Palladium and Copper Mediated Cross Couplings Using Dialkylphosphites



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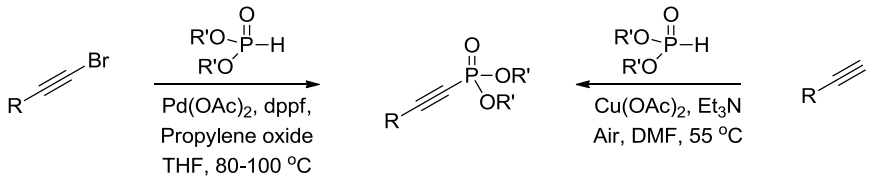
A thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

December 2013

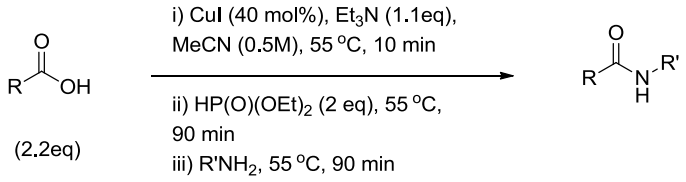
i. Abstract

Described herein are synthetic methodologies using palladium- and copper-mediated cross coupling reactions involving dialkylphosphites.

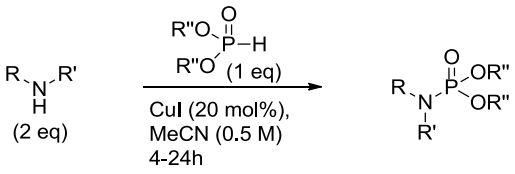
Chapter 1 discloses two methods for producing alknylphophonates. The first is a novel palladium mediated cross coupling of alkynylbromides with dialkylphosphites. The second is an improvement of a known[13] aerobic copper mediated cross coupling using terminal alkynes and dialkylphosphites.



Chapter 2 discloses a novel aerobic copper mediated amide synthesis method.



Chapter 3 discloses a novel aerobic copper mediated phosphoramidate synthesis method.



All of the above developed methodologies were found to produce their respective products in acceptable yields and tolerate a wide range of functionality.

The experimental section comprises the practical methods for effecting the above reactions and the experimental data for all of the compounds presented herein.

ii. Acknowledgements

First and foremost, I would like to thank Professor Chris Hayes, my supervisor, for his support over the past three years and contribution to the work performed during these studies.

I would also like to thank the Hayes group members, past and present, for their input throughout the years.

I would like to thank the analytical staff and service staff, without whom PhD studies would be significantly more challenging, if at all possible.

Finally, I would like to acknowledge the University of Nottingham and the EPSRC for funding.

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iii. Abbreviations

Abbreviation	Expansion
dppf	1,1'-bis(diphenylphosphino)ferrocene
DMTr	4,4'-Dimethoxytrityl
Ac	Acetyl
Bn	Benzyl
Bu	Butyl
Cbz	Carbobenzyloxy
DNA	Deoxyribonucleic Acid
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EWG	Electron withdrawing group
Et	Ethyl
EDTA	Ethylenediaminetetraacetic acid
HPLC	High performance liquid chromatography
^{i}Pr	Isopropyl
LiHMDS	Lithium bis(trimethylsilyl)amide
Me	Methyl
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
NMR	Nuclear magnetic resonance
Ph	Phenyl
RNA	Ribonucleic Acid

SM	Starting material
^{t}Bu	*tert*-Butyl
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
Boc	*tert*-Butyloxycarbonyl
THF	Tetrahydrofuran
TC	Thiophene-2-carboxylate
TFA	Trifluoroacetic Acid

1. Alkynylphosphonate synthesis

1.1. Introduction

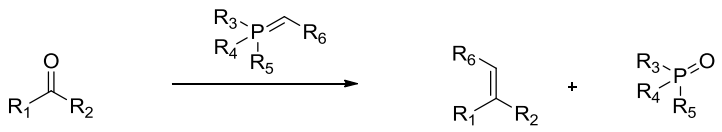
Compounds comprising phosphorus are of particular interest in the field of organic chemistry, with this interest continuing to expand in recent years. This is a direct result of developing applications for phosphorus compounds in numerous fields of synthetic chemistry, including the preparation of insecticides, agricultural chemicals, flame retardants, medicinal agents, reagents for olefination reactions, and chiral phosphorus ligands for stereospecific syntheses which utilise metal-based catalysis.

The recent expansion of the field of biochemistry, most likely through the development of greater computing power, has resulted in a more detailed understanding of the biological significance of biomolecules comprising phosphorus, most notably the nucleic acid polymers DNA and RNA. Improved understanding of the biochemistry of bio-systems inevitably leads to the development of systems designed to mimic and manipulate such systems for the purposes of biochemical probing and pharmaceutical progression.

Thus, there is clearly a great deal of chemical and biological potential associated with organophosphorus compounds. For this reason, it is necessary to continue to develop synthetic methods for producing such compounds.

1.1.1 Compounds comprising carbon-phosphorus bonds

A number of synthetically useful chemical transformations can be accomplished using compounds comprising at least one carbon-phosphorus bond. Of said transformations, the most utilised is the Wittig reaction (and the Horner-Wadsworth-Emmons variant) which produces olefins from keto-compounds using phosphorus ylide reagents (Scheme 1.1).[1]



Scheme 1.1 Cis or trans olefin can be selected through the use of an appropriate ylide.

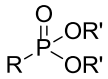
One of the major obstacles to extensively using compounds comprising carbon-phosphorus bonds in fine chemical synthesis is the production of such compounds. Classically, carbon-phosphorus bonds are formed by one of two means:

- Nucleophilic attack of a phosphorus(III) compound onto an electrophilic carbon; or
- Nucleophilic attack of a carbanionic species onto an electrophilic phosphorus(V) species.

Generally, such reactions will involve the use of an alkylhalide or a phosphoryl halide species, both of which are corrosive, toxic and generally incompatible with fine chemical synthesis. Engel *et al*. extensively review the classical methods for producing compounds comprising a C-P bond and as such is herein referred to in its entirety as a general guide to producing C-P bonds *via* classical methods.[2]

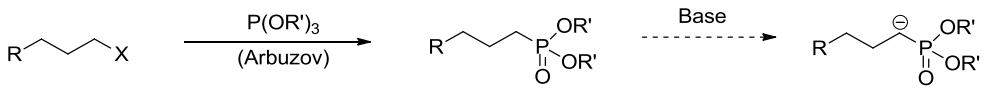
1.1.2 Organophosphonates

Of particular interest to us are organophosphonate compounds. These are compounds of the general formula depicted in scheme 1.2.



Scheme 1.2 R and R' represent a number of chemical groups, notably alkyl groups.

Organophosphonates are useful for synthetic transformations, such as the Horner-Wadsworth-Emmons olefination. However, our interest in organophosphonate compounds goes beyond simply using said moieties as functional group interconversion mediators; we are interested in highly functionalised organophosphonate compounds *per se*. It is fairly evident from scheme 1.3 that building complexity around an α-centre (to the phosphorus) would be an arduous challenge, and furthermore it would be borderline impossible to functionalise the β-position.



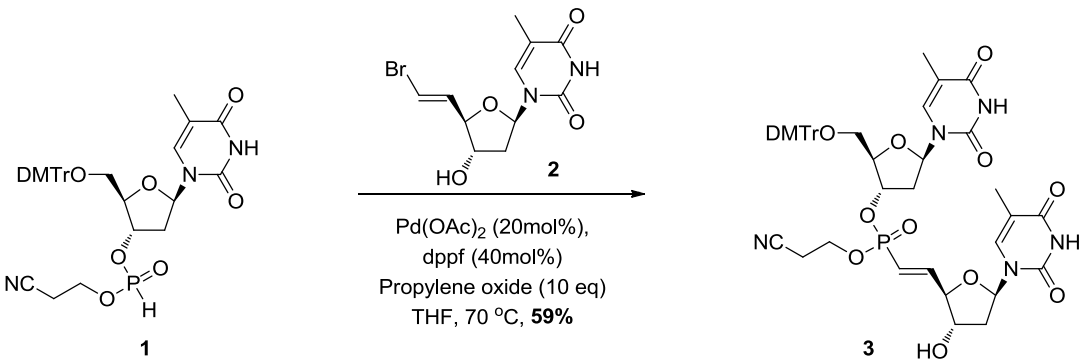
Scheme 1.3

Clearly, then, it would be of significant use if a more easily functionalized 'handle' could be used to increase the versatility and variability of both the α- and β- positions.

An alternative strategy towards producing highly functionalized organophosphonates is to use an α,β-unsaturated organophosphonate; manipulation of the α and β positions could be brought about *via* known transformations, for example hydroboration followed by metal-based cross coupling. However, synthesis of vinylphosphonates and alkynylphosphonates also classically suffer from requiring harsh reaction conditions, such as corrosive reagents and forcing conditions.[2,3]

More recent approaches toward forming α,β-unsaturated organophosphonates, particularly toward aryl and vinylphosphonates, have resulted in the development of milder carbon-phosphorus bond forming reaction conditions, such as metal mediated cross coupling reactions at lower temperatures.[4] These developments have proven to be

mild enough to allow the incorporation of carbon-phosphorus bonds into complex compounds. A particularly impressive metal-mediated synthesis of an α,β-unsaturated organophosphonate was performed within the Hayes group (scheme 1.4).[5]

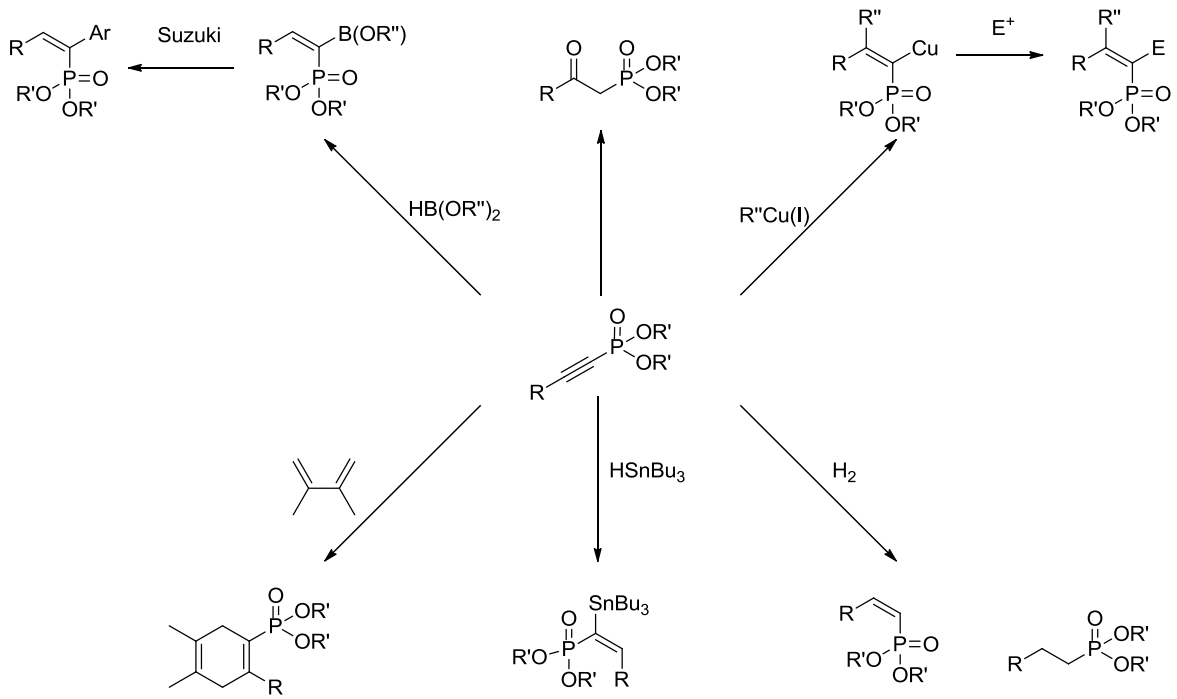


Scheme 1.4

However, one particular aspect pertaining to α,β-unsaturated organophosphonates which has remained relatively understudied, or may have been simply overlooked, is the synthesis of the alkynylphosphonate moiety. This is surprising as one would predict that the π-system in an alkynylphosphonate moiety would be of more synthetic value as a wider range of synthetic transformations exist for sp hybridised π-systems.

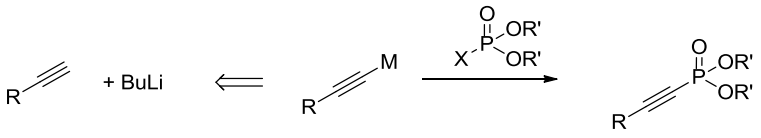
1.1.3 Alkynylphosphonates

Contrary to the above statement, there have been several syntheses of alkynylphosphontes (*via* classical methods) and manipulations thereof. Unsurprisingly, the alkynylphosphonate link has indeed been found to be a very versatile link, with high levels of substitution and functionalisation demonstrated in a wide range of systems (scheme 1.5).[6]



Scheme 1.5

The question which remains is thus: why has this highly manipulable moiety been sidelined in fine chemical synthesis? There may be a very simple answer for this – alkynylphosphonates are difficult to make. Synthesis of alkynylphosphonates typically requires a metallated alkyne (usually a lithiated terminal alkyne) and an electrophilic phosphorus(V) species (usually a P-X species, where X is a halogen) (scheme 1.6).[3]

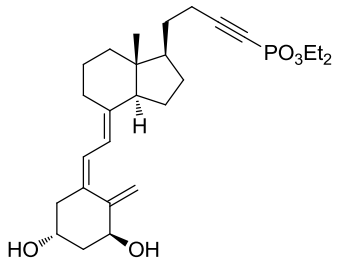


Scheme 1.6

The use of strong bases and corrosive reagents is generally avoided as far as practicably possible in fine chemical synthesis on the grounds that they can result in numerous

unwanted side reactions and can damage (expensive) equipment. Thus, developing a mild method for synthesising alkynylphosphonates would negate such a prejudice toward the use of this moiety and could foretell the emergence of a wider range of complex synthetic phosphonate-containing compounds.

Furthermore, the alkynylphosphonate link itself may prove to be an effective pharmaceutical bioisostere and/or efficacious moiety in the active sites in enzymes. To date, we are aware of only one medicinal chemistry compound, a calcitrol analogue, comprising an alkynylphosphonate link (scheme 1.7).[7]

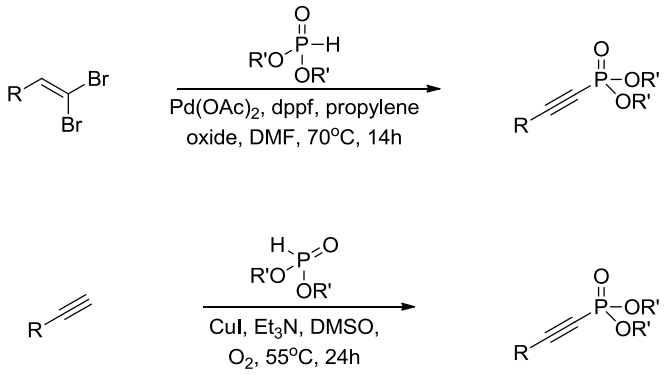


4

Scheme 1.7

The alkynylphosphonate link was found to improve the pharmacodynamics and pharmacokinetics of **4**; the alkyne link reduced metabolic activation (improving bioavailability) and the phosphonate lowered calcemic properties of the compound (demonstrating improved biological activity). Thus, the alkynylphosphonate moiety could yet prove to be a highly useful tool in the medicinal chemist's toolkit and as such requires the development of mild methods for synthesising this moiety.

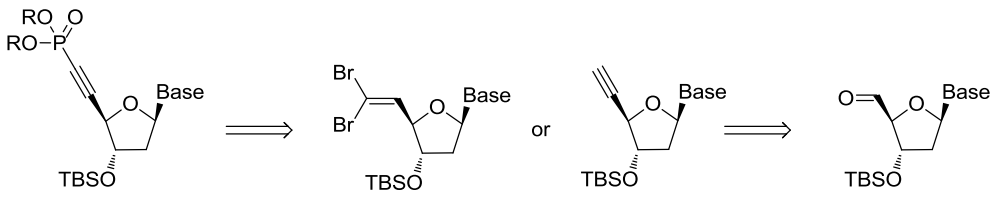
We are aware of two mild methods for synthesising alkynylphosphonates: a palladium mediated coupling of a 1,1-vinyldibromide with dialkylphosphites[8] and a copper mediated coupling of a terminal alkyne with dialkylphosphites[9] (scheme 1.8). Both of these reactions form the basis of this thesis.



Scheme 1.8

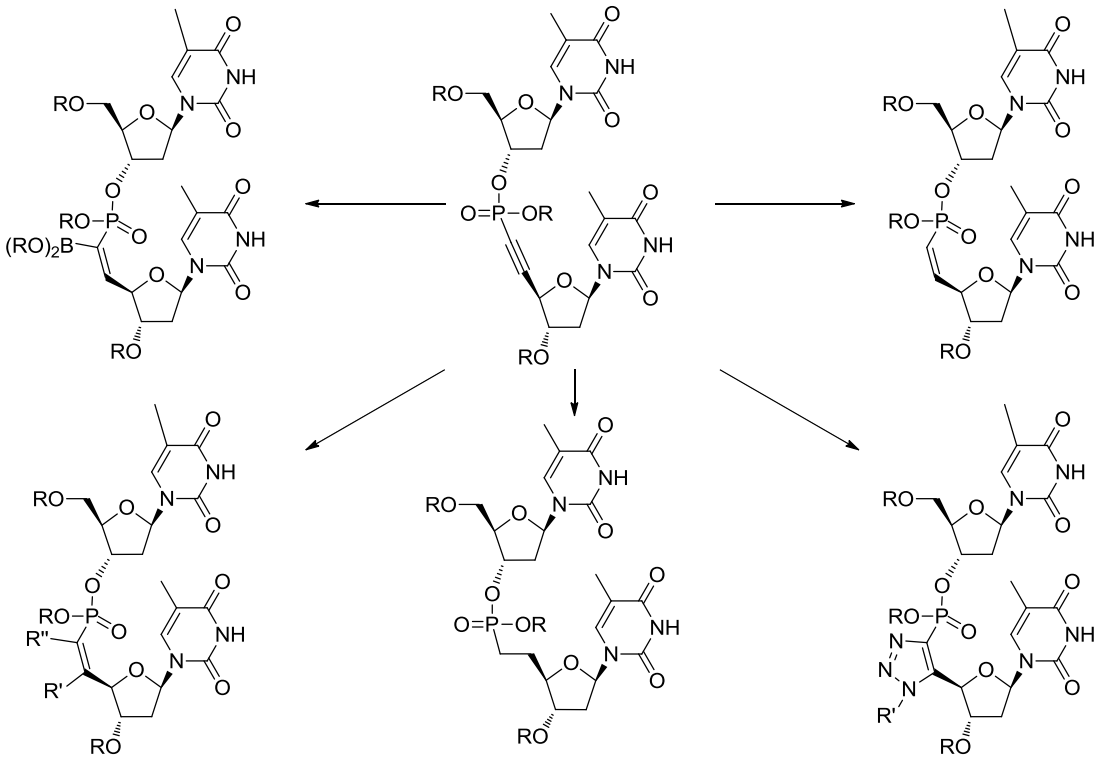
1.2 Aims and Objectives

The initial aim of this study was to synthesise a nucleoside comprising an alkynylphosphonate moiety through optimisation of one of the abovementioned literature methods.



Scheme 1.9

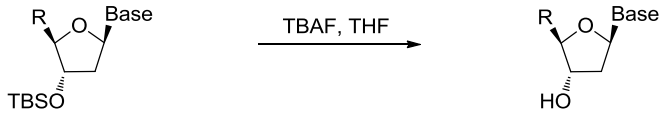
Our ultimate goal was to successfully synthesise an alkynylphosphonate linked dinucleotide, with the aim of both incorporating the dinucleotide into an oligonucleotide for biological evaluation and further manipulating the alkynylphosphonate link.



Scheme 1.10

1.3 Results and Discussion - Pd mediated cross coupling

Although the palladium mediated cross coupling to form an alkynylphosphonate linked dinucleotide had already been accomplished previously,[8] the 3' OH was protected with a TBDPS protecting group which was found to be irremovable under any standard conditions. To incorporate the dinucleotide into an oligonucleotide it would be imperative that the protecting group could be removed, thus we aimed to synthesise a dinucleotide with a more labile 3' protecting group. We were aware that, from analogous studies within the group, a TBS protecting group could be readily removed under fluoride deprotection conditions (scheme 1.11).

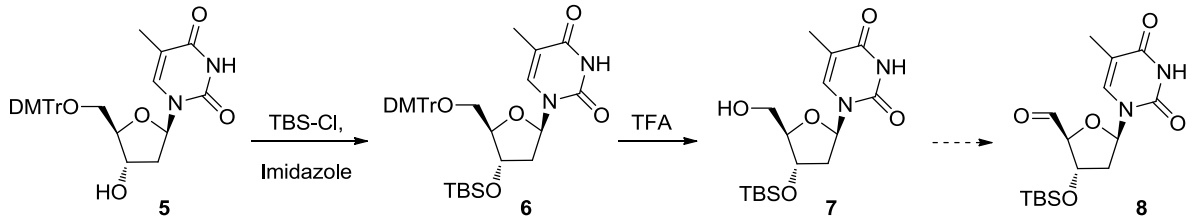


Scheme 1.11.

As such, our initial studies were towards synthesising a 3' TBS protected alkynylphosphonate linked dinucleotide.

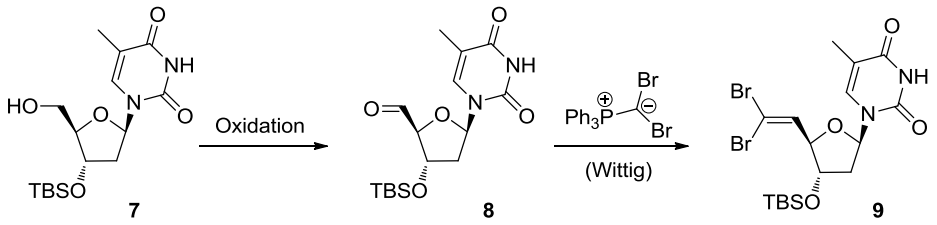
1.3.1 Precursor synthesis

Our proposed synthetic route passed through the 5' dehydro nucleotide **8**. Synthesis of the precursor alcohol **7** had been performed within the group previously using a protection and deprotection strategy (scheme 1.12).



Scheme 1.12

These reactions generally proceeded in high yields (70% - quantitative). However, transformation of alcohol **7** into vinyldibromide **9** proved to be far more challenging than initially expected (scheme 1.13).



7 **8** **9**

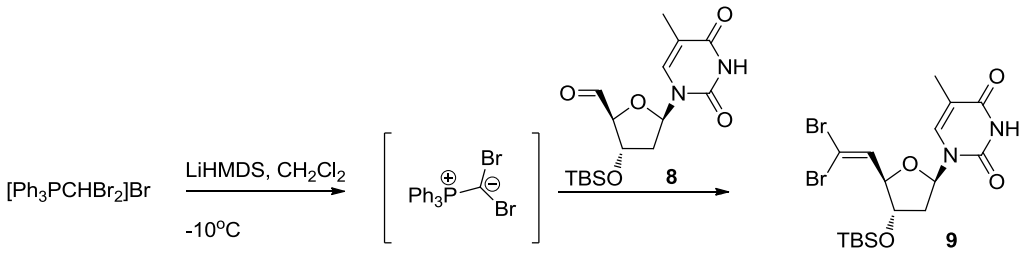
Scheme 1.13

A number of oxidation methods were used to produce aldehyde **8**. The most effective methods for forming **8** were found to be through the use of the Dess-Martin reagent or by performing a Moffat oxidation. However, any attempts to purify aldehyde **8** other than aqueous washing resulted in significant levels of decomposition. Thus, aldehyde **8** had to be progressed through to the next stage of the synthesis as a crude material.

Progressing aldehyde **8** to the next stage as a crude material proved to be a problem as it was not possible to dry the aldehyde to a completely anhydrous state (as determined by the persistent presence of a water peak in the ^{1}H NMR of the crude material). The Wittig reagent used in the next step was an unstabilised ylide, which was found to be unstable in the presence of water, thus optimisation of the Wittig reaction was required in order to produce the desired vinyldibromide **9**.

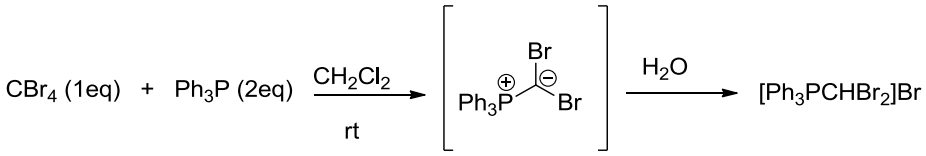
1.3.2 Forming the vinyldibromide

Our starting point was a synthesis previously used within the group, which formed the required ylide by deprotonating the precursor Wittig salt with a base (scheme 1.14).



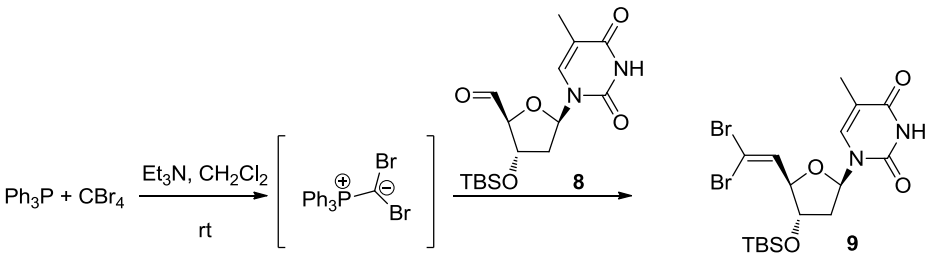
Scheme 1.14

As expected, results were somewhat capricious, yielding vinyldibromide **9** in a range of yields (29-51%); the quantity of water carried through by the crude aldehyde could not be controlled, thus the result was an unpredictable reaction. In addition to the reaction being capricious, the formation of the Wittig salt $[Ph_3PCHBr_2]Br$ was not trivial and as such required optimisation. Through trial and error with equivalents and reaction times we developed a solid, reproducible and scalable (up to ~8g) synthesis of the salt (scheme 1.15). Reacting Ph_3P with CBr_4 for 75-85 minutes before quenching with water produced $[Ph_3PCHBr_2]Br$ in excellent yields (84-98%).



Scheme 1.15

We were still dissatisfied with this synthesis on the ground that the vinyldibromide intermediate **9** would be a key reagent, thus it was unacceptable for the synthetic step which produced **9** to be low yielding and unpredictable. Fortunately, a further search of the available literature revealed a modified version of the Ramirez synthesis of vinyldibromides (scheme 1.16).[10]



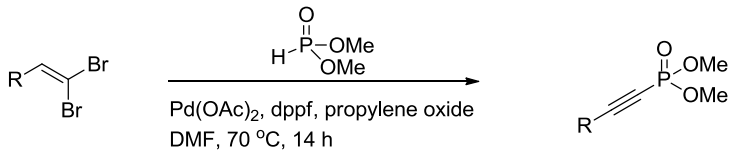
Scheme 1.16

This method was still rather capricious (as expected), however the yield of desired vinyldibromide **9** was consistently higher (55-82%). Furthermore, performing this reaction in the absence of light improved the reliability of this reaction, suggesting that at least one of the intermediates is sensitive to light. Due to the ease and general reliability of this method all further syntheses of vinyldibromides were performed under these reaction conditions.

1.3.3 Formation of Alkynylphosphonates

With the problematic synthesis of vinyldibromides somewhat resolved our focus was directed toward synthesising alkynylphosphonates. The first objective was to determine whether the 3'-TBS-5'-(1,1-dibromovinyl)nucleotide **9** would survive the literature coupling conditions. Initial studies utilised dimethyl phosphite as the coupling partner as it was known to couple effectively under the literature conditions.[8] This ensured that **9** was the only variable under scrutiny. Synthesis of **11** from **9** was found to be unpredictable, with yields ranging from 20-46% (Table 1.1, entry 1). This was attributed to the significantly acidic conditions which develop during the course of the reaction (2 molar equivalents of HBr are lost during the course of the reaction and propylene oxide is a relatively poor acid scavenger) causing deprotection of the TBS group. This hypothesis was somewhat corroborated by finding that replacing the TBS group with the more acid

stable TBDPS group increased the reliability of the reaction (consistently 46±5%, Table 1.1, entry 2). (Precursor **10** was independently synthesised through known methods[8] and subjected to identical coupling conditions).



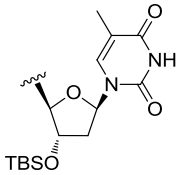
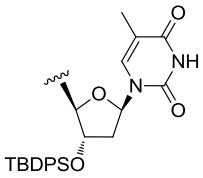
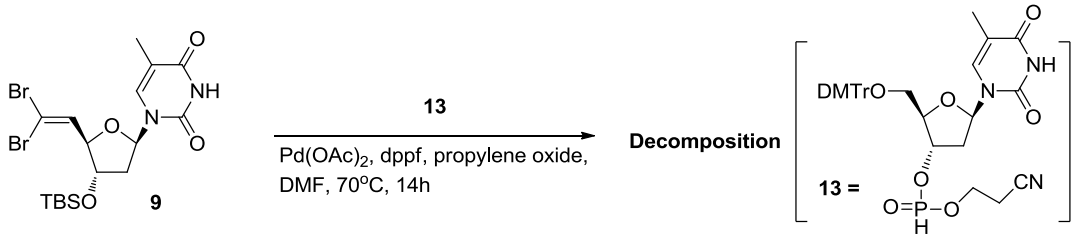
Entry	SM	R	Product	Yield (%)
1	**9**		**11**	20 - 46
2	**10**		**12**	46

Table 1.1. Reagents and conditions: vinydilbromide (1 eq), *H*-phosphonate (1.1 eq), $Pd(OAc)_2$ (0.2 eq), dppf (0.4 eq), propylene oxide (20 eq), DMF (0.5 M).

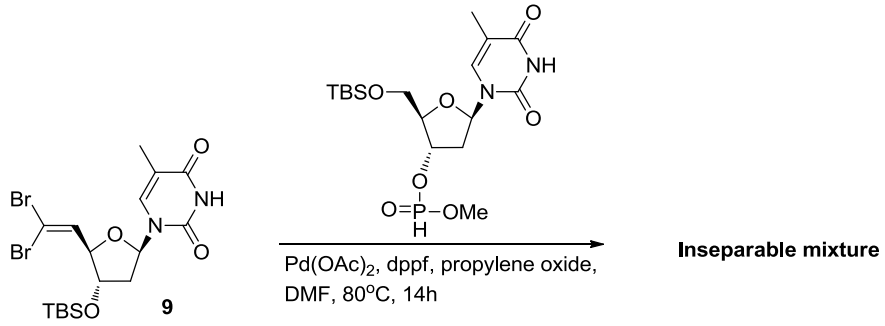
1.3.4 Towards an alkynylphosphonate linked dinucleotide

Regardless of the fact that the synthesis of alkynylphosphophosphonate **11** was capricious, we had successfully demonstrated that it was possible to form the desired link to some extent with the desired protecting group. As such, a test reaction toward the alkynylphosphonate linked dinucleotide was attempted (scheme 1.17).



Scheme 1.17 Compound **13** synthesised *via* known method.[5]

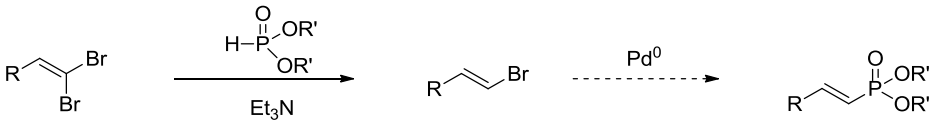
Following the hypothesis that the conditions become increasingly acidic during the course of the reaction, it is not particularly surprising that this reaction failed; the dimethoxytrityl group is incredibly acid sensitive and it is possible that the cyanoethyl protecting group falls off also. We reverted to the nucleotide phosphite which was used in the literature example (scheme 1.18),[8] in a last-ditch effort to produce a 3'-TBS protected dinucleotide. The desired alkynylphosphonate was detected (mass spectrometry & ^{31}P NMR), but isolation of the pure product proved to be impossible (scheme 1.18).



Scheme 1.18

1.3.5 Acid scavenging

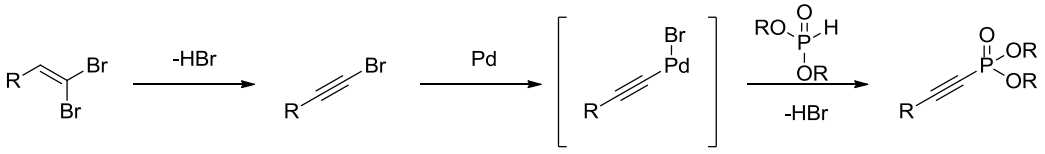
It was apparent that the problem associated with this method is poor acid scavenging. An obvious solution would have been to use a better base, i.e. an amine base. However, previous work within the group had already found that in the presence of an amine and a dialkylphosphite the vinyl-1,1-dibromide predominantly reduces to a trans-vinylbromide (scheme 1.19).



Scheme 1.19

1.4 Pd mediated synthesis - alkynylphosphonates from alkynylbromides

At this stage it was evident that a new synthetic strategy was required. As it was apparent that acid scavenging was a significant issue, we proposed that reducing the number of equivalents of acid produced *in situ* from two to one by deliberately removing one equivalent of HBr prior to coupling should reduce the overall acidity of the reaction and therefore improve the general applicability of the method (scheme 1.20).



Scheme 1.20

This new strategy posed two new problems:

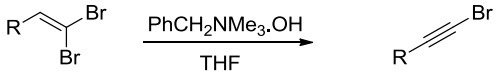
1. How to form the alkynylbromide, bearing in mind the effort required to form the vinyl-1,1-dibromide; and
2. What reaction conditions are necessary for optimal cross coupling and/or what conditions are tolerated – for example, can an amine base be used?

1.4.1 Synthesis of the alkynylbromide

Fortunately, the synthesis of alkynylbromides proved to be somewhat facile. After a thorough search of the literature it became apparent that two general strategies were employed for synthesising alkynylbromides. The first involved base mediated elimination of HBr from a vinyl-1,1-dibromide to form the alkynylbromide and the second involved bromination of a terminal alkyne.

Of these two general approaches, two specific literature preparations[11,12] were found to supersede all of the others.

Elimination of HBr from vinyl-1,1-dibromides using benzyltrimethylammonium hydroxide successfully produced a wide range of alkynylbromides in good to excellent yields (Table 1.2).[11]



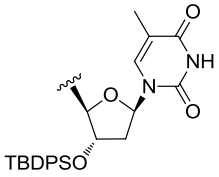
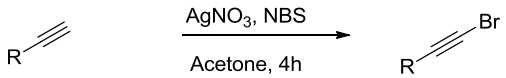
Entry	R	Product	Time (h)	Yield (%)
1	4-OMe-Ph	**14**	18	77
2	4-CN-Ph	**15**	2	67
3	Cyclohexyl	**16**	72	83
4	$Ph(CH_2)_2$	**17**	18	80
5	2-pyridyl	**18**	2	47
6		**19**	18	61

Table 1.2 Reagents and conditions: Vinyl dibromide (1 eq), benzyltrimethylammonium (2 eq, 40% w/w in MeOH), THF.

Similarly, bromination of terminal alkynes using silver nitrate (a silver acetylide is formed *in situ*) and N-bromosuccinimide (electrophilic bromine) produced a wide range of alkynylbromides in good to excellent yields (Table 1.3).[12]

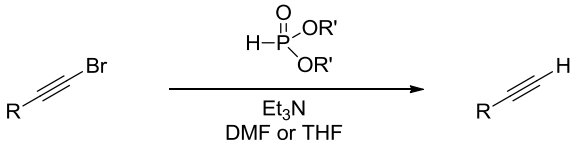


Entry	Terminal Alkyne	Product	Yield (%)
1	Phenylacetylene	**20**	71
2	1-Octyne	**21**	58
3	Methyl but-3-ynoate	**22**	82
4	5-Chloro-1-pentyne	**23**	55
5	1-Ethynylcyclohex-1-ene	**24**	66
6	5-TBSO-1-pentyne	**25**	93
7	5-TBDPSO-1-pentyne	**26**	71
8	5-AcO-1-pentyne	**27**	87

Table 1.3 Reagents and conditions: NBS (2 eq) and $AgNO_3$ (0.5 eq) in acetone.

1.4.2 Cross coupling conditions

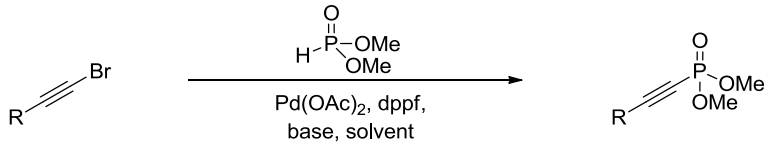
The primary purpose of using alkynylbromides was to lower the acidity of the cross coupling reaction mixture. We also hoped that the alkynylbromide species would be compatible with the amine base and dialkylphosphite combination. Unfortunately this was found not to be the case, as in the presence of Et_3N and a dialkylphosphite the alkynylbromide species was reduced, forming the corresponding terminal alkyne (scheme 1.21).



Scheme 1.21

1.4.3 Reaction optimisation

To determine the optimal cross coupling conditions the catalyst and ligand combination disclosed in the previous alkynylphosphonate synthesis[8] was used and the remaining variables were screened. Table 1.4 lists the key reactions for determining the optimal conditions.



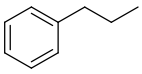
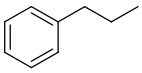
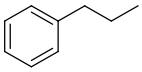
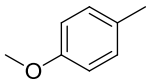
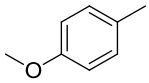
Entry	SM	R	Temp (°C)	Proton Scavenger	Solvent	Time (h)	Product	Yield (%)[a]
1	**17**		70	epoxyhexane	THF	3	**28**	18
2	**17**		70	epoxyhexane	THF	18	**28**	52
3	**17**		100	propylene oxide	THF	4	**28**	67
4	**14**		70	epoxyhexane	DMF	3	**29**	75
5	**14**		70	propylene oxide	THF	3	**29**	70

Table 1.4 [a] Isolated yield. Reagents and conditions: alkynylbromide (1 eq), dimethylphosphite (1 eq), $Pd(OAc)_2$ (0.2 eq), dppf (0.4 eq), epoxide (20 eq), solvent (0.3 M).

1.4.4 Base (Proton Scavenger)

We found that substantially increasing the number of equivalents of propylene oxide from three to twenty improved the reliability of the reaction. This was an acceptable

increase as propylene oxide is an inexpensive reagent (~£18/mol). We accepted that the acid scavenger would most likely need to be an epoxide species. To confirm that propylene oxide was a poor acid scavenger and not simply being lost through evaporation during course of the reaction, a number of examples utilised 1,2-epoxyhexane (b.p. 118-120 °C). From table 1.4 it is evident that the yield is not affected by the epoxide used thus it is not likely that propylene oxide is being lost during the reaction.

1.4.5 Solvent

The workup in the literature procedure[8] required that the reaction mixture be concentrated *in vacuo* and the residue purified by silica gel column chromatography. The solvent used in the preparation was DMF which is high boiling and thus difficult to fully remove *in vacuo*. Substitution for a lower boiling solvent would therefore make purification less challenging. Tetrahydrofuran was found to be a suitable replacement, with product yield only marginally diminished (table 1.4, entries 4 and 5).

1.4.6 Reaction time and temperature

Although the aromatic alkynylbromide coupled at 70 °C with low reaction time, the less reactive aliphatic substrate was sluggish (table 1.4, entries 1 and 2). As increased reaction time generated a higher yield of alkynylphosphonate the next obvious step was to attempt the same reaction at a higher temperature. Increasing the reaction temperature from 70 to 100 °C further improved the product yield whilst reducing the reaction time to 4 h (table 1.4, entry 3). From these results it was apparent that the optimal reaction time and temperature would be a function of trial and error for each substrate.

1.4.7 Catalyst and ligand

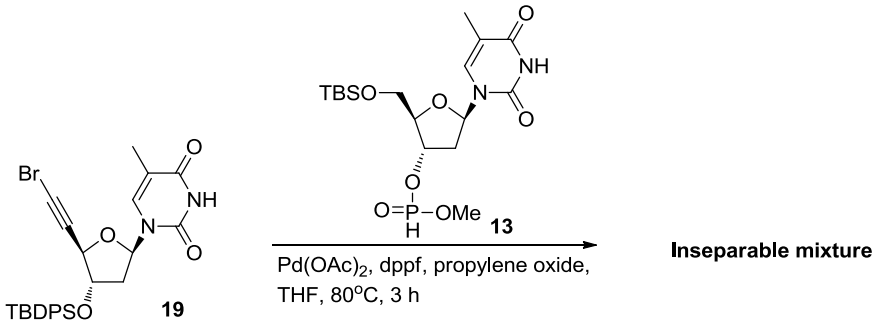
A number of alternative (and more expensive) palladium salts and ligands were screened, however none of the catalysts and ligand combinations tested demonstrated any improvement over the original catalyst/ligand combination.

1.4.8 Substrate range

With an optimal set of cross coupling reaction conditions determined it was necessary to determine the range of substrates which would be tolerated. Table 1.5 lists the alkynylbromides and dialkylphosphites (and their respective products) which were tolerated. In general, the reaction tolerated a wide range of functionality. Of note are entries 16-17, which tested the tolerance of the silyl groups. Again, the acid stable TBDPS group proved to be the superior protecting group.

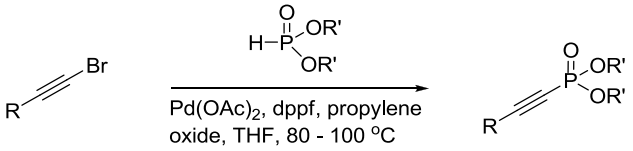
1.4.9 Alkynylphosphonate linked dinucleotide synthesis

At this stage a cross coupling toward the alkynylphosphonate linked dinucleotide was attempted. Disappointingly, the result was tantamount to that observed whilst using the vinyl-1,1-dibromonucleotide (c.f. scheme 1.18).



Scheme 1.22.

Evidently, a palladium mediated cross coupling strategy was not going to afford the desired alkynylphosphonate linked dinucleotide.



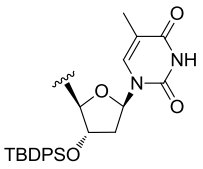
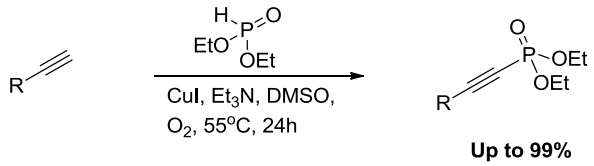
Entry	SM	R	R'	Temp (°C)	Product	Time (h)	Yield (%)
1	**20**	Ph	Me	80	**30**	4	70
2	**20**		Et	80	**31**	4	73
3	**14**	4-OMe-Ph	Me	80	**29**	3	70
4	**14**		Et	80	**32**	3	77
5	**14**		Bn	80	**33**	4	75
6	**15**	4-CN-Ph	Me	80	**34**	45min	53
7	**21**	$CH_3(CH_2)_5$	Me	100	**35**	4	94
8	**21**		Bn	100	**36**	4	61
9	**16**	Cyclohexyl	Me	100	**37**	4	61
10	**16**		Bn	100	**38**	4	49
11	**17**	$Ph(CH_2)_2$	Me	100	**28**	4	67
12	**18**	2-pyridyl	Me	80	**39**	45min	53
13	**22**	Methyl acetate	Me	100	**40**	3	56
14	**23**	$Cl(CH_2)_3$	Me	90	**41**	3	77
15	**24**	Cyclohexenyl	Me	90	**42**	3	78
16	**25**	$TBSO(CH_2)_3$	Me	90	**43**	3	36
17	**26**	$TBDPSO(CH_2)_3$	Me	90	**44**	3	60
18	**27**	$AcO(CH_2)_3$	Me	90	**45**	3	51
19	**19**		Me	90	**46**	3	57

Table 1.5. Reagents and conditions: alkynylbromide (1 eq), *H*-phosphonate (1 eq), $Pd(OAc)_2$ (0.2 eq), dppf (0.4 eq), propylene oxide (20 eq), THF (0.3 M).

