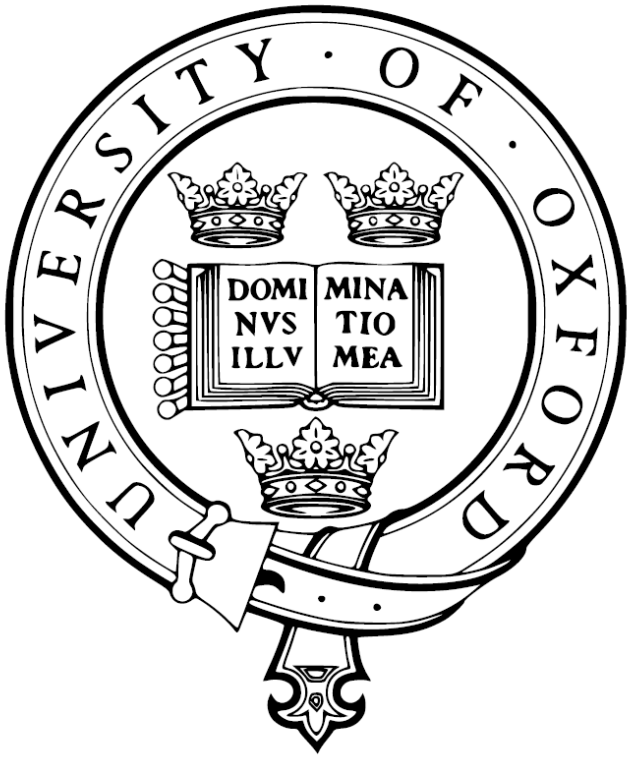
Novel Applications of Bifunctional Iminophosphorane Superbases in Enantioselective Catalytic Methodology



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Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from February 2017 until May 2021, 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.



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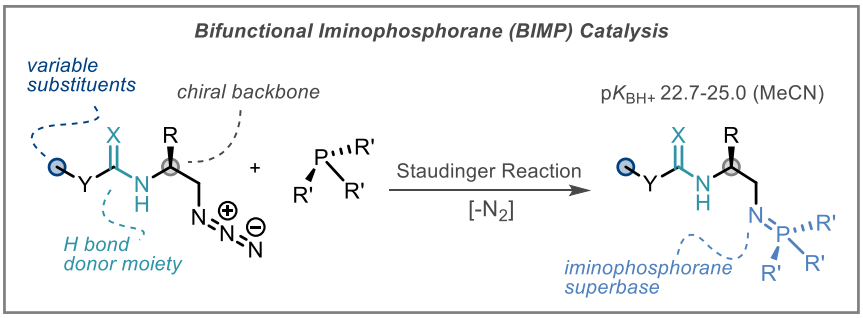
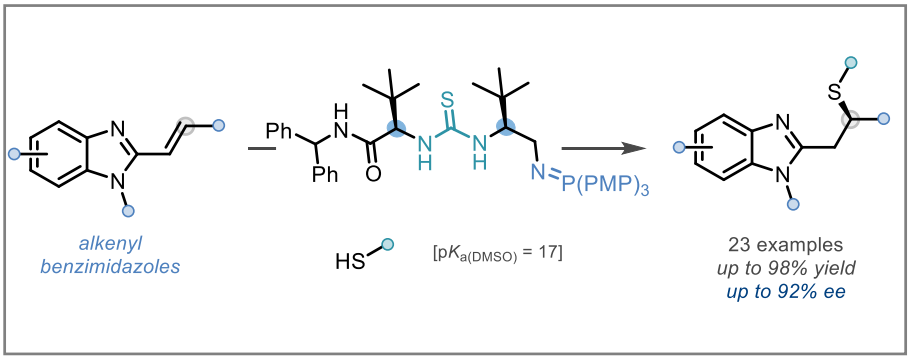
Abstract

Chapter 1 introduces enantioselective organocatalysis with a specific focus on bifunctional catalysts and chiral superbases. Subsequently, the discovery and applications of bifunctional iminophosphorane (BIMP) catalysts will be described.

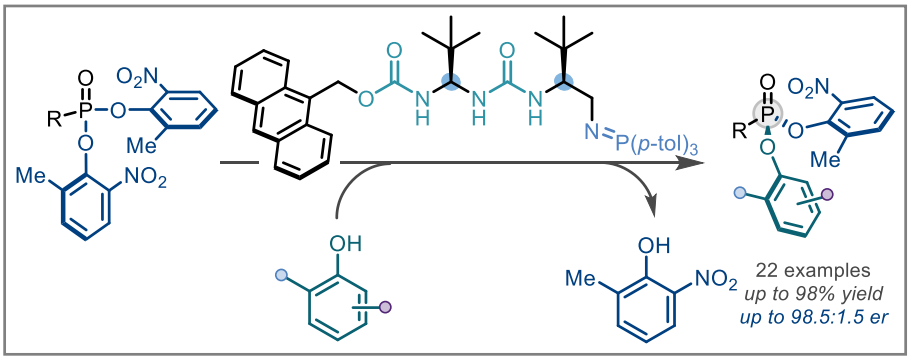


Chapter 2 focuses on the development of a novel enantioselective sulfa-Michael addition employing alkenyl-benzimidazoles as electrophiles. The work in this chapter will showcase a rare example of organocatalysed enantioselective addition to alkenyl heterocycles for the rapid generation of 3-D drug-like scaffolds.

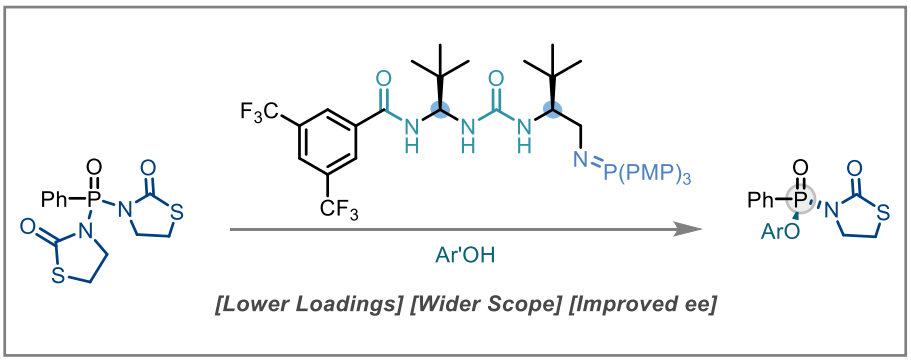


Chapter 3 introduces approaches to enantioselective P(V) synthesis, highlighting the strengths and shortcomings of current methods to then focus on the development of an unprecedented enantioselective nucleophilic desymmetrisation of phosphonate esters. The unique ability of a novel ureidopeptide BIMP catalyst to promote this reaction enantioselectively will be demonstrated against a wide array of other BIMPs as well as *Chinchona* alkaloid and phase transfer catalysts. The downstream

utility of the desymmetrised product will be demonstrated in the synthesis of numerous attractive nucleoside derived compounds.



Chapter 4 will disclose an improved enantioselective nucleophilic desymmetrisation of P(V) containing species. *Via* a superior BIMP catalyst scaffold and a thiazolidinone leaving group on the P(V) electrophiles, higher enantioselectivities, lower catalyst loadings, and improved nucleophile scope were obtained.



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To my esteemed collègue Pablo (aka Pabsy Pabs aka the Sheriff of ○○), thank you for your friendship throughout the years, G6 would not have been the same without you. An extra thank you for proofreading multiple chapters of this thesis. May you become the greatest Pokémon master in the world.

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future. Ken, you're the Yves-Saint-Laurent of DFT. I will riot if they don't retire the Amsterdam supercomputer in your honour when you finish your PhD. Tom, the fate of the (P(V)) world rests in your hands, with great BIMPs comes great responsibility.

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Finally, to my parents, without whom none of this would have been possible.

Abbreviations

(+)	Dextrorotary
(−)	Levorotatory
δ	NMR chemical shift
Δ	Heat
ν_{max}	Infrared absorption maximum
A	Adenine
AAA	Asymmetric Allylic Alkylation
Ac	Acetyl
ACC	Azide–Alkyne Cycloaddition
Am	Amyl
APCI	Atmospheric pressure chemical ionization
API	Active Pharmaceutical Ingredient
app	Apparent
Ar	Aryl
ARCM	Asymmetric Ring Closing Metathesis
$BAr^F{}_4$	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BDPP	2,4-Bis(diphenylphosphino)pentane

BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BIBOP	3,3'-tetrahydro-2,2'-bibenzo[d][1,3]oxaphosphole
BIMP	Bifunctional IMinoPhosphorane
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BQ	Benzoquinone
br	Broad
BTMG	2-*tert*-Butyl-1,1,3,3-tetramethylguanidine
Bz	Benzoyl
CAMP	methylcyclohexyl-*o*-anysilphosphine
cat	Catalyst
Cbz	Carboxybenzyl
CE	Cyanoethyl
CNS	Central Nervous System
cod	1,5-Cyclooctadiene
coe	Cyclooctene
COSY	COrrelation SpectroscopY
COVID-19	Coronavirus disease 2019
CPA	Chiral Phosphoric Acid

