New Catalytic Strategies for the Enantioselective Synthesis of Stereogenic-at-Phosphorus(V) Compounds



A thesis submitted in partial fulfilment of the requirement for the degree of Master's by Research (MSc by Research)

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Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from October 2020 until January 2022, under the supervision of Professor Darren J. Dixon. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.



Thomas Marsh

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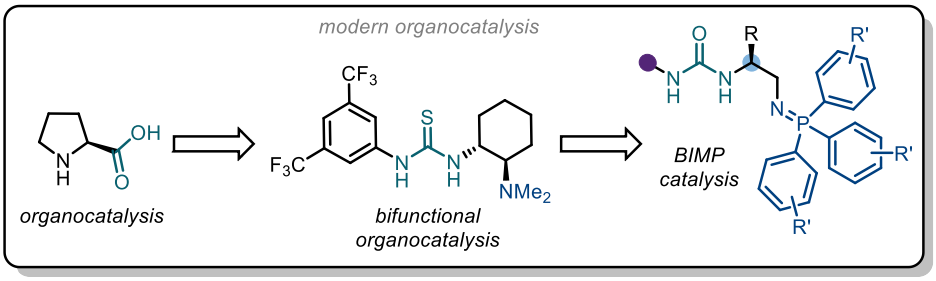
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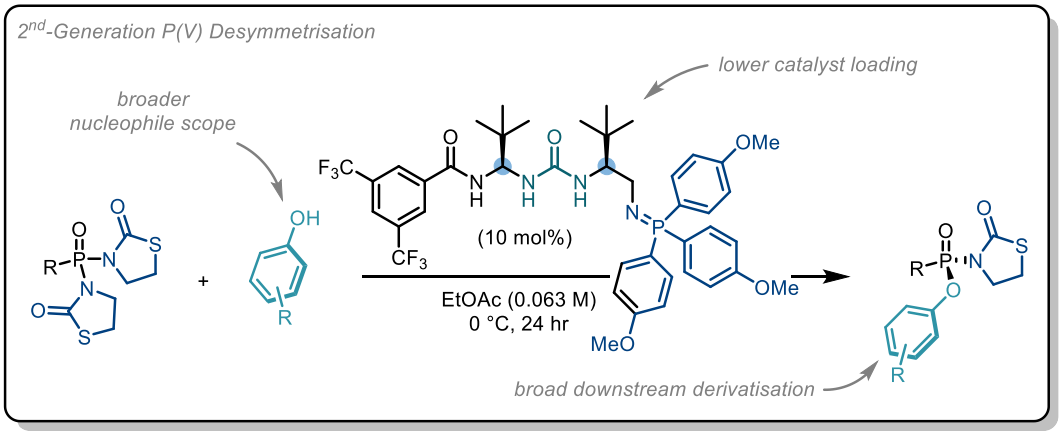
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Summary

Chapter 1 serves as an introduction to the field of enantioselective organocatalysis. Particular attention is given to the area of bifunctional organocatalysis and chiral organic superbase catalysis, leading into a discussion of bifunctional iminophosphoranes (BIMPs) as enabling catalysts within this class.



Chapter 2 introduces an improved 2nd-generation direct nucleophilic desymmetrisation method for the synthesis of molecules containing a P(V)-stereogenic centre, building upon previous work carried out in the group. This section outlines the importance of P(V) in both the pharmaceutical and agrochemical industries, and highlights the strengths and limitations of previous enantioselective desymmetrisation methods for the synthesis of stereogenic P(V) centres. Through a modified ureidopeptide BIMP catalyst framework, this work enabled lowered catalyst loadings, improved substrate scope, and broader downstream derivatisation of the desymmetrised products when compared to our 1st-generation P(V) desymmetrisation protocol.



Chapter 3 contains all the experimental procedures and analytical data for the work presented in this thesis.

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Abbreviations

(+)	Dextrorotary
(−)	Levorotatory
δ	NMR chemical shift
A	Adenine
AAA	Asymmetric Allylic Alkylation
AASI	Asymmetric allylic substitution-isomerisation
Ac	Acetyl
AAC	Azide-Alkyne Cycloaddition
API	Active Pharmaceutical Ingredient
Aq.	Aqueous
Ar	Aryl
ARCM	Asymmetric Ring Closing Metathesis
AZT	1-[(2*R*,4*S*,5*S*)-4-azido-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidine-2,4-dione
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BIMP	Bifunctional Iminophosphorane
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Br	Broad
BTMG	2-*tert*-Butyl-1,1,3,3-tetramethylguanidine
Bu	Butyl
n-BuLi	1-butyllithium
Bz	Benzoyl
CBL	Chiral Bidentate boryl Ligand
cod	1,5-Cyclooctadiene
coe	Cyclooctene
COSY	Correlation Spectroscopy
CMD	Concerted Metalation-Deprotonation
CPA	Chiral Phosphoric Acid
Cy	Cyclohexyl
d	Doublet
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCM	dichloromethane

dd	Doublet of doublets
ddd	Doublet of doublet of doublets
ddt	Doublet of doublet of triplets
$(DHQ)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIPEA	*N,N*-Disopropylethylamine
DKR	Dynamic Kinetic Resolution
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMTr	4,4'-Dimethoxytrityl
DNA	Deoxyribonucleic acid
DPP	Diphenylphosphinyl
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dq	Doublet of quartets
dt	Doublet of triplets
dT	Thymidine
E	Entgegen
ee	Enantiomeric excess
er	Enantiomeric ratio
es	Enantiospecificity
ESI	Electrospray ionisation
et al.	et alia
Et	Ethyl
eq.	Equivalents
fac	Facial
FCC	Flash column chromatography
FT	Fourier transform
G	Guanine
GC	Gas Chromatography
g	grams
h	heptet
n-Hexyl	1-hexyl
HMBC	Heteronuclear Multiple Bond Coupling
HMDS	Hexamethyldisilazane

HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coupling
i-Bu	isobutyl
IMDAF	Intramolecular Diels-Alder Addition of Furan
i-Pr	isopropyl
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
FT-IR	Fourier Transform Infrared
J	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium Diisopropylamide
LRMS	Low Resolution Mass Spectrometry
m	Multiplet
m	Meta
M	Molar
MBH	Morita-Baylis-Hillman
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mp	Melting Point
MS	Molecular Sieves
NOESY	Nuclear Overhauser Effect Spectroscopy
NHC	*N*-Heterocyclic Carbene
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
Nu	Nucleophile
o	Ortho
p	Para
p	pentet
Ph	Phenyl
Piv	Pivaloyl
PMP	Para-methoxy phenyl

ppm	Parts per million
Pr	Propyl
PyBox	(S,S)-2,6-Bis(4-isopropyl-2-oxazolin-2-yl)pyridine
q	Quartet
qd	Quartet of doublets
qt	Quarter of triplets
quant.	Quantitative
R	Rectus
R	Unspecified organic group
rr	Regioisomeric ratio
RCM	Ring-Closing-Metathesis
RNA	Ribonucleic acid
rt	Room temperature
s	Singlet
S	Sinister
Salox	salicycloxazoline
SARS	Severe Acute Respiratory Syndrome
SEGPHOS	5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
SPO	Secondary phosphine oxide
SMA	Sulfa-Michael Addition
T	Thymine
T	Temperature
T	triplet
$t_{1/2}$	Half-life
t-Bu	tert-Butyl
td	Triplet of doublets
tdd	Triplet of doublet of doublets
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMDS	Tetramethyldisiloxane
TMS	Trimethylsilyl

Tol	Tolyl
TS	Transition State
tt	triplet of triplets
UV	Ultraviolet
ν_{max}	Infrared absorption maximum
WHO	World Health Organization
Z	Zusammen

Chapter 1: Introduction

1.1 Introduction to Organocatalysis

Advances in the field of organic synthesis have shaped the way we live, dramatically improving life-expectancy, global food security, and quality of life over the last century. Complex molecules are routinely demanded for applications in the pharmaceutical, agrochemical, and fine chemical industries. In particular, chemical structures containing one or more stereogenic centres have unique importance across all areas of the chemical industry and new, expedient methods for their synthesis are constantly in demand.

Within the pharmaceutical and agrochemical industries, chiral molecules often exhibit enantio-dependent potency and physiological effects, owing to diastereomeric interactions between molecules *in vivo*. Historically, little consideration was given to this important effect and drug molecules were routinely marketed as racemic mixtures of both enantiomers with sometimes devastating consequences. Thalidomide (**1**, *Figure 1*), developed in the 1950s for the treatment of morning sickness in pregnant women, was sold for over a decade before it became clear that the drug caused appalling deformities in new-born children. It was subsequently found that both enantiomers of the drug had dramatically different biological effects and, whilst the (*R*)-enantiomer was an effective treatment for morning sickness, the (*S*)-enantiomer was teratogenic[1]. This tragic event highlighted the importance of single enantiomers in drug development, testing, and marketing, and today a detailed understanding of the various stereoisomers of a drug molecule is required for drug approval.



Figure 1: Structures of (*S*)- and (*R*)-thalidomide.

As such, methods for the synthesis of single enantiomers of molecules have a unique importance in synthetic organic chemistry (*Scheme 1*). Historically, this was achieved through chiral resolution (*Scheme 1**A***) [2,3] or chromatographic separation[4] using a chiral stationary phase *(Scheme 1**B***); whilst often straightforward, these methods necessarily result in the loss of 50% of the product mixture associated with the undesired enantiomer. Alternatively, chiral auxiliary methods, whereby a chiral molecule (often from the chiral pool) is covalently attached to a target molecule to induce asymmetry in a reaction, can be highly effective and often produce a high excess of the desired enantiomer (*Scheme 1**C***). However, this necessarily adds at least two steps to a synthetic sequence associated with attachment and removal of the auxiliary, thereby reducing overall yield[5,6].

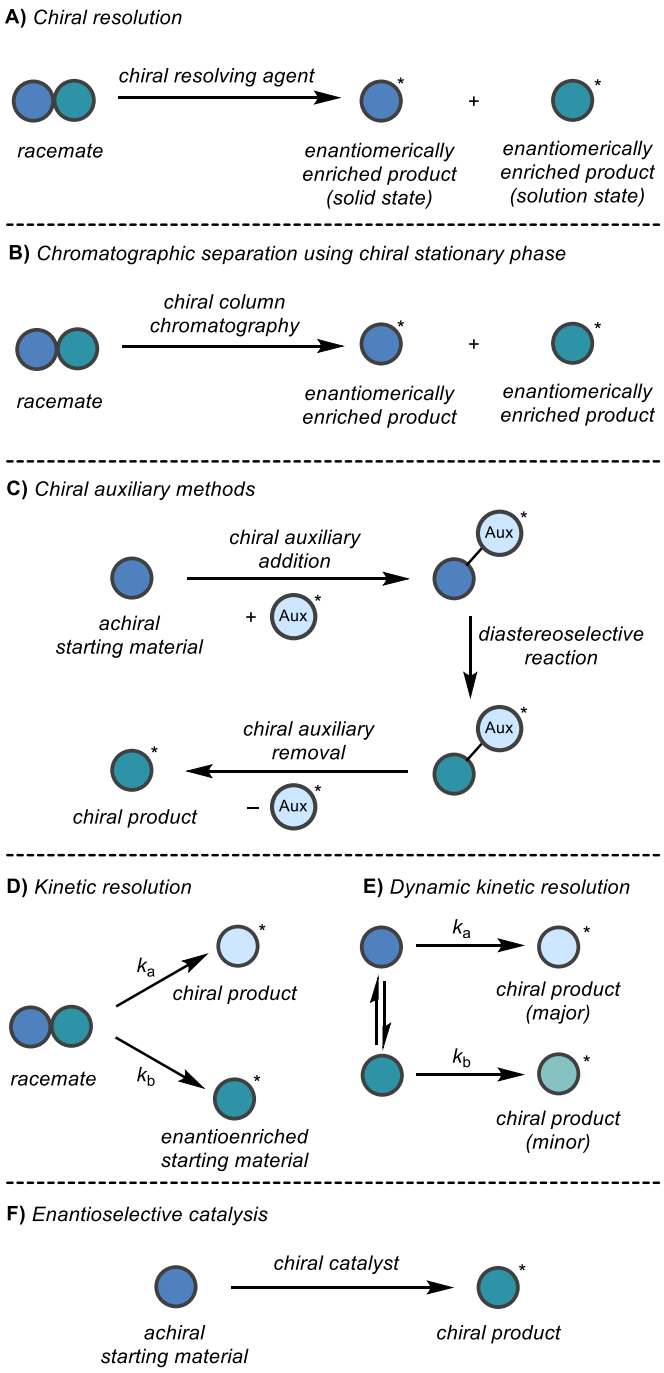
Kinetic resolution methods can also be used to achieve high levels of enantiomeric excess. Here, a chiral catalyst or chiral reagent reacts at different rates with each enantiomer in a racemic mixture, thereby generating both enantioenriched product and enantioenriched unreacted starting material (*Scheme 1**D***)[7]. Over the course of the reaction, the enantiomeric excess of the desired product will gradually fall as more of the undesired enantiomer of the starting material reacts, and the enantiomeric excess of the reactant will correspondingly rise. Therefore, to achieve a high enantiomeric excess of the desired product, there is an upper limit of the attainable product yield of around 50% and very high catalyst efficiencies are required to obtain both high yields and enantioselectivities[8]. In a dynamic kinetic resolution, the starting material is able to racemise, either under the reaction conditions or through interaction with the catalyst (*Scheme 1**E***). Because of this, both enantiomers of the starting material can be converted into a single desired enantiomer of the product, provided catalyst efficiency is high. However, this necessarily requires a facile racemisation mechanism, limiting the substrates that can be reacted using this method[9].

Over the past 50 years, methods utilising transition-metal catalysts for enantioselective synthesis have received widespread attention, culminating in the Nobel Prize in 2001 for Sharpless[10], Knowles[11], and Noyori[12] for their work on enantioselective metal catalysis. These enantioselective reactions are carried out on an achiral substrate, with chiral information relayed from a chiral ligand in combination with a precious metal catalyst (typically Pd, Rh, or Ir). Importantly, very high levels of enantioselectivity can be achieved with extremely low loadings of the metal catalyst (0.01 mol% is common) (*Scheme 1**F***)[13]. However, despite the sustained importance of this field to enantioselective synthesis, it has drawbacks related to the use of costly metal catalysts, the typical need for the complete removal of air and moisture from the reaction mixture, and the stringent requirements related for the removal of trace metal (sub ppm) in the final drug[14].

Enzymatic methods are also an important field in enantioselective synthesis, recently recognised through the award for the 2018 Nobel Prize to Francis Arnold 'for the directed evolution of enzymes'[15]. Historical drawbacks to the use of enzymes in enantioselective catalysis has been their low stability in both organic solvents and at high temperatures, as well as their extreme substrate specificity. However, advances in the field of directed evolution have resulted in broadly applicable and robust enzymatic catalysts for a wide range of chemical reactions[16]. Despite this, these methods require specialist equipment and training not typically available to synthetic organic chemists, limiting their widespread utility.

The 21st-century has also seen the development of the field of small-molecule organic catalysts ('organocatalysts')[17,18], emerging as a complementary method to metal- and enzyme-catalysed approaches. Organocatalysts are typically synthesised in a few steps starting from cheap and readily available chiral precursors and are stable to air and moisture, meaning they are often more user-friendly than their metal- and enzyme-based counterparts. These inherent advantages have led to the rapid development of the field of enantioselective organocatalysis for a broad range of important chemical

transformations and has recently been recognised by the award of the 2021 Nobel Prize to List and MacMillan 'for the development of asymmetric organocatalysis'.

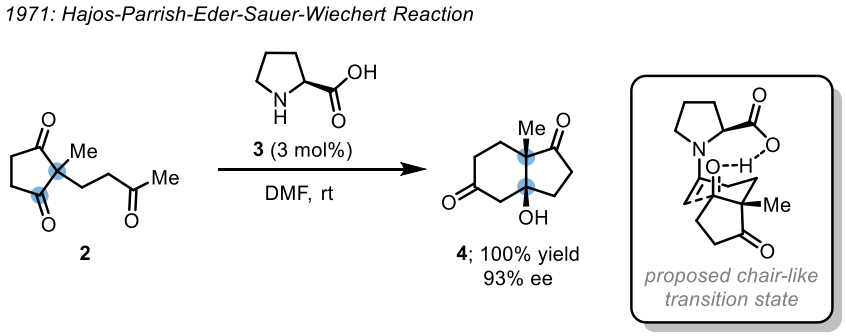


Scheme 1: Generic overview of synthetic methods for accessing chiral molecules. **A)** chiral resolution, **B)** chiral chromatographic separation using a chiral stationary phase, **C**) chiral auxiliary methods, **D)** kinetic resolution, **E)** dynamic kinetic resolution, **F)** enantioselective catalysis.

1.1.1 The Development of the Field of Organocatalysis

Early progress in the field of organocatalysis was made by Hajos and Parrish[19] and by Eder, Sauer, and Wiechert[20] (*Scheme 2*). These advances centred around the enantioselective intramolecular cyclisation of

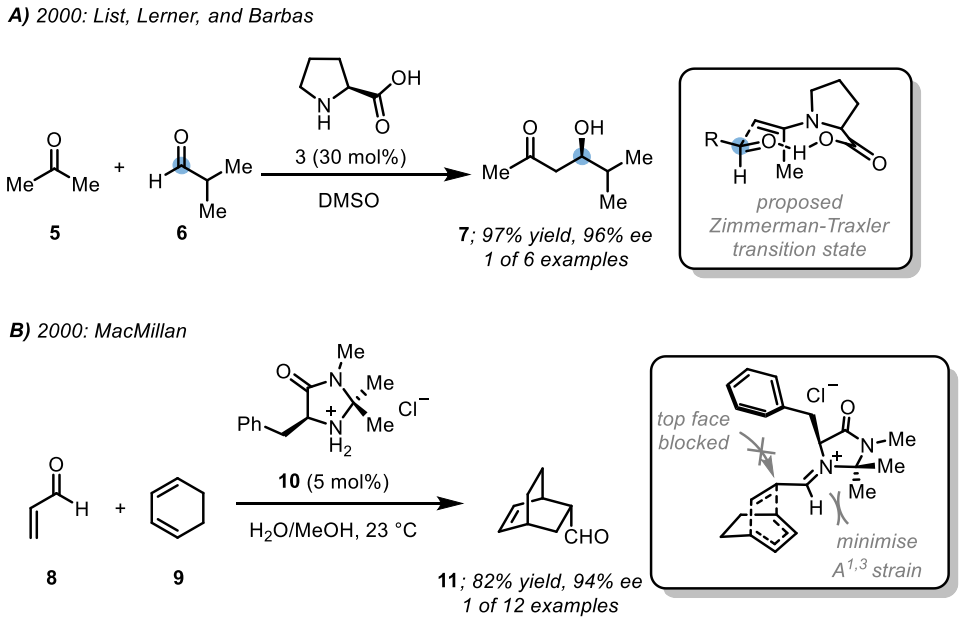
triketone **2** using (*S*)-proline catalyst **3**, with the reaction proceeding with a remarkable 100% yield and 93% ee. Later mechanistic work by Houk[21,22] revealed that the secondary amine first forms an enamine with the carbonyl of the methyl ketone, followed by a chair-like enamine aldol transition state in which attack of one of the prochiral ketones is favoured by an intramolecular hydrogen-bond between the proline carboxylic acid and the free ketone.



Scheme 2: (S)-proline catalysed Hajos-Parrish-Eder-Sauer-Wiechert reaction and proposed transition state.

Despite the simplicity of this transformation, the field of organocatalysis took nearly 30 years to develop. With some notable advances, particularly by Hiemstra & Wynberg[23], Inoue[24], and Jacobsen[25], it arguably was not until 2000 with the near-simultaneous disclosures from List, Lerner, and Barbas and MacMillan that the field truly began to develop (*Scheme 3*). List and co-workers, building upon the seminal work of Hajos, Parrish, Eder, Sauer, and Wiechert, disclosed an intermolecular condensation between acetone (**5**) and aldehyde **6**[26]. The authors proposed a mechanism of proline condensation with **5** to give the transient enamine, and nucleophilic attack on to the free **6** to form the aldol product **7**. Asymmetric induction is proposed to occur *via* a hydrogen bonded Zimmerman-Traxler chair-like transition state (*Scheme 3**A***). MacMillan, in a related approach, demonstrated the utility of iminium ion catalyst **10** in an enantioselective Diels-Alder cycloaddition reaction between α,β-unsaturated aldehyde **8** and diene **9**[27]. In the proposed mechanism, the authors suggest condensation of the secondary amine catalyst to the enal to form the activated iminium adduct, followed by a Diels-Alder cycloaddition. Asymmetry is induced through the steric blocking of one face of approach of the incoming diene (*Scheme 3**B***), with the iminium ion adopting a rigid *S*-trans conformation to minimise $A^{1,3}$ strain.

These seminal reports set the stage for further development and, to date, thousands of reactions utilising organocatalysts have been reported. For an overview of these methods, the reader is directed to numerous excellent reviews in the published literature[28–30].



Scheme 3: Seminal contributions to the field of organocatalysis by **A**) List, Lerner, Barbas' proline-catalysed enantioselective intermolecular aldol condensation, and **B**) MacMillan's enantioselective Diels-Alder reaction catalysed by a chiral iminium ion.

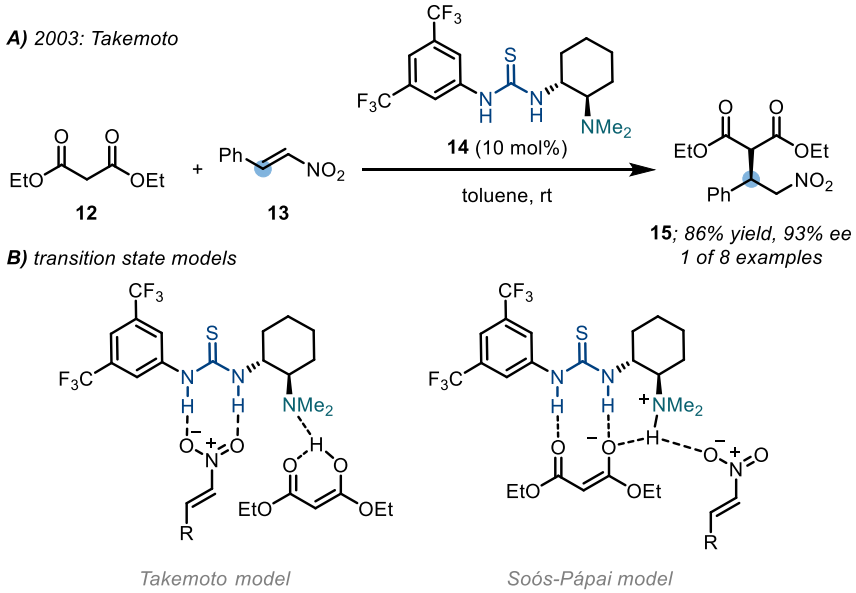
1.1.2 Bifunctional Organocatalysis

Among the many classes of organocatalysts, those bearing dual acid and base functionality have been particularly successful. The ability to simultaneously stabilise a reactive transition state through non-covalent interactions (such as hydrogen bonding, thereby lowering the LUMO of the reacting electrophile) and increase the reactivity of an incoming nucleophile (through, for example, deprotonation, thereby raising the HOMO of the reacting nucleophile) can lead to a significant enhancement in reaction rate. This 'push-pull' mechanism has dramatically broadened the landscape for organocatalytic reactions. Within dual acid/base bifunctional organocatalysis, there are two main catalyst classes: those combining a hydrogen bond donor group and a Brønsted base[31,32], and chiral phosphoric acids (CPAs)[33]. Dual hydrogen bond donor/Brønsted base bifunctional catalysts are the basis for this project.

1.1.3 The Development of Bifunctional Organocatalysis

The first explicitly designed dual hydrogen-bond donor/Brønsted base catalyst was reported by Takemoto *et al*[34] (**14**, *Scheme 4A*). This catalyst combined a basic tertiary amine and a 3,5-$(CF_3)_2C_6H_3$ thiourea moiety as the hydrogen-bond donor, enabling the enantioselective 1,4-addition of diethylmalonate (**12**) to nitroolefin **13**. The authors suggest that the catalyst works by simultaneously activating the nitroolefin *via* dual hydrogen bonding interactions and the malonate through deprotonation by the tertiary amine; significantly, presence of the thiourea and tertiary amine motifs in isolation gave poor yields of the desired product, supporting the importance bifunctional nature of the catalyst. Later computational studies by Soós and Pápai[35] propose an alternative mechanism whereby the

enol is instead bound to the thiourea *via* hydrogen-bonding interactions and the nitroolefin activated by the tertiary ammonium salt formed on deprotonation of the malonate. Despite the Soós and Pápai model being calculated to be 2.7 kcal/mol lower in energy than the Takemoto model, the mechanistic reality for related reactions likely depends upon the structure of the substrate and the catalyst, meaning a mix of the two pathways is often operative (*Scheme 4**B***).



Scheme 4: **A)** Takemoto's enantioselective addition of diethylmalonate to nitrostyrenes; **B)** Takemoto and Soós-Papai transition state models.

Following this seminal report by Takemoto, various alternative bifunctional organocatalysts have been reported, with those based on cinchona alkaloids being prominent[36,37]. An early proponent of this catalyst class was Deng and co-workers who, in 2004, reported a quinidine-based catalyst **16** for the conjugate addition of malonate esters to aromatic nitroolefins[38]. In this report, the authors found that a free hydroxyl group on the quinoline ring was crucial to high levels of enantiocontrol. Building upon this early report, numerous groups subsequently disclosed bifunctional cinchona-based catalyst systems for a range of synthetic transformations, including Chen[39], Connon[40], Dixon[41], Soós[39], Hiemstra[42], and Rawal[43] (*Figure 2*).

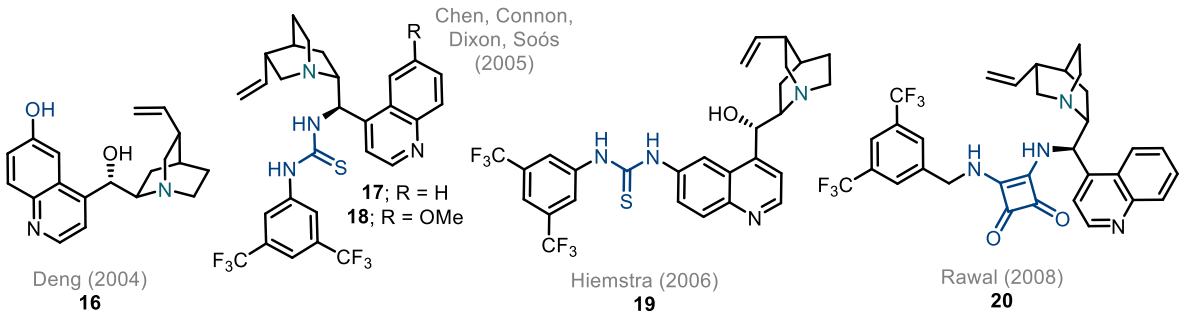


Figure 2: Representative structures of cinchona alkaloid bifunctional organocatalysts.

Collectively, bifunctional tertiary amine Brønsted base catalysts have found numerous applications throughout synthetic organic chemistry and have significantly broadened the scope of enantioselective polar addition reactions and the range of pronucleophiles and electrophiles that can be employed in these transformations.

1.2 Enantioselective Catalysis with Organic Superbases

Despite their success, tertiary amine bifunctional organocatalysts have a number of drawbacks. Most notably, they often require high catalyst loadings (10-20 mol%) and long reaction times (1-2 days is common). Similarly, due to the moderate basicity of the tertiary amine moiety, a narrow range of pronucleophiles are accessible to this strategy, limited by their high acidity and resultant low conjugate base reactivity; therefore, highly reactive electrophiles are often required for reactions to proceed efficiently[44].

One solution to this issue is through the replacement of the tertiary amine with an organic superbase. The term superbase refers loosely to any compound with a basicity higher than that of a proton sponge (**21**, pK_{BH^+} 18.7 in MeCN)[45,46]. However, a more specific alternative definition defines a superbase as any basic compound resulting from the combination of multiple basic moieties to afford new inherent properties[47]; for example, an amidine combines both basic amine and imine components, which, through resonance conjugation, generates a motif that is more basic than the two individual components in isolation[48].

The most commonly employed organic superbases have been amidines, guanidines, cyclopropenimines, and phosphazenes, in which the increased basicity arises from resonance stabilisation of the conjugate acid from neighbouring nitrogen lone pairs (*Figure 3*).

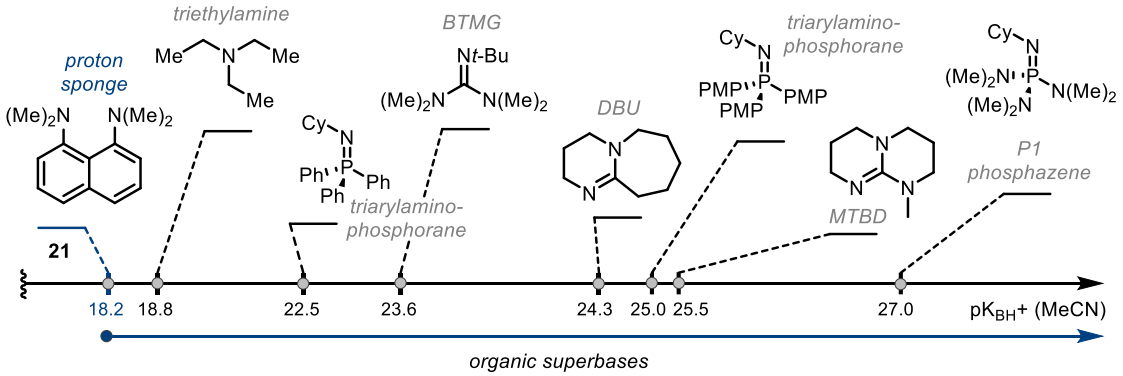


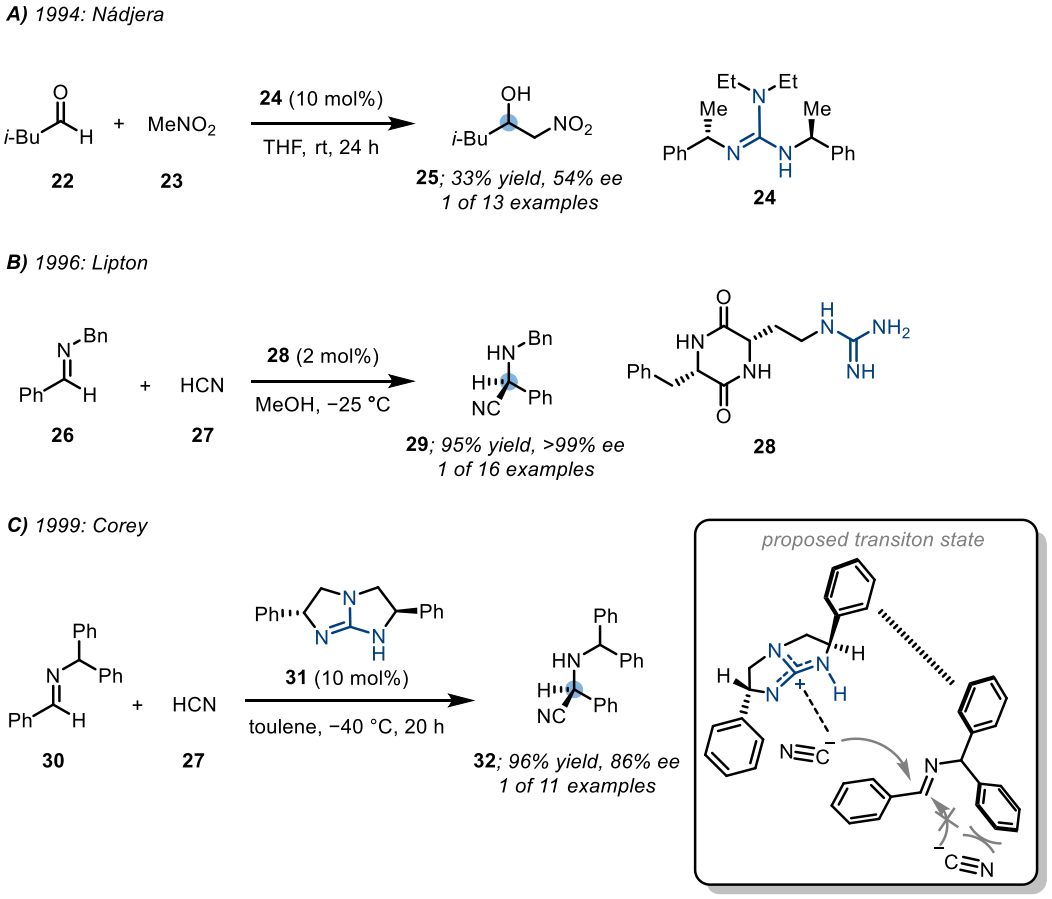
Figure 3: pK_{BH^+} scale for representative organic superbases. PMP = para-methoxy phenyl.

1.2.1 Guanidines

Traditionally, the most commonly employed superbasic moiety in organocatalysts has been guanidines[49,50]. Seminal work in this field was carried out by Nádjera in 1994, reporting modest

enantioselectivities in a nitro-aldol reaction[51] (*Scheme 5**A***). Later work by Lipton employed a chiral (*S*)-norarginine catalyst **28** in an enantioselective Strecker reaction of substituted imine **26**[52] (*Scheme 5**B***). Later in 1999, Corey disclosed C2-symmetric bicyclic guanidine catalyst **31** in the same reaction[53] (*Scheme 5**C***). Tan, building upon Corey's work, postulated that upon deprotonation of the incoming nucleophile, the resulting guanidinium moiety can engage in hydrogen bonding interactions with the imine, with the facial selectivity of attack dictated by steric blocking of one face of the electrophile[54,55]. In the years since Corey's publication, numerous groups have reported a number of chiral guanidine-based organocatalysts within various catalytic frameworks, including Ishikawa (**33**)[56,57], Terada (**34**, **35**)[58–62], Nagasawa (**35**)[63,64], and Feng (**36**)[65–67] (*Figure 4*).

Whilst effective, guanidines lie at the lower end of the basicity scale when compared to other superbasic motifs. To increase the range of pronucleophiles accessible to activation, numerous groups have reported incorporation of stronger superbases into their catalyst design, such as cyclopropenimines and phosphazenes.



Scheme 5: **A**) Nádjera's seminal guanidine-catalysed nitro-aldol reaction; **B**) Lipton's enantioselective Strecker addition; **C**) Corey's enantioselective Strecker addition using C2 symmetric guanidine catalyst **31**.

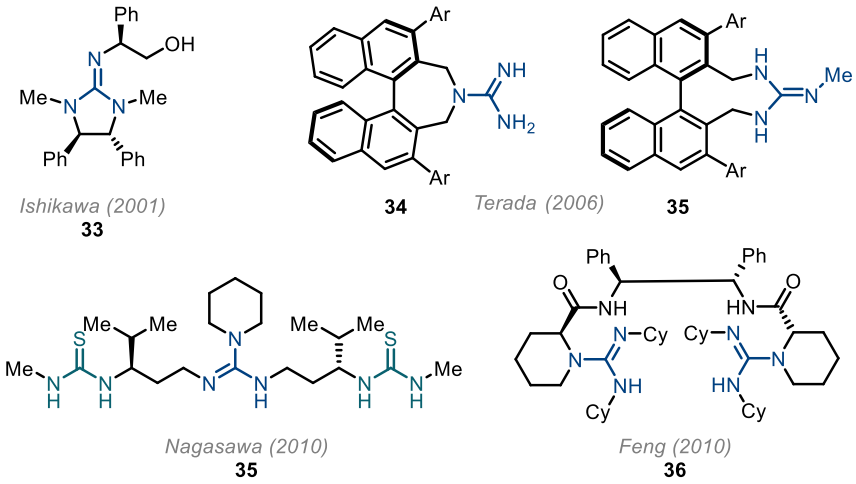
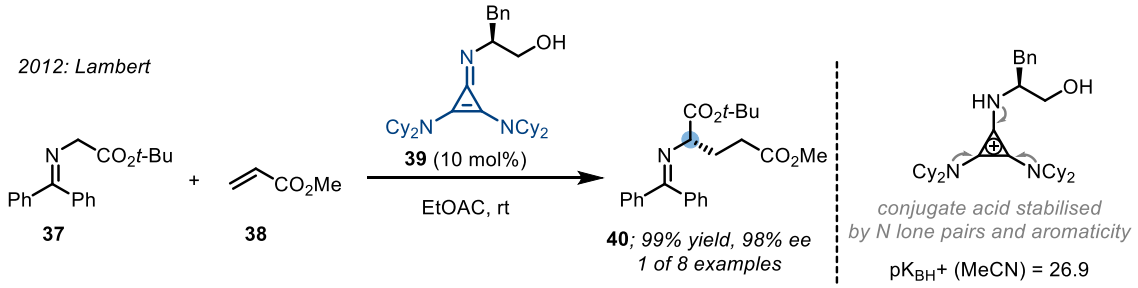


Figure 4: Representative structures of guanidine-based superbasic organocatalysts.

1.2.2 Cyclopropenimines

The first chiral cyclopropenimine catalyst **39** was disclosed by Lambert and co-workers in 2012[68]. Here, the authors demonstrated that the basicity of the cyclopropenimine was significantly higher than guanidines (pK_{BH^+} of 26.9 in MeCN compared to 23.6 for BTMG). This increased basicity arises due to the combined effect of a build-up of positive charge in the conjugate acid resulting in an aromatic cyclopropenium ion and resonance stabilisation of three N lone pairs. This catalyst was employed in the enantioselective 1,4-addition of glycine imine **37** to acrylate ester **38** with the reaction complete in 5 minutes, compared to 3 days for similar guanidine-based catalysts (*Scheme 6*). Using this catalyst, Lambert and co-workers later reported an analogous Mannich reaction to *N*-Boc aldimines using the same glycine imine nucleophile[69].



Scheme 6: Lambert's enantioselective 1,4 addition of glycine esters to acrylate esters using cyclopropenimine catalyst.

However, the stability of the 1st-generation of cyclopropenimines proved problematic, having a lifetime of 15 days in its neat state and only 7 hours in solution, precluding their widespread use. Lambert later addressed this issue through the design of 2nd-generation cyclopropenimine **41**, boasting improved solution and solid-state stability of 36 hours and greater than 5 years, respectively, whilst maintaining

high levels of catalytic efficiency and enantioselectivity (*Figure 5*). Jørgensen later employed 2nd-generation cyclopropenimines in the enantioselective [3+2] cycloaddition of 2-acyl cycloheptatrienes[70].

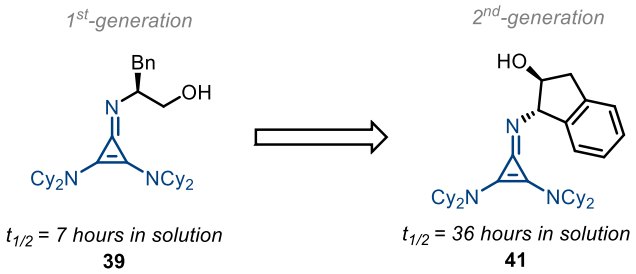


Figure 5: Lambert's 1st- and 2nd-generation cyclopropenimine catalyst structures.

1.2.3 Phosphazenes

Phosphazenes comprise a P(V) atom bonded to three amines and one imine group[71]. They are inherently more basic than amidines and guanidines, benefitting from resonance stabilisation of the multiple N lone pairs. Basicity can be further increased by linking together phosphazene units, in which the base strength increases with the increasing number of N atoms (*Figure 6*). These are labelled P1, P2, P3, and P4 phosphazenes depending on the number of units linked together.

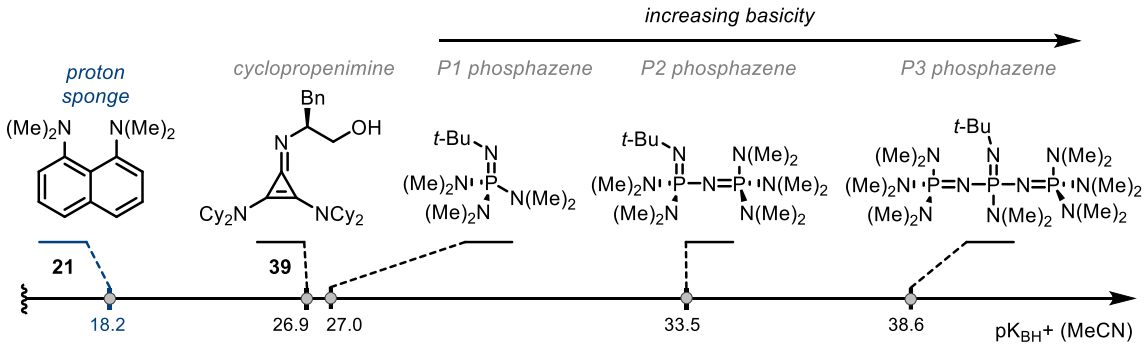
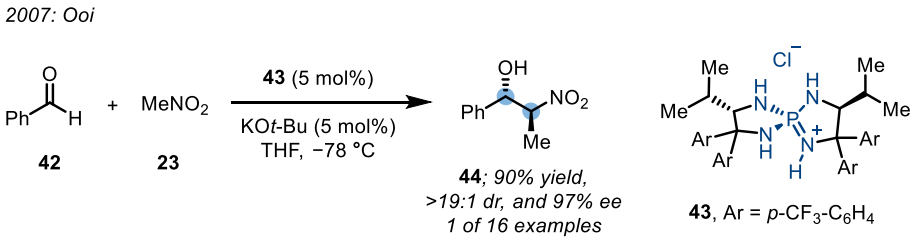


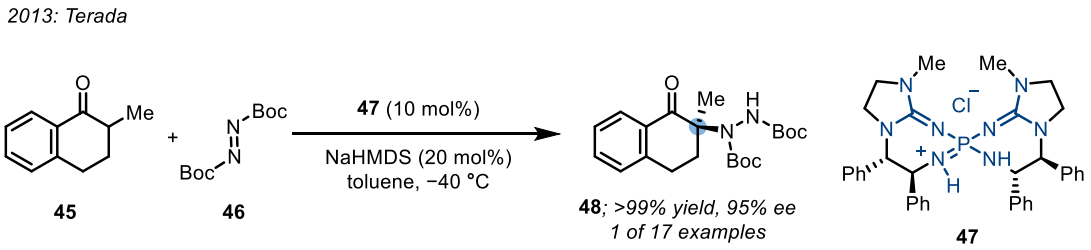
Figure 6: $pK_{BH}+$ scale for representative phosphazene organic superbases.

The first chiral phosphazene base **43** was employed by Ooi in 2007 in a highly enantioselective and diastereoselective Henry reaction[72] (*Scheme 7*). Asymmetric induction was proposed to occur through the formation of a hydrogen-bonded ion pair between the phosphazene conjugate acid and the deprotonated nucleophile **23**, which in turn preferentially attacks one enantiotopic face of the aldehyde electrophile **42**. Ooi's class of chiral spirocyclic phosphazene bases has subsequently been applied to a range of transformations, including enantioselective 1,4-[73], 1,6-[74], and 1,8-[75]conjugate addition, hydrophosphonylation of aldehydes[76], and the enantioselective oxidation of *N*-tosyl imines[77,78].



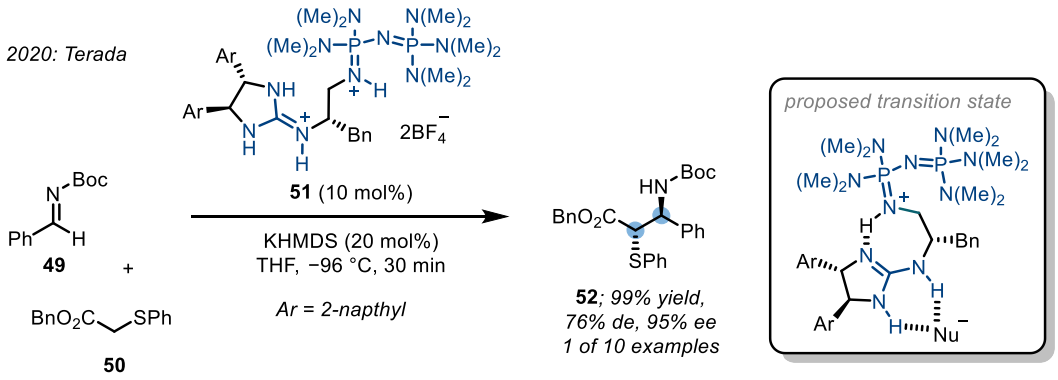
Scheme 7: Ooi's stereoselective Henry reaction using phosphazene superbase.

Later in 2013, Terada disclosed a stronger P-spirocyclic phosphazene base **47**, incorporating two guanidine units around the central P(V) atom[79,80]. This was used in the enantioselective amination of tetralone **45** with azodicarboxylate (**46**, *Scheme 8*). Significantly, under similar reaction conditions, Ooi's catalyst performed poorly, highlighting the importance of the increased basicity to the transformation. This catalyst has been employed in numerous enantioselective reactions, including a variety of enantioselective Mannich reactions[81,82] as well as a recently reported enantioselective hydrophosphinylation 1,1-vinyl azaheterocycle *N*-oxides[83].



Scheme 8: Terada's enantioselective amination of tetralones.

Recently, Terada has reported a new class of chiral phosphazene base **51**, combining a P2 phosphazene core with a tethered guanidine[84]. Asymmetric induction is proposed to occur through the formation of a rigid 7-membered ring on deprotonation of the nucleophile by the P2 phosphazene component, forming a chiral pocket. The guanidinium salt then engages in a hydrogen-bonded ion pair with the substrates. In their report, this catalyst was employed in the enantioselective Mannich-type reaction of *N*-Boc aldimine **49** and α-phenylthioacetate **50** (*Scheme 9*).

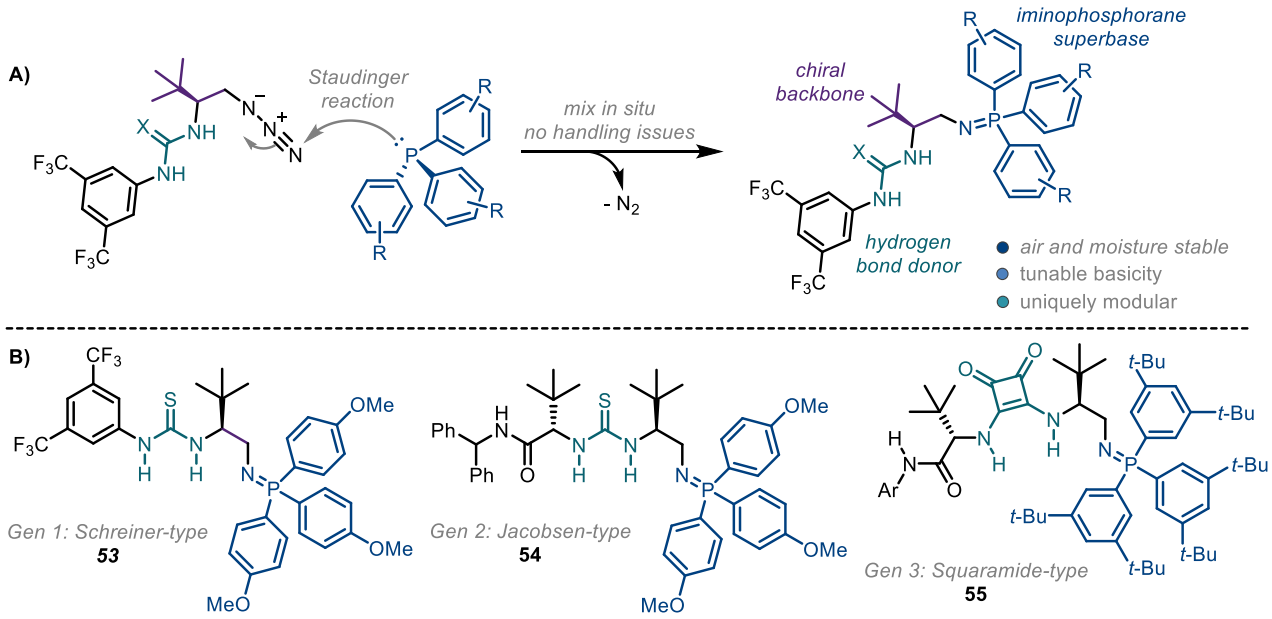


Scheme 9: Terada's enantioselective Mannich-type addition to *N*-Boc aldimines.