1.5 Copper mediated alkynylphosphonate synthesis

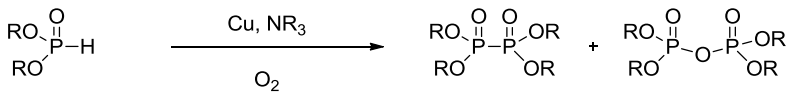
1.5.1 Introduction

Whilst developing the palladium mediated cross coupling of alkynylbromides with dialkylphosphites Han *et al*. published an aerobic copper mediated cross coupling of terminal alkynes with dialkylphosphites (scheme 1.23).[9]



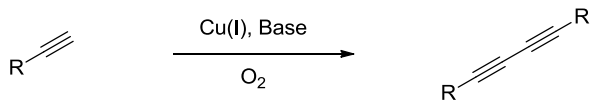
Scheme 1.23

A short time later Han *et al*. published another aerobic copper mediated cross coupling involving dialkylphosphites. In this instance, however, the products were either the pyrophosphate (P-O-P) or hypophosphate (P-P) (scheme 1.24).[13]



Scheme 1.24

Both of these transformations are interesting as they utilise almost identical reaction conditions but produce very different results. Coupling these findings with the very well-known Glaser homocoupling reaction (scheme 1.25)[14] raises some interesting mechanistic questions.

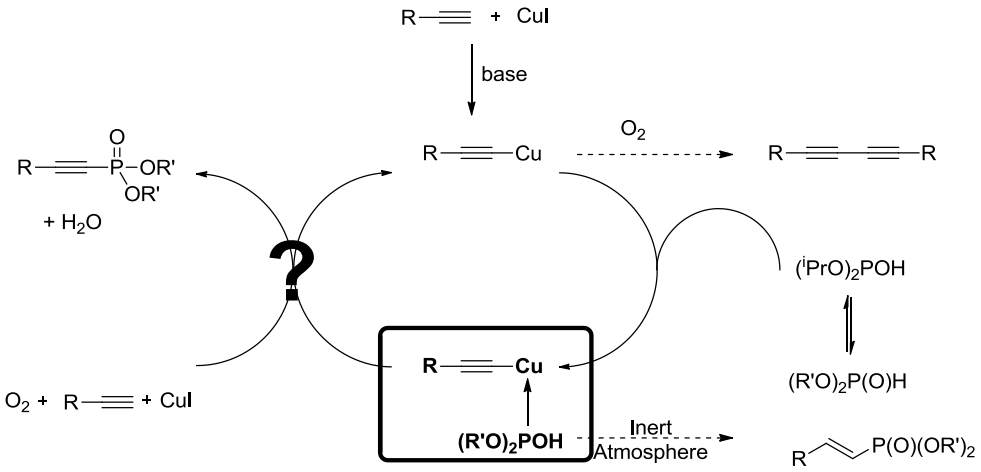


Scheme 1.25

With three very different outcomes stemming from three very similar starting points, it would be of use to firstly develop a mechanistic insight into reactions of this type before embarking on our own investigations into using Han's alkynylphosphonate synthesis method.

1.5.2 Han's Mechanism

The mechanism proposed in Han (scheme 1.26) was unusual in that both coupling partners were nucleophiles (highlighted in bold in the box). There was no indication as to how an oxidative coupling occurs (highlighted by '**?**'; the oxidation just 'happens'). At some point in this synthesis an oxidation step must occur. The question raised was thus: when and how does oxidation occur?



Scheme 1.26.

In an attempt to answer this we reverted to the literature in order to determine what, if anything, was known about reactions of this type.

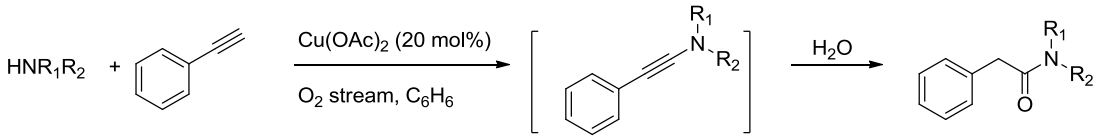
1.5.3 Cu^{II} mediated alkynylation reactions

Copper(I) species are generally accepted to oxidise to copper(II) in the presence of molecular oxygen.[15] Thus, we focused our initial search on aerobic copper(I/II) mediated alkynylation reactions, which appear to oxidatively couple two nucleophiles, in a bid to develop a more comprehensive understanding of the chemistry of such reactions.

1.5.4 Cu^{II} mediated alkynylation of amino compounds

Our attention was initially drawn to alkynylation reactions in which a nitrogen based species was the coupling partner. We expected that nitrogen, being in the same group as phosphorus, would share similar reactive trends with phosphorus.

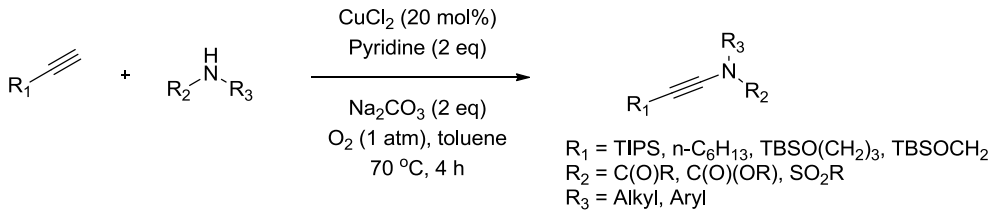
Peterson *et al*. demonstrated a copper mediated oxidative coupling of phenylacetlyene with amines, resulting in amides *via* hydrolysis of the intermediate ynamide (Scheme 1.27).[16]



Scheme 1.27

Although this is an interesting transformation, there was not much information disclosed in terms of useful mechanistic insight into the cross coupling to form the ynamine. However, there is clearly an oxidation step present in the mechanism.

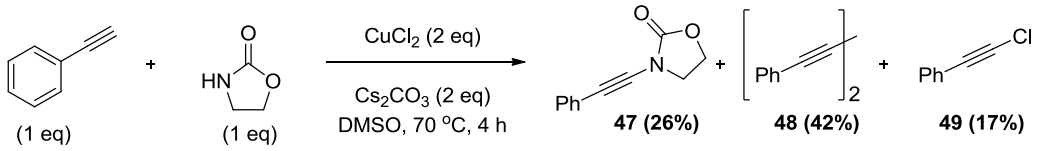
Stahl *et al.* demonstrated an aerobic copper(II) mediated cross coupling between terminal alkynes and electron deficient amido compounds (amides, carbamates, sulfonamides), producing ynamides (scheme 1.28).[17] Mizuno *et al.* later reported an improvement of this reaction simply by using $Cu(OH)_2$ as the catalyst, which reduced the general reaction stoichiometry.[18]



Scheme 1.28

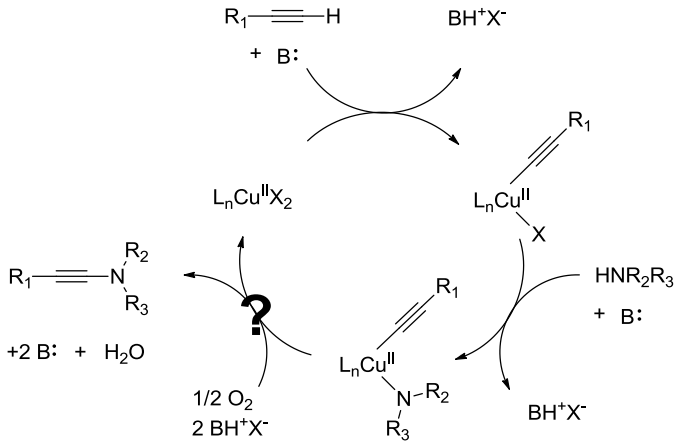
Initial studies by Stahl found that the desired ynamide could be formed in good yield (89%), however the reaction required a significant excess of the electron deficient amido component (5 equivalents). When a 1:1 ratio of alkyne : amido component was subjected to the reaction

conditions, the reaction composition changed, producing ynamide **47** (26%), homocoupled alkyne **48** (42%) and the unexpected chlorinated alkyne **49** (17%) (scheme 1.29).



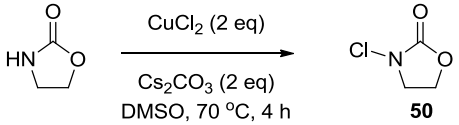
Scheme 1.29

Stahl suggested that **49** formed prior to cross coupling and was a reactive intermediate, however this theory was dismissed as attempts to use alkynyl chlorides directly as substrates resulted in negligible yields of ynamide. Stahl thus proposed a catalytic mechanism that featured sequential activation of the alkyne and nitrogen nucleophile, followed by C-N 'reductive' elimination (scheme 1.30; 'reductive' is used tentatively as the product of the elimination would be Cu^0 and not, as proposed by Stahl, Cu^{II}).



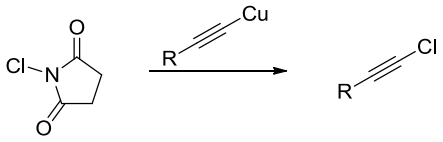
Scheme 1.30

This mechanism does not solve the mystery surrounding the oxidative coupling step, and in fact poses the new question: how is the alkynylchloride forming? One speculative argument is that an initial oxdative process forms **50** (scheme 1.31).



Scheme 1.31

Continuing with this speculative hypothesis, the chlorinated intermediate **50** closely resembles N-chlorosuccinimide, a reagent commonly used as a source of electrophilic chlorine. The resultant proposed chlorination is analogous to the bromination utilised in our palladium work (scheme 1.32, c.f. table 1.3).

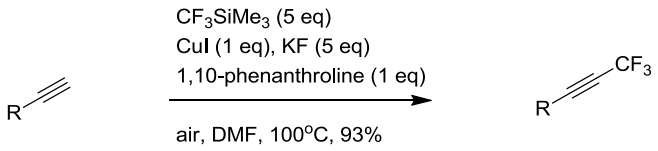


Scheme 1.32

This argument would explain both the formation of the alkynylchloride and the lack of reactivity when using alkynylchlorides directly as substrates. Furthermore, should this be the case then the requirement for such a vast excess of the electron deficient amino species may in part be to negate this side reaction by sacrificing some reagent to this side reaction whilst maintaining a sufficient quantity to perform the desired reaction through the desired (as of yet unknown) mechanism.

1.5.5 Trifluoromethylation of Alkynes

Quing *et al*. developed a mild and efficient method for trifluoromethylating terminal alkynes (scheme 1.33).[19] An interesting observation is that five equivalents of CF_3SiMe_3 (the partner coupling to the alkyne) are required to effect the transformation in good yields, with poor yields observed in the presence of fewer equivalents – c.f. Stahl *et al*.



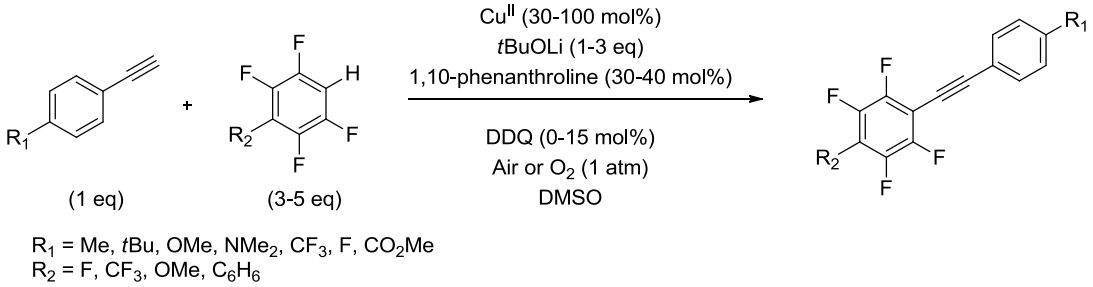
Scheme 1.33

The reaction allegedly proceeds *via* a Cu-CF_3 species and thus the cross coupling occurs between two nucleophilic species (assumedly the copper acetylide forms also) with an

oxidative coupling step involved somewhere in between. As before, no useful insight into the mechanistic aspects of this reaction was provided.

1.5.6 Alkynylation of Electron Deficient Aromatic Compounds

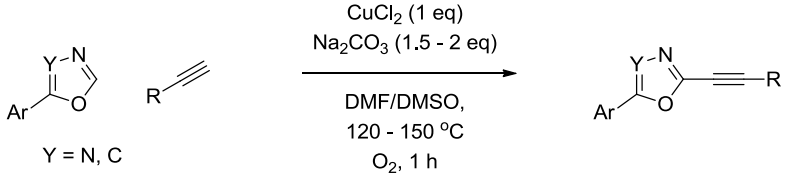
Hong *et al.*[20] and, independently, Miura *et al.*[21] developed very similar methods for the alkynylation of polyfluorinated aromatics (Scheme 1.34). Disappointingly, neither publication discusses either the possibility of side reactions or any mechanistic aspects of these reactions.



Scheme 1.34

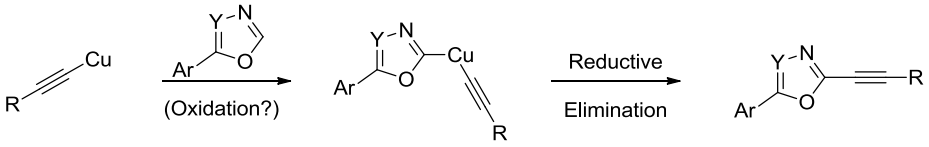
From the reaction conditions a fair assumption is that the first step of this mechanism is deprotonation of the highly electron deficient aromatic by ^{t}BuOLi. Drawing an analogy to other Cu-alkynylation reactions it could be envisaged that this species then binds copper to form the organocuprate. Such a mechanism would again involve the coupling of two nucleophilic species with an oxidative coupling step required somewhere in the mechanism.

Further examples of alkynylation of electron deficient aromatic compounds have been demonstrated by Miura *et al*. through the alkynylation of 1,3,4-oxadiazoles and 5-aryloxazoles with terminal alkynes (scheme 1.35).[22]



Scheme 1.35

The mechanism is thought to proceed through an (alkynyl)(heteroaryl)Cu(II) species (sheme 1.36), however, as mentioned above, a reductive elimination from the Cu^{II} species would produce Cu^{0} and the reaction would shut down.

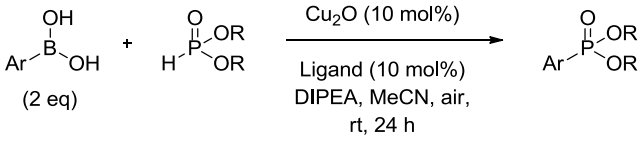


Scheme 1.36

Furthermore, there is no further discussion regarding how the initial oxidation to form the proposed (alkynyl)(heteroaryl)Cu(II) species occurs.

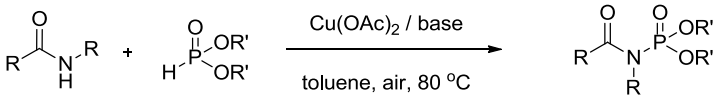
1.5.6 Cu^{II} mediated phosphorylation reactions

The initial search of the literature produced relatively little mechanistic insight into the copper mediated alkynylation reactions. As such, a further search was performed to determine what, if anything, was known about copper mediated phosphorylation reactions. This area appears to be a far less studied area of chemistry as apart from the couplings in schemes 1.23[9] and 1.24[13] we could only find two further aerobic copper mediated cross coupling reactions involving two nucleophiles, wherein one of the nucleophiles is a dialkylphosphite. The first is a copper-catalyzed addition of H-phosphonate diesters to boronic acids under the copper catalyst system Cu_2O/1,10-phenanthroline (scheme 1.37).[23]



Scheme 1.37

The second is a copper mediated coupling of an H-phosphonate diester to electron deficient amine producing an N-acylphosphoramidate (scheme 1.38).[24]



Scheme 1.38

Neither of these publications discuss any mechanistic aspects of these reactions, thus any mechanism we could postulate at this stage would be pure speculation.

1.5.7. General observation

The majority of the above copper mediated oxidative coupling reactions of two nucleophiles share one general common feature: they require at least one of the coupling partners to be electon deficient and in excess. It is not possible to determine the complete significance of this observation from the published results alone, however it appears to be a crucial requirement for the above reactions to work.

1.6 Results and Discussion – Copper Mediated Oxidative Cross Coupling

1.6.1 Towards Alkynylphosphonates

Considering the indeterminate mechanistic nature of copper mediated coupling reactions we decided to repeat an example from Han[9] and monitor it using ^{31}P NMR (note – ^{31}P NMR shifts for each species in the following test reactions can be found in references 9 and 13).

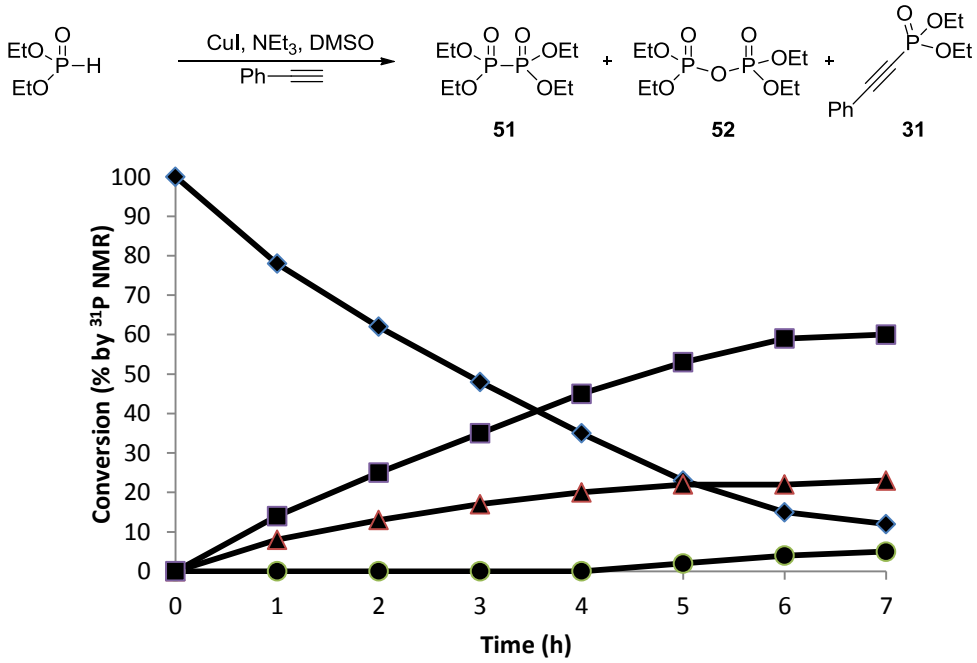
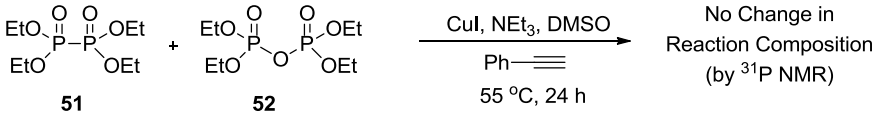


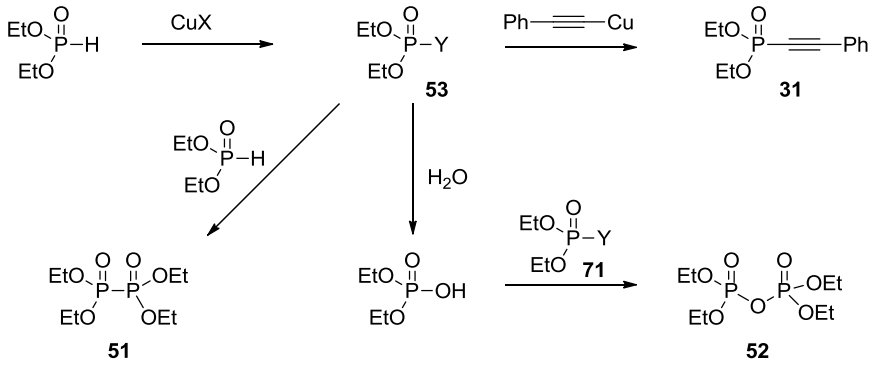
Figure 1.1 Reagents and conditions: 0.1 eq CuI, 0.2 eq Et_3N, 1.1 eq phenylacetylene and 1 eq dimethyl phosphite. Stirred at 55°C for 7 h, sampling hourly. Legend: ◆ Starting material, ■ Product **31**, ▲ Hypophosphate (P-P) **51**, ● Pyrophosphate (P-O-P) **52**

The predominant product was found to be the alkynylphosphonate, albeit in slightly lower yield (60%, by ^{31} P NMR) than that disclosed in Han *et al*. (83%). To account for the lower yield we initially postulated that the phosphorus by-products **51** and **52** may be reactive to the copper acetylide, which may have allowed the reaction to reach completion, albeit in a longer time frame. However, this theory was quickly dismissed (scheme 1.39).



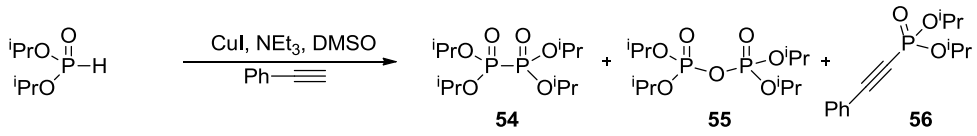
Scheme 1.39 Compounds **51** and **52** independently synthesised using literature conditions.[13]

The formation of **51** and **52** were reactive 'dead ends' – these compounds were irreversibly formed by-products. To rationalise all of the observed products we proposed that the dialkylphosphite could be oxidised to a reactive electrophilic phosphorus(V) species **53** (scheme 1.34, however c.f. speculative oxidation of the amido component in scheme 1.40).



Scheme 1.40 The nature of Y is unknown but we speculate that it is a leaving group.

If such a mechanism is in place then increasing the steric bulk surrounding the phosphorus by replacing Et with ^{i}Pr centre should, in theory, increase the formation of **56** whilst reducing the quantity of **54** and **55** due to increased steric hindrance in the transition state.



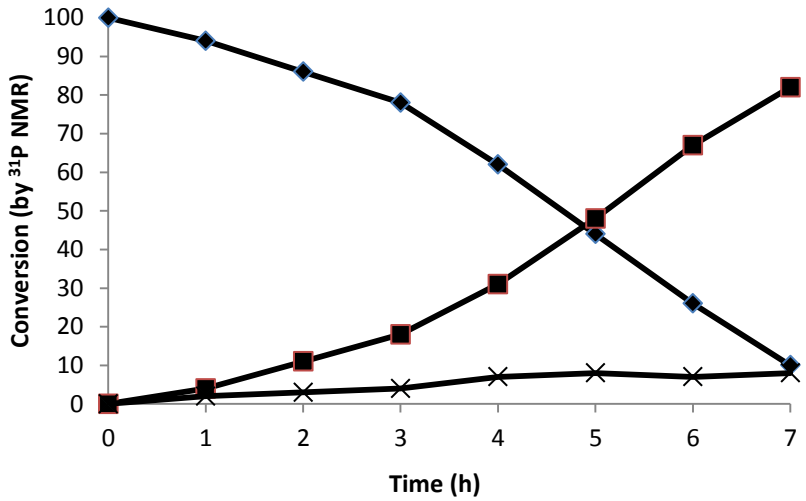


Figure 1.2 Reagents and conditions: 0.1 eq CuI, 0.2 eq Et_3N, 1.1 eq phenylacetylene and 1 eq diisopropyl phosphite. Stirred at 55°C for 7 h, sampling hourly. Legend: ◆ Starting material, ■ Product **56**, ▲ Hypophosphate (P-P) **54**, ● Pyrophosphate (P-O-P) **55**, X unknown byproduct.

As predicted, increasing the bulk surrounding the phosphorus centre increased the formation of **56** and reduced the formation of side products **54** and **55** (figure 1.2). A byproduct was also observed, however the identity of the byproduct was never confirmed. To confirm that the steric bulk surrounding the phosphorus centre was of significant importance, the above reaction was repeated, except in this case the steric bulk was significantly reduced by replacing ^{i}Pr with Me (figure 1.3).

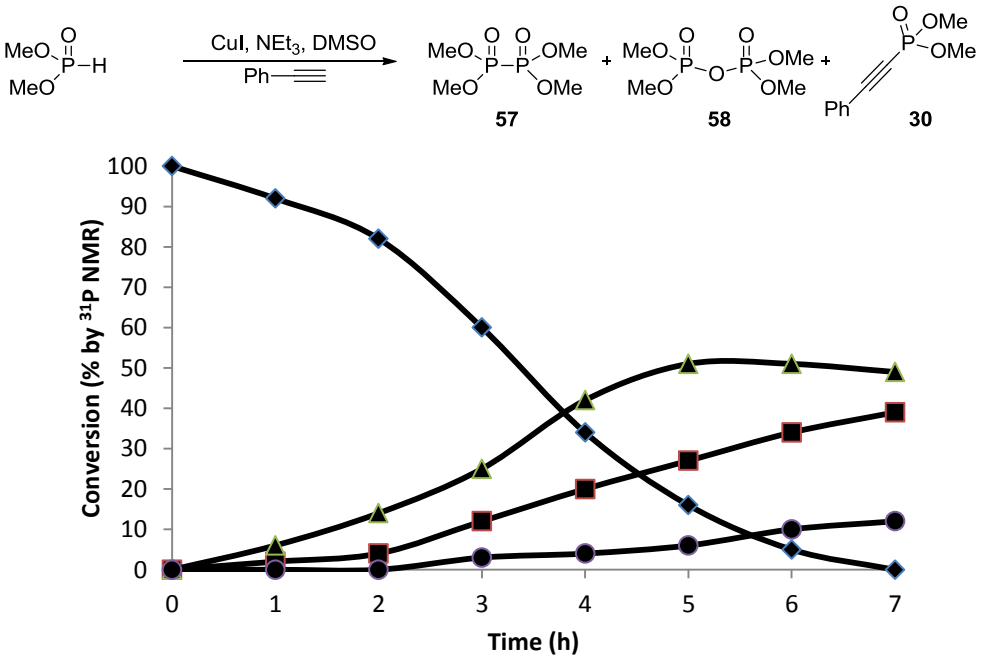
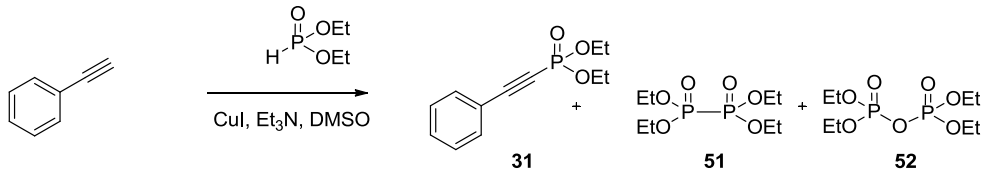


Figure 1.3 Reagents and conditions: 0.1 eq CuI, 0.2 eq Et_3N, 1.1 eq phenylacetylene and 1 eq dimethyl phosphite. Stirred at 55°C for 7 h, sampling hourly. Legend: ◆Starting material, ■ Product **30**, ▲ Hypophosphate (P-P) **57**, ● Pyrophosphate (P-O-P) **58**

Evidently, the final reaction composition is dependent on the steric bulk associated with the phosphite alkyl groups. This result was not disclosed in Han *et al.*, however, after reexamining the results in Han it was clear that the favoured phosphite was diisopropyl phosphite, with only one example of a less bulky phosphite, diethyl phosphite, which was the lowest yielding reaction. Thus, we proceeded to analyse each variable in this reaction both to gain a better understanding of the chemistry and to hopefully produce a set of reaction conditions which would tolerate both bulky and unhindered phosphites.

1.6.2 Effect of Concentration

The first variable examined was concentration of the reaction mixture.



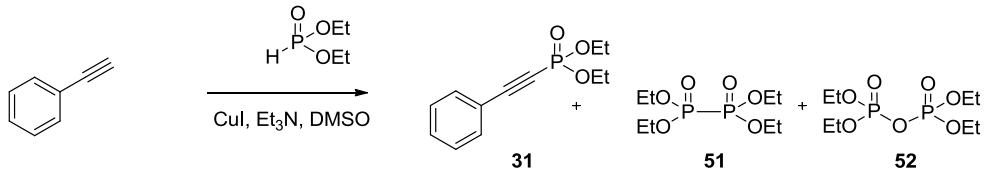
Entry	Concentration	HP(O)(OEt$_2$)	31	51	52
1	Neat	100	0	0	0
2	0.5M	0	70	25	5
3	0.25 M	0	84	16	0

Table 1.6 Conversions by ^{31}P NMR (%). Reagents and conditions: 0.1 eq CuI, 0.2 eq Et_3N, 1.1 eq phenylacetylene and 1 eq diethyl phosphite. Stirred at 55°C for 18 h.

Increasing the dilution improved the selectivity of the reaction toward the alkynylphosphonate. Whilst performing these reactions it was noted that a significant quantity of a yellow precipitate formed, which dissipated over time. The precipitate which formed was most likely the copper acetylide, thus increasing the dilution likely increased the quantity of solubilised acetylide. Referring to the proposed mechanism (scheme 1.34), increasing the concentration of solubilised acetylide in the reaction mixture would increase the quantity of acetylide available for reacting, consequently increasing the quantity of alkynylphosphonate produced.

1.6.3 Effect of Et_3N Loading

The amine could be acting as a ligand, base, initiator, proton mop, or a combination of all of the above. However, regardless of the role it was playing in the reaction, it was necessary to determine the effect of varying the level of Et_3N with regard to alkynylphosphonate formation.



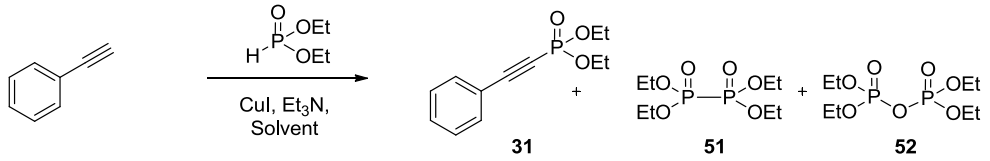
Entry	Equiv	HP(O)(OEt$_2$)	31	51	52
1	1.0[a]	0	60	0	0
2	0.2	0	84	16	0
3	0	0	62	38	0

Table 1.7 Conversions by ^{31}P NMR (%). Reagents and conditions: 0.25 M DMSO, 0.1 eq CuI, 1.1 eq phenylacetylene and 1 eq diethyl phosphite. Stirred at 55°C for 18 h. [a] Zero **51** or **52** observed, but observe two additional Phosphorus species at δ 20.2 and 19.9. Also recover 40% Glaser homocoupled product.

No significant conclusions could be drawn from this study other than that the original quantity of Et_3N used (20 mol%) was optimal.

1.6.4 Effect of Solvent

A number of solvents were screened to determine whether DMSO was in fact the best solvent.



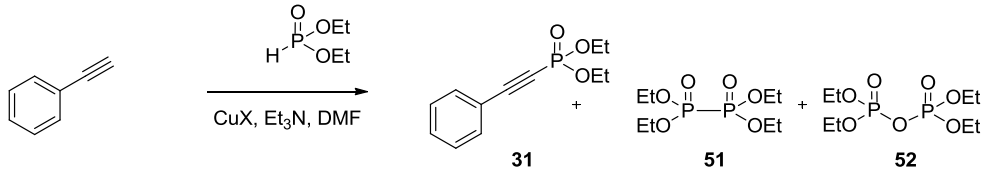
Entry	Solvent	HP(O)(OEt$_2$)	31	51	52
1	EtOH	100	0	0	0
2	MeOH	100	0	0	0
3	DMF	0	69	24	7
4	DMSO	0	84	16	0

Table 1.8 Conversions by ^{31}P NMR (%). Reagents and conditions: 0.25 M solvent, 0.1 eq CuI, 0.2 eq Et_3N, 1.1 eq phenylacetylene and 1 eq diethyl phosphite. Stirred at 55°C for 18 h.

It appeared that the polar aprotic solvents were in fact the best solvents for this reaction, possibly due to improved solubility of the catalyst or the copper acetylide in these solvents.

1.6.5 Effect of Catalyst

A screen of available copper(I) catalysts was performed in order to determine the importance of the ligand.

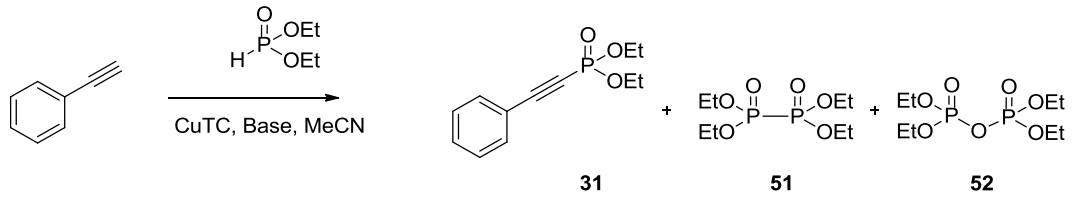


Entry	Catalyst	HP(O)(OEt$_2$)	31	51	52
1	CuI	0	69	24	7
2	CuBr	0	82	18	0
3	CuCl	0	71	24	5
4	CuTC[a]	12	74	14	0
5	CuTC[b]	15	76	9	0
6	CuTC[a,c]	5	88	7	0
7	CuTC[c,d]	72	38	0	0

Table 1.9 Conversions by ^{31}P NMR (%). Reagents and conditions: 0.25 M DMF, 0.1 eq Catalyst, 0.2 eq Et_3N, 1.1 eq phenylacetylene and 1 eq diethyl phosphite. Stirred at 55°C for 18 h. [a] 2.5h reaction time. [b] slow addition of the phosphite over 5 h. [c] Reaction diluted to 0.12 M. [d]5 mol% catalyst loading.

The thiophene-2-carboxylate ligand performed significantly better than the other catalysts tested, reducing side reactions and producing the desired product in 88% yield (by ^{31}P NMR). This was attributed to better solubility of the catalyst; the catalyst fully dissolved, a trait not observed with other catalysts. As such, a solubility screen of CuTC was performed in various other solvents: THF, MeCN, Et_2O, EtOAc and toluene. CuTC was found to be fully soluble in MeCN which, from a practical viewpoint, would make a significant improvement to the work up procedure; prior to workup studies (discussed below) the procedure required concentration of the reaction mixture *in vacuo* followed by silica gel column chromatography of the residue. As the reaction was performed in DMSO or DMF removal of these solvents *in vacuo* was never complete; traces of the solvent were always observed by ^{1}H NMR.

Consequently, a number of reactions using the previously determined optimal conditions were repeated in MeCN (selected examples in table 1.10).



Entry	Catalyst	Base	Conc^{n} (M)	HP(O)(OEt$_2$)	31	51	52
1	CuTC	Et_3N	0.12	35	40	15	10
2	CuTC[a]	Et_3N	0.25	0	74	10	9
3	CuTC[a]	Et_3N	0.5	0	75	8	7

Table 1.10 Conversions by ^{31}P NMR (%). Reagents and conditions: 0.1 eq Catalyst, 0.2 eq Et_3N, 1.1 eq phenylacetylene and 1 eq diethyl phosphite. Stirred at 55°C for 18 h. [a]The apparently missing 7-10% is due to an additional intermediate species observed in ^{31}P NMR (δ -10.8).

Although this reaction could be performed successfully in MeCN, it did not perform as well as it did in DMF or DMSO; the product selectivity was lower and the reaction was sluggish. However, whilst performing this reaction in acetonitrile an additional phosphorus species was observed in the ^{31}P NMR (δ -10.8). This was postulated to be the acylphosphonate species **59** formed by reaction of the electrophilic phosphorus species **53** with the thiophene-2-carboxylate ligand, evidence for which was found by mass spectrometry.

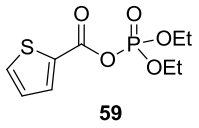
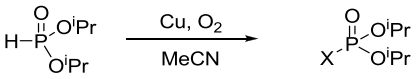


Figure 1.4

An independent synthesis of **59** confirmed its identity as the acylphosphonate (scheme 1.40). With this finding we aimed to discover the outcome of mixing copper salts with a dialkylphosphite under these reaction conditions. Diisopropyl phosphite was mixed with a

range of copper salts under air (Table 1.11). ^{31}P NMR studies were used to detect any new species which may have formed.



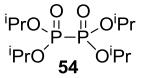
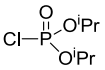
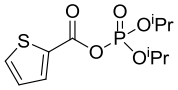
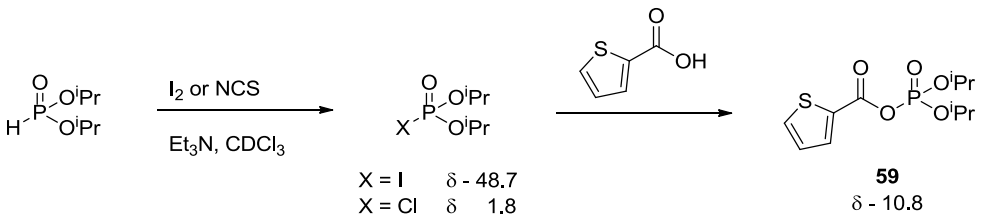
Catalyst	New Species (δ, ppm)	Proposed Structure
CuI	7.1[a]	 **54**
CuCl	1.9	
CuTC	- 10.9	
$Cu(OAc)_2$	-[b]	-

Table 1.11 Conditions: CuX (0.5 mmol), diisopropyl phosphite (0.5 mmol), MeCN (1 mL), 55 °C, 3 h. Reaction performed under air. CuTC = Cu(I) thiophene-2-carboxylate. ^{31}P NMR samples diluted in $CDCl_3$. [a]Only a minor product; still observe >90% SM by ^{31}P NMR. [b]Could not detect any species by ^{31}P NMR; assumably the phosphite binds the Cu(II) centre, which is paramagnetic thus significantly broadening the signals.

Oxidation of the phosphite was observed in both examples which used copper halides. The new species observed with CuCl was postulated to be the phosphoryl chloride, which was confirmed by an independent synthesis using N-chlorosuccinimide (NCS) (Scheme 1.41). No phosphoryl iodide was observed in the analogous reaction using CuI, however hypophosphate **54** was detected, which may have been the result of rapid nucleophilic trapping of the phosphoryl iodide (generated *in situ*) by unoxidised phosphite starting material.



Scheme 1.41 Chemical shifts correspond to shifts in the ^{31}P NMR of the crude reaction mixture.

The formation of the acylphosphonate was, in itself, an interesting finding. Although under these reaction conditions we propose that it may be acting as a phosphoryl transfer agent, acylphosphonates are known to react at the carbonyl and not the phosphoryl group, most notably in the production of amides. This shall be discussed in greater detail in chapter 2.

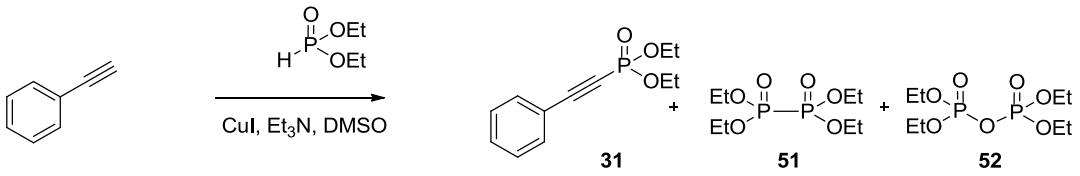
1.6.6 Work Up

One of the major issues associated with this methodology was isolation of the product. The workup procedure published in the supporting information made little sense:[8]

"A Representative Procedure: H-phosphonates (0.5 mmol), terminal alkyne (0.6 mmol), CuI or $Cu(OAc)_2 \cdot H_2O$(0.05 mmol) and a base (diethylamine or triethylamine, 0.1 mmol) were dissolved in commercial DMSO (1 mL) and stirred for 24 h at a temperature indicated under dry air atmosphere. **The resulting mixture was extracted with ethyl acetate or dichloromethane.** The organic layer was concentrated under vacuum and the crude product was purified by silica gel chromatography using a mixture of petroleum ether and ethyl acetate as eluent."

DMSO is completely miscible with ethyl acetate and dichloromethane and there is no indication of which (if any) aqueous extraction medium should be used. As such, various aqueous extractions were performed (neutral, acidic and basic) and the most successful to date was an extraction from saturated aqueous NH_4Cl. To quantify the success of using sat. NH_4Cl (aq) as the aqueous phase a repeat of the literature conditions was performed and the reaction mixture exactly halved, with each half subjected to a different workup procedure; one half was subjected to an aqueous workup from saturated NH_4Cl, the other half concentrated *in vacuo,* and both purified by column chromatography (Table 1.12). A common observation was the loss of approximately 40% isolated product with respect to the conversion to product. To ensure the product was stable on the acidic silica column, a sample of the clean product was passed through a silica gel column and recovered quantitatively. The

product could have been sticking to the catalyst, resulting in a loss on the column as a baseline copper salt. A number of attempts to chelate the copper prior to purification (using monodentate, bidentate, tridentate amines and EDTA) did not improve the yield, suggesting the product was not ligating to the copper.



Work up	HP(O)(OEt$_2$)	31	51	52	Isolated 31 (%)
Crude Mix	0	70	25	5	/
Aqueous	0	73	20	7	33
In Vacuo	0	71	23	6	35

Table 1.12 Conversions by ^{31}P NMR (%) of crude material and residue after each workup. Reagents and conditions: 0.1 eq CuI, 0.2 eq Et_3N, 1.1 eq phenylacetylene and 1 eq diisopropyl phosphite. Stirred at 55°C for 18 h.

1.6.7 Reaction Monitoring using an Internal Standard

The difference between the observed conversion by ^{31}P NMR of the crude mixture and the isolated yield made us question the reliability of using ^{31}P NMR as a method of determining the absolute yield. As such, one of the previous reactions was repeated with the inclusion of an internal standard (tri-n-butylphosphate, inert to the reaction conditions) (figure 1.5).

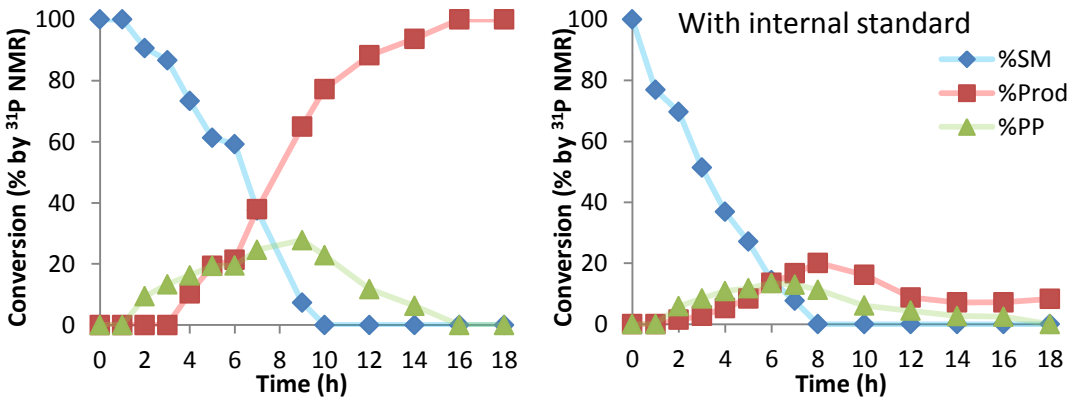


Figure 1.5 No internal standard (left) and with an internal standard (right). Reagents and conditions: Phenylacetylene (1.1eq), **dimethyl phosphite** (1eq), Et_3N (0.4eq), CuI (0.2eq), DMSO (0.5M), 55°C.

Using an internal standard immediately reveals a 'loss' of phosphorus species from the crude data. This may be due to some of the phosphorus binding the paramagnetic Cu^{II} species *in situ* thus causing signals to broaden and effectively become 'invisible' in the ^{31}P NMR. The maximum conversion (~ 20%) was closer to the isolated yield, explaining the previously observed reduction in isolated yield with respect to the conversion. To ensure this was a consistent result and not limited to dimethyl phosphite, the study was repeated using both diethyl (figure 1.6) and diisopropyl phosphite (figure 1.7). Again, the results demonstrate a more accurate correlation between the actual conversion to product and isolated yield. However, the findings in the optimisation study were not rendered invalid as the ratio of product to by-products remained consistent, albeit with a lower overall yield than expected.

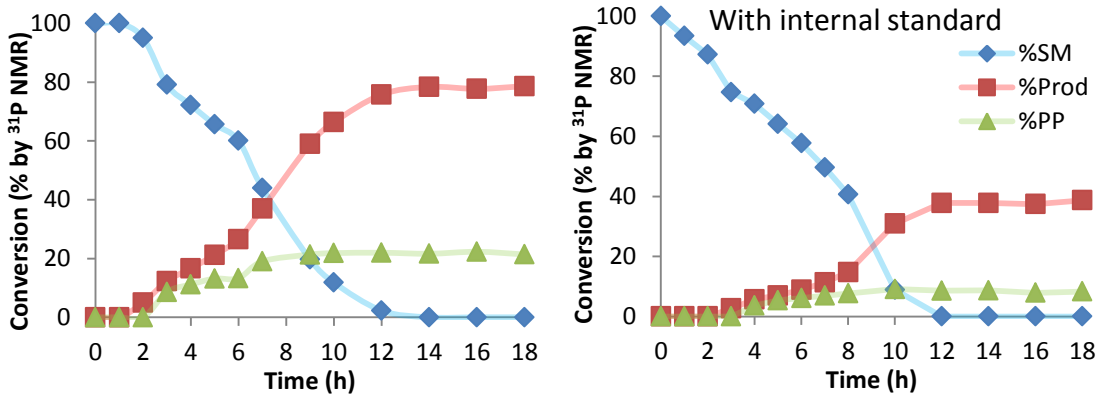


Figure 1.6 No internal standard (left) and with an internal standard (right). Reagents and conditions: Phenylacetylene (1.1eq), **diethyl phosphite** (1eq), Et_3N (0.4eq), CuI (0.2eq), DMSO (0.5M), 55°C.

