Approaches to Selective Phosphoryl Transfer

Thesis submitted for the degree of Doctor of Philosophy

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Declaration

This dissertation records the work carried out in the Department of Chemistry, University of Sheffield, between October 2012 and September 2017 and is original except where acknowledged by reference.

No part of this work is being, nor has been, submitted for a degree, diploma, or any other qualification at any other university.

Publications

Examining the origin of selectivity in the reaction of racemic alcohols with chiral N-phosphoryl oxazolidinones, S. Crook, N. J. Parr, J. Simmons, S. Jones, *Tetrahedron: Asymm.* **2014**, *25*, 1298-1308.

Acknowledgments

First of all I would like to say that this may be the hardest part of the Thesis, expressing how much I appreciate what everyone has done for me during my time in Sheffield is difficult, but I am truly grateful.

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Away from the department and key to everything are my Mum and Dad, without their support I would have never got through it all. I never say it enough, but thank you both for everything.

Abbreviations

Ac	Acetyl
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
ATR	Attenuated total reflection
Boc	*tert*-Butoxycarbonyl
Bn	Benzyl
cat.	Catalyst
Cy	Cyclohexyl
d	Doublet
de	Diastereomeric excess
DMAP	4-Dimethylaminopyridine
dr	Diastereomeric ratio
ee	Enantiomeric excess
EGF	Epidermal growth factor
eq	Equivalent(s)
Et	Ethyl
k	Equilibrium constant
h	Hour(s)
GC	Gas chromatography
hept	Heptet
Hz	Hertz
HMPT	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
i-Pr	Isopropyl
IR	Infrared
M	Molar concentration
m	Multiplet
Me	Methyl
mL	Millilitre(s)
Mol(s)	Mole(s)

mpt	Melting point
n-Bu	normal-Butyl
NCS	*N*-Chlorosuccinimide
NMI	*N*-Methylimidazole
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
Nu	Nucleophile
OXONE®	Potassium peroxymonosulfate
p	*Para*
p	Pentuplet
PEP	Phosphoenolpyruvate
Ph	Phenyl
pm	Picometres
PMB	*para*-Methoxybenzyl
q	Quartet
rt	Room temperature
s	Singlet
S_N2	Bimolecular nucleophilic substitution
TBDMS	*tert*-Butyldimethylsilyl
T	Temperature
t	Triplet
t-Bu	*tert*-Butyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
tol	Toluene
Tr	Trityl
Ts	*para*-Toluenesulfonyl
UV	Ultraviolet

Abstract

The work in this thesis describes the approaches made to produce a method for selective phosphorylation of alcohol substrates. Development of work into the asymmetric phosphorylation using *N*-phosphoryl oxazolidinones enabled a model to be proposed which accounted for the selectivity of these reactions, in which a combination of relay effects generate a transient chiral environment, this with the formation of diastereomeric reactive species and steric interactions between adjacent alkoxide moieties accounts for these selectivities. Modifications of the phosphoryl moiety were proposed from this model to improve the low selectivities of the *N*-phosphoryl oxazolidinone chiral auxiliaries, but no enhancement could be made due to a drop in reactivity when larger groups were incorporated.

A new proposal of using *P*-chiral auxiliaries was implemented to enhance the selectivity without affecting the reactivity. A new *P*-chiral oxazolidinone synthesis was optimised and reacted under the standard conditions. The selectivity of one diastereoisomer gave a 12% ee, similar to the selectivity of the *N*-phosphoryl oxazolidinones reinforcing the model proposed earlier whereas the other diastereoisomer with the larger group close to the stereodirecting group shut off the reactivity. This demonstrated that oxazolidinone chiral auxiliaries containing a stereodirecting group are not optimum and therefore the stereodirecting group was placed at the phosphate group. However a low selectivity similar to that of the other oxazolidinone was yielded.

This research moved to produce a trifunctional phosphorylation catalyst. Podand and polyether based catalysts were synthesised and tested to prove that trifunctional catalysis was occurring in these phosphorylation systems and a model was proposed which accounts for this trifunctional rate enhancement. These will allow for future catalysts to be designed bearing stereodirecting groups.

1. Introduction

1.1 Biological activation

Biological organisms have developed many complex signalling pathways and cascades that ultimately allow for survival under a variety of circumstances, many of which are regulated by phosphorylation. An example of one such selective phosphorylation signalling event is the propagation of cell proliferation, which is evoked by the release of Epidermal Growth Factor (EGF) in sites of growth within the body. EGF binds to an extracellular receptor which ultimately causes a conformational change of intracellular protein kinases, which then enables selective phosphorylation to mobilise the processes needed for growth (Figure 1).[1]

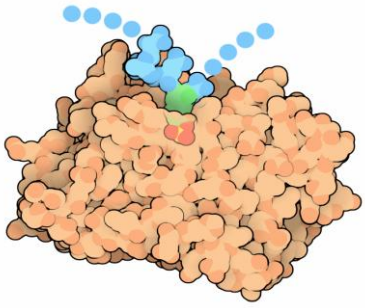
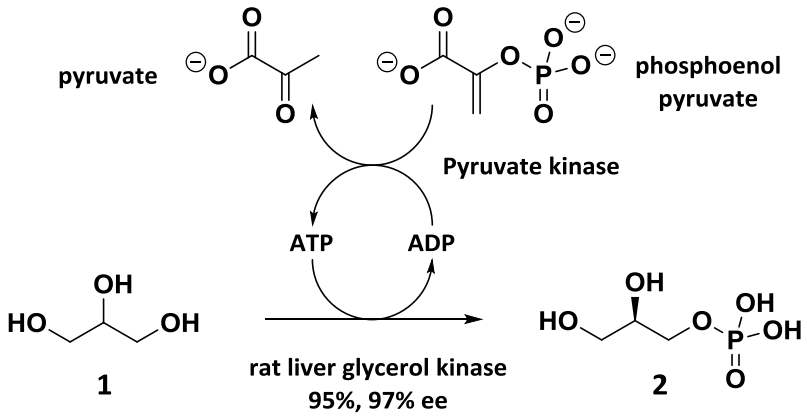


Figure 1. Example of phosphorylation of protein kinases.[2]

Selective phosphorylation using isolated enzymes has been utilised to enable the enantioselective introduction of phosphate groups on secondary alcohols on a multi-gram scale and in good yields.[3] These systems comprise of an enzyme which catalyses the transfer of the phosphate group onto the substrate, with a source of a phosphate or a cofactor. One example of this is rat liver glycerol kinase which phosphorylates glycerol **1** (Scheme 1).[4] Adenosine triphosphate (ATP) is most commonly used as a co-factor with another enzyme such as pyruvate kinase which catalyses the phosphate transfer from a phosphate source such as phosphoenolpyruvate (PEP) to the co-factor. However these systems are limited by the specificity of the enzymes for single substrates.



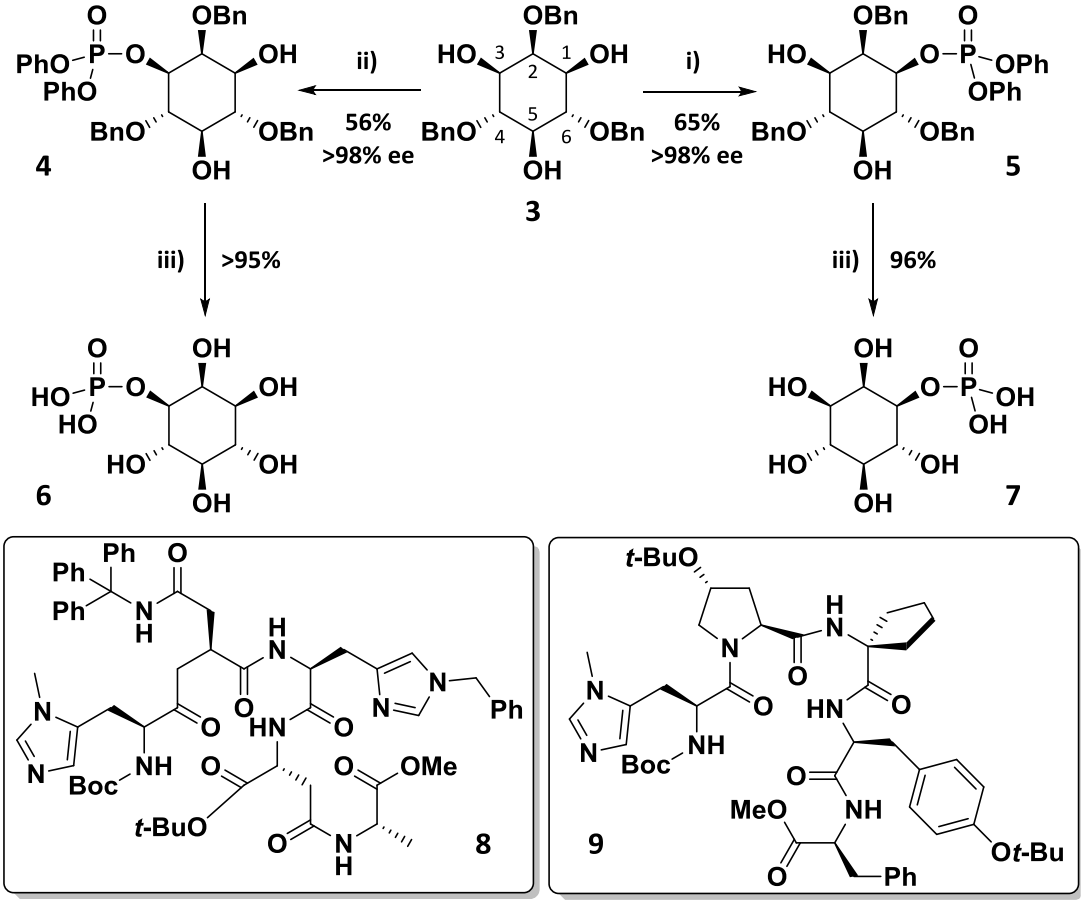
Scheme 1. Selective phosphorylation using enzymes.

1.2 Selective phosphorylation

Non-enzymatic selective phosphorylation examples are rare, with work from Miller *et al.* dominating this area. Miller and co-workers reported the use of short peptides as catalysts in the preparation of *myo*-inositol phosphates and their derivatives which are of interest due to the major role they play in cellular signalling events.[5][6]

A library of histidine-containing small peptides was prepared and screened for the regio- and enantioselective monophosphorylation of *meso*-*myo*-inositol-derived triol **3** (Scheme 2).[7] These gave a wide range of enantioselectivities for the monophosphorylation of the 1- and 3-hydroxyl groups. This illustrated that subtle changes in secondary structure of the peptide had a marked effect upon selectivity. The reaction of triol **3** with peptide **8** gave a ee of 90% for phosphorylation of the hydroxyl group at the 1-position. Optimisation of reaction conditions for peptide **8** gave a good yield and increased ee of the resultant monophosphate **5**. Removal of the benzyl groups and conversion to the phosphate monoester was carried out by a dissolved metal deprotection, leading to natural product D-I-1P **7** in excellent yield. This result led to an investigation into the selectivity of a wider range of peptides. On further screening of peptide libraries, catalyst **9** was discovered to afford 3-

monophosphate **4** in 56% yield and >98% ee. Birch reduction was employed to obtain D-I-3P **6** in excellent yield (Scheme 2).



Reaction conditions: i) diphenyl chlorophosphate, peptide **8** (0.020 eq), Et_3N, toluene; ii) diphenyl chlorophosphate, peptide **9** (0.0025 eq); iii) Li^0, NH_3, THF.

Scheme 2. Selective phosphorylation using small peptides.

This peptide screening led to the significant discovery that phosphorylation occurred at the 1- or 3-position, but never at the 5-position. This suggests that the catalytic activity is not regioselective but that it is enantioselective in the desymmetrisation of a *meso*-triol. While these two results were positive, the goal of site-selective catalysis was not yet achieved. For regioselective catalysis, a catalyst that could overcome the difference in energy barriers between the more reactive 1- and 3- positions and the less reactive 5- position would be required.

Miller *et al.* were able to exploit this energy difference to their advantage in the synthesis of enantiomerically pure phosphatidylinositol phosphates with saturated and unsaturated side chains, culminating in the total synthesis of both enantiomers of PI3P **10** (Figure 2).[8]

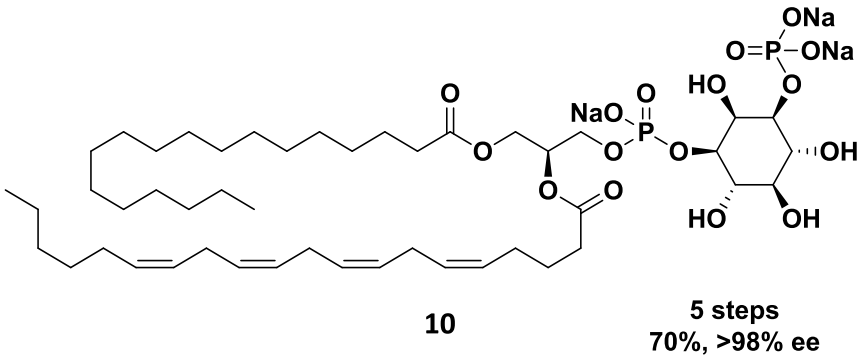


Figure 2. One of the enantiomers of PI3P that were synthesised.

Miller and co-workers were also able to demonstrate the versatility of monophosphate **5** as a synthetic intermediate in the synthesis of various deoxy-*myo*-inositol phosphates.[9] Selective thiocarbonylation was carried out at the more reactive 3-position or at both the 3- and 5-positions at which point a radical deoxygenation, followed by dissolved metal deprotection yielded 3-deoxy-D-*myo*-inositol-1-phosphate **11** and 3,5-dideoxy-D-*myo*-inositol-1-phosphate **12** as single enantiomers (Figure 3).

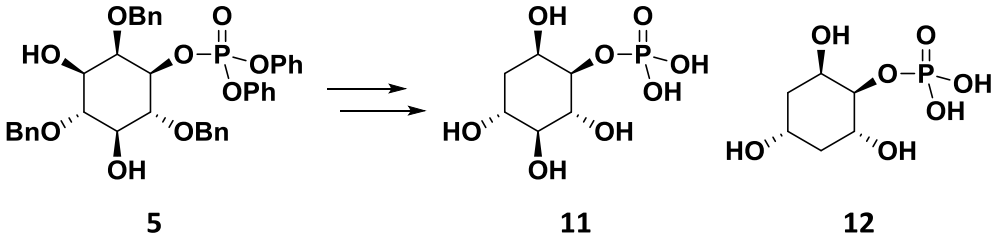
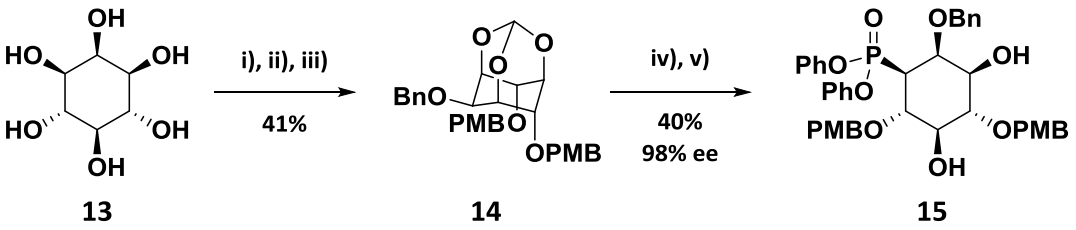


Figure 3. *myo*-inositol variants synthesised by using monophosphorylation.

Miller *et al.* continued this body of work in the synthesis of enantiomeric pairs of *myo*-inositol-triphosphates **17**, **18** and **19** and the enantiomeric pair of a *myo*-inositol-tetraphosphate **20**,[10] in which the key step was the preparation of a differentially protected *meso*-*myo*-inositol derived triol **13** (Scheme 3). The 1-, 3- and 5-hydroxyl groups were protected as an orthoester, which allowed the two more reactive hydroxyl groups at the 4- and 6-positions to be protected as PMB ethers and the less reactive 2-hydroxyl to be protected as a benzyl ether. Triol **13** was desymmetrised employing the previously developed small peptide catalysed asymmetric phosphorylation. Use of peptide **8** led to desymmetrised monophosphate **15** in 98% ee.



13 **14** **15**

Reaction conditions: i) $HC(OEt)_3$, TsOH; ii) NaH, PMBCl; iii) NaH, BnBr;
iv) HCl, MeOH; v) diphenyl chlorophosphate, peptide **8** (0.005 eq), Et_3N.

Scheme 3. Synthesis of protected *meso*-*myo*-inositol.

The principles learnt from earlier work were applied in the successful synthesis of D-I-3,5,6P3 **17**, D-I-3,4,5P3 **18**, D-I-3,4,6P3 **19** and D-I-3,4,5,6P4 **20** (Figure 4). The use of complementary peptide **9** in the desymmetrisation step led to the opposite enantiomer of desymmetrised monophosphate **16** in 98% ee. Reactions of synthetic intermediate, **16**, under analogous conditions led to the formation of the opposite enantiomers of all four *myo*-inositol polyphosphates.

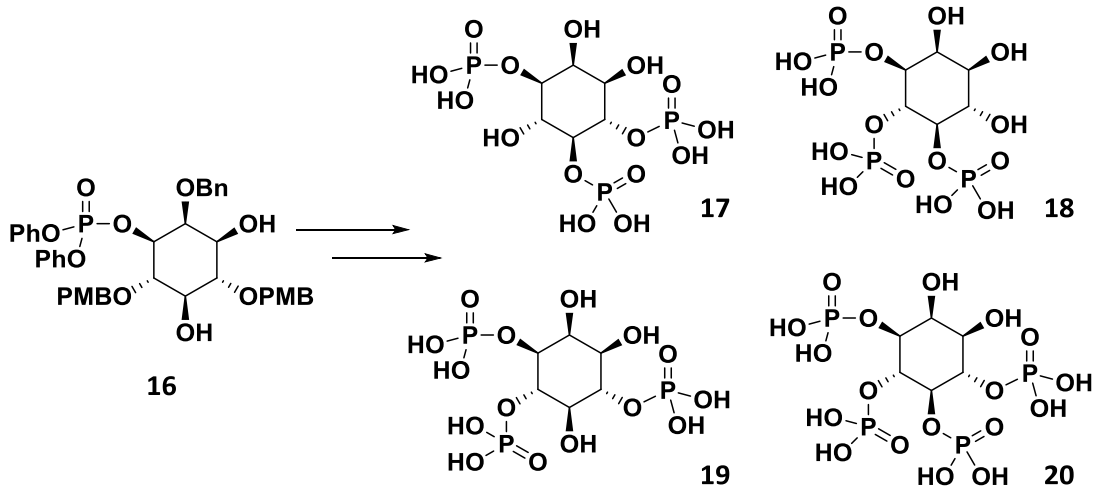


Figure 4. A number of inositols synthesised using principles from earlier work.

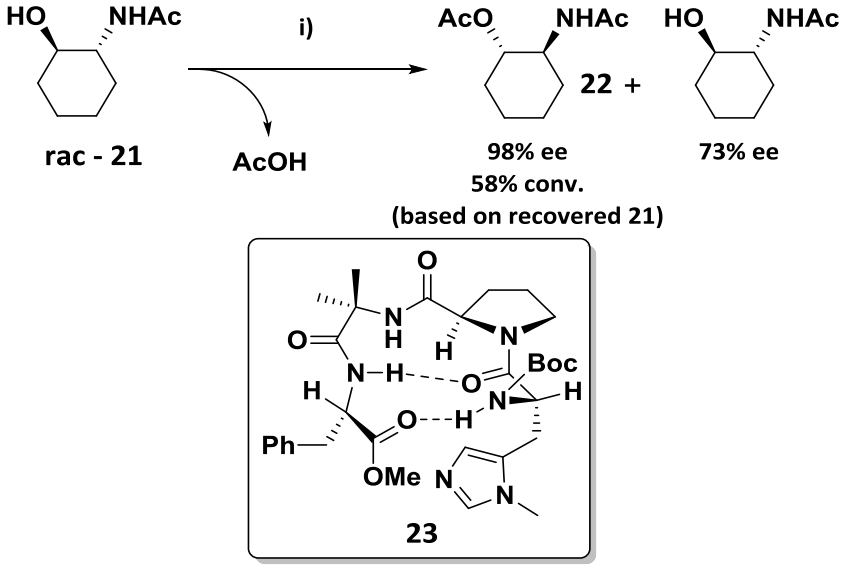
In summary, the work from Miller's group has allowed asymmetric phosphorylation to be carried out in good yield and excellent selectivity. However the methodology is extremely substrate specific, and results were only obtained with very specifically protected *meso*-*myo*-inositol derivatives. This work has shown that selective phosphorylation is possible and that it may one day be possible to phosphorylate much more complex sites.

1.3 Small peptide catalysed selective acylation

Initial work done by Miller *et al.* was conducted with small peptides with the aim to enable selective acylation. This eventually led to their work on selective phosphorylation. Miller's goal was to embed a nucleophile into a peptide sequence that would have a propensity to turn the catalytically active residue toward the functional groups within the peptide backbone and side chains.

A first generation of acylation catalysts were designed to contain a nucleophilic substructure. It was believed that since the stereogenic center of these histidine containing analogues was remote from the nucleophilic nitrogen, the 'folded' secondary structure was deemed necessary for the relay of stereochemical information during catalysis. Thus, an α-turn was selected as the initial platform for

the first generation catalysts. Kinetic resolution of *trans*-1,2-acetamidocyclohexanol **21** was used as the test reaction for these catalysts as it was speculated that the presence of a substrate amine would heighten affinity between catalyst **23** and the substrate through hydrogen bonding (Scheme 4).[11] Relatively selective catalysis was observed from these early catalysts but this also made the first generation catalysts highly substrate-specific. Thus catalysts with more 'folded' secondary structures were investigated.



Reaction conditions: i) Ac_2O, **23** (2.0 mol%), toluene.

Scheme 4. Acylation using small peptides.

It was from the comparison of more "folded" peptides **24** and **25**,[11] a study of peptide folding preference,[12][13] and with mechanistic investigations, that the hypothesis that the enhancement of the catalyst secondary structure (i.e., rigidity) led to increased selectivity (Figure 5). This hypothesis enabled the design of octapeptide catalysts biased to form α-hairpins. Using the D-Pro-Gly sequence, a number of catalysts were designed.[14] This new generation of catalysts had a high selectivity, but only for a limited set of substrates containing acetamides.[15] Any attempts of kinetic resolution upon unfunctionalised racemic alcohols with these catalysts yielded only nonselective reactions.

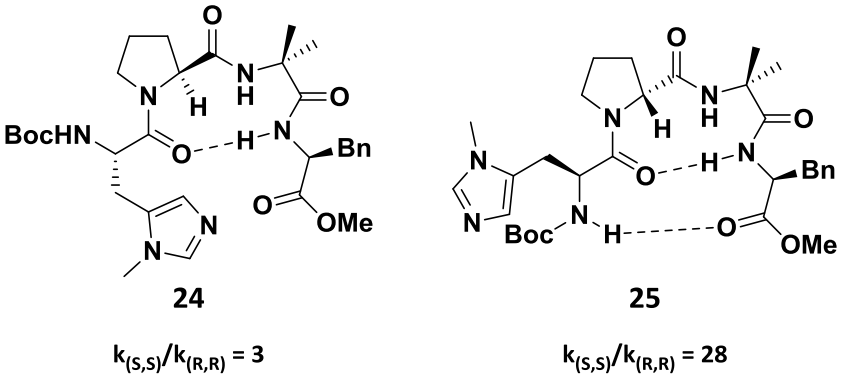
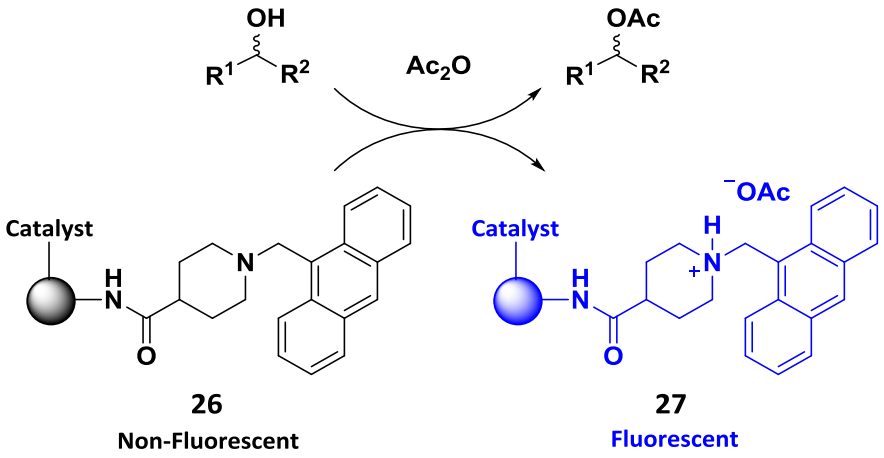


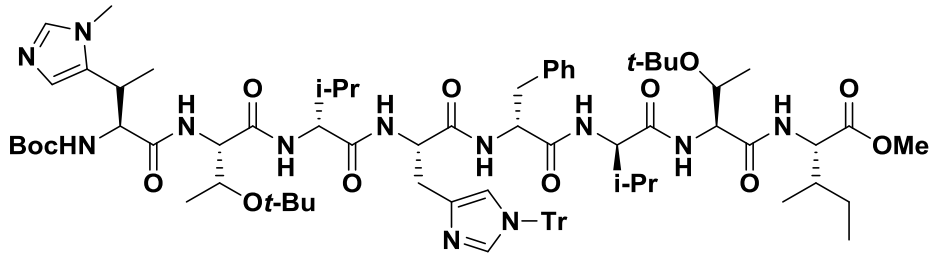
Figure 5. Rate comparison of peptide catalysts.

Thus the Miller group embarked upon a more generalised approach, using a combinatorial assay based on the concept of proton-activated fluorescence.[16][17] Due to the acyl transfer of acetic anhydride affording the ester and an equivalent of acetic acid on a per turnover basis (Scheme 5), a proton-activated fluorophore (aminomethylanthracene, **26**) was incorporated as a constituent of each bead-bound catalyst in a library that provided a real-time readout of catalytic activity.[18] This technique enabled screens of pooled beads to be performed under a fluorescence microscope, with the brightest beads correlating to those carrying the most active catalysts.[19][20] This enabled the Miller group to achieve a screen of diverse synthesised sensor-functionalised peptide library by using split-pool synthesis technique.[21][22]

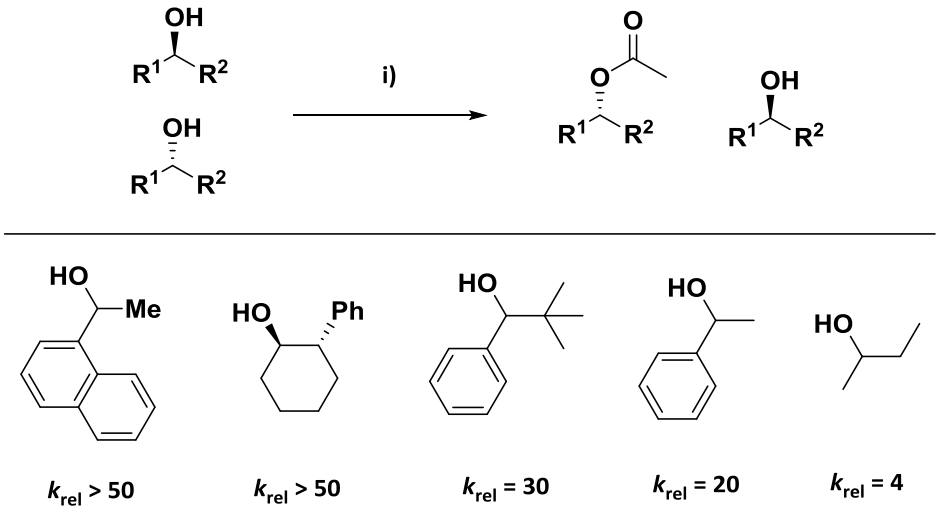


Scheme 5. Proton-activated fluorophore used as a sensor for acylation.

One of the highlights from this library technique was the discovery of peptide **28** (Scheme 6), which provided substantial k_{rel} values for a relatively diverse set of alcohols all without the acetamide moiety that was present in the first generation catalysts.[23] This result showed the vast potential of this technique.



28



Reaction conditions: i) acetic anhydride, **28** (2.5 mol%), toluene, -65 °C.

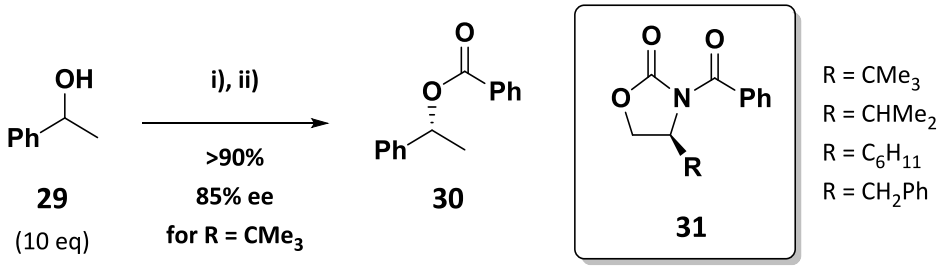
Scheme 6. Relative rates of acylation of alcohols with catalyst **28**.

This combinatorial approach was continued to find a number of catalysts which showed good activity and selectivity with a number of different substrates. Given the stereoselectivity that was seen in these acyl kinetic resolutions and that, in some cases, the selectivity could have been due to multidentate interactions between catalysts and substrates, the Miller group sought to extend the reaction scope to include “site-selective” and “regioselective” processes. Given that nucleophilic catalysis could be applied not only to acyl transfer but to other types of

group transfers, these catalysts were taken forward into the targeted asymmetric phosphorylation in the context of inositol phosphate synthesis described earlier.

1.4 Small molecule catalysed selective acylation

Although small peptide catalysis shows promise, the catalysts themselves have a very high molecular weight and are very substrate specific. Thus a way of performing acylation using lower molecular weight reagents would be preferred. One such example are Evans' auxiliaries that have been used in the kinetic resolution of racemic secondary alcohols as enantioselective acylating agents.[24] Differentially substituted *N*-benzoyl auxiliaries **31** were treated with ten equivalents of racemic 1-phenylethanol **29** along with one equivalent of *N*-methylpiperidine and $MgBr_2$**.**OEt_2. These reactions were completed within 30 minutes and appeared to show that the steric bulk of the stereodirecting group dictated the enantiomeric purity of the benzoate product **30** (Scheme 7). Ten equivalents of alcohol were initially employed to accentuate the selectivity of the reactions to enable the identification of the optimum oxazolidinone.

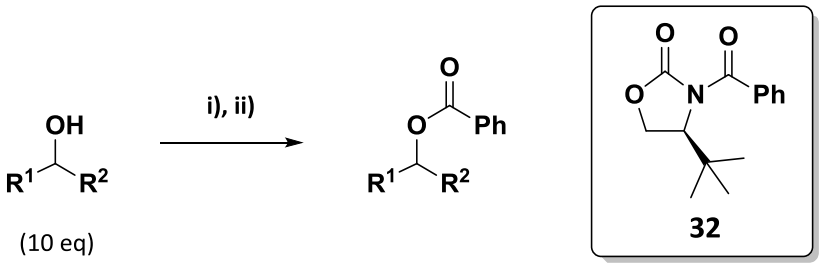


Reaction conditions: i) $MgBr_2.Et_2O$, *N*-methylpiperidine, CH_2Cl_2, rt;
ii) *N*-acyl oxazolidinone **31**.

Scheme 7. Acylation of 1-phenylethanol using oxazolidinone chiral auxiliaries.

The scope of these oxazolidinones was then investigated by screening a number of different alcohols, by employing the most selective auxiliary, *N*-acyl-(*S*)-4-*tert*-butyl-2-oxazolidinone **32**. A different methodology was also used, where alcohols were deprotonated with MeMgBr at 0 °C to give the alkoxide prior to addition of oxazolidinone **32** (Scheme 8, Table 1). Ten equivalents of the alcohol were

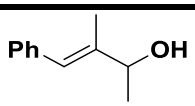
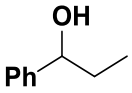
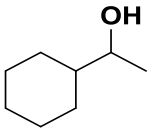
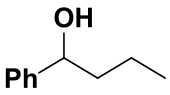
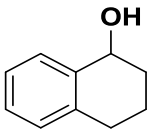
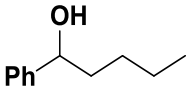
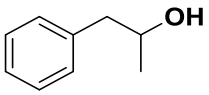
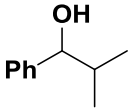
employed to make the methodology more practical. These reactions proceeded in good yield, with varying degrees of selectivity allowing the comparison of selectivities when the reactions have proceeded to completion, rather than attempting to quench the reactions at 50% conversion. The substrates obtained in the highest ee were phenyl *n*-alkyl carbinols.



Reaction conditions: i) MeMgBr, CH_2Cl_2, 0 °C; ii) *N*-acyl oxazolidinone **32**.

Scheme 8. Conditions for substrate screen.

Table 1. Selectivities of the alcohol substrates.

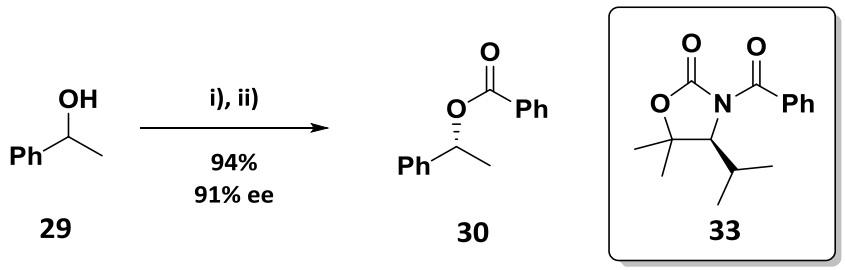
Entry	Substrate	ee (%)[α]	Entry	Substrate	ee (%)[α]
1		95	6		85
2		90	7		5
3		93	8		53
4		93	9		15
5		65			

[α]refers to the benzoate ester product.

Having observed the many advantages of Evans' auxiliaries, Davies *et al.* introduced an analogous type of auxiliary, named "SuperQuats". These contained a geminal

dimethyl group at the 5-position of the oxazolidinone,[25] this was also postulated to have a steric effect on the stereodirecting group at the 4-position, giving greater facial selectivity.

These auxiliaries have also been used as stoichiometric asymmetric acyl transfer reagents under the same conditions that Evans' used for asymmetric acylation. Ten equivalents of 1-phenylethanol **29** were pre-treated with one equivalent of MeMgBr to give the corresponding alkoxide, followed by subsequent addition of one equivalent of *N*-benzoyl-4-isopropyl-5,5-dimethyl-2-oxazolidinone **33** to afford the corresponding (*R*)-benzoate **30** in high yield and selectivity (Scheme 9).



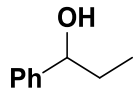
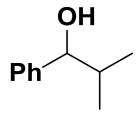
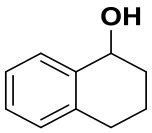
29 30 33

Reaction conditions: i) MeMgBr, CH_2Cl_2, 0 °C; ii) *N*-acyl oxazolidinone **33**.

Scheme 9. Acylation using the "SuperQuat" auxiliaries.

A further range of alcohols were then screened under the same conditions. This showed the same trend that had been observed for the Evans' auxiliaries, with phenyl *n*-alkyl carbinols giving the best results (Table 2). Comparison of the selectivity of the Evans' and Davies' auxiliaries indicated that *N*-benzoyl SuperQuat oxazolidin-2-one **33** generally exerts comparable levels of enantiocontrol to the corresponding *tert*-butyloxazolidin-2-one derivative **32**, and significantly higher levels of selectivity compared to the isopropyloxazolidin-2-one.

Table 2. Alcohol substrate screen using "SuperQuat" auxiliary **33**.

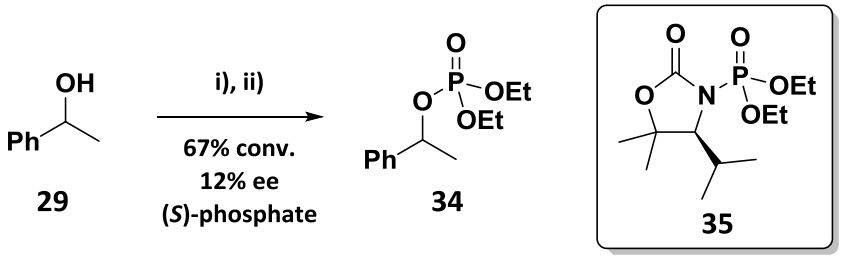
Entry	Substrate	ee (%)[α]
1		92
2		42
3		46

[α]refers to the benzoate ester product.