Cy	Cyclohexyl
δ	Delta
d	Doublet
dbtm	3,5-di-*tert*-butyl-4-methoxyphenyl
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
ddt	Doublet of doublet of triplets
DFT	Density functional theory
$(DHQ)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIPAMP	1,2-Bis[(2-methoxyphenyl)(phenylphosphino)]ethane
DIPAMPO	1,2-Bis[(2-methoxyphenyl)(phenylphosphino)]ethane oxide
DIPEA	*N*,*N*-Diisopropylethylamine
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
DPZ	5,6-Bis(5-methoxythiophen-2-yl)pyrazine-2,3-dicarbonitrile
dq	Doublet of quartets
dr	Diastereomeric ratio
dt	Doublet of triplets
dT	Thymidine
dtbbpy	4,4'-Di-*tert*-butyl-2,2'-dipyridyl
dtd	Doublet of triplet of doublets
dtdd	Doublet of triplet of doublet of doublets
DYKAT	Dynamic Kinetic Asymmetric Transformation
E	Entgegen
ee	Enantiomeric excess
ent	Enantiomer
er	Enantiomeric ratio
ESI	Electrospray ionisation
et al.	*et alia*
equiv.	Equivalents
fac	Facial
FCC	Flash Column Chromatography
FT	Fourier transform

G	Guanine
g	Grams
GII	Grubbs catalyst 2nd generation
hept	Heptuplet
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HGII	Hoveyda–Grubbs catalyst 2nd generation
HMBC	heteronuclear multiple bond coupling
HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coupling
HWE	Horner–Hadwsworth–Emmons
IMDAF	Intramolecular Diels−Alder Addition of Furan
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant
LDA	Lithium Diisopropylamide
LRMS	Low resolution mass spectrometry
m	Multiplet
m	Meta

M	Molar
m/*z*	Mass to charge ratio
MBH	Morita-Baylis-Hillman
m-CPBA	*meta*-Chloroperoxybenzoic acid
MIDA	Methyliminodiacetic acid
mp	Melting point
MPO	Methylphosphonate oligonucleotides
Ms	Methanesulfonyl
MS	Molecular sieves
n	Nonuplet
N	Normality
NHC	N-Heterocyclic Carbene
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMM	*N*-Methylmorpholine
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	Nucleophile
o	Ortho

p	Para
p	Pentet
PAMP	Phenyl *o*-Anisole Methyl Phosphine
PAMPO	Phenyl *o*-Anisole Methyl Phosphine Oxide
PDI	Polydispersity index
Pin	Pinacol
Piv	Pivaloyl
PMHS	Polymethylhydrosiloxane
PMP	*para*-Methoxy phenyl
PPA	Polyphosphoric acid
ppm	Parts per million
prep	Preparative
PSI	Phosphorous-Sulfur Incorporation
pyr	Pyridine
q	Quartet
qd	Quartet of doublets
qt	Quartet of triplets
quant.	Quantitative
R	Rectus
R	Unspecified organic group
RCM	Ring-Closing Metathesis

RNA	Ribonucleic acid
rr	Regioisomeric ratio
rt	Room temperature
s	Singlet
S	Sinister
SARS	Severe Acute Respiratory Syndrome
SCXRD	Single Crystal X-Ray Diffraction
SEGPHOS	5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
sept	Septuplet
SMA	Sulfa-Michael addition
SMD	Solvation Model based on Density
SPINOL	1,1'-spirobiindane-7,7'-diol
SPO	Secondary phosphine oxide
T	Thymine
T	Temperature
t	Triplet
$t_{1/2}$	Half-life
TADDOL	α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
td	Triplet of doublets

tdd	Triplet of doublet of doublets
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMDS	Tetramethyldisiloxane
TMS	Trimethylsilyl
tol	Tolyl
t_R	Retention time
Ts	*para*-Toluenesulfonyl
TS	Transition state
tt	Triplet of triplets
UV	Ultraviolet
w	Weight
WHO	World Health Organization
Z	Zusammen

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Chapter 1 : Introduction

1.1 General Introduction to Organocatalysis

1.1.1 On the importance of chirality

Over the last ~150 years chemistry has shaped the way we live. Major advances in pharmaceuticals, materials and agrochemicals have considerably extended the life expectancy, quality of life and provided food-security for billions of people around the world. Molecules of ever-increasing complexity have found their way in our everyday life. In particular, those containing one or more stereogenic centres are highly prevalent in all branches of the chemical industry, thus methods to synthesize single enantiomers/diastereomers of target molecules are of paramount importance for effective synthetic processes.

Chiral molecules often exhibit enantio-dependent potency or physiological properties as a consequence of diastereomeric *in vivo* interactions, therefore, the preparation of molecules in a highly enantioselective manner can also avoid unwanted adverse effects in patients.[1] An example of a drug demonstrating enantio-dependent properties is methamphetamine (**1**). Dextromethamphetamine (*S*-enantiomer) is an infamously powerful central nervous system (CNS) stimulant, and its production/consumption is prohibited in most countries. Levomethamphetamine, the *R*-enantiomer, on the other hand is an over-the-counter nasal decongestant in the US (**Figure 1**).[2]

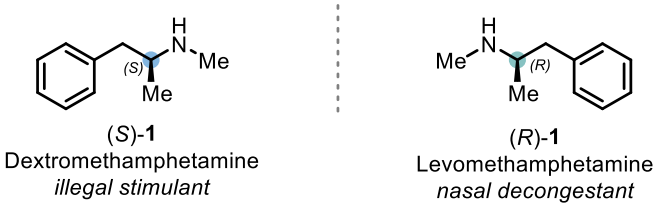


Figure 1. Structures of Dextromethamphetamine and Levomethamphetamine.

1.1.2 An overview of asymmetric synthesis

Ever since Louis Pasteur first laid the foundation for the field by resolving a racemic mixture of tartaric acid crystals by eye (Pasteur himself acting as a chiral resolving agent) the asymmetric synthesis of compounds has historically been achieved *via* chiral resolution[3] or by chromatographic separation on a chiral stationary phase (**Figure 2A**).[4,5] These methods however are intrinsically wasteful, as only a maximum 50% yield of the desired enantiomer can be obtained. Alternatively, the use of a chiral auxiliary, by which a chiral residue is covalently linked to a substrate to impart asymmetry, has also been a prevalent strategy, greatly contributing to the growth of the field (**Figure 2B**).[6,7] While attractive in its simplicity, and robust due to abundant literature precedent, the installation and removal of the auxiliary lengthens the synthetic sequence leading to the isolation of the target enantiomer in diminished yield and low atom economy,[8] but also in increased cost derived due to the stochiometric use of the auxiliary. In this regard, catalytic asymmetric approaches (by which enantioselectivity is imparted by a chiral catalyst) to enantioselective synthesis have long been seen as ideal direct routes to highly enantioenriched molecules (**Figure 2C**).

Arguably, transition metals (used in conjunction with chiral ligands) have dominated the field of asymmetric catalysis due to the impressive range of reactions enabled by this mode of catalysis together with the possibility to employ extremely low catalyst loadings thanks to the high catalytic activity and turnover number of the metal species.[9] In 2001 Noyori[10] and Knowles,[11] and Sharpless[12] were jointly awarded the Nobel prize for chemistry for their development of asymmetric hydrogenation and oxidation, respectively. Collectively these processes are employed in the synthesis of bioactive compounds on multi-tonne scale each year.[12] Despite these tremendous contributions, transition metal catalysed asymmetric reactions are often overly-reliant on the use of precious platinum group metals. These metals are a rare and finite resource whose mining is both extremely costly and ecologically damaging.[13] While considerable advances have been made to replace Pd, Rh and Ir with their first row counterparts, metals such as Ni and Co are still highly toxic and thus must be reduced to sub ppm levels in final drug compounds in order to meet stringent safety standards imposed by regulatory authorities.[14]

To circumvent these shortcomings, biocatalytic approaches employing catalytically active proteins known as enzymes have long been established as green alternatives for industrial processes. While

enzymes can show extremely high levels of both enantio- and site selectivity their performance is intrinsically substrate dependant due to the size and precise positioning of catalytically active residues in the active site. Enzymes can now be engineered to bind specific substrates thanks to great advances in the field of directed evolution for which Frances Arnold was jointly recognized with the Nobel prize in 2019.[15] This process however does require specialty equipment and complementary skillsets which are not always readily available in synthetic organic chemistry laboratories.