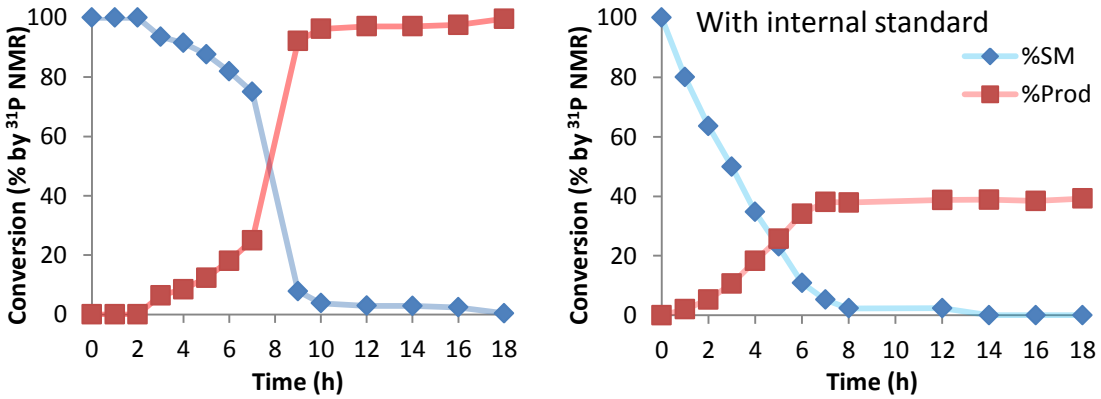
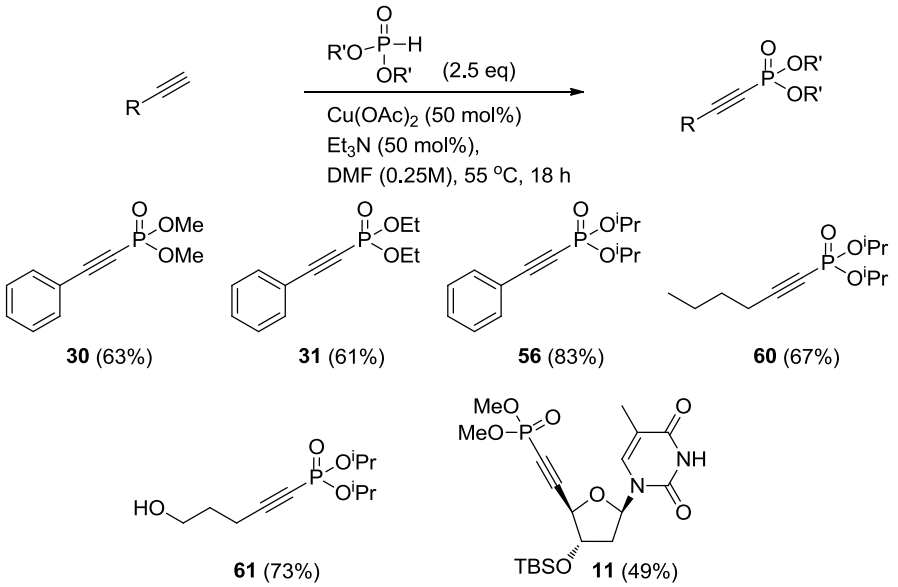


Figure 1.7 No internal standard (left) and with an internal standard (right). Reagents and conditions: Phenylacetylene (1.1eq), **diisopropyl phosphite** (1eq), Et_3N (0.4eq), CuI (0.2eq), DMSO (0.5M), 55°C.

Although these results were somewhat frustrating the outcome allowed us to develop a higher yielding and reproducible method. Evidently the phosphite was being 'lost', so an obvious solution was to increase the number of equivalents of phosphite. Increasing to 2.5 equivalents of phosphite increased the isolated yield, however, the reaction did not reach completion, with starting material phosphite observed in the ^{31}P NMR, even with extended heating (> 24 h). This suggested higher catalyst loadings were required. Further studies confirmed this theory, with the reaction requiring 50 mol% CuTC to reach completion. Replacing CuTC with $Cu(OAc)_2$ had no detrimental effect on the reaction and increasing the level of Et_3N to 50 mol% further improved the isolated yields. Thus, upon determining that the limiting factor was in fact the quantity of phosphite, a set of improved conditions were developed within a handful of experiments (scheme 1.42).



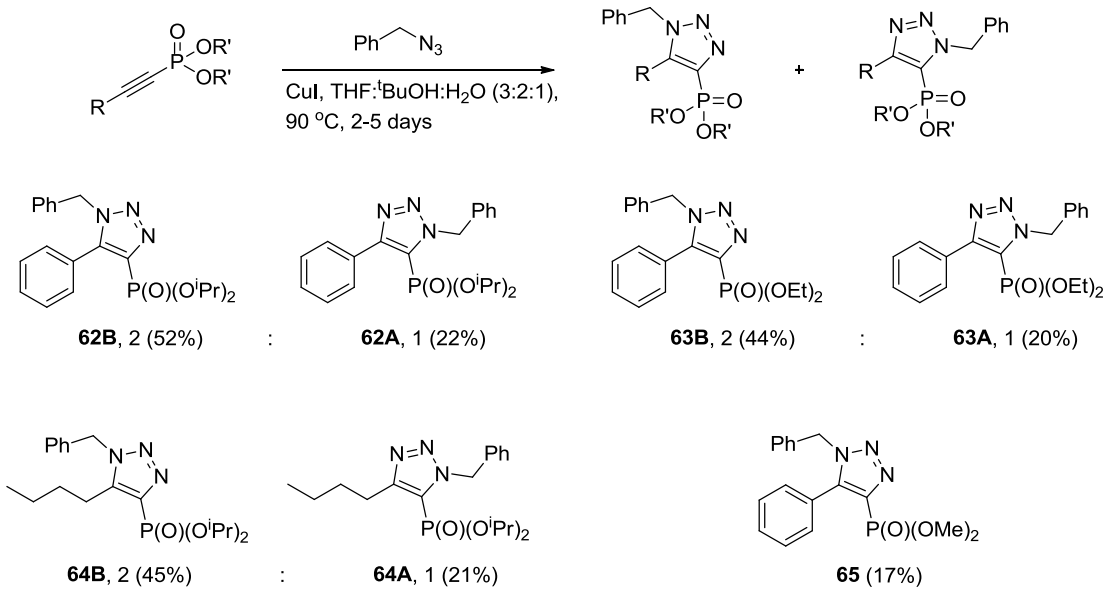
Scheme 1.42 Isolated yields in brackets.

Unfortunately, the late development of this method meant that no significant work towards an alkynylphosphonate linked dinucleotide could be performed.

1.7. Azide Alkyne Huisgen cycloaddition ('Click Chemistry')

Following the development of two mild methods for the synthesis of alkynylphosphonates studies towards modifying the link were initiated. Although a number of potential modifications were possible, initial studies focused on adding appendages to the alkynylphosphonate link through 'click' chemistry. Copper catalysed azide alkyne cycloaddition reactions have recently become a focal point in biochemistry and, in particular, have become the method of choice for labelling DNA due to its remarkable efficiency. They have been used to label oligonucleotides with fluorescent dyes, sugars, peptides and other reporter groups, to cyclise DNA, to synthesise DNA catenanes, to join oligonucleotides to PNA, and to produce analogues of DNA with modified nucleobases and backbones. Brown *et al.* cover this area in an extensive review.[25]

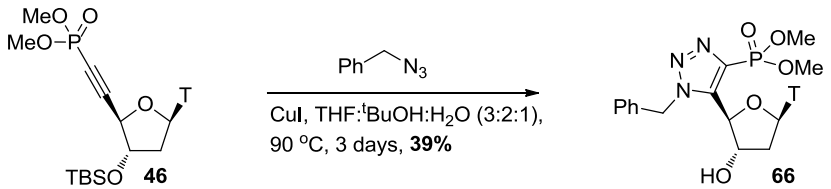
In this instance we were curious to determine whether the internal alkyne would cyclise, as most of the examples involved in modifying DNA use terminal alkynes. Utilising a standard set of conditions for Huisgen cycloadditions between terminal alkynes and azides, we immediatedly demonstrated cycloaddition onto the alkynylphosphonate link (scheme 1.43).



Scheme 1.43 Regioisomers identified using NOE and ratios determined by ^{1}H NMR of the crude reaction mixture. Regioisomers were easily separated by silica gel column chromatography. Isolated yields are given in parentheses.

The success of the cycloaddition is perhaps not particularly surprising as internal alkynes bearing an adjacent electron withdrawing substituent are known to cyclise with azides under forcing conditions.[26] However, this does prove that the alkynylphosphonate moiety survives long enough for cycloaddition to occur in good yields and does not simply decompose or undergo side reactions. The preferential formation of the 1,5 over the 1,4 regioisomer appeared to be reliant on the electronic properties of the triple bond and not controlled by steric hindrance. Further work screening various metals, electron donating and electron withdrawing groups would be necessary to determine whether this reaction could be tuned to be fully regioselective and higher yielding.

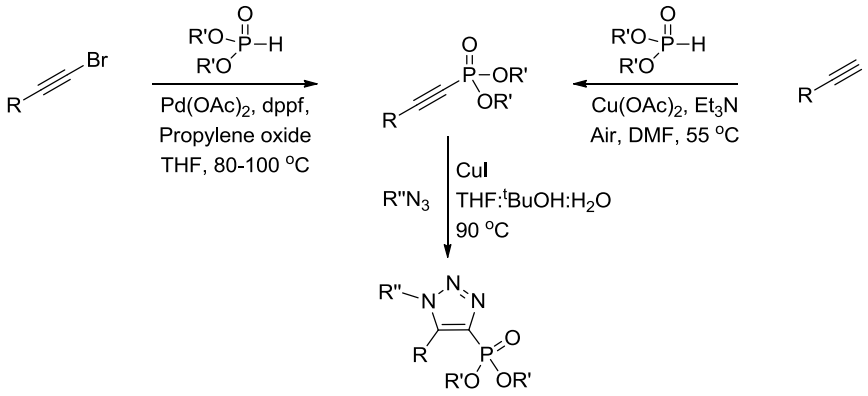
As the click reaction with alkynylphosphonates was found to be successful, a cycloaddition onto **32** was attempted. Cycloaddition was observed in moderate yield with loss of the 3' TBS protecting group (39%, ^{1}H NMR, ^{31}P NMR and mass spectrometry data, Scheme 1.44). Unfortunately, low levels of recovered material disallowed full characterisation, hence we can only express this as a tentative result. This does, however, demonstrate that the alkynylphosphonate moiety may be a useful link for directly conjugating biomarkers onto the backbone of DNA.



Scheme 1.44

1.8. Conclusions – Alkynylphosphonate Synthesis & Modification

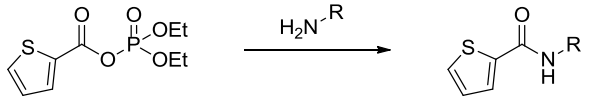
We have successfully developed two methods for producing alkynylphosphonates. Each method uses mild conditions and produces acceptable yields of product. Each method also has its own merits: Pd mediated cross coupling only requires one equivalent of phosphite (Cu requires 2.5 eq) and Cu mediated cross coupling does not require expensive metals or inert reaction conditions. Furthermore, we have shown that it is possible to functionalise the alkynylphosphonate link through the use of 'click' chemistry.



2. Amide synthesis

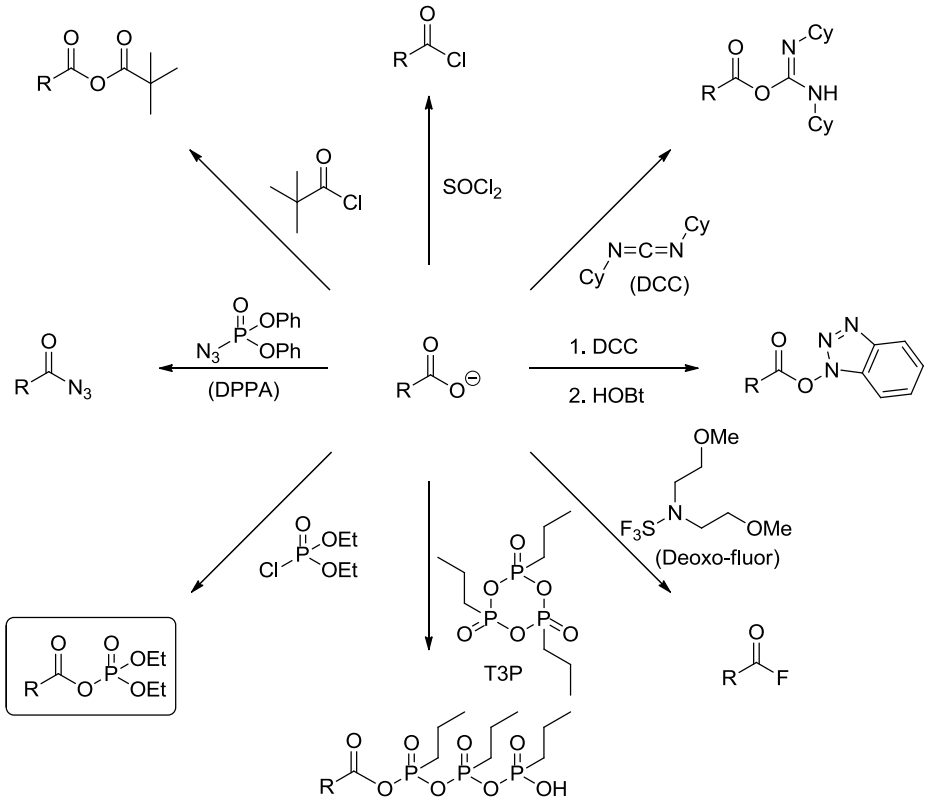
2.1 Introduction

During developmental studies of aerobic copper mediated alkynylphosphonate synthesis we observed an interesting result whilst attempting the cross coupling in MeCN; acylphosphonate species **59** was detected (figure 1.4). Acylphosphonate species have been successfully used as activated carboxylate species, so we speculated that it may be possible to develop this finding into another method of producing amides (scheme 2.1).



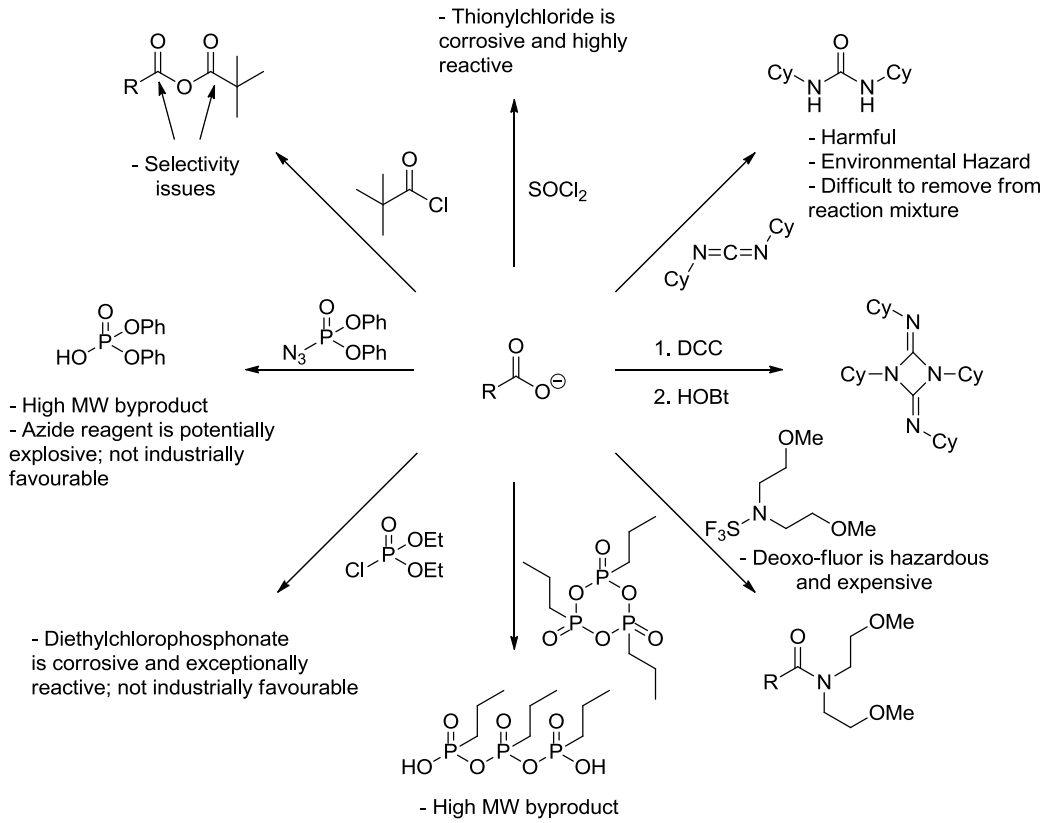
Scheme 2.1

However, there is already a wide range of simple and exotic reagents available for activating carboxylates, including reagents for forming dialkylacylphosphonates (scheme 2.2).[27]



Scheme 2.2 Selected examples of carboxylate activating reagents. For a full review see Bradley *et al*.[27]

With so many available coupling reagents why develop another? The answer is simple – there is still a high demand for amide coupling reagents which are cheap, stable, low molecular weight, high yielding, generate low levels of waste and minimize side reactions. Redrawing a modified version of the above schematic highlights some of the byproducts, waste products and general issues associated with the use of such reagents (scheme 2.3).



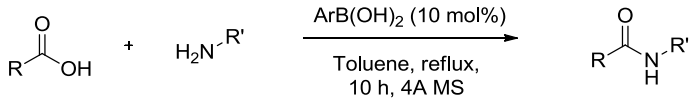
Scheme 2.3

A lot of effort continues to go into developing coupling reagents for the synthesis of amides and there is a good reason for this. Williams *et al.* performed an analysis of the reactions used for the preparation of drug candidate molecules in industry.[28] Of the 1039 reactions analysed, 128 (12%) of them were acylation reactions, of which 84 (66%) of these were amide formations. Thus, of all the reactions performed in drug synthesis approximately 8% of them are amide syntheses. A typical industrial drug synthesis route will use 10-12 steps, thus statistically almost every drug will require a step wherein an amide link is formed. The

fact that new coupling reagents and methods continue to be developed is a clear indicator that the formation of amides is still a synthetic problem for industry. Furthermore, with increasing regulations on the quantity of waste products being generated (i.e. poor atom efficiency reactions) the heavier, more exotic coupling reagents are becoming somewhat redundant. This point is highlighted by the fact that of the 84 amide reactions performed, 51 (61%) utilised the Schotten-Baumann reaction (high atom efficiency, high yielding), which is one of the oldest, if not the oldest amide synthesis procedure known.

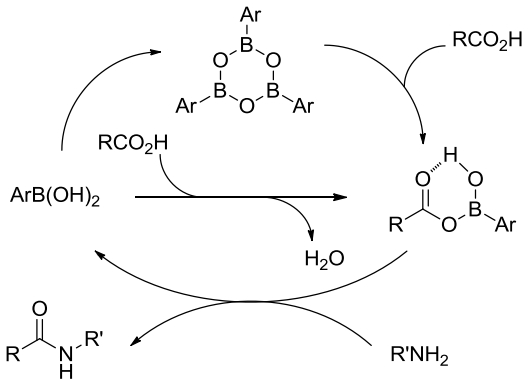
2.2 Recent developments in amide synthesis – catalytic approach

With the demand for better methods for producing amides from the pharmaceutical industry and the ever expanding field of peptide chemistry there is still clearly a significant need for better reagents and/or methods for producing amides. Recent developments have shyed away from using stoichiometric coupling reagents in favour of using catalytic systems. Yamamoto *et al*. developed the first boronic acid catalysed amide synthesis (scheme 2.4).[29]



Scheme 2.4

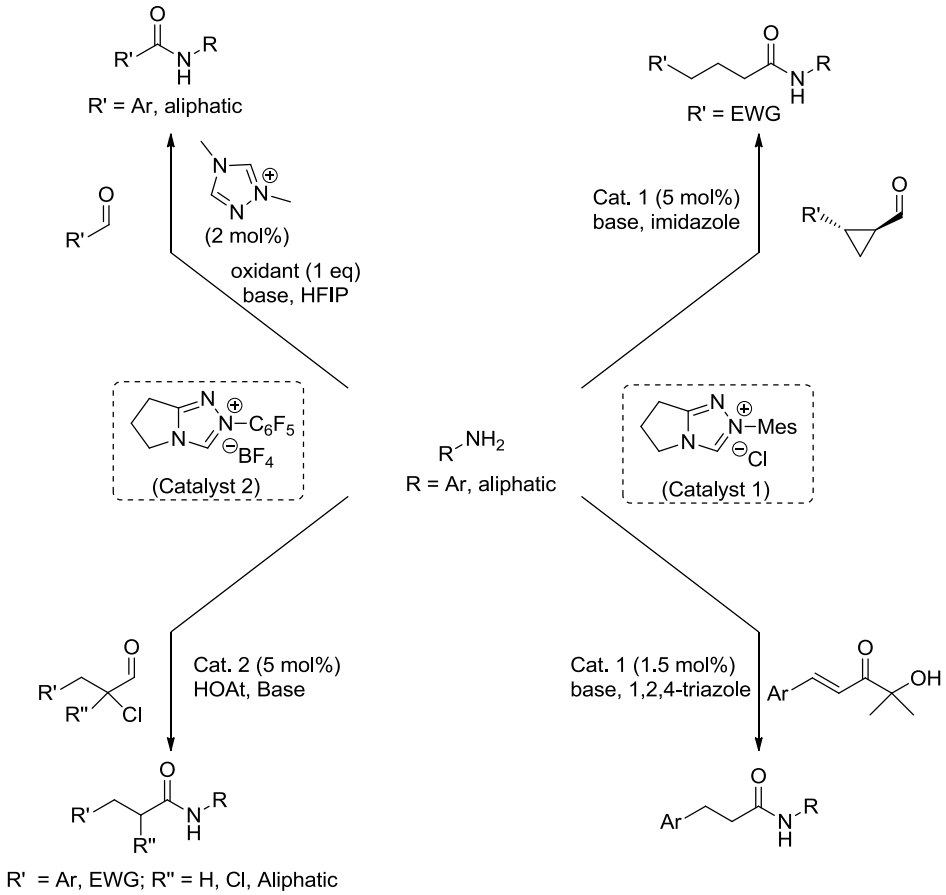
This reaction is assumed to proceed either *via* the boroxine species or by direct dehydration of the boronic acid with the carboxylic acid (scheme 2.5).



Scheme 2.5

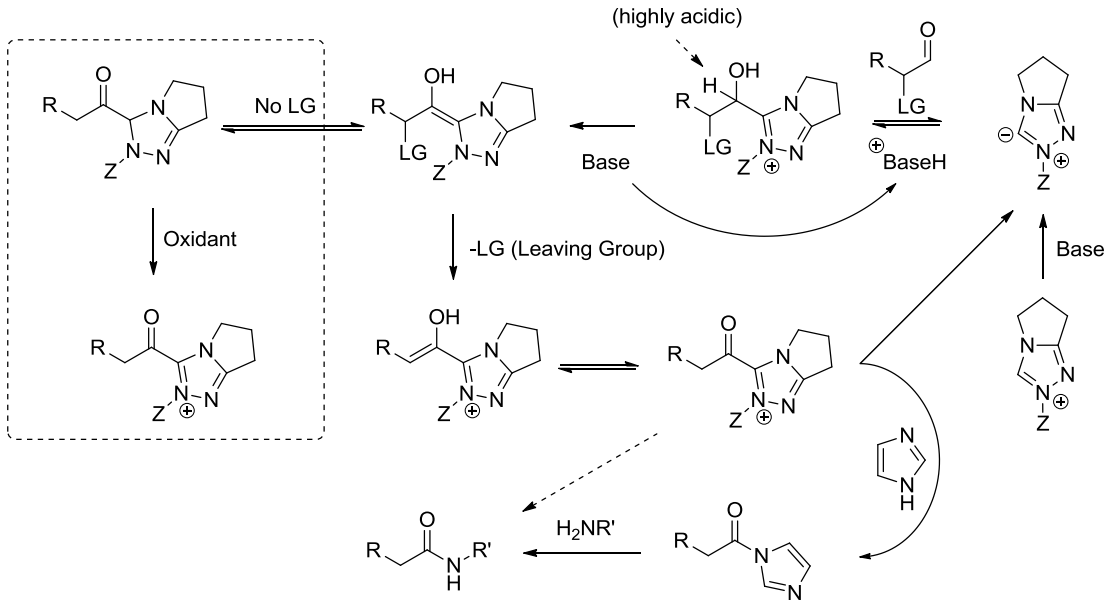
The substrate scope of the reaction seemed to be rather limited, with the majority of substrates comprising 'greasy' R groups. This method did demonstrate lactamisation of a number of amino acids in excellent yield, which is a useful result considering that most amino acid species are generally insoluble in most solvents. A recent review by Whiting *et al*. has revealed general improvements in boronic acid catalyzed amide synthesis,[30] however it appears that even with these improvements the method still tolerates only a limited substrate scope.

Another catalytic approach towards synthesising amides utilises N-heterocyclic carbenes as catalysts. A number of examples employing various precursor-types have been demonstrated using N-heterocyclic carbene mediated catalysis (scheme 2.6).[31]



Scheme 2.6

Again, the substrate scope is relatively limited as the starting materials are relatively complex and the reaction does not appear to tolerate R groups which are not 'greasy' (aliphatic or aromatic). Interestingly, all of these examples appear to proceed through a Stetter-like mechanistic cycle (scheme 2.7).



Scheme 2.7 The N-heterocyclic carbene catalyzed amidation reactions appear to generally follow this mechanistic cycle. The top left example, scheme 2.6, assumedly utilises an oxidant to rearomatise the NHC (dashed box) as there is no leaving group present; similar overall mechanism though.

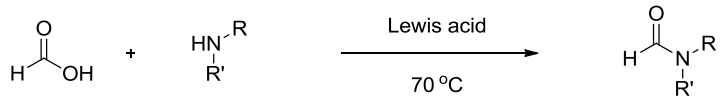
Further screening of the key variables, notably the catalyst and leaving group, may yet yield a more generally applicable methodology. Thus, the N-heterocyclic carbene approach deserves more attention; if further development improves the substrate scope (less complex starting materials and wider variety of substrates / products) then this certainly could be a strong contender for being the much sought after 'amide solution'.

2.3 Metal catalysed amide synthesis

Metal catalysed amide synthesis is a rapidly expanding area of research. There are many examples of various metals coupling various precursors to yield amides. A comprehensive review by Williams *et al.*[32] covers the majority of metal catalysed amide formations and is herein referred to in its entirety as a source of further information regarding this topic. A few

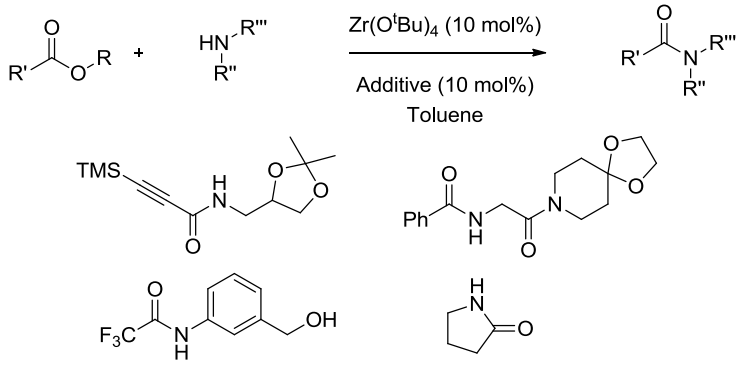
examples from this review which are somewhat relevant to this study are briefly discussed below.

The direct coupling of amines and carboxylic acids is inherently difficult to achieve using a metal catalyst as the natural equilibrium of the reaction between an acid, an amine and a metal is towards the corresponding ammonium-carboxylate salt and not a metal complex. Recent advances have determined that N-formylation can be achieved using a solvent-free reaction between formic acid and a range of amines in the presence of a metal salt; the initial discovery utilised ZnO,[33] however further advances have demonstrated that a whole host of Lewis acids are capable of mediating this reaction (scheme 2.8).[34]



Scheme 2.8

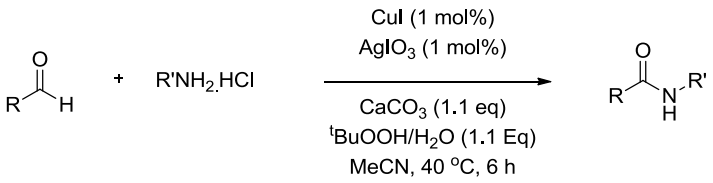
A number of metal catalysed reactions using esters as a starting material have proved to be highly successful,[35] with the most effective combination being group (IV) metal alkoxides in the presence of an activator (scheme 2.9).[36]



Scheme 2.9 Selected examples from the publication.

The mild reaction conditions and low reagent loadings, coupled to the wide range of functionality tolerance, including the formation of a lactam, instantly demonstrates a very powerful coupling system. The attractive use of metal catalysis for effecting the formation of

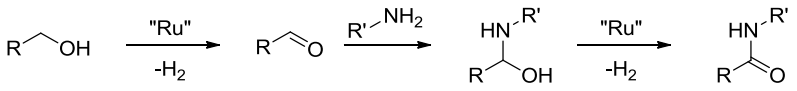
amides can also be found in a method developed by Wolf *et al*. which demonstrates an oxidative coupling between an aldehyde and an amine to form the corresponding amide (scheme 2.10).[37]



Scheme 2.10

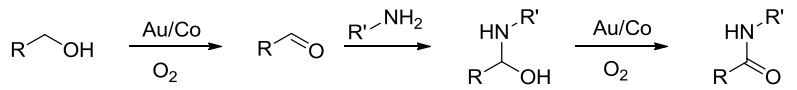
Although this method tolerated only a select group of substrates (yields decreased when an aliphatic or electron-poor arylaldehyde was used) and requires an aldehyde starting material, it did demonstrate the possibility of using abundant and cheap metals in catalytic quantities for generating amides.

More recently a flourish of publications demonstrating an oxidative coupling of alcohols with amines (and amine derivable precursors, such as nitro and azido compounds) to produce amides using ruthenium catalysts have surfaced.[38] The mechanism is proposed to proceed *via* sequential dehydrogenative oxidation processes (scheme 2.11).



Scheme 2.11

Kobayashi *et al*. have developed this concept further by utilizing an aerobic gold/cobalt system which performs sequential oxidation rather than dehydrogenation (scheme 2.12).[39]



Scheme 2.12

Thus, catalysis is clearly an attractive alternative to using one of the many stoichiometric amide coupling reagents. As mentioned at the start of this chapter, we speculated whether it would be possible to use the acylphosphonate observed in previous aerobic copper mediated

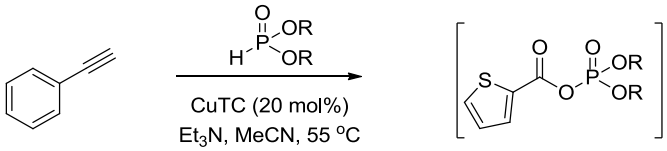
coupling reactions to produce amides. There are clear advantages to such a method if this is possible:

- the reaction is performed in air – no need for an inert atmosphere or any considerations regarding water (anhydrous conditions);
- dialkylphosphites are inexpensive reagents – diethyl phosphite (98%) is currently ~ £42 / 250 mL (Sigma-Aldrich);
- copper is an inexpensive and abundant metal;
- direct coupling of acid and amine – no need for complex starting materials.

As such, we proceeded to determine whether the aerobic copper-mediated system which produced acylphosphonate **59** could in fact be manipulated into becoming a general catalytic amide synthesis method.

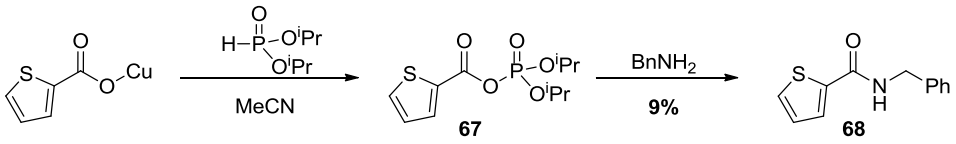
2.4 Results and Discussion – Aerobic copper mediated amide synthesis

We initially observed the acylphosphonate species whilst attempting to couple dialkyl phosphites with phenylacetylene using copper(I) thiophene-2-carboxylate (scheme 2.13).



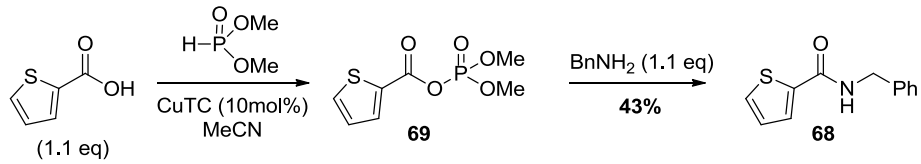
Scheme 2.13

In an initial attempt to form an amide from an acylphosphonate, diisopropylphosphite was reacted with stoichiometric CuTC until acylphosphonate **67** was detected (by mass spectrometry), followed by the addition of benzylamine (scheme 2.14).



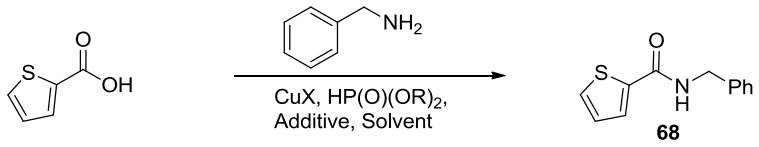
Scheme 2.14

Although the yield was low the fact that any amide was observed at all was a promising start. From previous empirical data we were aware that the steric bulk associated with the phosphite had a marked effect on reactivity (see chapter 1). A repeat using dimethyl phosphite confirmed this, and immediately (i.e. the next reaction attempted) it was apparent that the quantity of CuTC could be reduced to catalytic quantities (scheme 2.15).



Scheme 2.15

The marked improvement was a clear indicator that this reaction was highly dependent on the phosphite used. The significant improvement using the less-bulky phosphite was an excellent result as dimethyl phosphite is significantly less expensive than diisopropyl phosphite. From this success a number of optimisation reactions were performed (table 2.1).

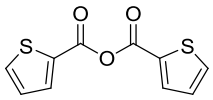


68

Entry	Acid (eq)	Amine (eq)	R (eq)	CuX (mol %)	Additive	Solvent	Yield (%)[a]
1	1.1	1.1	Me (1.0)	CuTC (10)	-	MeCN	43
2	1.2	1.0	Me (1.2)	CuTC (10)	-	MeCN	44
3	1.2	1.0	Me (1.2)	CuTC (10)	-	DMF	0
4	1.2	1.0	Me (1.2)	CuTC (10)	-	EtOAc	43
5	1.5	1.0	Me (1.5)	CuTC (20)	-	MeCN	46
6	1.5	1.0	Me (1.5)	CuI (20)	-	MeCN	22
7	1.5	1.0	Et (1.5)	CuI (20)	-	MeCN	36
8	1.0	1.2	Me (2.5)	CuI (20)	-	MeCN	31
9	2.0	1.0	Me (1.0)	CuI (20)	Et_3N (1.0)	MeCN	50
10	1.0	2.0	Et (1.2)	CuI (20)	-	MeCN	12 (73[b])
11	2.0	1.0	Et (1.0)	CuI (20)	Et_3N (1.0)	MeCN	55
12	**2.2**	**1.0**	**Et (2.0)**	**CuI (40)**	**Et_3N (1.1)**	**MeCN**	**68[c]**
13	4.4	1.0	Et (2.2)	CuI (40)	Et_3N (2.2)	MeCN	76[c]

Table 2.1. Conditions: Acid, amine, phosphite, copper salt and additives (where applicable) were dissolved in solvent (0.5M) and stirred at 55 °C for 4 h. [a]Isolated yield. [b]Corresponding phosphoramidate product – see chapter 3. [c]Thiophene-2-carboxylic acid, diethyl phosphite, Et_3N and CuI stirred at 55 °C for 90 mins prior to the addition of benzylamine.

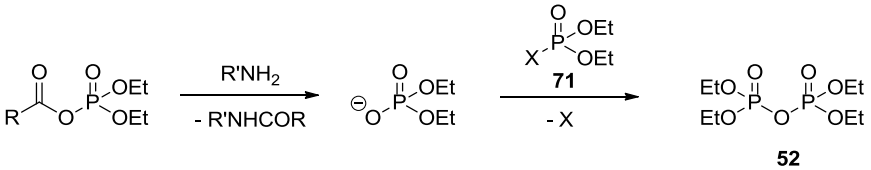
Using CuTC as the catalyst proved only to be useful for coupling to thiophene carboxylic acid. When switching to various other acids, 4 - 10% of the thiophene carboxylic amide was isolated as an often inseparable impurity. Replacing CuTC with CuI initially gave lower yields, however this was optimised to acceptable working levels as demonstrated in table 2.1. Preforming the acylphosphonate prior to addition of amine removed the initially capricious nature of this reaction and allowed for reproducible maximum yield (Table 2.1, Entry 12). Additionally, whilst preforming the reactive intermediate, the formation of the anhydride **70** (figure 2.1) was observed *via* mass spectrometry of the crude reaction mixture. This suggested more than one reactive pathway was present in forming the amide.



70

Figure 2.1

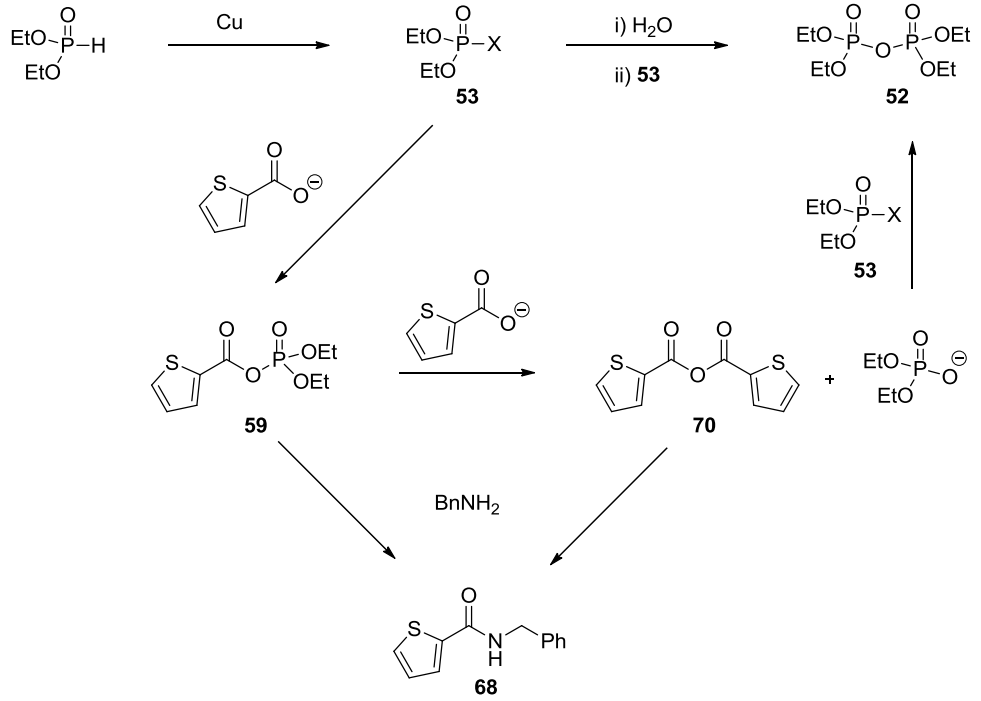
Although the reaction could be further improved to yield 76% amide (Table 2.1, Entry 13) the additional 2.2 equivalents of acid for an additional 8% yield did not seem practicable. Increasing the equivalents of phosphite led to improved yields, however the level of pyrophosphate **52** produced as a major byproduct increased significantly also. This was easily explained by the fact that as the reaction progresses the quantity of diethylphosphonate increases, which results in increased production of pyrophosphate **52** (scheme 2.16).



52

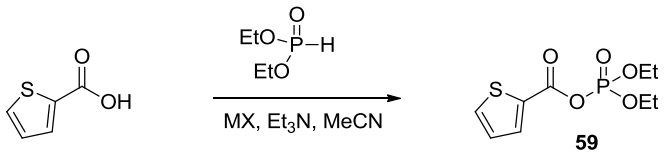
Scheme 2.16

From this data we were able to propose a reaction pathway which accounted for all of the observed species in the reaction (scheme 2.17).



Scheme 2.17

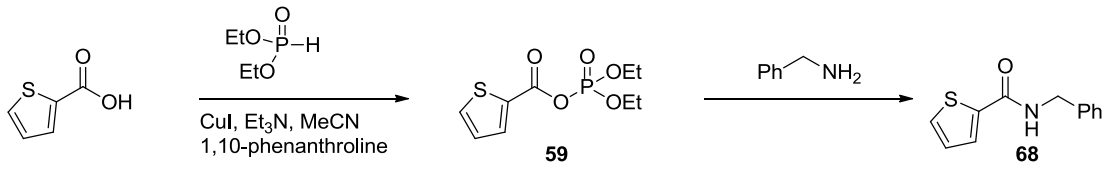
A number of first row transition metals were screened to determine whether any other metals could be used in this reaction. Unfortunately, none of the metal complexes tested demonstrated any catalytic turnover, with only a few showing trace oxidation of the phosphite by ^{31}P NMR and mass spectrometry (Table 2.2).



MX	59
$K_3Fe(CN)_6$	Zero
$FeCl_2$	Trace
$NiCl_2$	Trace
$CoCl_2$	Zero
$ZnCl_2$	Zero

Table 2.2 Reagents and conditions: Metal complex (20mol%), Et_3N (1.1 eq), Diethyl phosphite (1 eq), thiophene-2-carboxylic acid (1.2 eq), MeCN (0.5M), 55°C, 3h.

A further search of the literature for aerobic copper catalysed transformations found that a common feature was the addition of the 1,10-phenanthroline ligand to aid catalytic turnover. To determine whether this would enhance our conditions a standard reaction was performed with the addition of the ligand (scheme 2.18).

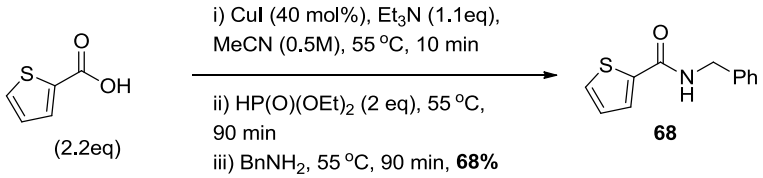


Scheme 2.18

Oxidation to the acylphosphonate intermediate **59** was successful, however the overall reaction was poor, with only 48% crude amide product isolated, which is significantly lower than the corresponding reaction without the ligand. This was attributed to effectively having an additional amine source in the reaction mixture which promotes byproduct (**51** and **52**) formation.

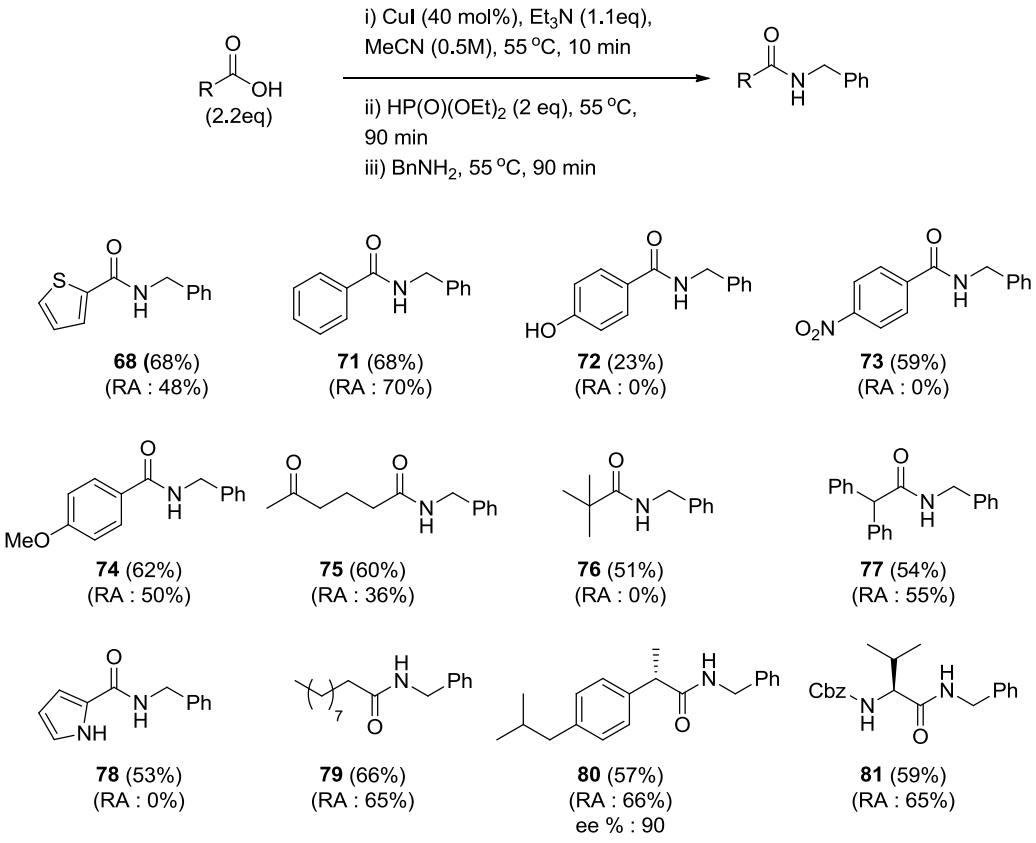
2.4.1 Generality of the Amide Synthesis method

Evidently, the best conditions for this reaction were those found in table 2.1, entry 12 (scheme 2.19).