The electronic effects of the reagents were then investigated using *p*-methoxybenzoyl as the acyl group, as the electron donating ability of the methoxy group was expected to suppress reactivity and promote selectivity. Results supported this, with enantiomeric excesses greater than or equal to those without the methoxy group.

1.5 Development of N-Phosphoryl Oxazolidinones

One aim of the Jones' group is to establish a small molecule approach to selective phosphorylation. A number oxazolidinones were screened and this first generation of chiral auxiliaries were tested by the formation of the magnesium bromoalkoxide, before the addition of the oxazolidinone. The highest selectivities were seen by oxazolidinone **35**, which gave an ee of 12% (Scheme 10); this was very low when compared to similar reactions with these oxazolidinones in acylation reactions.[26]



Reaction conditions: i) MeMgBr, Et_2O/ CH_2Cl_2, 2 h; ii) oxazolidinone **35**.

Scheme 10. Phosphorylation using a phosphorylating chiral auxiliary oxazolidinone.

Kinetic resolution of 1-phenylethanol **29** by asymmetric acylation was reported to proceed with 95% ee using Evans' acylating agent **32** and 91% ee using Davies' acylating agent **33**. A model for nucleophilic attack was proposed in order to account for the large discrepancy in selectivity between acylation and phosphorylation (Figure 6). As suggested in Evans' and co-workers paper, formation of a six-membered chelate between the two carbonyl groups of the *N*-acyl oxazolidinone to a magnesium cation would cause the trajectory of nucleophilic attack of the alkoxide to be proximal to the stereodirecting group, exerting a large influence on selectivity. In the case of the *N*-phosphoryl oxazolidinone, an $S_N2(P)$ trajectory of attack would be remote from the stereodirecting group, preventing a significant influence on selectivity.

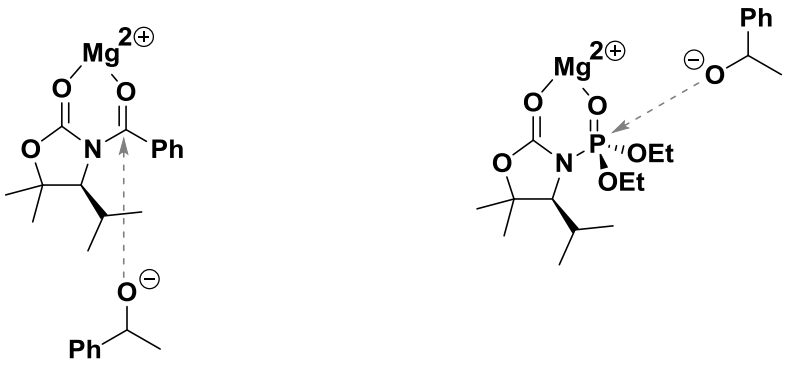
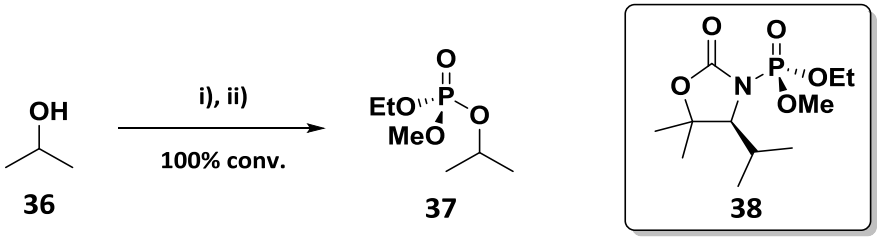


Figure 6. Model to account for the discrepancy in selectivities.

A study was completed that provided evidence supporting the suggestion that the phosphorylation of alkoxides, employing *N*-phosphoryl oxazolidinones as phosphorylating agents, proceeded *via* a concerted $S_N2(P)$ mechanism.[27] *P*-Chiral *N*-phosphoryl oxazolidinone **38** was prepared as a single diastereomer and the

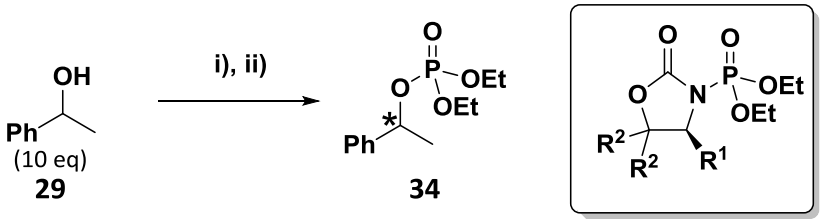
stereochemistry at phosphorus was confirmed by single crystal X-ray crystallography. Reaction with the chloromagnesium alkoxide of isopropanol **36** proceeded exclusively with inversion of configuration at phosphorus, in complete conversion (Scheme 11). This fact suggested that the reaction had proceeded *via* a concerted, $S_N2(P)$ type mechanism. The stereochemistry of the phosphate product **37** was confirmed by GC analysis, in comparison with the opposite enantiomer which was prepared by an alternate route.[28]



Reaction conditions: i) MeMgCl, Et_2O, -78 °C to rt;
ii) *N*-phosphoryl oxazolidinone **38**, CH_2Cl_2, 0 °C.

Scheme 11. Evidence for the $S_N2(P)$ mechanism.

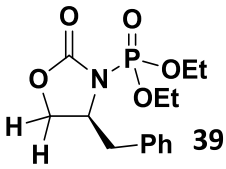
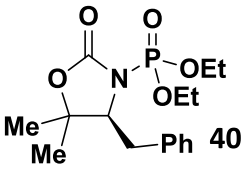
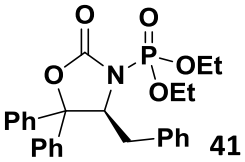
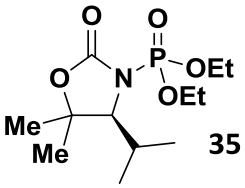
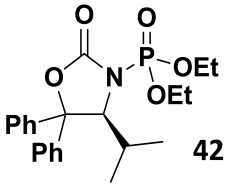
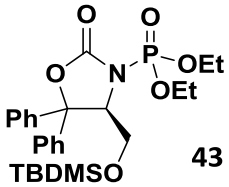
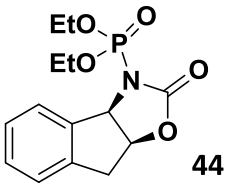
Further studies aimed to probe aspects of the mechanism of phosphorylation employing *N*-phosphoryl oxazolidinones and also to attempt to improve the selectivity of the methodology. 1-Phenylethanol **29** (10 eq) was employed as the substrate in conditions that were analogous to those employed by Davies in his work on kinetic resolution employing *N*-acyl oxazolidinones (Scheme 12).[29] The selectivity of the reaction was assessed by assaying the ee of the resulting phosphate ester **34** (Scheme 12, Table 3). However, the ee's of the phosphate products remained low (0 to 15%).



Reaction conditions: i) MeMgCl (1.1 eq), CH_2Cl_2, 0 °C to rt;
ii) *N*-phosphoryl oxazolidinone, CH_2Cl_2, 0 °C.

Scheme 12. Reaction conditions for the oxazolidinone screen.

Table 3. Yields and selectivities of each oxazolidinone.

Entry	*N*-Phosphoryl oxazolidinone	Yield (%) of product[a]	ee (%) of product[a]
1	 **39**	57 (50)	0 (2)
2	 **40**	67 (36)	3 (4)
3	 **41**	91 (74)	14 (15)
4	 **35**	69 (57)	8 (5)
5	 **42**	88 (87)	15 (15)
6	 **43**	62 (58)	11 (10)
7	 **44**	68 (59)	5 (5)

[a]Values in parentheses represent the results of duplicate reactions.

Although the selectivities were disappointing, a clear pattern emerged, that an increase in the steric bulk of the substituents on the oxazolidinone led to an increase in selectivity. Increasing the size of substituents at the 5-position gave a marked effect upon the selectivity of the reaction (Entries 1-3). Replacement of the benzyl group at the 4-position with an isopropyl group (Entries 4 and 5) also gave a slight increase in selectivity, whereas the TBDMS protected serine derived *N*-phosphoryl oxazolidinone (Entry 6) gave similar selectivity to the benzyl substituted oxazolidinone (Entry 4). This showed that the lone pair had no impact on the selectivity of the reaction by co-ordination to the magnesium counter ion, but was being governed by the steric influence of the OTBDMS group. Use of the aminoindanol derived *N*-phosphoryl oxazolidinone (Entry 7) afforded the phosphate in only 5% ee.

A model to explain the degree of selectivity was proposed (Figure 7), where the substituents at the 5-position of the *N*-phosphoryl oxazolidinone were shown to play a role in influencing the selectivity of the reaction. Without any substituents at the 5-position no selectivity is achieved. It was postulated that the substituents at the 5-position have a steric clash with the stereodirecting group at the 4-position, forcing it towards the phosphoryl group. The influence of the stereodirecting group could perturb the proximal ethoxy group whilst leaving the remote ethoxy group undisturbed, thus setting up a temporary asymmetric environment around phosphorus. This perturbation of the proximal ethoxy group could cause it to point out towards the trajectory of attack of the alkoxide or force it to adopt an alternate conformation. The latter is more likely due to the freedom of rotation of the ethoxy group, and it is this 'pseudo'-*P*-chirality that is hypothesised to account for the selectivity of the reaction.

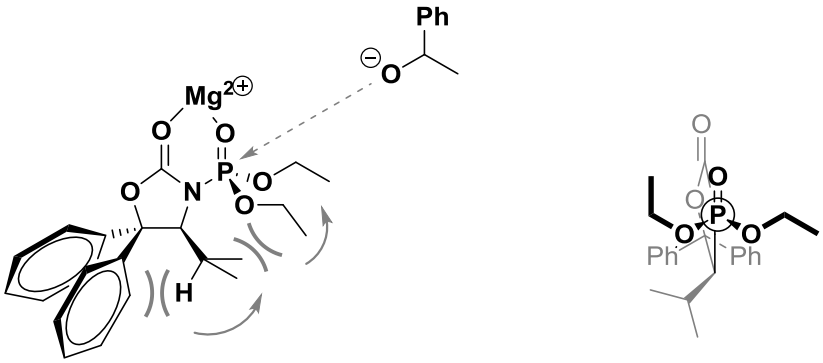
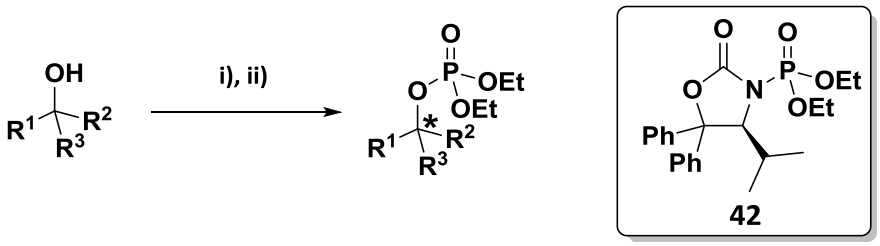


Figure 7. Proposed model to account for the selectivities.

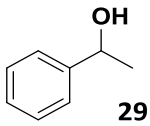
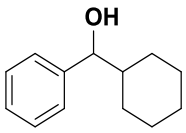
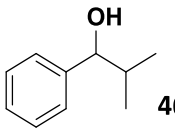
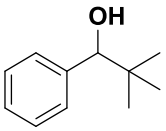
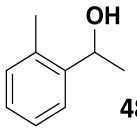
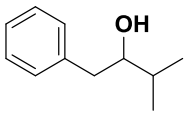
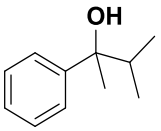
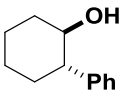
The phosphorylating reagents that gave the best selectivity in the phosphorylation of 1-phenylethanol **29** were (*S*)-4-benzyl-5,5-diphenyl-*N*-phosphoryl oxazolidinone **41** and (*S*)-4-isopropyl-5,5-diphenyl-*N*-phosphoryl oxazolidinone **42**. Isopropyl substituted *N*-phosphoryl oxazolidinone **42** is a solid, so was taken forward into an optimisation study to find the most selective conditions apply to a range of racemic alcohol substrates, in order to glean more information about the mechanism of the reaction. The first set of substrates were prepared by sodium borohydride reduction of the corresponding ketones, whilst other substrates were prepared *via* Grignard additions to a range of carbonyl compounds. These substrates were screened under the optimised reaction conditions (Scheme 13) and the results are summarised below (Table 4).



Reaction conditions: i) MeMgCl (1.1 eq), CH_2Cl_2, 0 °C to rt;
ii) *N*-phosphoryl oxazolinone **42**, CH_2Cl_2, 0 °C to rt.

Scheme 13. Reaction conditions for the substrate screen.

Table 4. Yields and selectivities of the alcohol substrates.

Entry	Substrate	Yield (%) of product[a]	ee (%) of product[a]
1	 **29**	88 (87)	15 (15)
2	 **45**	92 (19)	19 (18)
3	 **46**	83 (24)	20 (21)
4	 **47**	0 (0)	-
5	 **48**	0 (0)	-
6	 **49**	76 (75)	28 (28)
7	 **50**	0 (0)	-
8	 **51**	90 (89)	-

[a]Values in parentheses represent the results of duplicate reactions

Variation of the structure of the substrate had a considerable effect on the reactivity and selectivity of the procedure. As the size of the non phenyl R^2 substituent was increased, the selectivity of the phosphorylation increased. Moving from methyl to cyclohexyl led to an increase from 15% ee to 19% ee (Entries 1 and 2). A similar level of selectivity, 20% ee, was achieved when the R^2 substituent was

an isopropyl group (Entry 3). However, when the size of the R^2 substituent was further increased, to a *tert*-butyl group, conversion to the corresponding phosphate ester was minimal (Entry 4). It appeared that the optimum R^2 substituent, in terms of selectivity, was an isopropyl group. Increasing the size of the R^1 substituent to a *ortho*-tolyl group again caused a large decrease in reactivity, with minimal conversion to phosphate (Entry 5). As an alternative, the size of the R^1 substituent was decreased to a benzyl group, which afforded the corresponding phosphate ester in 28% ee (Entry 6). This was found to be the highest level of selectivity achieved. Entry 7 was used to test the feasibility of the asymmetric phosphorylation of tertiary alcohols but yielded only starting materials. Finally, cyclohexyl alcohol formed the corresponding phosphate ester in excellent yield, however the selectivity of the reaction could not be assayed, as no suitable chiral HPLC conditions were discovered (Entry 8).

Although an improvement in the selectivity of asymmetric phosphorylation was achieved, these results indicated that the optimised methodology was not yet a practical step for a synthetic strategy. However, the results have provided much insight into the way that the reaction works and should act as a foundation for the development of a highly selective phosphorylation procedure.

1.6 Aims

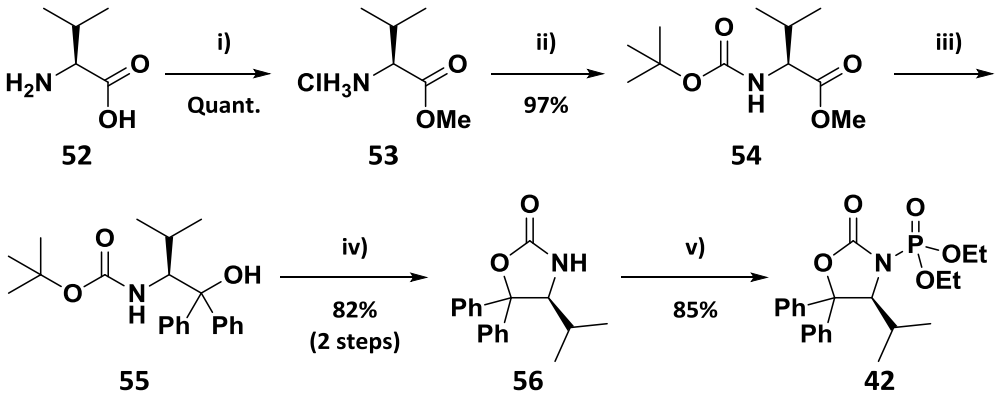
This project aims to further study selective phosphorylation using small molecule chiral auxiliaries. Firstly by expanding upon the work already done in this area, by synthesising a number of substrates which will hopefully elicit a greater understanding of the model proposed for this selective phosphorylation. Secondly by synthesising oxazolidinones with different groups on the phosphate, to elude if different size and shaped groups will yield higher selectivities. Lastly the project will focus upon expanding the work done on *P*-chiral oxazolidinones to further probe the model of selective phosphorylation, so that selective phosphorylation may be

understood and attempted on more complex molecules. The long term aim of this work is developing a framework for selective phosphorylation of proteins.

2. Asymmetric phosphorylation of alkoxides

2.1 Oxazolidinone synthesis

The L-valine derived phosphorylating agent (*S*)-4-isopropyl-5,5-diphenyl-*N*-phosphoryl oxazolidinone **42** was targeted due to it showing the highest degree of selectivity in previous work completed by the Jones group.[30] Thus, L-valine was treated with thionyl chloride in methanol to afford the corresponding methyl ester hydrochloride **53** quantitatively (Scheme 14). This was followed by reaction with di-*tert*-butyl dicarbonate under mildly basic conditions, which produced *N*-Boc-L-valine methyl ester **54** in excellent yield. This step not only protected the amine but also acted as the electrophilic centre for the ring closing step to form the desired oxazolidinone (Scheme 14). A double Grignard addition to the methyl ester **54** was carried out to afford the diphenyl alcohol **55**, which upon treatment with base, underwent reaction with the carbonyl of the Boc group to give (*S*)-4-isopropyl-5,5-diphenyl-2-oxazolidinone **56** in good yield over the two steps. The oxazolidinone **56** was phosphorylated using diethyl chlorophosphate and *n*-BuLi, giving (4*S*)-3-diethyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone **42** in good yield.

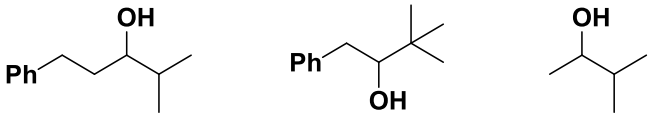


Reaction conditions: i) $SOCl_2$ (1.5 eq), MeOH, 0 °C to rt; ii) Boc_2O (1.05 eq), $NaHCO_3$ (3.0 eq), EtOH, 0 °C to rt; iii) PhMgBr (4.0 eq), THF, 0 °C to rt; iv) *t*-BuOK (1.1 eq), THF, 0 °C to rt; v) *n*-BuLi, THF, -78 °C to rt then diethyl chlorophosphate, -78 °C to rt.

Scheme 14. Synthesis of the *N*-phosphoryl oxazolidinone **42**.

2.2 Substrate synthesis

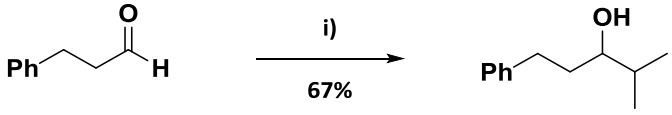
The alcohol substrates that were selected for screening were chosen to provide a greater understanding of the steric requirements of the reaction based upon previous work (Figure 8). The longer chain alcohol **57** was selected to probe the importance of the distance of the phenyl group from the reacting centre. The *tert*-butyl substrate **58** contains a bulkier side group, and substrate **59** was selected to explore if the presence of a phenyl group was important. Of these alcohols, **57** and **58** required synthesis, with the other being commercially available.



57 **58** **59**

Figure 8. Alcohol substrates chosen for screening.

Synthesis of alcohol **57** proceeded *via* addition of the Grignard reagent prepared from magnesium and 2-bromopropane with 3-phenylpropionaldehyde **60** to form the desired substrate **57** in good yield (Scheme 15).



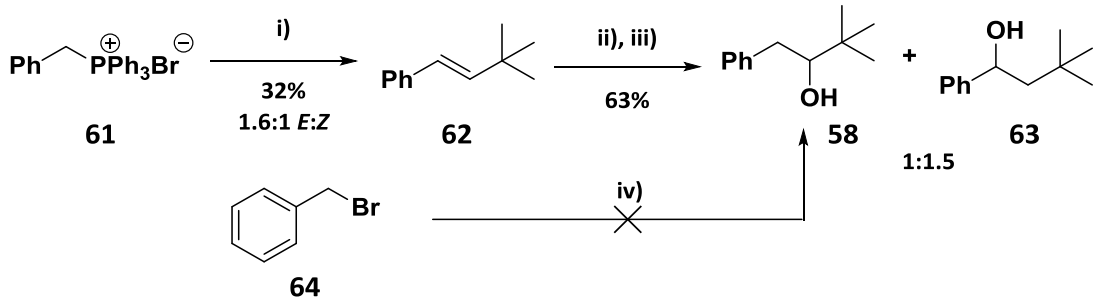
60 **57**

Reaction conditions: i) $(CH_3)_2CHMgBr$, THF, 0 °C to rt.

Scheme 15. Synthesis of 4-methyl-1-phenylpentan-3-ol **57**.

Synthesis of the alcohol **58** was initially attempted *via* a Wittig reaction to form the alkene **62**, which could then undergo hydroboration to give the desired alcohol (Scheme 16). However, this route gave poor yields of alkene in a 1.6:1 *E*:*Z* ratio (obtained from ^{1}H NMR data) which were inseparable and therefore gave the desired alcohol **58** as the minor product in the hydroboration step. Furthermore, separation of these two alcohol isomers proved difficult. Attempts to synthesise the

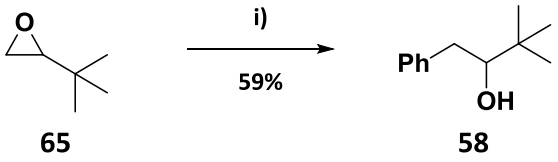
alcohol **58** *via* addition of a Grignard reagent to trimethylacetaldehyde failed to give the desired product.[31]



Reaction conditions: i) *t*-KOBu, THF, 0 °C to rt; then trimethylacetaldehyde, 0 °C to rt;
ii) BH_3.THF, THF then H_2O, rt; iii) NaOH, 30% H_2O_2, rt;
iv) $(CH_3)_2CHMgCl.LiCl$, THF, -15 °C, then trimethylacetaldehyde.

Scheme 16. Attempted synthesis of 3,3-dimethyl-1-phenyl butan-2-ol.

The alcohol **58** was synthesised *via* a regioselective Grignard addition to the commercially available epoxide 3,3-dimethyl-1,2-epoxybutane **65** (Scheme 17), giving the desired product in moderate yield.



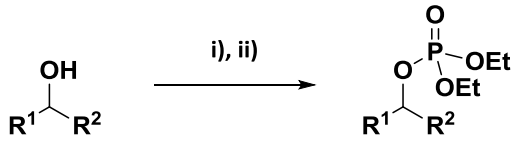
Reaction conditions: i) PhMgBr, CuBr THF, 0 °C to rt.

Scheme 17. Synthesis of the alcohol substrate 3,3-dimethyl-1-phenyl butan-2-ol **58**.

2.3 Preparation of racemic phosphate esters

Before asymmetric phosphorylation could be attempted, the corresponding phosphate esters were required in order to obtain reference data, including suitable methods to determine the enantiomeric purity. Each alcohol was deprotonated with *n*-BuLi before treatment with diethyl chlorophosphate to afford the corresponding phosphate ester (Scheme 18). This reaction gave the desired racemic phosphates in generally good yields (Table 5). Chiral HPLC conditions for the separation of the enantiomers of *O*-diethyl phosphoryl-4-methyl-1-phenylpentan-3-

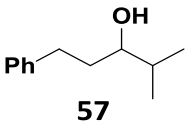
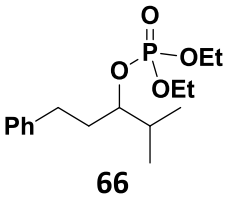
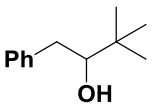
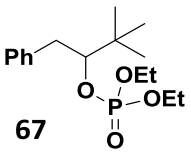
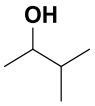
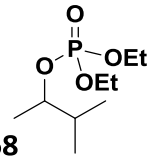
ol **66** and *O*-diethyl phosphoryl-3,3-dimethyl-1-phenyl butan-2-ol **67** were obtained by employing a Lux Cellulose-1 column. A range of chiral stationary phases were investigated for both GC and HPLC separation of *O*-diethyl phosphoryl-3-methylbutan-2-ol **68**, but conditions could not be found to separate the isomers.



Reaction conditions: i) *n*-BuLi, THF, -78 °C to rt; ii) diethyl chlorophosphate, -78 °C to rt.

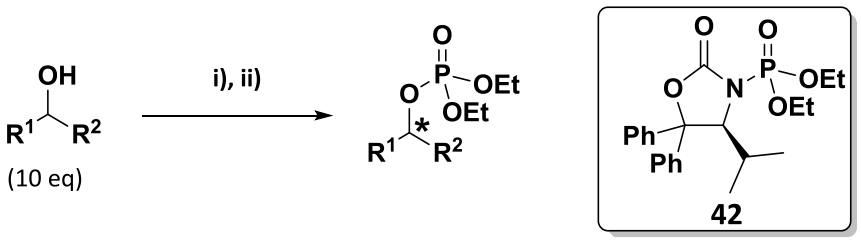
Scheme 18. General scheme for racemic phosphate synthesis.

Table 5. Substrates and racemic phosphates prepared.

Entry	Substrate	Phosphate	Yield (%)
1	 **57**	 **66**	91
2	 **58**	 **67**	80
3	 **59**	 **68**	86

2.4 Substrate screen

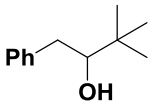
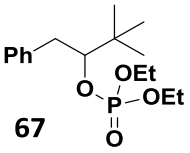
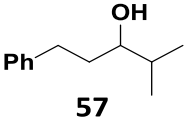
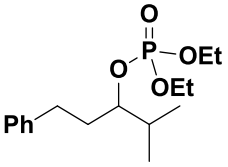
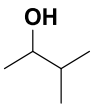
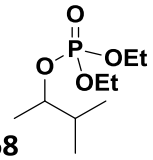
With conditions to analyse two of the phosphate esters in hand, the alcohol substrates were screened under the previously optimised conditions. The alcohol substrate (10 eq) was dissolved in CH_2Cl_2, and the alkoxide formed *via* addition of MeMgCl (1.1 eq) before the addition of (*S*)-4-isopropyl-5,5-diphenyl-*N*-phosphoryl oxazolidinone **42** (Scheme 19, Table 6).



Reaction conditions: i) MeMgCl (1.1 eq), CH_2Cl_2, 0 °C to rt, 1 h;
ii) *N*-phosphoryl oxazolidinone **42** (1.0 eq), CH_2Cl_2, 0 °C to rt.

Scheme 19. General scheme for selective phosphorylation of alcohol substrates.

Table 6. Substrates and the phosphates synthesised and their selectivities.

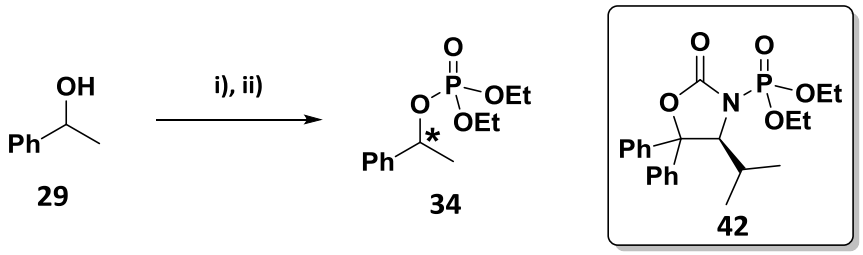
Entry	Substrate	Product	Yield (%) of product[a,b]	ee (%) of product[a,c]
1	 **58**	 **67**	0 (0)	-
2	 **57**	 **66**	66 (66)	14 (13)
3	 **59**	 **68**	74 (71)	-

[a]Values in parentheses represent the results of duplicate reactions. [b]Refers to isolated product. [c]Determined by chiral phase HPLC analysis.

In comparison to results previously obtained (Table 4) these new substrates have shown that there is a limit to the size of the large group that can be used before the reactivity is shut off (Entry 1). This could be due to the stereodirecting group affecting the positions of the groups on the phosphate, such that the trajectory of attack is blocked. Extending the benzyl chain backbone by another carbon atom led to a small decrease in selectivity, suggesting that the stereodirecting group is enforcing the phosphate groups into a position that is selective to certain substrates (Entry 2). No conditions were available to assay the selectivity although phosphate **68** (Entry 3) was isolated in good yield.

2.5 Dimeric model

Based on this study, a model was needed to explain the different reactivity and selectivity observed. This model is based upon the known structures of magnesium alkoxides and magnesium chloro-alkoxides which have been shown to adopt a dimeric tetrahedral species in the solid state and in solution.[32] However, magnesium complexes formed by reaction of alcohols with magnesium chloride have been shown to give octahedral complexes.[33] The actual species that exist under the conditions that have been explored in this study are unclear, which used conditions analogous to work conducted by both Evans and Davies, containing ten equivalents of alcohol with one equivalent of MeMgCl.[25] Further reactions were conducted that would enable an understanding of the nature of these reactive species. This was achieved by diminishing the quantities of alcohol and using THF as the solvent to ensure the presence of the same coordinating solvent in the previously reported structural studies (Scheme 20, Table 7).



Reaction conditions: i) MeMgCl, THF, 0 °C to rt, 1 h;
ii) *N*-phosphoryl oxazolidinone **42**, CH_2Cl_2, 0 °C to rt.

Scheme 20. Asymmetric synthesis of phosphate **34** using the oxazolidinone chiral auxiliary **42**.

Table 7. Study showing selectivity with reagent equivalencies.

Entry	Reagent equivalencies			ee (%) of product[a,b]
	1-phenylethanol 29	MeMgCl	42	
1	10	1	1	12 (12)
2	10	10	1	11 (13)
3	2	2	1	10 (10)

[a]Values in parentheses represent the results of duplicate reactions. [b]Determined by chiral phase HPLC analysis.

Reactions in this study proceeded to completion based upon the equivalents of oxazolidinone **42** with little change to the enantioselectivity of the reaction. Thus one can assume that the reactive species in all of these reactions is the same. Given that the reactive species is likely to be the dimeric tetrahedral based system when the alcohol is completely deprotonated due to there being no alcohol substrate present in the reaction (Entry 2), it seems reasonable to assume that this is the reactive species observed in all cases. If this assumption is correct, then once the phosphoryl oxazolidinone **42** is added to the reaction, displacement of the superfluous solvent ligands might occur leading to the formation of the complex **69** (Figure 9). This shows the position that the alkoxide nucleophile must be in to have the the correct trajectory for an intramolecular $S_N2(P)$ attack at the phosphorus

centre, which has been shown to occur with inversion of the stereochemistry in previous work completed by the Jones group.[26]

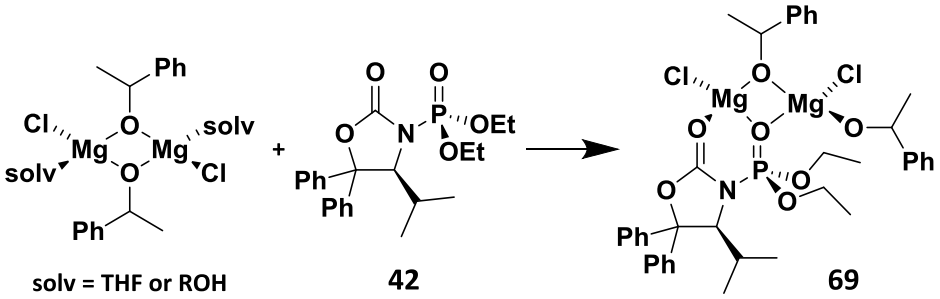


Figure 9. Possible formation of the dimeric tetrahedral based species **69**.

These assumptions and the knowledge that there is no reaction of the oxazolidinone leaving group and the phosphate product allow for models to be proposed that account for the crucial role that the 5,5-*gem*-disubstitution pattern plays in augmenting the selectivity in the reaction. The substituents at the 5-position have steric clash with the stereodirecting group at the 4-position, forcing it towards the phosphoryl group, in an analogous manner to that suggested by Davies.[25] The influence of this stereochemical relay may then perturb the conformation of one of the ethoxy groups, with this conformational bias setting up a transient chiral environment around the phosphorus atom that contributes towards the selectivity of the reaction (Figure 10).

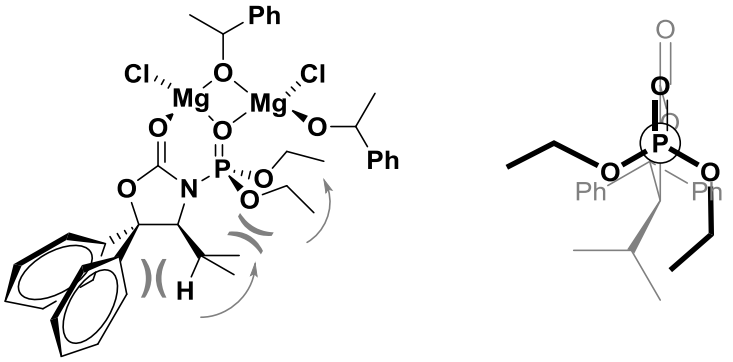


Figure 10. Possible model for the observed selectivity based upon a conformational enforced transient chiral environment.

This dimeric magnesium alkoxide model means that the reactive complexes formed with more complex alcohols can contain two chiral alkoxide moieties, leading to the possibility of forming diastereomeric reactive complexes which may enhance or reduce reactivity and selectivity (Figure 11). The interactions between the two alkoxide substrates in the reactive intermediate can then influence the selectivity of the reaction, which might explain why some of the best selectivities were observed with 3-methyl-1-phenyl-2-butanol **49** (Table 4, Entry 3). In this case, the increased size of the alcohol allows for better interaction between the two alkoxide moieties (Figure 11). It is possible that a combination of all of these models operate either in a cooperative or non-cooperative manner. Of course, if the reaction proceeded through a pentagonal bipyramidal intermediate, then similar arguments to these exist; however, these interactions now lead to differences in energies of the ensuing intermediates, or the activation energies for pseudo-rotation.

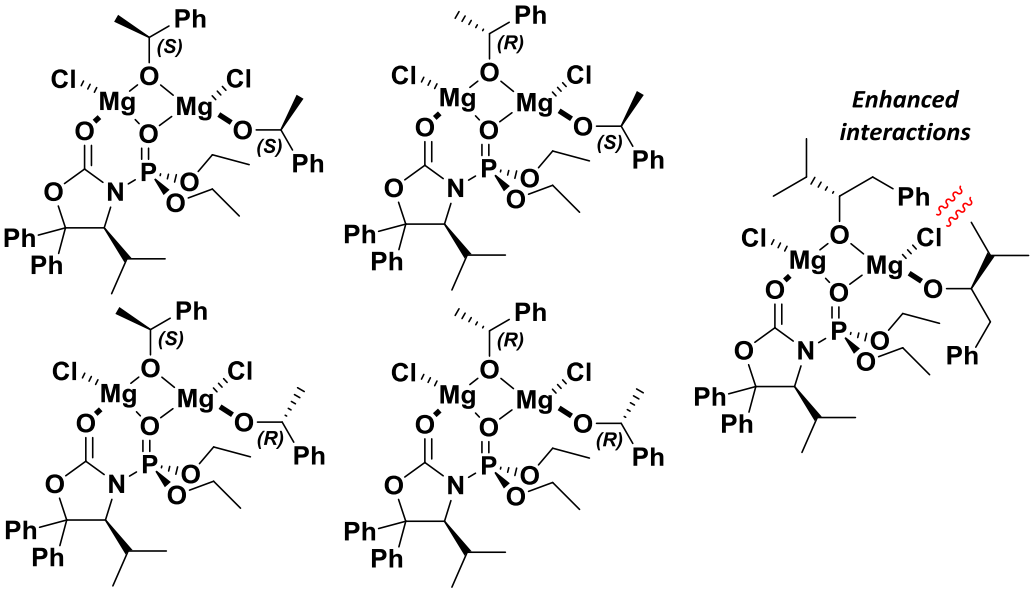
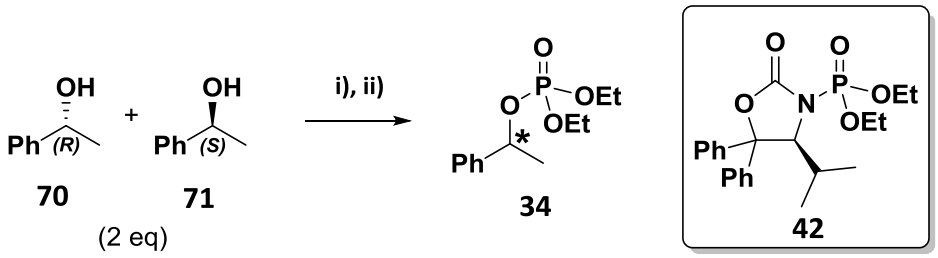


Figure 11. Possible diastereomeric reactive intermediates.