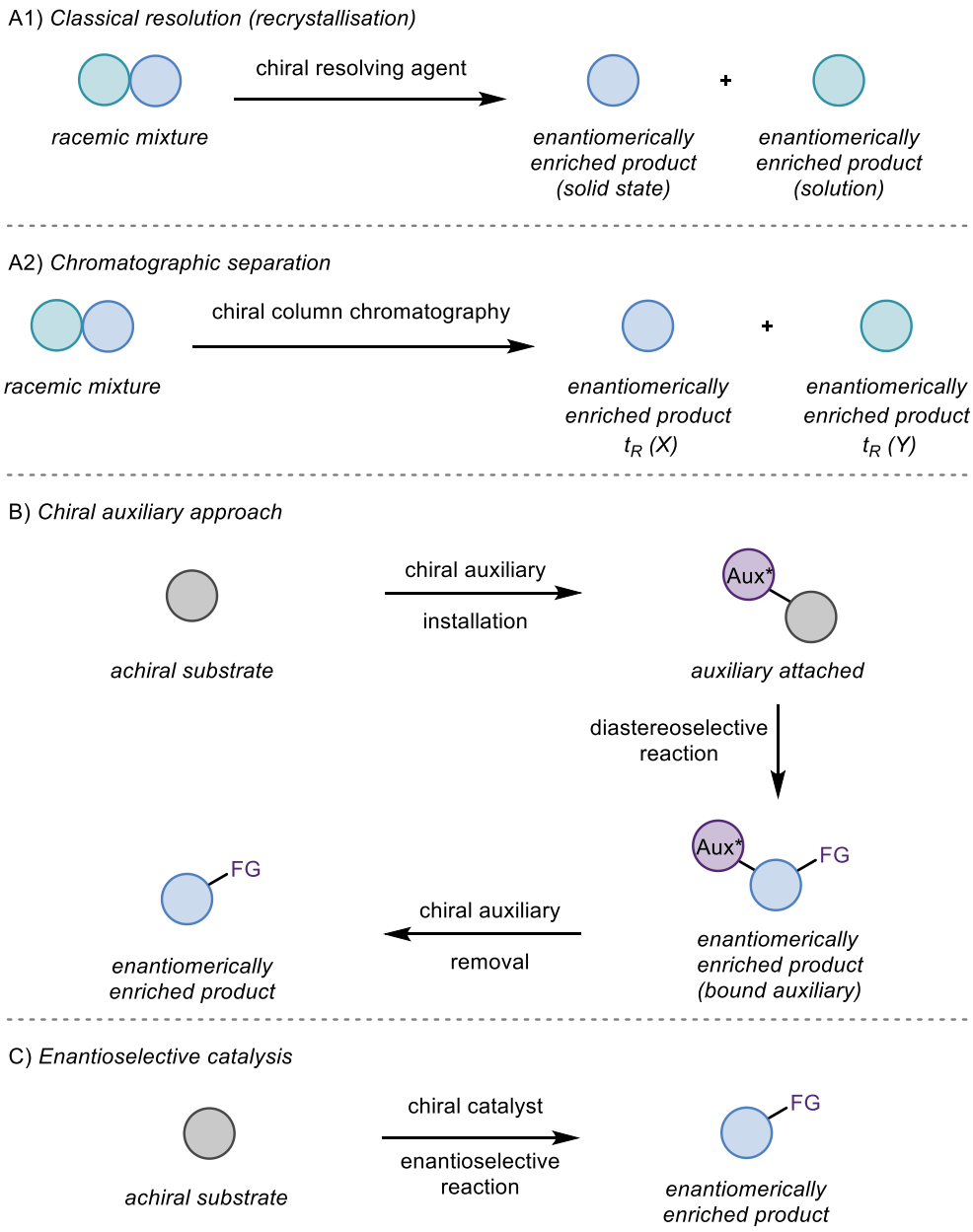


Figure 2. Approaches to asymmetric synthesis.

1.1.3 The dawn of organocatalysis

Chemists have long sought to emulate nature by designing metal-free catalysts which could perform biomimetic reactions with high levels of enantiocontrol by imitating enzymatic active sites with small molecules. This would overcome the inherent limitations of enzymatic processes such as substrate dependence and incompatibility with organic solvents or specific functional groups as well as cost and safety issues associated with transition metal catalysts. Indeed, since the popularisation of the term by MacMillan in 2000,[16] organocatalysis has flourished as a complementary and alternative approach to metal and enzyme catalysed processes.[17,18]

Organocatalysts can often be readily synthesised in a small number of steps from commercially available starting materials and be readily tuned for optimal catalyst performance. In addition, these catalysts are generally air and moisture stable and do not require rigorous oxygen and moisture exclusion from the reaction mixture and can therefore be more user-friendly for the experimental chemist compared to metal-based catalysts. These inherent advantages alongside the development of numerous distinct classes of organocatalysts for a wide range of disparate transformations have garnered considerable interest in these molecules by the synthetic community (**Figure 3**).

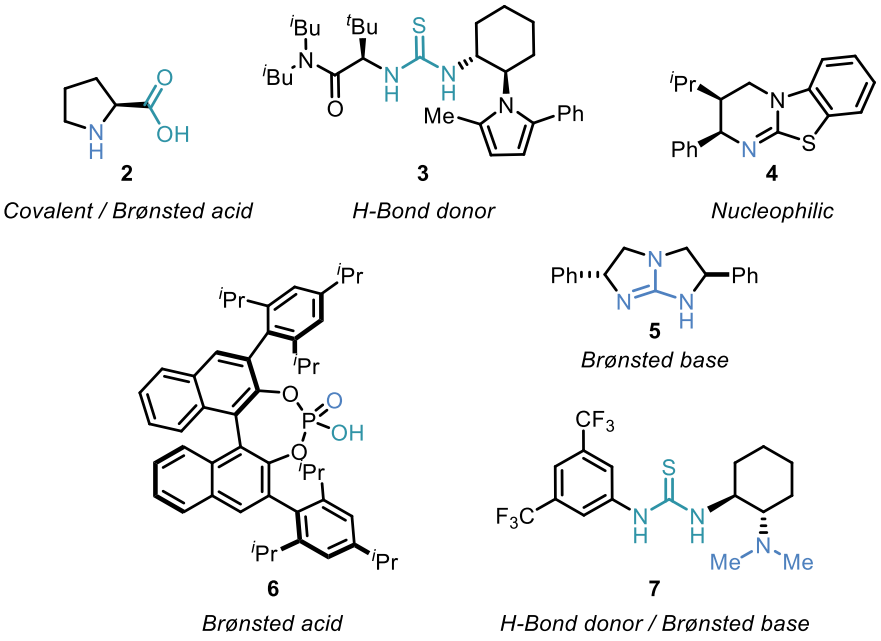
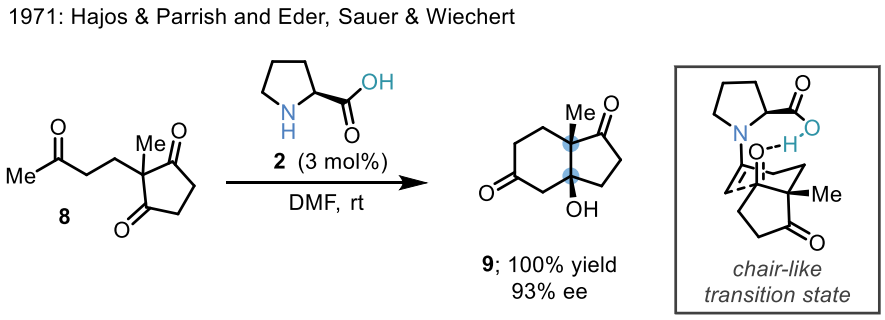


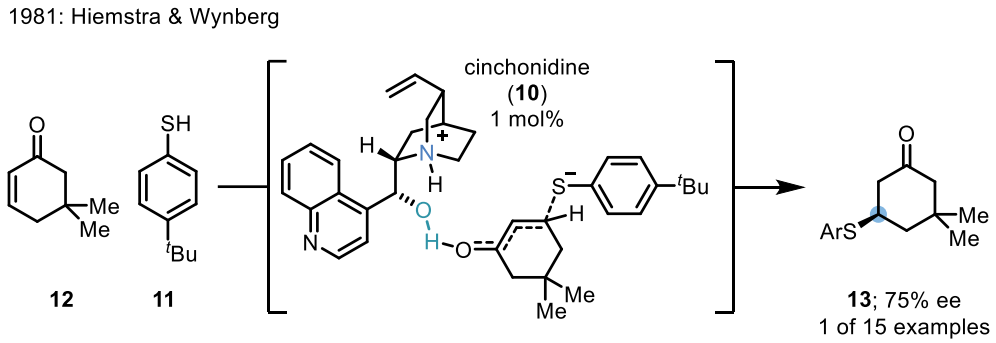
Figure 3. Examples of different classes of organocatalysts.

The field, however, was late to flourish and for its full potential to be widely recognised. Indeed, Dieter Seebach did not include organocatalysis among his vision for the future of synthetic methods in 1990.[19] This could be attributed to the fact that organocatalytic reactions were scarce in the early to mid 20th century with only sporadic reports focussing on individual transformations without extrapolating the fundamental catalytic concepts which could be applied to further reaction types.[20] Most famous among these are the almost simultaneous reports by Hajos and Parrish[21] and by Eder, Sauer and Wiechert[22] whereby triketone **8** was cyclized enantioselectively to medicinally relevant bi-cycle **9** in an impressive 93% ee by employing proline (**2**) as catalyst (**Scheme 1**). The reaction is believed to proceed *via* a chair-like transition state in which the proline derived enamine attacks one of the prochiral (enantiotopic) ketones discriminated by an intramolecular H-bonding interaction between the proline carboxylic acid residue and the carbonyl moiety.[23,24]



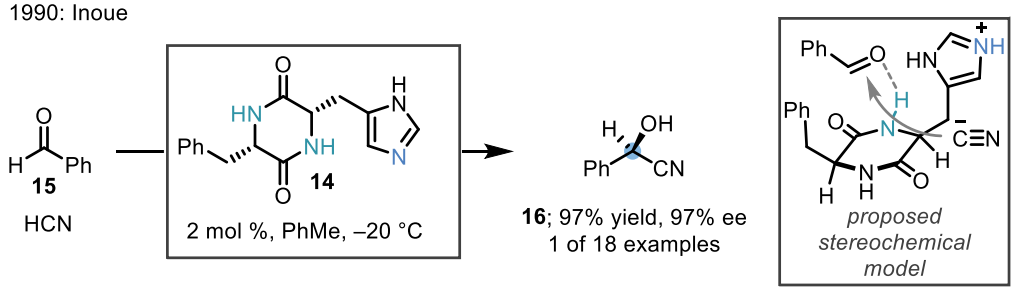
Scheme 1. The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

A comprehensive study by Hiemstra and Wynberg published in 1981,[25] demonstrated the use of cinchonidine (**10**) as catalyst for the sulfa-Michael addition of thiophenol **11** to enone **12** to afford adduct **13** with moderate levels of enantioselectivity. Most importantly the authors demonstrated, for the first time, that the hydroxyl group present on the catalyst was key for obtaining good levels of enantiocontrol. The authors postulated that an intermolecular H-bonding interaction from the cinchonidine hydroxyl group to the enone activated the electrophile, whilst an ionic interaction between the ammonium salt and the deprotonated thiol directed the nucleophile (**Scheme 2**).