1.2.4 Bifunctional Iminophosphorane Catalysis

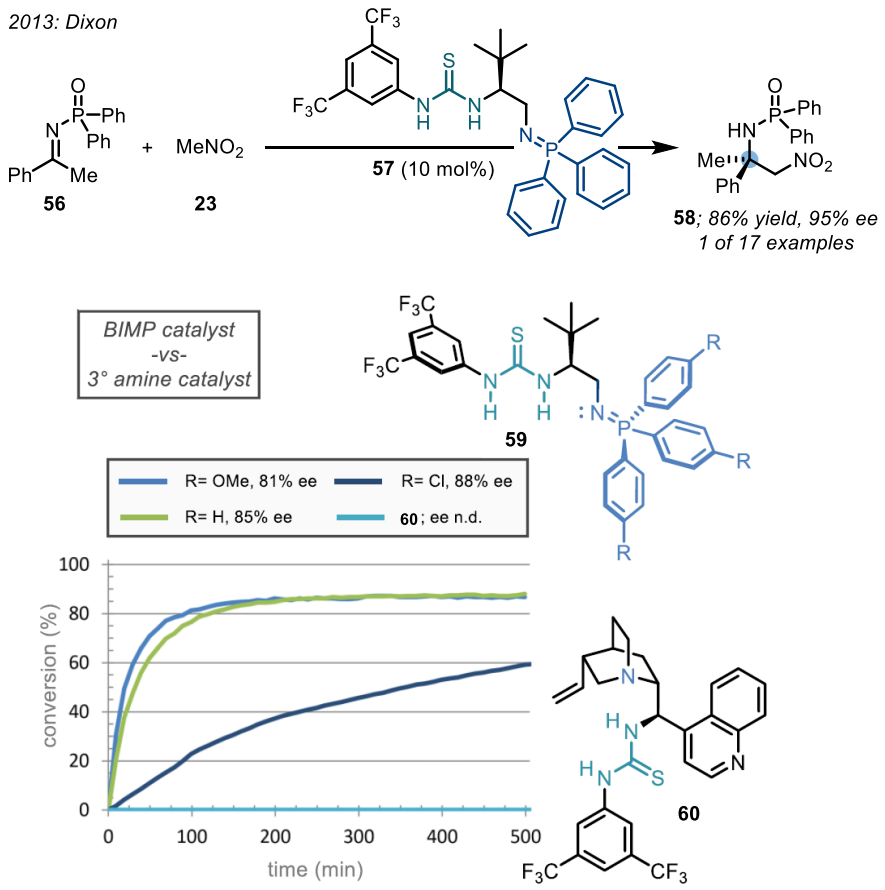
Despite their undoubted advantages, the aforementioned superbase catalysts have several drawbacks. Principally, their synthesis is often challenging and modularity in catalyst design is limited, preventing rapid screening for reaction development. Similarly, they are often unstable as their free base, requiring storage and handling as a salt. As such, they require an equal amount of strong inorganic base to activate the catalyst *in situ*, offsetting some of the advantages associated with the use of the organic superbase.

With these limitations in mind, the Dixon group has pioneered the development of a novel class of organic superbasic catalysts, the bifunctional iminophosphorane (BIMP)[85] (*Scheme 10*). By combining a hydrogen-bond donor motif and a tuneable superbasic iminophosphorane, BIMPs combine ease of synthesis, handling and storage, and unique catalyst modularity. The active iminophosphorane is formed through the *in situ* Staudinger reaction between an amino acid-derived organoazide and a readily available free phosphine; importantly, the basicity of this iminophosphorane can be tuned by variation of the employed phosphine, enabling late stage catalyst screening for a broad range of reactions. Mixing the organoazide and phosphine *in situ* allows for maximum tunability and no handling issues, though BIMP organocatalysts have been shown to be stable to both air and moisture and can be stored for over 2 years at −20 °C with no loss of activity[86]. Further, these catalyst frameworks offer unique modularity for rapid catalyst screening, enabling variation of the hydrogen-bond donor group, chiral backbone structure, and iminophosphorane basicity.



Scheme 10: **A)** Representative formation of BIMP catalyst; **B)** representative structures of 1st-,2nd-, and 3rd-generation BIMP catalysts.

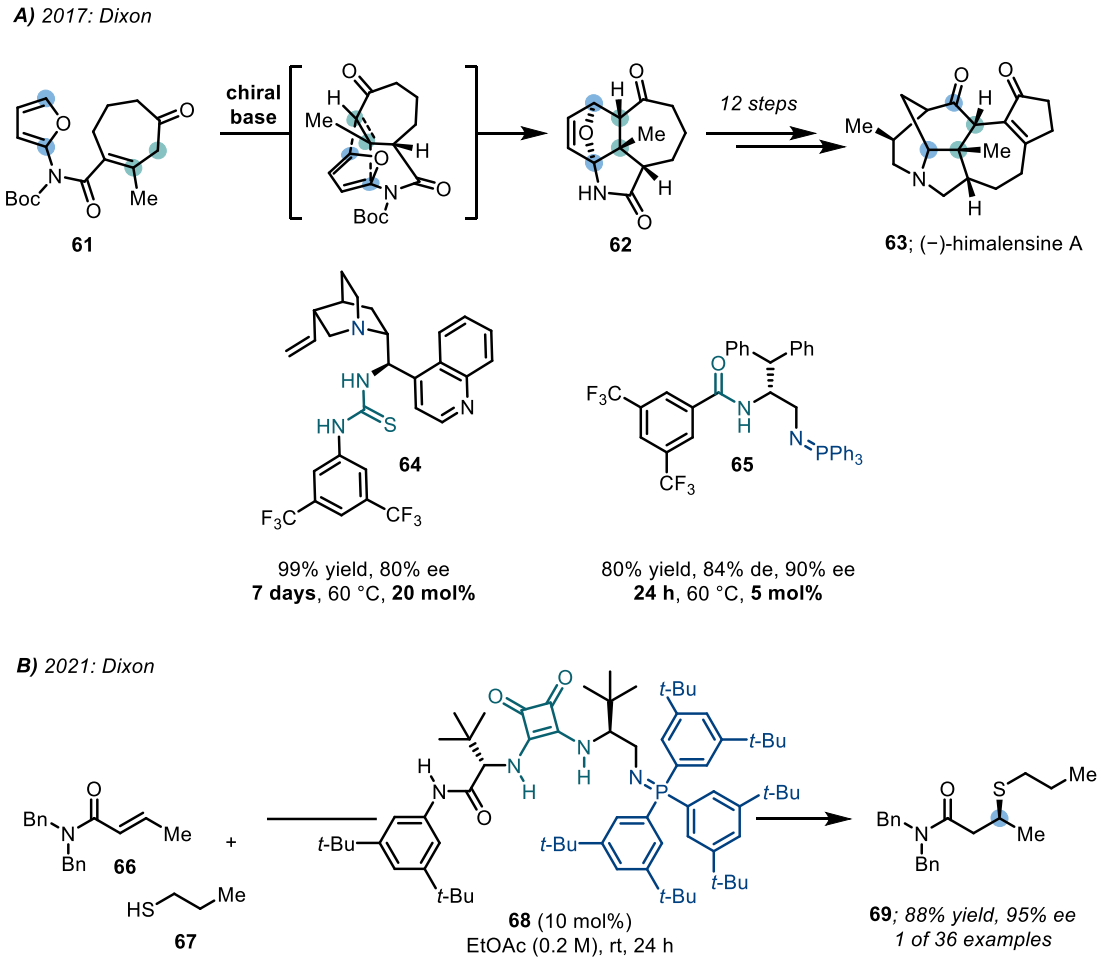
BIMP catalysts have been employed in a broad range of reaction classes. In 2013, Dixon and co-workers first demonstrated the utility of this catalyst class (**57**) in the enantioselective nitro-Mannich-type addition of **23** to *N*-DPP ketimine **56**, forming chiral amine product **58** [87]. Following screening of a library of BIMP catalysts, this protocol was able to deliver product in up to 97% yield and up to 95% ee. Importantly, the authors were able to demonstrate a significant rate enhancement for the BIMP catalysts **59** when compared to cinchona-based catalyst **60** due to their higher basicity, and the reaction rate was shown to be tuneable depending on the phosphine component of the iminophosphorane, with BIMPs possessing electron-rich phosphines reacting faster than electron-poor phosphines (*Scheme 11*).



Scheme 11: Dixon's enantioselective BIMP-catalysed nitromethane addition to N-DPP ketimines and representative rate enhancement effect of BIMP catalysts over cinchona analogues.

BIMP catalysts have also been utilised in the synthesis of a variety of natural products. For example, in 2017, Dixon reported the total synthesis of the alkaloid (−)-himalensine A[88] (**63**, *Scheme 12**A***). Key to this strategy was a novel base-catalysed enantioselective prototropic shift/intramolecular Diels-Alder cycloaddition cascade reaction of **61** to rapidly construct the ACD tricyclic ring system. Cinchona-derived tertiary amine catalyst **64** was shown to impart good levels of enantiocontrol in this step though with low overall reactivity, requiring 7 days for reaction completion. Identifying the low basicity of the tertiary amine base as the main issue, the authors instead employed 1st-generation BIMP catalyst **65**, achieving good yields of the desired product **62** with excellent levels of diastereoselectivity and enantioselectivity, using a low catalyst loading of 5 mol% and requiring only 24 hours for reaction completion.

Most recently, the Dixon group has reported an unprecedented enantioselective sulfa-Michael addition of alkyl thiol **67** to unactivated α,β-unsaturated amide **66** by employing a BIMP catalyst design incorporating a squaramide-based hydrogen-bond donor (**68**)[89]. Despite the low electrophilicity of the α,β-unsaturated amide, this protocol was able to deliver enantioenriched thiols in up to 99% yield and up to 95% ee, a result of the increased hydrogen-bond donor strength of the squaramide in comparison to urea- or thiourea-based catalysts (*Scheme 12**B***).



Scheme 12: **A)** Key base-catalysed enantioselective prototropic shift/Diels-Alder cycloaddition cascade in Dixon's total synthesis of (−)-himalensine A; **B)** Dixon's enantioselective sulfa-Michael addition of alkyl thiols to α,β-unsaturated amides.

1.2.5 Conclusions

The development of organocatalysis in the 21st-century has produced a vast array of methods for the enantioselective synthesis of chiral molecules. Amongst these strategies, bifunctional organocatalysts employing a Brønsted base and hydrogen bond donor have emerged as particularly versatile; however, traditional tertiary amine Brønsted bases deployed in these catalyst frameworks are limited by their low basicity and the subsequently narrow range of pronucleophiles accessible for activation. As such, numerous groups have focussed on the development of superbasic organocatalysts. Whilst effective, these catalysts typically suffer from low stability and short half-lives *in situ*, limiting their utility. One particularly versatile catalyst class is the bifunctional iminophosphoranes (BIMPs), combining a superbasic iminophosphorane motif (formed *in situ* with no handling issues) and a modular catalyst backbone, enabling rapid catalyst screening for reaction development.

We were interested in applying these versatile BIMP catalysts to novel reaction types not possible using traditional bifunctional organocatalysts. A particularly interesting area in this regard is the direct

enantioselective synthesis of stereogenic P(V) centres. Whilst numerous enantioselective catalytic methods have been published for access to compounds containing P(V)-stereogenic centres, these compounds often show low versality for downstream synthetic modification. By harnessing the BIMP catalyst framework, we hoped to contribute to this field through the development of a highly enantioselective, broad scope, and versatile method for the formation of P(V)-stereocentres, which additionally enable downstream derivatisation for ease of access to a wide range of important structures with pharmaceutical and agrochemical applications.

Chapter 2: Enantioselective Nucleophilic Desymmetrisation for the Synthesis of Stereogenic P(V)

2.1 The Importance of P(V)-Containing Molecules

P(V)-stereogenic compounds are prevalent throughout medicine and agrochemistry[90]. Pharmaceutically active compounds containing a P(V) stereocentre are widely employed as antivirals and anticancer agents such as Remdesivir (**70**) [91] and cyclophosphamide (**72**), the former an effective treatment for Ebola which has recently been approved as a treatment for SARS-CoV-2[92], and the latter a chemotherapy agent which is currently listed as a WHO essential medicine[93] (*Figure 7**A***). Stereogenic P(III) and P(V) compounds are also ubiquitous as ligands in enantioselective transition metal catalysis[94–96].

Within a pharmaceutical context, phosphates often represent the active form of antiviral and anticancer P(V)-containing APIs[97]. However, free phosphates show low stability and poor bioavailability due to their high polarity, preventing diffusion across the cell membrane; as such, P(V) drugs are generally administered in prodrug form[97]. Their higher lipophilicity enables diffusion across the cell membrane, whereby the biolabile prodrug motif is chemically or enzymatically cleaved *in vivo*, releasing the free phosphate[98]. Subsequent phosphorylation then generates the active triphosphate form of the drug. Various biolabile prodrugs have been developed to aid P(V) bioavailability and drug efficacy, including *cyclo*Sal[99], HepDirect[100], and ProTide[101] motifs (*Figure 7**B***). Importantly, the chirality of the P(V) stereocentre can have a dramatic effect on the rate of release of the active phosphate from the prodrug form, meaning the enantioselective synthesis of P(V)-stereogenic centres is of key importance[102].

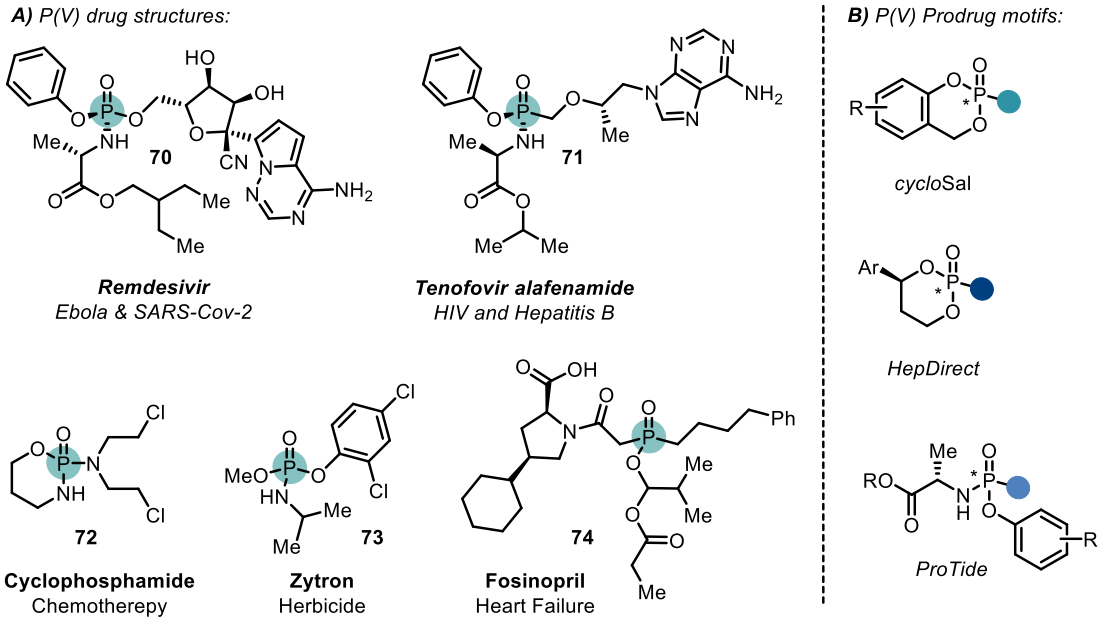


Figure 7: **A)** Representative P(V) drug structures; **B)** representative structures of commonly used P(V) prodrug motifs.

2.1.1 Synthesis of P(V)-Stereogenic Centres

Despite the tremendous progress made in the synthesis of stereogenic carbon atoms using enantioselective catalysis, in general the direct application of these methods to the formation of P(V)-stereogenic centres is challenging. The inherently longer C—P bond lengths may preclude the formation of a tight transition state, thereby reducing the energy difference between competing enantiomeric reaction pathways in the enantiodetermining catalytic step, giving low overall reaction enantioselectivity[103]. Similarly, the availability of low-lying 3d orbitals means P(V) may form high valence intermediates, thereby altering the catalytic cycle and making it challenging to directly implement catalytic enantioselective reaction systems developed specifically for the synthesis of stereogenic C centres. As such, there are relatively few reliable, broad scope, and highly enantioselective direct methods for forming P(V)-stereogenic centres.

Synthetic methods for accessing stereogenic P(V) compounds can generally be broken down into 5 classes: i) classical resolution and chromatographic separation, ii) chiral auxiliary methods, iii) direct functionalisation of secondary phosphine oxides, iv) diastereoselective coupling, and v) enantioselective desymmetrisation. Numerous advances have been made in these areas, including notable elegant recent examples from Baran[104–108], Merck[109], Miller[110], and Guant[111], vastly improving the ease of access P(V)-stereogenic centres. Only enantioselective desymmetrisation methods are within the scope of this thesis, but for a detailed overview of all of these methods the reader is referred to the numerous excellent reviews in the published literature[103,112–116].

As a branch of enantioselective catalysis, catalytic enantioselective desymmetrisation represents a potentially highly efficient means for accessing enantioenriched molecules[117–125]. Formally, this involves the conversion of a prochiral or meso compound into a chiral one by the removal of one or more symmetry elements, in which two enantiotopic functional groups are differentiated by means of a chiral catalyst[126]. This represents an attractive means for accessing P(V)-stereogenic molecules indirectly by the reaction of prochiral groups attached to P. If desymmetrisation occurs directly at the P(V) centre, then the simplified synthesis of symmetrical prochiral precursors can also beneficial. With these advantages in mind, the formation of chiral P(V) centres by desymmetrisation represents a potentially highly effective synthetic method.

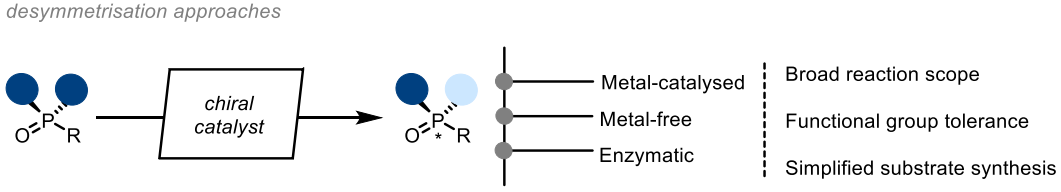


Figure 8: General overview of desymmetrisation approaches for the synthesis of P(V)-stereogenic molecules.

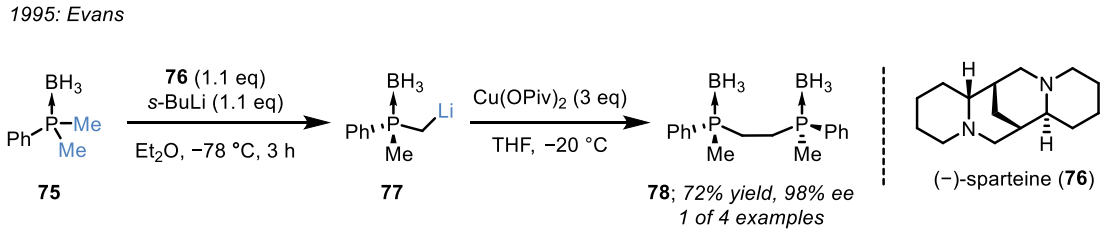
2.1.2 Indirect Enantioselective Desymmetrisation for Access to P(V) Stereocentres

In general, the majority of enantioselective desymmetrisation methods for accessing P(V) stereocentres employ indirect methods; that is, functionality is installed around the prochiral P(V) precursor and chirality introduced by the stereoselective reaction of these preinstalled functional groups. As such, reactivity occurs away from the central P(V) centre. Whilst various reaction types have been employed using this strategy, the P(V) precursors utilised may be classed as: i) BH_3-bound phosphines, ii) bis-alkyne substituted P(V) species, iii) bis-alkene substituted P(V) species, iv) bisphenol substituted P(V) species, v) phosphoramidic and phosphoric acids, and vi) bis aryl P(V) species.

2.1.3 Desymmetrisation of BH_3-Bound Phosphines

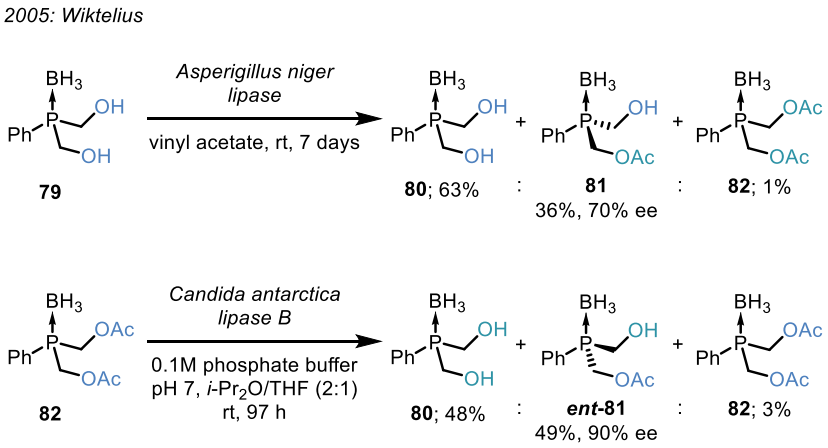
Early methodology focussed on the enantioselective desymmetrisation of BH_3-bound phosphines. These provide convenient precursors for accessing chiral phosphine ligands *via* reductive removal of the BH_3 group, minimising the need handling often air-sensitive free phosphines in ligand synthesis.

In an early approach, Evans[127] demonstrated the enantioselective deprotonation of prochiral alkyl groups around the P(V) centre using a *s*-BuLi alongside a (−)-sparteine additive (**76**), affording the chiral lithiated intermediate **77**. This was subsequently homodimerized using $Cu(OPiv)_2$ to afford the BH_3-bound bisphosphine (**78**, *Scheme 13*). Later, Imamoto[128] demonstrated a similar method for the synthesis of sterically hindered P-stereogenic bis(trialkylphosphine) ligands. In 2006, O'Brien[129] also showed the synthesis of P-stereogenic bisphosphines using *s*-BuLi as base and sub-stoichiometric quantities of a (+)- or (−)-sparteine surrogate[130].



Scheme 13: Evans' enantioselective deprotonation of prochiral alkyl phosphine oxides.

In 2005, Wiktelius[131] demonstrated an enzyme-mediated desymmetrisation of bis(hydroxymethyl)phenylphosphine-borane **79**. Using an *Aspergillus niger* lipase, the authors were able to achieve acetylation of these prochiral bis-alcohol P(V) precursors with a low 36% conversion and 70% ee. By instead using a *Candida Antarctica* lipase B enzyme, the authors were also able to demonstrate the reverse reaction; that is, deacetylation to yield the free alcohol. This proceeded with an improved 49% conversion and 90% ee (*Scheme 14*).



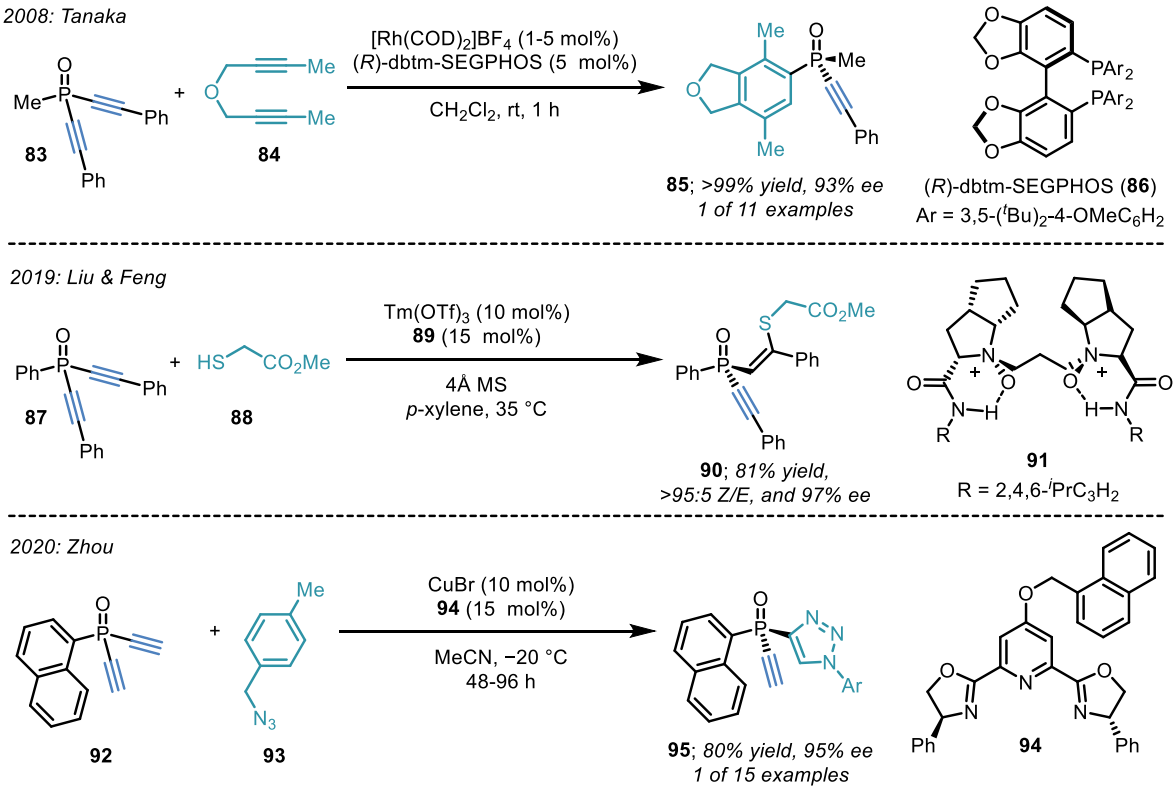
Scheme 14: Wiktelius's enzyme-mediated enantioselective desymmetrisation of prochiral BH_3-bound phosphines.

2.1.4 Desymmetrisation of Bis-Alkyne Substituted P(V) Species

In 2008, Tanaka[132] reported an elegant method for the enantioselective desymmetrisation of bis-alkyne P(V) species **83** using a Rh-catalysed [2+2+2] cycloaddition reaction. By employing 5 mol% of a $[Rh(COD)_2]BF_4$ catalyst precursor and 5 mol% (*R*)-dbtm-SEGPHOS (**86**) as chiral ligand, the authors were able to demonstrate excellent yields and enantioselectivities across a range of prochiral P(V) precursors (*Scheme 15**A***).

Later, in 2019, Liu & Feng[133] reported an enantioselective sulfa-Michael addition to prochiral bis-alkyne P(V) precursor **87** using a Tm(III) Lewis acid catalyst. Using 10 mol% $Tm(OTf)_3$ as catalyst precursor and 15 mol% ligand *N,N'*-dioxide catalyst **91**, the authors demonstrated moderate to good yields (up to 92% yield) and generally excellent stereoselectivity (up to >95:5 *Z:E* ratio and up to 97% ee) (*Scheme 15**B***). Using X-Ray crystal structures of the Tm(III)/ligand complex, the authors suggest coordination of the P=O bond of the prochiral P(V) precursor to the Lewis acidic Tm(III) centre, activating it towards nucleophilic attack, followed by enantioselective addition of the sulfur nucleophile.

In 2020, Zhou[134] demonstrated the Cu(I)-catalysed enantioselective azide-alkyne cycloaddition (CuAAC) of bis-alkyne substituted P(V) phosphine oxide **92** (*Scheme 15**C***). Using 10 mol% CuBr as the catalyst precursor and 12 mol% of PyBox ligand **94**, the authors were able to achieve an extremely broad scope reaction in generally good yields and excellent enantioselectivities. This reaction could also be extended to remote CuAAC of phosphole oxide-diynes, notable due to their potential applications in electronic devices. In addition to desymmetrisation, Zhou and co-workers were also able to demonstrate the kinetic resolution of mono-alkyne substituted P(V) phosphine oxides with up to 48% yield and 99% ee of the desired triazole product.



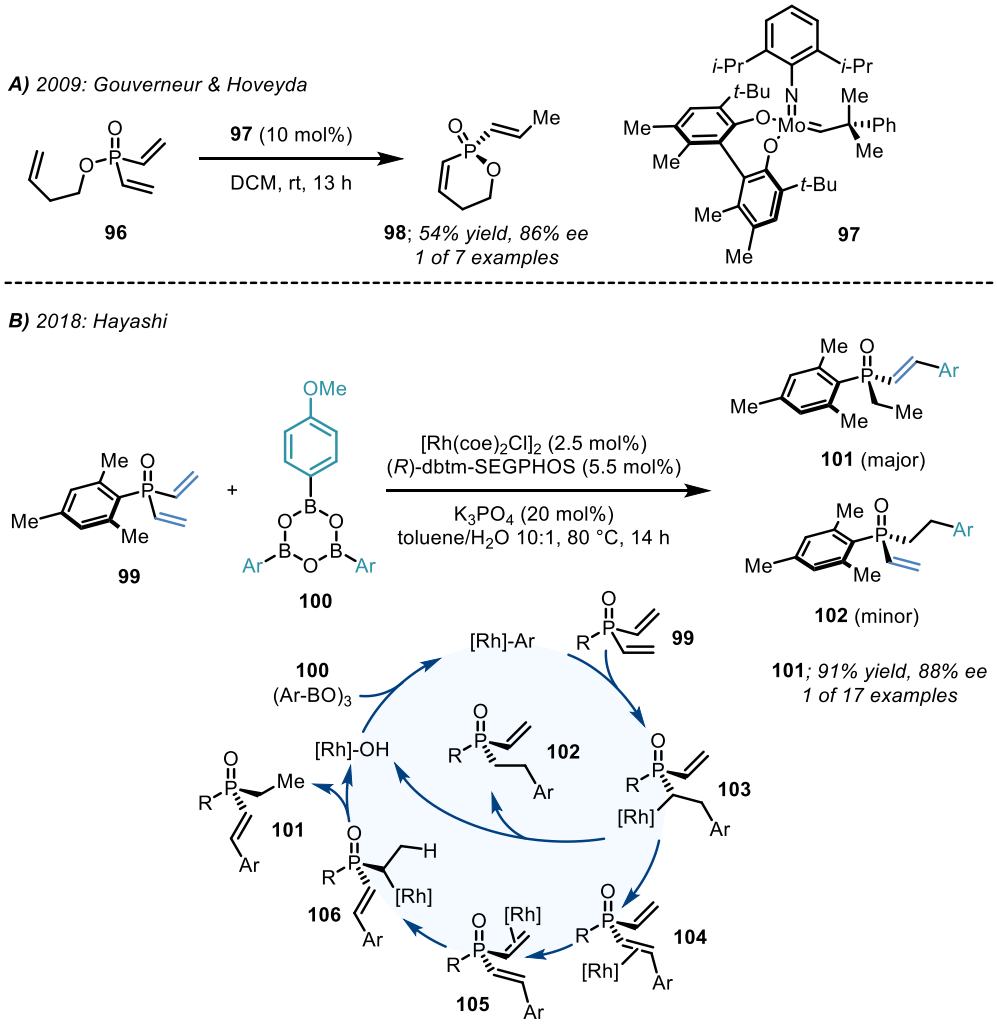
Scheme 15: Enantioselective desymmetrisation of bis-alkyne substituted phosphine oxides: **A**) Tanaka's enantioselective Rh-catalysed [2+2+2] cycloaddition; **B**) Liu & Feng's Tm(III)-catalysed sulfa-Michael addition; **C**) Zhou's enantioselective CuAAC.

2.1.5 Desymmetrisation of Bis-Alkene Substituted P(V) Species

In 2009, Gouverneur & Hoveyda[135] reported the first example of an enantioselective ring closing metathesis (ARCM) of bis-alkene P(V) phosphine oxide **96** to generate P(V)-stereogenic centres. By employing a bis-vinyl substituted P(V) centre alongside a tethered alkene, in the presence of 10 mol% of a chiral Mo catalyst **97**, the authors were able to achieve enantioselective ARCM in moderate to good yields (up to 88% yield) and moderate to good enantioselectivities (up to 96% ee) (*Scheme 16**A***).

In 2018, Hayashi[136] disclosed the enantioselective hydroarylation of similar bis-alkene substrate **99**. Using 2.5 mol% $[RhCl(coe)_2]_2$ as precatalyst and 5.5 mol% of **86** as chiral ligand, alongside triaryl boroxine **100** as aryl precursor, the authors were able to achieve hydroarylation of a range of substrates. However, this reaction generated a mixture of alkene and alkane products, resulting from incomplete alkene reduction by the Rh catalyst, though achieved good to excellent enantioselectivity for the synthesis of the stereogenic P(V) centre (up to 95% ee). Using deuterium labelling studies, the authors proposed a mechanistic cycle composing initial transmetallation of the Rh(I)/**86** complex to form the arylated active catalyst, followed by hydroarylation of the bis-vinyl prochiral P(V) precursor to form intermediate **103**. In the major product pathway, β-H elimination forms the arylated intermediate **104** and a Rh-H species, followed by subsequent Rh migration to the alternative alkene (**105**) and further reduction to the alkane

(**106**), generating the major hydroarylated product **101** following β-H elimination of the Rh catalyst. Premature protonolysis from intermediate **103** was postulated to lead to the formation of the undesired minor biproduct **102** (*Scheme 16**B***).



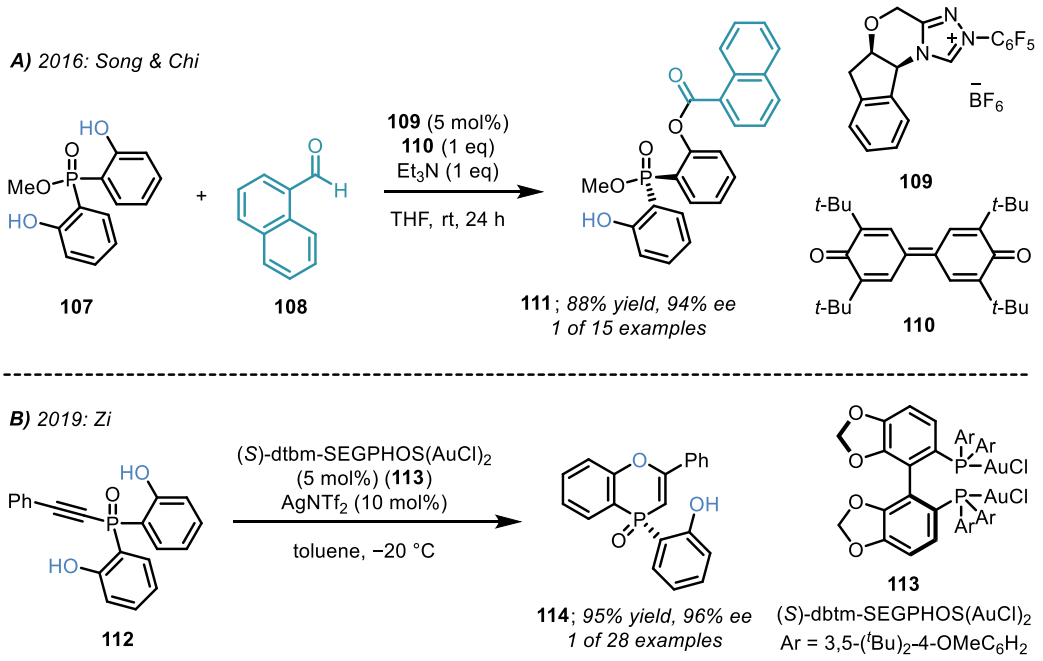
Scheme 16: Enantioselective desymmetrisation of bis-alkyne substituted P(V) species: **A**) Gouverneur and Hoveyda's enantioselective ARCM reaction; **B**) Hayashi's enantioselective hydroarylation of bis-alkyne phosphine oxides.

2.1.6 Desymmetrisation of Bisphenol Substituted P(V) Species

A popular class of substrates for P(V) desymmetrisation are those bound to two phenol groups. In 2016, Song & Chi[137] disclosed the synthesis of P(V)-stereogenic phosphinate **111** *via* *N*-Heterocyclic carbene (NHC)-catalysed enantioselective reaction of prochiral bisphenol substituted phosphinates with aldehydes. By employing 5 mol% NHC **109**, 1 eq quinone **110** as an external oxidising agent, and 1 eq NEt_3 as external base, the authors achieved good to excellent yields (up to 90% yield) and generally excellent enantioselectivities (up to 98% ee) for a range of aldehydes (**108**) and bisphenol phosphinates (**107**, *Scheme 17**A***). This reaction could also be extended to phosphinamides with up to 79% yield and 88% ee. Unfortunately, attempts to extend this methodology to bisphenol phosphine oxide precursors

led to severely reduced yields and enantioselectivity, and moving the phenol OH from the 2- to the 3- or 4- positions gave racemic product.

Later, in 2019, Zi[138] disclosed the enantioselective and regioselective hydroetherification of alkynes *via* the Au-catalysed desymmetrisation of prochiral bisphenol phosphine oxides. Using alkyne-bound bisphenol prochiral phosphine oxide precursor **112**, and 5 mol% (*S*)-dbtm-SEGPHOS(AuCl)$_2$ complex **112** and 10 mol% AgNTf$_2$ as external oxidant, the authors were able to achieve the regio- and enantioselective *6-endo-dig* intramolecular cyclisation of the phenolic nucleophile to the electrophilic alkyne, forming the P(V)-stereogenic heterocycle **114** (*Scheme 17**B***). This method could also be extended to include bis-alkyne substituted phosphine oxides, bearing only a single phenol component, with excellent enantioselectivity.



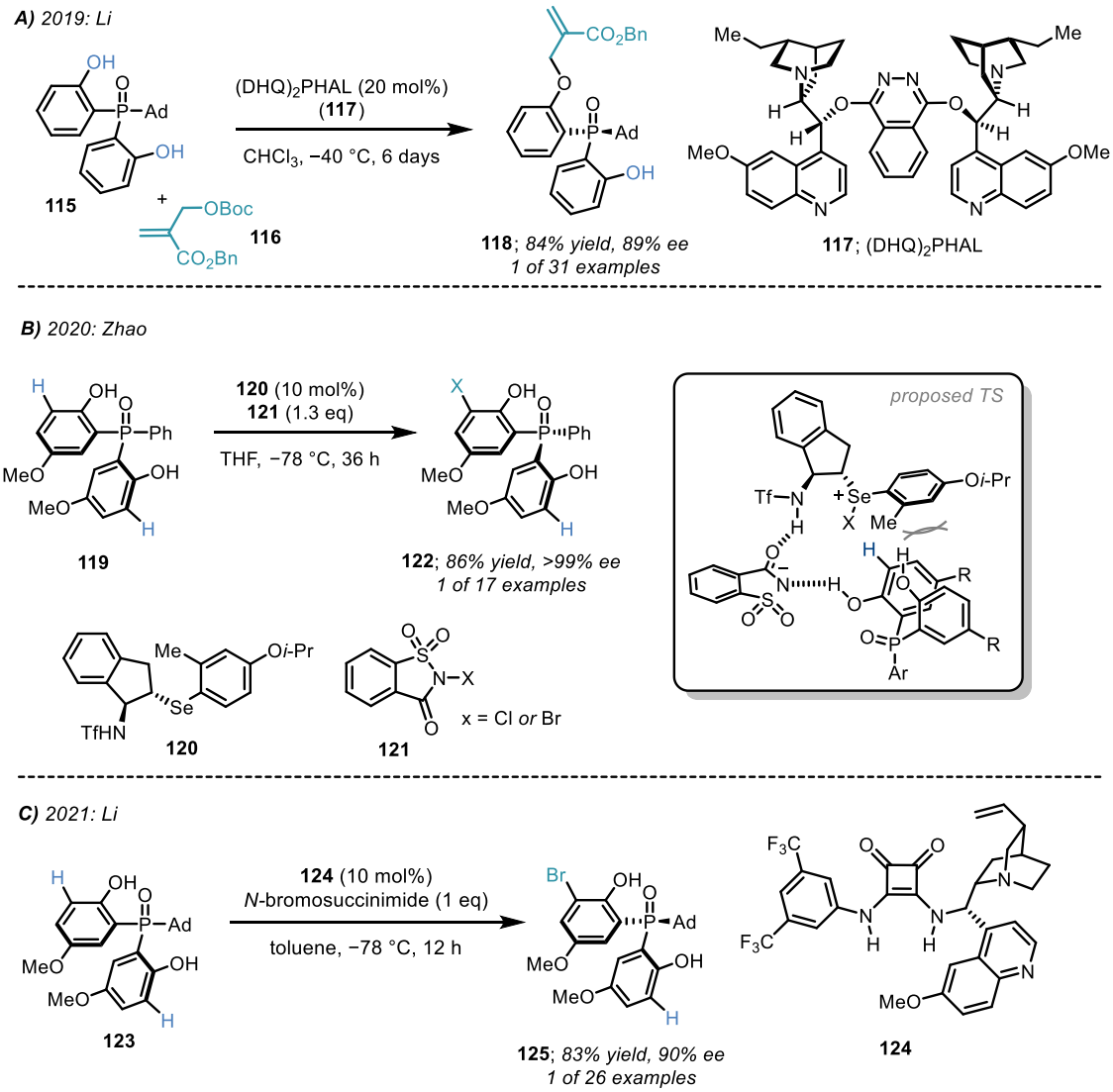
Scheme 17: **A**) Song & Chi's enantioselective NHC-catalysed synthesis of P(V) stereogenic phosphinates; **B**) Zi's enantioselective Au-catalysed hydroetherification.

Li has developed multiple organocatalytic desymmetrisations of bisphenol P(V) phosphine oxides. First, in 2019, Li disclosed a novel cinchona alkaloid-catalysed enantioselective desymmetrisation *via* a Morita-Baylis-Hillman (MBH) reaction[139]. Using 20 mol% (DHQ)$_2$PHAL (**116**) as the organocatalyst alongside MBH carbonate reagent **116**, the authors were able to achieve desymmetrisation of phosphine oxides bearing tertiary alkyl backbones (**115**) in good yields and enantioselectivities (*Scheme 18**A***). Unfortunately, however, the reactions were extremely slow under these conditions, taking 6 days, and attempts to alter the P(V) backbone with other functionality gave decreased selectivity.

In a related approach, Zhao has recently disclosed an unprecedented Se-catalysed enantioselective electrophilic aromatic halogenation reaction of prochiral biaryl phosphine oxides[140]. Using 10 mol% of

selenide catalyst **120**, in conjunction with *N*-chloro/*N*-bromosaccharin (**121**) as an external halogenating agent, the authors were able to demonstrate enantioselective electrophilic aromatic substitution bisphenol phosphine oxide **119** in up to 98% yield and up to >99% ee (*Scheme 18**B***). The authors postulate a mechanistic pathway involving initial halogenation of the selenide catalyst, followed by enantioselective halogenation of the phenol ring.

Later, in 2021, Li reported the *ortho*-selective enantioselective bromination of bisphenol phosphine oxides using cinchona-derived chiral squaramide catalyst **124**[141]. By employing 10 mol% **124** and *N*-bromosuccinimide (NBS) as the external brominating agent, enantioselective desymmetrisation of *ortho*-substituted bisphenol phosphine oxides (**123**) was demonstrated in up to 92% yield and 96% ee (*Scheme 18**C***). In the proposed mechanism, activation of NBS by the tertiary amine of the catalyst is followed by directed electrophilic aromatic substitution of the substrate, in which hydrogen bonding between the catalyst and the free phenol OH of the substrate were key to good levels of enantioselectivity.



Scheme 18: **A**) Li's enantioselective MBH reaction of bisphenol phosphine oxides; **B**) Li's organocatalytic electrophilic aromatic bromination; **C**) Zhao's Se-catalysed enantioselective electrophilic aromatic halogenation of biaryl phosphine oxides.

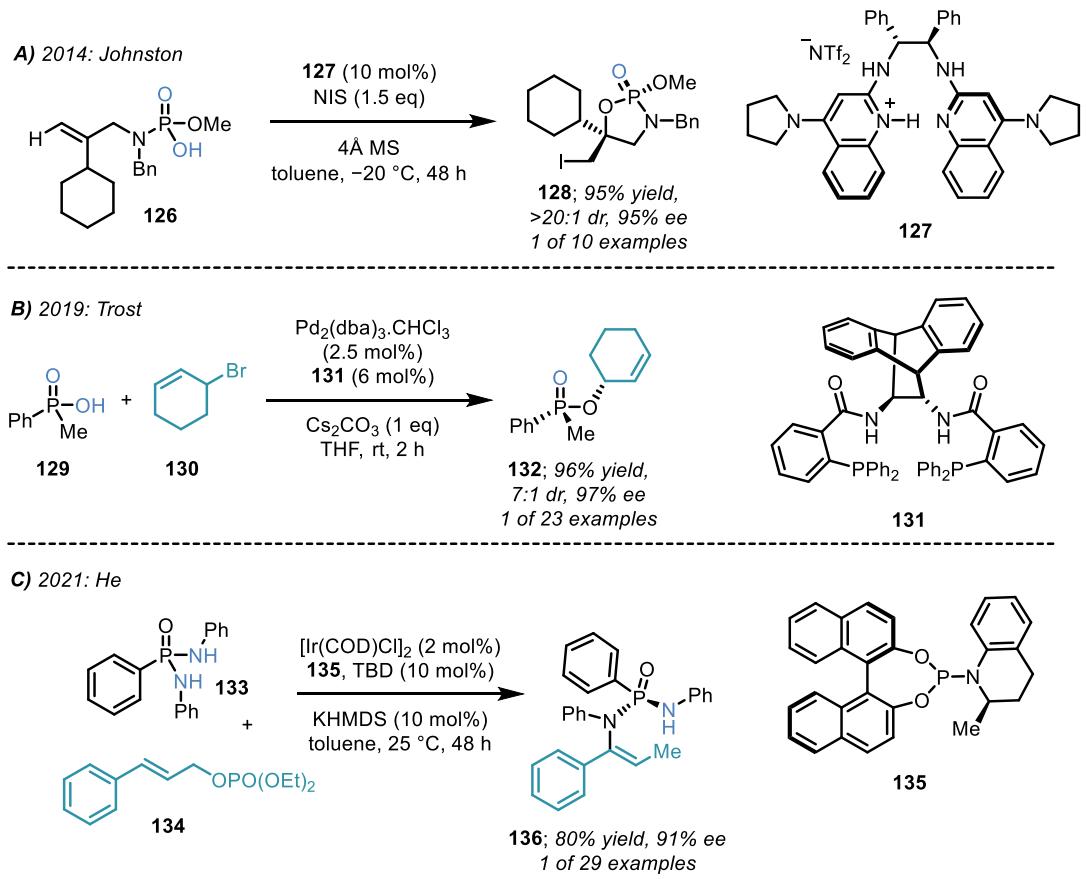
2.1.7 Desymmetrisation of Phosphoramidic Acids, Phosphinic Acids, and Phosphonamides

In addition to remote reactions of carbon and heteroatoms around the P(V) centre, a handful of methods have also been developed with reactivity occurring at heteroatoms directly bound to the P atom.

Johnston was the first to report such a transformation[142] with an enantioselective intramolecular Brønsted base-catalysed phosphoramidic acid addition to alkenes *via* a halogenative cyclisation[143]. Using prochiral substrate **126**, the authors were able to achieve enantioselective iodination of a distal alkene bound to the P(V) centre using a combination of 1.5 eq *N*-iodosuccinimide as the iodinating agent and 10 mol% chiral catalyst **127**. This was followed by stereospecific intramolecular *5-exo-trig* cyclisation to form heterocyclic product **128**, forming two stereocentres in a single reaction, including formation of a P(V)-stereogenic centre (*Scheme 19**A***).

Later, in 2019, Trost[144] reported the first intramolecular desymmetrisation of phosphinic acids (**129**) *via* a Pd-catalysed asymmetric allylic alkylation (AAA) strategy. With the optimised system of 2.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ as catalyst and 6 mol% of Trost ligand **131**, the authors were able to demonstrate the synthesis of a broad range of P(V) stereogenic phosphinates (**132**) bearing two stereocentres with up to 97% yield, 26:1 dr, and 99% ee in a single catalytic step; though, generally, the diastereoselectivity obtained was low across the substrate scope. In addition, the method required either 3-bromocyclohexene (**128**) or 3-bromocycloheptane as the electrophile, with linear alkylating agents giving diminished selectivity (*Scheme 19**B***).

Most recently, He[145] and co-workers have reported the enantioselective synthesis of P-stereogenic *N*-vinylphosphonamides using a novel asymmetric allylic substitution-isomerisation strategy. Using 2 mol% $[Ir(COD)Cl]_2$ as catalyst in conjunction with chiral phosphoramidate ligand **135**, and 1 eq KHMDS as external base, the authors demonstrated the formation of *N*-vinylphosphonamides (**136**) in up to 85% yield and 98% ee. Further, downstream reduction of the enantioenriched *N*-vinylphosphonamides enabled the facile synthesis of both diastereomers of P-/C-stereogenic centres with excellent enantioselectivity (*Scheme 19**C***).



Scheme 19: **A**) Johnston's enantioselective halogenative cyclisation; **B**) Trost's enantioselective AAA reaction; **C**) He's synthesis of *P*-stereogenic *N*-vinylphosphonamides via allylic substitution-isomerisation strategy.