To test if different percentages of the enantiomers would affect selectivity of the reaction a non-linear study of the enantiomers if 1-phenylethanol was conducted to discover if the interaction with other enantiomers of alcohol had an effect or if it was the pseudo chiral environment that enforced the selectivity of the reaction (Scheme 21, Table 8).



Reaction conditions: i) MeMgCl, THF, 0 °C to rt, 1 h;
ii) *N*-phosphoryl oxazolidinone **42**, CH_2Cl_2, 0 °C to rt.

Scheme 21. Asymmetric synthesis of phosphate **34** using different percentages of the enantiomers of 1-phenylethanol **70** and **71**.

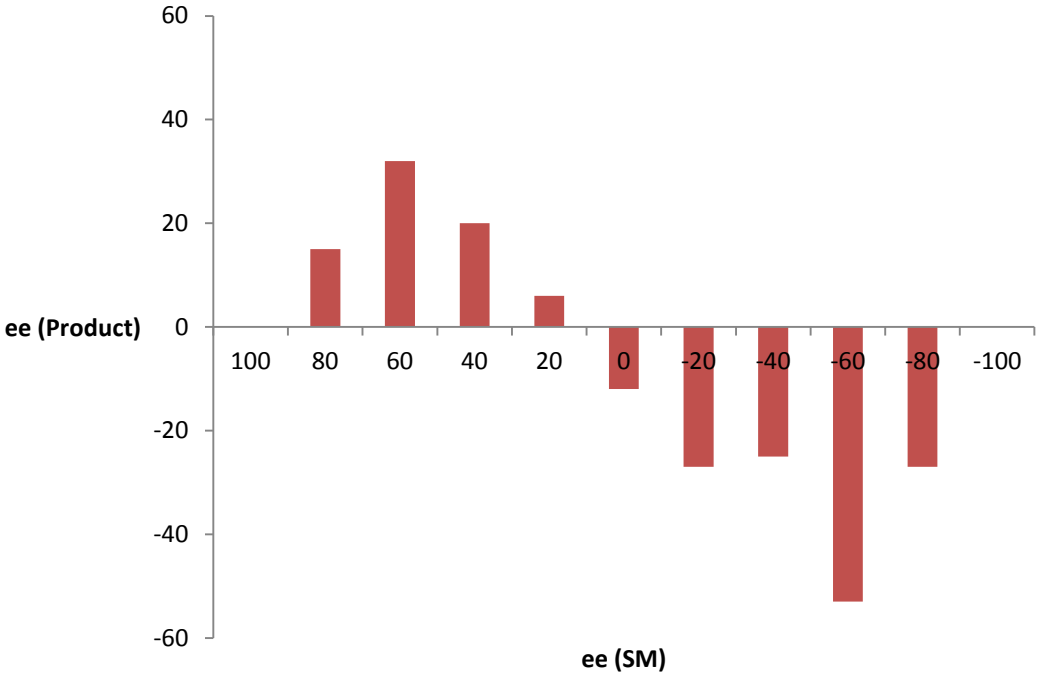
Table 8. Non-linear study of the enantiomers 1-phenylethanol.

Entry	ee (%) of (*S*)-SM used	ee (%) of (*S*)-product[a]	Difference
1	100	100	0
2	80	65	15
3	60	28	32
4	40	20	20
5	20	14	6
6	0	12	-12
7	-20	7	-27
8	-40	-15	-25
9	-60	-7	-53
10	-80	-53	-47
11	-100	-100	0

[a]Determined by chiral phase HPLC analysis.

These reactions were all quantitative and apart from an anomalous result for Entry 9 there is a clear asymmetric trend (Graph 1). There are two distinct peaks between the ee of the starting materials used and that of the ee of the product showing that there is an enhancement of the selectivity that is not due to the stereodirecting group of the oxazolidinone. It would appear that the interactions between the two alkoxide substrates in the reactive intermediate can influence the selectivity of the

reaction and that there is an optimum ee of each starting material around 60% and -60% respectfully that causes the greatest enhancement. That there is a clear interaction between different enantiomers of alkoxide substrates supports the proposed model.



Graph 1. Graphical representation of the non-linear study of the enantiomers of 1-phenylethanol.

2.6 Phosphoryl moiety

The proposed model to account for the selectivity suggests a transient asymmetric environment around the phosphorus atom (Figure 10). This pseudo-P-chirality arises from perturbation of one ethoxy group of the phosphate, causing it to either be forced out towards the trajectory of attack of the alkoxide or to adopt an alternate conformation, by the stereodirecting group at the 4-position of the oxazolidinone. If this proposed model holds true, then variation of the phosphoryl moiety could have a profound influence on the reaction.

Previous work undertaken found that the asymmetric phosphorylation of 1-phenylethanol **29** using *N*-phosphoryl oxazolidinones **72** and **73** (Figure 12) gave only starting materials at the end of the reaction. It was hypothesised that these analogues either blocked the trajectory of attack of the nucleophile or caused the trigonal bipyramidal intermediate to be too high in energy for the reaction to proceed.

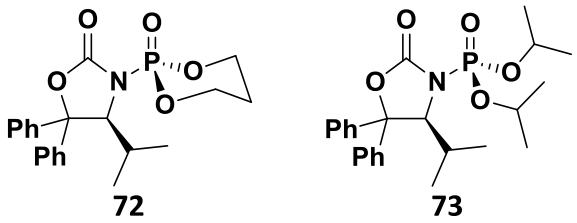


Figure 12. Different variations of the phosphoryl group on the oxazolidinones.

Thus it was hypothesised that incorporating a phosphoryl group that did not block the trajectory of the attack of the alkoxide, but was large enough to exert enhanced interactions with the alkoxide, would enhance the selectivities seen previously. It was proposed that a benzyl group would be the best candidate due to its steric bulk not being adjacent to the oxygen atom of the phosphate to allow attack of the alkoxide, but the large phenyl group could still interact with the auxiliary (Figure 13).

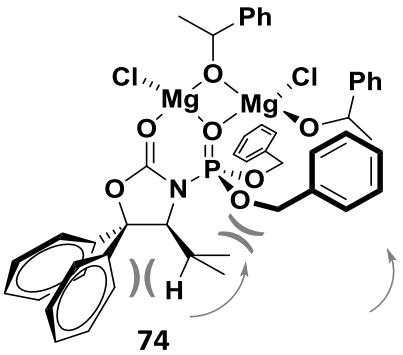
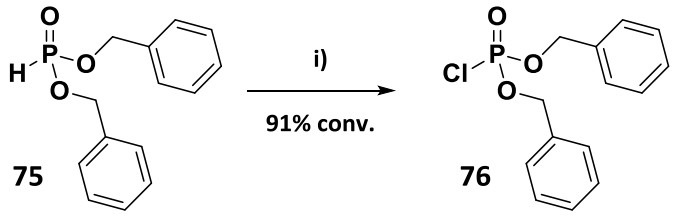


Figure 13. Dibenzyl variation in the dimeric model.

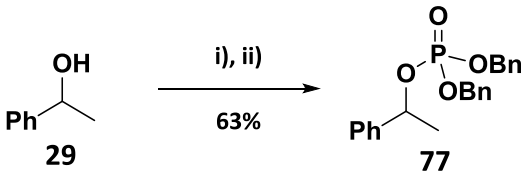
To test if the benzyl phosphate **74** gave enhanced selectivities, the corresponding chlorophosphate **76** was needed, which was synthesised from dibenzyl phosphite **75** using NCS (Scheme 22). The ^{1}H NMR spectrum of the crude reaction mixture showed that the dibenzyl chlorophosphate **76** was formed, but any attempts to purify the product by distillation or washings were unsuccessful, as within a few hours the product had completely decomposed.



Reaction conditions: i) NCS, toluene, rt.

Scheme 22. Synthesis of the dibenzyl chlorophosphate **76**.

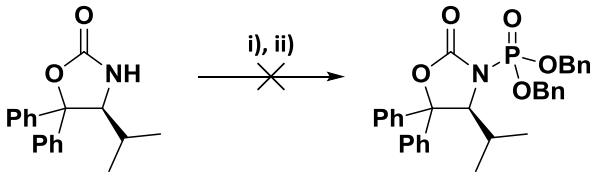
With challenges of purifying the compound due to its instability encountered, it was found that the product could be extracted using hexane and the impurities filtered off, although the chlorophosphate **76** was still unstable and had to be reacted quickly. Akin to the phosphorylation of 1-phenylethanol **29**, conditions for chiral HPLC were required to test the selectivities of the asymmetric reaction. Thus, the racemic synthesis of the dibenzylphosphate **77** was completed in good yield (Scheme 23), and HPLC conditions for the separation of the two enantiomers found.



Reaction conditions: i) MeMgCl, THF, 0 °C to rt; ii) dibenzyl chlorophosphate, 0 °C to rt.

Scheme 23. Synthesis of the racemic dibenzyl phosphate **77**.

Next, the oxazolidinone of the dibenzylphosphate **78** was required, the synthesis of which was analogous to the synthesis of the previously mentioned oxazolidinone **42**. The reaction gave the desired product **78** as determined from the ^{1}H NMR spectrum, however any attempts to purify the material proved fruitless, leading to decomposition (Scheme 24). The standard reaction with 1-phenylethanol **29** was attempted on the crude mixture but this led to a complex mixture of products. Thus, a new substituent was required that would be more stable to purification.

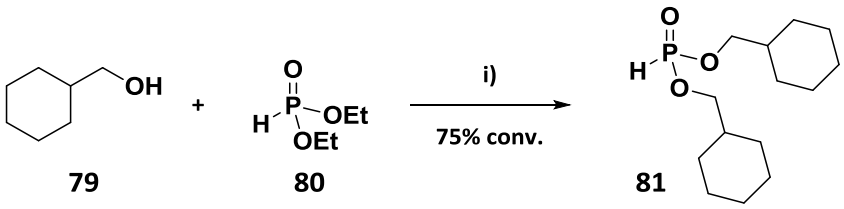


56 **78**

Reaction conditions: i) *n*-BuLi, THF, -78 °C to rt; ii) dibenzyl chlorophosphate **78**, -78 °C to rt.

Scheme 24. Attempted synthesis of the dibenzyl oxazolidinone auxiliary **78**.

A cyclohexylmethyl substrate was chosen as this would be structurally similar to a benzyl group but lack the reactivity of the benzyl centre. The initial route that was attempted was a substitution reaction with diethyl phosphite **80** to yield the dicyclohexylmethyl phosphite **81**, which could then be taken forward to the chlorophosphate **83** using the NCS method utilised in the benzyl phosphate synthesis (Scheme 25). This reaction gave the desired product but difficulties in separating the cyclohexyl phosphite **81** and the ethyl phosphite **80** in the purification process meant that the reaction would need to proceed to completion for it to be a viable route. However, this could not be achieved and other routes were therefore explored.

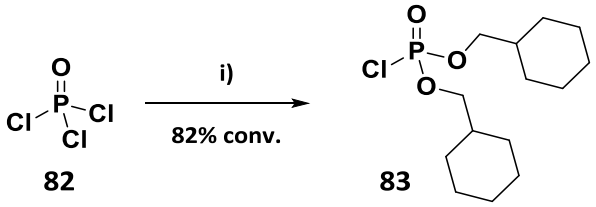


79 80 81

Reaction conditions: i) NaH, THF, rt.

Scheme 25. Synthesis of dicyclohexylmethyl phosphite **81**.

An alternative route started from phosphorus oxychloride **82**, which was reacted with two equivalents of cyclohexylmethanol **79** and triethylamine (Scheme 26). The crude material was distilled under vacuum to separate it from the small amounts of mono-substituted material left in the reaction. However it was found that the high temperatures required for separation decomposed the chlorophosphate **83**.

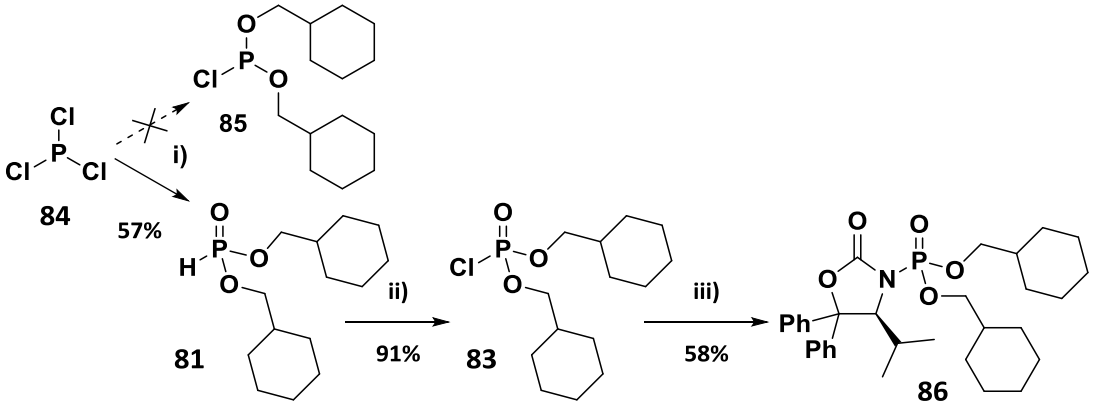


82 83

Reaction conditions: i) cyclohexylmethanol **79**, NEt_3, THF, rt.

Scheme 26. Synthesis of dicyclohexylmethyl chlorophosphate **83**.

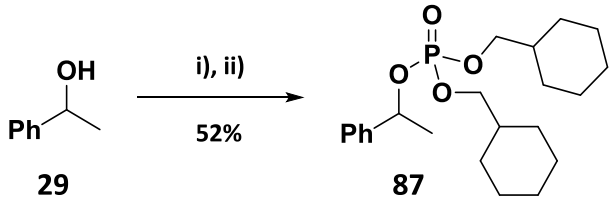
A similar strategy was attempted in which phosphorus trichloride **84** was used as the starting material with the intention of being oxidised once the di-substituted product had been formed, but this gave the unexpected phosphite product **81** (Scheme 27). However, this product could be purified and was subsequently chlorinated in good yield. The chlorophosphate **83** was then used in the reaction with the oxazolidinone **56** to give the desired product **86** in reasonable yield.



Reaction conditions: i) cyclohexylmethanol **79**, NEt_3, THF, rt; ii) NCS, toluene, rt; iii) oxazolidinone **56,** *n*-BuLi, THF, -78 °C to rt then **83**.

Scheme 27. Synthesis of the dicyclohexyl oxazolidinyl phosphate.

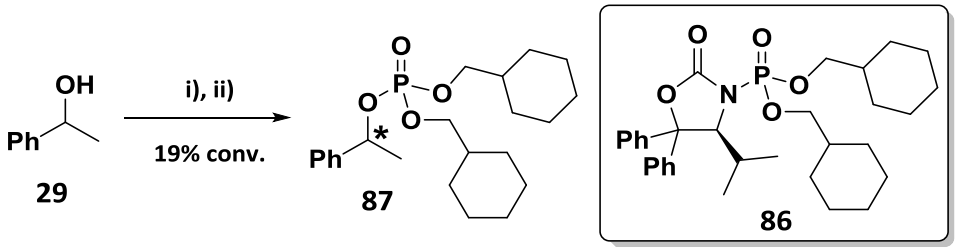
With the oxazolidinone **86** in hand, the racemic phosphate ester was required for the analysis of the asymmetric phosphorylation products, which was prepared by the reaction of the chlorophosphate **83** with 1-phenylethanol **29**, in a moderate yield after purification on silica gel. Conditions were then found which separated the phosphate **87** enantiomers by chiral HPLC so that the asymmetric reaction could be tested.



Reaction conditions: i) MeMgCl, CH_2Cl_2, rt; ii) chlorophosphate **83**.

Scheme 28. Synthesis of racemic dicyclohexylmethyl phosphate **87**.

The asymmetric variant of the reaction was completed under the previously optimised conditions using 1-phenylethanol **29** (Scheme 29), but the conversion of the reaction was very low, which is thought to be due to the large cyclohexylmethyl groups blocking the trajectory of attack of the alkoxide nucleophile (Figure 14). Analysis of the selectivity of the reaction remains unclear due to the low conversion of the reaction.



Reaction conditions: i) MeMgCl, CH_2Cl_2, rt; ii) oxazolidinone **86**.

Scheme 29. Asymmetric synthesis of dicyclohexylmethyl phosphate **87**.

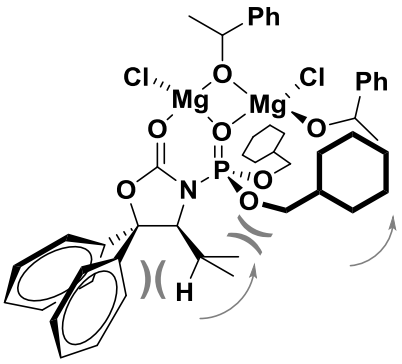


Figure 14. Cyclohexylmethyl group blocking the trajectory of the nucleophile.

2.7 Conclusion

A number of alcohol substrates were synthesised and phosphorylated to add further experimental evidence to aid the explanation of the stereoselectivity of the reactions of *N*-phosphoryl oxazolidinones with magnesium chloroalkoxides. Further reactions were conducted that enabled an understanding of the nature of dimeric tetrahedral magnesium reactive species present to enable the proposition of a model to account for the selectivities of these reactions. This proposes the generation of a transient chiral environment about the phosphorus centre propagated by the phenyl groups on the oxazolidinone, with the formation of diastereomeric reactive species and steric interactions between adjacent alkoxide moieties to account for these selectivities. These interactions were then supported by a non-linear experiment which shows a clear interaction between different enantiomers of alkoxide substrates.

Using the proposed model it was hypothesised that changing the phosphoryl moiety to a larger group connected by a linker could enhance the selectivity without blocking the trajectory of the nucleophile. Although these compounds were successfully synthesised it was found that even with this linker in place the reactivity was greatly reduced by these larger groups.

Using this model and the knowledge that two large groups on the phosphoryl moiety will greatly reduce the reactivity, a new proposal of using *P*-chiral auxiliaries may hold the key to providing enhanced levels of stereoselectivity. These would enable the attack of the nucleophile to be influenced without adding too much bulk.

3. *P*-Chiral phosphorylating agents

3.1 *P*-Chiral phosphoryl moiety

With the proposed model and knowledge of the problems that having too many large groups present on the phosphorus centre in previous phosphorylating agents it was thought that a greater degree of selectivity could be attained if a *P*-chiral phosphate source were used. These might enforce an environment around the phosphorus centre that would differentiate between the enantiomers of the substrates, as the substituents on the phosphorus atom could be tailored to the substrates so that only certain enantiomers would fit the binding model without blocking the trajectory of the nucleophile (Figure 15).

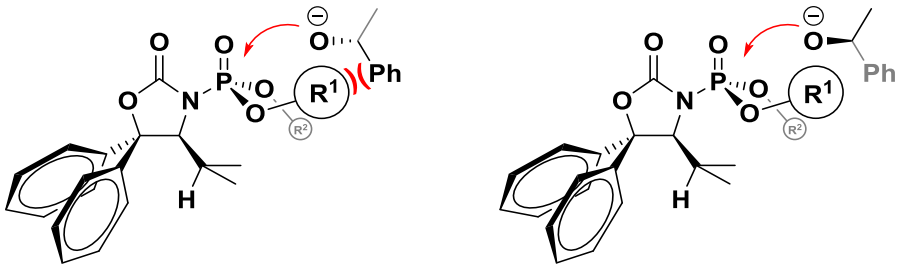
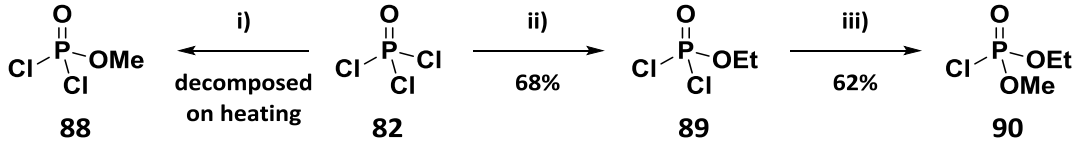


Figure 15. Model of transient chiral environment enhancing the selectivity.

A route was required that would enable the synthesis of *P*-chiral oxazolidinone compounds in high diastereomeric excess and that would enable separation of the diastereoisomers. Earlier work completed in Chapter 2 was adapted to attempt sequential addition of alcohol substrates to phosphorus oxychloride **82** to prepare methyl ethyl chlorophosphate **90** as these groups were small enough to not block the trajectory of the nucleophile but could test the impact of a *P*-chiral variant. Synthesis of this chlorophosphate was initially attempted *via* the addition of the methoxy group prior to that of the ethoxy group. However it was found that the methyl dichlorophosphate **88** decomposed at the temperatures required to distil the mono-substituted compound from the di-substituted impurities present. This method was then reversed so that the ethoxy group was added to the phosphorus oxychloride **82** to form the ethyl dichlorophosphate **89** before the addition of the methoxy group which did not decompose as quickly under the temperatures

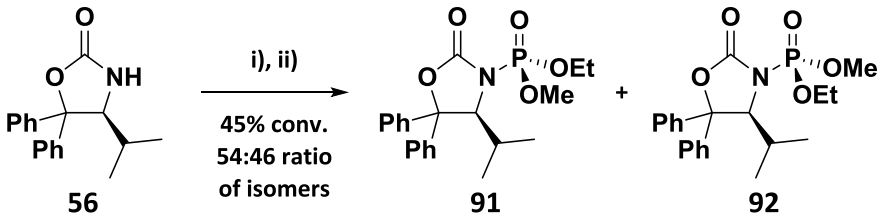
required for distillation. This gave the desired chlorophosphate **90** in reasonable yield after distillation (Scheme 30).



Reaction conditions: i) MeOH, NEt_3, THF; ii) EtOH, NEt_3, THF; iii) MeOH, NEt_3, THF.

Scheme 30. Synthesis of methyl ethyl chlorophosphate.

With the substrate in hand, the next step was to react this with the oxazolidinone **56** (Scheme 31). The reaction proceeded in good yield using *n*-BuLi and ^{1}H NMR spectroscopy indicated that there was a slight 54:46 preference for formation of one diastereoisomer, although the exact identity could not be confirmed.

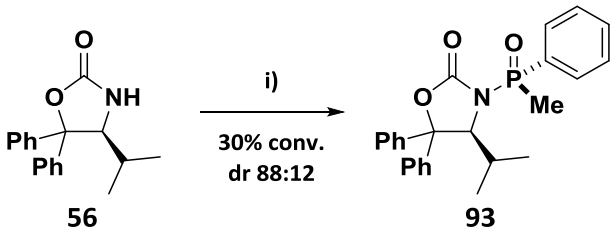


Reaction conditions: i) *n*-BuLi, THF, -78 °C to rt;
ii) methyl ethyl chlorophosphate **90** (1.1 eq), -78 °C to rt.

Scheme 31. Synthesis of *N*-phosphoryl methyl ethyl oxazolidinone auxiliaries.

The low conversion from this reaction could be due to a resolution of the chlorophosphate **90** with only one of the two isomers reacting with the oxazolidinone, unfortunately due to the reactive nature of the chlorophosphate this hypothesis could not be proven. However due to the only subtle difference in these diastereoisomers, separation could not be completed via any method and work moved into preparing compounds that would enable separation with a greater stereochemical bias. It was hypothesised that by using methodology as utilised in

previous work completed in the Jones group with phosphine oxide based oxazolidinones, similar high diastereoselectivity could be achieved (Scheme 32).[34]

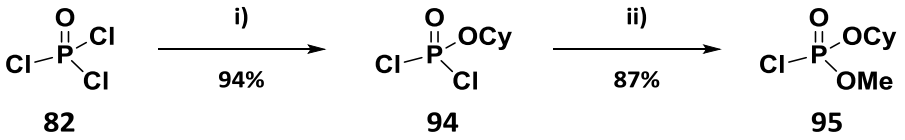


Reaction conditions: i) methyl(phenyl)phosphinic chloride, NEt_3, LiCl, THF, 0 °C to rt, 24 h.

Scheme 32. Synthesis of *N*-phosphinyl oxazolidinone **93**.[34]

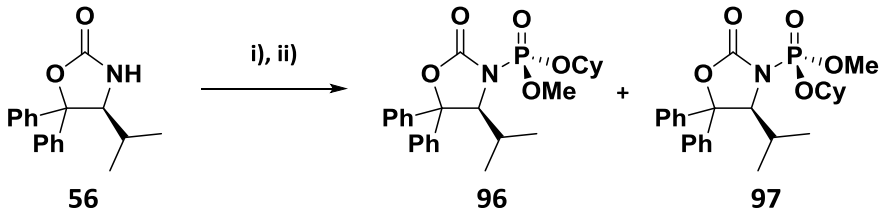
However, earlier work in Chapter 2 showed that if the groups on the phosphorus atom were too large then they could reduce the conversion of the reaction, thus groups were chosen to enhance selectivity but not shut off reactivity. The groups chosen were a small methyl group so that the trajectory of the nucleophile was not blocked, and a larger cyclohexyl group.

Synthesis of the methyl cyclohexyl chlorophosphate **95** proceeded in two steps (Scheme 33). Phosphorus oxychloride **82** was first converted into the dichloro compound **94** *via* the addition of cyclohexanol in the presence of distilled triethylamine. Methanol was then added using the same conditions to yield the reactive chlorophosphate **95** in good yields. This reactive reagent was then used in an optimisation study to explore the most selective way to make the target *N*-phosphoryl oxazolidinones **96**/**97** (Scheme 34).



Reaction conditions: i) CyOH, NEt_3, petroleum ether;
ii) MeOH, NEt_3, petroleum ether.

Scheme 33. Synthesis of cyclohexyl methyl chlorophosphate.



Reaction conditions: i) Base, Solvent, $Temp_1$, $Time_1$;
ii) cyclohexyl methyl chlorophosphate **95**, $Temp_2$, $Time_2$.

Scheme 34. General scheme for the synthesis of *N*-phosphoryl cyclohexyl methyl oxazolidinone auxiliaries.

3.2 Optimisation study

3.2.1 Base and concentration

The first aspect of the study looked at the different effects that the base had on the selectivity of the reaction. These initial reactions were conducted under the conditions which were used to synthesise the achiral phosphorylating agent **42** (Scheme 34, Table 9). The study continued by probing the differences that changing the equivalency and the solvent of the reaction would have and finally the effect of the concentration, by varying the amount of solvent.

Table 9. Effect of changing the base on the conversion and selectivity.

Entry	Base	Solvent	Concentration[b] (mmol dm^{-3})	Eq of chloro phosphate	Conversion (%)[c]	dr[c]
1	*n*-BuLi	THF	11.8	1	81	60:40
2	*t*-BuLi	THF	11.8	1	70	60:40
3	MeMgCl	THF	11.8	1	19	55:45
4	MeMgBr	THF	11.8	1	0	-
5	i-PrMgCl	THF	11.8	1	0	-
6	PhLi	THF	11.8	1	76	60:40
7	*n*-BuLi	THF	11.8	2	79	77:33
8[d]	*n*-BuLi	THF	11.8	2	77	73:27
9	*n*-BuLi	toluene	11.8	2	53	69:31
10	*n*-BuLi	Et_2O	11.8	2	67	72:28
11	*n*-BuLi	THF	78.8	2	58	70:30
12	*n*-BuLi	THF	50.7	2	62	70:30
13	*n*-BuLi	THF	23.6	2	74	71:29
14	*n*-BuLi	THF	5.9	2	94	69:31
15	*n*-BuLi	THF	3.0	2	89	68:32
16	*n*-BuLi	THF	1.8	2	88	66:34

[a]Reaction conditions: Base, solvent, -78 °C to rt for a $Time_1$ of 1 h then **95** at -78 °C then to rt for a $Time_2$ of 12 h. [b]Concentration of oxazolidinone. [c]Calculated from the ratio of integrals in the ^1H NMR spectrum. [d]$Time_1$ was 2 h in this case.

Use of isomeric *t*-BuLi base had essentially no effect on the selectivity of the reaction, and only a small effect on the conversion of the reaction (Entries 1 and 2). Moving to Grignard reagents demonstrated a clear reduction in conversion (Entries 3-5), with only the methylmagnesium chloride base (Entry 3) yielding any of the desired product. The last base (Entry 6) was found to give similar selectivity to the other lithium containing bases, but due to a slightly higher conversion, the optimal base taken forward in the study was *n*-BuLi.

Increasing the equivalencies of chlorophosphate in the reaction gave an enhancement in the selectivity of the reaction, without any effect on the conversion of the reaction and therefore all other reactions in this study were completed using 2 equivalents of the chlorophosphate (Entry 7). However it was found that increasing the duration of $Time_1$ did not give any enhancement in conversion of the reaction, suggesting that all of the oxazolidinone had been deprotonated in the first hour (Entry 8). Changing the solvent of the reaction to toluene or diethyl ether (Entries 9 and 10) gave a slightly reduced yield and similar selectivity in both cases.

The concentration used in the study thus far had been 11.8 mmol dm^{-3}, and increasing the concentration of the reaction gave a lower conversion and similar selectivities (Entries 11-13), but these results were affected by the decreasing solubility of the reagents. Decreasing the concentration of the reaction gave very high conversion, however this also caused a decrease in the selectivity (Entries 14-16). Thus, the most selective conditions for the reaction were found in Entry 7 and these chosen as the best to be taken forward.

3.2.2 Time and temperature

A study into the effect that the temperature had upon the reactivity and selectivity of the reaction was then undertaken.

Table 10. Time and temperature study to understand the conversion and selectivity over time.

		$Temp_2$ 0 °C		$Temp_2$ -30 °C		$Temp_2$ -78 °C	
Entry	**$Time_2$[a] (min)**	**Conversion (%)[b]**	**dr[b]**	**Conversion (%)[b]**	**dr[b]**	**Conversion (%)[b]**	**dr[b]**
1	15	93	64:36	75	69:31	8	69:31
2	30	94	64:36	83	68:32	10	76:24
3	45	92	64:36	85	68:32	14	76:24
4	60	93	64:36	85	68:32	18	76:24
5	75	93	64:36	85	69:31	21	76:24
6	90	94	64:36	87	68:32	24	77:23
7	105	94	64:36	85	68:32	27	76:24
8	120	90	64:36	93	69:31	29	76:24
9	135	95	64:36	87	68:32	32	76:24
10	150	93	67:33	89	67:33	35	76:24
11	165	94	64:36	89	68:32	39	76:24
12	180	95	64:36	88	68:32	42	75:25

[a]Reaction conditions: *n*-BuLi, THF, -78 °C to rt for a $Time_1$ of 1 h then **95** (2 eq) at $Temp_2$ for $Time_2$ stated. [b]Calculated from the ratio of integrals in the ^{1}H NMR spectrum.

When the temperature of $Temp_2$ was held at 0 °C, the reaction proceeded to completion almost immediately with a lower selectivity than observed in the previous optimisation study, implying that the reaction was occurring too quickly at this temperature. When $Temp_2$ was held at -30 °C, this led to a fast reaction but gave a slightly enhanced selectivity suggesting that slowing the reaction has enhanced the selectivity compared to higher temperatures. When the $Temp_2$ was held at -78 °C, the conversion was much lower and slowly increased with time with

a similar selectivity throughout. It is clear that reactions should be undertaken at -78 °C for the highest selectivity and that there is no benefit in stopping the reaction for a lower conversion for a higher selectivity compared to the most active conditions.

3.2.3 Additive effect

It has been shown in the past that reactions with the phosphorylated oxazolidinone can be enhanced depending on the counter-ion of the base used.[30] If the metal ion present is involved in the binding model and if chelate formation is important, then it is thought that pre-treatment with a Lewis acid additive could prove to be an important strategy. Therefore, treatment with a Lewis acid prior to the addition of the alkoxide nucleophile with range of Lewis acids were used in the most reactive reaction conditions (Table 11).

Table 11. Effect of Lewis acids on conversion and selectivity.

Entry	Additive	Conversion (%)[b]	dr[b]
1	$ZnCl_2$	0	-
2	$Cu(OTf)_2$	0	-
3	$SnCl_2$	0	-
4	$AgNO_3$	47	64:36
5	$MgCl_2$	59	68:32

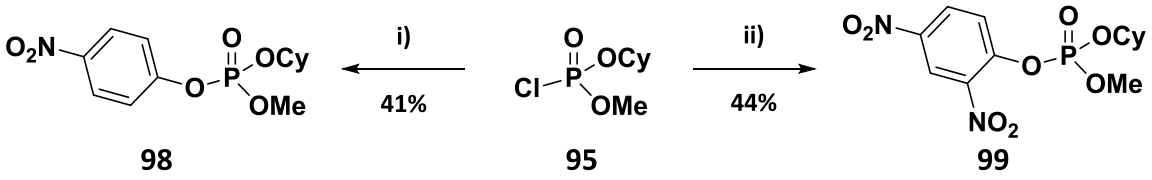
[a]Reaction conditions: *n*-BuLi, THF, Additive (1 eq), -78 °C to rt for a $Time_1$ of 1 h then **95** (2 eq) at -78 °C then to rt for a $Time_2$ of 12 h. [b]Calculated from the ratio of integrals in the ^1H NMR spectrum.

It was found that the addition of some additives to the reaction would shut down the reaction and only starting materials were recovered (Entires 1, 3 and 4). Silver nitrate or magnesium chloride did not give enhanced conversion and selectivity and give no benefit compared to the additive free reactions (Entries 2 and 5).

3.3 Leaving group ability

It was hypothesised that greater selectivities could be obtained by changing the electronic properties of the leaving group used. This change could be used to reduce the electrophilicity of the phosphate source and therefore slow the reaction, which could enable the stereodirecting group to have a greater affect on the selectivity at the slower reaction rate in a similar way to that witnessed in the temperature study. To reduce the reactivity of the chlorophosphate, nitrophenol based leaving groups were targeted as their leaving group ability could be tuned with the pK_a range of the mono and disubstituted being over 3.4 to 7.9.[35] [36]

Cyclohexyl methyl-4-nitrophenylphosphate **98** was synthesised *via* the same method used in the synthesis of the earlier chlorophosphates (Scheme 35). However the product **98** from this reaction was believed to be stable to column chromatography but was not obtained in a high yield due to the presence of unreacted p-nitrophenol starting material which eluted at a similar R_f to the product **98** on silica gel. A better leaving group that contained two nitro groups was also chosen for this study as its leaving group ability would be between that of the chloride and the single nitro-phenol leaving group.[36] Cyclohexyl methyl-2,4-dinitrophenylphosphate **99** was synthesised *via* the same method but also had the same purification problems as the single nitro-phenol compound **98**.



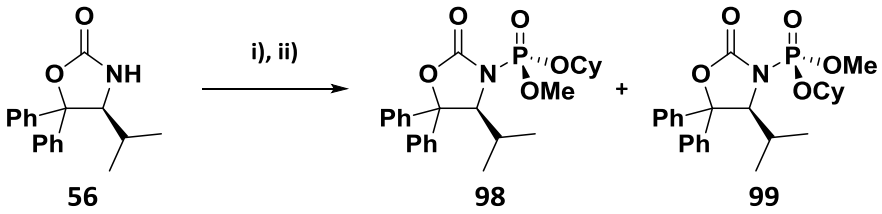
98 **95** **99**

Reaction conditions: i) *p*-nitrophenol, NEt_3, THF; ii) 2,4-dinitrophenol, NMI, NEt_3, THF.

Scheme 35. Synthesis of nitrophenol based reactive phosphates.