Scheme 2.19

To examine the generality of this reaction a screen of carboxylic acids was performed, keeping benzylamine constant (Scheme 2.20). The reaction generally produced acceptable yields (51 - 68%) and tolerated a wide range of functionality. Recovery of the excess acid was, in most cases, successful and facile.

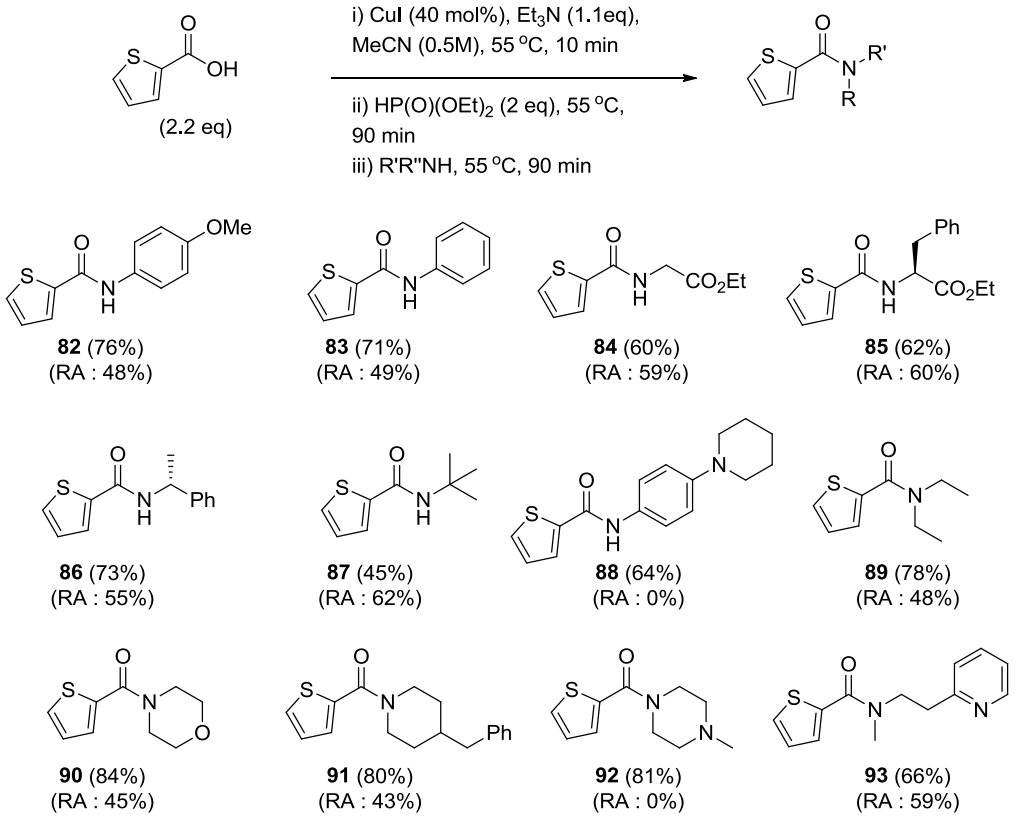


Scheme 2.20 RA = recovered acid.

Epimerisation of α-chiral centres is a problem which is regularly encountered whilst using common amide coupling reagents. To determine whether this method was prone to scrambling α-chiral centres an α-chiral acid was subjected to the coupling conditions. S-(+)-Ibuprofen was chosen as the test substrate as it is exceptionally prone to epimerization at the α-centre; the α-proton is particularly acidic as it is α to the carboxyl and is also in a benzylic position. Pleasingly, very little epimerization was observed (**80**, 90% ee as determined by chiral HPLC). This result was corroborated through the synthesis of compound **81** as said product possessed an $[\alpha]_D$ value which was comparable to enantiopure literature samples.

To further examine the generality of this reaction a screen of amines was performed, keeping thiophene-2-carboxylic acid constant (Scheme 2.21). Again, acceptable yields were observed

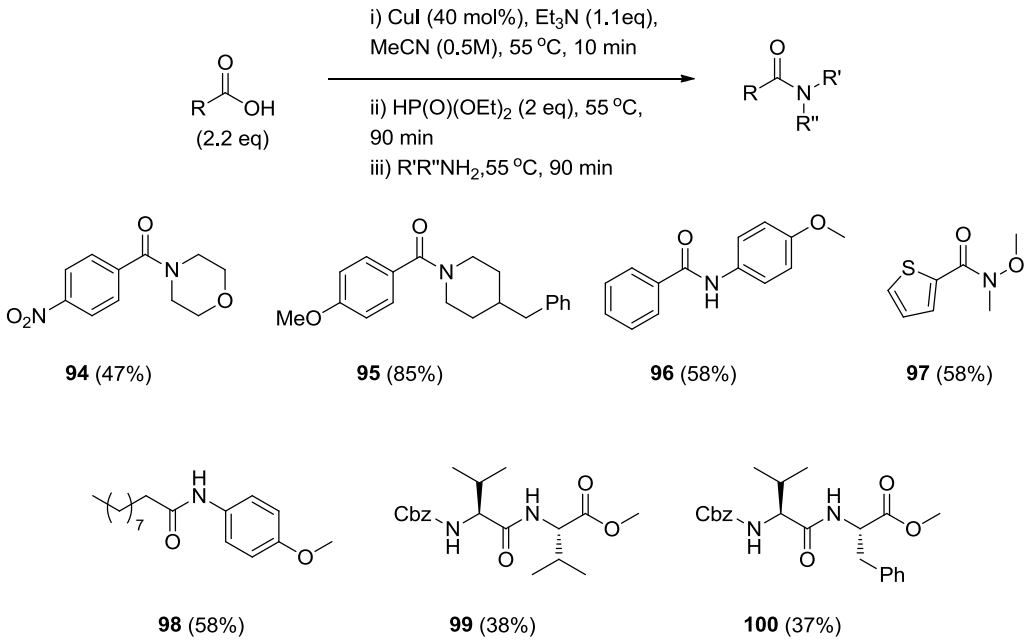
(45 - 84%) and a range of functionalities were tolerated. Interestingly, secondary amines generally gave higher yields than primary amines.



Scheme 2.21 RA = recovered acid.

A final set of amides was synthesised using various acids and amines to confirm the method remained general (scheme 2.22). Moderate to excellent yields were obtained, confirming the coupling can be used across a range of substrates.

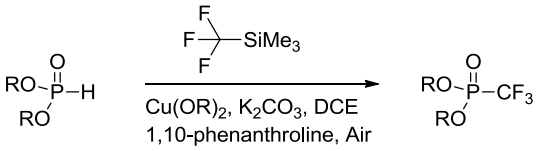
The synthesis of dipeptides was also possible, although the yields were only modest. Of the nitrogen protecting groups employed (Boc, Ac, Cbz) only the Cbz protected product could be isolated. We attributed this to the acid sensitivity of the Boc group (the pH of the reaction mix remains ~5 - 6 during the reaction) and solubility issues when using acetyl protection. To date, the highest yield achieved for peptide synthesis using this method remains at 38%.



Scheme 2.22

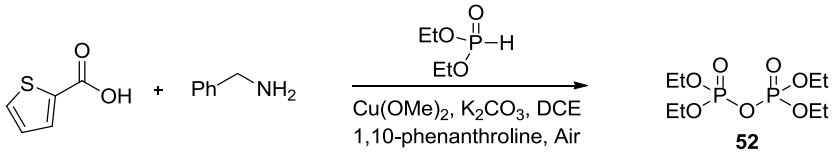
2.4.2 Amide Synthesis – Further Optimisation

More recently a method was published which utilised copper hydroxide and, more interestingly, copper alkoxides in the presence of air to catalyse the trifluoromethylation of phosphites (scheme 2.23).[40]



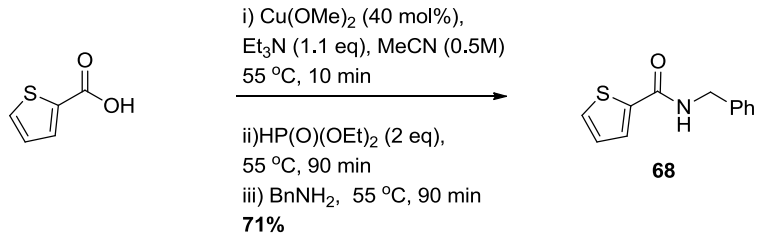
Scheme 2.23

Presumably a similar reaction mechanism is occurring to our system (oxidation of the phosphite to an electrophilic species as the initial step) thus copper alkoxides should catalyse the amide coupling. Applying the conditions reported in the publication in an attempt to form amide resulted in exclusive formation of **52** (scheme 2.24).



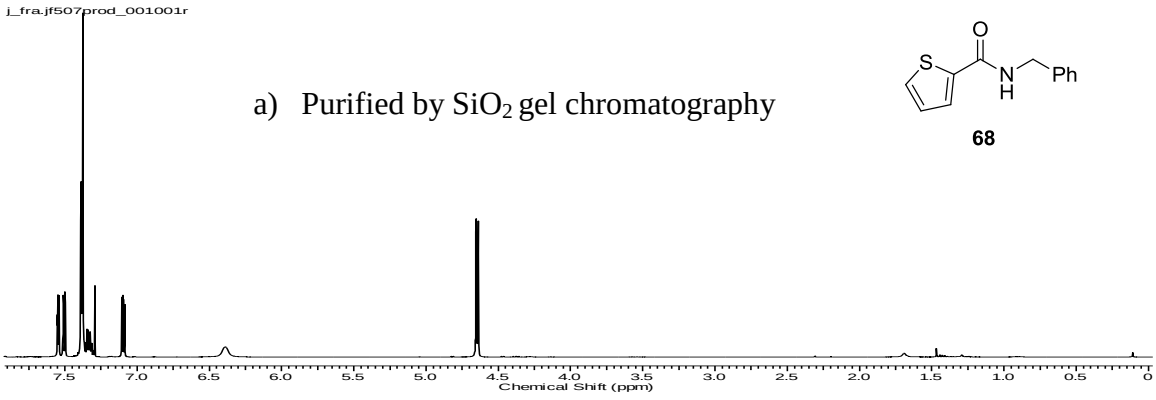
Scheme 2.24

As the reported literature conditions were unsuccessful for producing the amide, we repeated the reaction using our optimal conditions, replacing CuI with $Cu(OMe)_2$ (scheme 2.25).



Scheme 2.25

We found that $Cu(OMe)_2$ gave a slight improvement on using CuI and this prompted further investigations to determine whether further improvements could be made. An initial repeat of the reaction at half catalyst loading (20 mol%) found the reaction was as high yielding as before (72%). Reducing the quantity of diethyl phosphite from 2 to 1.1 equivalents resulted in a slight reduction in yield (61%). This was attributed to increased byproduct formation; pyrophosphate (P-P) was forming which was indicative of excessive quantities of base (based on previous empirical observations which are not reported herein). An easy solution to this issue was to reduce the loading of Et_3N from 1.1 to 0.5 equivalents. Disappointingly the yield remained unchanged (61%), however there was no need for chromatographic purification as washing the crude reaction mixture with saturated $NaHCO_3$ followed by 2M HCl resulted in an almost pure amide (>95% purity, figure 2.2).



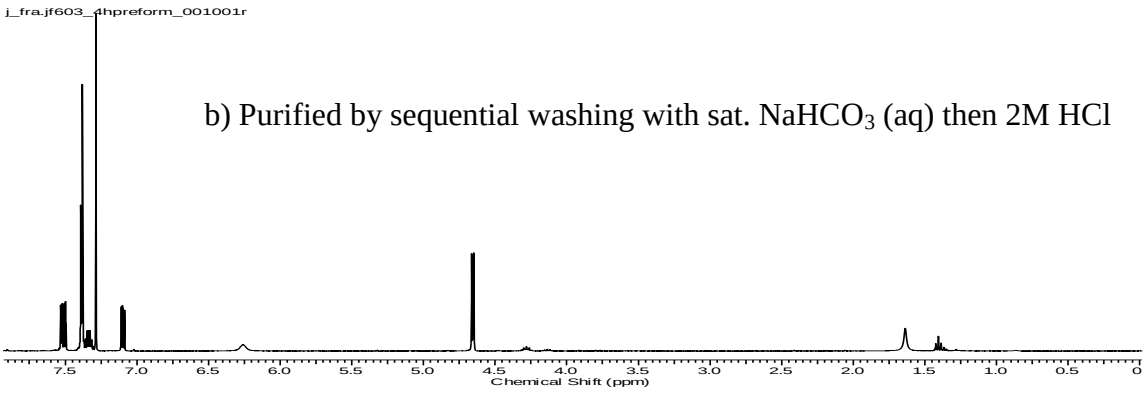


Figure 2.2 ^{1}H NMR of a) Product purified by column chromatography; b) product purified by aqueous washing.

The amide could be completely purified by recrystallization. This resulted in clean amide (>99% pure) in 54% yield. Reducing the loading of Et_3N further (0.2 equivalents) resulted in a diminished yield (48%) with hypophosphate (P-O-P) byproduct also being observed (10%). Finally, we aimed to improve the 'green chemistry' profile of this method further by running the reaction in one of the industrially preferred solvents. Acetonitrile is classed as usable, however switching to ethyl acetate or methanol would be preferential. Unfortunately, neither of these solvents proved useful for this transformation; ethyl acetate generated a slurry with a poorer impurity profile and methanol suppressed catalytic turnover. Interestingly, whilst using methanol as solvent, the major product that did form (albeit in low quantities) was diethylmethylphosphonate, suggesting the reactive intermediate phosphorus species was trapped by the solvent. This suggests further scope for this reaction set, however to date no further work has been performed.

As we had a particularly useful set of conditions for synthesising amides with minimal purification requirements our focus turned to utilising the method for array synthesis. This system preferentially utilises a filtration workup rather than aqueous and as such the development of a filtration-type workup procedure rather than aqueous was required. Using basic Al_2O_3 in combination with SiO_2 was insufficient for scrubbing the excess acid from the

reaction mixture, consistently yielding the amide with starting material acid as a major impurity. Replacing basic Al_2O_3 with Amberlyst® A-21 resin (a polymer supported alkylamine) did not improve the acid scavenging sufficiently and in fact increased the quantity of copper impurities (the product was green and signals were broadened in the ^1H NMR). Using a bilayer of silica and solid K_2CO_3 resulted in clean product being isolated, however passing solvent through the K_2CO_3 layer caused it to coagulate and thus the plug could not be flushed, resulting in low yield. This was easily remedied by premixing SiO_2 with K_2CO_3 (50/50, v/v) prior to loading. Initial results yielded amides with 90 – 100% purity, but increasing the polarity of some products required the plug to be flushed with acetone (in place of CH_2Cl_2) causing impurities to coelute (figure 2.3).

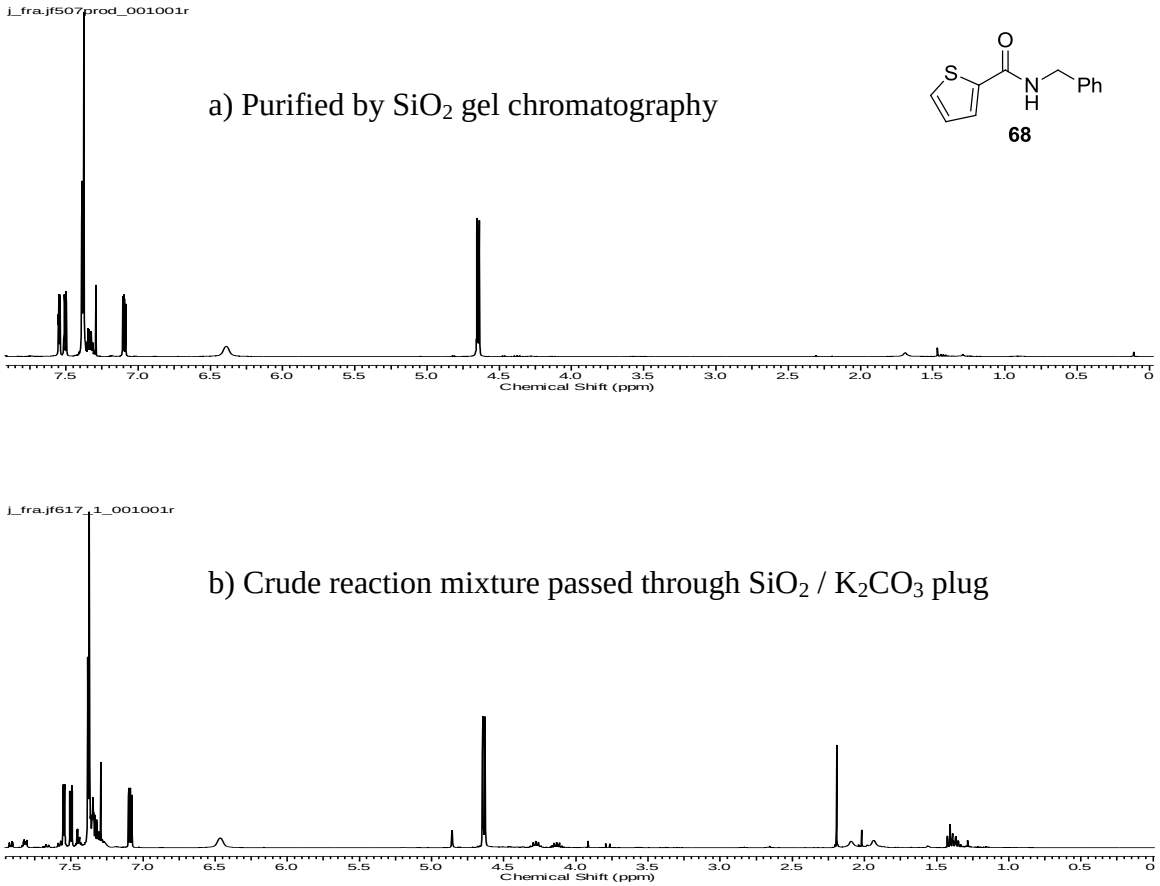


Figure 2.3 ^1H NMR of a) Product purified by column chromatography; b) product purified by passing crude reaction mixture through a plug of 50/50 (v/v) SiO_2/K_2CO_3 and eluting with acetone.

The products obtained were of relatively high purity (>80%), moderate to high yielding (up to 95%), and could be further purified by washing with saturated $NaHCO_3$ followed by 2M HCl. Additionally, the crude material could be recrystallised to generate clean amide (>99% pure) in 51% yield (figure 2.4).

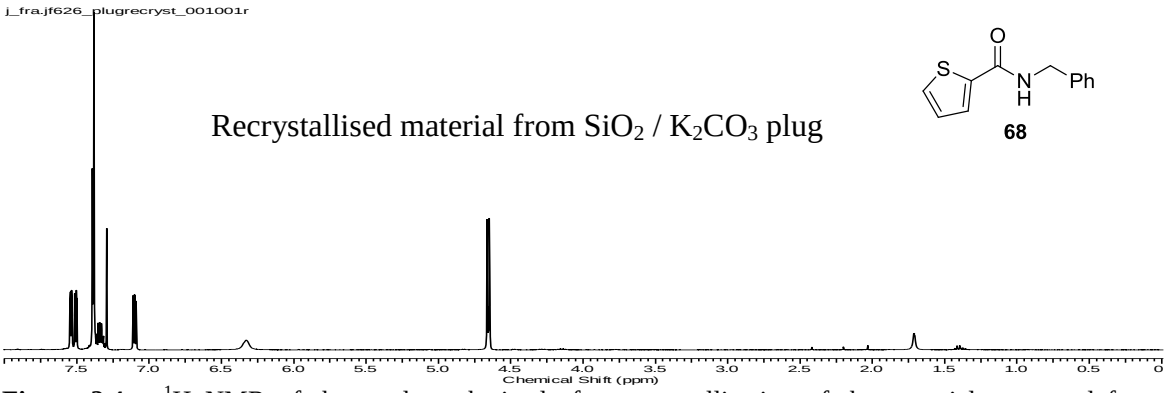


Figure 2.4 ^1H NMR of the product obtained after recrystallization of the material recovered from the SiO_2/K_2CO_3 plug.

The high purity of the recovered product from such a simple workup and purification strategy could be of significant benefit for high throughtput screening strategies as products obtained from this method could be advanced to further synthetic steps or biological testing with no further purification required. Furthermore, purification of these sorts could prove beneficial to the chemical industry in general as the solvent requirement for this purification method is far less than that of traditional purification techniques. To demonstrate this point, the solvent use of the initial coupling conditions (requiring aqueous workup and column chromatography) was compared to the solvent requirements for the aqueous workup and the plug filtration isolation/purification methods (figure 2.5).

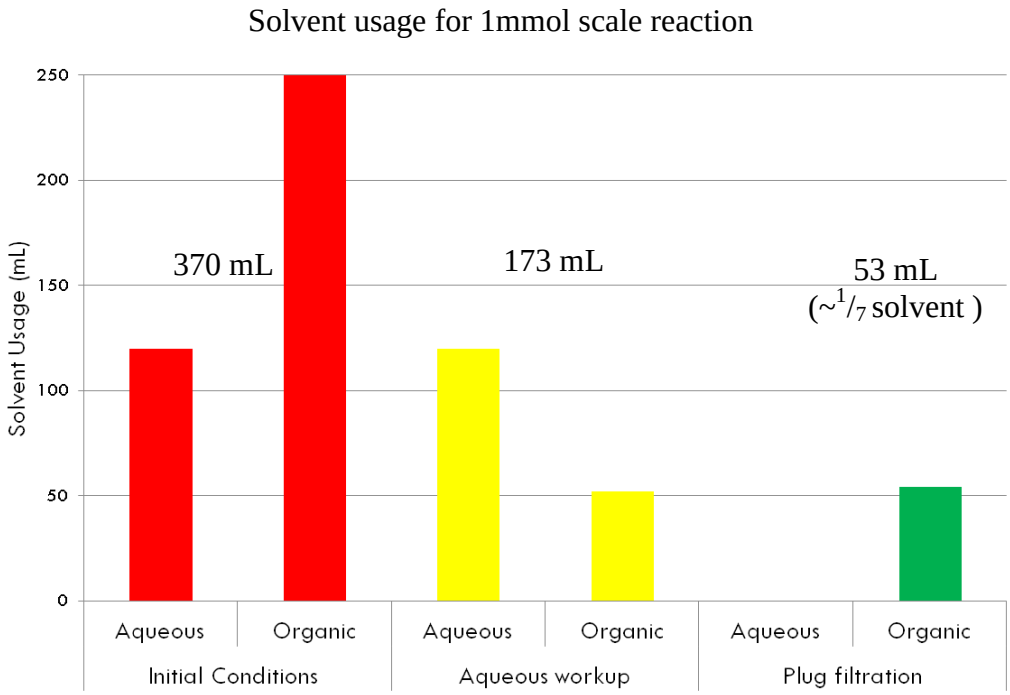
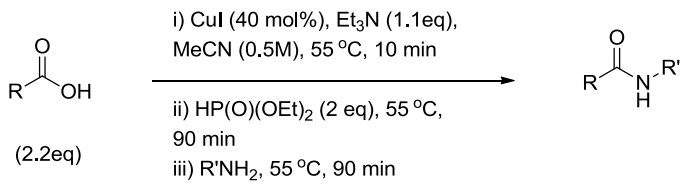


Figure 2.5. Typical solvent usage for a 1mmol scale amide coupling reaction. Initial conditions refer to scheme 2.17. Aqueous workup and plug filtration reaction conditions: $Cu(OMe)_2$ (20 mol%), Et_3N (0.5 eq), diethyl phosphite (1.1 eq), thiophene-2-carboxylic acid (2.2 eq), MeCN (0.5M), benzylamine (1 eq).

Amide synthesis *via* catalysis is an attractive concept. This copper catalysed amide coupling is still its infancy, yet, from the results obtained to date, it is worthy of further study. It uses cheap, low molecular weight coupling reagents alongside low solvent usage for purification, thus providing a more environmentally friendly ('green') amide formation strategy. Evidently, this is an area which requires further attention in order to maximise its potential.

2.5. Conclusions – Amide Synthesis

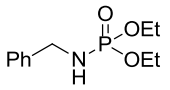
Mechanistic studies of the aerobic copper mediated synthesis of alkynylphosphonates allowed us to propose that the phosphite was being oxidised to a reactive electrophilic species. This in turn has allowed us to develop a novel methodology for the production of amides which is tolerant of a wide range of acids and amines.



3. Phosphoramidate synthesis

3.1 Introduction

A final observation of interest was the unexpected formation of the phosphoramidate product **101** observed during amide synthesis optimisation studies (table 2.1, entry 10).



101

Figure 3.1

3.2 Phosphoramidates – Brief overview

Phosphoramidates are a class of compounds which are relatively understudied. There are a handful of examples wherein the phosphoramidate moiety has been incorporated into a pharmaceutical compound,[41] however most of the study associated with this moiety can be found in modified nucleotide synthesis. A number of phosphoramidate and thiophosphoramidate linked dinucleotides have been reported (figure 3.2).[42]

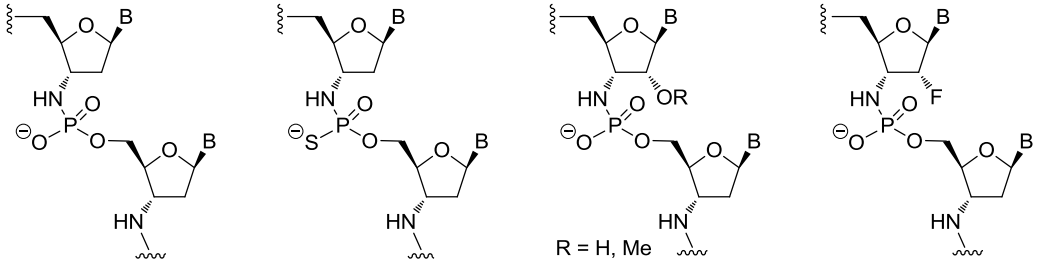
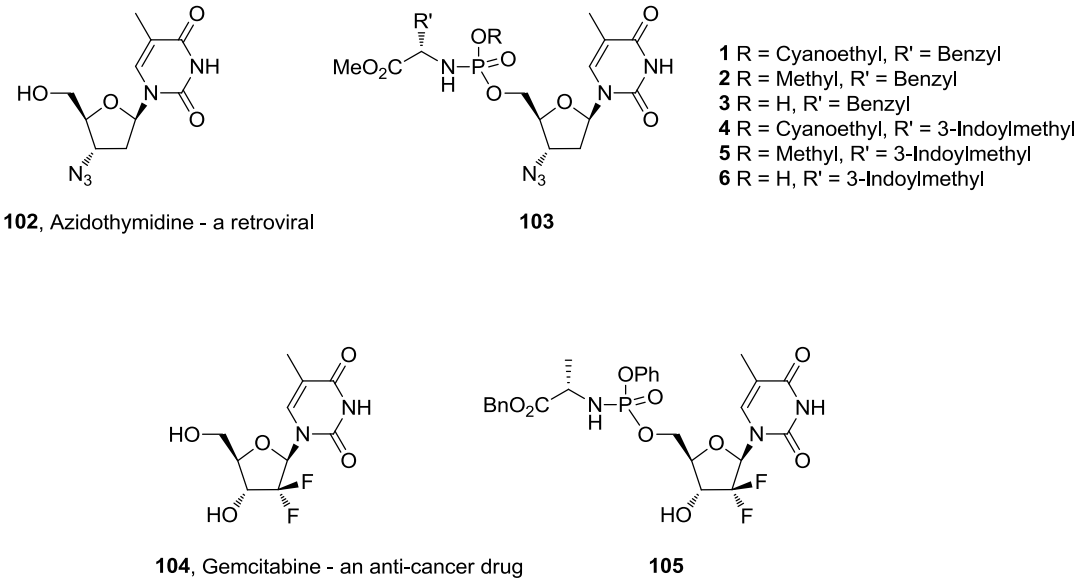


Figure 3.2

Oligonucleotides comprising one or more phosphoramidate link can significantly increase the nuclease stability of such compounds and form stable duplexes with their Watson-Crick counterparts. Oligonucleotide phosphoramidates and especially thio-phosphoramidates conjugated with lipid groups are cell-permeable and demonstrate high biological target specific activity in vitro. In vivo, these compounds show good bioavailability and efficient biodistribution to all major organs, while exerting acceptable toxicity at therapeutically relevant doses. An example of such a compound is the thiophosphoramidate 13-mer "Imetelstat", a telomerase inhibitor, which is a potent anticancer compound and is currently

in phase I/II clinical trials. A review by Gryaznov covers this area in exceptional detail and is herein referred to in its entirety as a source of further information for phosphoramidate linked nucleotides.[43]

In addition to phosphoramidate linked oligonucleotides demonstrating interesting biological properties, incorporation of a phosphoramidate moiety into a number of current modified nucleoside pharmaceticals have been demonstrated to increase their potenct (scheme 3.1).



Scheme 3.1 Two current examples of drugs with improved biological properties after incorporation of a phosphoramidate moiety.

The azidothymidine (AZT) prodrugs **103-1** to **103-6** were found to be non-cytotoxic at concentrations of 100 μM whilst inhibiting HIV-1 replication at concentrations of 0.08 – 30 μM.[44] Furthermore, cells treated with the active AZT diesters contained four fold more phosphorylated AZT than those treated with AZT, with no free AZT found in the sample (figure 3.3).[45] A similar observation is observed with the prodrug of Gemcitabine (**105**).[46] The increased accumulation of the prodrug can be attributed to the additional 'grease' attached to the drug, making it more lipophilic (in the case of the Gemcitabine prodrug, **105**, the lipophilicity was >1000 times that of Gemcitabine, **104**). This allows the prodrug to pass through the cell membrane by a passive diffusion mechanism instead of requiring active transport, as is required with the unmodified drug.

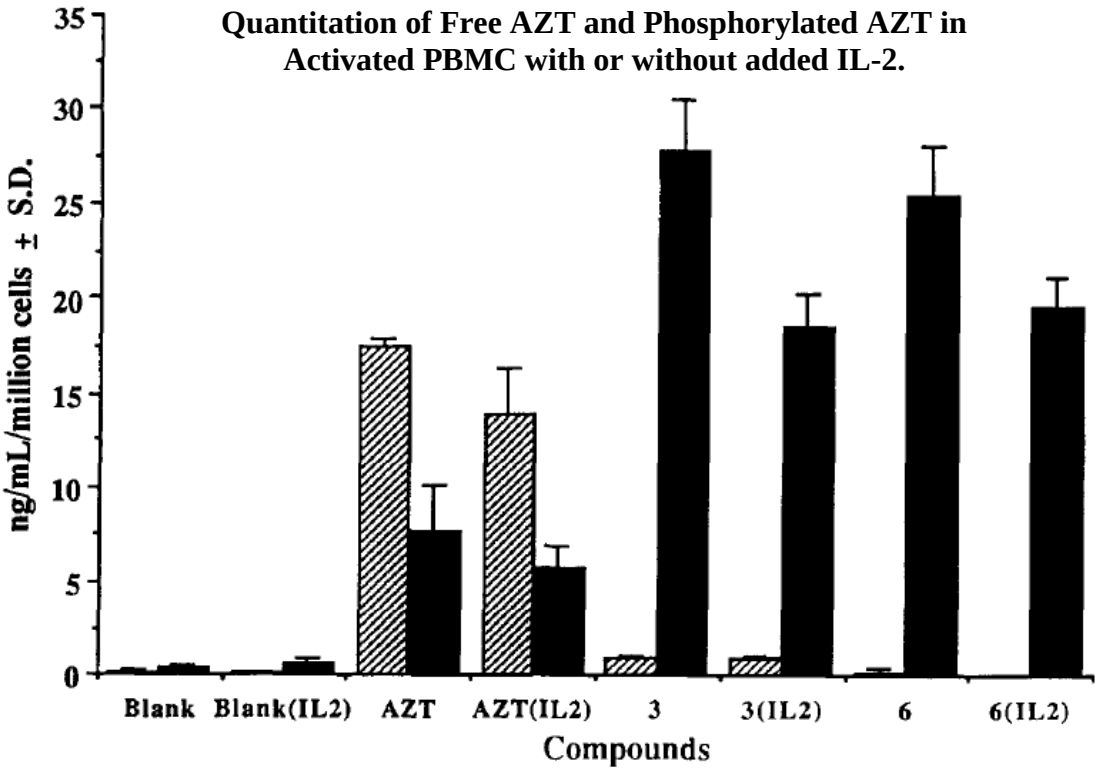
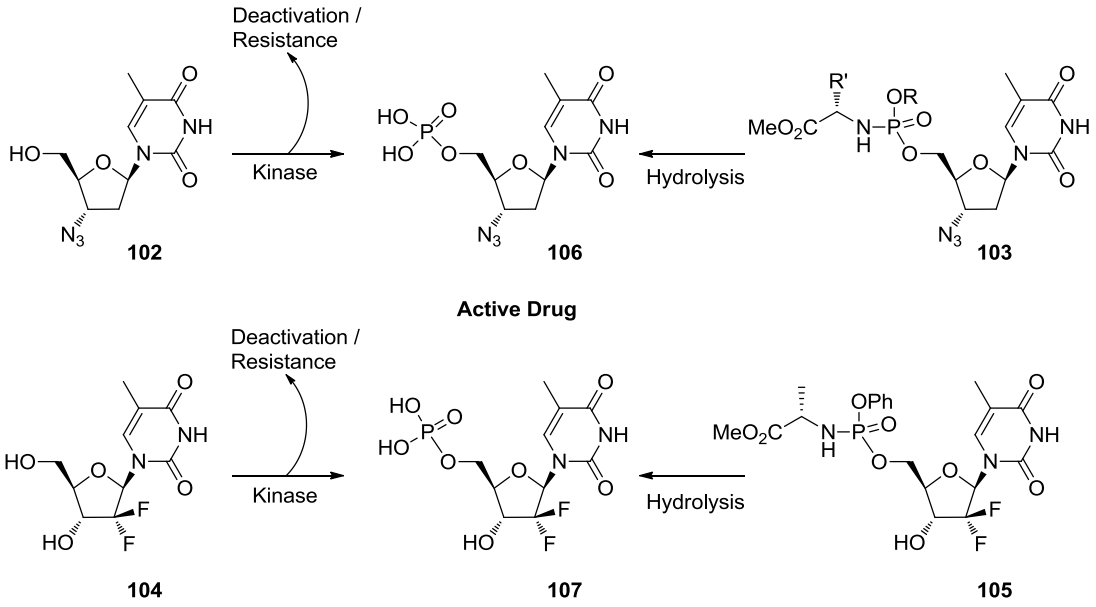


Figure 3.3 Striped blocks refer to the amount of free AZT nucleoside determined in the sample, while the solid blocks refer to the amount of phosphorylated AZT measured in the sample. The notation (IL2) refers to the results of experiments in which interleukin-2 (IL2) was added. Blank samples refer to untreated peripheral blood mononuclear cells (PBMC) grown under identical conditions. Graph: Reference 45.

The biological activity of modified nucleosides, for example AZT and Gemcitabine, requires intracellular metabolism to nucleoside 5'-mono, di- or triphosphates by kinase-mediated phosphorylation (**106** and **107**) to bind to their molecular targets.[47] However, inefficient intracellular phosphorylation of the nucleoside may reduce the efficacy of these agents. This may result either from the poor affinity of unnatural nucleoside to the kinase or from a decreased nucleoside kinase activity leading to drug resistance.[47] Thus, the use of the phosphoramidate prodrug delivers an already phosphorylated 5' nucleoside, removing the (often rate limiting) phosphorylation step (scheme 3.2).



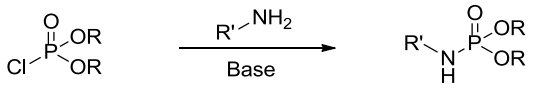
Scheme 3.2

Evidently, incorporation of a phosphoramidate moiety into pharmaceutical compounds can significantly improve the biological properties of said compounds. However, mild methods for their synthesis appear to be somewhat lacking.

3.3 Synthesis of the phosphoramidate link

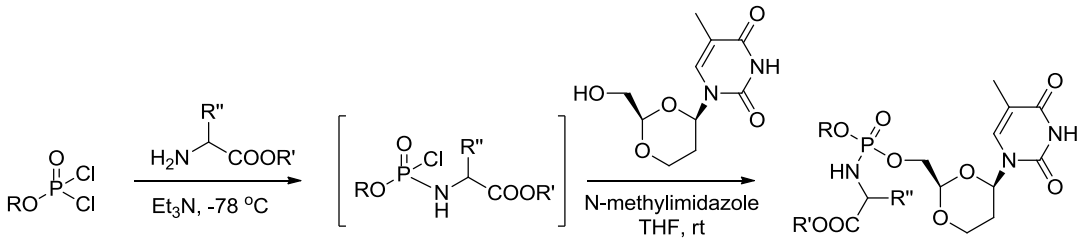
There appears to be only a few routes to producing compounds comprising the phosphoramidate moiety, using relatively standard chemistry. As mentioned above, Mizuno *et al*. have recently developed an aerobic copper mediated method for producing N-acylphosphoramidates (scheme 1.37),[24] however there was no mention of this method being applicable to amines to form phosphoramidates.

Phosphoramidates can be produced using a phosphoryl chloride and an amine (scheme 3.3).



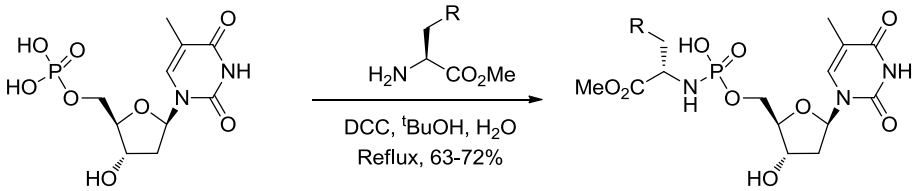
Scheme 3.3

As mentioned previously, phosphoryl chloride (halide) species are corrosive and not particularly applicable in large scale synthesis. However, the use of a phosphoryl chloride has been found to be effective in producing a nucleoside-type phosphoramidate product (scheme 3.4).[48]



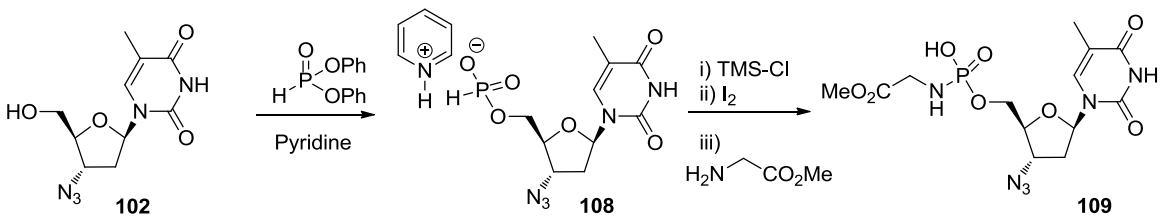
Scheme 3.4

Wagner *et al* demonstrated the formation of a phosphoramidate through the cross coupling of a phosphonate and amine using DCC (scheme 3.5).[49]



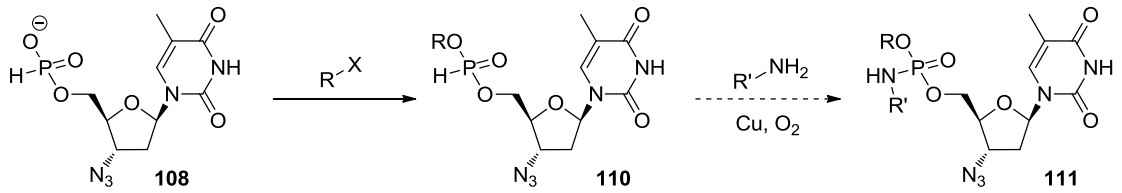
Scheme 3.5

These conditions are mild and produce good yields, but, as mentioned in chapter 2, the use of coupling reagents reduces atom efficiency and produces hazardous (and often inseparable) by-products. An alternative approach by Wagner utilised a method developed by Stawinski *et al*. wherein a transesterification to produce an H-phosphonate was followed by the production of a phosphoryl iodide *in-situ* which was then trapped by an amine (scheme 3.6).[50]



Scheme 3.6

The production of the phosphoryl iodide is not favourable as it is highly reactive and produces HI as a byproduct. However, the phosphite intermediate **108** is particularly interesting (scheme 3.7).



Scheme 3.7

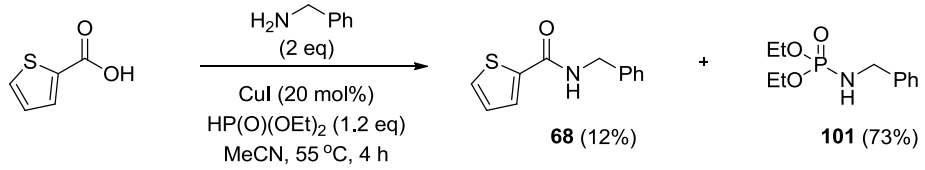
We could envisage alkylating the intermediate phosphite **108** to produce phosphite **110**, followed by copper mediated cross coupling with an amine to form **111**. Should it be possible to optimise the aerobic phosphoramidate cross coupling reaction then it becomes immediately apparent that:

- a wide range of compounds could be produced, in which both R and R' can easily be manipulated; and
- the method could be mild enough to tolerate a wide range of functionality.

As such, we proceeded to optimise this reaction.

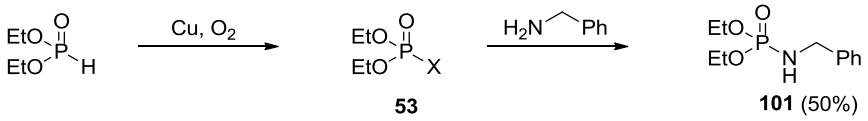
3.4 Results and discussion – copper mediated phosphoramidate synthesis.

The initial reaction which produced almost exclusively the phosphoramidate utilised an excess of benzylamine (table 2.1, entry 10, scheme 3.8).



Scheme 3.8

We proposed that the oxidised phosphite (reactive electrophilic phosphorus species generated *in situ*) was being trapped by the excess amine present in the reaction mixture (scheme 3.9).

