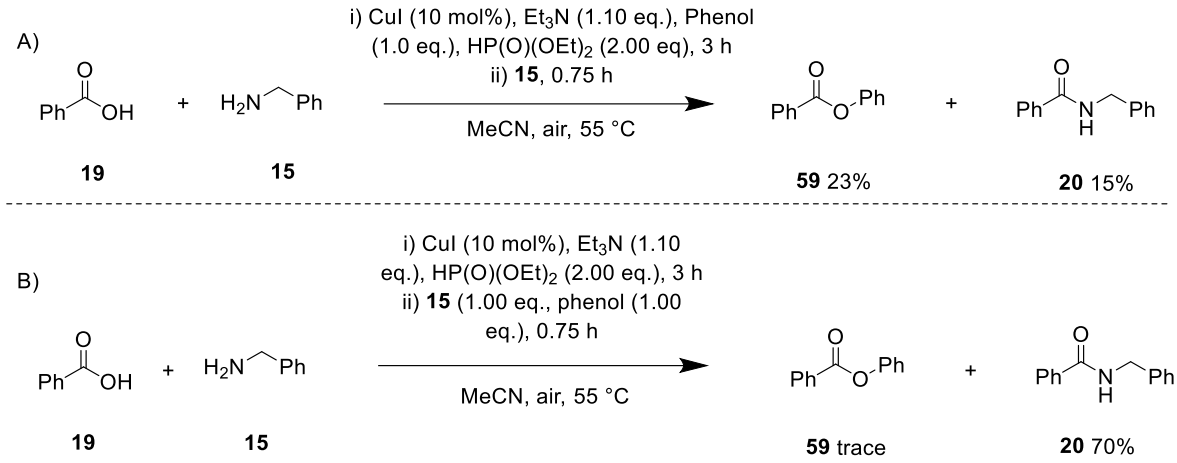


Scheme 27. *Attempted substrates when DMC was used as a solvent.*

2.2.4. Reaction with alcohols

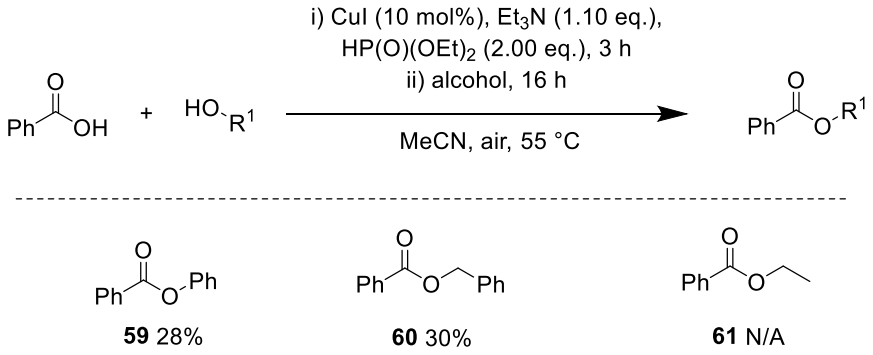
4-Hydroxybenzoic acid was unsuccessful during the amide coupling (Scheme 24) because of side esterification reactions. To further investigate the effect of phenolic groups on the amidation reaction, phenol was added to the reaction mixture at different time points (Scheme 28). Phenol addition at the start of the

reaction (Scheme 28, A) gave a mixture of ester and amide in low yields (23 and 15 % respectively). The addition of phenol at the same time as the amine had no impact on the amount of amide produced (Scheme 28, B), this is likely due to the stronger nucleophilicity of the amine compared to the phenol.



Scheme 28. *A) Addition of phenol at start of reaction. B) Addition of phenol at the same time as* ***15****.*

Attempts were made to synthesise esters directly (Scheme 29). However, only poor yields were obtained, even when the reaction was left for longer after alcohol addition. Therefore, no further studies were performed using alcohols. Alcohols are known to oxidised to aldehydes in the presence of copper but under these conditions no aldehyde was observed.[65]

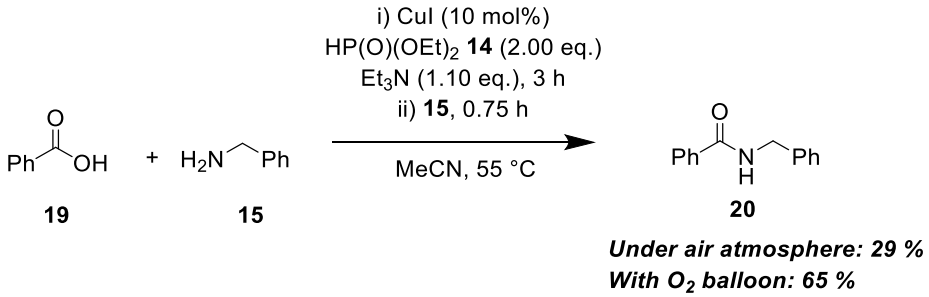


Scheme 29. *Attempted synthesis of esters.*

2.2.5. Scalability of amide coupling

Attempting to scale the synthesis of **20** by increasing the amount of benzylamine **15** from 0.50 mmol to 5.00 (10x scale) resulted in a significant decrease in yield from 68 % to 29 % (Scheme 30). Diethyl phosphite was still present after 3 h of heating a 55 °C, indicating the reaction rate had reduced. Due to the reaction

using oxygen as the terminal oxidant, it was envisaged that increasing the oxygen concentration would increase the rate of reaction. Therefore, performing the reaction under oxygen atmosphere resulted in full consumption of diethyl phosphite and the yield of **20** increased to 65 %. Performing the reaction at 0.5 mmol scale under oxygen atmosphere did not improve the yield of **20**.



Scheme 30. *Conditions used for scale up procedure* ***19*** *(12 mmol), HP(O)(OEt)₂* ***14*** *(10 mmol) and* ***15*** *(5 mmol).*

2.2.6. Solvent use and metrics

To improve the metrics of the amidation reaction, alternative methods of purification were used with the aim of reducing solvent waste. The original method used for purifying the amides consisted of an aqueous work up, followed by silica gel chromatography. Inherently this produced copious amounts of aqueous and organic waste (Fig 5, work up plus column).

Two alternative purification methods were performed (Fig 5) on *N*-benzylbenzamide **20** (reaction conditions were performed following procedure **A**, experimental). The first method consisted of concentrating the reaction mixture, then passing the residue through a short silica:K_2CO_3 (90:10 w/w) plug, using either Et_2O or EtOAc as the eluent. The trace organic impurities could be removed by washing with petrol to yield the pure amide. This approach is advantageous because the majority of waste produced can be disposed of through the silica waste stream.

The second method is applicable to amides that are insoluble in water (Fig 5, precipitation from reaction mixture). Na_2CO_3 solution was added to the cooled reaction mixture and the amide was precipitate from the reaction mixture. The crop was then filtered washed with Na_2CO_3 followed by washing with petrol.

Both methods successfully produced **20** without reducing the isolated yields (68 and 72% respectively) and significantly reduced solvent waste (Fig 5).

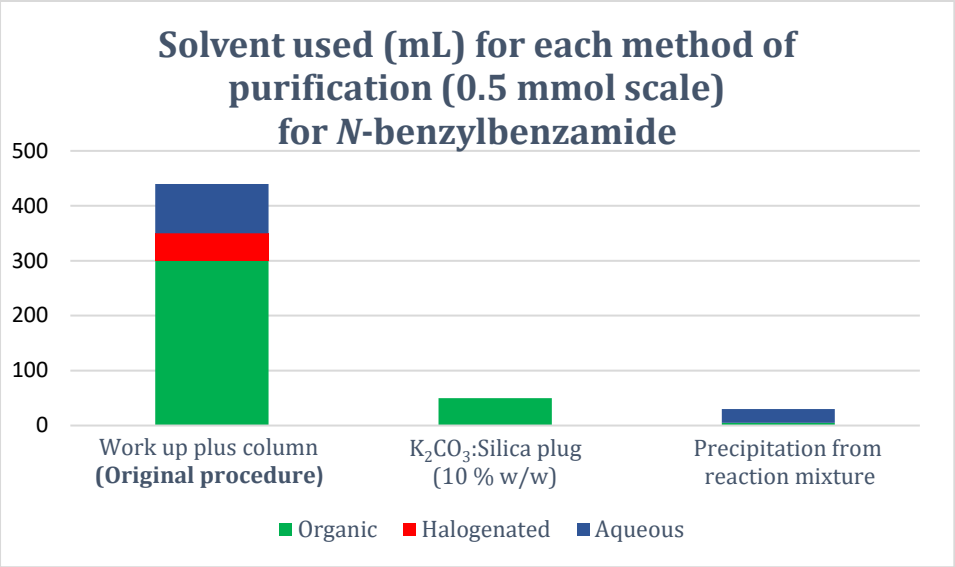


Fig 5. *The amount of solvent used (mL) for each method of purification.*

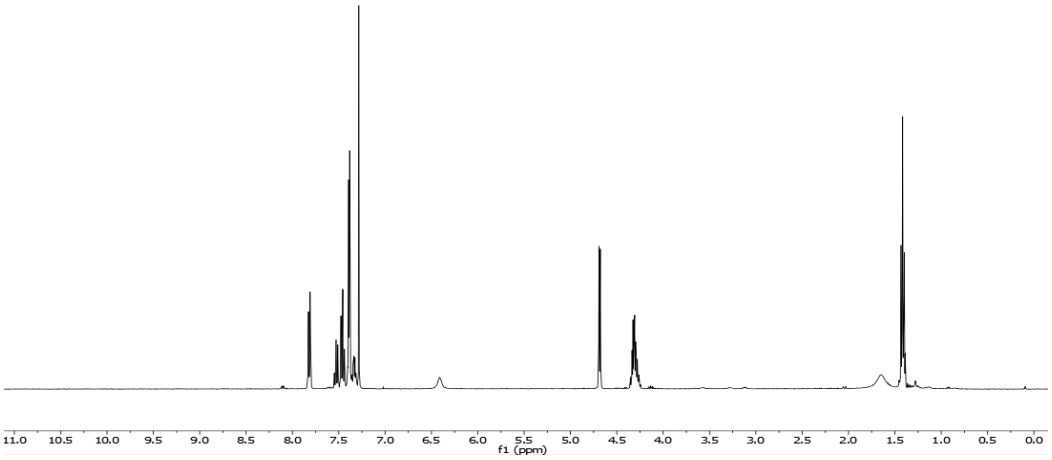


Fig 6. *^{1}H NMR spectrum of **20** after aqueous washing.*

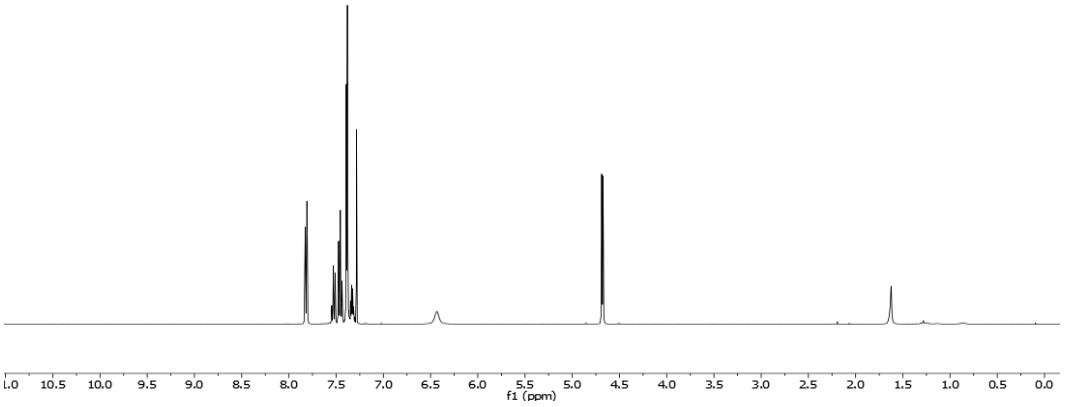


Fig 7. *^{1}H NMR spectrum of **20** after silica gel chromatography (work up plus column).*

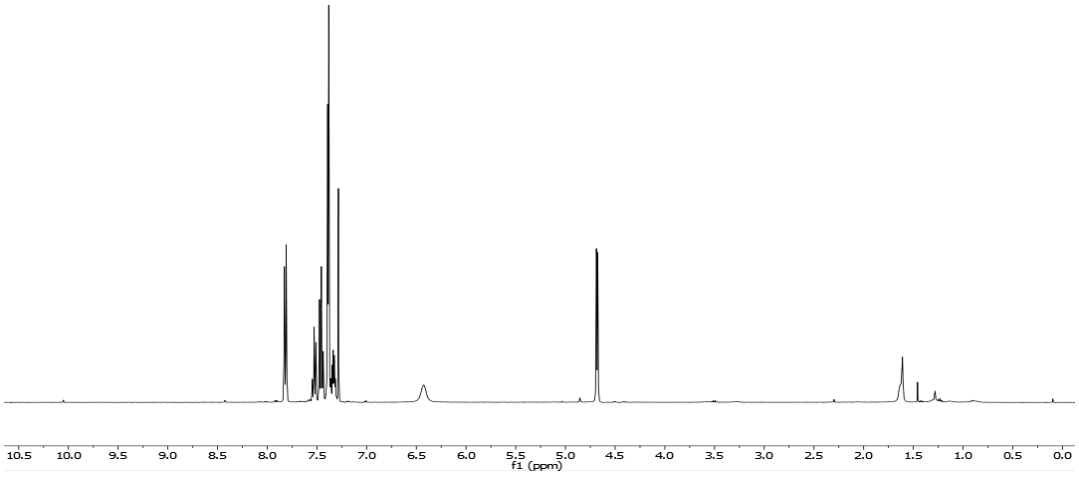


Fig 8. *^{1}H NMR spectrum of **20** after plug (silica:K_2CO_3, 90:10 w/w).*

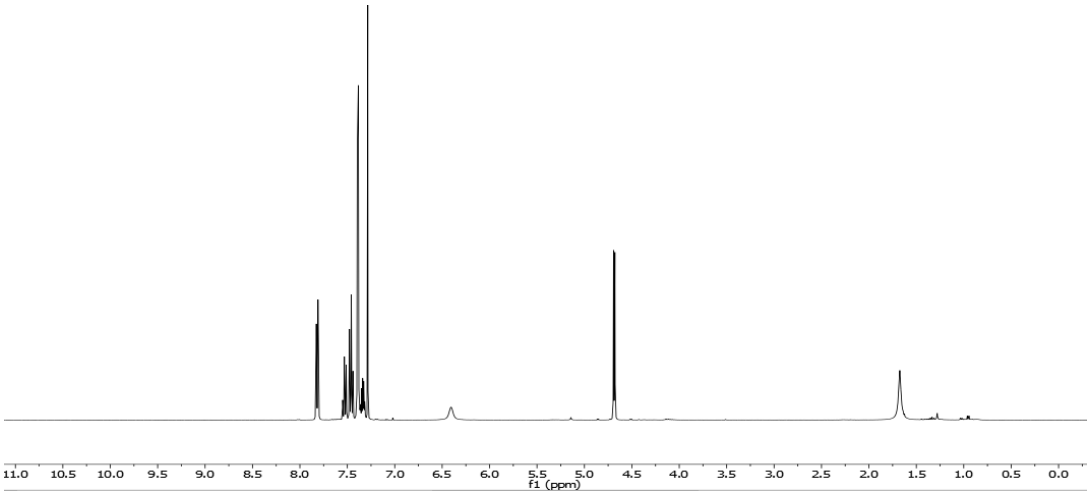


Fig 9. *^{1}H NMR spectrum of **20** after precipitation from reaction mixture.*

PMI intensity was used to compare common small scale amide coupling reagents (Fig 10) with the amide coupling developed in this thesis. The PMI values in Fig 10 excluded purification to simplify the analysis and because small scale reactions often show poor reaction efficiency in terms of PMI.[35] PMI=total mass input (Kg)/total mass product (Kg). Results shown in blue required further purification by aqueous work up. Results shown in red required column chromatography and results shown in green required no further purification (Fig 10).

Despite this work giving a lower yield of **20** (68 %) than the other methods (Fig 10), the obtained PMI value for this work is competitive with the other stoichiometric coupling reactions described. In addition, this work is advantageous over the other stoichiometric coupling reactions because chromatography was not required for purification of **20**.[66,67,68]

Catalytic amide reactions such as, the borate catalysed approach developed by Sheppard supersede stoichiometric coupling reactions (Fig 10) in terms of PMI but are limited because high temperatures and the removal of water are required during the reaction.[59]

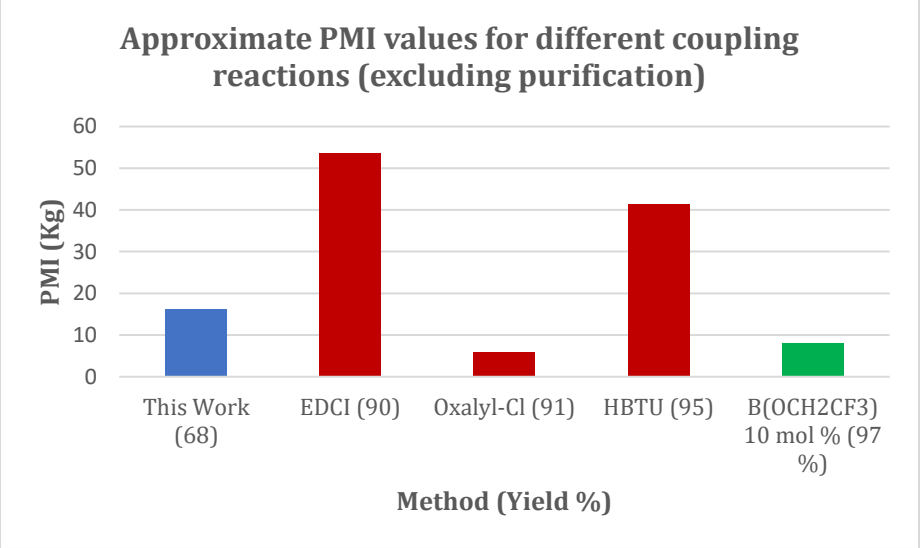


Fig 10. *Process mass intensity (PMI) values of small-scale coupling reagents for the synthesis of N-benzyl benzamide* ***20****.*[66,67,68] *PMI for B(OCH₂CF₃) 10 mol % was reported by Sheppard for the synthesis of N-(cyclohexylmethyl)picolinamide* ***13****.*[59]

As explained earlier solvent use has the largest impact on PMI, this point is further illustrated by Fig 11, which combines the PMI values obtained from this work and the different purification methods.

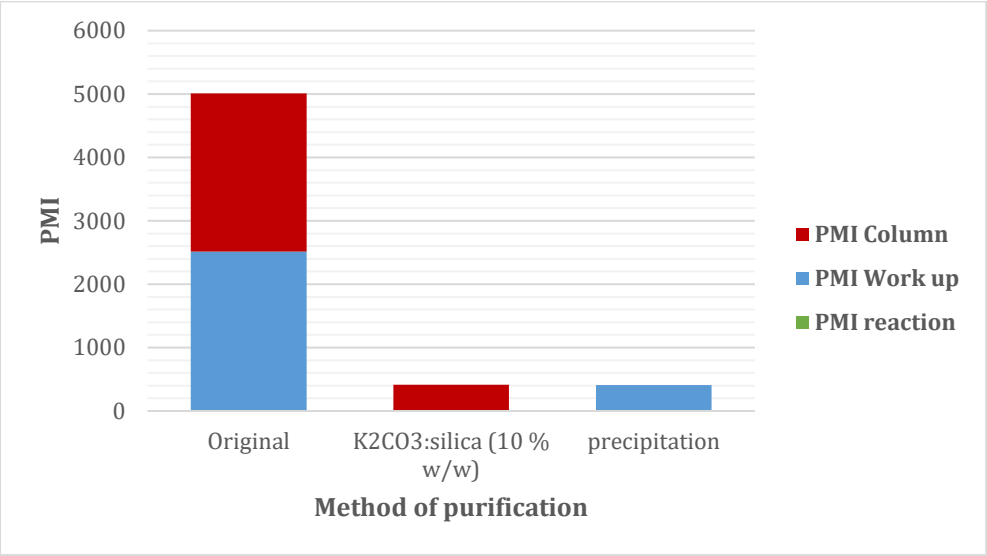


Fig 11. *PMI values of for the synthesis of N-benzylbenzamide* ***20*** *including different purification methods.*

2.3. Mechanistic insight and intermediates

One of the main limitations of the reaction is due to the formation of dimeric species. The formation of acid anhydrides such as **25** meant that an excess of acid and phosphite were required for the amidation to proceed efficiently.

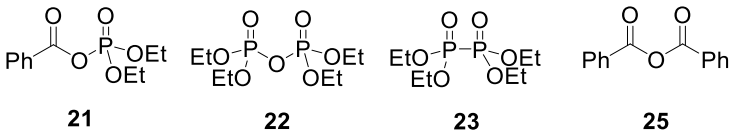
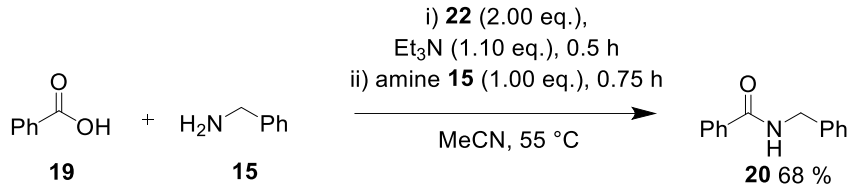


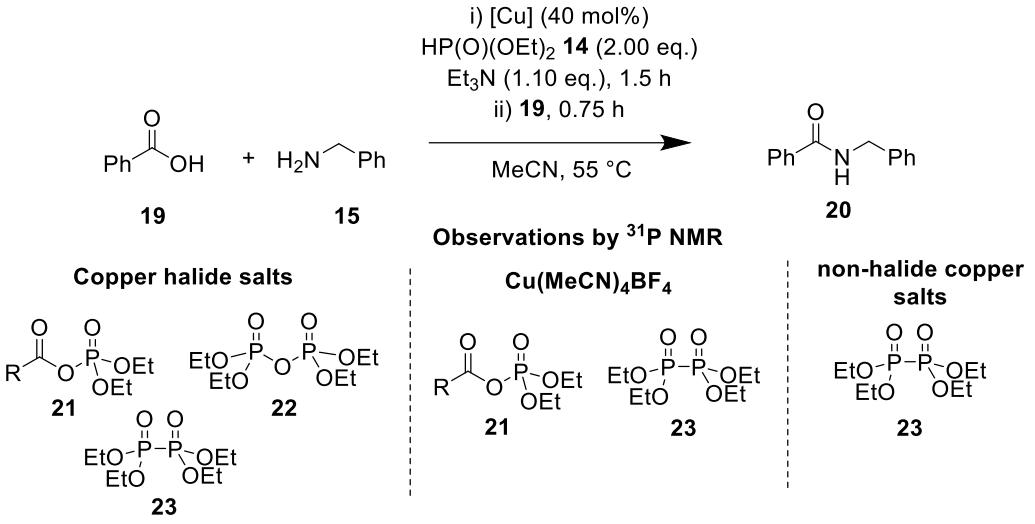
Fig 12. *Observed by-products and intermediates in reaction before the addition of benzyl amine* ***15****. By-products were observed by* ^{31}P *NMR,* ^{1}H *NMR and MS.*

It was envisaged that pyrophosphate **22** could act as an electrophile for the carboxylic acid to generate acyl phosphate **21**, during the copper catalysed reaction. To investigate this hypothesis, tetraethyl pyrophosphate (**22**, TEPP) was reacted in the present of benzoic acid **19** and benzyl amine **15**. Interestingly, **20** was isolated in a 68% yield (Scheme 31). This result indicates that **22** has the ability to participate in the copper catalysed amide reaction.



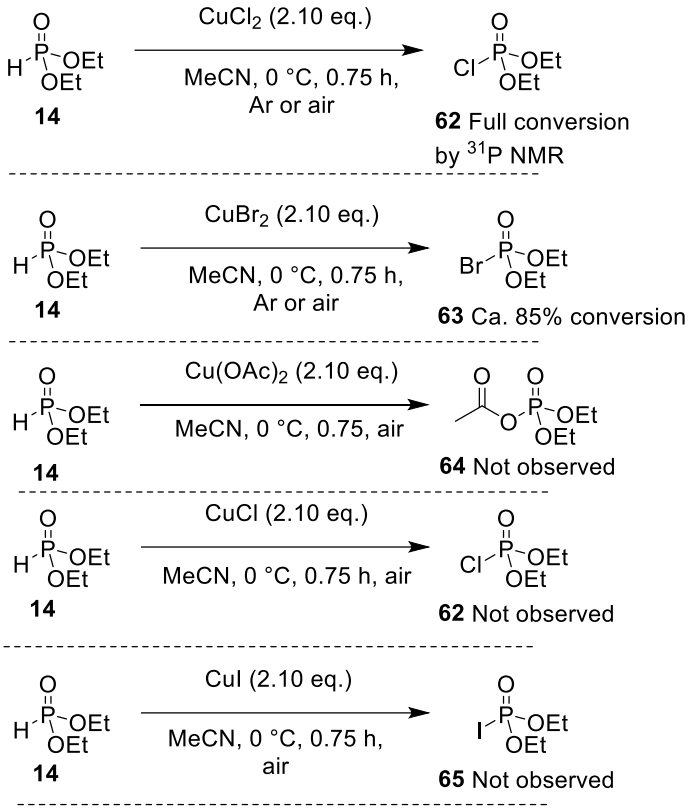
Scheme 31. *The reaction using TEPP* ***22*** *as a coupling reagent.*

As highlighted in Table 3, the formation of **22** was only observed when copper halide salts were used. Hypophosphate **23** could be observed in the presence of all copper catalysts but it was the only product detected when Cu_2O and $Cu(MeO)_2$ were used as catalysts. When $Cu(MeCN)_4BF_4$ was used both acyl phosphate **21** and hypophosphate **23** were present, but no pyrophosphate **22** was detected by ^{31}P NMR.



Scheme 32. *Breakdown of products observed by* ^{31}P *NMR when halide and non-halide copper catalysts were used.*

A plausible hypothesis for the formation of **22** is *via* the formation of a diethyl phosphoryl halide which can react with water and itself to produce the pyrophosphate. To further investigate the behaviour of copper salts in the presence of diethyl phosphite a series of stoichiometric copper experiments were performed (Scheme 33).



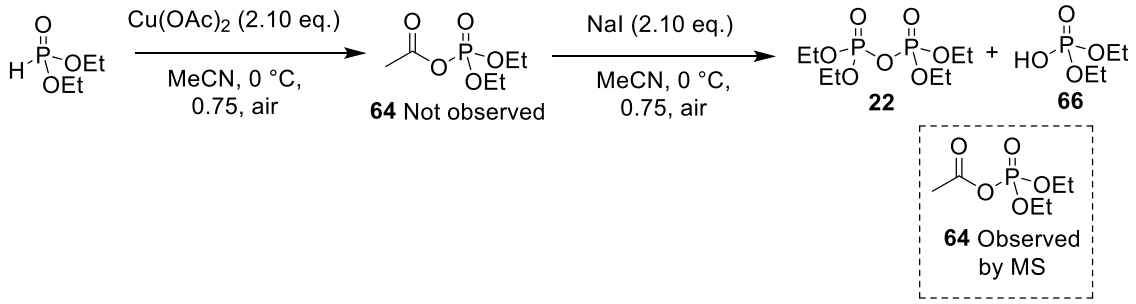
Scheme 33. *Diethyl phosphite addition to Cu salts measured by ^{31}P NMR. Chemical shifts are provided in the experimental.*

Initially, Cu(II)salts were reacted with **14** (Scheme 33). $CuCl_2$ and $CuBr_2$ both reacted readily with **14** to give the corresponding phosphoryl halides **62** and **63** under aerobic conditions. $CuCl_2$ was more reactive than $CuBr_2$. To investigate whether oxygen played a role in this transformation $CuCl_2$ and $CuBr_2$ were subjected to inert atmosphere. The oxidation of **14** still proceeded efficiently, giving phosphoryl halides **62** and **63**. No reaction was observed when $Cu(OAc)_2$ was combined with **14** under aerobic conditions.

The results highlighted in Scheme 33 indicate that Cu(II) is the active catalyst, and copper carboxylates do not readily react with dialkyl phosphite **14** in the presence of Cu(II). The formation of phosphoryl halide intermediates would also explain why the coupling works better in the presence of copper halide salts. Despite this observation, acyl phosphate **21** was observed by ^{31}P NMR when $Cu(MeCN)_4BF_4$ was used. Therefore, the formation of the phosphorus halide is likely not the only mechanism. However, the role of BF_4 counter anion is yet to be determined.

When Cu(I) halide salts (CuI and CuCl) were reacted with **14** (Scheme 33) no oxidation of diethyl phosphite **14** was observed under aerobic conditions. Therefore, the generation of acyl phosphates must arise from Cu(II).

CuI_2 is not commercially available because it is unstable. Cu(II) in the presence of iodide reduces Cu(II) to Cu(I) to give molecular iodine and CuI. It is possible that Cu(II) oxidises iodine and this promotes the cross-dehydrogenative coupling observed between a carboxylic acid and diethyl phosphite **14**. To further investigate this hypothesis NaI was added to $Cu(OAc)_2$ and **14** (Scheme 34). The reaction mixture turned black and oxidation of **14** was observed by ^{31}P NMR. No acyl phosphate **64** was observed by ^{31}P NMR, but the adduct of **64** was detected by MS (ESI^+). The ^{31}P NMR consisted of mostly a new signal at 0.14 ppm and some pyrophosphosphate **22**. The new peak at 0.14 ppm is believed to be diethyl hydrogen phosphate **66**, which was not observed in any of the previous Cu experiments (stoichiometric and catalytic).



Scheme 34. *Addition of NaI (2.10 eq.) to a mixture of $Cu(OAc)_2$ and diethyl phosphite **14**. Products were detected by ^{31}P NMR and/or MS.*

EPR measurements were taken at each stage of the reaction as a method to measure changes in oxidation at Cu (Fig 13). At the start of the reaction only benzoic acid and CuI were present in the reaction mixture, no Cu(II) was detected. The addition of Et_3N promoted the oxidation to Cu(II), this presence of Cu(II) was also evident due to the instantaneous colour change from pale yellow to blue. The addition of diethyl phosphite resulted in a slight reduction of the intensity of the Cu(II) signal. After 0.5 h the Cu(II) signals had almost completely disappeared but the formation of additional 'sharp' signals around 3000 Gauss may indicate the presence of radicals. Additional hyperfine splitting appeared to indicate the formation of a new species; possibly indicating phosphorus binding

to the copper. Leaving the reaction for 2.5 h resulted in an almost colourless solution and EPR showed most of the Cu(II) had converted to Cu(I). However, future work is required to determine the exact nature of the copper species observed at 0.5 h and 2.5 h after acyl phosphate addition. In addition, the generation of x-ray crystal structures may help divulge information about the active catalyst.

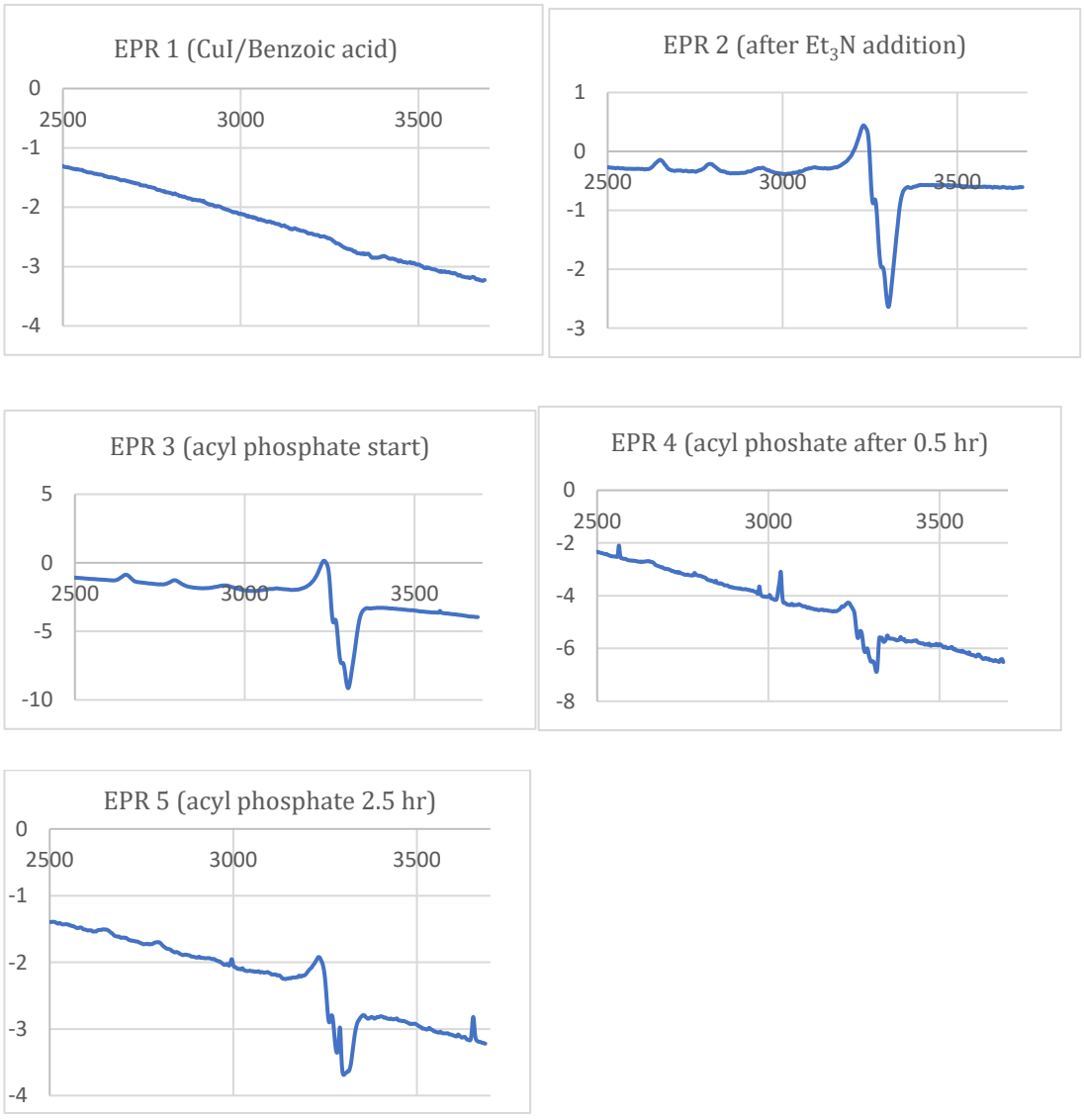


Fig 13. *EPR spectra for the copper catalysed reaction between benzoic acid* ***19*** *and acyl phosphate* ***21****. X axis= Magnetic field (Gauss), Y axis= dX/dB.*

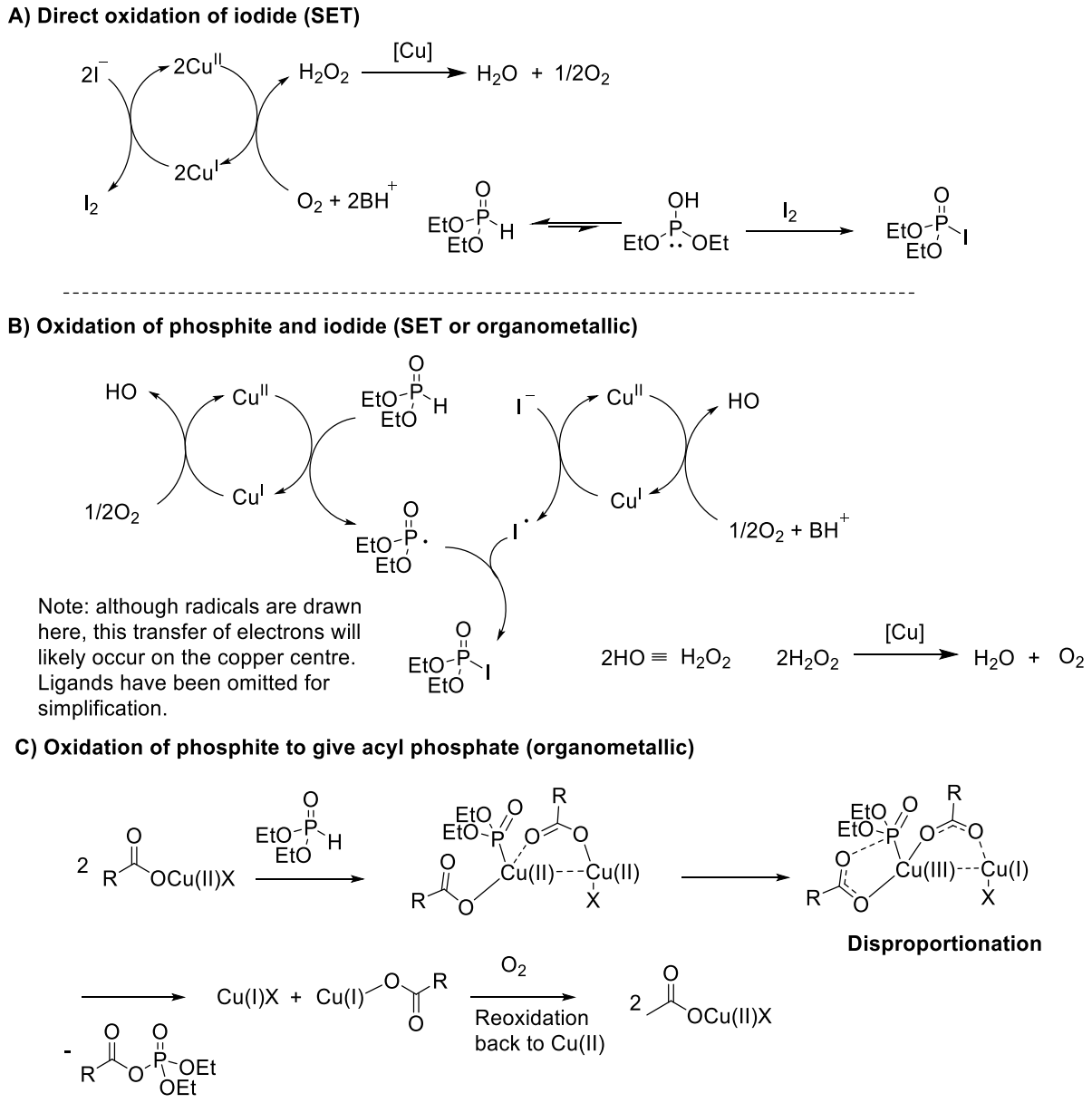
In 2015, Stahl published a review on the mechanisms of copper-catalysed aerobic oxidations. Here is a brief summary of Stahl's findings.[69] Stahl emphasises 3 different classes of reactions: 1) Single electron transfer (SET) for oxidative functionalisation of electron rich substrates; 2) oxidative carbon-heteroatom

bond-forming reactions that proceed via disproportion of two Cu(II) species to give Cu(I) and Cu(III) (organometallic pathway); 3) methods for aerobic oxidation of alcohols and amines, that use Cu(II) in the presence of a redox active co-catalyst. Stahl summarises the two mechanisms (SET and organometallic pathway) that can occur during C-H oxidation (on page 1762).[69] Stahl explains that the two mechanisms have obvious differences, but they also share common features. For example, in both cases two-copper(II) species participate in the two-electron reaction, and the role of O_2 is to re-oxidise Cu(I) to Cu(II). The examples reviewed by Stahl highlight that the first Cu(II) activates the substrate via formation of a Cu-substrate adduct and the second Cu(II), oxidises this intermediate. In the SET pathway the electron is removed from the substrate to the copper centre. In the organometallic pathway, the electron is removed from the metal centre during the oxidation step, converting Cu(II) to Cu(III).[69]

Based on the evidence obtained from this study, and comparing against Stahl's review, it is difficult to gauge which pathway applies here (SET electron transfer or organometallic). It may be that both mechanisms apply. The evidence that two copper centres are involved in the catalytic cycle was illustrated earlier when a mixture of $CuCl_2$ (5 mol %) and CuCl (5 mol %) were found to increase reactivity, when compared to $CuCl_2$ (10 mol %) or CuCl (10 mol %).

Halides are redox active and may undergo SET transfer with Cu(II). The evidence from this study highlights that Cu(II) halide salts give phosphorus halides, which can react with carboxylates to give acyl phosphates. Two mechanisms can be derived from the SET pathway. The first possibility is the direct oxidation of iodide, to either give molecular iodine or hypervalent iodine, which could react with diethyl phosphite **14** (Scheme 35, A). The second possibility is the generation of phosphorus centred radicals (or equivalent species) that react with iodide around the copper centre (Scheme 35, B). In this case, both phosphorus and iodine would each donate 1 e^- to the Cu/O_2 oxidant. This second possibility may also follow the 'organometallic pathway'. Finally, the other possibility is that phosphorus donates two e^- directly onto the copper centre *via* disproportionation of the Cu. In this case, the direct reaction with the carboxylate may occur (Scheme 35, C). In this final case the counter anion (X^-) may merely

adjust the redox properties of the copper to facilitate this transformation and not necessarily undergo any chemical change. Scheme 35 applies Stahl's summary to this experiment.



Scheme 35. *Speculative mechanisms for the activation of diethyl phosphite with ligands and potential bridging copper oxygen species omitted for simplicity. B= base (e.g. Et3N).*

2.4. Conclusions and future work

A general method for the synthesis of amides from carboxylic acids has been developed using a practical amount of copper catalyst (10 mol%), generating moderate to good yields. The reaction has been applied to a wide variety of substrates with few problems. It is also possible to use simple techniques to purify the amides that minimise solvent use.

It is possible to scale the reaction but using higher quantities of substrate and solvent requires an increased concentration of oxygen, to increase the rate of reaction.

It appears that the generation of diethyl phosphoryl halide may play a key role in the reaction mechanism but there are other alternatives. The nature of the copper species mediating this reaction is unknown, the reaction is either single electron transfer or proceeds *via* a Cu(III) equivalent. Further investigation into the nature of the copper catalyst will provide better insight into the mechanism. This would involve characterising the redox properties of the copper by cyclic voltammetry, then exploring the EPR experiments in more detail. This could be done by evaluating the reaction between diethyl phosphite and different copper(II) catalysts under different reaction conditions. The generation and analysis of x-ray crystal structures may provide insight into the catalyst structure.

Grignard Additions to Acyl Phosphates

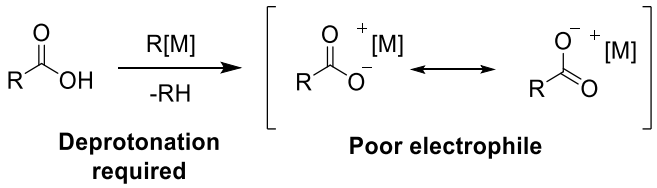
3. Introduction to ketones

Ketones are useful substrates that can undergo many different chemical transformations to produce a wide range of intermediates or final products.[70,71] Our recent success generating amides from carboxylic acids, made us wonder whether it would be possible to synthesise ketones from acyl phosphates, *via* the addition of a suitable organometallic nucleophile.

3.1. Organometallic additions to common acyl derivatives

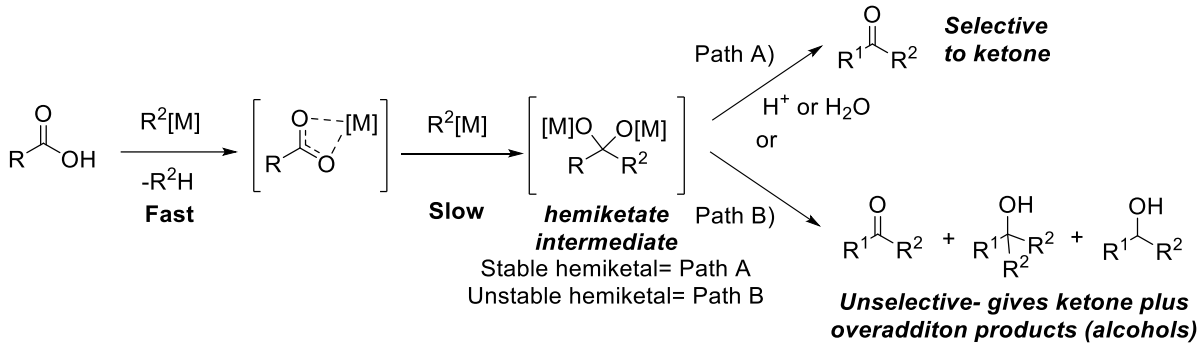
3.1.1. Organometallic additions to carboxylic acids

The direct addition of organometallic reagents to carboxylic acids to produce ketones is challenging. This is because proton on the carboxylic acid will consume 1.00 equivalent of organometallic unless a suitable base is chosen to first deprotonate the carboxylic acid. There is also the requirement to overcome the limited electrophilicity of the carboxylate anion (Scheme 35).