3.3.2 Phosphorylation

With the two nitrophenol phosphates **98** and **99** in hand, both were taken forward into the most selective conditions from the optimisation study, with the aim of exploring the effect of changing the electronics of the leaving group on the reaction conversion and selectivity (Scheme 36, Table 12).



Reaction conditions: i) *n*-BuLi, THF, -78 °C to rt, 1 h;
ii) cyclohexyl methyl nitrophosphate **96** or **97**, $Temp_2$.

Scheme 36. Synthesis of *N*-phosphoryl cyclohexyl methyl oxazolidinone auxiliaries using nitrophosphates.

Table 12. Effects of changing the leaving group on the conversion and selectivity.

Entry	$Temp_2$ (°C)	Leaving group on phosphate	Conversion (%)[b]	dr[b]
1	-78	chloride	79	78:22
2	-78	4-nitrophenol	0	-
3	0	4-nitrophenol	10	69:31
4	-78	2,4-dinitrophenol	42	84:16
5	0	2,4-dinitrophenol	63	72:28

[a]Reaction conditions: *n*-BuLi, THF, -78 °C to rt for a $Time_1$ of 1 h then **95**/**98**/**99** (2 eq) at $Temp_2$ for a $Time_2$ of 12 h. [b]Calculated from the ratio of integrals in the ^{1}H NMR spectrum.

It was found that the use of the 4-nitrophenol leaving group shut off the reactivity of the phosphate at low temperatures (Entry 2) and at 0 °C only gave a very small conversion (Entry 3), suggesting the change in leaving group ability had a marked effect on the reactivity when compared to the chloride leaving group (Entry 1). The 2,4-dinitrophenol variant gave a good conversion at 0 °C as well as only a slightly

lower selectivity than chlorophosphate reactions at -78 °C (Entries 4 and 5). When the conditions that were found in the optimisation study were applied to this 2,4-dinitrophenol variant, a lower conversion was obtained but a very high diastereomeric ratio of 84:16 (Entry 4). These results show that a change in the leaving group ability has a significant effect on the selectivity of the reaction. The slower reaction rate when the dinitrophenol leaving group is used could enable the stereodirecting group on the oxazolidinone to have a greater effect on the position of the larger cyclohexyl group on the phosphate, which has lead to an enhancement in selectivity.

Even higher selectivities might be obtained if a larger number of equivalencies of electrophile were used, by biasing the amount of the enantiomer that reacts at a faster rate with the oxazolidinone **56**, and so various equivalencies were investigated (Table 13).

Table 13. Effect of large equivalencies and leaving group on the conversion and selectivity.

Entry	$Temp_2$ (°C)	Eq of phosphate	Leaving group	Conversion (%)[b]	dr[b]
1	0	10	4-nitrophenol	20	67:33
2	-78	10	4-nitrophenol	14	57:43
3	0	10	2,4-dinitrophenol	72	77:23
4	-78	10	2,4-dinitrophenol	63	84:16
5	-78	10	chloride	84	87:13

[a]Reaction conditions: *n*-BuLi, THF, -78 °C to rt for a $Time_1$ of 1 h then phosphate **95**/**98**/**99** as stated at $Temp_2$ for a $Time_2$ of 12 h. [b]Calculated from the ratio of integrals in the ^{1}H NMR spectrum.

Use of higher equivalencies in the reaction gave higher conversion for the 4-nitrophenol derivative, however these were still at or below 20% for both low temperature reactions, and the selectivities were not enhanced greatly (Entries 1 and 2). The dinitro variant gave much higher conversions than observed in previous

studies, with the 0 °C reaction giving a good conversion and a good selectivity (Entry 3). However reaction at -78 °C gave the best results with a good conversion, and a selectivity of 84:16 (Entry 4). Although this result was very encouraging, problems with the work up and purification meant that it was very difficult to separate the products and the nitrophosphate, and therefore this was not the most viable route to the diastereoisomers. The chloride group was then subjected to the higher equivalencies which gave very high conversions and selectivities, higher than that of the nitro variants (Entry 5). Not only were these the best results for forming the diastereoisomers but the work up and purification were much easier than for the nitro versions.

The diastereomeric *P*-chiral oxazolidinones **96** and **97** were separated by repeated column chromatography and crystallisation. A crystal structure of the minor diastereoisomers **97** formed in the reactions was obtained and identified as the (*S*)-*P* stereochemistry (Figure 16).

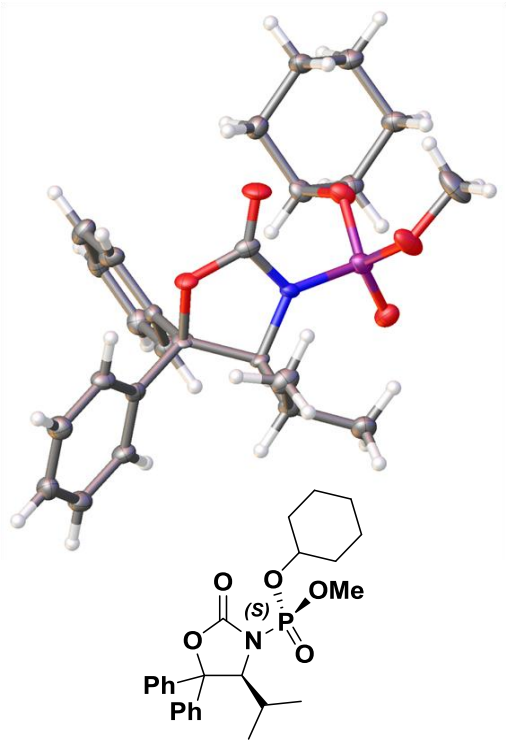


Figure 16. Crystal structure of the minor *P*-chiral oxazolidinone **97**.

A model to account for the preference of the (*R*)-*P* stereochemistry can be suggested, in which the co-ordination of the counter-ion is key to the selectivity of the reaction (Figure 17). In the synthesis of the minor diastereoisomer this co-ordination to the lithium aggregate which have been recorded in the literature places the larger cyclohexyl group in contact with the isopropyl stereodirecting group of the oxazolidinone and therefore the rate of reaction is reduced.[37] In the synthesis of the major (*R*)-*P* diastereoisomer, it is the smaller methyl group which is in contact with the stereodirecting group which leads to the selectivity of the reaction.

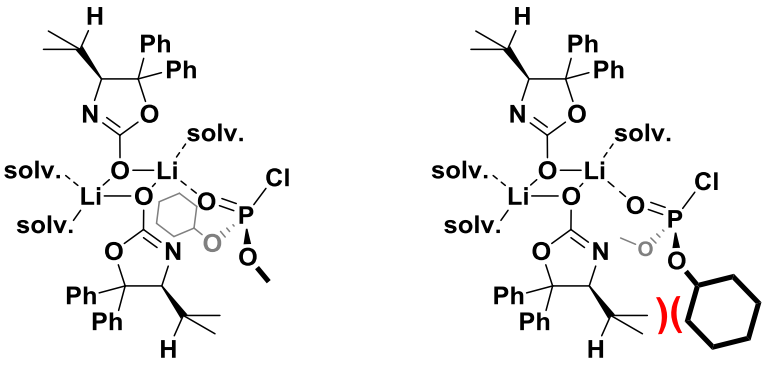
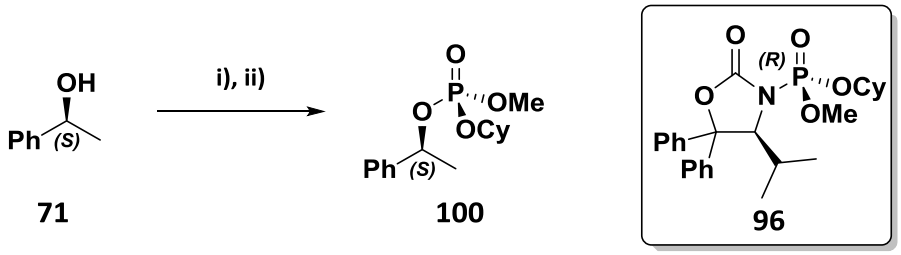


Figure 17. Model to account for the selectivity of diastereoisomers.

3.4 Substrate test

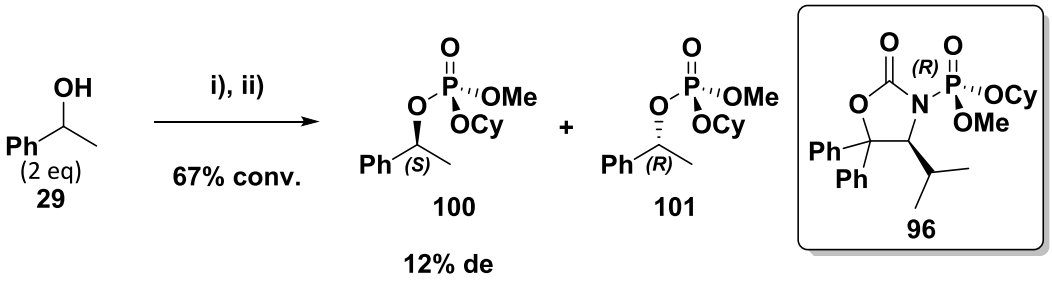
With the diastereoisomers in hand, these could then be taken forward in a test with the alcohol substrate 1-phenylethanol **29**. In order to determine which isomer was formed (by the ^{1}H NMR spectrum), (*S*)-1-phenylethanol **71** was reacted with the (*R*)-*P* cyclohexyl methyl oxazolidinone **96** to form one diastereoisomer in good yield (Scheme 37). This was assumed to be the (*S*)-(*R*)$_{P}$ product obtained by inversion of stereochemistry, further supporting the evidence of these reactions proceeding *via* an S_N2 reaction at phosphorus, which has been explored by previous work in the Jones group.[26]



Reaction conditions: i) MeMgCl, THF, 1 h; ii) oxazolidinone **96**.

Scheme 37. Synthesis of one diastereoisomer **100** for assignment of asymmetric reactions.

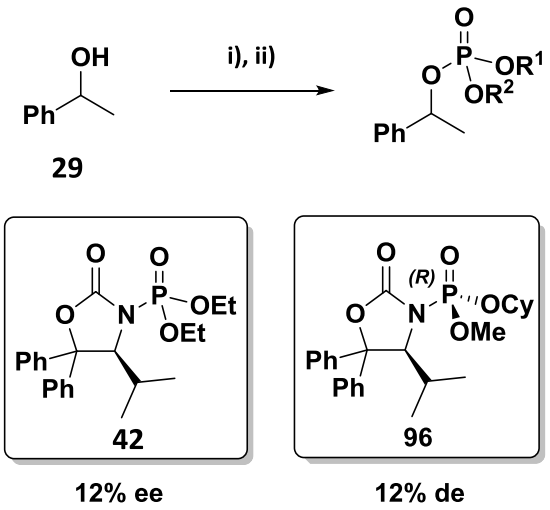
With the ability to analyse the products of the reaction with the single oxazolidinone diastereoisomer, the reaction of racemic 1-phenylethanol **29** with the (*R*)-*P* oxazolidinone **96** was completed under the standard reaction conditions (Scheme 38).[30]



Reaction conditions: i) MeMgCl, THF, 1 h; ii) oxazolidinone **96**.

Scheme 38. Asymmetric synthesis of phosphates **100**/**101** using the (*R*)-*P* oxazolidinone **96**.

This reaction proceeded with good conversion and the selectivity was determined from the crude ^{1}H NMR spectrum and found to be 12% de for the (S)-C product **100**. This selectivity has not been enhanced compared to that of the diethyl oxazolidinones in Chapter 2 for which model has been proposed which describes the selectivity of the reaction (Figure 10).[30] The change to (*R*)-*P* oxazolidinone **96** does not seem to effect the selectivity of the reaction compared to that of the diethyl oxazolidinone **42** reaction with 1-phenylethanol **29**, having a 12% de and 12% ee respectively (Scheme 39).



Reaction conditions: i) MeMgCl, THF, 1 h; ii) oxazolidinone **42**/**96**.

Scheme 39. Comparable selectivities of phosphate chiral auxiliaries.

It appears that the group furthest from the stereodirecting group is not affecting the selectivity of the reaction and even the larger cyclohexyl group is not large enough to influence the trajectory of the nucleophile. However, the change from the ethyl group to the smaller methyl group has not had a marked effect. The fact that these selectivities are very similar suggests that both are reacting *via* the same model and that the effect of the stereodirecting group upon the group adjacent to it on the phosphate is what causes the selectivity of this reaction (Figure 18).

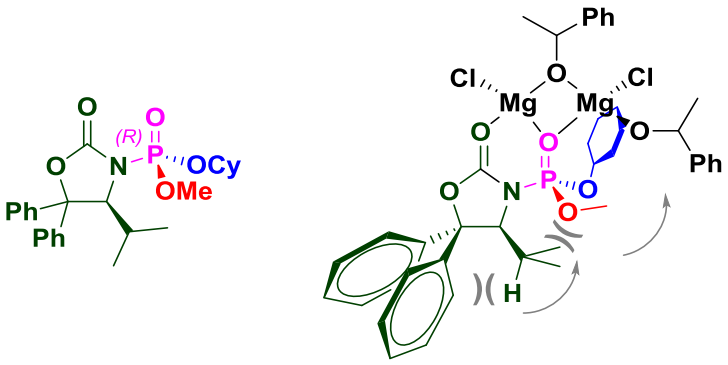
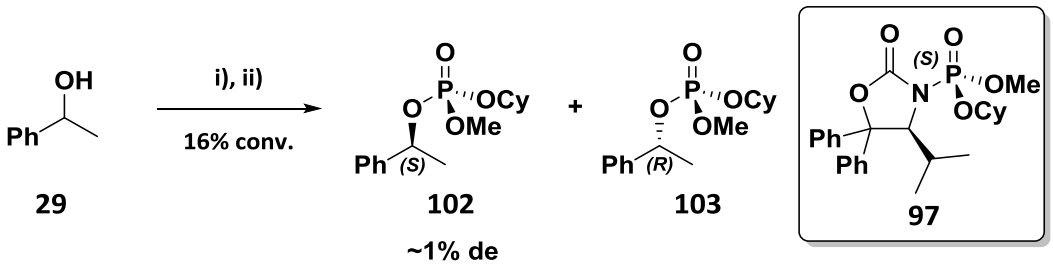


Figure 18. Visual representation of the positions of the groups on the (*R*)-*P* oxazolidinone **96** upon attack of 1-phenylethanol **29** nucleophile.

The (*S*)-*P* oxazolidinone **97** which has the larger cyclohexyl group closer to the stereodirecting group and whose position is believed to be responsible for the selectivity of the reaction was also reacted under the standard conditions (Scheme 40).



Reaction conditions: i) MeMgCl, THF, 1 h; ii) oxazolidinone **97**.

Scheme 40. Asymmetric synthesis of phosphates **102**/**101** using the (*S*)-*P* oxazolidinone **97**.

However it was found that when the (*S*)-*P* oxazolidinone **97** was used, the reactivity dramatically dropped off and a very poor conversion was obtained that made analysis of the reaction selectivity from the ^{1}H NMR spectrum very difficult. This result shows that the cyclohexyl group is indeed in a position that affects the trajectory of the nucleophile, but that it is too large and is blocking the attack and reducing the reactivity dramatically (Figure 19).

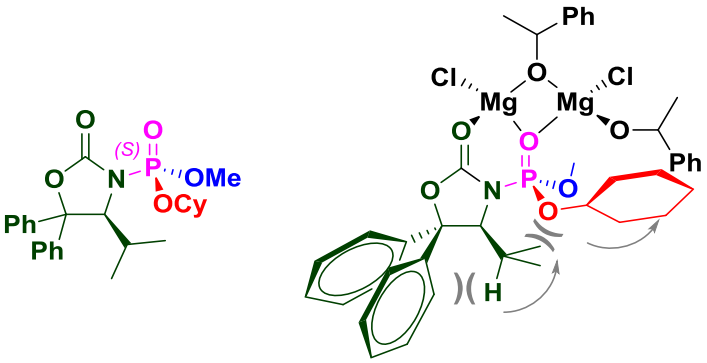
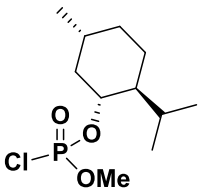


Figure 19. Visual representation of the positions of the groups on the (*S*)-*P* oxazolidinone **97** upon attack of the 1-phenylethanol **29** nucleophile.

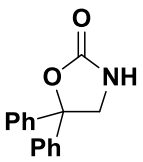
3.5 P-Chiral stereodirecting group

It appears that when the *P*-chiral cyclohexyl methyl diastereoisomer with a large group close to the isopropyl stereodirecting group was used, the reactivity was shut off. Additionally if the group is on the other side of the molecule, it is too far away from the reaction pathway to affect the selectivity of the reaction. Thus, a new course of action was undertaken to enhance the selectivity without reducing the reactivity. It was hypothesised that instead of using the stereodirecting group on the oxazolidinone, this could be placed on the phosphate to enhance the selectivity without reducing reactivity. Menthol was chosen as the stereodirecting group due its commercial availability and its tendency to form crystals that could then be separated. The other group was chosen to be a small methyl group, so that the reactivity was not reduced by it blocking the trajectory of the nucleophile. Thus the targets for this study were chosen to be the (*R*)-*P* and (*S*)-*P* menthyl methyl oxazolidinones **104** and **105**.

The required menthyl methyl chlorophosphate **106** could be prepared *via* the method used for other *P*-chiral chlorophosphates (Figure 20). This required an oxazolidinone that did not contain any stereodirecting group, but retained the diphenyl groups that might enhance the solubility of the molecule yet not influence the phosphorylation reaction (Figure 20).



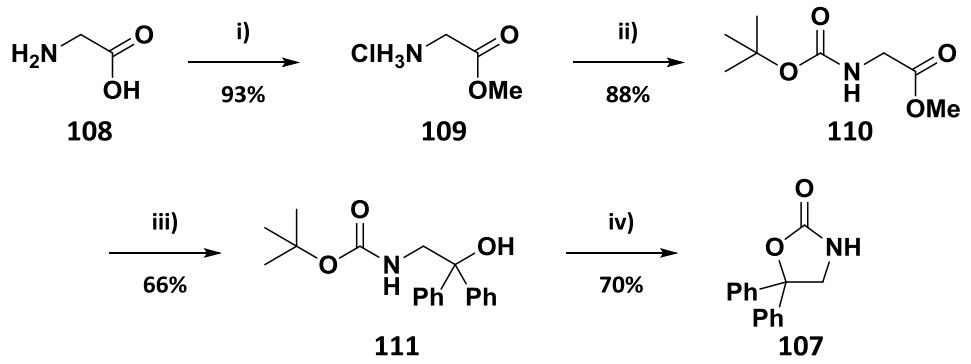
106



107

Figure 20. Auxiliary and chlorophosphate targets **106** and **107**.

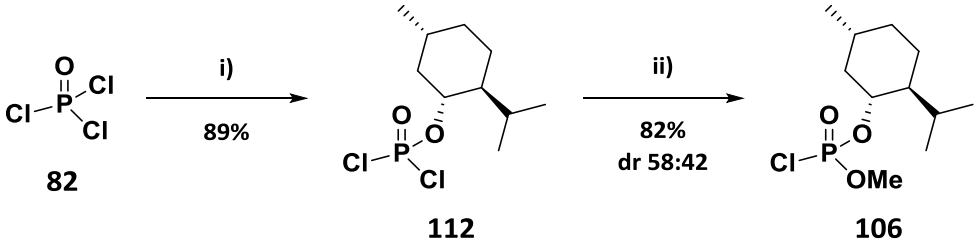
Synthesis of the oxazolidinone followed literature precedence from glycine in good yield over 4 steps (Scheme 41).[29][38]



Reaction conditions: i) $SOCl_2$, MeOH, 0 °C to rt; ii) Boc_2O, $NaHCO_3$, EtOH, 0 °C to rt; iii) PhMgBr, THF, 0 °C to rt; iv) *t*-BuOK, THF, 0 °C to rt.

Scheme 41. Synthesis of oxazolidinone **107**.

Next, the chlorophosphate **106** was synthesised using the method that had been optimised for the synthesis of cyclohexyl methyl chlorophosphate **95** (Scheme 42).



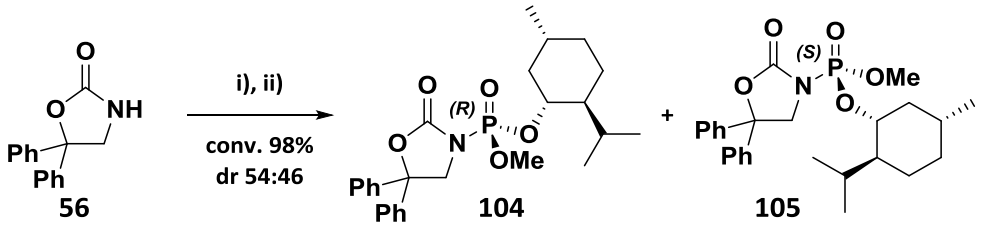
Reaction conditions: i) menthol, NEt_3, petroleum ether; ii) MeOH, NEt_3, petroleum ether.

Scheme 42. Synthesis of menthyl methyl chlorophosphate **106**.

Synthesis of the menthyl methyl chlorophosphate **106** was completed in good yield without any need for further purification, giving a diastereomeric ratio of 58:42. This new reactive intermediate was then taken forward into the synthesis of the phosphorylating reagent.

Phosphorylation of the oxazolidinone **56** with the chlorophosphate **106**, under the conditions optimised in previous work gave a very high conversion of 98% and by analysis of the crude ^{1}H NMR spectrum, the ratio of the two diastereoisomers was found to be 54:46 (Scheme 43). This is a higher conversion a when the stereodirecting group was on the oxazolidinone auxiliary, however the

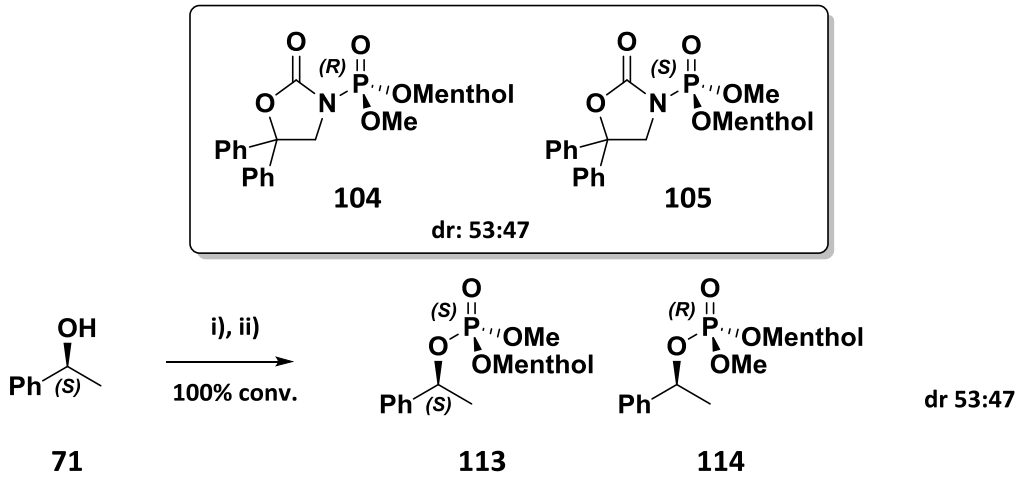
diastereoselectivity of the reaction is lower which suggests that the stereodirecting group on the menthol is not exerting as much of a stereochemical bias. Purification of these diastereoisomers was then attempted, however no separation could be obtained from recrystallisation, silica gel, alumina or any method using HPLC.



Reaction conditions: i) *n*-BuLi, THF, -78 °C to rt;
ii) menthyl methyl chlorophosphate **106** (2 eq), -78 °C to rt.

Scheme 43. Synthesis of the *N*-phosphoryl menthyl methyl oxazolidinone auxiliary **104**/**105**.

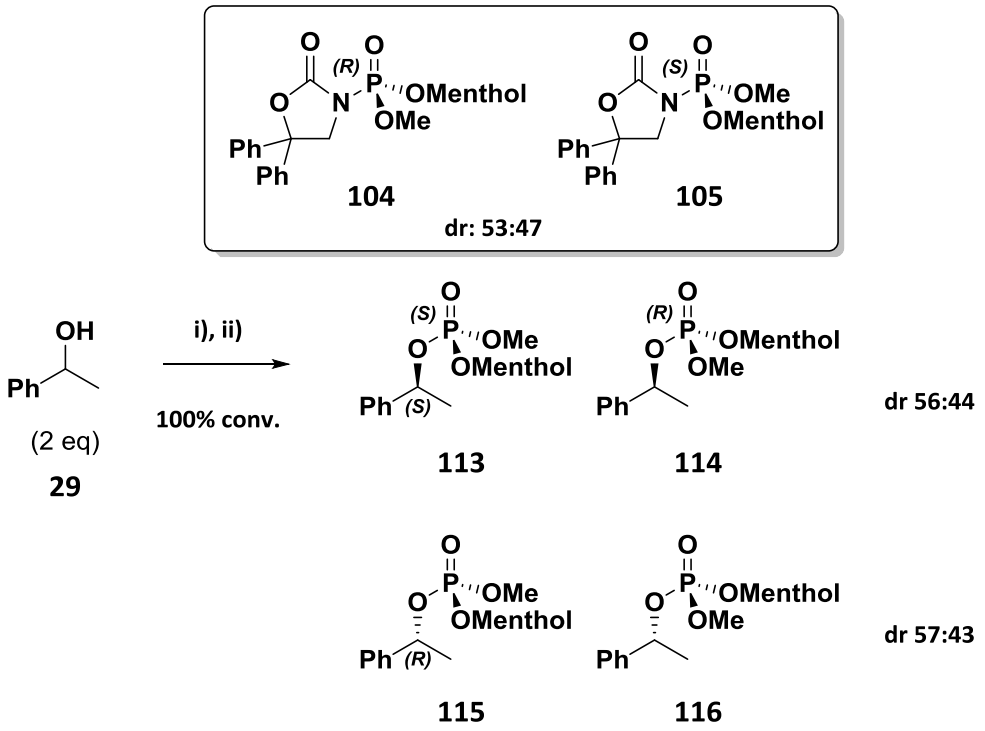
Although single diastereoisomers of the desired menthyl methyl oxazolidinone **104**/**105** could not be obtained, a mixture was tested with the 1-phenylethanol **29** substrate. A mixture of the two diastereoisomers with a dr of 53:47 was used, and this sample was first reacted with (*S*)-1-phenylethanol **71** so that the ^{1}H NMR data could be used to analyse the racemic reaction (Scheme 44).



Reaction conditions: i) MeMgCl, THF, 1 h; ii) oxazolidinones **104** and **105** (1 eq.).

Scheme 44. (*S*)-1-Phenylethanol substrate test.

This reaction proceeded to completion and retained the diastereomeric ratio of the starting material, meaning that the reaction proceeded cleanly *via* the $S_N2(P)$ pathway. This data could then be used to analyse the mixtures of the racemic reaction; although there was no way to determine the stereochemical identity of the diastereoisomers formed, through previous work into P-chiral phosphorylating agents there is a clear difference in the peaks of the methoxy groups in the ^{1}H NMR and this trend is seen in these phosphates and therefore an assumption can be made of the identity of the phosphates enabling some understanding of the reaction.



Reaction conditions: i) MeMgCl, THF, 1 h; ii) oxazolidinones **104** and **105** (1 eq.).

Scheme 45. Racemic 1-phenylethanol **29** test reaction with mixture of diastereoisomers of oxazolidinone.

Analysis of the crude ^{1}H NMR data of the racemic reaction, by measuring the integration of cleanly separated methoxy peaks, and comparison of this with the (*S*)-1-phenylethanol **71** reaction, enabled logical assignment of each

diastereoisomer (Scheme 45). The (S_C)-phosphates had a diastereomeric ratio of 56:44 which is an enhancement on the initial ratio of the oxazolidinones, showing that there is selectivity for one enantiomer of 1-phenylethanol over the other. The diastereomeric ratio in the (*R*)-*C* phosphate was found to be 57:43 which is the same selectivity change seen in the (*S*)-*C* phosphate. This value may be significant as the same enhancement in selectivity is seen in both enantiomers of 1-phenylethanol but for the opposite enantiomer at phosphorus, implying that the selectivity comes from the *P*-chiral environment of the reactive intermediate and each oxazolidinone diastereoisomer is selective for one enantiomer of 1-phenylethanol **29**. The selectivity therefore does not appear to be enforced by the stereodirecting group of the menthol group, but the *P*-chiral environment of the intermediate. This can be further quantified if the enantiomeric excess is calculated for each enantiomer of phosphate as if each were separate reactions. This would give a 12% ee and a 13% ee for the two enantiomers in this reaction, which is almost identical to the reaction of 1-phenylethanol **29** with the original diethyl oxazolidinone **56** which gave a 15% ee through the proposed transient chiral environment at phosphorus. This suggests that placing the stereodirecting group onto the substituents of the phosphate is not a viable option to enhance the selectivity of the reaction.

3.6 Conclusion

A dimeric magnesium model has been proposed that accounts for the low selectivity of the phosphorylating reactions with oxazolidinone auxiliaries, and from this proposal a number of changes have been attempted to enhance the selectivity of these reactions. These initially included changing the phosphoryl moiety with the aim that a larger group could enhance the selectivity without blocking the trajectory if a linker was incorporated. However it was found that the reactivity was reduced by these larger groups and this led to the proposal of *P*-chiral auxiliaries, as these would enable the attack of the nucleophile to be influenced without adding too much bulk, due to changing one of the groups on the phosphorus to a small methoxy group.

A new route to different *P*-chiral auxiliaries was designed and the synthesis was optimised to discover the most selective conditions to form the diastereomeric oxazolidinones **96** and **97**. After separation of the two separate auxiliaries, they were tested on the 1-phenylethanol substrate **29** to see if the model of the transient chiral environment held true and if selectivities could indeed be enhanced *via* this method. This study found that when the larger group was placed on the opposite side to the stereodirecting group on the oxazolidinone the selectivity was not enhanced. This suggests that it does not play a key role in determining selectivity and is positioned away from the trajectory of the nucleophile. However the other diastereoisomer with the large cyclohexyl group next to the stereodirecting group greatly reduced the reactivity, even with the much smaller methyl group on the other side of the phosphate. This shows that the selectivity of this reaction cannot be enhanced *via* these methods as the effect of the stereodirecting group can only lead to a small selectivity with small groups but when any larger groups are added the reactivity is shut off.

It was then hypothesised that if a stereodirecting group was added into the phosphate group instead of the oxazolidinone auxiliary then it could affect the selectivity of the reaction without reducing reactivity. A new auxiliary was

synthesised and although there were problems in the purification of this compound, it was tested with the standard 1-phenylethanol substrate **29**. The results from this showed that the opposite phosphorus diastereoisomers gave a selectivity preference for the different enantiomers of 1-phenylethanol. This selectivity is also similar to previously tested diethyl and cyclohexyl methyl oxazolidinones, which suggests that the stereoselectivity is due to the *P*-chiral environment in each case.

The selectivity of these reactions are still low even with the augmentations that have been completed from the proposed dimeric magnesium model. These auxiliaries seem to suffer from a 'catch 22' that larger groups are needed to influence the selectivity of the reaction but once these groups are incorporated they block the trajectory of the nucleophile and the reactivity is shut off.

This is in complete contrast with work done with oxazolidinones with acyl groups which have been shown to give high yields and selectivities as they react *via* the Bürgi-Dunitz angle and therefore affected by the stereodirecting group unlike the phosphorylation variants which are hampered by the S_N2 trajectory. A new catalyst that may affect this S_N2 trajectory is required that does not reduce the reactivity.

Alternatively an oxazolidinone that does not give its selectivity from a transient chiral environment but from an enforced chiral environment may be one way to get around the problems that these auxiliaries have encountered (Figure 21).

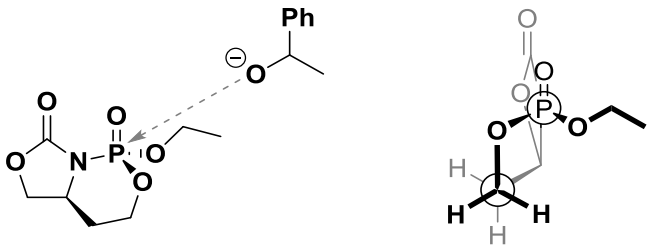


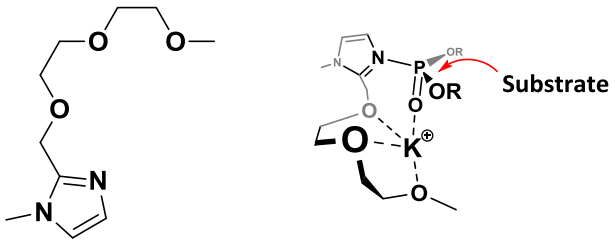
Figure 21. Oxazolidinone with enforced chiral environment.

4. Trifunctional catalysis

4.1 Introduction

With the issues involved in the oxazolidinone phosphorylating agents not being able to produce high selectivity without shutting off the reactivity, a new approach to selective phosphorylation was needed, the inspiration for this coming from previous work within the Jones group. This work focused on the concept of bifunctional catalysis using cation templated nucleophilic catalysis. Using a bifunctional catalyst is a powerful option for designing efficient asymmetric catalysts which provides effective simultaneous activation of reaction components. Compared with conventional catalysts, bifunctional catalysts generally exhibit enhanced catalytic activity and higher levels of stereodifferentiation under mild conditions due to the cooperative effect involved, which makes them attractive targets for next-generation catalysts for prospective applications.[39][40] Jacobsen *et al.* have produced an enantioselective catalyst containing hydrogen-bond donors that are enabled by the addition of an anion, which activates an 'on-off' catalytic cycle between an inactive aggregate resting state that is dissociated to form the active catalyst species.[41]

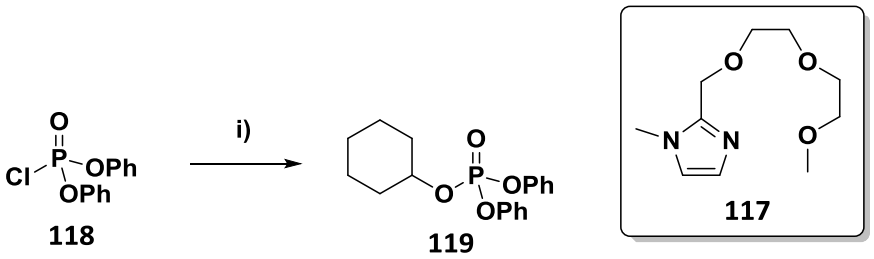
With influence from the literature, this work investigated an *N*-methyl imidazole derived bifunctional catalyst **117** for efficient asymmetric phosphoryl transfer, possessing the potential to act as a nucleophilic catalyst and cation coordination template (Figure 22).



117

Figure 22. Polyether bifunctional catalyst **117** from previous work with possible binding model.

In this previous work, the optimal solvent was CH_2Cl_2 using KPF_6 as potassium cation source, at a catalyst loading of 10 mol%. (Scheme 46).

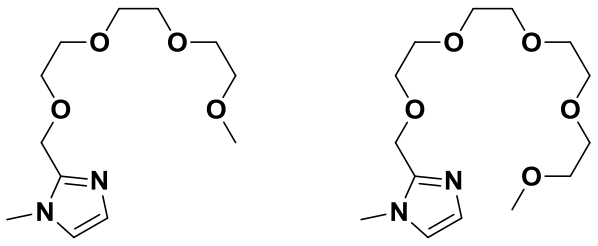


Reaction conditions: i) Catalyst **117** (10 mol%), cyclohexanol, additive (10 mol%), NEt_3 (1 eq), CH_2Cl_2, 30 °C, 24 h.

Scheme 46. Catalytic phosphorylation of cyclohexanol to study the cooperative effect.

This catalyst **117** showed a decreased rate compared to that of the lone NMI reaction which was thought to be due to the steric bulk of the polyether side chain. However there was a clear cooperative effect occurring when comparing the rate of reaction of the catalyst with and without the potassium additive, showing that these catalysts function as bifunctional phosphorylation agents. These conditions were taken forward in an alcohol substrate screen to demonstrate that these catalysts were not substrate specific, using both diethyl and diphenyl chlorophosphates. The results showed that these types of catalysts could phosphorylate a range of primary, secondary and phenolic alcohols in high yields.

This led to the synthesis of longer chain catalysts variants with four **120** and five **121** oxygen atoms in the polyether (Figure 23). Testing was completed under the same conditions to see how the chelation of the potassium ion and its relative position to the imidazole group would affect the conversion of the reaction.