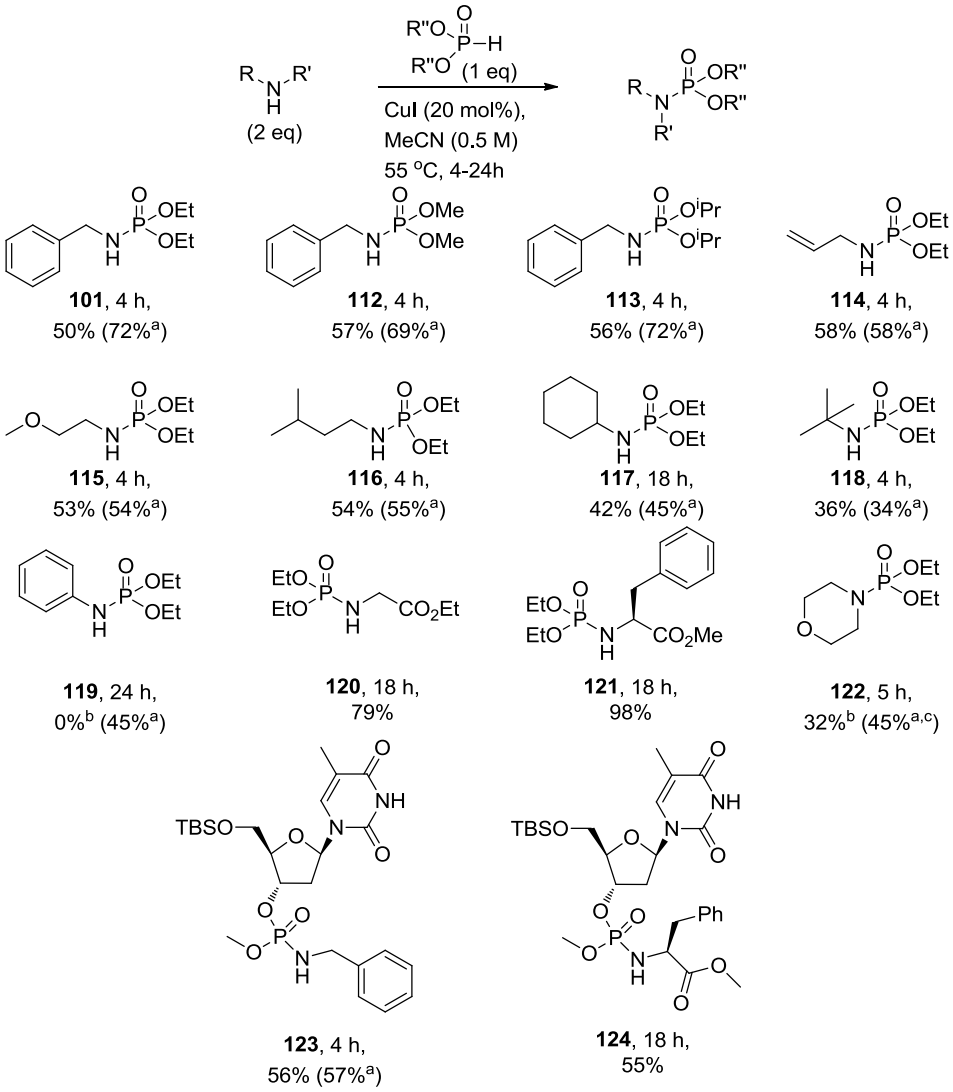


Scheme 3.9

Removing the acid entirely resulted in exclusive production of **101**, albeit in slightly lower yield (50%), which corroborated our hypothesis. From this result, a screen of amino acids against a number of phosphites was performed (scheme 3.11). Pleasingly, all of the primary amines tested generated acceptable yields of the corresponding phosphoramidate, however secondary amines proved to be less successful, with lower yields observed. Of the phosphites screened, only the reactions involving diphenyl phosphite were unsuccessful.

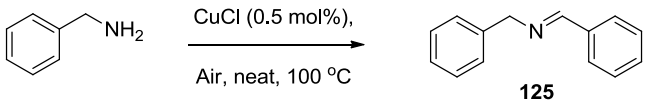
We speculated that the observed reduction in yield upon removal of the acid was due to a buffering effect caused by formation of the corresponding ammonium-carboxylate salt. From this speculative hypothesis we proposed that adding an equivalent of acid to the reaction mixture could increase the yield of phosphoramidate generated. Testing this hypothesis, we immediately determined that addition of an equivalent of acetic acid to the reaction increased the yield of **101**. Furthermore, addition of an equivalent of acetic acid allowed aniline to

couple to diethyl phosphite to form **119** in moderate yield. As such, a number of the examples were repeated with the addition of one equivalent of acetic acid.



Scheme 3.11 [a]1 eq AcOH added to the reaction mixture. [b]Aniline polymerises, forming a black insoluble polymer. [c] Product isolated with 8% (determined by ^{1}H NMR) inseparable tetraethyl hypodiphosphate.

For some of the examples addition of an equivalent of acetic acid increased the yield of phosphoramidate, however most produced identical results to the reaction wherein no acid was present. An alternative explanation to that proposed initially is that the amines which generate higher yields with an equivalent of acid are themselves prone to oxidation by copper. Adimurhy *et al*. demonstrated copper mediated oxidation of amines, including oxidation of benzylamine to **125** (scheme 3.12).[51]



125

Scheme 3.12

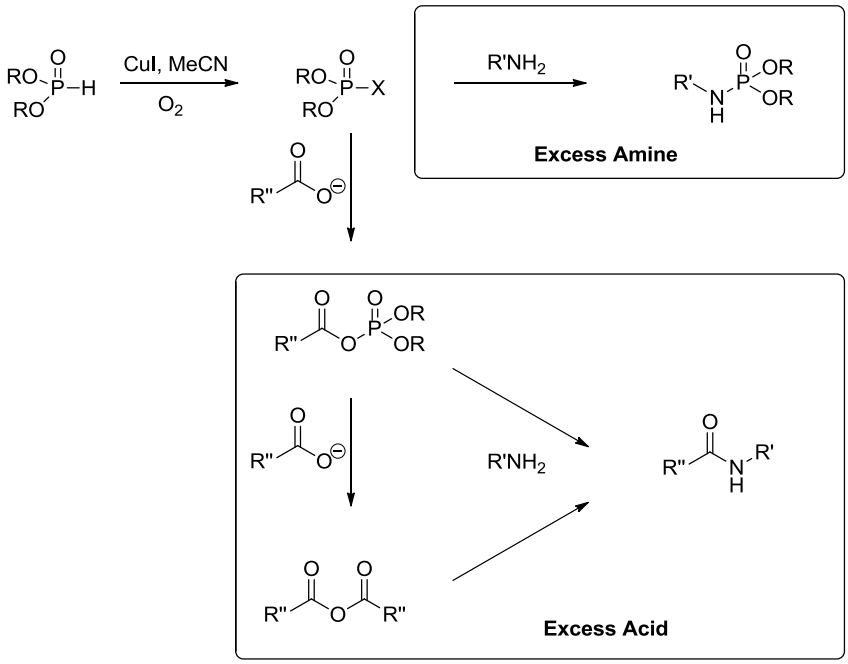
An equivalent of acid could reduce the rate of oxidation of the amine (*via* protonation, 'deactivating' the lone pair) hence increasing the lifetime of the amine in the reaction vessel. Future studies on this system should investigate the effect of varying the salt generated *in situ*.

3.5 Nucleoside phosphoramidates

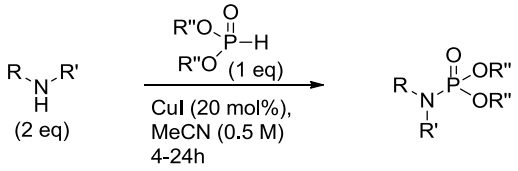
The most interesting of the results obtained was the production of nucleosides comprising a phosphoramidate link (**123** and **124**). This strongly implies that the initial proposition in scheme 3.7, wherein the R and R' groups are easily manipulated, is a realistic possibility, and requires further attention.

3.6. Conclusions – Phosphoramidate Synthesis

During the optimisation studies towards forming amides (Chapter 2) it was observed that in the presence of excess amine the preferential reaction product was the corresponding phosphoramidate product rather than the (then desired) amide product (table 2.1, entry 10). We herein propose that the mechanism of formation of the amide and phosphoramidate is similar in both instances, with both requiring an electrophilic phosphorus intermediate.



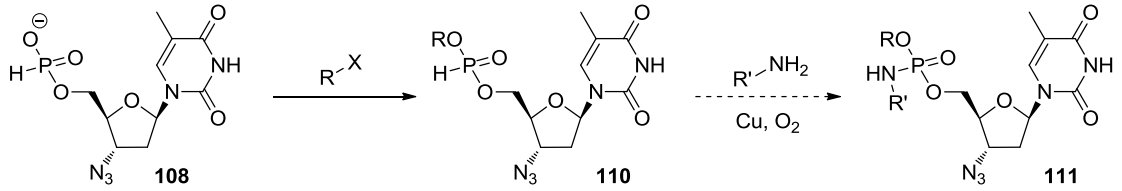
This has been developed into a general method for forming phosphoramidates, and tolerates a wide range of amines and phosphites.



4. Future Work

Continuing to develop the aerobic copper mediated amide synthesis would be a wise use of research resources. Should this method be developed to the level where the yields are consistently high whilst maintaining low solvent usage during purification then it will stand apart from the current methodology: cheap catalyst, cheap low molecular weight stoichiometric coupling reagent, good atom efficiency, no inert atmosphere required, low toxicity aqueous soluble byproduct, and good functionality tolerance.

Further studies into determining whether it is possible to produce various nucleosides comprising a phosphoramidate moiety *via* our novel copper mediated phosphoramidate synthesis should at least be attempted.



Should this prove successful then it may allow the production of a wider range of biologically active compounds of this type.

5. Experimental

Starting materials were obtained from commercial suppliers and used without further purification unless otherwise stated. THF was distilled from K/benzophenone. CH_2Cl_2 was distilled from CaH_2. Reactions were performed under an argon atmosphere unless stated otherwise. All couplings utilising copper were performed under air and under non-anhydrous conditions.

Thin layer chromatography (TLC) was carried out on Merck silica gel pre-coated sheets SIL G/UV_{254}. They were visualised by exposure to UV light (254 nm) followed by staining with basic potassium permanganate and/or vanillin as appropriate. Flash column chromatography was carried out using Merck silica gel 60, 35-70 μm particles as the stationary phase with solvents of analytical purity. All petrol used was petroleum ether (boiling point: 40-60 $^{\circ}$C) and all water was previously deionised.

NMR spectra were obtained as dilute solutions in the appropriate solvent at 25 $^{\circ}$C unless otherwise stated. ^{1}H NMR and ^{13}C spectra were recorded on a Brücker DPX 400 MHz, AV400 MHz, AVIII 400 MHz, AVIII 500 MHz or Jeol EX 270 MHz spectrometer. All chemical shifts were recorded on the δ-scale using residual solvent as an internal standard ($CDCl_3$: δ_H 7.28, δ_C 77.16; $(CD_3)_2SO$: δ_H 2.50, δ_C 39.43; D_3COD: δ_H 3.31, δ_C 49.05; C_6D_6: δ_H 7.16, δ_C 128.06). All coupling constants are reported in hertz (Hz), and multiplicities were labelled s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), dd (double doublet), dt (double triplet), dq (double quartet), ddd (double double doublet), m (multiplet). The prefixes br (broad), app (apparent) and quat (quaternary) were used. Assignments were made based on chemical shift and where appropriate, with the benefit of DEPT sequences and correlation techniques (COSY, HMQC, HMBC).

Infrared spectra were recorded on a Perkin-Elmer 1600 FT spectrometer, as dilute solutions in $CHCl_3$ unless otherwise stated.

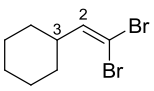
Mass spectra were recorded using a MicroTOF 61 spectrometer using electrospray (ES^+) or (ES^-) or electron ionisation techniques.

5.1 Preparation of vinyldibromide precursors.

General procedure (A)

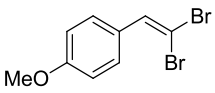
To a stirring solution of Ph_3P (2 eq) in CH_2Cl_2 (1.7 M) was added CBr_4 (1 eq) in CH_2Cl_2 (0.9 M) at 0 °C and the resulting solution stirred in the dark for 25 minutes. Et_3N (0.65 eq) was added and the mixture stirred in the dark for a further 15 minutes at 0 °C before addition of the aldehyde (1 eq) in CH_2Cl_2 (0.7 M). The mixture was stirred at 0 °C for 25 minutes before warming to room temperature, where the reaction was stirred in the dark for 18 h. The mixture was concentrated *in vacuo* and the residue purified by silica gel column chromatography.

1,1-Dibromo-2-cyclohexylethene



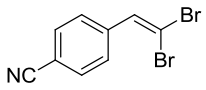
As general procedure **(A)**. To a stirring solution of Ph_3P (2.62 g, 10.0 mmol) in CH_2Cl_2 (7 mL) was added CBr_4 (1.66 g, 5.0 mmol) in CH_2Cl_2 (7 mL). Et_3N (835 μL, 6.0 mmol) was added and the mixture stirred for 15 mins before addition of cyclohexanecarboxaldehyde (540 μL, 4.5 mmol) in CH_2Cl_2 (7 mL). Recovered 874 mg (74%) product as a clear colourless oil. R_f 0.65 (petrol); ^{1}H NMR (400 MHz, $CDCl_3$) 6.25 (1H, d, *J* 9.0, C^2H), 2.30 (1H, app. tdt, *J* 11.0, 9.0 and 3.6, C^3H), 1.80 - 1.61 (5H, m, $C^{Cy}H_2$) and 1.38 - 1.08 (5H, m, $C^{Cy}H_2$); *m/z* (EI) 270 (M+, 56%), 268 (M+, 100), 266 (M+, 48), 214 (21), 212 (39), 210 (21), 199 (30), 189 (37), 187 (38), 133 (80), 131 (76), 107 (37), 87 (27), 79 (65), 77 (20), 67 (62) and 65 (30); (Found M+ 265.9294. $C_9H_7{}^{79}BrO$ requires 265.9300). Data for 1,1-Dibromo-2-cyclohexylethene are in agreement with literature.[52]

1-(2,2-dibromovinyl)-4-methoxybenzene



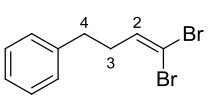
As general procedure **(A)**. To a stirring solution of Ph_3P (4.89 g, 19.0 mmol) in CH_2Cl_2 (12 mL) was added CBr_4 (3.14 g, 9.5 mmol) in CH_2Cl_2 (12 mL). Et_3N (1.4 mL, 10.0 mmol) was added and the mixture stirred for 15 mins before addition of 4-methoxybenzaldehyde (894 μL, 7.35 mmol) in CH_2Cl_2 (11 mL). Recovered 1.64 g (77%) product as a yellow crystalline solid. R_f 0.40 (Et_2O : Petrol, 1 : 10); m.p. 32 - 34 $^{\circ}$C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.53 (2H, d, *J* 9.0, *ArH*), 7.43 (1H, s, *CH*), 6.91 (2H, d, *J* 9.0, *ArH*) and 3.85 (3H, s, *OCH_3*); ^{13}C NMR (400 MHz, $CDCl_3$) 159.7 (C), 136.3 (CH), 129.9 (2CH), 127.9 (C), 113.8 (2CH), 87.3 (C) and 55.3 (CH_3). Data for 1-(2,2-dibromovinyl)-4-methoxybenzene are in agreement with literature.[53]

4-(2,2-Dibromovinyl)benzonitrile



As general procedure **(A)**. To a stirring solution of Ph_3P (4.16 g, 15.8 mmol) in CH_2Cl_2 (10 mL) was added CBr_4 (2.63 g, 7.9 mmol) in CH_2Cl_2 (10 mL). Et_3N (1.17 mL, 8.4 mmol) was added and the mixture stirred for 15 mins before addition of 4-cyanobenzaldehyde (800 mg, 6.1 mmol) in CH_2Cl_2 (9.2 mL). Recovered 1.42 g (80%) product as a white solid. R_f 0.42 (Et_2O : petrol, 1 : 10); m.p. 78 - 80 $^{\circ}$C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.62 - 7.73 (4H, m, *ArH*) and 7.52 (1H, s, *$C^{l'}H$*); ^{13}C NMR (100 MHz, $CDCl_3$) 139.6 (C), 135.2 (CH), 132.2 (CH), 128.9 (CH), 118.5 (C), 112.0 (C) and 93.5 (C). Data for 4-(2,2-dibromovinyl)benzonitrile are in agreement with literature.[54]

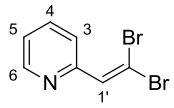
(4,4-dibromobut-3-enyl)benzene



As general procedure **(A)**. To a stirring solution of Ph_3P (3.144 g, 12.0 mmol) in CH_2Cl_2 (8.5 mL) was added CBr_4 (1.990 g, 6.0 mmol) in CH_2Cl_2 (8.5 mL) at 0 $^{\circ}$C. Et_3N (974 μL, 7.0 mmol) was added and the mixture stirred for 15 mins before addition of cinnamaldehyde (658 μL, 5 mmol) in CH_2Cl_2 (7 mL). Recovered 1.35 g,

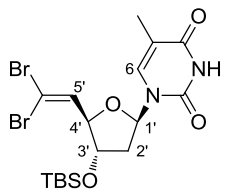
(93%) product as a clear colourless oil. R_f 0.30 (petrol); ^{1}H NMR (400 MHz, $CDCl_3$) 7.30 - 7.40 (2H, t, *J* 7.3, *ArH*), 7.18 - 7.27 (3H, m, *ArH*), 6.44 (1H, t, *J* 7.2, C^2H), 2.76 (2H, t, *J* 7.8, C^4H_2) and 2.41 - 2.48 (2H, app. q, *J* 7.6, C^3H_2); ^{13}C NMR (400 MHz, $CDCl_3$) 140.6 (C), 137.6 (CH), 128.5 (CH), 128.4 (CH), 126.3 (CH), 89.5 (C), 34.7 (CH_2), 33.9 (CH_2). Data for (4,4-dibromobut-3-enyl)benzene are in agreement with literature.[55]

2-(2,2-Dibromovinyl)pyridine



As general procedure **(A)**. To a stirring solution of Ph_3P (3.91 g, 14.9 mmol) in CH_2Cl_2 (8.8 mL) was added CBr_4 (2.47 g, 7.47 mmol) in CH_2Cl_2 (8.8 mL) at 0 °C. Et_3N (1.14 mL, 8.22 mmol) was added and the mixture stirred for 15 mins before addition of 2-pyridinecarboxaldehyde (800 mg, 7.47 mmol). Recovered 1.19 g (61%) product as a light green oil. R_f 0.71 (petrol : EtOAc, 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) 8.63 (1H, m, C^6H), 7.72 - 7.76 (1H, m C^5H), 7.70 (1H, dd, *J* 8.2 and 1.8, C^3H) 7.65 (1H, s, $C^{1'}H$) 7.22 - 7.26 (1H, m, C^4H); ^{13}C NMR (100 MHz, $CDCl_3$) 153.9 (C), 149.6 (CH), 137.2 (CH), 136.3 (CH), 123.5 (CH), 122.9 (CH) and 93.1 (C). Data for 2-(2,2-dibromovinyl)pyridine are in agreement with literature.[56]

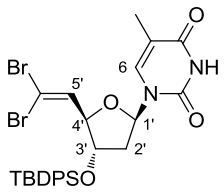
(1'*R*, 3'*S*, 4'*R*)-3'-(Tert-butyldimethylsilyloxy)-5'-(2,2-dibromovinyl) thymidine (9)



Dess-Martin Periodinane (263 mg, 0.62 mmol) was added in one portion to a stirring solution of 3'-TBS tymidine (200 mg, 0.56 mmol) in CH_2Cl_2 (4.3 mL). The reaction was stirred at room temperature for 1 h, after which time it was quenched with saturated solutions of $Na_2S_2O_3$ (15 mL) and $NaHCO_3$ (15 mL) and stirred for 15 minutes. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), the combined organic extracts dried (Na_2SO_4) and the volatiles removed *in vacuo*, generating **8** (198 mg, 100 %) as a white foam. **8** was taken through to the next step without purification as a crude material.

To a stirred solution of Ph_3P (537 mg, 2.05 mmol) in CH_2Cl_2 (1.4 mL) at 0 °C was added CBr_4 (341 mg, 1.03 mmol) in DCM (1.4 mL) slowly. The reaction was stirred at 0°C for 30 minutes, before addition of Et_3N (214 μL, 1.53 mmol). The mixture was stirred at 0 °C for 15 minutes, and **8** (198 mg, 0.56 mmol) in CH_2Cl_2 (1.4 mL) added. The mixture was stirred at 0 °C for 15 minutes before warming to room temperature where it was stirred for 18 h. The reaction was quenched with water (3 mL), stirred for 30 minutes, then extracted with CH_2Cl_2 (3 x 20mL). The combined organic extracts were dried (Na_2SO_4), the volatiles removed *in vacuo*, and the remaining residue purified by column chromatography (EtOAc:hexane 1:1) to afford product **9** (234 mg, 82%) as a white solid; R_f 0.38 (EtOAc:hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (1H, br s, *NH*), 7.10 (1H, d, *J* 1.3, C^6H), 6.53 (1H, d, *J* 8.5, $C^{5'}H$), 6.10 (1H, t, *J* 6.8, $C^{1'}H$), 4.56 (1H, dd, *J* 8.5 and 3.6, $C^{4'}H$), 4.31-4.37 (1H, m, $C^{3'}H$), 2.34-2.41 (1H, m, $C^{2'}H_2$), 2.18-2.29 (1H, m, $C^{2'}H_2$), 1.97 (3H, d, *J* 1.3, CH_3), 0.93 (9H, s, $SiMe_2{}^tBu$), 0.14 (3H, s, $SiMe_2{}^tBu$) and 0.12 (3H, s, $SiMe_2{}^tBu$); HRMS *m/z* (ES^+) Found M+Na 530.9930, $C_{17}H_{26}{}^{79}Br_2N_2O_4SiNa$ requires 530.9921) Data for product **23** are in agreement with literature.[57]

(1'*R*, 3'*S*, 4'*R*)-3'-(Tert-butyldiphenylsilyloxy)-5'-(2,2-dibromovinyl) thymidine (10)



Dess-Martin Periodinane (263 mg, 0.62 mmol) was added in one portion to a stirring solution of 3'-OTBDPS Thymidine (200 mg, 0.56 mmol) in CH_2Cl_2 (4.3 mL). The reaction was stirred at room temperature for 1 h, after which time it was quenched with saturated solutions of $Na_2S_2O_3$ (15 mL) and $NaHCO_3$ (15 mL) and stirred for 15 minutes. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), the combined organic extracts dried (Na_2SO_4) and the volatiles removed *in vacuo*, generating the 5'-aldehyde (198 mg, 100 %) as a white foam. The aldehyde was taken through to the next step without purification as a crude material.

To a stirred solution of Ph_3P (537 mg, 2.05 mmol) in CH_2Cl_2 (1.4 mL) at 0 °C was added CBr_4 (341 mg, 1.03 mmol) in CH_2Cl_2 (1.4 mL). The reaction was stirred at 0°C for 30 minutes, before addition of Et_3N (214 μL, 1.53 mmol). The mixture was stirred at 0 °C for 15 minutes, and the aldehyde (198 mg, 0.56 mmol) in CH_2Cl_2 (1.4 mL) added. Recovered 120 mg (45%) **10** as a white solid; R_f 0.26 (Et_2O : Petrol, 5 : 1); m.p, 69 - 72 °C; [α_D] (c 0.7) 24.2; υ_{max} /cm^{-1} ($CHCl_3$ soln) 3391, 3011, 2933, 2861, 1691, 1471, 1428, 1364, 1271, 1113, 1051 and 920; ^{1}H NMR (400 MHz, $CDCl_3$) 8.08 - 8.21 (1H, br. s,), 7.67 (4H, d, *J* 6.5, *ArH*), 7.39 - 7.52 (6H, m, *ArH*), 6.91 (1H, d, *J* 1.3, C^6H), 6.25 (1H, d, *J* 8.8, $C^{5'}H$), 6.20 (1H, t, *J* 6.8, $C^{1'}H$), 4.66 (1H, dd, *J* 8.8 and 4.0, $C^{4'}H$), 4.27 (1H, dt, *J* 6.8 and 4.0, $C^{3'}H$), 2.36 (1H, ddd, *J* 10.4, 6.8 and 3.3, $C^{2'}H_2$), 1.90 - 1.99 (1H, m, $C^{2'}H_2$), 1.89 (3H, d, *J* 1.3, CH_3) and 1.11 (9H, s, $SiPh_2{}^tBu$); ^{13}C NMR (100 MHz, $CDCl_3$) 164.0 (C), 150.3 (C), 135.8 (CH), 135.7 (CH), 135.4 (CH), 134.9 (CH), 132.9 (C), 132.6 (C), 130.2 (CH), 128.0 (CH), 111.2 (C), 95.8 (C), 85.9 (CH), 85.7 (CH), 75.8 (CH), 41.1 (CH_2), 26.9 (CH_3), 19.1 (C) and 12.6 (CH_3); HRMS *m/z* (ES$^+$) Found M+Na 655.0214. $C_{27}H_{30}O_4{}^{79}Br_2SiN_2Na$ requires 655.0234.

5.2 Preparation of alkynylbromide precursors.

General Procedure (B)

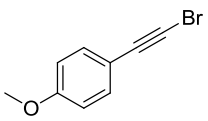
To a stirring solution of vinyldibromide (1 eq) in THF (0.7 M) was added benzyltrimethylammonium hydroxide (2 eq, 40%w/w in MeOH) and the mixture stirred at room temperature for 2-72 h. The reaction mixture was diluted with Et_2O, washed with saturated $NaHCO_3$ and the organic layer dried ($MgSO_4$). The volatiles were removed *in vacuo* and the residue purified by silica gel column chromatography.

General Procedure (C)

To a stirring solution of terminal alkyne (1 eq) in acetone (0.08 M) was added $AgNO_3$ (0.5 eq) and N-bromosuccinimide (2 eq). The resulting solution was stirred for 4 h at room

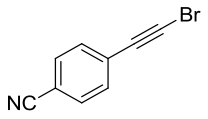
temperature before pouring the reaction mixture onto saturated NH_4Cl and extracting with Et_2O. The organic was dried ($MgSO_4$), the volatiles removed in vacuo and the residue purified by silica gel column chromatography.

1-(bromoethynyl)-4-methoxybenzene (14)



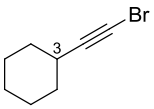
As general procedure **(B)**. To a stirring solution of 1-(2,2-dibromovinyl)-4-methoxybenzene (1.0 g, 3.5 mmol) in THF (5 mL) was added benzyltrimethylammonium hydroxide (3.125 mL, 7.0 mmol). The mixture was stirred for 3 h. Recovered 683 mg (94%) product as a light yellow solid. R_f 0.58 (hexane : EtOAc, 7 : 3); m.p. 26 – 29 $^{\circ}$C. υ_{max} /cm^{-1} ($CHCl_3$ soln) 2840, 1606, 1572, 1510, 1462, 1291, 1250, 1173, 1032 and 833; ^{1}H NMR (400MHz, $CDCl_3$) 7.40 (2H, d, *J* 9.1, *ArH*), 6.85 (2H, d, *J* 9.1, *ArH*) and 3.83 (3H, s, *OCH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 159.9 (C), 133.5 (CH), 114.8 (C), 113.9 (CH), 79.9 (C), 55.3 (CH_3) and 47.9 (C); *m/z* (EI) 212 (M+, 88%), 210 (M+, 90), 197 (55), 195 (58), 169 (44), 167 (45%) and 88 (100); (Found M+ 209.9673, $C_9H_7{}^{79}BrO$ requires 209.9675).

4-(Bromoethynyl)benzonitrile (15)



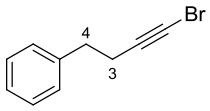
As general procedure **(B)**. To a stirring solution of 4-(2,2-dibromovinyl)benzonitrile (350 mg, 1.21 mmol) in THF (1.8 mL) was added benzyltrimethylammonium hydroxide (1.09 mL, 2.42 mmol). The mixture was stirred for 2 h. Recovered 173 mg (67%) as a white solid. R_f 0.29 (petrol : Et_2O, 10 : 1); m.p. 72-74 $^{\circ}$C; υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2232, 2203, 1605, 1501, 1407, 1270, 1195, 1176, 1020, 929 and 840; ^{1}H NMR (400 MHz, $CDCl_3$) 7.63 (2H, d, *J* 8.5, *ArH*) and 7.55 (2H, d, *J* 8.5, *ArH*); ^{13}C NMR (100 MHz, $CDCl_3$) 132.6 (CH), 132.0 (CH), 127.6 (C), 118.3 (C), 112.1 (C), 78.6 (C) and 55.4; *m/z* (EI) 207 (M+, 97%), 205 (M+, 90), 126 (45), 195 (58) and 99 (15); (Found M+ 204.9523, $C_9H_4{}^{79}BrN$ requires 204.9522).

(Bromoethynyl)cyclohexane (16)



As general procedure **(B)**. To a stirring solution of 1,1-Dibromo-2-cyclohexylethene (1.2 g, 4.48 mmol) in THF (6.4 mL) was added benzyltrimethylammonium hydroxide (4.0 mL, 8.96 mmol). The mixture was stirred for 72 h. Recovered 699 mg (83%) product as a clear colourless oil. R_f 0.61 (petrol); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3008, 2938, 2859, 1709, 1450, 1258, 1157, 1053, 963 and 907; ^{1}H NMR (400 MHz, CDCl) 2.33 - 2.43 (1H, m, C^3H), 1.77 - 1.87 (2H, m, $C^{Cy}H_2$), 1.65 - 1.76 (2H, m, $C^{Cy}H_2$), 1.41 - 1.59 (3H, m, $C^{Cy}H_2$) and 1.27 - 1.39 (3H, m, $C^{Cy}H_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 84.4 (C), 37.8 (C), 32.3 (CH_2), 30.2 (CH), 25.4 (CH_2) and 24.8 (CH_2); *m/z* (EI) 188 (M+, 15%), 186 (15), 133 (7), 131 (7), 107 (10), 105 (9), 91 (24) and 79 (100). (Found M+ 186.0034. $C_8H_{12}{}^{79}Br$ requires 186.0039).

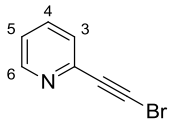
(1-Bromobut-2-ynyl)benzene (17)



As general procedure **(B)**. To a stirring solution of 4,4-dibromobut-3-enyl)benzene (800 mg, 2.76 mmol) in THF (8 mL) was added benzyltrimethylammonium hydroxide (1.34 mL, 3.0 mmol). The mixture was stirred for 18 h. Recovered 463 mg (80 %) as a clear colourless oil; R_f 0.29 (petrol); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3012, 2932, 1498, 1454, 1194, 1078 and 909; ^{1}H NMR (400 MHz, $CDCl_3$) 7.31 - 7.37 (2H, m, *ArH*), 7.22 - 7.28 (3H, m, *ArH*), 2.87 (2H, t, *J* 7.5, C^4H_2) and 2.53 (2H, t, *J* 7.5, C^3H_2); ^{13}C NMR (100 MHz, $CDCl_3$) 140.3 (C), 128.5 (CH), 128.4 (CH), 126.4 (CH), 79.6 (C), 38.7 (C), 34.7 (CH_2) and 21.9 (CH_2); *m/z* (EI) 210 (M+, 2%), 208 (M+, 2), 129 (100), 91 (37) and 65 (14); (Found M+ 207.9881, $C_{10}H_9{}^{79}Br$ requires 207.9882).

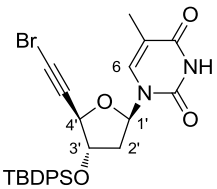
2-(Bromoethynyl)pyridine (18)

As general procedure **(B)**. To a stirring solution of 2-(2,2-dibromovinyl)pyridine (450 mg, 1.72 mmol) in THF (5 mL) was added benzyltrimethylammonium hydroxide (0.92 mL, 2.06



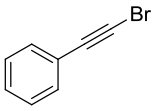
mmol). The mixture was stirred for 2 h. Recovered 146 mg (47%) as a light green oil. R_f 0.63 (EtOAc : petrol, 1 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 2986, 2207, 1584, 1566, 1463, 1428, 1256, 1151, 1092, 1045, 992 and 900; ^{1}H NMR (400 MHz, $CDCl_3$) 8.56 (1H, ddd, *J* 4.8, 1.8, 1.2, *C*^{6}*H*) 7.65 (1H, app. td, *J* 7.8, 1.8, *C*^{4}*H*) 7.42 (1H, app. dt, *J* 7.8, 4.8, 1.2, *C*^{3}*H*) 7.25 (1H, ddd, *J* 7.8, 4.8, 1.2, *C*^{5}*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 150.1 (CH), 142.7 (C), 136.2 (CH), 127.4 (CH), 123.3 (CH), 79.7 (C) and 51.7 (C); *m/z* (EI) 184 (33%), 183 (M+, 97), 181 (100), 103 (15), 102 (20) and 86 (13); (Found M+ 180.9522, $C_7H_4{}^{79}Br$ requires 180.9522).

(1'*R*, 3'*S*, 4'*R*)-5'-(bromoethynyl)-3'-(tert-butyldiphenylsilyloxy) thymidine (19)



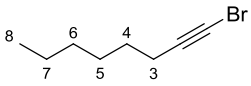
As general procedure **(B)**. To a stirring solution of **10** (200 mg, 0.39 mmol) was added benzyltrimethylammonium hydroxide (229 μL, 0.50 mmol). The mixture was stirred for 18 h. Recovered 103 mg (61%) as a light yellow solid. R_f 0.41 (Et_2O : petrol, 3 : 1); m.p. 164-167 $^{\circ}$C; [α_D] (c 0.7) 31.3; υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2933, 2860, 1691, 1471, 1428, 1364, 1295, 1270, 1239, 1187, 1113, 1057, 980, 952, 909; ^{1}H NMR (400 MHz,$CDCl_3$) 8.89 - 8.92 (1H, br. s., *NH*), 7.66 (4H, m, *ArH*), 7.41 - 7.52 (6H, m, *ArH*), 7.40 (1H, d, *J* 1.3, *C*^{6}*H*), 6.56 (1H, dd, *J* 8.2 and 5.9, *C*$^{1'}$*H*), 4.63 (1H, app. s, *C*$^{4'}$*H*), 4.51 (1H, app. d, *J* 4.3, *C*$^{3'}$*H*), 2.41 - 2.52 (1H, m, *C*$^{2'}$*H*$_2$), 1.98 - 2.09 (1H, m, *C*$^{2'}$*H*$_2$), 1.93 (3H, d, *J* 1.3, *CH*$_3$) and 1.11 (9H, s, $SiPh_2{}^tBu$); ^{13}C NMR (100 MHz, $CDCl_3$) 163.7 (C), 150.3 (C), 135.7 (CH), 135.6 (CH), 132.6 (C), 132.5 (C), 130.3 (CH), 128.0 (CH), 111.3 (C), 86.8 (CH), 78.3 (CH), 77.6 (CH), 50.1 (C), 40.5 (CH_2), 26.8 (CH_3), 19.04 (C) and 12.9 (CH_3); HRMS *m/z* (ES$^+$) Found M + Na 575.0961. $C_{27}H_{29}O_4N_2Si^{79}BrNa$ requires 575.0972.

(Bromoethynyl)benzene (20)



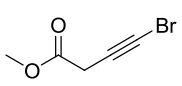
As general procedure **(C)**. To a stirring solution of phenylacetylene (400 mg, 3.92 mmol) in acetone (50 mL) was added $AgNO_3$ (337 mg, 1.98 mmol) and N-bromosuccinimide (1.05 g, 3.92 mmol). Recovered 500 mg (71%) product as a colourless clear oil. R_f 0.46 (petrol); ^{1}H NMR (400 MHz, $CDCl_3$) 7.45 - 7.50 (2H, dd, *J* 7.5 and 1.5 *ArH* and *ArH*) and 7.30 - 7.40 (3H, m, *ArH*); ^{13}C NMR (100 MHz, $CDCl_3$) 132.0 (CH), 128.7 (CH), 128.4 (CH), 122.7 (C), 80.1 (C) and 49.7 (C). Data for (bromoethynyl)benzene are in agreement with literature.[58]

1-Bromooct-1-yne (21)



As general procedure **(C)**. To a stirring solution of 1-octyne (200 mg, 1.82 mmol) in acetone (22 mL) was added $AgNO_3$ (155 mg, 0.91 mmol) and N-bromosuccinimide (648 mg, 3.64 mmol). Recovered 198 mg (58%) product as a colourless clear oil. R_f 0.63 (petrol); υ_{max} /cm^{-1} ($CHCl_3$ soln) 2933, 2861, 1467, 1430 and 1379; ^{1}H NMR (400 MHz, $CDCl_3$) 2.22 (2H, t, *J* 7.0, C^3H_2), 1.48 - 1.59 (2H, m, C^4H_2), 1.23 - 1.45 (6H, m, C^5H_2, C^6H_2 and C^7H_2) and 0.88 - 0.95 (3H, m, C^8H_2); ^{13}C NMR (400 MHz, $CDCl_3$) 80.5 (C). 37.4 (C), 31.3 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 22.5 (CH_2), 19.7 (CH_2) and 14.0 (CH_3); *m/z* (EI) 161 (9 %), 159 (9), 147(7), 145(6), 134 (9), 132 (9), 119 ([M+] - C_5H_{10}, 9), 117 ([M+] - C_5H_{10}, 9) and 79 (100).

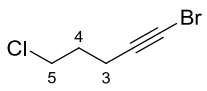
Methyl 4-bromobut-3-ynoate (22)



As general procedure **(C)**. To a stirring solution of methyl but-3-ynoate (200 mg, 2.04 mmol) in acetone (26 mL) was added $AgNO_3$ (173 mg, 1.02 mmol) and N-bromosuccinimide (726 mg, 4.08 mmol). Recovered 294 mg (82%) product as a colourless clear oil. R_f 0.33 (petrol : Et_2O, 10 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3045, 2945, 1747, 1378, 1359, 1240, 1057, 1027, 964 and 909; ^{1}H NMR (400 MHz, $CDCl_3$) 4.72 (2H, s,

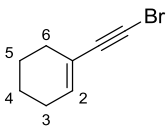
CH₂) and 2.13 (3H, s, *CH₃*); ^{13}C NMR (100 MHz, $CDCl_3$) 170.1 (C), 74.1 (C), 52.8 (CH_2), 47.1 (C) and 20.6 (CH_3); Product too unstable for elemental and mass spectroscopic analysis.

1-bromo-5-chloropent-1-yne (23)



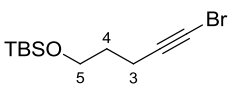
As general procedure **(C)**. To a stirring solution of 5-chloropent-1-yne (200 mg, 1.95 mmol) in acetone (26 mL) was added $AgNO_3$ (167 mg, 0.98 mmol) and N-bromosuccinimide (694 mg, 3.90 mmol). Recovered 193 mg (55%) product as a colourless clear oil. R_f 0.62 (petrol : Et_2O, 9 : 1), ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR 3.66 (2H, t, *J* 6.5, *5³H₂*), 2.43 (2H, t, *J* 6.5, *C³H₂*) and 1.99 (2H, app. quin, *J* 6.5, *C⁴H₂*); ^{13}C NMR (100 MHz, $CDCl_3$) 78.4 (C), 43.5 (CH_2), 39.0 (C), 31.0 (CH_2) and 17.1 (CH_2). Data are in agreement with literature.[59]

1-(bromoethynyl)cyclohex-1-ene (24)



As general procedure **(C)**. To a stirring solution of 1-ethynylcyclohex-1-ene (200 mg, 1.89 mmol) in acetone (24 mL) was added $AgNO_3$ (162 mg, 0.95 mmol) and N-bromosuccinimide (673 mg, 3.78 mmol). Recovered 230 mg (66%) product as a colourless clear oil. R_f 0.50 (petrol); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2939, 2862, 2843, 1448, 1436, 1349, 1138, 1076, 1046, 920 and 844; ^{1}H NMR (400 MHz, $CDCl_3$) 6.16 (1H, app. spt, *J* 1.9, *C²H*) 2.04 - 2.18 (4H, m, *C³H₂* and *C⁶H₂*) 1.52 - 1.69 (4H, m, *C⁴H₂* and *C⁵H₂*); ^{13}C NMR (100 MHz, $CDCl_3$) 136.4 (CH), 120.5 (C), 81.9 (C), 46.2 (C), 28.9 (CH_2), 25.6 (CH_2), 22.2 (CH_2) and 21.4 (CH_2); *m/z* (EI) 186 (3%), 184 (4), 130 (10), 129 (100), 128 (10), 105 (6) and 91 (12); (Found M+ 183.9888. $C_8H_9{}^{79}Br$ requires 183.9882).

(5-bromopent-4-ynyloxy)(tert-butyl)dimethylsilane (25)

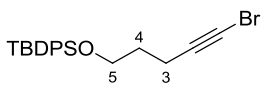


To a stirring solution of 4-pentyn-1-ol (200 mg, 2.38 mmol) in DMF (5.4 mL) was added imidazole (324 mg, 4.76 mmol) and the solution stirred at room temperature for 5 mins before addition of tert-butyldimethylsilyl chloride (466 mg, 3.09

mmol). The solution was stirred at room temperature for 2 h before being diluted with Et_2O and washed with water. The organic was dried ($MgSO_4$), volatiles removed in vacuo and the residue purified by silica gel column chromatography. Recovered 352 mg (75%) product as a clear colourless oil. R_f 0.28 (petrol : Et_2O, 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) 3.73 (2H, t, *J* 6.0, C^5H_2), 2.30 (2H, td, *J* 7.3 and 2.8 C^3H_2), 1.96 (1H, t, *J* 2.8, *C*≡*CH*) 1.76 (2H, tt, *J* 7.3 and 6.0, C^4H_2), 0.93 (9H, s, $SiMe_2{}^tBu$) and 0.09 (6H, s, $SiMe_2{}^tBu$); ^{13}C NMR (100 MHz, $CDCl_3$) 84.3 (C), 68.2 (C), 61.4 (CH_2), 31.5 (CH_2), 25.9 (CH), 18.3 (C) and 14.9 (C). Data are in agreement with literature.[60]

As general procedure **(C)**. To a stirring solution of tert-butyldimethyl(pent-4-yn-1-yloxy)silane (200 mg, 1.01 mmol) in acetone (13.5 mL) was added $AgNO_3$ (87 mg, 0.51 mmol) and N-bromosuccinimide (360 mg, 2.02 mmol). Recovered 258 mg (93%) product as a colourless clear oil. R_f 0.68 (petrol : Et_2O 4 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3012, 2956, 2930, 2885, 2858, 1472, 1464, 1256, 1106, 959 and 837; ^{1}H NMR (400 MHz, $CDCl_3$) 3.70 (2H, t, *J* 5.9, C^5H_2), 2.31 (2H, t, *J* 7.2, C^3H_2), 1.73 (3H, tt, *J* 7.2 and 5.9, C^4H_2), 0.90 - 0.93 (9H, s, $SiMe_2{}^tBu$) and 0.06 - 0.08 (6H, s, $SiMe_2{}^tBu$); ^{13}C NMR (400 MHz, $CDCl_3$) 80.9 (C), 61.3 (CH_2), 37.7 (C), 31.3 (CH_2), 26.0 (CH_3), 18.3 (C) and 16.1 (CH_2); *m/z* (EI) 221(16%), 219 (16), 193 (20), 191 (21), 169 (73), 167 (72), 163 ([M+]-TBS, 33), 161 ([M+]-TBS, 25), 139 (43), 137 (43), 135 (18), 133 (19), 83 ([M+]-TBS, -Br, 100).

(5-Bromopent-4-ynyloxy)(tert-butyl)diphenylsilane (26)

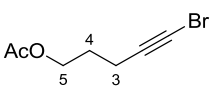


To a stirring solution of 4-pentyn-1-ol (200 mg, 2.38 mmol) in DMF (5.4 mL) was added imidazole (324 mg, 4.76 mmol) and the solution stirred at room temperature for 5 mins before addition of tert-butyldiphenylsilyl chloride (787 mg, 2.86 mmol). The solution was stirred at room temperature for 2 h before being diluted with Et_2O and washed with water. The organic was dried ($MgSO_4$), volatiles removed in vacuo and the residue purified by silica gel column chromatography. Recovered 590 mg

(76%) product as a clear colourless oil. R_f 0.64 (petrol : Et_2O, 10 : 1); ^1H NMR (400 MHz, $CDCl_3$) 7.70 (4H, dd, *J* 7.9 and 1.6, *ArH*), 7.38 - 7.48 (6H, m, *ArH*), 3.78 (2H, t, *J* 6.0, C^5H_2) 2.38 (2H, td, *J* 7.3 and 2.8, C^3H_2), 1.94 (1H, t, *J* 2.8, *C≡CH*), 1.81 (2H, tt, *J* 7.3 and 6.0, C^4H_2) and 1.08 (9H, s, $SiPh_2{}^tBu$); ^{13}C NMR (100 MHz, $CDCl_3$) 135.6 (CH), 133.9 (C), 129.6 (CH), 127.7 (CH), 84.3 (C), 68.3 (CH), 62.3 (CH_2), 31.5 (CH_2), 26.9 (CH3), 19.3 (C), 15.0 (CH_2). Data are in agreement with literature.[61]

As general procedure **(C)**. To a stirring solution of tert-butyldiphenyl(pent-4-yn-1-yloxy)silane (300 mg, 0.93 mmol) in acetone (11 mL) was added $AgNO_3$ (80 mg, 0.47 mmol) and N-bromosuccinimide (331 mg, 1.86 mmol). Recovered 291 mg (78%) product as a colourless clear oil. R_f 0.64 (Petrol : Et_2O, 10 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3073, 3011, 2932, 2859, 1473, 1428, 1390, 1362, 1110 and 909; ^1H NMR (400 MHz, $CDCl_3$) 7.70 (4H, dd, *J* 7.9 and 1.8, *ArH*), 7.39 - 7.47 (6H, m, *ArH*), 3.76 (2H, t, *J* 6.0, C^5H_2), 2.40 (2H, t, *J* 7.2, C^3H_2) 1.78 (2H, tt, *J* 7.2 and 6.0, C^4H_2) 1.08 (9H, s, $SiPh_2{}^tBu$); ^{13}C NMR (100 MHz, $CDCl_3$) 135.6 (CH), 133.8 (C), 129.6 (CH), 127.7 (CH), 80.0 (C), 62.13 (CH_2), 37.8 (C), 31.2 (CH_2), 26.8 (CH_3), 19.2 (C) and 16.2 (CH_2); *m/z* (EI) 221(16%), 263 (100), 245 (53), 235 (51), 217 (55), 211 (42), 181 (97), 163 ([M+] - TBDPS, 5) and 161 ([M+] - TBDPS, 5).