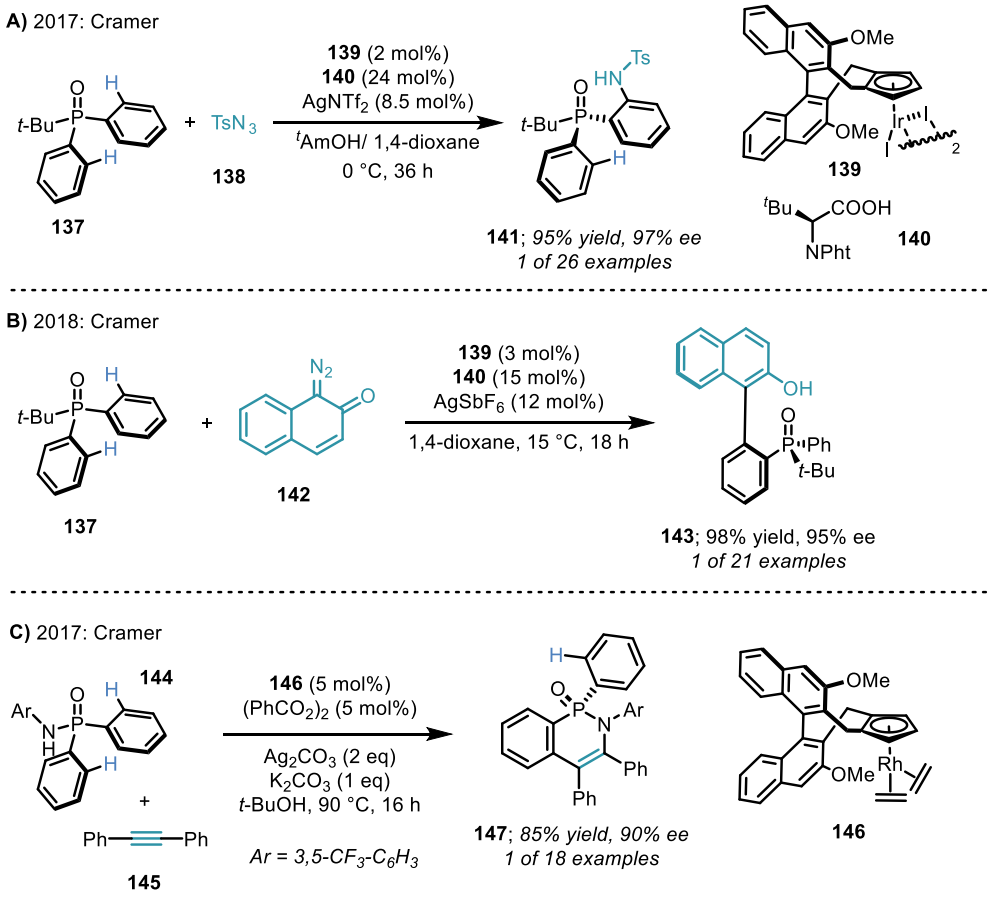
2.1.8 Desymmetrisation of Biaryl P(V) Substituted Species

By far the most employed method for stereogenic P(V) synthesis by indirect enantioselective desymmetrisation is the functionalisation of bis-aryl-substituted P(V) species through C-H activation methods. Given the breadth of this method of P(V) desymmetrisation, only the most important and recent examples are discussed. For an excellent overview of these methods, the reader is referred to recent reviews in the published literature[114,146].

Cramer has made numerous advances in this area. In 2017, building on work from Chang[147], Cramer reported a highly enantioselective Cp^{x}Ir(III)-catalysed C−H activation of prochiral phosphine oxides[148]. Combining prochiral biaryl phosphine oxide **137** and various aryl azides (**138**), alongside 2 mol% Cp^{x}Ir(III) catalyst **139** (incorporating a Cramer-type chiral Cp^x ligand), 24 mol% of chirality matched chiral carboxylic acid **140**, and 8.5 mol% $AgNTf_2$ for iodine abstraction, the authors were able to achieve enantioselective C−H amidation across a broad range of substrates with generally excellent yields (up to 95% yield) and excellent enantioselectivities (up to 98% ee) (*Scheme 20**A***). Importantly, the authors found that chirality-matched carboxylic acid ligand **140**, alongside the chiral Cp^x ligand, were key to achieving high levels of enantioselectivity, with achiral or mismatched chiral acids giving significantly diminished yields and stereocontrol. Cramer later used this same catalyst system for the enantioselective desymmetrisation of bis-aryl phosphine oxides, this time utilising *o*-quinone diazide **142** as the coupling

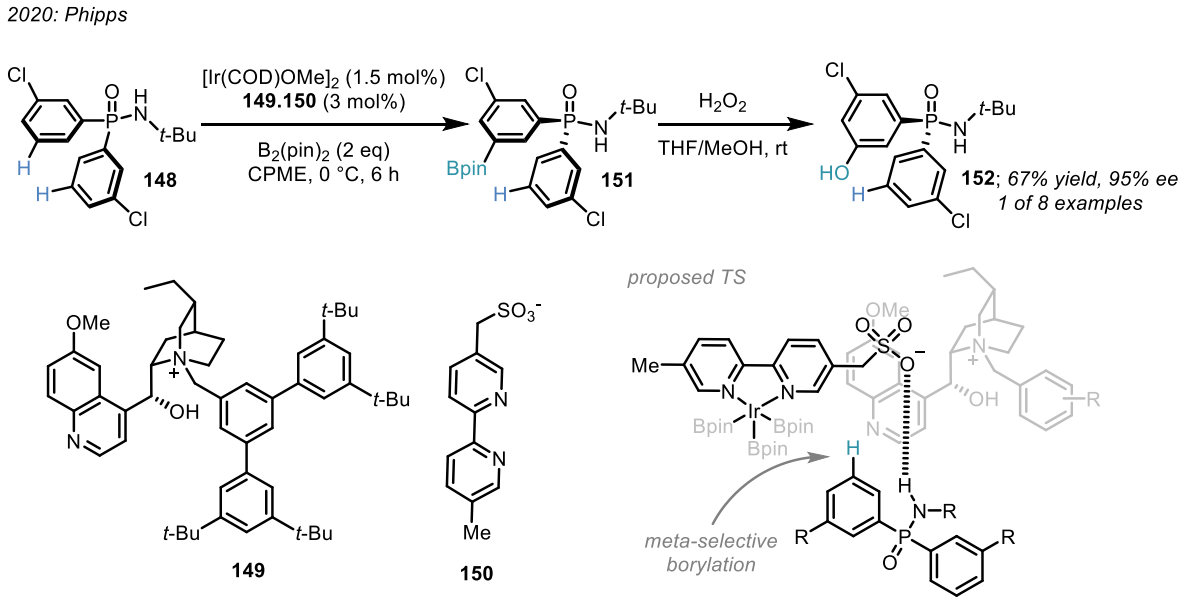
partner to form axially and P(V)-chiral products (**143**)[149]. Using a similar set of reaction conditions (3 mol% Cp^{x}Ir(III) catalyst **139**, 15 mol% chiral acid **140**, and 12 mol% $AgSbF_6$), the authors were able to demonstrate phosphine oxide arylation with, again, excellent yields (up to 97% yield) and stereoselectivity (>20:1 dr and up to 99% ee) (*Scheme 20**B***).

Building on earlier work from Han[150], Cramer has also disclosed the enantioselective desymmetrisation of phosphinamides, with an external alkyne as the coupling partner, to form enantioenriched stereogenic at P(V)/*N*-containing heterocycles[151]. Using biaryl phosphinamide **144** – and harnessing a fluorinated substituent on N to act as a directing group – alongside 5 mol% Cp^{x}Rh(III) catalyst **146**[152], 5 mol% benzoyl peroxide, K_2CO_3 as base, and Ag_2CO_3 as the external oxidant, the authors demonstrated enantioselective desymmetrisation for P(V)-stereogenic heterocycle formation with a range of alkynes and phosphine oxides in moderate to good yields (up to 86% yield) and good enantioselectivity (up to 92% ee) (*Scheme 20**C***). The authors demonstrated the utility of this unique class of products through the stereospecific reduction (97% es) of the P(V) centre to P(III) using DBU/$HSiCl_3$, giving potential as a novel ligand class for various metal-catalysed reactions.



Scheme 20: **A**) Cramer's enantioselective C−H amidation of biaryl phosphine oxides; **B**) Cramer's enantioselective C−H arylation; **C**) Cramer's enantioselective desymmetrisation of phosphinamides.

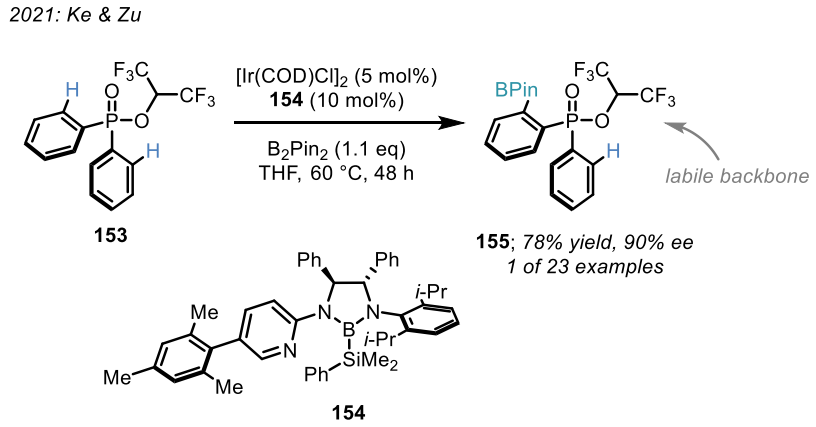
In 2020, Phipps and co-workers reported an elegant chiral counter-cation approach for the enantioselective desymmetrisation of biaryl phosphinamides by an Ir-catalysed *meta*-selective C−H borylation/oxidation[153]. By employing 1.5 mol% of an $[Ir(COD)OMe]_2$ catalyst, anionic bipyridine ligand **150**, and cinchona-based chiral cation **149**, the authors were able to demonstrate *meta*-selective borylation of a range of *meta*-substituted prochiral biaryl phosphinamides (**148**). Subsequent oxidation with H_2O_2 then generated the corresponding phenol product **152**. The sulfonate anion of the anionic bipyridine ligand was postulated to hydrogen bond to the acidic N−H of the phosphinamide, orientating the substrate for *meta*-selective borylation. The formation of a strong ion pair between the sulfonate anion and chiral cinchona ammonium cation was postulated to form a chiral pocket, enabling the enantioselective desymmetrisation of the prochiral substrate (*Scheme 21*).



Scheme 21: Phipps' enantioselective meta-borylation using chiral counterion catalysis.

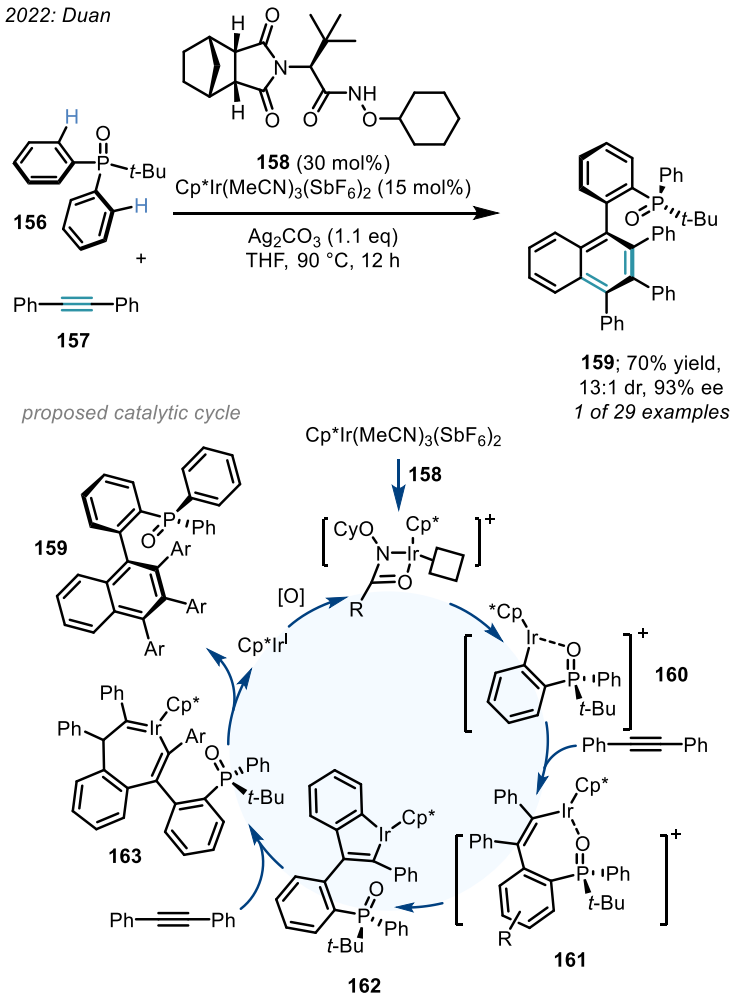
Ke & Zu[154] have recently disclosed the *ortho*-selective enantioselective C−H borylation of diarylphosphinates. In this challenging transformation, judicious choice of both ligand and catalyst were required to overcome the small steric bias between the aryl group and the OR group of the phosphinate during C−H activation. However, by employing 5 mol% $[IrCl(COD)]_2$ and 10 mol% of chiral bidentate boryl ligand (CBL, **152**) alongside $B_2(pin)_2$ as the external borylating agent, the authors were able to achieve selective C−H borylation in moderate to good yields and in generally excellent ee (up to 92% ee) for a broad range of prochiral biaryl phosphinates (**153**). Key to this approach was use of labile 1,1,1,3,3,3-hexafluoropropan-2-yl on the phosphinate backbone, enabling facile downstream substitution of the formed P(V) stereocentre with various alkoxide nucleophiles, followed by additional downstream synthetic modification (*Scheme 22*). The bulky CBL ligand **154** was proposed to facilitate the

formation of a 14-electron Ir(III) intermediate, followed by coordination with the P=O bond of the phosphinate and subsequent enantioselective aryl C−H oxidative addition.



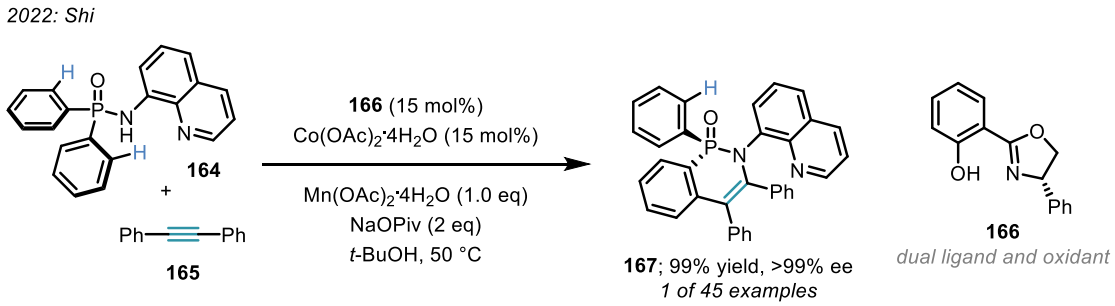
Scheme 22: Ke & Zu's ortho-selective C−H borylation of diarylphosphinates.

In 2022, Duan and co-workers[155] reported an elegant enantioselective oxidative double C−H activation strategy between prochiral biaryl phosphine oxides (**156**) and diarylacetylenes (**157**) for the synthesis of P- and axially- chiral products (**159**). During reaction screening, the authors observed formation of P- and axially chiral biaryl phosphine oxides **159** as opposed to the originally desired monoalkenylation products. Extensive catalyst and ligand screening revealed $Cp^*Ir(MeCN)_3(SbF_5)_2$ and chiral amide ligand **158**, alongside $AgCO_3$ as external oxidant, to be optimal for this transformation. The authors were able to demonstrate the synthesis of a structurally diverse range of biaryl phosphine oxides in good to excellent yields (up to 92% yield) and good to excellent stereoselectivity (up to >20:1 dr and up to 95% ee). Following mechanistic studies, the authors propose a double oxidative C−H activation process, in which the chiral Ir catalyst first undergoes enantioselective CMD (concerted metalation-deprotonation) C−H oxidation to the prochiral biaryl phosphine oxide **156** to form intermediate **160**. Reaction of **160** with alkyne **157** then formed the intermediate alkenyl species **161**, followed by a second oxidative C−H activation to the phenyl group of the alkyne to form 5-membered iridacycle **162**. Finally, the insertion of a second alkyne forms 7-membered iridacycle **163**, and subsequent reductive elimination generates the P- and axially- chiral product **159** alongside a Cp^*Ir^{I} species, which is oxidised to Cp^*Ir^{III} by Ag_2CO_3 to complete the catalytic cycle (*Scheme 23*).



Scheme 23: Duan's oxidative double C-H activation for enantioselective desymmetrisation of biaryl phosphine oxides.

Recently, Shi[156] has also reported an unprecedented cobalt/Salox-catalysed C−H annulation strategy for the enantioselective desymmetrisation of biarylphosphinamides. Key to this strategy was the use of a Salox ligand **166**, which was proposed to: i) stabilise the catalytically active octahedral Co^{III} intermediate following *in situ* oxidation of the $Co^{II}(OAc)_2{\cdot}4H_2O$ precursor by $Mn(OAc)_2{\cdot}4H_2O$, and ii) provide high levels of enantiocontrol through the incorporation of a chiral element adjacent to the metal centre. By incorporating an 8-aminoquinoline directing group on the prochiral biarylphosphinamide, in conjunction with 10 mol% $Co^{II}(OAc)_2.4H_2O$, 15 mol% Salox ligand **166**, 1 eq $Mn(OAc)_3{\cdot}2H_2O$ as external oxidant, and 2 eq NaOPiv as additive, the authors were able to achieve excellent yields (up to 99%) and near-perfect enantioselectivity (consistently up to >99% ee) for this C−H annulation strategy with various alkynes (*Scheme 24*).



Scheme 24: Shi's cobalt-Salox C−H annulation for the enantioselective desymmetrisation of biarylphosphinamides.

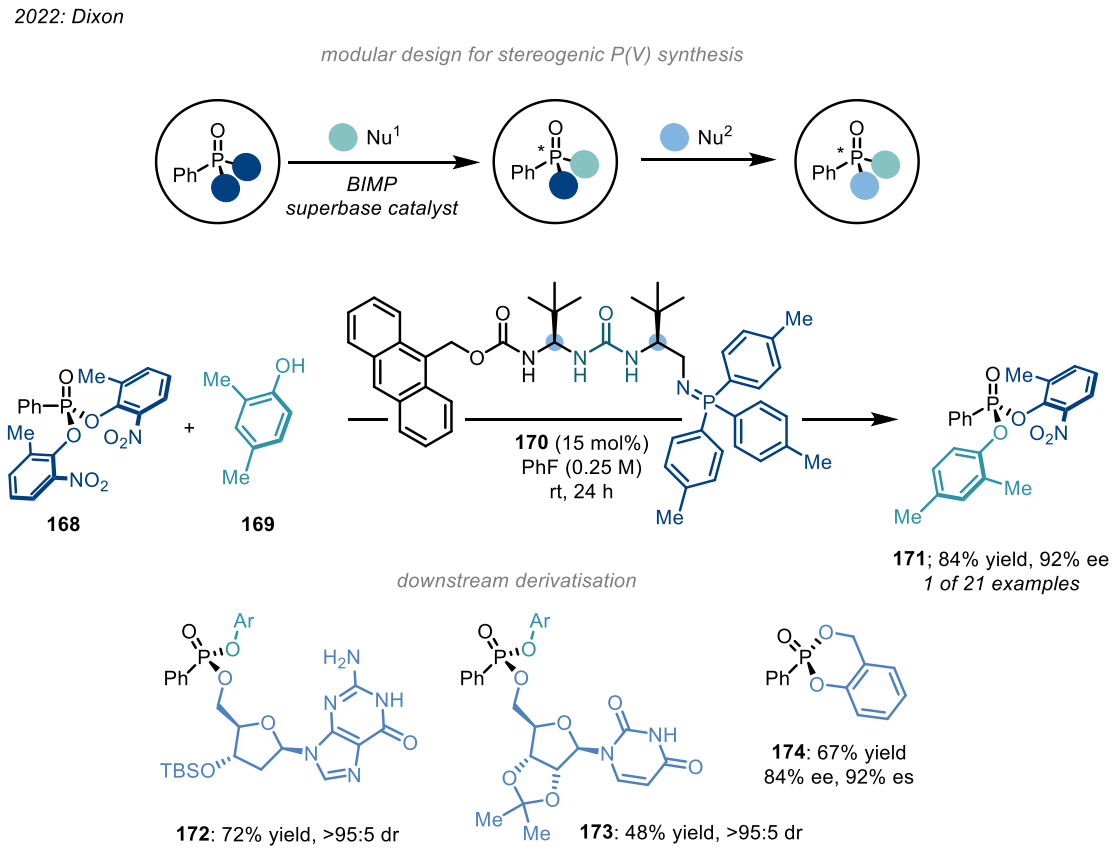
2.1.9 Direct Enantioselective Desymmetrisation for the Synthesis of Stereogenic P(V)

Whilst elegant, these indirect desymmetrisation methods require the pre-installation of functional groups around the P(V) centre, limiting the overall scope of these reactions and adding numerous steps to the synthetic sequence. A more efficient strategy would be desymmetrisation with reactivity occurring directly at P, enabling a modular approach to stereogenic P(V) synthesis in which the chiral centre is formed in a single catalytic step, followed by downstream derivatisation of the enantioenriched P(V) atom.

To this end, it wasn't until 2021 that Dixon first reported an unprecedented direct enantioselective desymmetrisation of phosphonate esters[157] (*Scheme 25*). By employing a novel ureidopeptide BIMP catalyst **168**, Dixon and co-workers were able to apply a two-step nucleophilic displacement strategy for stereogenic P(V) synthesis. The first step involved enantioselective nucleophilic desymmetrisation of a prochiral P(V) precursor **168** with *ortho*-substituted phenol nucleophiles (**169**) for stereogenic P(V) formation (**171**). This was then followed by downstream enantiospecific nucleophilic substitution of **171** for modular, direct access to P(V) stereocentres possessing P−O, P−S, and P−N linkages. Importantly, the superbasicity of the BIMP catalyst proved key to this transformation, with cinchona-derived catalysts giving severely diminished reactivity.

Computational studies indicated several non-covalent interactions were important for the observed reactivity and stereoselectivity. Firstly, partial deprotonation of the incoming phenol nucleophile by the superbasic iminophosphorane was shown to generate an activated nucleophile for attack at the P(V) centre. Second, hydrogen bonding interactions between the ureidopeptide backbone and both the P=O bond of the phosphonate and the Lewis basic NO_2 groups of the leaving group, along with additional π-π stacking interactions between the aromatic phenol leaving group and the anthracenyl catalyst backbone, were shown to stabilise the intermediate transition state during nucleophilic attack. Lastly, orientation of the aryl substituents on the phosphonate ester either towards (leading to the (*S*)-enantiomer of the product) or away (leading to the (*R*)-enantiomer of the product) from the BIMP

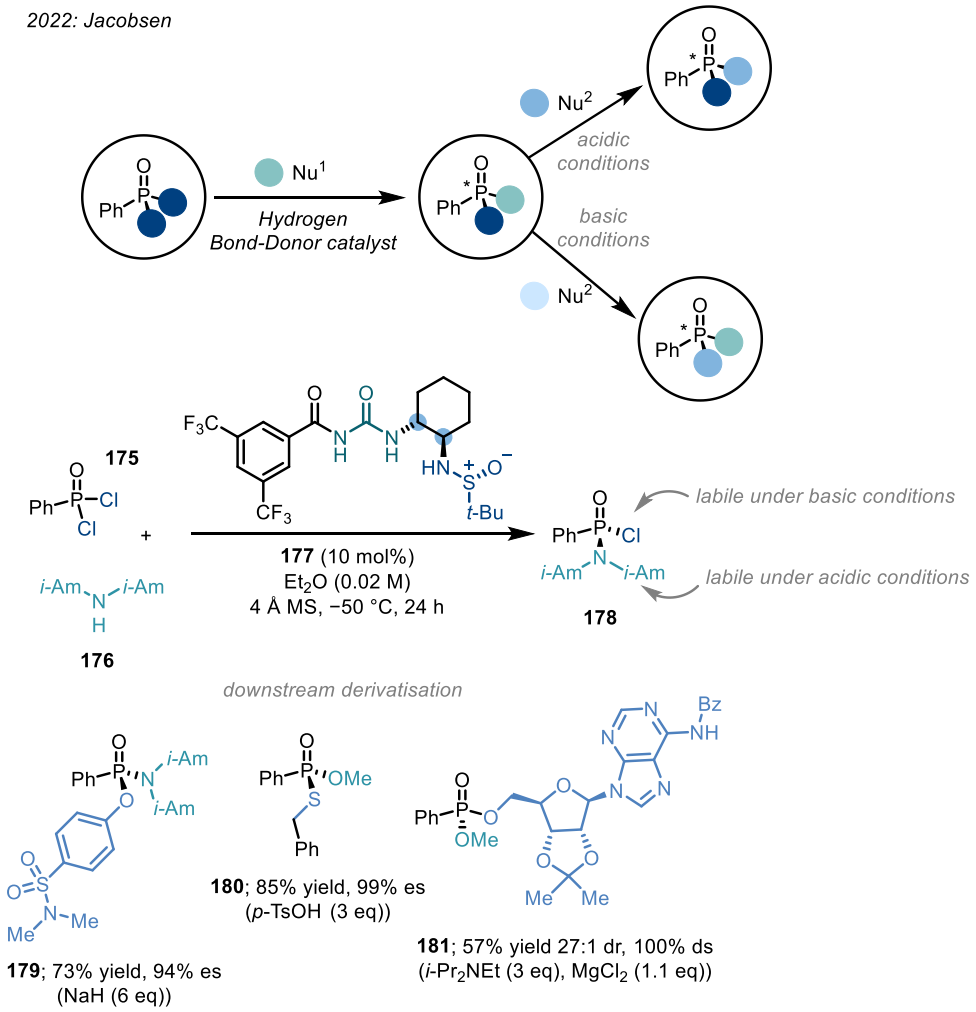
catalyst framework allowed for differentiation of the two phenolic leaving groups in the enantiodetermining step.



Scheme 25: Dixon's 1st-generation nucleophilic enantioselective desymmetrisation of prochiral phosphonate esters.

In a conceptually similar approach, Jacobsen later reported a direct enantioselective nucleophilic desymmetrisation of simple phosphonyl dichlorides (**175**) with secondary amines to form chlorophosphonamidates (**178**), employing a bifunctional sulfinamido urea catalyst **177**[158] (*Scheme 26*). Despite the ready availability of the phosphoryl chloride starting materials in this desymmetrisation approach, only P(V) electrophiles possessing aromatic substituents gave good yields and stereoselectivities in the reaction, with alkyl phosphoryl chlorides have severely diminished ee's. Further, the nucleophile scope was largely limited to diisoamylamine (**176**), with other secondary amines generally giving diminished yields and/or enantioselectivities. Similarly to Dixon's 1st-generation desymmetrisation, the authors were able to demonstrate the unique modularity and orthogonality of the chlorophosphonamidates products, whereby the chloro substituent could be displaced under basic conditions and the amine under acidic conditions in a two-step, one-pot synthetic sequence. For ease of isolation, the chlorophosphonamidate products were not isolated directly and were instead reacted directly *in situ*, requiring 5-10 equivalents of the corresponding metalated nucleophile. This modular

strategy enabled straightforward access to a variety of enantioenriched drug compounds *via* downstream modification of the formed stereogenic P(V) centre.



Scheme 26: Jacobsen's nucleophilic enantioselective desymmetrisation of prochiral phosphoryl chlorides.

2.1.10 Limitations of 1st-Generation BIMP-Catalysed Nucleophilic Desymmetrisation

Despite its conceptual novelty, Dixon's 1st-generation catalyst system had several limitations. The phenolic leaving group that was employed effectively deactivated the BIMP catalyst and prevented efficient catalyst turnover due to its low pK_a relative to the incoming nucleophile. Because of this, high catalyst loadings of 15 mol% were required. Further, whilst high yields and enantioselectivities were obtained for desymmetrisation, this required phenol nucleophiles possessing *ortho*-alkyl substituents, thereby limiting the overall scope of the transformation. Lastly, downstream derivatisation was limited to *O*-, *S*-, and *N*-centred nucleophiles, with *C*-centred nucleophiles leading to unwanted side reactions; this prevented access to synthetically important P-stereogenic phosphinates, phosphine oxides, and phosphines.

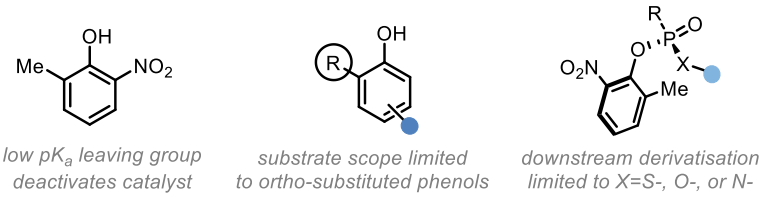
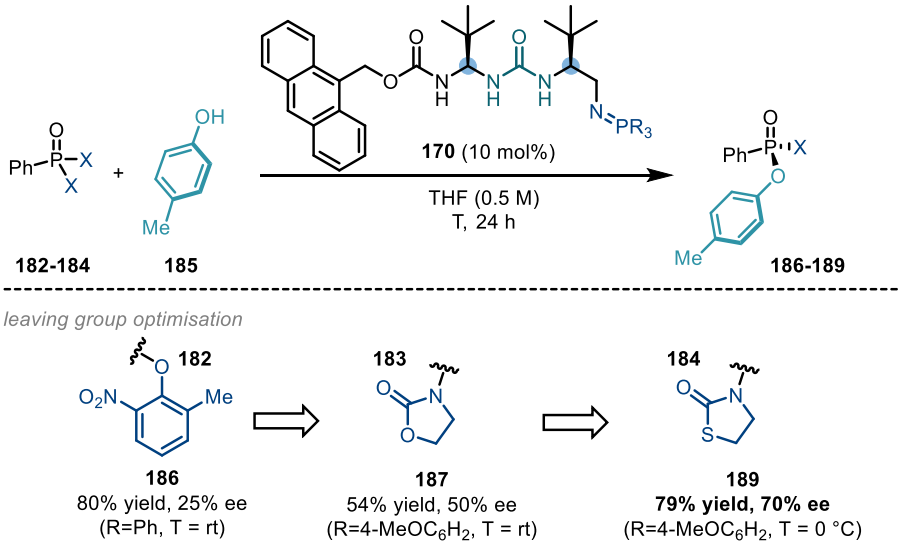


Figure 9: Limitations of 1st-generation for BIMP-catalysed direct enantioselective desymmetrisation.

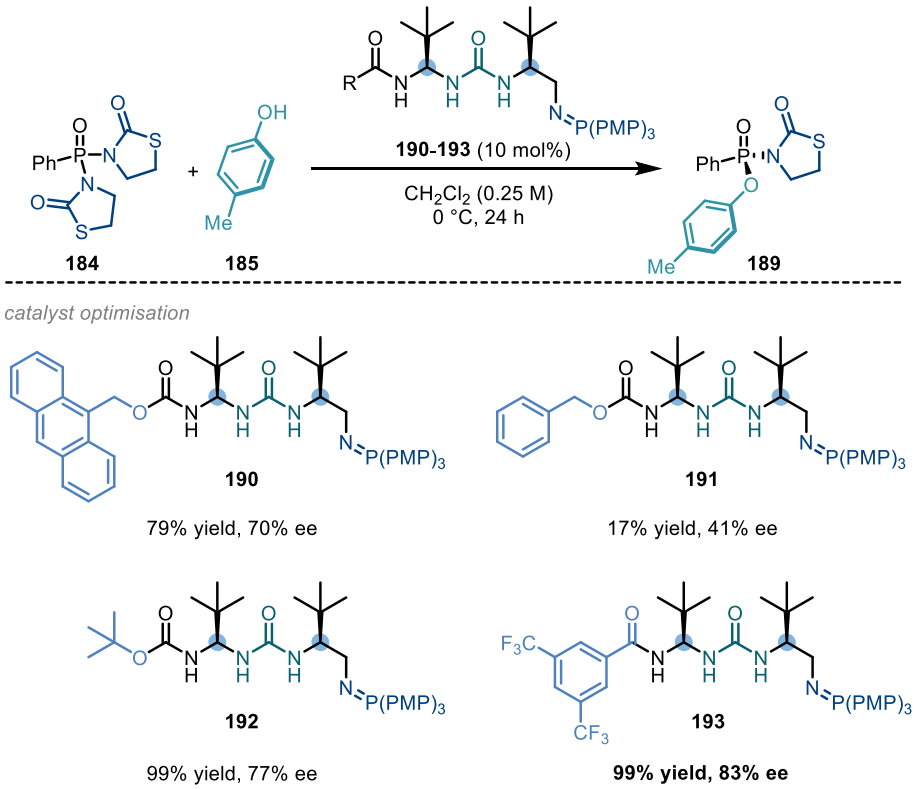
2.1.11 Development of 2nd-Generation System

With these limitations in mind, we began development of our 2nd-generation catalyst system[159]. Following a screening of leaving groups, thiazolidinone-derived **184** was found to give the highest levels of enantioselectivity (*Scheme 27*). This is postulated to occur due to the higher pK_a leaving group relative to the incoming nucleophile, in which build-up of the concentration of the leaving group throughout the reaction does not inhibit deprotonation of the relatively low pK_a phenolic nucleophile by the iminophosphorane. This results in more efficient catalyst recycling throughout the catalytic cycle and, therefore, higher observed enantioselectivity.



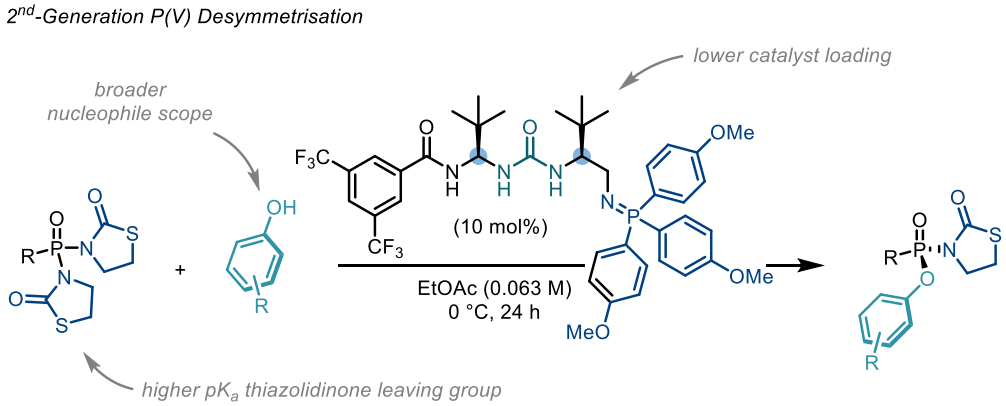
Scheme 27: Optimisation of leaving group for 2nd-generation enantioselective desymmetrisation. All optimisation carried out by Dr Michele Formica.

Further tuning of the BIMP ureidopeptide catalyst revealed that catalyst **193** – possessing both a more acidic 3,5-$(CF_3)_2C_6H_3$-substituted amide and a more basic *p*-methoxyphenyl (**PMP**) substituted iminophosphorane – was optimal for the transformation (*Scheme 28*). Changing solvent to EtOAc and diluting the reaction to 0.063M also gave a further improvement in both yield and enantioselectivity up to 99% yield and 96% ee.

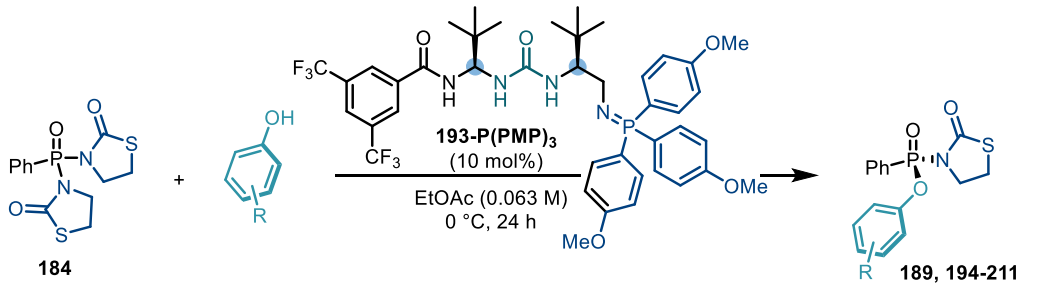


Scheme 28: Optimisation of catalyst backbone for 2nd-generation enantioselective desymmetrisation. All optimisation carried out by Dr Michele Formica.

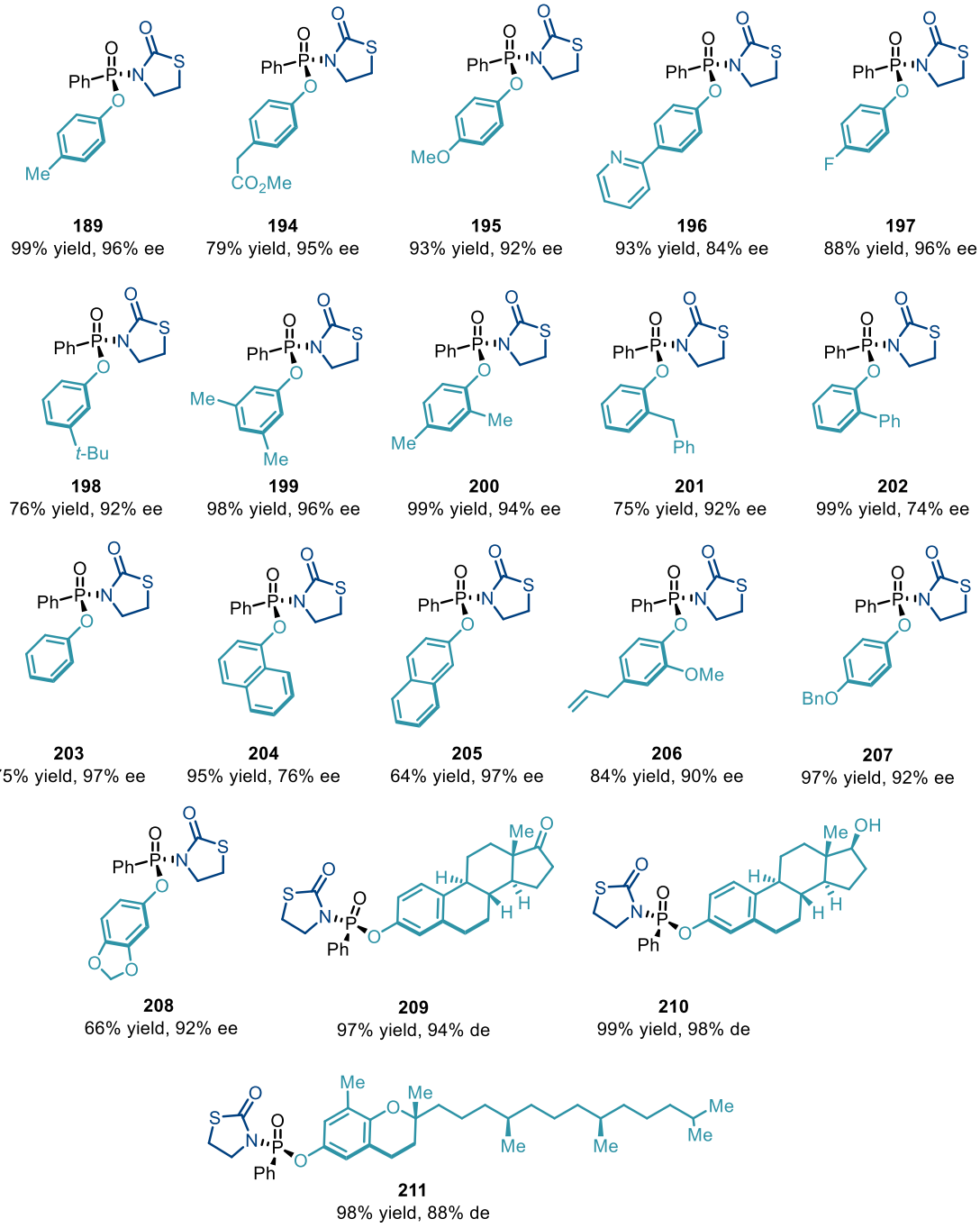
Using these optimised reaction conditions (*Scheme 29*), an initial exploration of the nucleophile scope for the enantioselective desymmetrisation step showed that our 2nd-generation catalyst accommodates a significantly broader range of phenol nucleophiles with both excellent yield and good to excellent enantioselectivity (*Scheme 30*), without the requirement for an *ortho*-alkyl substituent. This represents a significant improvement over our 1st-generation system.



Scheme 29: Improvements for 2nd-generation BIMP-catalysed nucleophilic desymmetrisation.



Substrate Scope



Scheme 30: Nucleophile scope for 2nd-generation BIMP-catalysed direct nucleophilic desymmetrisation of prochiral phosphonate esters. All work carried out by Dr Michele Formica.

2.2 Project Aims

Building upon our initial developments for the 2nd-generation desymmetrisation reaction, the aims of this project were to further explore the scope for this transformation. We were keen to explore the scope of the reaction with respect to the P(V) electrophile, incorporating aliphatic and, importantly, aromatic C backbones.

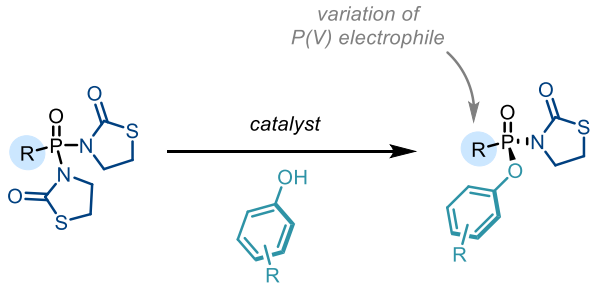


Figure 10: Scope of P(V) electrophile.

Pivoting upon this initial desymmetrisation reaction, the enantioenriched product was then well-positioned for a second enantiospecific nucleophilic displacement of the remaining thiazolidinone leaving group, which we envisioned would give downstream access to P(V)-stereogenic compounds containing a broad range of P–O, P–S, P–N, and P–C bonds. Particular focus was placed on expanding the scope of nucleophiles that could be deployed for this second nucleophilic displacement, and in forging key P–C bonds, especially given that this was a significant limitation of our 1st-generation reaction system.

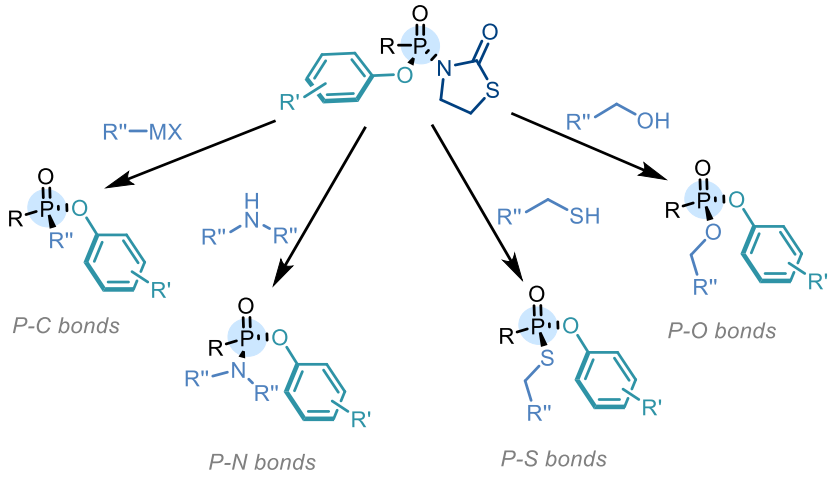
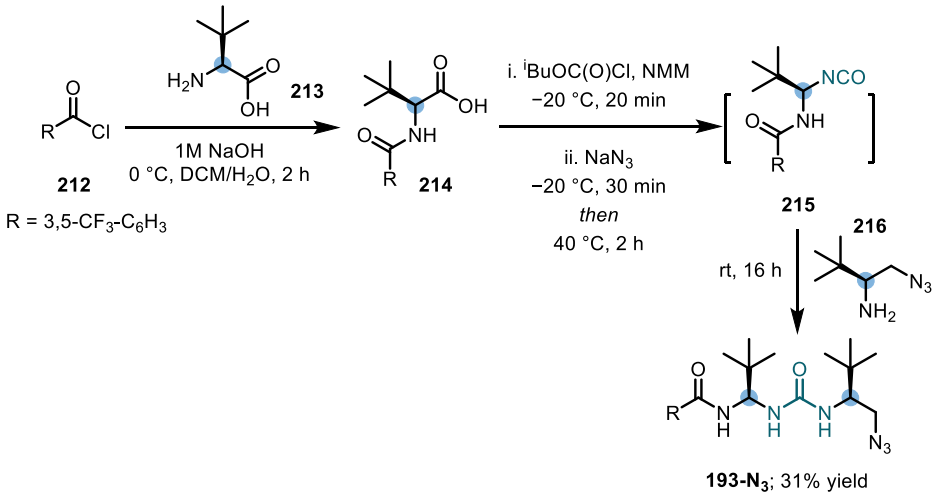


Figure 11: Possible downstream derivatisation of enantioenriched P(V) stereocentre.

2.3 Results and Discussion

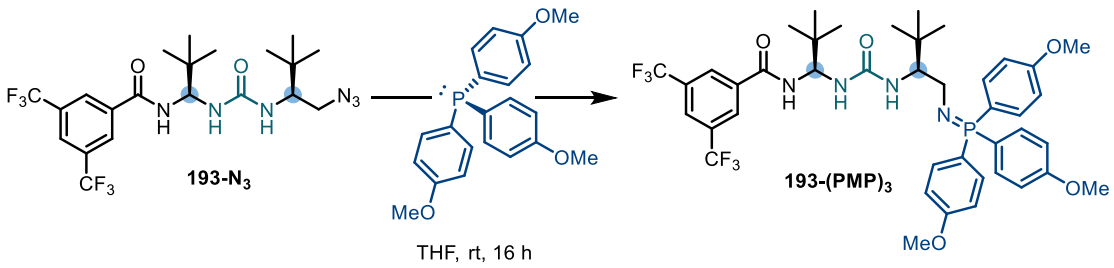
2.3.1 Preparation of BIMP Catalyst

2nd-Generation ureidopeptide BIMP precatalyst **193-N_3** was prepared according to the literature procedure[159,160]. Commercially available acid chloride **212** was reacted with (*S*)-tert-leucine (**213**) under Schotten-Baumann conditions to afford carboxylic acid **214**. **214** was treated with *iso*butyl chloroformate and *N*-methyl morpholine to form the mixed anhydride *in situ*, followed by treatment with NaN_3. The crude acyl azide was subsequently refluxed to afford isocyanate **215** *via* a Curtius rearrangement[161] and **215** was then combined with amino azide **216**[160]. Pure ureidopeptide precatalyst **193-N_3** was obtained by recrystallisation from EtOAc in 31% overall yield (*Scheme 31*).



Scheme 31: Synthesis of ureidopeptide BIMP precatalyst **193-N_3**.

Prior to desymmetrisation, azide **193-N_3** was combined with tris(4-methoxyphenyl)phosphine [**P(PMP)$_3$**] in THF and stirred overnight at room temperature to afford active ureidopeptide BIMP catalyst **193-P(PMP)$_3$** *in situ via* the Staudinger reaction (*Scheme 32*). Solvent was removed under a stream of nitrogen and **193-P(PMP)$_3$** used directly without further purification.

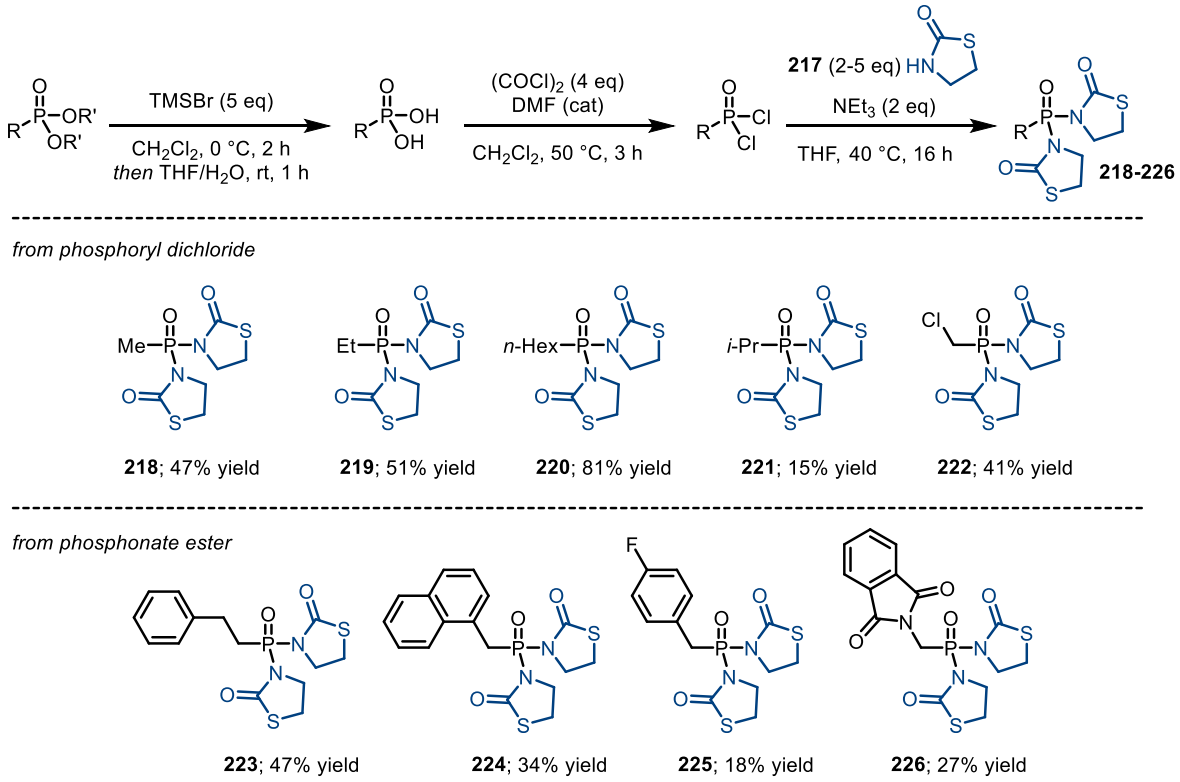


Scheme 32: Synthesis of ureidopeptide BIMP catalyst **193-P(PMP)$_3$**.