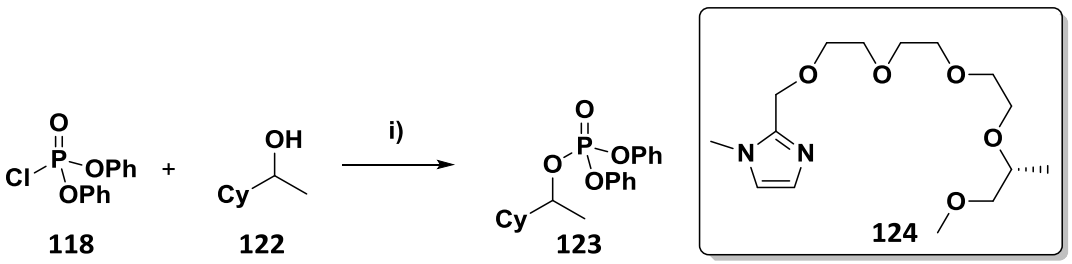


120 **121**

Figure 23. Longer chain polyether bifunctional catalysts.

This showed that the rate of the reaction in the presence of the longer chain catalyst **120** was faster than that of the catalyst **117** with a shorter polyether chain, but when the chain was further lengthened, the catalyst **121** gave a slight decrease in the rate of reaction which was deemed to be due to steric effects.

These longer chain catalysts were tested with a number of metal additives, the optimum ones being $Mg(OTf)_2$ and KPF_6 with the catalyst **120** containing four oxygen atoms in the polyether chain. With this knowledge, an attempt was made to prepare an asymmetric phosphorylation catalyst **124** with a stereodirecting group on the opposite side of the polyether chain to that of the *N*-methylimidazole group, with the hope that when the polyether formed the coordinated reactive intermediate, it would affect the stereoselectivity of the reaction (Scheme 47).



118 **122** **123** **124**

Reaction conditions: i) Catalyst **124** (10 mol%), $Mg(OTf)_2$ (10 mol%), NEt_3 (1 eq), CH_2Cl_2, -10 °C, 15 min.

Scheme 47. Attempted asymmetric phosphorylation.

The reaction gave no selectivity with or without the magnesium additive, indicating that the stereodirecting group had no effect upon the incoming alcohol nucleophile. This is understandable as the methyl group is perhaps too small to affect the stereoselectivity (Figure 24).

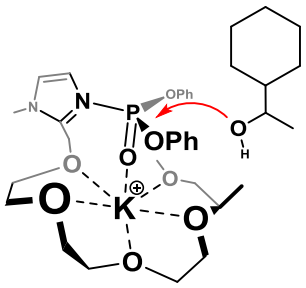
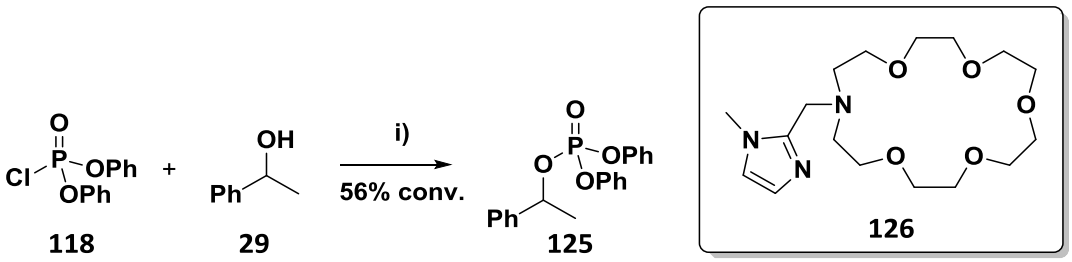


Figure 24. Possible binding model for asymmetric catalyst **124**.

The final catalyst **126** investigated was an aza-crown that would negate the need for the molecule to preorganise into the coordinating position around the metal additive required to catalyse the reaction (Scheme 48).



Reaction conditions: i) Catalyst **126** (10 mol%), $Mg(OTf)_2$ (10 mol%), NEt_3 (1 eq), CH_2Cl_2, -10 °C, 15 min.

Scheme 48. Phosphorylation of 1-phenylethanol **29** using an aza-crown catalyst **126**.

Using the aza-crown as the catalyst without any additive gave a good conversion, but once the metal additive was introduced the conversion was drastically reduced. This is believed to be due to the aza-crowns forming a more thermodymamically stable intermediate and hence the catalyst was slower to react with the nucleophile.

4.2 Aims

There is clear potential for adapting and investigating these catalysts. One possibility is the use of trifunctional catalysts that function by first co-ordinating to a phosphate source, locating it in a position where a nucleophilic catalyst can then catalyse the reaction. A new trifunctional mode of action would add a base that would deprotonate the alcohol substrate for phosphorylation, which would enable the possibility of future functionalisation of the base close to the trajectory of the nucleophile (Figure 25).

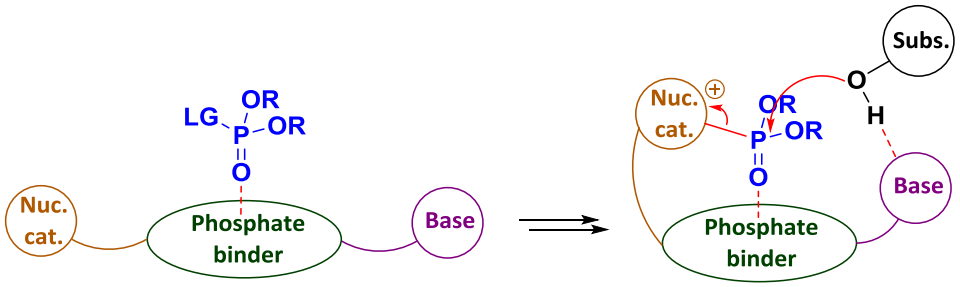


Figure 25. Proposed function of trifunctional catalysis.

4.3 Catalyst synthesis

In the first instance, a trifunctional catalyst was targeted to support the hypothesis. A number of trifunctional catalysts together with appropriate 'control' catalysts, were proposed with different heteroatoms within the chain (Figure 26). The chain length was chosen from the bifunctional catalysts that gave the highest conversion. The heteroatoms in the linker to the catalytic imidazoles were chosen to be either oxygen atoms or nitrogen atoms as this would allow further investigation of the geometry of the trifunctional catalyst and determine whether the heteroatoms in the linker have an effect on reactivity and selectivity.

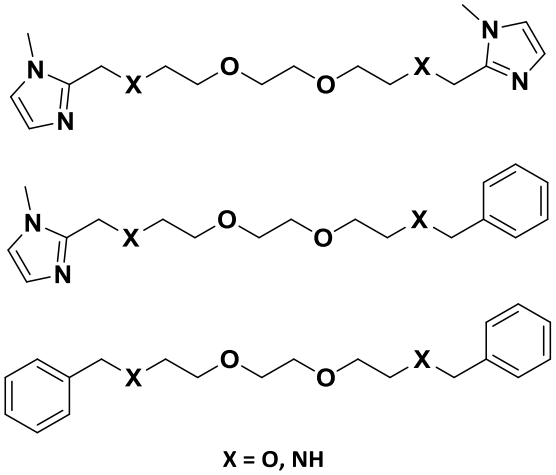
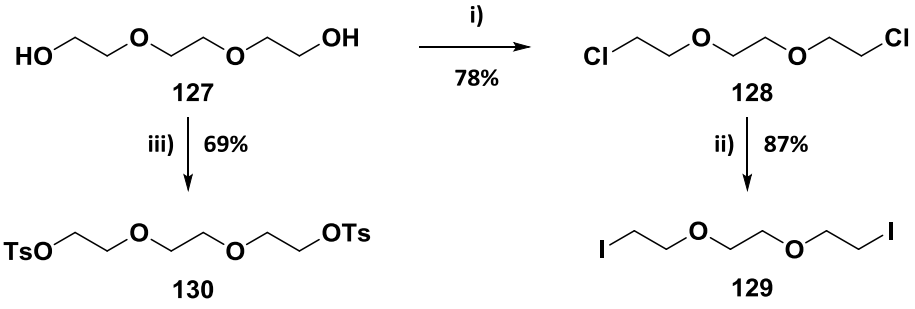


Figure 26. Catalysts and controls to be synthesised to probe trifunctional catalysis.

A final catalyst was designed to discover if a trifunctional podand catalyst would be able to bypass the thermodynamically stable intermediate formed when the bifunctional podand catalyst was used in previous work. The aim of this was to test if not having to reorganise into a coordinating position around the metal additive would enhance selectivity.

Synthesis of these polyethers required a polyether chain with two leaving groups at either end, so that different groups could be added to create the target catalysts and control compounds. A number of different leaving groups were placed on the termini of these chains, these being chloride, tosylate and iodide (Scheme 49).

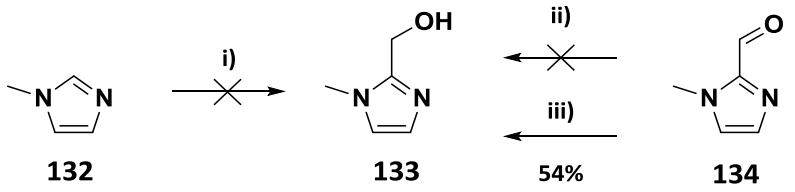


Reaction conditions: i) $SOCl_2$, pyridine, hexane, reflux, 12 h; ii) NaI, acetone, reflux, 72 h; iii) TsCl, DMAP (10 mol%), NEt_3, CH_2Cl_2, rt, 72 h.

Scheme 49. Chlorination, tosylation and iodination of the polyether backbone.

The dichlorination of the alcohol groups proceeded cleanly and the product **128** was obtained in good yield, without the need for further purification after work-up. This dichloro compound **128** was taken forward into the iodination step so that a better leaving group could be utilised in these reactions. This reaction gave the di-iodo compound **129** in good yield and was ready to be taken forward into subsequent reactions without further purification. As a very reactive intermediate this compound **129** had to be used immediately after synthesis. Finally the ditosylate **130** was obtained in a good yield as a crystalline solid that could be stored without sign of decomposition until it was required in the subsequent reactions.

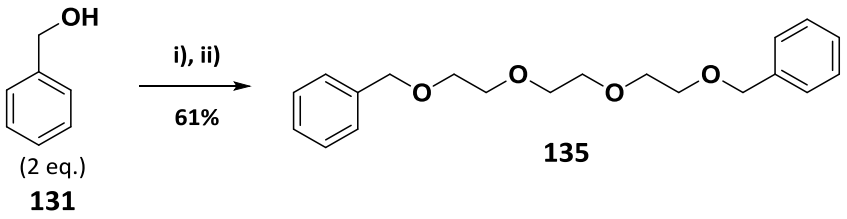
The end groups required were either commercially available benzyl alcohol **131**, or the 1-methyl-1*H*-imidazole-2-methanol **133**. An attempt to prepare the latter by reaction with paraformaldehyde failed to yield any of the desired alcohol, which could have been due to ineffective cracking of paraformaldehyde (Scheme 50). Therefore a different route was investigated starting from the commercially available aldehyde **134**, followed by reduction. The initial attempts at reducing the aldehyde **134** with sodium borohydride were not successful as the product was lost in the work up procedure. It was found that using lithium aluminium hydride gave the desired product **133** in a reasonable yield after some changes in the work up procedure that used minimal amounts of water.



Reaction conditions: i) paraformaldehyde, reflux, 12 h;
ii) $NaBH_4$, MeOH, rt, 6 h; iii) $LiAlH_4$, THF, rt, 2 h.

Scheme 50. Attempted synthesis of 1-methyl-1H-imidazole-2-methanol **133** from *N*-methylimidazole **132** and 1-methylimidazole-2-carboaldehyde **134**.

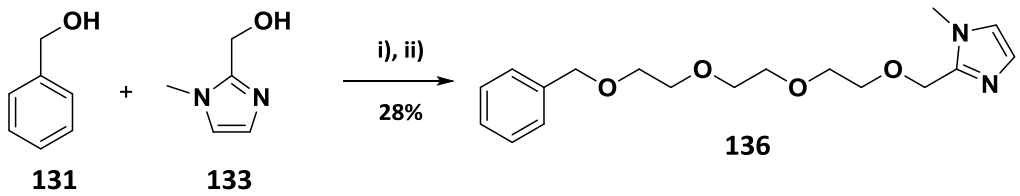
With the imidazole alcohol **133** in hand, the polyether catalysts were then constructed. Reaction of the two equivalents of benzyl alcohol gave the dibenzyl polyether (Scheme 51).



Reaction conditions: i) NaH, THF, 0 °C, 10 min;
ii) 1,2-*bis*(2-Tosylethoxy)-ethane **130**, THF, 0 °C to rt, 12 h.

Scheme 51. Synthesis of the dibenzyl control compound **135**.

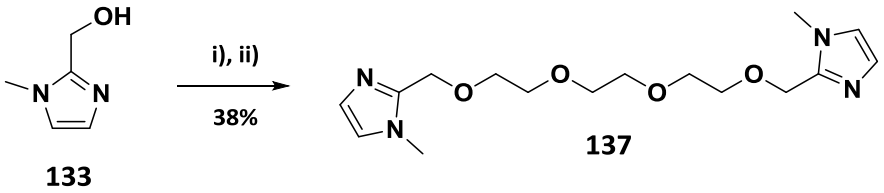
This gave the dibenzyl polyether **135** in good yield after continuous extraction and then purification on silica gel, and the same technique was used with the differently substituted polyether by using an equivalent of both the imidazole benzyl alcohol **131** and alcohol **133** (Scheme 52). This gave the differently substituted polyether **136** after continuous extraction and a difficult purification on silica gel from the similar amounts of disubstituted products that were formed under these reaction conditions.



Reaction conditions: i) NaH, THF, 0 °C, 10 min;
ii) 1,2-*bis*(2-Tosylethoxy)-ethane **130,** THF, 0 °C to rt, 12 h.

Scheme 52. Synthesis of the differently substituted polyether **136**.

The final compound required was the catalyst containing two imidazole groups (Scheme 53). The diimidazole polyether catalyst **137** was obtained after continuous extraction in a poor yield due to the presence of the two imidazole groups which made purification on silica gel more difficult.

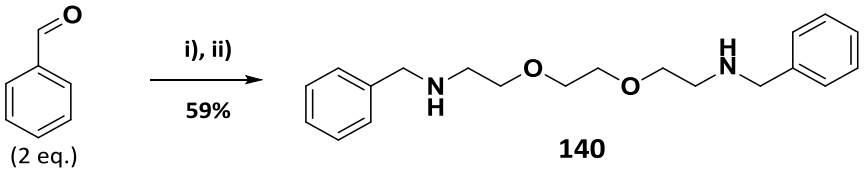


133 **137**

Reaction conditions: i) NaH, THF, 0 °C, 10 min;
ii) 1,2-*bis*(2-Tosylethoxy)-ethane **130,** THF, 0 °C to rt, 12 h.

Scheme 53. Synthesis of the catalyst containing two imidazole units **137**.

The nitrogen containing catalysts required a different reductive amination method, with starting materials being commercially available. The dibenzyl control was synthesised using two equivalents of distilled benzaldehyde **138** with the diamine **139** (Scheme 54).

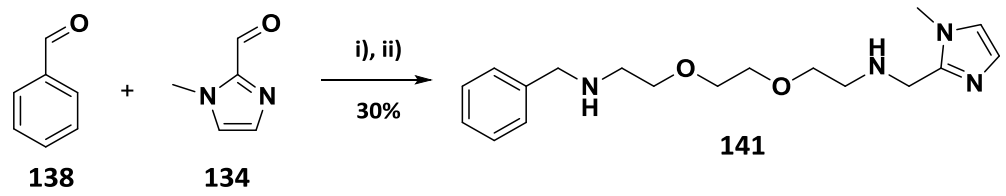


(2 eq.) **138** **140**

Reaction conditions: i) 1,2-*bis*(2-aminoethoxy)ethane **139**, MeOH, rt, 12 h;
ii) $NaBH_4$, 0 °C to rt, 2 h.

Scheme 54. Synthesis of the dibenzylamino catalyst **140**.

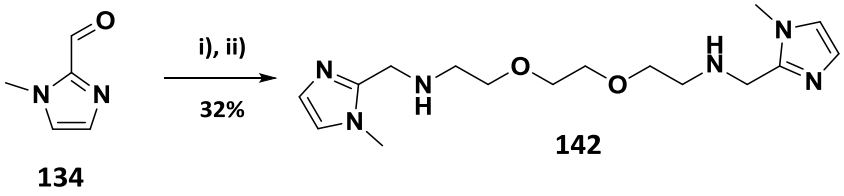
This gave the dibenzylamino catalyst **140** in good yield after continuous extraction and purification on silica gel. The next catalyst was the differentially substituted variant and this was synthesised *via* the same method used earlier with one equivalent of both benzaldehyde **138** and imidazole aldehyde **134** (Scheme 55). This gave the differently substituted catalyst **141** in reasonable yield after the problems that were with the polyether variant and further purification from di-substituted products that were formed.



Reaction conditions: i) 1,2-*bis*(2-aminoethoxy)ethane **139**, MeOH, rt, 12 h; ii) $NaBH_4$, 0 °C to rt, 2 h.

Scheme 55. Synthesis of the differently substituted catalyst **141**.

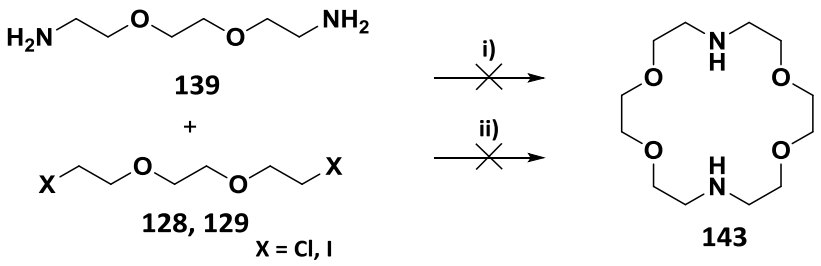
The final catalyst **142** was synthesised in a low yield by a similar method due to reoccurring problems and the purification process on silica gel (Scheme 56). All three of the nitrogen containing catalysts **140**, **141** and **142** were taken forward to the catalyst screening process.



Reaction conditions: i) 1,2-*bis*(2-aminoethoxy)ethane **139**, MeOH, rt, 12 h;
ii) $NaBH_4$, 0 °C to rt, 2 h.

Scheme 56. Synthesis of the diimidazole catalyst **142**.

The final catalyst to complete the study was the podand **143**. Initially the attempts to synthesise the podand catalyst **143** consisted of creating the framework and then functionalising so that different groups on the nitrogen could be installed. This would be achieved by ring closing of a diamine and a polyether with two leaving groups, using electrophiles synthesised earlier. The first of these was the electrophile with two chloro groups **128** (Scheme 57).

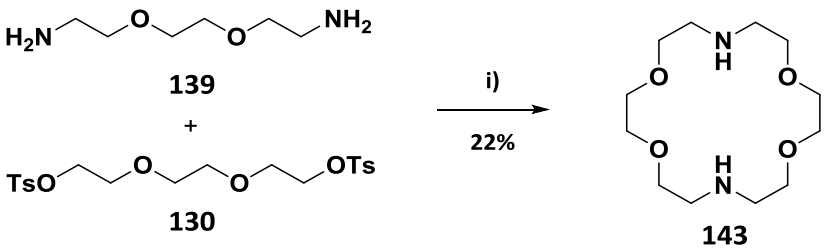


Reaction conditions: i) 1,2-*bis*(2-Chloroethoxy)-ethane, NaI, Na_2CO_3, MeCN, rt, 12 h;
ii) 1,2-*bis*(2-Iodoethoxy)-ethane, NaI, Na_2CO_3, MeCN, rt, 12 h.

Scheme 57. Attempted synthesis of the unfunctionalised podand **143** *via* the di-chloride electrophile **128** and di-iodo electrophile **129**.

However this method gave only traces of the product **143** compared to the unreacted starting materials based on analysis of the ^{1}H NMR spectrum, therefore the more reactive di-iodo polyether **129** was utilised. This method gave a small amount of the desired podand **143** with a smaller amount of unreacted starting materials. The product was found in the aqueous layer after reducing to dryness under reduced pressure and analysis of the complex ^{1}H NMR spectrum. However, no method could be found to purify this.

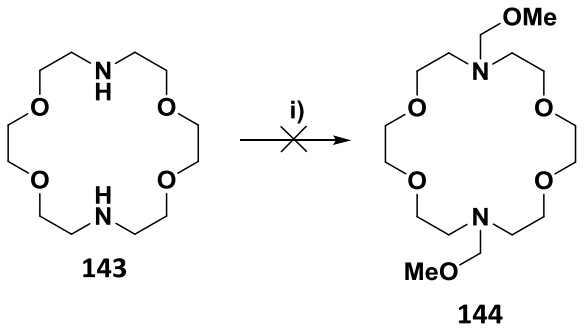
A recent literature report detailed that certain crown compounds could be templated with metals that would be the correct size for the ring required.[42] The pore size of the podand **143** is the correct size for a potassium ion, whereas the sodium ions being used thus far would be small in comparison of the pore size. A potassium source was therefore introduced into the reactions, and this greatly improved the conversion of the reaction. The problem of extraction was solved by using a method of continuous extraction, and all of these changes were taken forward into the reaction with the stable ditosyl electrophile **130** (Scheme 58).



Reaction conditions: i) 1,2-*bis*(2-Tosylethoxy)-ethane, KI, K_2CO_3, MeCN, rt, 12 h.

Scheme 58. Synthesis of the unfunctionalised podand **143**.

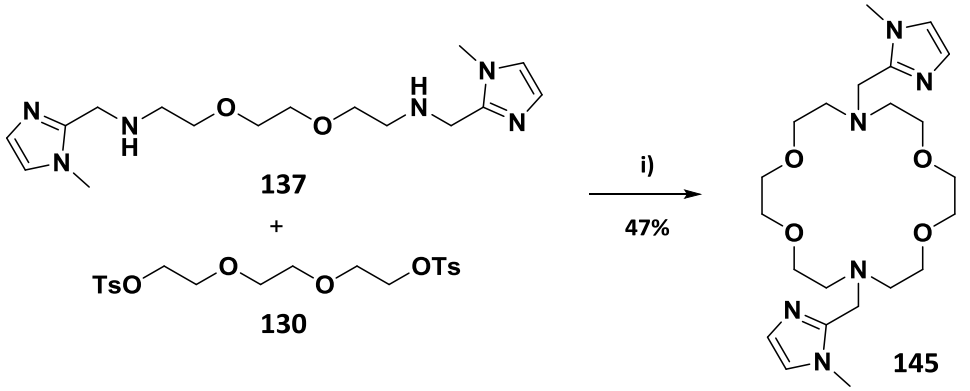
This new templating technique worked well and there was enough crude material to enable continuous extraction. This podand **143** was then taken forward into a compound that could be further functionalised into the target podand (Scheme 59).



Reaction conditions: i) paraformaldehyde, MeOH, reflux, 12 h.

Scheme 59. Attempted functionalisation of the podand **144**.

However this method, alongside other attempts to functionalise this podand with different groups did not give the desired product and therefore a different method was required, involving using the nitrogen containing polyether catalyst **137** to make the desired podand **145** that contained two imidazoles (Scheme 60).



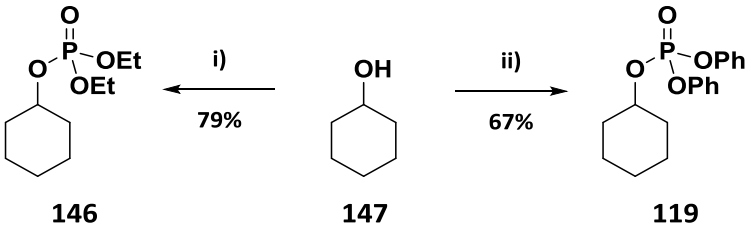
Reaction conditions: i) KI, K_2CO_3, MeCN, rt, 12 h.

Scheme 60. Synthesis of the podand catalyst **145**.

This gave the podand catalyst **145** in a reasonable yield using the templating and continuous extraction method and after purification on alumina due to the product not eluting on silica gel.

4.4 Catalyst screening

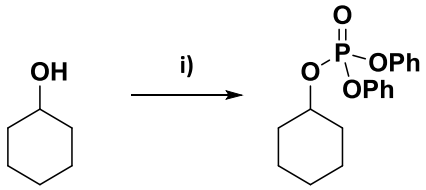
The catalysts and the controls required to test if trifunctional catalysis was occurring were taken forward into a screen with cyclohexanol, as in previous work. This screening required synthesis of reference phosphate products and determination of which of these phosphate products would be suitable to be taken forward into *in situ* monitoring of the reaction (Scheme 61).



Reaction conditions: i) diethyl chlorophosphate, NEt_3, imidazole, THF, 0 °C to rt, 12 h;
ii) diphenyl chlorophosphate, NEt_3, imidazole, THF, 0 °C to rt, 12 h.

Scheme 61. Synthesis of the potential phosphates **146** and **119** for the catalyst screen.

Both phosphate products **146** and **119** were synthesised in good yields and were analysed *via* IR spectroscopy to evaluate which of them would be suitable for *in situ* monitoring using ReactIR to determine rates of reaction. It was found that the diethyl chlorophosphate peak was indistinguishable from that of the diethyl phosphate product **146** and therefore was not a viable option for monitoring the reaction. However, the diphenyl variant **119** had peaks for the diphenyl chlorophosphate at 970 cm^{-1} and 1182 cm^{-1} that could be distinguished from those of the diphenyl phosphate product **119** which gave peaks at 950 cm^{-1} and 1192 cm^{-1}. This was chosen as the phosphate source in the study in which catalysts and additives were screened under standard conditions (Scheme 62, Table 14). Reactions were left for 15 minutes and then quenched and analysed by ^{1}H NMR spectroscopy to determine the conversion.

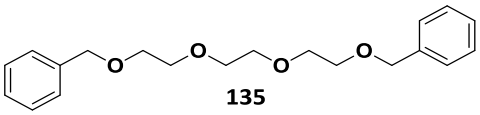
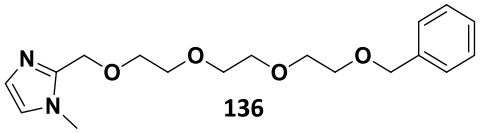
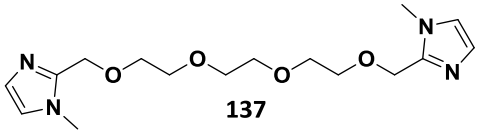
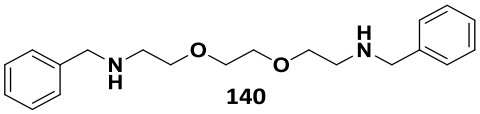
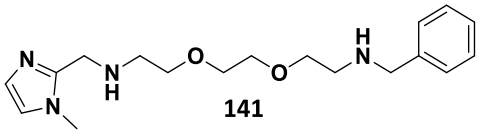
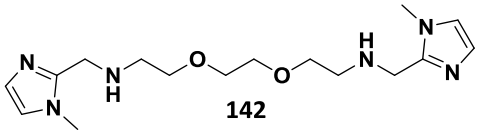
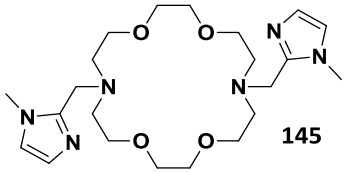


147 **119**

Reaction conditions: i) Catalyst (10 mol%), additive (10 mol%), NEt_3, CH_2Cl_2, -10 °C then diphenyl chlorophosphate, 15 min.

Scheme 62. Conditions for the catalyst screen.

Table 14. Conversions of the catalyst screen reactions.

Entry	Catalyst	Conversions (%)[a,b] with additive		
		None	KPF_6	$Mg(OTf)_2$
1	None	5 (4)	2 (3)	3 (3)
2	NMI **132**	100 (100)	96 (97)	100 (100)
3	 **135**	0 (0)	0 (0)	0 (0)
4	 **136**	48 (44)	73 (67)	68 (72)
5	 **137**	45 (47)	82 (81)	84 (84)
6	 **140**	4 (3)	4 (4)	4 (4)
7	 **141**	18 (17)	27 (29)	30 (34)
8	 **142**	20 (17)	46 (45)	53 (57)
9	 **145**	14 (14)	19 (20)	20 (22)

[a]Values in parentheses represent the results of duplicate reactions. [b]Calculated from ratios of integrals of the proton adjacent to the alcohol and phosphate respectively in the ^{1}H NMR spectrum.

At this temperature, the rates of the background reactions were minimal with and without metal additives whilst the reaction with the NMI catalyst proceeded to completion as expected (Entries 1 and 2). With the oxygen containing polyether catalysts, the system containing two benzyl groups **135** gave no conversion showing

that the polyether backbone does not catalyse the reaction with or without additive present (Entry 3). The catalyst with one imidazole group and one control benzyl group **136** gave a conversion of 48% without any additives present (Entry 4). Conversion was enhanced with this system to around 70% for both KPF_6 and $Mg(OTf)_2$ additives. Both of these gave very similar conversions throughout the study, suggesting that the difference in ionic radius of 86 pm for Mg^{2+} and 152 pm for K^+ does not have a large effect on the rates of the reaction.[43] The third polyether catalyst containing two imidazole groups **137** gave a conversion similar to that of the bifunctional catalyst **136** when no additive was present (Entry 5). In the presence of the additives, there was a large rate enhancement and conversions of over 80% were seen for both KPF_6 and $Mg(OTf)_2$ additives. This is a clear increase in conversion compared to that of the catalyst containing only one imidazole unit, suggesting that trifunctional catalysis was indeed enhancing the rate of the reaction. The likelihood that this enhancement is due to the presence of two imidazole groups instead of trifunctional catalysis seems unlikely, since there was no clear difference in conversion between the catalyst containing two imidazole groups and the control group containing one before the addition of the metal additives. It is therefore thought that trifunctional catalysis is being achieved in this system.

The nitrogen containing catalysts also gave minimal conversion for the control catalyst containing two benzyl groups **140** without and with additives (Entry 6). The catalyst with one imidazole and one benzyl group **141** gave a conversion of 18% which is much lower than that of the same type of catalyst in the polyether series **136**, showing that the presence of the nitrogen has a marked effect on the rate of the reaction (Entry 7). This could be due to a number of factors that the presence of the hydrogen could have upon the reactive intermediate, it could be causing a steric clash in the trifunctional binding model or the electronics of the system could be varied enough to affect the conversion. If the amine of some of the catalyst has been partially protonated this could affect the electronics of the catalyst and its

coordination to the potassium cation which would reduce the conversion of the reaction. In the presence of the metal additives, an increase in conversion for both additives was similar and at around 30%, and follow the trend seen with bifunctional catalysts and the polyether variant. This was also witnessed with the final nitrogen based catalyst which has two imidazole groups **142**, which gave a similar conversion of 20% to the mono-imidazole catalyst **141** in the absence of any additive (Entry 8). Even though the conversion was lower than the polyether variant **137**, it was once again a clear enhancement when additives were present compared to that of the catalyst with one imidazole group **141**, providing further evidence for trifunctional catalysis taking place in these systems.

The podand containing two imidazole groups **145** gave a conversion with no additive of 14% which is low when compared to the earlier work (Entry 9). This only had one imidazole on the podand which had a conversion of 56% under similar conditions (Scheme 48). This could be due to the presence of potassium ions from the synthesis of this podand, although the catalyst was washed several times before use, it is still possible that some remained and affected the overall conversion of the reaction. When additives were used, the conversion was not greatly enhanced and conversions of only 20% were witnessed for both additives. This is believed to be due to the podand creating a more stable intermediate when a metal ion is contained within the podand, with both imidazole groups binding to the metal ion from above and below the ring (Figure 27).

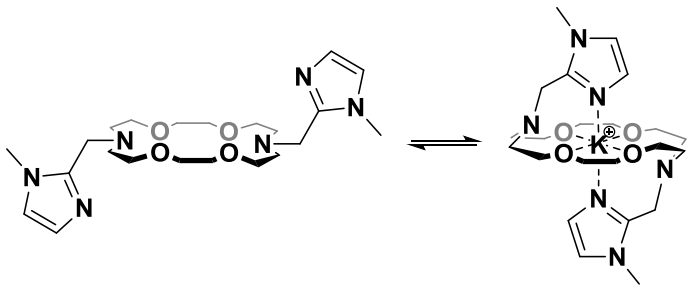
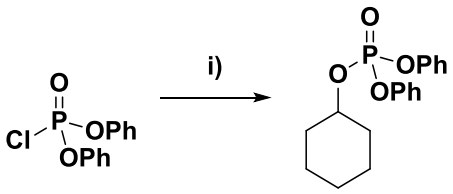


Figure 27. Imidazole binding reducing podand reactivity.

This means that the nucleophilic catalyst **145** is in a thermodynamically stable resting state and therefore the conversion will be reduced. It is hard to distinguish if the conversion of the reaction with no additive present being similar to that of the reactions with additives present could be due to the presence of potassium remaining in the system from the synthesis or that the additive containing reactions do not enhance the conversion. However it is clear that these podand catalysts are not a viable option for trifunctional catalysis.

With the results from the catalyst screen showing evidence of trifunctional catalysis, the next step was to more accurately monitor the reaction so the rate of reaction could be observed and compared. The most reactive polyether catalyst **137** was chosen for this study and would be monitored by ReactIR by the peak for the diphenyl chlorophosphate at 1182 cm^{-1}, which is clear under the reaction conditions (Scheme 63, Table 15). This reaction is assumed to be a first order reaction meaning the rate of reaction depends linearly on one reactant concentration and therefore the concentration of the diethyl phosphate product **119** is directly proportional to that of the diphenyl chlorophosphate. With the knowledge of the concentration of diphenyl chlorophosphate in the reaction mixture before the injection of cyclohexanol **147**, the rate constant could be calculated from the concentration of the starting material during the reaction using Equation 1.7 (Figure 28).

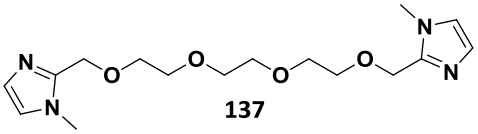
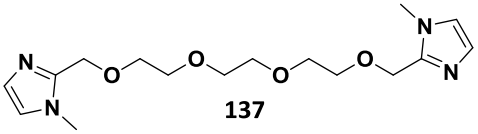


119

Reaction conditions: i) Catalyst **137** (10 mol%), additive (10 mol%), NEt_3, CH_2Cl_2, -10 °C, 15 min.

Scheme 63. Conditions for the rate of reaction study.

Table 15. Rate constants of the reactions.

Entry	Catalyst/additive	Rate constant (s^{-1})[b]
1	None	$1.0 \times 10^{-5} \pm 3.7 \times 10^{-4}$
2	$Mg(OTf)_2$	$1.0 \times 10^{-5} \pm 3.7 \times 10^{-4}$
3	 **137**	$2.0 \times 10^{-4} \pm 3.8 \times 10^{-4}$
4	 **137** + $Mg(OTf)_2$	$1.1 \times 10^{-3} \pm 3.9 \times 10^{-4}$
5	NMI	$4.2 \times 10^{-3} \pm 3.2 \times 10^{-4}$

[a]Reaction conditions: catalyst (10 mol%), additive (10 mol%), NEt_3, CH_2Cl_2, -10 °C then diphenyl chlorophosphate, 15 min. [b]Calculated from ReactIR data using Equation 1.7.

$$Rate = -\frac{d[A]}{dt} = k[A] \tag{1.1}$$

$$\frac{d[A]}{[A]} = -k\,dt \tag{1.2}$$

$$\int_{[A]_0}^{[A]} \frac{d[A]}{[A]} = -\int_{t_0}^{t} k\,dt \tag{1.3}$$

$$\int_{[A]_0}^{[A]} \frac{1}{[A]}\,d[A] = -\int_{t_0}^{t} k\,dt \tag{1.4}$$

$$\int \frac{1}{x} = ln(x) \tag{1.5}$$

$$ln[A] - ln[A]_0 = -kt \tag{1.6}$$

$$\ln[A] = -kt + \ln[A]_0 \tag{1.7}$$

Figure 28. Derivation of the equation used to calculate the rate of reaction for the first order reaction.