5-Bromopent-4-ynyl acetate (27)



4-pentyn-1-ol (250mg, 2.98 mmol) and acetic anhydride (310 μL, 3.28 mmol) were charged to a reaction vessel and stirred at 80°C for 18 h. The reaction was diluted with Et_2O, washed with water and the organic dried ($MgSO_4$). The volatiles were removed in vacuo and the residue purified by silica gel column chromatography. Recovered 149 mg (40%) as a clear colourless oil. R_f 0.25 (Petrol : Et_2O, 10 : 1); ^1H NMR (400 MHz, $CDCl_3$) 4.19 (2H, t, *J* 6.7, C^5H_2), 2.31 (2H, td, *J* 6.7 and 2.6, C^3H_2), 2.07 (3H, s, OCH_3), 1.98 (1H, t, *J* 2.6, *C≡CH*) and 1.87 (2H, app. quin, *J* 6.7, C^4H_2);

^{13}C NMR (100 MHz, $CDCl_3$) 171.1 (C), 83.0 (C), 69.0 (CH), 63.0 (CH_2), 27.5 (CH_2), 20.9 (CH_3) and 15.2 (CH_2). Data are in agreement with literature.[62]

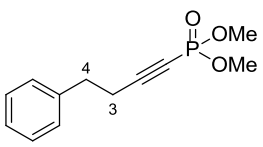
As general procedure **(C)**. To a stirring solution of pent-4-yn-1-yl acetate (130 mg, 1.03 mmol) in acetone (12 mL) was added $AgNO_3$ (88 mg, 0.52 mmol) and N-bromosuccinimide (367 mg, 2.06 mmol). Recovered 146 mg (69%) product as a colourless clear oil. R_f 0.37 (petrol : Et_2O, 10 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2964, 1735, 1391, 1368, 1250, 1046 and 909; ^{1}H NMR (400 MHz, $CDCl_3$) 4.15 (2H, t, *J* 6.3, C^5H_2), 2.32 (2H, t, *J* 7.0, C^3H_2), 2.06 (3H, s, OCH_3) and 1.85 (2H, tt, *J* 7.0 and 6.3, C^4H_2); ^{13}C NMR (100 MHz, $CDCl_3$) 171.0 (C), 78.84 (C), 63.0 (CH_2), 38.7 (C), 27.3 (CH_2), 20.9 (CH_3) and 16.5 (CH_2); *m/z* (EI) 205 ([M+] - H, 2%), 203 ([M+] - H, 2%), 192 ([M+] - CH_3, 56), 190 ([M+] - CH_3, 163 ([M+] – CH_3CO, 11), 161 ([M+] – CH_3CO, 11), 146 ([M+] – CH_3COO, 100), 144 ([M+] – CH_3COO, 100), 125 (16), 83 (15) and 65 (87).

5.3 Preparation of alkynylphosphonates – Palladium

General Procedure (D)

$Pd(OAc)_2$ (0.2 eq) and dppf (0.4 eq) were charged to a screw cap Reacti-vial^{TM} vessel, THF added and the mixture stirred at room temperature for 20 minutes. Alkynylphosphonate (1 eq), *H*-Phosphonate (1 eq) and propylene oxide (20 eq) were dissolved in THF (0.28 M) and the solution added to the catalyst mixture. The reaction was stirred at 80 - 100 $^{\circ}$C for 0.5 - 4 h before cooling to room temperature and concentrating in vacuo. The residue was purified by silica gel column chromatography.

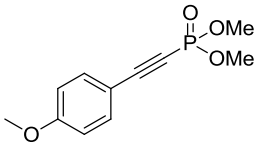
Dimethyl 4-phenylbut-1-ynylphosphonate (28)



As general procedure **(D)**. $Pd(OAc)_2$ (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. (4-Bromobut-3-ynyl)benzene (100 mg, 0.48

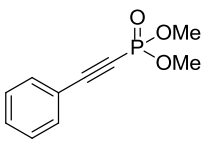
mmol), dimethyl phosphite (50 μL, 0.48 mmol) and propylene oxide (672 μL, 9.6 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 100 $^{\circ}$C for 4 h. Recovered 114 mg (67%) as a yellow oil. R_f 0.30 (EtOAc:petrol 2:1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3010, 2955, 2854, 2436, 2208, 1603, 1496, 1455, 1423, 1423, 1266, 1039, 928, 909 and 843; ^{1}H NMR (400 MHz, $CDCl_3$) 7.31 - 7.36 (2H, m, *ArH*), 7.21 - 7.28 (3H, m, *ArH*), 3.74 (6H, d, *J* 12.3, *OCH*$_3$), 2.93 (2H, t, *J* 7.8, *C*^{4}*H*$_2$) and 2.69 (2H, td, *J* 7.8 and 4.5, *C*^{3}*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 139.3 (C), 128.6 (CH), 128.4 (CH), 126.8 (CH), 102.9 (d, *J* 53, C), 70.0 (d, *J* 302, C), 53.2 (d, *J* 6, CH_3), 33.6 (CH_2), 21.3 (CH_2); ^{31}P NMR (161 MHz, $CDCl_3$) -3.19; HRMS *m/z* (ES$^+$) Found M + Na 261.0647. $C_{12}H_{15}O_3PNa$ requires 261.0651.

Dimethyl (4-methoxyphenyl)ethynylphosphonate (29)



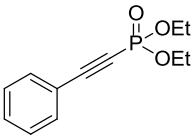
As general procedure **(D)**. $Pd(OAc)_2$ (22 mg, 0.10 mmol) and dppf (111 mg, 0.20 mmol) were dissolved in THF (1 mL) and stirred at room temperature for 20 mins. 1-(Bromoethynyl)-4-methoxybenzene (100 mg, 0.48 mmol), dimethyl phosphite (52 μL, 0.48 mmol) and propylene oxide (672 μL, 9.6 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 80°C for 4 h. Recovered 81 mg (70%) as a yellow oil. R_f 0.11 (EtOAc:Petrol, 1:1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2955, 2184, 1604, 1510, 1463, 1297, 1256, 1174, 1034, 871 and 837; ^{1}H NMR (400 MHz, C_6D_6) 7.34 (2H, d, *J* 8.5, *ArH*), 6.59 (2H, d, *J* 8.5, *ArH*), 3.62 (6H, d, *J* 14.4, *POCH*$_3$) and 3.25 (3H, s, *OCH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 161.6 (C), 134.5 (CH), 114.3 (CH), 111.5 (C), 100.7 (d, *J* 54, C), 75.7 (d, *J* 303, C), 55.4 (CH_3) and 53.3 (d, *J* 5, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) -2.18; HRMS *m/z* (ES$^+$) Found M+Na 263.0443. $C_{11}H_{13}O_4PNa$ requires 263.0444.

Dimethyl phenylethynylphosphonate (30)



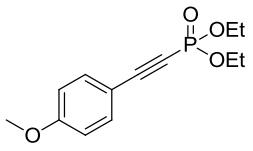
As general procedure **(D)**. $Pd(OAc)_2$ (25 mg, 0.11 mmol) and dppf (122 mg, 0.22 mmol) were dissolved in THF (1 mL) and stirred at room temperature for 20 mins. (Bromoethynyl)benzene (100 mg, 0.55 mmol), dimethyl phosphite (57 μL, 0.55 mmol) and propylene oxide (771 μL, 11.0 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 80°C for 3 h. Recovered 81 mg (70%) as a yellow oil. R_f 0.24 (EtOAc : petrol, 1 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2955, 2414, 2189, 1523, 1491, 1424, 1264, 1241, 1038, 929 and 864; ^{1}H NMR (100 MHz, $CDCl_3$) 7.57 - 7.61 (2H, m, *ArH*), 7.45 - 7.51 (1H, m, *ArH*), 7.37 - 7.42 (2H, m, *ArH*) and 3.87 (6H, d, *J* 12.3, *OCH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 132.7 (CH), 130.9 (CH), 128.6 (CH), 119.3 (C), 99.9 (d, *J* 53, C), 76.9 (d, *J* 301, C) and 53.5 (d, *J* 6, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) -2.74; HRMS *m/z* (ES^+) Found M+Na 233.0338, $C_{10}H_{11}O_3PNa$ requires 233.0338.

Diethyl phenylethynylphosphonate (31)



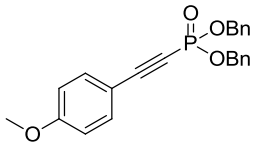
As general procedure **(D)**. $Pd(OAc)_2$ (25 mg, 0.11 mmol) and dppf (122 mg, 0.22 mmol) were dissolved in THF (1 mL) and stirred at room temperature for 20 mins. (Bromoethynyl)benzene (100 mg, 0.55 mmol), diethyl phosphite (72 μL, 0.55 mmol) and propylene oxide (771 μL, 11.0 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 80°C for 2 h. Recovered 97 mg (73%) as a yellow oil. R_f 0.31 (Et_2O : petrol, 3 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3007, 2189, 1490, 1444, 1394, 1258, 1165, 1027, 979 and 859; ^{1}H NMR (400 MHz, $CDCl_3$) 7.55 - 7.61 (2H, m, *ArH*), 7.46 (1H, m, *ArH*), 7.36 - 7.42 (2H, m, *ArH*), 4.20 - 4.30 (4H, m, *CH*$_2$CH$_3$) and 1.43 (6H, td, *J* 7.1, 0.7, CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 132.7 (CH), 130.7 (CH), 128.6 (CH), 119.5 (C), 99.1 (d, *J* 53, C), 63.3 (d, *J* 5, CH_2) and 16.1 (d, *J* 7, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) -6.00; HRMS *m/z* (ES^+) Found M+Na 261.0658, $C_{12}H_{15}O_3PNa$ requires 261.0651.

Diethyl ((4-methoxyphenyl)ethynyl)phosphonate (32)



As general procedure **(D)**. $Pd(OAc)_2$ (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-(Bromoethynyl)-4-methoxybenzene (100 mg, 0.48 mmol), diethyl phosphite (62 μL, 0.48 mmol) and propylene oxide (672 μL, 9.6 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 80°C for 3 h. Recovered 97 mg (77%) as a light yellow oil. R_f 0.21 (EtOAc : petrol, 1 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3008, 2184, 1605, 1510, 1297, 1255, 1173, 1030, 979, 909 and 867; ^{1}H NMR (400 MHz, $CDCl_3$), 7.51 (2 H, d, *J* 8.8, *ArH*), 6.89 (2 H, d, *J* 8.8, *ArH*), 4.22 (4 H, dqd, *J* 8.8, 7.0 and 1.0, *CH_2*CH_3) and 1.41 (6 H, td, *J* 7.0 and 0.6, CH_2*CH_3*); ^{13}C NMR (100 MHz, $CDCl_3$) 131.5 (C), 134.4 (CH), 114.2 (CH), 111.3 (C), 100.7 (d, *J* 54, C), 77.2 (d, *J* 301, C), 63.1 (d, *J* 6, CH_2), 55.4 (CH_3) and 16.1 (d, *J* 7, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) -5.40; HRMS *m/z* (ES^+) Found M+Na 291.0765. $C_{13}H_{17}O_4PNa$ requires 291.0757.

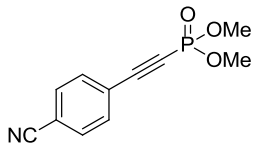
Dibenzyl (4-methoxyphenyl)ethynylphosphonate (33)



As general procedure **(D)**. $Pd(OAc)_2$ (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-(Bromoethynyl)-4-methoxybenzene (100 mg, 0.48 mmol), dibenzyl phosphite (126 mg, 0.48 mmol) and propylene oxide (672 μL, 9.6 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 80°C for 4 h. Recovered 142 mg (75%) as a yellow oil. R_f 0.37 (EtOAc:Petrol 1:1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3156, 2254, 2184, 1794, 1710, 1605, 1457, 1381, 1363, 1094, 1045, 995 and 893; ^{1}H NMR (400 MHz, C_6D_6) 7.39 - 7.34 (4H, m, *ArH*), 7.29 - 7.23 (2H, m, *ArH*), 7.21 - 7.11 (8H, m, *ArH*), 6.54 (2H, d, *J* 9.1, *ArH*), 5.21 (4H, d, *J* 8.8, *CH_2*) and 3.21 (3H, s, *OCH_3*); ^{13}C NMR (400 MHz, $CDCl_3$) 161.5 (C), 135.3 (C, d, *J* 7), 134.5 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 114.3 (CH), 111.1 (C), 100.7 (d, *J* 54, C), 76.9 (d, *J* 306, C), 68.5 (d, *J* 5, CH_2) and

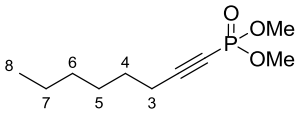
55.4 (CH_3); ^{31}P NMR (400 MHz, $CDCl_3$) -4.87; HRMS *m/z* (ES^+) Found M+Na 415.1066. $C_{23}H_{21}O_4PNa$ requires 415.1070.

Dimethyl (4-cyanophenyl)ethynylphosphonate (34)



As general procedure **(D)**. $Pd(OAc)_2$ (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. 4-(Bromoethynyl)benzonitrile (100 mg, 0.49 mmol), dimethyl phosphite (51 μL, 0.49 mmol) and propylene oxide (686 μL, 9.8 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 80°C for 45 mins. Recovered 61 mg (53%) as a light yellow solid. R_f 0.24 (EtOAc : petrol, 1 : 1); m.p. 72 – 75 $^\circ$C; υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2415, 2233, 2194, 1521, 1502, 1477, 1424, 1271, 1241, 1039, 929, 864 and 843; ^{1}H NMR (400 MHz, $CDCl_3$) 7.65 - 7.70 (4H, d, *J* 1.2, *ArH*) and 3.86 (6H, d, *J* 12.3, *OCH_3*); ^{13}C NMR (100 MHz, $CHCl_3$) 133.2 (CH), 132.2 (CH), 124.0 (d, *J* 5, C), 117.7 (C), 114.3 (C), 96.8 (d, *J* 52, C), 81.0 (d, *J* 297, C) and 53.7 (d, *J* 6, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) -4.08; HRMS *m/z* (ES^+) Found M+Na 258.0278. $C_{11}H_{10}O_3NPNa$ requires 258.0291.

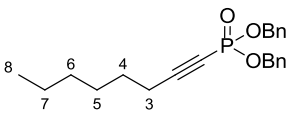
Dimethyl(oct-1-ynyl)phosphonate (35)



As general procedure **(D)**. $Pd(OAc)_2$ (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), dimethyl phosphite (55 μL, 0.53 mmol) and propylene oxide (743 μL, 10.6 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 100°C for 4 h. Recovered 109 mg (94%) as a light yellow oil. R_f 0.26 (EtOAc : petrol, 2 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 2954, 2252, 2205, 1711, 1457, 1362, 1090, 1045 and 896; ^{1}H NMR (400 MHz, $CDCl_3$) 3.79 (6H, d, *J* 12.3, *OCH_3*), 2.37 (2H, td, *J* 7.1 and 4.5, *C^3H_2*), 1.54 - 1.67 (2H, m, *C^4H_2*), 1.36 - 1.48 (2H, m,

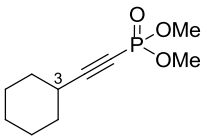
C^5H_2), 1.20 - 1.36 (4H, m, C^6H_2 and C^7H_2) and 0.88 - 0.93 (3H, m, C^8H_2); ^{13}C NMR (100 MHz, $CDCl_3$) 104.3 (d, *J* 54, C), 69.0 (d, *J* 304, C), 53.2 (d, *J* 6, CH_3), 31.1 (CH_2), 28.4 (CH_2), 27.4 (CH_2), 22.4 (CH_2), 19.2 (CH_2) and 14.0 (CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) -2.86; HRMS *m/z* (ES^+) Found M + Na 241.0976. $C_{10}H_{19}O_3PNa$ requires 241.0964.

Dibenzyl oct-1-ynylphosphonate (36)



As general procedure **(D)**. $Pd(OAc)_2$ (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), dibenzyl phosphite (139 mg, 0.53 mmol) and propylene oxide (743 μL, 10.6 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 100°C for 4 h. Recovered 120 mg (61%) as a light yellow oil. R_f 0.51 (EtOAc : petrol, 1 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2933, 2861, 2207, 1521, 1498, 1456, 1423, 1380, 1258, 1010 and 929; ^{1}H NMR (400 MHz, $CDCl_3$) 7.32 - 7.40 (10H, m, *ArH*) 5.09 (4H, d, *J* 8.5, OCH_2Ph), 2.31 (2H, td, *J* 7.2 and 4.4, C^3H_2) 1.49 - 1.59 (2H, app. quin., *J* 7.31, C^4H_2), 1.33 - 1.42 (2H, m, C^5H_2) 1.23 - 1.32 (4H, m, C^6H_2 and C^7H_2) and 0.89 (3H, t, *J* 6.7 Hz, C^8H_2); ^{13}C NMR (100 MHz, $CDCl_3$) 135.7 (C), 128.5 (CH), 128.4 (CH), 127.9 (CH), 104.3 (d, *J* 54, C), 70.1 (d, *J* 307, C), 68.2 (d, *J* 6, CH_2), 31.2 (CH_2), 28.5 (CH_2), 27.3 (CH_2), 22.4 (CH_2), 21.1 (CH_2), 19.3 (CH_2) and 14.0 (CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) -5.62; HRMS *m/z* (ES^+) Found M + Na 393.1587. $C_{22}H_{27}O_3PNa$ requires 393.1590.

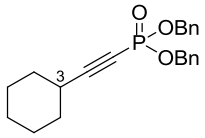
Dimethyl cyclohexylethynylphosphonate (37)



As general procedure **(D)**. $Pd(OAc)_2$ (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. (Bromoethynyl)cyclohexane (100 mg, 0.53 mmol), dimethyl phosphite (55 μL, 0.53 mmol) and propylene oxide (743 μL, 10.6 mmol) were dissolved in

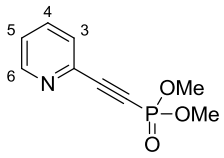
THF (2 mL), added to the catalyst mixture and stirred at 100°C for 4 h. Recovered 69 mg (61%) as a light yellow oil. R_f 0.39 (EtOAc : Petrol, 2 : 1) ; υ_{max} /cm^{-1} ($CHCl_3$ soln) 3234, 2281, 1711, 1620, 1455, 1361, and 1327; ^{1}H NMR (400 MHz ,$CDCl_3$) 3.80 (6H, d, *J* 12.3, *POCH*$_3$), 2.62 - 2.50 (1H, m, *C*^{3}*H*), 1.94 - 1.81 (2H, m,*C*^{Cy}*H*$_2$), 1.79 - 1.68 (2H, m, *C*^{Cy}*H*$_2$), 1.62 - 1.48 (3H, m, *C*^{Cy}*H*$_2$) and 1.37 (3H, m, *C*^{Cy}*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 107.7 (d, *J* 51, C), 68.6 (d, *J* 304, C), 53.2 (d, *J* 5, CH_3), 31.3 (CH_2), 29.3 (d, *J* 4, CH), 25.5 (CH_2) and 24.5 (CH_2); ^{31}P NMR (161 MHz, $CDCl_3$) -2.59; HRMS *m/z* (ES^+) Found M+Na 239.0819. $C_{10}H_{17}O_3PNa$ requires 239.0808.

Dibenzyl cyclohexylethynylphosphonate (38)



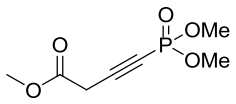
As general procedure **(D)**. $Pd(OAc)_2$ (22 mg, 0.10 mmol) and dppf (111 mg, 0.20 mmol) were dissolved in THF (1 mL) and stirred at room temperature for 20 mins. (Bromoethynyl)cyclohexane (100 mg, 0.53 mmol), dibenzyl phosphite (139 mg, 0.53 mmol) and propylene oxide (743 μL, 10.6 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 100 °C for 4 h. Recovered 95 mg (49%) as a light yellow oil. R_f 0.42 (petrol : EtOAc, 2 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2938, 2858, 2415, 2202, 1522, 1499, 1454, 1380, 1257, 1011, 928, 929 and 848; ^{1}H NMR (400 MHz, $CDCl_3$) 7.31 - 7.42 (10H, m, *ArH*), 5.10 (4H, d, *J* 8.8, O*CH*$_2$Ph), 2.47 - 2.56 (1H, m, *C*^{3}*H*), 1.75 - 1.87 (2H, m, *C*^{Cy}*H*$_2$), 1.64 - 1.74 (2H, m, *C*^{Cy}*H*$_2$), 1.43 - 1.56 (3H, m, *C*^{Cy}*H*$_2$), 1.26 - 1.38 (3H, m, *C*^{Cy}*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 141.0 (C), 135.7 (C), 128.5 (CH), 127.9 (CH), 127.6 (CH), 127.0 (CH), 107.7 (d, *J* 53, C), 69.3 (d, *J* 306, C), 68.3 (d, *J* 6, CH_2), 65.3 (CH_2), 31.3 (CH_2), 31.2 (CH_2), 25.5 (CH_2) and 24.5 (CH_2); ^{31}P NMR (161 MHz, $CDCl_3$) -5.27; HRMS *m/z* (ES^+) Found M+Na 391.1430. $C_{22}H_{25}O_3PNa$ requires 391.1434.

Dimethyl pyridin-2-ylethynylphosphonate (39)



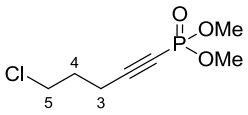
As general procedure **(D)**. $Pd(OAc)_2$ (25 mg, 0.11 mmol) and dppf (122 mg, 0.22 mmol) were dissolved in THF (1 mL) and stirred at room temperature for 20 mins. 2-(Bromoethynyl)pyridine (100 mg, 0.55 mmol), dimethyl phosphite (56 μL, 0.55 mmol) and propylene oxide (771 μL, 11.0 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 80 $^{\circ}$C for 45 mins. Recovered 62 mg (53%) as a yellow oil. R_f 0.02 (EtOAc : petrol, 1 : 1, with 1% Et_3N); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3684, 3011, 2414, 2200, 1581, 1521, 1476, 1463, 1429, 1241, 1046, 929, 873 and 848; ^{1}H NMR (400 MHz, $CDCl_3$) 8.67 (1H, d, *J* 4.0, *C^{6}H*), 7.76 (1H, app. t, *J* 7.0, *C^{4}H*), 7.63 (1H, d, *J* 7.0, *C^{3}H*), 7.39 (1H, dd, *J* 7.0 and 4.0, *C^{5}H*), 3.89 (6H, d, *J* 12.3, *OCH$_3$*); ^{13}C NMR (100 MHz, $CDCl_3$) 150.6 (CH), 140.3 (C), 136.5 (CH), 128.7 (CH), 125.0 (CH), 97.5 (d, *J* 51, C), 76.3 (d, *J* 294, C) and 53.7 (d, *J* 6, CH_3); ^{31}P NMR (16, $CDCl_3$) -3.90; HRMS *m/z* (ES$^+$) Found M + Na 234.0286. $C_9H_{10}NO_3PNa$ requires 234.0291.

Methyl 4-(dimethoxyphosphoryl)but-3-ynoate (40)



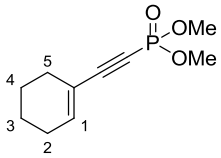
As general procedure **(D)**. $Pd(OAc)_2$ (25 mg, 0.11 mmol) and dppf (122 mg, 0.22 mmol) were dissolved in THF (1 mL) and stirred at room temperature for 20 mins. Methyl 4-bromobut-3-ynoate (100 mg, 0.57 mmol), dimethyl phosphite (57 μL, 0.57 mmol) and propylene oxide (800 μL, 11.4 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 90 $^{\circ}$C for 3 h. Recovered 74 mg (56%) as a light yellow oil. R_f 0.17 (EtOAc : petrol, 1 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3010, 2956, 2855, 2221, 1749, 1448, 1377, 1357, 1270, 1242, 1051 and 846; ^{1}H NMR (400 MHz, $CDCl_3$) 4.78 (2H, d, *J* 4.1, *CH$_2$*), 3.81 (6H, d, *J* 12.3, *P(O)OCH$_3$*) 2.12 (3H, s, *C(O)OCH$_3$*); ^{13}C NMR (100 MHz, $CDCl_3$) 169.7 (C), 94.7 (d, *J* 51, C), 75.5 (d, *J* 358, C), 53.6 (d, *J* 6, CH_3), 51.3 (d, *J* 5, CH_2) and 20.5 (CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) -4.72; HRMS *m/z* (ES$^+$) Found M + Na 229.0229. $C_7H_{11}O_5PNa$ requires 229.0236.

Dimethyl 5-chloropent-1-ynylphosphonate (41)



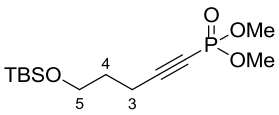
As general procedure **(D)**. $Pd(OAc)_2$ (25 mg, 0.11 mmol) and dppf (122 mg, 0.22 mmol) were dissolved in THF (1 mL) and stirred at room temperature for 20 mins. 1-Bromo-5-chloropent-1-yne (100 mg, 0.55 mmol), dimethyl phosphite (56 μL, 0.55 mmol) and propylene oxide (771 μL, 11.0 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 90 $^{\circ}$C for 3 h. Recovered 101 mg (77%) as a light yellow oil. R_f 0.14 (EtOAc : petrol, 2 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2956, 2210, 1447, 1267, 1186, 1040, 909 and 844; ^{1}H NMR (400 MHz, $CDCl_3$) 3.77 (6H, d, *J* 12.3, *OCH*$_3$), 3.63 (2H, t, *J* 6.8, *C*^{5}*H*$_2$), 2.57 (2H, td, *J* 6.8, 4.5, *C*^{3}*H*$_2$), 2.04 (2H, app. quin, *J* 6.8, *C*^{4}*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 101.6 (d, *J* 53, C), 70.2 (d, *J* 302, C), 53.3 (d, *J* 5, CH_3), 43.1 (CH_2) and 30.1 (CH_2), 16.7 (CH_2); ^{31}P NMR (161 MHz, $CDCl_3$) -3.53; HRMS *m/z* (ES$^+$) Found M + Na 233.0102. $C_7H_{12}{}^{35}ClO_3PNa$ requires 233.0105.

Dimethyl cyclohexenylethynylphosphonate (42)



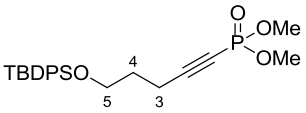
As general procedure **(D)**. $Pd(OAc)_2$ (25 mg, 0.11 mmol) and dppf (122 mg, 0.22 mmol) were dissolved in THF (1 mL) and stirred at room temperature for 20 mins. 1-(Bromoethynyl)cyclohex-1-ene (100 mg, 0.54 mmol), dimethyl phosphite (56 μL, 0.54 mmol) and propylene oxide (757 μL, 10.8 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 90 $^{\circ}$C for 3 h. Recovered 91 mg (78%) as a light yellow oil. R_f 0.28 (EtOAc : petrol, 2 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3010, 2951, 2854, 2174, 1717, 1626, 1449, 1436, 1262, 1185, 1040, 921 and 868; ^{1}H NMR (400 MHz, $CDCl_3$) 6.44 - 6.50 (1H, m, *C*^{1}*H*), 3.80 (6H, d, *J* 12.0, *OCH*$_3$), 2.13 - 2.20 (4H, m, *C*^{2}*H*$_2$ and *C*^{5}*H*$_2$) and 1.57 - 1.70 (4H, m, *C*^{3}*H*$_2$ and *C*^{4}*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 142.4 (CH), 118.3 (C), 102.3 (d, *J* 52, C), 74.1 (d, *J* 304, C), 53.3 (d, *J* 6, CH_3), 27.9 (CH_2), 25.9 (CH_2), 21.8 (CH_2) and 21.0 (CH_2); ^{31}P NMR (161 MHz, $CDCl_3$) -1.94; HRMS *m/z* (ES$^+$) Found M + Na 237.0652. $C_{10}H_{15}O_3PNa$ requires 237.0651.

Dimethyl 5-(tert-butyldimethylsilyloxy)pent-1-ynylphosphonate (43)



As general procedure **(D)**. $Pd(OAc)_2$ (16 mg, 0.07 mmol) and dppf (80 mg, 0.14 mmol) were dissolved in THF (0.5 mL) and stirred at room temperature for 20 mins. (5-Bromopent-4-ynyloxy)(tert-butyl)dimethylsilane (100 mg, 0.36 mmol), dimethyl phosphite (37 μL, 0.36 mmol) and propylene oxide (504 μL, 7.2 mmol) were dissolved in THF (1.7 mL), added to the catalyst mixture and stirred at 90 $^{\circ}$C for 3 h. Recovered 44 mg (36%) as a light yellow oil. R_f 0.50 (EtOAc : petrol, 1 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3012, 2956, 2931, 2857, 2207, 1463, 1258, 1195, 1106, 1040, 928 and 839; ^{1}H NMR (400 MHz, $CDCl_3$) 3.79 (6H, d, *J* 12.0, *OCH*$_3$), 3.70 (2H, t, *J* 5.8, *C*^{5}*H*$_2$), 2.48 (2H, td, *J* 7.2, 4.4, *C*^{3}*H*$_2$), 1.80 (2H, tt, *J* 7.2, 5.8, *C*^{4}*H*$_2$), 0.90 (9H, s, SiMe$_2$^{t}*Bu*) and 0.07 (6H, s, Si*Me*$_2$^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) 103.7 (d, *J* 53, C), 69.1 (d, *J* 304, C), 61.0 (CH_2), 53.2 (d, *J* 5, CH_3), 30.5 (CH_2), 25.8 (CH_3) and 15.7 (CH_2); ^{31}P NMR (161, $CDCl_3$) -3.07; HRMS *m/z* (ES$^+$) Found M + Na 329.1297. $C_{13}H_{27}O_4PSiNa$ requires 329.1308.

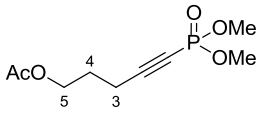
Dimethyl 5-(tert-butyldiphenylsilyloxy)pent-1-ynylphosphonate (44)



As general procedure **(D)**. $Pd(OAc)_2$ (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. (5-Bromopent-4-ynyloxy)(tert-butyl)diphenylsilane (100 mg, 0.50 mmol), dimethyl phosphite (51 μL, 0.50 mmol) and propylene oxide (700 μL, 10.0 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 90 $^{\circ}$C for 3 h. Recovered 129 mg (60%) as a light yellow oil. R_f 0.29 (EtOAc : Petrol, 1 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2956, 2933, 2859, 2208, 1428, 1265, 1110, 1040, 909 and 842; ^{1}H NMR (400 MHz, $CDCl_3$) 7.66 (4H, dd, *J* 7.9 and 1.6, *ArH*), 7.37 - 7.48 (6H, m, *ArH*), 3.76 (6H, d, *J* 12.3, *OCH*$_3$), 3.75 (2H, t, *J* 5.8, *C*^{5}*H*$_2$), 2.55 (2H, td, *J* 7.2, 4.4, *C*^{3}*H*$_2$), 1.85 (2H, tt, *J* 7.2 and 5.8, *C*^{4}*H*$_2$), 1.07 (9H, s, SiPh$_2$^{t}*Bu*); ^{13}C NMR (100 MHz, $CDCl_3$) 135.5 (CH), 133.5 (C), 129.8 (CH), 127.8 (CH), 103.7 (d, *J* 53, C), 69.2 (d, *J* 303, C), 62.0 (CH_2), 53.2 (d, *J* 6, CH_3), 30.4

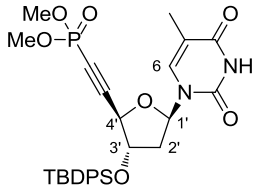
(CH_2), 26.8 (CH_3), 19.2 (C) and 15.9 (CH_2); ^{31}P NMR (161 MHz, $CDCl_3$) -3.08; HRMS *m/z* (ES^+) Found M + Na 453.1618. $C_{23}H_{31}O_4PSiNa$ requires 453.1621.

5-(Dimethoxyphosphoryl)pent-4-ynyl acetate (45)



As general procedure **(D)**. $Pd(OAc)_2$ (27 mg, 0.12 mmol) and dppf (133 mg, 0.24 mmol) were dissolved in THF (1.5 mL) and stirred at room temperature for 20 mins. 5-Bromopent-4-ynyl acetate (100 mg, 0.62 mmol), dimethyl phosphite (64 μL, 0.62 mmol) and propylene oxide (869 μL, 12.4 mmol) were dissolved in THF (2 mL), added to the catalyst mixture and stirred at 90 $^{\circ}$C for 2 h. Recovered 75 mg (51%) as a light yellow oil. R_f 0.19 (EtOAc : petrol, 2 : 1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2956, 2854, 2210, 1737, 1368, 1249, 1044, 951 and 843; ^{1}H NMR (400 MHz, $CDCl_3$) 4.15 (2H, t, *J* 6.1, *C^{5}H$_2$*), 3.78 (6H, d, *J* 12.3, *P(O)OCH$_3$*), 2.47 (2H, td, *J* 7.1 and 4.4, *C^{3}H$_2$*), 2.06 (3H, s, *C(O)OCH$_3$*) and 1.93 (2H, tt, *J* 7.1 and 6.1, *C^{4}H$_2$*); ^{13}C NMR (100 MHz, $CDCl_3$) 170.9 (C), 102.1 (d, *J* 53, C), 70.0 (d, *J* 302, C), 62.6 (CH_2), 53.2 (d, *J* 6, CH_3), 26.7 (CH_2), 20.9 (CH_3) and 16.2 (CH_2); ^{31}P NMR (161, $CDCl_3$) -3.42; HRMS *m/z* (ES^+) Found M + Na 257.0557. $C_9H_{15}O_5PNa$ requires 257.0549.

Dimethyl ((1'*R*, 3'*S*, 4'*R*)-5'-ethynyl-3'-(tert-butyldiphenylsilyloxy) thymidine) phosphonate (46)

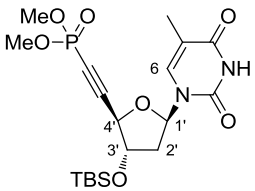


As general procedure **(D)**. $Pd(OAc)_2$ (5 mg, 0.02 mmol) and dppf (22 mg, 0.04 mmol) were dissolved in THF (0.2 mL) and stirred at room temperature for 20 mins. **19** (50 mg, 0.09 mmol), dimethyl phosphite (9 μL, 0.09 mmol) and propylene oxide (127 μL, 1.8 mmol) were dissolved in THF (0.3 mL), added to the catalyst mixture and stirred at 90 $^{\circ}$C for 2 h. Recovered 30 mg (57%) as a light yellow oil. R_f 0.12 (EtOAc : Petrol, 3 : 1); [α_D] (c 0.7) 12.4; υ_{max} / cm^{-1} ($CHCl_3$ soln) 3393, 3008, 2957, 2934, 2860, 2206, 1692, 1471, 1395, 1365, 1308, 1271, 1113, 1046, 909 and

845; ^{1}H NMR (400 MHz, $CDCl_3$) 8.30 - 8.35 (1H, br. s, *NH*), 7.65 - 7.69 (4H, m, *ArH*), 7.42 - 7.54 (6H, m, *ArH*), 7.29 (1H, d, *J* 1.3, $C^{6}H$), 6.64 (1H, dd, *J* 8.7 and 5.6, $C^{1'}H$), 4.67 (H, d, *J* 3.3, $C^{4'}H$), 4.60 (1H, d, *J* 4.0, $C^{3'}H$), 3.76 (6H, dd, *J* 12.3 and 5.0, OCH_3), 2.41 - 2.56 (1H, m, $C^{2'}H_2$), 2.01 - 2.12 (1H, m, $C^{2'}H_2$), 1.96 (3H, d, *J* 1.3, CH_3) and 1.13 (9H, s, $SiPh_2{}^{t}Bu$); ^{13}C NMR (100 MHz, C_6D_6) 163.4 (C), 150.5 (C), 136.0 (CH), 134.4 (CH), 132.6 (C), 130.4 (CH), 111.6 (C), 96.0 (d, *J* 48, C), 86.7 (CH), 78.5 (d, *J* 269, C), 78.3 (CH), 76.2 (CH), 52.6 (d, *J* 5, CH_3), 39.6 (CH_2), 26.7 (CH_3), 19.0 (C) and 12.5 (CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) -5.07; HRMS *m/z* (ES^+) Found M + Na 605.1853. $C_{29}H_{35}O_7N_2SiPNa$ requires 605.1843.

5.4 Formation of alkynylphosphonate – Copper

Dimethyl ((1'*R*, 3'*S*, 4'*R*)-5'-ethynyl-3'-(tert-butyldimethylsilyloxy) thymidine) phosphonate (11)

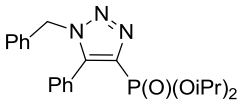


$Cu(OAc)_2$ (132 mg, 0.72 mmol), Et_3N (198 µL, 1.42 mmol), (1'*R*, 3'*S*, 4'*R*)-5'-ethynyl-3'-(tert-butyldimethylsilyloxy) thymidine (500 mg, 1.42 mmol) and dimethyl phosphite (520 µL, 5.68 mmol) were dissolved in DMF (18 mL) and the reaction stirred at 55 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated *in vacuo*. The residue was loaded onto a silica gel column and eluted (Et_2O) yielding the product (320 mg, 49%) as an oily solid. R_f – 0.05 (Et_2O); [α_D] (c 0.5) 9.1; υ_{max} / cm^{-1} ($CHCl_3$ soln) 3392, 3010, 2956, 2932, 2858, 1692, 1470, 1270, 1186, 1129, 1107, 1045 and 842; ^{1}H NMR (400 MHz, $CDCl_3$) 8.18 (1H, br. s., *NH*), 7.37 (1H, d, *J* 1.1, $C^{6}H$), 6.49 (1H, dd, *J* 8.4 and 5.8, $C^{1'}H$), 4.66 (1H, d, *J* 3.3, $C^{4'}H$), 4.62 (1H, app. d, *J* 4.6, $C^{3'}H$), 3.85 (6H, dd, *J* 12.3 and 2.4, $(OMe)_2$), 2.39-2.49 (1H, m, $C^{2'}H$), 2.16 - 2.25 (1 H, m, $C^{2'}H$), 2.00 (3H, d, *J* 1.1, CH_3), 0.92 (9H, s, $SiMe_2{}^{t}Bu$) and 0.14 (6 H, s, $SiMe_2{}^{t}Bu$); ^{13}C NMR (100 MHz, $CDCl_3$) 163.8 (C), 150.4 (C), 134.8 (CH), 111.7 (C), 96.2 (C, d, *J* 49), 86.7 (CH), 77.2 (C, d, *J* 295), 77.2 (CH, d, *J* 2), 76.5 (CH, d, *J* 4), 53.4 (CH_3, app. dd, *J* 8 and 6), 40.3 (CH_2), 25.5 (CH_3), 17.8 (C), 12.4 (CH_3), -5.0 (CH_3) and -5.1

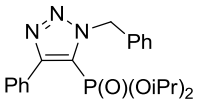
(CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) -4.95; HRMS *m/z* (ES^+) Found M + Na 481.1511. $C_{19}H_{31}O_7N_2SiPNa$ requires 481.1530.

5.5 Click chemistry

Diisopropyl 1-benzyl-5-phenyl-1H-1,2,3-triazol-4-ylphosphonate, 62 B, and diisopropyl 1-benzyl-4-phenyl-1H-1,2,3-triazol-5-ylphosphonate, 62 A



62B



62A

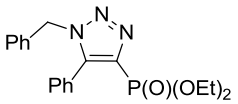
Diisopropyl phenylethynylphosphonate (200 mg, 0.75 mmol), benzyl azide (198 mg, 1.5 mmol) and copper iodide (72 mg, 0.38 mmol) were charged to a 1 mL screwcap Reactivial^{TM} under argon. A mixture of THF : ^{t}BuOH : H_2O (3:2:1) (1 mL) was added and the vial sealed under argon. The mixture was stirred vigorously at 90 °C for 2 days. After cooling to room temperature the reaction mixture was directly loaded onto a silica gel column and the products eluted (Et_2O) yielding **62A** (65 mg, 22%) and **62B** (156 mg, 52%) as separable regioisomers (2 : 1 ratio of **62B** : **62A** from ^{1}H NMR of the crude; regioisomers determined by NOE spectroscopy).

Data for compound 62B: Yellow oil. R_f - 0.15 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 2986, 2938, 1481, 1387, 1302, 1245, 1105, 1020 and 909; ^{1}H NMR (400 MHz, $CDCl_3$) 7.51 - 7.38 (3H, m, *ArH*), 7.32 - 7.22 (5H, m, *ArH*), 7.06 - 6.98 (2H, m, *ArH*), 5.44 (2H, s, Ph*CH*$_2$), 4.75 (2H, d.spt., *J* 7.8 and 6.3, P(O)(O*CH*(CH_3)$_2$)$_2$), 1.27 (6H, d, *J* 6.2 P(O)(OCH(*CH*$_3$)$_2$)) and 1.17 (6 H, d, *J* 6.2, P(O)(OCH(*CH*$_3$)$_2$)) ; ^{13}C NMR (100 MHz, $CDCl_3$) 143.1 (C, d, *J* 33), 137.5 (C, d, *J* 242), 135.3 (C), 130.5 (CH), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.0 (CH), 126.5 (C), 72.1 (CH, d, *J* 6), 52.5 (CH_2), 24.5 (CH_3, d, *J* 4) and 24.1 (CH_3, d, *J* 5); ^{31}P NMR (161 MHz, $CDCl_3$) 5.49; HRMS *m/z* (ES^+) Found M + Na 422.1606. $C_{21}H_{26}N_3O_3PNa$ requires 422.1604.

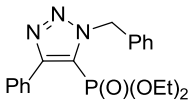
Data for compound 62A: Yellow oil. R_f – 0.47 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 2985, 1497, 1456, 1388, 1377, 1254, 1179, 1142, 1101, 995 and 909; ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 - 7.78 (2H, m, *ArH*), 7.46 - 7.37 (5H, m, *ArH*), 7.36 - 7.26 (3H, m, *ArH*), 6.08 (2H, s, Ph*CH*$_2$),

4.35 (2H, d.spt., *J* 7.8 and 6.1, P(O)(O*CH*(CH_3)$_2$)$_2$), 1.20 (6H, d, *J* 6.2, P(O)(OCH(*CH_3*)$_2$)) and 0.84 (6H, d, *J* 6.2, P(O)(OCH(*CH_3*)$_2$)); ^{13}C NMR (100 MHz, $CDCl_3$) 154.0 (C, d, *J* 18), 136.9 (C), 131.3 (C), 130.1 (CH), 129.7 (CH), 129.4 (CH), 129.1 (CH), 128.9 (CH), 123.4 (C, d, *J* 218), 73.4 (CH, d, *J* 5), 54.9 (CH_2), 24.7 (CH_3, d, *J* 4) and 24.0 (CH_3, d, *J* 5); ^{31}P NMR (161 MHz, $CDCl_3$) 1.86; HRMS *m/z* (ES^+) Found M + Na 422.1597. $C_{21}H_{26}N_3O_3PNa$ requires 422.1604.

Diethyl 1-benzyl-5-phenyl-1H-1,2,3-triazol-4-ylphosphonate, 63 B, and diethyl 1-benzyl-4-phenyl-1H-1,2,3-triazol-5-ylphosphonate, 63 A



63B



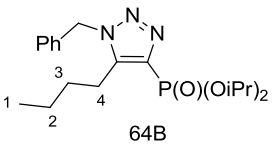
63A

Diethyl phenylethynylphosphonate (200 mg, 0.84 mmol), benzyl azide (222 mg, 1.68 mmol) and copper iodide (80 mg, 0.42 mmol) were charged to a 1 mL screwcap Reactivial^{TM} under argon. A mixture of THF : ^{t}BuOH : H_2O (3:2:1) (1 mL) was added and the vial sealed under argon. The mixture was stirred vigorously at 90 °C for 3 days. After cooling to room temperature the reaction mixture was directly loaded onto a silica gel column and the products eluted (gradient: 3:1 Petrol:Et_2O to 10% MeOH in Et_2O) yielding **63A** (62 mg, 20%) and **63B** (136 mg, 44%) as separable regioisomers (2 : 1 ratio of **63B** : **63A** from ^{1}H NMR of the crude; regioisomers determined by NOE spectroscopy).