2.4 Scope of the Desymmetrisation Reaction

2.4.1 P(V) Electrophile Synthesis

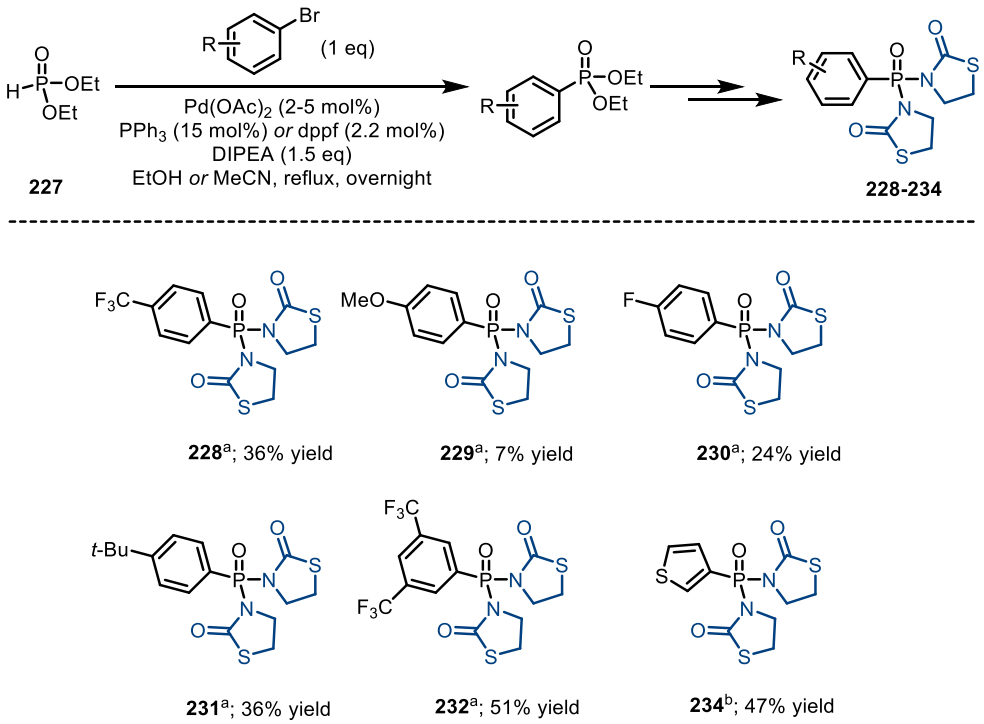
To explore the scope of the desymmetrisation reaction with respect to the P(V) electrophile, a library of novel phosphoryl bisthiazolidinones bearing different aliphatic and benzylic backbones were synthesised (**218**-**226**, *Scheme 33*). Phosphoryl bisthiazolidinones **218**-**222** were formed from the corresponding phosphoryl dichlorides in moderate to good yields. P(V) electrophiles **223**-**226** were instead synthesised from commercially available phosphonate esters over a 3-step, one-pot procedure[162]. Ester cleavage with TMS-Br was followed by hydrolysis with H_2O and subsequent chlorination with oxalyl chloride and catalytic DMF, whereby the crude phosphoryl dichloride was coupled with thiazolidinone **217** in the presence of NEt_3 to yield the corresponding phosphoryl bisthiazolidinones. Depending on the substrate, 2-5 equivalents of NEt_3 were required in the final step in order to quench any remaining residual acid from previous steps.



Scheme 33: Synthesis of P(V) electrophiles. [a] 5 eq of NEt_3 were used in the final step, [b] reaction carried out at rt, yields reported over 3 steps.

Phosphoryl bisthiazolidinones **228**-**234** bearing aromatic backbones were synthesised *via* Pd-catalysed Hirao coupling of commercially available diethyl phosphite **227** and the corresponding aryl bromide[163,164] *(Scheme 34)*. The formed phosphonate esters were subsequently converted to the corresponding phosphoryl bisthiazolidinones *via* the phosphoryl dichlorides according to the aforementioned procedure. The low yield for substrate **229** was due to poor conversion from the phosphoryl dichloride,

likely due to the low electrophilicity of the P(V) centre due to the relatively electron-donating aromatic backbone.



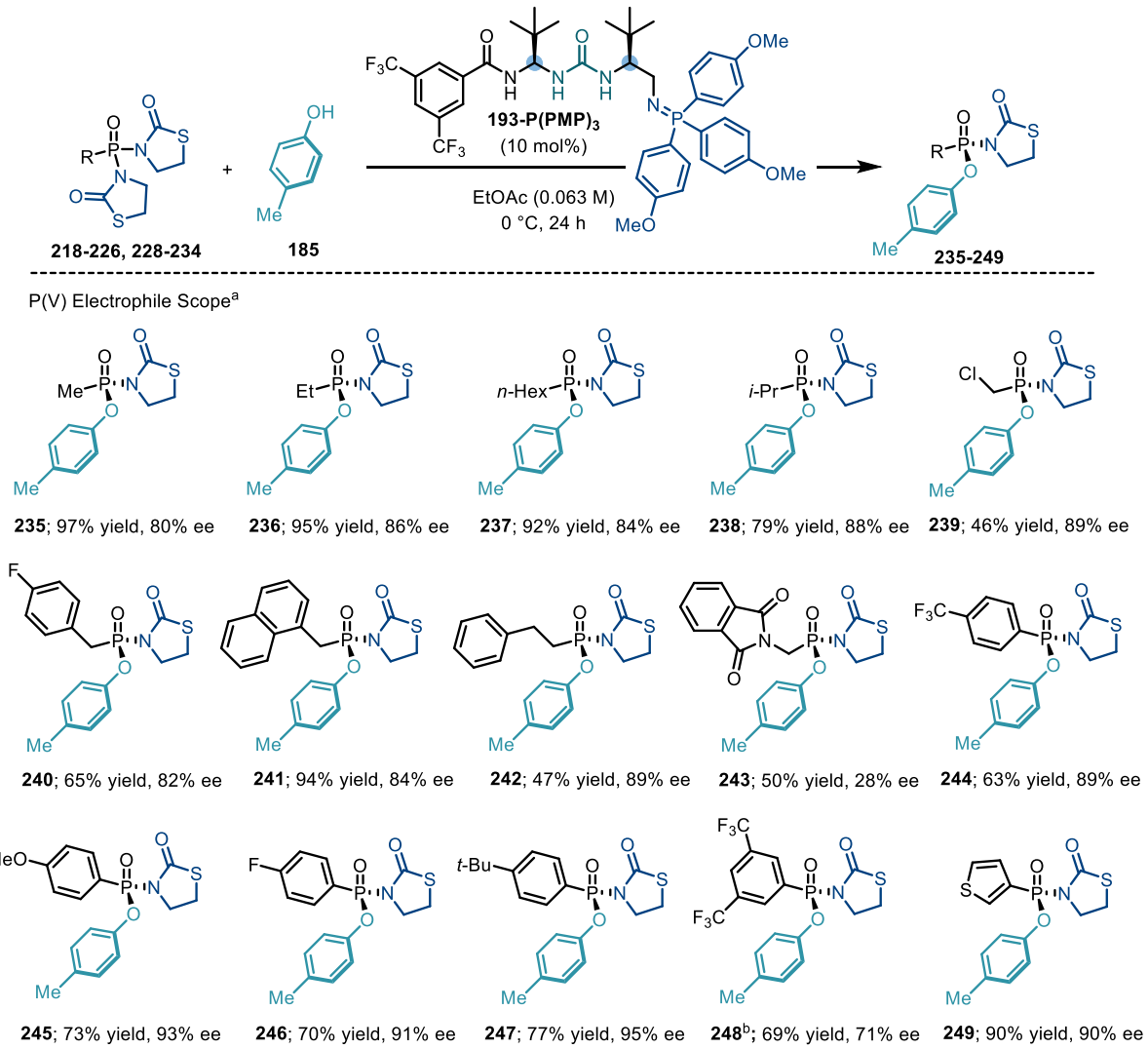
Scheme 34: Synthesis of P(V) electrophiles *via* Hirao coupling. [a] $Pd(OAc)_2$ (5 mol%), PPh_3 (15 mol%), 1 eq aryl bromide, 1.2 eq diethyl phosphite, DIPEA (1.5 eq), EtOH, reflux, overnight; [b] $Pd(OAc)_2$ (2 mol%), dppf (2.2 mol%), 1 eq aryl bromide, 1.2 eq diethyl phosphite, DIPEA (1.5 eq), MeCN, reflux, overnight. All yields reported over 4 steps.

2.4.2 Scope with Respect to P(V) Electrophile

With a library of phosphoryl bisthiazolidinones in hand, and deploying reaction conditions previously optimised in the group[159], the scope of the desymmetrisation reaction with respect to the P(V) electrophile was explored (*Scheme 35*). Pleasingly, linear and branched alkyl substituents bearing Me (**218**), Et (**219**), *n*-Hex (**220**), and a sterically hindered *i*-Pr (**221**) group were well-tolerated, forming the corresponding desymmetrised products **235**-**238** in 79-97% yield and 80-88% ee. Chloromethyl-bearing substrate **222** gave the corresponding product **239** in a low yield of 49% and moderate 78% ee, a result of diminished reactivity of the substrate as opposed to competitive side reactions on the backbone.

Substrates **224** and **225** bearing benzylic substituents were also well-tolerated, forming the corresponding products **240** and **241** in 65% yield and 82% ee and 94% yield and 84% ee, respectively. In addition, phenylethyl-derived substrate **223** reacted smoothly, forming product **242** in a slightly diminished 47% yield and excellent 89% ee. Unfortunately, phthalimide-derived substrate **226** formed the corresponding product **243** with moderate 50% yield significantly diminished 28% ee, most likely a result of interference of catalyst binding to the substrate due to competitive hydrogen-bonding to the Lewis basic phthalimide moiety.

Moving on to P(V) electrophiles bearing aromatic backbones, we were pleased to find that substrates **228-231**, bearing a variety of electron rich and electron poor aromatic groups, were well-tolerated under the reaction conditions, forming products **244**-**247** in 63-89% yield and excellent 89-95% ee. Substrate **232** bearing a strongly electron-withdrawing aromatic backbone gave diminished enantioselectivity at 0 °C; instead, the reaction was carried out at −20 °C and the reaction time extended to 3 days to compensate for a slower reaction rate, forming the corresponding desymmetrised product **248** in 69% yield and 71% ee. We were also pleased to find that heteroaromatic electrophile **234** was well-tolerated, forming product **249** in excellent 90% yield and 90% ee.

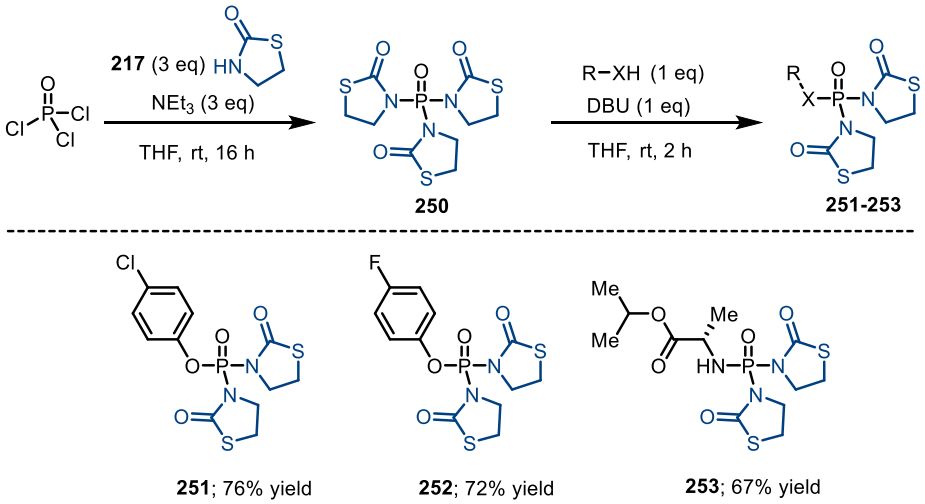


Scheme 35: P(V) electrophile scope for BIMP-catalysed desymmetrisation (0.1 mmol scale). All yields are isolated yields; ee was determined by HPLC on a chiral stationary phase. [a] Reaction carried out at 0 °C for 24 hr; [b] reaction carried out at −20 °C for 3 days.

2.4.3 Unsuccessful P(V) Electrophiles

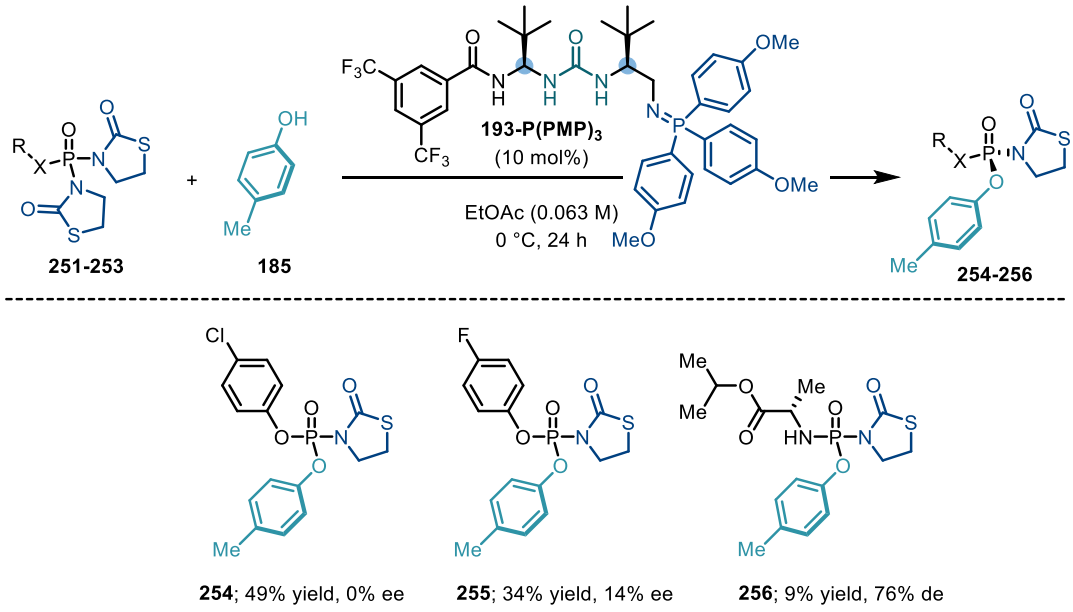
Attempts to extend this methodology to include P(V) electrophiles containing non-carbon backbones proved unsuccessful. The corresponding substrates were synthesised by a 2-step sequence: first, reaction

of $POCl_3$ with with 3 eq **217** and 3 eq NEt_3 as base generated the intermediate phosphoryl tristhiazolidinone **250**, followed by nucleophilic displacement of one thiazolidinone group with 1 eq of the corresponding nucleophile and 1 eq DBU as base (*Scheme 36*).



Scheme 36: Synthesis of P(V) electrophiles possessing non-carbon backbones.

Phenol-derived substrates **251** and **252** formed the corresponding desymmetrised products **254** and **255** in moderate 49% and 34% yields, respectively, but severely diminished 0% ee and 14% ee, respectively. Alanine-derived substrate **253** formed product **256** in severely diminished 9% yield but moderate 76% de. The low reactivity but good diastereoselectivity in this reaction is likely due to the lower electrophilicity of substrate **253** resulting from the strong electron donation from the N atom (*Scheme 37*).

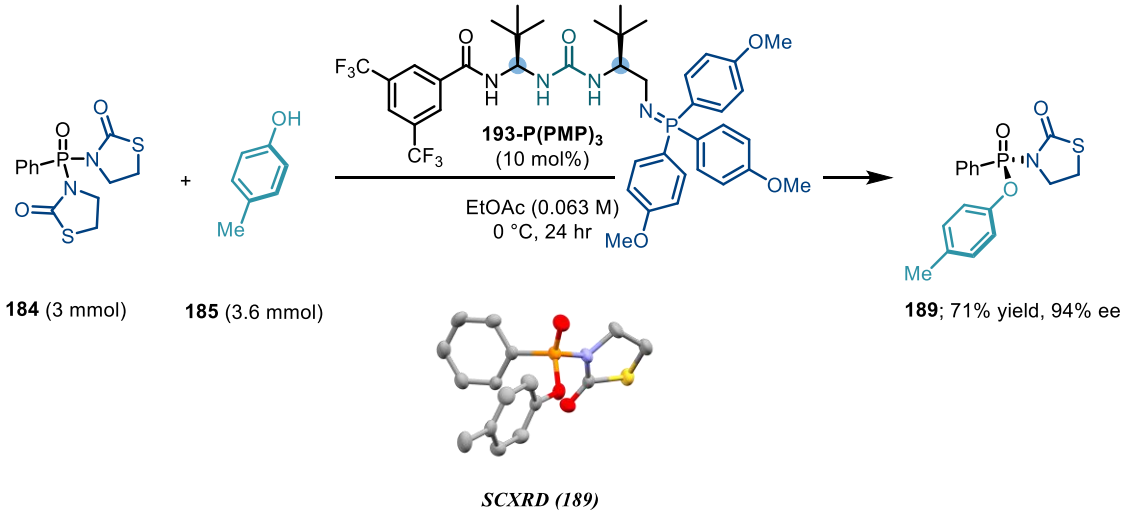


Scheme 37: Unsuccessful P(V) electrophile scope for BIMP-catalysed desymmetrisation.

2.4.4 Reaction Scale-Up

Having established the scope of this desymmetrisation reaction with respect to the P(V) electrophile, attention was turned to reaction scale-up using model substrate **184**. However, using our previously optimised reaction conditions and repeating on a 3 mmol (1 g) scale initially formed product **189** in diminished 56% yield and 85% ee. Pleasingly, increasing the temperature for iminophosphorane formation during precatalyst activation to 40 °C to ensure full conversion led to a significantly improved 71% yield and 94% ee (*Scheme 38*).

A small amount of **189** was recrystallised to enantiopurity by slow evaporation from CH_2Cl_2/hexane and subsequently analysed by single crystal X-Ray diffraction. Product configuration was confirmed as (*R*) and the stereochemical configuration of all related products was assigned by analogy.



Scheme 38: Reaction scale-up and single crystal X-Ray diffraction of compound **189** (hydrogen atoms omitted for clarity).

2.5 Derivatisation

2.5.1 Aliphatic Alcohols

Following demonstration of the broad scope of our desymmetrisation strategy with respect to the P(V) electrophile and phenol nucleophile, attention was then turned to the stereospecific* nucleophilic displacement of the second thiazolidinone leaving group of **189**, thereby enabling modular downstream derivatisation of the enantioenriched P(V) centre.

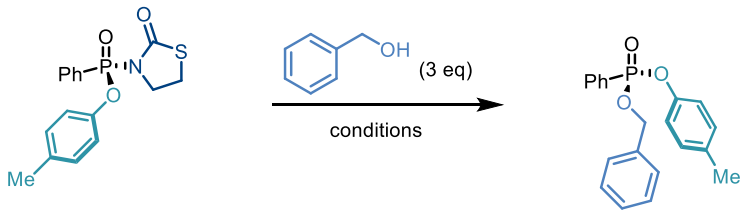
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* Enantiospecificity (es) is defined as: $es = \frac{\text{ee of derivatised product}}{\text{ee of starting material}} \times 100\%$

All displacement reactions are assumed to react with inversion of configuration at P(V), by analogy with our previous work[157].

Beginning with BnOH as a model nucleophile and utilising substitution conditions reported for our 1st-generation P(V) desymmetrisation[157], we observed moderate yield of the corresponding derivatised product **257** with minor racemisation at the P(V) centre (*Table 1*, *entry 1*). Increasing reaction time to 16 hours gave only a slight improvement in yield and increased P(V) racemisation (*entry 2*). Further lowering the temperature to 20 °C gave no improvement in es (*entry 3*) and decreasing *t*BuMgCl and BnOH equivalents gave diminished yield (*entry 4*). Following literature precedent, Et_2AlCl as an additive in neat pyridine gave no conversion to product (*entry 5*)[165]. Pleasingly, switching to DBU as base and increasing base and BnOH equivalents gave significantly improved yield and es (*entry 6*). Increasing reaction temperature to 40 °C gave significant racemisation at the P(V) stereocentre (*entry 7*).

Table 1: Optimisation of reaction conditions for nucleophilic displacement of second thiazolidinone leaving group with BnOH. Reactions carried out in THF (0.1 M), unless stated otherwise, with equal nucleophile and base equivalents. Reactions carried out on 0.05 mmol scale. All yields are isolated yields.

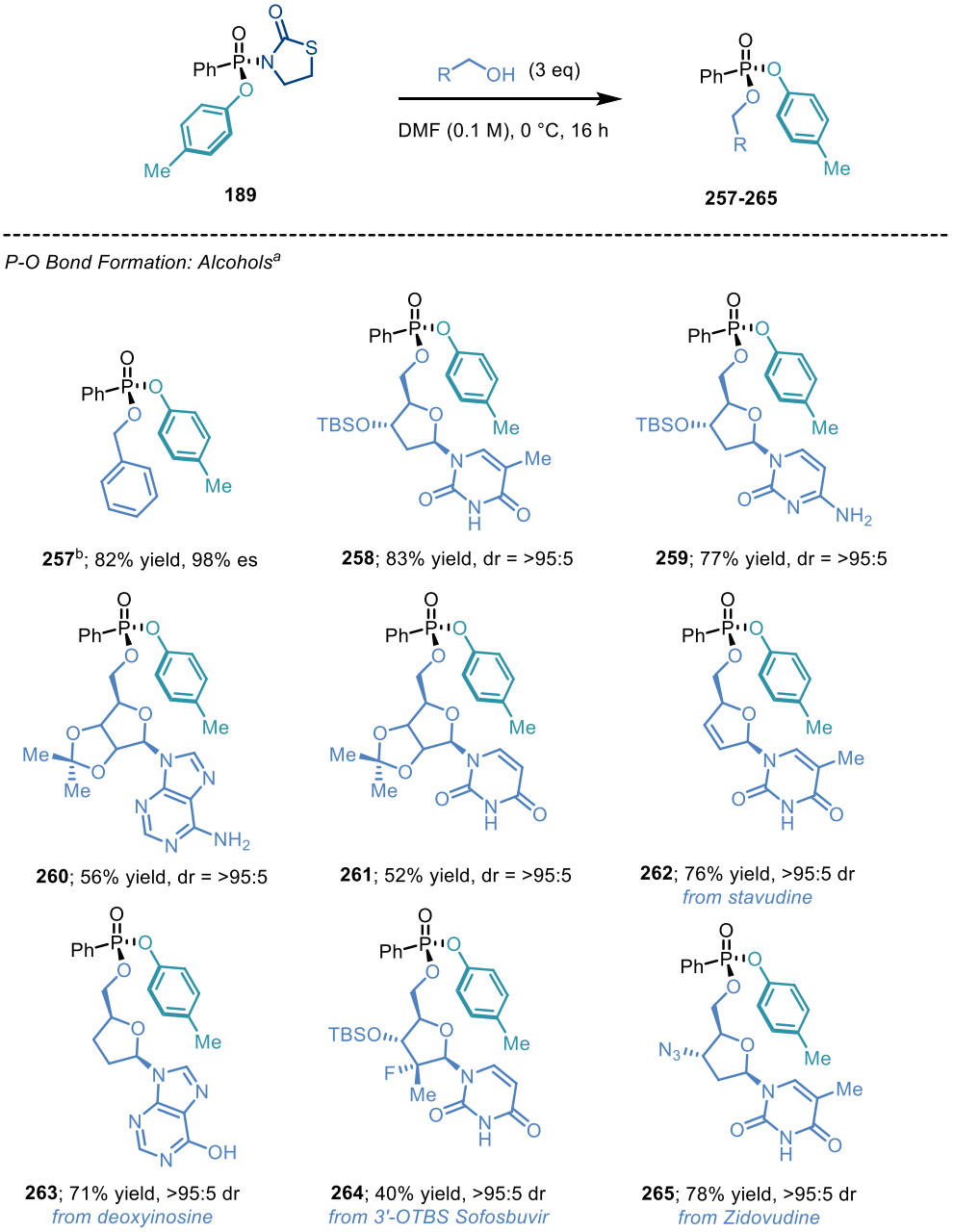


189 **257**

Entry	Base	Time / hr	Temp / ° C	Yield / %	es / %
1	*t*-BuMgCl (2.0 eq)	1	0	49	92
2	*t*-BuMgCl (2.0 eq)	16	0	65	88
3	*t*-BuMgCl (2.0 eq)	16	−20	60	88
4	*t*-BuMgCl (1.0 eq)	16	0	49	86
5	Pyridine (0.4M), Et_2AlCl (0.5 eq), BnOH (1.2 eq)	16	0	/	/
6	**DBU (3 eq)**	**16**	**0**	**82**	**98**
7	DBU (3 eq)	16	40	60	56

With these optimised conditions in hand, the scope of the derivatisation using aliphatic alcohols was explored (*Scheme 39*). 3'-OTBS-Protected deoxythymidine and deoxycytidine nucleophiles were well-tolerated following a solvent switch to DMF to aid solubility, forming the corresponding products **258** and **259** >95:5 dr and 77% and 83% yields, respectively. Acetal protected RNA nucleosides adenosine and uridine were also tolerated, forming the corresponding products **260** and **261** in >95:5 dr and 56% yield and 52% yield, respectively. A number of key drug motifs were also incorporated (**262**-**265**) in 40-

86% yield and >95:5 dr, highlighting the utility of this modular approach to enantioenriched P(V)-containing drug structures. Of particular note are 3'-OTBS-Sofosbuvir (**264**) and AZT (zidovudine)-derived (**265**) backbones, both important antivirals for the treatment of hepatitis C and HIV/AIDS, respectively[166,167].



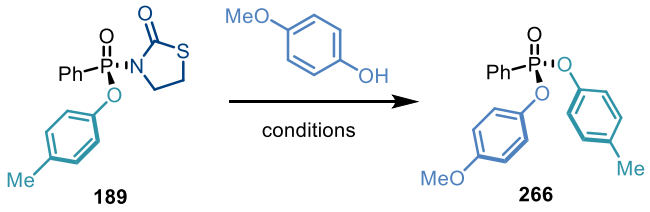
Scheme 39: Scope for alcohol derivatisation of enantioenriched P(V) phosphonate **189**. All reaction carried out on 0.05 mmol scale. All yields are isolated yields. [a]3 eq nucleophile, 3 eq DBU, DMF (0.1 M), rt, 16 h; [b]3 eq nucleophile, 3 eq DBU, THF (0.1 M), 0 °C, 16 h.

2.5.2 Phenols

With stereospecific substitution having been demonstrated for aliphatic alcohols, focus was then shifted towards phenols. Using 4-methoxyphenol as a model nucleophile and the previously optimal reaction

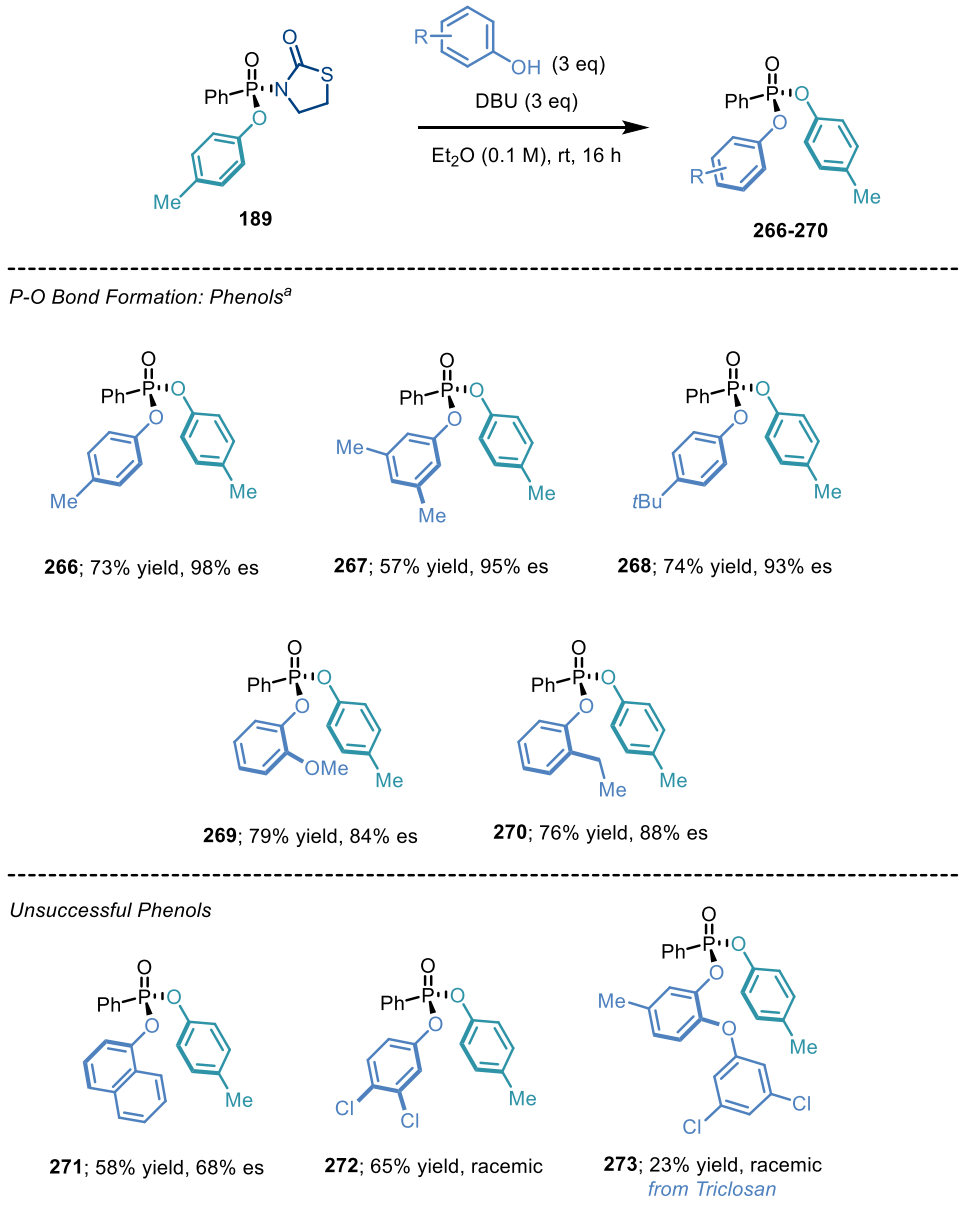
conditions gave good yield of product **266** but unfortunately led to significant racemisation at P (*Table 2*, *entry 1*). Changing base to BEMP gave no significant improvement (*entry 2*). Solvents were observed to have a profound effect on both yield and es, with high polarity solvents MeCN (*entry 3*) and DMF (*entry 4*) giving quantitative yields but almost complete racemisation at P. Pleasingly, however, changing solvent to Et_2O gave moderate yield of **266** with complete stereoretention (*entry 5*). Carrying out the reaction at room temperature gave a significant improvement in yield and minimal loss in es (*entry 6*), but further attempts to improve conversion by raising the reaction temperature to 40 °C led to complete racemisation at P (*entry 7*).

Table 2: Optimisation of reaction conditions for nucleophilic displacement of second thiazolidinone leaving group with 4-methoxyphenol (3 eq). Reactions progressed for 16 hr and carried out on 0.05 mmol scale. All yields are isolated yields.



Entry	Solvent (0.1 M)	Base (3 eq)	Temp / ° C	Yield / %	es / %
1	THF	DBU	0	72	81
2	THF	BEMP	0	72	85
3	MeCN	DBU	0	quant.	15
4	DMF	DBU	0	quant.	racemic
5	Et_2O	DBU	0	20	100
6	**Et_2O**	**DBU**	**rt**	**73**	**98**
7	Et_2O	DBU	40	81	racemic

With these optimised conditions in hand, the substrate scope was probed (*Scheme 40*). Pleasingly, a range of electron-rich phenolic nucleophiles reacted smoothly, affording the corresponding products **267**-**270** in 41-87% yield and 84-95% es. Unfortunately, however, attempts to employ extend to even moderately electron-poor phenols as nucleophiles led to significant racemisation at P, despite moderate to good yields (**271**-**273**).

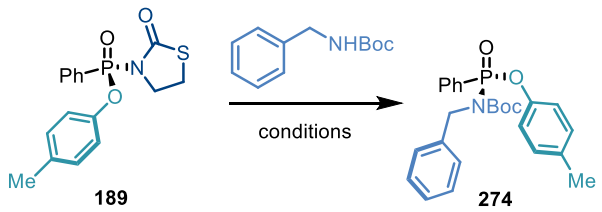


Scheme 40: Scope for phenol derivatisation of enantioenriched P(V) phosphonate **189**. All reaction carried out on 0.05 mmol scale. All yields are isolated yields. [a]3 eq nucleophile, 3 eq DBU, Et_2O (0.1 M), 0 °C, 16 h.

2.5.3 Amines

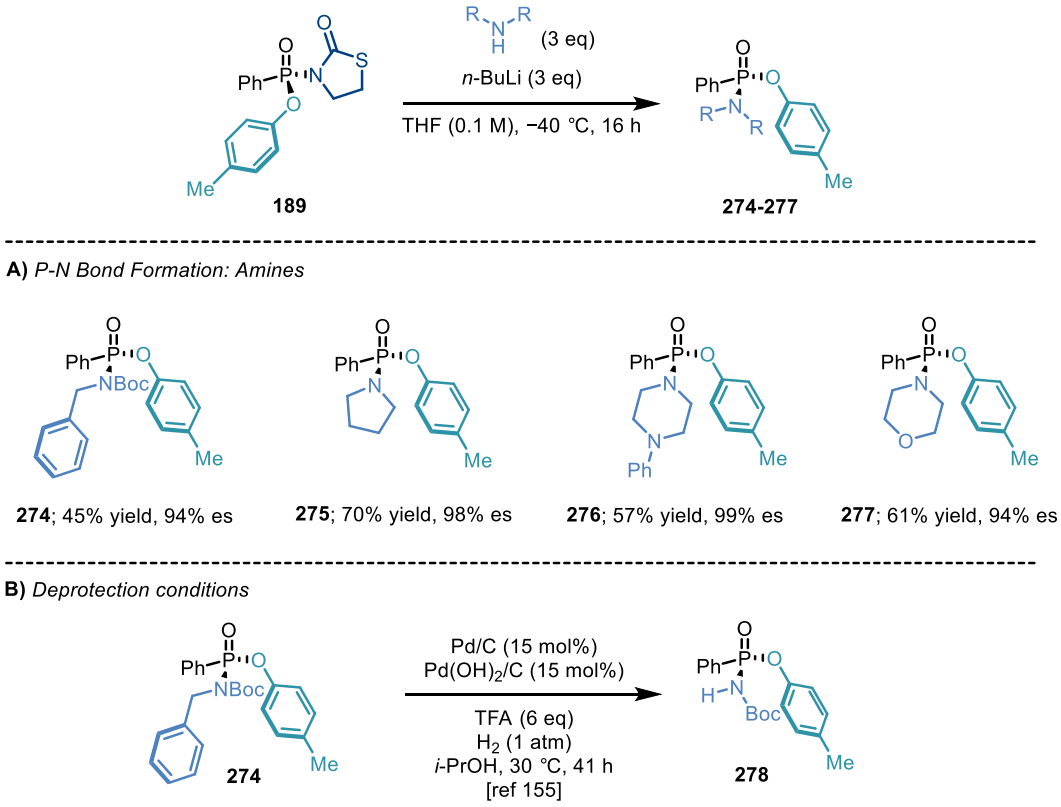
Next, attention was turned to P−N bond formation by addition of amine nucleophiles. Using *N*-Boc benzylamine as a model nucleophile and DBU as base gave negligible conversion to the corresponding product **274** (*Table 3*, *entry 1*). Switching to *t*-BuMgCl as base improved conversion but led to significant racemisation at P (*entry 2*). Pleasingly, switching to 1.5 eq *n*-BuLi as base gave a large increase in both yield and es (*entry 3*) and an optimal balance between reaction rate and es was found when the reaction was carried out at −40 ° C (*entry 6*).

Table 3: Optimisation of reaction conditions for nucleophilic displacement of second thiazolidinone leaving group with *N*-Boc benzyl amine. All reactions carried out in THF (0.1 M) for 16 hr, with equal nucleophile and base equivalents. All reactions carried out on 0.05 mmol scale. All yields are isolated yields.



Entry	Base	Temp / ° C	Yield / %	es / %
1	DBU (3 eq)	rt	No reaction	/
2	*t*-BuMgCl (2 eq)	0	32	34
3	*n*-BuLi (1.5 eq)	0	64	79
4	*n*-BuLi (1.5 eq)	−20	50	79
5	*n*-BuLi (1.5 eq)	−78	No reaction	/
6	***n*-BuLi (1.5 eq)**	**−40**	**45**	**94**

With these optimised conditions in hand, the scope of the amine addition was explored. Pleasingly, a range of medicinally relevant secondary amines could be incorporated, including pyrrolidine (**275**, 70% yield, 98% es), 1-phenyl piperazine (**276**, 57% yield, 99% es), and morpholine (**277**, 46% yield, 94% es) (*Scheme 41*). Whilst attempts to extend this methodology to primary amines proved unsuccessful, substrate **274** may be readily deprotected under conditions reported by Jacobsen[158].

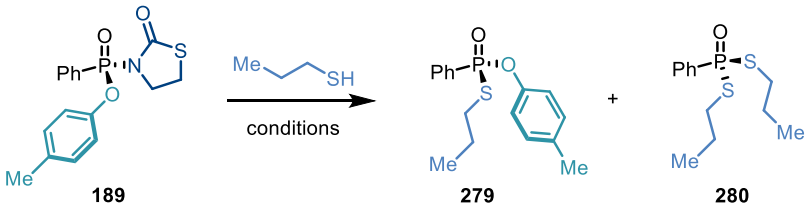


Scheme 41: **A)** Scope for amine derivatisation of enantioenriched P(V) phosphonate **189**. All reaction carried out on 0.05 mmol scale. All yields are isolated yields. **B)** Jacobsen's reported hydrogenolysis conditions for amine deprotection.

2.5.4 Thiols

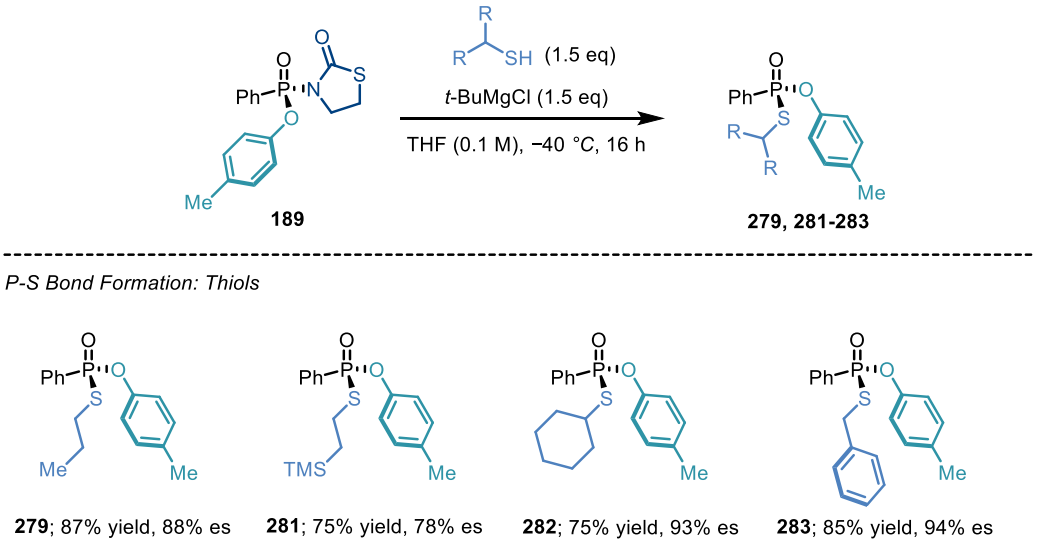
Next, P−S bond formation by nucleophilic addition of thiols was attempted. Using propane thiol as a model nucleophile and *n*-BuLi as base, double thiol addition to the P centre was observed (**280**) (*Table 4*, *entry 1*). Lowering thiol and base equivalents gave a similar result (*entry 2*). Switching base to DBU gave no reaction (*entry 3*), with attempts to increase conversion through higher base and nucleophile equivalents proving unsuccessful (*entry 4*). Finally, switching to *t*-BuMgCl as base pleasingly gave clean conversion to the desired monoaddition product **279**, with minimal racemisation at P (*entry 5*).

Table 4: Optimisation of reaction conditions for nucleophilic displacement of second thiazolidinone leaving group with propane thiol. All reactions carried out in THF (0.1 M) for 16 hr, with equal nucleophile and base equivalents. All reactions carried out on 0.05 mmol scale. All yields are isolated yields.



Entry	Base	Temp / ° C	Yield / %	es / %
1	*n*-BuLi (1.5 eq)	−40	Double addition (**280**)	/
2	*n*-BuLi (1.0 eq)	−40	Double addition (**280**)	/
3	DBU (1.5 eq)	rt	No reaction	/
4	DBU (3.0 eq)	rt	No reaction	/
5	***t*-BuMgCl (1.5 eq)**	**−40**	**87**	**88**

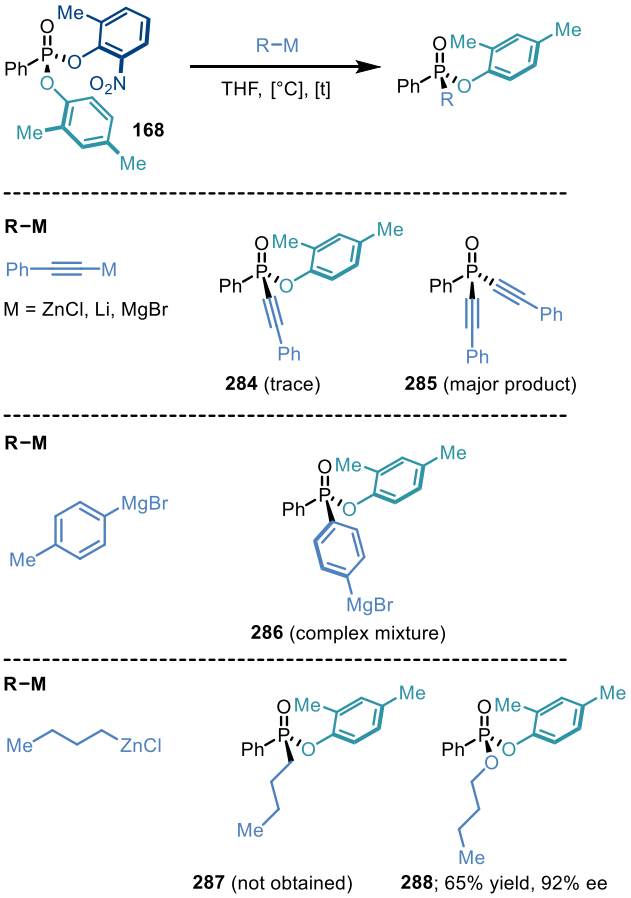
A range of primary, secondary, and benzylic thiols were well-tolerated under these optimised reaction conditions, forming the corresponding products **280**-**284** in 75-88% yield, 78-94% es (*Scheme 42*).



Scheme 42: Scope for thiol derivatisation of enantioenriched P(V) phosphonate **189**. All reaction carried out on 0.05 mmol scale. All yields are isolated yields.

2.5.5 Grignard Reagents

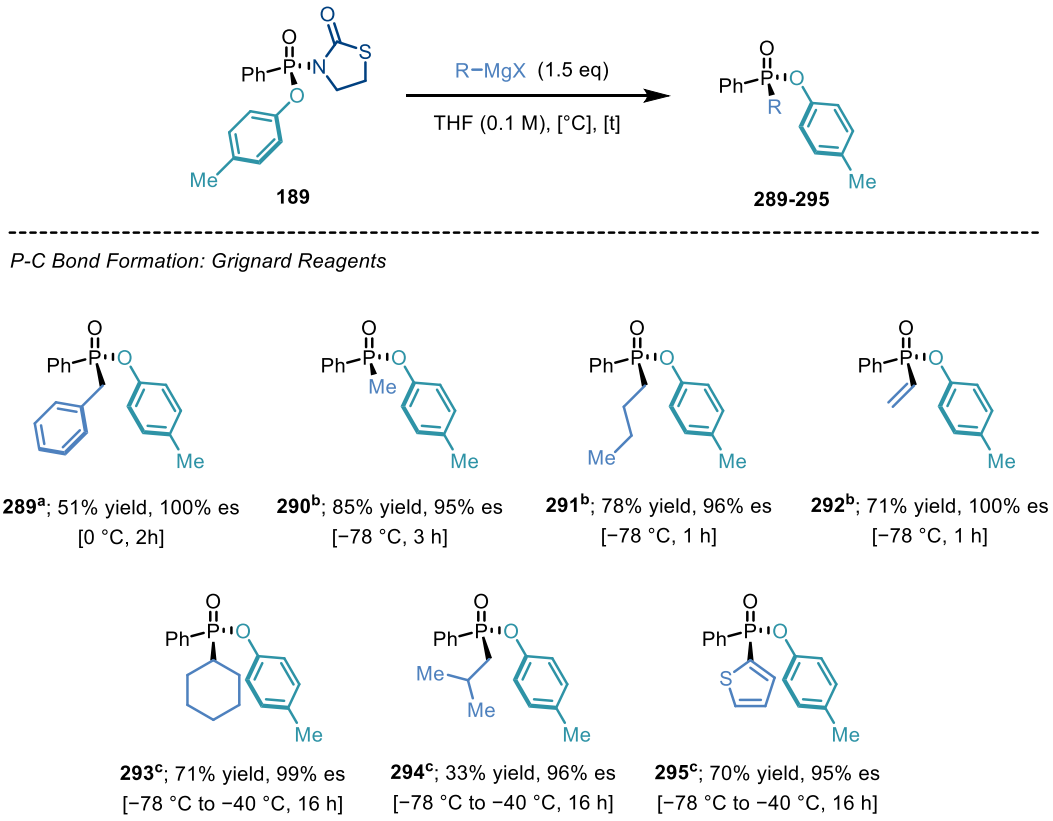
Lastly, attention was turned to Grignard reagent addition. A significant limitation of our 1st-generation catalyst system was the inability to forge P-C bonds *via* downstream derivatisation of the formed chiral phosphonate due to the formation of unwanted side products (*Scheme 43*). It was hoped that Grignard reagent addition would be facilitated in our 2nd-generation reaction system by switching to a thiazolidinone leaving group, thereby enabling rapid access to P-C bonds, found in a variety of phosphinates, phosphine oxides, and phosphines.



Scheme 43: Unsuccessful attempts to from P–C bonds using 1st-generation system. All work carried out by Dr Michele Formica.

Starting with BnMgCl as a nucleophile, we were pleased to observe clean formation of the corresponding product **289** in 51% yield and 100% es using THF as solvent at 0 °C for 2 h (*Scheme 44*). Unfortunately, however, switching nucleophile to MeMgBr led to significant racemisation at P. Lowering the reaction temperature to −78 °C proved necessary to minimise racemisation, and increasing the reaction time to 3 hours was needed to compensate for a slower reaction rate, forming product **290** in 85% yield and 87% es. With these optimised conditions, *n*-BuMgCl and vinylMgCl reacted smoothly, forming products **291** and **292** in 71% yield and 100% es and 78% yield and 96% es, respectively.

More sterically hindered 2° CyMgCl, however, gave low yields of the desired product at −78 °C; instead, reacting at −40 °C overnight gave the optimal balance between reaction yield and racemisation P, forming the corresponding product **293** in 71% yield and 99% es. Using these reaction conditions, *i*-BuMgCl 2-thiophenylMgCl could both be incorporated, forming the corresponding products **294** and **295** in 33% yield and 96% es and 70% yield and 95% es, respectively.



Scheme 44: Scope for Grignard derivatisation of enantioenriched P(V) phosphonate **189**. All reactions carried out on 0.05 mmol scale. All yields are isolated yields. [a]1.5 eq nucleophile, THF (0.1 M), 0 °C, 2 hr; [b]1.5 nucleophile, THF (0.1 M), −78 °C, 3 hr; [c]1.5 eq nucleophile, THF (0.1 M), −40 °C, 16 h.

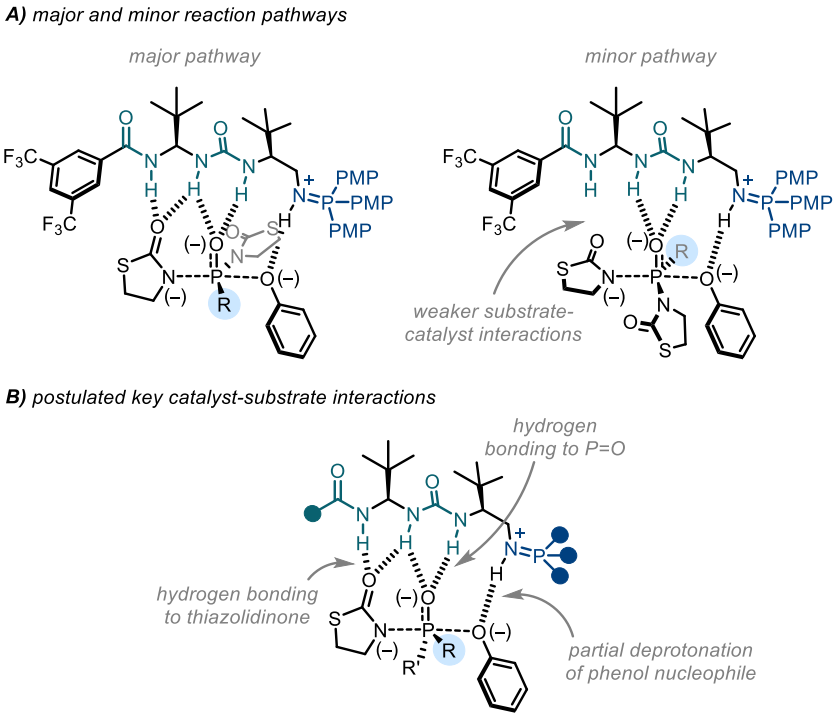
Overall, a broad range of P−C bonds could be forged *via* this enantiospecific downstream nucleophilic displacement, including the incorporation of structurally diverse, commercially available aliphatic, vinylic, benzylic, and aromatic Grignard reagents. This represents a significant improvement over our 1st-generation reaction system, enabling potentially facile downstream access to important phosphinates, phosphine oxides, and phosphines with medicinal, agrochemical, and synthetic applications.