The rate constants for the background reaction and the reaction with only the $Mg(OTf)_2$ additive had the same rate at this temperature (Entries 1 and 2). Combination of the catalyst **137** and $Mg(OTf)_2$ gave an order of magnitude increase in the rate of the reaction compared to that using only the catalyst **137** (Entries 3 and 4), and comes close to the rate of the reaction with only the NMI catalyst (Entry 5).

A binding model has been suggested which accounts for the rate enhancement, in which the additive enables one imidazole group to act as a nucleophilic catalyst whilst the other imidazole group can enhance the rate of reaction by acting as a base for the proton on the incoming nucleophile (Figure 29).

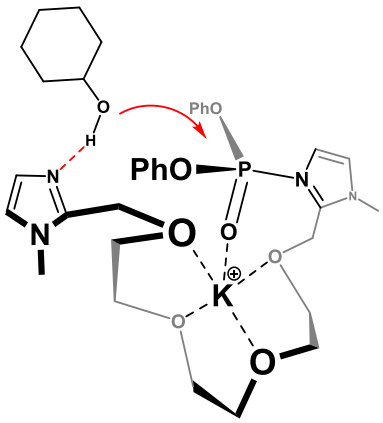


Figure 29. Proposed binding model for trifunctional catalysis.

This is important when looking to the future of selective phosphorylation as there are many adaptations that could influence the reactive intermediate and therefore be used as effective selective phosphorylation catalysts.

4.5 Conclusion

Podand and polyether catalysts have been designed and synthesised from readily available starting materials to probe if trifunctional catalysis is a viable option for phosphorylation, and to investigate if they would enhance the rate of reaction compared to that of bifunctional catalysts. Results from this study have shown that trifunctional catalysis is a viable option for phosphorylation and that there is a clear rate enhancement compared to that of bifunctional catalysts.

Different heteroatoms being incorporated into the polyether backbone have a marked effect upon the rate of the reaction. The clear rate enhancement of the reaction from bifunctional to that of the trifunctional catalysts shows that the addition of the third functionality of the base into the catalysts enhances the rate. This also enables another appendage to be included which can be tailored to enhance the rate of reaction and the addition of stereogenic centres that could give an enantioselective synthesis of phosphates.

A model has been proposed which accounts for this enhancement in the rate of reaction and this model suggests the changes to the catalysts could both enhance the rate and allow for the catalysts to be used as asymmetric phosphorylation agents in the future.

4.6 Future Work

This work supports the hypothesis that these catalysts are undergoing trifunctional catalysis can be adapted for asymmetric and selective phosphorylation. This could be achieved by adding large phenyl groups to the polyether chain or the linker connecting the imidazoles.

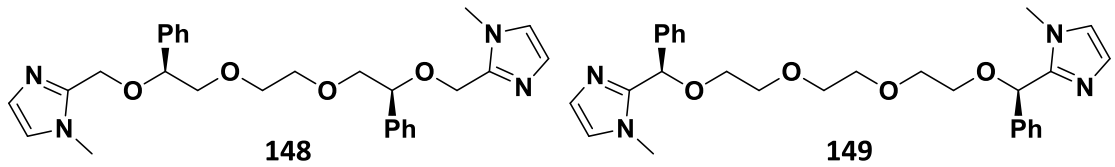


Figure 30. Possible asymmetric trifunctional catalysts **148** and **149**.

There is also potential for the nucleophilic catalyst and base to contain a stereogenic centre which could lead to asymmetric catalysts which would be in a position close to the nucleophile and therefore should be able to affect the trajectory of the nucleophile.

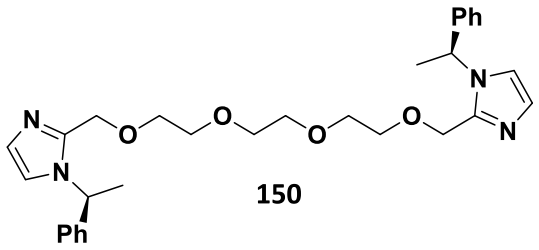


Figure 31. A possible variant **150** that could act as an asymmetric phosphorylation catalyst.

There is the potential to change many aspects of the catalyst, from the chain length of the polyether backbone to the nucleophilic catalyst and base that are connected to them. These catalysts have the potential of being selective asymmetric phosphorylation agents.

5. Experimental

All reactions were performed under a nitrogen atmosphere using acetone washed, flame dried glassware with magnetic stirring and if required heated through the use of Dry Syn™ blocks. All reagents used were supplied from commercial suppliers and used without further purification or as indicated prepared in the laboratory. Reactions that were performed at 0 °C and -78 °C used water/ice baths and acetone/dry ice baths, respectively. All solvents used in the course of the project were obtained from the departmental Grubbs solvent system and stored under a positive pressure of nitrogen. Reagents that were susceptible to air were titrated against a standard solution to determine the concentration of the reagent.

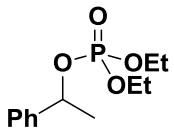
Analytical thin layer chromatography (TLC) was carried out utilising aluminium backed Merck TLC plates (silica gel 60 F254) and visualised with UV light (254 nm) or basic $KMnO_4$ solution. Flash column chromatography was performed using Silica Gel (30 – 70 μm) as the stationary phase unless stated. Columns were typically packed as a slurry, and the eluent used for a particular purification noted within the individual experimental details for each reaction.

All ^{1}H, ^{13}C, ^{31}P spectra were obtained using either a Bruker AV250 or AV400 spectrometer. Unless specifically stated, all samples were ran at 20 °C using deuteriated chloroform as the solvent. Chemical shifts are expressed in parts per million (ppm) as δ values relative to tetramethylsilane (TMS) as an external standard.

Mass spectrometry was performed by the University of Sheffield Mass Spectrometry Service using the method of electrospray ionisation on a Waters LCT Mass Spectrometer unless otherwise stated. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR. Specific rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589 nm (Na D-line) and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on a Gallenkamp apparatus and are uncorrected.

Determination of the enantiomeric excess of the *P*-chiral phosphates was performed using a Gilson HPLC chain with an ABI Analytical Spectroflow 783 UV detector. The chiral column used for each compound is stated for each compound and the wavelength at which the detector was set was 254 nm. In all cases, a mixture of hexane and propan-2-ol were used as the mobile phase, the exact ratio of which is described in the individual experimental details. Mobile phase flow, unless specified otherwise, was 1.0 $cm^3\,min^{-1}$.

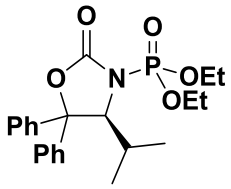
_O_-Diethyl phosphoryl-1-phenylethanol, 34.[26]



1-Phenylethanol **29** (6.00 g, 49.0 mmol) was dissolved in THF (20 mL) with stirring and the solution was cooled to -78 °C. MeMgCl (2.80 mL, 2.0 M in THF, 5.5 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 1 h, before being cooled to -78 °C. Diethyl chlorophosphate (0.86 g, 0.6 mL, 5.0 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 2 h, before being quenched by the addition of $NH_4Cl_{(aq)}$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (10 mL), brine (10 mL) and dried over $MgSO_4$. The solution was filtered and the solvent was removed under reduced pressure, and following flash column chromatography on silica gel (2:3, EtOAc: petroleum ether 40 − 60 °C) the title compound (1.23 g, 96%) was obtained as a clear oil; ν_{max} (ATR)/ cm^{-1} 2982, 2933, 1450; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.17 (td, 3H, *J* 7.1, $J_{H\text{-}P}$ 0.9, OCH_2CH_3), 1.27 (td, 3H, *J* 7.1, $J_{H\text{-}P}$ 0.9, OCH_2CH_3), 1.62 (d, 3H, *J* 6.5, $CHCH_3$), 3.88 − 4.11 (m, 4H, 2 x OCH_2CH_3), 5.46 (p, 1H, *J* 6.5, $J_{C\text{-}P}$ 6.5, $CHCH_3$), 7.27 − 7.38 (m, 5H, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 141.6 (d, $J_{C\text{-}P}$ 5.1, Ar*C*) , 128.3 (2 x Ar*C*H), 127.0 (Ar*C*H), 125.7 (2 x Ar*C*H), 76.6 (d, $J_{C\text{-}P}$ 5.1, $CHCH_3$), 63.5 (d, $J_{C\text{-}P}$ 5.1, OCH_2CH_3), 24.1 ($CHCH_3$), 15.9 [d, $J_{C\text{-}P}$

8.1, OCH_2CH_3], 15.8 (d, $J_{C\text{-}P}$ 8.1, OCH_2CH_3); ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -1.82; *m/z* (ES^+) 259.1093 (100%, MH^+. $C_{12}H_{20}O_4P$ requires 259.1099). All data was in accordance with the literature.

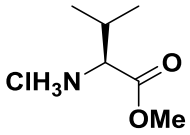
(4*S*)-3-Diethyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone, 42.[30]



(*S*)-4-Isopropyl-5,5-diphenyl-2-oxazolidinone **56** (3.70 g, 13.1 mmol) was stirred as a suspension in THF (250 mL) and cooled to -78 °C. *n*BuLi (5.30 mL, 2.5M in hexanes, 14 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 1 h, before being cooled to -78 °C. Diethyl chlorophosphate (2.10 mL, 14 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring overnight, before being quenched by the addition of $NH_4Cl_{(aq)}$ (50 mL). The resulting mixture was extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (30 mL), brine (30 mL) and dried over $MgSO_4$. The filtered solvent was removed under reduced pressure, following flash column chromatography on silica gel (1:2, EtOAc: petroleum ether 40 − 60 °C) the title compound (3.53 g, 64%) was obtained as a white solid; mpt 106-108 °C; $[\alpha]^{22}_D$ -152 (*c* 0.5, $CHCl_3$); ν_{max} (ATR)/ cm^{-1} 2982, 1758, 1430; ^1H NMR (400 MHz; $CDCl_3$) δ_H 0.79 [d, 3H, *J* 6.8, $CH(CH_3)_2$], 0.92 (td, 3H, *J* 7.1, $J_{H\text{-}P}$ 0.8, OCH_2CH_3), 1.05 [d, 3H, *J* 6.8, $CH(CH_3)_2$], 1.35 [td, 3H, *J* 7.1, $J_{H\text{-}P}$ 1.1, OCH_2CH_3], 1.97 [hept-d, 1H, *J* 6.8, $J_{H\text{-}P}$ 2.4, $CH(CH_3)_2$], 3.04 − 3.08 (m, 1H, $OCHHCH_3$), 3.44 − 3.50 (m, 1H, $OCHHCH_3$), 4.25 − 4.33 (m, 2H, OCH_2CH_3), 4.98 (dd, 1H, $J_{H\text{-}P}$ 3.3, *J* 2.4, CHNP), 7.24 − 7.44 (m, 8H, ArCH), 7.65 − 7.67 (d, 2H, *J* 7.4, ArCH); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.6 (C=O), 143.3 (ArC), 138.3 (ArC), 128.8 (2 x ArCH), 128.4 (2 x ArCH), 128.3 (ArCH), 127.8 (ArCH), 125.5 (2 x ArCH), 125.4 (2 x ArCH), 90.6 (CAr_2), 69.4 (d, $J_{C\text{-}P}$ 3.0, CHN), 65.1 (d, $J_{C\text{-}P}$ 7.1, OCH_2CH_3), 63.3 (d, $J_{C\text{-}P}$ 5.1,

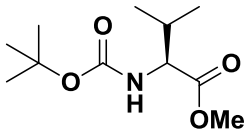
O*C*H$_2$CH$_3$), 30.0 [CH(*C*H$_3$)$_2$], 21.1 [CH(*C*H$_3$)$_2$], 16.1 (d, $J_{C\text{-}P}$ 7.5, 2 x OCH$_2$*C*H$_3$), 15.7 [d, $J_{C\text{-}P}$ 7.2, 2 x OCH$_2$*C*H$_3$], 15.6 [*C*H(CH$_3$)$_2$]; ^{31}P NMR (101 MHz; CDCl$_3$) δ_P -4.30; *m/z* (ES$^+$) 463 (15%), 436 (18), 435 (76), 419 (24), 418.1772 (100%, MH$^+$. $C_{22}H_{29}NO_5P$ requires 418.1783), 319 (3). All data was in accordance with the literature.

L-Valine methyl ester hydrochloride, 53.[44]



L-Valine (5.02 g, 42.9 mmol) was stirred as a suspension in MeOH (200 mL) and the mixture was cooled to 0 °C. Thionyl chloride (7.66 g, 4.70 mL, 64.4 mmol) was added dropwise. The resulting solution was allowed to warm to rt and left to stir for 48 h. The solvent was removed under reduced pressure to give the title compound (7.12 g, 99%) as a white solid that required no further purification; mp 164 - 166 °C (lit.[44] , 166 - 168 °C);$[\alpha]_D^{22}$ +15 (*c* 4.0, H$_2$O) [lit.[44], +16 (*c* 4.12, H$_2$O)]; ^{1}H NMR (250 MHz; D$_2$O) δ_H 0.83 [d, 3H, *J* 7.0, CH(C*H*$_3$)$_2$], 0.84 [d, 3H, *J* 7.0, CH(C*H*$_3$)$_2$], 2.05 – 2.22 [m, 1H, C*H*(CH$_3$)$_2$], 3.65 (s, 3H, OC*H*$_3$), 3.83 (d, 1H, *J* 4.7, C*H*N). All data was in accordance with the literature.

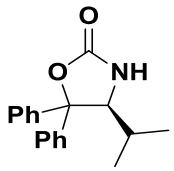
***N*-Boc-L-valine methyl ester, 54.**[45]



L-Valine methyl ester hydrochloride **53** (29.0 g, 173.0 mmol) was dissolved in EtOH (200 mL) and the resulting solution was cooled to 0 °C. Sodium hydrogen carbonate (43.6 g, 519.0 mmol) was added as a single portion, immediately followed by di-*tert*-butyl dicarbonate (39.6 g, 181.4 mmol). The reaction mixture was allowed to warm to rt and left to stir for 48 h, before being filtered through Hyflo Super Cel®. The

solvent was removed under reduced pressure, the residue redissolved in Et_2O (50 mL) and again filtered through Hyflo Super Cel®. The solvent was removed under reduced pressure and following purification by flash column chromatography on silica gel (1:9, EtOAc: petroleum ether 40 − 60 °C) the title compound (39.9 g, 97 %) was obtained as a clear oil; $[\alpha]^{22}_{D}$ +11.7 (*c* 2.5, $CHCl_3$) [lit.[45], +12.9 (*c* 2.43, $CHCl_3$)]; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.87 [d, 3H, *J* 6.9, $CH(CH_3)_2$], 0.94 [d, 3H, *J* 6.9, $CH(CH_3)_2$], 1.43 [s, 9H, $C(CH_3)_3$], 2.09 – 2.14 [m, 1H, $CH(CH_3)_2$], 3.72 (s, 3H, CO_2CH_3), 4.21 (dd, 1H, *J* 8.6, 4.8, CHNH), 5.01 (d, 1H, *J* 8.6, NH). All data was in accordance with the literature.

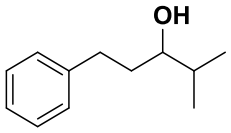
(*S*)-4-Isopropyl-5,5-diphenyl-2-oxazolidinone, 56.[46]



Magnesium turnings (0.34 g, 13.84 mmol) were stirred in THF (35 mL) under an atmosphere of nitrogen. Bromobenzene (2.17 g, 1.45 mL, 13.84 mmol) was added dropwise to the reaction mixture, which was heated to initiate an exothermic reaction. The remaining bromobenzene was diluted with THF (70 mL) and the resulting solution was added to the reaction vessel at a rate as to ensure heating at a steady reflux. Once addition was complete, the reaction mixture was cooled to 0 °C. *N*-Boc-L-Valine methyl ester **54** (0.64 g, 2.77 mmol) was dissolved in THF (35 mL) and the resulting solution was added dropwise to the reaction vessel. The reaction mixture was allowed to warm to rt and left stirring for 48 h, before being quenched by addition of $NH_4Cl_{(aq)}$ (50 mL). The resulting mixture was extracted with EtOAc (3 × 40 mL), washed with brine (25 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was dissolved in THF (125 mL) and cooled to 0 °C. KO^tBu (0.36 g, 3.19 mmol) was added as a single portion and the reaction was left stirring at this temperature for 1 h, before being allowed to warm

to rt and left stirring overnight. The reaction was quenched with $NH_4Cl_{(aq)}$ (30 mL), the organic solvent was removed under reduced pressure and the resulting mixture was filtered. The residual solid was washed with H_2O (20 mL), methanol (20 mL) and CH_2Cl_2 (20 mL) to give the title compound (2.30 g, 83%) as a fluffy white solid that did not require further purification; 250 - 252 °C (lit.[46], 252 - 253 °C); $[\alpha]^{22}_D$ -250.0 (*c* 0.2, $CHCl_3$) [lit.[46], -255.2 (*c* 0.2, $CHCl_3$)]; ν_{max} (ATR)/cm^{-1} 3288, 2962, 1742, 1452; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.68 (d, 3H, *J* 6.8, CHC*H*$_3$), 0.87 (d, 3H, *J* 6.8, CHC*H*$_3$), 1.83 – 1.91 [m, 1H, C*H*$(CH_3)_2$], 4.34 (d, 1H, *J* 3.6, C*H*NH), 5.53 (s, 1H, N*H*), 7.25 – 7.40 (m, 8H, ArC*H*), 7.53 – 7.55 (d, 2H, *J* 7.4, ArC*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.4 (O*C*N), 143.8 (Ar*C*), 139.1 (Ar*C*), 128.5 (2 x Ar*C*H), 128.2 (Ar*C*H), 128.1 (2 x Ar*C*H), 127.7 (Ar*C*H), 126.3 (2 x Ar*C*H), 125.7 (2 x Ar*C*H), 89.4 (*C*Ar_2), 65.8 (*C*HN), 29.6 [*C*$(CH_3)_2$], 20.8 [C(*C*$H_3)_2$], 15.6 [C(*C*$H_3)_2$]; *m/z* (ES^+) 345 (17%), 323 (100), 299 (9), 282.1491 (78%, MH^+. $C_{18}H_{20}NO_2$ requires 282.1494), 221 (13), 150 (6). All data in accordance with the literature.

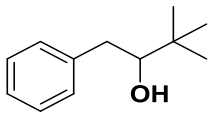
4-Methyl-1-phenylpentan-3-ol, 57.[47]



Magnesium turnings (2.72 g, 112 mmol) were stirred in THF (20 mL) under an atmosphere of nitrogen. 2-Bromopropane (13.78 g, 10.5 mL, 112 mmol) was added dropwise to the reaction mixture, which was heated to initiate an exothermic reaction. The remaining 2-bromopropane was diluted with THF (150 mL) and the resulting solution was added to the reaction vessel at a rate as to ensure heating at a steady reflux. The reaction mixture was cooled to 0 °C. 3-Phenylpropionaldehyde (5.01 g, 37.3 mmol) was dissolved in THF (35 mL) and the resulting solution was added dropwise to the reaction vessel. The reaction mixture was allowed to warm to rt and left stirring for 48 h, before being quenched by addition of $NH_4Cl_{(aq)}$ (50 mL). The resulting mixture was extracted with EtOAc (3 × 40 mL), washed with brine

(25 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Following purification by flash column chromatography on silica gel (1:8, EtOAc: petroleum ether 40 − 60 °C) the title compound (5.20 g, 78 %) was obtained as a faint yellow oil; ν_{max} (ATR)/cm^{-1} 3364, 2956, 2870, 1604, 1496, 1454; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.94 (d, 3H, *J* 6.8, C*H*$_3$), 0.95 (d, 3H, *J* 6.8, C*H*$_3$), 1.41 (s, 1H, O*H*), 1.67 – 1.87 [m, 3H, C*H*$(CH_3)_2$ and C*H*$_2$], 2.68 [ddd, 1H, *J* 13.7, 9.8 and 6.8, CH*H*], 2.88 (ddd, 1H, *J* 13.7, 9.8 and 5.4, CH*H*), 3.43 (ddd, 1H, *J* 8.9, 5.2, 3.5, C*H*OH), 7.20 – 7.34 (m, 5H, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 142.4 (Ar*C*), 128.5 (2 x Ar*C*H), 128.4 (2 x Ar*C*H), 125.8 (Ar*C*H), 76.2 (*C*HOH), 36.0 (*C*H_2Ar), 33.7 [*C*H$(CH_3)_2$], 32.5 (*C*H_2COH), 18.8 (*C*H_3), 17.2 (*C*H_3); *m/z* (EI^+) 178.1365 (4%, M^+. $C_{12}H_{18}O$ requires 178.1358), 160 (18), 117 (43), 104 (56), 92 (35), 91 (100), 83 (32). All data was in accordance with the literature.

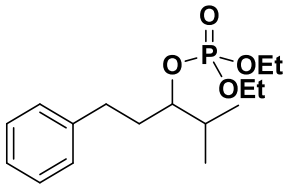
3,3-Dimethyl-1-phenylbutan-2-ol, 58.[48]



Magnesium turnings (4.86 g, 200 mmol) were stirred in THF (35 mL) under an atmosphere of nitrogen. Bromobenzene (31.40 g, 21 mL, 200 mmol) was added dropwise to the reaction mixture, which was heated to initiate an exothermic reaction. The remaining bromobenzene was diluted with THF (125 mL) and the resulting solution was added to the reaction vessel at a rate as to ensure heating at a steady reflux. The reaction mixture was cooled to 0 °C and copper (I) bromide (3.81 g, 20 mmol) was added portionwise. The reaction was left to stir for 30 minutes at below 7 ^oC, before being cooled to 0 °C and 3,3-dimethyl-1,2-epoxybutane (1.00 g, 1.22 mL, 10 mmol) was added dropwise to the reaction vessel. The reaction mixture was allowed to warm to rt and left stirring for 12 h, before being quenched by addition of HCl (1M, 50 mL). The resulting mixture was extracted with EtOAc (3 × 30 mL), washed with $NaHCO_{3(aq)}$ (30 mL), dried over $MgSO_4$, filtered

and the solvent was removed under reduced pressure and following flash column chromatography on silica gel (1:9, EtOAc: petroleum ether 40 − 60 °C) the title compound (1.05 g, 59%) was obtained as a yellow oil; ν_{max} (ATR)/cm^{-1} 3563, 3457, 3027, 2953, 2863, 1604, 1494, 1478; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.04 [br s, 9H, C(C*H*$_3$)$_3$], 1.54 (br s, 1H, CHO*H*), 2.50 (dd, 1H, *J* 13.6 and 10.7, C*H*H), 2.95 (dd, 1H, *J* 13.6 and 2.0, CH*H*), 3.47 (dd, 1H, *J* 10.7 and 2.0, C*H*O), 7.24 – 7.28 (m, 3H, Ar*H*), 7.33 – 7.37 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 139.9 (Ar*C*), 129.4 (2 x Ar*C*H), 128.6 (Ar*C*H), 126.3 (2 x Ar*C*H), 80.6 (*C*HOH), 38.4 (*C*H$_2$Ar), 34.8 [*C*(CH$_3$)$_3$], 25.9 [3 x C(*C*H$_3$)$_3$]; *m/z* (EI$^+$) 178.1355 (1%, M$^+$. $C_{12}H_{18}O$ requires 178.1358), 160 (10%), 145 (15), 121 (12), 103 (13), 92 (100), 91 (67). All data was in accordance with the literature.

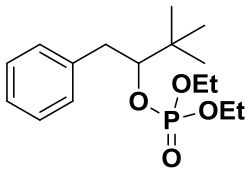
***O*-Diethyl phosphoryl-1-phenyl-4-methyl-3-pentanol, 66.**



4-Methyl-1-phenylpentan-3-ol **57** (0.501 g, 2.80 mmol) was dissolved in THF (30 mL) with stirring and the solution was cooled to -78 °C. MeMgCl (0.15 mL, 2 M in THF, 0.30 mmol) was added dropwise and the solution was allowed to warm to rt for 1 h, before being cooled to -78 °C. Diethyl chlorophosphate (0.048 g, 0.05 mL, 0.28 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 2 h, before being quenched by the addition of saturated $NH_4Cl_{(aq)}$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (10 mL), brine (10 mL) and dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure and following flash column chromatography on silica gel (2:3, EtOAc: petroleum ether 40 − 60 °C) the title compound (0.08 g, 91%) was obtained as a clear oil; ν_{max} (ATR)/cm^{-1} 2963, 1480, 1455; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.96 [d, 3H,

J 6.8, CH(C*H*$_3$)$_2$], 0.99 [d, 3H, *J* 6.8, CH(C*H*$_3$)$_2$], 1.37 [td, 6H, *J* 7.1 and $J_{H\text{-}P}$ 0.5, OCH$_2$C*H*$_3$], 1.88-2.05 [m, 3H, C*H*$_2$CHOP and C*H*(CH$_3$)$_2$], 2.69 (ddd, 1H, *J* 13.8, 11.0 and 5.9, ArC*H*H), 2.81 (ddd, 1H, *J* 13.8, 11.0 and 5.5, ArCH*H*) 4.11-4.18 (m, 4H, 2 x OC*H*$_2$CH$_3$), 4.31 (ddd, 1H, *J* 12.1, 7.8, 4.4, C*H*OP), 7.19-7.33 (m, 5H, Ar*H*); ^{13}C NMR (101 MHz; CDCl$_3$) δ_C 141.9 (Ar*C*), 128.4 (2 x Ar*C*H), 128.4 (2 x Ar*C*H), 125.9 (Ar*C*H), 83.9 (d, $J_{C\text{-}P}$ 6.1, CHOP), 63.6 (O*C*H$_2$CH$_3$), 63.5 (O*C*H$_2$CH$_3$), 33.5 (d, $J_{C\text{-}P}$ 4.0, Ar*C*H$_2$), 31.9 [d, $J_{C\text{-}P}$ 3.0, *C*H(CH$_3$)], 31.7 (*C*H$_2$CO), 17.7 [CH(*C*H$_3$)], 17.5 [CH(*C*H$_3$)], 16.2 (OCH$_2$*C*H$_3$), 16.2 (OCH$_2$*C*H$_3$); ^{31}P NMR (101 MHz; CDCl$_3$) δ_P -1.30; *m/z* (EI$^+$) 378 (27%), 337 (44), 315.1714 (100%, MH$^+$. $C_{16}H_{28}O_4P$ requires 315.1725), 196 (24), 155 (8); Chiral HPLC: Lux 3µm Cellulose-1, 2% i-PrOH in hexane; 1 mL/min; retention times 9.7 min and 12.5 min.

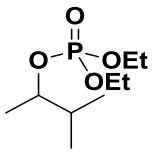
_O_-Diethyl phosphoryl-1-phenyl-3,3-dimethyl-2-pentanol, 67.



3-Dimethyl-1-phenylbutan-2-ol **58** (0.50 g, 2.8 mmol) was dissolved in THF (30 mL) with stirring and the solution was cooled to -78 °C. MeMgCl (0.02 g, 0.16 mL, 1.9 M in THF, 0.30 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 1 h, before being cooled to -78 °C. Diethyl chlorophosphate (0.05 g, 0.04 mL, 0.28 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 2 h, before being quenched by the addition of $NH_4Cl_{(aq)}$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (10 mL), brine (10 mL) and dried over $MgSO_4$. This was filtered, the solvent was removed under reduced pressure and following flash column chromatography on silica gel (2:5, EtOAc: petroleum ether 40 − 60 °C) the title compound (0.07 g, 80%) was obtained as a clear oil; ν_{max} (ATR)/cm^{-1} 2963, 1480,

1455, 1396, 1367, 1259; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.02 [s, 9H, C(C*H*$_3$)$_3$], 1.06 (td, 3H, *J* 7.1 and 1.1, OCH$_2$C*H*$_3$), 1.26 (td, 3H, *J* 7.1 and 1.1, OCH$_2$C*H*$_3$), 2.80 (dd, 1H, *J* 14.5 and 8.8, ArC*H*H), 3.02 (ddd, 1H, *J* 14.5, 3.5 and 2.1, ArCH*H*), 3.37-3.47 (m, 1H, OC*H*H), 3.58-3.67 (m, 1H, OCH*H*), 3.93-4.00 (m, 2H, OC*H*$_2$CH$_3$), 4.50 (td, 1H, *J* 8.8 and 3.5, C*H*OP), 7.19-7.29 (m, 5H, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 138.7 (Ar*C*), 129.6 (2 x Ar*C*H), 128.3 (2 x Ar*C*H), 126.3 (Ar*C*H), 88.1 (d, $J_{C\text{-}P}$ 8.1, *C*HOP), 63.3 (d, $J_{C\text{-}P}$ 6.1, OCH$_2$CH$_3$), 62.9 (d, $J_{C\text{-}P}$ 6.1, OCH$_2$CH$_3$), 37.8 (*C*H$_2$Ar), 35.8 [d, $J_{C\text{-}P}$ 4.0, *C*(CH$_3$)$_3$], 26.2 [3 x C(*C*H$_3$)$_3$], 16.1 (d, $J_{C\text{-}P}$ 8.1, OCH$_2$*C*H$_3$), 16.0, (d, $J_{C\text{-}P}$ 8.1, OCH$_2$*C*H$_3$); ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -1.60; *m/z* (ESI$^+$) 378 (18%), 360 (5), 337 (12), 315.1726 (100%, MH$^+$. $C_{16}H_{28}O_4P$ requires 315.1725), 196 (13), 155 (5); Chiral HPLC Lux 3µm Cellulose-1, 1% iPrOH in hexane; 1 mL/min; retention times 17.3 min and 19.7 min.

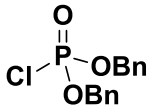
_O_-Diethyl phosphoryl-3-methylbutan-2-ol, 68.



3-Methylbutan-2-ol (0.50 g, 5.67 mmol) was dissolved in THF (30 mL) with stirring and the solution was cooled to 0 °C. MeMgCl (0.046 g, 0.24 mL, 2.6 M in THF, 0.62 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 1 h, before being cooled to 0 °C. Diethyl chlorophosphate (0.067 g, 0.08 mL, 0.57 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for overnight before being quenched by the addition of $NH_4Cl_{(aq)}$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (10 mL), brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and following flash column chromatography on silica gel (1:1, EtOAc: petroleum ether 40 − 60 °C) the title compound (0.12 g,

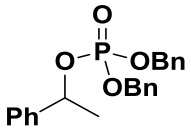
86%) was obtained as a clear oil; ν_{max} (ATR)/ cm^{-1} 2963, 2916, 2849, 1673, 1463; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.93 [d, 6H, *J* 6.8, CH(CH_3)$_2$], 1.27 (d, *J* 6.4, 3H, CHCH_3), 1.33 (td, 6H, *J* 7.1, $J_{H\text{-}P}$ 0.6, 2 x OCH_2CH_3), 1.80-1.86 [m, 2H, C*H*(CH_3)$_2$], 4.04-4.11 (m, 4H, 2 x OCH_2CH_3), 4.31 (m, 1H, C*H*OP); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 80.2 (*C*HOP), 63.5 (2 x OCH_2CH_3), 33.8 [*C*H(CH_3)$_2$], 31.4 (CH*C*H_3), 17.8 [CH(CH_3)$_2$], 17.6 [CH(CH_3)$_2$], 16.1 (2 x OCH_2CH_3); ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -1.46; *m/z* (ES^+) 237 (7%), 225.1260 (68%, MH^+. $C_9H_{22}O_4P$ requires 225.1256), 196 (100), 181 (16), 168 (8), 155 (21), 140 (7).

Dibenzyl chlorophosphate, 76.[49]



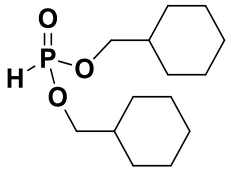
N-Chlorosuccinimide (0.30 g, 2.2 mmol) was dissolved in toluene (20 mL) and dibenzyl phosphite (0.53 g, 0.45 mL, 2.0 mmol) was added dropwise. The reaction was left to stir for 3 h, filtered to remove a precipitate. The solvent was removed under reduced pressure, the residue was triturated with hexanes (30 mL), the precipitate filtered off, and the solvent evaporated under reduced pressure to give title compound (0.54 g, 91 %) as a clear oil that did not require further purification; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 5.21 (dd, 2H, *J J* 16.1, $J_{H\text{-}P}$ 9.0, 2 x C*H*HO), 5.18 (dd, 2H, *J* 16.1, $J_{H\text{-}P}$ 9.0, 2 x CH*H*O), 7.38 (s, 10H, Ar*H*); ^{31}P NMR (101 MHz; $CDCl_3$) δ_P 4.82. All data was in accordance with the literature.

***O*-Dibenzyl phosphoryl-1-phenylethanol, 77.**



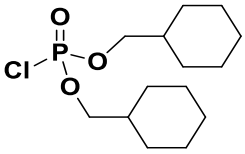
1-Phenylethanol (0.082 g, 0.67 mmol) was dissolved in THF (20 mL) with stirring and the solution was cooled to -78 °C. MeMgCl (0.35 mL, 2.1 M in THF, 0.74 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 1 h, before being cooled to -78 °C. Dibenzyl chlorophosphate **76** (0.2 g, 0.67 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 2 h, before being quenched by the addition of $NH_4Cl_{(aq)}$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (10 mL), brine (10 mL) and dried over $MgSO_4$. The solution was filtered and the solvent was removed under reduced pressure, and following flash column chromatography on silica gel (3:17, EtOAc: petroleum ether 40 − 60 °C) the title compound (0.097 g, 38%) was obtained as a clear oil; ν_{max} (ATR)/ cm^{-1} 2982, 2933, 1450; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.61 (d, 3H, *J* 6.5, CHC*H*$_3$), 4.88 (d, 2H, *J* 7.7, OC*H*$_2$Ar), 4.91-5.10 (m, 2H, OC*H*$_2$Ar), 5.51 (dq, 1H, $J_{C\text{-}P}$ 7.2, *J* 6.6, C*H*CH$_3$), 7.19 − 7.40 (m, 15H, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 144.1 (Ar*C*), 136.0 (Ar*C*), 135.7 (Ar*C*), 128.6 (4 x Ar*C*H), 128.5 (4 x Ar*C*H), 128.5 (2 x Ar*C*H), 128.0 (Ar*C*H), 127.9 (Ar*C*H), 127.5 (Ar*C*H), 126.4 (2 x Ar*C*H), 74.7 (*C*HCH$_3$), 69.6 (d, $J_{C\text{-}P}$ 5.5, O*C*H$_2$Ph), 69.2 (d, $J_{C\text{-}P}$ 4.9, O*C*H$_2$Ph), 24.7 (CH*C*H$_3$); ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -1.76.

Dicyclohexylmethyl phosphite, 81.



Triethylamine (5.57 g, 7.80 mL, 55.0 mmol) in THF (20 mL) was added dropwise to a solution of cyclohexanemethanol (6.28 g, 6.80 mL, 55 mmol) and phosphorus trichloride (3.78 g, 2.40 mL, 27.5 mmol) in THF (100 mL) cooled to 0 °C. The reaction mixture was then warmed to rt and left to stir overnight, before being filtered to remove salts. The solvent was removed under reduced pressure, and the crude material distilled under reduced pressure (2.5 mbar, 150 °C) to give the title compound (4.19 g, 57%) as a clear oil; ν_{max} (ATR)/ cm^{-1} 2923, 2851, 1642; ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 0.94-1.33 (m, 10H, Cy*H*), 1.57-1.78 (m, 12H, Cy*H*), 3.86 (ddd, 4H, *J* 7.9, 6.3 and 1.7, OCH_2), 6.80 (d, 1H, $J_{P\text{-}H}$ 692.5, P*H*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 70.7 (d, $J_{C\text{-}P}$ 8.0, 2 x *C*H_2Cy), 38.5 (d, $J_{C\text{-}P}$ 7.0, 2 x Cy-*C*H), 29.2 (2 x Cy-*C*H_2), 29.2 (2 x Cy-*C*H_2), 26.3 (2 x Cy-*C*H_2), 25.5 (4 x Cy-*C*H_2); ^{31}P NMR ($CDCl_3$, 101 MHz): δ_P 8.19; *m/z* (EI^+) 338 (52%), 316 (100), 292 (22), 275.1767 (275, MH^+. $C_{14}H_{28}O_3P$ requires 275.1776.

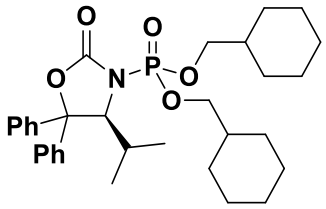
Dicyclohexylmethyl chlorophosphate, 83.