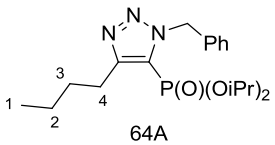
Data for compound 63B: Yellow oil. R_f – 0.09 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3003, 1498, 1481, 1455, 1415, 1394, 1246, 1052, 1028, 978 and 909; ^{1}H NMR (400 MHz, $CDCl_3$) 7.56 - 7.41 (3H, m, *ArH*), 7.32 - 7.23 (5H, m, *ArH*), 7.08 - 7.01 (2H, m, *ArH*), 5.46 (2H, s, Ph*CH_2*), 4.21 - 4.05 (4 H, m, P(O)(O*CH_2*CH_3)$_2$) and 1.23 (6 H, td, *J* 7.2 and 0.6, P(O)(OCH$_2$*CH_3*)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 143.6 (C, d, *J* 33), 136.5 (C, d, *J* 241), 135.2 (C), 130.7 (CH), 130.5 (CH), 129.4 (CH), 129.2 (CH), 129.0 (CH), 128.1 (CH), 126.3 (C), 63.4 (CH_2, d, *J* 6), 52.7 (CH_2) and 16.7 (CH_3, d, *J* 7); ^{31}P NMR (161 MHz, $CDCl_3$) 7.29; HRMS *m/z* (ES^+) Found M + Na 394.1279. $C_{19}H_{22}N_3O_3PNa$ requires 394.1291.

Data for compound 63A: Yellow oil. R_f – 0.47 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3007, 1534, 1498, 1476, 1457, 1394, 1256, 1171, 1103, 1022 and 982; ^1H NMR (400 MHz, $CDCl_3$) 7.79 - 7.72 (2H, m, *ArH*), 7.46 - 7.37 (5H, m, *ArH*), 7.36 - 7.27 (3H, m, *ArH*), 6.03 (2H, s, Ph*CH*$_2$), 3.95 - 3.83 (2H, m, P(O)(O*CH*$_2$CH$_3$)), 3.72 - 3.60 (2H, m, P(O)(O*CH*$_2$CH$_3$)) and 0.99 (6 H, td, *J* 7.1 and 0.8, P(O)(OCH$_2$*CH*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 154.0 (C, d, *J* 19), 136.3 (C), 130.7 (C), 129.7 (CH), 129.5 (CH), 129.1 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 122.0 (C, d, *J* 218), 63.5 (CH_2, d, *J* 5), 54.6 (CH_2) and 16.2 (CH_3, d, *J* 7); ^{31}P NMR (161 MHz, $CDCl_3$) 4.21; HRMS *m/z* (ES^+) Found M + H 372.1460. $C_{19}H_{23}N_3O_3P$ requires 372.1472.

Diisopropyl 1-benzyl-5-butyl-1H-1,2,3-triazol-4-ylphosphonate, 64 B, and diisopropyl 1-benzyl-4-butyl-1H-1,2,3-triazol-5-ylphosphonate, 64 A



64B



64A

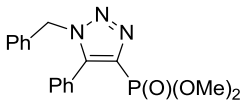
Diisopropyl hex-1-ynylphosphonate (200 mg, 0.81 mmol), benzyl azide (218 mg, 1.62 mmol) and copper iodide (77 mg, 0.41 mmol) were charged to a 1 mL screwcap Reactivial^{TM} under argon. A mixture of THF : ^{t}BuOH : H_2O (3:2:1) (1 mL) was added and the vial sealed under argon. The mixture was stirred vigorously at 90 °C for 4 days. After cooling to room temperature the reaction mixture was directly loaded onto a silica gel column and the products eluted (gradient: 3:1 Petrol:Et_2O to 100% Et_2O) yielding **64A** (63 mg, 21%) and **64B** (139 mg, 45%) as separable regioisomers (2 : 1 ratio of **64B** : **64A** from ^1H NMR of the crude; regioisomers determined by NOE spectroscopy).

Data for compound 64B: Yellow oil. R_f – 0.30 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 2986, 2936, 2875, 1498, 1387, 1246, 1180, 1142, 1104, 1000 and 909; ^1H NMR (400 MHz, $CDCl_3$) 7.38 - 7.29 (3H, m, *ArH*), 7.19 - 7.12 (2 H, m, *ArH*), 5.52 (2 H, s, Ph*CH*$_2$), 4.76 (2H, d.spt., *J* 8.3 and 6.1, P(O)(O*CH*(CH$_3$)$_2$)$_2$), 2.81 (2 H, t, *J* 7.6, *C*^{4}*H*$_2$), 1.39 - 1.24 (16 H, m, *C*^{2}*H*$_2$, *C*^{3}*H*$_2$ and

P(O)(OCH(CH_3)$_2$)$_2$) and 0.82 (3H, t, *J* 7.2, C^1H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 144.8 (C, d, *J* 35), 136.2 (C, d, *J* 239), 135.1 (C), 129.5 (CH), 129.0 (CH), 121.7 (CH), 72.0 (CH, d, *J* 5), 52.3 (CH_2), 31.6 (CH_2), 24.5 (CH_3, d, *J* 4), 24.3 (CH_2, d, *J* 5) and 14.0 (CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 5.86; HRMS *m/z* (ES^+) Found M + Na 402.1912. $C_{19}H_{30}N_3O_3PNa$ requires 402.1917.

Data for compound 64A: Yellow oil. R_f – 0.57 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 2985, 2935, 2874, 1498, 1457, 1388, 1377, 1257, 1178, 1143, 1103, 993 and 909; ^{1}H NMR (400 MHz, $CDCl_3$) 7.34 - 7.24 (5H, m, *ArH*), 5.84 (2H, s, PhCH_2), 4.47 (2H, d.spt., *J* 7.9 and 6.3, P(O)(O*CH*(CH_3)$_2$)$_2$), 2.84 (2H, td, *J* 7.9 and 1.0 Hz, C^4H_2), 1.77 - 1.68 (2H, m, C^3H_2), 1.40 (2H, tq, *J* 7.5 and 7.3, C^2H_2), 1.27 (6H, d, *J* 6.2, P(O)(OCH(CH_3)$_2$)), 1.03 (6H, d, *J* 6.2, P(O)(OCH(CH_3)$_2$)) and 0.93 (3H, t, *J* 7.3, C^1H_2); ^{13}C NMR (100 MHz, $CDCl_3$) 155.0 (C, d, *J* 20), 135.9 (C), 128.6 (CH), 128.1 (CH), 128.1 (CH), 122.9 (C, d, *J* 222), 72.1 (CH, d, *J* 5), 53.6 (CH_2), 31.4 (CH_2), 25.7 (CH_2), 23.9 (CH_3, d, *J* 4), 23.5 (CH_3, d, *J* 5), 22.6 (CH_2) and 13.9 (CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 2.79; HRMS *m/z* (ES^+) Found M + Na 402.1911. $C_{19}H_{30}N_3O_3PNa$ requires 402.1917.

Dimethyl 1-benzyl-5-phenyl-1H-1,2,3-triazol-4-ylphosphonate (65)



Dimethyl phenylethynylphosphonate (200 mg, 0.95 mmol), benzyl azide (251 mg, 1.90 mmol) and copper iodide (91 mg, 0.48 mmol) were charged to a 1 mL screwcap Reactivial^{TM} under argon. A mixture of THF : ^{t}BuOH : H_2O (3:2:1) (1 mL) was added and the vial sealed under argon. The mixture was stirred vigorously at 90 °C for 2 days. After cooling to room temperature the reaction mixture was directly loaded onto a silica gel column and the products eluted (Et_2O) yielding **x** (54 mg, 17%) as a light yellow oil. R_f – 0.12 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3008, 1498, 1445, 1256, 1172, 1102 and 1022; ^{1}H NMR (400 MHz, $CDCl_3$) 7.54 - 7.42 (3H, m, *ArH*), 7.31 - 7.23 (5H, m, *ArH*), 7.06 - 6.99 (2H, m, *ArH*), 5.46 (2 H, s, PhCH_2), 3.75 (4 H, s, P(O)(*OMe*)) and

3.73 (4 H, s, P(O)(*OMe*)); ^{13}C NMR (100 MHz, $CDCl_3$) 143.9 (C, d, *J* 34), 135.5 (C, d, *J* 242), 135.1 (C), 130.8 (CH), 130.3 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.0 (CH), 125.9 (C), 53.8 (CH_3, d, *J* 6) and 52.5 (CH_2); ^{31}P NMR (161 MHz, $CDCl_3$) 9.94; HRMS *m/z* (ES^+) Found M + Na 366.0970. $C_{17}H_{18}N_3O_3PNa$ requires 366.0978.

5.6 Formation of amides

Amide Formation - General Procedure E

To a stirring suspension of CuI (38 mg, 0.2 mmol) in MeCN (1 mL) was added carboxylic acid (1.1 mmol) and Et_3N (76 µL, 0.55 mmol). The solution was stirred at 55 °C for 10 minutes before addition of diethyl phosphite (129 µL, 1.0 mmol). The reaction was stirred at 55 °C for 90 minutes before addition of amine (0.5 mmol). The reaction was stirred at 55 °C for a further 90 minutes before cooling to room temperature and diluting with CH_2Cl_2 (50 mL). The organic was washed with saturated aqueous Na_2CO_3 (30 mL), 2M HCl (30 mL), brine (30 mL), then dried ($MgSO_4$). Removal of the volatiles *in vacuo* left the crude amide, which was purified by silica gel column chromatography.

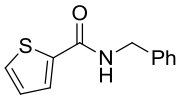
Amide Formation - General Procedure F

To a stirring suspension of CuI (38 mg, 0.2 mmol) in MeCN (1 mL) was added carboxylic acid (1.1 mmol) and Et_3N (76 µL, 0.55 mmol). The solution was stirred at 55 °C for 10 minutes before addition of diethyl phosphite (129 µL, 1.0 mmol). The reaction was stirred at 55 °C for 90 minutes before addition of amine (0.5 mmol). The reaction was stirred at 55 °C for a further 90 minutes before cooling to room temperature and diluting with CH_2Cl_2 (50 mL). The organic was washed with saturated aqueous Na_2CO_3 (30 mL), brine (30 mL), then dried ($MgSO_4$). Removal of the volatiles *in vacuo* left the crude amide, which was purified by silica gel column chromatography.

Carboxylic Acid Recovery

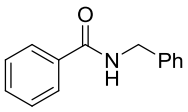
The basic aqueous layer was acidified using 2M HCl to pH ~3. For acids which crashed out of solution recovery was achieved by filtration. For acids which remained in solution recovery was achieved by extraction with CH_2Cl_2, dried over Na_2SO_4, and solvent removed leaving the acid starting material.

N-benzylthiophene-2-carboxamide (68)



As general procedure **E**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and benzylamine (55 µL, 0.5 mmol) used as coupling partners. Recovered 74 mg (68%) product as a white solid. m.p. 118-121 °C (Lit.[63] 119 – 120 °C). R_f 0.48 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3449, 3011, 1651, 1534, 1504 and 1268; ^{1}H NMR (400 MHz, $CDCl_3$) 7.53 (1H, dd, *J* 3.7, 1.13, *ArH*), 7.49 (1H, dd, *J* 5.0, 1.1, *ArH*) 7.38 - 7.35 (4H, m, *ArH*), 7.34 - 7.29 (m, 1 H, *ArH*), 7.08 (1H, dd, *J* 5.0, 3.7, *ArH*), 6.38 (1H, br. s, *NH*) and 4.63 (d, *J* 5.8, *CH_2*); ^{13}C NMR (100 MHz, $CDCl_3$) 161.8 (C), 138.8 (C), 138.1 (C), 130.0 (CH), 128.8 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH) and 44.0 (CH_2); HRMS *m/z* (ES^+) Found M + H 218.0622. $C_{12}H_{12}NOS$ requires 218.0634.

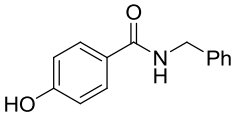
N-benzylbenzamide (71)



As general procedure **E**. Benzoic acid (134 mg, 1.1 mmol) and benzylamine (55 µL, 0.5 mmol) used as coupling partners. Recovered 72 mg (68%) product as a white solid. m.p. 101-103 °C (Lit.[64] 101 – 102 °C). R_f 0.31 (Et_2O:Petrol, 3:2); υ_{max} / cm^{-1} ($CHCl_3$ soln) 3453, 3068, 3011, 1658, 1519, 1487 and 1275; ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 - 7.77 (2H, m, *ArH*), 7.57 - 7.48 (1H, m, *ArH*), 7.48 - 7.41 (2H, m, *ArH*), 7.38 (4 H, m, *ArH*), 7.35 - 7.30 (1 H, m, *ArH*), 6.49 (1 H, br. s, *NH*) and 4.67 (2 H, d, *J* 5.65, *CH_2*); ^{13}C NMR (100 MHz, $CDCl_3$) 167.4 (C), 138.2 (C), 134.4 (C), 131.6 (CH), 128.8 (CH), 128.6

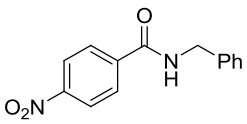
(CH), 128.0 (CH), 127.7 (CH), 127.0 (CH) and 44.2 (CH_2); HRMS *m/z* (ES^+) Found M + Na 234.08

N-benzyl-4-hydroxybenzamide (72)



As general procedure **E**. 4-Hydroxybenzoic acid (152 mg, 1.1 mmol) and benzylamine (55 µL, 0.5 mmol) used as coupling partners. Recovered 26 mg (23%) as a light yellow oil. R_f 0.26 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3590, 3455, 3011, 1654, 1610, 1530, 1498, 1265 and 1172; ^{1}H NMR (400 MHz, $CDCl_3$) 8.19 (1H, br. s, *NH*), 7.64 (2H, d, *J* 8.7, *ArH*), 7.36 - 7.27 (4H, m, *ArH*), 6.86 (2H, d, *J* 8.7, *ArH*), 6.59 - 6.52 (1H, m, *ArH*) and 4.62 (2H, d, *J* 5.7, *CH_2*); ^{13}C NMR (100 MHz, $CDCl_3$) 168.1 (C), 160.1 (C), 137.9 (C), 129.0 (CH), 128.8 (CH), 127.9 (CH), 127.7 (CH), 125.3 (C), 115.7 (CH) and 44.3 (CH_2); HRMS *m/z* (ES^+) Found M + Na 250.0834. $C_{14}H_{13}NONa$ requires 250.0838.

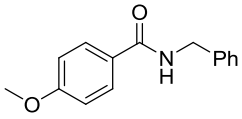
N-benzyl-4-nitrobenzamide (73)



As general procedure **E**. 4-Nitrobenzoic acid (184 mg, 1.1 mmol) and benzylamine (55 µL, 0.5 mmol) used as coupling partners. Recovered 76 mg (59%) product as a white solid. m.p. 140-142 °C (Lit.[65] 139 – 140 °C).. R_f 0.28 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3448, 3011, 1671, 1604, 1528, 1485, 1348 and 1272; ^{1}H NMR (400 MHz, $CDCl_3$) 8.28 (2H, d, *J* 9.2, *ArH*), 7.96 (2H, d, *J* 9.2, *ArH*), 7.42 - 7.31 (5H, m, *ArH*), 6.60 (1H, br. s., *NH*) and 4.67 (2H, d, *J* 5.7, *CH_2*); ^{13}C NMR (100 MHz, $CDCl_3$) 165.4 (C), 149.7 (C), 139.9 (C), 137.5 (C), 129.0 (CH), 128.2 (CH), 128.0 (CH), 128.0 (CH), 123.9 (CH) and 44.5 (CH_2); HRMS *m/z* (ES^+) Found M + Na 279.0741. $C_{14}H_{12}N_2O_3Na$ requires 279.0740.

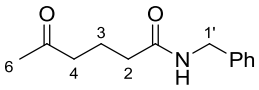
N-benzyl-4-methoxybenzamide (74)

As general procedure **E**. 4-Methoxybenzoic acid (167 mg, 1.1 mmol) and benzylamine (55 µL, 0.5 mmol) used as coupling partners. Recovered 75 mg (62%) product as a white solid.



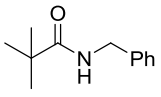
m.p. 126-129 °C (Lit.[66] 126 – 128 °C). R_f 0.18 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3691, 3455, 3008, 2928, 1652, 1606, 1528, 1498, 1464, 1255, 1177 and 1031; ^1H NMR (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.91, *ArH*), 7.39 - 7.27 (5H, m, *ArH*), 6.92 (2H, d, *J* 8.9, *ArH*), 6.44 (1H, br. s, *NH*), 4.64 (2 H, d, *J* 5.7, CH_2) and 3.85 (3 H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 166.9 (C), 162.2 (C), 138.5 (C), 128.8 (CH), 128.8 (CH), 127.9 (CH), 127.6 (CH), 126.7 (C), 113.8 (CH), 55.4 (CH_3) and 44.1 (CH_2); HRMS *m/z* (ES^+) Found M + Na 264.0988. $C_{15}H_{15}NO_2Na$ requires 264.0995.

N-benzyl-5-oxohexanamide (75)



As general procedure **E**. 4-Acetylbutyric acid (143 mg, 1.1 mmol) and benzylamine (55 µL, 0.5 mmol) used as coupling partners. Recovered 66 mg (60%) as an oily solid. R_f 0.31 (CH_2Cl_2:MeOH, 95:5); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3691, 3445, 3011, 1713, 1668, 1514, 1455, 1361 and 1242; ^1H NMR (400 MHz, $CDCl_3$) 7.48 - 7.16 (5H, m, *ArH*), 5.97 (1H, br. s, *NH*), 4.44 (2H, d, *J* 5.8, $C^{1'}H_2$), 2.54 (2H, t, *J* 7.3, C^2H_2), 2.26 (2H, t, *J* 7.3, C^4H_2), 2.14 (3H, s, C^6H_3) and 1.94 (2H, quin, *J* 7.30, C^3H_2); ^{13}C NMR (100 MHz, $CDCl_3$) 208.6 (C), 172.2 (C), 138.3 (C), 128.7 (CH), 127.8 (CH), 127.5 (CH), 43.6 (CH_2), 42.5 (CH_2), 35.4 (CH_2), 30.0 (CH_3) and 19.7 (CH_2); HRMS *m/z* (ES^+) Found M + Na 242.1154. $C_{13}H_{17}NO_2Na$ requires 242.1151.

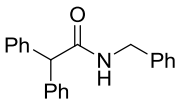
N-benzylpivalamide (76)



As general procedure **E**. Pivalic acid (112 mg, 1.1 mmol) and benzylamine (55 µL, 0.5 mmol) used as coupling partners. Recovered 49 mg (51%) product as a white solid. m.p. 79-82 °C (Lit.[67] 79 – 81 °C).. R_f 0.32 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3466, 3009, 2967, 1653, 1513, 1455, 1366 and 1192; ^1H NMR (400 MHz, $CDCl_3$) 7.30 (5H, m, *ArH*), 5.95 (1H, br. s, *NH*), 4.47 (2 H, d, *J* 5.7, CH_2) and 1.26 (9 H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 178.3 (C), 138.7 (C), 128.7 (CH), 127.7 (CH), 127.5 (CH), 43.6

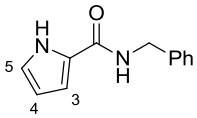
(CH_2), 38.7 (C) and 27.7 (CH_3); HRMS *m/z* (ES^+) Found M + Na 214.1199. $C_{12}H_{17}NONa$ requires 214.1202.

N-benzyl-2,2-diphenylacetamide (77)



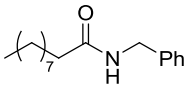
As general procedure **E**. Diphenylacetic acid (233 mg, 1.1 mmol) and benzylamine (55 µL, 0.5 mmol) used as coupling partners. Recovered 81 mg (54%) product as a white solid. m.p. 127-129 °C (Lit.[68] 126 – 128 °C). R_f 0.34 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3428, 3008, 1749, 1670, 1602, 1510, 1497, 1454, 1125 and 1031; ^1H NMR (400 MHz, $CDCl_3$) 7.40 - 7.26 (13H, m, *ArH*), 7.25 - 7.17 (2H, m, *ArH*), 5.00 (1H, s, *CH*) and 4.52 (2 H, d, *J* 5.8, *CH_2*); ^{13}C NMR (100 MHz, $CDCl_3$) 171.8 (C), 139.4 (C), 138.1 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 59.2 (CH) and 43.9 (CH_2); HRMS *m/z* (ES^+) Found M + Na 324.1348. $C_{21}H_{19}NONa$ requires 324.1359.

N-benzyl-1H-pyrrole-2-carboxamide (78)



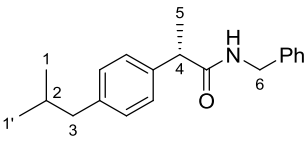
As general procedure **E**. 2-Pyrrolecarboxylic acid (122 mg, 1.1 mmol) and benzylamine (55 µL, 0.5 mmol) used as coupling partners. Recovered 53 mg (53%) product as a white solid. m.p. 127-129 °C. R_f 0.20 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3452, 3091, 1716, 1648, 1557, 1514, 1414, 1331, 1113 and 1087; ^1H NMR (400 MHz, $CDCl_3$) 10.11 (1 H, br. s, *NH*), 7.41 - 7.27 (5H, m, *ArH*), 6.91 (1H, td, *J* 2.6, 1.4, *C^5H*), 6.60 (1H, ddd, *J* 3.8, 2.6, 1.4, *C^4H*) 6.38 (1 H, br. s, *NH*), 6.23 (1 H, dt, *J* 3.8, 2.6, *C^3H*) and 4.64 (2 H, d, *J* 5.9, *CH_2*); ^{13}C NMR (100 MHz, $CDCl_3$) 161.3 (C), 138.5 (C), 128.8 (CH), 127.8 (CH), 127.6 (CH), 125.7 (C), 121.9 (CH), 109.7 (CH), 109.1 (CH) and 43.4 (CH_2); HRMS *m/z* (ES^+) Found M + Na 223.0843. $C_{12}H_{12}N_2ONa$ requires 223.0842.

N-benzyldecanamide (79)



As general procedure **E**. Decanoic acid (189 mg, 1.1 mmol) and benzylamine (55 µL, 0.5 mmol) used as coupling partners. Recovered 86 mg (66%) product as a white solid. m.p. 61-63 °C (Lit.[69] 60 – 62 °C).. R_f 0.18 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3691, 3448, 3010, 2928, 2856, 1665, 1513, 1456 and 1243; ^{1}H NMR (400 MHz, $CDCl_3$) 7.39 - 7.25 (5H, m, *ArH*), 5.75 (1H, br. s., *NH*), 4.46 (2H, d, *J* 5.7, CH_2), 2.22 (2H, t, *J* 7.4, CH_2), 1.67 (2 H, app. quin, *J* 7.3, CH_2), 1.36 - 1.24 (12 H, m, CH_2) and 0.90 (3 H, t, *J* 6.8, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 173.0 (C), 138.5 (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) and 14.1 (CH_3); HRMS *m/z* (ES^+) Found M + Na 284.1972. $C_{17}H_{27}NONa$ requires 284.1985.

(S)-N-benzyl-2-(4-isobutylphenyl)propanamide (80)



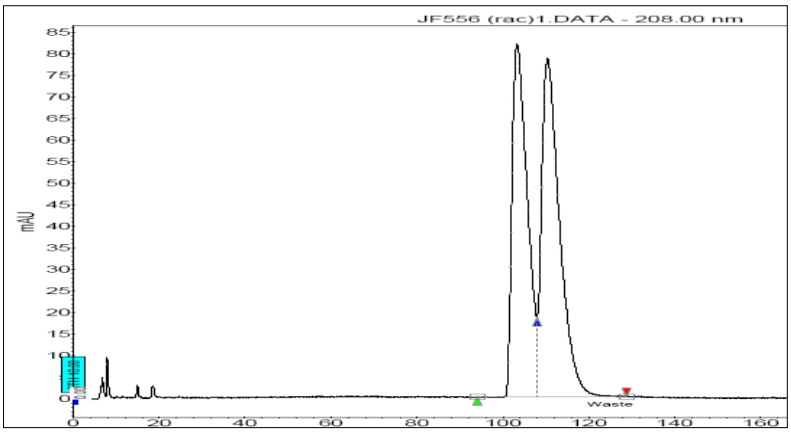
To a stirring suspension of CuI (38 mg, 0.2 mmol) in MeCN (1 mL) was added (S)-(+)-ibuprofen (227 mg, 1.1 mmol) and Et_3N (76 µL, 0.55 mmol). The solution was stirred at 55 °C for 10 minutes before addition of diethyl phosphite (129 µL, 1.0 mmol). The reaction was stirred at 55 °C for 90 minutes before addition of benzylamine (55 µL, 0.5 mmol). The reaction was stirred at 55 °C for a further 90 minutes before cooling to room temperature and diluting with CH_2Cl_2 (50 mL). The organic was washed with aqueous $NaHCO_3$ (pH 9, 30 mL), 2M HCl (30 mL), brine (30 mL), then dried (Na_2SO_4). Removal of the volatiles *in vacuo* left the crude amide, which was purified by silica gel column chromatography.

Recovered 84 mg (57%) as a white waxy solid. R_f 0.24 (3:2 Et_2O:Petrol); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3432, 3010, 2958, 2932, 2870, 1666, 1512, 1455, 1242 and 909; $[\alpha]_{589}^{22}$ +12.4 (c 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.33 - 7.21 (4H, m, *ArH*), 7.18 - 7.11 (3H, m, *ArH*), 5.79 (1H, br. s, *NH*), 4.42 (1H, d, *J* 5.8, C^6H_2), 3.62 (1H, q, *J* 7.2,C^4H), 2.49 (2H, d, *J* 7.2,

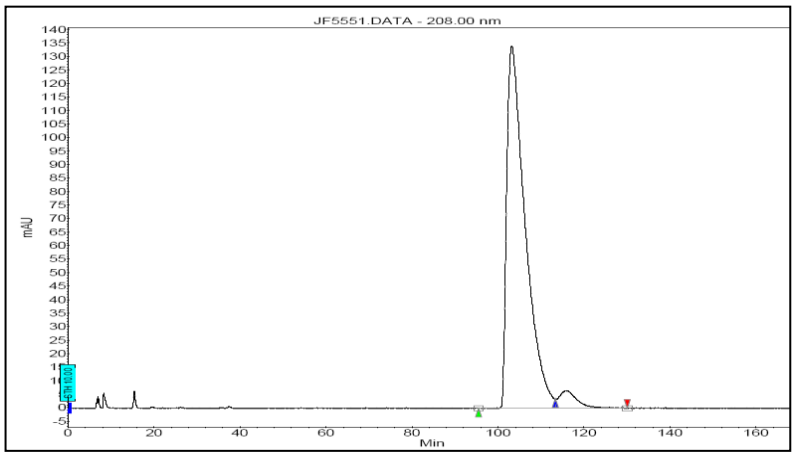
C^3H_2), 1.89 (1 H, app. d sep, *J* 13.50 and 6.8, C^2H), 1.58 (3H, d, *J* 7.2, C^5H_3) and 0.94 (6 H, d, *J* 6.8, C^1H_3 and $C^{1'}H_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 174.4 (C), 140.7 (C), 138.4 (C), 138.3 (C), 129.6 (CH), 128.5 (CH), 127.3 (CH)m 127.2 (CH), 46.7 (CH), 44.9 (CH_2), 43.4 (CH_2), 30.1 (CH), 22.3 (CH_3) and 18.4 (CH_3); HRMS *m/z* (ES^+) Found M + Na 318.1825. $C_{20}H_{25}NONa$ requires 318.1828.

HPLC (Chiralcel OD-H column. Hexane/isopropanol 99/1. Flow rate of 0.5 mL/min. Temperature at 25 °C. UV detection at 208 nm)

Racemic Mixture (prepared from racemic ibuprofen):

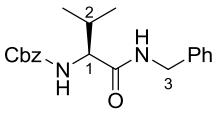


Chiral product (Prepared from (S)-(+)-ibuprofen):



Peak (time, mins)	Area (mAU.min)	Area (%)
103	665.4	95.4
116	32.1	4.6

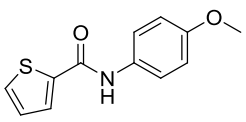
(S)-benzyl 1-(benzylamino)-3-methyl-1-oxobutan-2-ylcarbamate (81)



To a stirring suspension of CuI (0.2 mmol) in MeCN (1 mL) was added Cbz-L-Valine (276 mg, 1.1 mmol) and Et_3N (76 µL, 0.55 mmol). The solution was stirred at 55 °C for 10 minutes before addition of diethyl phosphite (129 µL, 1.0 mmol). The reaction was stirred at 55 °C for 90 minutes before addition of benzylamine (55 µL, 0.5 mmol). The reaction was stirred at 55 °C for a further 90 minutes before cooling to room temperature and diluting with CH_2Cl_2 (50 mL). The organic was washed with aqueous $NaHCO_3$ (pH 9, 30 mL), 2M HCl (30 mL), brine (30 mL), then dried (Na_2SO_4). Removal of the volatiles *in vacuo* left the crude amide, which was purified by silica gel column chromatography.

Recovered 101 mg (59%) as a white solid. m.p. 172 – 174 °C (Lit.[70] 174 – 176 °C). R_f 0.57 (3:2 Et_2O:Petrol); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3435, 3011, 2968, 1716, 1676, 1505, 1455, 1242, 1096 and 1028; $[\alpha]_{589}^{22}$ -16.8 (c 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.41 - 7.22 (10H, m, *ArH*), 6.35 (1H, br. s., *NH*Bn), 5.41 (1H, d, *J* 7.5, *NH*Cbz), 5.13 - 5.01 (2H, s, CH_2 (Cbz)), 4.50 (1H, dd, *J* 14.3 and 6.0, C^3H_2), 4.41 (1H, dd, *J* 14.3 and 6.0, C^3H_2), 4.03 (1H, t, *J* 7.5, C^1H), 2.17 (1H, d sep, *J* 7.5 and 6.8, C^2H), 0.99 (3 H, d, *J* 6.8, CH_3) and 0.94 (3 H, d, *J* 6.8, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 171.2 (C), 156.6 (C), 138.0 (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); HRMS *m/z* (ES^+) Found M + Na 363.1677. $C_{20}H_{24}N_2O_3Na$ requires 363.1679.

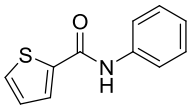
N-(4-methoxyphenyl)thiophene-2-carboxamide (82)



As general procedure **E**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and 4-Methoxyaniline (62 mg, 0.5 mmol) used as coupling partners. Recovered 89 mg (76%) product as a white solid. m.p. 139-141 °C (Lit.[71] 139 – 140 °C). R_f 0.27 (Et_2O:Petrol, 3:1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3439, 3008, 2929, 1661, 1599, 1530,

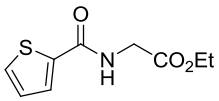
1515, 1422 and 1246; ^{1}H NMR (400 MHz, $CDCl_3$) 7.71 (1H, br. s, *NH*), 7.63 (1H, dd, *J* 3.6, 0.9, *ArH*), 7.55-7.50 (3H, m, *ArH*), 7.12 (1H, dd, *J* 4.9, 3.6, *ArH*), 6.90 (2H, d, *J* 9.1, *ArH*), 3.82 (3 H, s, *OCH_3*); ^{13}C NMR (100 MHz, $CDCl_3$) 159.9 (C), 156.7 (C), 139.3 (C), 130.6 (C), 130.5 (CH), 128.3 (CH), 127.8 (CH), 122.2 (CH), 114.3 (CH) and 55.5 (CH_3); HRMS *m/z* (ES^+) Found M + Na 256.0406. $C_{12}H_{11}NO_2SNa$ requires 256.0403.

N-phenylthiophene-2-carboxamide (83)



As general procedure **E**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and aniline (46 µL, 0.5 mmol) used as coupling partners. Recovered 72 mg (71%) product as a white solid. m.p. 138-140 °C (Lit.[72] 136 – 138 °C). R_f 0.47 (Et_2O:Petrol, 4:1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3691, 3606, 3009, 2927, 2855, 1667, 1599, 1530, 1515, 1441, 1315 and 1244; ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 (1H, br. s., *NH*), 7.66 (1H, dd, *J* 3.8, 1.1, *ArH*), 7.65 - 7.63 (1H, m, *ArH*), 7.63 - 7.61 (1H, m, *ArH*), 7.55 (1H, dd, *J* 4.9, 1.1, *ArH*), 7.37 (1 H, ddt, *J* 8.4, 7.5, 1.9, *ArH*), 7.16 (1 H, tt, *J* 7.4, 1.1, *ArH*) and 7.12 (1H, dd, *J* 5.0, 3.8, *ArH*); ^{13}C NMR (100 MHz, $CDCl_3$) 160.0 (C), 139.3 (C), 137.6 (C), 130.8 (CH), 129.1 (CH), 128.5 (CH), 127.9 (CH), 124.6 (CH) and 120.3 (CH); HRMS *m/z* (ES^+) Found M + Na 226.0297. $C_{11}H_9NOSNa$ requires 226.0297.

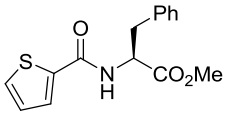
Ethyl 2-(thiophene-2-carboxamido)acetate (84)



To a stirring suspension of CuI (76 mg, 0.4mmol) in MeCN (1 mL) was added thiophene-2-carboxylic acid (282 mg, 2.2 mmol) and Et_3N (151 µL, 1.1 mmol). The solution was stirred at 55 °C for 10 mins before addition of diethyl phosphite (257 µL, 2.0 mmol). The reaction was stirred at 55 °C for 90 mins before addition of glycine ethyl ester hydrochloride (140 mg, 1 mmol) and Et_3N (69 µL, 1.0 mmol). The reaction was stirred at 55 °C for 90 mins before cooling to room temperature and diluting with CH_2Cl_2 (50 mL). The organic was washed with saturated aqueous Na_2CO_3 (30 mL), 2M

HCl (30 mL), brine (30 mL), then dried ($MgSO_4$). Removal of the volatiles *in vacuo* left the crude product which was purified by silica gel column chromatography. Recovered 129 mg (60%) product as a white solid. m.p. 88-90 °C (Lit.[73] 88 – 89 °C). R_f 0.46 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3435, 3009, 1741, 1654, 1534, 1505, 1442, 1420, 1397, 1379 and 1241; ^1H NMR (400 MHz, $CDCl_3$) 7.57 (1H, dd, *J* 3.8, 1.1, *ArH*), 7.49 (1H, dd, *J* 5.0, 1.1, *ArH*), 7.08 (1H, dd, *J* 5.0, 3.8, *ArH*), 6.70 (1H, br. s, *NH*), 4.26 (2H, q, *J* 7.1 Hz, O*CH*$_2$CH$_3$), 4.21 (2H, d, *J* 5.1, *CH*$_2$) and 1.31 (3H, t, *J* 7.1, OCH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 170.0 (C), 161.9 (C), 138.1 (C), 130.4 (CH), 128.6 (CH), 127.7 (CH), 61.7 (CH_2), 41.7 (CH_2) and 14.16 (CH_3); HRMS *m/z* (ES^+) Found M + Na 236.0362. $C_9H_{11}NO_3SNa$ requires 236.0352.

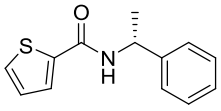
(S)-methyl 3-phenyl-2-(thiophene-2-carboxamido)propanoate (85)



To a stirring suspension of CuI (38 mg, 0.2mmol) in MeCN (1 mL) was added thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and Et_3N (76 µL, 0.55 mmol). The solution was stirred at 55 °C for 10 mins before addition of diethyl phosphite (129 µL, 2.0 mmol). The reaction was stirred at 55 °C for 90 mins before addition of L-phenylalanine methyl ester hydrochloride (108 mg, 0.5 mmol) and Et_3N (69 µL, 0.5 mmol). The reaction was stirred at 55 °C for 90 mins before cooling to room temperature and diluting with CH_2Cl_2 (50 mL). The organic was washed with saturated aqueous Na_2CO_3 (30 mL), 2M HCl (30 mL), brine (30 mL), then dried ($MgSO_4$). Removal of the volatiles *in vacuo* left the crude product which was purified by silica gel column chromatography. Recovered 96 mg (62%) product as a white solid. m.p. 86-89 °C. R_f 0.46 (Et_2O); $[\alpha]_{589}^{22}$ +74.5 (c 1.2, $CHCl_3$) υ_{max} /cm^{-1} ($CHCl_3$ soln) 3692, 3430, 3011, 2956, 1742, 1653, 1531, 1500, 1439, 1421, 1365, 1241 and 1016; ^1H NMR (400 MHz, $CDCl_3$) 7.50 (1H, dd, *J* 5.0, 1.2, *ArH*), 7.48 (1H, dd, *J* 3.8, 1.2, *ArH*), 7.35 - 7.25 (3 H, m, *ArH*), 7.17 (2 H, dd, *J* 7.9, 1.5, *ArH*), 7.08 (1 H, dd, *J* 5.0, 3.8, *ArH*), 6.55 (1 H, d, *J* 7.6, *NH*), 5.08 (1 H, dt, *J* 7.6, 5.7, *CH*), 3.78 (1 H, s, *OCH*$_3$) and 3.26 (2 H, dd, *J* 9.0, 5.7, *CH*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 172.0

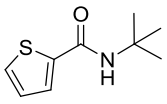
(C), 161.3 (C), 138.3 (C), 135.8 (C), 130.5 (CH), 129.4 (CH), 128.7 (CH), 128.5 (CH), 127.7 (CH), 127.3 (CH), 53.5 (CH), 52.5 (CH_3) and 31.0 (CH_2); HRMS *m/z* (ES^+) Found M + Na 312.0667. $C_{15}H_{15}NO_3SNa$ requires 312.0665.

(R)-N-(1-phenylethyl)thiophene-2-carboxamide (86)



As general procedure **E**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and (R)-α-Methylbenzylamine (64 µL, 0.5 mmol) used as coupling partners. Recovered 84 mg (73%) product as a white solid. m.p. 122-124 °C (Lit.[74] 127 – 128 °C). R_f 0.33 (Et_2O:Petrol, 3:2); $[\alpha]_{589}^{22}$ +11.8 (c 1.2, $CHCl_3$) υ_{max} /cm^{-1} ($CHCl_3$ soln) 3692, 3441, 3011, 1650, 1531, 1496, 1451, 1421, 1356 and 1256; ^{1}H NMR (400 MHz, $CDCl_3$) 7.52 (1H, dd, *J* 3.8, 1.1, *ArH*), 7.47 (1H, dd, *J* 5.0, 1.1, *ArH*), 7.42 - 7.34 (4 H, m, *ArH*), 7.32 - 7.26 (1 H, m, *ArH*), 7.06 (1H, dd, *J* 5.0, 3.8, *ArH*), 6.35 (1 H, d, *J* 6.9, *NH*), 5.32 (1 H, quin, *J* 6.9 *CH*) and 1.61 (3H, d, *J* 6.9, *CH_3*); ^{13}C NMR (100 MHz, $CDCl_3$) 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) and 21.7 (CH_3); HRMS *m/z* (ES^+) Found M + Na 254.0609. $C_{13}H_{13}NOSNa$ requires 254.0610.

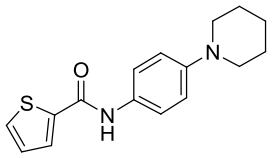
N-*tert*-butylthiophene-2-carboxamide (87)



As general procedure **E.** Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and *tert*-butylamine (53 µL, 0.5 mmol) used as coupling partners. Reaction required 24 h stirring after addition of amine. Recovered 41 mg (45%) product as a white solid. m.p. 144-145 °C (Lit.[75] 147 – 148 °C). R_f 0.41 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3443, 3008, 2969, 2929, 1653, 1532, 1504, 1456, 1394 and 1288; ^{1}H NMR (400 MHz, $CDCl_3$) 7.45-7.43 (3H, m, *ArH*), 7.06 (2H, dd, *J* 5.0, 3.6, *ArH*), 5.79 (1 H, br. s, *NH*) and 1.48 (9 H, s, *CH*); ^{13}C NMR (100 MHz, $CDCl_3$) 161.3 (C), 140.6 (C), 129.4 (CH), 127.5 (CH),

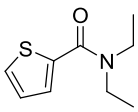
127.4 (CH), 52.0 (C) and 29.0 (CH_3); HRMS *m/z* (ES^+) Found M + Na 206.0613. $C_{13}H_{14}N_2OSNa$ requires 206.0610.

N-(4-(piperidin-1-yl)phenyl)thiophene-2-carboxamide (88)



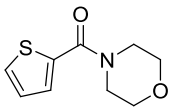
As general procedure **F**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and 4-(1-piperidinyl) aniline (88 mg, 0.5 mmol) used as coupling partners. Recovered 91 mg (64%) product as a white solid. m.p. 179-182 °C. R_f 0.51 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 2930, 2856, 1658, 1516, 1422, 1317 and 1242; ^1H NMR (400 MHz, $CDCl_3$) 7.64 (1H, br. s., *NH*), 7.61 (1H, d, *J* 3.5, *ArH*), 7.52 (1H, dd, *J* 5.0, 1.1, *ArH*), 7.48 (2H, d, *J* 9.0, *ArH*), 7.12 (1 H, dd, *J* 5.0, 3.5 *ArH*), 6.94 (2 H, d, *J* 9.0, *ArH*), 3.15 (4 H, t, *J* 5.5, *CH_2*), 1.73 (4 H, quin, *J* 5.5, *CH_2*) and 1.53 - 1.64 (2 H, m, *CH_2*); ^{13}C NMR (100 MHz, $CDCl_3$) 159.8 (C), 149.6 (C), 139.6 (C), 130.3 (CH), 129.4 (C), 128.2 (CH), 127.8 (CH), 121.7 (CH), 117.0 (CH), 51.0 (CH_2), 25.8 (CH_2) and 24.3 (CH_2); HRMS *m/z* (ES^+) Found M + Na 309.1032. $C_{16}H_{18}N_2OSNa$ requires 309.1032.

N,N-diethylthiophene-2-carboxamide (89)



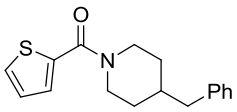
As general procedure **E**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and diethylamine (52 µL, 0.5 mmol) used as coupling partners. Recovered 71 mg (78%) product as a white solid. m.p. 54-57 °C (Lit.[76] 50 – 52 °C). R_f 0.25 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 1607, 1525, 1460, 14445, 1436 and 1282; ^1H NMR (400 MHz, $CDCl_3$) 7.43 (1H, dd, *J* 5.0, 1.1, *ArH*), 7.33 (1H, dd, *J* 3.8, 1.1, *ArH*), 7.05 (1H, dd, *J* 5.0, 3.6, *ArH*), 3.56 (4H, q, *J* 7.3, *CH_2*) and 1.27 (6 H, t, *J* 7.1, *CH_3*); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) 163.0 (C), 138.8 (C), 129.6 (CH), 128.5 (CH), 127.7 (CH), 41.2 (CH_2) and 13.0 (CH_3); HRMS *m/z* (ES^+) Found M + Na 206.0620. $C_9H_{13}NOSNa$ requires 206.0610.

Morpholino(thiophen-2-yl)methanone (90)



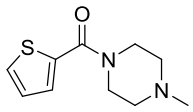
As general procedure **E**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and morpholine (43 µL, 0.5 mmol) used as coupling partners. Recovered 83 mg (84%) product as an oily solid. R_f 0.31 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2862, 1617, 1524, 1458, 1435, 1414, 1276, 1255, 1115, 1002 and 909; ^{1}H NMR (400 MHz, $CDCl_3$) 7.45 (1H, dd, *J* 5.0, 1.1, *ArH*), 7.28 (1H, dd, *J* 3.6, 1.1, *ArH*), 7.04 (1H, dd, *J* 5.0, 3.6, *ArH*) and 3.79 - 3.68 (8H, m, *CH_2*); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) 162.1 (C), 136.7(C), 129.4 (CH), 128.9 (CH), 126.9 (CH), 65.8 (CH_2) and 45.0 (CH_2); HRMS *m/z* (ES^+) Found M + Na 220.0398. $C_9H_{11}NO_2SNa$ requires 220.0403.