Scheme 35. *General scheme depicting the relative reactivity of organometallic nucleophiles with carboxylic acids.*

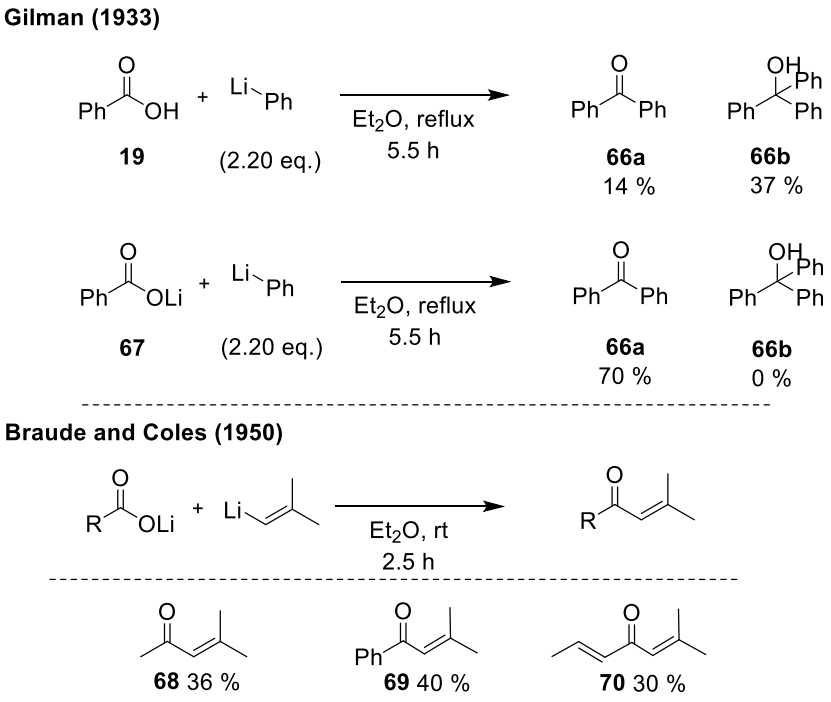
To successfully prepare ketones from organometallic reagents the ketone must not form during the reaction. Therefore, a stable intermediate that collapses on work up is required (Scheme 36). This is because ketones are more reactive than carboxylate anions. Therefore, the organometallic reagent reacts quicker with ketones than the relatively unreactive carboxylate anions. For example, Grignard reagents can react with ketones to produce tertiary alcohols, alternatively they can reduce ketones to secondary alcohols.[72]



Scheme 36. *Overview of organometallic additions to carboxylic acids.*

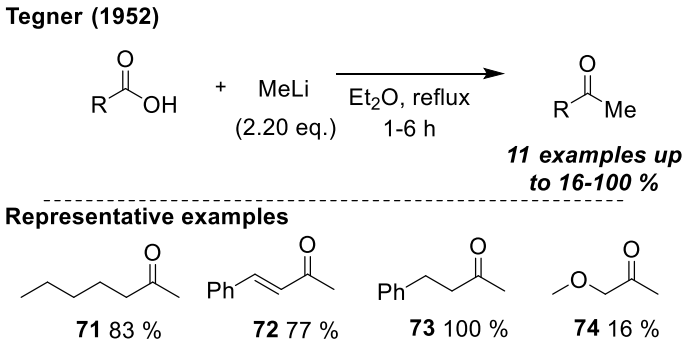
3.1.2. Organolithium addition to carboxylic acids

Organolithium additions to carboxylic acids and carboxylate anions have been studied for nearly 90 years. In 1933, Gilman first showed that reacting benzoic acid with phenyllithium (2.00 eq.) produced a mixture of benzophenone **66a** (37 %) and triphenyl methanol **66b** (14 %) (Scheme 37). However, lithium benzoate **19** was more effective and gave benzophenone **66a** in 70 % yield with no tertiary alcohol (Scheme 37).[73] In 1950, Braude and Coles reported reacting isobutenyl-lithium with lithium carboxylates (Scheme 37), this gave modest yields of ketones (30-40 %).[74]



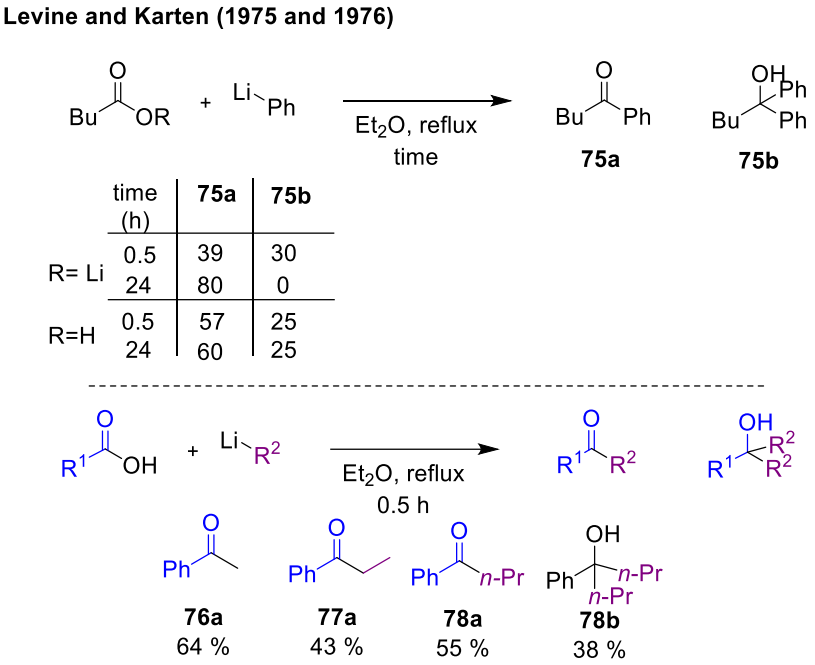
Scheme 37. *Early preparations of ketones by reacting lithium carboxylates with organolithiums.*[73,74]

Over the years, multiple papers have employed methyllithium to prepare ketones from carboxylic acids.[75] One of the earliest successes was reported by Tegner in 1952 (Scheme 38), who reacted MeLi (2.00 eq.) with carboxylic acids to give ketones in good yields (up to 100 %). Acetic acid and formic acid gave no ketone but longer chain aliphatic acids and cinnamic acid were successful at giving methyl ketones.[76]



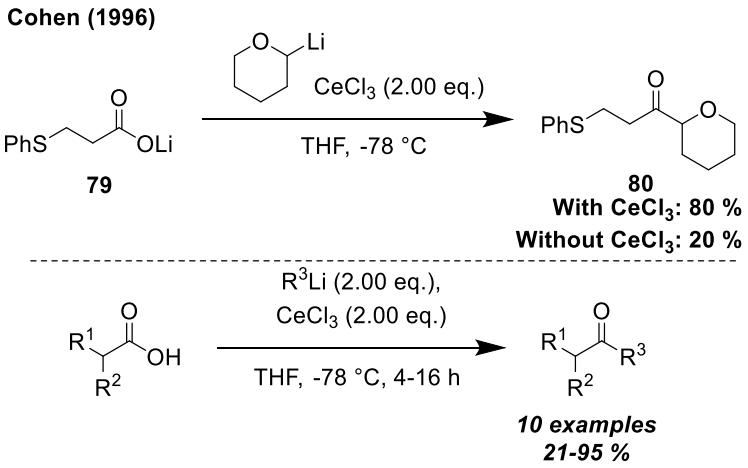
Scheme 38. *Reaction between methyllithium and carboxylic acids.*

In 1975, Levine and Karten revisited the reaction between lithium carboxylates and phenyl lithium (Scheme 39).[77,78] In summary, the lithium carboxylates gave better yields of ketone than when carboxylic acids were used. Interestingly, reacting lithium butyrate with phenyllithium gave better selectivity to the ketone **75a** compared to the tertiary alcohol **75b** when the reaction was left for 24 h instead of 0.5 h (Scheme 39). The authors postulated the better selectivity was because the 0.5 h reaction still had an excess of phenyllithium during hydrolysis of the hemiketal intermediate. As a result, the excess phenyllithium had reacted with the ketone **75a** during work up.[77,78] In a follow up paper Levine and Karten (1976) attempted to react more carboxylic acids with a variety of organolithium reagents (2.00 eq.). They had limited success, with almost all examples producing a mixture of alcohol and ketone. Only MeLi and EtLi reacted with benzoic acid to form exclusively ketone, extending the chain length beyond this resulted in tertiary alcohol formation (Scheme 39).[78]



Scheme 39. *Reaction of lithium butyrate or benzoic acid with phenyllithium.*[77,78]

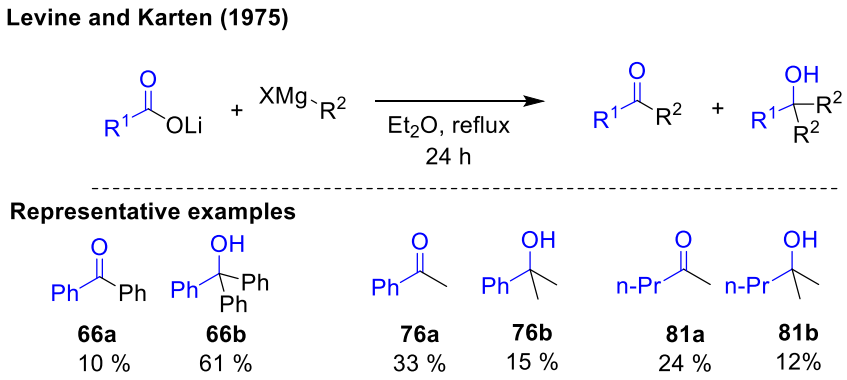
In 1933, Gilman predicted cerium would enhance the reactivity of organolithium reactions with carboxylates.[73] However, it wasn't until 1996 when Gilman's hypothesis was proven and cerium was used to prepare ketones from carboxylic acids. Cohen showed that the addition of stoichiometric cerium could greatly improve the reaction between lithium carboxylates (Scheme 40). In addition to lithium carboxylates, carboxylic acids were also tolerated in good yields. Earlier literature was only successful at reacting methyllithium with carboxylic acids, whereas in this case n-butyllithium and cyclic lithium reagents were also tolerated (Scheme 40).[79]



Scheme 40. *Cerium(III)chloride promoted organolithium addition to carboxylic acids.*[79]

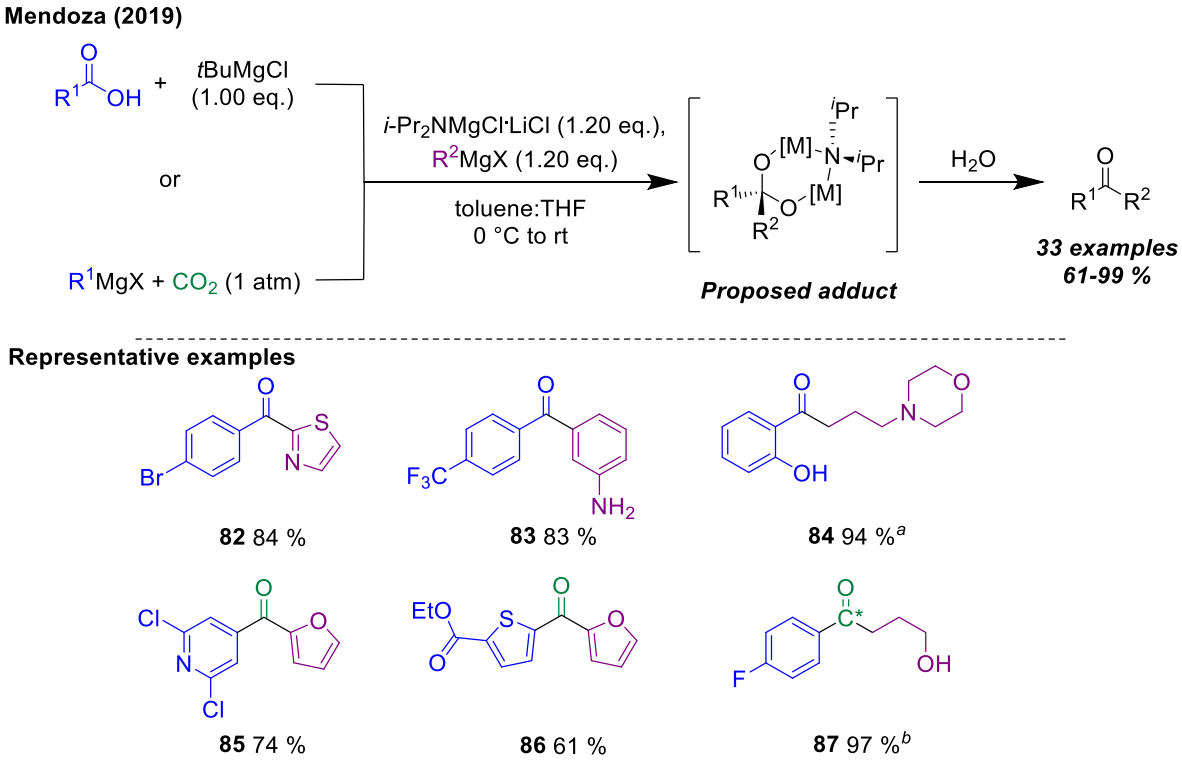
3.1.3. Grignard addition to carboxylic acids

Grignard reagents are preferred nucleophiles for direct organometallic acylation than organolithium reagents, due to their enhanced stability and better functional group tolerance, particularly in large scale processes.[80] Despite the advantages of using Grignard reagents to make ketones, the earlier examples of reacting carboxylates with Grignard reagents were largely unsuccessful because of tertiary alcohol formation. Levine and Karten illustrated this in 1975 by reacting Grignard reagents with lithium carboxylates, all examples were low yielding and produced significant amounts of tertiary alcohol (Scheme 41).[77]



Scheme 41. *Grignard addition to lithium carboxylates.*

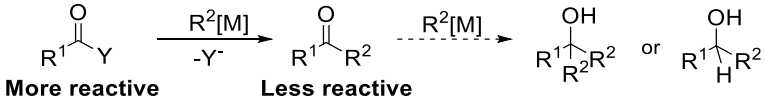
Recently, Mendoza (2019) has demonstrated quite an elegant solution for directly adding Grignard reagents to carboxylate salts to give ketones. The reaction is believed to proceed *via* the formation of a stable metal-diisopropylamine complex (Scheme 42). The carboxylate salts were generated *in situ* from carboxylic acids and *t*BuMgCl (1.00 eq.), or *via* Grignard addition to CO_2 (Scheme 41).[81]



Scheme 41. *Direct addition of Grignard reagents to carboxylate anions and proposed intermediate.*[81] *[a]t-BuMgCl (2.00 eq.) was used. [b]Radiolabeled $^{13}CO_2$ (1 atm) was used.*

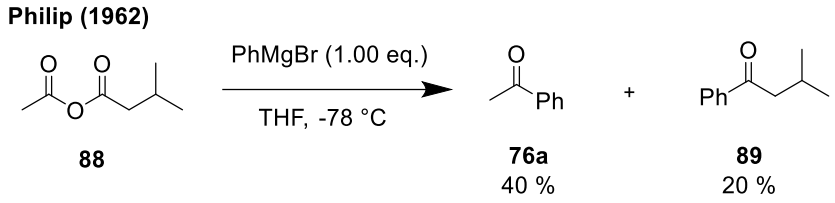
3.1.4. Grignard additions to acid chlorides and anhydrides

Acid chlorides and anhydrides are more reactive to many organometallic reagents than the product ketone and over addition can, in theory, be avoided by changing solvent, additives and temperature.[82]



Scheme 42. *Representation of highly reactive carboxylic acid derivatives for ketone synthesis.*

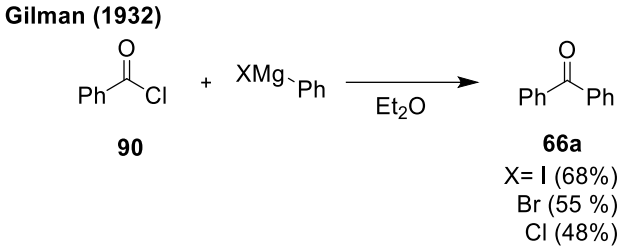
Although acid anhydrides can give ketones, Grignard additions to anhydrides result in poor yields.[83–85] This is because the carbonyl carbon of the anhydride is closer, in terms of relative reactivity, to an ester rather than an acyl chloride. Due to the lower reactivity of acid anhydrides over addition is more likely to occur. Acid anhydrides also sacrifice 1 equivalent of acid. Mixed acid anhydrides can present selectivity issues (Scheme 43). A combination of the said reasons means that acid anhydrides are relatively poor candidates in organomagnesium/lithium chemistry.[83]



Scheme 43. *Example of Grignard addition to mixed acid anhydride at low temperature.*[83]

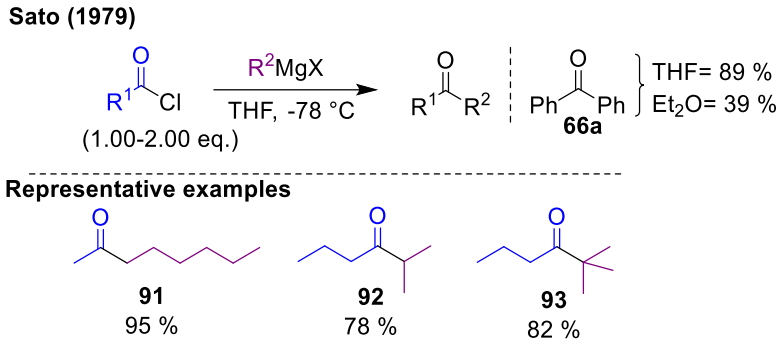
In terms of relative reactivity, acyl chlorides are more reactive than anhydrides. Organolithium reagents can produce ketones from acyl chlorides but due to their high basicity and reactivity, enolization or 1,2-addition to the ketone is more likely, thus, resulting in diminished yields.[82] Due to the advantages of Grignard reagents over organolithium,[81] this section will focus on the development of reacting acyl chlorides with Grignard reagents.

In 1932, Gilman reported the synthesis of benzophenone **66a** with 68 % yield from phenyl magnesium iodide, 55 % from phenyl magnesium bromide and 48 % from phenyl magnesium chloride (Scheme 44). The reaction was described as instantaneous and the formation of the ketone in the reaction mixture was an issue because of over addition to the tertiary alcohol.[86]



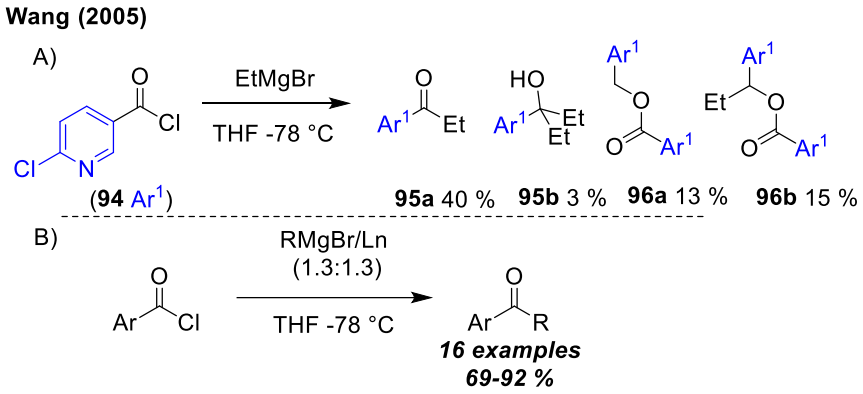
Scheme 44. *Synthesis of benzophenone from benzoyl chloride.*

Over the next 40 years, the direct addition of Grignard reagents to acyl chlorides to make ketones had limited success because the high reactivity of the acid chloride resulted in side reactions, such as tertiary alcohol formation.[82] It wasn't until 1979, when Sato reported that performing Grignard reactions with acyl chlorides at -78 °C in THF produced almost quantitative yields of the desired ketone (Scheme 45), a significant improvement to previously used ether.[87] This approach has been applied to acid chlorides bearing an ester functionality and selectivity was maintained. However, when aliphatic ketones were prepared, an excess of acid chloride (1.30 to 2.00 eq.) was required to give satisfactory yields.[88]



Scheme 45. *Addition of Grignard reagents to acyl chlorides at low temperature in THF.*

Wang (2005) demonstrated more complex substrates were not applicable using the conditions reported by Sato. The addition of EtMgBr to 6-chloronicotinoyl chloride in THF at -78 °C (Scheme 46A) resulted in a 40 % yield of ketone **95a**, with a mixture of tertiary alcohol **95b** (3 %) and esters **96a/b** (28 %). The addition of a ligand, (bis[2-(N,N-dimethylamino)ethyl] ether) to chelate to the magnesium, significantly increased the yield (from 40 to 92 %).[89] This approach was applied to a variety of aromatic acyl chlorides and alkyl/aryl Grignard reagents (Scheme 46B).

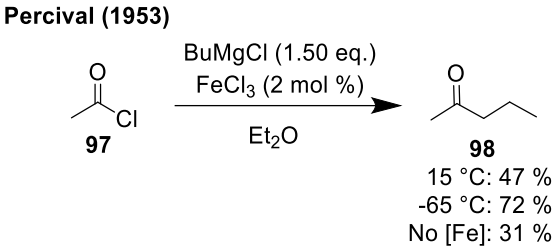


Scheme 46. *A) Reaction of ethyl magnesium bromide with aryl chloride (Ar¹=6-chloronicotinoyl chloride.) B) Modified conditions presented by Wang (Ar= Aryl, R= Alkyl or Aryl, Ln= bis[2-(N,N-dimethylamino)ethyl] ether).*[90]

3.1.5. Ketones from acid chlorides and Grignard reagents using iron or nickel catalysts

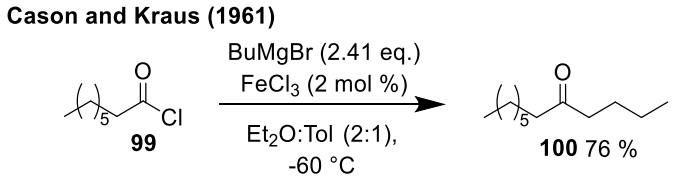
In the years following Gilmans initial reaction between acid chlorides and Grignards, iron chloride showed promise at improving selectivity to the ketone. In 1944, Kharasch reported the first iron catalysed acylation from mesitoyl

chloride and methyl magnesium iodide.[91,92] In 1953, Percival replicated the conditions with aliphatic ketones (Scheme 47). However, enolization and addition to the ketone was an issue when preparing aliphatic ketones.[93] Reducing the temperature to -65 °C minimised side reactions and resulted in a moderate improvement in yield.



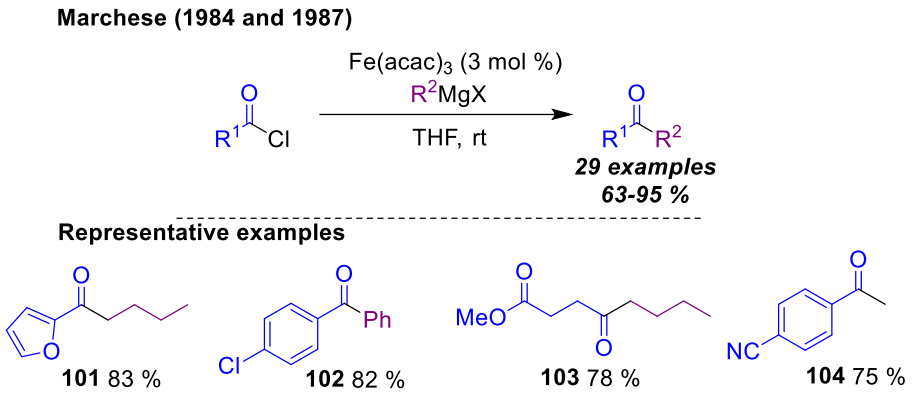
Scheme 47. *Iron-catalysed addition of BuMgCl to acetyl chloride.*[93]

In 1961, Cason and Kraus investigated the $FeCl_3$ catalysed method by using ether:toluene (2:1) at low temperature (-60 °C). The chosen substrates were capryl chloride and BuMgBr. The most successful result was 76 % of ketone and only 3 % tertiary alcohol (Scheme 48).[94]



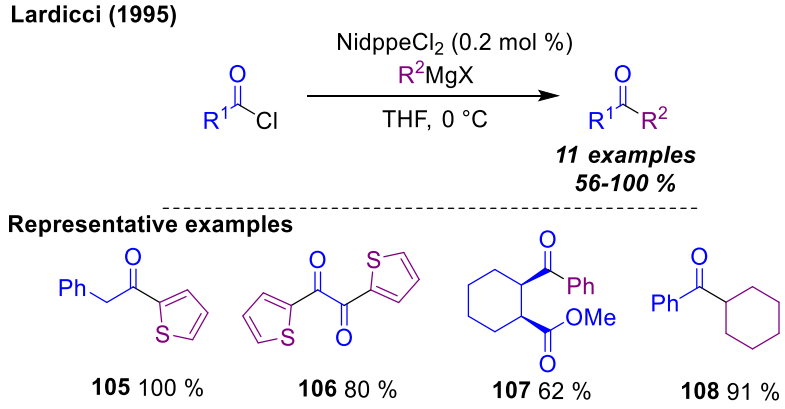
Scheme 48. *Iron-catalysed BuMgBr addition to capryl chloride.*[94]

In 1984, Marchese significantly improved the iron-catalysed Grignard coupling to acyl chlorides, by using $Fe(acac)_3$ at room temperature without an excess of acid chloride (Scheme 49).[95,96] $Fe(acac)_3$ is also less hygroscopic and easier to handle than $FeCl_3$. THF was the solvent used, this further illustrates that THF is more effective than ether at preparing ketones from Grignard reagents and acid chlorides.[92] Marchese further expanded the scope of the iron-catalysed reaction in 1987, by incorporating functional groups that can also react with Grignard reagents, such as esters and nitriles (Scheme 49).[96]



Scheme 49. *Iron-catalysed reaction between acid chlorides and Grignard reagents.*[95,96]

Similarly, to iron, a small amount of nickel catalyst is also reported to improve selectivity to ketone from acid chlorides and Grignard reagents (Scheme 50).[97] Ladicci illustrated this in 1995, by subjecting Grignard reagents to a Ni[0] catalyst ($NidppeCl_2$) and was able to achieve up to quantitative yields of ketone (Scheme 50).[97] Although high yields were observed at mild temperatures and low catalyst loadings, typical reaction conditions were run dilute at 0.01 M initial concentration. The iron-catalysed example by Marchese was run at 0.1 M initial concentration, which is still slightly diluted but 10 times more concentrated than the Ladicci's method.[95,97]

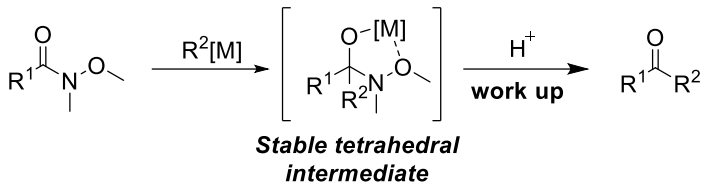


Scheme 50. *Nickel-catalysed reaction between acid chlorides and Grignard reagents.*[97]

3.1.6. Weinreb amides

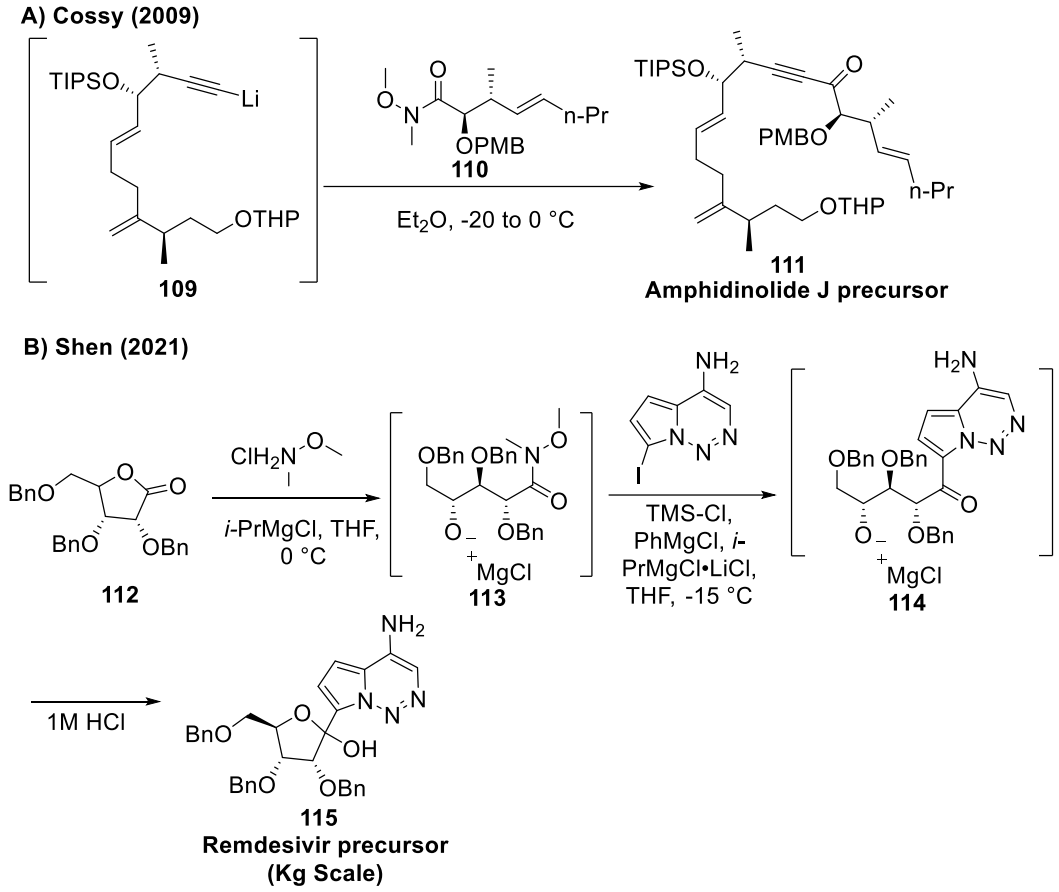
In 1981, Weinreb and Nahm shown that *N*-methoxy-*N*-methylamides, commonly known as Weinreb amides, are effective acylating reagents for Grignard and organolithium additions without generating over addition products. Reactions were performed at 0.1 M initial concentration.[98] Weinreb amides form a stable

tetrahedral intermediate that collapses on work up (Scheme 51). This mechanism was proved by Collum (2006) using in situ IR, and NMR spectroscopy.[99]



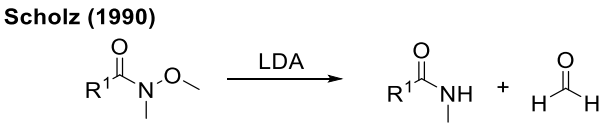
Scheme 51. *Formation of stable metal chelate by organometallic addition to Weinreb amides ([M]= Mg or Li).*

Weinreb amides are perhaps the most common acyl donor used to produce ketones *via* direct organometallic addition, because of their stability and resistance to over addition. They have been employed in many synthetic procedures and can produce ketones with high levels of complexity.[100,101] Applications include; preparation of intermediate ketones in natural product synthesis (Scheme 52, A), and active pharmaceutical ingredients (API's).[102,103,104] Recently, a Weinreb amide has been used in the concise synthesis of a key precursor for Remdesivir **115** (Scheme 52, B), an FDA approved drug for treatment of COVID-19.[104]



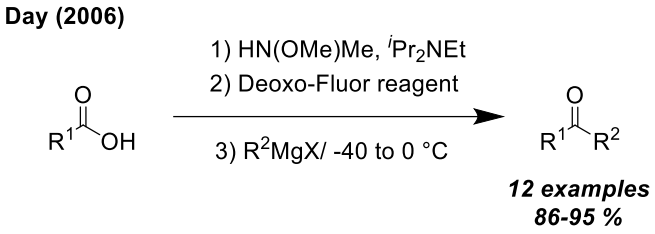
Scheme 52. *Examples of Weinreb amides in natural product synthesis (A),*[103] *and API manufacture (B).*[104]

Weinreb amides can decompose in the presence of a strong hindered base (for example, LDA) because E2-elimination occurs to produce formaldehyde by cleavage the N-O bond (Scheme 53).[105]



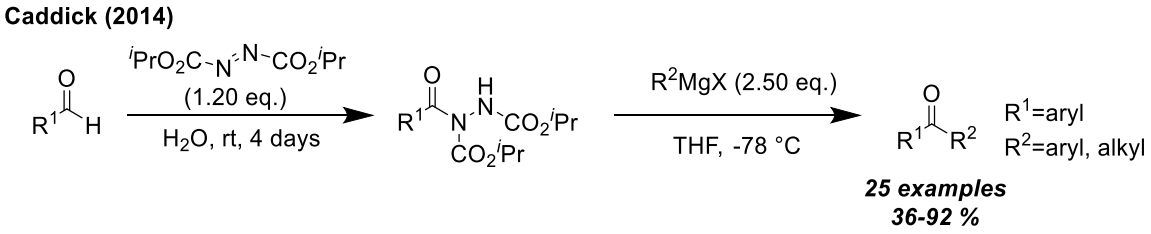
Scheme 53. *Decomposition of Weinreb amide in the presence of lithium diisopropylamine (LDA).*[105]

In order to avoid multiple purification steps, attempts have been made to find more direct strategies that employ Weinreb amides (or similar compounds) as acyl donors. Day (2006) reported *in situ* generation of Weinreb amides from carboxylic acids, however, the reported method, uses stoichiometric fluorinating (Deoxo-fluor®) reagent to generate acyl fluorides in situ (Scheme 54). In addition, 6-7 equivalents of Grignard were used to achieve the reported yields.[106]



Scheme 54. *One-pot synthesis of ketones from carboxylic acids, using Deoxo-Fluor® and HN(OMe)Me.*[106]

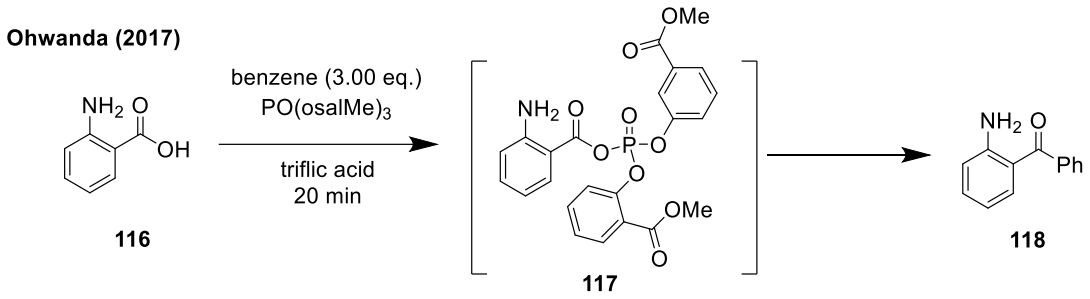
In 2014, Caddick demonstrated aromatic acyl hydrazides can selectively generate ketones from Grignard reagents (Scheme 55).[72] The logic behind Caddick's method is the same as the Weinreb amide approach- the formation of a stable tetrahedral intermediate to produce ketones. The Grignard additions were performed at 0.05 M initial concentration. The acyl hydrazides were prepared in one-step from aldehydes and diispropylazodicarboxylate (DIAD). No additives were used in the preparation of acyl hydrazides; however, long reaction times were required to prepare the starting reagent (Scheme 55).[72]



Scheme 55. *Acyl hydrazides for ketone synthesis.*[72]

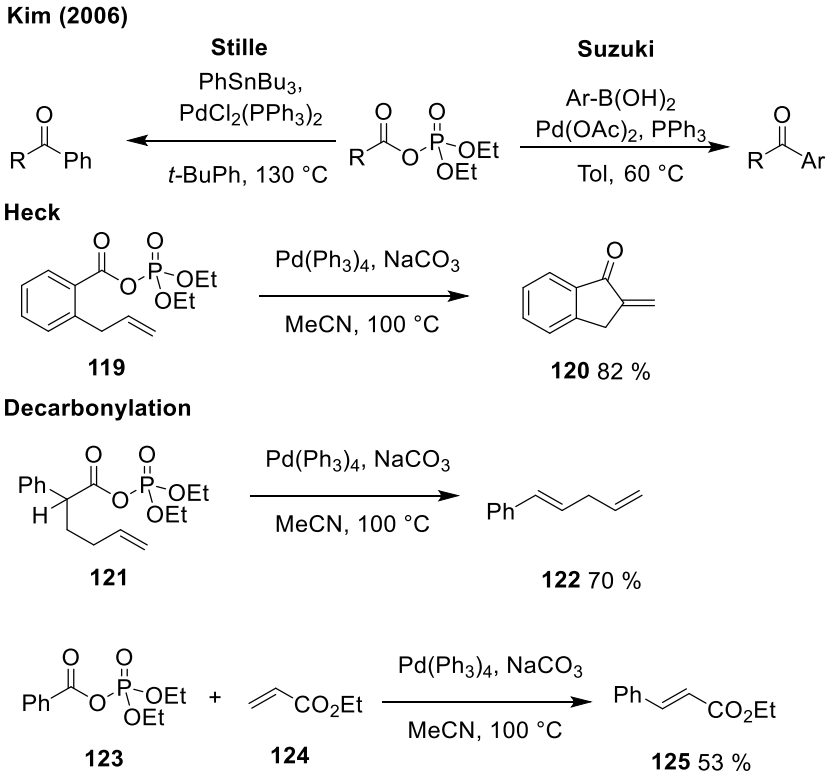
3.2. Ketones from acyl phosphates

Reports of acyl phosphates as acylating reagents in the literature are rather limited. There are some examples of Friedel-Crafts acylation (Scheme 56).[107,108] However, these reactions are limited by difficult to control regioselectivity and the use of stoichiometric Lewis acids.[109] The direct addition of nucleophiles to acylating reagents overcomes the limitations with Friedel-Crafts acylations and allows for the synthesis of non-aromatic ketones.



Scheme 56. *Friedel-Crafts acylation of aminocarboxylic acids using phosphate ester.*[108]

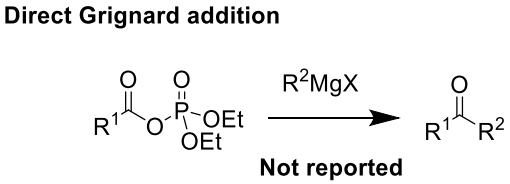
One report employs palladium catalysts to generate ketones from acyl phosphates, in the form of a Suzuki or Stille-type coupling (Scheme 57). The same report demonstrated that Heck reactions were possible. However, coupling of alkenes **121** and **124** resulted in decarbonylation giving **122** and **125**.[110]



Scheme 57. *Palladium cross-coupling reactions using acyl phosphates.*[110]

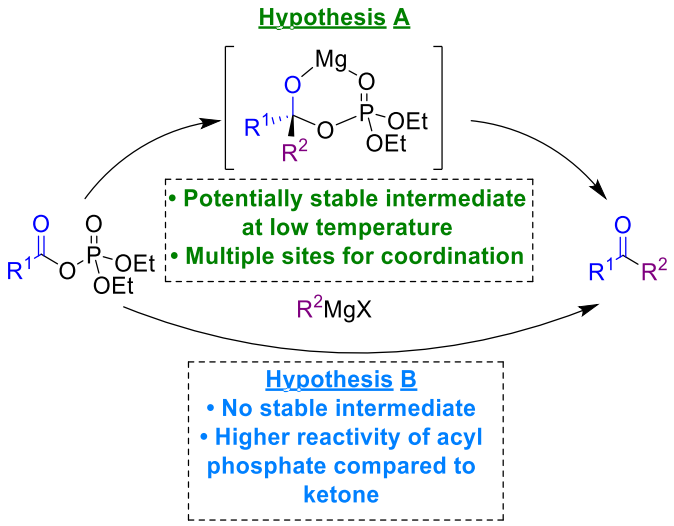
Despite palladium catalysis being an effective method for synthesising ketones, palladium is a rare earth element and is listed on the periodic table of endangered elements. In contrast to palladium, magnesium is more abundant in the earth's crust, therefore, finding effective ways of using Grignard reagents is desirable

from a sustainability perspective. To the best of our knowledge, there are no reports that react Grignard reagents with acyl phosphates.



Scheme 58. *Direct Grignard addition to acyl phosphates.*

Acyl phosphates are advantageous over Weinreb amides because they can be prepared in one-step from carboxylic acids, without requiring stoichiometric coupling reagents.[111] We decided to investigate whether we could use acyl phosphates to selectively generate ketones from organometallic reagents. Hypothesising that acyl phosphates could either form a stable intermediate, or that they would react with Grignard reagents faster than Grignard reagents react with ketones (Scheme 59).



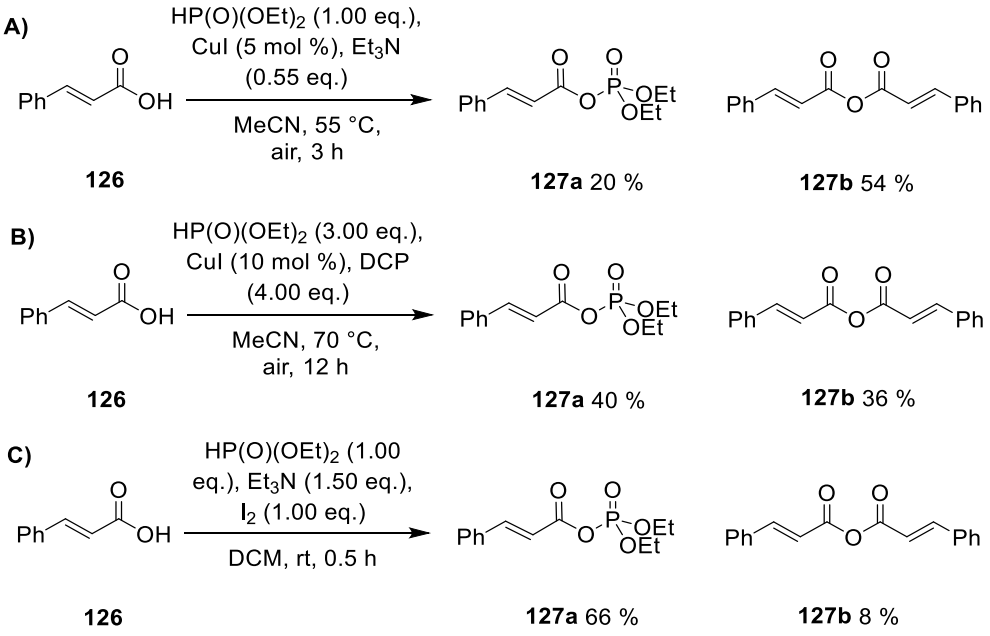
Scheme 59. *Potential pathways for the synthesis of ketones from acyl phosphates.*

The aim of this work is to efficiently prepare acyl phosphates from an appropriate phosphorus(III) reagent, and develop a convenient and effective method that can produce a variety of ketones from the isolated acyl phosphates by nucleophilic substitution with Grignard reagents. Typically, nucleophilic substitution reactions between Grignard reagents and common acyl donors are performed at low concentrations (<0.1 M) to avoid over addition. We aim to perform the reactions at higher concentrations because this will minimise solvent use.

4. Direct organometallic addition to acyl phosphates

4.1. Acyl phosphate synthesis

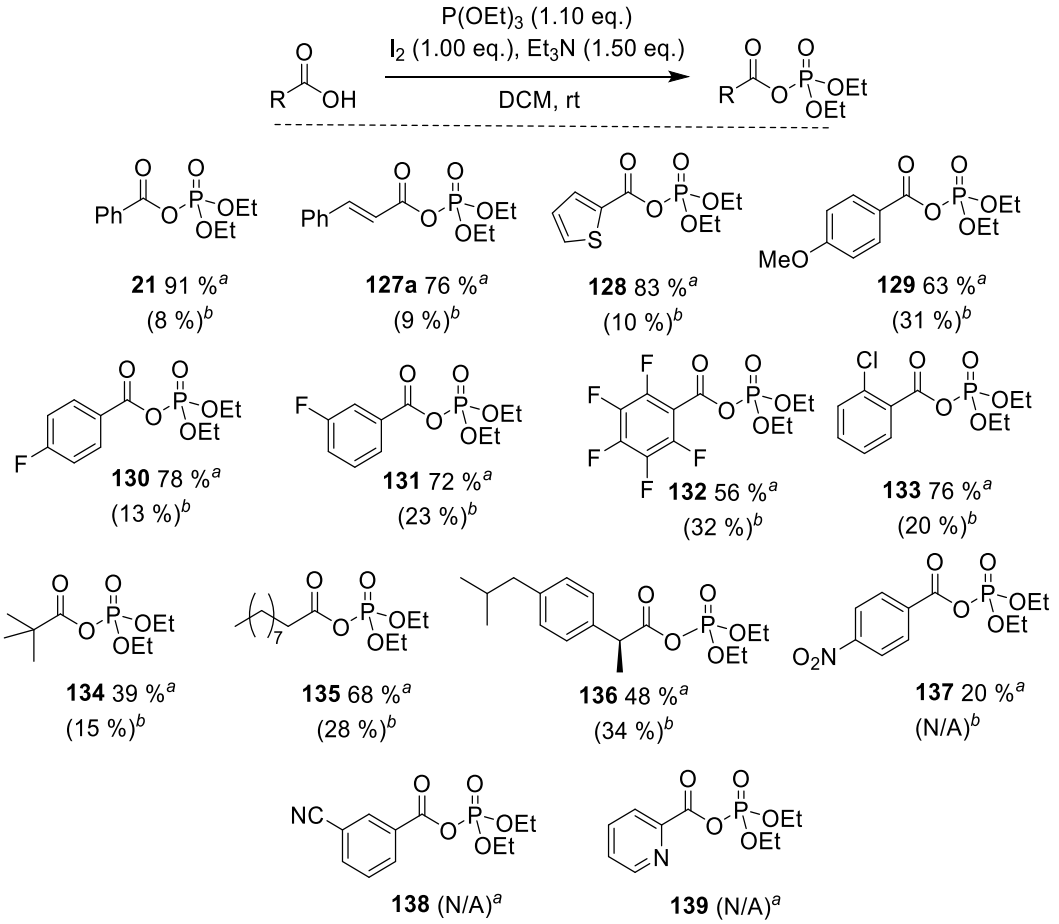
First a suitable method for preparing and isolating acyl phosphates was required. Three methods were attempted (Scheme 60). The two copper-catalysed methods (Scheme 60, A and B) produced the lowest yield of acyl phosphate **127a** because of competing formation of acid anhydride **127b**. The Arbuzov method used by Peng to prepare amides from acyl phosphate intermediates was then attempted.[38] This method gave the highest yield and best selectivity to the acyl phosphate **127a**. As a result, the conditions shown (Scheme 60, C) were used to prepare additional acyl phosphates.



Scheme 60. *Conditions used to determine appropriate method for preparing acyl phosphates.*

Several acyl phosphates were synthesised (Scheme 61), all were purified by column chromatography with no sign of degradation. Phenyl or thiophene carboxylic acids gave in acyl phosphates **21** and **128** in 91 % and 83 % yield respectively, in addition, a 10 % acid anhydride impurity was present in both cases. Using a more electron rich aromatic such as, 4-methoxyphenyl gave a slightly lower yield of acyl phosphate **129** (63 %) and more acid anhydride was also recovered (31 %). 4-Fluorobenzoic acid and 3-Fluorobenzoic acid produced acyl phosphates **130** and **131** in 78 % and 72 % yield. Applying the reaction to a

significantly more electron deficient aromatic such as perfluorophenyl carboxylic acid gave **132** in 56 % yield with 32 % of acid anhydride. 2-Chlorobenzoic acid produced similar results as 3-fluoro and 4-fluoro aromatics and gave **133** in 76 % yield.



Scheme 61. *Acyl phosphate synthesis at 10 mmol scale, yields were from isolated substrates. [a]Acyl phosphate recovered. [b]Acid anhydride recovered.*

In addition to simple aromatic acid phosphates, aliphatic and benzylic phosphates **134-136** were also prepared (Scheme 61). The incorporation of a *tert*-butyl group gave **134** in 39 %, but no significant increase in acid anhydride was observed. Longer chain unsubstituted aliphatic compounds showed good recovery and gave **135** in a 68 % yield. Ibuprofen was used to prepare **136** in 48 % yield. The lower yields associated with **134** and **136** can be justified because of steric hinderance from the additional methyl substituents α to the carbonyl.

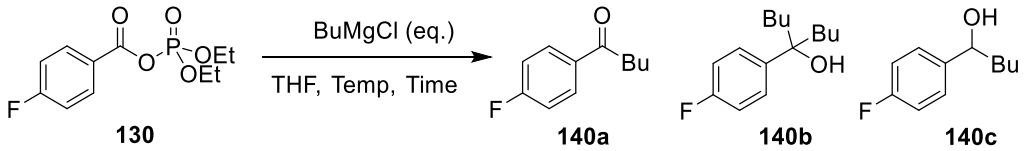
Substrates bearing nitro **137**, cyano **138** or pyridine **139** were not successfully isolated because the polar nature of the substrates resulted in an inability to

separate from anhydride and phosphate impurities. The major phosphate impurity observed was pyrophosphate **22** (^{31}P NMR δ -13.12 ppm).

4.2. Optimisation of Grignard addition to acyl phosphates

4.2.1. Monitoring by ^{19}F NMR

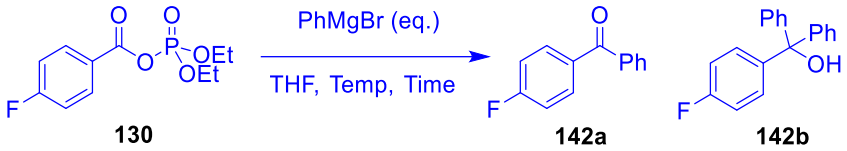
Initially, we investigated the reaction of **130** with nBuMgCl using ^{19}F NMR to monitor the formation of ketone and over addition products (Table 7).[72] Reactions were performed using an initial concentration of 0.75 M. α,α,α-Trifluorotoluene was used as an internal standard. Performing the reaction at -10 °C using BuMgCl (1.0 eq.) produced almost exclusively ketone **140a** compared to tertiary alcohol **140b**, however, trace amounts other compounds and poor mass recovery resulted in an NMR yield of ketone **140a** 60 % (entry 1). Reducing the temperature to -78 °C resulted in a greater mass recovery and cleaner ^{19}F NMR, giving ketone **140a** 83 % by NMR. Further increasing the amount of nBuMgCl (entries 3,4), resulted in a greater quantity of **140b** compared to the amount of **140a**. The addition of BuMgCl (2.0 eq.) and leaving the reaction for longer (entry 5) resulted in almost exclusively **140b**. The addition of nBuMgCl (3.0 eq.) and leaving for 15 minutes resulted in more secondary alcohol **140c**, along with a mixture of **140a** and **140b** (entry 6).



Entry	BuMgCl (eq.)	Temperature (°C)	Time (h)	**130** (-102.8)[a]	**140a** (-105.7)[a]	**140b** (-117.5)[a]	**140c** (-115.4)[a] (lit.)[112]
1[b]	1.0	-10	0.25	0	60 (55)[c]	0.6	0
2	1.0	-78	0.25	5	83 (67)[c]	4	0
3	1.5	-78	0.25	0	74	6	0.4
4	2.0	-78	0.25	0	60	6	0
5	2.0	-78	1.00	0	0	77 (67)[c]	4
6	3.0	-78	0.25	0	29	55	11

Table 7. *Composition of products observed in crude mixture using ^{19}F NMR. α,α,α-Trifluorotoluene was used as an internal standard. [a]Chemical shift. [b]Multiple unknown compounds present. [c]Isolated yield.*

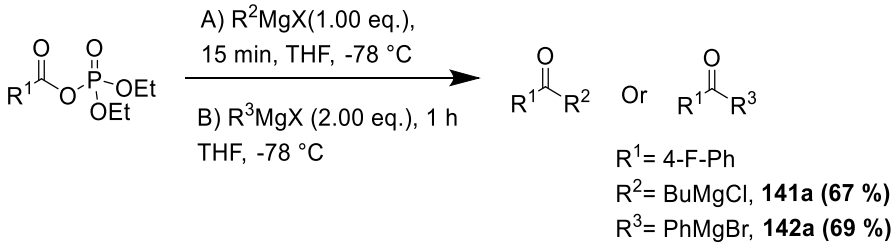
To compare, Matthew Wilkins investigated reacting PhMgBr with **130** to give 4-F-benzophenone (**142a**). Based on the results shown in Table 8, BuMgCl is more reactive towards acyl phosphate **140** than PhMgBr. PhMgBr performed best when (2.00 eq.) was added at -78 °C, because full conversion to **142a** was observed with no tertiary alcohol **142b**. Results shown in blue were obtained by Matthew Wilkins.



Entry	BuMgCl/PhMgBr (eq.)	Temperature (°C)	Time (h)	Relative integration of ketone(**a**):tertiary alcohol(**b**) in ^{19}F NMR			
				141a	**141b**	**142a**	**142b**
1	1.0	-10	0.15	0.93	0.01	0.91 (51)[a]	0.08
2	1.0	-78	0.15	0.95	0.03	0.96	0
3	2.0	-78	0.15	0.9	0.10	0.98 (56)[a]	0
4	2.0	-78	1.00	0	0.92	100 (57)[a]	0

Table 8. *Relative integration of ketone to tertiary alcohol observed in ^{19}F NMR. [a]Isolated yield. Relative integration given in this table because no internal standard was used.*[1]

When entry 4 was repeated, the ketone **142a** was obtained with a higher isolated yield (69 %) than Matthew's attempt. Based on the data obtained by the ^{19}F NMR studies, we determined that the conditions shown in Scheme 62 represent optimal conditions for reacting alkyl and aryl Grignard reagents to the respective acyl phosphates.