N-Chlorosuccinimide (0.56 g, 4.2 mmol) was dissolved in toluene (20 mL) and dicyclohexylmethyl phosphite **81** (0.91 g, 3.82 mmol) was added dropwise and left to stir for 3 h, before being filtered to remove precipitate and the solvent was removed under reduced pressure. Extracted with hexanes (2 x 30 mL) which was removed under reduced pressure to give the title compound (1.07 g, 91 %) as a clear oil that was used immediately without further purification; ^{1}H NMR ($CDCl_3$,

250 MHz) δ_H 0.96-1.33 (m, 10H, CyH), 1.65-1.78 (m, 12H, Cy*H*), 3.90-4.06 (m, 4H, OC*H*$_2$); ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 74.5 (d, $J_{C\text{-}P}$ 7.0, 2 x O*C*H$_2$Cy), 38.0 (d, $J_{C\text{-}P}$ 8.0, 2 x Cy-*C*H), 29.0 (2 x Cy-*C*H$_2$), 29.0 (2 x Cy-*C*H$_2$), 26.2 (2 x Cy-*C*H$_2$), 25.4 (4 x Cy-*C*H$_2$); ^{31}P NMR ($CDCl_3$, 101 MHz) δ_P 5.22.

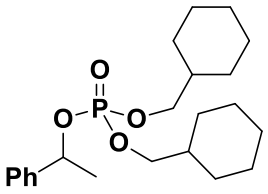
(4*S*)-3-Dicyclohexylmethyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone, 86.



(*S*)-4-Isopropyl-5,5-diphenyl-2-oxazolidinone **56** (0.37 g, 1.30 mmol) was stirred as a suspension in THF (250 mL) and cooled to -78 °C. MeMgCl (0.18 g, 2.8 M in THF, 0.5 mL, 1.43 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 1 h, before being cooled to -78 °C. Dicyclohexylmethyl chlorophosphate **83** (0.40 g, 1.30 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring overnight, before being quenched by the addition of $NH_4Cl_{(aq)}$ (50 mL). The resulting mixture was extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (30 mL), brine (30 mL) and dried over $MgSO_4$. The filtered solvent was removed under reduced pressure and following flash column chromatography on silica gel (1:2, EtOAc: petroleum ether 40 − 60 °C) the title compound (0.42 g, 58%) was obtained as a white solid; mpt 120-121 °C; $[\alpha]_D^{22}$ -100.0 (*c* 1.0, $CHCl_3$); ν_{max} (ATR)/ cm^{-1} 2922, 2850, 1767, 1450, 1368, 1022; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.52-0.69 (m, 2H, CyH), 0.82 [d, 3H, *J* 6.8, CH(C*H*$_3$)$_2$], 0.94-1.48 [m, 13H, CyH and CH(C*H*$_3$)$_2$], 1.60-1.80 (m, 10H, CyH), 1.96 [pent-d, 1H, *J* 6.8, 2.1, C*H*(CH$_3$)$_2$], 2.67 (dt, 1H, *J* 9.7 and 6.4, OC*H*HCy), 3.21 (dt, 1H, *J* 9.7 and 6.4, OCH*H*Cy), 4.01-4.07 (m, 2H, OC*H*$_2$Cy), 5.01 (dd, 1H, *J* 2.1 $J_{H\text{-}P}$ 0.9, C*H*N), 7.26-7.45 (m, 8H, ArC*H*), 7.26-7.45 (d, 2H, *J* 8.7, ArC*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 154.5 (d, $J_{C\text{-}P}$ 8.1,

C=O), 143.3 (Ar*C*), 138.4 (Ar*C*), 128.8 (2 x Ar*C*H), 128.4 (2 x Ar*C*H), 127.7 (Ar*C*H), 125.5 (5 x Ar*C*H), 90.5 [d, $J_{C\text{-}P}$ 7.0, *C*$(Ar)_2$], 73.9 (d, $J_{C\text{-}P}$ 8.0, *C*H_2Cy), 71.7 (d, $J_{C\text{-}P}$ 8.0, *C*H_2Cy), 69.1 (d, $J_{C\text{-}P}$ 3.0, *C*HN), 38.3 (d, $J_{C\text{-}P}$ 7.0, Cy-*C*H), 37.5 (d, $J_{C\text{-}P}$ 8.0, Cy-*C*H), 30.0 [*C*H(*C*$H_3)_2$], 29.1 (2 x Cy-*C*H_2), 28.8 (2 x Cy-*C*H_2), 26.3 (Cy-*C*H_2), 26.2 (Cy-*C*H_2), 25.5 (2 x Cy-*C*H_2), 25.3 (2 x Cy-*C*H_2), 21.1 (*C*H_3), 15.6 (*C*H_3); ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -4.14; *m/*z (ES^+) 617 (29%), 571 (50), 554.3014 (100%, MH^+. $C_{32}H_{45}NO_5P$ requires 554.3035).

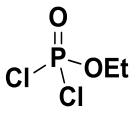
_O_-Dicyclohexyl methyl phosphoryl-1-phenylethanol, 87.



1-Phenylethanol (0.08 g, 0.65 mmol) was dissolved in THF (20 mL) with stirring and the solution was cooled to -78 °C. MeMgCl (0.26 mL, 2.8 M in THF, 0.72 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 1 h, before being cooled to -78 °C. Dicyclohexyl methyl chlorophosphate **83** (0.2 g, 0.65 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 2 h, before being quenched by the addition of $NH_4Cl_{(aq)}$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (10 mL), brine (10 mL) and dried over $MgSO_4$. The solution was filtered and the solvent was removed under reduced pressure and following flash column chromatography on silica gel (1:1, EtOAc: petroleum ether 40 − 60 °C) the title compound (0.24 g, 94%) was obtained as a clear oil; ν_{max} (ATR)/ cm^{-1} 2980, 2932, 1452; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 0.76-1.01 (m, 4H, Cy*H*), 1.06-1.31 (m, 6H, Cy*H*), 1.53 (d, 3H, *J* 6.5, C*H*CH_3), 1.57-1.82 (m, 12H, Cy*H*), 3.64-3.87 (m, 4H, OC*H*$_2$Cy), 4.91-5.10 (m, 2H, OC*H*$_2$Ar), 5.51 (p, 1H, *J* 6.9, C*H*CH_3), 7.19 − 7.40 (m, 5H, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 141.6 (d, $J_{C\text{-}P}$ 5.1, Ar*C*) , 128.3 (2 x Ar*C*H), 127.0 (Ar*C*H), 125.7 (2

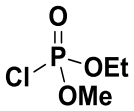
x Ar*C*H), 76.6 (d, $J_{C\text{-}P}$ 5.0, *C*HCH$_3$), 73.9 (d, $J_{C\text{-}P}$ 8.0, *C*H$_2$Cy), 71.7 (d, $J_{C\text{-}P}$ 8.0, *C*H$_2$Cy), 38.3 (d, $J_{C\text{-}P}$ 8.0, Cy-*C*H), 37.5 (d, $J_{C\text{-}P}$ 8.0, Cy-*C*H), 29.2 (2 x Cy-*C*H$_2$), 28.9 (2 x Cy-*C*H$_2$), 26.3 (Cy-*C*H$_2$), 26.2 (Cy-*C*H$_2$), 25.5 (2 x Cy-*C*H$_2$), 25.2 (2 x Cy-*C*H$_2$), 24.3 (CH*C*H$_3$); ^{31}P NMR (101 MHz; CDCl$_3$) δ_P -1.42.

Ethyl dichlorophosphate, 89.[26]



A solution of triethylamine (6.58 g, 9.10 mL, 65.1 mmol) and ethanol (3.80 mL, 65.1 mmol) in petroleum ether 40 – 60 °C (100 mL) was added over 1 h to a solution of phosphorus oxychloride (9.96 g, 6.10 mL, 65.1 mmol) in petroleum ether 40 – 60 °C (50 mL) at -30 °C under nitrogen. The solution was warmed to rt and allowed to stir for 2 h, filtered under nitrogen and the solvent removed under reduced pressure. The remaining colourless oil was purified by distillation (38 °C, 0.3 mbar) (lit.[50] 117 °C, 760 mmHg) to give the title compound (8.58 g, 68%) as a colourless oil; ^{1}H NMR (250 MHz; CDCl$_3$) δ_H 1.48 (td, 3H, *J* 7.1, $J_{P\text{-}H}$ 1.4, CH$_2$C*H*$_3$), 4.41 (dq, 2H, $J_{C\text{-}P}$ 10.9, *J* 7.1, C*H*$_2$CH$_3$); ^{13}C NMR (CDCl$_3$, 101 MHz): δ_C 68.6 (d, $J_{C\text{-}P}$ 9.1, O*C*H$_2$CH$_3$), 15.6 (d, $J_{C\text{-}P}$ 9.1, OCH$_2$*C*H$_3$); ^{31}P NMR (CDCl$_3$, 101 MHz) δ_P 6.79. All data was in accordance with the literature.

Ethyl methyl chlorophosphate, 90.[26]

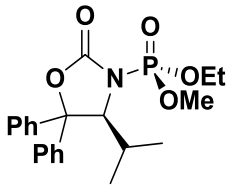


A solution of triethylamine (3.36 mL, 2.44 mL, 24.1 mmol) and methanol (0.77 mL, 24.1 mmol) in petroleum ether 40 – 60 °C (50 mL) was added over 1 h to a solution of ethyl dichlorophosphate **89** (3.92 g, 24.1 mmol) in petroleum ether 40 – 60 °C (50 mL) at -30 °C under nitrogen. The solution was warmed to rt and allowed to stir for 3 h, filtered under nitrogen and the solvent removed under reduced pressure. The remaining colourless oil was purified by distillation (22 °C, 0.02 mbar) (lit.[26] 22 °C, 0.3 mmHg) to give the title compound (2.82 g, 62%) as a colourless oil; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.40 (td, 3H, *J* 7.1, $J_{P\text{-}H}$ 1.2, CH_2CH_3), 3.89 (d, 3H, $J_{H\text{-}P}$ 13.7, OCH_3), 4.18-4.36 (m, 2H, 2 x CH_2CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 66.1 (d, $J_{C\text{-}P}$ 6.0, OCH_2CH_3), 55.4 (d, $J_{C\text{-}P}$ 6.0, OCH_3), 15.7 (d, $J_{C\text{-}P}$ 8.0, OCH_2CH_3); ^{31}P NMR ($CDCl_3$, 101 MHz) δ_P 5.97; *m/z* (ES^+) 421 (30%), 389 (8), 281 (100), 182(22). All data was in accordance with the literature.

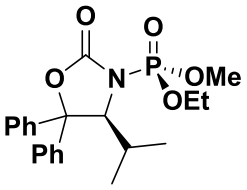
(R_P,4*S*)-3-Methyl ethyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone 91 and (S_P,4*S*)-3-Methyl ethyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone 92.

(*S*)-4-*Iso*propyl-5,5-diphenyl-2-oxazolidinone **56** (1.00 g, 3.55 mmol) was stirred as a suspension in THF (250 mL) and cooled to -78 °C. *n*-BuLi (1.56 mL, 2.5 M in hexanes, 3.91 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 1 h, before being cooled to -78 °C. Ethyl methyl chlorophosphate **90** (0.62 g, 3.91 mmol) in THF (10 mL) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring overnight, before being quenched by the addition of saturated $NH_4Cl_{(aq)}$ (50 mL). The resulting mixture was extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (30 mL), brine (30 mL) and dried over $MgSO_4$.

The filtered solvent was removed under reduced pressure, to give a crude product mixture of diastereoisomers as a white solids.

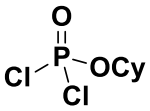


(R_P,4*S*)-3-Methyl ethyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.83 [d, 3H, *J* 6.9, CH(C*H*$_3$)$_2$], 1.19 [d, 3H, *J* 6.9, CH(C*H*$_3$)$_2$], 1.32 (t, 3H, *J* 7.1, CH_2CH_3), 1.95 [hd, 1H, C*H*(CH$_3$)$_2$], 3.92 (d, 3H, *J* 11.7, OC*H*$_3$), 4.04 – 4.28 (m, 2H, C*H*$_2$CH$_3$), 5.04-5.06 (m, 1H, C*H*NP), 7.24 − 7.44 (m, 8H, ArC*H*), 7.67-7.70 (m, 2H, ArC*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 154.6 (*C*=O), 143.3 (Ar*C*), 138.4 (Ar*C*), 128.9 (2 x Ar*C*H), 128.4 (3 x Ar*C*H), 127.7 (Ar*C*H), 125.6 (2 x Ar*C*H), 125.5 (2 x Ar*C*H), 90.5 (*C*Ar$_2$), 78.0 (*C*H$_3$O), 69.0 (d, $J_{C\text{-}P}$ 3.3, *C*HN), 64.3 (*C*H$_2$CH$_3$), 54.9 (d, $J_{C\text{-}P}$ 7.0, *C*H), 33.3 (*C*H$_2$), 32.4 (d, $J_{C\text{-}P}$ 6.1, *C*H$_2$), 30.1 [*C*H(CH$_3$)$_2$], 24.9 (*C*H$_2$), 23.4 (2 x *C*H$_2$), 21.1 [CH(*C*H$_3$)$_2$], 16.3 (CH$_2$*C*H$_3$), 15.5 [CH(*C*H$_3$)$_2$]; ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -3.19;



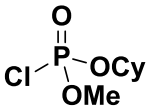
(S_P,4*S*)-3-Methyl ethyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.83 [d, 3H, *J* 6.9, CH(C*H*$_3$)$_2$], 1.19 [d, 3H, *J* 6.9, CH(C*H*$_3$)$_2$], 1.32 (t, 3H, *J* 6.9, CH_2CH_3), 1.95 [m, 1H, C*H*(CH$_3$)$_2$], 3.68 (d, 3H, *J* 11.6, OC*H*$_3$), 4.04 – 4.28 (m, 2H, C*H*$_2$CH$_3$), 5.04-5.06 (m, 1H, C*H*NP), 7.24 − 7.44 (m, 8H, ArC*H*), 7.67-7.70 (m, 2H, ArC*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 154.6 (*C*=O), 143.3 (Ar*C*), 138.4 (Ar*C*), 128.9 (2 x Ar*C*H), 128.4 (3 x Ar*C*H), 127.7 (Ar*C*H), 125.6 (2 x Ar*C*H), 125.5 (2 x Ar*C*H), 90.5 (*C*Ar$_2$), 78.0 (*C*H$_3$O), 69.0 (d, $J_{C\text{-}P}$ 3.3, *C*HN), 64.3 (*C*H$_2$CH$_3$), 54.9 (d, $J_{C\text{-}P}$ 7.0, *C*H), 33.3 (*C*H$_2$), 32.4 (d, $J_{C\text{-}P}$ 6.1, *C*H$_2$), 30.1 [*C*H(CH$_3$)$_2$], 24.9 (*C*H$_2$), 23.4 (2 x *C*H$_2$), 21.1 [CH(*C*H$_3$)$_2$], 16.3 (CH$_2$*C*H$_3$), 15.5 [CH(*C*H$_3$)$_2$]; ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -3.34;

Cyclohexyl dichlorophosphate, 94.[51]



A solution of triethylamine (8.40 mL, 6.07 g, 60.0 mmol) and cyclohexanol (6.25 mL, 6.01 g, 60.0 mmol) in petroleum ether 40 – 60 °C (100 mL) was added over 1 h to a solution of phosphorus oxychloride (5.60 mL, 9.20 g, 60.0 mmol) in petroleum ether 40 – 60 °C (50 mL) at -30 °C under a nitrogen atmosphere. The solution was warmed to rt and allowed to stir for 2 h, filtered under nitrogen and the solvent removed under reduced pressure to give the title compound (12.28 g, 94%) as a colourless oil that was used without further purification; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.30-1.48 (m, 3H, Cy*H*), 1.52-1.59 (m, 1H, Cy*H*), 1.71-1.89 (m, 4H, Cy*H*), 2.02-2.07 (m, 2H, Cy*H*), 4.77-4.86 (m, 1H, Cy*H*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 84.2 [d, $J_{C\text{-}P}$ 9.8, O*C*H], 32.8 [d, $J_{C\text{-}P}$ 4.9, 2 x *C*H_2], 24.7 (2 x *C*H_2), 23.2 (*C*H_2); ^{31}P NMR ($CDCl_3$, 101 MHz) δ_P 5.70. All data was in accordance with the literature.

Cyclohexyl methyl chlorophosphate, 95.

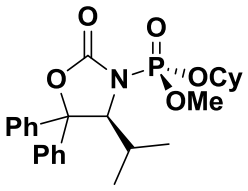


A solution of triethylamine (7.61 mL, 5.52 g, 54.56 mmol) and methanol (2.21 mL, 1.75 g, 54.56 mmol) in petroleum ether 40 – 60 °C (50 mL) was added over 1 h to a solution of cyclohexyl dichlorophosphate **94** (11.84 g, 54.56 mmol) in petroleum ether 40 – 60 °C (50 mL) at -30 °C under nitrogen. The solution was warmed to rt and allowed to stir for 3 h, filtered under nitrogen and the solvent removed under reduced pressure, to give the title compound (10.18 g, 88%) as a yellow oil that was used without further purification; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.23-1.41 (m, 3H, C*H*H and CH_2), 1.47-1.54 (m, 1H, C*H*H), 1.58-1.66 (m, 2H, CH_2), 1.71-1.77 (m, 2H, CH_2), 1.93-2.03 (m, 2H, CH_2), 3.87 (d, 3H, $J_{H\text{-}P}$ 13.8, OCH_3), 4.54-4.63 [m, 1H,

C*H*(CH_2)$_2$]; ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 80.6 [d, $J_{C\text{-}P}$ 7.5, O*C*H], 55.3 (d, $J_{C\text{-}P}$ 6.9, O*C*H_3), 33.0 [d, $J_{C\text{-}P}$ 4.7, OCH(*C*H_2)$_2$], 32.7 [d, $J_{C\text{-}P}$ 4.7, OCH(*C*H_2)$_2$], 24.9 (2 x *C*H_2), 23.3 (*C*H_2); ^{31}P NMR ($CDCl_3$, 101 MHz) δ_P 4.92; *m/z* (ES^+) 230 (6%), 213.0441 (12%, MH^+. $C_7H_{15}ClO_3P$ requires 213.0442), 133 (32), 130 (100).

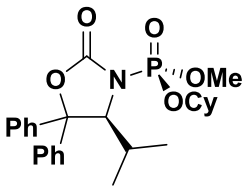
(R_P,4*S*)-3-Methyl cyclohexyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone 96 and (S_P,4*S*)-3-Methyl cyclohexyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone 97.

(*S*)-4-Isopropyl-5,5-diphenyl-2-oxazolidinone **56** (0.10 g, 0.36 mmol) was stirred as a suspension in THF (250 mL) and cooled to -78 °C. *n*BuLi (0.16 mL, 2.5 M in hexanes, 0.39 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 1 h, before being cooled to -78 °C. Cyclohexyl methyl chlorophosphate **95** (0.16 g, 0.73 mmol) in THF (10 mL) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring overnight, before being quenched by the addition of saturated $NH_4Cl_{(aq)}$ (50 mL). The resulting mixture was extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (30 mL), brine (30 mL) and dried over $MgSO_4$. The filtered solvent was removed under reduced pressure, to give a crude product mixture of diastereoisomers as a white solids which were separated by reapeated flash column chromatography on silica gel (1:2, EtOAc: petroleum ether 40 – 60 °C)



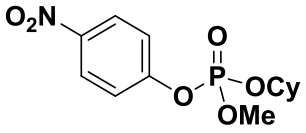
(R_P,4*S*)-3-Methyl cyclohexyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone (0.052 g, 32%); mpt 116-118 °C; $[\alpha]^{22}_D$ -140 (*c* 0.5, $CHCl_3$); ν_{max} (ATR)/ cm^{-1} 2931, 2857, 1762, 1449; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.83 [d, 3H, *J* 6.9, CH(C*H*$_3$)$_2$], 1.03-1.17 (m, 3H, Cy*H*), 1.19 [d, 3H, *J* 6.9, CH(C*H*$_3$)$_2$], 1.32-1.45 (m, 3H, Cy*H*), 1.55-1.64 (m, 2H, Cy*H*), 1.78-1.83 (m, 2H, Cy*H*), 1.95 [hd, 1H, *J* 6.9, 2.1, C*H*(CH_3)$_2$], 3.52-3.60 [m,

1H, C*H*(CH_2)$_2$], 3.92 (d, 3H, *J* 11.7, OC*H*$_3$), 5.05 (dd, 1H, $J_{H\text{-}P}$ 3.2, *J* 2.3, C*H*NP), 7.24 – 7.44 (m, 8H, ArC*H*), 7.67-7.70 (m, 2H, ArC*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 154.6 (d, *J* 7.7, *C*=O), 143.3 (Ar*C*), 138.4 (Ar*C*), 128.9 (2 x Ar*C*H), 128.4 (3 x Ar*C*H), 127.7 (Ar*C*H), 125.6 (2 x Ar*C*H), 125.5 (2 x Ar*C*H), 90.5 (*C*Ar$_2$), 78.0 (*C*H$_3$O), 69.0 (d, $J_{C\text{-}P}$ 3.3, *C*HN), 54.9 (d, $J_{C\text{-}P}$ 7.0, *C*H), 33.3 (*C*H$_2$), 32.4 (d, $J_{C\text{-}P}$ 6.1, *C*H$_2$), 30.1 [*C*H(CH_3)$_2$], 24.9 (*C*H$_2$), 23.4 (2 x *C*H$_2$), 21.1 [CH(*C*H$_3$)$_2$], 15.5 [CH(*C*H$_3$)$_2$]; ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -4.09; *m/z* (ESI$^+$) 503 (10%), 480 (21), 458.2093 (13%, MH$^+$. $C_{25}H_{33}NO_5P$ requires 458.2091), 376 (100).



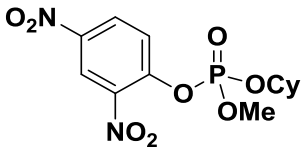
(S_P,4*S*)-3-Methyl cyclohexyl phosphoryl-4-isopropyl-5,5-diphenyl-2-oxazolidinone (0.015 g, 9%); mpt 176-178 °C; $[\alpha]^{22}_D$ -100 (*c* 0.5, $CHCl_3$); ν_{max} (ATR)/ cm^{-1} 2946, 2860, 1761, 1449; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.83 [d, 3H, *J* 6.7, CH(C*H*$_3$)$_2$], 1.10 [d, 3H, *J* 7.1, CH(C*H*$_3$)$_2$], 1.23-1.40 (m, 3H, Cy*H*), 1.47-1.53 (m, 1H, Cy*H*), 1.59-1.69 (m, 2H, Cy*H*), 1.72-1.80 (m, 2H, Cy*H*), 1.94-2.01 [m, 3H, Cy*H*, C*H*(CH_3)$_2$], 3.02 (d, 3H, *J* 11.9, OC*H*$_3$), 4.61-4.69 [m, 1H, OC*H*(CH_2)$_2$], 5.01 (dd, 1H, $J_{H\text{-}P}$ 3.1, *J* 2.5, C*H*NP), 7.25-7.30 (m, 3H, ArC*H*), 7.33-7.40 (m, 3H, ArC*H*), 7.45 (d, 2H, *J* 7.4, Ar*C*H), 7.69-7.72 (m, 2H, Ar*C*H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 154.5 (d, $J_{C\text{-}P}$ 7.5, *C*=O), 143.3 (Ar*C*), 138.3 (Ar*C*), 128.8 (2 x Ar*C*H), 128.4 (3 x Ar*C*H), 127.8 (Ar*C*H), 125.6 (2 x Ar*C*H), 125.5 (2 x Ar*C*H), 90.5 (d, $J_{C\text{-}P}$ 7.3, *C*Ar$_2$), 79.0 (d, $J_{C\text{-}P}$ 7.4, *C*H$_3$), 69.3 (d, $J_{C\text{-}P}$ 3.2, *C*HN), 53.1 (d, $J_{C\text{-}P}$ 5.9, O*C*H), 33.3 (d, $J_{C\text{-}P}$ 4.2, *C*H$_2$), 33.2 (d, $J_{C\text{-}P}$ 4.6, *C*H$_2$), 30.0 [*C*H(CH_3)$_2$], 25.1 (*C*H$_2$), 23.4 (2 x *C*H$_2$), 21.2 [CH(*C*H$_3$)$_2$], 15.6 [CH(*C*H$_3$)$_2$]; ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -3.65; *m/z* (ESI$^+$) 531 (8%), 503 (12), 480 (39), 458.2096 (32%, MH$^+$. $C_{25}H_{33}NO_5P$ requires 458.2091), 376 (100), 124 (57).

Cyclohexyl methyl-4-nitrophenylphosphate, 98.



A solution of triethylamine (4.89 mL, 3.54 g, 35.1 mmol), *N*-methylimidazole (0.28 mL, 0.29 g, 3.51 mmol) and 4-nitrophenol (4.88 g, 35.1 mmol) in petroleum ether 40 – 60 °C (50 mL) was added over 1 h to a solution of cyclohexyl methyl chlorophosphate **95** (7.46 g, 35.1 mmol) in petroleum ether 40 – 60 °C (50 mL) at -30 °C. The solution was warmed to rt and allowed to stir for 3 h, filtered under nitrogen and the solvent removed under reduced pressure. Following flash chromatography on silica gel (1:3, EtOAc: petroleum ether 40 – 60 °C) the title compound (2.36 g, 21%) was obtained as yellow oil; ν_{max} (ATR)/cm^{-1} 2939, 2860, 1592, 1520, 1491; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.23-1.43 (m, 3H, C*H*$_2$ an C*H*H), 1.50-1.66 (m, 3H, C*H*$_2$ and CH*H*), 1.72-1.82 (m, 2H, C*H*$_2$), 1.92-2.02 (m, 2H, C*H*$_2$), 3.89 (d, 3H, *J* 11.5, OC*H*$_3$), 4.51-4.59 [m, 1H, OC*H*$(CH_2)_2$], 7.40 [2H, $(AX)_2$, 2 x ArC*H*], 8.26 [2H, $(AX)_2$, 2 x ArC*H*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 155.6 (d, $J_{C\text{-}P}$ 6.4, Ar*C*O), 144.6 (Ar*C*), 125.6 (2 x Ar*C*H), 120.6 (d, $J_{C\text{-}P}$ 5.4, 2 x Ar*C*H), 79.4 (d, $J_{C\text{-}P}$ 6.4, O*C*H), 55.0 (d, $J_{C\text{-}P}$ 6.4, O*C*H$_3$), 33.2 (d, $J_{C\text{-}P}$ 4.5, *C*H$_2$), 33.1 (d, $J_{C\text{-}P}$ 4.6, *C*H$_2$), 24.9 (*C*H$_2$), 23.4 (*C*H$_2$); ^{31}P NMR ($CDCl_3$, 101 MHz) δ_P -6.81; *m/z* (ES^+) 338 (100%, MNa^+), 316.0946 (30%, MH^+. $C_{13}H_{19}NO_6P$ requires 316.0945), 275 (25).

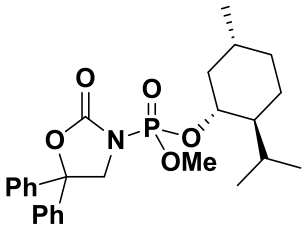
Cyclohexyl methyl-2,4-dinitrophenylphosphate, 99.



A solution of triethylamine (6.48 mL, 4.71 g, 46.55 mmol), *N*-methylimidazole (0.37 mL, 0.38 g, 4.55 mmol) and 2,4-dinitrophenol (6.48 g, 46.55 mmol) in petroleum ether 40 – 60 °C (50 mL) was added over 1 h to a solution of cyclohexyl methyl

chlorophosphate **95** (9.90 g, 46.55 mmol) in petroleum ether 40 – 60 °C (50 mL) at -30 °C. The solution was warmed to rt and allowed to stir for 3 h, filtered under nitrogen and the solvent removed under reduced pressure. Following flash chromatography on silica gel (1:1, EtOAc: petroleum ether 40 – 60 °C) the title compound (6.82 g, 41%) was obtained as yellow oil; ν_{max} (ATR)/cm^{-1} 3114, 2940, 2861, 1607, 1533; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.23-1.43 (m, 3H, Cy*H*), 1.50-1.66 (m, 3H, Cy*H*), 1.72-1.81 (m, 2H, Cy*H*), 1.92-2.02 (m, 2H, Cy*H*), 3.94 (d, 3H, $J_{H\text{-}P}$, 11.7, OC*H*$_3$), 4.55-4.63 [m, 1H, OCH$(CH_2)_2$], 7.87 (dd, 1H, *J* 9.2 and *J* 0.9, ArC*H*), 8.47 (dd, 1H, *J* 9.2 and *J* 2.7, ArC*H*), 8.82 (dd, 1H, *J* 2.7 and *J* 0.9, ArC*H*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 148.3 (Ar*C*), 148.2 (Ar*C*), 143.6 (Ar*C*), 128.8 (Ar*C*H), 123.3 (d, $J_{C\text{-}P}$ 2.3, Ar*C*H), 121.6 (Ar*C*H), 80.5 (d, $J_{C\text{-}P}$ 6.9, O*C*H), 55.7 (d, $J_{C\text{-}P}$ 6.8, O*C*H$_3$), 33.2 (d, $J_{C\text{-}P}$ 4.1, *C*H$_2$), 33.0 (d, $J_{C\text{-}P}$ 4.7, *C*H$_2$), 24.9 (*C*H$_2$), 23.4 (2 x *C*H$_2$); ^{31}P NMR ($CDCl_3$, 101 MHz) δ_P -7.85; *m/z* (ESI$^+$) 378 (32%), 316.0797 (6%, MH$^+$. $C_{13}H_{18}N_2O_8P$ requires 316.0795), 279 (100).

3-Menthyl methyl phosphoryl-5,5-diphenyl-2-oxazolidinone 104/105.



5,5-diphenyl-2-oxazolidinone **107** (0.50 g, 1.78 mmol) was stirred as a suspension in THF (30 mL) and cooled to -78 °C. *n*BuLi (0.78 mL, 2.5 M in hexanes, 1.95 mmol) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring for 1 h, before being cooled to -78 °C. (1*R*)-Menthyl methyl chlorophosphate **106** (0.96 g, 3.56 mmol) in THF (10 mL) was added dropwise and the solution was allowed to warm to rt. The reaction mixture was left stirring overnight, before being quenched by the addition of saturated $NH_4Cl_{(aq)}$ (50 mL). The resulting mixture was extracted with EtOAc (3 × 60 mL). The combined organic

extracts were washed with $NaHCO_{3(aq)}$ (30 mL), brine (30 mL) and dried over $MgSO_4$. The filtered solvent was removed under reduced pressure, followed by flash column chromatography on silica gel (1:3, EtOAc: petroleum ether 40 – 60 °C) to give a mix of diastereoisomers of the title compound (0.052 g, 32%) as a white solid;

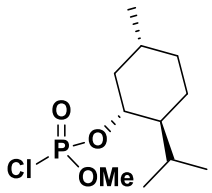
Diastereoisomer A:

ν_{max} (ATR)/ cm^{-1} 2952, 2869, 1772, 1450, 1268, 998; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.60 (d, 3H, *J* 6.9, CH_3), 0.75-1.29 [m, 9H, CH(CH_3)$_2$, CH_2, C*H*], 1.35-1.43 (m, 1H, CH_2), 1.60-1.70 (m, 2H, CH_2), 1.84-1.87 (m, 1H, CH_2), 1.96-2.08 (m, 1H, CH_2), 2.12-2.20 [m, 1H, C*H*(CH_3)$_2$]; 3.76 (d, 3H, *J* 8.8, OCH_3), 4.20-4.31 (m, 1H, OC*H*), 4.49-4.59 (m, 2H, NCH_2), 7.32-7.47 (m, 10H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.2 (*C*=O), 141.4 (Ar*C*), 141.3 (Ar*C*), 128.8 (4 x Ar*C*H), 128.6 (2 x Ar*C*H), 125.4 (4 x Ar*C*H), 85.7 (*C*Ph$_2$), 81.2 (d, $J_{C\text{-}P}$ 7.2, O*C*H$_3$), 57.3 (d, $J_{C\text{-}P}$ 4.0, *C*H$_2$), 54.4 (d, $J_{C\text{-}P}$ 6.0, *C*H), 48.2 (*C*H), 42.6 (*C*H$_2$), 33.8 (*C*H$_2$), 31.6 (*C*H), 25.4 (*C*H), 22.7 (*C*H$_2$), 21.9 (*C*H$_3$), 20.9 (*C*H$_3$), 15.5 (*C*H$_3$); ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -3.92; *m/z* (ESI^+) 494.2077 (34%, MNa^+. $C_{26}H_{34}NO_5P$ requires 494.2067), 334 (100%).

Diastereoisomer B:

ν_{max} (ATR)/ cm^{-1} 2952, 2869, 1772, 1450, 1268, 998; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.75-1.29 [m, 13H, CH(CH_3)$_2$, CH_2, C*H*], 1.35-1.43 (m, 1H, CH_2), 1.60-1.70 (m, 2H, CH_2), 1.84-1.87 (m, 1H, CH_2), 2.12-2.20 [m, 1H, C*H*(CH_3)$_2$], 3.73 (d, 3H, *J* 8.8, OCH_3), 4.20-4.31 (m, 1H, OC*H*), 4.49-4.59 (m, 2H, NCH_2), 7.32-7.47 (m, 10H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.1 (*C*=O), 141.4 (Ar*C*), 141.3 (Ar*C*), 128.8 (4 x Ar*C*H), 128.5 (2 x Ar*C*H), 125.3 (4 x Ar*C*H), 85.6 (*C*Ph$_2$), 80.7 (d, $J_{C\text{-}P}$ 6.9, *C*H$_3$O), 57.3 (d, $J_{C\text{-}P}$ 4.0, *C*H$_2$), 54.4 (d, $J_{C\text{-}P}$ 6.0, *C*H), 48.1 (*C*H), 42.0 (*C*H$_2$), 33.8 (*C*H$_2$), 31.4 (*C*H), 25.4 (*C*H), 22.7 (*C*H$_2$), 21.9 (*C*H$_3$), 20.9 (*C*H$_3$), 15.5 (*C*H$_3$); ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -4.06; *m/z* (ESI^+) 494.2077 (34%, MNa^+. $C_{26}H_{34}NO_5P$ requires 494.2067), 334 (100%).

(1*R*)-Menthyl methyl chlorophosphate, 106.



A solution of triethylamine (1.70 mL, 1.23 g, 12.15 mmol) and methanol (0.49 mL, 0.39 g, 12.15 mmol) in petroleum ether 40 – 60 °C (50 mL) was added over 1 h to a solution of (1*R*)-menthyl dichlorophosphate **112** (3.32 g, 12.15 mmol) in petroleum ether 40 – 60 °C (50 mL) at -30 °C under nitrogen. The solution was warmed to rt and allowed to stir for 3 h, filtered under nitrogen and the solvent removed under reduced pressure, to give the title compound (2.84 g, 87%) as a clear yellow oil that was used without further purification;

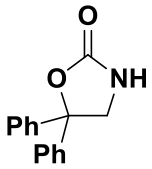
Diastereoisomer A:

ν_{max} (ATR)/cm^{-1} 2955, 2922, 2870, 1456, 1287, 999; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.82-1.17 (m, 8H, CH_2 and CH_3), 1.23 (dd, 1H, *J* 11.6, 4.8, C*H*), 1.39-1.51 (m, 2H, CH_2), 1.61-1.73 (m, 3H, CH_2), 1.96-2.02 (m, 1H, CH_2), 2.09-2.23 (m, 2H, C*H* and *C*H_2), 2.30-2.35 (m, 1H, C*H*), 3.90 (d, 3h, *J* 13.8, CH_3), 4.65 (m, 1H, OC*H*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 83.0 (d, $J_{C\text{-}P}$ 8.4, O*C*H_3), 55.2 (*C*H), 48.4 (*C*H_2), 41.9 (*C*H_2), 33.8 (*C*H_2), 31.6 (*C*H), 25.7 (*C*H), 23.0 (*C*H_2), 21.9 (*C*H_3), 20.9 (*C*H_3), 15.8 (*C*H_3); ^{31}P NMR ($CDCl_3$, 101 MHz) δ_P 5.58.