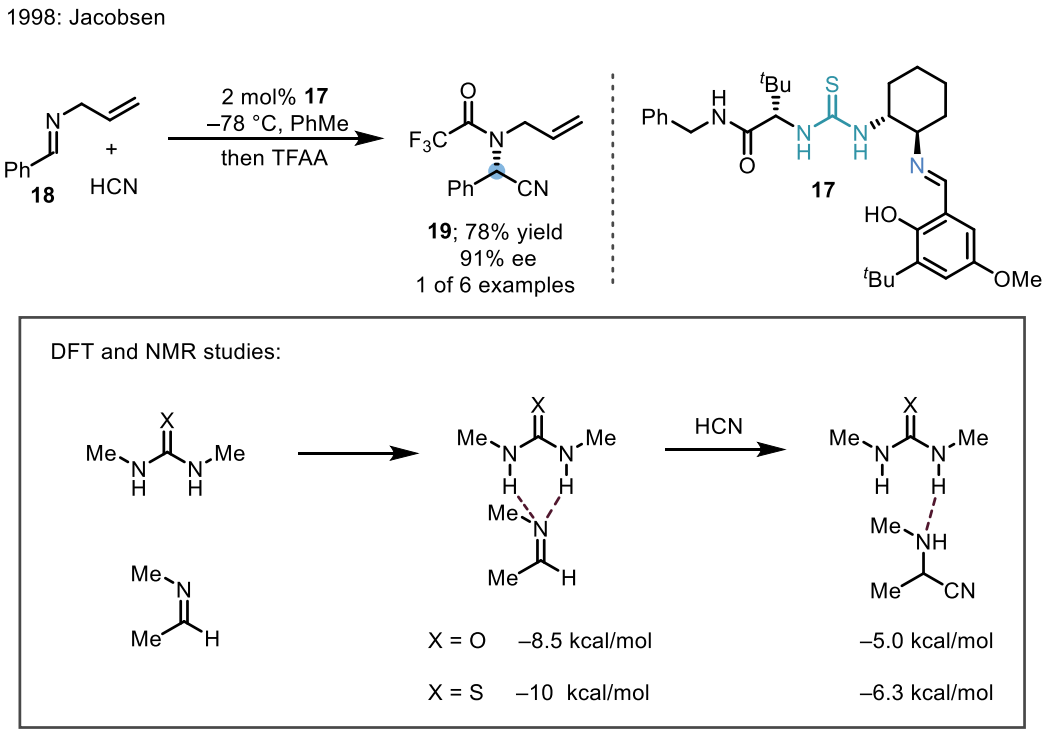
Scheme 2. Hiemstra & Wynberg's cinchonidine catalysed sulfa-Michael addition to enones. Ar= 4-*tert*-butyl-C_6H_4.

Another early example demonstrating the importance of non-covalent interactions in organocatalysis was demonstrated by Inoue in 1981[26] and further expanded upon in 1990.[27] The authors disclosed an elegant metal-free hydrocyanation of aldehydes catalysed by a small cyclic diketopiperazine (**14**) (synthesised by condensation of L-phenylalanine and L-histidine) designed to mimic oxynitrilase.[28,29] By employing only 2 mol% of diketopiperazine catalyst **14**, Inoue demonstrated the hydrocyanation of benzaldehyde (**15**) to cyanohydrin **16** in 97% yield and 97% ee. H-bonding was again invoked as the key non-covalent interaction directing the stereochemical outcome of the reaction. It was proposed that the aldehyde carbonyl moiety was hydrogen bound to the conformationally rigid keto piperazine N−H, with the sterically more demanding phenyl group pointing away from the concave face of the catalyst. The nucleophile could then attack one face of the aldehyde preferentially affording enantioenriched product **16**.[30] Non aromatic aldehydes were also found to participate in the reaction albeit with reduced levels of enantiocontrol (**Scheme 3**).



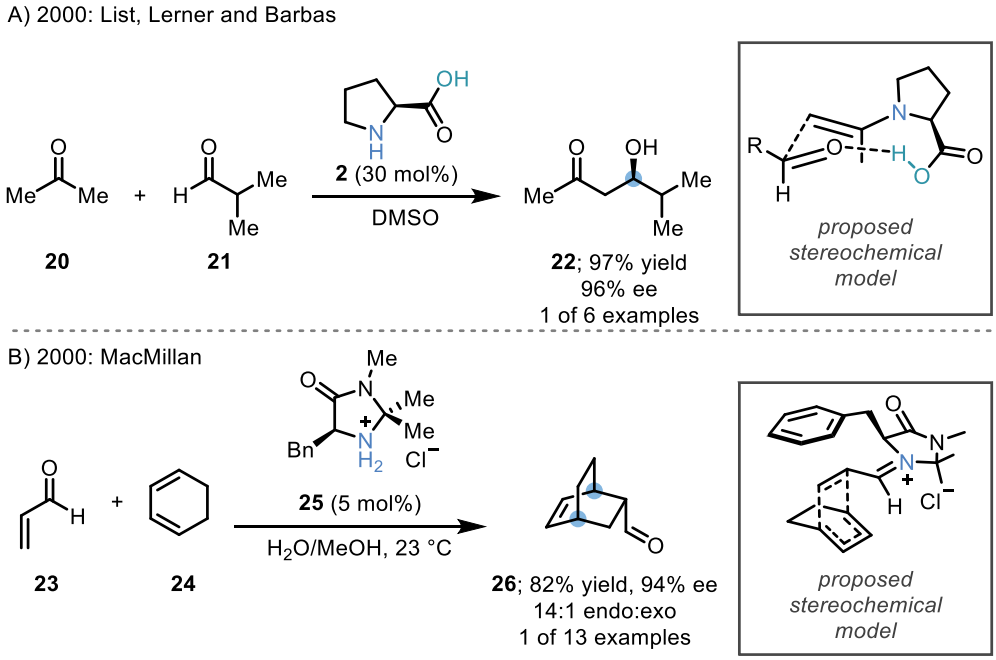
Scheme 3. Inoue's hydrocyanation of benzaldehyde.

Following Inoue's report, in 1998, Jacobsen serendipitously discovered and subsequently developed the first example of (thio)urea hydrogen-bonding catalysis in an asymmetric Strecker reaction.[31] Thus, while in search of novel metal ligands to perform the aforementioned transformation the authors discovered that the ligand scaffold itself was catalytically competent. Indeed, after extensive optimization of the catalyst structure 2 mol% of thiourea-bearing Schiff base **17** promoted the addition of HCN to imine **18** and (following acylation with TFAA) afforded enantioenriched product **19** in 78% yield and 91% ee (**Scheme 4**, top). Subsequent DFT and NMR studies revealed that substrate binding to the (thio)urea moiety *via* H-bonding was energetically favourable by 8.5 to 10.0 kcal/mol whilst product binding was found to be less energetically favourable allowing for catalyst turnover to occur (**Scheme 4**, bottom).[32] This catalyst class was later found to be applicable to the addition of a wide range of pronucleophiles to imines including silyl-ketene acetals,[33] phosphites[34] and nitroalkanes[35] as well as indoles in an acyl Pictet–Spengler reaction.[36]



Scheme 4. Jacobsen's asymmetric Strecker reaction and summary of DFT and NMR studies elucidating the role of the H-bond donor.

Arguably, and despite these advances, it wasn't until 2000, with the almost simultaneous disclosure of two reports, (the first by List, Lerner and Barbas (**Scheme 5A**)[37] and the second from MacMillan (**Scheme 5B**)[16]) that the field of organocatalysis began to rapidly develop.



Scheme 5. A) List, Lerner and Barbas' proline catalysed enantioselective intermolecular aldol reaction. B) MacMillan's organocatalysed enantioselective Diels-Alder reaction.

In their seminal report, List and co-workers described a proline catalysed aldol reaction between ketones and aldehydes. The authors proposed the condensation of proline (**2**) with acetone (**20**) which, following tautomerisation to the corresponding nucleophilic enamine, attacked the non-enolisable aldehyde **21** affording aldol product **22** in excellent yield and with high levels of enantiocontrol. The excellent enantioselectivity of the reaction resulted from a key H-bond interaction between the proline carboxylic acid residue and the aldehyde carbonyl thereby activating it. The two coupling partners are thus arranged in a Zimmerman-Traxler chair-like transition state with the bulky substituent on the aldehyde occupying a pseudo-equatorial position thus dictating the absolute stereochemical configuration of alcohol **22**. The authors demonstrated the generality of their method involving enamine catalysis[38] on a variety of aromatic and aliphatic aldehydes in up to 97% yield and 96% ee.

MacMillan, in a complementary approach, demonstrated the generality of iminium catalysis[39] in a Diels-Alder cycloaddition between α,β-unsaturated enals such as **23** and cyclohexadiene (**24**). The reaction proceeded smoothly at room temperature with only 5 mol% of imidazolidinone·HCl catalyst **25**. The authors proposed that, upon condensation with the enal, the structurally defined catalyst places the bulkier vinyl substituent opposite the gem-dimethyl group to avoid energetically unfavourable allylic 1,3 strain while the benzyl group blocks the *si* face of the iminium to attack allowing for the formation of bicyclic aldehyde **26** with excellent enantioselectivities and endo selectivity.