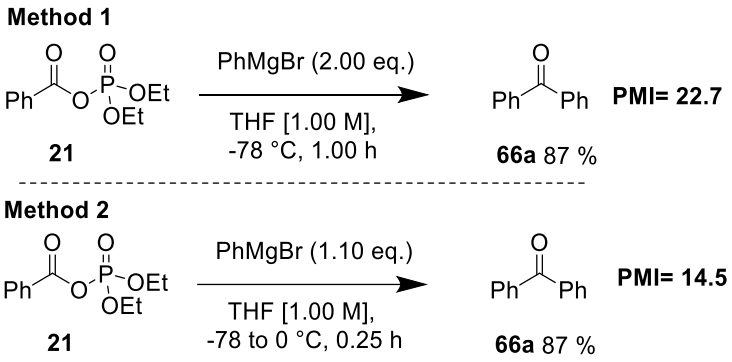
Scheme 62. *Optimised conditions for alkyl and aryl Grignards.*

[1] Results in Blue were obtained by Matthew Wilkins.

4.2.2. Metrics

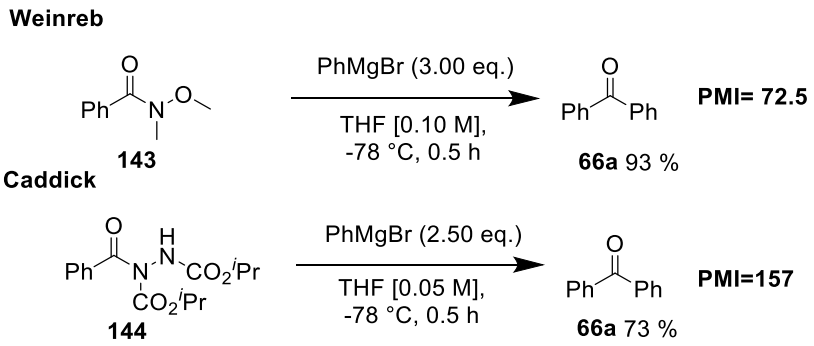
Process mass intensity (PMI) was used to compare Grignard additions to acyl phosphates with previously published literature. PMI=total mass input (Kg)/total mass product (Kg). Benzophenone **66a** was the product ketone used to compare 'this work' with the surrounding literature. Purification was omitted based on the assumption that **66a** can be purified the same way for each of the methods examined.

The optimised reaction between **21** and PhMgBr (2.00 eq.) gave benzophenone **66a** in 80 % yield (Scheme 63, method 1). A reduced loading of PhMgBr (1.10 eq.) and warming to 0 °C gave **66a** in 87 % yield (Scheme 63, method 2). Both reactions were run at 1.00 M initial concentration. Method 1 gave a PMI value of 22.7 and method 2 gave a reduced PMI value of 14.5.



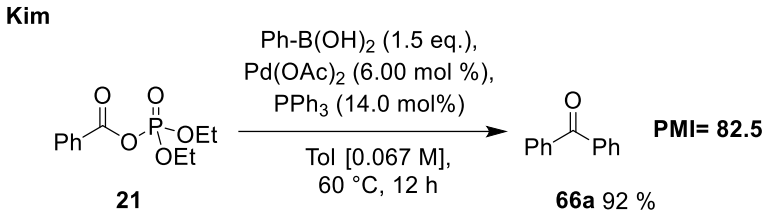
Scheme 63. *Synthesis of benzophenone* ***66a*** *using a reduced loading.*

The Weinreb and Caddick methods prepared **66a** with an initial concentration of (0.10 M and 0.05 M in THF respectively).[72,98] Both reactions gave significantly poorer PMI values (Scheme 64) than this work (Scheme 63).



Scheme 64. *Weinreb and Caddick methods for the synthesis of benzophenone* ***66a.***[72,98]

The Suzuki reaction to synthesise **66a** from acyl phosphates uses a catalyst, and therefore could be considered to be sustainable (Scheme 65).[110] However, excess boronic acid (1.5 eq.) and a low concentration [0.067 M] resulted in a higher PMI value (82.5) than using a Weinreb amide (72.5).



Scheme 65. *Suzuki cross-coupling between acyl phosphate* ***21*** *and phenyl boronic acid.*[110]

As shown from the graph (Fig 12), method 1 and method 2 have significantly lower PMI values than the reported methods. This is due to a reduction in the number of equivalents of Grignard added and a reduction in solvent use.

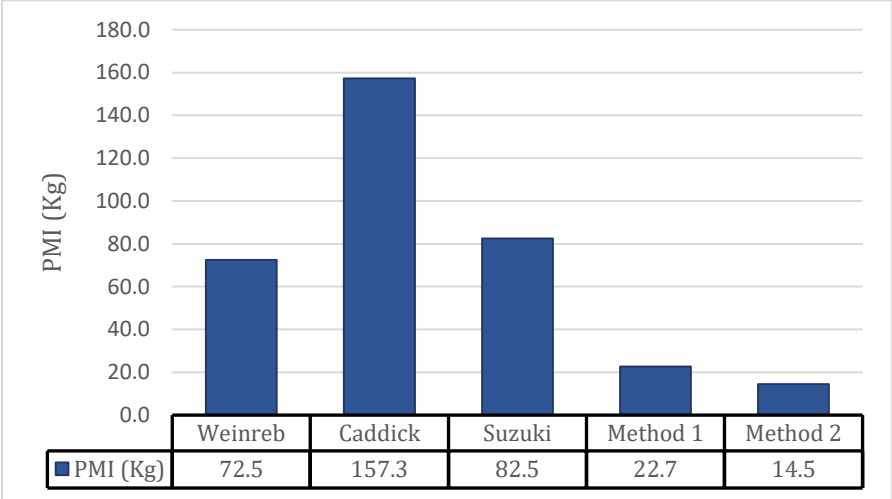


Fig 12. *PMI calculations (excluding purification) for reported benzophenone synthesis via Weinreb*[98]*, Caddick*[72] *and Suzuki*[110] *vs PMI for method 1 and method 2.*

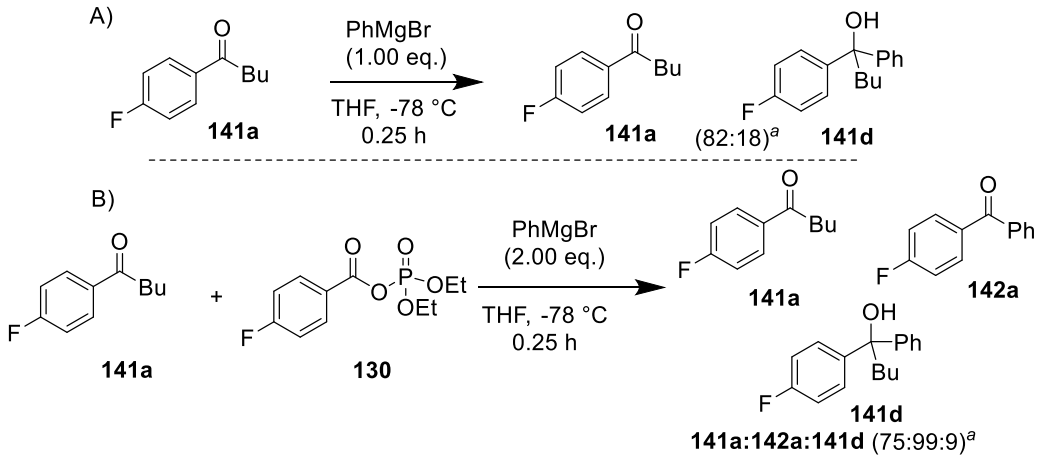
4.3. The reactivity of acyl phosphates vs acid chlorides

4.3.1. Competition reactions between ketones and acyl phosphates

We decided to investigate the reactivity of the acyl phosphate, questioning whether a stable intermediate was likely, or whether the phosphate was simply more reactive than the ketone formed? Results from Table 8 show the reaction will not tolerate higher equivalents of alkyl Grignard, but higher equivalents of aryl Grignard are tolerated.

To determine whether a stable intermediate was likely, a competition experiment between acyl phosphate **130** and ketone **141a** was performed (Scheme 66), postulating that if the Grignard reacts with both **130** and the ketone **141a** under the optimised conditions, a stable intermediate would be more likely. Alternatively, if the Grignard only reacts with **130a** and not the ketone under the standard conditions, the reaction is more likely to proceed selectively due to the acyl phosphate being more reactive than the ketone generated.

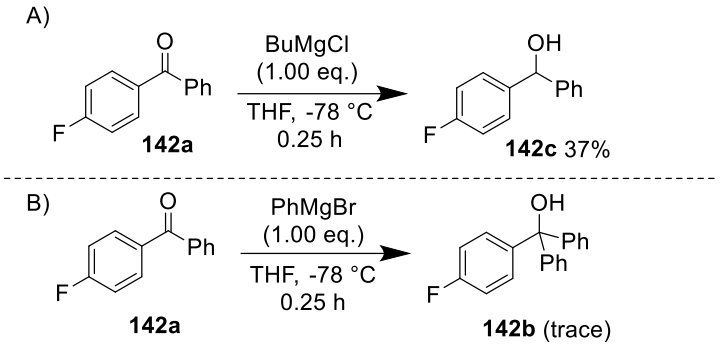
Initially, 1.00 M **141a** in THF (1.00 eq.) was reacted with PhMgBr (1.00 eq.) at -78 °C. This achieved approximately 18 % conversion to the tertiary alcohol **141d** by ^{19}F NMR (Scheme 47a). The next reaction used an equal amount of ketone **141a** (1.00 eq.) and acyl phosphate **130** (1.00 eq.) which was then reacted with PhMgBr (2.00 eq.), this gave about 5 % tertiary alcohol (Scheme 47b.), highlighting the addition to acyl phosphate is more favoured than the addition to the ketone.



Scheme 64. *A) Reaction between **141a** and PhMgBr. B) Competition reaction between **141a** and **130** in the presence of PhMgBr. Relative integration of products, normalised using α,α,α-trifluorotoluene as an internal standard.*

The deprotonation of **141a** is a competing reaction that would regenerate the ketone upon work up. However, attempting to react BuMgCl (1.00 eq.) with a non-enolizable ketone (**142a**) resulted in approximately 37 % conversion to the secondary alcohol **142c** (Scheme 65A), and therefore did not provide a sufficient benchmark to prove/disprove our hypothesis. The presence of **142c** was identified by ^{1}H NMR (δ 5.80 (s) and 2.46 (br. s.) ppm) and ^{19}F NMR (δ -114.9

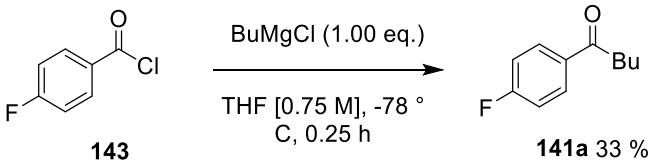
ppm), the chemical shifts matched literature values.[113] Interestingly, when **142a** was subjected to PhMgBr at -78 °C no addition to the ketone occurred (Scheme 65B).



Scheme 65. *BuMgCl and PhMgBr additions to aryl ketone* ***142a***

4.3.2. Comparison with acid chlorides using ^{19}F NMR

To further understand the reactivity between acyl phosphates and Grignard's reagents, a comparative study between 4-fluorobenzoyl chloride **143** and acyl phosphate **130** was performed. Initially, 4-fluorobenzoyl chloride **143** was reacted with BuMgCl at -78 °C using the same conditions as the analogous acyl phosphate reaction **130** (Scheme 66). The reaction was conducted at 0.75 M initial concentration and gave a low yield of ketone **141a** 33 %. The same reaction using acyl phosphate **130** gave **141a** in 68 % yield.

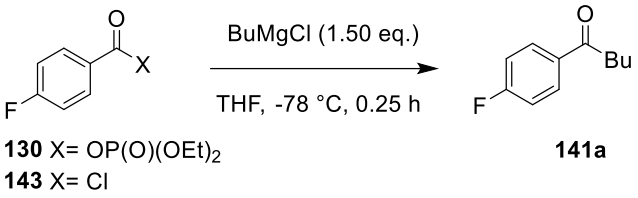


Scheme 66. *BuMgCl addition to acid chloride.*

Based on the previous observations it is apparent that BuMgCl reacts with **141a** to give over-addition products at low temperature and was therefore, the selected nucleophile for the comparative studies.

^{19}F NMR was used to evaluate the crude material in both acid chloride **143** and acyl phosphate **130** reactions (Scheme 67). BuMgCl was used in excess (1.50 eq.) for both experiments under the optimised conditions (THF, -78 °C, 0.75 M initial concentration). The quality of the acyl phosphate spectrum (Fig 13, A) was much

cleaner than the acid chloride spectrum (Fig 13, B). The acyl phosphate spectrum only possessed ca. 5 % tertiary alcohol at 117.5 ppm (Fig 21, A).



Scheme 67. *Conditions used for ^{19}F NMR comparison between acyl phosphate* ***130*** *and acid chloride* ***143****.*

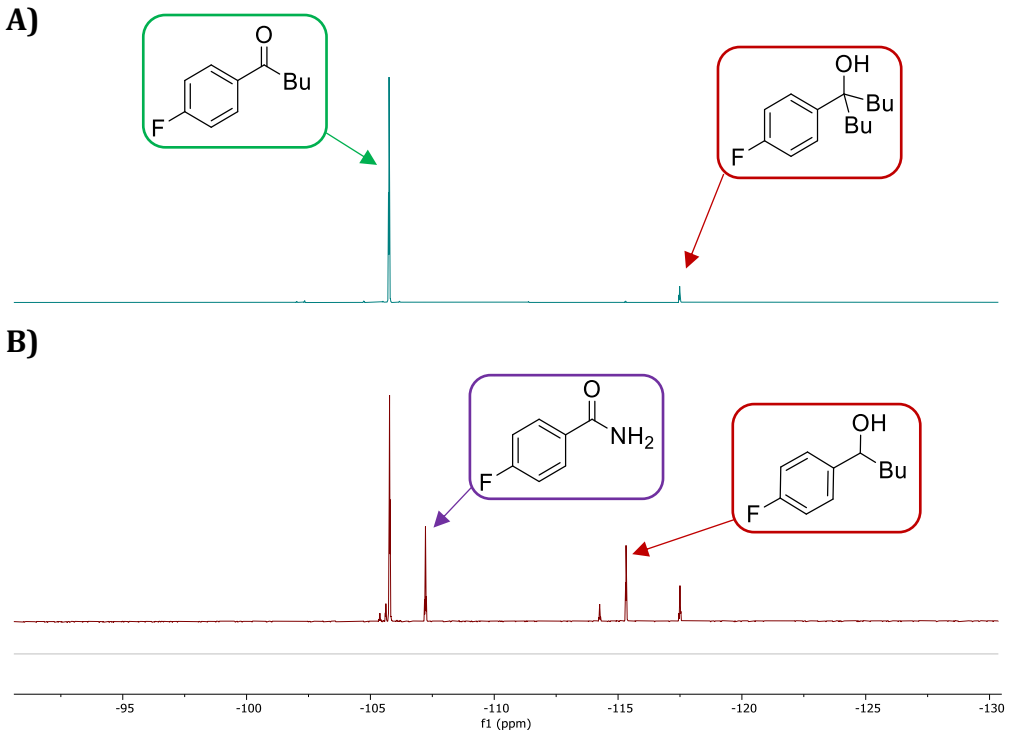


Fig 13. *A) Reaction between acyl phosphate* ***130*** *and BuMgCl (1.50 eq.) at -78 °C. B) Reaction between acid chloride* ***143*** *and BuMgCl (1.50 eq.) at -78 °C.*

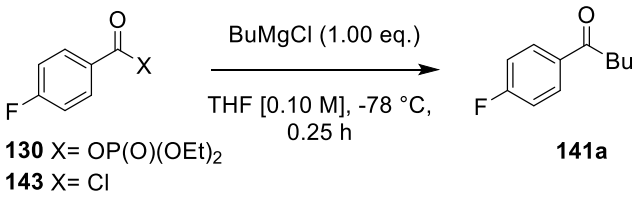
The addition of BuMgCl to 4-Fluorobenzoyl chloride (**143**) produced a mixture of compounds. The secondary alcohol (**141c**) accounted for around 20 % of the crude mixture. No reduction to the secondary alcohol was observed when using acyl phosphate **130**. The tertiary alcohol (**141b**) was also more prominent in the acid chloride reaction accounting for 10 % of the impurities. The acid chloride crude spectrum contained 24 % 4-fluorobenzamide (107.2 ppm) indicating the reaction had not gone to completion and the unreacted acid chloride had instead

reacted with the ammonium chloride quench. The acid chloride spectrum (Fig 13B) also contained some unknown impurities.

Interestingly, no evidence of unreacted acyl phosphates was visible in the crude mixture of the acyl phosphate reaction. Indicating Grignard reagents are more reactive to acyl phosphates than acid chlorides, the other alternative is that the acyl phosphates are destroyed upon work up.

4.3.3. ReactIR and kinetics

Next, ReactIR was used to monitor both acyl phosphate **130** and acid chloride **143** reactivity with BuMgCl (1.00 eq.) at -78 °C (Scheme 67). Measurements were taken every 30 s (128 scans). The intensity of the carbonyl peaks for the acyl donor (**130** (1746 cm^{-1}) or **143** (1779 cm^{-1})) were measured to show consumption of the acyl donor. The appearance of the carbonyl for the ketone **141a** (1689 cm^{-1}) was used to measure ketone formation. The acyl phosphate **130** reaction with BuMgCl was quick, therefore the following reactions were performed at 0.10 M initial concentration to get a better indication of what is happening during the reaction.



Scheme 67. *Reactions investigated by ReactIR, initial concentration [0.10 M].*

The relative peak heights from the carbonyl stretches were then converted into concentrations for starting material consumption (Fig 14) and ketone formation (Fig 15). A 5-point calibration graph was prepared to calculate ketone formation (See appendices).

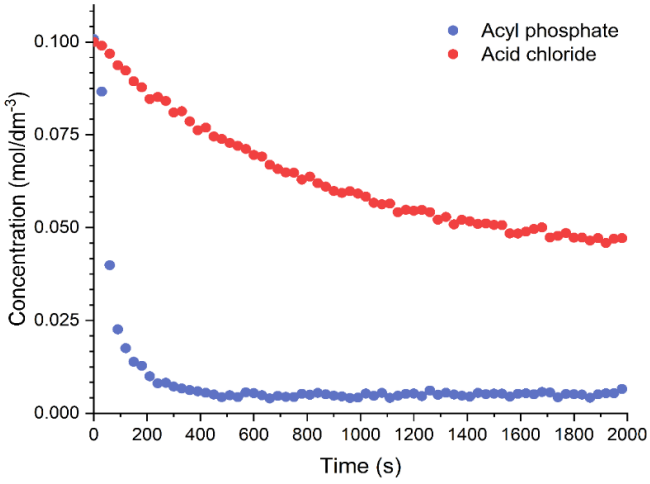


Fig 14. *Graph showing relative consumption of acyl phosphate* ***130*** *(blue) and acid chloride* ***143*** *(red). Reactions performed at -78 °C, initial concentration [0.1 M] and BuMgCl (1.00 eq.) was added in one portion.*

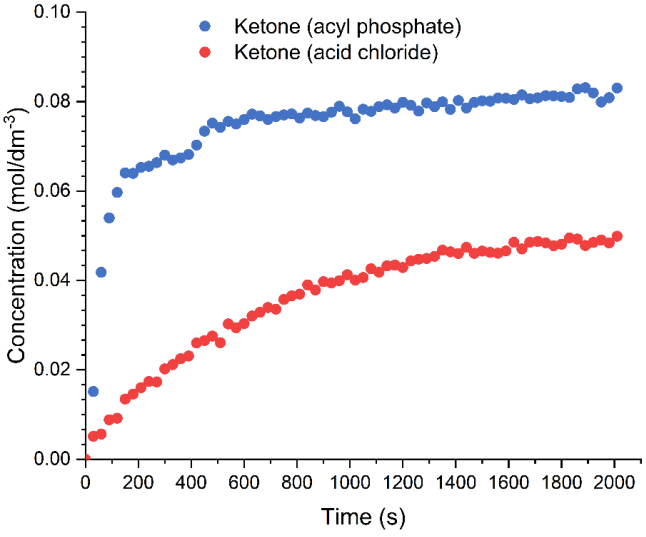


Fig 15. *Graph showing formation of ketone* ***141a*** *from acyl phosphate* ***130*** *and acid chloride* ***143****.*

It is clear from Fig 14 that Grignard reagents are more reactive towards acyl phosphates than acid chlorides. Both acyl phosphate **130** and acid chloride **143** display 2nd order kinetics with respect to consumption of the acyl donor. Plotting this data using the integrated rate law (Equation 1) revealed that acyl phosphate **130** has a rate constant k = 436x10^{-3} M^{-1}s^{-1} ± 11.4x10^{-3} (Fig 16), whereas acyl chloride **143** has a rate constant k = 7.22x10^{-3} M^{-1}s^{-1} ± 0.0083x10^{-3} (Fig 17).

$$\frac{1}{[A]} = \frac{1}{[A]_0} + kt$$

Equation 1. *Integrated rate law (2nd order) used to plot linear graphs. A= acyl donor (**130** or **143**)*

In addition to the integrated rate law, a non-linear fit was also used to calculate k and the results were similar with acyl phosphate **130** k = 485x10^{-3} M^{-1}s^{-1} ±10.7x10^{-3} (Fig 18) and acid chloride **143** k = 7.32x10^{-3} M^{-1}s^{-1} 0.0083x10^{-3} (Fig 19).

$$t_{\frac{1}{2}} = \frac{1}{k[A]_0}$$

Equation 2. *half-life ($t_{1/2}$) derived from 2nd order rate law.*

At 0.1 M acyl phosphate **130** has a calculated half-life ($t_{1/2}$) between 20-23 s, comparatively acid chloride **143** has a half-life between 1366-1388 s in the presence of BuMgCl (1.00 eq.). The data provided in this study shows that the reaction between BuMgCl and acyl phosphate **130** is around 60-70 times faster than the equivalent reaction using acid chloride **143**.

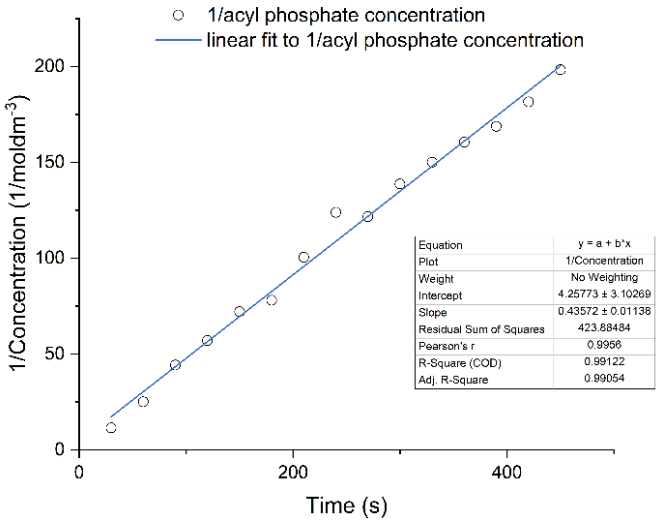


Fig 16. *Integrated rate graph for acyl phosphate **130** in the presence of BuMgCl. Rate constant k = 4.36x10^{-1} M^{-1}s^{-1}.*

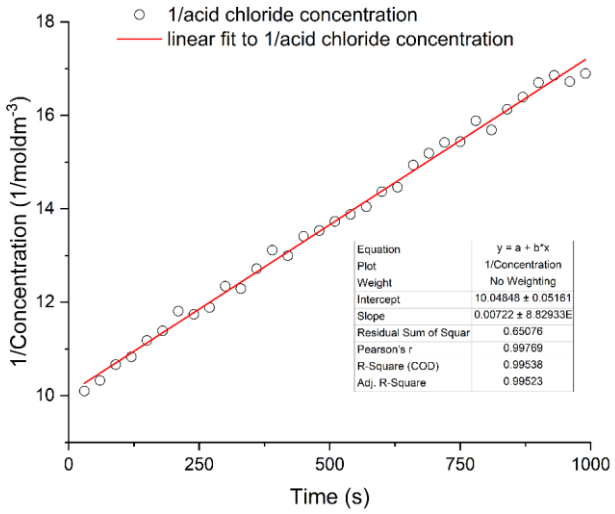


Fig 17. *Integrated rate graph for acid chloride* ***143*** *in the presence of BuMgCl. Rate constant* $k = 7.22 \times 10^{-3}\ M^{-1}s^{-1}$

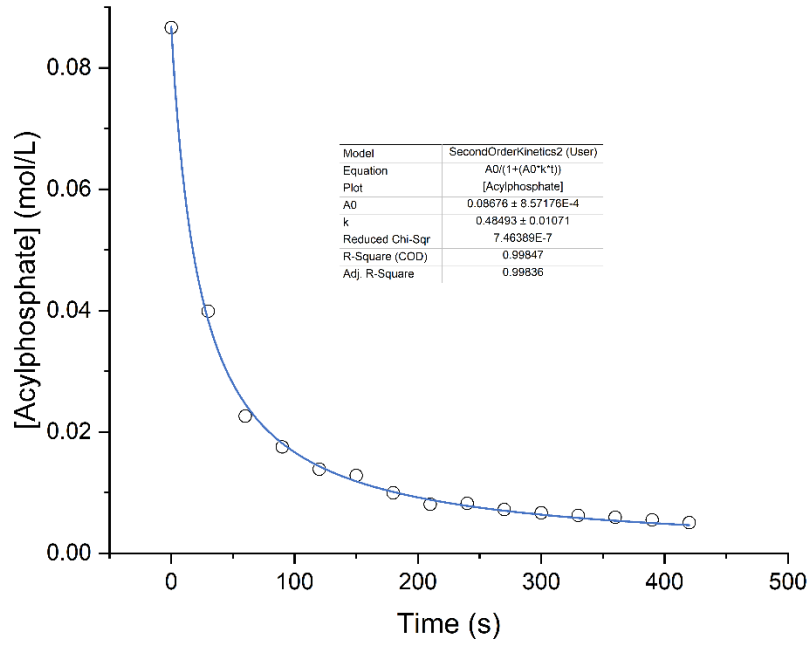


Fig 18. *Non-linear fit for acyl phosphate* ***130*** *in the presence of BuMgCl. Rate constant* $k = 4.85 \times 10^{-1}\ M^{-1}s^{-1}$.

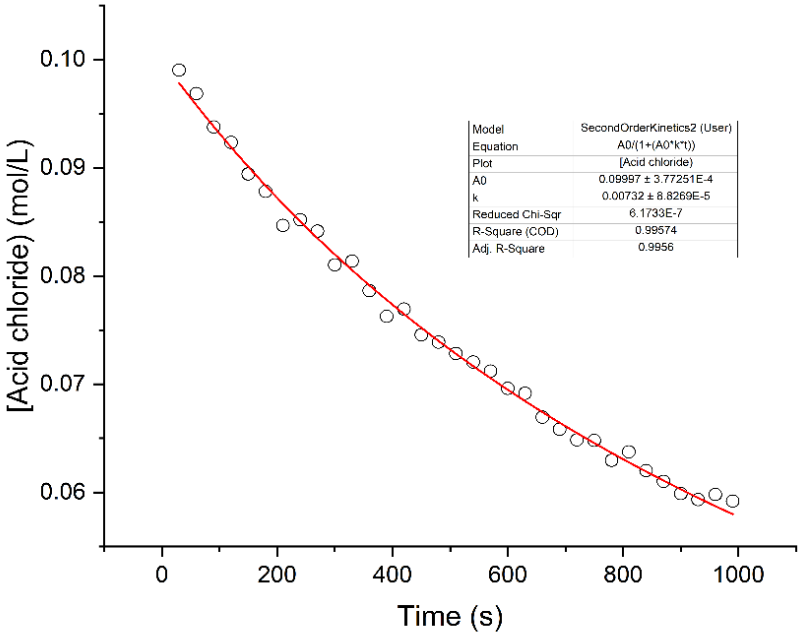


***Fig 19**. Non-linear fit for acid chloride **143** in the presence of BuMgCl. Rate constant $k = 7.32x10^{-3}$ $M^{-1}s^{-1}$.*

The ReactIR data suggests that a stable intermediate is not the factor that dictates the selectivity towards the ketone, but the selectivity is in fact because acyl phosphates are highly reactive towards Grignard reagents. Acid chlorides are regarded as potent electrophiles, yet in this reaction the acyl phosphate is clearly the more potent electrophile.

The presence of the phosphate group could influence the reaction by disrupting the Schenck equilibrium. It is believed that the dimeric alkyl magnesium species more reactive than the monomeric form.[114,115] Dioxane is known to force the Schlenck equilibrium to the dialkyl magnesium perhaps the phosphate could incorporate similar properties.[116] However, the Schlenk equilibrium is more complex than simple dimers and monomers, the formation of oligomers adds to this complexity.[80,115]

In addition to the Schlenk equilibrium there is still ambiguity between the mechanism of Grignard additions to ketones.[114] It is debated whether the reaction proceeds *via* a concerted two-electron mechanism or by single electron

transfer. Without performing the necessary experiments, it would be impossible to tell which mechanism applies to Grignard addition to acyl phosphates.

Woerpel recently showed that most Grignard additions occur *via* a two-electron mechanism. Exceptions include Turbo Grignard reagents and perfluorophenyl ketones, which proceed *via* a mixture of two electron or single electron processes.[117] Assuming the reaction proceeds *via* a two-electron process polarity and electronegativity would define parameters for the reactivity of Grignard reagents. At this point it is unclear what the exact effect the polar phosphate group has on the nucleophilicity of the Grignard reagent, however, it is known that chelating agents can supress Grignard addition to ketones.[89] Perhaps the enhanced reactivity is observed because the phosphate group serves a dual purpose:

1) Coordination of the acyl phosphate to the magnesium allows for better orientation to the π* acceptor (carbonyl).
2) Coordination of the phosphate leaving group to the Grignard reagent supresses reactivity to the ketone.

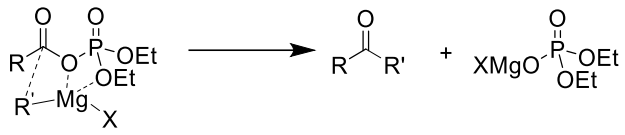
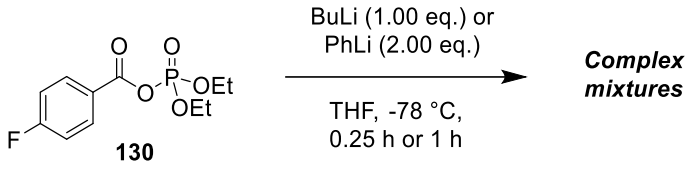


Fig 20. *Illustration depicting possible coordination effects of phosphates with Grignard reagents (X=Cl, Br, R' etc.).*

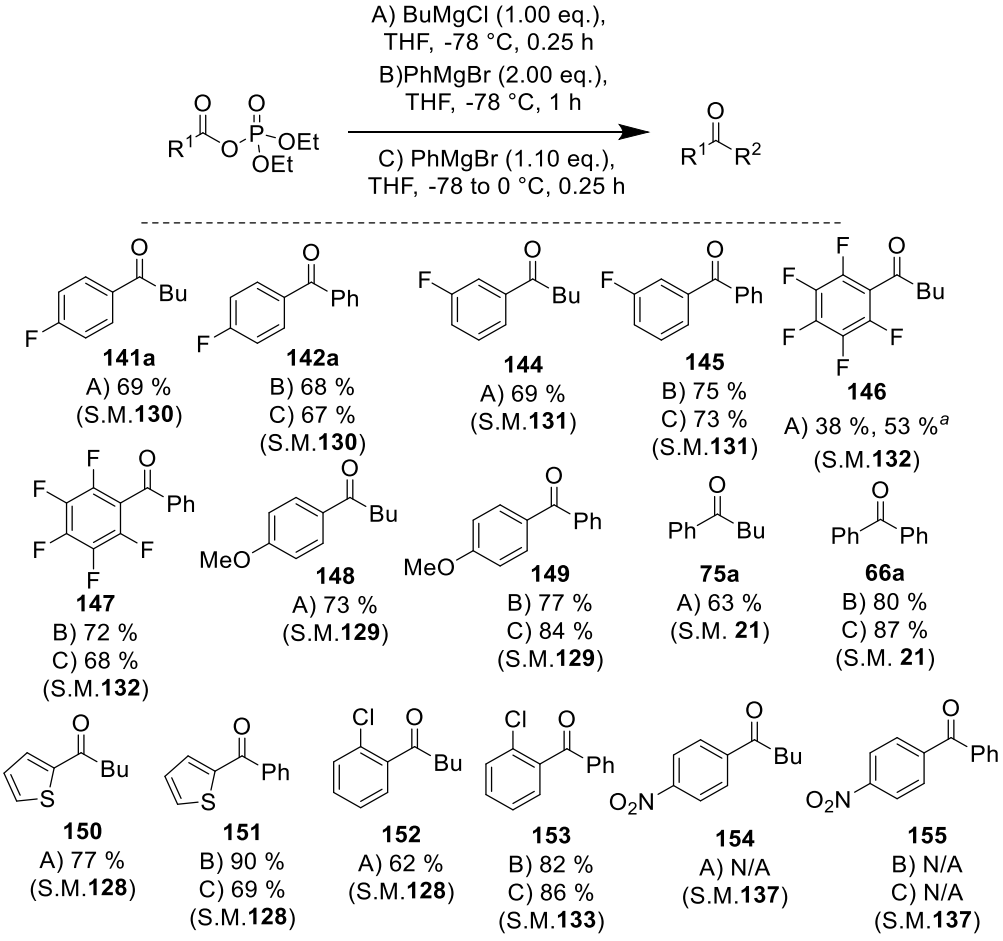
4.4. Substrate Scope

The addition of organolithiums (BuLi and PhLi) to **130** resulted in complex mixtures of products, with the tertiary alcohol being the major by-product in both cases (Scheme 68). Perhaps, the more basic nature of organolithiums combined with a lesser ability to coordinate to the phosphate compared to organomagnesium results in a less selective reaction.



Scheme 68. *Organolithium additions to acyl phosphates.*

A variety of aromatic acyl phosphates were reacted with BuMgCl and PhMgBr respectively (Scheme 69). Fluorine containing aromatics were used, addition of BuMgCl to the 3-Fluorophenyl substituted acyl phosphate **131** gave a slightly lower yield of ketone **145** (58 %), compared to the 4-Fluorophenyl substituted acyl phosphate **130** that resulted in a 68 % yield of **141a**. The phenyl additions to **131** were higher yielding, producing ketone **145** in 75 and 73 % yield.



Scheme 69. *BuMgCl and PhMgBr additions to aromatic acyl phosphates (S.M.=acyl phosphate).* [a]*BuMgCl (1.50 eq.) was used.*

Addition of PhMgBr to perfluorophenyl substituted acyl phosphate **132** gave similar yields of ketone **147** (72 and 68 %) as additions to 4-fluorophenyl **130**

and 3-fluorophenyl **131** derivatives (Scheme 69). However, BuMgCl addition to **132** only resulted in a 38 % yield of ketone **146**; in addition to the low yield trace amounts of multiple unknown impurities were also observed. The presence of unknown impurities could either be due to single electron transfer processes because of a lower energy π* orbital of **132**, or the more electron deficient carbonyl is susceptible to over addition.[117] It was postulated that enolization could be an issue because of a more electron deficient product ketone (**132**), as a result more of the Grignard reagent would be consumed before addition to the ketone, to counteract this, the equivalents of BuMgCl were increased from 1.00 to 1.50 resulting in a modest improvement in yield, isolating **146** in a 53 % yield.

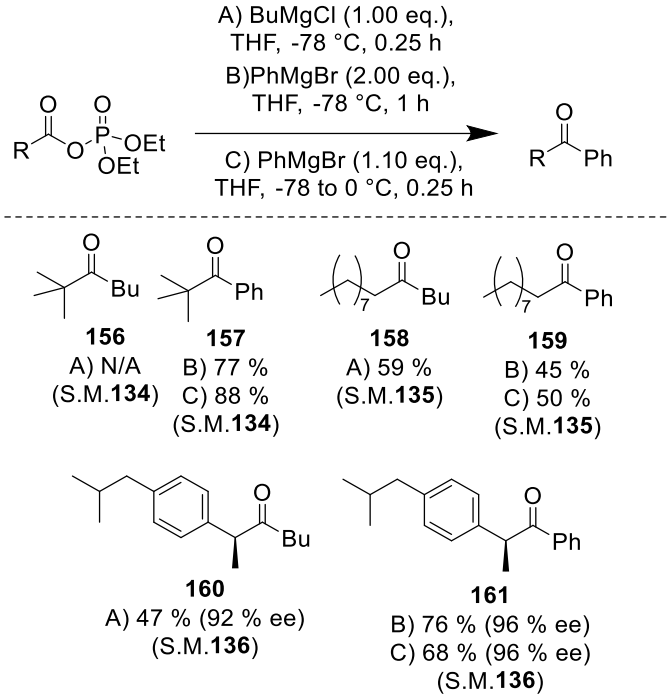
In theory, the use of more electron rich aromatic acyl phosphates (**129** and **128**) may produce less acidic ketones that would be less susceptible to deprotonation, therefore, resulting in higher yields of ketone. This hypothesis was supported because ketones **148** and **150** were isolated in 73 % and 78 % yields, respectively.

PhMgBr additions to phenyl- and 2-chlorophenyl- **21** and **152** produced ketones in over 80 % yield, whereas BuMgCl additions to **21** and **152** gave poorer yields, 63 % and 62 % respectively. Additions to nitro substituted acyl phosphate **137** resulted a complex mixture because the nitro group is also susceptible to reduction.

On average PhMgBr additions were approximately 15 % higher yielding than the BuMgCl additions to aromatic acyl phosphates. This can be attributed to the enolization of the product ketones that are quickly formed in solution.

Grignard reagents were also reacted with aliphatic and benzylic acyl phosphates (Scheme 70). Compound **156** was not isolated due to difficulty handling the product ketone. The addition of PhMgBr to *tert*-butyl acyl phosphate **134** resulted in high yields of **157** (77 % and 88 % respectively). The same addition to decanoyl phosphate **135** gave **158** in 45-50 % yield and about 10 % tertiary alcohol was isolated. The higher yields obtained from **157** are likely because there are no enolizable protons in the product, in addition the steric hinderance

from the *tert*-butyl group could prevent over addition. **135** and BuMgCl gave a modest yield of **159** (59 %).



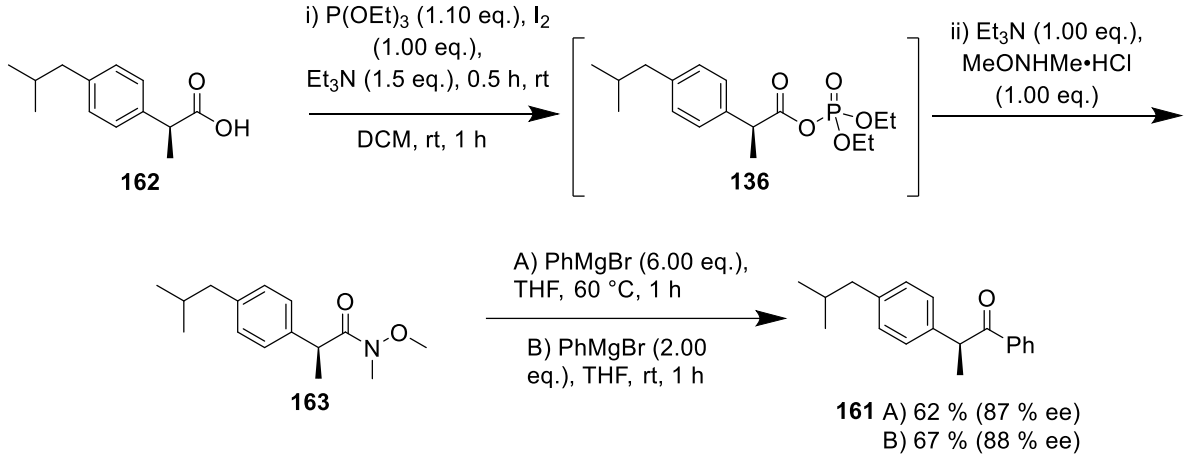
Scheme 70. *BuMgCl and PhMgBr additions to aliphatic acyl phosphates.*

Using a methyl substituted benzylic acyl phosphate such as **136** produced **161** in 76 % (96 % ee) and 68 % yield (96 % ee) with only trace amounts of over addition observed, highlighting that low sterically hindered unsubstituted aliphatic ketones are more prone to over addition (Scheme 70). The level of epimerisation with BuMgCl addition to **136** was slightly lower and gave **160** 47 % (92 % ee).

The enantiomeric excess observed with both Grignard additions to **136** was higher than the enantiomeric excess observed with the benzyl amine derivative (**5**) that was prepared using the copper catalysed approach in Chapter 1. This result is surprising because the mechanism for epimerisation of **5**, **160** and **161** occurs *via* deprotonation of the α-hydrogen, Grignard reagents are strongly basic and ketones are more electron withdrawing than amides, therefore, it was expected epimerisation would occur more readily when preparing ketones **160** and **161**. Although it is possible that epimerisation could occur during carboxylic acid activation/acyl phosphate formation, the high enantiomeric excess observed

from the product ketones shows that that the enantiomeric excess was not eroded during acyl phosphate stage.

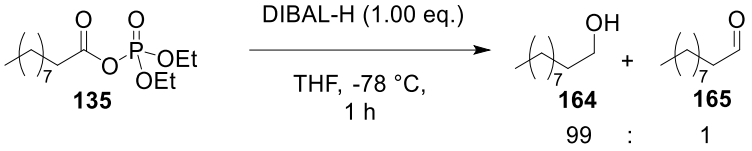
To further investigate the effects of Grignard reagents and the ability to epimerise amides, Weinreb amide **163** was prepared from the acyl phosphate intermediate **136** and then reacted with PhMgBr (Scheme 71). Unfortunately, chiral separation was not achieved with the starting Weinreb amide, despite this, a comparison of the overall procedure (Weinreb vs acyl phosphate) can still be made.



Scheme 71. *Preparation of Weinreb amide from (S)-ibuprofen* ***162*** *and acyl phosphate. Then subsequent Grignard addition to* ***163****.*

The conditions used for reacting **163** with PhMgBr (6.00 eq.) were taken from the original Weirneb paper, which proceeded to perform the addition at elevated temperature (Scheme 71). The enantiomeric excess (ee) of **161** was 87 % when 6.00 equivalents were used. To make the results more comparable to the acyl phosphate example the number of equivalents were reduced to 2.00 (Scheme 50, conditions B) and the ee of **161** was 88 %. Weinreb amides form a stable intermediate, and because the temperature and excess Grignard reagent do not significantly affect ee, the stable intermediate does not contribute to epimerisation. These results show that the more direct route of activating (S)-ibuprofen **162** to give acyl phosphate **136**, and subsequent ketone **161** formation results in less chance of epimerisation than preparing the amide **163** followed by a subsequent Grignard addition.

Weinreb amides can undergo selective reduction to the aldehyde in the presence of strong reducing agents, such as DIBAL-H and $LiAlH_4$ because of the formation of a stable tetrahedral intermediate. A short investigation was performed to see if acyl phosphates also selectively reduce to aldehydes (Scheme 72). Decanoyl phosphate **135** was subjected to DIBAL-H (1.00 eq.) at -78 °C, however, **135** was almost exclusively reduced to the alcohol **164**. The full reduction to **164** ultimately proves that a stable intermediate does not govern the selective formation of ketones from acyl phosphates.



Scheme 72. *Decanoyl phosphate reduction in the presence of DIBAL-H.*

4.5. Conclusions and future work

Performing an Arbuzov reaction can isolate acyl phosphates in good to excellent yields. Subsequently, the isolated acyl phosphates are suitable electrophiles for Grignard addition to ketones. Grignard addition to acyl phosphates performs best at a reduced temperature because selectivity to ketone is almost exclusive. Acyl phosphates can be stored at -18 °C without decomposing.

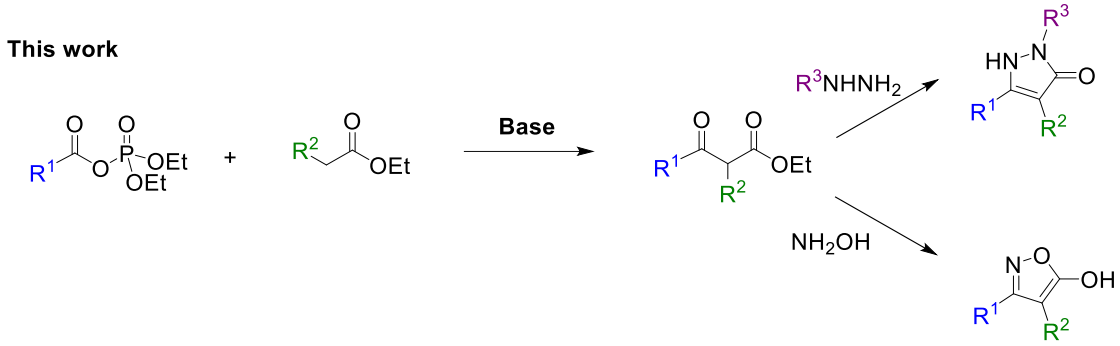
Acyl phosphates are about 60 times more reactive towards Grignard reagents than acid chlorides, this enhanced reactivity ultimately leads to a selective method for ketone formation when in the presence of Grignard reagents. α-Chiral acyl phosphates and the respective ketones are resistant to epimerisation, when in the presence of Grignard reagents.

Acyl phosphates are prone to reduction to alcohols in the presence of DIBAL-H at low temperature. Organolithiums are unsuitable nucleophiles for the synthesis of ketones from acyl phosphates. The addition of Grignard reagents to α,β-unsaturated acyl phosphates leads to 1,4-addition. Perhaps trans-metalating Grignard reagents with other metals such as lanthanides could improve selectivity to the 1,2-addition over the 1,4-addition.

Acyl Phosphates and Diazophosphonates for the synthesis of heterocycles

5.1. Acyl phosphates for β-ketoester synthesis

Due to the success of reacting Grignard reagents with acyl phosphates to make ketones, we decided to expand the study to other nucleophiles. β-ketoesters are formed from enolates and are used for the preparation of heterocycles. Herein is a summary of how β-ketoesters are prepared by acylation.



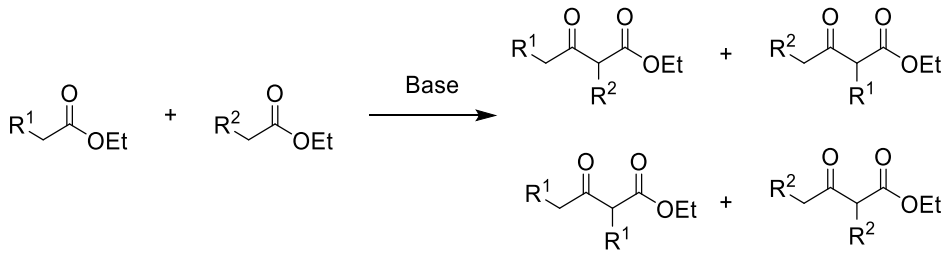
Scheme 73. *Proposed route to the synthesis of β-ketoesters from acyl phosphates, followed by condensation to 5-membered heterocycles.*

5.2. Synthesis of β-ketoesters by acylation

The first β-ketoester synthesis was by Heinrich Geuther in 1863, who discovered that ethyl acetate condenses with itself in the presence of sodium to produce ethyl acetoacetate.[118] The role of sodium and its effects on ethyl acetate was debated for many years after this discovery.[119] In 1887, Claisen discovered 1,3-dicarbonyls can be prepared by reacting esters with acetone in the presence of sodium ethoxide, Claisen postulated that sodium was not directly responsible for the condensation of ethyl acetate but serves only to generate sodium ethoxide, from traces of alcohol in the ester.[120] Other researchers contested this proposal because they found the reaction between sodium and ethyl acetate formed ethyl acetoacetate in higher yields, when compared to the reaction between ethyl acetate and sodium ethoxide.[121,122] The role of sodium on ethyl acetate wasn't fully realised until 1931, when McElvain studied sodium's effects on 'the acetoacetic ester condensation,' he found that sodium reduced ethyl acetate to

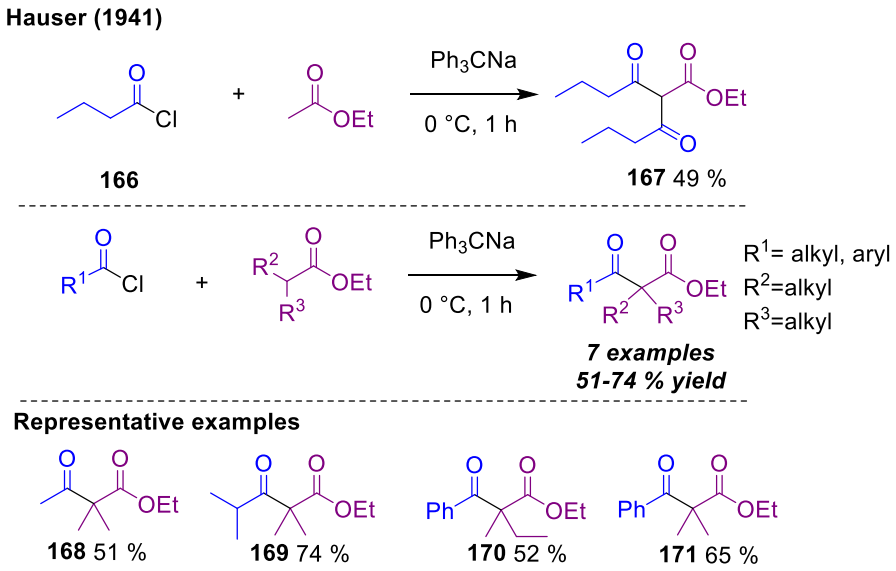
sodium ethoxide. McElvain proved Claisen's hypothesis correct.[122] The reaction between esters and enolates is now formally known as the Claisen-condensation.