(4-benzylpiperidin-1-yl)(thiophen-2-yl)methanone (91)



As general procedure **E**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and 4-benzylpiperidine (88 µL, 0.5 mmol) used as coupling partners. Recovered 114 mg (80%) product as an oily solid. R_f 0.25 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3002, 1605, 1524, 1446, 1243, 1054, 1030 and 1011; ^{1}H NMR (270 MHz, $(CD_3)_2SO$, 90 °C) 7.66 (1H, dd, *J* 5.0, 1.2, *ArH*), 7.35 - 7.24 (3H, m, *ArH*), 7.23 - 7.14 (3H, m, *ArH*), 7.09 (1H, dd, *J* 5, 3.7, *ArH*), 4.22 (2H, d, *J* 13.4, *CH_2*), 3.03 - 2.89 (2H, m, *CH_2*), 2.58 (2H, d, *J* 7.2, *CH_2*), 1.87 (1H, ttt, 11.0, 7.2, 3.7, *CH*), 1.74 – 1.59 (2H, m, *CH_2*), 1.30 – 1.10 (2H, m, *CH_2*); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) 163.5 (C), 139.9 (C), 137.6 (C), 129.1 (CH), 128.4 (CH), 128.4 (CH), 128.2 (CH), 126.6 (CH), 126.1 (CH), 43.0 (CH_2), 38.4 (CH) and 32.3 (CH_2); HRMS *m/z* (ES^+) Found M + Na 308.1075. $C_{17}H_{19}NOSNa$ requires 308.1080.

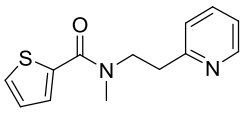
(4-methylpiperazin-1-yl)(thiophen-2-yl)methanone (92)



As general procedure **F**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and N-methylpiperazine (55 µL, 0.5 mmol) used as coupling partners.

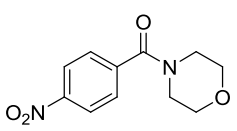
Recovered 85 mg (81%) product as a light yellow oil. R_f 0.12 (Et_2O:MeOH, 9:1); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3010, 2945, 2803, 1614, 1523, 1461, 1439, 1294, 1266, 1242, 1139, 1003 and 909; ^{1}H NMR (400 MHz, $CDCl_3$) 7.43 (1H, dd, *J* 5.0, 1.1, *ArH*), 7.28 (1H, dd, *J* 3.6, 1.1, *ArH*), 7.03 (1H, dd, *J* 5.0, 3.6, *ArH*), 3.76 (4H, t, *J* 5.0, *CH_2*), 2.44 (4H, t, *J* 5.0, *CH_2*), 2.32 (3 H, s, *CH_3*); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) 162.0 (C), 136.8 (C), 128.4 (CH), 128.2 (CH), 126.4 (CH), 54.1 (CH_2), 44.9 (CH_3) and 44.3 (CH_2); HRMS *m/z* (ES^+) Found M + Na 233.0722. $C_{13}H_{14}N_2OSNa$ requires 233.0719.

N-methyl-N-(2-(pyridin-2-yl)ethyl)thiophene-2-carboxamide (93)



As general procedure **F**. Thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and 2-(2-methylethylamino) pyridine (69 µL, 0.5 mmol) used as coupling partners. Recovered 81 mg (66%) product as a light yellow oil. R_f 0.18 (Et_2O:MeOH, 95:5); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 1613, 1525, 1477, 1436, 1400, 1242 and 1060; ^{1}H NMR (400 MHz, $CDCl_3$) 8.55 (1H, d, *J* 4.0, *ArH*), 7.62 (1H, td, *J* 7.7, 1.9, *ArH*), 7.44 (1H, dd, *J* 5.0, 0.9, *ArH*), 7.32 (1H, dd, *J* 3.8, 1.1, *ArH*), 7.21 (1H, br. s, *NH*), 7.16 (1 H, ddd, *J* 7.5, 5.0, 0.9, *ArH*), 7.04 (1 H, dd, *J* 5.0, 4.0, *ArH*), 3.94 (2H, t, *J* 7.4, *ArH*) and 3.15 (5 H, m, *CH_2* and *CH_3*); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) 162.7 (C), 158.2 (C), 148.5 (CH), 137.7 (C), 135.9 (CH), 128.5 (CH), 128.2 (CH), 126.4 (CH), 122.6 (CH), 121.0 (CH), 54.2 (CH_2), 48.7 (CH_3) and 35.3 (CH_2); HRMS *m/z* (ES^+) Found M + Na 247.0905. $C_{13}H_{14}N_2OSNa$ requires 247.0900.

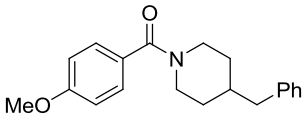
Morpholino(4-nitrophenyl)methanone (94)



As general procedure **E**. 4-Nitrobenzoic acid (184 mg, 1.1 mmol) and morpholine (43 µL, 0.5 mmol) used as coupling partners. Recovered 56 mg (47%) product as a white solid. m.p. 106-108 °C (Lit.[77] 104 – 106 °C).. R_f 0.16 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3011, 2927, 2861, 1635, 1602, 1527, 1459, 1435, 1353, 1280, 1261,

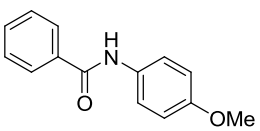
1023, 1013, 863 and 839; ^{1}H NMR (270 MHz, $(CD_3)_2SO$, 90 °C) 8.26 (2H, d, *J* 8.8, *ArH*), 7.68 (2H, d, *J* 8.8, *ArH*), 3.66-3.60 (4H, m, *CH_2*), 3.48 (4H, br. s., *CH_2*); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) 167.4 (C), 148.0 (C), 142.1 (C), 128.6 (CH), 124.0 (CH), 66.2 (CH_2), 47.7 (CH_2.) and 42.2 (CH_2); HRMS *m/z* (ES^+) Found M + Na 259.0686. $C_{11}H_{12}N_2O_4Na$ requires 259.0689.

(4-benzylpiperidin-1-yl)(4-methoxyphenyl)methanone (95)



As general procedure **E**. 4-Methoxybenzoic acid (167 mg, 1.1 mmol) and 4-benzylpiperidine (88 µL, 0.5 mmol) used as coupling partners. Recovered 132 mg (85%) product as a white solid. m.p. 80-83 °C. R_f 0.27 (Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3007, 2933, 1611, 1438, 1250, 1174, 1032 and 840; ^{1}H NMR (270 MHz, $(CD_3)_2SO$, 90 °C) 7.36- 7.23 (4H, m, *ArH*), 7.22 – 7.13 (3H, m, *ArH*), 6.96 (1H, d, *J* 8.8, *ArH*), 4.03 (2H, d, *J* 13.1, *CH_2*), 3.8 (3H, s, *OCH_3*), 2.87 (2H, ddd, *J* 13, 12.2, 2.7, *CH_2*), 2.57 (2H, d, *J* 7.2, *CH_2*), 1.83 (1H, ttt, 11.0, 7.2, 3.7), 1.62 (2H, m, *CH_2*), 1.17 (2H, app. qd, *J* 12.1, 4.3); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) 169.0 (C), 160.2 (C), 140.3 (C), 129.2 (CH), 128.9 (CH), 128.6 (C), 128.4 (CH), 126.1 (CH), 113.8 (CH), 55.4 (CH_3), 44.2 (CH_2), 42.3 (CH_2), 37.8 (CH) and 32.16 (CH_2); HRMS *m/z* (ES^+) Found M + Na 332.1615. $C_{20}H_{23}NO_2Na$ requires 332.1621.

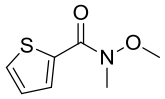
N-(4-methoxyphenyl)benzamide (96)



As general procedure **E**. Benzoic acid (134 mg, 1.1 mmol) and 4-methoxyaniline (62 mg, 0.5 mmol) used as coupling partners. Recovered 66 mg (58%) product as a white solid. m.p. 155-158 °C (Lit.[78] 157 – 158 °C). R_f 0.27 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3439, 3008, 1670, 1514, 1412, 1248 and 1035; ^{1}H NMR (400 MHz, $CDCl_3$) 7.88 (1H, d, *J* 8.7, *ArH*), 7.75 (1H, br. s, *NH*), 7.60 - 7.53 (3H, m, *ArH*), 7.53 - 7.47 (2H, m, *ArH*), 6.93 (2 H, d, *J* 8.7, *ArH*) and 3.84 (3 H, s, O*CH_3*);

^{13}C NMR (100MHz, $CDCl_3$) 165.6 (C), 156.6 (C), 135.0 (C), 131.8 (CH), 131.0 (C), 128.8 (CH), 127.0 (CH), 122.0 (CH), 114.2 (CH) and 55.5 (CH_3); HRMS *m/z* (ES^+) Found M + Na 250.0834. $C_{14}H_{13}NO_2Na$ requires 250.0838.

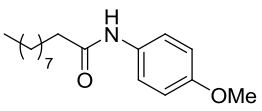
N-methoxy-N-methylthiophene-2-carboxamide (97)



To a stirring suspension of CuI (38 mg, 0.2 mmol) in MeCN (1 mL) was added thiophene-2-carboxylic acid (141 mg, 1.1 mmol) and Et_3N (76 µL, 0.55 mmol). The solution was stirred at 55 °C for 10 minutes before addition of diethyl phosphite (129 µL, 1.0 mmol). The reaction was stirred at 55 °C for 90 minutes before addition of Et_3N (76 µL, 0.5 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (97 mg, 0.5 mmol). The reaction was stirred at 55 °C for a further 90 minutes before cooling to room temperature and diluting with CH_2Cl_2 (50 mL). The organic was washed with aqueous $NaHCO_3$ (2 x 30 mL), 2M HCl (30 mL), then dried (Na_2SO_4). Removal of the volatiles *in vacuo* left the crude amide, which was purified by silica gel column chromatography.

Recovered 50 mg (58%) as a light yellow oil. R_f 0.40 (3:2 Et_2O:Petrol); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3008, 2939, 1616, 1519, 1459, 1423, 1386, 1239 and 982; ^{1}H NMR (400 MHz, $CDCl_3$) 7.97 (1H, dd, *J* 3.8 and 1.3, *ArH*), 7.55 (1H, dd, *J* 5.0 and 1.3, *ArH*), 7.11 (1 H, dd, *J* 5.0 and 3.8, *ArH*), 3.78 (3 H, s, N*CH*$_3$) and 3.37 (3 H, s, O*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 162.2 (C), 134.3 (CH), 133.2 (C), 132.2 (CH), 126.7 (CH), 61.5 (CH_3) and 33.0 (CH_3); HRMS *m/z* (ES^+) Found M + Na 194.0255. $C_7H_9NO_2NaS$ requires 194.0246.

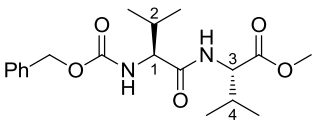
N-(4-methoxyphenyl)decanamide (98)



As general procedure **E**. Decanoic acid (189 mg, 1.1 mmol) and 4-methoxyaniline (62 mg, 0.5 mmol) used as coupling partners. Recovered 80 mg (58%) product as a white solid. m.p. 98-99 °C (Lit.[69] 102 – 103 °C). R_f 0.39 (Et_2O:Petrol, 3:2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3437, 3011, 2929, 2856, 1679, 1514 and

1246; ^{1}H NMR (400 MHz, $CDCl_3$) 7.42 (2H, d, *J* 8.9, *ArH*), 7.13 (1H, br. s, *NH*), 6.87 (2H, d, *J* 9.0, *ArH*), 3.80 (3H, s, *OCH*$_3$), 2.34 (2H, t, *J* 7.5, *CH*$_2$), 1.73 (2H, quin, *J* 7.5, *CH*$_2$), 1.44 - 1.19 (12H, m, *CH*$_2$) and 0.90 (3 H, t, *J* 6.8, *CH*$_3$); ^{13}C NMR (100MHz, $CDCl_3$) 171.3 (C), 156.3 (C), 131.1 (C), 121.7 (CH), 114.1 (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), 25.8 (CH_2), 22.7 (CH_2) and 14.1 (CH_3); HRMS *m/z* (ES^+) Found M + Na 300.1930. $C_{17}H_{27}NO_2Na$ requires 300.1934.

(S) - methyl 2 - ((S) - 2 - (benzyloxycarbonylamino) 3 - methylbutanamido) - 3 – methylbutanoate (Cbz-Val-Val-OMe) (99)

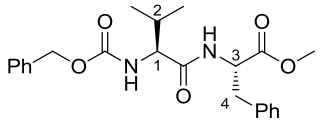


To a stirring suspension of CuI (0.2 mmol) in MeCN (1 mL) was added Cbz-L-Valine (276 mg, 1.1 mmol) and Et_3N (76 µL, 0.55 mmol). The solution was stirred at 55 °C for 10 minutes before addition of diethyl phosphite (129 µL, 1.0 mmol). The reaction was stirred at 55 °C for 90 minutes before addition of Et_3N (69 µL, 0.5 mmol) and L-Valine methyl ester hydrochloride (84 mg, 0.5 mmol). The reaction was stirred at 55 °C for a further 90 minutes before cooling to room temperature and diluting with CH_2Cl_2 (50 mL). The organic was washed with aqueous $NaHCO_3$ (pH 9, 30 mL), 2M HCl (30 mL), brine (30 mL), then dried (Na_2SO_4). Removal of the volatiles *in vacuo* left the crude amide, which was purified by silica gel column chromatography.

Recovered 69 mg (38%) as a white solid. m.p. 102 – 104 °C (Lit.[79] 106 – 107 °C). R_f 0.50 (3:2 Et_2O:Petrol); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3430, 3011, 2969, 2936, 2876, 1735, 1682, 1504, 1467, 1439, 1392, 1373, 1337, 1314, 1147, 1095 and 1027; $[\alpha]_{589}^{22}$ -33.6 (c 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) 7.40 - 7.29 (5H, m, *ArH*), 6.50 (1H, d, *J* 8.5, C(O)*NH*), 5.45 (1H, d, *J* 8.7, Cbz*NH*), 5.13 (2H, s, Ph*CH*$_2$), 4.56 (1H, dd, *J* 8.5 and 5.0, *C*^{3}*H*), 4.10 (1H, app. t, *J* 7.6, *C*^{1}*H*), 3.75 (3H, s, *OMe*), 2.24 - 2.07 (2H, m, *C*^{2}*H* and *C*^{4}*H*) and 1.03 - 0.83 (12 H, m, CH(*CH*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 172.3 (C), 171.4 (C), 156.5 (C), 136.4 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 67.2 (CH_2), 60.5 (CH), 57.3 (CH), 52.3 (CH), 31.3 (CH), 19.3

(CH_3), 19.0 (CH_3), 18.0 (CH_3) and 17.9 (CH_3); HRMS *m/z* (ES^+) Found M + Na 387.1887. $C_{19}H_{28}N_2O_5Na$ requires 387.1890.

(S) - methyl 2 - ((S) – 2 - (benzyloxycarbonylamino) – 3 - methylbutanamido) – 3 – phenylpropanoate (Cbz-Val-Phe-OMe) (100)



To a stirring suspension of CuI (0.2 mmol) in MeCN (1 mL) was added Cbz-L-Valine (276 mg, 1.1 mmol) and Et_3N (76 µL, 0.55 mmol). The solution was stirred at 55 °C for 10 minutes before addition of diethyl phosphite (129 µL, 1.0 mmol). The reaction was stirred at 55 °C for 90 minutes before addition of Et_3N (69 µL, 0.5 mmol) and L-Phenylalanine methyl ester hydrochloride (107 mg, 0.5 mmol). The reaction was stirred at 55 °C for a further 90 minutes before cooling to room temperature and diluting with CH_2Cl_2 (50 mL). The organic was washed with aqueous $NaHCO_3$ (pH 9, 30 mL), 2M HCl (30 mL), brine (30 mL), then dried (Na_2SO_4). Removal of the volatiles *in vacuo* left the crude amide, which was purified by silica gel column chromatography.

Recovered 77 mg (37%) as a white solid. m.p. 141 – 144 °C (Lit.[80] 142 – 143 °C). R_f 0.63 (3:2 Et_2O:Petrol); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3428, 3011, 2967, 1739, 1680, 1501, 1455, 1366, 1242, 1181, 1107 and 1028; $[\alpha]_{589}^{22}$ +99.7 (c 1.00, MeOH); ^1H NMR (400 MHz, $CDCl_3$) 7.32 - 7.42 (5H, m, *ArH*), 7.21 - 7.31 (3H, m, *ArH*), 7.11 (2H, d, *J* 6.8, *ArH*), 6.24 (1H, d, *J* 7.8, C(O)*NH*), 5.30 (1H, d, *J* 8.3, Cbz*NH*), 5.13 (2H, s, PhCH_2), 4.89 (1H, dt, *J* 7.8 and 6.0, C^3H), 3.99 (1H, dd, *J* 8.3 and 6.5, C^1H), 3.74 (3 H, s, *OMe*), 3.05 - 3.20 (2 H, m, C^4H_2), 2.10 (1 H, d.sxt., *J* 6.7 and 6.5, C^2H), 0.95 (3H, d, *J* 6.7, CHCH_3) and 0.89 (3H, d, *J* 6.7, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 171.8 (C), 170.1 (C), 156.4 (C), 136.4 (C), 135.7 (C), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.4 (CH), 67.2 (CH_2), 60.4 (CH), 53.2 (CH), 52.5 (CH_3), 38.1 (CH_2), 31.2 (CH), 19.2 (CH_3) and 17.8 (CH_3); HRMS *m/z* (ES^+) Found M + Na 435.1882. $C_{23}H_{28}N_2O_5Na$ requires 435.1890.

5.7 Phosphoramidate synthesis

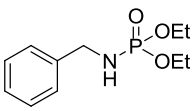
General Procedure G

To a stirring suspension of CuI (38 mg, 0.2 mmol) in MeCN (2 mL) was added phosphite (1 mmol) and amine (2 mmol). The mixture was stirred at 55 °C for 4-18 h before cooling to room temperature and diluting with $CHCl_3$ (50 mL). The organic was washed with 2M HCl (30 mL), saturated $NaHCO_3$ (30 mL), then dried (Na_2SO_4). Removal of the volatiles *in vacuo* left the crude product which was purified by silica gel column chromatography (gradient: Et_2O to 5-10% MeOH in CH_2Cl_2).

General Procedure H

As general procedure **G** with the addition of acetic acid (57 μL, 1 mmol) prior to addition of amine and phosphite.

Diethyl benzylphosphoramidate (101)

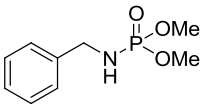


Using general procedure **G** recover 122 mg (50%) product.

Using general procedure **H** recover 174 mg (72%) product.

Benzylamine (218 μL, 2 mmol) and diethyl phosphite (129 μL, 1 mmol) used as coupling partners. Product is a yellow oil. R_f – 0.46 (10% MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3424, 2993, 1603, 1496, 1455, 1414, 1247, 1057, 1029 and 971; ^{1}H NMR (400 MHz, $CDCl_3$) 7.38 - 7.25 (5 H, m, *ArH*), 4.16 - 3.99 (6 H, m, *CH_2* and O*CH_2*CH_3), 3.03 - 3.16 (1 H, m, *NH*), 1.32 (6 H, td, *J* 7.1 and 0.8, OCH_2*CH_3*); ^{13}C NMR (100 MHz, $CDCl_3$) 139.6 (C), 128.5 (CH), 127.3 (CH), 127.2 (CH), 62.3 (d, *J* 5, CH_2), 45.3 (CH_2) and 16.1 (d, *J* 7, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 8.49; HRMS *m/z* (ES^+) Found M + Na 266.0912. $C_{11}H_{18}NO_3PNa$ requires 266.0917.

Dimethyl benzylphosphoramidate (112)

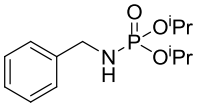


Using general procedure **G** recover 123 mg (57%) product.

Using general procedure **H** recover 149 mg (69%) product.

Benzylamine (218 μL, 2 mmol) and dimethyl phosphite (92 μL, 1 mmol) used as coupling partners. Product is a yellow oil. R_f – 0.45 (10% MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3424, 3001, 2954, 1455, 1414, 1252, 1063, 1038 and 853; ^{1}H NMR (400 MHz, $CDCl_3$) 7.36 - 7.25 (5 H, m, *ArH*), 4.10 (2 H, dd, *J* 10.0 and 7.0, CH_2), 3.70 (6 H, d, *J* 11.2, *OMe*) and 3.26 - 3.12 (1 H, m, *NH*); ^{13}C NMR (100 MHz, $CDCl_3$) 139.5 (C), 128.6 (CH), 127.4 (CH), 127.3 (CH), 53.0 (d, *J* 5, CH_3) and 45.3 (CH_2); ^{31}P NMR (161 MHz, $CDCl_3$) 11.13; HRMS *m/z* (ES^+) Found M + Na 238.0606. $C_9H_{14}NO_3PNa$ requires 238.604.

Diisopropyl benzylphosphoramidate (113)

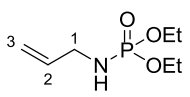


Using general procedure **G** recover 151 mg (56%) product.

Using general procedure **H** recover 196 mg (72%) product.

Benzylamine (218 μL, 2 mmol) and diisopropyl phosphite (168 μL, 1 mmol) used as coupling partners. Product is a yellow solid. m.p. 48 – 50 °C (Lit.[81] 48.5 – 50 °C). R_f – 0.44 (10% MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3009, 2985, 1497, 1454, 1413, 1387, 1376, 1244, 1106, 1019 and 993; ^{1}H NMR (400 MHz, $CDCl_3$) 7.38 - 7.23 (5 H, m, *ArH*), 4.65 (2 H, dspt, *J* 7.5 and 6.2, O*CH*(CH_3)$_2$), 4.11 (2 H, dd, *J* 9.0 and 7.0, CH_2), 2.88 - 2.73 (1 H, m, *NH*), 1.36 (6 H, d, *J* 6.2, OCH(*CH*$_3$)$_2$) and 1.31 (6 H, d, *J* 6.2, OCH(*CH*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 139.8 (C), 128.5 (CH), 127.3 (2CH [overlapping]), 70.9 (d *J* 6, CH), 45.5 (CH_2) and 23.8 (t, *J* 4, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 6.52; HRMS *m/z* (ES^+) Found M + Na 294.1222. $C_{13}H_{22}NO_3PNa$ requires 294.1230.

Diethyl allylphosphoramidate (114)

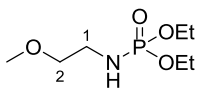


Using general procedure **G** recover 111 mg (58%) product.

Using general procedure **H** recover 111 mg (58%) product.

Allylamine (149 μL, 2 mmol) and diethyl phosphite (129 μL, 1 mmol) used as coupling partners. Product is as a yellow oil. R_f – 0.61 (10% MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3425, 3010, 1411, 1250, 1096, 1030 and 971; ^{1}H NMR (400 MHz, $CDCl_3$) 5.90 - 5.79 (1 H, m,C^2H), 5.20 (1 H, dq, *J* 17.1 and 1.6, C^3H_2), 5.07 (1 H, dq, *J* 10.3 and 1.4, C^3H_2), 4.09 - 3.98 (4 H, m, O$CH_2$$CH_3$), 3.50 (2 H, dddt, *J* 10.3, 6.9, 5.4 and 1.6, C^1H_2), 2.96 - 2.84 (1 H, m, *NH*)and 1.29 (6 H, td, *J* 7.1and 0.8. OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 136.1 (CH), 115.3 (CH_2), 62.2 (d, *J* 5, CH_2), 43.7 (CH_2) and 16.1 (d, *J* 7, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 8.81; HRMS *m/z* (ES^+) Found M + Na 216.0767. $C_7H_{16}NO_3PNa$ requires 216.0760.

Diethyl 2-methoxyethylphosphoramidate (115)

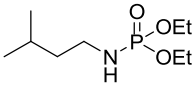


Using general procedure **G** recover 113 mg (53%) product.

Using general procedure **H** recover 114 mg (54%) product.

2-Methoxyethylamine (174 μL, 2 mmol) and diethyl phosphite (129 μL, 1 mmol) used as coupling partners. Product is as a yellow oil. R_f – 0.72 (10% MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3421, 2993, 2932, 1602, 1416, 1393, 1245, 1058, 1030 and 970; ^{1}H NMR (400 MHz, $CDCl_3$) 4.10 - 3.99 (4 H, m, O$CH_2$$CH_3$), 3.41 (2 H, td, *J* 5.0 and 0.6, C^2H_2), 3.34 (3 H, s, *OMe*), 3.09 - 2.99 (3 H, m, C^1H_2 and *NH*) and 1.30 (6 H, td, *J* 7.1 and 0.8, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 72.6 (d, *J* 6, CH_2), 62.2 (d, *J* 5, CH_2), 58.7 (CH_3), 41.0 (CH_2) and 16.1 (d, *J* 7, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 9.13; HRMS *m/z* (ES^+) Found M + Na 234.0873. $C_7H_{18}NO_4PNa$ requires 234.0866.

Diethyl isopentylphosphoramidate (116)

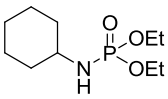


Using general procedure **G** recover 120 mg (54%) product.

Using general procedure **H** recover 123 mg (55%) product.

Isoamylamine (232 μL, 2 mmol) and diethyl phosphite (129 μL, 1mmol) used as coupling partners. Recovered 120 mg (54%) as a yellow oil. R_f – 0.40 (5% MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3425, 2992, 2961, 2873, 1469, 1413, 1369, 1240, 1096, 1058, 1031 and 969; ^{1}H NMR (400 MHz, $CDCl_3$) 4.11 - 3.99 (4 H, m, O*CH*$_2$CH$_3$), 2.90 (2 H, dq, *J* 9.5 and 7.0, *CH*$_2$), 2.59 (1 H, m, *NH*), 1.63 (1 H, spt, *J* 7.0, *CH*), 1.37 (2 H, q, *J* 7.0, *CH*$_2$), 1.31 (6 H, t, *J* 7.0, *CH*$_3$) and 0.89 (6 H, d, *J* 6.7, OCH$_2$*CH*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$) 62.1(d, *J* 5, CH_2), 40.7 (d, *J* 6, CH_2), 39.5 (CH_2), 25.4 (CH), 22.3 (CH_3) and 16.2 (d, *J* 7, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 9.15; HRMS *m/z* (ES^+) Found M + Na 246.1231. $C_9H_{22}NO_3PNa$ requires 246.1230.

Diethyl cyclohexylphosphoramidate (117)

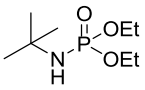


Using general procedure **G** recover 104 mg (42%) product.

Using general procedure **H** recover 106mg (45%) product.

Cyclohexylamine (229 μL, 2 mmol) and diethyl phosphite (129 μL, 1 mmol) used as coupling partners. Recovered 104 mg (42%) as a tan oily solid. R_f – 0.17 (5% MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3413, 2991, 2936, 2857, 1602, 1561, 1451, 1420, 1393, 1300, 1245, 1105, 1030 and 967; ^{1}H NMR (400 MHz, $CDCl_3$) 4.10 - 3.97 (4 H, m, O*CH*$_2$CH$_3$), 3.02 - 2.88 (1 H, m, *CH*), 2.55 (1 H, t, *J* 9.7, *NH*), 1.96 - 1.85 (3 H, m, *CyCH*$_2$), 1.68 (3 H, dt, *J* 13.0 and 3.7), 1.55 (1 H, dt, *J* 13.0 and 3.7, *CyCH*$_2$), 1.34 -1.22 (8 H, m, *CyCH*$_2$ and OCH$_2$*CH*$_3$) and 1.07 - 1.19 (3 H, m, *CyCH*$_2$); ^{13}C NMR (400 MHz, $CDCl_3$) 62.1 (d, *J* 5, CH_2), 50.5 (CH), 35.7 (CH_2), 25.3 (CH_2), 24.9 (CH_2) and 16.2 (d, *J* 7, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 8.20; HRMS *m/z* (ES^+) Found M + Na 258.1228. $C_{10}H_{22}NO_3PNa$ requires 258.1230.

Diethyl tert-butylphosphoramidate (118)

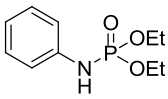


Using general procedure **G** recover 76 mg (36%) product.

Using general procedure **H** recover 72 mg (34%) product.

Tert-butylamine (210 μL, 2 mmol) and diethyl phosphite (129 μL, 1 mmol) used as coupling partners. Recovered 76 mg (36%) product as a yellow oil. R_f – 0.29 (5% MeOH in CH_2Cl_2); /cm^{-1} ($CHCl_3$ soln) 3404, 3010, 2986, 2908, 1408, 1390, 1244, 1031, 987 and 909; ^{1}H NMR (400 MHz, $CDCl_3$) 4.12 - 3.98 (4 H, m, O*CH*$_2$CH$_3$), 2.58 (1 H, d, *J* 6.8, *NH*), 1.30 (6 H, td, *J* 7.1 and 0.7, OCH$_2$*CH*$_3$) and 1.25 (9 H, d, *J* 0.8, *CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 62.0 (d, *J* 5, CH_2), 50.6 (C), 31.3 (d, *J* 5, CH_3) and 16.2 (d, *J* 8, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 6.95; HRMS *m/z* (ES^+) Found M + Na 232.1076. $C_8H_{20}NO_3PNa$ requires 232.1073.

Diethyl phenylphosphoramidate (119)

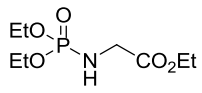


Using general procedure **G** recover 0 mg (0%) product.

Using general procedure **H** recover 104 mg (45%) product.

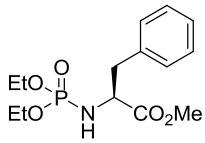
Aniline (182 μL, 2 mmol) and diethyl phosphite (129 μL, 1 mmol) used as coupling partners. Recovered 98 mg (42%) as a tan oily solid. R_f – 0.32 (5% MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3692, 3607, 3412, 2998, 2361, 1602, 1500, 1479, 1398, 1298, 1252, 1026 and 976; ^{1}H NMR (400 MHz, $CDCl_3$) 7.26 (2 H, t, 8.6, *ArH*), 7.04 – 7.00 (2 H, m, *ArH*), 6.97 (1 H, tt, *J* 7.3 and 1.1, *ArH*), 6.17 (1 H, d, *J* 9.0, *NH*), 4.04 - 4.25 (4 H, m, O*CH*$_2$CH$_3$), 1.33 (6 H, td, *J* 7.2 and 0.8, OCH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 139.7 (C), 129.2 (CH), 121.5 (CH), 117.3 (CH), 62.7 (d, *J* 5, CH_2) and 16.1 (d, *J* 7, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 2.28; HRMS *m/z* (ES^+) Found M + Na 252.0759. $C_{10}H_{16}NO_3PNa$ requires 252.0760.

Ethyl 2-(diethoxyphosphorylamino)acetate (120)



To a stirring suspension of CuI (38 mg, 0.2 mmol) in MeCN (2 mL) was added diethyl phosphite (129 μL, 1 mmol), glycine ethyl ester hydrochloride (280 mg, 2 mmol) and Et_3N (277 μL, 2 mmol). The mixture was stirred at 55 °C for 18 h before cooling to room temperature and diluting with $CHCl_3$ (50 mL). The organic was washed with 2M HCl (30 mL), saturated $NaHCO_3$ (30 mL), then dried (Na_2SO_4). Removal of the volatiles *in vacuo* left the crude product which was purified by column chromatography (gradient: Et_2O to 5% MeOH in CH_2Cl_2) yielding the product (189 mg, 79%) as a yellow oil. R_f – 0.46 (5 % MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3415, 2993, 2940, 2909, 1742, 1444, 1419, 1394, 1372, 1320, 1252, 1148, 1058, 1029 and 972; ^1H NMR (400 MHz, $CDCl_3$) 4.18 (2 H, q, *J* 7.2, $CO_2CH_2CH_3$), 4.11 - 4.01 (4 H, m, $P(O)OCH_2CH_3$), 3.67 (2 H, dd, *J* 9.9and 6.3, CH_2), 3.32 - 3.20 (1 H, m, *NH*), 1.29 (6 H, td, *J* 7.0 and 0.8, $P(O)OCH_2CH_3$) and 1.25 (3 H, t, *J* 7.2, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 170.9 (d, *J* 8, C), 62.5 (d, *J*, CH_2), 61.4 (CH_2), 43.0 (CH_2), 16.1 (d, *J* 7, CH_3) and 14.1 (CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 7.68; HRMS *m/z* (ES^+) Found M + Na 262.0811. $C_8H_{18}NO_5PNa$ requires 262.0815.

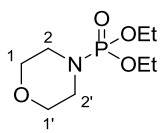
(S)-methyl 2-(diethoxyphosphorylamino)-3-phenylpropanoate (121)



To a stirring suspension of CuI (38 mg, 0.2 mmol) in MeCN (2 mL) was added diethyl phosphite (129 μL, 1 mmol), L-phenylalanine methyl ester hydrochloride (432 mg, 2 mmol) and Et_3N (277 μL, 2 mmol). The mixture was stirred at 55 °C for 18 h before cooling to room temperature and diluting with $CHCl_3$ (50 mL). The organic was washed with 2M HCl (30 mL), saturated $NaHCO_3$ (30 mL), then dried (Na_2SO_4). Removal of the volatiles *in vacuo* left the crude product which was purified by column chromatography (gradient: Et_2O to 5% MeOH in CH_2Cl_2) yielding the product (310 mg,

98%) as a tan oil. R_f – 0.46 (5 % MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3401, 2996, 1743, 1603, 1497, 1443, 1426, 1245, 1128, 1058, 1030 and 973; $[\alpha]_{589}^{22}$ +15.4 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.36 - 7.09 (5 H, m, *ArH*), 4.18 - 4.06 (1 H, m, *CH*), 4.04 - 3.86 (3 H, m, O*CH*$_2$$CH_3$), 3.82 - 3.69 (1 H, m, O*CH*$_2$$CH_3$), 3.72 (3 H, s, *OMe*), 3.19 (1 H, t, *J* 10.3, *NH*), 3.07 (1 H, ddd, *J* 13.6, 5.5 and 1.3, Ph*CH*$_2$), 2.97 (1 H, dd, *J* 13.6 and 7.0, Ph*CH*$_2$) and 1.24 (6 H, dtd, *J* 12.9, 7.0 and 0.8, OCH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 173.1 (C), 136.0 (C), 129.4 (CH), 128.4 (CH), 127.0 (CH), 62.3 (d, *J* 5, CH_2), 55.6 (CH), 52.1 (CH_3), 40.5 (d, *J* 6, CH_2) and 16.0 (d, *J* 8, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 6.79; HRMS *m/z* (ES^+) Found M + Na 338.1116. $C_{14}H_{22}NO_5PNa$ requires 338.1128.

Diethyl morpholinophosphonate (122)

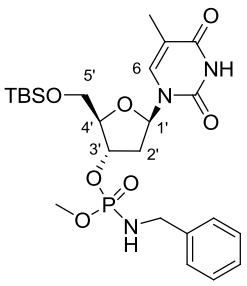


Using general procedure **G** recover 71 mg (32%) product with tetraethyl hypodiphosphate (8% by ^{1}H NMR) as an inseparable impurity.

Using general procedure **H** recover 101 mg (45 %) product. with tetraethyl hypodiphosphate (7% by ^{1}H NMR) as an inseparable impurity.

Morpholine (173 μL, 2 mmol) and diethyl phosphite (129 μL, 1mmol) used as coupling partners. Product is a yellow oil. R_f – 0.61 (10% MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3691, 3606, 2995, 2915, 2860, 1637, 1602, 1444, 1393, 1299, 1250, 1164, 1139, 1062, 1029 and 975; ^{1}H NMR (400 MHz, $CDCl_3$) 4.09 - 3.95 (4 H, m, O*CH*$_2$$CH_3$), 3.61 (4 H, td, *J* 4.7 and 1.1, C^1H_2 and $C^{1'}H_2$), 3.14 - 3.04 (4 H, m, C^2H_2 and $C^{2'}H_2$)and 1.28 (6 H, td, *J* 7.1 and 0.8, OCH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 67.0 (d, *J* 6, CH_2), 62.4 (d, *J* 5, CH_2), 44.6 (CH_2) and 16.2 (d, *J* 7, CH_3); ^{31}P NMR (161 MHz, $CDCl_3$) 7.77; HRMS *m/z* (ES^+) Found M + Na 246.0869. $C_8H_{18}NO_4PNa$ requires 246.0866.

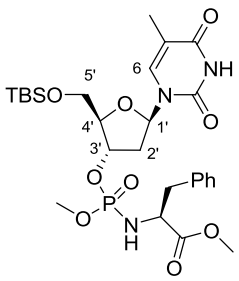
Phosphoramidate 123



To a stirring suspension of CuI (10 mg, 0.05 mmol) in MeCN (0.5 mL) was added 5' – OTBS – 3' – methyl phosphonate thymidine (109 mg, 0.25 mmol) and benzylamine (56 μL, 0.5 mmol). The mixture was stirred at 55 °C for 18 h before cooling to room temperature and diluting with a mixtre of IPA : $CHCl_3$ (1:5, 30 mL). The organic was washed with 2M HCl (20 mL), saturated $NaHCO_3$ (20 mL), then dried (Na_2SO_4). Removal of the volatiles *in vacuo* left the crude product which was purified by column chromatography (gradient: Et_2O to 3% MeOH in Et_2O) yielding the product (76 mg, 56%) as a white solid (1:1 mixture of diastereoisomers). m.p. 47 - 50 °C; R_f – 0.15 (3% MeOH in Et_2O); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3399, 3010, 2956, 2932, 2859, 1689, 1520, 1471, 1322, 1258, 1129, 1051, 1011, 976 and 834; [Diastereoisomer denoted with *] ^{1}H NMR (400 MHz, $CDCl_3$) 9.57 (0.5 H, br. s., *NH*), 9.55 (0.5 H, br. s., *NH**), 7.48 (0.5 H, d, *J* 1.1, C^6H), 7.47 (0.5 H, d, *J* 1.1, C^6H*), 7.37 – 7.24 (5 H, m, *ArH* and *ArH**), 6.35 (1 H, app. ddd, *J* 9.0, 5.2 and 3.7, $C^{1'}H$ and $C^{1'}H$*), 4.94 (0.5 H, t, *J* 6.3, $C^{4'}H$), 4.90 (0.5 H, t, *J* 6.5, $C^{4'}H$*), 4.28 (0.5 H, d, *J* 1.4, $C^{3'}H$), 4.17 (0.5 H, d, *J* 1.4, $C^{3'}H$*), 4.11 (2 H, app. dd, *J* 10.8 and 7.2, PhCH_2NH and PhCH_2NH*), 3.88 (2 H, app. dd, *J* 3.5 and 2.2, $C^{5'}H$ and $C^{5'}H$*), 3.73 (3 H, s, *OMe*), 3.70 (3 H, s, *OMe**), 3.70 - 3.62 (0.5 H, m, PhCH_2NH), 3.59 – 3.50 (0.5 H, m, PhCH_2NH*), 2.54 (0.5 H, dd, *J* 13.4 and 5.1, $C^{2'}H_2$), 2.35 (0.5 H, dd, *J* 13.2 and 5.5, $C^{2'}H_2$*), 2.15 – 2.03 (0.5 H, m, $C^{2'}H_2$), 2.03 – 1.93 (0.5 H, m, $C^{2'}H_2$*), 1.91 (3 H, s, CH_3 and CH_3*), 0.92 (9 H, s, $(CH_3)_3$$CSiMe_2$ and $(CH_3)_3$$CSiMe_2$*) and 0.11 (6 H, s, $(CH_3)_3CSiMe_2$ and $(CH_3)_3CSiMe_2$*); ^{13}C NMR (100 MHz, $CDCl_3$) 163.91 (C), 163.89 (C*), 150.4 (C and C*), 139.22 (C), 139.17 (C*), 134.99 (C), 134.96 (C*), 128.6 (CH and CH*), 127.4 (CH and CH*), 127.22 (CH), 127.18 (CH*), 111.04 (C), 111.02 (C*), 86.0 (d, *J* 4, CH), 85.7 (d, *J* 5, CH), 84.5 (CH and CH*), 77.5 (d, *J* 5, CH), 77.1(d, *J* 5, CH), 63.3 (CH_2 and CH_2*), 53.2 (dd, *J* 5 and 4, CH_3 and CH_3*), 45.21 (CH_2),

45.17 (CH_2*), 39.4 (d, *J* 5, CH_2), 39.2 (d, *J* 6, CH_2), 25.9 (CH_3 and CH_3*), 18.2 (C and C*) and 12.4 (CH_3 and CH_3*); ^{31}P NMR (161 MHz, $CDCl_3$) 9.67 and 9.42; HRMS *m/z* (ES^+) Found M + Na 562.2112. $C_{24}H_{38}N_3O_7PSiNa$ requires 562.2109.

Phosphoramidate 124



To a stirring suspension of CuI (10 mg, 0.05 mmol) in MeCN (0.5 mL) was added 5' – OTBS – 3' – methyl phosphonate thymidine (109 mg, 0.25 mmol), L-phenylalanine methyl ester hydrochloride (108 mg, 0.5 mmol) and Et_3N (64 μL, 0.5 mmol). The mixture was stirred at 55 °C for 18 h before cooling to room temperature and diluting with a mixtre of IPA : $CHCl_3$ (1:5, 30 mL). The organic was washed with 2M HCl (20 mL), saturated $NaHCO_3$ (20 mL), then dried (Na_2SO_4). Removal of the volatiles *in vacuo* left the crude product which was purified by column chromatography (gradient: Et_2O to 5% MeOH in CH_2Cl_2) yielding the product (85 mg, 55%) as a white solid (1:1 mixture of diastereoisomers). m.p. 55 - 58 °C; R_f – 0.44 (5% MeOH in CH_2Cl_2); υ_{max} /cm^{-1} ($CHCl_3$ soln) 3396, 3043, 2956, 2932, 2859, 1743, 1689, 1520, 1470, 1322, 1259, 1129, 1050, 1011 and 835; [Diastereoisomer denoted with *] ^{1}H NMR (400 MHz, $CDCl_3$) 8.70 (1 H, br. s., *NH* and *NH**), 7.51 (0.5 H, d, *J* 1.1, C^6H), 7.47 (0.5 H, d, *J* 1.1, C^6H*), 7.37 – 7.15 (5 H, m, *ArH* and *ArH**), 6.34 – 6.28 (1 H, m, $C^{1'}H$ and $C^{1'}H$*), 4.90 (0.5 H, t, *J* 6.0, $C^{4'}H$), 4.81 (0.5 H, t, *J* 6.5, $C^{4'}H$*), 4.21 (0.5 H, d, *J* 1.5, $C^{3'}H$), 4.15 (0.5 H, d, *J* 1.0, $C^{3'}H$*), 4.15 – 4.10 (0.5 H, m, *NH*), 4.09 – 4.00 (0.5 H, m, *NH*), 3.85 (1 H, app. td, *J* 5.9 and 2.1, PhCH_2 and PhCH_2*), 3.77 (1.5 H, s, CO_2Me), 3.75 (1.5 H, s, CO_2Me*), 3.60 (1.5 H, d, *J* 11.3, *OMe*), 3.45 (1.5 H, d, *J* 11.3, *OMe**), 3.33 (1 H, td, *J* 10.4 and 7.3, *CH* and *CH**), 3.13-3.04 (1 H, m, $C^{5'}H$ and $C^{5'}H$*), 3.01 – 2.89 (1 H, m, $C^{5'}H$ and $C^{5'}H$*), 2.48 (0.5 H, dd, *J* 13.4 and 5.3, $C^{2'}H_2$), 2.29 (0.5 H, dd, *J* 14.0 and 5.7, $C^{2'}H_2$*), 2.10 – 2.00 (0.5 H, m, $C^{2'}H_2$), 2.00-1.93 (0.5 H, m, $C^{2'}H_2$*), 1.93 (3 H, s, CH_3 and CH_3*), 0.94 (4.5 H, s, $(CH_3)_3$CSiMe$_2$), 0.93 (4.5 H, s, $(CH_3)_3$CSiMe$_2$*) and 0.14 – 0.11(6 H, m, $(CH_3)_3$C*SiMe$_2$* and

$(CH_3)_3CSiMe_2$*); ^{13}C NMR (100 MHz, $CDCl_3$) 173.0 (C and C*), 163.54 (C), 163.53 (C*), 150.19 (C), 150.16 (C*), 135.9 (C), 135.8 (C*), 135.1 (CH and CH*), 129.5 (CH), 129.4 (CH*), 128.63 (CH), 128.59 (CH*), 127.18 (CH and CH*), 111.05 (C and C*), 86.1 (d, *J* 4, CH), 85.8 (d, *J* 5, CH*), 84.55 (CH), 84.54 (CH*), 77.9 (d, *J* 6, CH), 77.4 (d, *J* 5, CH*), 63.4 (CH_2), 63.3 (CH_2*), 55.8 (C), 55.6 (CH*), 53.3 (d, *J* 5, CH_3), 53.1 (d, *J* 5, CH_3*), 52.4 (CH_3), 52.3 (CH_3*), 40.43 (CH_2), 40.36 (CH_2*), 39.4 (d, *J* 5, CH_2), 39.2 (d, *J* 5, CH_2*), 25.9 (CH_3 and CH_3*), 18.3 (C and C*) and 12.5 (CH_3 and CH_3*); ^{31}P NMR (161 MHz, $CDCl_3$) 8.06 and 7.63; HRMS *m/z* (ES^+) Found M + Na 634.2325. $C_{27}H_{42}N_3O_9PSiNa$ requires 634.2320.

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