Collectively these two reports, together with the seminal publications previously highlighted, paved the way for the field organocatalysis to flourish. Thousands of enantioselective metal-free reactions have since been reported by numerous groups around the world and, as of today, organocatalysis has been cemented as one of the pillars of modern homogeneous catalysis alongside transition metal and bio-catalysis.[40–42]

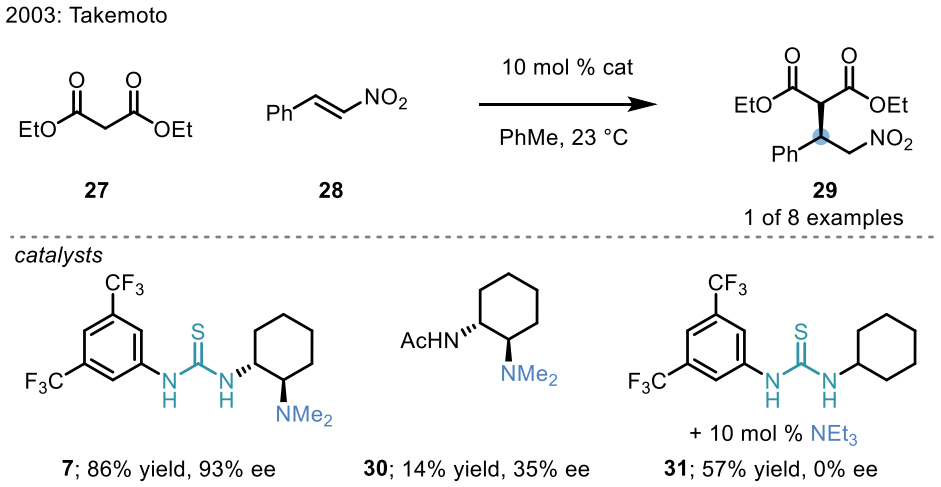
1.2 Bifunctional Organocatalysis

1.2.1 Early approaches

Among the numerous organocatalysts developed over the last two decades, bifunctional organocatalysts, which combine two catalytic residues within the same catalyst scaffold, have been particularly successful. Within this class of catalysts there exist two main families: the first are catalysts combining H-bond donor and Brønsted base residues[43,44] and the second are chiral phosphoric acids (CPAs) which, while extremely versatile, will not be discussed further within the context of this thesis.[45]

Takemoto was the first to report an explicitly designed bifunctional H-bond donor/Brønsted base organocatalyst. Takemoto's catalyst (**7**) combines a tertiary amine with the 3,5-$(CF_3)_2C_6H_3$ thiourea moiety. The addition of a Brønsted base within the catalyst scaffold allowed for activation of the pro-nucleophile *via* deprotonation, thus providing a distinct advantage over previous thiourea catalyst which only operate *via* a "pull" mechanism. This concept was demonstrated in the 1,4-addition of diethylmalonate **27** to nitro-olefins such as nitro-styrene **28** to afford enantioenriched **29** (**Scheme 6**).[46] Noticeably, when **30** was used as catalyst both the yield and ee were drastically decreased thus showing that the thiourea moiety was key for both substrate activation and enantiofacial control. Finally, when

thiourea **31** and 10 mol% triethylamine were employed as co-catalysts the yield was only moderate, clearly demonstrating the superior performance of the bifunctional catalyst which combines two catalytic components within a single molecular construct.



Scheme 6. Takemoto's enantioselective addition of malonates to nitrostyrenes.

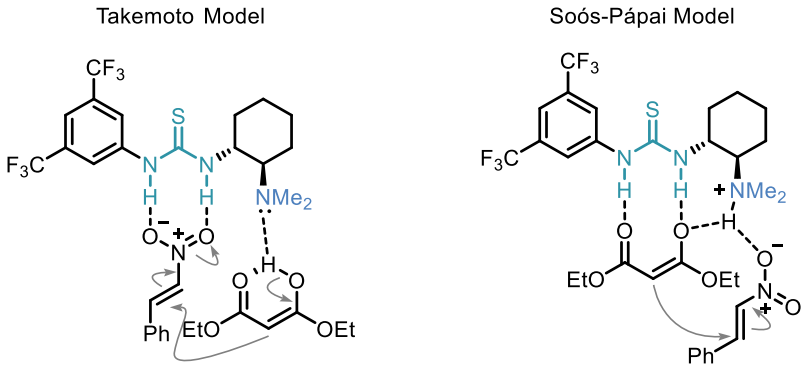


Figure 4. Alternative binding modes as proposed by Takemoto (left) and Soós and Pápai (right).

The authors postulated that the catalyst activates the electrophile (*via* H-bonding interactions) and the nucleophile (*via* deprotonation by the tertiary amine) simultaneously allowing for preferential attack of the enol to one face of the nitro-olefin as enforced by the chiral scaffold (**Figure 4**, left). Soós and Pápai later proposed an alternative mechanism based on computational studies (**Figure 4**, right).[47] While the calculations revealed that in both models, the rate determining step was the formation of the carbon-carbon bond, a novel transition state model whereby the tertiary ammonium salt binds the nitro-olefin and the enol is bound to the thiourea by H-bonds was found to be 2.7 kcal/mol more energetically favourable than the one proposed by Takemoto. These two models are not mutually exclusive, as both

lead to the same enantiomer of the product illustrating that the solution state of catalyst **7** is indeed far more complex than illustrative representations lead to believe.

1.2.2 *Cinchona* alkaloid derived bifunctional organocatalysts

Following Takemoto's landmark discovery in 2003 a suite of highly active bifunctional catalysts were disclosed by numerous other research groups from around the world.[48] Amongst these, one particularly prominent catalyst family were those derived from naturally occurring and abundant *Cinchona* alkaloids (**Figure 5**).[49,50] These catalysts exploit the quinuclidine core of the *Cinchona* alkaloids as an efficient chiral base while making use of the multiple synthetic handles present in the natural product to install a hydrogen-bond donor moiety and fine-tune the catalyst structure.

As an early proponent of this class of catalysts, in 2004, Deng employed catalyst **32** in the conjugate addition of malonate esters to aromatic nitro-olefins.[51] The authors claimed the free hydroxyl group on the quinoline ring activates the electrophile and is crucial for obtaining high levels of enantiocontrol.

The subsequent year, catalysts **33** and **34**, which combine a thiourea H-bond donor with the *Cinchona* scaffold, was disclosed almost simultaneously by four research groups. Soós employed **34** in a highly enantioselective (up to 98% ee) Michael addition of nitromethane to chalcone derivatives.[52] Chen later demonstrated the efficacy of catalyst **33** in the mildly enantioselective 1,4-addition of thiophenol to α,β-unsaturated enones and imides.[53] Finally, Connon[54] and Dixon[55] reported that **34** or **33** respectively, could promote the conjugate addition of malonate esters to nitro-olefins with excellent levels of enantiocontrol. Importantly, in all cases, the presence of both the Brønsted base and the H-bond donor was crucial for obtaining high levels of reactivity and enantiocontrol.

Further catalyst modifications were then introduced by Hiemstra and Rawal. Hiemstra demonstrated the use of catalyst **35**, which bears a thiourea motif on the quinoline ring, in the enantioselective Henry reaction of nitromethane to aromatic aldehydes.[56] Rawal instead introduced squaramides as novel, highly effective hydrogen bond donors.[57] Indeed only 0.5 mol% of catalyst **36** was required to promote the enantioselective conjugate of 1,3-dicarbonyl compounds to nitro-olefins in 8 to 24 hours.

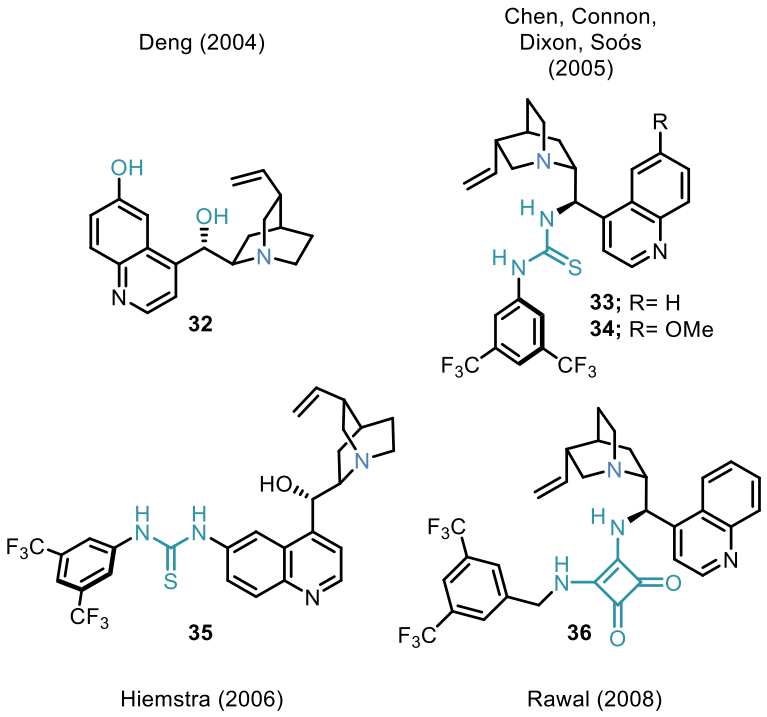


Figure 5. Representative *Cinchona* alkaloid derived bifunctional organocatalysts.