The condensation of two different esters, both containing α-hydrogens, can be problematic due to their similar reactivity a mixture of condensation products can occur (Scheme 74).[120,123]



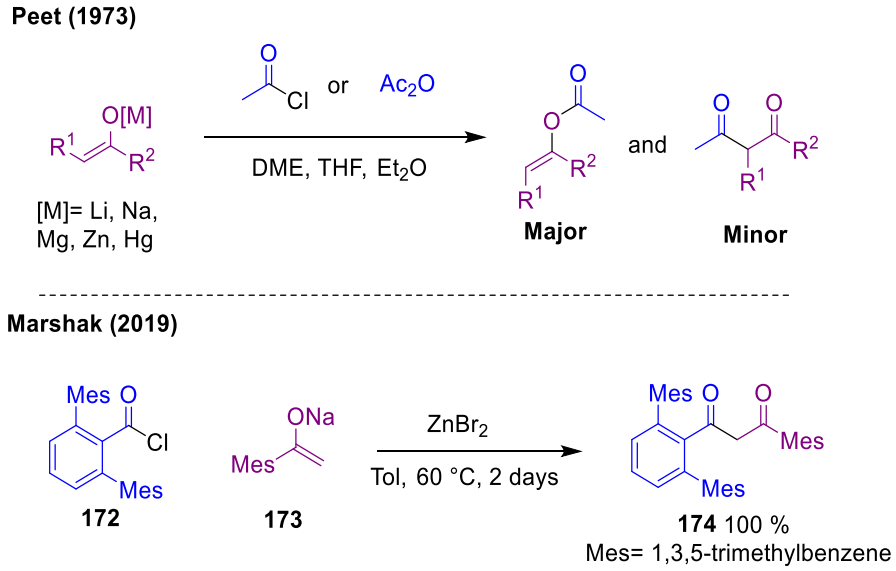
Scheme 74. *The classical Claisen-condensation results in undesired mixture of condensation products.*

The use of acid chlorides for acylating esters was explored by Hauser in 1941, utilising triphenylmethyl sodium as a base.[124] Hauser postulated that the higher electrophilicity of acid chlorides would selectively undergo condensation with esters, but instead he found that acylation of ethyl acetate with acid chlorides gave mainly bis-acylated acetate.[124–127] Using α,α-disubstituted esters gave β-ketoesters in good yields (Scheme 75).[124]



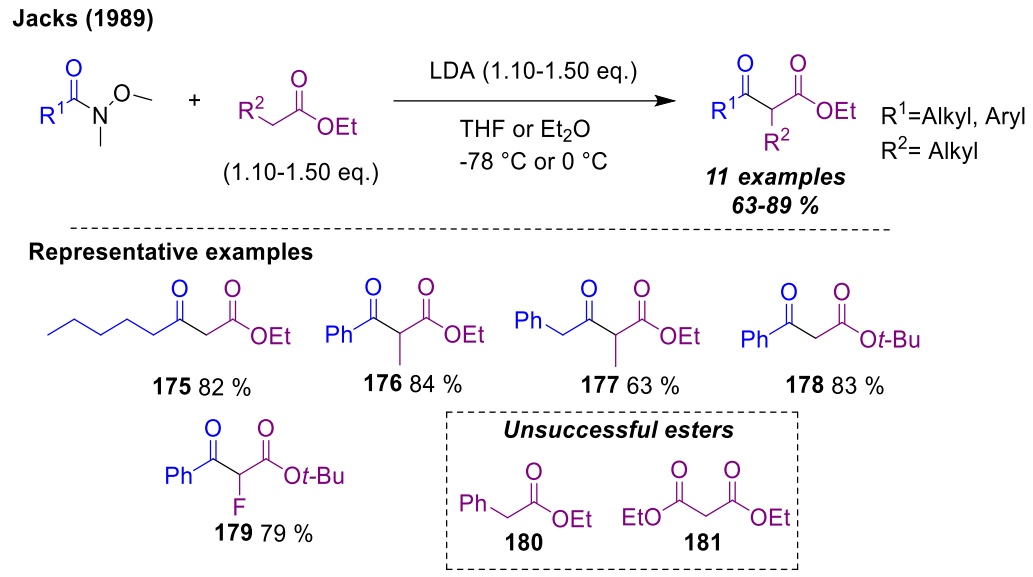
Scheme 75. *Reaction of acid chlorides and sodium ester enolates.*[124]

It is widely reported that reacting acid chlorides with metal enolates generated from ketones can produce significant amounts of *O*-acylated product as opposed to *C*-acylated 1,3-diketones, with the exception of sterically hindered enolates which favour C-acylation (Scheme 76).[128–131] Polar solvents such as DMF or DMSO also favour *O*-acylation.[132]



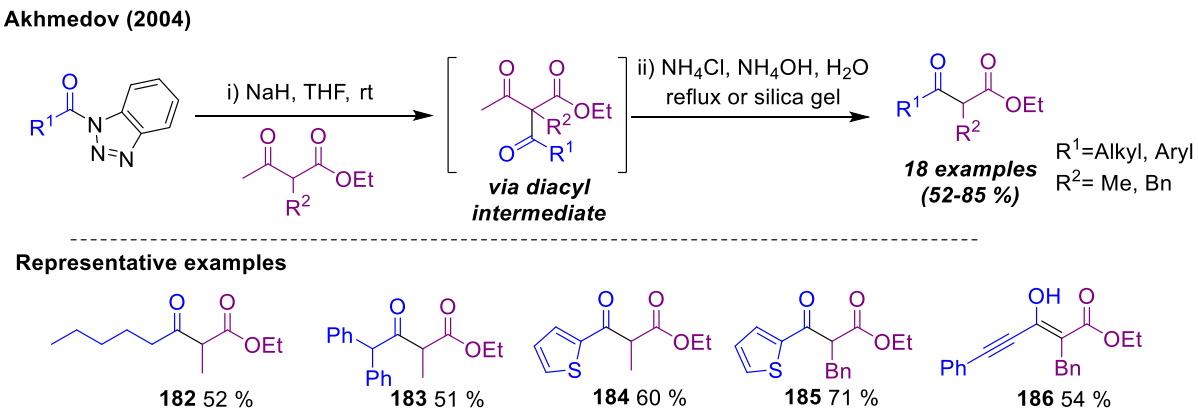
Scheme 76. *Metal enolate reactions with acid chlorides.*

To combat the inherent difficulty of using acid chlorides to C-acylate esters and ketones, alternative acylating reagents have been examined. For example, Jacks showed that Weinreb amides are effective at acylating lithium ester enolates (Scheme 77) producing high yields of β-ketoesters (63-89 %). However, reacting ethyl phenylacetate **180** and diethyl malonate **181** at -78 ^{0}C resulted in a 0 % yield due to self-condensation of the ester.[133]



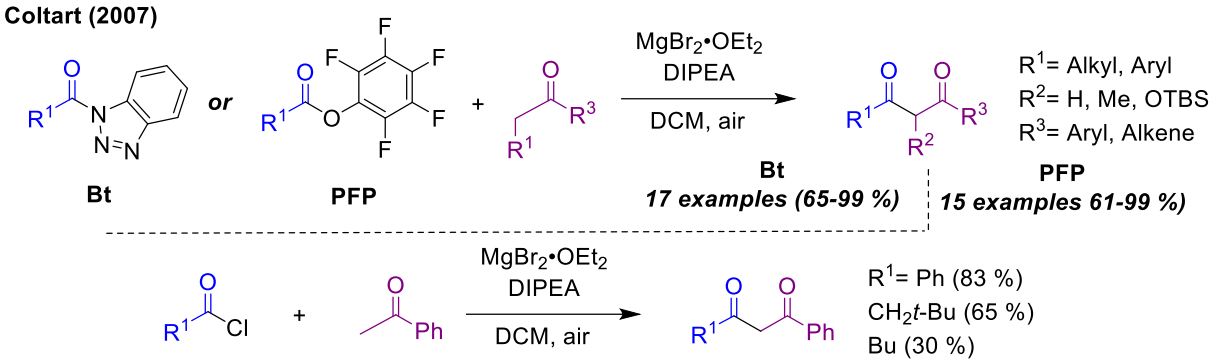
Scheme 77. *Reaction of Weinreb amides with lithium enolates.*[133]

In 2004, Akhmedov showed acylbenzotriazoles (Bt) are effective at producing β-ketoesters from methyl, benzyl and acetyl acetoesters in high yields (52-85 %), claiming no other acylated by-products were detected (Scheme 78).[134] This method proceeds *via C*-acylation followed by deacetylation by heating at reflux with ammonium chloride and ammonium hydroxide. It was proposed that the benzotriazole promotes deacetylation by reacting with the acetyl group on the tricarbonyl. Applying Akhmedov's approach to acetyl acetones to produce 1,3-diketones was successful for two aromatic and one sulphide example, however, other acyl benzotriazoles were prone to *O*-acylation.[134] The use of benzotriazoles also possesses some safety concerns due to risk of explosion.



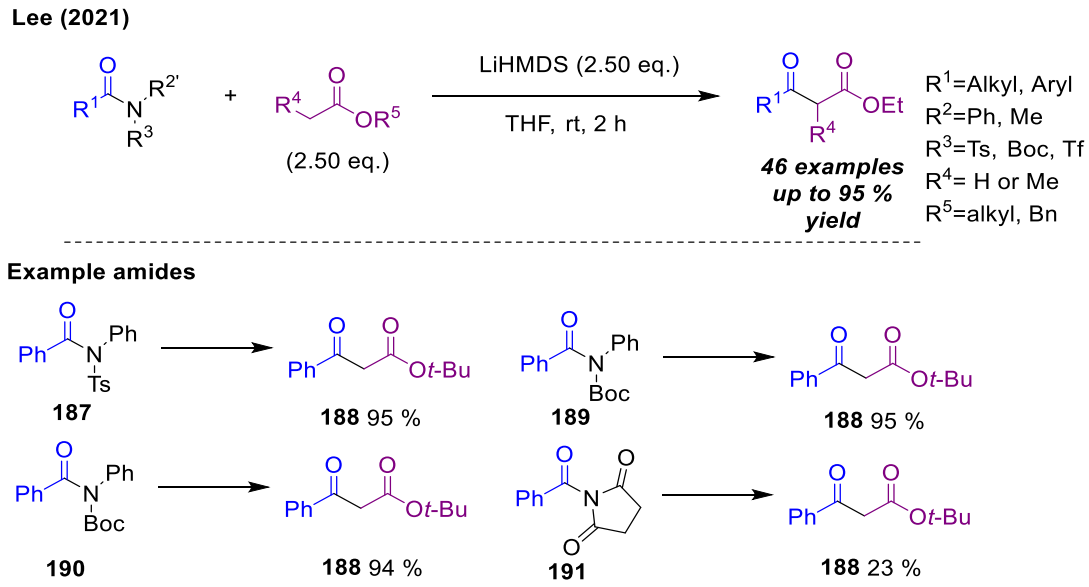
Scheme 78. *C-Acylations and deacetylation of acetylacetoesters using benzotriazole.*[134]

A more convenient application for preparing 1,3-diketones from acyl benzotriazoles was developed by Coltart. This approach used DIPEA in the presence of a Lewis acid (Scheme 79). Applying the same methodology to pentafluorophenyl esters (PFP) was also effective, acid chlorides however, were less effective because of bis-acylation.[135]



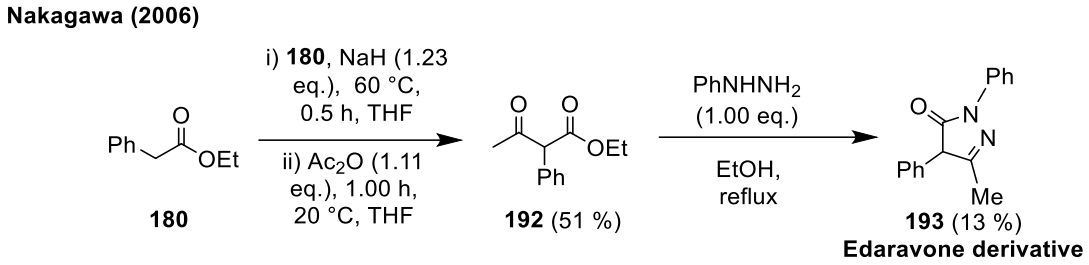
Scheme 79. *Soft-enolization approach to 1,3-diketones from acyl benzotriazoles and acid chlorides.*[135]

Recently, Lee reported tertiary amides bearing tosyl, triflate and boc groups can also effectively produce β-ketoesters from esters at room temperature using LiHMDS as a base (Scheme 80).[136] Both aliphatic and aromatic amides were tolerated and produced high yields overall, however, no α-aryl esters were reported, presumably because of the tendency for α-aryl esters to self-condense.



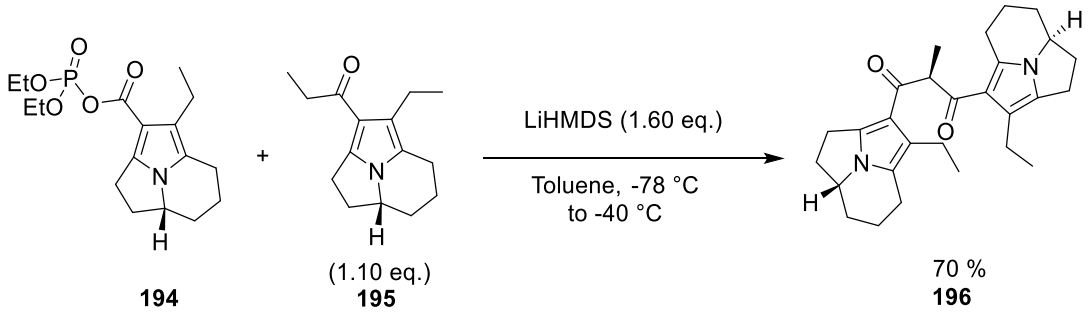
Scheme 80. *Addition of lithium enolates to tosyl, triflic and boc protected amides.*[136]

In the presence of poorly electrophilic acylating reagents (such as amides) self-condensation of ethyl phenylacetate occurs.[133] However, the reaction between ethyl phenylacetate and acetic anhydride or benzoyl chlorides has been reported in several medicinal chemistry related papers (Scheme 81).[137,138,139] Self-condensation is avoided by using a more potent acylating reagent (such as acid chlorides or acid anhydrides) because the nucleophile diverts from reacting with the ester and instead, reacts with the acylating reagent. Acyl phosphates are also potent acylating reagents and could serve as viable alternatives to acid chlorides, acid anhydrides or amides for the synthesis of β-ketoesters.



Scheme 81. *Preparation of β-ketoester **192** from acetic anhydride and subsequent condensation to Edaravone derivative **193**.*

To the best of our knowledge acyl phosphates have not been used to prepare β-ketoesters, but during the synthesis of myrmicarin alkaloids Movassaghi demonstrated the use of an acyl phosphate **194** to selectively C-acylate a ketone **195** for the preparation of a 1,3-diketone intermediate **196** (Scheme 82). The acyl phosphate **194** was more effective at coupling with **195** to give **196** than acid chloride and esters because *O*-acylation occurred when the acid chloride and esters were reacted with **195**. The acyl phosphate **194** was prepared from highly toxic diethyl cyanophosphate (DECP).[140]



Scheme 82. *Synthesis of natural product intermediate **196** from acyl phosphate **194**.*

5.3. Heterocycles from β-ketoesters

β-ketoesters are important for the synthesis of biologically active heterocycles. In 1883, Knorr discovered the first pyrazole derivative by reacting phenyl hydrazine with ethyl acetoacetate to produce 3-methyl-1-phenylpyrazolin-5(4*H*)-one **197**, the *N*-methyl derivative (phenazone **198**) was commercialised as an analgesic (Fig 21).[141] Isoxazolone derivatives can also be prepared by condensing hydroxylamine with β-ketoesters. Since the discovery of the first pyrazole derivative many drugs that contain 5-membered heterocycles have been commercialised such as the anti-inflammatory agent celecoxib **199** and the antibacterial agent sulfisoxazole **200**.

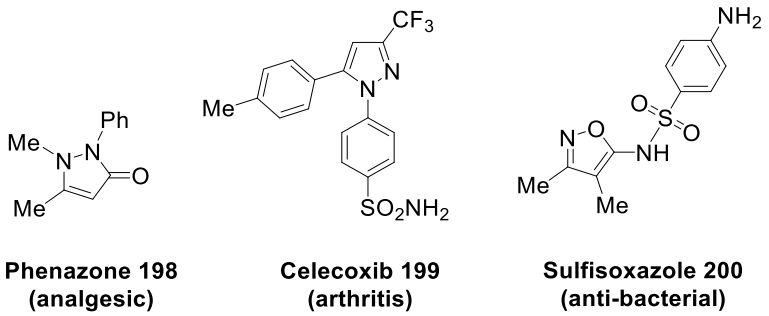


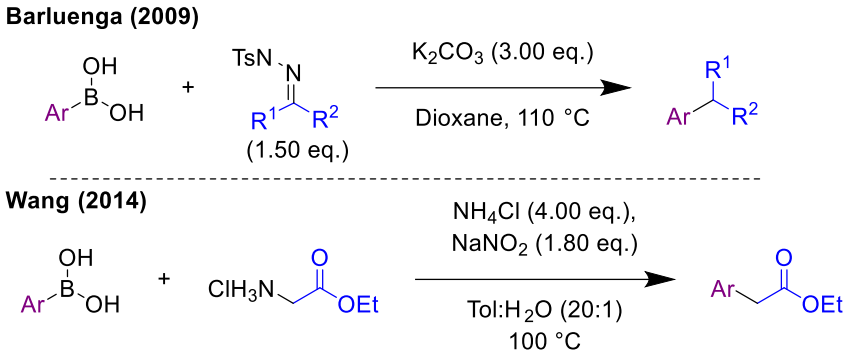
Fig 21. *Commercial pyrazole and isoxazole derivatives;* ***198****- phenazone (analgesic),*[142] ***199****-celecoxib (arthritis)*[143] *and* ***200****- sulfisoxazole (anti-bacterial).*[144]

The main aim of this study is to prepare α-substituted β-ketoesters from acyl phosphates and α-aryl esters. However, due to the utility of 1,3-dicarbonyls in pyrazole and isoxazole synthesis, attempts will be made to synthesise the respective 3,4-isoxazolols and 4,5-pyrazolones from β-ketoesters.

6. β-ketoesters and heterocycles

6.1. Synthesis of α-aryl esters

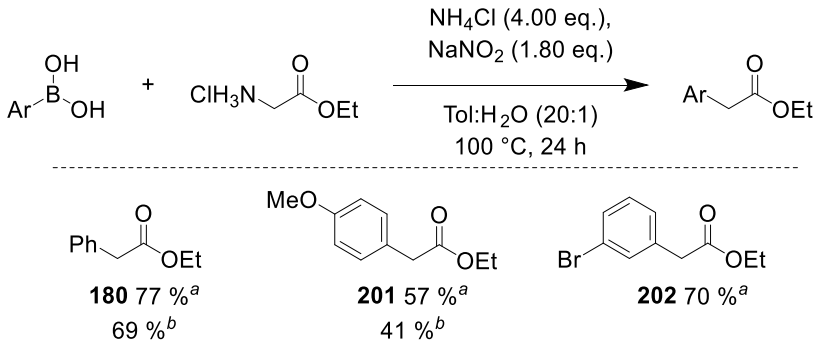
The first objective was to find an appropriate method to prepare α-aryl esters that would then be used to prepare enolates. In 2009, Barluenga published a method for coupling boronic acids from tosyl-hydrazones, that had been converted to diazo-compounds *in-situ via* a Bamford-Stevens reaction, to generate carbon-carbon bonds without the use of transition metals.[145] Then in 2014, Wang also showed that boronic acids could undergo a de-nitrogenative coupling with glycine by *in-situ* diazotisation (Scheme 83).[146]



Scheme 83. *Reaction of tosyl hydrazones and amines with aryl boronic acids by in-situ diazotisation.*[145,146]

Arylboronic acids and glycine are readily accessible starting materials and can be used to prepare α-arylesters, even when the aryl acetic acid fragment to perform a trans-esterification reaction is not readily available. Therefore, Wang's method was used as a starting point to prepare the α-aryl esters used in this study.

The esters were synthesised on a 5.00-10.0 mmol scale using slightly modified Wang conditions; NH_4Cl, $NaNO_2$ and glycine hydrochloride were first heated to 50 °C before sequential addition of boronic acid and water. This sequential addition of reagents was more effective than adding all reagents at the start (as carried out by Wang).[146]



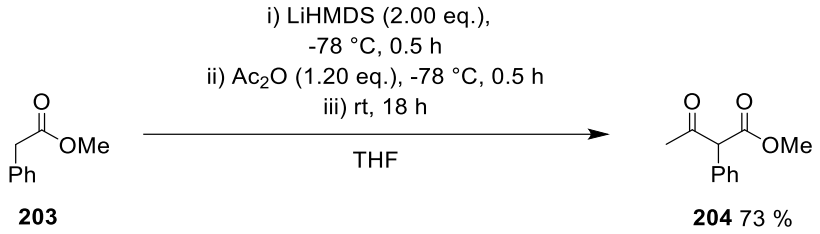
Scheme 84. *Synthesis of α-arylesters using Wang conditions.*[146] [a]*Reaction heated to 50 °C before addition of boronic acid and water.* [b]*All reagents at the start before heating.*

6.2. Synthesis of β-ketoesters from acyl phosphates

6.2.1. Optimisation

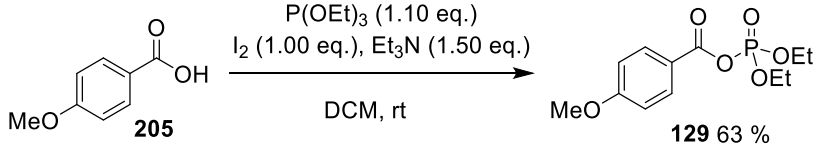
Having prepared the esters, the next step was to determine appropriate conditions for the acyl phosphate reaction. Initially, a trial reaction between

methyl phenylacetate **203** and acetic anhydride was performed. LiHMDS (2.00 eq.) was used to deprotonate **203** and the enolate was reacted with acetic anhydride in the presence of THF resulted in a 73 % yield of β-ketoester **204** (Scheme 85). Ester **203** was added to an excess of LiHMDS to maximise enolate concentration and minimise ester **203** concentration. The reaction was also performed at -78 °C to avoid self-condensation of the ester.



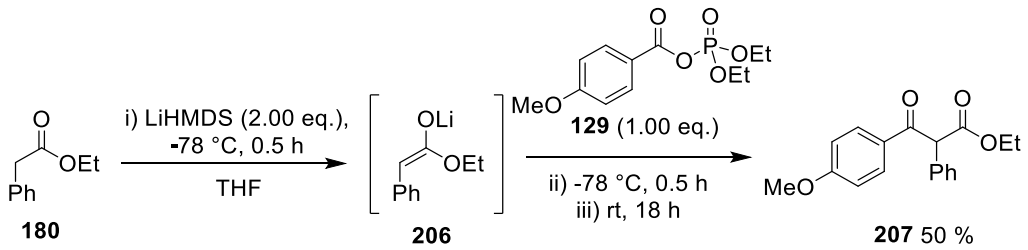
Scheme 85. *Reaction of methyl phenylacetate **203** with acetic anhydride in the presence of LiHMDS to give **204**.*

Diethyl (4-methoxybenzoyl)phosphate **129** was selected for the initial optimisation of reaction because the characteristic signals for the 4-methoxyphenyl group would assist in NMR analysis of reaction products. Acyl phosphates were prepared using the Arbuzov conditions (Scheme 86).



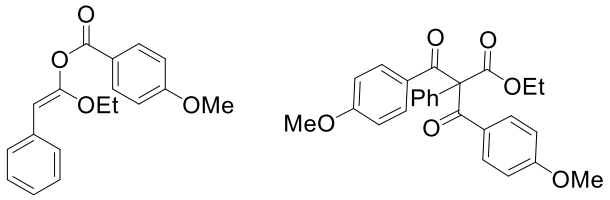
Scheme 86*. Conditions used to prepare acyl phosphate **129**.*

Treating ethyl phenylacetate **180** with LiHMDS (2.00 eq.) and reacting with acyl phosphate **129** gave the desired β-ketoester **207** 50 % yield (Scheme 64).



Scheme 88. *Reaction of **129** with **180** in the presence of LiHMDS and isolation of **207** by quenching with [a]NH4Cl(sat.) or [b]2M HCl.*

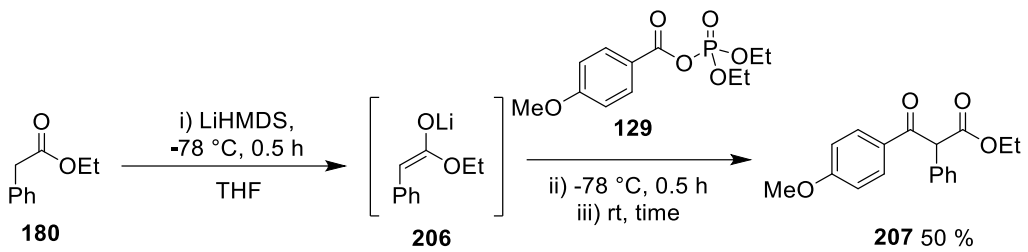
Analysis of the crude reaction mixture by ^{31}P NMR showed diethyl phosphate δ 0.98 ppm plus two other unknown phosphorus impurities at -1.13 and -9.38 ppm, in a ratio of 5:1:0.25. The additional phosphorus impurities indicate that the phosphate group undergoes side reactions, albeit in low quantities. 4-Methoxybenzoic acid **205** was also present in the crude reaction mixture. Presumably 4-methoxybenzoic acid **205** was produced from the decomposition of **129**, however, it is also possible that **205** could be generated from the decomposition of the *O*-acetylated ketene acetal **208**, or from decomposition of the diacetyl **209** (Fig 22).



208 **209**

Fig 22. *Potential by-products arising from O-acylation **208** or bis-acylaton **209**. *Both could decompose during work up to give 4-methoxybenzoic acid **205**.*

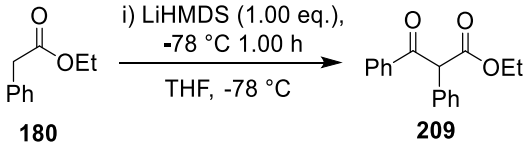
At this point, further optimisation of the reaction between acyl phosphate **129** and ethyl phenylacetate **180** to give **207** was performed (Table 8). It was not necessary to leave the reaction for 18 hours because warming to room temperature and quenching immediately resulted in a 53 % yield of **207** (entry 2). However, it was necessary to allow the reaction to warm from -78 ^{0}C to room temperature because quenching at a higher temperature resulted in a lower yield of 42 % yield (entry 1). Reducing the number of equivalents of base to 1.50 (entry 3) resulted in a higher yield isolated yield of **207** 57 %.



Entry	Acyl phosphate (eq.)	Ester (eq.)	Base (eq.)	Yield %
1	1.00	1.00	LiHMDS (2.00)	42
2	1.00	1.00	LiHMDS (2.00)	53
3	**1.00**	**1.00**	**LiHMDS (1.50)**	**57**
4	1.00	1.00	LiHMDS (1.00)	39
5	1.00	1.00	KHMDS (2.00)	41
6	1.00	1.00	KHMDS (1.50)	40
7	1.00	1.00	NaHMDS (2.00)	28
8	2.00	1.00	LiHMDS (1.50)	57
9	1.00	2.00	LiHMDS (3.00)	58

***Table 8**. Optimisation of reaction between ethyl phenyl acetate **180** and **129** to give β-ketoester **207**.*

Further decreasing the amount of LiHMDS to 1.00 equivalent (Table 8, entry 4) resulted in a lower yield (39 %). It was also evident that other side reactions had occurred because of additional peaks in the ^{1}H NMR spectrum. Self-condensation of **180** was also evident and was assigned due to an additional α-proton at 6.12 ppm (^{1}H NMR) and an additional carbonyl peak at 189.6 ppm (^{13}C NMR).



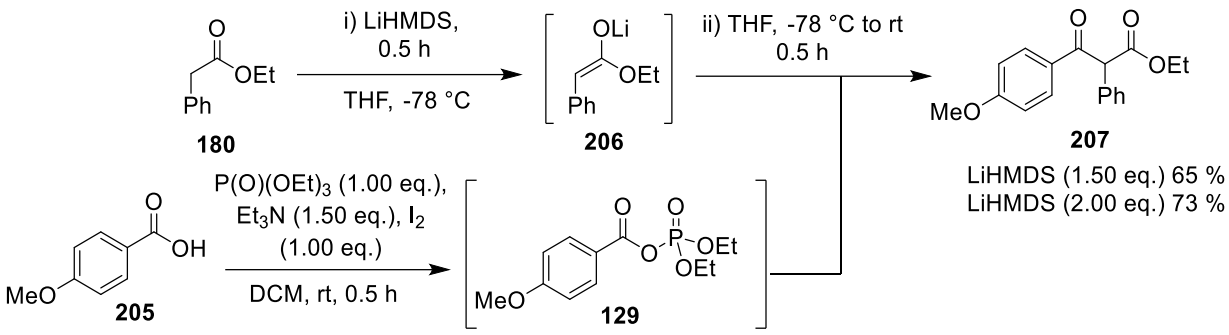
***Scheme 89.** Claisen ester condensation product **209**.*

Attempting to use the potassium and sodium HMDS salts as a base resulted in poorer yields compared to LiHMDS (entries 5 and 7 gave 41 % and 28 % respectively).

The addition of excess acyl phosphate **129** (2.00 eq.) or excess ester **180** (2.00 eq.) also showed little improvement, indicating neither phosphate nor ester are significantly limiting the reaction under these reaction conditions. Further

exploration into alternative solvents may improve selectivity towards β-ketoester. Entry 3 gave the highest yield of **207** and was selected as the optimal conditions for further exploration.

To improve the efficiency of the overall transformation, the crude acyl phosphate mixture **129** was combined with the enolate **206** (Scheme 90).

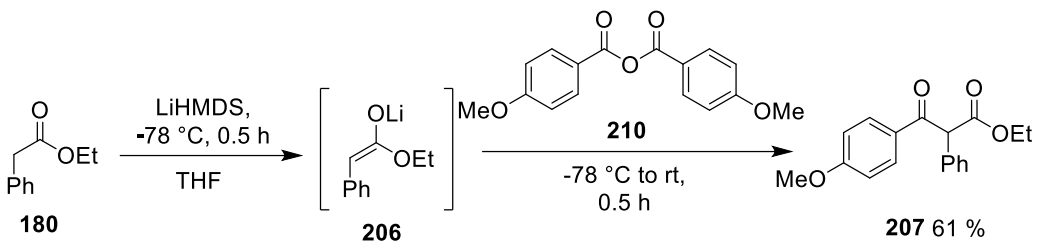


Scheme 90. *Simplified (telescoped) procedure for the synthesis of β-ketoester **207** from 4-methoxybenzoic acid **205** and ester **180**.*

Interestingly, a higher yield of β-ketoester **207** (65 %) was obtained when the purification step (column chromatography) for the acyl phosphate **129** was avoided (Scheme 90). It was a possibility that some LiHMDS was consumed due to the presence of other proton sources (for example, Et_3N salts or water from the previous step). To counteract the potential presence of addition proton sources, LiHMDS was increased to 2.00 equivalents this gave a slightly higher 73 % yield (Scheme 90).

The crude Arbuzov conditions (Scheme 90) contains an approximate ratio of 2:1, acyl phosphate:acid anhydride.[2] It was hypothesised that the presence of the 4-methoxybenzoic anhydride **210** could contribute to the higher yield observed when the crude mixture was used rather than the pure acyl phosphate **129**. To further the investigate effect that the acid anhydride **210** has on the reaction, **210** replaced acyl phosphate **129** and reacted with enolate **206**. Using acid anhydride **210** gave a similar yield of β-ketoester **195** (61 %) to the acyl phosphate reaction (Scheme 91).

[2] Relative amounts of acyl phosphate and acid anhydride were estimated by isolated material from the Arbuzov reaction (Scheme 61).

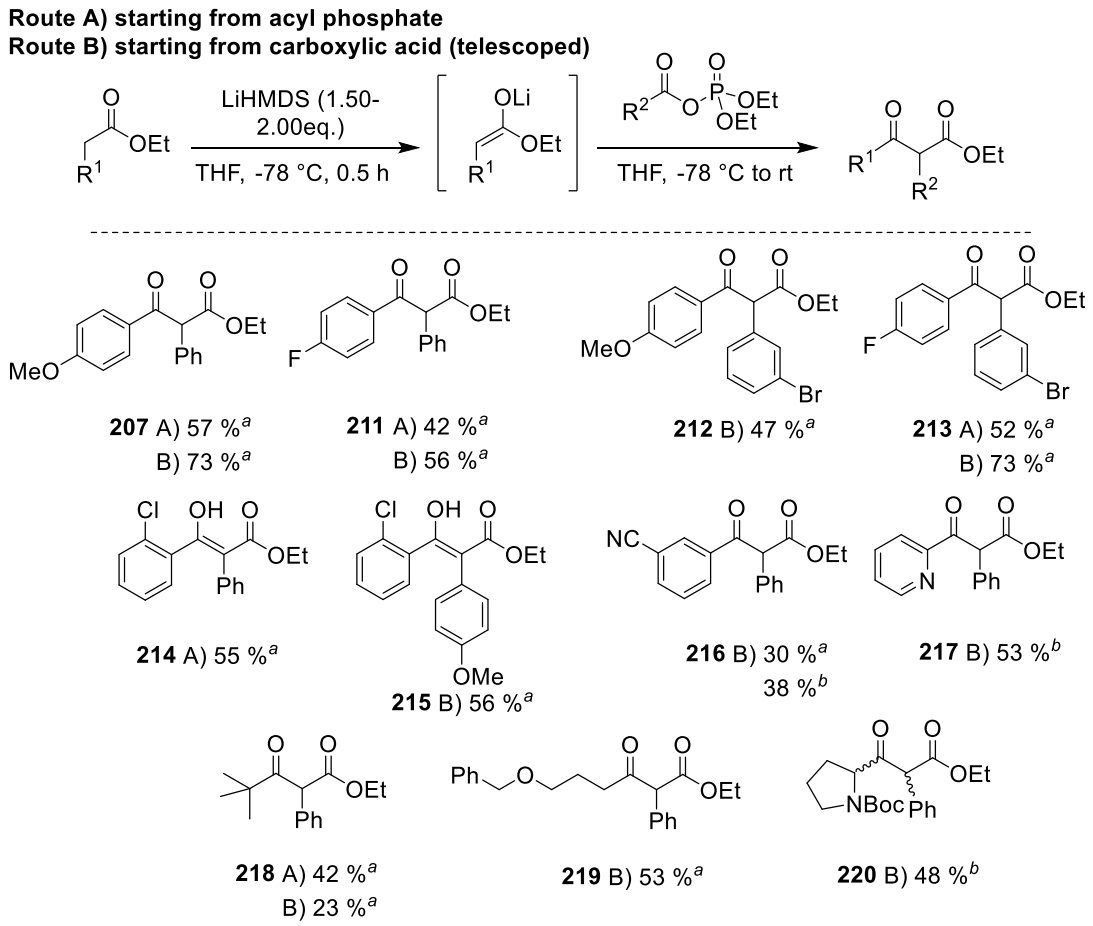


Scheme 91. *Reaction of acid anhydride **210** with ethyl phenyl acetate **180** to give **207**.*

Since no significant increase in yield was observed when using the acid anhydride **210**, it is difficult to gauge whether the presence of acid anhydride does improve the simplified (telescoped) reaction. The presence of other phosphorus by-products, such as **22**, could also influence selectivity to the β-ketoester *via* coordination to the Li-enolate. Further work investigating the effect of phosphates on enolate additions could lead to a better understanding of why an increase in yield was observed in the telescoped reaction. However, despite the possibility of coordinating effects from phosphates, it should not be ruled out that the acyl phosphate crude mixture could have contained less moisture upon addition to the reaction than when the pure acyl phosphate was used.

6.2.2. Substrate scope β-ketoesters

Several β-ketoesters were synthesised from the corresponding acyl phosphates (Scheme 92, route A) and/or carboxylic acids (Scheme 92, route B). The preparation of 4-fluorophenyl derivatives **211** and **213** also resulted in the telescoped step (Scheme 92, route B) producing a better yield than when the pure acyl phosphate was used (Scheme 92, route A). The Arbuzov reaction used to prepare diethyl (4-fluorobenzoyl)phosphate **130** resulted in an 8.5:1 ratio (acyl phosphate: acid anhydride) and the preparation of diethyl (4-methoxybenzoyl)phosphate contained a 2:1 ratio (acyl phosphate: acid anhydride), yet both telescoped reactions proceeded in >70 % yield. The improved yield for both reactions increase the likelihood that the presence of phosphates is advantageous for enolate additions.



Scheme 92. *Substrate scope β-ketoesters; [a]2 M HCl used to quench the reaction, [b]Sat. NH_4Cl used to quench the reaction.*

207 and **213** were both obtained in over >70 % when using route B, it was also expected **212** would give similar results. Unfortunately, this was not the case and **212** was produced in a modest yield (47 %), perhaps the presence of moisture from the crude material may have resulted in a poorer yield than expected.

The synthesis of β-ketoesters from diethyl (2-chlorobenzoyl)phosphate **133** gave **214** and **215** in 55 % and 56 % yield respectively. Interestingly, both **214** and **215** were present as mostly enol (ca. 1:2, keto:enol) in $CDCl_3$, perhaps the halogen bonding effects from the 2-chlorosubstituted aromatic and the carbonyl results in a more favoured enol tautomer. The other β-ketoesters were present as the keto tautomer >80 % in $CDCl_3$.

Acyl phosphates bearing cyano and 2-pyridine groups were difficult to isolate because the acid anhydride and phosphate impurities were inseparable from the product acyl phosphate. But since no purification of the acyl phosphate is

required, starting from the carboxylic acid (Scheme 92, route B) allowed for the synthesis of **216** and **217** (38 % and 53 % overall yield).

Reacting ethyl phenyl acetate **195** with diethyl pivoylphosphate **134** gave **218** in a 42 % yield, comparatively, starting from pivalic acid (Scheme 91, route B) resulted in an even poorer yield (23 %). The lower isolated yield obtained from route B is due to a poor yield from the Arbuzov step (i). The steric hinderance from the *tert*-butyl group likely impedes both acyl phosphate **134** and pivalic anhydride's ability to react with the enolate of **195**.

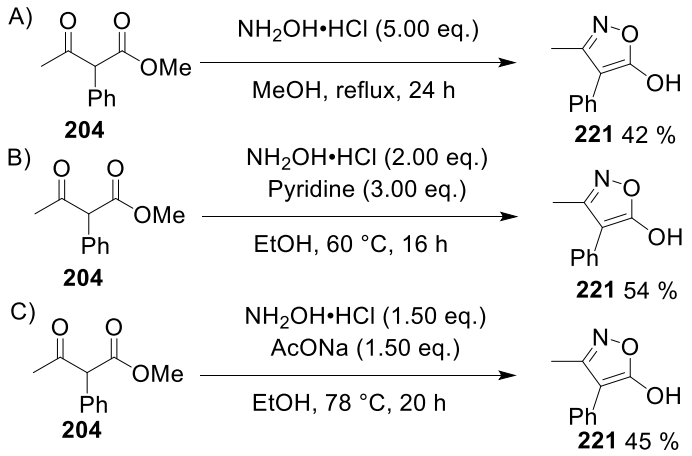
Conveniently carboxylic acids containing α-hydrogens were also compatible because 4-(benzyloxy)butyric acid gave **219** in a 53 % yield, and Boc-protected proline gave a similar yield of **220** (48 %). No evidence of additional acylation was observed.

6.3. Synthesis of 5-membered heterocycles

6.3.1. Synthesis of isoxazolols from β-ketoesters

After preparing and isolating β-ketoesters, the next step was to prepare 5-membered heterocycles. Initially, isoxazoles derivatives were prepared by condensing β-ketoesters with hydroxylamine.

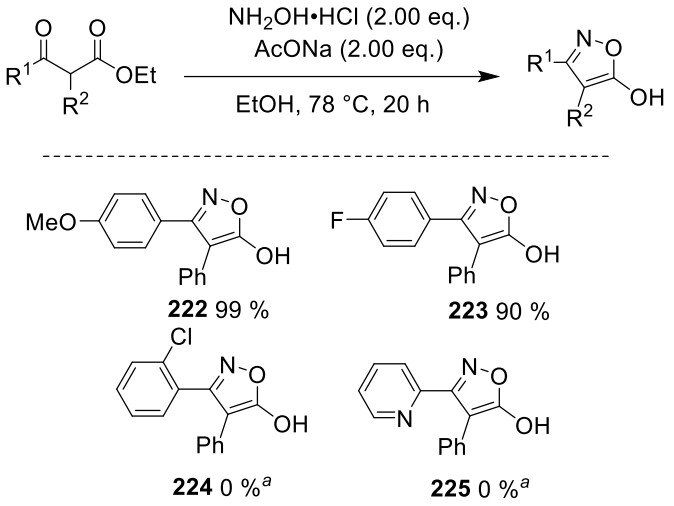
Initial screening of approaches using literature conditions were performed by reacting methyl 2-phenylacetoacetate **204** with hydroxylamine hydrochloride.[147,148,149] The resultant heterocycle **221** was isolated by recrystallisation from EtOAc. Using pyridine as an acid-base buffer (Scheme 93, B) gave the highest yield of **221** (54 %).



Scheme 93. *Conditions used to synthesise isoxazole* ***132****. References: conditions A,*[147] *conditions B*[148] *and conditions C.*[149] *Regiochemistry tentatively assigned by literature values.*

Attempts were then made to prepare 3-(4-methoxyphenyl)-4-phenylisoxazol-5-ol **222**, 3-(4-fluorophenyl)-4-phenylisoxazol-5-ol **223** and 3-(2-chlorophenyl)-4-phenylisoxazol-5-ol **224**, however, only **223** was isolated in reasonable purity (68 % yield) with trace amounts of unknown impurities. The other substrates were unsuccessfully isolated and present as complex mixtures of impurities.

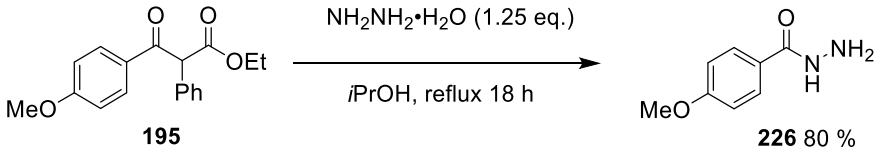
As a result, the reaction was repeated using a sodium acetate buffer instead (Scheme 93, conditions C) but 2.00 equivalents of hydroxylamine were used. Pleasingly **222** was isolated in quantitative yield (Scheme 94). 3-(4-fluorophenyl)-4-phenylisoxazol-5-ol **223** was also isolated in 90 % yield. However, under the same conditions **224** and **225** were obtained as complex mixtures (Scheme 94). All successfully isolated examples were present as the OH tautomer, assignment was made based on the broad singlets around 13 ppm (^{1}H NMR). No CH corresponding to the isoxazolone tautomer was present.[148] The results show that the synthesis of 3,4-aryl isoxazolols can be problematic.



Scheme 94. *Synthesis of 3,4-isoxazolols. [a]Isoxazolol was not isolated clean. Regiochemistry tentatively assigned by literature values.*[139]

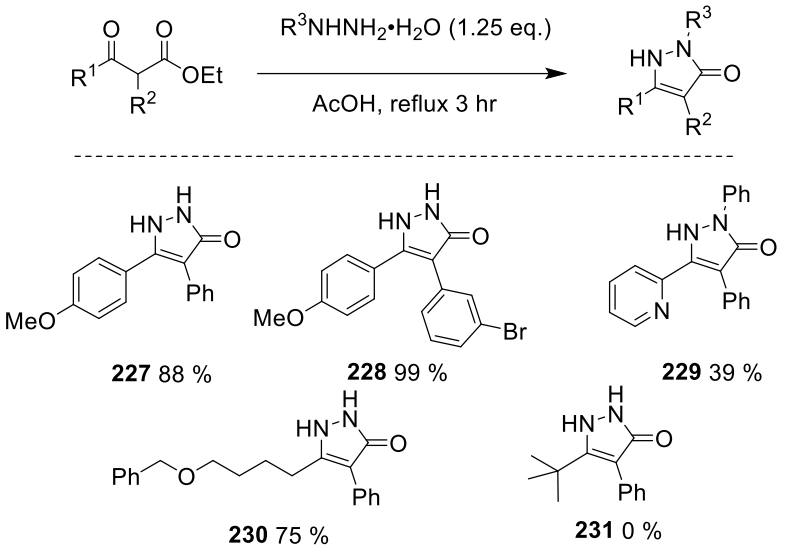
6.3.2. Synthesis of pyrazolones from β-ketoesters

Due to the difficultly isolating clean samples of isoxazolols, the focus was switched to synthesising pyrazolone's. First, **195** was reacted with hydrazine hydrate under by refluxing in the presence of isopropanol.[150] However, these conditions resulted in acyl hydrazide **226** (80 %) from a retro-Claisen condensation reaction (Scheme 95). **226** was identified by MS (ESI^+) and characteristic ^1H NMR shifts at δ 9.62 ppm (NH) and 4.46 (NH_2). The ^1H NMR data matches the literature.[151]



Scheme 95. *Retro-Claisen condensation of **195** with hydrazine to give hydrazide **226**.*

It was postulated that more acidic conditions were required to promote the hydrolysis. Therefore, the reaction was repeated but using acetic acid instead of isopropanol and the desired pyrazolone **227** was isolated in 88 % yield (Scheme 94). Attempting these conditions was successful for the following pyrazolones **228-230**. However, applying the same conditions to *tert*-butyl- **231** resulted in recovery of starting material when left for 3 h or 24 h (Scheme 96).



Scheme 96. *Pyrazolones from β-ketoesters. Regiochemistry of* ***229*** *tentatively assigned by similar literature values.*[152]

6.4. Pyrazoles from diazophosphonates

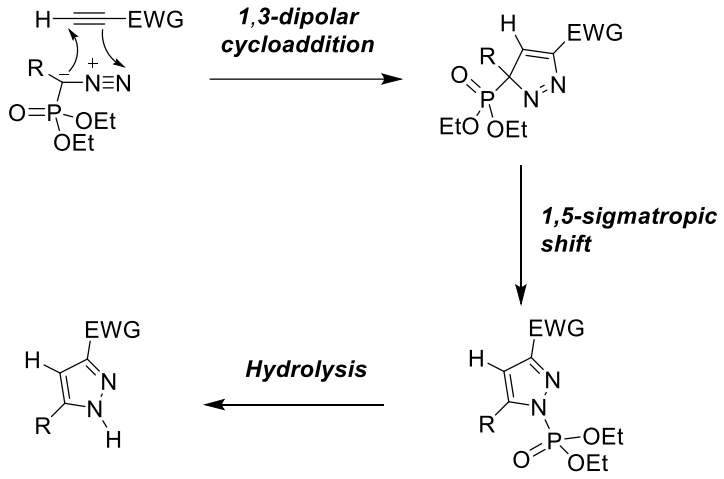
6.4.1. Pyrazoles from diazo compounds and diazophosphonates

The synthesis of pyrazole derivatives from 1,3-dicarbonyls is not the only method available. The cycloaddition reaction between diazoalkanes and alkynes, first discovered by Buchner in 1889, is a highly effective method that produces pyrazoles without breaking any σ bonds.[153] Diazoalkanes, however, are notoriously unstable and possess many safety concerns due to risk of explosion. Incorporating electron withdrawing groups α to the diazo can increase the stability of the diazo group.

Diazophosphonates, first discovered in 1967, are most known for their application in the Seyferth-Gilbert homologation for the synthesis of alkynes.[154,155,156] Diazophosphonates have enhanced stability compared to diazoalkanes because of the electron withdrawing nature of the phosphorus. The enhanced stability of diazophosphonates led us to the hypothesis that diazophosphonates could be used as surrogates for diazoalkanes in pyrazole synthesis, the full study can be found using reference [133].