2.6 Mechanistic Considerations

In considering the mechanism for the desymmetrisation reaction, a number of key interactions are likely operative. Firstly, the superbasic iminophosphorane likely facilitates partial or complete deprotonation

of the incoming phenolic nucleophile, generating the corresponding phenolate and thereby forming a stronger nucleophile with which to attack the P(V) centre. Secondly, the ureidopeptide catalyst framework likely interacts with the prochiral P(V) substrate *via* dual hydrogen bonding interactions, both to the P=O bond and to the carbonyl of the thiazolidinone leaving group.

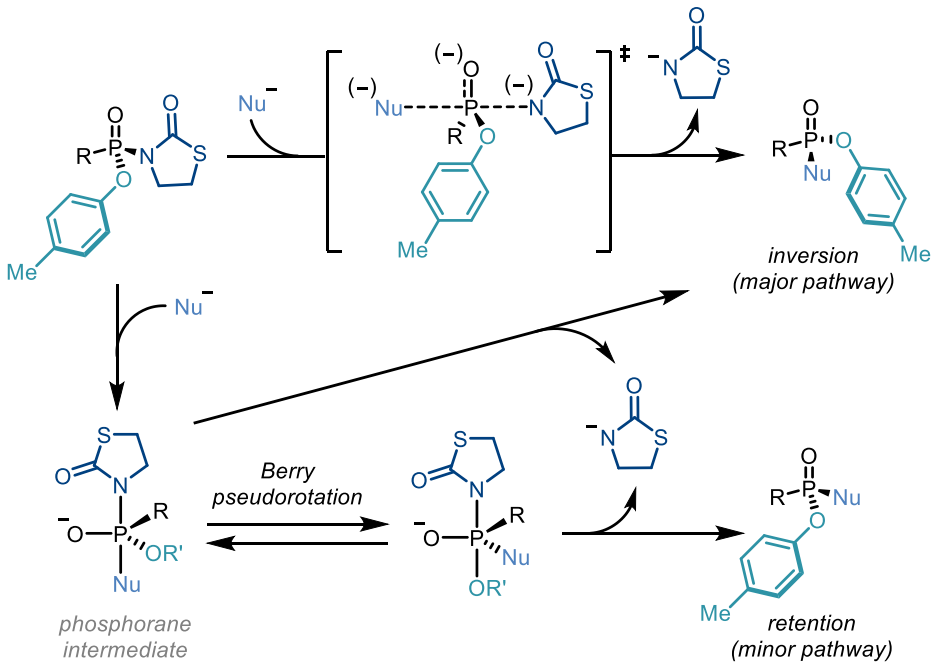
Analogously to our 1st-generation system, this is postulated to lower the activation energy barrier for nucleophilic attack by the incoming phenolate nucleophile. Assuming nucleophilic attack is the enantiodetermining step, the P(V) backbone may be orientated either away (leading to the major (*R*)-enantiomer) or towards (leading to the minor (*S*)-enantiomer) the catalyst framework in two diastereomerically distinguishable reactant complexes. Computational studies for our 1st-generation system indicated that the major transition state shows substrate binding through both the P=O carbonyl and Lewis basic leaving group through hydrogen bonding interactions, whereas the minor transition state is bound solely through the substrate P=O bond. In a similar fashion, it is postulated that the sum of the stabilising non-covalent interactions between the substrate and the catalyst framework for the major (*R*)-enantiomer are stronger than those for the corresponding (*S*)-enantiomer, therefore leading to the observed enantioselectivity in the our 2nd-generation catalyst system (*Scheme 45*). However, the exact reason for the broader nucleophile scope with our 2nd-generation system is unclear at this stage, in particular the lack of a requirement for an *ortho*-substituted phenol to obtain products with high enantioselectivity. This question is currently being studied computationally and results will be disclosed in due course.



Scheme 45: **A)** Overview of the postulated major (*R*-enantiomer) and minor (*S*-enantiomer) reaction pathways for the desymmetrisation reaction. Orientation of the P(V) backbone group away from the catalyst framework is proposed to maximise favourable non-covalent interactions between the substrate and the catalyst. **B)** Postulated key interactions in the substrate complex.

Racemisation of the P(V) stereocentre was a persistent challenge during downstream derivatisation with various nucleophiles. Importantly, variation in the nucleophile type, nucleophile structure, and changes in the solvent and temperature had often dramatic and largely unpredictable effects on the observed enantiospecificity of the nucleophilic displacement.

Nucleophilic substitution reactions at tetracoordinate P(V) species (S_N@P(V)) exist on a continuum between synchronous attack of the nucleophile and loss of the leaving group, analogous to an S_N2 reaction at stereogenic C and leading to Walden inversion of the P(V) centre, and an asynchronous, stepwise addition-elimination mechanism, proceeding through a 5-coordinate phosphorane intermediate[168,169]. In the majority of cases, S_N@P(V) reactions proceed through a largely concerted reaction pathway, thereby leading to inversion of configuration, and, analogously to our 1st-generation system, inversion is likely the dominant pathway for the derivatisation reactions in our 2nd-generation reaction system. However, there are numerous reports in the published literature of certain P(V) systems undergoing significant racemisation or even complete retention of configuration on nucleophilic substitution. This may be explained by the formation of a 5-coordinate trigonal bipyramidal (TBP) phosphorane intermediate on addition of the nucleophile, followed by exchange of the axial and equatorial ligands through Berry pseudorotation(s)[170–176], and subsequent loss of the leaving group. In the extreme case, this process may lead to complete retention of configuration if one of the enantiomeric phosphorane intermediates is significantly energetically favoured[177], though in the majority of cases this instead would lead to varying levels of P(V) racemisation (*Scheme 46*). Computational studies by Bickelhaupt *et al.*[178–182] have shown that the degree of (a)synchronicity in S_N@P(V) reactions is highly dependent on the steric environment around the P(V) centre (arising from both the P(V) substituents and the incoming nucleophile), the reaction solvent, and reaction temperature. This is consistent with the strong dependence of P(V) racemisation during downstream derivatisation on the reaction conditions, which largely had to be optimised for each class of nucleophile. Given that P(V) racemisation was not a significant issue during downstream derivatisation in our 1st-generation reaction system, the challenges associated with this transformation in our 2nd-generation system may be traced to the higher pK_a thiazolidinone leaving group, which, given it is a poorer leaving group, may bias the reaction pathway for nucleophilic displacement towards an asynchronous mechanism.



Scheme 46: Proposed racemisation pathway for P(V) derivatisation.

2.7 Scope and Limitations of Present Methodology

Our 2nd-generation desymmetrisation system represents a significant improvement in terms of both scope of the desymmetrisation reaction and downstream derivatisation when compared to our 1st-generation system. Switching to a higher *p*K$_a$ thiazolidinone leaving group has enabled us to lower catalyst loading from 15 mol% to 10 mol%, a result of improved catalyst turnover due to better *p*K$_a$ matching between the iminophosphorane and the leaving group. Similarly, changes to both the catalyst structure and the leaving group have resulted in a far broader range of phenol nucleophiles being tolerated for desymmetrisation, which was previously limited to *ortho*-substituted phenols for our 1st-generation catalyst. Significantly, the thiazolidinone group has facilitated broad downstream derivatisation of the formed chiral phosphonates, thereby representing a truly modular system with the ability for rapid access to P–S, P–O, and P–C bonds, which represent important motifs in a variety of P(V)-containing medicinal and agrochemical compounds.

However, our 2nd-generation system still presents a few limitations. Firstly, despite the range of phenol nucleophiles tolerated by the system being broad, strongly electron-poor phenols led to trace product or no reaction due to their low nucleophilicity. Similarly, the system is limited to phenolic nucleophiles, with non-aromatic alcohols being insufficiently activated by the current BIMP catalyst; ultimately, this limits access to a range of important chiral phosphonate drug structures. Secondly, the system does not tolerate P(V) electrophiles bearing non-carbon backbones, which result in low yields or racemisation of the P centre. Again, this represents a limitation in the ability to easily access many medicinally important chiral phosphonates using this methodology, such a ProTide, HepDirect, and *cyclo*Sal prodrug motifs.

Lastly, despite the significant scope for downstream derivatisation with a range of nucleophiles, racemisation of P was a recurring problem, requiring careful tuning of the reaction conditions to minimise this effect. Given racemisation was not a significant issue with our 1st-generation system, this is likely due to the higher pK_a, and therefore poorer leaving group ability, of the thiazolidinone leaving group employed. With these limitations in mind, there is still scope for reaction improvement through further catalyst and leaving group optimisation.

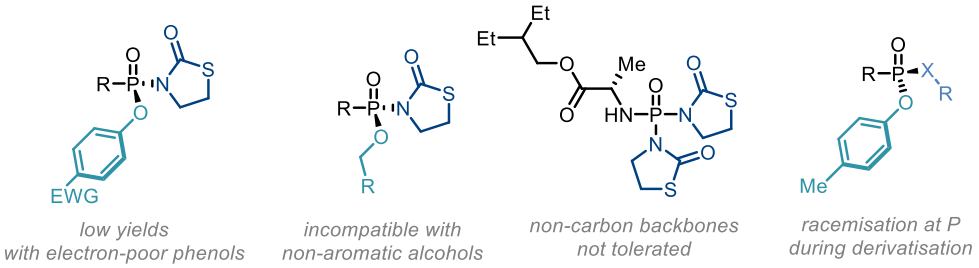
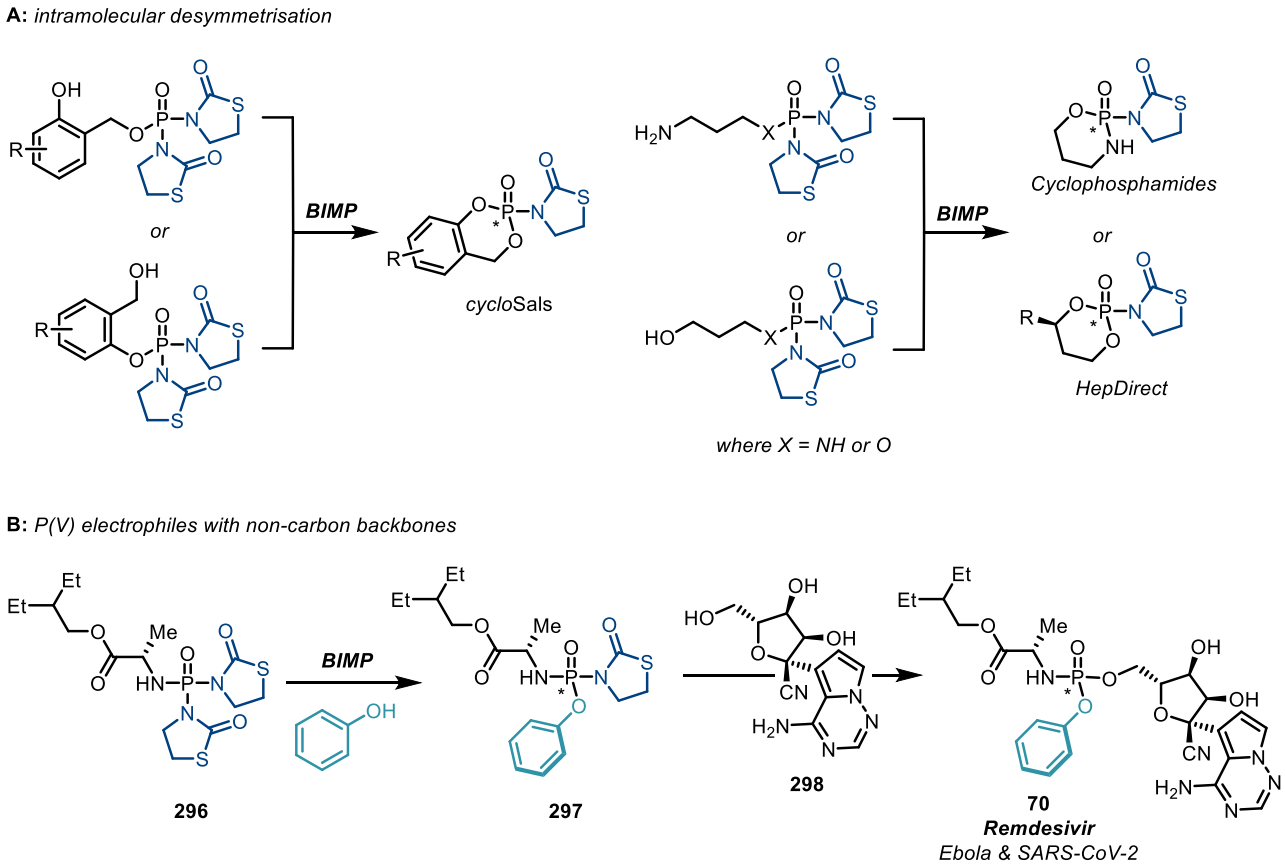


Figure 12: Overview of the limitations of current methodology.

2.8 Conclusions and Future Work

In conclusion, a 2nd-generation enantioselective catalytic desymmetrisation for direct access to enantioenriched P(V) stereocentres is described. Through use of a prochiral P(V) electrophile containing two thiazolidinone leaving groups and harnessing a bifunctional iminophosphorane (BIMP) superbase catalyst, this desymmetrisation protocol delivers consistently high yields (up to 99% isolated yield) and enantiomeric excess (up to 97% ee) with a broad range of nucleophiles and P(V) electrophiles. The reaction was successfully scaled up to 3.0 mmol (1g scale), delivering product in 71% yield and 94% ee. In addition, the unique modularity of this system was demonstrated, with downstream nucleophilic displacement of the second thiazolidinone leaving group enabling stereoselective access to a broad range of chiral P(V) compounds containing P–O, P–N, P–S, and P–C linkages.

Future directions of this work will target the synthesis of *cyclo*Sal prodrugs through an intramolecular enantioselective desymmetrisation. Extension of this method may also enable related intramolecular desymmetrisation reactions using aliphatic alcohols and amines, opening access to HepDirect prodrugs and cyclophosphamides (*Scheme 47**A***). Further catalyst and leaving group optimisation may also enable the desymmetrisation of P(V) electrophiles bearing non-carbon backbones such as **296**, giving access to medicinally important phosphonate prodrugs, such as Remdesivir (*Scheme 47**B***). Computational studies are also underway aimed at elucidating the origin of the increased nucleophile scope of the 2nd-generation system.



Scheme 47: Potential future work for access to medicinally important P(V)-containing drug and prodrug structures.

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Chapter 3: Experimental Details

General Techniques: Reactions were carried out under a nitrogen atmosphere unless stated otherwise. Glassware was oven-dried and cooled under vacuum then purged with nitrogen before use. Room temperature refers to 22 ± 2 °C. Inert atmosphere techniques, such as Schlenk technique, were used for the handling of air/moisture sensitive reagents. Reactions carried out at 0 °C were cooled using an ice bath or carried out in a 0 °C fridge, those at –10/–15 °C were cooled using a mixture of ice and NaCl or carried out in a freezer at the described temperature, and those at –78 °C were carried out using a solid CO_2/acetone bath. Reactions carried out at high temperatures were heated using an oil bath or, preferably, using DrySyn® heating blocks. Reaction temperatures refer to external temperatures, for example of a heating block or oil bath, not of internal reaction temperatures.

Nomenclature and Numbering: Compounds are named following IUPAC nomenclature as generated by ChemDraw. Carbon atoms are numbered in a systematic way where possible to ease comparison between related compounds in a synthetic sequence, not necessarily in accordance with IUPAC conventions.

Solvents and Reagents: Where solvent dryness was important, CH_2Cl_2 (DCM), Et_2O, methanol, THF, and toluene were either obtained from dry solvent bottles with septa (Aldrich), an MBRAUN-SPS solvent purification system in which solvent is passed through an activated alumina column under nitrogen, or by standing over 3 Å molecular sieves under an atmosphere of nitrogen. Reagents were used as obtained without further purification unless stated otherwise. Chromatography: Thin layer chromatography (TLC) was carried out using Merck aluminium backed DC60 F254 plates (particle size 0.2 mm). TLC sheets were visualised by UV light, then developed by staining with potassium

permanganate on silica. Purification by flash column chromatography (FCC) was carried out using Merck silicagel 60 F254 (particle size 43–60 μm).

Characterisation: Proton (^{1}H), carbon (^{13}C), fluorine (^{19}F) and phosphorous (^{32}P) spectra were recorded on Bruker AVG400 (400/101 MHz), Bruker AVH400 (400/101 MHz), Bruker AVF400 (400/101 MHz), Bruker AVB500 (500/126 MHz), Bruker AVC500 (500/126 MHz), and Bruker DPX200 (200 MHz) NMR spectrometers. Spectra are referenced to the residual solvent peak ($CHCl_3$: δ_H 7.26, δ_C 77.16; C_7D_7H: δ_H 2.08, δ_C 20.43; $(CD_3)_2CO$: δ_H 2.05, δ_C 206.26; C_6D_5H: δ_H 7.16; CD_2HOD: 3.31, δ_C 49.00). Chemical shifts (δ) are given in parts per million (ppm, ± 0.01) and coupling constants (*J*) are given in Hertz (Hz, ± 0.1 as measured on Mestrenova, without rounding). The following convention is used to report chemical shifts: δ (multiplicity, number of protons, coupling constant(s), assignment), with chemical shifts reported in descending order. When a large roof effect was observed, it was included after the multiplicity. Peak assignments were made based on chemical shifts, integrations, coupling constants, and two-dimensional techniques such as COSY and HSQC. Where necessary, additional experiments such as HMBC, nOe, and NOESY were also used. Peak multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (h), nonuplet (n), a combination e.g. doublet of doublets (dd), or as a multiplet (m) over a peak range. Additionally, peaks may be described as broad (br), or apparent (app)

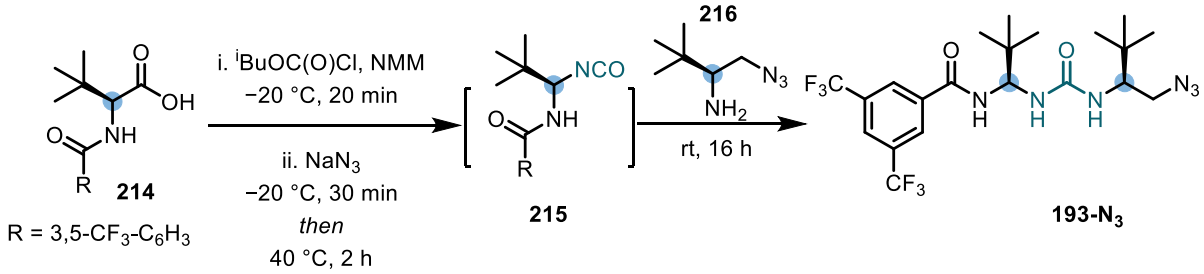
Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer. Selected diagnostic absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Low-resolution mass spectra were acquired using a Micromass LCT Premier spectrometer (ESI). High resolution mass spectra were recorded by Chemistry Research Laboratory staff using a Bruker Daltronics MicroTOF spectrometer (ESI). Mass to charge ratios (m/z) are reported in Daltons. Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celcius (°C). Optical rotations were recorded using a Perkin Elmer 241 optical activity polarimeter at 25 °C.

$[\alpha]_D^T$ values are reported in 10^{-1} deg cm^2 g^1; concentrations (c) are quoted in g/100 mL; D refers to the D-line of sodium (589 nm); Temperatures (T) are given in degrees Celsius (°C). (+) and (–) compound number prefixes indicate the sign of the optical rotation.

Enantiomeric excesses were determined by HPLC analysis on an Agilent 1200 Series instrument using a chiral stationary phase column specified in the individual experiment or by GC analysis on an Agilent 7820A instrument employing a chiral stationary phase column specified in the individual experiment and by comparing the samples with the appropriate racemic mixtures.

3.1 Catalyst Synthesis

193-N_3: *N*-((*R*)-1-(3-((*S*)-1-azido-3,3-dimethylbutan-2-yl)ureido)-2,2-dimethylpropyl)-3,5-bis(trifluoromethyl)benzamide



To a vigorously stirred solution of (*S*)-*tert*-leucine (**213**, 2.00 g, 15.2 mmol) in 1M aq. NaOH (9.58 mL) at 0 °C was added 4.0 mL of CH_2Cl_2. Stirring was stopped and 3,5-bis(trifluoromethyl)benzoyl chloride (**212**, 4.42 g, 2.9 mL, 16.0 mmol) was injected into the organic layer. Vigorous stirring was immediately resumed and maintained at room temperature. After 2 hr (upon complete conversion of the SM as assessed by TLC) the reaction was cooled to 0 °C and quenched with 1M aq. HCl until the solution was <pH 2. Et_2O (15.0 mL) was added, and the organic phase was separated. The aqueous phase was further extracted with 2 x 15.0 mL Et_2O. The combined organic phases were washed with brine (30.0 mL), dried over $MgSO_4$ and filtered. The resulting solution was concentrated *in vacuo* to afford the crude product **214** which was further purified by FCC (CH_2Cl_2 to 9:1 CH_2Cl_2:MeOH) to afford pure **214** in 44% yield (2.51 g, 6.70 mmol).

According to a modified literature procedure[160], to a solution of **214** (371 mg, 1.0 mmol, 1.0 eq) in THF (4 mL) at -20 °C were added sequentially isobutyl chloroformate (130 µL, 1.0 mmol, 1.0 eq) and *N*-methylmorpholine (110 µL, 1.0 mmol, 1.0 eq) and stirring was maintained for 20 min. To the reaction mixture was added sodium azide (98 mg, 1.5 mmol, 1.5 eq) in H_2O (1.0 mL) and stirring was maintained for 30 min at -20 °C. The organic layer was then separated, the volatiles removed *in vacuo*, dissolved in CH_2Cl_2 (15.0 mL) and washed with water (10.0 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to 5 mL. The reaction mixture was heated to reflux for 2 h and then the reaction mixture was cooled to rt and the crude amino azide (**216**, 156 mg, 1.00 mmol, 1.00 eq) as a solution in Et_2O (4.0 mL) was added dropwise. The reaction mixture was stirred at rt overnight and then the volatiles removed *in vacuo*. The crude was recrystallised from hot EtOAc, cooled to rt, filtered, and washed with pentane to obtain **193-N_3** as a white solid in 31% yield (246 mg, 0.31 mmol).

$[\alpha]_D^{25}$ = −2.00 (c = 0.95, DMSO); **Mp** 248 - 250 °C ; **^{1}H NMR** (400 MHz, DMSO-*d6*) δ 8.78 (dd, *J* = 17.6, 8.2 Hz, 1H, NH), 8.46 – 8.37 (m, 2H, *ortho*-ArCH), 8.29 (dd, *J* = 2.0, 1.1 Hz, 1H, *para*-ArCH), 6.28 (dd, *J* = 9.6, 3.3 Hz, 1H, NH), 6.19 (dd, *J* = 9.4, 6.3 Hz, 1H, NH), 5.58 (t, *J* = 8.7 Hz, 1H, NCHN), 3.59 (td, *J* = 9.4, 3.4 Hz, 1H, $CHC(CH_3)$), 3.40 (dd, *J* = 12.7, 3.4 Hz, 1H, $CHaCHbN_3$), 3.22 – 3.10 (m, 1H, $CHaCHbN_3$), 0.95 (s, 9H, $C(CH_3)_3$), 0.86 (s, 9H, $C(CH_3)_3$; **^{13}C NMR** (101 MHz, DMSO-*d6*) δ 163.0 (C=O), 157.0 (C=O), 137.0 (ArC), 130.3 (d, J = 33.3 Hz, CCF_3), 128.3 (ArCH), 124.6 (ArCH), 123.1 (q,

J = 272.9 Hz, CF_3), 64.0 (NCHN), 56.8 (CH_2), 51.7 ($CHC(CH_3)_3$), 36.0 ($C(CH_3)_3$), 34.2 ($C(CH_3)_3$), 26.4 ($C(CH_3)_3$), 25.6 ($C(CH_3)_3$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.29; **IR** ν_{max}/cm^{-1}: 3320, 2969, 2094, 1642 (C=O), 1546, 1277, 1132, 699, 681; **HRMS** (ESI+): calcd. for $C_{21}H_{29}N_6O_2F_6$ $[M+H]^+$ 511.2251, found 511.2248.

3.2 Substrate Synthesis

3.2.1 General Procedure I: Synthesis of P(V) electrophiles

General Procedure I-A: Substrate synthesis from phosphoryl dichloride

The corresponding phosphonic dichloride (1 eq) and 1,3-thiazolidin-2-one (**217**, 2 eq) were dissolved in THF and cooled to 0 °C. Et_3N (2 eq) was added dropwise resulting in the formation of a white precipitate. The reaction mixture was then allowed to warm to room temperature or 40 °C (as specified in the individual experiment) and stirred for 14 hr. Solvent was removed *in vacuo* and the resulting crude was dissolved in CH_2Cl_2 (40.0 mL) and was washed sequentially with saturated aq. Na_2CO_3 (15.0 mL), brine (15.0 mL), 2M aq. HCl (15.0 mL), then brine (15.0 mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by trituration in cold ethanol and washed with pentane to afford the pure phosphonate.

General Procedure I-B: Substrate synthesis from phosphonate ester

The corresponding phosphonate ester (1 eq) was dissolved in dry CH_2Cl_2 (0.125 M), cooled to 0 °C then TMS-Br was added (5 eq). The solution was stirred for a further 2 hr. Volatiles were removed *in vacuo* and the crude was stirred in THF:H_2O (10:1) (0.3 M) for 1 hr. Volatiles were removed *in vacuo* and azeotroped with toluene to remove all traces of water and dried under high vacuum for 12 hr. The crude phosphonic acid was dissolved in CH_2Cl_2 (0.5 M) and a catalytic amount of DMF was added. The solution was heated to 50 °C, oxalyl chloride (4 eq) was added dropwise over 30 min, and the solution was stirred for a further 3 hr. Volatiles were removed *in vacuo* and the crude phosphoryl dichloride was converted to the desired phosphonic ester following **General Procedure I-A**.

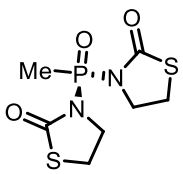
General Procedure I-C: Substrate synthesis from diethyl phosphite

According to a modified literature procedure[164], $Pd(OAc)_2$ (5 mol%) and PPh_3 (15 mol%) were combined under nitrogen atmosphere and dissolved in dry EtOH. The corresponding aryl bromide (1 eq), diethyl phosphite (1.2 eq) and DIPEA (1.5 eq) were subsequently added and the reaction mixture refluxed overnight. Solvent was removed *in vacuo* and the crude reaction mixture was diluted with EtOAc then was sequentially with 1M HCl, sat aq $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and volatiles were removed *in vacuo* before purification by flash column chromatography. Product was converted to the desired phosphonate following **General Procedure I-B.**

General Procedure I-D: Substrate synthesis from diisopropyl phosphite

According to a modified literature procedure[163], $Pd(OAc)_2$ (2 mol%) and dppf (2.2 mol%) were combined under nitrogen atmosphere and dissolved in dry MeCN. The corresponding aryl bromide (1 eq), diethyl phosphite (1.2 eq) and DIPEA (1.5 eq) were subsequently added and the reaction mixture refluxed overnight. Solvent was removed *in vacuo* and the crude reaction mixture was diluted with EtOAc then was sequentially with 1M HCl, sat aq $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and volatiles were removed *in vacuo* before purification by flash column chromatography to afford the pure phosphonate. Product was converted to the desired phosphonate following **General Procedure I-B.**

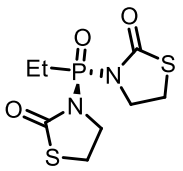
218: 3,3'-(methylphosphoryl)bis(oxazolidin-2-one)



218 was synthesised following **General Procedure I-A**. Methyl phosphonic dichloride (0.34 mL, 3.80 mmol) was used as dichloride, 1,3-thiazolidin-2-one (0.78 g, 7.60 mmol) was used as nucleophile, Et_3N (1.00 mL, 7.6 mmol) as the base in THF (10.0 mL), stirring at 40 °C. FCC 95:5 CH_2Cl_2: Acetone. White solid (0.34 g, 1.30 mmol, 17% yield).

Mp 168 – 170 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 – 3.98 (m, 4H, $NC\underline{H_2}CH_2S$), 3.49 – 3.34 (m, 4H, $NCH_2C\underline{H_2}S$), 2.02 (d, *J* = 17.1 Hz, 3H, CH_3P); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.3 (C=O), 47.8 (d, *J* = 5.1 Hz, $N\underline{C}H_2CH_2S$), 29.0 (d, *J* = 8.6 Hz, $NCH_2\underline{C}H_2S$), 15.3 (d, *J* = 114.2 Hz, CH_3P); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.31; **IR** (film) υ_{max}/cm^{-1}: 1659 (C=O), 1364, 1300, 1234 (P=O), 1151, 1101, 985, 873, 753, 689; **HRMS** (ESI+): calcd. for $C_7H_{12}O_3N_2PS_2$ 267.0021 $[M+H]^+$, found 267.0022.

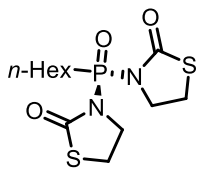
219: 3,3'-(ethylphosphoryl)bis(oxazolidin-2-one)



219 was synthesised following **General Procedure I-A**. Ethyl phosphonic dichloride (0.80 mL, 7.60 mmol) was used as dichloride, 1,3-thiazolidin-2-one (1.60 g, 15.0 mmol) was used as nucleophile, Et_3N (2.00 mL, 15.0 mmol) as the base in THF (40.0 mL), stirring at 40 °C. FCC 95:5 CH_2Cl_2: Acetone. White solid (0.91 g, 3.20 mmol, 43% yield).

Mp 140 – 142 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.12 – 3.95 (m, 4H, $NC\underline{H_2}CH_2S$), 3.49 – 3.33 (m, 4H, $NCH_2C\underline{H_2}S$), 2.33 (dq, *J* = 15.3, 7.6 Hz, 2H, $CH_3C\underline{H_2}P$), 1.33 – 1.15 (m, 3H, $C\underline{H_3}CH_2P$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.3 (C=O), 48.0 (d, *J* = 4.4 Hz, $N\underline{C}H_2CH_2S$), 29.3 (d, *J* = 7.9 Hz, $NCH_2\underline{C}H_2S$), 21.3 (d, *J* = 110.0 Hz, $CH_3\underline{C}H_2P$), 5.1 (d, *J* = 6.5 Hz, $\underline{C}H_3CH_2P$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 26.65; **IR** (film) υ_{max}/cm^{-1}: 1670 (C=O), 1363, 1218 (P=O), 1103, 1020, 830, 757, 689; **HRMS** (ESI+): calcd. for $C_8H_{14}O_3N_2PS_2$ 281.0178 $[M+H]^+$, found 281.0177.

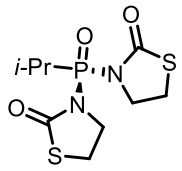
220: 3,3'-(hexylphosphoryl)bis(oxazolidin-2-one)



220 was synthesised following **General Procedure I-A**. Hexyl phosphonic dichloride (0.16 g, 0.94 mmol) was used as dichloride, 1,3-thiazolidin-2-one (0.18 g, 1.80 mmol) was used as nucleophile, Et_3N (0.23 mL, 1.8 mmol) as the base in THF (10.0 mL), stirring at 40 °C. FCC 95:5 CH_2Cl_2: Acetone. White solid (0.28 g, 0.76 mmol, 80% yield).

Mp 60 - 64 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.07 – 3.99 (m, 4H, NC$\underline{H_2}CH_2S$), 3.47 – 3.33 (m, 4H, $NCH_2C\underline{H_2}S$), 2.40 – 2.24 (m, 2H, C$\underline{H_2}CH_2P$), 1.73 – 1.58 (m, 2H, $CH_3CH_2CH_2C\underline{H_2}$), 1.50 – 1.37 (m, 2H, C$\underline{H_2}$P), 1.36 – 1.23 (m, 4H, $CH_3C\underline{H_2}CH_2$, $CH_3CH_2C\underline{H_2}$), 0.96 – 0.81 (m, 3H, $C\underline{H_3}CH_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.1 (C=O), 47.9 (d, *J* = 4.3 Hz, N$\underline{C}H_2CH_2S$), 31.2 ($CH_3\underline{C}H_2$), 30.1 (d, *J* = 18.2 Hz, $\underline{C}H_2CH_2P$), 29.1 (d, *J* = 7.9 Hz, $NCH_2\underline{C}H_2S$), 27.8 (d, *J* = 108.1 Hz, CH_2P), 22.4 ($CH_3CH_2\underline{C}H_2$), 20.8 (d, *J* = 5.0 Hz, $\underline{C}H_2CH_2CH_2P$), 14.0 ($\underline{C}H_3CH_2$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 25.09; **IR** (film) υ_{max}/cm^{-1}: 2930, 1676 (C=O), 1358, 1234 (P=O), 1145, 1102, 977, 834, 766; **HRMS** (ESI+): calcd. for $C_{12}H_{22}O_3N_2PS_2$ 337.0804 $[M+H]^+$, found 337.0805.

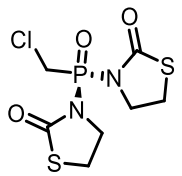
221: 3,3'-(*iso*propylphosphoryl)bis(oxazolidin-2-one)



221 was synthesised following **General Procedure I-A**. Isopropyl phosphonic dichloride (0.64 g, 4.00 mmol) was used as dichloride, 1,3-thiazolidin-2-one (0.83 g, 8.0 mmol) was used as nucleophile, Et_3N (1.1 mL, 8.00 mmol) as the base in THF (20.0 mL), stirring at 40 °C. FCC 95:5 CH_2Cl_2: Acetone. White solid (0.17 g, 0.59 mmol, 15% yield).

Mp 130 - 134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.04 (td, *J* = 7.0, 1.4 Hz, 4H, NC$\underline{H_2}CH_2S$), 3.46 – 3.33 (m, 4H, $NCH_2C\underline{H_2}S$), 2.93 – 2.76 (m, 1H, $(CH_3)_2C\underline{H}P$), 1.36 – 1.19 (m, 6H, $(C\underline{H_3})_2CHP$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.8 (C=O), 48.1 (d, *J* = 3.9 Hz, N$\underline{C}H_2CH_2S$), 29.2 (d, *J* = 7.2 Hz, $NCH_2\underline{C}H_2S$), 26.5 (d, *J* = 106.3 Hz, $(CH_3)_2\underline{C}HP$), 14.9 (d, *J* = 3.9 Hz, $(\underline{C}H_3)_2CHP$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 31.13; **IR** (film) υ_{max}/cm^{-1}: 2976, 1665 (C=O), 1467, 1239, 1215 (P=O), 1144, 1100, 1038, 1020, 974, 944, 877, 720, 697, 686; **HRMS** (ESI+): calcd. for $C_9H_{16}O_3N_2PS_2$ 295.0333 $[M+H]^+$, found 295.0335.

222: 3,3'-((chloromethyl)phosphoryl)bis(thiazolidin-2-one)

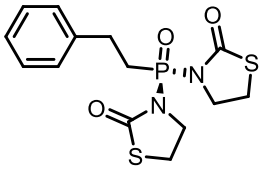


222 was synthesised following **General Procedure I-A**. Chloromethyl phosphonic dichloride (0.41 g, 4.00 mmol) was used as dichloride, 1,3-thiazolidin-2-one (0.83 g, 8.00 mmol) was used as nucleophile, Et_3N (1.10.0 mL, 8.00 mmol) as the base in THF (20.0 mL), stirring at 40 °C. FCC 95:5 CH_2Cl_2: Acetone. White solid (0.49 g, 1.60 mmol, 41% yield).

Mp 160 - 162 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.25 (d, *J* = 8.1 Hz, 2H, $ClCH_2P$), 4.16 – 3.95 (m, 4H, NC$\underline{H_2}CH_2S$), 3.46 (t, *J* = 7.0 Hz, 4H, $NCH_2C\underline{H_2}S$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.3 (d, *J* = 2.6 Hz, C=O), 47.6 (d, *J* = 4.0 Hz, N$\underline{C}H_2CH_2S$), 36.8 (d, *J* = 121.7 Hz, $NCH_2\underline{C}H_2S$), 29.4 (d, *J* = 8.1 Hz, $ClCH_2P$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.78; **IR** (film) υ_{max}/cm^{-1}: 1691 (C=O), 1345, 1288, 1251

(P=O), 1227, 1162, 1096, 1025, 854, 705, 688; **HRMS** (ESI+): calcd. for $C_7H_{11}O_3N_2ClPS_2$ 300.9632 $[M+H]^+$, found 300.9633.

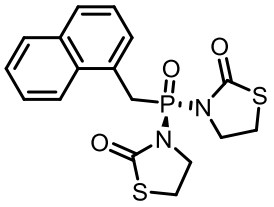
223: 3,3'-(phenethylphosphoryl)bis(thiazolidin-2-one)



223 was synthesised according to **General Procedure I-B**. Diethyl phenylethylphosphonate ester (0.46 g, 2.0 mmol) was used and 1,3-thiazolidin-2-one (0.41 g, 4.00 mmol) was used as nucleophile at 40 °C. FCC 95:5 CH_2Cl_2: acetone. FCC 95:5 CH_2Cl_2:MeOH, off-white solid (0.33 g, 0.94 mmol, 47% yield).

Mp 204 - 206 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 5H, ArH), 4.01 – 3.84 (m, 4H, $NC\underline{H_2}CH_2S$), 3.39 – 3.18 (m, 4H, $NCH_2C\underline{H_2}S$), 3.10 – 2.96 (m, 2H, $ArCH_2$), 2.79 – 2.63 (m, 2H, $ArCH_2C\underline{H_2}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (C=O), 139.4 (d, J = 14.6 Hz, $Ar\underline{C}CH_2$), 128.8 (ArC), 128.3 (ArC) 126.8 (ArC), 47.6 (d, J = 4.3 Hz, $N\underline{C}H_2CH_2S$), 29.2 (d, J = 107.7 Hz, CH_2P), 28.9 (d, J = 8.1 Hz, $NCH_2\underline{C}H_2S$), 27.2 (d, J = 4.6 Hz, $ArCH_2$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 23.64; **IR** (film) υ_{max}/cm^{-1}: 1676 (C=O), 1437, 1359, 1281, 1240 (P=O), 1220, 1146, 1104, 943, 836, 743, 698; **HRMS** (ESI+): calcd. for $C_{14}H_{18}O_3N_2PS_2$ 357.0491 $[M+H]^+$, found 357.0492.

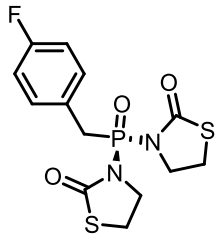
224: 3,3'-((naphthalen-1-ylmethyl)phosphoryl)bis(thiazolidin-2-one)



224 was synthesised according to **General Procedure I-B**. Diethyl (1-naphthylmethyl)phosphonate ester (0.50 g, 1.00 mmol) was used and 1,3-thiazolidin-2-one (0.37 g, 3.60 mmol) was used as nucleophile at room temperature. FCC 95:5 CH_2Cl_2:MeOH, off-white solid (0.24 g, 0.60 mmol, 34%, yield).

Mp 166 - 168 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 8.5, 1.2 Hz, 1H, ArH), 7.89 – 7.78 (m, 2H, ArH), 7.64 – 7.55 (m, 1H, ArH), 7.56 – 7.42 (m, 3H, ArH), 4.31 (d, J = 19.2 Hz, 2H, CH_2P), 3.90 – 3.52 (m, 4H, $NC\underline{H_2}CH_2S$), 3.33 – 2.98 (m, 4H, $NCH_2C\underline{H_2}S$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.34 (d, J = 1.7 Hz, C=O), 133.91 (d, J = 3.4 Hz, ArC), 132.41 (d, J = 5.3 Hz, ArC), 129.19 (d, J = 8.1 Hz. ArCH), 128.7 (d, J = 4.8 Hz, ArCH) 128.6 (s, ArCH), 126.76 (ArC), 126.18 (ArCH), 125.46 (d, J = 11.0 Hz, ArCH), 125.33 (d, J = 4.7 Hz, ArCH), 124.33 (d, J = 2.1 Hz, ArCH), 47.68 (d, J = 3.9 Hz, $N\underline{C}H_2CH_2S$), 32.09 (d, J = 103.9 Hz, CH_2P), 28.94 (d, J = 7.8 Hz, $NCH_2\underline{C}H_2S$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 20.02; **IR** (film) υ_{max}/cm^{-1}: 2982, 1691 (C=O), 1445, 1356, 1282, 1245 (P=O), 1221, 1137, 1100, 871, 786; **HRMS** (ESI+): calcd. for $C_{17}H_{18}O_3N_2PS_2$ 393.0491 $[M+H]^+$, found 393.0489.

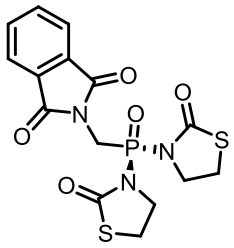
225: 3,3'-((4-fluorobenzyl)phosphoryl)bis(thiazolidin-2-one)



225 was synthesised according to **General Procedure VIII-B**. Diethyl (4-fluorobenzyl)phosphonate ester (0.26 g, 1.10 mmol) was used and 1,3-thiazolidin-2-one (0.23 g, 2.20 mmol) was used as nucleophile at room temperature. FCC 95:5 CH_2Cl_2:MeOH, off-white solid (69.0 mg, 0.19 mmol, 18% yield).

Mp 184 - 186 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H, ArCH), 7.10 – 7.02 (m, 2H, ArCH), 3.94 – 3.63 (m, 4H, NC$\underline{H_2}$CH_2S), 3.83 – 3.73 (m, 2H, CH_2P), 3.41 – 3.12 (m, 4H, NCH_2C$\underline{H_2}$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (C=O), 162.4 (d, *J* = 251.5 Hz, ArCF), 132.0 – 131.7 (m, ArCH), 124.5 – 124.9 (m, Ar$\underline{C}$CH_2) 115.9 (dd, *J* = 21.7, 3.5 Hz, ArCH), 47.7 (d, *J* = 3.8 Hz, N$\underline{C}$H$_2$CH$_2$S), 34.3 (d, *J* = 104.1 Hz, CH_2P), 29.1 (d, *J* = 7.9 Hz, NCH$_2\underline{C}$H$_2$S); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -113.98 – -114.12 (m); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 20.26 (d, *J* = 6.5 Hz); **IR** (film) υ_{max}/cm^{-1}: 2982, 1676 (C=O), 1509, 1361, 1361, 1239 (P=O), 1148, 1105, 828, 779, 699; **HRMS** (ESI+): calcd. for $C_{13}H_{15}O_3N_2PS_2F$ 361.0240 $[M+H]^+$, found 361.0241.

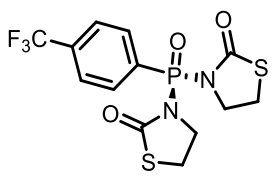
226: 2-((bis(2-oxothiazolidin-3-yl)phosphoryl)methyl)isoindoline-1,3-dione



226 was synthesised according to **General Procedure I-B**. Dimethyl (phthalimidomethyl)phosphonate ester (400 mg, 1.50 mmol) was used and 1,3-thiazolidin-2-one (0.31 g, 3.00 mmol) was used as nucleophile at room temperature. FCC 95:5 CH_2Cl_2:MeOH, off-white solid (0.17 g, 0.41 mmol, 27% yield).

Mp 208 - 210 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H, ArH), 7.78 – 7.71 (m, 2H, ArH), 4.73 (d, *J* = 8.4 Hz, 2H, CH_2P), 4.06 (td, *J* = 7.1, 1.4 Hz, 4H, NC$\underline{H_2}$CH_2S), 3.52 – 3.38 (m, 4H, NCH_2C$\underline{H_2}$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8 (d, *J* = 2.0 Hz, C=O thiazolidinone), 167.4 (C=O phthalimide), 134.6 (ArCH), 131.95 (ArC), 123.9 (ArCH), 47.9 (d, *J* = 4.7 Hz, N$\underline{C}$H$_2$CH$_2$S), 36.1 (d, *J* = 122.4 Hz, CH_2P), 29.6 (d, *J* = 8.3 Hz, NCH$_2\underline{C}$H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.18; **IR** (film) υ_{max}/cm^{-1}: 2931, 1676 (C=O), 1374, 1285, 1233 (P=O), 1145, 1102, 977, 833, 693; **HRMS** (ESI+): calcd. for $C_{15}H_{14}O_5N_3PS_2Na$ 434.0005 $[M+Na]^+$, found 434.0005.

228: 3,3'-((4-(trifluoromethyl)phenyl)phosphoryl)bis(thiazolidin-2-one)

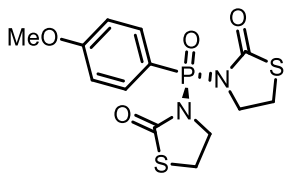


228 was synthesised according to **General Procedure I-C**. Diethyl (4-trifluoromethyl)phenyl phosphonate (0.55 g, 1.96 mmol) was used and 1,3-thiazolidin-2-one (0.40 g, 3.92 mmol) was used as nucleophile at 40 °C. FCC 6:4 Pentane: EA. White solid (0.28 g, 0.70 mmol, 36% yield).

Mp 127 – 130 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.27 – 8.17 (m, 2H, ArH), 7.83 – 7.76 (m, 2H, ArH), 4.06 – 3.82 (m, 4H, NC$\underline{H_2}$CH_2S), 3.52 – 3.29 (m, 4H, NCH_2C$\underline{H_2}$S); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.84 (C=O), 133.14 (d, *J* = 12.0 Hz, ArC), 126.34 – 124.95 (m, ArC), 48.87 (d, *J* = 5.8 Hz, N$\underline{C}$H$_2$CH$_2$S), 29.37 (d, *J* = 9.1 Hz, NCH$_2\underline{C}$H$_2$S); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -63.47 – -63.50 (m); **^{31}P NMR** (162

MHz, $CDCl_3$) δ 8.71 – 8.57 (m); **IR** (film) υmax/cm-1: 1678 (C=O), 1324, 1249 (P=O), 1132, 1111, 1064, 839, 710; (ESI+): calcd. for C13H13O3N2F3P1S2 397.0052[M+Na]+, found 397.0051.

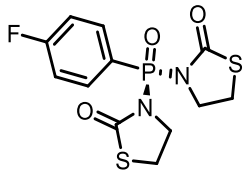
229: 3,3'-((4-methoxyphenyl)phosphoryl)bis(thiazolidin-2-one)



229 was synthesised according to **General Procedure I-C**. Diethyl (4-methoxyphenyl) phosphonate (0.38 g, 2.00 mmol) was used and 1,3-thiazolidin-2-one (0.41 g, 4.00 mmol) was used as nucleophile at 40 °C. FCC 6:4 Pentane: EA. White solid (51 mg, 0.14 mmol, 7% yield).

Mp 120 – 124 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.94 (m, 2H, ArH), 7.06 – 6.97 (m, 2H, ArH), 4.01 – 3.88 (m, 4H, NC$\underline{H_2}CH_2S$), 3.47 – 3.27 (m, 4H, $NCH_2C\underline{H_2}S$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.58 (C=O), 134.38 (d, *J* = 13.2 Hz, ArC), 114.47 (d, *J* = 16.6 Hz, ArC), 55.49 (Ar$\underline{C}H_3$), 49.02 (d, *J* = 6.0 Hz, N$\underline{C}H_2CH_2S$), 29.10 (d, *J* = 9.0 Hz, $NCH_2\underline{C}H_2S$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 10.82; $NCH_2\underline{C}H_2S$); **IR** (film) υmax/cm-1: 2981, 2889, 1682 (C=O), 1381, 1239 (P=O), 1150, 1119, 1096, 837**;** **HRMS** (ESI+): calcd. for C13H16O4N2P1S2 359.0284[M+H]+, found 359.0283.

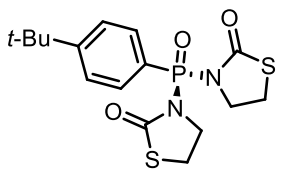
230: 3,3'-((4-fluorophenyl)phosphoryl)bis(thiazolidin-2-one)



230 was synthesised according to **General Procedure I-C**. Diethyl (4-fluoro)phenyl phosphonate (0.46 g, 2.00 mmol) was used and 1,3-thiazolidin-2-one (0.41 g, 4.00 mmol) was used as nucleophile at 40 °C. FCC 6:4 Pentane: EA. Off-white solid (0.16 g, 0.47 mmol, 24% yield).