Diastereoisomer B:

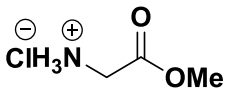
ν_{max} (ATR)/cm^{-1} 2955, 2922, 2870, 1456, 1287, 999; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.82-1.17 (m, 8H, CH_2 and CH_3), 1.29 (dd, 1H, *J* 12.1, 4.8, C*H*), 1.39-1.51 (m, 2H, CH_2), 1.61-1.73 (m, 3H, CH_2), 1.96-2.02 (m, 1H, CH_2), 2.09-2.23 (m, 2H, C*H* and *C*H_2), 2.30-2.35 (m, 1H, C*H*), 3.90 (d, 3h, *J* 13.8, CH_3), 4.65 (m, 1H, OC*H*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 82.8 (d, $J_{C\text{-}P}$ 8.0, O*C*H_3), 55.2 (*C*H), 48.3 (*C*H_2), 42.4 (*C*H_2), 33.8 (*C*H_2), 31.6 (*C*H), 25.7 (*C*H), 23.0 (*C*H_2), 21.8 (*C*H_3), 20.8 (*C*H_3), 15.7 (*C*H_3); ^{31}P NMR ($CDCl_3$

5,5-Diphenyl-2-oxazolidinone, 107.[38]



N-Boc-2-amino-1,1-diphenylethanol **111** (3.73 g, 11.90 mmol) was dissolved in THF (50 mL) and the resulting solution was cooled to 0 °C. KO^{t}Bu (1.47 g, 13.09 mmol) was added as a single portion and the reaction was left stirring at this temperature for 1 h, before being allowed to warm to rt and left stirring overnight. The reaction was quenched with $NH_4Cl_{(aq)}$ (30 mL), The resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (30 mL), brine (30 mL) and dried over $MgSO_4$ before being filtered and the solvent was removed under reduced pressure. Following recrystallisation from hexane/EtOAc the title compound (1.99 g, 70%) was obtained as a pale yellow solid; 195-197 °C (lit.[38], 196-197 °C); ν_{max} (ATR)/cm^{-1} 2801, 2674, 1735, 1451, 1294, 1231, 1078; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.23 (s, 2H,CH_2), 5.92 (s, 1H, N*H*), 7.21-7.45 (m, 10H, Ar*H*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 158.8 (*C*=O), 142.4 (2 x Ar*C*), 128.7 (4 x Ar*C*H), 128.3 (2 x Ar*C*H), 125.5 (4 x Ar*C*H), 86.6 (*C*Ar$_2$), 53.5 (*C*H$_2$); *m/z* (ESI$^+$) 262.1 (6%), 240.1019 (100%, MH$^+$. $C_{15}H_{13}NO_2$ requires 240.1019), 196.1 (23), 146.0 (5). All data was in accordance with the literature.

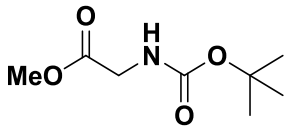
Glycine methyl ester hydrochloride, 109.[52]



Glycine (20 g, 266.4 mmol) was stirred as a suspension in MeOH (200 mL) and the mixture was cooled to 0 °C. Thionyl chloride (31.70 g, 19.35 mL, 266.4 mmol) was added dropwise. The resulting solution was allowed to warm to rt and left to stir for 48 h. The solvent was removed under reduced pressure and the title compound (31.08 g, 93%) was obtained as a white solid; ^{1}H NMR (400 MHz; D_2O) δ_H 3.79 (s, 3H,

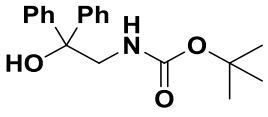
C*H*$_3$), 3.89 (s, 2H, C*H*$_2$); ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 168.6 (*C*=O), 53.3 (*C*H$_3$), 39.9 (*C*H$_2$). All data was in accordance with the literature.

_N_-Boc-glycine methyl ester, 110.[53]



Glycine methyl ester hydrochloride **109** (31.1 g, 247.5 mmol) was dissolved in EtOH (200 mL) and the resulting solution was cooled to 0 °C. Sodium hydrogen carbonate (59.4 g, 272.3 mmol) was added as a single portion, immediately followed by di-tert-butyl dicarbonate (22.9 g, 272.3 mmol). The reaction mixture was allowed to warm to rt and left to stir for 48 h, before being filtered through Hyflo Super Cel®. The solvent was removed under reduced pressure, the residue redissolved in Et_2O (50 mL) and again filtered through Hyflo Super Cel®. The solvent was removed under reduced pressure to give the title compound (41.2 g, 88 %) as a clear oil; ν_{max} (ATR)/cm^{-1} 2979, 1694, 1513, 1367, 1157; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.45 [s, 9H, C(C*H*$_3$)$_3$], 3.75 (s, 3H, C*H*$_3$), 3.92 (d, 2H, *J* 5.6, C*H*$_2$), 5.09 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 170.9 (*C*=O), 155.7 (*C*=O), 80.0 [*C*(CH$_3$)$_3$], 52.2 (*C*H$_3$), 42.3 (*C*H$_2$), 28.3 (*C*H$_3$); *m/z* (ESI$^+$) 233 (18%), 212.0890 (6%, MNa$^+$. $C_8H_{15}NO_4$ requires 212.0893), 134 (100). All data was in accordance with the literature.

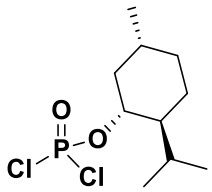
_N_-Boc-2-amino-1,1-diphenylethanol, 111.[38]



Magnesium turnings (5.14 g, 211.4 mmol) were stirred in THF (35 mL) under an atmosphere of nitrogen. Bromobenzene (33.19 g, 22.2 mL, 211.4 mmol) was added dropwise to the reaction mixture, which was heated to initiate an exothermic

reaction. The remaining bromobenzene was diluted with THF (70 mL) and the resulting solution was added to the reaction vessel at a rate as to ensure heating at a steady reflux. Once addition was complete, the reaction mixture was cooled to 0 °C. *N*-Boc-glycine methyl ester **110** (10.0 g, 52.9 mmol) was dissolved in THF (35 mL) and the resulting solution was added dropwise to the reaction vessel. The reaction mixture was allowed to warm to rt and left stirring for 48 h, before being quenched by addition of $NH_4Cl_{(aq)}$ (50 mL). The resulting mixture was extracted with EtOAc (3 × 40 mL), washed with brine (25 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure and following recrystallisation from hexane/EtOAc the title compound (10.93 g, 66%) was obtained as a white solid; 99-102 °C (lit.[38], 100-102 °C); ν_{max} (ATR)/cm^{-1} 2676, 1676, 1530, 1355, 1252, 1057; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.41 [s, 9H, C(C*H*$_3$)$_3$], 3.48 (s, 1H, O*H*), 3.96 (d, 2H, *J* 6.2, C*H*$_2$), 4.79 (s, 1H, N*H*), 7.25-7.30 (m, 2H, Ar*H*), 7.34-7.37 (m, 4H, Ar*H*), 7.44-7.46 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 157.2 (Ar*C*), 157.1 (Ar*C*), 144.7 (*C*=O), 128.4 (4 x Ar*C*H), 127.3 (2 x Ar*C*H), 126.2 (4 x Ar*C*H), 80.0 [*C*(CH$_3$)$_3$], 50.4 (*C*H$_2$), 28.3 (*C*H$_3$); *m/z* (ESI$^+$) 336.1570 (12%, MNa$^+$. $C_{19}H_{23}NO_3$ requires 336.1570), 240.1 (100%), 196.1 (15). All data was in accordance with the literature.

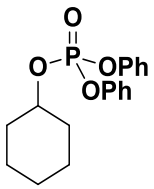
(1*R*)-Menthyl dichlorophosphate, 112.[51]



A solution of triethylamine (2.02 g, 2.79 mL, 20 mmol) and *D*-menthol (3.13 g, 20 mmol) in petroleum ether 40 – 60 °C (100 mL) was added over 1 h to a solution of phosphorus oxychloride (3.07 g, 1.87 mL, 20 mmol) in petroleum ether 40 – 60 °C (50 mL) at -30 °C under nitrogen. The solution was warmed to rt and allowed to stir for 2 h, filtered under nitrogen and the solvent removed under reduced pressure to give the title compound (5.06 g, 93%) as a colourless oil that was used without

further purification; ν_{max} (ATR)/cm^{-1} 2953, 2928, 2871, 1456, 1293, 991; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.83-1.17 (m, 8H, CH_2 and CH_3), 1.33-1.55 (m, 3H, C*H* and CH_2), 1.61-1.77 (m, 3H, CH_2), 1.96-2.02 (m, 1H, CH_2), 2.06-2.23 (m, 2H, C*H* and *C*H_2), 2.33-2.39 (m, 1H, C*H*), 4.65 (ddd, 1H, *J* 20.6, 10.6 and 4.6, OC*H*); ^{13}C NMR ($CDCl_3$, 101 MHz); δ_C 86.7 (d, $J_{C\text{-}P}$ 10.9, *C*H), 48.3 (d, $J_{C\text{-}P}$ 8.2, *C*H_2), 42.2 (*C*H_2), 33.7 (*C*H_2), 31.8 (*C*H), 25.8 (*C*H), 23.1 (*C*H_2), 21.8 (*C*H_3), 20.8 (*C*H_3), 15.8 (*C*H_3); ^{31}P NMR ($CDCl_3$, 101 MHz) δ_P 7.14. All data was in accordance with the literature.

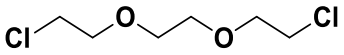
Cyclohexyl diphenyl phosphate, 119.[54]



A solution of diphenyl chlorophosphate (4.94 mL, 5.90 g, 21.97 mmol) in THF (20 mL) was added dropwise to a solution of cyclohexanol (2.08 mL, 2.00 g, 19.97 mmol), triethylamine (2.79 mL, 2.02 g, 19.97 mmol) and N-methylimidazole (0.16 mL, 0.16 g, 2.00 mmol) that was cooled to 0 °C. The solution was allowed to warm to rt and left stirring for 2 h, before being quenched by the addition of $NH_4Cl_{(aq)}$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (10 mL), brine (10 mL) and dried over $MgSO_4$. The solution was filtered and the solvent was removed under reduced pressure, and following flash column chromatography on silica gel (1:2, EtOAc: petroleum ether 40 – 60 °C) the title compound (4.47 g, 67%) was obtained as a clear oil; ν_{max} (ATR)/ cm^{-1} 2934, 2860, 1590, 1487, 1283, 1188, 1009, 999, 937; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.23-1.40 (m, 3H, 3 x Cy*H*), 1.48-1.66 (m, 3H, 3 x Cy*H*), 1.69− 1.79 (m, 2H, 2 x Cy*H*) 1.90-2.01 (m, 2H, 2 x Cy*H*), 4.61-4.69 [m, 1H, C*H*$(CH_2)_2$], 7.18-7.28 (m, 6H, Ar*H*), 7.33-7.38 (m, 4H, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 150.8 (Ar*C*), 150.7 (Ar*C*), 129.7 (4 x Ar*C*H), 125.2 (2 x Ar*C*H), 120.2 (2 x Ar*C*H), 120.1 (2 x

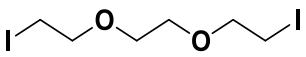
Ar*C*H), 79.5 (d, $J_{C\text{-}P}$ 6.6, *CH*O), 33.2 (*C*H_2), 33.1 (*C*H_2), 25.0 (*C*H_2), 23.4 (2 x *C*H_2); ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -12.67. All data was in accordance with the literature.

1,2-*bis*(2-Chloroethoxy)ethane, 128.[55]



A solution of thionyl chloride (1.93 mL, 3.17 g, 26.64 mmol) in hexane (20 mL) was added dropwise over 3 h to a solution of triethyleneglycol (1.59 mL, 2.00 g, 13.32 mmol) and pyridine (2.15 mL, 2.11 g, 26.64 mmol) in hexane (150 mL). The mixture was brought to reflux for 12 h and then cooled to rt before being quenched by the dropwise addition of hydrochloric acid (6.3 mL, 11.8 M) diluted with H_2O (50 mL). The resulting mixture was extracted with Hexane (3 × 20 mL) and the combined organic extracts dried were washed with H_2O (3 x 30 mL) before being dried with $MgSO_4$, which was filtered and the solvent removed under reduced pressure to give the title compound (3.89 g, 78%) was obtained as a lucid oil that required no further purification; ν_{max} (ATR)/ cm^{-1} 2865, 1298, 1108; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.65-3.68 (m, 4H, 2 x ClC*H*$_2$), 3.72 (s, 4H, OC*H*$_2$C*H*$_2$O), 3.78-3.81 (m, 4H, 2 x OC*H*$_2$CH$_2$Cl); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 71.4 (2 x O*C*H$_2$), 70.6 (2 x O*C*H$_2$), 42.7 (2 x Cl*C*H$_2$). All data was in accordance with the literature.

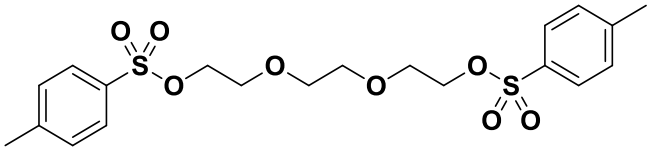
1,2-b*is*(2-Iodoethoxy)ethane 129.[56][57]



1,2-bis(2-Chloroethoxy)ethane **128** (1.64 g, 8.76 mmol) was dissolved in acetone (100 mL) and sodium iodide (6.56 g, 43.78 mmol) was added to the solution before being heated to 40 °C and stirred for 72 h. The solution was allowed to return to rt before the solvent was removed under reduced pressure and H_2O (10 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (4 x 50 mL) and the

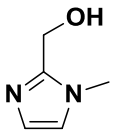
combined extracts were washed with brine (30 mL) and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. To give the title compound (2.82 g, 87%) as a yellow oil that required no further purification; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.28-3.31 (m, 4H, 2 x IC*H*$_2$), 3.70 (s, 4H, OC*H*$_2$C*H*$_2$O), 3.78-3.81 (m, 4H, 2 x OC*H*$_2$CH$_2$I). All data was in accordance with the literature.

1,2-b*is*(2-Tosylethoxy)ethane, 130.[57]



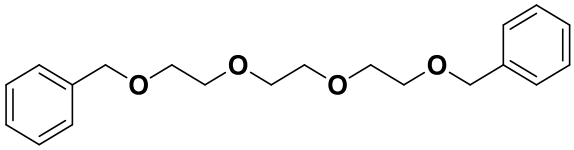
Triethylene glycol (7.97 mL, 10.00 g, 66.6 mmol) was added dropwise to a solution of tosyl chloride (27.95 g, 146.6 mmol), 4-dimethylaminopyridine (6.07 g, 33.3 mmol) and triethylamine (40.87 mL, 29.65 g, 293.0 mmol) in CH_2Cl_2 (100 mL) that was cooled to 0 °C. The reaction mixture was allowed to warm to rt and stirred for 72 h. The solution was allowed to return to rt before being quenched and washed with $HCl_{(aq)}$ (5 x 50 mL, 1 M), then the combined organic extracts were washed with brine (50 mL) and dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. Upon recrystallisation from diethyl ether:CH_2Cl_2 (10:1) the title compound (10.63 g, 67%) was obtained as white crystals; mpt 80-82 °C; ν_{max} (ATR)/ cm^{-1} 2957, 2929, 2897, 2871, 1596, 1439, 1349, 1171; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.46 (s, 6H, 2 x C*H*$_3$), 3.53 (s, 4H, OC*H*$_2$C*H*$_2$O), 3.66-3.68 (m, 4H, 2 x OC*H*$_2$CH$_2$OTs), 4.14-4.16 (m, 4H, 2 x OCH$_2$C*H*$_2$OTs), 7.36 (d, 4H, *J* 8.1, Ar*H*), 7.80 (d, 4H, *J* 8.1, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 144.9 (2 x Ar*C*S), 132.9 (2 x Ar*C*CH$_3$), 129.9 (4 x Ar*C*H$_2$), 128.0 (4 x Ar*C*H$_2$), 70.7 (2 x *C*H$_2$), 69.2 (2 x *C*H$_2$), 68.7 (2 x *C*H$_2$), 21.6 (2 x *C*H$_3$). All data was in accordance with the literature.

1-Methyl-1*H*-imidazole-2-methanol, 133.[58]



To a suspension of $LiAlH_4$ (0.35 g, 9.08 mmol) in THF (10 mL) was added dropwise to a solution of 1-methylimidazole-2-carboxaldehyde (0.50 g, 4.54 mmol) in THF (20 mL) that was cooled to 0 °C. The solution was stirred for 5 minutes before H_2O (0.4 mL), 15% aqueous NaOH (0.4 mL) then H_2O (1.2 mL) were added dropwise sequentially and the solution was allowed to warm to rt and left stirring for 2.5 h. $MgSO_4$ was then added to the mixture and the solid was removed by vacuum filtration. Upon recrystallisation from EtOAc:hexane the title compound (0.273 g, 54%) was obtained as white crystals; mpt 115-116 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.66 (s, 6H, NC*H*$_3$), 4.60 (s, 4H, OC*H*$_2$), 6.84 (d, 2H, *J* 1.2, Im*H*), 6.91 (d, 2H, *J* 1.2, Im*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 144.5 (Im*C*), 127.3 (Im*C*H), 122.1 (Im*C*H), 56.0 (*C*H$_2$), 32.9 (*C*H$_3$). All data was in accordance with the literature.

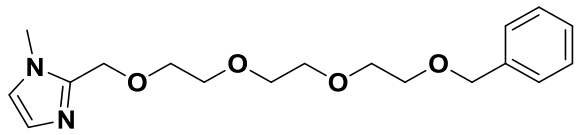
1,2-b*is*[2-(Phenylmethoxy)ethoxy]ethane, 135.



Sodium hydride (0.30 g, 7.42 mmol) was added portionwise to a solution of benzyl alcohol (0.70 mL, 0.73 g, 6.75 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred for 10 minutes before the dropwise addition of 1,2-bis(2-tosylethoxy)ethane **130** (0.50 g, 3.37 mmol) in THF (5 mL) and left stirring at rt for 12 h, at which point the reaction was quenched with H_2O (20 mL). Extracted with EtOAc (3 x 30 mL) and the combined organic washings were dried with $MgSO_4$ and filtered, before the solvent was removed under reduced pressure and following

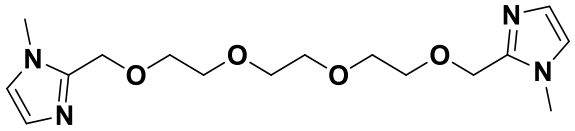
flash column chromatography on silica gel (1:99, MeOH:CH_2Cl_2) the title compound (0.67 g, 61%) was obtained as a yellow oil; ν_{max} (ATR)/ cm^{-1} 2862, 1717, 1453, 1350, 1091; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.64-3.67 (m, 4H, C*H*$_2$), 3.70-3.72 (m, 8H, C*H*$_2$), 4.59 (s, 4H, ArC*H*$_2$), 7.28-7.40 (m, 10H, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 138.3 (2 x Ar*C*), 128.4 (4 x Ar*C*H), 127.8 (4 x Ar*C*H), 127.6 (2 x Ar*C*H), 73.3 (2 x *C*H$_2$), 70.7 (4 x *C*H$_2$), 69.4 (2 x *C*H$_2$); *m/z* (ESI$^+$) 348.2 (100%), 331.1911 (5%, MH$^+$. $C_{20}H_{26}O_4$ requires 331.1904).

1-Methyl-2-(12-phenyl-2,5,8,11-tetraoxadodecan-1-yl)-1H-imidazole, 136.



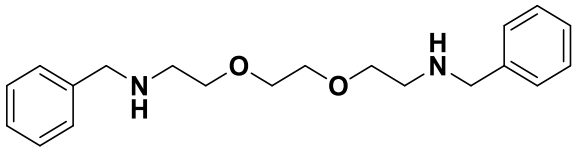
Sodium hydride (2.62 g, 6.54 mmol) was added portionwise to a solution of 1-methyl-1H-imidazole-2-methanol **133** (0.3 g, 2.73 mmol) and benzyl alcohol (0.28 mL, 0.30 g, 2.73 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred for 10 minutes before the dropwise addition of 1,2-bis(tosylethoxy)ethane **130** (0.40 g, 2.73 mmol) in THF (5 mL) and left stirring at rt for 12 h, at which point the reaction was quenched with H_2O (20 mL). Extracted with EtOAc (3 x 30 mL) and the combined organic washings were dried with $MgSO_4$ and filtered, before the solvent was removed under reduced pressure and following flash column chromatography on silica gel (1:99, MeOH:CH_2Cl_2) the title compound (0.39 g, 28%) was obtained as a yellow oil; ν_{max} (ATR)/ cm^{-1} 2865, 1717, 1498, 1349, 1276, 1088; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.60-3.71 (m, 12H, C*H*$_2$), 4.58 (s, 2H, PhC*H*$_2$), 4.66 (s, 2H, ImC*H*$_2$), 6.81 (s, 1H, Im*H*), 6.96 (s, 1H, Im*H*), 7.28-7.32 (m, 2H, Ar*H*), 7.35-7.36 (m, 3H, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 144.6 (ArC), 138.2 (Im*C*), 128.4 (2 x Ar*C*H), 127.8 (2 x Ar*C*H), 127.6 (Ar*C*H), 127.2 (Im*C*H), 122.1 (Im*C*H), 73.2 (*C*H$_2$), 70.6 (2 x *C*H$_2$), 70.5 (*C*H$_2$), 70.4 (*C*H$_2$), 69.2 (*C*H$_2$), 69.1 (*C*H$_2$), 64.9 (*C*H$_2$), 32.9 (*C*H$_3$); *m/z* (ESI$^+$) 363 (22%), 349 (38), 335.1968 (100%, MH$^+$. $C_{18}H_{26}N_2O_4$ requires 335.1965), 214 (47).

1,2-*bis*[2-(1-Methyl-1H-imidazole)methoxy]ethane, 137.



Sodium hydride (0.19 g, 4.74 mmol) was added portionwise to a solution of 1-methyl-1H-imidazole-2-methanol **133** (0.44 g, 3.96 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred for 10 minutes before the dropwise addition of 1,2-bis(tosylethoxy)ethane **130** (0.29 g, 1.98 mmol) in THF (5 mL) and left stirring at rt for 12 h, at which point the reaction was quenched with H_2O (5 mL). Extracted with EtOAc (3 x 15 mL) and the combined organic washings were dried with $MgSO_4$ and filtered, before the solvent was removed under reduced pressure and following flash column chromatography on silica gel (1:99, MeOH:CH_2Cl_2) the title compound (0.26 g, 38%) was obtained as a yellow oil; ν_{max} (ATR)/ cm^{-1} 3108, 2866, 1500, 1451, 1416, 1346, 1284, 1082; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.56-3.63 (m, 12H, OC*H*$_2$), 3.68 (s, 6H, NC*H*$_3$), 4.61 (s, 4H, OC*H*$_2$Im), 6.85 (d, 2H, *J* 1.2, Im*H*), 6.92 (d, 2H, *J* 1.2, Im*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 144.5 (2 x Im*C*), 127.3 (2 x Im*C*H), 122.1 (2 x Im*C*H), 70.5 (2 x *C*H_2), 70.3 (2 x *C*H_2), 69.1 (2 x *C*H_2), 65.0 (2 x *C*H_2), 32.9 (2 x *C*H_3); *m/z* (ESI$^+$) 361 (2%), 349 (38), 339.2030 (20%, MH^+. $C_{16}H_{26}N_4O_4$ requires 335.2056), 245 (8) 170 (100).

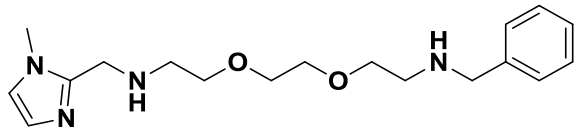
1,2-*bis*(2-Benzylaminoethoxy)ethane, 140.[59][60]



1,2-bis(2-Aminoethoxy)ethane (1.42 mL, 2.07 g, 14.0 mmol) was added dropwise to a solution of benzaldehyde (2.88 mL, 3.00 g, 28.0 mmol) in MeOH (30 mL). The reaction mixture was stirred for 12 h before it was cooled to 0 °C for the portionwise addition of $NaBH_4$ (1.59 g, 42 mmol) and left stirring for 2 h at which

point the reaction was quenched with H_2O (20 mL) and the solvents removed to dryness by reduced pressure. Extraction was completed after the addition of H_2O (30 mL) by washing with CH_2Cl_2 in a continuous fashion, the combined organic washings were dried with $MgSO_4$ and filtered, before the solvent was removed under reduced pressure and following flash column chromatography on silica gel (1:9, MeOH:EtOAc) the title compound (2.71 g, 59%) was obtained as a yellow oil; ν_{max} (ATR)/ cm^{-1} 3027, 2863, 1452, 1109; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.02 (s, 2H, N*H*) 2.82 (t, 4H, *J* 5.2, C*H*$_2$NH), 3.61-3.64 (m, 8H, 2 x OC*H*$_2$CH$_2$NH and OC*H*$_2$C*H*$_2$O), 3.82 (s, 4H, OC*H*$_2$Ar), 7.24-7.34 (m, 10H, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 140.2 (2 x Ar*C*), 128.4 (4 x Ar*C*H), 128.2 (4 x Ar*C*H), 126.9 (2 x Ar*C*H), 70.6 (2 x *C*H$_2$), 70.3 (2 x *C*H$_2$), 53.9 (2 x *C*H$_2$), 48.7 (2 x *C*H$_2$).

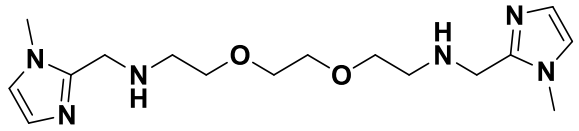
1-Methyl-2-(12-phenyl-5,8-dioxa-2,11-diazadodecan-1-yl)-1H-imidazole, 141.



1,2-bis(2-Aminoethoxy)ethane (0.46 mL, 0.67 g, 4.54 mmol) was added dropwise to a solution of 1-methyl-2-imidazolecarboxaldehyde (0.50 g, 4.54 mmol) in MeOH (30 mL) at 0 °C. The reaction mixture was stirred allowed to warm to rt for 2 h before it was cooled to 0 °C for the dropwise addition of benzaldehyde (0.46 mL, 0.48 g, 4.54 mmol), the reaction mixture was once again allowed to warm to rt for 2 h before being cooled to 0 °C for the portionwise addition of $NaBH_4$ (0.34 g, 9.08 mmol) and left stirring at rt for 12 h at which point the reaction was quenched with H_2O (20 mL) and the solvents removed to dryness by reduced pressure. Extraction was completed after the addition of H_2O (30 mL) by washing with CH_2Cl_2 in a continuous fashion, the combined organic washings were dried with $MgSO_4$ and filtered, before the solvent was removed under reduced pressure and following flash column chromatography on silica gel (1:9, MeOH:CH_2Cl_2) the title compound (0.59 g, 30%) was obtained as a yellow oil; ν_{max} (ATR)/ cm^{-1} 2864, 1648, 1496, 1453, 1283, 1099;

^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.86 (s, 2H, N*H*), 2.81-2.84 (m, 4H, CH_2NH), 3.58-3.64 (m, 8H, 2 x OCH_2CH_2NH and OCH_2CH_2O), 3.67 (s, 3H, NCH_3), 3.82 (s, 4H, OCH_2Ar), 3.87 (s, 4H, OCH_2Im), 6.82 (d, 1H, *J* 1.2, Im*H*), 6.93 (d, 1H, *J* 1.2, Im*H*), 7.23-7.28 (m, 1H, Ar*H*), 7.31-7.36 (m, 4H, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 146.5 (Im*C*CH_2), 140.1 (Ar*C*CH_2), 128.4 (2 x Ar*C*H), 128.2 (2 x Ar*C*H), 127.1 (Im*C*H), 127.0 (Ar*C*H), 121.2 (Im*C*H), 70.5 (2 x *C*H_2), 70.3 (*C*H_2), 70.2 (Ar*C*H_2), 53.8 (*C*H_2), 48.6 (2 x *C*H_2), 45.6 (*C*H_2), 32.7 (*C*H_3); *m/z* (ESI$^+$) 355 (12%), 333.2283 (72%, MH^+. $C_{18}H_{28}N_4O_2$ requires 333.2285), 243 (81), 167 (100). All data was in accordance with the literature.

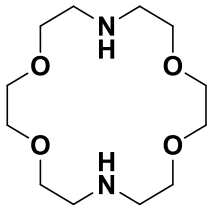
1-Methyl-2-[12-(1-methyl-1H-imidazol-2-yl)-5,8-dioxa-2,11-diazadodecan-1-yl]-1H-imidazole, 142.



1,2-bis(2-Aminoethoxy)ethane (0.20 mL, 0.29 g, 1.97 mmol) was added dropwise to a solution of 1-methyl-imidazocarboxaldehyde (0.43 g, 3.74 mmol) in MeOH (30 mL). The reaction mixture was stirred for 2 h before it was cooled to 0 °C for the portionwise addition of $NaBH_4$ (0.2 g, 4.74 mmol) and left stirring at rt for 12 h at which point the reaction was quenched with H_2O (20 mL) and the solvents removed to dryness by reduced pressure. Extraction was completed after the addition of H_2O (30 mL) by washing with CH_2Cl_2 in a continuous fashion, the combined organic washings were dried with $MgSO_4$ and filtered, before the solvent was removed under reduced pressure and following flash column chromatography on silica gel (1:9, MeOH:CH_2Cl_2) the title compound (0.21 g, 32%) was obtained as a yellow oil; ν_{max} (ATR)/ cm^{-1} 2859, 2032, 1652, 1456, 1282, 1084; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.58 (s, 2H, N*H*), 2.81 (t, 4H, *J* 5.2, CH_2NH), 3.56-3.58 (m, 8H, 2 x OCH_2CH_2NH and OCH_2CH_2O), 3.67 (s, 6H, NCH_3), 3.86 (s, 4H, ImCH_2), 6.81 (d, 2H, *J* 1.1, Im*H*), 6.90 (d, 2H, *J* 1.1, Im*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 146.4 (2 x Im*C*), 127.0 (2 x Im*C*H), 121.2 (2 x Im*C*H), 70.4 (2 x *C*H_2), 70.2 (2 x *C*H_2), 48.6 (2 x *C*H_2), 45.5 (2 x *C*H_2), 32.8 (2

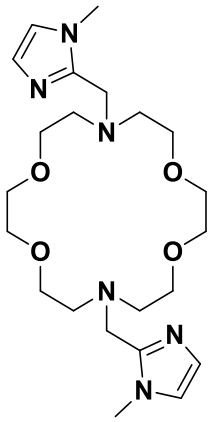
x CH_3); *m/z* (ESI^+) 337.2351 (90%, MH^+. $C_{16}H_{28}N_6O_2$ requires 337.2347), 243.2 (34%), 169 (100).

1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane, 143.[61]



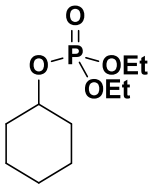
Potassium carbonate (4.16 g, 30.10 mmol) and potassium iodide (5.00 g, 30.10 mmol) was added portionwise to a solution of 1,2-b*is*(2-tosylethoxy)ethane **130** (6.90 g, 15.05 mmol), 1,2-bis(2-aminoethoxy)ethane (2.23 g, 15.05 mmol) in MeCN (250 mL). The mixture was brought to reflux for 72 h and then cooled to rt before solvents removed to dryness by reduced pressure. Extraction was completed after the addition of H_2O (30 mL) by washing with CH_2Cl_2 in a continuous fashion, the combined organic washings were dried with $MgSO_4$ and filtered, before the solvent was removed under reduced pressure. Upon recrystallisation from heptane the title compound (0.87 g, 22%) was obtained as a white solid; mpt 111-113 °C; ^1H NMR (400 MHz; $CDCl_3$) δ_H 2.80 (t, 8H, *J* 5.5, NC*H*$_2$), 3.51-3.53 (m, 16H, OC*H*$_2$), 2.09 (s, 2H, N*H*); *m/z* (ES^+) 263.1982 (100%, MH^+. $C_{12}H_{27}N_2O_4$ requires 263.1971), 261.1 (91). All data was in accordance with the literature.

7,16-*bis*(1-Methyl-1H-imidazol-2-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, 145.



Potassium carbonate (0.21 g, 1.52 mmol) and potassium iodide (0.25 g, 1.52 mmol) was added portionwise to a solution of 1-methyl-2-[12-(1-methyl-1H-imidazol-2-yl)-5,8-dioxa-2,11-diazadodecan-1-yl]-1H-imidazole **142** (0.26 g, 0.76 mmol), 1,2-bis(tosylethoxy)ethate **130** (0.35 g, 0.76 mmol) in MeCN (50 mL). The mixture was brought to reflux for 12 h and then cooled to rt before being filtered by Buchner filtration to remove the solids before solvents removed to dryness by reduced pressure. A small amount of H_2O (1 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were dried with $MgSO_4$ and filtered before the solvent was removed under reduced pressure and following flash column chromatography on alumina (basic aluminium oxide 50 – 200 μm, 1:9, MeOH:CH_2Cl_2) the title compound (0.16 g, 47%) was obtained as a yellow oil; ν_{max} (ATR)/ cm^{-1} 2821, 2350, 1500, 1454, 1355, 1285, 1106; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.80 (t, 8H, *J* 5.5, NC*H*$_2$), 3.51-3.53 (m, 16H, OC*H*$_2$), 3.72 (s, 6H, C*H*$_3$), 3.76 (s, 4H, ImC*H*$_2$), 6.82 (d, 2H, *J* 1.0, Im*H*), 6.91 (d, 2H, *J* 1.0, Im*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 145.6 (2 x Im*C*), 126.9 (2 x Im*C*H), 121.6 (2 x Im*C*H), 70.6 (4 x *C*H$_2$), 69.7 (4 x *C*H$_2$), 54.0 (4 x *C*H$_2$), 52.3 (2 x *C*H$_2$), 33.0 (2 x *C*H$_3$); *m/z* (ESI$^+$) 495.3 (16%), 451.3028 (100%, MH$^+$. $C_{22}H_{38}N_6O_4$ requires 451.3027), 357.3 (19), 226.2 (100).

Cyclohexyl diethyl phosphate, 146.[54]



A solution of diethyl chlorophosphate (3.2 mL, 3.79 g, 21.97 mmol) in THF (20 mL) was added dropwise to a solution of cyclohexanol (2.1 mL, 2.00 g, 19.97 mmol), triethylamine (2.8 mL, 2.02 g, 19.97 mmol) and N-methylimidazole (0.16 mL, 0.16 g, 2.00 mmol) that was cooled to 0 °C. The solution was allowed to warm to rt and left stirring for 2 h, before being quenched by the addition of $NH_4Cl_{(aq)}$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (10 mL), brine (10 mL) and dried over $MgSO_4$. The solution was filtered and the solvent was removed under reduced pressure, and following flash column chromatography on silica gel (1:1, EtOAc: petroleum ether 40 – 60 °C) the title compound (3.73 g, 79%) was obtained as a clear oil; ν_{max} (ATR)/ cm^{-1} 2983, 2936, 2861, 1450, 1393, 1370, 1257, 1166, 997; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.16-1.40 (m, 3H, 3 x Cy*H*), 1.35 (t, 3H, *J* 7.1, OCH_2CH_3), 1.36 (t, 3H, *J* 7.1, OCH_2CH_3), 1.50-1.59 (m, 3H, 3 x Cy*H*), 1.71− 1.80 (m, 2H, 2 x Cy*H*), 1.91-2.02 (m, 2H, 2 x Cy*H*), 4.11 (app. pent., 4H, *J* 7.1 and 7.1 OCH_2CH_3), 4.33-4.42 [m, 1H, $CH(CH_2)_2$]; ^{13}C NMR (101 MHz; $CDCl_3$) δ_C 77.2 (d, $J_{C\text{-}P}$ 6.0, *C*HO), 63.5 (CH_2CH_3), 63.4 (CH_2CH_3), 33.4 (CH_2), 33.3 (CH_2), 25.1 (CH_2), 23.6 (2 x CH_2), 16.2 (CH_2CH_3), 16.1 (CH_2CH_3); ^{31}P NMR (101 MHz; $CDCl_3$) δ_P -1.67. All data was in accordance with the literature.

6. References

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