The final part of this thesis briefly describes the cycloaddition reaction between diazophosphonates and alkynes. The reaction proceeds by a dipolar [3+2] cycloaddition between diazophosphonates and alkynes, followed by

aromatisation, which is achieved by the migration of the phosphorus group *via* a [1,5]-sigmatropic shift to produce the N-phosphoryl pyrazole (Scheme 97). The phosphoryl group attached to the nitrogen heterocycle is labile and can be cleaved under mild conditions in the presence of NaOH (1.00 eq.) to produce the N-H pyrazole (work up).[157]

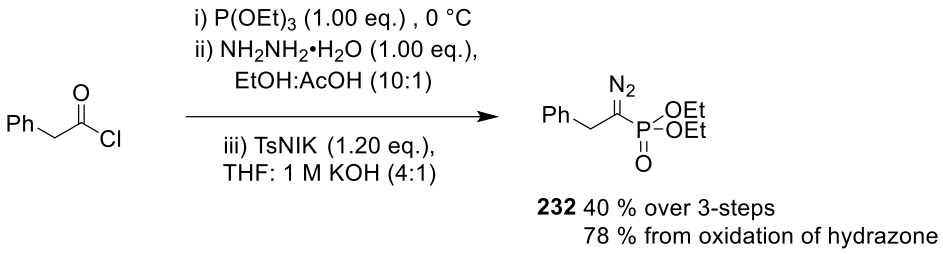


Scheme 97. *Proposed mechanism for the preparation of N-H pyrazoles from diazophosphonates.*[157]

6.4.2. Preparation of diazophosphonates

Diazophosphonate **232** was conveniently prepared by oxidation/dehydration from the corresponding hydrazone using Iodamine-T (TsNIK). Iodamine-T was recently developed by Moody to circumvent using heavy metal oxidants (HgO, $Pb(OAc)_4$, Ni_2O_3, CrO_2) to oxidise hydrazones.[158]

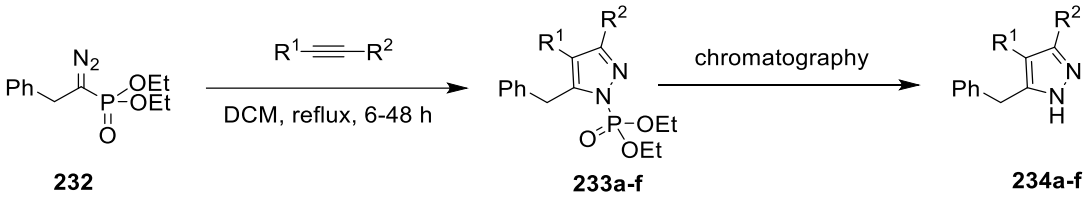
When the pure hydrazone was used no column chromatography was required for the oxidation and **232** was isolated in 78 % yield. However, flash column chromatography was required when crude hydrazine mixture (Scheme 97, ii) was used to prepare **232**. Telescoping the reaction resulted in a 40 % yield over 3-steps starting from phenyl acetylchloride (Scheme 98). *The same method for preparing diazophosphonates was also performed in flow by incorporating TsNIK onto a solid support resin.[157]



Scheme 98. *Batch preparation of diazophosphonate* ***232****.*

6.4.3. 1,3-dipolar cycloaddition of diazophosphonates with alkynes

Initially, the cycloaddition reactions were performed by refluxing **232** and alkynes in DCM, followed by chromatography to isolate the N-Phosphoryl pyrazoles. All the N-Phosphoryl pyrazoles were present as a mixture to N-P and N-H pyrazole because some of the N-P pyrazole had already hydrolysed (Table 9).[157] As expected more electron deficient alkynes proceeded more readily than TMS- and phenyl acetylenes.



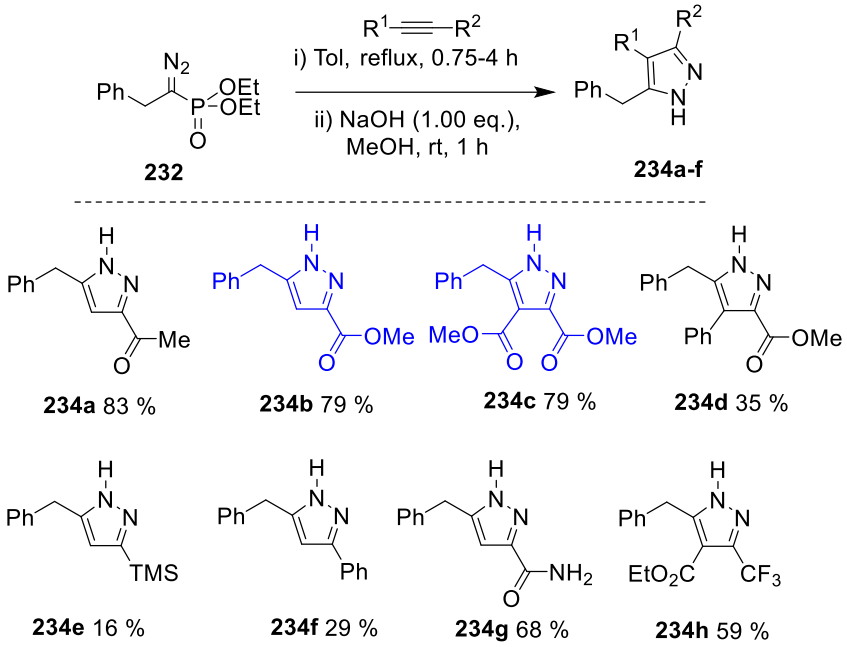
R^1	R^2	**233/234**	Total yield % (**233+234**)	Ratio (**233:234**)
H	COMe	a	75	78:22
H	CO_2Me	b	86	86:14
CO_2Me	CO_2Me	c	83	77:23
Ph	CO_2Me	d	15	72:28
H	$SiMe_3$	e	12	99:1
H	Ph	f	8	81:19

Table 9. *1,3-dipolar cycloaddition of* ***234*** *with alkynes.*[3]

At this point, the procedure was simplified by the addition of a hydrolysis step to give NH pyrazoles. In addition, the reaction was performed in toluene to increase the rate of reaction. The following pyrazoles (**234a-f**) were produced (Scheme 99), with the addition of two new substrates (**234g** and **234h**). All unsymmetrical alkynes were regioselective with the most electron deficient

[3] *Results in blue were obtained by Katie Ruffell and Frances Smith.*

group on the C-3 position. **234a-c** were produced efficiently from the corresponding alkynes. Methyl phenylpropiolate produced **234d** in a lower yield (35 %) because of steric hinderance.



Scheme 99. *1,3-dipolar cycloaddition of alkynes and* ***234*** *to give N-H pyrazoles.*[4] *Results in blue were performed by Katie Ruffell and Frances Smith.*

TMS- and phenyl- acetylenes still proceeded to give poor yields (**234e-f**), due to a competing Bamford-Stevens reaction that produced diethyl (E)-styryl phosphonate (Scheme 99), at high temperatures. Both examples (**234e-f**) were refluxed in toluene for 4 hr before base work up and both reactions gave diethyl (E)-styryl phosphonate in 48 % yield, that was present with a diethyl methylphosphonate impurity (ca. 10 %). Diethyl methylphosphonate was assigned by ^{31}P NMR δ 0.47 ppm and ^{1}H NMR δ 3.77 (3H, dd, $J_{(H\text{-}P)}$ 11.0, 0.9, CH_3). Aliphatic alkynes (oct-1-yne and hex-3-yne) failed to give any pyrazole and only resulted in the Bamford-Stevens product.

Methyl-3-trifluoromethylpropiolate directed the trifluoromethyl group to C-3 over the carbonyl due to the strong inductive effects of the C-3 group. The

[4] *Results in blue were obtained by Katie Ruffell and Frances Smith.*

regiochemistry of **234h** was unambiguously assigned due to the observed coupling between CF_3 and C^3 (143.0 ppm, $J_{(C\text{-}F)}$ 38 Hz) by ^{13}C NMR.

Additional diazophonates and alkynes were explored by co-authors of the paper; examples include, aromatic and aliphatic diazophosphonates, strained alkynes and first-in-class intramolecular cyclisations.[157]

The ^1H NMR spectrum below (Fig 23) is the crude spectrum of **234e** prior to the hydrolysis step. This data highlights that even when a poor $LUMO_{dipolarphile}$ was used, the only by-product during the cyclisation was diethyl (E)-styryl phosphonate. For more efficient reactions such as, **234h** no diethyl (E)-styryl phosphonate was observed in the crude material.

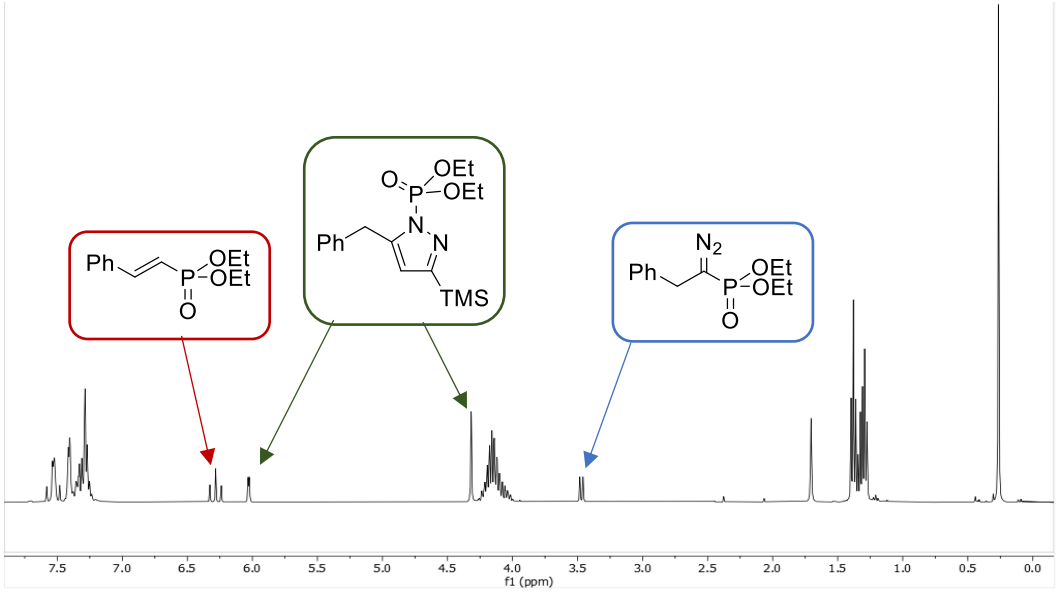


Fig 23. *Crude ^1H NMR Spectrum of **233e** before treatment of base to give **234e**.*

6.5. Conclusions and future work

β-Ketoesters could efficiently be synthesised from acyl phosphosphates and esters in moderate yields. Quenching with ammonium chloride produced cleaner crude material than HCl work up but sacrificed some product β-ketoester. Movassaghi highlighted that 1,3-dicarbonyls can be prepared in the presence of toluene, perhaps optimisation by using toluene or other solvents may further improve the reaction.[140]

In some cases, the yield was improved when crude acyl phosphate mixtures were used, further investigation is required, to determine whether the better yield is

from additional coordination of phosphate impurities or simply because of lower residual moisture.

The synthesis of substituted 3,4-isoxazolols from α-aryl substituted β-ketoesters was problematic due to competing reactions and inefficient condensations. Further exploration into more optimal condensation procedures is required.

Experimental (Chapter IV)

7. Experimental

Starting materials were obtained from commercial suppliers unless otherwise stated. All petrol used was petroleum ether (boiling point: 40-60 °C) and all water was previously deionised.

All copper-catalysed reactions were performed in a Radley's carousel tube (150 mm) under air and non-anhydrous conditions, unless otherwise stated. All other reactions were performed in a round bottom flask under argon atmosphere, unless otherwise stated.

Column chromatography was perform using Merck silica gel 60. Pore size, 40-63μm. Thin layer chromatography (TLC) was performed using Merck silica gel plates 60 F_{254}.

Fourier-transformed infrared (FTIR) spectra were obtained using a Bruker Alpha FTIR spectrometer with a single reflection attenuated total reflectance (ATR) module.

High resolution mass spectra were obtained using a Bruker microTOF spectrometer using electrospray ionisation (ESI).

Chiral HPLC data was obtained using Agilent 1100 series. Wavelengths were recorded at 210, 250 and 280 nm. All chromatograms were obtained using Chiral OJ-H column at 25 °C. All reported data were calculated from chromatograms at 250 nm. Percentages were calculated from integrated peak area.

NMR data was collected using either a Bruker AV400, AV-3-400 or AV-3-400HD. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) are reported in Hz. All chemical shifts were recorded using the residual solvent as the internal standard ($CDCl_3$: δ_H 7.28, δ_C 77.16; $DMSO_{d\text{-}6}$: δ_H 2.50, δ_C 39.43).

7.1. Amides procedures and assignments

General procedure 1A

To a stirring suspension of CuI (9.50 mg, 50.0 μmol) in MeCN (1.00 mL), carboxylic acid (1.10 mmol) and Et_3N (76 μL, 0.55 mmol) were added at 55 °C. The solution was stirred for 5 min before the addition of diethyl phosphite (129 μL, 1.00 mmol). The reaction was stirred vigorously for 3 h before the amine (0.50 mmol) was added. The reaction was stirred for a further 0.75 h before cooling to room temperature and diluting with DCM (50 mL). The organic layer was washed with saturated Na_2CO_3 (30 mL), 2M HCl (30 mL) and brine (30 mL), then dried ($MgSO_4$). Volatiles were removed under reduced pressure to recover the crude product, which was purified by silica gel chromatography using the solvent system provided.

General procedure 1B

To a stirring suspension of CuI (38.0 mg, 0.20 mmol) in MeCN (1.00 mL), carboxylic acid (1.10 mmol) and Et_3N (76 μL, 0.55 mmol) were added at 55 °C. The solution was stirred for 5 min before the addition of diethyl phosphite (129 μL, 1.00 mmol). The reaction was stirred vigorously for 1.5 h before amine (0.50 mmol) was added. The reaction was stirred for a further 0.75 h before cooling to room temperature and diluting with DCM (50 mL). The organic layer was washed with saturated Na_2CO_3 (30 mL), 2M HCl (30 mL) and brine (30 mL), then dried ($MgSO_4$). Volatiles were removed under reduced pressure to recover the crude product, which was purified by silica gel chromatography using the solvent system provided.

General procedure 1C

To a stirring suspension of CuI (9.50 mg, 50 μmol) in MeCN (1.00 mL), carboxylic acid (1.10 mmol) and Et_3N (76 μL, 0.55 mmol) were added at 55 °C. The solution was stirred for 5 min before the addition of diethyl phosphite (129 μL, 1.00 mmol). The reaction was stirred vigorously for 3 h before the amine (0.50 mmol) was added. The reaction was stirred for a further 0.75 h before cooling to room

temperature and diluting with DCM (50 mL). The organic layer was washed with saturated Na_2CO_3 (30 mL), and brine (30 mL), then dried (Na_2SO_4). Volatiles were removed under reduced pressure to recover the crude product, which was purified by silica gel chromatography using the solvent system provided.

General procedure 1D

To a stirring suspension of CuI (9.5 mg, 50 μmol) in MeCN (1 mL), carboxylic acid (1.10 mmol) and Et_3N (76 μL, 0.55 mmol) were added at 55 °C. The solution was stirred for 5 min before the addition of diethyl phosphite (129 μL, 1.00 mmol). The reaction was stirred vigorously for 3 h before the amine (0.50 mmol) was added. The reaction was stirred for a further 0.75 h before cooling to room temperature and diluting with DCM (50 mL). The organic layer was washed with saturated Na_2CO_3 (30 mL), then 2M HCl (30 mL). The HCl wash was basified to ~pH 9 then extracted with DCM (3x50 mL), the organic layer was dried (Na_2SO_4) and volatiles removed under reduced pressure to give amide without further need for purification.

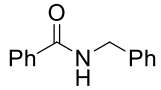
General procedure 1E

To a stirring suspension of CuI (9.5 mg, 50 μmol) in MeCN (1 mL), carboxylic acid (1.10 mmol) and Et_3N (76 μL, 0.55 mmol) were added at 55 °C. The solution was stirred for 5 min before the addition of diethyl phosphite (129 μL, 1.00 mmol). The reaction was stirred vigorously for 3 h. Et_3N (69 μL, 0.50 mmol) and amine (0.50 mmol) were added. The reaction was stirred for a further 0.75 h before cooling to room temperature and diluting with DCM (50 mL). The organic layer was washed with saturated Na_2CO_3 (30 mL), 2M HCl (30 mL) and brine (30 mL), then dried (Na_2SO4). Volatiles were removed under reduced pressure to recover the crude product, which was purified by silica gel chromatography using the solvent system provided.

General procedure 1F

To a stirring suspension of CuI (38 mg, 0.20 mmol) in MeCN (1 mL), carboxylic acid (1.10 mmol) and Et_3N (76 µL, 0.55 mmol) were added at 55 °C. The solution was stirred for 5 min before the addition of diethyl phosphite (129 µL, 1.00 mmol). The reaction was stirred vigorously for 1.5 h. Et_3N (69 µL, 0.50 mmol) and amine (0.50 mmol) were added. The reaction was stirred for a further 0.75 h before cooling to room temperature and diluting with DCM (50 mL). The organic layer was washed with saturated Na_2CO_3 (30 mL), 2M HCl (30 mL) and brine (30 mL), then dried (Na_2SO4). Volatiles were removed under reduced pressure to recover the crude product, which was purified by silica gel chromatography using the solvent system provided.

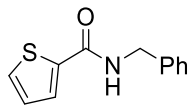
***N*-Benzylbenzamide 20**



Following procedure **1A**. Benzoic acid (134 mg, 1.10 mmol) and benzyl amine (55 µL, 0.50 mmol) were used as coupling partners. R_f 0.44 (Et_2O:Petrol, 6:4); Recovered 72 mg (68%) as a white solid. mp. 102-104 °C (lit:[159] 104 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84-7.80 (2 H, m, Ar*H*), 7.56-7.50 (1H, m, Ar*H*), 7.49-7.43 (2H, m, Ar*H*), 7.40-7.35 (4H, m, Ar*H*), 7.35-7.31 (1H, m, Ar*H*), 6.38 (1H, br. s., N*H*), 4.68 (2H, d, *J* 5.7, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4 (C), 138.1 (C), 134.4 (C), 131.6 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 127.0 (CH), 44.2 (CH_2); MS (ESI^+) calcd. for $C_{14}H_{14}NO$ $[M+H]^+$ 212.1070 found, 212.1074. Spectroscopic data are in accordance with literature.[159]

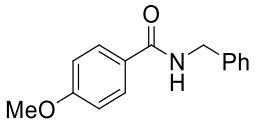
Following procedure **1B**. Recovered 72 mg as a white solid (68%).

N-Benzylthiophene-2-carboxamide 26



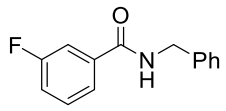
Following procedure **1A**. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and benzyl amine (55 µL, 0.50 mmol) were used as coupling partners. R_f 0.48 (Et_2O:Petrol, 6:4). Recovered 68 mg (63%) as a white solid. mp. 114-116 °C (lit:[160] 114-115 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, dd, *J* 3.7, 1.2, Ar*H*), 7.50 (1H, dd, *J* 5.0, 1.2, Ar*H*), 7.41-7.37 (4H, m, Ar*H*), 7.36-7.30 (1H, m, Ar*H*), 6.24 (1H, br. s., N*H*) and 4.66 (2 H, d, *J* 5.7, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (C), 138.7 (C), 138.0 (C), 130.0 (CH), 128.8 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.7 (CH), 44.0 (CH_2); MS (ESI$^+$) calcd. for $C_{12}H_{12}NOS$ $[M+H]^+$ 218.0634 found, 218.0635. Spectroscopic data are in accordance with literature.[160]

N-Benzyl-4-methoxybenzamide 27



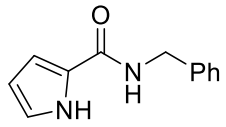
Following procedure **1A**. 4-methoxybenzoic acid (167 mg, 1.10 mmol) and benzyl amine (55 µL, 0.50 mmol) were used as coupling partners. R_f 0.20 (Et_2O:Petrol, 6:4). Recovered 68 mg (56%). mp. 126-128 °C (lit:[161] 124-125 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.76 (2H, m, Ar*H*), 7.39-7.29 (5H, m, Ar*H*), 6.96-6.89 (2H, m, Ar*H*), 6.45 (1H, br. s., N*H*), 4.64 (2H, *d, J* 5.7, C*H*$_2$) and 3.86 (3H, s, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (C), 162.2 (C), 138.4 (C), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 126.7(C), 113.8 (CH), 55.4 (CH_3), 44.0 (CH_2); MS (ESI$^+$) calculated for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1176, found 242.1174. Spectroscopic data are in accordance with literature.[161]

_N_-Benzyl-3-fluorobenzamide 28



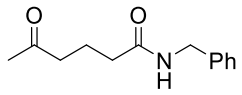
Following procedure **1A**. 3-Fluorobenzoic acid (154 mg, 1.10 mmol) and benzylamine (55 µL, 0.50 mmol) were used a coupling partners. R_f 0.46 (Et_2O:Petrol, 3:2). Recovered 69 mg (60%) as a white solid. mp. 92-94 (lit.,[162] 91-92 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.51 (2 H, m, Ar*H*), 7.46-7.31 (6 H, m, Ar*H*), 7.22 (1 H, tdd, *J,* 8.3 ,2.6 ,1, Ar*H*), 6.41 (1 H, br. s., N*H*), and 4.67 (1 H, d, *J*, 5.6, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (d, $J_{(C-F)}$ 2.3, C), 162.8 (d, $J_{(C-F)}$ 248.0, CF), 138.0 (C), 136.8 (d, $J_{(C-F)}$ 7.0, C), 130.4 (d, $J_{(C-F)}$ 7.8, CH), 129.0 (CH), 128 (CH), 127.9 (CH), 122.5 (CH), 118.8 (d, *J* 21.4, CH), 114.6 (d, $J_{(C-F)}$ 23, CH), 44.4 (CH_2); ^{19}F NMR ($CDCl_3$) δ -111.1; MS (ESI$^+$) calcd. for $C_{14}H_{12}FNONa$ $[M+Na]^+$ 252.0795, found 252.0802. Spectroscopic data are in accordance with literature.[162]

_N_-Benzyl-1*H*-pyrrole-2-carboxamide 29



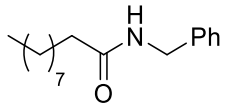
Following procedure **1A**. Pyrrole-2-carboxylic acid (122 mg, 1.10 mmol) and benzyl amine (55 µL, 0.50 mmol) were used as coupling partners. R_f (Et_2O:Petrol, 7:3) 0.26. Recovered 46 mg (46%) as a white solid. mp. 126-128 °C (lit.,[163] 128-130 °C); υ_{max} (ATR)/cm^{-1} 3376, 3267, 3086, 2923, 1706, 1613, 1556; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (1H, br. s., N*H*), 7.35-7.41 (4H, m, Ar*H*), 7.34-7.29 (1H, m, Ar*H*), 6.96-6.93 (1H, m, Ar*H*), 6.58-6.56 (1H, m, Ar*H*), 6.27-6.23 (1H, m, Ar*H*), 6.21 (1H, br. s., N*H*), 4.65 (2H, d, *J* 5.6, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (C), 138.2 (C), 128.8 (CH), 127.8 (CH), 127.6 (CH), 125.8 (C), 121.6 (CH), 109.9 (CH), 108.8 (CH), 43.4 (CH_2); MS (ESI$^+$) calculated for $C_{12}H_{13}N_2O$ $[M+H]^+$ 201.1022 found, 201.1019.

N-Benzyl-5-oxohexanamide 30



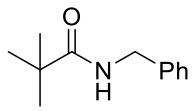
Following procedure **1A**. 4-Acetylbutyric acid (147.6 µL, 1.10 mmol) and benzyl amine (55 µL, 0.50 mmol) were used as coupling partners. Purified using Et_2O:Petrol, 90:10 to Et_2O:MeOH, 90:10); R_f 0.30 (DCM:MeOH, 95:5). Recovered 58 mg (53%) as a waxy solid. mp. 32-35 °C; υ_{max} (ATR)/cm^{-1} 3133, 3090, 2925, 1702, 1634, 1551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.33 (2H, m, Ar*H*), 7.32-7.27 (3H, m, Ar*H*), 5.89 (1H, br. s., N*H*), 4.45 (2H, d, *J* 5.7, C*H*$_2$), 2.54 (2H, t, *J* 7.3, C*H*$_2$), 2.26 (2H, t, *J* 7.3, C*H*$_2$), 2.14 (3H, s, C*H*$_3$) and 1.94 (2H, quin, *J* 7.30, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6 (C), 172.2 (C), 138.3 (C), 128.7 (CH), 127.8 (CH), 127.6 (CH), 43.6 (CH_2), 42.5 (CH_2), 35.4 (CH_2), 30.0 (CH_3), 19.7 (CH_2); MS (ESI$^+$) calcd. for $C_{13}H_{17}NO_2Na$ $[M+Na]^+$ 242.1151, found 242.1151.

N-Benzyldecanamide 31



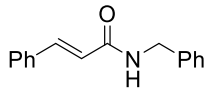
Following procedure **1A**. Decanoic acid (189 mg, 1.10 mmol) and benzyl amine (55 µL, 0.50 mmol) were used as coupling partners. R_f 0.29 (Et_2O:Petrol, 7:3). Recovered 84 mg (65%) as a colourless solid. mp. 60-62 °C (lit:[164] 60-62 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (5H, m, Ar*H*), 5.70 (1H, br. s., N*H*), 4.47 (2H, d, *J* 5.7, C*H*$_2$), 2.23 (2H, t, *J*, 7.4, C*H*$_2$), 1.68 (2H, app. quint, *J*, 7.3, C*H*$_2$), 1.36-1.24 (12H, m, C*H*$_2$) and 0.90 (3H, t, *J*, 6.8, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (C), 138.4 (C), 128.7 (CH), 127.9 (CH), 127.5 (CH), 43.6 (CH_2), 36.9 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 25.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3); MS (ESI$^+$) calcd. for $C_{17}H_{27}NONa$ $[M+Na]^+$ 284.1985, found 284.1982. $C_{17}H_{27}NONa$. Spectroscopic data are in accordance with literature.[165]

***N*-Benzylpivalamide 32**



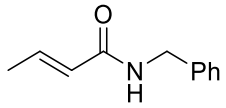
Following procedure **1A**. Pivalic acid (112 mg, 1.10 mmol) and benzyl amine (55 µL, 0.50 mmol) were used as coupling partners. R_f 0.28 (Et_2O:Petrol, 5:5); Recovered 58 mg (60%) as a yellow solid. mp. 80-82 °C (lit:[166] 81-82 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.33 (5H, m, Ar*H*), 5.92 (1H, br. s., N*H*), 4.46 (2H, d, *J* 5.6, C*H*$_2$), 1.25 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C), 138.7 (C), 128.7 (CH), 127.7 (CH), 127.5 (CH), 43.6 (CH_2), 38.7 (C), 27.7 (CH_3); MS (ESI^+) calcd. for $C_{12}H_{18}NO$ $[M+H]^+$ 192.1383, found 192.1386. Spectroscopic data are in accordance with literature.[166]

(*E*)-*N*-Benzyl-cinnamamide 33



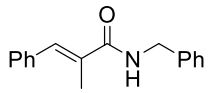
Following procedure **1A**. Trans-cinnamic acid (163 mg, 1.10 mmol) and benzyl amine (55 µL, 0.50 mmol) were used as coupling partners. R_f 0.23 (Et_2O:Petrol, 6:4). Recovered 92 mg (78%) as a white solid. mp. 98-100 °C (lit.,[167] 98-99 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, d, *J* 15.6, C*H*), 7.54-7.49 (2H, m, Ar*H*), 7.43-7.30 (8H, m, Ar*H*), 6.44 (1H, d, *J* 15.6, *CH*), 5.97 (1H, br. s., N*H*), 4.60 (1H, d, *J* 5.8, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C), 141.5 (CH), 138.2 (C), 134.8 (C), 129.8 (CH), 128.9 (CH), 128.8 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 120.4 (CH), 43.9 (CH_2); MS (ESI^+) calculated for $C_{16}H_{16}NO$ $[M+H]^+$ 238.1226, found 238.1233. Spectroscopic data are accordance with literature.[167]

(*E*)-*N*-Benzylbut-2-enamide 34



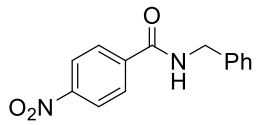
Following procedure **1A**. 2-Butenoic acid (95 mg, 1.1 mmol) and benzyl amine (55 µL, 0.55 mmol) were used as coupling partners. R_f (Et_2O:petrol, 1:2) 0.38. Recovered (62 mg, 71 %) as a white solid. mp. 114-116 °C; υ_{max} (ATR)/cm^{-1} 3260, 3081, 3061, 3028, 1670, 1624, 1554, 1493; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (5H, m, Ar*H*), 6.91 (1H, dq, *J* 15.3, 6.9, C*H*), 5.83 (1H, dq, *J* 15.3, 1.7, C*H*), 5.72 (1H, br. s., N*H*), 4.53 (2H, d, *J* 5.7, C*H*$_2$), 1.88 (3H, dd, *J* 6.9, 1.7, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (C), 140.5 (CH), 138.3 (C), 128.7 (CH), 127.9 (CH), 127.5 (CH), 124.8 (CH), 43.6 (CH_2), 17.8 (CH_3); MS (ESI^+) calcd. for $C_{11}H_{14}NO$ $[M+H]^+$ 176.1070 found 176.1079.

(*E*)-*N*-benzyl-α-methylcinnamic amide 35



Following procedure **1A**. α-Methylcinnamic acid (186 mg, 1.10 mmol) and benzyl amine (55 µL, 0.55 mmol) were used as coupling partners. R_f 0.30 (Et_2O:petrol, 6:4). Recovered (88 mg, 64 %) as a white solid. mp. 118-120 (lit.,[57] 120-121 °C); υ_{max} (ATR)/cm^{-1} 3280, 3060, 3031, 1612, 1536, 1488, 1451; ^{1}H NMR (400 MHz, $CDCl_3$) 7.45-7.30 (11H, m, Ar*H*C*H*), 6.16 (1H, br. s., N*H*), 4.61 (2H, d, *J* 5.6, C*H*$_2$), 2.14 (3H, s, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 169.2 (C), 138.2 (C), 136.0 (C), 134.2 (CH), 131.8 (C), 129.4 (CH), 128.8 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 44.1 (CH_2), 14.1 (CH_3); MS (ESI^+) calcd. for $C_{17}H_{17}NONa$ $[M+Na]^+$ 274.1202, found 274.1207.

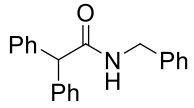
***N*-Benzyl-4-nitrobenzamide 36**



Following procedure **1A**. 4-Nitrobenzoic acid (177 mg, 1.10 mmol) and benzylamine (55 µL, 0.50 mmol) were used as coupling partners. R_f 0.40 (Et_2O:Petrol, 6:4). Recovered 50 mg (39%) as a white powder. mp. 138-140 °C (lit:[168] 137-142 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (2H, *d, J* 8.8, Ar*H*), 7.98 (2H, *d, J* 8.8, Ar*H*), 7.45-7.32 (5H, m, Ar*H*), 6.45 (1H, br. s., N*H*), 4.7 (2H, *d, J* 5.7, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C), 149.7 (C), 139.9 (C), 137.4 (C), 129.0 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 123.9 (CH), 44.6 (CH_2); MS (ESI^-) calcd. for $C_{14}H_{11}N_2O_3$ $[M-H]^-$ 255.0775, found 255.0765. Spectroscopic data are in accordance with literature.[168]

Following procedure **1B**. Recovered 76 mg (59%) as a white powder. Spectroscopic data identical to previous procedure.

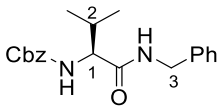
***N*-Benzyl-2,2-diphenylacetamide 37**



Following procedure **1A**. Diphenylacetic acid (233 mg, 1.10 mmol) and benzylamine (55 µL, 0.50 mmol) were used as coupling partners. R_f 0.34 (Et_2O:Petrol, 6:4); Recovered 51 mg (34%) as a white solid. mp. 124-126 °C (lit:[56] 130 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (13H, m, Ar*H*), 7.25-7.20 (2H, m, Ar*H*) 5.90 (1H, br. s., N*H*), 4.99 (1H, s, C*H*) and 4.52 (1H, d, *J* 5.7, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 139.4 (C), 138.1 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.4 (CH), 127.3 (CH), 59.3 (CH), 43.9 (CH_2); MS (ESI^+) calcd. for $C_{21}H_{20}NO$ $[M+H]^+$ 302.1539, found 302.1542. Spectroscopic data are in accordance with literature.[56]

Following procedure **1B**. Recovered 72 mg (48%) as a white solid. Spectroscopic data matches previous procedure.

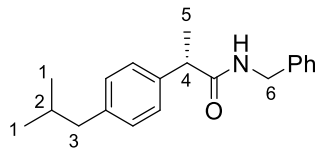
(*S*)-Benzyl-1-(benzylamino)-3-methyl-1-oxobutan-2-ylcarbamate 38



Following procedure **1A** but Na_2SO_4 used as drying agent. Cbz-L-Valine (276 mg, 1.10 mmol) and benzyl amine (55 μL, 0.50 mmol) were used as coupling partners. R_f 0.57 (Et_2O:Petrol, 6:4). Recovered 73 mg (35%) as a white solid. mp. 162-164 (lit:[169] 169 °C); $[\alpha]_{589}^{22}$ -16.7 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.25 (10H, m, Ar*H*), 6.17 (1H, br.s., N*H*Bn), 5.35 (1H, d *J 8.5,* N*H*Cbz), 5.16-5.08 (2H, s, C*H*$_2$(Cbz)), 4.51 (1H, dd, *J* 14.5 and 5.7, C^3*H*$_2$), 4.44 (1H, dd, *J* 14.5 and 5.7, C^3*H*$_2$), 4.00 (1H, dd, *J* 8.8 and 6.0, C^1*H*), 2.20 (1H, m, C^2*H*), 0.99 (3H, d, *J* 6.8, C*H*$_3$) and 0.94 (3H, d, *J* 6.8, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C), 156.6 (C), 137.9 (C), 136.3 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 67.3 (CH_2), 60.8 (CH), 43.8 (CH_2), 31.1 (CH), 19.5 (CH_3) and 18.0 (CH_3); MS (ESI$^+$) calcd. for $C_{20}H_{25}N_2O_3$ $[M+H]^+$ 341.1860, found 341.1867 expected. HPLC (hexane:*i*PrOH 99:1 (4 min) gradient up to 90:10 (20 min), 1 mL/Min, chiral OJ-H) t_R (S)= 22.04 min (99.6 %), t_R (R)= 26.32 min (0.04%). Spectroscopic data are in accordance with literature.[169]

Following procedure **1B**. Recovered 120 mg (68%) as a white solid. Spectroscopic data identical to previous procedure.

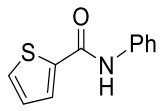
(*S*)-*N*-Benzyl-2-(4-isobutylphenyl)propenamide 5



Following procedure **1A** but Na_2SO_4 used as drying agent. 99% (S)-ibuprofen (227 mg, 1.10 mmol) and benzyl amine (55 μL, 0.50 mmol) were used as coupling partners. R_f 0.24 (Et_2O:Petrol, 6:4). Recovered 61 mg (41%, 95% e.r.) as a waxy solid. mp. 48-50 °C (lit.,[58] 77-78 °C); $[\alpha]_{589}^{22}$ 12.3 (c 1.00, $CHCl_3$) [lit.,[57] 7.2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.20 (5H, m, Ar*H*), 7.17-7.11 (4H, m, Ar*H*), 5.63 (1H, br. s., N*H*), 4.41 (2H, d, *J*, 5.7, C^6H_2), 3.60 (1H, q, *J*, 7.2, C^4H), 2.47 (2H, d, *J*, 7.2, C^3H_2), 1.86 (1H, app. nonet, *J* 6.8, C^2H), 1.57 (3H, d, *J*, 7.2, C^5H_3) and 0.92 (6H, d, *J*, 6.8, C^1H_3 and $C^{1'}H_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (C), 140.7 (C), 138.4 (C), 138.3 (C), 129.6 (CH), 128.5 (CH), 127.3 (CH), 127.3 (CH) 127.2 (CH), 46.7 (CH), 44.9 (CH_2), 43.4 (CH_2), 30.1 (CH), 22.3 (CH_3), 18.4 (CH_3); MS (ESI^+) calcd. for $C_{20}H_{26}NO$ $[M+H]^+$ 296.2014, found 296.2011. Spectroscopic data are accordance with literature.[57] HPLC (hexane:*i*PrOH 99:1 (4 min) gradient up to 90:10 (20 min), 1 mL/Min, chiral OJ-H) t_R (R)= 18.69 min (4.8 %), t_R (S)= 21 min (95.2 %).

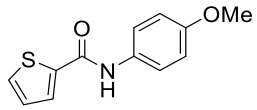
Following procedure **1B**. but Na_2SO_4 used as drying agent. 99% (S)-ibuprofen (227 mg, 1.10 mmol) and benzylamine (55 μL, 0.50 mmol) were used as coupling partners. Recovered 93 mg (63 %). Spectroscopic data identical to previous procedure.

***N*-Phenylthiophene-2-carboxamide 40**



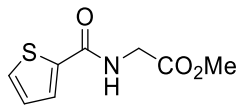
Following procedure **1A**. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and aniline (50 µL, 0.50 mmol) were used as coupling partners. R_f 0.48 (Et_2O:Petrol, 1:1). Recovered 79 mg (72%) as an off-white solid. mp. 139-140 °C (lit.,[170] 136-138 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, br. s., N*H*), 7.68-7.61 (3H, m, Ar*H*), 7.57 (1H, dd, *J* 5.0, 1.2, Ar*H*), 7.42-7.35 (2H, m, Ar*H*), 7.21-7.13 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (C), 139.4 (C), 137.7 (C), 130.8 (CH), 129.3 (CH), 128.6 (CH), 128.0 (CH), 124.8 (CH), 120.3 (CH); MS (ESI^+) calcd. for $C_{11}H_{10}NOS$ $[M+H]^+$ 204.0478, found 204.0479. Spectroscopic data are in accordance with the literature.[170]

***N*-(4-Methoxyphenyl)thiophen-2-carboxamide 41**



Following procedure **1A**. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and 4-methoxyaniline (62 mg, 0.50 mmol) were used as coupling partners. R_f- 0.40 (Et_2O:Petrol, 3:1). Recovered 80 mg (69%) as a slightly orange solid. mp. 138-140 °C (lit.,[171] 139-140 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, br. s., N*H*), 7.63 (1H, d, *J* 3.3, Ar*H*), 7.57-7.49 (3H, m, Ar*H*), 7.14 (1H, dd, *J* 5.0, 3.7, Ar*H*), 6.95-6.89 (2H, m, Ar*H*), 3.83 (3H, s, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (C), 156.7(C), 139.3 (C), 130.6 (C), 130.5 (CH), 128.3 (CH), 127.8 (CH), 122.2 (CH), 114.3 (CH), 55.5 (CH_3); MS (ESI^+) calcd. for $C_{12}H_{11}NO_2SNa$ $[M+Na]^+$ 256.0403, found 256.0407. Spectroscopic data are in accordance with the literature.[171]

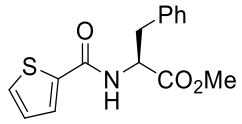
Methyl-2-(thiophene-2-carboxamido)acetate 42



Following procedure **1E**. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and glycine methyl ester hydrochloride (63 mg, 0.50 mmol) were used as coupling partners. R_f 0.38 (Et_2O:Petrol, 9:1). Recovered 64 mg (64%) as a white solid. mp. 92-94 °C (lit.,[172] 94-96 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, dd, *J* 3.7, 1.1, Ar*H*), 7.53 (1H, dd, *J* 5.0, 1.1, Ar*H*), 7.11 (1H, dd, *J* 5.0, 3.7, Ar*H*), 6.53 (1H, br. s., N*H*), 4.25 (2H, d, *J* 5.1, C*H*$_2$), 3.83 (1H, s, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C), 161.9 (C), 138.0 (C), 130.5 (CH), 128.6 (CH), 127.7 (CH), 52.6 (CH_3), 41.6 (CH_2); MS (ESI$^+$) calcd. for $C_8H_9NO_3SNa$ $[M+Na]^+$ 222.0195, found 222.0194.

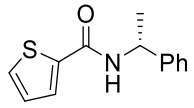
Following procedure **1F**. Recovered 59 mg (59%) as a white solid. Spectroscopic data identical to previous procedure.

(*S*)-Methyl-3-phenyl-2-(thiophene-2-carboxamido) propanoate 43



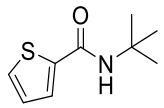
Following procedure **1E**. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and L-phenyl alanine methyl ester hydrochloride (108 mg, 0.50 mmol) were used as coupling partners. R_f 0.46 (Et_2O:Petrol, 7.3). Recovered 79 mg (55%) as a white solid. mp. 82-84 °C; $[\alpha]_{589}^{23}$ +74.4 (c 1.00, $CHCl_3$); υ_{max} (ATR)/cm^{-1} 3282, 3108, 2949, 1732, 1622, 1540, 1497; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, *J* 5.0, 1.2, Ar*H*), 7.48 (1H, dd, *J* 3.8, 1.2, Ar*H*), 7.35-7.25 (3H, m, Ar*H*), 7.18-7.13 (2H, m, Ar*H*), 7.09 (1H, *dd, J* 5.0, 3.8, Ar*H*), 6.44 (1H, *d* 7.6, N*H*), 5.11-5.05 (1H, m, C*H*), 3.78 (3H, s, OC*H*$_3$) and 3.21-3.33 (2H, m, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 161.3 (C),138.3 (C) 135.8 (C) 130.4 (CH), 129.4 (CH), 128.7 (CH), 128.5 (CH), 127.7 (CH), 127.3 (CH), 53.4 (CH), 52.5 (CH_3), 38.0 (CH_2); MS (ESI$^+$) calcd. for $C_{15}H_{16}NO_3S$ $[M+H]^+$ 290.0845, found 290.0844. HPLC (hexane:*i*PrOH 90:10 gradient up to 80:20 (20 min), 1 mL/Min, chiral OJ-H) t_R (S)= 22 min (98.2 %), t_R (R)= 27 min (1.8%).

(R)-*N*-(1-Phenylethyl)thiophene-2-carboxamide 44



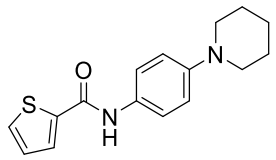
Following procedure **1C**. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and (R)-α-methyl benzamide (64 µL, 0.50 mmol) were used as coupling partners. R_f 0.34 (Et_2O:Petrol, 6:4). Recovered 62 mg (54%) as a white solid. mp. 126-128 °C (lit.,[173] 127-128 °C); $[\alpha]_{589}^{23}$ +11.5 (c 1.00, $CHCl_3$) [lit:[173] +11.7 (c 0.62, $CHCl_3$)][173] υ_{max} (ATR)/cm^{-1} 3289, 3085, 3064, 2915, 1630, 1551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, *J*, 3.7, 1.2, Ar*H*), 7.49 (1H, dd, *J* 5.0, 1.1, Ar*H*), 7.44-7.36 (4H, m, Ar*H*), 7.28-7.33 (1H, m, Ar*H*), 7.09 (1H, dd, *J* 5.0, 3.7, Ar*H*), 6.16 (1H, br. s, N*H*), 5.34 (1H, app. quint, *J* 6.9, C*H*), 1.64 (3H, d, *J*, 6.9, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1 (C), 143.0 (C), 139.1 (C), 130.0 (CH), 128.8 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 126.3 (CH), 49.3 (CH), 21.7 (CH_3); MS (ESI^+) calcd. for $C_{13}H_{13}NO_3SNa$ $[M+Na]^+$ 254.0610, found 254.0615. HPLC (hexane:*i*PrOH 85:15 (22 min) gradient up to 75:25 (35 min), 1 mL/Min, chiral OJ-H) t_R (R)= 26 min (99.98 %), t_R (S)= 33 min (0.02%).

***N*-(*tert*-Butyl)thiophene-2-carboxamide 45**



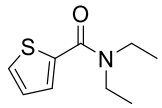
Following procedure **1A**, but the reaction was left stirring for 16 hours after amine addition. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and tert-butylamine (53 µL, 0.50 mmol) were used as coupling partners. R_f 0.41 (Et_2O:Petrol, 6:4). Recovered 62 mg (68%) as a white solid. mp. 146-148 °C (lit.,[174] 147-148 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (2H, m, Ar*H*), 7.07 (1H, dd, *J* 5.0, 3.7, Ar*H*), 5.81 (1 H, br. s., N*H*), 1.49 (9H, s, (C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (C), 140.3 (C), 129.4 (CH), 127.5 (CH), 127.4 (CH), 52.0 (C), 29.0 (CH_3); MS (ESI^+) calcd. for $C_9H_{13}NOSNa$ $[M+Na]^+$ 206.0610, found 206.0619. Spectroscopic data are in accordance with literature.[174]

N-(4-Piperidinyl-1-yl)phenyl)thiophene-2-carboxamide 46



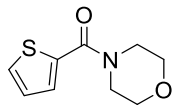
Following procedure **1C**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and N-(4-aminophenyl)piperidine (88 mg, 0.50 mmol) were used as coupling partners. R_f 0.45 (Et_2O:Petrol, 9:1); Recovered 100 mg (70%) as a white solid. mp. 154-157 °C; υ_{max} (ATR)/cm^{-1} 3282, 2929, 2852, 2802, 1621, 1513; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.59 (1H, m, Ar*H*), 7.56 (1H, br. s., N*H*), 7.54 (1H, dd, *J* 5.0, 1.1, Ar*H*), 7.49 (2H, d, *J* 9.0, Ar*H*), 7.14 (1H, dd, *J* 5.1, 1.1, Ar*H*), 6.98-6.93 (2H, m, Ar*H*), 3.19-3.12 (4H, m, C*H*$_2$), 1.79-1.70 (4H, m, C*H*$_2$), 1.65-1.56 (2H, m, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7 (C), 149.6 (C), 139.5 (C), 130.3 (CH), 129.4 (C), 128.1 (CH), 127.4 (CH), 121.6 (CH), 117.0 (CH), 51.0 (CH_2), 25.8 (CH_2), 24.2 (CH_2); MS (ESI^+) calcd. for $C_{16}H_{18}N_2OSNa$ $[M+Na]^+$ 309.1032, found 309.1032.

N,N-Diethylthiophene-2-carboxamide 47



Following procedure **1A**. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and diethyl amine (52 μL, 0.50 mmol) were used as coupling partners. R_f 0.25 (Et_2O:Petrol, 6:4). Recovered 51 mg (56%) as a pale-yellow oil. υ_{max} (ATR)/cm^{-1} 3075, 2972, 2933, 2873, 1602, 1523, 1473; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, dd, *J* 5.0, 1.2, Ar*H*), 7.34 (1H, dd, *J* 3.8, 1.2, Ar*H*), 7.05 (1H, m, Ar*H*), 3.56 (4H, q, *J* 7.1, C*H*$_2$), 1.27 (6H, t, *J* 7.1, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (C), 138.3 (C), 128.2 (CH), 127.9 (CH), 126.7 (CH), 42.2 (CH_2), 13.7 (CH_3); MS (ESI^+) calcd. for $C_9H_{14}NOS$ $[M+H]^+$ 184.0791, found 184.0788.

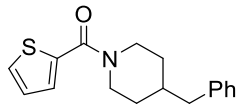
Morpholino(thiophen-2-yl)methanone 48



Following procedure **1A**. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and morpholine (43 μL, 0.50 mmol) were used as coupling partners. R_f 0.42 (Et_2O:Petrol, 9:1). Recovered 68 mg (69%) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3024, 3005, 2862, 1613, 1524, 1414, 1276; ^1H NMR (400 MHz, DMSO-*d6*) δ 7.77 (1H, dd, *J* 5.0, 1.1, Ar*H*), 7.43 (1H, dd, *J* 3.6, 1.1, Ar*H*), 7.13 (1H, dd, *J* 5.0, 3.6, Ar*H*), 3.67-3.63 (8H, m, C*H*$_2$); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 162.4 (C), 136.9 (C), 129.6 (CH), 129.2 (CH), 127.1 (CH), 66.1 (CH_2), 45.2 (CH_2); MS (ESI^+) calcd. for $C_9H_{12}NO_2S$ $[M+H]^+$ 198.0583, found 198.0583.

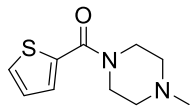
Following procedure **1B**. Recovered 65 mg (66%) as a colourless oil. Spectroscopic data identical to previous procedure.

(4-Benzylpiperidin-1-yl)(thiophen-2-yl)methanone 49



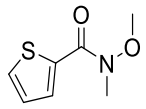
Following procedure **1A**. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and 4-benzylpiperidine (88 μL, 0.50 mmol) were used as coupling partners. R_f 0.25 (Et_2O:Petrol, 6:4). Recovered 111 mg (77%) as a waxy solid. mp. 62-64 °C; υ_{max} (ATR)/cm^{-1} 3083, 3050, 2934, 2911, 2858, 1585, 1523, 1436; ^1H NMR (400 MHz, DMSO-*d6*, 80°C) δ 7.67 (1H, d, *J* 5.0, Ar*H*), 7.34 (1H, d, *J* 3.7, Ar*H*), 7.29 (2H, t, *J* 7.5, Ar*H*), 7.22-7.16 (4H, m, Ar*H*), 7.1 (1H, t, *J* 5.0, Ar*H*), 4.23 (2H, d, *J* 13.3, C*H*$_2$), 2.96 (2H, t, *J* 12.7, C*H*$_2$), 2.58 (2H, d, 7.2, C*H*$_2$), 1.87 (1H, ttt, *J* 11.2, 7.2, 4.1, C*H*), 1.67 (2H, d, *J* 13.3, C*H*$_2$), 1.26-1.14 (2H, m, C*H*$_2$); ^{13}C NMR (100 MHz, DMSO-*d6*, 80°C) δ 161.9 (C), 139.6 (C), 137.6 (C), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 126.4 (CH), 125.4 (ArH), 44.6 (CH_2), 41.6 (CH_2), 36.9 (CH), 31.4 (CH_2); MS (ESI^+) calcd. for $C_{17}H_{19}NOSNa$ $[M+Na]^+$ 308.1080, found 308.1083.