Mp 108 – 116 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 – 8.02 (m, 2H, ArH), 7.25 – 7.18 (m, 2H, ArH), 4.03 – 3.84 (m, 4H, NC$\underline{H_2}CH_2S$), 3.50 – 3.27 (m, 4H, $NCH_2C\underline{H_2}S$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.81 (C=O), 135.36 (dd, *J* = 13.3, 9.2 Hz, ArC), 116.57 (dd, *J* = 21.6, 17.0 Hz, ArC), 49.03 (d, *J* = 6.0 Hz, N$\underline{C}H_2CH_2S$), 29.29 (d, *J* = 9.0 Hz, $NCH_2\underline{C}H_2S$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 9.49 (d, *J* = 1.9 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -102.70 (d, *J* = 2.0 Hz); **IR** (film) υmax/cm-1: 2981, 1682 (C=O), 1249 (P=O), 1150, 1127, 1097, 837; **HRMS** (ESI+): calcd. for C12H13O3N2F1P1S2 347.0084 [M+H]+, found 347.0084.

231: 3,3'-((4-(*tert*-butyl)phenyl)phosphoryl)bis(thiazolidin-2-one)

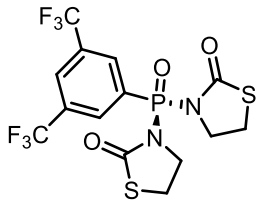


231 was synthesised according to **General Procedure I-C**. Diethyl (4-tert-butyl)phenyl phosphonate (0.54 g, 2.00 mmol) was used and 1,3-thiazolidin-2-one (0.41 g, 4.00 mmol) was used as nucleophile at 40 °C. FCC 6:4 Pentane: EA. Off-white solid (0.28 g, 0.72 mmol, 36% yield).

Mp 180 – 184 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.91 (m, 2H, ArH), 7.59 – 7.52 (m, 2H, ArH), 4.04 – 3.84 (m, 4H, NC$\underline{H_2}CH_2S$), 3.50 – 3.25 (m, 4H, $NCH_2C\underline{H_2}S$), 1.34 (s, 9H, ArC(C$\underline{H_3}$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.77 (C=O), 157.88 (ArC), 132.25 (d, *J* = 12.0 Hz, ArC), 126.15 (d, *J* = 15.8 Hz, ArC), 124.55 (d, *J* = 165.7 Hz, ArC), 49.19 (d, *J* = 6.1 Hz,N$\underline{C}H_2CH_2S$), 35.39 (Ar$\underline{C}$(CH$_3$)$_3$), 31.13 (ArC($\underline{C}$H$_3$)$_3$), 29.30 (d, *J* = 8.9 Hz, $NCH_2\underline{C}H_2S$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 10.83; **IR** (film)

υmax/cm-1: 2980, 1685 (C=O), 1244 (P=O), 1097, 835; **HRMS** (ESI+): calcd. for C16H22O3N2PS2 385.0804 [M+H]+, found 385.0800.

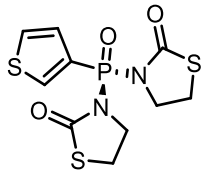
232: 3,3'-((3,5-bis(trifluoromethyl)phenyl)phosphoryl)bis(thiazolidin-2-one)



232 was synthesised according to **General Procedure I-C**. Diethyl (3,5-trifluoromethyl)phenyl phosphonate (1.0 g, 2.86 mmol) was used and 1,3-thiazolidin-2-one (0.59 g, 5.72 mmol) was used as nucleophile at 40 °C. FCC 6:4 Pentane: EA. White solid (0.68 g, 1.47 mmol, 51% yield).

Mp 190 – 194 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 14.4 Hz, 2H, ArH) 8.12 (s, 1H, ArH), 4.07 – 3.89 (m, 4H, NC$\underline{H_2}$$CH_2$S), 3.53 – 3.35 (m, 4H, $NCH_2C\underline{H_2}$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.77 (C=O), 133.20 – 132.83 (m, ArC), 127.93 – 126.32 (m, ArC), 48.51 (d, *J* = 5.7 Hz, N$\underline{C}H_2CH_2$S), 29.39 (d, *J* = 9.2 Hz, $NCH_2\underline{C}H_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 6.94; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.85 – -62.89 (m); **IR** (film) υmax/cm-1: 2981, 1678 (C=O), 1277, 1248 (P=O), 1128, 1091; **HRMS** (ESI+): calcd. for C14H12O3N2F6PS2 464.9926 [M+H]+, found 464.9926.

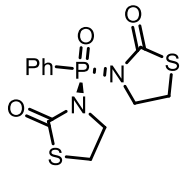
234: 3,3'-(thiophen-3-ylphosphoryl)bis(thiazolidin-2-one)



234 was synthesised according to **General Procedure I-D**. Diethyl (4-thiophene) phosphonate (0.88 g, 4.00 mmol) was used and 1,3-thiazolidin-2-one (0.83 g, 8.00 mmol) was used as nucleophile at 40 °C. FCC 6:4 Pentane: EA. Pale yellow solid (0.63 g, 1.88 mmol, 47% yield).

Mp 240 – 242 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (ddd, *J* = 8.8, 2.9, 1.2 Hz, 1H, ArH), 7.67 – 7.60 (m, 1H, ArH), 7.53 – 7.44 (m, 1H, ArH), 4.06 – 3.85 (m, 4H, NC$\underline{H_2}$$CH_2$S), 3.49 – 3.27 (m, 4H, $NCH_2C\underline{H_2}$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.59 (C=O), 138.39 (d, *J* = 18.6 Hz, ArC), 129.37 (d, *J* = 18.6 Hz, ArC), 127.89 (d, *J* = 20.3 Hz, ArC), 48.84 (d, *J* = 6.4 Hz, N$\underline{C}H_2CH_2$S), 29.23 (d, *J* = 9.3 Hz, $NCH_2\underline{C}H_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.24; **IR** (film) υmax/cm-1: 2981, 1678 (C=O), 1365, 1238 (P=O), 1101, 833; **HRMS** (ESI+): calcd. for C10H12O3N2P1S3 334.9742 [M+H]+, found 334.9739.

184: 3,3'-(phenylphosphoryl)bis(oxazolidin-2-one)



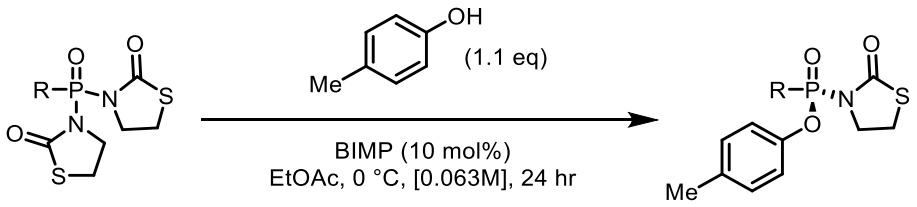
According to a modified literature procedure, **217** (1.55 g, 15 mmol) was dissolved in THF (12.0 mL) and cooled to 0 °C. THF (12 mL) was then added followed by the dropwise addition of phenylphosphoryl dichloride (1.06 mL, 7.5 mmol). The resulting solution was warmed to rt and stirred for 16 hr. The resulting suspension was poured over ice cold saturated $NaHCO_3$ (200 mL) resulting in the precipitation of the crude product which was filtered and washed with H_2O (2 x 100 mL). The resulting solid triturated with cold EtOH (20 mL), filtered, washed with cold EtOH (10 mL) and then pentane (50 mL). Recrystallisation from toluene afforded the pure **184** in 55% yield (1.35 g, 4.13 mmol).

Mp 158 – 160 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (dt, *J* = 14.1, 6.7 Hz, 2H, ArH), 7.66 – 7.59 (m, 1H, ArH), 7.53 (dp, *J* = 7.8, 3.7 Hz, 2H, ArH), 4.04 – 3.81 (m, 4H, NC$\underline{H_2}$$CH_2$S), 3.44 – 3.25 (m, 4H,

$NCH_2C\underline{H_2}S$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8 (C=O), 134.0 (d, *J* = 3.2 Hz, ArC), 132.3 (d, *J* = 11.5 Hz, ArC), 129.1 (d, *J* = 15.5 Hz, ArC), 127.9 (d, *J* = 162.9 Hz, ArC), 49.1 (d, *J* = 6.0 Hz, $N\underline{C}H_2CH_2S$), 29.3 (d, *J* = 8.9 Hz, $NCH_2\underline{C}H_2S$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 10.57; **IR** υ_{max}/cm^{-1}: 3319, 2970, 1674 (C=O), 1642, 1547, 1249 (P=O), 1126, 1139, 1092, 668, 657; **HRMS** (ESI+): calcd. for $C_{12}H_{13}O_3N_2NaPS_2$ 350.9997 $[M+Na]^+$, found 350.9998.

3.3 Desymmetrisations

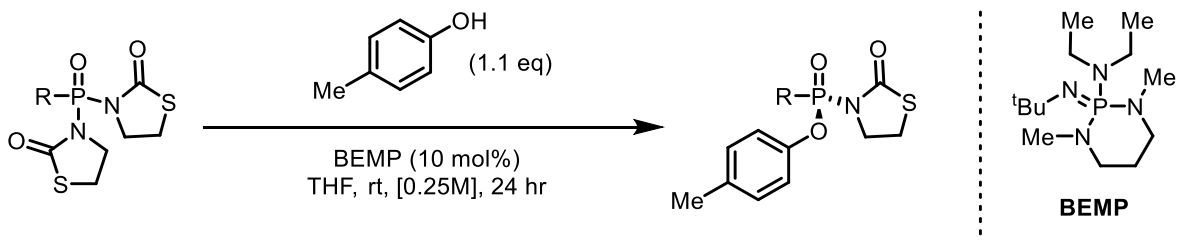
3.3.1 General Procedure II: Enantioselective Desymmetrisation



To the corresponding organoazide (**193-N_3**, 5.0 mg, 0.01 mmol) and P(PMP)$_3$ (3.5 mg, 0.01mmol) under argon atmosphere was added THF (0.4 mL) and the reaction mixture was stirred for 24 h. The formation of the organocatalysts was monitored by TLC. Upon completion volatiles were removed under a stream of N_2 yielding the expected iminophosphorane **193-P(PMP)$_3$** which was used without further purification.

To the corresponding P(V) electrophile (0.10 mmol) and BIMP organocatalyst **193-P(PMP)$_3$** (0.010 mmol) under argon atmosphere was added EtOAc (1.6 mL) and phenol (0.10 mmol, 1.0 equivalents) then the reaction was stirred at 0 °C for 24 h. The reaction mixture was loaded directly onto silica gel and purified by flash column chromatography as specified in the individual experiment to afford pure desymmetrised phosphonate ester. The two enantiomers were separated by chiral HPLC using conditions specified in the individual experiment.

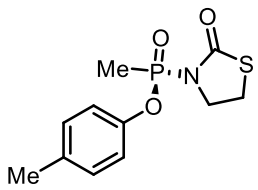
3.3.2 General Procedure III: Racemic Desymmetrisation



To the corresponding P(V) electrophile (0.10 mmol) and 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) (4.5 μL, 0.010 mmol) under argon was added THF (0.4 mL) and the corresponding phenol (0.11 mmol) and the reaction was stirred at 22 °C for 24 h. Volatiles were removed under a stream of N_2 and the crude product was purified by flash column

chromatography as specified in the individual experiment to afford the racemic desymmetrised phosphonate ester product. The two enantiomers were separated by chiral HPLC using conditions specified in the individual experiment.

235: *p*-tolyl (*R*)-methyl(2-oxothiazolidin-3-yl)phosphinate

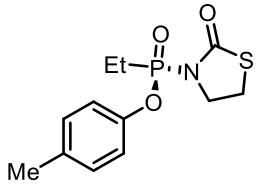


235 was synthesised following **General Procedure II**. **218** (26.6 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL). FCC CH_2Cl_2: Acetone 95:5. Colourless oil (26.4 mg, 0.097 mmol, 97% yield, 80% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (major) = 9.26 min, t (minor) = 11.13 min.

[α]$_D^{25}$ = +92.6 (c = 0.33, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.05 (m, 4H, ArCH), 4.05 – 3.68 (m, 2H, NC$\underline{H_2}$CH$_2$S), 3.33 – 3.06 (m, 2H, NCH$_2$C$\underline{H_2}$S), 2.32 (s, 3H, ArCH$_3$), 1.97 (d, *J* = 17.9 Hz, 3H, CH$_3$P); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.8 (C=O), 147.3 (d, *J* = 9.8 Hz, ArCO), 135.4 (d, *J* = 1.9 Hz, Ar$\underline{C}$CH$_3$), 130.4 (d, *J* = 1.7 Hz, ArCH), 120.6 (d, *J* = 4.1 Hz, ArCH), 48.1 (d, *J* = 3.9 Hz, N$\underline{C}$H$_2$CH$_2$S), 29.0 (d, *J* = 7.6 Hz, NCH$_2\underline{C}$H$_2$S), 20.8 (ArCH$_3$), 13.2 (d, *J* = 131.6 Hz, CH$_3$P); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 26.12; **IR** (film) υ_{max}/cm^{-1}: 2981, 1687 (C=O), 1506, 1259 (P=O), 1201, 1113, 925, 825, 746; **HRMS** (ESI+): calcd. for $C_{11}H_{15}O_3NPS$ 272.0505 $[M+H]^+$, found 272.0503.

236: *p*-tolyl (*R*)-ethyl(2-oxothiazolidin-3-yl)phosphinate

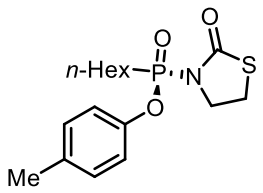


236 was synthesised following **General Procedure II**. **219** (28.0 mg, 0.1 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL). FCC CH_2Cl_2: Acetone 95:5. Colourless oil (27.2 mg, 0.095 mmol, 95% yield, 86% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (major) = 8.32 min, t (minor) = 11.42 min.

[α]$_D^{25}$ = +28.9 (c = 0.07, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.05 (m, 4H, ArCH), 4.05 – 3.71 (m, 2H, NC$\underline{H_2}$CH$_2$S), 3.36 – 3.04 (m, 2H, NCH$_2$C$\underline{H_2}$S), 2.41 – 2.22 (m, 5H, ArCH$_3$, CH$_3$C$\underline{H_2}$), 1.34 – 1.21 (m, 3H, C$\underline{H_3}$CH$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.67 (C=O), 147.39 (d, *J* = 10.4 Hz, ArCO), 135.20 (ArCCH$_3$), 130.30 (d, *J* = 1.7 Hz, ArCH), 120.64 (d, *J* = 4.1 Hz, ArCH), 48.48 (d, *J* = 3.5 Hz, NC$\underline{H_2}$CH$_2$S), 29.11 (d, *J* = 7.1 Hz, NCH$_2$C$\underline{H_2}$S), 20.78 (ArCH$_3$), 19.9 (d, *J* = 128.3 Hz, CH$_3\underline{C}$H$_2$P), 5.5 (d, *J* = 6.0 Hz, $\underline{C}$H$_3$CH$_2$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 30.45; **IR** (film) υ_{max}/cm^{-1}: 2980, 2917, 2849, 1680 (C=O), 1504, 1257, 1226 (P=O), 1194, 1161, 1146, 1102, 917, 819, 665, 641; **HRMS** (ESI+): calcd. for $C_{12}H_{17}O_3NPS$ 286.0661 $[M+H]^+$, found 286.0662.

237: *p*-tolyl (*R*)-hexyl(2-oxothiazolidin-3-yl)phosphinate

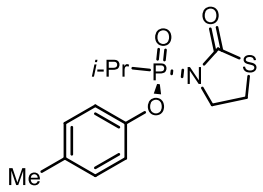


237 was synthesised following **General Procedure II**. **220** (32.2 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). FCC CH_2Cl_2: Acetone 95:5. Colourless oil (30.0 mg, 0.092 mmol, 92% yield, 84% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (major) = 7.27 min, t (minor) = 9.64 min.

[α]$_D^{25}$ = +56.8 (c = 0.36, $CHCl_3$); **1H NMR** (400 MHz, $CDCl_3$) δ 7.16 – 7.04 (m, 4H, ArH), 4.03 – 3.71 (m, 2H, NC$\underline{H_2}$CH$_2$S), 3.32 – 3.04 (m, 2H, NCH$_2$C$\underline{H_2}$S), 2.39 – 2.21 (m, 5H, ArCH$_3$, CH$_2$C$\underline{H_2}$P), 1.83 – 1.57 (m, 2H, C$\underline{H_2}$CH$_2$CH$_2$P), 1.49 – 1.38 (m, 2H, C$\underline{H_2}$CH$_2$P), 1.36 – 1.26 (m, 4H, CH$_3$C$\underline{H_2}$CH$_2$, CH$_3$CH$_2$C$\underline{H_2}$), 0.95 – 0.81 (m, 3H, ArCH$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9 (C=O), 147.5 (d, *J* = 10.4 Hz, ArCO), 135.3 (d, *J* = 1.9 Hz, Ar$\underline{C}$CH$_3$), 130.4 (d, *J* = 1.6 Hz, ArCH), 120.8 (d, *J* = 4.1 Hz, ArCH), 48.5 (d, *J* = 3.5 Hz, N$\underline{C}$H$_2$CH$_2$S), 31.3 (CH$_3$$\underline{C}H_2$), 30.2 (d, *J* = 17.8 Hz, $\underline{C}$H$_2$CH$_2$P), 29.2 (d, *J* = 7.1 Hz, NCH$_2$$\underline{C}H_2$S), 26.7 (d, *J* = 126.0 Hz, CH$_2$$\underline{C}H_2$P), 22.5 (d, *J* = 4.8 Hz, CH$_3$CH$_2$$\underline{C}H_2$), 21.5 (d, *J* = 4.7 Hz, $\underline{C}$H$_2$CH$_2$CH$_2$P), 20.9 (ArCH$_3$), 14.1 (d, *J* = 6.6 Hz, $\underline{C}$H$_3$CH$_2$); **^{31}P NMR** (162 MHz, CDCl3) δ 204.10; **IR** (film) υ_{max}/cm^{-1}: 2928, 1690 (C=O), 1506, 1221 (P=O), 1201, 1114, 925, 825; **HRMS** (ESI+): calcd. for $C_{16}H_{25}NO_3PS$ 342.1287 $[M+H]^+$, found 342.1285.

238: *p*-tolyl (*R*)-isopropyl(2-oxothiazolidin-3-yl)phosphinate

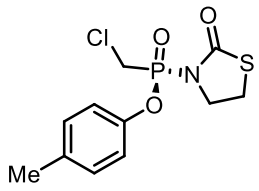


238 was synthesised following **General Procedure II**. **221** (29.4 mg, 0.1 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.1 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). FCC CH_2Cl_2: Acetone 95:5. Colourless oil (23.6 mg, 0.079 mmol, 79% yield, 88% ee).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (minor) = 7.60 min, t (major) = 8.50 min.

[α]$_D^{25}$ = +35.5 (c = 0.54, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.04 (m, 4H, ArH), 3.98 – 3.73 (m, 2H, NC$\underline{H_2}$CH$_2$S), 3.30 – 3.04 (m, 2H, NCH$_2$C$\underline{H_2}$S), 2.87 – 2.69 (m, 1H, C$\underline{H}$(CH$_3$)$_2$), 2.32 (s, 3H, ArCH$_3$), 1.45 – 1.17 (m, 6H, CH(C$\underline{H_3}$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.7 (C=O), 147.7 (d, *J* = 11.5 Hz, ArCO), 135.2 (d, *J* = 1.7 Hz, ArCCH$_3$), 130.4 (d, *J* = 1.6 Hz, ArCH), 120.7 (d, *J* = 4.1 Hz, ArCH), 49.0 (d, *J* = 3.1 Hz, N$\underline{C}$H$_2$CH$_2$S), 29.4 (d, *J* = 6.6 Hz, NCH$_2$$\underline{C}H_2$S), 26.1 (d, *J* = 127.0 Hz, $\underline{C}$H(CH$_3$)$_2$), 20.9 (ArCH$_3$), 15.2 (d, *J* = 2.6 Hz, CH($\underline{C}$H$_3$)$_2$), 14.9 (d, *J* = 5.5 Hz, CH($\underline{C}$H$_3$)$_2$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 33.22; **IR** (film) υ_{max}/cm^{-1}: 1686 (C=O), 1506, 1220 (P=O), 1200, 1116, 926, 825; **HRMS** (ESI+): calcd. for $C_{13}H_{19}O_3NPS$ 300.0818 $[M+H]^+$, found 300.0819.

239: *p*-tolyl (*R*)-(chloromethyl)(2-oxothiazolidin-3-yl)phosphinate

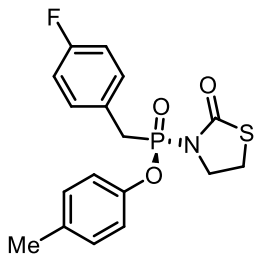


239 was synthesised following **General Procedure II**. **222** (30.7 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). FCC CH_2Cl_2: Acetone 95:5. Colourless solid (14.1 mg, 0.046 mmol, 46% yield, 78% ee).

HPLC Conditions: CHIRALCEL OD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (major) = 9.25 min, t (minor) = 16.91 min.

$[\alpha]_D^{25}$ = +43.4 (c = 0.65, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12 – 6.98 (m, 4H, ArH), 4.17 – 3.83 (m, 4H, NCH_2CH_2S, $ClCH_2P$), 3.33 – 3.12 (m, 2H, NCH_2CH_2S), 2.26 (s, 3H, $ArCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9 (C=O), 146.9 (d, *J* = 10.0 Hz, ArCO), 135.7 (d, *J* = 1.8 Hz, $ArCCH_3$), 130.4 (d, *J* = 1.5 Hz, ArCH), 120.3 (d, *J* = 4.3 Hz, ArCH), 48.7 (d, *J* = 3.7 Hz, NCH_2CH_2S), 34.3 (d, *J* = 147.5 Hz, $ClCH_2P$), 29.2 (d, *J* = 7.7 Hz, NCH_2CH_2S), 20.7 ($ArCH_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 15.25; **IR** (film) υ_{max}/cm^{-1}: 1682 (C=O), 1505, 1274 (P=O), 1197, 1114, 948, 824; **HRMS** (ESI+): calcd. for $C_{11}H_{14}O_3NClPS$ 306.0115 $[M+H]^+$, found 306.0117.

240: *p*-tolyl (*R*)-(4-fluorobenzyl)(2-oxothiazolidin-3-yl)phosphinate

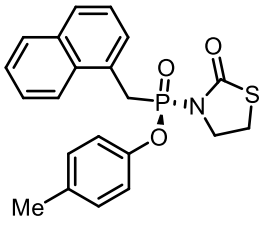


240 was synthesised following **General Procedure II**. **225** (20.0 mg, 0.056 mmol) was used as phosphonate, 4-methylphenol (5.6 mg, 0.056 mmol) was used as nucleophile, **193-P(PMP)$_3$** (4.3 mg, 0.005 mmol) was used as catalyst in EtOAc (0.80 mL). FCC CH_2Cl_2: Acetone 95:5. Colourless oil (13.2 mg, 0.036 mmol, 65% yield, 82% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (major) = 18.25 min, t (minor) = 22.53 min.

$[\alpha]_D^{25}$ = +1.7 (c = 0.58, $CHCl_3$); **^{1}H NMR** (400 MHz, CDCl3) δ 7.34 (ddd, *J* = 8.5, 5.3, 2.9 Hz, 2H, ArH), 7.17 – 6.99 (m, 6H, ArH), 3.85 – 3.41 (m, 4H, NCH_2CH_2S, CH_2P), 3.13 – 2.94 (m, 2H, NCH_2CH_2S), 2.32 (s, 3H, $ArCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9 (C=O), 162.3 (d, *J* = 246.4 Hz, ArCF), 147.4 (d, *J* = 10.7 Hz, ArCO), 135.3 ($ArCCH_3$), 131.8 – 131.2 (m, ArCH), 130.3 (d, *J* = 1.5 Hz, ArCH), 125.6(d, *J* = 8.6 Hz, $ArCCH_2$), 120.6 (d, *J* = 4.3 Hz, ArCH), 115.8 (dd, *J* = 21.5, 3.6 Hz, ArCH), 48.6 (d, *J* = 3.5 Hz, NCH_2CH_2S), 33.0 (d, *J* = 124.7 Hz, CH_2P), 29.1 (d, *J* = 7.2 Hz, NCH_2CH_2S), 20.8 ($ArCH_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.64 (d, *J* = 6.5 Hz); **IR** (film) υ_{max}/cm^{-1}: 2982, 1685 (C=O), 1602, 1506, 1262 (P=O), 1201, 1112, 944, 854, 688; **HRMS** (ESI+): calcd. for $C_{17}H_{18}O_3NPSF$ 366.0724 $[M+H]^+$, found 366.0725.

241: *p*-tolyl (*R*)-(naphthalen-1-ylmethyl)(2-oxothiazolidin-3-yl)phosphinate

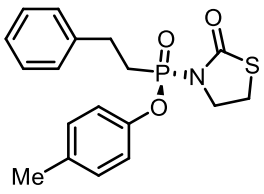


241 was synthesised following **General Procedure II. 224** (39.0 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). FCC CH_2Cl_2: Acetone 95:5. Colourless oil (25.2 mg, 0.063 mmol, 63% yield, 84% ee).

HPLC Conditions: CHIRALPAK IB, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (major) = 11.27 min, t (minor) = 15.39 min.

[α]$_D^{25}$ = – 25.7 (c = 0.71, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 8.6, 1.1 Hz, 1H, NaphH), 7.89 – 7.77 (m, 2H, NaphH), 7.64 – 7.42 (m, 4H, NaphH), 7.12 (s, 4H, ArH), 4.24 – 4.12 (d, *J* = 20.0 Hz, 2H, CH_2P), 3.69 – 3.33 (m, 2H, $NC\underline{H_2}CH_2S$), 3.03 – 2.82 (m, 2H, $NCH_2C\underline{H_2}S$), 2.31 (d, *J* = 1.0 Hz, 3H, $ArCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (C=O), 147.5 (d, *J* = 10.6 Hz, ArCO), 135.2 (d, *J* = 1.8 Hz, ArC), 133.9 (d, *J* = 3.3 Hz, ArC), 132.3 (d, *J* = 5.3 Hz, ArCH), 130.3 (d, *J* = 1.4 Hz, ArCH), 128.9 (d, *J* = 8.3 Hz, ArCH), 128.6 (ArCH), 128.3 (d, *J* = 4.8 Hz, ArCH), 126.4 (d, *J* = 9.7 Hz, ArC), 126.0 (ArCH), 125.4 (d, *J* = 4.7 Hz, ArCH), 124.5 (d, *J* = 2.2 Hz, ArCH), 120.5 (d, *J* = 4.4 Hz, ArCH), 48.6 (d, *J* = 3.5 Hz, $N\underline{C}H_2CH_2S$), 31.0 (d, *J* = 125.2 Hz, CH_2P), 29.0 (d, *J* = 7.1 Hz, $NCH_2\underline{C}H_2S$), 20.8 ($ArCH_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.07; **IR** (film) υ_{max}/cm^{-1}: 1683 (C=O), 1505, 1264 (P=O), 1198, 1110, 927, 804, 781; **HRMS** (ESI+): calcd. for $C_{21}H_{21}O_3NPS$ 398.0974 $[M+H]^+$, found 398.0972.

242: *p*-tolyl (*R*)-(2-oxothiazolidin-3-yl)(phenethyl)phosphinate

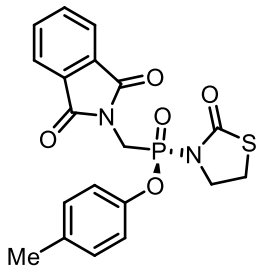


242 was synthesised following **General Procedure II**. **223** (35.6 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (0.80 mL). FCC CH_2Cl_2: Acetone 95:5. Colourless oil (25.1 mg, 0.069 mmol, 69% yield, 89% ee).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (major) = 13.33 min, t (minor) = 19.04 min.

[α]$_D^{25}$ = +76.1 (c = 0.62, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.11 (m, 5H, ArH), 7.08 – 6.98 (m, 4H, ArH), 3.65 – 3.50 (m, 2H, $NC\underline{H_2}CH_2S$), 3.12 – 2.84 (m, 4H, $NCH_2C\underline{H_2}S$, $ArC\underline{H_2}CH_2P$), 2.80 – 2.39 (m, 2H, $ArCH_2C\underline{H_2}P$), 2.25 (s, 3H, $ArCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.57 (C=O), 147.21 (d, *J* = 10.3 Hz, ArCO), 139.7 (d, *J* = 14.6 Hz, $Ar\underline{C}CH_2CH_2P$), 135.2 (d, *J* = 1.8 Hz, $Ar\underline{C}CH_3$), 130.2 (d, *J* = 1.6 Hz, ArCH), 128.6 (ArCH), 128.2 (ArCH), 126.5 (ArCH), 120.6 (d, *J* = 4.1 Hz, ArCH), 48.0 (d, *J* = 3.8 Hz, $N\underline{C}H_2CH_2S$), 28.7 (d, *J* = 7.4 Hz, $Ar\underline{C}H_2CH_2P$), 27.7 (d, *J* = 126.0 Hz, $ArCH_2\underline{C}H_2P$), 27.7 (d, *J* = 3.9 Hz, $NCH_2\underline{C}H_2S$), 20.7 (ArCH3); **^{31}P NMR (**162 MHz, $CDCl_3$) δ 27.27; **IR** (film) υ_{max}/cm^{-1}: 2982, 1685 (C=O), 1506, 1252 (P=O), 1202, 1115, 940, 823, 746, 697; **HRMS** (ESI+): calcd. for $C_{18}H_{21}O_3NPS$ 362.0974 $[M+H]^+$, found 362.0971.

243: *p*-tolyl (*R*)-((1,3-dioxoisoindolin-2-yl)methyl)(2-oxothiazolidin-3-yl)phosphinate

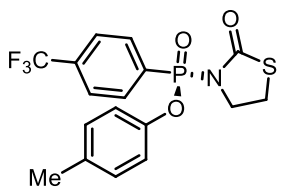


243 was synthesised following **General Procedure II**. **226** (21.0 mg, 0.05 mmol) was used as phosphonate, 4-methylphenol (5.4 mg, 0.05 mmol) was used as nucleophile, **193-P(PMP)$_3$** (4.3 mg, 0.005 mmol) was used as catalyst in EtOAc (0.80 mL). FCC CH_2Cl_2: Acetone 95:5. Colourless oil (20.9 mg, 0.050 mmol, 50% yield, 28% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 mL/min, λ = 220 nm, t (major) = 19.45 min, t (minor) = 27.03 min

^{1}H NMR (400 MHz, CDCl3) δ 7.93 – 7.72 (m, 4H, ArH), 7.13 (d, *J* = 1.1 Hz, 4H, ArH), 4.67 – 4.50 (m, 2H, CH2P), 4.06 – 3.75 (m, 2H, NC$\underline{H_2}CH_2S$), 3.44 – 3.13 (m, 2H, $NCH_2C\underline{H_2}S$), 2.32 (d, *J* = 1.1 Hz, 3H, $ArCH_3$); **^{13}C NMR** (101 MHz, CDCl3) δ 175.6 (C=O phtalimide), 167.4 (C=O thioazolidinone), 147.3 (d, *J* = 10.5 Hz, ArCO), 135.7 (d, *J* = 1.6 Hz, ArCCH3), 134.4 (ArCH), 132.1 (ArC), 130.5 (ArCH), 123.8 (ArCH), 120.6 (d, *J* = 4.5 Hz, ArCH), 48.0 (d, *J* = 4.7 Hz, N$\underline{C}H_2CH_2S$), 34.5 (d, *J* = 146.1 Hz, CH_2P), 29.5 (d, *J* = 7.7 Hz, $NH_2\underline{C}H_2S$), 20.9 ($ArCH_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 15.05; **IR** (film) υ_{max}/cm^{-1}: 1721 (C=O), 1692 (C=O), 1505, 1402, 1219 (P=O), 1192, 1118, 947, 720; **HRMS** (ESI+): calcd. for $C_{19}H_{18}N_2O_5PS$ 417.0678 $[M+H]^+$, found 417.0667.

244: *p*-tolyl (*R*)-(2-oxothiazolidin-3-yl)(4-(trifluoromethyl)phenyl)phosphinate



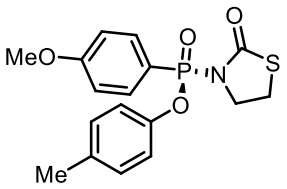
224 was synthesised following **General Procedure II. 228** (39.6 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). FCC pentane:EtOAC 6:4. Colourless oil (25.2 mg, 0.063 mmol, 63% yield, 89% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (minor) = 9.16 min, t (major) = 14.23 min.

$[\alpha]_D^{25}$ = +13.6 [c = 1.1, $CHCl_3$]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.17 (m, 2H, ArH), 7.77 (dd, *J* = 8.2, 3.9 Hz, 2H, ArH), 7.24 – 7.12 (m, 4H, ArH), 4.15 – 3.91 (m, 2H, NC$\underline{H_2}CH_2S$), 3.35 – 3.13 (m, 2H, $NCH_2C\underline{H_2}S$), 2.34 (s, 3H, $ArC\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.32 (C=O), 147.34 (d, *J* = 9.5 Hz, Ar$\underline{C}$O), 135.78 (d, *J* = 1.6 Hz, ArC), 133.25, 130.61 (d, *J* = 1.4 Hz, ArC), 125.30 (d, *J* = 3.8 Hz, ArC), 120.65 (d, *J* = 4.6 Hz , ArC), 48.67 (d, *J* = 4.5 Hz, N$\underline{C}H_2CH_2S$), 29.23 (d, *J* = 7.8 Hz, $NCH_2\underline{C}H_2S$), 20.95 (Ar$\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 10.39; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.38; **IR** (film) υ_{max}/cm^{-1}: 2981, 1383, 1251 (P=O), 1153, 1073, 955**; HRMS** (ESI+): calcd. for $C_{17}H_{16}O_3NF_3PS$ 402.0535 $[M+H]^+$, found 402.0530.

245: *p*-tolyl (*R*)-(4-methoxyphenyl)(2-oxothiazolidin-3-yl)phosphinate

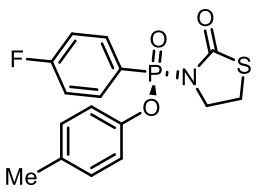


245 was synthesised following **General Procedure II. 229** (35.8 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). FCC pentane:EtOAC 1:1. Colourless oil (26.7 mg, 0.073 mmol, 73% yield, 93% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 mL/min, λ = 220 nm, t (minor) = 10.28 min, t (major) = 17.59 min.

[α]$_D^{25}$ = +81.0 [c = 0.1, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 7.96 (m, 2H, ArH), 7.23 – 7.11 (m, 4H, ArH), 7.05 – 6.95 (m, 2H, ArH), 4.12 – 3.89 (m, 2H, NC$\underline{H_2}$CH_2S), 3.86 (s, 3H, ArOC$\underline{H_3}$), 3.31 – 3.11 (m, 2H, NCH_2C$\underline{H_2}$S), 2.33 (s, 3H, ArC$\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.08 (C=O), 163.73 (d, *J* = 3.6 Hz, ArC), 147.76 (ArC), 135.27 (ArC), 134.88 (d, *J* = 12.8 Hz, ArC), 130.42 (ArC), 120.75 (d, *J* = 4.5 Hz, ArC), 118.38 (d, *J* = 191.4 Hz, ArC), 114.05 (d, *J* = 17.1 Hz, ArC), 55.53 (ArO$\underline{C}$H$_3$), 48.83 (d, *J* = 4.6 Hz, N$\underline{C}$H$_2$CH$_2$S), 29.07 (d, *J* = 7.7 Hz, NH$_2\underline{C}$H$_2$S), 20.93 (Ar$\underline{C}$H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.49; **IR** (film) υ_{max}/cm-1: 2981, 1383, 1251 (P=O), 1153, 1074, 955; **HRMS** (ESI+): calcd. for $C_{17}H_{19}O_4NPS$ 364.0767 $[M+H]^+$, found 364.0767.

246: *p*-tolyl (*R*)-(4-fluorophenyl)(2-oxothiazolidin-3-yl)phosphinate

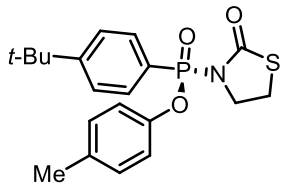


246 was synthesised following **General Procedure II. 230** (34.6 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). FCC pentane:EtOAC 6:4. Colourless oil (24.7 mg, 0.070 mmol, 70% yield, 91% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (minor) = 10.04 min, t (major) = 20.86 min.

[α]$_D^{25}$ = +137.5 [c = 0.08, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 8.05 (m, 2H, ArH), 7.24 – 7.11 (m, 6H, ArH), 4.12 – 3.90 (m, 2H, NC$\underline{H_2}$CH_2S), 3.33 – 3.14 (m, 2H, NCH_2C$\underline{H_2}$S), 2.34 (d, *J* = 1.0 Hz, 3H, ArC$\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.20 (C=O), 147.50 (d, *J* = 9.3 Hz, ArC), 135.79 – 135.45 (m, ArC), 130.53 (ArC), 120.70 (d, *J* = 4.5 Hz, ArC), 116.05 (d, *J* = 17.3 Hz, ArC), 115.84 (d, *J* = 17.4 Hz, ArC), 48.76 (d, *J* = 4.6 Hz, N$\underline{C}$H$_2$CH$_2$S), 29.14 (d, *J* = 7.8 Hz, NH$_2\underline{C}$H$_2$S), 20.94 (Ar$\underline{C}$H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 11.77 (d, *J* = 1.5 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -103.99 – -104.12 (m); **IR** (film) υ_{max}/cm^{-1}: 2981, 1383, 1251 (P=O), 1153, 1073, 955; **HRMS** (ESI+): calcd. for $C_{16}H_{16}O_3NFPS$ 352.0567 $[M+H]^+$, found 352.0563.

247: *p*-tolyl (*R*)-(4-(tert-butyl)phenyl)(2-oxothiazolidin-3-yl)phosphinate

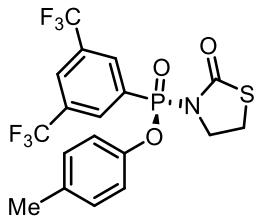


247 was synthesised following **General Procedure II. 231** (38.4 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). FCC pentane:EtOAC 6:4. Colourless oil (30.1 mg, 0.077 mmol, 77% yield, 95% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (minor) = 9.86 min, t (major) = 15.63 min.

[α]$_D^{25}$ = +182.0 [c = 0.1, $CHCl_3$] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 2H, ArH), 7.57 – 7.48 (m, 2H, ArH), 7.24 – 7.11 (m, 4H, ArH), 4.13 – 3.91 (m, 2H, NC$\underline{H_2}$CH_2S), 3.33 – 3.11 (m, 2H, NCH_2C$\underline{H_2}$S), 2.33 (s, 3H, ArC$\underline{H_3}$), 1.34 (s, 9H, ArC(C$\underline{H_3}$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.90 (C=O), 156.98 (d, *J* = 3.5 Hz, Ar$\underline{C}$O), 147.58 (d, *J* = 9.6 Hz, ArC), 135.16 (d, *J* = 1.7 Hz, ArC), 132.42 (d, *J* = 11.5 Hz, ArC), 130.30 (d, *J* = 1.4 Hz, ArC), 125.46 (d, *J* = 16.2 Hz, ArC), 123.95 (d, *J* = 186.1 Hz, ArC), 120.65 (d, *J* = 4.5 Hz, ArC), 48.70 (d, *J* = 4.5 Hz, N$\underline{C}$H$_2$CH$_2$S), 35.17 (Ar$\underline{C}$(CH$_3$)$_3$), 31.05 (ArC($\underline{C}$H$_3$)$_3$), 28.98 (d, *J* = 7.7 Hz, NCH$_2\underline{C}$H$_2$S), 20.81 (Ar$\underline{C}$H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.31; **IR** (film) υ_{max}/cm^{-1}: 2981, 1383, 1250 (P=O), 1154, 1073, 956; **HRMS** (ESI+): calcd. for $C_{20}H_{25}O_3NPS$ 390.1287 $[M+H]^+$, found 390.1291.

248: *p*-tolyl (*R*)-(3,5-bis(trifluoromethyl)phenyl)(2-oxothiazolidin-3-yl)phosphinate

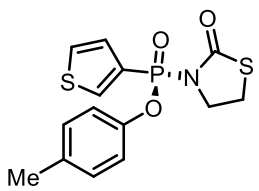


248 was synthesised following **General Procedure II. 232** (39.6 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **193-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL) at -20 °C for 3 days. FCC pentane:EtOAC 1:1. Colourless oil (32.3 mg, 0.069 mmol, 69% yield, 71% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 7.21 min, t (major) = 8.76 min.

[α]$_D^{25}$ = +126.0 [c = 0.1, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 – 8.52 (m, 2H, ArH), 8.10 (s, 1H, ArH), 7.25 – 7.16 (m, 4H, ArHS), 4.17 – 3.91 (m, 2H, NC$\underline{H_2}$CH_2S), 3.36 – 3.15 (m, 2H, NCH_2C$\underline{H_2}$S), 2.36 (s, 3H, ArC$\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.59 (C=O), 147.00 (d, *J* = 9.5 Hz, Ar$\underline{C}$O), 136.19 (d, *J* = 1.6 Hz, ArC), 133.57 – 132.99 (m, ArC), 132.06 (dd, *J* = 33.9, 16.3 Hz), 130.74 (d, *J* = 1.5 Hz, ArC), 130.66 (d, *J* = 187.4 Hz), 127.23 – 126.81 (m, ArC), 122.95 (d, *J* = 270.8 Hz, Ar$\underline{C}$F$_3$), 120.64 (d, *J* = 4.4 Hz, ArC), 48.57 (d, *J* = 4.5 Hz, N$\underline{C}$H$_2$CH$_2$S), 29.31 (d, *J* = 8.1 Hz, NCH$_2\underline{C}$H$_2$S), 20.96 (Ar$\underline{C}$H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 8.08; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.88; **IR** (film) υ_{max}/cm^{-1}: 2981, 1383, 1251 (P=O), 1158, 1073, 955; **HRMS** (ESI+): calcd. for $C_{18}H_{15}O_3NF_6PS$ 470.0409 $[M+H]^+$, found 470.0407.

249: *p*-tolyl (*R*)-(2-oxothiazolidin-3-yl)(thiophen-3-yl)phosphinate

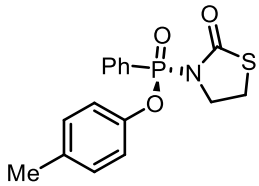


249 was synthesised following **General Procedure II. 234** (33.4 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **A1** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). FCC pentane:EtOAC 1:1. Colourless oil (30.6 mg, 0.090 mmol, 90% yield, 90% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 19.17 min, t (major) = 30.96 min.

$[\alpha]_D^{25}$ = +137.5 [c = 0.08, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (ddd, *J* = 8.8, 2.9, 1.2 Hz, 1H, ArH), 7.63 (ddd, *J* = 5.2, 4.2, 1.2 Hz, 1H, ArH), 7.47 – 7.39 (m, 1H, ArH), 7.21 – 7.10 (m, 4H, ArH), 4.14 – 3.86 (m, 2H, $NC\underline{H}_2CH_2S$), 3.33 – 3.14 (m, 2H, $NCH_2C\underline{H}_2S$), 2.32 (s, 3H, $ArC\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.19 (C=O), 147.49 ($Ar\underline{C}O$), 137.88 (d, *J* = 19.2 Hz, ArC), 135.43, 130.44 (d, *J* = 1.5 Hz, ArC), 130.21 (d, *J* = 18.7 Hz, ArC), 128.12 (d, *J* = 193.2 Hz, ArC), 126.83 (d, *J* = 21.1 Hz, ArC), 120.75 (d, *J* = 4.5 Hz, ArC), 48.65 (d, *J* = 5.0 Hz, $N\underline{C}H_2CH_2S$), 29.13 (d, *J* = 8.1 Hz, $NCH_2\underline{C}H_2S$), 20.93 ($Ar\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 6.80; **IR** (film) υ_{max}/cm^{-1}: 2981, 1383, 1251 (P=O), 1153, 1073, 955; **HRMS** (ESI+): calcd. for $C_{14}H_{15}O_3NPS_2$ 340.0225 $[M+H]^+$, found 340.0224.

189: *p*-tolyl-(*R*)-(2-oxooxazolidin-3-yl)(phenyl)phosphinate



3.05 mmol scale: BIMP **193-P(PMP)$_3$** (259 mg, 0.31 mmol) and **184** (1.00 g, 3.05 mmol) were used as electrophile was dissolved EtOAc (48.0 mL) and cooled to 0 °C, then 4-methylphenol (380 mg, 3.60 mmol) was added and the reaction was stirred at 0 °C for 24 hr. The reaction was then quenched with 1M aq. AcOH (0.31 mL) and all volatiles were removed *in vacuo*. The crude product was purified by FCC (CH_2Cl_2: Acetone 95:5). Colourless Oil (711 mg, 2.13 mmol, 71% yield, 94% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 240 nm, t (minor) = 15.90 min, t (major) = 17.10 min. **$[\alpha]_D^{25}$** = +148.9 (c = 0.47, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 7.99 (m, 2H, phenyl ArCH), 7.66 – 7.56 (m, 1H, ArCH), 7.56 – 7.43 (m, 2H, ArCH), 7.22 – 7.17 (m, 2H, ArCH), 7.16 – 7.11 (m, 2H, ArCH), 4.01 (ddtd, *J* = 43.6, 10.9, 7.1, 1.2 Hz, 2H, $NC\underline{H}_2CH_2S$), 3.33 – 3.11 (m, 2H, $NCH_2C\underline{H}_2S$), 2.32 (d, *J* = 1.0 Hz, 3H, $ArCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (C=O), 147.5 (d, *J* = 9.6 Hz, ArCO), 135.4 (d, *J* = 1.7 Hz, ArC), 133.5 (d, *J* = 3.2 Hz, ArCH), 132.6 (d, *J* = 11.1 Hz, ArCH), 130.4 (d, *J* = 1.3 Hz, ArCH), 128.5 (d, *J* = 16.0 Hz, ArCH), 127.3 (d, *J* = 183.3 Hz, CP), 120.7 (d, *J* = 4.5 Hz, ArCH), 48.7 (d, *J* = 4.6 Hz, $N\underline{C}H_2CH_2S$), 29.1 (d, *J* = 7.8 Hz, $NCH_2\underline{C}H_2S$), 20.9 ($ArCH_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.85; **IR** (film) υ_{max}/cm^{-1}:1687 (C=O), 1504, 1256 (P=O), 1200, 1128, 944, 826, 729, 696; **HRMS** (ESI+): calcd. for $C_{16}H_{16}O_3NNaPS$ 356.0481 $[M+Na]^+$, found 356.0481.

Single crystal X-ray diffraction data for compound 189

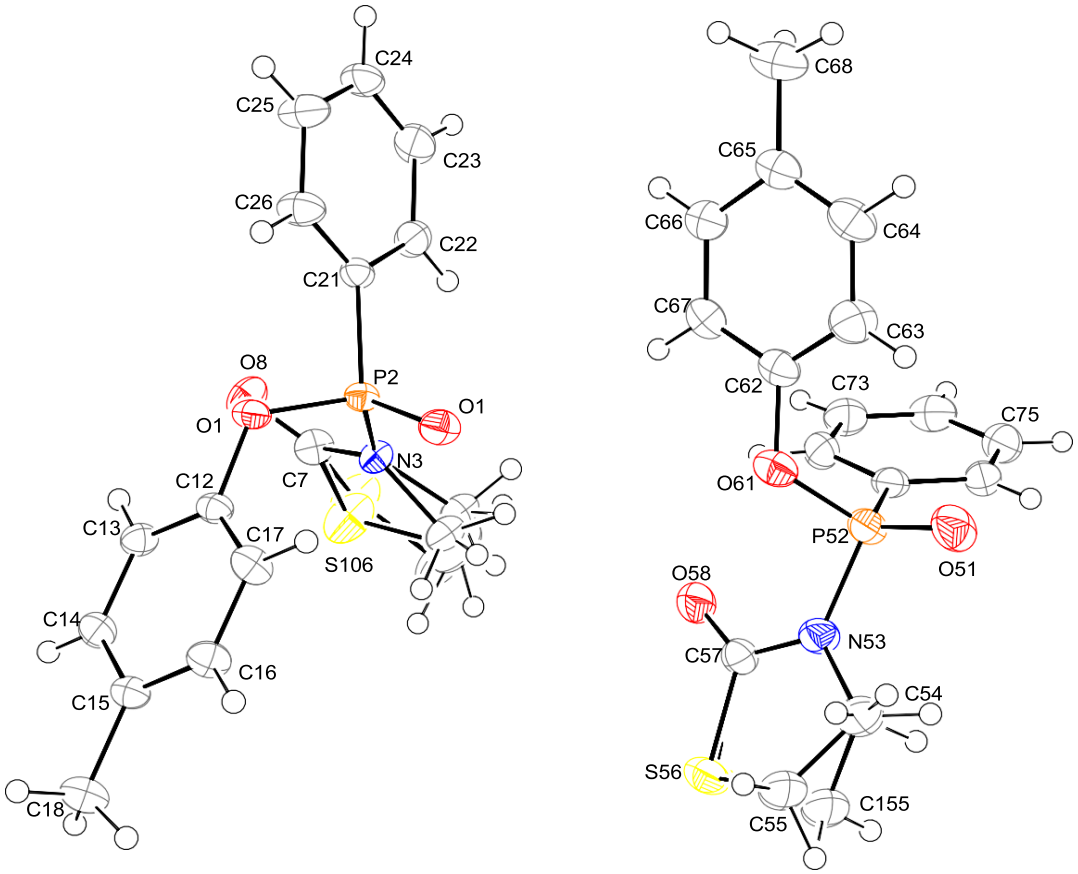


Table 1. Crystal data and structure refinement for **189**.