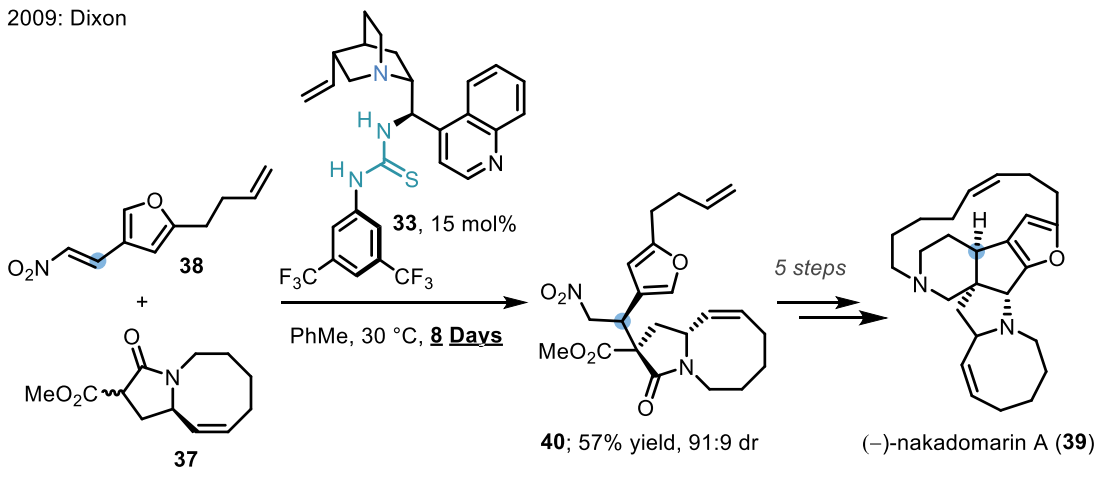
Collectively, the bifunctional tertiary amine Brønsted base catalysts highlighted above, alongside further seminal contributions by Pedrosa,[58] Berkessel[59] and Jacobsen,[60] have been responsible for a plethora of significant reports on enantioselective polar addition reactions over the past decade.

1.2.3 Limitations of tertiary amine bifunctional organocatalysis

Despite their success, however, some severe limitations of tertiary amine Brønsted base H-bond donor catalysts exist, such as high catalyst loadings (usually 10-20 mol%) and long reaction times (1-2 days).[48] An inherent limitation of utilizing a Brønsted base catalyst incorporating chiral tertiary amines is the narrow range of pronucleophiles accessible, limited by their high acidity and resulting in conjugate bases of only moderate nucleophilicity.[61] As previously illustrated, good catalytic performance was observed with β-ketoesters (pK_a of 14.2 in DMSO) pro-nucleophiles and highly electrophilic nitro olefins at cryogenic temperatures when using bifunctional *Cinchona*-derived catalysts. In contrast, when similar catalysts were employed with a lower acidity pro-nucleophile such as nitromethane (pK_a of 17.2 in DMSO) in conjugate additions to chalcones, substantial reaction times (122 hours) were required to obtain substantial yield of product at room temperature.[52] The activation of higher pK_a pronucleophiles

is even more challenging, with reported methods being scarce and often relying on Lewis acid co-catalysis.[62]

Due to this reactivity issue, highly reactive electrophiles such as imines derived from aldehydes, nitro-styrenes, enals and enones are commonplace, with numerous groups including our own resorting to the use of carboxylic acid derivatives possessing electron withdrawing groups (i.e. N-acyl pyrazoles,[63] and fluorinated[64] or aryl esters[65]) to increase electrophilicity. This approach, however, results in poor atom economy and requires extra synthetic steps for activating group installation and removal. Furthermore, there are cases in which such groups cannot be installed. An example of this is a key Michael addition between **37** and nitro-olefin **38** in Dixon's total synthesis of (−)-nakadomarin A (**39**) in which bifunctional *Cinchona* derived catalyst **33** delivered the desired adduct **40** with 91:9 dr but with a long reaction time of 8 days (**Scheme 7**).[66]



Scheme 7. Dixon's diastereoselective addition of malonamide **37** to nitro-olefin **38** en-route to (−)-nakadomarin A.

Addressing these issues would be highly beneficial, allowing for chiral Brønsted base catalysts to become more widespread as an alternative to transition metal catalysts within a large-scale industrial setting. One solution that addresses the limits of reactivity of bifunctional organocatalysts is to consider catalyst designs that incorporate superbasic functionalities as alternative Brønsted bases to tertiary amines.[67]

1.3 Enantioselective Superbase Catalysis

1.3.1 Definition of superbases

The term superbase is loosely defined to include any compound with a basicity higher than that of proton sponge (**41**, pK_{BH^+} 18.7 in MeCN).[67] This definition encompasses a variety of strong organic bases such as guanidines and phosphazines (**Figure 6**).[68]

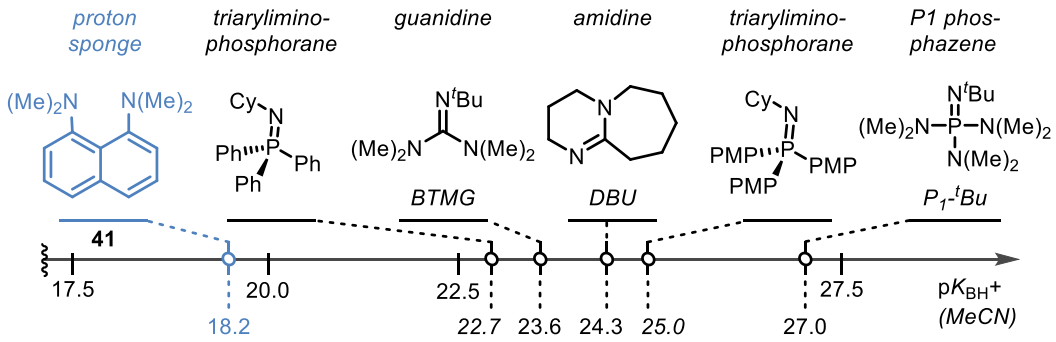
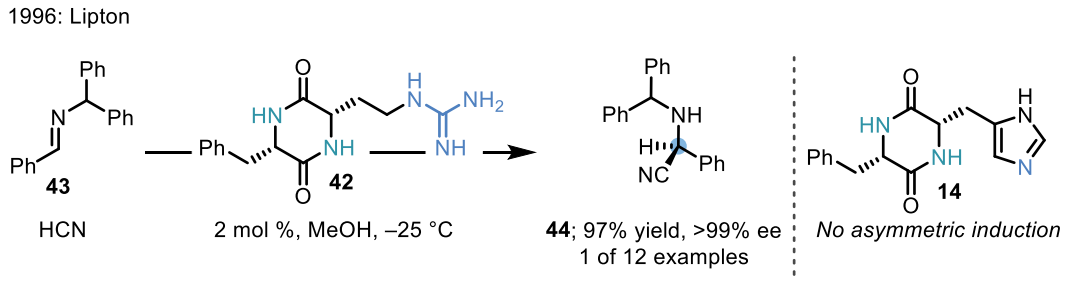


Figure 6. pK_{BH^+} scale of representative organosuperbases in MeCN. PMP= *para*-methoxy phenyl.

1.3.2 Chiral guanidine catalysis

The superbasic moiety most incorporated into organocatalysts are guanidines.[69,70] Guanidines possess increased basicity compared to tertiary amines due to increased resonance stabilisation of the protonated guanidinium cation from the additional nitrogen lone pairs. The first pioneering study of chiral guanidine as a Brønsted based catalysts was reported by Nádjera in 1994, with modest enantioselectivities being achieved in a nitro-aldol reaction.[71] The first highly enantioselective guanidine catalysed reaction was described by Lipton,[i] who employed (*S*)-norarginine derived catalyst **42** to promote an enantioselective *Strecker* reaction utilising substituted imines (**43**) affording 1,2-addition product **44**. Lipton found that replacing the imidazole moiety from Inoue's catalyst (**14**) (which provided no asymmetric induction in this reaction) with a more basic guanidine was key to accelerate proton transfer and thus promote high levels of reactivity and enantioselectivity (**Scheme 8**).[72]

[i] It is worth highlighting that, despite Lipton's report having been cited 288 times (as of May 2021), in the hands of other authors the method was found to be poorly reproducible,[152] thus casting doubt on the validity of Lipton's studies.



Scheme 8. Lipton's guanidine catalysed asymmetric Strecker reaction.

Three years later, in 1999, Corey disclosed the use of bicyclic guanidine **5** in the same reaction.[73] An analogous catalyst (**45**) was later utilized by Tan for the enantioselective conjugate addition of secondary phosphine oxides (SPOs) to nitrostyrenes.[74] Tan later postulated that, upon deprotonation of the nucleophile, the resulting guanidinium cation can act as a hydrogen bond donor directing nucleophilic attack.[75] In the years following Corey's report, a number of chiral guanidine catalysts were disclosed (**Figure 7**).

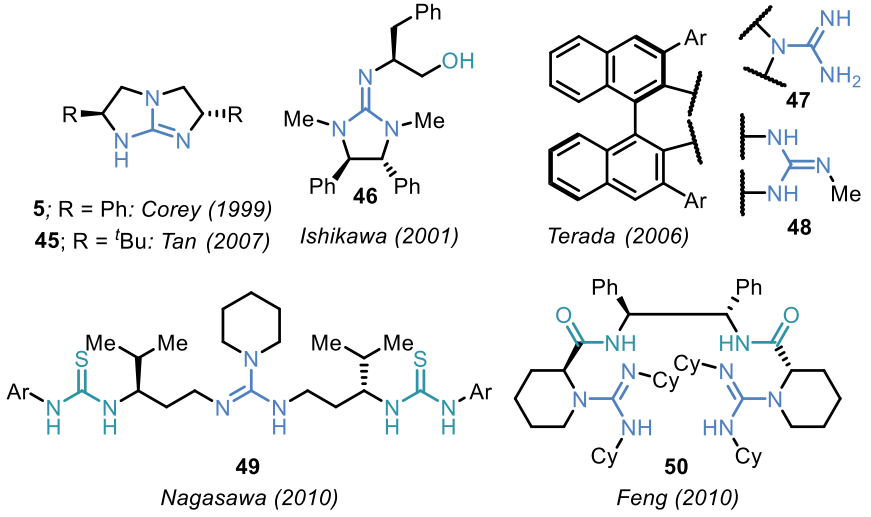


Figure 7. A selection of representative guanidine derived superbase catalysts. **47**; Ar = 4-(3,5-*t*-$Bu_2C_6H_3)C_6H_4$. **48**; Ar = 3,5-(3,5-di-*tert*-butylphenyl)$_2C_6H_3$.