(4-Methylpiperazin-1yl)thiophen-2-ylmethanone 50



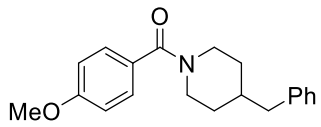
Following procedure **1D**. Thiophene-2-carboxylic acid (141 mg, 1.1o mmol) and N-methylpiperizine (55.5 µL, 0.50 mmol) were used as coupling partners. R_f 0.20 (Et_2O:MeOH, 9:1). Recovered 71 mg (68%) as a pale-yellow oil. υ_{max} (ATR)/cm^{-1} 2982, 2932, 2910, 1624, 1481, 1442, 1055; ^1H NMR (400 MHz, $DMSO_{d6}$) δ 7.75 (1H, d, *J* 5.0, Ar*H*), 7.40-7.37 (1H, m, Ar*H*), 7.12 (1H, dd, *J* 5.1, 3.6, Ar*H*), 3.63 (4H, m, C*H*$_2$), 2.37 (4H, t, *J* 5.1, C*H*$_2$), 2.22 (3H, s, C*H*$_3$); ^{13}C NMR (100 MHz, DMSO) δ 162.2 (C), 137.1 (C), 129.4 (CH), 129.0 (CH), 127.1 (CH), 54.5 (CH_2), 45.4 (CH_3), 44.8 (CH_2); MS (ESI^+) calcd. for $C_{10}H_{14}N_2OSNa$ $[M+Na]^+$ 233.0719, found 233.0722.

***N*-Methoxy-*N*-methylthiophene-2-carboxamide 51**



Following procedure **1E**. Thiophene-2-carboxylic acid (141 mg, 1.10 mmol) and N,O-dimethylhydroxylamine hydrochloride (49 mg, 0.50 mmol) were used as coupling partners. Rf 0.40 (Et_2O:Petrol, 6:4). Recovered 59 mg (68%) as a pale-yellow oil. υ_{max} (ATR)/cm^{-1} 2991, 2936, 1603, 1518, 1423, 1378; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, dd, *J* 3.8, 1.3, Ar*H*), 7.57 (1H, dd, *J* 5.1, 1.3, Ar*H*), 7.12 (1H, dd, 5.1, 3.8, Ar*H*), 3.80 (1H, s, NC*H*$_3$), 3.39 (1H, s, OC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (C), 134.4 (CH), 133.5 (C), 132.3 (CH), 126.8 (CH), 61.7 (NCH_3), 33.2 (OCH_3); MS (ESI^+) calcd. for $C_7H_9NO_2SNa$ $[M+Na]^+$ 194. 0246, found 194.0247.

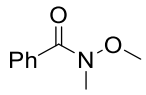
(4-Benzylpiperidin-1-yl)(4-methoxyphenyl)methanone 52



Following procedure **1A** but Na_2SO_4 used as drying agent. 4-methoxybenzoic acid (167 mg, 1.10 mmol) and 4-benzylpiperidine (88 μL, 0.50 mmol) were used as coupling partners. R_f (0.28, Et_2O). Recovered 75 mg (48%) as a white solid. mp. 82-84 °C; υ_{max} (ATR)/cm^{-1} 3083, 3049, 3003, 2964, 2867, 1588, 1513, 1430; ^1H NMR (400 MHz, $DMSO_{d-6}$, 80°C) δ 7.38-7.24 (4H, m, Ar*H*), 7.13-7.12 (3H, m, Ar*H*), 7.03-6.93 (2H, m, Ar*H*), 4.03 (2H, d, 13.1, CH_2), 3.08 (3H, s, CH_3), 2.87 (2H, td, *J* 13.1, 2.6, CH_2), 2.57 (2H, d, *J* 7.2, CH_2), 1.88-1.76 (1H, m, C*H*), 1.23-1.12 (2H, m, CH_2); ^{13}C NMR (100 MHz, $DMSO_{d-6}$, 80°C) δ 169.4 (C), 160.6 (C), 140.5 (C), 129.4 (CH) 129.2 (C), 129.1 (CH), 128.6 (CH), 126.3 (CH), 114.3 (CH), 55.8 (CH_3), 45.1 (CH_2), 42.5(CH_2), 37.8 (CH), 32.2 (CH_2); MS (ESI^+) calcd. for $C_{20}H_{24}NO_2$ $[M+H]^+$ 310.1802, found 310.1802.

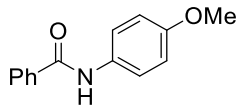
Following procedure **1B** but Na_2SO_4 used as drying agent. Recovered 77 mg (50%) as a white solid. Spectroscopic data identical to previous procedure.

***N*-Methoxy-*N*-methylbenzamide 53**



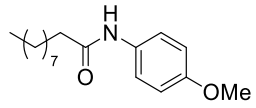
Following procedure **1E**. Benzoic acid (134 mg, 1.10 mmol) and hydroxylamine hydrochloride 49 mg (0.50 mmol) were used as coupling partners. R_f 0.46 (Et_2O:Petrol, 6:4). Recovered 54 mg (65 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3060, 2970, 2935, 1634, 1602, 1446, 1414, 1377, 1287, 1213, 977, 787, 704; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.65 (2H, m, Ar*H*), 7.56 – 7.32 (3H, m, Ar*H*), 3.55 (3H, s, OCH_3), 3.36 (3H, s, NCH_3); ^{13}C NMR(101 MHz, $CDCl_3$) δ 170.0 (C), 134.1 (C), 130.6 (CH), 128.1 (CH), 128.0 (CH), 61.0 (OCH_3), 33.8 (NCH_3); MS (ESI^+) calcd. for $C_9H_{11}NO_2Na$ $[M+Na]^+$ 188.0682, found 188.0686. Spectroscopic data are in accordance with literature.[175]

N-(4-Methoxyphenyl)benzamide 54



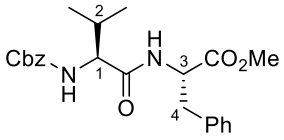
Following procedure **1A**. Benzoic acid (134 mg. 1.1 mmol) and 4-methoxyaniline (62 mg, 0.50 mmol) were used as coupling partners. R_f 0.29 (Et_2O:Petrol, 6:4); Recovered 63 mg as a white solid (56%). mp. 148-150 °C (lit.,[176] 152-154 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.91 (2H, m, Ar*H*), 7.75 (1H, br. s., N*H*), 7.60-7.54 (3H, m, Ar*H*), 7.54-7.48 (2H, m, *ArH*), 6.97-6.91 (2H, m, *ArH*), 3.83 (3H, s, OC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (C), 156.7(C), 135.0 (C), 131.7 (CH), 131.0 (C), 128.8 (CH), 127.0 (CH), 122.0 (CH), 114.3 (CH), 55.5 (OCH_3); MS (ESI$^+$) calcd. for $C_{14}H_{13}NO_2Na$ $[M+Na]^+$ 250.0838, found 250.0848.

N-(4-Methoxyphenyl)decanamide 55



Following procedure **1A**. Decanoic acid (189 mg, 1.10 mmol) and 4-methoxyaniline (62 mg, 0.50 mmol) were used as coupling partners. Rf 0.36 (Et_2O:Petrol, 1:1). Recovered 75 mg (54%) as a white solid. mp. 102-104 °C (lit.,[164] 102-103 °C); υ_{max} (ATR)/cm^{-1} 3315, 2968, 2954, 2927, 2847, 1652, 1540, 1515; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* 8.8, Ar*H*), 7.03 (1H, br. s., N*H*), 6.88 (2H, d, *J* 8.9, Ar*H*), 3.81 (3H, s, OC*H*$_3$), 2.35 (2H, t, *J* 7.6, C*H*$_2$), 1.74 (2H, quin, *J* 7.5, Ar*H*), 1.19-1.43 (12H, m, C*H*$_2$), 0.90 (3H, t, *J* 6.6, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C), 156.4 (C), 131 (C).1, 121.7 (CH), 114.2 (CH), 55.5 (CH_3), 37.7 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.4(CH_2), 29.3 (CH_2), 29.3 (CH_2), 25.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3); MS (ESI$^+$) calcd. for $C_{11}H_{15}NO_2Na$ $[M+Na]^+$ 300.1934, found 300.1934.

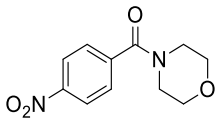
(S)-Methyl-2-((S)-2(benzyloxycarbonylamino)-3-methylbutanamido)-3-phenylpropanoate (Cbz-Val-Phe-OMe) 56



Following procedure **1E**. Cbz-L-Val (276 mg, 1.1 mmol) and L-phenylalanine methyl ester hydrochloride (108 mg, 0.50 mmol) were used as coupling partners. R_f 0.61 (Et_2O:Petrol, 6:4); Recovered 73 mg (35%) as a white solid. mp. 139-140 °C (lit.,[177] 138-139 °C); $[\alpha]_{589}^{23}$ +37.7 (c 1.00, $CHCl_3$) [lit:[177] +37 (c 1.00, $CHCl_3$)][177]; υ_{max} (ATR)/cm^{-1} 3296, 2966, 2922, 2844, 1733, 1690, 1649, 1534, 1498, 1467, 1454; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.32 (5H, m, Ar*H*), 7.31-7.21 (3H, m, Ar*H*), 7.11 (2H, d, Ar*H*), 6.26 (1H, d, *J* 7.8, C(O)N*H*), 5.31 (1H, d, *J* 8.3, CBzN*H*), 5.13 (2H, s, PhC*H*$_2$), 4.90 (1H, dt, *J* 7.8, 5.9, C^3*H*), 4.00 (1H, m, C^1*H*), 3.74 (3H, s, OC*H*$_3$), 3.19-3.07 (2H, m, C^4*H*$_2$), 2.16-2.03 (1H, m, C^2*H*), 0.95 (3H, d, *J* 6.7, CHC*H*$_3$), 0.89 (3H, d, *J* 6.7, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (C), 170.8 (C), 156.3 (C), 136.2 (C), 135.5 (C), 129.2 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 67.1 (CH_2), 60.2 (CH), 53.2 (CH_3), 37.9 (CH_2), 31.1 (CH), 19.1 (CH_3), 17.6 (CH); MS (ESI^+) calcd. for $C_{23}H_{29}N_2O_5$ $[M+H]^+$ 413.2071, found 413.2073.

Following procedure **1F**. Recovered 79 mg (38%). Spectroscopic data identical to previous procedure.

Morpholino(4-nitrophenyl)methanone 57



Following procedure **1A**. 4-Nitrobenzoic acid (184 mg, 1.10 mmol) and morpholine (43 μL, 0.50 mmol) were used as coupling partners. R_f 0.31 (Et_2O:Petrol,6:4). Recovered 42 mg (36%) as a white solid. mp. 104-106 °C (lit.,[178] 104-106 °C); ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.32-8.25 (2H, m, Ar*H*), 7.72-7.66 (2H, m, Ar*H*), 3.71-3.59 (4H, br. s., *CH*$_2$), 3.59-3.50 (2H, br. s., C*H*$_2$), 3.32-3.23 (2H, br. s., C*H*$_2$); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 167.6 (C), 148.3 (C), 142.4 (C), 128.9 (CH),

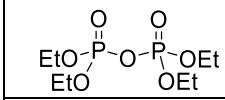
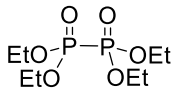
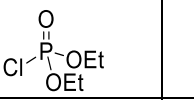
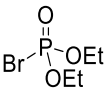
124.3 (CH), 66.4 (CH_2), 47.9 (CH_2), 42.5 (CH_2); MS (ESI^+) calcd. for $C_{11}H_{13}N_2O_4$ $[M+H]^+$ 259.0870, found 259.0879. Spectroscopic data are in accordance with literature.[179]

7.2. Chapter I- additional experiments

Stoichiometric Cu experiments

In a 150 mm Radley's tube, copper salt (2.10 mmol) was added, followed by acetonitrile (1.00 mL). The suspension was stirred at 0 ^{0}C for 0.25 h under air or argon atmosphere. Then diethyl phosphite (129 µL, 0.50 mmol) was added and the suspension stirred for 0.75 h. Aliquots were taken for analysis at 0.25 h and 0.75 h and measured by ^{31}P NMR.

Observed compounds by ^{31}P NMR (162 MHz, $CDCl_3$)

			
δ -13.31[24]	δ 6.57[24]	δ 4.27[17]	δ 7.51[17]

EPR experiment

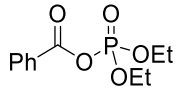
In a 150 mm Radley's carousel tube open to air, CuI (18 mg, 0.10 mmol) in MeCN (2.00 mL) were stirred at 55 °C. An aliquot (0.10 mL) was taken, diluted with MeCN to 0.5 mL and the solution frozen with liquid nitrogen, then EPR was ran (no response). Benzoic acid (269 mg, 2.2 mmol) was added, then aliquot and measurement were taken (no Response). Et_3N (152 µL, 1.10 mmol) was added, reaction mixture turned blue then aliquot and measurement were taken (Response indicative of Cu(II)). Diethyl phosphite (258 µL, 2.00 mmol) was added then aliquot and measurement taken, aliquots were then taken at 0.5 h and 3.0 h, before addition of benzylamine (110 µL, 1.00 mmol) and a final measurement was taken.

7.3. Acyl phosphates procedures and assignments

General procedure

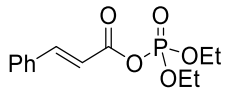
In a 100 mL round bottom flask, carboxylic acid (10 mmol) and Iodine (10 mmol) were dissolved in anhydrous DCM (50 mL) at 0 °C. Triethylphosphite (1.88 mL, 11 mmol) and Et_3N (15 mmol) were added to the reaction and allowed to warm to rt. The reaction was stirred at rt for 0.5-0.75 h. Upon completion the reaction mixture was concentrated onto celite then purified using silica gel chromatography, using the solvent system provided.

Diethyl benzoylphosphate 21



Following general procedure. Benzoic acid (1.34 g, 10.0 mmol) was used. Purified using EtOAc:Petrol (1:2 then 1:1). R_f 0.24 (EtOAc:Petrol, 1:2). Recovered 2.35 g (91 %) as a pale yellow oil; υ_{max} (ATR)/cm^{-1} 2985, 2913, 1743, 1599, 1478, 1282, 1009; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (2H, d, *J* 7.2, Ar*H*), 7.66 (1H, t, *J* 7.5, Ar*H*), 7.50 (2H, t, 7.8, Ar*H*), 4.44-4.34 (4H, m, C*H*$_2$), 1.44 (6H, t, 7.1, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1 (d, $J_{(C\text{-}P)}$ 8.3, C), 134.5 (CH), 130.7 (CH), 128.8 (CH), 128.2 (d, $J_{(C\text{-}P)}$ 8.3, C), 65.4 (d, $J_{(C\text{-}P)}$ 5.9, CH_2), 16.2 (d, $J_{(C\text{-}P)}$ 6.9, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -7.72 (quint, *J* 8.1); MS (ESI^+) calcd. for $C_{11}H_{15}O_5P$ $[M+Na]^+$ 281.0549, found 281.0547. Spectroscopic data are in accordance with literature.[41]

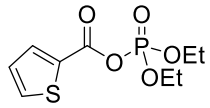
Diethyl (E)-cinnamoylphosphate 127a



Following general procedure, (E)-cinnamic acid (1.48 g, 10.0 mmol) and triethyl phosphite (1.71 mL, 10.0 mmol) were used. Recovered 2.16 g (76 %) as a pale-yellow oil. R_f 0.32 (1:2, EtOAc:Petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* 15.9, C*H*), 7.60 – 7.53 (2H, m, Ar*H*), 7.51 – 7.38 (3H, m, Ar*H*), 6.44 (1H, dd, *J* 15.9, 2.1, C*H*), 4.42-4.28 (4H, m, C*H*$_2$), 1.43 (6H, td, *J* 7.1, 1.1, C*H*$_3$);^{13}C NMR (101 MHz,

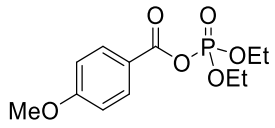
$CDCl_3$) δ 160.9 (d, $J_{(C-P)}$ 8.1, C), 149.1 (CH), 133.6 (C), 131.4 (CH), 129.1 (CH), 128.6 (CH), 116.1 (d, $J_{(C-P)}$ 9.1, CH), 65.20 (d, $J_{(C-P)}$ 5.8, CH_2), 16.12 (d, $J_{(C-P)}$ 6.9, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -7.96 (quint, *J* 8.3); MS (ESI^+) calcd. for $C13H_{17}O_5PNa$ $[M+Na]^+$ 307.0711, found 307.0711.

Diethyl (2-thiophenecarbonyl)phosphate 128



Following general procedure. Thiophene-2-carboxylic acid (1.28 g, 10.0 mmol) was used. Recovered 2.18 g (83 %) as a colourless oil. R_f 0.27 (1:1, petrol:EtOAc); υ_{max} (ATR)/cm^{-1} 3093, 2985, 2913, 1730, 1519, 1478, 1282, 999; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, dd, *J* 3.8, 1.3, Ar*H*), 7.72 (1H, dd, *J* 5.0, 1.3, Ar*H*), 7.16 (1H, dd, *J* 5.0, 3.8, Ar*H*), 4.36 (4H, dq, *J* 8.4, 7.1, C*H₂*), 1.42 (6H, td, *J* 7.1, 1.3, C*H₃*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (d, $J_{(C-P)}$ 7.6, C), 136.2 (CH), 135.3 (CH), 131.6 (d, $J_{(C-P)}$ 9.9, C), 128.4 (CH), 65.5 (d, $J_{(C-P)}$ 5.9, CH_2), 16.1 (d, $J_{(C-P)}$ 6.9, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -8.58 (quint, *J* 8.6); MS (ESI^+) calcd. for $C_9H_{13}O_5P_1S_1$ $[M+Na]^+$ 287.0114, found 287.0116. Spectroscopic data are in accordance with literature.[41]

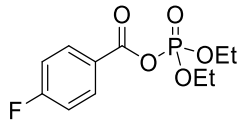
Diethyl (4-methoxybenzoyl)phosphate 129



Following general procedure. 4-Methoxybenzoic acid (1.52 g, 10.0 mmol) was used. Recovered 1.80 g (63 %) as a colourless oil. R_f 0.43 (2:1, EtOAc:pent); υ_{max} (ATR)/cm^{-1} 2925, 2855, 1772, 1459, 1412, 1394, 1165, 1137, 1103, 1024, 985, 917, 819, 752; ^1H NMR (400 MHz, $CDCl_3$) 8.04 – 7.97 (2H, m, Ar*H*), 6.98 – 6.91 (2H, m, Ar*H*), 4.42 – 4.29 (2H, m, C*H₂*), 3.88 (1H, s, OC*H₃*), 1.41 (3H, td, *J* 7.1, 1.1, C*H₃*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7 (C), 160.6 (C), 133.0 (CH), 120.3 (C), 114.1 (CH), 65.19 (d, $J_{(C-P)}$ 5.8, CH_2), 55.59 (OCH_3), 16.13 (d, $J_{(C-P)}$ 6.9, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -7.63 (p, *J* 8.2); MS (ESI^+) calcd. for $C_{12}H_{18}O_5P$ $[M+H]^+$

289.0836, found 289.0835. Spectroscopic data are in accordance with literature.[41]

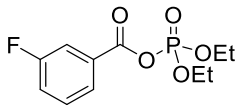
Diethyl (4-fluorobenzoyl)phosphate 130



Following general procedure. 4-Fluorobenzoic acid (1.4 g, 10.0 mmol) was used. Purified using EtOAc:Petrol (4:6 then 1:1), R_f 0.25 (EtOAc:Petrol, 1:1). Recovered 2.17 g (78 %) as a pale-yellow oil. υ_{max} (ATR)/cm^{-1} 2987, 2914, 1745, 1602, 1507, 1479, 1445, 1414, 1395, 1371, 1284, 1242, 1155, 1083, 1019, 960, 863, 815, 761, 683, 632; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.06 (2H, m, Ar*H*), 7.17 (2H, t, *J* 8.6, Ar*H*), 4.38 (4H, tt, *J* 7.2, 1.2, C*H*$_2$), 1.43 (6H, td, *J* 7.2, 1.1, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (d, $J_{(C\text{-}F)}$ 257, C), 160.1 (d, $J_{(C\text{-}P)}$ 8.3, C), 133.4 (d, $J_{(C\text{-}F)}$ 9.7, CH), 124.4 (dd, *J* 8.3$_{(C\text{-}P)}$, 2.9$_{(C\text{-}F)}$, C), 116.1 (d, $J_{(C\text{-}F)}$ 22.2, CH), 65.4 (d, $J_{(C\text{-}P)}$ 5.9, CH_2), 16.1 (d, $J_{(C\text{-}P)}$ 6.9, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ - 7.78 (p, *J* 8.5); ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.39 (ddd, *J* 8.5, 5.5, 3.1); MS (ESI^+) calcd. for $C_{11}H_{14}F_1O_5PNa$ $[M+Na]^+$ 299.0455, found 299.0460.

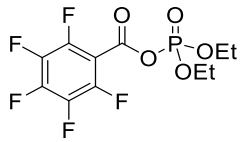
4-Fluorobenzoic acid (4.2 g, 30 mmol) and iodine (7.6 g, 30 mmol) were dissolved in anhydrous DCM (150 mL). Triethylphosphite (5.65 mL, 33 mmol) and triethyl amine (6.28 mL, 45 mmol) were added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 45 minutes. The reaction mixture was concentrated onto Celite then purified using silica gel chromatography (EtOAc:Pet, 4:6 then 1:1). Recovered 6.15 g (74 %) as a pale-yellow oil. Spectroscopic data identical to previous procedure.

Diethyl(3-Fluorobenzoyl)phosphate 131



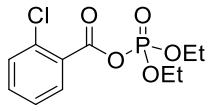
Following general procedure. 3-Fluorobenzoic acid (1.40 g, 10.0 mmol) was used. Recovered 1.99 g (72 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 2987, 2914, 1748, 1593, 1485, 1443, 1395, 1371, 1266, 1186, 1156, 1019, 963, 918, 823, 776, 748, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1 H, d, *J* 7.8, Ar*H*), 7.72 (1H, d, *J* 9.0, Ar*H*), 7.48 (2 H, td, *J* 8.2, 5.5 Hz, Ar*H*), 7.35 (1 H, td, *J* 8.2, 1.4, Ar*H*), 4.42-4.32 (4 H, m, C*H*$_2$), 1.42 (6 H, t, 7.1, C*H*$_3$);^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, $J_{(C-F)}$ 244.9, CF), 160.0 (m, C) 130.5 (d, $J_{(C-F)}$ 7.7, CH), 130.3 (m, C), 126.4 (CH), 121.7 (d, *J* 20.8, CH), 117.3 (d, $J_{(C-F)}$ 23.4, CH), 65.5 (d, $J_{(C-P)}$ 5.4, CH_2), 16.1 (d, $J_{(C-P)}$ 6.4, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -7.89 (quint, *J* 8.7); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.32 (td, *J* 8.7, 5.5); MS (ESI$^+$) calcd. for $C_{11}H_{14}F_1O_5P$ [M+Na]$^+$ 299.0455, found 299.0460.

Diethyl(2,3,4,5,6-pentafluorobenzoyl)phosphate 132



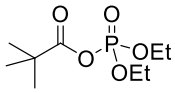
Following general procedure. 2,3,4,5,6-Pentafluorobenzoic acid (2.10 g, 10.0 mmol) was used. Recovered a 10:1 mixture of acyl phosphate and acid anhydride (2.49 g, 56.3 % acyl phosphate and 5.6 % acid anhydride). R_f 0.21 (pent:EtOAc, 8:2); υ_{max} (ATR)/cm^{-1} 2990, 2915, 1762, 1737, 1650, 1523,1499, 1446, 1294, 1028, 1003, 928, 821, 752, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43-4.28 (4H, m, C*H*$_2$), 1.46 – 1.29 (6H, m, C*H*$_3$); ^{31}C NMR (101 MHz, $CDCl_3$) δ 153.4-153.1 (m, C), 149.51 – 143.46 (m, CF), 146.88 – 142.23 (m, CF), 139.86 – 135.47 (m, CF), 106.3 – 105.9 (m, C) 66.02 (d, $J_{(C-P)}$ 6.1, CH_2), 15.93 (d, $J_{(C-P)}$ 6.9, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -9.50 (quint, *J* 8.8); ^{19}F NMR (376 MHz, $CDCl_3$) δ -135.74 (dp, *J* 19.2, 7.7), -144.71 (dtt, *J* 20.9, 14.2, 6.6), -159.57 (dqd, *J* 26.9, 13.5, 7.2); MS (ESI+) calcd. for $C_{11}H_{11}F_5O_5P$ [M+H]$^+$ 359.0259, found 359.0261.

Diethyl(2-chlorobenzoyl)phosphate 133



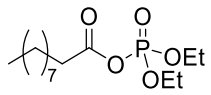
Following general procedure. 2-Chlorobenzoic acid (1.56 g, 10 mmol) and triethyl phosphite (1.88 mL, 11 mmol) were used. Recovered 2.23 g (76 %) as a pale-yellow oil. R_f 0.28 (6:4, pent:EtOAc); υ_{max} (ATR)/cm^{-1} 2985, 2933, 1758, 1590, 1571, 1277,1235, 1007, 952, 860, 784, 684, 667, 650; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.99 (1H, m, Ar*H*), 7.47-7.54 (2H, m, Ar*H*), 7.33-7.40 (1H, m, Ar*H*), 4.32-4.43 (4H, m, C*H*$_2$), 1.37-1.45 (6H, m, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (C, d, $J_{(C-P)}$ 8.1), 135.28 (C, d, $J_{(C-P)}$ 2.3), 134.2 (CH), 132.8 (CH), 131.7 (CH), 127.3 (C, dd, $J_{(C-P)}$ 8.7, 2.9), 126.9 (CH), 65.50 (CH_2, d, $J_{(C-P)}$ 5.9), 16.11 (CH_3, d, $J_{(C-P)}$ 7.1); ^{31}P NMR δ -8.35 (quint, J 8.2); MS (ESI^+) calcd. for $C_{11}H_{15}O_5PCl$ $[M+H]^+$ 293.0340, found 293.0338. Spectroscopic data are in accordance with literature.[41]

Diethyl pivoylphosphate 134



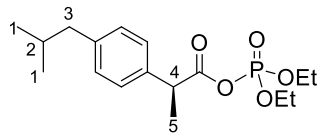
Following general procedure. Pivalic acid (1.02 g, 10 mmol) was used. Recovered 1.49 g as a mixture of acyl phosphate (39 %) and acid anhydride (15 %). R_f 0.29 (DCM:MeOH 95:5); υ_{max} (ATR)/cm^{-1} 2979, 2937, 2876, 1808, 1762,1741, 1480, 1481, 1397, 1383, 1285, 1120, 1196, 1113, 1017, 954, 885, 818, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17-4.27 (4H, m, C*H*$_2$), 1.33 (6H, tt, *J* 7.1, 1.2, C*H*$_3$), 1.22 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (d, $J_{(C-P)}$ 10.8, C), 65.0 (d, $J_{(C-P)}$ 5.9, CH_2), 39.9 (d, $J_{(C-P)}$ 6.1, C), 26.6 ($(CH_3)_3$), 16.0 (d, $J_{(C-P)}$ 6.7, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -7.76 (quint, *J* 8.8); MS (ESI^+) calcd. for $C_9H_{19}O_5P_1$ $[M+Na]^+$ 261.0862, found 261.0864.

Diethyl decanoylphosphate 135



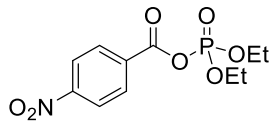
Following general procedure. Decanoic acid (1.72 g, 10 mmol was used. Columned as gradient 9:1 to 7:3. Recovered 2.1 g (68 %) as a pale-yellow oil. R_f 0.56 (7:3, pent:EtOAc); υ_{max} (ATR)/cm^{-1} 2925, 2855, 1773, 1460, 1394, 1370, 1280, 1165, 1137, 1103, 1025, 995, 917, 819, 752, 665, 646; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 – 4.20 (4H, m, C*H*$_2$), 2.45 (2H, td, *J* 7.3, 2.4, C*H*$_2$), 1.65 (2H, q, *J* 7.3, C*H*$_2$), 1.41 – 1.20 (18H, m, C*H*$_2$, C*H*$_3$), 0.88 (3H, td, *J* 6.9, 2.6, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.02 (d, $J_{(C-P)}$ 9.9, C), 65.10 (d, $J_{(C-P)}$ 5.8, CH_2), 35.00 (d, $J_{(C-P)}$ 6.7, CH_2), 31.83 (CH_2), 29.33 (CH_2), 29.21 (CH_2), 29.16 (CH_2), 28.83 (d, $J_{(C-P)}$ 7.4, CH_2), 24.25 (d, $J_{(C-P)}$ 3.0, CH_2), 22.65 (CH_2), 16.05 (d, $J_{(C-P)}$ 6.8, CH_3), 14.09 (CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -8.34 (quint, *J* 8.2); MS (ESI^+) calcd. for $C_{14}H_{29}O_5PNa$ $[M+Na]^+$ 331.1645, found 331.1643.

(*S*)-(diethyl phosphoric) (*S*)-2-(4-isobutylphenyl)propanoic anhydride 136



Following general procedure. (S)-Ibuprofen (2.06 g, 10.0 mmol) was used. Column performed as a gradient 95:5 to 8:2 (petrol:EtOAc). Recovered 1.64 g (48 %) as a colourless oil. R_f 0.36 (8:2, Petrol:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (2H, d, *J* 8.2, Ar*H*), 7.13 (2H, d, *J* 8.2, Ar*H*), 4.21 – 4.04 (4H, m, OC*H*$_2$), 3.79 (1 H, q, *J* 7.1, C^4*H*), 2.46 (2H, d, *J* 7.1, C^3*H*$_2$), 1.85 (1H, app. nonet, *J* 6.8, C^2*H*), 1.54 (3H, d, *J* 7.1, C^5*H*$_3$), 1.27 (6H, tt, *J* 7.1, 1.0, CH_2C*H*$_3$), 0.90 (6H, d, *J* 6.8, C^1*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) 168.8 (C), 141.2 (C), 136.0 (C), 129.6 (CH), 127.3 (CH), 65.0 (dd, $J_{(C-P)}$ 9.0, 5.9, CH_2), 46.1 (d, $J_{(C-P)}$ 6.8, CH), 45.0 (CH_2) 30.2 (CH), 22.3 (CH_3), 18.0 (CH_3) , 15.9 (d, *J* 6.8, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -8.64 (quint, *J* 8.5); MS (ESI^+) calcd. for $C_{17}H_{27}O_5PNa$ $[M+Na]^+$ 365.1488, found 365.1487.

Diethyl(4-nitrobenzoyl)phosphate 137



Following general procedure. 4-Nitrobenzoic acid (1.67 g, 10.0 mmol) was used. Purification was achieved by column chromatography followed by recrystallisation from $CHCl_3$ and Et_2O. Recovered 0.60 g (20 %) as a cream solid. R_f 0.18 (95:5 DCM:MeOH); υ_{max} (ATR)/cm^{-1} 3115, 3062, 2985, 2823, 2660, 2547, 1685, 1600, 156, 1494, 1423, 1369, 1275, 1167, 1013, 978, 931, 877, 859, 820, 798, 787; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 – 8.40 (2 H, m, Ar*H*), 8.39 – 8.34 (2 H, m, Ar*H*), 3.20 (4 H, q, *J* 7.3, C*H*$_2$), 1.49 (6 H, t, *J* 7.3, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (C), 151.6 (C), 133.5 (C), 131.8 (CH), 124.2 (CH), 46.3 (CH_2), 16.1 (CH_3); ^{31}P NMR (162 MHz, $CDCl_3$); δ -7.95 (quint, *J* 8.6); MS (ESI$^-$) calcd. for $C_{11}H_{13}NO_7P$ [M-H]$^-$ 302.0435, found 302.0436.

7.4. Ketones procedures and assignments

General procedure A

In a two neck round bottom flask, acyl phosphate (1.00 mmol) was dissolved in THF (1.5 mL) at -78 °C. Alkyl Grignard (1.00 mmol, 2 M, 0.5 mL) was added dropwise. The reaction was stirred for 0.25 h. The reaction was quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was further purified using silica gel chromatography using the solvent system provided.

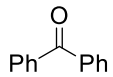
General procedure B

In a two neck round bottom flask, acyl phosphate (1.00 mmol) was dissolved in THF (1 mL) at -78 °C. Aryl Grignard (2.00 mmol, 1 M, 1.0 mL) was added dropwise. The reaction was stirred for 1 h. The reaction was quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was further purified using silica gel chromatography using the solvent system provided.

General procedure C

In a two neck round bottom flask, acyl phosphate (1.00 mmol) was dissolved in THF (1 mL) at -78 °C. Aryl Grignard (1.10 mmol, 1 M, 0.55 mL) was added dropwise. The reaction was stirred for 0.25 h then allowed to warm to 0 °C. The reaction was quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was further purified using silica gel chromatography using the solvent system provided.

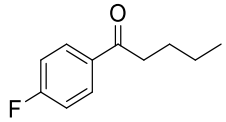
Benzophenone 66a



Following procedure **B**, diethyl benzoylphosphate (258 mg, 1.10 mmol) and PhMgBr (2.00 mmol) were used as coupling partners. R_f 0.33 (98:2, Petrol:EtOAc). Recovered 146 mg (80 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3059, 1655, 1577, 1489, 1317, 1274, 1203, 1176, 1149 999, 974, 918, 848, 810, 763, 700, 637; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.80 (4H, m, Ar*H*), 7.61 (2H, t, *J* 7.5, Ar*H*), 7.51 (4H, t, *J* 7.5, Ar*H*); ^{13}C NMR (101 MHz, Chloroform-d) δ 196.76 (C), 137.62 (C), 132.44 (CH), 130.08 (CH), 128.30 (CH); MS (ESI^+) calculated for $C_{13}H_{10}ONa$ $[M+Na]^+$ 205.0624, found 205.0639. Spectroscopic data are in accordance with literature.[180]

Following procedure **C**, diethyl benzoylphosphate (276 mg, 1.00 mmol) and PhMgBr (1.10 mmol) were used as coupling partners. Recovered 158 mg (87 %) as a colourless oil. Spectroscopic data matches previous procedure.

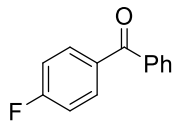
4-(Fluorophenyl)-1-pentanone 141a



Following procedure **A,** diethyl (4F-benzoyl)phosphate (276 mg, 1.00 mmol) and BuMgCl (1.00 mmol) were used as coupling partners. R_f 0.41 (Pet:EtOAc, 95:5);

Recovered 120 mg (67 %) as a waxy colourless solid. mp. 26-28 °C; υ_{max} (ATR)/cm^{-1} 3075, 2959, 2934, 2883, 2874, 2663, 1674, 1593, 1505, 1467, 1459, 1376, 1341, 1300, 1271, 1230,1203, 1156, 1113, 1098, 979, 822, 759, 592; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.96 (2H, m, Ar*H*), 7.19 – 7.08 (2H, m, Ar*H*), 2.95 (2H, t *J* 7.4, C*H*$_2$), 1.79 – 1.67 (2H, m, C*H*$_2$), 1.49 – 1.35 (2H, m, C*H*$_2$), 0.97 (3H, t, *J* 7.4, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0 (C), 165.6 (d, $J_{(C-F)}$ 254.7, CF), 133.5 (d, $J_{(C-F)}$ 3.0, C), 130.7 (d, $J_{(C-F)}$ 9.2, CH), 115.61 (d, $J_{(C-F)}$ 21.7, CH), 38.3 (CH_2), 26.4 (CH_2), 22.5 (CH_2), 13.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$); δ -105.75 (tt, *J* 8.4, 5.4); MS (ESI$^+$) calcd. For $C_{11}H_{14}FO$ $[M+H]^+$ 181.1029, found 181.1027. Spectroscopic data are in accordance with literature.[81]

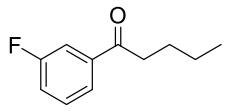
4-Fluorobenzophenone 142a



Following procedure **B**, diethyl (4F-benzoyl)phosphate (552 mg, 2.00 mmol) and PhMgBr (4.00 mmol) were used as coupling partners. R_f 0.50 (Pet:EtOAc, 95:5). Recovered 272 mg (68 %) as a waxy white solid. mp 44-46 °C; υ_{max} (ATR)/cm^{-1} 3069, 2928, 1646, 1595, 1501, 1445,1406, 1319, 1297, 1242, 1150,1027, 1000, 978, 923, 849,7293, 697, 677, 631; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.83 (2H, m, Ar*H*), 7.82 – 7.76 (2H, m, Ar*H*), 7.64 – 7.58 (1H, m, Ar*H*), 7.56 – 7.47 (2H m, Ar*H*), 7.23 – 7.13 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3 (C), 165.4 (d, $J_{(C-F)}$ 254.1, CF), 137.5 (C), 133.8 (d, *J* 3.2, C), 132.7 (d, *J* 9.2, CH), 132.5 (CH), 129.90 (CH), 128.38 (CH), 115.48 (d, $J_{(C-F)}$ 21.9, CH); ^{19}F NMR (162 MHz, $CDCl_3$) δ -105.93 (tt, *J* 8.6, 5.4); MS (ESI$^+$) calcd. For $C_{11}H_{10}FO$ $[M+H]^+$ 201.0710, found 201.078. Spectroscopic data are in accordance with literature.[81]

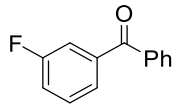
Following procedure **C,** diethyl (4F-benzoyl)phosphate (276 mg, 1.00 mmol) and PhMgBr (1.10 mmol) were used as coupling partners. Recovered Spectroscopic data matches the previous procedure.

3-(Fluorophenyl)-1-pentanone 144



Following procedure **A**, diethyl (3F-benzoyl)phosphate (276 mg, 1.00 mmol) and BuMgCl (1.00 mmol) were used as coupling partners. R_f 0.59 (98:2, Pent:EtOAc). Recovered 104 mg (58 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3062, 3025, 2966, 2900, 2889, 1673, 1594, 1467, 1416, 1383, 1340, 1247, 1219, 1120, 1094, 951, 848, 730, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, dt, *J* 7.6, 1.6, Ar*H*), 7.66 (1H, ddd, *J* 9.6, 2.7, 1.6, Ar*H*), 7.46 (1H, td, *J* 8.0, 5.5, Ar*H*), 7.32 – 7.23 (1H, m, Ar*H*), 3.01 – 2.93 (2H, t, *J* 7.3, C*H*$_2$), 1.82 – 1.68 (2H, m, C*H*$_2$), 1.52 – 1.37 (2H, m, C*H*$_2$), 0.98 (3H, t, *J* 7.3, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.25 (C), 162.89 (d, $J_{(C-F)}$ 247.4, CF), 139.17 (C), 130.21 (d, $J_{(C-F)}$ 7.6, CH), 123.79 (d, $J_{(C-F)}$ 2.9, CH), 119.88 (d, $J_{(C-F)}$ 21.4, CH), 114.81 (d, $J_{(C-F)}$ 22.2, CH), 38.49 (CH_2), 26.33 (CH_2), 22.43 (CH_2), 13.92 (CH); MS (ESI$^+$) calcd. for $C_{11}H_{13}FONa$ $[M+Na]^+$ 203.0843, found 203.0829. Spectroscopic data are in accordance with literature.[181]

3-Fluorobenzophenone 145

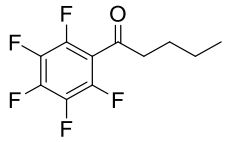


Following procedure **B**, diethyl (3F-benzoyl)phosphate (276 mg, 1.00 mmol) and PhMgBr (2.00 mmol) were used as coupling partners. R_f 0.66 (98:2, Petrol:EtOAc). Recovered 151 mg (75 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3070, 2930, 1662, 1587, 1483, 1443, 1315, 1281, 1210, 1159, 1120, 1078, 966, 889, 861, 837, 808, 784, 725, 634; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (2H, m, Ar*H*), 7.67 – 7.56 (2H, m, Ar*H*), 7.54 – 7.47 (4H, m, Ar*H*), 7.30 (1H, tdd, *J* 8.3, 2.7, 1.0, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3 (d, $J_{(C-F)}$ 2.2, C), 162.5 (d, $J_{(C-F)}$ 248.1, CF), 139.7 (d, $J_{(C-F)}$ 6.3, C), 137.0 (CH), 132.8 (CH), 130.0 (d, *J* 7.4, CH), 128.4 (CH), 125.85 (d, $J_{(C-F)}$ 3.1, CH), 119.5 (d, $J_{(C-F)}$ 21.3, CH), 116.8 (d, $J_{(C-F)}$ 22.4, CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.92 (td, *J* 8.8, 5.4); MS (ESI$^+$) calculated for

$C_{13}H_9FONa$ $[M+Na]^+$ 223.0535, found 223.0536. Spectroscopic data are in accordance with literature.[182]

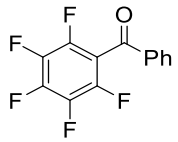
Following procedure **C**, diethyl (3F-benzoyl)phosphate (276 mg, 1.00 mmol) and PhMgBr (2.00 mmol) were used. Recovered 145 mg (73 %) as a colourless oil. Spectroscopic data identical to previous.

1-(Perfluorophenyl)pentan-1-one 146



Following procedure **A**, diethyl(2,3,4,5,6-pentafluorobenzoyl)phosphate (359 mg, 1.00 mmol) and BuMgCl 2 M in THF (0.75 mL, 1.50 mmol) were used. R_f 0.43 (pent:EtOAc). Recovered 130 mg (52 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (2H, tt, *J* 7.3, 1.3, C*H*$_2$), 1.71 (2H, quint, *J* 7.3, C*H*$_2$), 1.48 – 1.34 (2H, m, C*H*$_2$), 0.95 (3H, t, *J* 7.3, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3 (C), 146.3 – 142.28 (dm, CF), 144.4-140.7 (dm, CF), 139.2-135.6 (dm, CF), 115.6-115.0 (m, C), 45.0-44.8 (m, CH_2), 25.6 (CH_2), 22.1 (CH_2), 13.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -141.13 to -141.70 (m), -150.13 (tt, *J* 20.6, 3.4), -159.66 to -160.28 (m). Spectroscopic data are in accordance with literature.[183]

(Perfluorophenyl)(phenyl)methanone 147

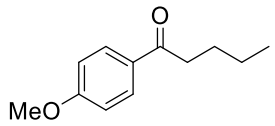


Following procedure **B**, diethyl(2,3,4,5,6-pentafluorobenzoyl)phosphate (359 mg, 1.00 mmol) and PhMgBr (2.00 mmol) were used. R_f 0.42 (9:1, petrol:EtOAc) Recovered 195 mg (72 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3067, 2927, 1750, 1680, 1650, 1597, 1493, 1412, 1322, 1237, 1178, 1113, 994, 982, 909, 817, 755, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, ddt, *J* 7.5, 1.4, 0.7, Ar*H*), 7.76 – 7.66 (1H, m, Ar*H*), 7.60 – 7.51 (2H, m, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.3 (C), 143.8 (dtd, *J* 252.0, 8.1, 4.2, CF), 144.09 – 140.92 (dm, CF), 139.68-135.99 (dm,

CF), 135.9 (C), 135.1 (CH), 129.7 (CH), 129.1 (CH), 114.64 – 113.60 (m, C); ^{19}F NMR (377 MHz, $CDCl_3$) δ -139.51 to -140.08 (m), -149.84 to -150.78 (m), -159.38 to -160.18 (m); MS (ESI$^+$) Calcd. for $C_{13}H_5F_5ONa$ $[M+Na]^+$ 295.0158, found 295.0154. Spectroscopic data are in accordance with literature.[184]

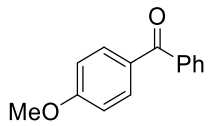
Following procedure **2C**, diethyl(2,3,4,5,6-pentafluorobenzoyl)phosphate (359 mg, 1.00 mmol) and PhMgBr (1.10 mmol) were used. Recovered 181 mg (68 %) as a colourless oil. Spectroscopic data identical to previous.

4-(Methoxyphenyl)-1-pentanone 148



Following procedure **C**. Diethyl(4-methoxybenzoyl)phosphate (288 mg, 1.00 mmol) and BuMgCl (1.00 mmol) were used as coupling partners. R_f 0.19 (96:4) Petrol:EtOAc). Recovered 140 mg (73 %) as a white solid. mp 28-30 °C**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.92 (2H, m, ArH), 6.99 – 6.90 (2H, m, ArH), 3.89 (3H, s, CH_3), 2.93 (2H, t, *J* 7.4, 1H), 1.73 (2H, quint, *J* 7.4, CH_2), 1.43 (2H, sext, *J* 7.4, CH_2), 0.97 (3H, t, *J* 7.4, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.29 (C), 163.31 (C), 130.33 (CH), 130.22 (C), 113.67 (CH), 55.46 (CH_3), 38.04 (CH_2), 26.77 (CH_2), 22.56 (CH_2), 13.97 (CH_3); MS (ESI$^+$) Calcd. for $C_{12}H_{17}O_2$ $[M+H]^+$ 193.1223, found 193,1227. Spectroscopic data are in accordance with literature.[185]

4-Methoxybenzophenone 149

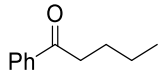


Following procedure **B**. Diethyl(4-methoxybenzoyl)phosphate (288 mg, 1.00 mmol) and PhMgBr (2.00 mmol) were used as coupling partners. R_f 0.2 (95:5 Petrol:EtOAc). Recovered 165 mg (77 %) as a white solid. mp 48-50 °C (lit., 60-61°C)[182]; υ_{max} (ATR)/cm^{-1} 3058, 3014, 2970, 2834, 1648, 1595, 1576, 1505, 1417, 1279, 1180, 1000, 973, 916, 842, 817, 693, 676; ^{1}H NMR δ 7.86 (2H, d, *J* 8.8 Hz, C*H*), 7.78 (2H, d, *J* 7.6 Hz, C*H*), 7.66 – 7.54 (1H, m, C*H*), 7.50 (2H, t, *J* 7.6 Hz,

C*H*), 6.99 (2H, d, *J* 8.8 Hz, C*H*), 3.91 (3H, s, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6 (C), 163.2 (C), 138.3 (C), 132.6 (CH), 131.9 (CH), 130.2 (CH), 129.7 (CH), 128.2 (CH), 113.6 (CH), 55.5 (CH_3); MS (ESI$^+$) calcd. for $C_{11}H_{12}O_2Na$ $[M+Na]^+$ 235.0730, found 235.0731. Spectroscopic data are in accordance with literature.[182]

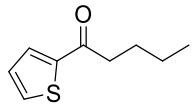
Following procedure **2C**. Diethyl(4-methoxybenzoyl)phosphate (288 mg, 1.00 mmol) and PhMgBr (1.10 mmol) were used as coupling partners. Recovered 177 mg (84 %) as a white solid. Spectroscopic data matches previous procedure.

1-Phenylpentan-1-one 75A



Following procedure **A**, diethyl benzoylphosphate (258 mg, 1.00 mmol) and BuMgCl (1.00 mmol) were used as coupling partners. R_f 0.57 (98:2, pent:EtOAc). Recovered 103 mg (63 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3067, 2968, 2873, 1686, 1360, 1260, 1168, 989, 843, 764, 729, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.95 (2 H, m, Ar*H*), 7.63 – 7.52 (1 H, m, Ar*H*), 7.48 (2 H, dd, *J* 8.3, 6.8, Ar*H*), 3.03 – 2.96 (2 H, t, *J* 7.3, C*H*$_2$), 1.75 (2 H, quint, *J* 7.3, C*H*$_2$), 1.52 – 1.37 (2 H, m, C*H*$_2$), 0.98 (3 H, t, *J* 7.3, C*H*$_3$); ^{13}C NMR δ $_C$ (101 MHz, $CDCl_3$) 200.63 (C), 137.11 (C), 132.87 (CH), 128.56 (CH), 128.07 (CH), 38.35 (CH_2), 26.50 (CH_2), 22.50 (CH_2), 13.96 (CH_3); MS (ESI$^+$) Cald. for $C_{11}H_{15}O$ $[M+H]^+$ 163.1123, found 163.1126. Spectroscopic data are in accordance with literature.[180]

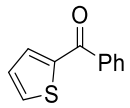
1-(Thiophen-2-yl)pentan-1-one 150



Following procedure **A**, diethyl(thiophene-2-carbonyl)phosphate (264 mg, 1.00 mmol) and BuMgCl (1.00 mmol) were used as coupling partners. R_f 0.37 (9:1 Petrol:EtOAc). Recovered 130 mg (77 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3041, 2958, 2928, 2872, 1656, 1518, 1460, 1412, 1358, 1198, 1062, 854, 788, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, dd, *J* 3.8, 1.1, Ar*H*), 7.63 (1H, dd, *J* 5.0, 1.1, Ar*H*), 7.14 (1H, dd, *J* 5.0, 3.8, Ar*H*), 2.96 – 2.87 (2H, t, *J* 7.3, C*H*$_2$), 1.81 – 1.69

(2H, m, C*H*$_2$), 1.51 – 1.36 (2H, m, C*H*$_2$), 0.96 (3H, t, *J* 7.3, C*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.60 (C), 144.53 (C), 133.35 (CH), 131.69 (CH), 128.05 (CH), 39.15 (CH_2), 26.89 (CH_2), 22.47 (CH_2), 13.91 (CH_3); MS (ESI$^+$) calcd. for $C_9H_{13}OS$ $[M+H]^+$ 168.0682 found 168.0678. Spectroscopic data are in accordance with literature.[186]

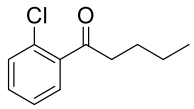
2-Benzoylthiophene 151



Following procedure **B**, diethyl(thiophene-2-carbonyl)phosphate (264 mg, 1.00 mmol) and PhMgBr (2.00 mmol) were used as coupling partners. R_f 0.33 (9:1 Petrol:EtOAc). Recovered 171 mg (90 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3069, 2958, 2931, 2872, 1697, 1590, 1467, 1432, 1242, 1294, 1162, 1094, 1036, 1012, 754, 698, 595; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.85 (2H, m, Ar*H*), 7.75 (1H, dd, *J* 5.0, 1.1, Ar*H*), 7.68 (dd, *J* 3.8, 1.2, Ar*H*), 7.66 – 7.58 (1H, m, Ar*H*), 7.57 – 7.48 (2H, m, Ar*H*), 7.19 (1H, dd, *J* 5.0, 3.8, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.3 (C), 143.65 (C), 138.15 (C), 134.90 (CH), 134.26(CH), 132.30 (CH), 129.20 (C), 128.44 (C), 127.99 (C); MS (ESI$^+$) calcd. for $C_{11}H_8OSNa$ $[M+Na]^+$ 211.0188, found 211.0187. Spectroscopic data are in accordance with literature.[72]

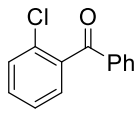
Following procedure **C**, diethyl(thiophene-2-carbonyl)phosphate (264 mg, 1.00 mmol) and PhMgBr (1.10 mmol) were used as coupling partners. Recovered 130 mg (69 %) as a colourless oil. Spectroscopic data matches the previous procedure.