Identification code	**189**	
Empirical formula	C16 H16 N O3 P S	
Formula weight	333.35	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.0831(2) Å	□ = 90°.
	b = 13.1723(2) Å	□ = 95.9373(17)°.
	c = 13.3341(2) Å	□ = 90°.
Volume	1586.80(5) $Å^3$	
Z	4	
Density (calculated)	1.395 Mg/m^3	
Absorption coefficient	2.870 mm^{-1}	
F(000)	696	
Crystal size	0.19 x 0.16 x 0.10 mm^3	
Theta range for data collection	4.732 to 76.677°.	
Index ranges	-11<=h<=11, -16<=k<=16, -16<=l<=16	
Reflections collected	33015	
Independent reflections	6600 [R(int) = 0.049]	
Completeness to theta = 75.143°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.75 and 0.65	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6600 / 17 / 418	
Goodness-of-fit on F^2	0.9948	
Final R indices [I>2sigma(I)]	R1 = 0.0291, wR2 = 0.0761	
R indices (all data)	R1 = 0.0310, wR2 = 0.0779	
Absolute structure parameter	-0.001(7)	
Largest diff. peak and hole	0.06 and -0.06 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)for 7420. U(eq) is defined as one third of the trace of the *ortho*gonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6204(1)	5012(1)	7236(1)	28
P(2)	7413(1)	4847(1)	8040(1)	20
N(3)	8938(2)	5436(1)	7715(1)	24
C(7)	10244(2)	5456(2)	8353(1)	28
O(8)	10425(2)	5071(1)	9171(1)	36
O(11)	7131(1)	5257(1)	9124(1)	24
C(12)	6866(2)	6290(2)	9303(1)	22
C(13)	7863(2)	6779(2)	9992(1)	25
C(14)	7598(2)	7788(2)	10226(1)	25
C(15)	6373(2)	8309(2)	9767(1)	23
C(16)	5404(2)	7789(2)	9074(2)	28
C(17)	5637(2)	6773(2)	8840(1)	27
C(18)	6126(2)	9411(2)	10013(2)	31
C(21)	7874(2)	3556(2)	8331(1)	22
C(22)	8865(2)	3032(2)	7798(1)	32
C(23)	9100(3)	2003(2)	7972(2)	39
C(24)	8362(3)	1497(2)	8669(2)	36
C(25)	7386(3)	2020(2)	9212(2)	40
C(26)	7144(2)	3043(2)	9046(2)	34
O(51)	5548(2)	5063(2)	2277(1)	44
P(52)	6816(1)	5213(1)	3027(1)	30
N(53)	7022(2)	6467(2)	3277(1)	32
C(57)	8090(2)	6868(2)	3964(1)	30
O(58)	9051(2)	6395(1)	4456(1)	40
O(61)	6664(2)	4798(1)	4134(1)	33
C(62)	6547(2)	3747(2)	4320(2)	30
C(63)	5529(2)	3150(2)	3760(2)	41
C(64)	5474(2)	2118(2)	3988(2)	42
C(65)	6398(2)	1696(2)	4760(2)	34
C(66)	7396(3)	2326(2)	5318(2)	40
C(67)	7474(3)	3352(2)	5106(2)	40

C(68)	6372(3)	577(2)	4985(2)	46
C(71)	8491(2)	4674(2)	2666(1)	28
C(72)	9708(2)	4454(2)	3355(2)	33
C(73)	10948(2)	3997(2)	3023(2)	39
C(74)	10979(3)	3751(2)	2033(2)	41
C(75)	9770(3)	3963(2)	1337(2)	41
C(76)	8531(2)	4424(2)	1652(2)	33
C(4)	9170(20)	5842(17)	6706(10)	30
C(104)	8870(5)	6108(3)	6824(3)	30
C(5)	10560(30)	6450(30)	6730(30)	50
C(105)	10443(6)	6245(6)	6589(4)	50
S(6)	11766(11)	5938(11)	7752(10)	47
S(106)	11593(3)	6170(3)	7783(2)	47
C(55)	6043(7)	8127(4)	3445(5)	44
C(155)	6568(5)	8256(3)	2899(3)	44
C(54)	5930(30)	7196(9)	2792(18)	44
C(154)	5927(16)	7205(6)	2812(12)	44
S(56)	7880(20)	8203(7)	4080(20)	41
S(156)	7900(16)	8209(5)	4002(16)	41

Table 3. Bond lengths [Å] and angles [°] for 7420.

O(1)-P(2)	1.4695(13)	C(24)-H(241)	0.929
P(2)-N(3)	1.6832(15)	C(25)-C(26)	1.379(3)
P(2)-O(11)	1.5880(12)	C(25)-H(251)	0.949
P(2)-C(21)	1.7843(17)	C(26)-H(261)	0.926
N(3)-C(7)	1.387(2)	O(51)-P(52)	1.4584(15)
N(3)-C(4)	1.482(9)	P(52)-N(53)	1.6928(17)
N(3)-C(7)	1.387(2)	P(52)-O(61)	1.5927(15)
N(3)-C(104)	1.478(3)	P(52)-C(71)	1.7896(19)
C(7)-O(8)	1.199(2)	N(53)-C(57)	1.370(3)
C(7)-S(6)	1.785(8)	N(53)-C(54)	1.480(9)
C(7)-O(8)	1.199(2)	N(53)-C(57)	1.370(3)
C(7)-S(106)	1.777(2)	N(53)-C(154)	1.480(6)
O(11)-C(12)	1.407(2)	C(57)-O(58)	1.209(2)
C(12)-C(13)	1.381(2)	C(57)-S(56)	1.778(8)
C(12)-C(17)	1.374(2)	C(57)-O(58)	1.209(2)
C(13)-C(14)	1.391(2)	C(57)-S(156)	1.775(6)
C(13)-H(131)	0.951	O(61)-C(62)	1.413(2)
C(14)-C(15)	1.394(2)	C(62)-C(63)	1.374(3)
C(14)-H(141)	0.922	C(62)-C(67)	1.376(3)
C(15)-C(16)	1.389(3)	C(63)-C(64)	1.395(3)
C(15)-C(18)	1.510(2)	C(63)-H(631)	0.949
C(16)-C(17)	1.395(3)	C(64)-C(65)	1.376(3)
C(16)-H(161)	0.916	C(64)-H(641)	0.926
C(17)-H(171)	0.946	C(65)-C(66)	1.387(3)
C(18)-H(181)	0.956	C(65)-C(68)	1.505(3)
C(18)-H(182)	0.979	C(66)-C(67)	1.385(3)
C(18)-H(183)	0.942	C(66)-H(661)	0.919
C(21)-C(22)	1.387(2)	C(67)-H(671)	0.929
C(21)-C(26)	1.391(3)	C(68)-H(683)	0.957
C(22)-C(23)	1.388(3)	C(68)-H(682)	0.972
C(22)-H(221)	0.948	C(68)-H(681)	0.954
C(23)-C(24)	1.374(3)	C(71)-C(72)	1.392(3)
C(23)-H(231)	0.926	C(71)-C(76)	1.395(3)
C(24)-C(25)	1.385(3)	C(72)-C(73)	1.389(3)

C(72)-H(721)	0.940	O(1)-P(2)-C(21)	116.14(8)
C(73)-C(74)	1.362(3)	N(3)-P(2)-C(21)	108.34(8)
C(73)-H(731)	0.945	O(11)-P(2)-C(21)	100.53(7)
C(74)-C(75)	1.391(4)	P(2)-N(3)-C(7)	121.69(12)
C(74)-H(741)	0.928	P(2)-N(3)-C(4)	126.6(8)
C(75)-C(76)	1.383(3)	C(7)-N(3)-C(4)	111.1(8)
C(75)-H(751)	0.933	P(2)-N(3)-C(7)	121.69(12)
C(76)-H(761)	0.918	P(2)-N(3)-C(104)	121.08(17)
C(4)-C(5)	1.499(10)	C(7)-N(3)-C(104)	116.35(17)
C(4)-H(41)	0.973	N(3)-C(7)-O(8)	125.35(16)
C(4)-H(42)	0.970	N(3)-C(7)-S(6)	112.6(4)
C(104)-C(105)	1.505(5)	O(8)-C(7)-S(6)	121.3(4)
C(104)-H(1041)	0.964	N(3)-C(7)-O(8)	125.35(16)
C(104)-H(1042)	0.967	N(3)-C(7)-S(106)	109.34(15)
C(5)-S(6)	1.788(10)	O(8)-C(7)-S(106)	125.29(17)
C(5)-H(51)	0.974	P(2)-O(11)-C(12)	122.02(11)
C(5)-H(52)	0.971	O(11)-C(12)-C(13)	116.89(15)
C(105)-S(106)	1.814(4)	O(11)-C(12)-C(17)	121.13(16)
C(105)-H(1051)	0.954	C(13)-C(12)-C(17)	121.93(16)
C(105)-H(1052)	0.981	C(12)-C(13)-C(14)	118.56(16)
C(55)-C(54)	1.502(10)	C(12)-C(13)-H(131)	119.0
C(55)-S(56)	1.794(10)	C(14)-C(13)-H(131)	122.4
C(55)-H(551)	0.971	C(13)-C(14)-C(15)	121.36(16)
C(55)-H(552)	0.964	C(13)-C(14)-H(141)	120.4
C(155)-C(154)	1.502(10)	C(15)-C(14)-H(141)	118.3
C(155)-S(156)	1.807(9)	C(14)-C(15)-C(16)	118.11(16)
C(155)-H(1551)	0.967	C(14)-C(15)-C(18)	120.53(17)
C(155)-H(1552)	0.965	C(16)-C(15)-C(18)	121.35(17)
C(54)-H(541)	0.979	C(15)-C(16)-C(17)	121.46(17)
C(54)-H(542)	0.966	C(15)-C(16)-H(161)	118.7
C(154)-H(1541)	0.961	C(17)-C(16)-H(161)	119.9
C(154)-H(1542)	0.965	C(16)-C(17)-C(12)	118.56(16)
		C(16)-C(17)-H(171)	121.1
O(1)-P(2)-N(3)	108.46(7)	C(12)-C(17)-H(171)	120.4
O(1)-P(2)-O(11)	115.79(7)	C(15)-C(18)-H(181)	111.0
N(3)-P(2)-O(11)	106.95(7)	C(15)-C(18)-H(182)	109.7

H(181)-C(18)-H(182)	107.3	O(58)-C(57)-S(56)	122.7(4)
C(15)-C(18)-H(183)	112.0	N(53)-C(57)-O(58)	125.86(18)
H(181)-C(18)-H(183)	109.3	N(53)-C(57)-S(156)	109.8(3)
H(182)-C(18)-H(183)	107.4	O(58)-C(57)-S(156)	124.3(3)
P(2)-C(21)-C(22)	120.82(14)	P(52)-O(61)-C(62)	120.97(12)
P(2)-C(21)-C(26)	119.64(13)	O(61)-C(62)-C(63)	121.56(19)
C(22)-C(21)-C(26)	119.34(16)	O(61)-C(62)-C(67)	116.92(18)
C(21)-C(22)-C(23)	119.79(18)	C(63)-C(62)-C(67)	121.5(2)
C(21)-C(22)-H(221)	119.4	C(62)-C(63)-C(64)	118.4(2)
C(23)-C(22)-H(221)	120.8	C(62)-C(63)-H(631)	121.4
C(22)-C(23)-C(24)	120.63(18)	C(64)-C(63)-H(631)	120.2
C(22)-C(23)-H(231)	118.3	C(63)-C(64)-C(65)	121.6(2)
C(24)-C(23)-H(231)	121.1	C(63)-C(64)-H(641)	118.9
C(23)-C(24)-C(25)	119.74(18)	C(65)-C(64)-H(641)	119.5
C(23)-C(24)-H(241)	119.7	C(64)-C(65)-C(66)	118.3(2)
C(25)-C(24)-H(241)	120.6	C(64)-C(65)-C(68)	121.6(2)
C(24)-C(25)-C(26)	120.1(2)	C(66)-C(65)-C(68)	120.1(2)
C(24)-C(25)-H(251)	121.1	C(65)-C(66)-C(67)	121.3(2)
C(26)-C(25)-H(251)	118.8	C(65)-C(66)-H(661)	118.8
C(21)-C(26)-C(25)	120.41(18)	C(67)-C(66)-H(661)	119.9
C(21)-C(26)-H(261)	119.4	C(66)-C(67)-C(62)	118.9(2)
C(25)-C(26)-H(261)	120.2	C(66)-C(67)-H(671)	119.6
O(51)-P(52)-N(53)	109.32(9)	C(62)-C(67)-H(671)	121.5
O(51)-P(52)-O(61)	116.81(9)	C(65)-C(68)-H(683)	110.7
N(53)-P(52)-O(61)	99.83(8)	C(65)-C(68)-H(682)	112.2
O(51)-P(52)-C(71)	113.26(10)	H(683)-C(68)-H(682)	106.5
N(53)-P(52)-C(71)	111.12(9)	C(65)-C(68)-H(681)	110.7
O(61)-P(52)-C(71)	105.70(8)	H(683)-C(68)-H(681)	110.0
P(52)-N(53)-C(57)	124.38(13)	H(682)-C(68)-H(681)	106.5
P(52)-N(53)-C(54)	119.4(5)	P(52)-C(71)-C(72)	122.96(15)
C(57)-N(53)-C(54)	116.1(5)	P(52)-C(71)-C(76)	117.51(16)
P(52)-N(53)-C(57)	124.38(13)	C(72)-C(71)-C(76)	119.46(18)
P(52)-N(53)-C(154)	120.2(3)	C(71)-C(72)-C(73)	119.63(18)
C(57)-N(53)-C(154)	115.2(3)	C(71)-C(72)-H(721)	120.6
N(53)-C(57)-O(58)	125.86(18)	C(73)-C(72)-H(721)	119.7
N(53)-C(57)-S(56)	111.4(4)	C(72)-C(73)-C(74)	120.7(2)

C(72)-C(73)-H(731)	119.0	C(104)-C(105)-H(1052)	109.5
C(74)-C(73)-H(731)	120.2	S(106)-C(105)-H(1052)	108.1
C(73)-C(74)-C(75)	120.3(2)	H(1051)-C(105)-H(1052)	108.9
C(73)-C(74)-H(741)	120.3	C(5)-S(6)-C(7)	92.1(11)
C(75)-C(74)-H(741)	119.5	C(105)-S(106)-C(7)	92.5(2)
C(74)-C(75)-C(76)	119.82(19)	C(54)-C(55)-S(56)	109.0(9)
C(74)-C(75)-H(751)	120.2	C(54)-C(55)-H(551)	109.7
C(76)-C(75)-H(751)	119.9	S(56)-C(55)-H(551)	108.5
C(71)-C(76)-C(75)	120.1(2)	C(54)-C(55)-H(552)	111.4
C(71)-C(76)-H(761)	119.2	S(56)-C(55)-H(552)	108.5
C(75)-C(76)-H(761)	120.7	H(551)-C(55)-H(552)	109.6
N(3)-C(4)-C(5)	111.8(17)	C(154)-C(155)-S(156)	104.6(5)
N(3)-C(4)-H(41)	108.4	C(154)-C(155)-H(1551)	111.7
C(5)-C(4)-H(41)	109.9	S(156)-C(155)-H(1551)	109.6
N(3)-C(4)-H(42)	108.7	C(154)-C(155)-H(1552)	111.0
C(5)-C(4)-H(42)	108.7	S(156)-C(155)-H(1552)	110.5
H(41)-C(4)-H(42)	109.4	H(1551)-C(155)-H(1552)	109.4
N(3)-C(104)-C(105)	106.1(3)	C(55)-C(54)-N(53)	105.8(8)
N(3)-C(104)-H(1041)	109.2	C(55)-C(54)-H(541)	109.5
C(105)-C(104)-H(1041)	112.1	N(53)-C(54)-H(541)	107.9
N(3)-C(104)-H(1042)	108.2	C(55)-C(54)-H(542)	113.5
C(105)-C(104)-H(1042)	110.6	N(53)-C(54)-H(542)	111.5
H(1041)-C(104)-H(1042)	110.5	H(541)-C(54)-H(542)	108.5
C(4)-C(5)-S(6)	105.3(14)	C(155)-C(154)-N(53)	109.6(7)
C(4)-C(5)-H(51)	111.1	C(155)-C(154)-H(1541)	108.1
S(6)-C(5)-H(51)	110.3	N(53)-C(154)-H(1541)	109.0
C(4)-C(5)-H(52)	109.9	C(155)-C(154)-H(1542)	111.0
S(6)-C(5)-H(52)	110.9	N(53)-C(154)-H(1542)	110.9
H(51)-C(5)-H(52)	109.4	H(1541)-C(154)-H(1542)	108.3
C(104)-C(105)-S(106)	106.5(4)	C(55)-S(56)-C(57)	90.3(5)
C(104)-C(105)-H(1051)	114.1	C(155)-S(156)-C(57)	94.0(4)
S(106)-C(105)-H(1051)	109.6		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 7420. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + .. + 2 hr k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	24(1)	25(1)	35(1)	1(1)	-5(1)	1(1)
P(2)	19(1)	17(1)	25(1)	1(1)	1(1)	1(1)
N(3)	24(1)	24(1)	22(1)	4(1)	1(1)	1(1)
C(7)	21(1)	29(1)	34(1)	2(1)	2(1)	-1(1)
O(8)	28(1)	47(1)	32(1)	10(1)	-5(1)	-1(1)
O(11)	28(1)	17(1)	30(1)	1(1)	8(1)	1(1)
C(12)	23(1)	18(1)	27(1)	0(1)	8(1)	-1(1)
C(13)	24(1)	23(1)	28(1)	3(1)	0(1)	3(1)
C(14)	23(1)	25(1)	29(1)	-2(1)	2(1)	-3(1)
C(15)	22(1)	20(1)	30(1)	0(1)	9(1)	-1(1)
C(16)	20(1)	25(1)	37(1)	-1(1)	2(1)	5(1)
C(17)	18(1)	27(1)	35(1)	-5(1)	0(1)	-2(1)
C(18)	25(1)	23(1)	46(1)	-3(1)	4(1)	0(1)
C(21)	23(1)	18(1)	25(1)	-1(1)	-2(1)	3(1)
C(22)	40(1)	29(1)	27(1)	1(1)	9(1)	8(1)
C(23)	49(1)	31(1)	37(1)	-4(1)	6(1)	17(1)
C(24)	45(1)	20(1)	41(1)	0(1)	-3(1)	9(1)
C(25)	45(1)	25(1)	51(1)	9(1)	13(1)	2(1)
C(26)	34(1)	24(1)	46(1)	2(1)	15(1)	3(1)
O(51)	39(1)	41(1)	50(1)	-8(1)	-11(1)	-1(1)
P(52)	29(1)	25(1)	34(1)	-3(1)	-1(1)	1(1)
N(53)	31(1)	26(1)	38(1)	-1(1)	-4(1)	7(1)
C(57)	34(1)	28(1)	29(1)	-3(1)	7(1)	3(1)
O(58)	44(1)	36(1)	37(1)	-4(1)	-10(1)	3(1)
O(61)	35(1)	26(1)	41(1)	-4(1)	10(1)	0(1)
C(62)	30(1)	27(1)	35(1)	-4(1)	12(1)	-1(1)
C(63)	32(1)	41(1)	48(1)	3(1)	-1(1)	-7(1)
C(64)	35(1)	37(1)	52(1)	-7(1)	2(1)	-14(1)
C(65)	32(1)	30(1)	42(1)	-5(1)	15(1)	-1(1)
C(66)	46(1)	33(1)	39(1)	0(1)	-1(1)	-1(1)
C(67)	48(1)	33(1)	37(1)	-6(1)	-2(1)	-7(1)

C(68)	45(1)	29(1)	67(2)	-2(1)	19(1)	-4(1)
C(71)	36(1)	20(1)	31(1)	1(1)	7(1)	-1(1)
C(72)	39(1)	32(1)	28(1)	-3(1)	5(1)	6(1)
C(73)	37(1)	34(1)	45(1)	2(1)	4(1)	5(1)
C(74)	45(1)	33(1)	49(1)	4(1)	20(1)	4(1)
C(75)	57(1)	37(1)	31(1)	-1(1)	19(1)	-6(1)
C(76)	43(1)	29(1)	28(1)	2(1)	4(1)	-7(1)
C(4)	30(2)	30(2)	29(1)	9(1)	2(1)	-2(1)
C(104)	30(2)	30(2)	29(1)	9(1)	2(1)	-2(1)
C(5)	31(1)	73(3)	45(2)	26(2)	3(1)	-7(2)
C(105)	31(1)	73(3)	45(2)	26(2)	3(1)	-7(2)
S(6)	24(1)	66(1)	50(1)	19(1)	0(1)	-15(1)
S(106)	24(1)	66(1)	50(1)	19(1)	0(1)	-15(1)
C(55)	52(2)	35(2)	45(2)	3(2)	3(1)	15(1)
C(155)	52(2)	35(2)	45(2)	3(2)	3(1)	15(1)
C(54)	45(1)	36(1)	48(1)	1(1)	-8(1)	13(1)
C(154)	45(1)	36(1)	48(1)	1(1)	-8(1)	13(1)
S(56)	49(1)	27(1)	47(3)	-7(1)	3(1)	3(1)
S(156)	49(1)	27(1)	47(3)	-7(1)	3(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for 7420.

	x	y	z	U(eq)
H(131)	8703	6417	10289	31
H(141)	8247	8133	10682	31
H(161)	4601	8127	8765	33
H(171)	4971	6422	8369	33
H(181)	5418	9714	9522	48
H(182)	5731	9463	10667	48
H(183)	7012	9787	10055	48
H(221)	9377	3384	7319	38
H(231)	9753	1666	7598	47
H(241)	8527	807	8775	42
H(251)	6892	1691	9715	48
H(261)	6480	3391	9400	41
H(631)	4870	3427	3232	50
H(641)	4808	1708	3602	51
H(661)	8015	2050	5835	48
H(671)	8153	3758	5491	49
H(683)	7301	270	4889	69
H(682)	6198	442	5680	68
H(681)	5593	249	4572	70
H(721)	9715	4641	4035	39
H(731)	11788	3885	3489	47
H(741)	11807	3440	1818	49
H(751)	9801	3808	657	50
H(761)	7717	4555	1204	41
H(41)	8320	6264	6474	36
H(42)	9226	5277	6245	36
H(1041)	8418	6743	6980	35
H(1042)	8289	5772	6273	35
H(51)	10375	7167	6847	59
H(52)	10990	6374	6096	59

H(1051)	10623	6871	6264	59
H(1052)	10718	5683	6163	60
H(551)	5865	8728	3029	53
H(552)	5348	8105	3944	53
H(1551)	5820	8759	2996	53
H(1552)	7049	8428	2309	53
H(541)	6224	7363	2126	53
H(542)	4947	6907	2706	53
H(1541)	5063	7190	3173	54
H(1542)	5630	7033	2117	53

Table 6. Hydrogen bonds for 7420 [Å and °].

D-H..A	d(D-H)	d(H..A)	d(D..A)	<(DHA)
C(18)-H(181)..O(51)#1	0.96	2.51	3.378(7)	151
C(18)-H(183)..O(8)#2	0.94	2.48	3.324(7)	150
C(55)-H(551)..O(1)#1	0.97	2.53	3.282(7)	135
C(155)-H(551)..O(1)#1	0.92	2.53	3.409(7)	161
C(55)-H(1551)..O(1)#1	1.03	2.47	3.282(7)	135
C(155)-H(1551)..O(1)#1	0.97	2.47	3.409(7)	165

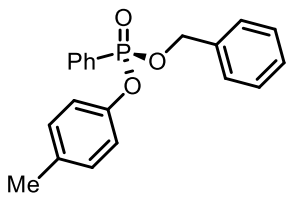
Symmetry transformations used to generate equivalent atoms:#1 -x+1,y+1/2,-z+1 #2 -x+2,y+1/2,-z+2

3.4 Derivatisation

3.4.1 General Procedure IV: Alcohols

As specified in the individual experiment, phosphonate **189** (1 eq) and alcohol (3 eq) were dissolved in THF, DMF, or a THF:DMF mixture, and DBU (3 eq) was added. The reaction mixture was subsequently allowed to stir at room temperature or 0 °C overnight. On reaction completion, solvent was removed *in vacuo* and the crude reaction mixture was loaded directly onto silica and purified by flash column chromatography as specified in the individual experiment to afford the pure derivatised phosphonate.

257: Benzyl *p*-tolyl (*R*)-phenylphosphonate



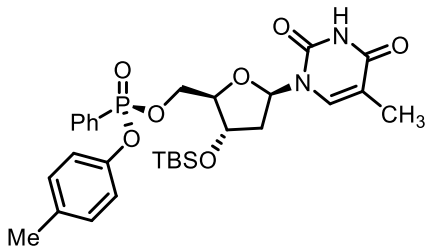
257 was synthesised according to **General Procedure IV**. **189** (17 mg, 0.05 mmol) was used as phosphonate, benzyl alcohol (31 μL, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in THF (0.5 mL) at 0 °C overnight. FCC 99:1 CH_2Cl_2: Acetone. Colourless oil (13.6 mg, 0.041 mmol, 82% yield, 91% ee, 98% es).

HPLC Conditions: CHIRALPAK OD-H, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (minor) = 8.91 min, t (major) = 14.88 min.

$[\alpha]_D^{25}$ = +22.3 [c = 1.06, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.82 (m, 2H, ArH), 7.61 – 7.51 (m, 1H, ArH), 7.51 – 7.40 (m, 2H, ArH), 7.38 – 7.29 (m, 4H, ArH), 7.09 – 6.97 (m, 4H, ArH), 5.27 – 5.12 (m, 2H, Ar$\underline{C}H_2$O), 2.28 (s, 3H, Ar$\underline{C}H_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.09 (d, *J* = 7.0 Hz, Ar$\underline{C}$OP), 134.58 (Ar$\underline{C}CH_2$O), 132.92 (d, *J* = 3.2 Hz, ArC), 132.19 (d, *J* = 10.1 Hz, ArC), 130.23 (ArC), 128.69 (d, *J* = 4.8 Hz, ArC), 128.55 (d, *J* = 3.4 Hz, ArC), 128.09 (ArC), 120.46 (d, *J* = 4.2 Hz, ArC), 68.14 (d, *J* = 5.6 Hz, Ar$\underline{C}H_2$O), 20.84 (Ar$\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 15.93; **IR** (film) υ_{max}/cm^{-1}:

1506, 1262 (P=O), 1204, 1131, 1010, 923, 656; **HRMS** (ESI+): calcd. for $C_{20}H_{21}O_2NP$ 338.1304 $[M+H]^+$, found 338.1301.

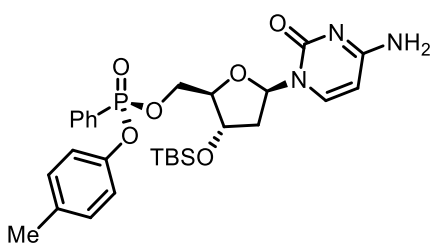
258: ((2*R*,3*S*,5*R*)-3-((tert-butyldimethylsilyl)oxy)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl)methyl *p*-tolyl (*R*)-phenylphosphonate



258 was synthesised according to **General Procedure IV**. **189** (17 mg, 0.05 mmol) was used as phosphonate, 3'-OTBS-5'-OH thymidine (53 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in THF (0.5 mL) at 0 °C overnight. FCC 9:1 CH_2Cl_2:MeOH. Colourless oil (24.4 mg, 0.042 mmol, 83% yield, 97:3 dr).

$[\alpha]_D^{25}$ = +6.7 [c = 0.09, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (s, 1H, NH), 7.93 – 7.82 (m, 2H, ArH), 7.65 – 7.56 (m, 1H, ArH), 7.55 – 7.44 (m, 3H, ArH), 7.12 – 6.97 (m, 4H, ArH), 6.38 (dd, *J* = 9.1, 5.2 Hz, 1H, TBSOCHCH$_2$C<u>H</u>O), 5.19 – 5.10 (m, 1H, TBSOC<u>H</u>CH$_2$CHO), 4.27 – 4.20 (m, 1H, TBSOCHC<u>H$_2$</u>CHO), 3.89 – 3.65 (m, 3H, TBSOCHC<u>H$_2$</u>CHO), 2.48 – 2.38 (m, 1H, POC<u>H$_2$</u>), 2.29 (s, 3H, POArC<u>H$_3$</u>), 2.11 – 1.99 (m, 1H, POC<u>H$_2$</u>), 1.90 (d, *J* = 1.2 Hz, 3H, NCHCC<u>H$_3$</u>), 0.89 (s, 9H, OSi(CH$_3$)$_2$C(C<u>H$_3$</u>)$_3$), 0.08 (d, *J* = 3.5 Hz, 6H, OSi(C<u>H$_3$</u>)$_2$C(C<u>H$_3$</u>)$_3$)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.49 (NH<u>C</u>OCCH$_3$), 150.18 (NH<u>C</u>ON), 147.80 (Ar<u>C</u>OP), 134.97 (ArC), 134.86 (ArC), 133.22 (ArC), 131.95 (d, *J* = 10.4 Hz, ArC), 130.23 (ArC), 128.73 (d, *J* = 15.6 Hz, ArC), 120.35 (d, *J* = 4.3 Hz, ArC), 111.17 (ArC), 86.12 (TBSOCHCH$_2$<u>C</u>HO), 84.55 (TBSOCHCH$_2$CHO<u>C</u>H), 63.14 (PO<u>C</u>H$_2$), 39.50 (TBSOCH<u>C</u>H$_2$CHO), 25.90 (OSi(CH$_3$)$_2$C(<u>C</u>H$_3$)$_3$), 20.69 (OSi(CH$_3$)$_2$<u>C</u>(CH$_3$)$_3$), 18.29 (POAr<u>C</u>H$_3$), 12.45 (NCHC<u>C</u>H$_3$), -5.48 (d, *J* = 6.1 Hz, OSi(<u>C</u>H$_3$)$_2$C(CH$_3$)$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.08, 15.85; **IR** (film) υ_{max}/cm^{-1}: 2981, 2889, 1383, 1251 (P=O), 1152, 1073, 955; **HRMS** (ESI+): calcd. for $C_{29}H_{40}O_7N_2PSi$ 587.2337 $[M+H]^+$, found 587.2337.

259: ((2*R*,3*S*,5*R*)-5-(4-amino-2-oxopyrimidin-1(2*H*)-yl)-3-((tert-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)methyl *p*-tolyl (*R*)-phenylphosphonate

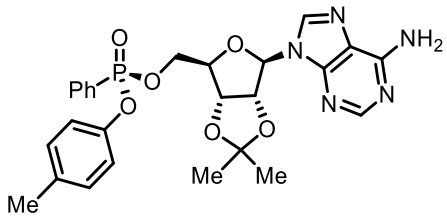


259 was synthesised according to **General Procedure IV**. **189** (17 mg, 0.05 mmol) was used as phosphonate, 3'-OTBS-5'-OH deoxycytidine (51 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in THF (0.5 mL) at room temperature overnight. FCC 9:1 CH_2Cl_2:MeOH. Colourless oil (22.1 mg, 0.039 mmol, 77% yield, 96:4 dr).

$[\alpha]_D^{25}$ = +52.0 [c = 0.1, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.78 (m, 2H, ArH), 7.66 – 7.54 (m, 2H, ArH), 7.54 – 7.44 (m, 2H, ArH), 7.10 – 6.96 (m, 4H, ArH), 6.20 (t, *J* = 6.2 Hz, 1H, TBSOCHCH$_2$C<u>H</u>O), 5.47 (d, *J* = 7.4 Hz, 1H, TBSOCHCH$_2$CHOC<u>H</u>) 4.66 (s, 2H, NH$_2$), 4.41 – 4.20 (m, 2H, TBSOCHC<u>H$_2$</u>CHO), 4.06 – 3.99 (m, 1H, TBSOC<u>H</u>CH$_2$CHO), 2.44 – 2.31 (m, 1H, POC<u>H$_2$</u>),

2.26 (s, 3H, POArC$\underline{H}_3$), 2.00 – 1.89 (m, 1H, POC$\underline{H}_2$), 0.83 (s, 9H, OSi(CH$_3$)$_2$C(C$\underline{H}_3$)$_3$), 0.01 (d, *J* = 6.7 Hz, 6H, OSi(C$\underline{H}_3$)$_2$C(CH$_3$)$_3$).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.69 (N$\underline{C}$NH$_2$), 155.93 (N$\underline{C}$ON), 148.04 (Ar$\underline{C}$OP), 140.82 (N$\underline{C}$HCHCNH$_2$), 135.05 (ArC), 133.43 (d, *J* = 3.1 Hz, ArC), 132.02 (d, *J* = 10.2 Hz, ArC), 130.37 (ArC), 128.96 (d, *J* = 15.6 Hz, ArC), 126.67 (d, *J* = 191.7 Hz, ArC), 120.21 (d, *J* = 4.4 Hz, ArC), 94.37 (NCH$\underline{C}$HCNH$_2$), 86.40 (TBSOCHCH$_2\underline{C}$HO), 85.32 (d, *J* = 7.7 Hz, TBSOCHCH$_2$CHO$\underline{C}$H), 71.23 (TBSO$\underline{C}$HCH$_2$CHO), 65.15 (d, *J* = 5.9 Hz, PO$\underline{C}$H$_2$), 41.77 (TBSOCHCH$_2$CHO), 25.76 (OSi(CH$_3$)$_2$C($\underline{C}$H$_3$)$_3$), 20.78 (POAr$\underline{C}$H$_3$), 17.99 (OSi(CH$_3$)$_2\underline{C}$(CH$_3$)$_3$), -4.76 (d, *J* = 28.5 Hz, OSi($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ -158.58, -158.89; **IR** (film) υ_{max}/cm^{-1}: 2981, 2361, 2342, 1650 (C=O), 1506, 1394, 1254 (P=O), 1203, 1132, 685; **HRMS** (ESI+): calcd. for $C_{28}H_{39}O_6N_3PSi$ 572.2340 [M+H]$^+$, found 572.2330.

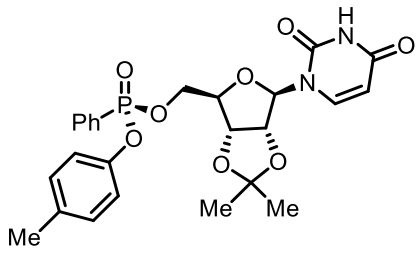
260: ((3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl *p*-tolyl (*R*)-phenylphosphonate



260 was synthesised according to **General Procedure IV**. **189** (17 mg, 0.05 mmol) was used as phosphonate, ((3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dio xol-4-yl)methanol (46 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in THF (0.5 mL) at room temperature overnight. FCC 9:1 CH_2Cl_2:MeOH. Colourless oil (15.1 mg, 0.028 mmol, 56% yield, 96:4 dr).

[α]$_D^{25}$ = 1.0 [c = 0.1, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (s, 1H, N$\underline{C}$HNCNH$_2$), 7.89 (s, 1H, N$\underline{C}$HNCCNH$_2$), 7.81 – 7.70 (m, 2H, ArH), 7.59 – 7.50 (m, 1H, ArH), 7.47 – 7.36 (m, 2H, ArH), 7.03 – 6.89 (m, 4H, ArH), 6.08 (d, *J* = 2.5 Hz, 1H, CHCHCHC$\underline{H}$N), 6.02 (s, 2H, NH$_2$), 5.21 (dd, *J* = 6.3, 2.5 Hz, 1H, CHCHC$\underline{H}$CHN), 5.01 (dd, *J* = 6.3, 2.8 Hz, 1H, CHC$\underline{H}$CHCHN), 4.54 – 4.48 (m, 1H, C$\underline{H}$CHCHCHN), 4.36 – 4.29 (m, 2H, POC$\underline{H}_2$), 2.24 (s, 3H, POArC$\underline{H}_3$), 1.59 (s, 3H, O$_2$C(C$\underline{H}_3$)$_2$), 1.36 (s, 3H, O$_2$C(C$\underline{H}_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.60 ($\underline{C}$NH$_2$), 153.28 (N$\underline{C}$HNCNH$_2$), 149.29 (ArC), 148.01 (Ar$\underline{C}$OP), 139.37 (ArC), 133.30 (ArC), 132.07 (d, *J* = 10.4 Hz, ArC), 130.26 (ArC), 128.75 (d, *J* = 15.7 Hz, ArC), 120.16 (d, *J* = 4.4 Hz, ArC), 119.92 (ArC), 114.66 (ArC), 91.46 (CHCHCH$\underline{C}$HN), 85.56 (d, *J* = 7.7 Hz, $\underline{C}$HCHCHCHN), 84.46 (CHCH$\underline{C}$HCHN), 81.55 (CH$\underline{C}$HCHCHN), 65.91 (d, *J* = 5.6 Hz, PO$\underline{C}$H$_2$), 27.18 (O$_2$C($\underline{C}$H$_3$)$_2$), 20.76 (Ar$\underline{C}$H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.43, 16.27; **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2342, 1652 (C=O), 1382, 1252 (P=O), 1215, 1133, 1072, 942; **HRMS** (ESI+): calcd. for $C_{26}H_{29}O_6N_5P$ 538.1850 [M+H]$^+$, found 538.1838

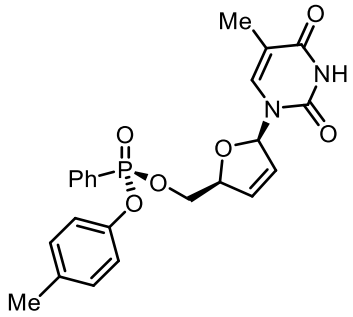
261: ((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl *p*-tolyl (*R*)-phenylphosphonate



261 was synthesised according to **General Procedure IV**. **189** (17 mg, 0.05 mmol) was used as phosphonate, 1-((3aR,4R,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)pyrimidine-2,4(1H,3H)-dione (43 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in THF:DMF (9:1, 0.5 mL) at room temperature overnight. FCC 9:1 CH_2Cl_2:MeOH. Colourless oil (13.4 mg, 0.026 mmol, 52% yield, 96:4 dr).

$[\alpha]_D^{25}$ = +11.7 [c = 0.12, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47 (s, 1H, NH), 7.91 – 7.80 (m, 2H, ArH), 7.64 – 7.57 (m, 1H, ArH), 7.54 – 7.45 (m, 2H, ArH), 7.29 (d, *J* = 8.1 Hz, 1H, NHCHCHCO), 7.10 – 6.99 (m, 4H, ArH), 5.81 (d, *J* = 2.9 Hz, 1H, CHCHCHCHN), 5.51 (d, *J* = 8.1 Hz, 1H, NCHCHCO), 4.81 (dd, *J* = 6.5, 2.7 Hz, 1H, CHCHCHCHN), 4.66 (dd, *J* = 6.4, 2.9 Hz, 1H, CHCHCHCHN), 4.44 – 4.35 (m, 3H, CHCHCHCHN, $POCH_2$), 2.28 (s, 3H, $POArCH_3$), 1.56 (s, 3H, $O_2C(CH_3)_2$), 1.33 (d, *J* = 0.9 Hz, 3H, $O_2C(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.73 (NCONHCO), 149.93 (NCONHCO), 140.96 (NCHCHCO), 132.12 (d, *J* = 10.4 Hz, ArC), 130.41 (ArC), 128.95 (d, *J* = 15.6 Hz, ArC), 120.22 (d, *J* = 4.4 Hz, ArC), 114.80 ($O_2C(CH_3)_2$), 102.59 (NCHCHCO), 93.03 (CHCHCHCHN), 85.06 (CHCHCHCHN), 84.62 (CHCHCHCHN), 80.61 (CHCHCHCHN), 65.94 ($POCH_2$), 25.38 ($O_2C(CH_3)_2$), 20.84 ($POArCH_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.31, 16.10; **IR** (film) υ_{max}/cm^{-1}: 2981, 2888, 1383, 1251 (P=O), 1152, 1074, 955; **HRMS** (ESI+): calcd. for $C_{25}H_{28}O_8N_2P$ 515.1278 $[M+H]^+$, found 515.1573.

262: ((2*S*,5*R*)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methyl *p*-tolyl (*R*)-phenylphosphonate

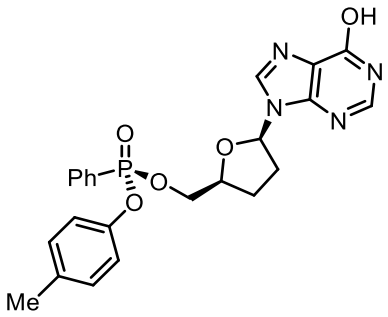


262 was synthesised according to **General Procedure IV**. **189** (17 mg, 0.05 mmol) was used as phosphonate, sanilvudine (34 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in THF (0.75 mL) at room temperature overnight. FCC 95:5 CH_2Cl_2:MeOH. Colourless oil (16.6 mg, 0.038 mmol, 76% yield, 96:4 dr).

$[\alpha]_D^{25}$ = +30.0 [c = 0.11, $CHCl_3$]; **^{1}H NMR** (400 MHz, MeOD) δ 7.92 – 7.80 (m, 2H, ArH), 7.74 – 7.63 (m, 1H, ArH), 7.63 – 7.50 (m, 2H, ArH), 7.37 – 7.32 (m, 1H, NCHCCH$_3$), 7.15 – 6.99 (m, 4H, ArH), 7.00 – 6.94 (m, 1H, NH), 6.45 (dt, *J* = 6.1, 1.8 Hz, 1H, CHCHCHCHN), 6.06 – 5.97 (m, 1H, CHCHCHCHN), 5.12 – 5.04 (m, 1H, CHCHCHCHN), 4.45 – 4.29 (m, 2H, $POCH_2$), 2.30 (s, 3H, $POArCH_3$), 1.57 (d, *J* = 1.2 Hz, 3H, NCHCCH$_3$); **^{13}C NMR** (151 MHz, MeOD) δ 166.27 (C(CH$_3$)CONH), 152.79 (NCONHCO), 148.98

(d, *J* = 7.6 Hz, ArCOP), 137.81 (ArC), 136.58 (d, *J* = 1.4 Hz, ArC), 134.79 (d, *J* = 3.2 Hz, ArC), 134.50 (ArC), 133.03 (d, *J* = 10.3 Hz, ArC), 131.20 (ArC), 130.13 (d, *J* = 15.4 Hz, ArC), 128.36 (ArC), 127.29 (d, *J* = 190.4 Hz, ArC), 121.54 (d, *J* = 4.2 Hz, ArC), 111.77 (ArC), 91.18 (CHCHCHCHN), 86.18 (d, *J* = 8.2 Hz, CHCHCHCHN), 68.29 (d, *J* = 5.6 Hz, POCH$_2$), 20.70 (POArCH$_3$), 12.26 (NCHCCH$_3$); **^{31}P NMR** (162 MHz, MeOD) δ 16.56, 16.35; **IR** (film) υ_{max}/cm^{-1}: 2981, 2888, 1383, 1252 (P=O), 1072, 956; **HRMS** (ESI+): calcd. for $C_{23}H_{24}O_6N_2P$ 455.1366 [M+H]$^+$, found 455.1365.

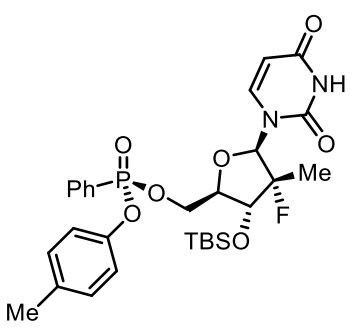
263: ((2*S*,5*R*)-5-(6-hydroxy-9*H*-purin-9-yl)tetrahydrofuran-2-yl)methyl *p*-tolyl (*R*)-phenylphosphonate



263 was synthesised according to **General Procedure IV**. **189** (17 mg, 0.05 mmol) was used as phosphonate, didanosine (35.4 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in DMF (0.75 mL) at room temperature overnight. FCC 95:5 CH_2Cl_2:MeOH. Colourless oil (16.0 mg, 0.036 mmol, 71% yield, 96:4 dr).

[α]$_D^{25}$ = +49.2 [c = 0.12, $CHCl_3$]; **^{1}H NMR** (400 MHz, MeOD) δ 8.17 (s, 1H, NCHNC(OH)), 8.00 (s, 1H, NCHNCC(OH)), 7.84 – 7.71 (m, 2H, ArH), 7.69 – 7.60 (m, 1H, ArH), 7.55 – 7.45 (m, 2H, ArH), 7.12 – 6.93 (m, 4H, ArH), 6.34 – 6.25 (m, 1H, CHCH$_2$CH$_2$CHN), 4.51 – 4.42 (m, 1H, CHCH$_2$CH$_2$CHN), 4.42 – 4.29 (m, 2H, POCH$_2$), 2.65 – 2.53 (m, 2H, CHCH$_2$CH$_2$CHN), 2.33 – 2.15 (m, 5H, CHCH$_2$CH$_2$CHN, ArCH$_3$).**^{13}C NMR** (151 MHz, MeOD) δ 158.91 (C(OH)), 149.48 (ArC), 149.31 (d, *J* = 7.6 Hz, ArCOP), 146.48 (NCHNC(OH)), 140.22 (ArC), 136.28 (d, *J* = 1.5 Hz, ArC), 134.56 (d, *J* = 3.2 Hz, ArC), 133.03 (ArC), 131.18 (ArC), 129.90 (d, *J* = 15.7 Hz, ArC), 127.46 (d, *J* = 192.3 Hz, ArC), 125.90 (ArC), 121.29 (d, *J* = 4.4 Hz, ArC), 87.29 (CHCH$_2$CH$_2$CHN), 81.20 (d, *J* = 7.6 Hz, CHCH$_2$CH$_2$CHN), 68.69 (d, *J* = 5.9 Hz, POCH$_2$), 32.77 (CHCH$_2$CH$_2$CHN), 26.77 (CHCH$_2$CH$_2$CHN), 20.67 (NCHNC(OH)); **^{31}P NMR** (162 MHz, MeOD) δ 16.73, 16.49; **IR** (film) υ_{max}/cm^{-1}: 2981, 2888, 1383, 1252 (P=O), 1152, 1073, 955; **HRMS** (ESI+): calcd. for $C_{23}H_{24}O_5N_4P$ 467.1479 [M+H]$^+$, found 467.1478.

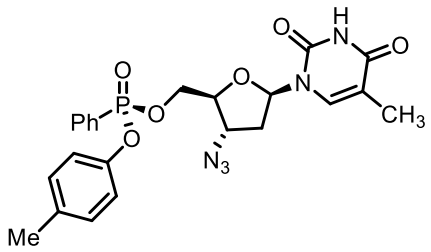
264: ((2*R*,3*R*,4*R*,5*R*)-3-((tert-butyldimethylsilyl)oxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-4-methyltetrahydrofuran-2-yl)methyl *p*-tolyl (*R*)-phenylphosphonate



264 was synthesised according to **General Procedure IV**. **189** (17 mg, 0.05 mmol) was used as phosphonate, 1-((2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-3-fluoro-5-(hydroxymethyl)-3-methyl tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (56 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in THF:DMF (9:1, 1.0 mL) at room temperature overnight. FCC 99:1 CH_2Cl_2:MeOH. Colourless oil (12.2 mg, 0.020 mmol, 40% yield, 96:4 dr).

[α]$_D^{25}$ = +71.4 [c = 0.14, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (s, 1H, NH), 7.92 – 7.82 (m, 2H, ArH), 7.70 – 7.59 (m, 1H, ArH), 7.58 – 7.51 (m, 2H, ArH), 7.46 (d, *J* = 8.2 Hz, 1H, NCHCHCO), 7.04 (q, *J* = 8.7 Hz, 4H, ArH), 6.23 – 6.10 (m, 1H, TBSOCHC(FCH_3)CHN), 5.18 (d, *J* = 8.2 Hz, 1H, NCHCHCO), 4.72 – 4.61 (m, 1H, POCH_2), 4.38 – 4.27 (m, 1H, POCH_2), 4.15 (d, *J* = 9.0 Hz, 1H, TBSOCHC(FCH_3)CHN), 4.01 – 3.89 (m, 1H, CHCH(OTBS)C(FCH_3)CHN), 2.28 (s, 3H, ArCH_3), 0.92 (s, 9H, OSi(CH_3)$_2$C(CH_3)$_3$), 0.15 (d, *J* = 10.2 Hz, 6H, OSi(CH_3)$_2$C(CH_3)$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.25 (NCHCHCO), 149.99 (NCONHCO), 147.95 (ArCOP), 138.76 (ArC), 136.15 (ArC), 134.93 (ArC), 133.60 (ArC), 132.05 (d, *J* = 10.1 Hz, ArC), 130.30 (ArC), 129.03 (d, *J* = 15.5 Hz, ArC), 119.92 (d, *J* = 4.4 Hz, ArC), 100.23 (NCHCHCO), 89.44 (CHCH(OTBS)CH(FCH_3)CH), 62.61 (POCH_2), 25.60 (, OSi(CH_3)$_2$C(CH_3)$_3$), 20.67 (ArCH_3), 17.97 (, OSi(CH_3)$_2$C(CH_3)$_3$), 16.90 (CH(OTBS)C(FCH_3)CH), -4.34 (d, *J* = 23.9 Hz, , OSi(CH_3)$_2$C(CH_3)$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.09, 15.93; **IR** (film) υ_{max}/cm^{-1}: 2981, 2888, 1383, 1251 (P=O), 1152, 1073, 956; **HRMS** (ESI+): calcd. for $C_{29}H_{39}O_7N_2FPSi$ 605.2243 $[M+H]^+$, found 605.2239.