Ishikawa subsequently developed bifunctional chiral guanidine catalyst **46**.[76] The incorporation of a hydroxyl H-bond donor was essential to obtain high levels of enantioselectivity (up to 97% ee) in the addition of glycine imine to acrylic esters.[77] It is worth noting that no reactivity was observed in the

presence of 20 mol% of quinine, demonstrating the superior performance of guanidine based catalysts compared to those bearing tertiary amines in this reaction.

Terada introduced axially chiral guanidines **47** and **48** in 2006. Seven membered guanidine **47** was found to be optimal in the asymmetric electrophilic amination of 1,3-dicarbonyl compounds[78] while nine-membered guanidine **48** was an efficient catalyst in the 1,4-addition of 1,3-dicarbonyls to nitroolefins.[79] A H-bonded ion pair between the chiral guanidinium cation and the deprotonated nucleophile anion was, once again, invoked by the authors to explain the origins of enantioselectivity.[78] These catalysts were found to be proficient in a variety of asymmetric transformations such as a Henry reaction with benzaldehydes,[80] the aldol reaction between furanones and aldehydes[81] and α-amination of α-ketoesters.[82]

Nagasawa disclosed bifunctional guanidine **49** which possesses the Brønsted base nestled within a C_2 symmetric scaffold bearing two thioureas as H-bond donor groups. **49** was effective in catalysing the Mannich reaction between N-Boc imines and malonates,[83] as well as promoting the 1,4-type Friedel-Crafts reaction between phenols and nitroolefins.[84]

Also in 2010, Feng introduced a highly versatile, DCC derived, chiral bis-guanidine catalyst **50** for the enantioselective (up to 99% ee) inverse-electron-demand hetero-Diels-Alder reaction of chalcones with azlactones.[85] Later, the same authors described the use of an analogous catalyst in the direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactams with alkylidene malonates[86] and then demonstrated the use of the $HBAr^{F}_4$ salt of **50** in the asymmetric oxyamination of azlactones[87].

1.3.3 Further advances in enantioselective superbase catalysis

Despite the development of numerous elegant catalytic systems incorporating guanidines and amidines[88–90] as alternative Brønsted basic sites to tertiary amines, these functional groups have a relatively low pK_{BH^+} when compared to other known superbasic motifs (**Figure 8**). In a bid to further boost catalyst performance, various designs for chiral catalysts incorporating stronger superbases such as cyclopropenimines and phosphazenes have been disclosed.[91–95]

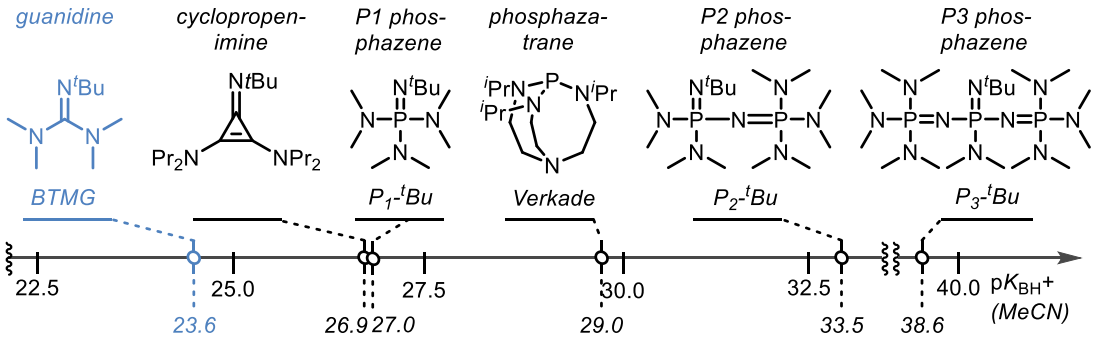
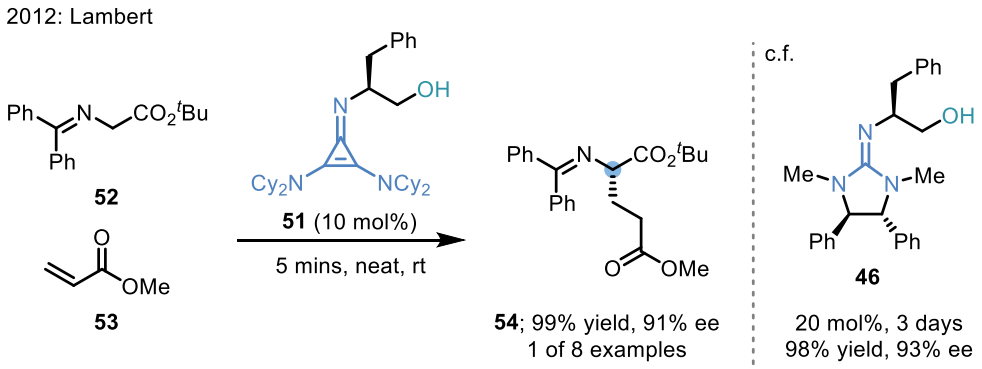


Figure 8. Representative organosuperbases with higher pK_{BH^+} than BTMG in MeCN.



Scheme 9. Lambert's chiral cyclopropenimine catalysed asymmetric 1,4-addition of glycine imines to acrylate esters and comparison with Ishikawa's guanidine-based catalyst.

The basicity of cyclopropenimines had been calculated by Maksić in 1999 to exceed that of guanidines.[96,97] This greater basicity is due to the developed positive charge being stabilized within the resulting aromatic cyclopropenium ion in addition to three N lone pairs. It was not until 2012, however, that this was verified experimentally by Lambert, which showed that the basicity of cyclopropenimine is comparable to that of a P1-phosphazene (26.9 vs 27.0 pK_{BH^+} in MeCN).[98] In the same report, Lambert disclosed the first chiral cyclopropenimine catalyst, **51** (incorporating the same alcohol based H-bond donor employed in 2001 by Ishikawa) which was shown to be crucial for substrate binding and enantiocontrol by later in-depth DFT-calculations.[99] The authors employed this novel catalyst to high effect, demonstrating it's far superior performance to catalyst **51** in the enantioselective 1,4-addition of glycine imines (**52**) to acrylate esters (**53**) which afforded Michael addition product **54** (**Scheme 9**). The same catalyst was later applied again by Lambert in an analogous Mannich reaction to N-Boc aldimines using the same nucleophile[99] and by Jørgensen in the enantioselective [3+2] cycloaddition of 2-acyl

cycloheptatrienes to azomethine ylides.[100] In both of these reactions, cyclopropenimine catalyst **51** was demonstrated to vastly outclass known *Cinchona*-derived bifunctional organocatalysts.

Unfortunately, as is commonly observed in multiple superbase catalysts of high pK_{BH^+}, **51** was observed to decompose over time in the solid state ($t_{1/2}$=15 days at rt and 8 months at −20 °C) and even more dramatically in solution ($t_{1/2}$= 7 hr). This drawback led Lambert and co-workers to later disclose a new catalyst (**55**) which utilises a more stable chiral scaffold, resulting in greatly improved stability ($t_{1/2}$ of > 5 years at rt and 36 hours in solution) whilst maintaining high catalytic activity in the enantioselective 1,4-addition of glycine imines to a variety of Michael acceptors (**Figure 9**).[101] Lambert has also disclosed higher-order cyclopropenimines showing exceptionally high basicity (up to 42.1 pK_{BH^+} in MeCN), these however are yet to be employed in enantioselective catalysis.[101]

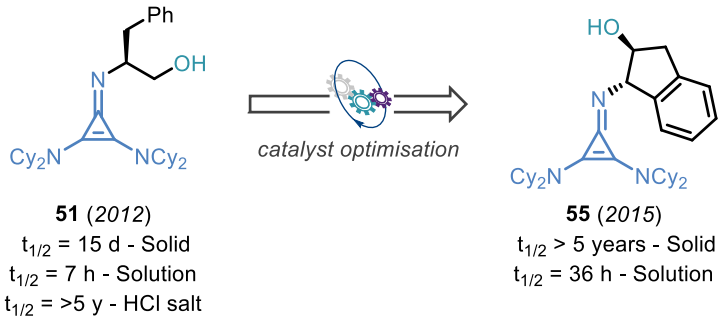


Figure 9. Improved stability of Lambert's second-generation chiral cyclopropenimine catalyst.