2-(Chlorophenyl)-1-pentanone 152



Following procedure **A**. Diethyl(2-chlorobenzoyl)phosphate (292 mg, 1.00 mmol) and BuMgCl (1.00 mmol) were used as coupling partners. R_f 0.41 (Pent:EtOAc, 96:4). Recovered 122 mg (62 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3068, 2958, 2931, 2872, 1697, 1590, 1510, 1466, 1379, 1204, 1113, 1036, 947, 755, 734, 698, 642; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, td, *J* 7.5, 1.8, Ar*H*), 7.38 (1H, td, *J* 7.5, 1.8, Ar*H*), 7.33 (1H, td, *J* 7.5 1.8, Ar*H*), 2.95 (2H, t, *J* 7.3, CH_2), 1.70 (2H, p, *J* 7.3, CH_2), 1.48-1.34 (2H, m, CH_2), 0.95 (3H, t, *J* 7.3, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.00 (C), 139.9 (CH), 131.4 (CH), 130.7 (C), 130.5 (CH), 128.7 (CH), 126.9 (CH), 42.8 (CH_2), 26.3 (CH_2), 22.3 (CH_2), 13.89 (CH_3); MS (ESI^+): calcd for $C_{11}H_{13}ClONa$ $[M+Na]^+$ 219.0547, found 219.0548. Spectroscopic data are in accordance with literature.[187]

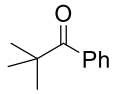
2-Chlorobenzophenone 153



Following procedure **B**. Diethyl(2-Chlorobenzoyl)phosphate (292 mg, 1.00 mmol) and PhMgBr (2.00 mmol) were used as coupling partners. R_f 0.26 (96:4 Petrol:EtOAc). Recovered 176 mg (82 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3060, 1659, 1594, 1580, 1314, 1296, 1280, 1057, 949, 762, 742, 729, 701, 696, 630; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.79 (2 H, m, C*H*), 7.66 – 7.59 (1 H, m, C*H*), 7.53 – 7.44 (4 H, m, CH), 7.43 – 7.38 (2 H, m, C*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.28 (C), 138.62 (C), 136.49 (CH), 133.71 (CH), 131.32 (C), 131.14 (CH), 130.08 (CH), 129.13 (CH), 128.63 (C), 126.69 (CH); MS (ESI^+) calcd. for $C_{13}H_{10}OCl$ $[M+H]^+$ 217.0415, found 217.0415. Spectroscopic data are in accordance with literature.[188]

Following procedure **C**. Diethyl(2-Chlorobenzoyl)phosphate (292 mg, 1.00 mmol) and PhMgBr (1.10 mmol) were used as coupling partners. Recovered 187 mg (86 %) as a colourless oil. Spectroscopic data identical to previous.

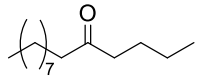
2,2-Dimethylpropiophenone 157



Following procedure **B**, diethyl pivoylphosphate (238 mg, 1.00 mmol) and PhMgBr (2.00 mmol) were used as coupling partners. R_f 0.30 (95:5 Petrol:EtOAc). Recovered 124 mg (77 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3062, 2989, 2932, 2872, 1673, 1477, 1395, 1366, 1191, 1176, 1002, 731, 697, 647, 619; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (2H, m, Ar*H*), 7.55 – 7.36 (3H, m, Ar*H*), 1.37 (9H, s, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3 (C), 138.6 (C), 130.8 (CH), 128.1 (CH) 127.8 (CH), 44.2 (C), 28.0 (CH_3); MS (ESI^+) calcd. for $C_{11}H_{16}O$ $[M+H]^+$ 163.1123, found 163.1119.

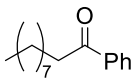
Following procedure **C**, diethyl pivoylphosphate (238 mg, 1.00 mmol) and PhMgBr (1.10 mmol) were used. Recovered 143 mg (88 %) as a colourless oil.

Tetradeca-5-one 158



Following procedure **A**, diethyl decanoylphosphate (308 mg, 1.00 mmol) and BuMgCl (1.00 eq.) used. Recovered 125 mg (59 %) as a colourless solid. R_f 0.47 (98:2, Petrol:EtOAc). mp. 28-30 °C; υ_{max} (ATR)/cm^{-1} 2957, 2917, 2870, 2849, 1700, 1467, 1317, 1131, 1041, 1013, 833, 680; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (4 H, td, J 7.3, 2.2, CH_2), 1.64 – 1.50 (4 H, m, CH_2), 1.40 – 1.20 (14 H, m, CH_2), 0.92 (3 H, t, J 7.3, CH_3), 0.89 (3H, t, *J* 6.9, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.8 (C), 42.8 (CH_2), 42.5 (CH_2), 31.9 (CH_2), 29.44 (CH_2), 29.4 (CH_2), 29.3 ($2CH_2$), 26.0 (CH_2), 23.9 (CH_2), 22.7 (CH_2), 22.4 (CH_2), 14.1 (CH_3), 13.9 (CH_3); MS calcd. for $C_{14}H_{28}O$ $[M+Na]^+$ 235.2032 found 235.2031.

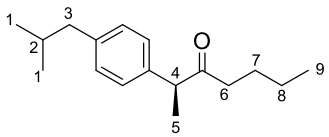
Decanophenone 159



Following procedure **B**, diethyl decanoylphosphate (308 mg, 1.00 mmol) and PhMgBr (2.00 eq.) were used. R_f 0.42 (98:2, petrol:EtOAc). Recovered 105 mg (45 %) as a waxy white solid. mp. 36-38 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.95 (2H, m, Ar*H*), 7.60 – 7.54 (1H, m, Ar*H*), 7.48 (2H, t, *J* 7.6, Ar*H*), 2.98 (2H, t, *J* 7.4, CH_2), 1.76 (2H, quint, *J* 7.4, CH_2), 1.53 – 1.15 (12H, m, CH_2), 0.90 (3H, t, *J* 6.6, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.61 (C), 137.11 (C), 132.84 (CH), 128.54 (CH), 128.06 (CH), 38.65 (CH_2), 31.89 (CH_2), 29.50 (CH_2), 29.48 (CH_2), 29.40 (CH_2), 29.30 (CH_2), 24.41 (CH_2), 22.68 (CH_2), 14.12 (CH_3); MS (ESI$^+$) calcd. for $C_{16}H_{25}O$ $[M+H]^+$ 233.1903, theoretical 233.1900.

Following procedure **C**, diethyl decanoylphosphate (308 mg, 1.00 mmol) and PhMgBr (1.10 mmol) were used. Recovered 115 mg (50 %) as a waxy white solid.

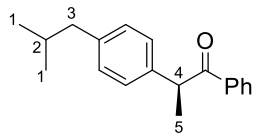
(*S*)-2-(4-Isobutylphenyl)heptan-3-one 160



Following procedure **A**. Acyl phosphate (342 mg, 1.00 mmol) and BuMgCl (1.00 eq.) were used. R_f 0.57 (96:4, petrol:EtOAc). Recovered 116 mg (47 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3022, 2966, 2900, 2870, 1719, 1151, 1463, 1419, 1367, 1167, 1105, 1061, 1029, 922, 882, 848, 756, 596; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.06 (4H, m, Ar*H*), 3.74 (1H, q, *J* 7.0 Hz, C^4*H*), 2.47 (2H, d, *J* 7.2, C$^6H_2$), 2.36 (2H, td, *J* 7.2, 4.5, C$^7H_2$), 1.86 (1H, app. nonet, *J* 6.8 Hz, C^2*H*), 1.56 – 1.42 (2H, m, C$^8H_2$), 1.39 (3H, d, *J* 7.0 Hz, C$^5H_3$), 1.30 – 1.12 (2H, m, C$^3H_2$), 0.91 (6H, d, *J* 6.8, C$^1H_3$), 0.82 (3H, t, *J* 7.2, C$^9H_3$);^{13}C NMR (101 MHz, $CDCl_3$) δ 211.38 (C), 140.52 (C), 137.92 (C), 129.57 (CH), 127.58 (CH), 52.62 (CH), 45.03 (CH_2), 40.64 (CH_2), 30.20 (CH), 26.03 (CH_2), 22.37 (CH_3), 22.17 (CH_2), 17.40 (CH_3), 13.77 (CH_3); MS (ESI$^+$) Calculated for $C_{17}H_{26}ONa$ $[M+Na]^+$ 269.1876 found 269.1870; HPLC (hexane (100

%), 0.25 mL/Min, chiral OJ-H) t_R (R)= 24.75 min (3.88 %), t_R (S)= 26.47 min (96.12%).

(S)-2-(4-Isobutylphenyl)-1-phenylpropan-1-one 161



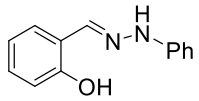
Following procedure **B**, acyl phosphate (342 mg, 1.00 mmol) and PhMgBr (2.00 mmol) were used. R_f 0.55 (95:5, petrol:EtOAc). Recovered 200 mg (76 %) as a waxy colourless solid; mp. 46-48°C; υ_{max} (ATR)/cm^{-1} 3062, 3025, 2966, 2889, 1673, 1617, 1594, 1467, 1416, 1383, 1307, 1247, 1219, 1175, 1120, 951, 848, 790, 730, 657, 636, 616; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.96 (2H, m, Ar*H*), 7.54 – 7.45 (1H, m Ar*H*), 7.40 (2H, dd, *J* 8.1, 6.8, Ar*H*), 7.22 (2H, d, *J* 8.1 Hz, Ar*H*), 7.09 (2H, d, *J* 8.1, Ar*H*), 4.69 (1H, q, *J* 6.8, C^4H), 2.43 (2H, d, *J* 6.8, C^3H), 1.84 (1 H, app. nonet, *J* 6.8, C^2H), 1.55 (3H, d, *J* 6.8, C^5H), 0.89 (6H, d, *J* 6.8, C^1H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6 (C), 140.3 (C), 138.6 (C), 136.6 (C), 132.7 (CH), 129.7 (CH), 128.8 (CH), 128.4 (CH), 127.5 (CH), 47.5 (C^4H), 45.0 (C^3H_2), 30.1 (C^2H), 22.40 (C^1H_3), 19.54 (C^5H_3); MS (ESI^+) Calculated for $C_{19}H_{22}ONa$ $[M+Na]^+$ 289.1563, found 289.1561; HPLC (hexane (100 %), 1 mL/Min, chiral OJ-H) t_R (R)= 13.87 min (2.39 %), t_R (S)= 15.62 min (97.61%).

Following procedure **C**, acyl phosphate (342 mg, 1.00 mmol) and PhMgBr (1.10 mmol) were used. Recovered 180 mg (68 %) waxy colourless solid. Spectroscopic data identical to previous. HPLC (hexane (100 %), 1 mL/Min, chiral OJ-H) t_R (R)= 13.87 min (2.06 %), t_R (S)= 15.62 min (97.94%).

7.5. Chapter 2- additional experiments

Titration of Grignard reagents

Salicylaldehyde phenylhydrazone

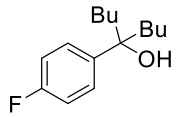


Reagent was prepared using literature procedure and dried under high vacuum.[189]

Titration procedure

An accurately weighed sample of salicylaldehyde phenylhydrazone (60-80 mg) was dissolved in anhydrous THF (10 mL) and stirred at room temperature under argon atmosphere. The Grignard reagent was added slowly to the solution using a syringe. Initially a yellow colour formed (monoanion), the end point was observed when the colour changes from yellow to dark orange.

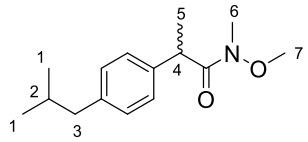
Dibutyl 4-fluorobenzyl alcohol 141b



In a two neck round bottom flask, diethyl 4-fluorobenzoyl phosphate (278 mg, 1.00 mmol) was dissolved in THF (1.5 mL) at -78 °C. BuMgCl (2.00 mmol, 2 M) was added dropwise. The reaction was stirred for 1.00 h. The reaction was quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL), dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography, R_f 0.26 pent:EtOAc (95:5). Recovered 160 mg (67 %) as a colourless oil; υ_{max} (ATR)/cm^{-1} 3469, 2956, 2933, 2862, 1603, 1508, 1466, 1406, 1379, 1342, 1225, 119, 1097, 1034, 1014, 884, 817, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (2H, m, Ar*H*), 7.08 – 6.99 (2H, m, Ar*H*), 1.96 – 1.69 (4H, m, C*H*$_2$), 1.67 (1 H, s, O*H*), 1.36 – 1.14 (6H, m, C*H*$_2$), 1.11 – 0.80 (8H, m, C*H*$_3$); ^{13}C NMR

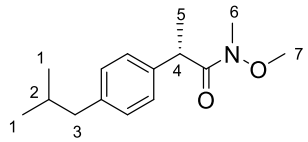
(101 MHz, $CDCl_3$) δ 161.4 (d, $J_{(C-F)}$ 244.4, C), 142.1 (d, $J_{(C-F)}$ 3.2, C), 126.9 (d, $J_{(C-F)}$ 7.7, CH), 114.7 (d, $J_{(C-F)}$ 21.0, CH), 76.8 (C), 42.8 (CH_2), 25.6 (CH_2), 23.0 (CH_2), 14.0 (CH_3); ^{19}F NMR (376 MHz, CDCl3) δ -117.47 (tt, J 8.7, 5.4, CF).

2-(4-Isobutylphenyl)-*N*-methoxy-*N*-methylpropanamide 163



R/S-ibuprofen (1.24 g, 6.00 mmol) and iodine (1.52 g, 6.00 mmol) in DCM (30 mL). Triethyl phosphite (1.13 mL, 6.60 mmol) and Et_3N (1.25 mL, 9.00 mmol) were added at 0 °C. Reaction was stirred for 0.75 h at rt, then N,O-dimethylhydroxylamine hydrochloride (0.585 g, 6.00 mmol) and Et_3N (836 µL, 6.00 mmol) were added. The reaction was stirred for 1 h at rt. DCM was added (30 mL), washed with Na_2CO_3 (30 mL), 2 M HCl (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification was achieved by silica gel chromatography, R_f 0.21 (9:1, petrol:EtOAc). Recovered 768 mg (52 %) as a colourless oil.^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* 8.1, Ar*H*), 7.10 (2H, d, *J* 8.1, Ar*H*), 4.13 (1H, m, C*H*), 3.42 (3H, s, C*H*$_3$), 3.18 (3H, s, C*H*$_3$), 2.45 (2H, d, *J* 7.2, C*H*$_2$), 1.86 (1H, app. nonet, *J* 6.8, C*H*), 1.45 (3H, d, *J* 7.1, C*H*$_3$), 0.90 (6H, dd, *J* 6.6, 1.0, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3 (C), 140.1 (C), 139.1 (C), 129.3 (CH), 127.3 (CH), 61.1 (C^7H_3), 45.1 (C^3H_2), 41.6 (C^4H), 32.3 (C^6H_3), 30.2 (C^2H), 22.4 (C^1H_3), 19.6 (C^5H_3); MS (ESI^+) calcd. for $C_{15}H_{24}NO_2$ $[M+H]^+$ 250.1802, found 250.1806. Spectroscopic data is in accordance with literature.[190] Failed to separate enantiomers on Chiral OJ-H column.

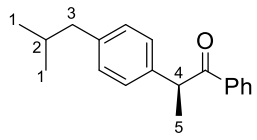
(*S*)-2-(4-isobutylphenyl)-*N*-methoxy-*N*-methylpropanamide 163



Following above procedure using S-ibuprofen (1.24 g, 6.00 mmol). Recovered 1.15 g (77 %) as a colourless oil. Spectroscopic data identical to previous.

Spectroscopic data are in accordance with literature.[190] Failed to separate enantiomers on Chiral OJ-H column.

(S)-2-(4-isobutylphenyl)-1-phenylpropan-1-one 161



(S)-2-(4-isobutylphenyl)-N-methoxy-N-methylpropanamide (249 mg, 1.00 mmol) in THF (10 mL). PhMgBr (2.00 eq.) was added at 0 °C. Reaction was stirred at 0 °C for 1 h. Quench 2 M HCl (10 mL), extracted EtOAc (3 x 10 mL), washed brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purified by silica gel chromatography (96:4, pent:EtOAc). Recovered 143 mg (68 %) as a colourless solid. Spectroscopic data matches previous.

HPLC Chiral OJ-H column at 25 °C (250 nm), Flow rate 1 mL/min. Hexane (100 %). (R)-enantiomer: retention time- 13.87 min; peak area- 141.68 (6.06 %). (S)-enantiomer: retention time 15.62 min; peak area- 2186.16 (93.9 %).

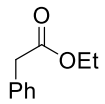
(S)-2-(4-isobutylphenyl)-N-methoxy-N-methylpropanamide (82 mg, 0.329 mmol) in THF (10 mL). PhMgBr (6.00 eq.) was added at rt. Reaction heated to 65 °C and stirred for 1 h. Quench 2 M HCl (10 mL), extracted EtOAc (3 x 10 mL), washed brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purified by silica gel chromatography (96:4, pent:EtOAc). Recovered 54 mg (62 %) as a colourless solid. Spectroscopic data matches previous. HPLC (hexane (100 %), 1 mL/Min, chiral OJ-H) t_R (R)= 13.87 min (6.44 %), t_R (S)= 15.62 min (93.56 %).

ReactIR

In a nitrogen flushed flame dried multi-neck Schlenck tube, equipped with a magnetic stirrer and a diamond ReactIR probe that was situated so the probe tip was about 1-2 cm from the bottom of the flask. The flask was placed under argon atmosphere, anhydrous THF (9 mL) was added and cooled to -78 °C (-72 °C internal). Interval time was set to 30 s. A blank of the THF solution was taken. Acid chloride or acyl phosphate (1.00 mmol) in THF (1 mL) were added and an average peak height was taken over 10 measurements. BuMgCl (1.00 mmol, 0.50 mL) was added in one-portion and measurements were taken every 30 s (128 scans) until no change in IR spectrum was observed.

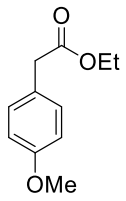
7.6. α-Aryl esters procedure and assignments

Ethyl phenylacetate 180



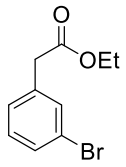
In a 50 mL round bottom flask, sodium nitrite (1.034 g, 19.0 mmol) and glycine ethyl ester hydrochloride (2.094 g, 15 mmol) in toluene (24 mL) were stirred at 50 °C for 5 min. NH_4Cl (2.14 g, 40.0 mmol), phenyl boronic acid (1.29 g, 10.0 mmol) and water (1.2 mL) were added sequentially. The reaction mixture was heated to 100 °C and stirred for 24 h, then cooled to room temperature, concentrated under reduced pressure and purified by silica gel chromatography, R_f 0.44 (95:5 pent:EtOAc). Recovered 1.268 g (77 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (5 H, m, Ar*H*), 4.18 (2 H, q, *J* 7.2, CH_2), 3.64 (2 H, s, CH_2), 1.28 (3 H, t, *J* 7.2, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.64 (C), 134.18 (C), 129.25 (CH), 128.56 (CH), 127.05 (CH), 60.86 (CH_2), 41.46 (CH_2), 14.19 (CH_3); MS (ESI$^+$) calcd. for $C_{10}H_{11}O_3$ $[M+H]^+$ 165.0910, found 165.0906. Spectroscopic data are in accordance with the literature.[146]

Ethyl 2-(4-methoxyphenyl)acetate 201



In a 25 mL round bottom flask, sodium nitrite (655 mg, 9.50 mmol) and glycine ethyl ester hydrochloride (1.047 g, 7.50 mmol) in toluene (12.0 mL) were stirred at 50 ^{0}C for 5 min. NH_4Cl (1.07 g, 2.0 mmol), (4-methoxyphenyl)boronic acid (756 mg, 5.00 mmol) and water (1.20 mL) were added sequentially. The reaction was heated to 100 °C for 24 h, then cooled to room temperature, concentrated under reduced pressure and purified by silica gel chromatography, R_f 0.2 (pent:EtOAc). Recovered 550 mg (57 %) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.19 (2 H, m, Ar*H*), 6.92 – 6.84 (2 H, m, Ar*H*), 4.17 (2 H, q, *J* 7.1, C*H*$_2$), 3.82 (3 H, s, C*H*$_3$), 3.57 (2 H, s, C*H*$_2$), 1.27 (3 H, t, *J* 7.1, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.98 (C), 158.67 (C), 130.27 (CH), 126.25 (C), 113.99 (CH), 60.80 (CH_2), 55.27 (CH_3), 40.54 (CH_2), 14.20 (CH_3); MS (ESI$^+$) calcd. for $C_{10}H_{13}O_3$ $[M+H]^+$ 181.0865, found 181.0863. Spectroscopic data are in accordance with literature.[146]

Ethyl 2-(3-bromophenyl)acetate 202



In a 25 mL round bottom flask, sodium nitrite (655 mg, 9.50 mmol) and glycine ethyl ester hydrochloride (1.047 g, 7.50 mmol) in toluene (12.0 mL) were stirred at 50 ^{0}C for 5 min. NH_4Cl (1.07 g, 2.0 mmol), (3-bromophenyl)boronic acid (1.004 g, 5.00 mmol) and water (1.20 mL) were added sequentially. The reaction was heated to 100 °C for 24 h, then cooled to room temperature, concentrated under reduced pressure and purified by silica gel chromatography, R_f 0.45 (98:2, pent:EtOAc). Recovered 848 mg (70 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (1 H, m, Ar*H*), 7.44 – 7.39 (1 H, m, Ar*H*), 7.28 – 7.16 (2 H, m, Ar*H*), 4.18 (2 H, q, *J* 7.1, C*H*$_2$), 3.60 (2 H, s, C*H*$_2$), 1.28 (3 H, t, *J* 7.1, C*H*$_3$); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 170.9 (C) 136.3 (C), 132.3 (CH), 130.2 (CH), 130.1 (CH), 128.0 (CH), 122.5 (C), 61.1 (OCH_2), 40.9 (CH_2), 14.2 (CH_3). MS (ESI^+) calcd. for $C_9H_{10}BrO_2$ $[M+H]^+$ 228.9864, found 228.9860. Spectroscopic data are in accordance with literature.[146]

7.7. β-Ketoesters procedures and assignments

Procedure 3A

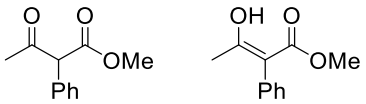
Ester (1.00 mmol) in THF (1.5 mL) was added dropwise to LiHMDS 1 M THF (2.00 mmol) at −78 °C. The reaction was stirred for 0.5 h before acyl phosphate (1.00 mmol) in THF (1.5 mL) was added in one portion. The reaction was stirred for a further 0.5 h before warming to rt. Upon completion 2 M HCl (10 mL) was added, extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using the solvent system provided.

Procedure 3B

Step 1, carboxylic acid (2.00 mmol) and iodine (2.00 mmol) were dissolved in DCM (10 mL). Distilled triethyl phosphite (2.00 mmol) and triethyl amine (3.00 mmol) were added at 0 °C. The reaction mixture was stirred at rt for 0.75 h minutes then poured onto cold water (10 mL) and DCM (10 mL) was added, dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was stored under high vacuum.

Step 2, ester (2.00 mmol) in THF (3.0 mL) was added dropwise to LiHMDS 1 M THF (4.00 mmol) at −78 °C. The reaction was stirred for 0.5 h before the crude mixture (2.00 mmol) in THF (3.0 mL) was added in one portion. The reaction was stirred for a further 0.5 h before warming to rt. Upon completion 2 M HCl (10 mL) was added, extracted with EtOAc (3 x 20 mL), washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using the solvent system provided.

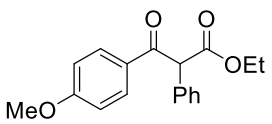
Methyl 2-phenylacetoacetate and methyl (Z)-3-hydroxy-3-phenylbut-2-enoate 204



Methyl phenylacetate (1.32 g, 8.80 mmol) in THF (13.5 mL) was added dropwise to LiHMDS 1 M THF (19.0 mL, 19.0 mmol) at –78 °C. The reaction was stirred for 30 minutes before acetic anhydride (851 µL, 9.00 mmol) in THF (13.5 mL) was added in one portion. The reaction was stirred for a further 30 minutes before warming to rt. The reaction was stirred for 18 hours then, NH_4Cl (50 mL) was added, extracted with EtOAc (3 x 50 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by silica gel chromatography, R_f 0.48 (95:5, pent:EtOAc). Recovered 1.24 g (73 %) as a colourless oil.

Present as a mixture of keto:enol (52:48) in $CDCl_3$. Aromatic signals are overlapped. ^{1}H NMR (keto) (400 MHz, $CDCl_3$) δ 7.49-7.27 (5H, m, Ar*H*(overlapped)), 4.94 (3H, s, OC*H*$_3$), 2.21 (C*H*$_3$); ^{1}H NMR (enol) (400 MHz, CDCl3) δ 13.06 (1H, d, *J* 0.9, O*H*), 7.49 – 7.27 (3H, m, Ar*H*(overlapped)), 7.22 – 7.15 (2H, m, Ar*H*), 3.71 (3H, s, OC*H*$_3$), 1.88 (3H, d, *J* 0.9, C*H*$_3$); ^{13}C NMR (keto+enol) (101 MHz, CDCl3) δ 201.4 (C(keto)), 174.1 (C(enol)), 173.0 (C(enol), 169.0(C(keto)), 135.1 (C), 132.6 (C), 131.2 (CH), 129.3 (CH), 129.0 (CH), 128.4 (CH), 128.2 (CH), 127.1 (CH), 104.1 (C(enol)), 65.7(CH(keto)), 52.6 (OCH_3(keto)), 51.8 (OCH_3(enol)), 28.8 (CH_3(keto)), 19.9 (CH_3(enol)); MS (ESI$^+$) calcd. for $C_{11}H_{13}O_3$ $[M+H]^+$ 193.0865, found 193.193.0862. Spectroscopic data are in accordance with literature.[191]

Ethyl 3-(4-methoxyphenyl)-3-oxo-2-phenylpropanoate 207

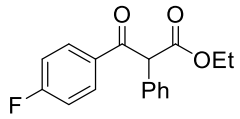


Following procedure **3A**. Ethyl phenylacetate (168 mg, 1.00 mmol) and diethyl (4-methoxybenzoyl) phosphate (288 mg, 1.00 mmol) were used. R_f 0.32 (8:2, pent:EtOAc). Recovered 171 mg (57 %) as a pale-yellow oil. υ_{max} (ATR)/cm^{-1}

3065, 3029, 2967, 2885, 1733, 1684, 1515, 1495, 1355, 1342, 1256, 1193, 1068, 1013, 981, 882, 792, 675, 647; present as keto (100 %) in $CDCl_3$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.93 (2H, m, Ar*H*), 7.54 – 7.21 (5H, m, Ar*H*), 6.95 – 6.87 (2H, m, Ar*H*), 5.59 (1H, s, C*H*), 4.31 – 4.19 (2H, m, C*H*$_2$), 3.85 (3H, s, OC*H*$_3$), 1.27 (3H, t, J 7.1, C*H*$_3$); ^{13}C NMR (101 MHz, CDCl3) δ 191.83 (C), 169.03 (C), 163.80 (C), 133.40 (C), 131.35 (CH), 129.55 (CH), 128.79 (CH), 128.60 (C), 128.02 (C), 113.93 (CH), 61.69 (CH_2), 60.35 (CH), 55.51 (CH_3), 14.09 (CH_3); MS (ESI^+) calcd. for $C_{18}H_{19}O_4$ $[M+H]^+$ 299.1278, found 299.1275.

Following procedure **3B**. 4-methoxybenzoic acid (304 mg, 2.00 mmol) was used in step 1. Ethyl phenylacetate (328 mg, 2.00 mmol) was used in step 2. Recovered 438 mg (73 %) as a pale-yellow oil. Spectroscopic data identical to previous.

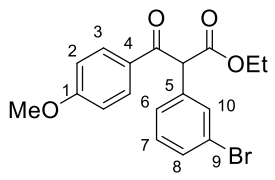
Ethyl 3-(4-fluorophenyl)-3-oxo-2-phenylpropanoate 211



Following procedure **3A**. Ethyl phenylacetate (164 mg, 1.00 mmol) and diethyl (4-fluorobenzoyl) phosphate (276 mg, 1.00 mmol) were used. R_f 0.35 (8:2, pent:Et_2O). Recovered 132 mg (46 %) as a pale-yellow oil. υ_{max} (ATR)/cm^{-1} 3066, 3032, 2982, 2936, 1733, 1681, 1596, 1409, 1180, 1027, 1010, 946, 828, 697; Present as a mixture of keto:enol (ca. 94:6) in $CDCl_3$; ^1H NMR (keto) (400 MHz, $CDCl_3$) δ 8.06 – 7.95 (2H, m, Ar*H*), 7.45 – 7.33 (5H, m, Ar*H*), 7.18 – 7.06 (2H, m, Ar*H*), 5.57 (1H, s, C*H*), 4.26 (2H, q, *J* 7.1, C*H*$_2$), 1.27 (3H, t, *J* 7.1, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.79 (C), 168.64 (C), 165.88 (d, $J_{(C-F)}$ 256.0, C), 132.84 (C), 132.07 (d, $J_{(C-F)}$ 3.0, C), 131.65 (d, $J_{(C-F)}$ 9.5, CH), 129.53 (CH), 128.92 (CH), 128.25 (CH), 115.92 (d, *J* 22.0, CH), 61.86 (CH_2), 60.62 (CH), 14.05 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.06 (tt, *J* 8.4, 5.3, CF(keto), -110.24 (tt, *J* 8.5, 5.5, CF(enol)); MS (ESI^+) calcd. for $C_{17}H_{16}FO_3$ $[M+H]^+$ 287.1083, found 287.1085.

Following procedure **3B**. 4-fluorobenzoic acid (280 mg, 2.00 mmol) was used in step 1. Ethyl phenyl acetate (328 mg, 2.00 mmol) was used in step 2. Recovered 245 mg (42 %) as a pale-yellow oil. Spectroscopic data identical to previous.

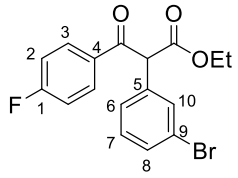
Ethyl 2-(3-bromophenyl)-3-(4-methoxyphenyl)-3-oxopropanoate 212



Following procedure **3B**. 4-methoxybenzoic acid (304 mg, 2.00 mmol) was used in step 1. Ethyl-2-(3-bromophenyl)acetate (486 mg, 2.00 mmol) was used in step 2. R_f 0.23 (9:1, pent:EtOAc). Recovered 340 mg (47 %) as a pale-yellow oil.

υ_{max} (ATR)/cm^{-1} 2979, 2936, 2840, 1738, 1672, 1597, 1510, 1473, 1391, 1367, 1322, 1305, 1288, 1257, 1216, 1167, 1115, 1094, 1075, 1028, 998, 952, 872, 835, 794, 753, 684, 666, 644, 621; Present as a mixture of keto:enol (ca. 96:4) in $CDCl_3$; ^{1}H NMR (keto) (400 MHz, $CDCl_3$) δ 8.00 – 7.92 (2H, m, Ar*H*), 7.60 (1H, s, Ar*H*), 7.45 (1H, dt, *J* 7.8, 1.0, Ar*H*), 7.37 (1H, dt, *J* 7.8, 1.3, Ar*H*), 7.24 (1H, t, *J* 7.8, Ar*H*), 6.97 – 6.89 (2H, m, Ar*H*), 5.55 (1H, s, CH), 4.24 (2H, q, *J* 7.1, CH_2), 1.26 (3H, t, *J* 7.1, CH_3); ^{13}C NMR (keto) (101 MHz, $CDCl_3$) δ 191.1 (C), 168.5 (C), 164.0 (C^1), 135.4 (C^5), 132.5 (C^{10}H), 131.3 (C^2H), 131.2 (C^8H), 130.2 (C^6H), 128.4 (C^4), 128.3 (C^7H), 122.7 (C^9), 114.1 (C^3H), 61.9 (OCH_2), 59.6 (CH), 55.6 (OCH_3), 14.1 (CH_3). MS (ESI^+) calcd. for $C_{18}H_{17}BrO_4Na$ $[M+Na]^+$ 399.0208, found 399.0195.

Ethyl 2-(3-bromophenyl)-3-(4-fluorophenyl)-3-oxopropanoate 213

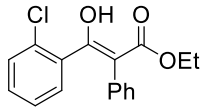


Following procedure **3A**. Diethyl(4-fluorobenzoyl)phosphate (276 mg, 1.00 mmol) was used. R_f 0.37 (9:1, pent:EtOAc) 374 mg (53 %) as a pale yellow oil. υ_{max} (ATR)/cm^{-1} 3019, 2983, 1733, 1685, 1635, 1598, 1570, 1507, 1475, 1445, 1428, 1370, 1321, 1287, 1259, 1215, 1183, 1158, 1095, 1075, 1027, 1008, 844, 751, 684, 668, 667, 622; Present as a mixture of keto:enol (ca. 85:15) in $CDCl_3$; ^{1}H NMR (keto) (400 MHz, $CDCl_3$) δ 8.05 – 7.95 (2H, m, Ar*H*), 7.61 – 7.54 (1H, m, Ar*H*), 7.48 (1H, ddd, *J* 7.9, 2.0, 1.1, Ar*H*), 7.36 (1H, dt, *J* 7.7, 1.4, Ar*H*), 7.27 – 7.23 (1H, m, Ar*H*), 7.20 – 7.07 (2H, m, Ar*H*), 5.53 (1H, s, C*H*), 4.38 – 4.09 (2H, m, CH_2), 1.27 (3H,

td, *J* 7.2, 3.2, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.08 (C), 168.06 (C), 166.04 (d, $J_{(C-F)}$ 256.7, C^1), 134.84 (C^5), 132.53 (C^7H), 131.86 (d, $J_{(C-F)}$ 2.9, C^4), 131.63 (d, $J_{(C-F)}$ 9.5, C^3H), 131.45 (C^{10}H), 130.34 (C^8H), 128.24 (C^6H), 122.79 (C^9), 116.09 (d, $J_{(C-F)}$ 22.0, C^2H), 62.12 (CH_2), 59.88 (CH), 14.02 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.46 (tt, *J* 8.3, 5.3, CF(keto)), -109.51 (tt, *J* 8.6, 5.4, CF(enol)); MS (ESI^+) calcd. for $C_{17}H_{14}{}^{79}BrFO_3Na$ $[M+Na]^+$ 387.0003, found 387.0002.

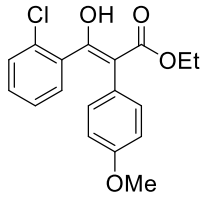
Following procedure **3A**. 4-Fluorobenzoic acid (280 mg, 2.00 mmol) was used in step 1. Ethyl-2-(3-bromophenyl)acetate (486 mg, 2.00 mmol) was used in step 2. Recovered 527 mg (72 %) as a pale-yellow oil. Spectroscopic data identical to previous.

Ethyl (Z)-3-(2-chlorophenyl)-3-hydroxy-2-phenylacrylate 214



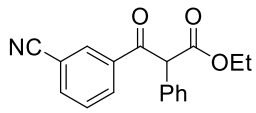
Following procedure **3A**. Diethyl (2-chlorobenzoyl) phosphate (292 mg, 1.00 mmol) and ethyl phenylacetate (164 mg, 1.00 mmol) were used. R_f 0.51 (94:6, pent:EtOAc). Recovered 165 mg (55 %) as a yellow oil. υ_{max} (ATR)/cm^{-1} 3064, 2983, 2648, 1732, 1686, 1590, 1434, 1407, 1369, 1285, 1249, 1196, 1068, 1014, 982, 901, 861, 811, 792, 741, 698, 642; Present as a mixture of keto:enol (ca. 1:2) in $CDCl_3$; ^{1}H NMR (enol) (400 MHz, $CDCl_3$) δ 13.32 (1H, s, O*H*), 7.46 – 7.23 (4 H, m, Ar*H*), 7.23 – 7.02 (5H, m, Ar*H*), 4.32 (2H, q, *J* 7.2, C*H*$_2$), 1.29 (3H, t, *J* 7.1, C*H*$_3$)-aromatic protons are overlapped with keto; ^{13}C NMR (enol) (101 MHz, $CDCl_3$) δ 172.8 (C), 170.3 (C), 138.2 (C) 134.5 (C), 131.3 (CH), 130.2 (CH), 129.8 (CH), 129.6 (CH), 128.7 (CH), 128.3 (C), 127.5 (CH), 126.2 (CH), 106.9 (C), 69.4 (C), 61.3 (CH_2), 14.2 (CH_3); MS (ESI^+) calcd. for $C_{17}H_{16}ClO_3$ $[M+H]^+$ 303.0782, found 303.0787.

Ethyl (Z)-3-(2-chlorophenyl)-3-hydroxy-2-(4-methoxyphenyl)acrylate 215



Following procedure **3B**. 2-Chlorobenzoic acid (313 mg, 2.00 mmol) was used in step 1. Ethyl-2-(4-methoxyphenyl)acetate (388 mg, 2.00 mmol) was used in step 2. R_f 0.24 (95:5, pent:EtOAc). Recovered 383 mg (56 %) as a yellow oil. υ_{max} (ATR)/cm^{-1} 2981, 2935, 2834, 1743, 1702, 1637, 1609, 1584, 1512, 1466, 1395, 1373, 1332, 1279, 1244, 1176, 1141, 1109, 1095, 1057, 992, 949, 915, 834, 736, 692; Present as a mixture of keto:enol (ca. 1:2) in $CDCl_3$; ^{1}H NMR (enol) (400 MHz, $CDCl_3$) δ 13.25 (1 H, s, O*H*), 7.42 – 7.35 (1 H, m, Ar*H*), 7.18 (1 H, ddd, *J* 8.0, 6.2, 2.9, Ar*H*), 7.12 – 7.07 (2 H, m, Ar*H*) 7.04 – 6.95 (2 H, m, Ar*H*), 6.71 – 6.62 (2 H, m, Ar*H*), 4.31 (2 H, q, *J* 7.1, C*H*$_2$), 3.73 (1 H, s, C*H*$_3$), 1.29 (3 H, t, *J* 7.1, C*H*$_3$)- aromatic protons are overlapped with keto; ^{13}C NMR (enol) (101 MHz, $CDCl_3$) δ 173.0 (C), 170.0 (C), 158.2 (C), 132.30 (CH), 131.89 (C), 131.0 (CH), 130.6 (CH), 130.05 (CH), 126.2 (CH), 112.9 (CH), 106.5 (C), 62.9 (C), 61.2 (OCH_2), 55.0 (OCH_3), 14.2 (CH_3); MS (ESI^+) calcd. for $C_{18}H_{17}ClO_4Na$ $[M+Na]^+$ 355.0708, found 355.0717.

Ethyl 3-(3-cyanophenyl)-3-oxo-2-phenylpropanoate 216

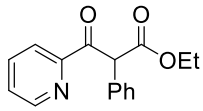


3-cyanobenzoic acid (2.00 mmol) and iodine (2.00 mmol) were dissolved in DCM (10 mL). Distilled triethyl phosphite (2.00 mmol) and triethyl amine (3.00 mmol) were added at 0 ^{0}C. The reaction mixture was stirred at rt for 45 minutes then poured onto cold water (10 mL) and DCM (10 mL) was added, dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was stored under high vacuum until use. Ethyl phenyl acetate (328 mg, 2.00 mmol) in THF (3.0 mL) was added dropwise to 1 M LiHMDS (4.00 mmol) at –78 ^{0}C. The reaction was stirred for 30 minutes before the crude mixture in THF (10.0 mL) was added

slowly. The reaction was stirred for a further 30 minutes before warming to rt. The reaction was stirred at rt overnight, then sat. NH_4Cl (20 mL) was added, extracted with EtOAc (3 x 20 mL), washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification was obtained by silica gel chromatography, R_f 0.25 (9:1, pent:EtOAc). Recovered 230 mg (38 %) as a pale yellow oil; υ_{max} (ATR)/cm^{-1} 3068, 2982, 2937, 2232, 1733, 1688, 1640, 1580, 1497, 1477, 1454, 1368, 1263, 1194, 1019, 754, 699, 678; Present as a mixture of keto:enol (ca. 5:1) in $CDCl_3$; ^{1}H NMR (Keto) (400 MHz, $CDCl_3$) δ 8.24 (1H, t, *J* 1.5, Ar*H*), 8.18 (1H, dt, *J* 8.0, 1.5, Ar*H*), 7.83 (1H, dt, *J* 7.8, 1.5, Ar*H*), 7.59 (1H, t, *J* 7.8, Ar*H*), 7.48 – 7.29 (5H, m, Ar*H*), 5.55 (1H, s, C*H*), 4.33 – 4.21 (2H, m, C*H*$_2$), 1.28 (3H, t, *J* 7.2, C*H*$_3$); ^{13}C NMR (Keto) (101 MHz, $CDCl_3$) δ 191.5 (C), 168.1 (C), 136.3 (CH), 132.8 (CH), 132.5 (CH), 132.1 (C), 129.8 (CH), 129.5 (CH), 129.1 (CH), 128.6 (CH), 117.7 (C), 113.4 (C), 62.1 (CH_2), 60.7 (CH), 14.0 (CH_3); MS (ESI^+) cald. for $C_{18}H_{15}NO_3Na$ $[M+Na]^+$ 316.0944, found 316.0947.

As above procedure but the reaction was quenched with 2 M HCl (20 mL). Recovered 175 mg (30 %) as a yellow oil. Spectroscopic data identical to previous.

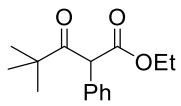
Ethyl 3-(2-pyridine)-3-oxo-2-phenylpropanoate 217



Following procedure **3B**. Picolinic acid (220 mg, 2.00 mmol) was used in the first step. Ethyl phenyl acetate (328 mg, 2.00 mmol) was used in the second step. NH_4Cl (20 mL) was used to quench reaction, then extracted with EtOAc (3 x 20 mL), washed brine (20 mL), dried (Na_2SO_4). The residue was purified using silica gel chromatography R_f 0.33 (9:1, pent:EtOAc). Recovered 285 mg (53 %) as an orange oil. υ_{max} (ATR)/cm^{-1} 3060, 3032, 2981, 2938, 1743, 1726, 1601, 1582, 1497, 1390, 1367, 1275, 1250, 1215, 1187, 1151, 1092, 1076, 1028, 1010, 995, 946, 917, 8912, 840, 766, 735, 699, 618, 600; Present as keto (100 %) in $CDCl_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (1H, ddd, J 4.8, 1.7, 1.1, Ar*H*), 8.10 (1H, dt, J 7.8, 1.1, Ar*H*), 7.84 (1H, td, J 7.8, 1.7, Ar*H*), 7.48 (3H, ddt, J 6.1, 3.3, 1.7, Ar*H*), 7.42 – 7.28 (3H, m, Ar*H*), 6.21 (1H, s, C*H*), 4.28-4.14 (2H, m, C*H*$_2$), 1.23 (3H, t, J 7.1, C*H*$_3$);

^{13}C NMR (101 MHz, CDCl3) δ 194.48 (C), 169.46 (C), 152.10 (C), 148.87 (CH), 137.06 (CH), 132.99 (C), 130.05 (CH), 128.52 (CH), 127.88 (CH), 127.44 (CH), 122.83 (CH), 61.47 (CH_2), 58.54 (CH), 14.14 (CH_3); MS (ESI$^+$) calcd. for $C_{16}H_{16}NO_3$ $[M+H]^+$ 270.1125, found 270.1135.

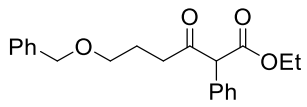
4,4-Dimethyl-3-oxo-2-phenyl-valeric acid ethyl ester 218



Following procedure **3A**. Diethyl pivoylphosphate (238 mg, 1.00 mmol) and ethyl phenyl acetate (164 mg, 1.00 mmol) were used. R_f 0.34 (95:5, pent:EtOAc). Recovered 105 mg (42 %) as a pale-yellow oil. υ_{max} (ATR)/cm^{-1} 3065, 3030, 2971, 2935, 2906, 2872, 1744, 1703, 1585, 1497, 1455, 1395, 1366, 1342, 1299, 1270, 1224, 1194, 1153, 1113, 1095, 1077, 1056, 1027, 999, 941, 896, 731, 698; Present as Keto (100 %) in $CDCl_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (5 H, m, Ar*H*), 5.22 (1 H, s, C*H*), 4.25-4.11 (2 H, m, C*H*$_2$), 1.26 (3 H, t, *J* 7.1, C*H*$_3$), 1.18 (9 H, s, C(C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.02 (C), 168.68 (C), 133.16 (C), 129.46 (CH), 128.56 (CH), 127.92 (CH), 61.59 (CH_3), 58.58 (CH), 45.82 (C), 26.40 (CH_3), 14.04 (CH_3); MS (ESI$^+$) calcd. for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1305, found 271.1307.

Following procedure **3B**. Pivalic acid (204 mg, 2.00 mmol) was used in the first step. Ethyl phenyl acetate (328 mg, 2.00 mmol) was used in the second step. Recovered 115 mg (23 %) as a pale-yellow oil. Spectroscopic data identical to previous procedure.

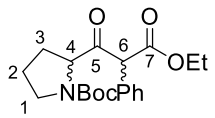
Ethyl 6-oxybenzyl-3-oxo-2-phenyl-hexanoate 219



Following procedure **3B**. 4-(benzyloxy)butyric acid (354 μL, 2.00 mmol) was used in the first step. Recovered 360 mg (53 %) as a colourless oil.

υ_{max} (ATR)/cm^{-1} 3534, 3062, 3030, 2981, 2861, 1731, 1716, 1601, 1495, 1477, 1395, 1369, 1292, 1255, 1203, 1171, 1097, 1075, 1026, 915, 885, 858, 812, 790, 731, 716, 698; Present as a mixture of keto:enol (ca. 5:1) in $CDCl_3$; ^{1}H NMR (keto) δ H (400 MHz, CDCl3) 7.57 – 7.27 (10H, m, Ar*H*), 4.75 (1H, s, C*H*), 4.43 (2H, s, PhC*H*$_2$), 4.38 – 4.12 (2H, m, OC*H*$_2$CH$_3$), 3.51 – 3.36 (2H, m, OC*H*$_2$), 2.64 (2H, t, *J* 7.1, C(O)C*H*$_2$), 1.97 – 1.81 (2H, m, C*H*$_2$), 1.37 – 1.23 (3H, m, C*H*$_3$); ^{13}C NMR (keto) δ $_C$ (101 MHz, $CDCl_3$) 203.48 (C), 168.57 (C), 138.36 (C), 132.64 (C), 129.46 (CH), 128.83 (CH), 128.38 (CH), 128.21 (CH), 127.64 (CH), 127.59 (CH), 72.83 (CH_2), 68.95 (CH_2), 65.04 (CH), 61.60 (CH_2), 38.33 (CH_2), 23.82 (CH_2), 14.10 (CH_3); MS (ESI$^+$) calcd. for $C_{21}H_{24}O_4Na$ [M+Na]$^+$ 363.1572, found 363.1575.

tert-Butyl-2-(3-ethoxy-3-oxo-2-phenylpropanoyl)pyrrolidine-2-carboxylate 220

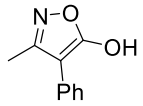


Following procedure **3B**. Boc-pro-OH (430 mg, 2.00 mmol) was used in the step 1. Ethyl phenyl acetate (328 mg, 2.00 mmol) was used in step 2. R_f 0.29 (9:1, pent:EtOAc). Recovered 352 mg (49 %) as a yellow oil. Recovered as a mixture of diastereomers (52:48 by ^{1}H NMR). υ_{max} (ATR)/cm^{-1} 2977, 2933, 2879, 174, 1692, 1639, 1599, 1495, 1477, 1454, 1391, 1366, 1340, 1305, 1258, 1216, 1201, 1159, 1119, 1093, 1045, 1025, 978, 920, 854, 771, 732, 702, 623; present as a mixture of keto:enol (ca. 10:1) in $DMSO_{d-6}$)^{1}H NMR (keto)both diastereomers (a+b)-(500 MHz, DMSO-80 °C) δ 7.47 – 7.27 (10H, m, Ar*H*$_{(a+b)}$), 5.21 (1H, s, C^6*H*$_a$), 5.15 (1H, s, C^6*H*$_b$), 4.47 (1H, dd, *J* 9.0, 4.0, C^4*H*$_a$), 4.43 (1H, dd, *J* 9.0, 4.0, C^4*H*$_b$), 4.22 – 4.08 (4H, m, OC*H*$_{2(a+b)}$), 3.49-3.36 (1H, m, C*H*$_2$), 3.37 – 3.26 (2H, m, C*H*$_2$), 3.20 (1H, br. s, C*H*$_2$), 3.07 (1H, br. s, C*H*$_2$), 2.17 (1H, s, C*H*$_2$), 1.99 (1H, m, C*H*$_2$), 1.93 (1H, m, C*H*$_2$), 1.83 – 1.69 (4H, m, C*H*$_2$), 1.51 – 1.34 (18H, m, C(C*H*$_3$)$_{3(a+b)}$), 1.27 – 1.09 (6H, m, C*H*$_{3(a+b)}$); ^{13}C NMR both diastereomers (a+b)- (126 MHz, DMSO-80°C) δ 203.2 (C^5$_{(a)}$), 202.7 (C^5$_b$), 168.4 (C^7$_{(a)}$), 168.1 (C^7$_{(b)}$), 153.9 (2C$_{(a+b)}$), 133.2 (C$_{(a)}$), 133.0 (C$_{(b)}$), 130.0 (CH$_{(a)}$), 130.0 (CH$_{(b)}$), 128.8 (CH$_{(a)}$), 128.8 (CH$_{(b)}$), 128.3 (2CH$_{(a+b)}$), 79.7 (C$_{(a)}$), 79.4 (C$_{(b)}$), 65.5 (C^{4}H$_{(b)}$), 65.5 (C^{4}H$_{(a)}$), 61.52 (C^{6}H$_{(b)}$), 61.47 (OCH$_{2(a)}$), 61.2 (C^{6}H$_{(a)}$), 61.0 (OCH$_{2(b)}$), 47.6 (C^{1}H$_{2(b)}$) , 47.1 (C^{1}H$_{2(a)}$), 29.3 (C^{3}H$_{2(b)}$), 28.70

($C^3H_{2(a)}$), 28.5 ($CH_{3(a/b)}$), 28.4 ($CH_{3(a/b)}$), 23.8 ($2C^2H_{2(a+b)}$), 14.3 ($CH_{3(a+b)}$); MS (ESI^+) calcd. for $C_{20}H_{27}NO_5Na$ $[M+Na]^+$ 384.1787 found 384.1789.