265: ((2*S*,3*S*,5*R*)-3-azido-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl)methyl *p*-tolyl (*R*)-phenylphosphonate



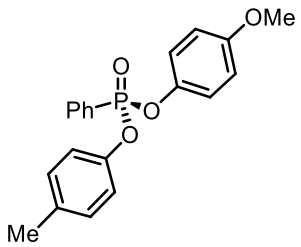
265 was synthesised according to **General Procedure IV**. **189** (17 mg, 0.05 mmol) was used as phosphonate, AZT (40 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in THF (0.5 mL) at 0 °C overnight. FCC 99:1 CH_2Cl_2:MeOH. Colourless oil (19.3 mg, 0.039 mmol, 78% yield, 96:4 dr).

[α]$_D^{25}$ = +119.0 [c = 0.1, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.80 (s, 1H, NH), 7.92 – 7.81 (m, 2H, ArH), 7.67 – 7.57 (m, 1H, ArH), 7.56 – 7.46 (m, 2H, ArH), 7.36 (q, *J* = 1.2 Hz, 1H, ArH), 7.11 – 6.97 (m, 4H, ArH), 6.22 (t, *J* = 6.6 Hz, 1H, N_3CHCH$_2$CHO), 4.45 – 4.36 (m, 2H, N_3CHCH_2CHO), 4.36 – 4.30 (m, 1H, N_3CHCH$_2$CHOCH), 4.11 – 4.03 (m, 1H, N_3CHCH$_2$CHO), 2.47 – 2.36 (m, 1H, POCH_2), 2.27 (s, 3H, POArCH_3), 2.24 – 2.14 (m, 1H, POCH_2), 1.76 (d, *J* = 1.2 Hz, 3H, NCHCCH_3CO). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.58 (NHCOCCH$_3$), 150.25 (NHCONCH), 148.04 (ArCOP), 135.20 (d, *J* = 8.3 Hz, ArC), 133.65 (ArC), 132.09 (d, *J* = 10.4 Hz, ArC), 130.43 (ArC), 129.07 (d, *J* = 15.6 Hz, ArC), 126.47 (d, *J* = 190.1 Hz, ArC), 120.19 (d, *J* = 4.4 Hz, ArC), 111.56 (ArC), 84.87 (N_3CHCH$_2$CHO), 82.58 (d, *J* = 7.0 Hz, N_3CHCH$_2$CHOCH), 65.40 (POCH_2), 60.58 (N_3CHCH$_2$CHO), 37.70 (N_3CHCH$_2$CHO), 20.81 (POArCH_3), 12.47 (NCHCCH_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.70, 16.63; **IR** (film) υ_{max}/cm^{-1}: 2981, 2889, 1383, 1251 (P=O), 1152, 1073, 355; **HRMS** (ESI+): calcd. for $C_{23}H_{25}O_5N_5P$ 498.1537 $[M+H]^+$, found 498.1531.

3.4.2 General Procedure V: Phenols

Phosphonate **189** (1 eq) and phenol (3 eq) were dissolved in Et_2O and DBU (3 eq) was added. The reaction mixture was subsequently allowed to stir at room temperature or 0 °C overnight. On reaction completion, the crude reaction mixture was loaded directly onto silica and purified by flash column chromatography as specified in the individual experiment to afford the pure derivatised phosphonate.

266: 4-methoxyphenyl *p*-tolyl (*S*)-phenylphosphonate

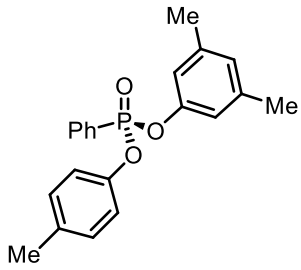


266 was synthesised according to **General Procedure V**. **189** (17 mg, 0.05 mmol) was used as phosphonate, 4-methoxyphenol (18.6 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in Et_2O (0.5 mL) at 0 °C overnight. FCC 95:5 CH_2Cl_2: Acetone. Colourless oil (13 mg, 0.036 mmol, 73% yield, 92% ee, 98% es).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 70/30, 1 mL/min, λ = 220 nm, t (minor) = 12.41 min, t (major) = 22.77 min.

$[\alpha]_D^{25}$ = -1.0 [c = 0.2, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.89 (m, 2H, ArH), 7.64 – 7.54 (m, 1H, ArH), 7.54 – 7.44 (m, 2H, ArH), 7.14 – 6.99 (m, 6H, ArH), 6.83 – 6.75 (m, 2H, ArH), 3.75 (s, 3H, ArOC$\underline{H}_3$), 2.29 (d, *J* = 0.8 Hz, 3H, ArC$\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.88 (Ar$\underline{C}$OCH$_3$), 144.03 (Ar$\underline{C}$OP), 134.78 (Ar$\underline{C}$OP), 133.20 (d, *J* = 3.2 Hz, ArC), 132.45 (d, *J* = 10.1 Hz, ArC), 130.28 (ArC), 128.71 (d, *J* = 15.6 Hz, ArC), 127.21 (d, *J* = 192.0 Hz, Ar$\underline{C}$P), 121.67 (d, *J* = 4.2 Hz, ArC), 120.46 (d, *J* = 4.5 Hz, ArC), 114.79 (ArC), 55.73 (ArO$\underline{C}$H$_3$), 20.85 (Ar$\underline{C}$H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.08; **IR** (film) υ_{max}/cm^{-1}: 2981, 1383, 1252 (P=O), 1152, 1073, 956; **HRMS** (ESI+): calcd. for $C_{20}H_{20}O_4P$ 355.1094 $[M+H]^+$, found 355.1092.

267: 3,5-dimethylphenyl *p*-tolyl (*S*)-phenylphosphonate



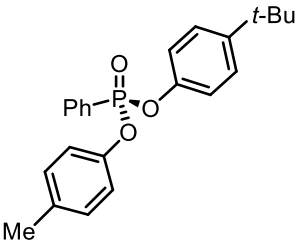
267 was synthesised according to **General Procedure V**. **189** (17 mg, 0.05 mmol) was used as phosphonate, 3,5-dimethylphenol (16.8 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in Et_2O (0.5 mL) at room temperature overnight. FCC 95:5 CH_2Cl_2: Acetone. Colourless oil (10 mg, 0.028 mmol, 57% yield, 89% ee, 95% es).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 23.60 min, t (major) = 24.30 min.

$[\alpha]_D^{25}$ = +3.3 [c = 0.15, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.90 (m, 2H, ArH), 7.64 – 7.56 (m, 1H, ArH), 7.55 – 7.44 (m, 2H, ArH), 7.11 – 7.02 (m, 4H, ArH), 6.83 – 6.74 (m, 3H, ArH), 2.29 (s, 3H, Ar$\underline{C}$H$_3$), 2.25 (s, 6H, Ar(C$\underline{H}_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.39 (d, *J* = 7.1 Hz, Ar$\underline{C}$O), 148.37 (d, *J* = 7.6 Hz, Ar$\underline{C}$O), 139.64 (ArC), 134.75 (ArC), 133.15 (d, *J* = 3.2 Hz, ArC), 132.42 (d, *J* = 10.3 Hz, ArC), 130.25 (ArC), 128.68 (d, *J* = 15.8 Hz, ArC), 127.40 (d, *J* = 192.7 Hz, ArC), 126.89 (ArC), 120.53 (d, *J* = 4.4 Hz, ArC), 118.28 (d, *J* = 4.6 Hz, ArC), 21.35 (Ar(C$\underline{H}_3$)$_2$), 20.85 (Ar$\underline{C}$H$_3$); **^{31}P NMR**

(162 MHz, $CDCl_3$) δ 11.53; **IR** (film) υ_{max}/cm^{-1}: 2981, 1383, 1251 (P=O), 1153, 1073, 955; **HRMS** (ESI+): calcd. for $C_{21}H_{22}O_3P$ 353.1301 $[M+H]^+$, found 353.1298.

268: 4-(tert-butyl)phenyl *p*-tolyl (*S*)-phenylphosphonate

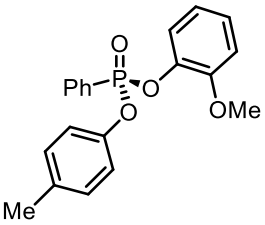


268 was synthesised according to **General Procedure V**. **189** (17 mg, 0.05 mmol) was used as phosphonate, 4-tert-butylphenol (22.6 mg, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in Et_2O (0.5 mL) at room temperature overnight. FCC 95:5 CH_2Cl_2: Acetone. Colourless oil (14.0 mg, 0.036 mmol, 74% yield, 87% ee, 93% es).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 6.81 min, t (major) = 8.22 min.

$[\alpha]_D^{25}$ = -8.3 [c = 0.06, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.91 (m, 2H, ArH), 7.64 – 7.55 (m, 1H, ArH), 7.55 – 7.44 (m, 2H, ArH), 7.31 – 7.27 (m, 2H, ArH), 7.12 – 7.05 (m, 6H, ArH), 2.29 (s, 3H, $ArC\underline{H}_3$), 1.27 (s, 9H, $ArC(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.53 – 147.68 (m, $Ar\underline{C}OP$), 134.76 (ArC), 133.17 (d, *J* = 3.3 Hz, ArC), 132.44 (d, *J* = 10.3 Hz, ArC), 130.27 (ArC), 128.71 (d, *J* = 15.8 Hz, ArC), 127.40 (d, *J* = 192.5 Hz, $Ar\underline{C}P$), 126.68 (ArC), 120.51 (d, *J* = 4.5 Hz, ArC), 120.09 (d, *J* = 4.4 Hz, ArC), 34.50 ($Ar\underline{C}(CH_3)_3$), 31.52 ($ArC(\underline{C}H_3)_3$), 20.86 ($Ar\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 11.80; **IR** (film) υ_{max}/cm^{-1}: 2981, 1383, 1252 (P=O), 1152, 1073, 955; **HRMS** (ESI+): calcd. for $C_{23}H_{26}O_3P$ 381.1614 $[M+H]^+$, found 381.1610.

269: 2-methoxyphenyl *p*-tolyl (*S*)-phenylphosphonate

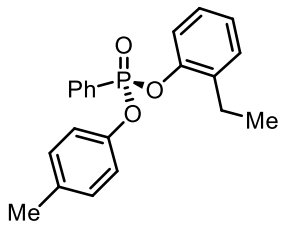


269 was synthesised according to **General Procedure V**. **189** (17 mg, 0.05 mmol) was used as phosphonate, 2-methoxyphenol (16.4 μL, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in Et_2O (0.5 mL) at room temperature overnight. FCC 95:5 CH_2Cl_2: Acetone. Colourless oil (14.8 mg, 0.040 mmol, 79% yield, 79% ee, 84% es).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 mL/min, λ = 220 nm, t (minor) = 16.84 min, t (major) = 12.67 min.

$[\alpha]_D^{25}$ = +5.0 [c = 0.3, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 2H, ArH), 7.63 – 7.53 (m, 1H, ArH), 7.53 – 7.43 (m, 2H, ArH), 7.20 (dt, *J* = 8.0, 1.6 Hz, 1H, ArH), 7.15 – 7.04 (m, 5H, ArH), 6.90 – 6.80 (m, 3H, ArH), 3.69 (s, 3H, $ArOC\underline{H}_3$), 2.29 (d, *J* = 0.9 Hz, 3H, $ArC\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.93 ($Ar\underline{C}O$), 148.38 ($Ar\underline{C}O$), 139.90 ($Ar\underline{C}O$), 134.65 (ArC), 132.97 (d, *J* = 3.3 Hz, ArC), 132.45 (d, *J* = 10.5 Hz, ArC), 130.18 (ArC), 128.44 (d, *J* = 15.9 Hz, ArC), 125.92 (d, *J* = 1.7 Hz, ArC), 122.09 (d, *J* = 3.2 Hz, ArC), 121.59 (ArC), 120.93 (d, *J* = 1.7 Hz, ArC), 120.61 (d, *J* = 4.4 Hz, ArC), 120.25 (ArC), 114.68 (ArC), 112.91 (ArC), 110.88 (ArC), 55.85 ($Ar\underline{C}OCH_3$), 20.86 ($Ar\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.17; **IR** (film) υ_{max}/cm^{-1}: 2981, 1382, 1251 (P=O), 1152, 1073, 1073, 956; **HRMS** (ESI+): calcd. for $C_{20}H_{20}O_4P$ 355.1094 $[M+H]^+$, found 355.1095.

270: 2-ethylphenyl *p*-tolyl (*S*)-phenylphosphonate



270 was synthesised according to **General Procedure V**. **189** (17 mg, 0.05 mmol) was used as phosphonate, 2-ethylphenol (17.8 μL, 0.15 mmol) as alcohol, DBU (22 μL, 0.15 mmol) as base in Et_2O (0.5 mL) at room temperature overnight. FCC 95:5 CH_2Cl_2: Acetone. Colourless oil (13.4 mg, 0.042 mmol, 76% yield, 83% ee, 88% es).

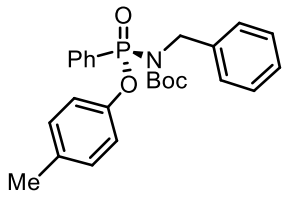
HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (minor) = 13.51 min, t (major) = 17.21 min.

$[\alpha]_D^{25}$ = +13.3 [c = 0.09, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 7.92 (m, 2H, ArH), 7.65 – 7.57 (m, 1H, ArH), 7.54 – 7.46 (m, 2H, ArH), 7.32 – 7.27 (m, 1H, ArH), 7.22 – 7.17 (m, 1H, ArH), 7.15 – 7.00 (m, 6H, ArH), 2.62 (q, *J* = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 2.28 (s, 3H, $ArC\underline{H}_3$), 1.14 (t, *J* = 7.5 Hz, 3H, $CH_2C\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.89 (d, *J* = 7.7 Hz, Ar<u>C</u>O), 148.37 (*J* = 7.1 Hz, Ar<u>C</u>O), 135.37 (ArC), 134.82 (ArC), 133.23 (ArC), 132.31 (d, *J* = 10.3 Hz, ArC), 130.26 (ArC), 129.82 (ArC), 128.77 (d, *J* = 15.7 Hz, ArC), 127.08 (ArC), 125.23 (ArC), 120.55 (d, *J* = 4.4 Hz, ArC), 120.44 (d, *J* = 2.8 Hz, ArC), 23.39 ($Ar\underline{C}H_2CH_3$), 20.85 ($ArCH_2\underline{C}H_3$), 14.27 ($Ar\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 11.37; **IR** (film) υ_{max}/cm^{-1}: 2981, 1382, 1251 (P=O), 1152, 1073, 956; **HRMS** (ESI+): calcd. for $C_{21}H_{22}O_3P$ 353.1301 $[M+H]^+$, found 353.1301.

3.4.3 General Procedure V: Amines

Under a nitrogen atmosphere, amine (1.5 eq) was dissolved in THF and cooled to 78 °C. *n*-BuLi (1.5 eq) was added and the mixture allowed to stir for 20 mins before addition to a 78 °C solution of **189** (1 eq) dissolved in THF. The reaction mixture was allowed to stir at 78 °C for 30 mins, then slowly warmed to 40 °C and stirred at 40 °C overnight. On reaction completion, the crude mixture was loaded directly onto silica and purified by flash column chromatography as specified in the individual experiment to afford the pure derivatised phosphinate. Unless otherwise stated, all amines were distilled prior to use.

274: *tert*-butyl (*R*)-benzyl(phenyl(*p*-tolyloxy)phosphoryl)carbamate



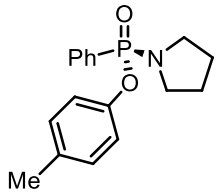
274 was synthesised according to **General Procedure V**. **189** (8.5 mg, 0.025 mmol) was used as phosphonate, tert-butyl benzylcarbamate (7.8 mg, 0.38 mmol) as amine, *n*-BuLi (2.4 M in hexanes, 15.7 μL, 0.038 mmol) as base in THF (0.5 mL). FCC 7:3 pentane:EtOAc. Colourless oil (4.9 mg, 0.011 mmol, 45% yield, 88% ee, 94% es).

HPLC Conditions: CHIRALPAK OD, hexane/isopropanol = gradient 98/2 to 70/30, 1 mL/min, λ = 220 nm, t (minor) = 13.99 min, t (major) = 11.83 min.

$[\alpha]_D^{25}$ = -54.0 [c = 0.05, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.68 (m, 2H, ArH), 7.56 – 7.47 (m, 1H, ArH), 7.45 – 7.37 (m, 2H, ArH), 7.36 – 7.31 (m, 2H, ArH), 7.25 – 7.20 (m, 3H, ArH), 7.05 (s,

4H, ArH), 4.92 – 4.75 (m, 2H, ArC$\underline{H}_2$N), 2.31 (d, *J* = 1.0 Hz, 3H, ArC$\underline{H}_3$), 1.20 (s, 9H, NC(C$\underline{H}_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.78 (ArC), 132.24 (ArC), 131.46 (d, *J* = 10.6 Hz, ArC), 130.27 (ArC), 128.87 (ArC), 128.38 – 128.10 (m, ArC), 127.29 (ArC), 120.77 (d, *J* = 4.6 Hz, ArC), 83.11 (N$\underline{C}$(CH$_3$)$_3$), 48.71 (Ar$\underline{C}$H$_2$N), 27.96 (NC($\underline{C}$H$_3$)$_3$), 20.90 (Ar$\underline{C}$H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.28; **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2342, 1382, 1251 (P=O), 1155, 1072, 954; **HRMS** (ESI+): calcd. for $C_{25}H_{28}O_4NNaP$ 460.1648 $[M+Na]^+$, found 460.1646.

275: *p*-tolyl (*R*)-phenyl(pyrrolidin-1-yl)phosphinate

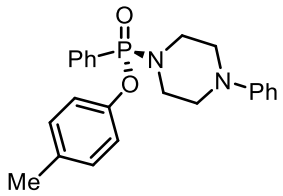


275 was synthesised according to **General Procedure V**. **189** (17 mg, 0.05 mmol) was used as phosphonate, pyrrolidine (6.3 μL, 0.075 mmol) as amine, *n*-BuLi (2.4 M in hexanes, 31 μL, 0.075 mmol) as base in THF (0.5 mL). FCC 6:4 pentane:EtOAc. Colourless oil (10.5 mg, 0.035 mmol, 70% yield, 92% ee, 98% es).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 16.02 min, t (major) = 13.75 min.

$[\alpha]_D^{25}$ = -33.6 [c = 0.14, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 2H, ArH), 7.56 – 7.41 (m, 3H, ArH), 7.21 – 7.04 (m, 4H, ArH), 3.31 – 3.12 (m, 4H, N(C$\underline{H}_2$)$_2$(CH$_2$)$_2$), 2.30 (s, 3H, ArC$\underline{H}_3$), 1.82 – 1.72 (m, 4H, N(CH$_2$)$_2$(C$\underline{H}_2$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.05 (ArC), 133.92 (ArC), 131.91 (d, *J* = 3.1 Hz, ArC), 131.53 (d, *J* = 9.6 Hz, ArC), 130.20 (ArC), 128.56 (d, *J* = 14.4 Hz, ArC), 120.21 (d, *J* = 5.0 Hz, ArC), 46.87 (d, *J* = 4.7 Hz, N($\underline{C}$H$_2$)$_2$(CH$_2$)$_2$), 26.39 (d, *J* = 8.3 Hz, N(CH$_2$)$_2$($\underline{C}$H$_2$)$_2$), 20.86 (Ar$\underline{C}$H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 18.65; **IR** (film) υ_{max}/cm^{-1}: 2981, 2361, 2342, 1382, 1251 (P=O), 1126, 1126, 955; **HRMS** (ESI+): calcd. for $C_{17}H_{21}O_2NP$ 302.1304 $[M+H]^+$, found 302.1302.

276: *p*-tolyl (*R*)-phenyl(4-phenylpiperazin-1-yl)phosphinate



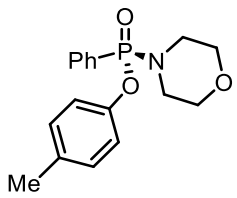
276 was synthesised according to **General Procedure V**. **189** (17 mg, 0.05 mmol) was used as phosphonate, N-phenylpiperazine (7.6 μL, 0.075 mmol) as amine, *n*-BuLi (2.4 M in hexanes, 31 μL, 0.075 mmol) as base in THF (0.5 mL). FCC 9:1 CH_2Cl_2: Acetone. Colourless oil (11.1 mg, 0.028 mmol, 57% yield, 93% ee, 99% es).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 14.52 min, t (major) = 11.08 min.

$[\alpha]_D^{25}$ = -75.8 [c = 0.12, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.84 (m, 2H, ArH), 7.61 – 7.43 (m, 3H, ArH), 7.25 – 7.09 (m, 6H, ArH), 6.90 – 6.82 (m, 3H, ArH), 3.43 – 3.18 (m, 4H, PN(C$\underline{H}_2$)$_2$(CH$_2$)$_2$), 3.02 (t, *J* = 5.0 Hz, 4H, PN(CH$_2$)$_2$(C$\underline{H}_2$)$_2$N), 2.31 (s, 3H, ArC$\underline{H}_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 151.50, 148.73 (d, *J* = 8.3 Hz), 134.32, 132.25 (d, *J* = 3.1 Hz), 131.60 (d, *J* = 9.8 Hz), 130.34 (ArC), 129.31 (ArC), 128.75 (d, *J* = 14.5 Hz, ArC), 120.48 (ArC), 120.31 (d, *J* = 4.9 Hz, ArC), 116.72 (ArC), 49.82 (d, *J* = 5.7 Hz, PN(CH$_2$)$_2$($\underline{C}$H$_2$)$_2$O), 44.24 (d, *J* = 2.3 Hz, PN($\underline{C}$H$_2$)$_2$(CH$_2$)$_2$O), 20.88 (Ar$\underline{C}$H$_3$); **^{31}P NMR** (162 MHz,

$CDCl_3$) δ 19.27; **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2342, 1505, 1381, 1237 (P=O), 1074, 974; **HRMS** (ESI+): calcd. for $C_{23}H_{26}O_2NP$ 393.1726 $[M+H]^+$, found 393.1726.

277: *p*-tolyl (*R*)-morpholino(phenyl)phosphinate



277 was synthesised according to **General Procedure V**. **189** (17 mg, 0.05 mmol) was used as phosphonate, morpholine (6.6 μL, 0.075 mmol) as amine, *n*-BuLi (2.4 M in hexanes, 31 μL, 0.075 mmol) as base in THF (0.5 mL). FCC 9:1 CH_2Cl_2: Acetone. Colourless oil (9.7 mg, 0.031 mmol, 61% yield, 88% ee, 94% es).

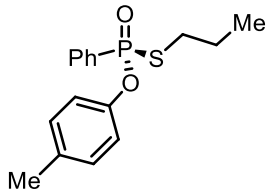
HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 18.01 min, t (major) = 12.00 min.

$[\alpha]_D^{25}$ = -23.3 [c = 1.14, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 2H, ArH), 7.59 – 7.52 (m, 1H, ArH), 7.52 – 7.45 (m, 2H, ArH), 7.21 – 7.10 (m, 4H, ArH), 3.52 (td, *J* = 4.7, 1.1 Hz, 4H, $N(CH_2)_2(C\underline{H}_2)_2O$), 3.25 – 3.06 (m, 4H, $N(CH_2)_2(C\underline{H}_2)_2O$), 2.32 (s, 3H, $ArC\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.66 (ArC), 132.30 (ArC), 130.34 (ArC), 128.76 (d, *J* = 14.7 Hz, ArC), 120.26 (d, *J* = 4.8 Hz, ArC), 66.98 (d, *J* = 5.4 Hz, $N(CH_2)_2(\underline{C}H_2)_2O$), 44.26 ($N(\underline{C}H_2)_2(CH_2)_2O$), 20.87 ($Ar\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 18.96; **IR** (film) υ_{max}/cm^{-1}: 2980, 2918, 2851, 2360, 2342, 1692 (C=O), 1506, 1242 (P=O), 1204, 1114, 971, 914; **HRMS** (ESI+): calcd. for $C_{17}H_{21}O_3NP$ 318.1254 $[M+H]^+$, found 318.1250.

3.4.4 General Procedure VI: Thiols

Under a nitrogen atmosphere, thiol (1 eq) was dissolved in THF and cooled to 78 °C. *t*-BuMgCl (1 eq) was added and the mixture allowed to stir for 20 mins before addition to a 78 °C solution of **189** (1 eq) dissolved in THF. The reaction mixture was allowed to stir at 78 °C for 30 mins, then slowly warmed to 40 °C and stirred at 40 °C overnight. On reaction completion, the crude mixture was loaded directly onto silica and purified by flash column chromatography as specified in the individual experiment to afford the pure derivatised phosphonothioate.

279: *S*-propyl *O*-(*p*-tolyl) (*R*)-phenylphosphonothioate

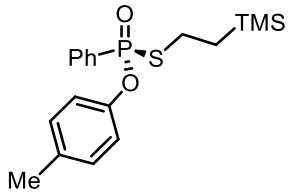


279 was synthesised according to **General Procedure VI**. **189** (17 mg, 0.05 mmol) was used as phosphonate, propane thiol (4.6 μL, 0.05 mmol) as amine, *t*-BuMgCl (2 M in THF, 38 μL, 0.075 mmol) as base in THF (0.5 mL). FCC 6:4 pentane:EtOAc. Colourless oil (13.3 mg, 0.043 mmol, 87% yield, 83% ee, 88% es).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 14.92 min, t (major) = 10.96 min.

[α]$_D^{25}$ = -56.0 [c = 0.15, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.93 (m, 2H, ArH), 7.63 – 7.46 (m, 3H, ArH), 7.20 – 7.08 (m, 4H, ArH), 2.86 – 2.66 (m, 2H, $SC\underline{H}_2CH_2CH_3$), 2.31 (s, 3H, $ArC\underline{H}_3$), 1.55 (h, *J* = 7.3 Hz, 2H, $SCH_2C\underline{H}_2CH_3$), 0.87 (t, *J* = 7.3 Hz, 3H, $SCH_2CH_2C\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.32 ($Ar\underline{C}O$), 134.77 (ArC), 132.74 (ArC), 131.36 (d, *J* = 11.0 Hz, ArC), 130.13 (ArC), 128.58 (d, *J* = 14.9 Hz, ArC), 120.79 (d, *J* = 4.8 Hz, ArC), 32.46 (d, *J* = 2.8 Hz, $S\underline{C}H_2CH_2CH_3$), 23.99 (d, *J* = 5.5 Hz, $SCH_2\underline{C}H_2CH_3$), 20.76 ($Ar\underline{C}H_3$), 13.09 ($SCH_2CH_2\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 43.42; **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2342, 1382, 1250 (P=O), 1164, 955; **HRMS** (ESI+): calcd. for $C_{16}H_{20}O_2PS$ 307.0916 $[M+H]^+$, found 307.0911.

281: *O*-(*p*-tolyl) S-(2-(trimethylsilyl)ethyl) (*R*)-phenylphosphonothioate

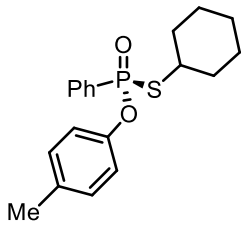


281 was synthesised according to **General Procedure VI**. **189** (17 mg, 0.05 mmol) was used as phosphonate, 2-(trimethylsilyl)ethane thiol (8 μL, 0.05 mmol) as amine, *t*-BuMgCl (2 M in THF, 38 μL, 0.075 mmol) as base in THF (0.5 mL). FCC 6:4 pentane:EtOAc. Colourless oil (13.6 mg, 0.037 mmol, 75% yield, 73% ee, 78% es).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 8.93 min, t (major) = 7.40 min.

[α]$_D^{25}$ = -47.2 [c = 0.29, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (ddt, *J* = 13.9, 7.0, 1.4 Hz, 2H), 7.63 – 7.46 (m, 3H), 7.21 – 7.09 (m, 4H), 2.91 – 2.72 (m, 2H), 2.31 (s, 3H), 0.87 – 0.78 (m, 2H), -0.07 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.52 ($Ar\underline{C}O$), 134.92 (ArC), 132.84 (ArC), 131.50 (d, *J* = 11.0 Hz, ArC), 130.28 (ArC), 128.73 (d, *J* = 14.8 Hz, ArC), 121.02 (d, *J* = 4.8 Hz, ArC), 27.45 ($S\underline{C}H_2CH_2$), 20.91 ($Ar\underline{C}H_3$), 19.43 ($SCH_2\underline{C}H_2$), -1.79 ($Si(\underline{C}H_3)_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 43.02; **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2342, 1504, 1237 (P=O), 1197, 1165, 1118, 912, 858, 669; **HRMS** (ESI+): calcd. for $C_{18}H_{26}O_2PSSi$ 365.1154 $[M+H]^+$, found 365.1154.

282: *S*-cyclohexyl *O*-(*p*-tolyl) (*R*)-phenylphosphonothioate



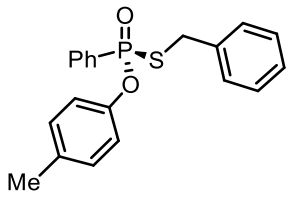
282 was synthesised according to **General Procedure VI**. **189** (17 mg, 0.05 mmol) was used as phosphonate, cyclohexanethiol (6.1 μL, 0.05 mmol) as amine, *t*-BuMgCl (2 M in THF, 38 μL, 0.075 mmol) as base in THF (0.5 mL). FCC 6:4 pentane:EtOAc. Colourless oil (13 mg, 0.038 mmol, 75% yield, 87% ee, 93% es).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 16.64 min, t (major) = 12.23 min.

[α]$_D^{25}$ = -40.9 [c = 0.11, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.91 (m, 2H, ArH), 7.62 – 7.45 (m, 3H, ArH), 7.18 – 7.04 (m, 4H, ArH), 3.37 – 3.23 (m, 1H, $SC\underline{H}(CH_2)_2(CH_2)_2CH_2$), 2.31 (s, 3H, $ArC\underline{H}_3$), 1.95 – 1.79 (m, 2H), 1.71 – 1.56 (m, 3H), 1.54 – 1.08 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.47 ($Ar\underline{C}O$), 134.80 (ArC), 132.73 (ArC), 131.47 (d, *J* = 11.1 Hz, ArC), 130.21 (ArC), 128.67 (d, *J* =

15.0 Hz, ArC), 121.03 (d, *J* = 4.7 Hz, ArC), 45.65 (d, *J* = 2.7 Hz, S<u>C</u>H(CH$_2$)$_2$(CH$_2$)$_2$CH$_2$), 35.31, 25.97, 25.39, 20.91; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 42.78; **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2342, 1382, 1238 (P=O), 955; **HRMS** (ESI+): calcd. for $C_{19}H_{24}O_2PS$ 347.1229 $[M+H]^+$, found 347.1225.

283: *S*-benzyl O-(*p*-tolyl) (*R*)-phenylphosphonothioate

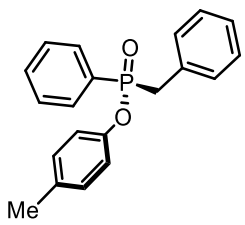


283 was synthesised according to **General Procedure VI**. **189** (17 mg, 0.05 mmol) was used as phosphonate, benzyl mercaptan (5.9 μL, 0.05 mmol) as amine, *t*-BuMgCl (2 M in THF, 38 μL, 0.075 mmol) as base in THF (0.5 mL). FCC 6:4 pentane:EtOAc. Colourless oil (15.1 mg, 0.043 mmol, 85% yield, 88% ee, 94% es).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (minor) = 21.75 min, t (major) = 13.37 min.

[α]$_D^{25}$ = -56.9 [c = 0.13, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.88 (m, 2H, ArH), 7.62 – 7.43 (m, 3H, ArH), 7.23 – 7.05 (m, 9H, ArH), 4.07 – 3.92 (m, 2H, SC<u>H</u>$_2$Ph), 2.32 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.28 (Ar<u>C</u>O), 136.86 (ArC), 135.06 (ArC), 132.93 (d, *J* = 3.3 Hz, ArC), 131.53 (d, *J* = 11.2 Hz, ArC), 130.32 (ArC), 129.03 (ArC), 128.89 – 128.56 (m, ArC), 127.61 (ArC), 120.98 (d, *J* = 4.7 Hz, ArC), 34.71 (d, *J* = 2.5 Hz, S<u>C</u>H$_2$Ph), 20.92 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 42.23; **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2342, 1382, 1250 (P=O), 1164, 955, 773, 669; **HRMS** (ESI+): calcd. for $C_{20}H_{20}O_2PS$ 355.0916 $[M+H]^+$, found 355.0912.

289: *p*-tolyl (*S*)-benzyl(phenyl)phosphinate



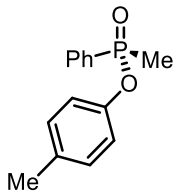
Under a nitrogen atmosphere, **189** (17 mg, 0.050 mmol) was dissolved in Et_2O (0.5 mL) and cooled to 0 °C. Benzyl magnesium chloride (1M in 2-methyl THF, 55 μL, 0.055 mmol) was then added and the reaction mixture stirred at 0 °C for 4 hours. On reaction completion, the crude mixture was loaded directly onto silica and purified by FCC (6:4 pentane:ethyl acetate) to afford p-tolyl (S)-benzyl(phenyl)phosphinate (**289**) as a white solid (8.2 mg, 0.025 mmol, 51% yield, 92% ee, 100% es).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (minor) = 14.54 min, t (major) = 18.96 min.

[α]$_D^{25}$ = -14.0 [c = 0.1, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.60 (m, 2H, ArH), 7.55 – 7.45 (m, 1H, ArH), 7.42 – 7.33 (m, 2H, ArH), 7.25 – 7.19 (m, 3H, ArH), 7.16 – 7.09 (m, 2H, ArH), 7.00 (s, 4H, ArH), 3.47 (d, *J* = 17.9 Hz, 2H, ArC<u>H</u>$_2$O), 2.24 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.86 (d, *J* = 8.9 Hz, Ar<u>C</u>O), 134.16 (ArC), 132.66 (d, *J* = 2.8 Hz, ArC), 132.33 (d, *J* = 9.8 Hz, ArC), 131.15 (d, *J* = 7.6 Hz, ArC), 130.32 – 130.18 (m, ArC), 129.56 (d, *J* = 127.2 Hz, ArC), 128.64 – 128.40 (m, ArC), 127.04 (d, *J* = 3.4 Hz, ArC), 120.36 (d, *J* = 4.8 Hz, ArC), 38.36 (d, *J* = 95.1 Hz, Ar<u>C</u>H$_2$P), 20.80

(Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 38.52; **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2341, 1382, 1233 (P=O), 1154, 1071, 955; **HRMS** (ESI+): calcd. for $C_{20}H_{20}O_2P$ 323.1195 $[M+H]^+$, found 323.1195.

290: *p*-tolyl (*S*)-methyl(phenyl)phosphinate

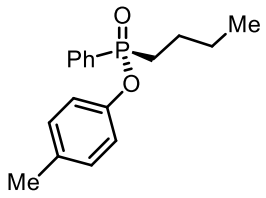


Under a nitrogen atmosphere, **189** (8.5 mg, 0.025 mmol) was dissolved in THF (0.25 mL) and cooled to 78 °C. Methyl magnesium bromide (3M in Et_2O, 9 μL, 0.028 mmol) was then added and the reaction mixture stirred at −78 °C for 3 hours. On reaction completion, the crude mixture was loaded directly onto silica and purified by FCC (95:5 CH_2Cl_2:acetone) to afford p-tolyl (S)-methyl(phenyl)phosphinate (**290**) as a colourless oil (6 mg, 0.024 mmol, 97% yield, 87% ee, 95% es).

HPLC Conditions: CHIRALPAK OD, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 14.70 min, t (major) = 22.50 min.

$[\alpha]_D^{25}$ = -46.7 [c = 0.39, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 2H, ArH), 7.58 – 7.51 (m, 1H, ArH), 7.51 – 7.43 (m, 2H, ArH), 7.07 – 6.97 (m, 4H, ArH), 2.25 (s, 3H, ArC<u>H</u>$_3$), 1.83 (d, *J* = 14.4 Hz, 3H, C<u>H</u>$_3$P); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.66 (ArC), 131.48 (d, *J* = 10.4 Hz, ArC), 128.77 (d, *J* = 13.1 Hz, ArC), 120.55 (d, *J* = 4.5 Hz, ArC), 20.81 (Ar<u>C</u>H$_3$), 16.13 (16.13 (d, *J* = 102.0 Hz, Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 41.39; **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2342, 1682 (C=O), 1506, 1215 (P=O), 1125, 918, 748; **HRMS** (ESI+): calcd. for $C_{14}H_{16}O_2P$ 247.0882 $[M+H]^+$, found 247.0881.

291: *p*-tolyl (*S*)-butyl(phenyl)phosphinate



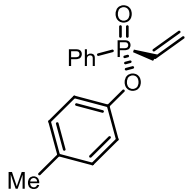
Under a nitrogen atmosphere, **189** (8.5 mg, 0.025 mmol) was dissolved in THF (0.25 mL) and cooled to 78 °C. Butyl magnesium chloride (2M in THF, 14 μL, 0.028 mmol) was then added and the reaction mixture stirred at −78 °C for 1 hour. On reaction completion, the crude mixture was loaded directly onto silica and purified by FCC (7:3 pentane:ethyl acetate) to afford p-tolyl (S)-butyl(phenyl)phosphinate (**291**) as a colourless oil (5.6 mg, 0.019 mmol, 78% yield, 88% ee, 96% es).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (minor) = 14.97 min, t (major) = 11.90 min.

$[\alpha]_D^{25}$ = -29.8 [c = 0.5, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 – 7.72 (m, 2H, ArH), 7.50 – 7.44 (m, 1H, ArH), 7.43 – 7.36 (m, 2H, ArH), 6.94 (s, 4H, ArH), 2.18 (s, 3H, ArC<u>H</u>$_3$), 2.13 – 1.86 (m, 2H, PC<u>H</u>$_2$CH$_2$), 1.69 – 1.42 (m, 2H, PCH$_2$C<u>H</u>$_2$), 1.41 – 1.24 (m, 2H, PCH$_2$CH$_2$C<u>H</u>$_2$), 0.81 (t, *J* = 7.3 Hz, 3H, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.87 (d, *J* = 8.9 Hz, Ar<u>C</u>O), 134.07 (ArC), 132.53 (d, *J* = 2.8 Hz, ArC), 131.90 (d, *J* = 10.1 Hz, ArC), 130.65 (d, *J* = 124.3 Hz, ArC), 130.21 (ArC), 128.73 (d, *J* = 12.6 Hz, ArC), 120.46 (d, *J* = 4.7 Hz, ArC), 29.76 (d, *J* = 99.7 Hz, P<u>C</u>H$_2$CH$_2$), 24.19 – 23.72 (m, PCH$_2$<u>C</u>H$_2$), 20.81 (PCH$_2$CH$_2$<u>C</u>H$_2$), 13.70 (CH$_2$<u>C</u>H$_2$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 43.99; **IR** (film)

υ_{max}/cm^{-1}: 2981, 2888, 1383, 1253 (P=O), 1152, 1073, 955; **HRMS** (ESI+): calcd. for $C_{17}H_{22}O_2P$ 289.1352 $[M+H]^+$, found 289.1350.

292: *p*-tolyl (*S*)-phenyl(vinyl)phosphinate

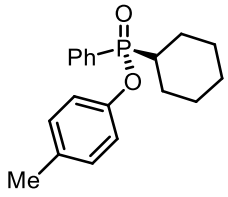


Under a nitrogen atmosphere, **189** (8.5 mg, 0.025 mmol) was dissolved in THF (0.25 mL) and cooled to 78 °C. Vinyl magnesium bromide (1M in THF, 28 μL, 0.028 mmol) was then added and the reaction mixture stirred at −78 °C for 1 hour. On reaction completion, the crude mixture was loaded directly onto silica and purified by FCC (95:5 CH_2Cl_2:acetone) to afford p-tolyl (S)-phenyl(vinyl)phosphinate (**292**) as a colourless oil (4.6 mg, 0.018 mmol, 71% yield, 92% ee, 100% es).

HPLC Conditions: CHIRALPAK OD-H, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (minor) = 14.88 min, t (major) = 8.91 min.

$[\alpha]_D^{25}$ = +38.6 [c = 0.16, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.75 (m, 2H, ArH), 7.54 – 7.45 (m, 1H, ArH), 7.45 – 7.37 (m, 2H, ArH), 7.04 – 6.94 (m, 4H, ArH), 6.47 – 6.01 (m, 3H, PC<u>H</u>C<u>H</u>$_2$), 2.20 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.64 (d, *J* = 8.5 Hz, Ar<u>C</u>O), 135.83 (d, *J* = 2.2 Hz, ArC), 134.38 (ArC), 132.73 (d, *J* = 2.8 Hz, ArC), 131.84 (d, *J* = 10.3 Hz, ArC), 130.28 (Ar<u>C</u>P), 130.26 (ArC), 129.49 (d, *J* = 132.4 Hz, P<u>C</u>HCH$_2$), 128.75 (d, *J* = 13.3 Hz, PCH<u>C</u>H$_2$), 120.61 (d, *J* = 4.6 Hz, ArC), 20.84 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 28.75; **IR** (film) υ_{max}/cm^{-1}: 2981, 1383, 1252 (P=O), 1152, 1073, 955; **HRMS** (ESI+): calcd. for $C_{15}H_{16}O_2P$ 259.0882 $[M+H]^+$, found 259.0882.

293: *p*-tolyl (*S*)-cyclohexyl(phenyl)phosphinate

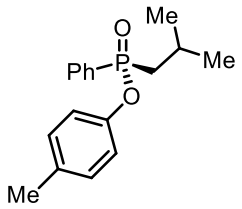


Under a nitrogen atmosphere, **189** (8.5 mg, 0.025 mmol) was dissolved in THF (0.25 mL) and cooled to 78 °C. Cyclohexyl magnesium chloride (1M in THF, 28 μL, 0.028 mmol) was then added. The reaction mixture was stirred at −78 °C for 1 hour, then slowly warmed to −40 °C and stirred at −40 °C overnight. On reaction completion, the crude mixture was loaded directly onto silica and purified by FCC (6:4 pentane:ethyl acetate) to afford p-tolyl (S)-cyclohexyl(phenyl)phosphinate (**293**) as a colourless oil (5.6 mg, 0.018 mmol, 71% yield, 91% ee, 99% es).

$[\alpha]_D^{25}$ = +121.1 [c = 0.45, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 2H, ArH), 7.58 – 7.48 (m, 1H, ArH), 7.50 – 7.40 (m, 2H, ArH), 7.06 – 6.96 (m, 4H, ArH), 2.24 (s, 3H, ArC<u>H</u>$_3$), 2.18 – 2.09 (m, 1H, Alk<u>H</u>), 2.08 – 1.93 (m, 1H, Alk<u>H</u>), 1.90 – 1.65 (m, 4H, Alk<u>H</u>), 1.57 (s, 4H, Alk<u>H</u>), 1.52 – 1.28 (m, 1H, Alk<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.56 (d, *J* = 9.5 Hz, ArC), 130.16 (ArC), 128.59 (d, *J* = 12.1 Hz, ArC), 120.27 (ArC), 39.48 (P<u>C</u>H(CH$_2$)$_2$(CH$_2$)$_2$CH$_2$), 29.86 (PCH(<u>C</u>H$_2$)$_2$(CH$_2$)$_2$CH$_2$), 26.26 (d, *J* = 15.1 Hz, PCH(CH$_2$)$_2$(<u>C</u>H$_2$)$_2$CH$_2$), 25.93 (PCH(CH$_2$)$_2$(CH$_2$)$_2$<u>C</u>H$_2$), 20.79 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162

MHz, $CDCl_3$) δ 45.14; **IR** (film) υ_{max}/cm^{-1}: 2981, 2889, 2360, 2342, 1690 (C=O), 1505, 1382, 1255 (P=O), 1216, 1128, 954, 729; **HRMS** (ESI+): calcd. for $C_{19}H_{24}O_2P$ 315.1508 $[M+H]^+$, found 315.1507.

294: *p*-tolyl (*S*)-isobutyl(phenyl)phosphinate

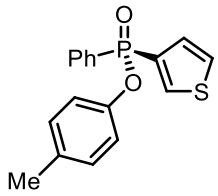


Under a nitrogen atmosphere, **189** (8.5 mg, 0.025 mmol) was dissolved in THF (0.25 mL) and cooled to 78 °C. Isobutyl magnesium chloride (2M in THF, 14 μL, 0.028 mmol) was then added. The reaction mixture was stirred at −78 °C for 1 hour, then slowly warmed to −40 °C and stirred at −40 °C overnight. On reaction completion, the crude mixture was loaded directly onto silica and purified by FCC (6:4 pentane:ethyl acetate) to afford p-tolyl (S)-isobutyl(phenyl)phosphinate (**294**) as a colourless oil (2.4 mg, 0.008 mmol, 33% yield, 88% ee, 96% es).

HPLC Conditions: CHIRALPAK AD, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (minor) = 15.90 min, t (major) = 13.10 min.

$[\alpha]_D^{25}$ = +33.8 [c = 0.16, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 2H, ArH), 7.57 – 7.41 (m, 3H, ArH), 6.99 (s, 4H, ArH), 2.24 (d, *J* = 0.8 Hz, 3H, $ArC\underline{H}_3$), 2.21 – 1.89 (m, 3H, $C\underline{H}_2C\underline{H}(CH_3)_2$), 1.14 – 0.94 (m, 6H, $CH_2CH(C\underline{H}_3)_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.81 (d, *J* = 9.1 Hz, $Ar\underline{C}O$), 134.00 (ArC), 132.46 (d, *J* = 2.7 Hz, ArC), 131.84 (d, *J* = 10.2 Hz, ArC), 131.32 (d, *J* = 123.2 Hz, ArC), 130.16 (ArC), 128.71 (d, *J* = 12.5 Hz, ArC), 120.50 (d, *J* = 4.5 Hz, ArC), 38.79 (d, *J* = 98.7 Hz, $\underline{C}H_2CH(CH_3)_2$), 24.59 (d, *J* = 11.4 Hz, $CH_2CH(\underline{C}H_3)_2$), 24.35 (d, *J* = 9.7 Hz, $\underline{C}H_2CH(\underline{C}H_3)_2$), 23.56 (d, *J* = 3.2 Hz, $CH_2\underline{C}H(CH_3)_2$), 20.79 ($Ar\underline{C}H_3$); **^{31}P NMR** (243 MHz, $CDCl_3$) δ 43.18 (p, *J* = 12.5 Hz); **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2341, 1384, 1258 (P=O), 1133, 942; **HRMS** (ESI+): calcd. for $C_{17}H_{22}O_2P$ 289.1352 $[M+H]^+$, found 289.1351.

295: *p*-tolyl (*R*)-phenyl(thiophen-2-yl)phosphinate



Under a nitrogen atmosphere, **189** (8.5 mg, 0.025 mmol) was dissolved in THF (0.25 mL) and cooled to 78 °C. 2-Thienyl magnesium bromide (1M in THF, 38 μL, 0.038 mmol) was then added. The reaction mixture was stirred at −78 °C for 1 hour, then slowly warmed to −40 °C and stirred at −40 °C overnight. On reaction completion, the crude mixture was loaded directly onto silica and purified by FCC (9:1 CH_2Cl_2:acetone) to afford p-tolyl (R)-phenyl(thiophen-2-yl)phosphinate (**295**) as a colourless oil (5.5 mg, 0.017 mmol, 70% yield, 87% ee, 95% es).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 14.34 min, t (major) = 15.53 min.

$[\alpha]_D^{25}$ = +69.0 [c = 0.1, $CHCl_3$]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.89 (m, 2H, ArH), 7.70 (td, *J* = 4.8, 1.1 Hz, 1H, ArH), 7.66 (ddd, *J* = 7.5, 3.6, 1.1 Hz, 1H, ArH), 7.59 – 7.51 (m, 1H, ArH), 7.51 – 7.43 (m, 2H, ArH), 7.15 (ddd, *J* = 4.8, 3.6, 2.6 Hz, 1H, ArH), 7.13 – 6.99 (m, 4H, ArH), 2.26 (d, *J* = 0.8 Hz,

3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.14 (d, *J* = 11.8 Hz, ArC), 134.49 (ArC), 134.14 (d, *J* = 6.1 Hz, ArC), 132.73 (ArC), 131.77 (d, *J* = 10.6 Hz, ArC), 130.25 (ArC), 128.73 (d, *J* = 14.1 Hz, ArC), 128.35 (d, *J* = 16.2 Hz, ArC), 120.64 (d, *J* = 4.8 Hz, ArC), 20.84 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 23.60; **IR** (film) υ_{max}/cm^{-1}: 2981, 2360, 2342, 1382, 1237 (P=O), 1167, 954; **HRMS** (ESI+): calcd. for $C_{17}H_{16}O_2PS$ 315.0603 $[M+H]^+$, found 315.0600.