7.8. Heterocycles from β-ketoesters procedures and assignments

3-Methyl-4-phenylisoxazol-5-ol Lab number 221

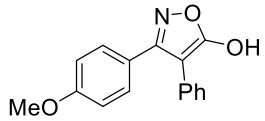


Methyl-3-oxo-2-phenyl butanoate (776 mg, 4.03 mmol) and $NH_2OH{\cdot}HCl$ (1.390 g, 20.0 mmol) in MeOH (20.0 mL) was stirred at reflux for 24 hours. The reaction mixture was cooled to room temperature then concentrated under reduced pressure. Water (10 mL) was added then triturated with Pent:EtOAc (10:1). The solid was dissolved in EtOAc, dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallised from EtOAc:Pent to give 300 mg (43 %) as an off-white solid. mp. 108-110 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 12.75 (1H, s, O*H*), 7.58 – 7.51 (2H, m, Ar*H*), 7.44 – 7.34 (2H, m, Ar*H*), 7.30 – 7.20 (1H, m, Ar*H*), 2.33 (3H, s, C*H*$_3$); ^{13}C NMR (101 MHz, DMSO) δ 170.4 (C), 159.9 (C), 131.1 (C), 128.8 (CH), 127.4 (CH), 126.6 (CH), 12.4 (CH_3); MS (ESI^+) $C_{10}H_{10}NO_2$ $[M+H]^+$ 176.0706, found 176.0709.

Methyl-3-oxo-2-phenyl butanoate (412 mg, 2.00 mmol), $NH_2OH{\cdot}HCl$ (278 mg, 4.00 mmol) and pyridine (483 µL, 6 mmol) in EtOH (2 mL) were stirred at 60 ^{0}C for 16 hours. The reaction mixture was cooled to room temperature and poured onto water (10 mL), extracted with 3 x 10 mL), washed with 2 M HCl (10 mL), brine (10 mL) then dried (Na_2SO_4). Recrystallised from EtOAc:Pent to give 190 mg (54 %) as white needle like crystals. Spectroscopic data identical to previous.

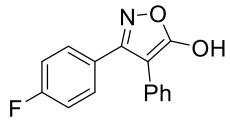
Methyl-3-oxo-2-phenyl butanoate (412 mg, 2.00 mmol), $NH_2OH{\cdot}HCl$ (207 mg, 4.00 mmol) and sodium acetate (246 mg, 4.00 mmol) in EtOH (5 mL) were heated to 78 ^{0}C for 20 hours. Reaction mixture was concentrated under reduced pressure. Recrystallised from EtOAc:Pent to give 158 mg (45 %) as an off-white solid. Spectroscopic data identical to previous.

3-(4-Methoxyphenyl)-4-phenylisoxazol-5-ol 222



Ethyl 3-(4-methoxyphenyl)-3-oxo-2-phenylpropanoate (90 mg, 0.302 mmol) in EtOH (0.75 mL). Sodium acetate (49 mg, 0.604 mmol) and $NH_2OH{\cdot}HCl$ (42 mg, 0.604 mmol) were added. Reaction stirred at 80 °C for 15 hours. Reaction concentrated under reduced pressure and purified by flash column chromatography R_f 0.25 (EtOAc:MeOH, 9:1). Recovered 80 mg (99 %) as a white solid. mp. 150-152 °C; υ_{max} (ATR)/cm^{-1} 3051, 2938, 2839, 1672, 1660, 1606, 1565, 1491, 1308, 1256, 1177, 1111, 1072, 1021, 971, 916, 840, 795, 696, 592; ^{1}H NMR (400 MHz, DMSO) δ 7.42 – 7.36 (2H, m, Ar*H*), 7.35 – 7.28 (4H, m, Ar*H*), 7.27 – 7.20 (1H, m, Ar*H*), 7.07 – 6.99 (2H, m, Ar*H*), 3.80 (3H, s, OC*H*$_3$), OH hydrogen missing; ^{13}C NMR (101 MHz, DMSO) δ 171.15 (C), 161.77 (C), 160.69 (C), 130.78 (C), 129.90 (CH), 128.82 (CH), 128.72 (CH), 127.04 (CH), 119.96 (C), 114.99 (CH), 55.87 (CH_3); MS (ESI^+): calcd for $C_{16}H_{14}NO_3$ $[M+H]^+$ 268.0976, found 268.0968. Spectroscopic data are in accordance with literature.[139]

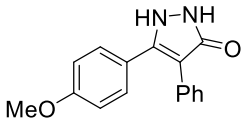
3-(4-Fluorophenyl)-4-phenylisoxazol-5-ol 223



Ethyl 3-(4-fluorophenyl)-3-oxo-2-phenylpropanoate (80 mg, 0.279 mmol), sodium acetate (46 mg, 0.558 mmol) and $NH_2OH{\cdot}HCl$ (39 mg, 0.558 mmol) in EtOH (0.7 mL) was stirred at 78 ^{0}C for 18 hours. The reaction mixture was cooled to room temperature, concentrated under reduced pressure then purified by column chromatography, R_f 0.15 (EtOAc:MeOH, 9:1). Recovered 64 mg (90 %) as a cream solid. mp. 134-136 °C; υ_{max} (ATR)/cm^{-1} 3067, 2921, 2734, 1659, 1601,1562, 1528, 1508, 1463, 1443, 1431, 1311, 1281, 1233, 1182, 1159, 1096, 1072, 1037, 964, 937, 913, 813, 695, 676, 638, 624; ^{1}H NMR (400 MHz, DMSO) δ 12.93 (1H, br. s., O*H*), 7.56 – 7.45 (2H, m, Ar*H*), 7.42 – 7.19 (7H, m, Ar*H*); ^{13}C NMR (101 MHz, DMSO) δ 170.7 (C), 166.4 ($J_{(C\text{-}F)}$ 265.0, CF), 165.5 (C), 130.94 (d, $J_{(C\text{-}F)}$ 9.0, CH), 130.4 (C), 128.9 (CH), 128.7 (CH), 127.1 (CH), 119.9 (C), 116.72 (d, $J_{(C\text{-}F)}$

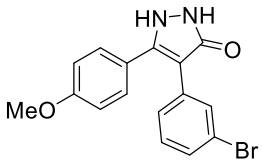
22.2, CH); ^{19}F NMR (377 MHz, DMSO) δ -109.15; MS (ESI$^+$) $C_{11}H_{10}FNO_2$ $[M+H]^+$ 256.0768, found 256.0771.

5-(4-Methoxyphenyl)-4-phenyl-1,2-dihydro-3*H*-pyrazol-3-one 227



Ethyl 3-(4-methoxyphenyl)-3-oxo-2-propanoate 38 mg (0.128 mmol) was dissolved in acetic acid (0.5 mL). Hydrazine hydrate (17 µL, 0.161 mmol) was added at room temperature and then the reaction was stirred at reflux for 3 hours. The reaction mixture was cooled to room temperature, poured onto $NaHCO_3$ (5 mL), extracted with EtOAc (3 x10 mL), washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel chromatography, R_f 0.19 (EtOAc). Recovered 30 mg (88 %) as a white solid. Mp. 205-207 °C ; υ_{max} (ATR)/cm^{-1} 3315, 3052, 2932, 2838, 2699, 1601, 1564, 1516, 1460, 1377, 1290, 1235, 1177, 1133, 1015, 996, 964, 943, 833, 802, 775, 698, 665, 631; ^{1}H NMR (400 MHz, DMSO) δ 11.90 (1H, s, N*H*), 9.91 (1H, s, N*H*), 7.31 – 7.23 (6H, m, Ar*H*), 7.15 (1H, ddd, *J* 8.6, 5.6, 2.3, Ar*H*), 6.98 – 6.90 (2H, m, Ar*H*), 3.77 (3H, s, C*H*$_3$); ^{13}C NMR (101 MHz, DMSO) δ 159.6 (C), 140.1 (C), 133.4 (C), 131.8 (C), 129.3 (CH), 129.2 (CH), 128.5 (CH), 125.8 (CH), 123.4 (C), 114.5 (CH), 102.6 (C), 55.6 (OCH_3); MS (ESI$^+$) calcd. for $C_{16}H_{14}N_2O_2Na$ $[M+Na]^+$ 289.0947, found 289.0944.

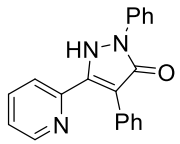
4-(3-Bromophenyl)-5-(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrazol-3-one 228



Ethyl 3-(4-methoxyphenyl)-3-oxo-2-propanoate (101 mg, 0.267 mmol) was dissolved in acetic acid (0.5 mL). Hydrazine hydrate (26 µL, 0.334 mmol) was added at room temperature and then mixture was stirred at reflux for 3 hours. The reaction mixture was cooled to room temperature, poured onto $NaHCO_3$ (5 mL), extracted with EtOAc (3 x10 mL), washed with brine (10 mL), dried

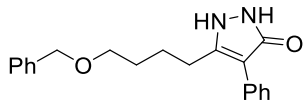
(Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel chromatography, R_f 0.28 (98:2, EtOAc:MeOH). Recovered 91 mg (99 %) as a white solid. mp. 208-210 °C; υ_{max} (ATR)/cm^{-1} 3308, 2972, 2942, 2840, 2586, 1600, 1518, 1497, 1468, 1417, 1380, 1283, 1254, 1232, 1175, 10901076, 1031, 996, 939, 894, 802, 782, 747, 723, 686, 661, 642, 631; ^{1}H NMR (400 MHz, DMSO) δ 12.01 (1H, s, N*H*), 10.17 (1H, s, N*H*), 7.47 (1H, dd, J 2.3, 1.3, Ar*H*), 7.35 – 7.32 (1H, m, Ar*H*), 7.31 – 7.26 (2H, m, Ar*H*), 7.25 – 7.17 (2H, m, Ar*H*), 6.98 (2H, d, J 8.6, Ar*H*), 3.78 (3H, s, CH_3); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 159.8 (C), 140.4 (C), 136.0 (C), 131.9 (C), 131.2 (CH), 130.6 (CH), 129.5 (CH), 128.4 (CH), 127.7 (CH), 123.0 (C), 121.9 (C), 114.7 (CH), 101.1 (C), 55.7 (CH_3); MS (ESI^+) calcd. for $C_{16}H_{14}BrN_2O_2$ [M+H^+]: 345.0233, found 345.0229.

2,4-Diphenyl-5-(pyridine-2-yl)-1,2-dihydro-3*H*-pyrazol-one 229



Ethyl 3-oxo-2-phenyl-3-(pyridine-2-yl)propanoate (131 mg, 0.486 mmol) was dissolved in acetic acid (0.6 mL). Phenyl hydrazine (67 μL, 0.608 mmol) was added at room temperature and then mixture was stirred at reflux for 45 minutes. The reaction mixture was cooled to room temperature, poured onto cold water (6 mL), extracted with EtOAc (3 x 40 mL), washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Residue was purified by silica gel chromatography, R_f 0.25 (EtOAc). Recovered 60 mg (39 %) as an orange solid. mp. 76-78 °C; υ_{max} (ATR)/cm^{-1} 3282, 3230, 3010, 2938, 1641, 1593, 1545, 1493, 1373, 1303, 1237, 1177, 1153, 999, 888, 864, 790, 753, 713, 691, 655, 613, 562; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (1H, s, N*H*), 8.54 – 8.37 (1H, m, Ar*H*), 7.87 – 7.77 (3H, m, Ar*H*), 7.71 – 7.66 (1H, m, Ar*H*), 7.53 (2H, t, *J* 7.9, Ar*H*), 7.38 – 7.28 (6H, m, Ar*H*), 7.23 (1H, dt, *J* 8.7, 4.2, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (C), 149.6 (C), 149.3 (CH), 137.4 (C), 136.6 (CH), 129.7 (CH), 129.4 (CH), 129.1 (CH), 128.4 (CH), 127.9 (C), 126.1 (CH), 123.9 (CH), 123.2 (CH), 120.9 (CH), 120.3 (C), 108.7 (C); MS (ESI^+) calcd. for $C_{20}H_{15}N_3ONa$ $[M+Na]^+$ 336.1107, found 336.1108.

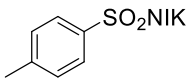
5-(4-(Benzyloxy)butyl)-4-phenyl-1,2-dihydro-3*H*-pyrazol-3-one 230



Ethyl 7-(benzyloxy)-3-oxo-2-phenylheptanoate (71 mg, 0.208 mmol) was dissolved in acetic acid (0.5 mL). Hydrazine hydrate (21 µL, 0.261 mmol) was added at room temperature and then mixture was stirred at reflux for 3 hours. The reaction mixture was cooled to room temperature, poured onto $NaHCO_3$ (5 mL), extracted with EtOAc (3 x10 mL), washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallised from aqueous EtOH. Recovered 48 mg (75 %) as a white solid. mp. 86-88 °C; υ_{max} (ATR)/cm^{-1} 3027, 2922, 2854, 2710, 1732, 1599, 1509, 1494, 1432, 1360, 1328, 1293, 1274, 1257, 1226, 1207, 1180, 1089, 1031, 911, 764, 732, 694, 663; ^{1}H NMR (400 MHz, DMSO) δ 11.44 (1H, s, N*H*), 9.81 (1H, s, N*H*), 7.41 – 7.19 (10H, m, Ar*H*), 4.37 (2H, s, C*H*$_2$), 3.38 (2H, t, *J* 6.1, C*H*$_2$), 2.74 – 2.66 (2H, m, C*H*$_2$), 1.89 – 1.74 (2H, m, C*H*$_2$), 1.21 – 1.06 (2H, m, C*H*$_2$); ^{13}C NMR (101 MHz, DMSO) δ 172.2 (C), 140.3 (C), 134.9 (C), 128.8 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 126.3(C), 125.6 (CH), 103.0 (C), 72.4 (CH_2), 69.5 (CH_2), 29.0 (CH_2), 22.7 (CH_2), 14.6 (CH_2); MS (ESI$^+$) calcd. for $C_{20}H_{23}N_2O_2$ $[M+H]^+$ 323.1760, found 323.1763.

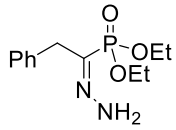
7.9. Preparation of diazophosphonates

Potassium *N*-iodo *p*-toluenesulphonamide (Iodamine-T, TsNIK)



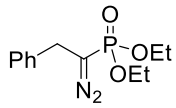
Reagent was prepared by Kyran Whymark, who followed the literature procedure.[158]

Diethyl (E/Z)-(1-hydrazineylidene-2-phenylethyl)phosphonate



Triethyl phosphite (1.70 mL, 10.0 mmol) was added dropwise to phenyl acetyl chloride (1.33 mL, 10.0 mmol) at 0 °C. Reaction was stirred at room temperature for 1 h before diluting with EtOH (10 mL). Then the keto-phosphonate solution was added dropwise to a solution of hydrazine hydrate (610 µL, 10.0 mmol) in EtOH:AcOH (10:1, 11 mL) at 0 °C. Then stirred for 2 h at room temperature. The reaction mixture was poured onto cold water (20 mL), extracted with DCM (3 x 20 mL), dried (Na_2SO_4) and then concentrated under reduced pressure. Purified by column chromatography, R_f 0.19 (pent:EtOAc, 2:8). Recovered diethyl (E)-(1-hydrazineylidene-2-phenylethyl)phosphonate 789 mg (29 %) as a pale-yellow oil, which was used in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.13 (5H, m, Ar*H*), 6.03 (2H, br. s., N*H*$_2$), 4.27 – 4.08 (4H, m, C*H*$_2$), 3.80 (2H, d, *J* 11.7, C*H*$_2$), 1.34 (1H, t, *J* 7.0,); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (d, $J_{(C\text{-}P)}$ 235.7, CN), 134.6 (d, $J_{(C\text{-}P)}$ 3.7, C), 129.0 (CH), 128.2 (CH), 127.0 (CH), 62.53 (d, $J_{(C\text{-}P)}$ 6.1, CH_2), 32.67 (d, $J_{(C\text{-}P)}$ 22.3, CH_2), 16.34 (d, *J* 6.3, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 12.13 (m). Spectroscopic data are in accordance with the literature.[158]

Diethyl (1-diazo-2-phenylethyl)phosphonate 232



Diethyl (E)-(1-hydrazineylidene-2-phenylethyl)phosphonate (530 mg, 1.96 mmol) and TsNIK (789 mg, 2.35 mmol) in THF (10 mL). 1 M KOH (2 mL) was slowly added to the stirring suspension and stirred at rt. After 1.5 h the reaction mixture was diluted with KOH (20 mL) and extracted with ether (3 x 20 mL). The combined organic extracts were washed with KOH (20 mL), brine (30 mL) then dried (Na_2SO_4) and concentrated under reduced pressure to give **6a** 409 mg (78 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (5H, m, Ar*H*), 4.25 – 3.88 (4H, m, OC*H*$_2$), 3.47 (2H, d, *J* 9.9, C*H*$_2$), 1.32 (6H, t, *J* 7.1, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4 (d, $J_{(C\text{-}P)}$ 3.5, C), 128.8 (CH), 128.4 (CH), 127.2 (CH), 62.5 (CH_2, d,

$J_{(C\text{-}P)}$ 5.6, CH_2), 41.8 (d, $J_{(C\text{-}P)}$ 233.0, CN), 30.2 (d, $J_{(C\text{-}P)}$ 8.6, CH_2), 16.2 (d, J 6.7, CH_3); MS (ESI^+) calcd. for $C_{12}H_{18}N_2O_3P$ $[M+H]^+$ 269.1050, found 269.1048. Spectroscopic data are in accordance with literature.[158]

Triethyl phosphite (857 µL, 5.00 mmol) was added dropwise to phenyl acetyl chloride (661 µL, 5.00 mmol) at 0 °C. Reaction was stirred at room temperature for 2 h, then diluted with EtOH (5 mL) and added dropwise to a solution of hydrazine hydrate (310 µL, 5.00 mmol) in EtOH:AcOH (10:1, 5.5 mL) at 0 °C. Then stirred for 3 days at room temperature. The reaction mixture was poured onto cold water (20 mL), extracted with DCM (3 x 20 mL), dried (Na_2SO_4) and then concentrated under reduced pressure to give the crude hydrazone.

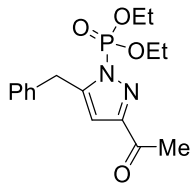
The crude hydrazone was dissolved in THF (20 mL) and TSNIK (1.84 g, 5.00 mmol) added. 1 M KOH (5 mL) was added dropwise at 0 °C and then stirred at rt for 1.5 h. The reaction mixture was diluted with 1 M KOH (20 mL), extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purified by flash column chromatography R_f 0.32 (1:1 Pent:EtOAc). Recovered 610 mg (46 %) as a yellow oil. Spectroscopic data identical to previous.

7.10. Pyrazoles procedures and assignments

General procedure for pyrazole synthesis

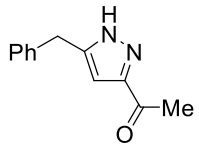
The alkyne (0.550 mmol) in toluene (1 mL) was added to diethyl (1-diazo-2-phenylethyl)phosphonate **140** (134 mg, 0.500 mmol) at room temperature, and the mixture stirred at reflux for 0.75 - 4 h. The reaction was concentrated under reduced pressure, dissolved in MeOH (1 mL) and NaOH (20 mg, 0.5 mmol) in water (0.4 mL) was added. Then stirred at rt for 2 hr and poured into cold water (10 mL), extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography gave the NH pyrazole.

Diethyl (3-acetyl-5-benzyl-1*H*-pyrazol-1-yl)phosphonate 233a



3-Butyn-2-one (43 µL, 0.550 mmol) in DCM (1 mL) was added to **140** (134 mg, 0.500 mmol) at room temperature, and the mixture stirred at reflux for 20 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification by column chromatography, R_f 0.33 (pent:EtOAc, 7:3). Recovered 97 mg (58 %) as a yellow oil. υ_{max} (ATR)/cm^{-1} 3219, 3142 ,2987 ,2914, 1682, 1604, 1572, 1454, 1401, 1371, 1354, 1163, 1100, 1026, 978, 943, 814, 754, 719, 696, 611, 509; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.23 (5 H, m, Ar*H*), 6.46 (1H, d, *J* 3.7, C^4*H*), 4.31 (2H, s, C*H*$_2$), 4.28-4.12 (4H, m, C*H*$_2$), 2.59 (3H, s, C(O)C*H*$_3$) , 1.33 (3H, td, *J* 7.1, 1.1, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2 (C), 154.8 (d, $J_{(C\text{-}P)}$ 12.4, C), 151.8 (d, $J_{(C\text{-}P)}$ 12.7, C), 137.4 (C), 129.1 (CH), 128.6 (CH), 126.9 (CH), 108.2 (d, $J_{(C\text{-}P)}$ 7.3, C^{4}H), 65.7 (d, $J_{(C\text{-}P)}$ 6.3, CH_2), 32.9 (CH_2), 26.3 (CH_3), 15.9 (d, $J_{(C\text{-}P)}$ 6.8, CH_3); MS (ESI$^+$): calcd. for $C_{16}H_{21}N_2O_4P$ [M+Na]$^+$ 359.1131, found 359.1131.

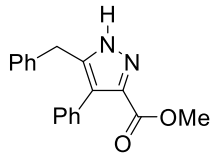
1-(5-Benzyl-1*H*-pyrazol-3-yl)ethan-1-one 234a



Following procedure. 3-Butyn-2-one (32 µL, 0.410 mmol) and diazo (100 mg, 0.373 mmol) were used and the reaction was stirred for 2 h. Purified by silica gel chromatography, R_f 0.26 (pent:EtOAc, 7:3). Recovered 62 mg (83 %) as a white solid. mp 72-74 °C; υ_{max} (ATR)/cm^{-1} 3221, 3137, 3114, 3060, 3032, 2994, 2926, 2848, 1669, 1570, 1477,1452, 1441, 1404, 1353, 1324, 1301, 1211, 1174, 1071, 1020, 990, 948, 903, 833, 804, 774, 720, 695, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (5H, m, Ar*H*), 6.60 (1H, s, C^4*H*), 4.08 (2H, s, C*H*$_2$), 2.54 (3H, s, C(O)C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6 (C), 148.6 (C), 147.3 (C), 137.9 (C), 128.9 (CH),

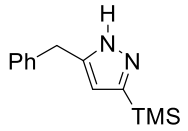
128.7 (CH), 126.9 (CH), 106.5 (C^4H), 33.2 (CH_2), 26.7 (CH_3); MS (ESI^+): calcd. for $C_{12}H_{12}N_2O$ $[M+H]^+$ 201.1022, found 201.1024.

Methyl 5-benzyl-4-phenyl-1*H*-pyrazole-3-carboxylate 234d



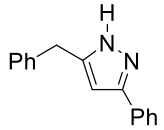
Following general procedure. Methyl 3-phenylpropiolate (148 mg, 0.927 mmol) and diazo (226 mg, 0.854 mmol) were used, and the reaction was stirred at reflux for 4 h. Purified by column chromatography, pent:Et_2O (1:1). Recovered 86 mg (35 %) as a white solid. υ_{max} (ATR)/cm^{-1} 3246, 3162, 3062, 3027, 2949, 1704, 1604, 1564, 1486, 1445, 1431, 1339, 1298, 1193, 1153, 1117, 1086, 1030, 985, 952, 864, 795, 694, 666, 619; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.55 (2H, m, Ar*H*), 7.43-7.39 (3H, m, Ar*H*), 7.36-7.24 (5H, m, Ar*H*), 4.3 (2H, s, C*H*$_2$), 3.73 (3H, s, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2 (C), 151.1 (C), 137.6 (C^3), 130.9 (CH), 130.2 (C), 129.0 (CH), 128.3 (CH), 128.7 (CH), 128.1 (CH), 126.8 (CH), 126.4 (C), 108.5 (C^4), 51.1 (OCH_3), 33.3 (CH_2); MS (ESI^+): calcd for $C_{18}H_{16}N_2O_2$ $[M+H]^+$ 293.1285, found 293.1288.

5-Benzyl-3-(trimethylsilyl)-1*H*-pyrazole 234e



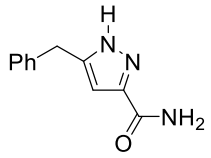
Following general procedure. Trimethylsilylacetylene (76 μL, 0.550 mmol) and **140** (134 mg, 0.500 mmol) were used, and the reaction was stirred at reflux for 4 h. Purified by column chromatography (7:3 pent:EtOAc). Recovered 18 mg (16%) as a white solid. mp 84-86 °C; υ_{max} (ATR)/cm^{-1} 3147, 3056, 2960, 2901, 2792, 1494, 1453, 1407, 1245, 1009, 837, 758, 714, 630; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.18 (5H, m, Ar*H*), 6.30 (1H, br. s., N*H*), 6.20 (1H, s, C^4H), 4.05 (2H, s, C*H*$_2$), 0.32 (9H, s, $SiMe_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (C), 144.5 (C), 139.6 (C), 128.8 (CH), 128.5 (CH), 126.3 (CH), 111.9 (C^4H), 34.0 (CH_2), -1.19 (CH_3): MS (ESI^+): calcd. for $C_{13}H_{19}N_2Si$ $[M+H]^+$ 231.1312, found 231.1317.

5-Benzyl-3-phenyl-1*H*-pyrazole 234f



Following general procedure. Phenyl acetylene (60 µL, 0.550 mmol) and **140** (134 mg, 0.500 mmol) were used, and the reaction was stirred at reflux for 4 h. Purified by column chromatography, R_f 0.59 (pent:EtOAc, 6:4). Recovered 34 mg (29%) as a white solid. mp 82-84 °C; υ_{max} (ATR)/cm^{-1} 3244, 3059, 3025, 2921, 1584, 1567, 1149, 1071, 1019, 960, 763, 715, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.61 (2H, m, Ar*H*), 7.48–7.20 (8H, m, Ar*H*), 6.39 (1H, s, C^4*H*), 4.07 (2H, s, C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2 (C), 147.4 (C), 138.5 (C), 132.0 (C), 128.76 (CH), 128.75 (CH), 128.7 (CH), 128.0 (CH), 126.7 (CH), 125.6 (CH), 102.1 (C^{4}H), 33.2 (CH_2); MS (ESI$^+$): calcd. for $C_{16}H_{14}N_2Na$ $[M+Na]^+$ 257.1049, found 257.1050.

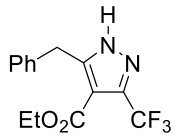
5-Benzyl-1*H*-pyrazole-3-carboxamide 234g



Propiolamide (37 mg, 0.530 mmol) in toluene (1 mL) was added to diethyl (1-diazo-2-phenylethyl)phosphonate **140** (130 mg, 0.485 mmol) at room temperature, and the mixture stirred at reflux for 3 h. The reaction was concentrated under reduced pressure, dissolved in MeOH (1 mL) and NaOH (20 mg, 0.500 mmol) in water (0.4 mL) was added. Then stirred at rt for 2 h and poured into cold water (10 mL), extracted with EtOAc (3 x 10 mL), dried (Na2SO4) and concentrated under reduced pressure. The crude material was triturated with Pent:Et_2O (1:1) to give 66 mg (68 %) as a white solid. mp 154-156 °C; υ_{max} (ATR)/cm^{-1} 3374, 3193, 3138, 3112, 3036, 2857, 1679, 1639, 1601, 1507, 1494, 1455, 1406, 1349, 1288, 1274, 1177, 1071, 993, 817, 783, 718, 660; ^{1}H NMR (400 MHz, CD_3OD) δ 7.36–7.24 (3H, m, Ar*H*), 7.27–7.19 (2H, m, Ar*H*), 6.51 (1H, s, C^4*H*), 4.04 (2H, s, C*H*$_2$); ^{13}C NMR (101 MHz, CD_3OD) δ 166.0 (C), 146.3 (C),

144.3 (C), 138.2 (C), 128.3 (CH), 128.2 (CH), 126.3 (CH), 104.3 (C^4H), 31.0 (CH_2); MS (ESI^+): calcd for $C_{11}H_{12}N_3O$ $[M+H]^+$ 202.0975, found 202.0976.

Ethyl 5-benzyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate 234h



Following general procedure. Ethyl 4,4,4-trifluorobut-2-ynoate (79 μL, 0.550 mmol) and **140** (134 mg, 0.500 mmol) were used, and the reaction was stirred at reflux for 0.75 h. Purified by column chromatography (9:1 pent:EtOAc). Recovered 88 mg (59 %) as a colourless oil. υ_{max} (ATR)/cm^{-1} 3200, 3031, 2983, 1708, 1604, 1571, 1498, 1475, 1370, 1132, 1095, 1001, 751, 719, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 10.53 (1H, s, N*H*), 7.47–7.11 (5H, m, Ar*H*), 4.38 (2H, s, C*H*$_2$), 4.36 (2H, q, *J* 7.2, OC*H*$_2$$CH_3$), 1.38 (3H, t, *J* 7.2, OCH_2C*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8 (C), 149.4 (C), 142.8 (q, $J_{(C\text{-}F)}$ 38, C^3), 135.5 (C), 129.1 (CH), 128.9 (CH), 127.5 (CH), 120.5 (q, $J_{(C\text{-}F)}$ 269.7, CF_3), 109.1 (C^4), 60.9 (OCH_2), 31.8 (CH_2), 13.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3; MS (ESI^+): calcd for $C_{14}H_{14}F_3N_2O_2$ $[M+H]^+$ 299.1002, found 299.1004.

8. Appendices

Appendix-A (PMI calculations)

PMI values (Ketone work, results and discussion) were calculated in Kg using the equation PMI=Total mass input (Kg)/Total mass product (Kg). PMI values from literature and reaction were calculated using the optimised conditions (for the synthesis of N-benzylbenzamide) and the data (Kg) is shown below

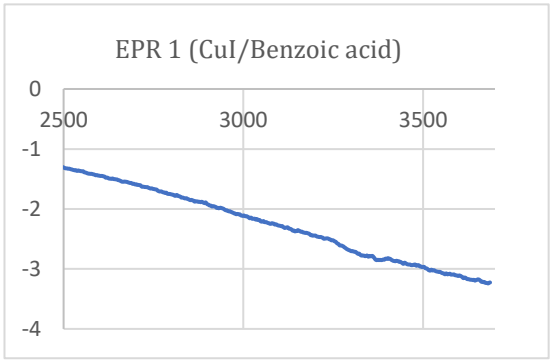
This work					
Start rxt	RMM	mmol	Amount (g)	Amount (Kg)	
CuI	190.45	0.05	0.0095225	9.5225E-06	
Benzoic acid	122.123	1.1	0.1343353	0.00013434	
Et3N	101.19	0.55	0.0556545	5.5655E-05	
Diethyl phosphite	137.09	1	0.13709	0.00013709	
Benzylamine	107.15	0.5	0.053575	5.3575E-05	
MeCN (1 mL)			0.786	0.000786	**Total mass rxt start (Kg)**
	Product				**0.001176177**
N-Benzylbenzamide	RMM	Amount (g)	**Amount (Kg)**		PMI
	211.26	0.0718284	**7.18284E-05**		16.37482249
Yield %					
68					

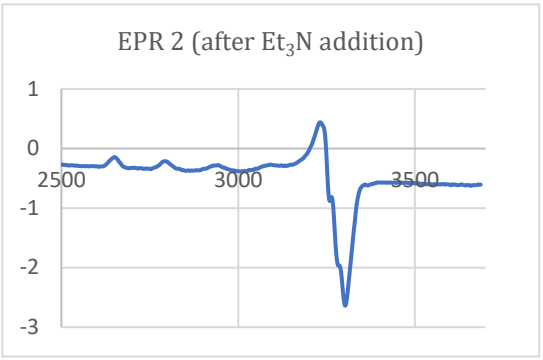
Oxalyl-Cl[66]				
Start rxt	rmm	mmol	amount g	amount Kg
Benzoic acid	122.12	5	0.6106	0.000611
Benzyl amine	107.15	5	0.53575	0.000536
Ph3O	278.3	5	1.3915	0.001392
MeCN			2.37	0.00237
oxalyl-Cl	126.93	6.5	0.825045	0.000825
Total start	total mass Kg			
Reagent	**0.005733**			
Mass Product	RMM	mmol	g	Total Kg
Product	211.26	4.54	0.96	**0.00096**
PMI				
5.971765625				

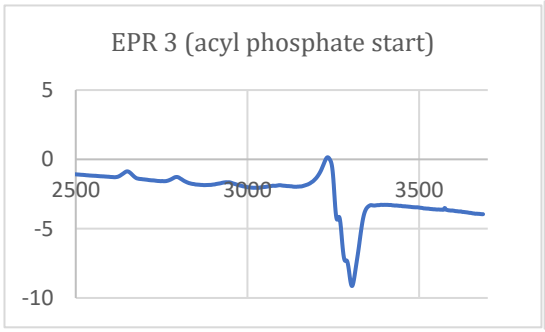
EDCI[67]				
Start rxt	rmm	mmol	amount g	amount Kg
Benzoic acid	122.12	4.8	0.586176	0.000586
DMF			37.76	0.03776
Benzyl amine	107.15	4	0.4286	0.000429
EDCI	155.245	4.8	0.745176	0.000745
HOBt	135.12	10	1.3512	0.001351
				0
Total start	total mass Kg			
Reagent	**0.040871152**			
Mass Product	RMM	mmol	g	Total Kg
Product	211.26	3.6	0.760536	**0.000761**
PMI				
53.73993079				

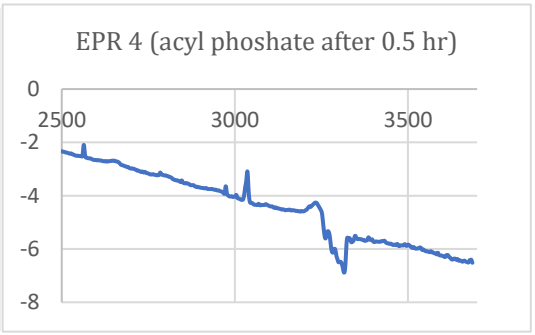
HBTU[68]				
Start rxt	rmm	mmol	amount g	amount Kg
Benzoic acid	122.12	14	1.70968	0.00171
Benzyl amine	107.15	9.3	0.984	0.000984
Et3N	101.19	18.7	1.892253	0.001892
MeCN			31.6	0.0316
HBTU	379.247	9.3	3.526997	0.003527
Total start	total mass Kg			
Reagent	**0.039713**			
Mass Product	RMM	mmol	g	Total Kg
Product	211.26	9	1.9	**0.0019**
PMI				
20.90154				

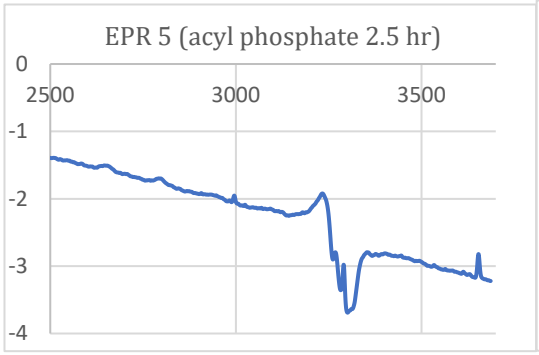
Appendix-B (EPR experiment)

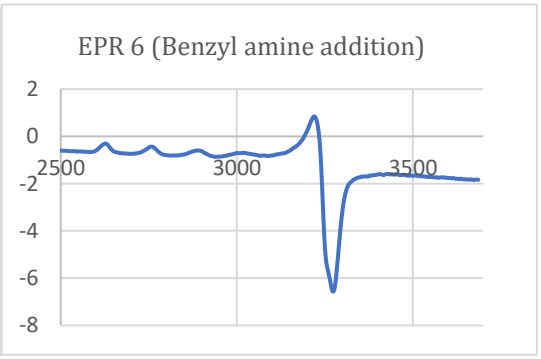












Appendix-C (PMI ketones)

PMI values (Ketone work, results and discussion) were calculated in Kg using the equation PMI=Total mass input (Kg)/Total mass product (Kg). PMI values from literature and reaction were calculated using the optimised conditions (for the synthesis of benzophenone) and the data (Kg) is shown below. Purification of Benzophenone was excluded assuming all crude materials can be purified in the same way.

Weinreb[98]

Weinreb	Acyl donor	Grignard	THF (Grignard)	THF (start)	Total mass input (Kg)
Yield 93 %	0.00016508	0.00054393	0.002667	0.00889	0.01226601
Mass product (Kg)					**PMI**
0.00016926					72.4684509

Caddick[72]

Caddick	Acyl donor	Grignard	THF (Grignard)	THF (start)	Total mass input (Kg)
Yield 73 %	0.00030814	0.000226638	0.00111125	0.00889	0.010536028
Mass product (Kg)					
0.000067					**PMI**
					157.2541418

Suzuki[110]

Suzuki	Acyl donor	nucleophile	Pd(Ac)	THF	PPh3	Total mass input (Kg)
Yield 92 %	0.0000258	0.000018289	0.000001	0.0013335	0.000004	0.001383
mass product						
0.000017					**PMI**	
					81.32876471	

Method 1 (this work)

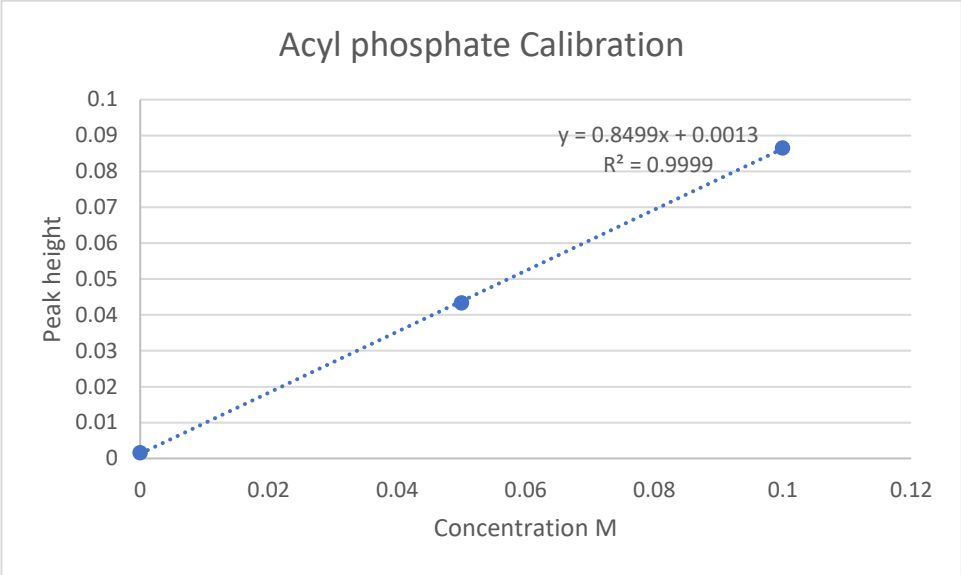
Method 1	Acyl donor	Grignard	THF (Grignard)	THF (Start)	Total mass Input (Kg)
Yield 80 %	0.00025806	0.00036262	0.001778	0.000889	0.00328768
Mass product Kg					
0.000145					**PMI**
					22.67365517

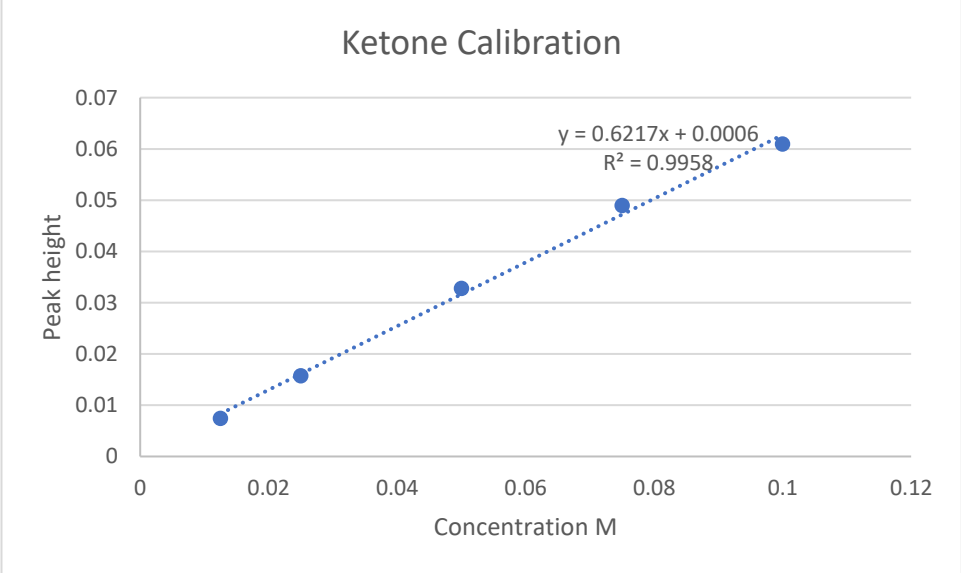
Method 2 (this work)

Method 1	Acyl donor	Grignard	THF (Grignard)	THF (Start)	Total mass input (Kg)
Yield 88 %	0.00025806	0.00019944	0.0009779	0.000889	0.00232440
Mass product (Kg)					
0.00016				**PMI**	14.52750625

Appendix-D (calibration graphs for ReactIR)

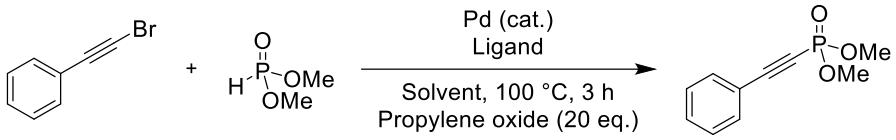
Calibrations graphs for ReactIR experiments.





Appendix-E

Addition work performed during my PhD which does not contribute to the main body of work is presented (below). The palladium-catalysed cross coupling of dialkylphosphites and secondary phosphine oxides has been investigated. A series of ligands and solvents were screened.

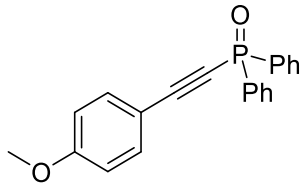


Entry	Catalyst (mol %)	Ligand (mol %)	Solvent	Yield[a] %
1	$Pd(OAc)_2$ (20)	TPP (40)	THF	61
2	$Pd(OAc)_2$ (20)	TFP (40)	THF	0[b] (86)[c]
3	$Pd(OAc)_2$ (20)	dppe (40)	THF	15
4	**$Pd(OAc)_2$ (20)**	**dppf (40)**	**THF**	**73**
5	$Pd(PPh_3)_4$ (20)	--	THF	0 (85)[c]
6	$Pd(OAc)_2$ (10)	dppf (40)	THF	59
7	$Pd(OAc)_2$ (10)	dppf (20)	THF	68
8	$Pd(OAc)_2$ (5)	dppf (40)	THF	28
9	$Pd(OAc)_2$ (5)	dppf (10)	THF	60 (23)[c]
10	$Pd(OAc)_2$ (20)	dppf (40)	Toluene	65
11	$Pd(OAc)_2$ (20)	dppf (40)	DMF	38

Table: *[a]Isolated yield. [b]Trace amounts of product observed in crude NMR. [c]Recovered starting material.*

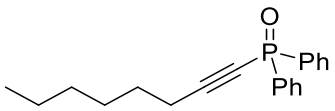
This route was also applied to the following secondary phosphine oxides. Typically, cross-coupling reactions for dialkyl phosphites or secondary phosphine oxides only really work for one or the other, however, the palladium catalysed method can couple both phosphine oxides and dialkyl phosphites.

[2-(4-methoxyphenyl)ethynyl]diphenylphosphine oxide



$Pd(OAc)_2$ (22 mg, 0.11 mmol) and dppf (111 mg, 0.20 mmol) were dissolved in THF (1 mL) and stirred at room temperature for 20 mins. (1-Bromoethynyl)-4-methoxybenzene (100 mg, 0.48 mmol), diphenyl phosphine oxide (97 mg, 0.48 mmol) and propylene oxide (672 μL, 9.6 0.48 mmol) were dissolved in THF (2 mL), and added to the catalyst mixture then stirred at 100 °C for 3 h. The reaction mixture was concentrated and purified *via* silica gel chromatography, R_f 0.22 (EtOAc:Petrol, 2:1). Recovered a pale-yellow oil that was triturated with pentane to produce a white solid, 108 mg (68 %). mp 110-112 ^{0}C. υ_{max} /cm^{-1} 3071, 3009, 2969, 2935, 2838, 2162, 1601, 1505, 1195. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.88 (4H, m, Ar*H*), 7.60-7.48 (8H, m, Ar*H*), 6.94 – 6.88 (2H, m, Ar*H*), 3.86 (3H, s, C*H*$_3$).^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5 (C), 134.4 (d, $J_{(C-P)}$ 2.3, CH), 133.3 (d, $J_{(C-P)}$ 122.0, C), 132.2 (d, $J_{(C-P)}$ 2.7, CH), 131.0 (d, *J* 11.4, CH), 128.6 (d, $J_{(C-P)}$ 13.2, CH), 114.3 (CH), 111.8 (d, $J_{(C-P)}$ 4.1, C), 106.2 (d, $J_{(C-P)}$ 30.9, C), 81.7 (d, $J_{(C-P)}$ 173.0, C), 55.5 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.25. HRMS (ESI) Calculated for $C_{21}H_{17}O_2PNa$ [M+Na]: expected 355.0858 found 355.0852.

(oct-1-yn-1-yl)diphenylphosphine oxide



$Pd(OAc)_2$ (22 mg, 0.10 mmol) and dppf (111 mg, 0.20 mmol) were dissolved in THF (1 mL) and stirred at room temperature for 20 mins. 1-Bromooct-1-yne (100 mg, 0.53 mmol), diphenyl phosphine oxide (107 mg, 0.53 mmol) and propylene oxide (743 μL, 10.6 mmol) were dissolved in THF (2 mL), and added to the catalyst mixture then stirred at 80 °C for 4 h. The reaction mixture was concentrated and purified *via* silica gel chromatography, R_f 0.27 (EtOAc:Petrol, 2:1). Recovered 90 mg (55 %) as a pale-yellow oil. υ_{max} /cm^{-1} 3056, 2927, 2857, 2190, 1482, 1204,1119. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (4H, dd, *J* 13.5, 7.1, Ar*H*), 7.58-7.43 (6H, m, Ar*H*), 2.47 (2H, td, *J* 7.1, 2.5, CH_2), 1.65 (2H, p, *J* 7.1, CH_2), 1.44 (2H, p, *J* 7.1, CH_2), 1.37 – 1.24 (4H, m, CH_2), 0.92 – 0.87 (3H, m, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.6 (d, $J_{(C-P)}$ 129.0, C), 132.0 (CH), 130.9 (d, $J_{(C-P)}$ 10.9, CH), 128.55 (d, $J_{(C-P)}$ 13.4, CH), 109.89 (d, $J_{(C-P)}$ 29.8, C), 75.00 (d, $J_{(C-P)}$ 178.0, C), 31.15 (CH_2), 28.54 (CH_2), 27.55 (CH_2), 22.47 (CH_2), 19.8 (CH_2), 14.0 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.57. HRMS (ESI) Calculated for $C_{20}H_{24}OP$ [M+H]: expected 311.1559 found 311.1565.

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