Phosphazene bases were first introduced by Schwesinger in 1985 and comprise of a P(V) atom bonded to three amines and one imine group.[102] Phosphazenes are inherently stronger bases than amidines and guanidines and their basicities can be further increased by the addition of other phosphazene units (**Figure 8**). The higher the number of N atoms the larger the increase in basicity.[103]

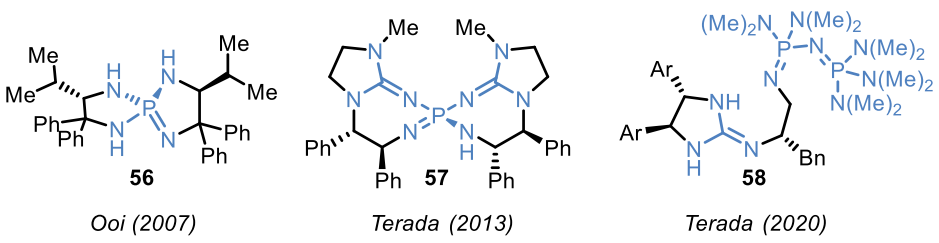
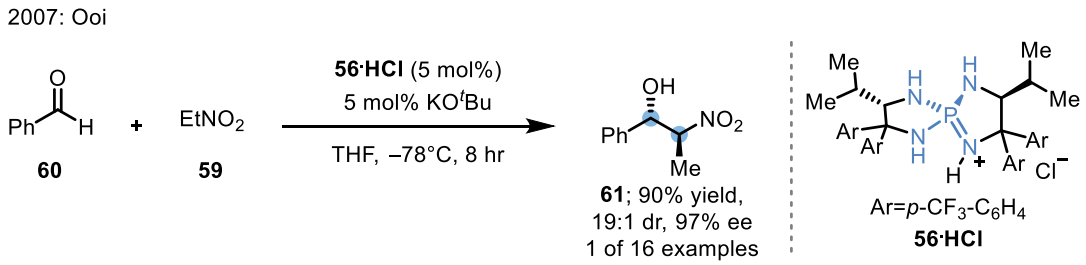


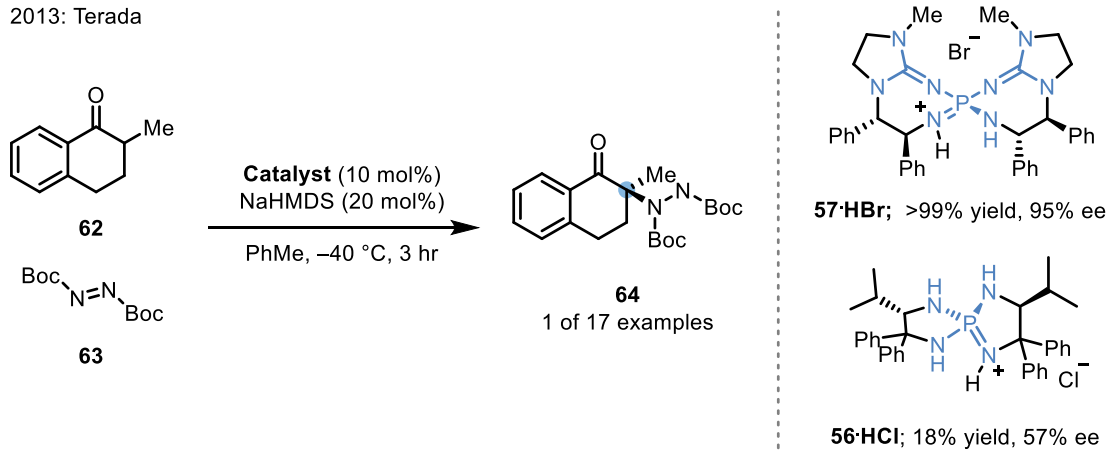
Figure 10. Representative chiral phosphazene superbase catalysts.

The first chiral phosphazene base was introduced by Ooi in 2007 (**Figure 10**).[104] The novel spirocyclic phosphazine (**56**) salt was synthesized from a L-valine-derived diamine and PCl_5. Its use as a chiral Brønsted base was demonstrated in a highly enantio- and diastereoselective Henry reaction where **56·HCl** was free-based *in-situ* with KO*t*Bu to generate the active catalyst (**Scheme 10**). The authors postulated that the phosphonium salt generated upon deprotonation of $EtNO_2$ (**59**) forms a H-bonded ion-pair[105] with the nucleophile, which, in turn preferentially attacks one face of **60** to deliver **61** with high enantioselectivity. This class of catalysts was later applied to a range of reactions including: the enantioselective hydrophosphonylation of aldehydes,[106] asymmetric 1,4-, 1,6-, and 1,8-conjugate additions,[107–109] an asymmetric Payne-type oxidation of N-tosyl imines[110,111], and most recently a glycolate aldol reaction of sulfur-substituted enediolates with aldehydes.[112]

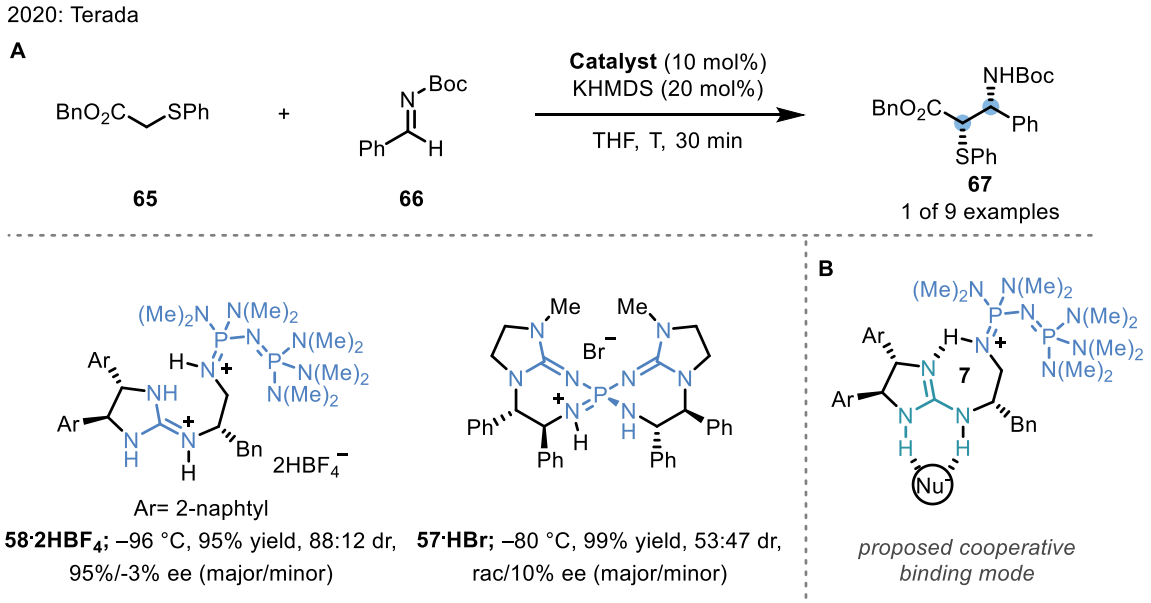


Scheme 10. Ooi's chiral phosphazene catalysed direct Henry reaction.

In 2013, inspired by the work of Kolomeitsev and Leito,[113] Terada disclosed an even stronger P-spiro chiral phosphazene compared to Ooi's by incorporating two guanidine subunits around the central P atom (**57**).[114,115] The superior performance of this highly basic catalyst was demonstrated in the enantioselective amination (up 98% ee) of tetralones such as **62** with azodicarboxylate **63**. The catalyst (**57**) was introduced in the reaction mixture as the HBr salt and free-based in-situ with 20 mol% of NaHMDS. It is worth noting, that under the same reaction conditions, Ooi's catalyst (**56**) performed poorly affording product **64** in only 18% yield and 57% ee (**Scheme 11**). This class of catalysts was subsequently employed in a variety of asymmetric Mannich-type reactions employing 2- alkoxycarbonyl-1,3-dithiane,[116] 2-alkyl thionolactones,[117] 2-benzylpyridine N- oxides,[118] and β,γ-epoxysulfones as nucleophiles.[119] Most recently, Terada also demonstrated the effectiveness of this catalyst class in enantioselective reprotonation applied to the asymmetric hydrophosphinylation of 1,1-vinyl azaheterocycle *N*-oxides.[120]



Scheme 11. Comparison between Terada's and Ooi's chiral phosphazene catalysts in the enantioselective amination of tetralone **62**.



Scheme 12. A) Terada's enantioselective direct Mannich-type reaction of α-phenylthioacetates. B) Proposed catalyst cooperative binding mode.

In 2020, Terada disclosed a new chiral phosphazene base, this time incorporating a P2- Schwesinger base in combination with a guanidine (**58**) (**Scheme 12**). This interesting design relies upon the interaction between the two basic functionalities, which, upon deprotonation of the nucleophile by the P2 moiety results in the formation a rigid 7-membered ring H-bond network creating a tight chiral pocket and allowing for the resulting guanidinium salt to form a H-bonded ion pair with the substrates (**Scheme 12B**).[121] The effectiveness of this catalyst was shown in the enantioselective direct Mannich-type reaction

of α-phenylthioacetates such as **65** to *N*-Boc aldimines (**66**) where 10 mol% **58**·2HBF$_4$ was free-based *in situ* by 20 mol% KHMDS. Mannich product **67** was obtained with higher ee when using **58** over chiral phosphazene **57** while maintaining similar levels of reactivity (**Scheme 12A**). The authors also demonstrated the use of a homologous catalyst incorporating a P3 base in the Mannich-type reaction of α-phenylthioacetamide which, whilst promising, only delivered the desired adduct in 58% yield and with moderate levels of enantio- and diastereoselectivity.

1.3.4 Limitations of chiral superbase catalysis

While collectively, novel chiral catalysts incorporating superbasic motifs have overcome many of the limitations imposed by tertiary amine-based catalysts, their often-challenging syntheses and lack of modularity have hampered penetration of these catalysts into mainstream use. In addition, the incorporation of highly basic functionalities such a cyclopropenamines and phosphazines leads to difficulty in handling and storage of the free-base catalyst. Groups such as those of Ooi and Terada have circumvented this issue by storing their catalysts as inorganic acid salts. Because of this, an equal amount of alkali metal Brønsted base such as KO*t*Bu or NaHMDS is required to generate the catalyst *in-situ* partially obviating the use of an organic superbase, especially given that highly active chiral ligands for alkali metal bases already exist.[122–126]

1.4 Bifunctional Iminophosphorane Catalysis

Recognizing the limitations of chiral tertiary amine bifunctional organocatalysts as well as chiral superbase catalysts (either through insufficient pronucleophile activation or ineffective enantiocontrol through lack of tunability) the Dixon group conceived a novel class of bifunctional superbase catalysts: bifunctional iminophosphoranes (BIMPs).[127]

By combining an inactive amino acid derived chiral organoazide bearing a tuneable H-bond donor group with an inactive, yet widely available, phosphine *via* a Staudinger reaction the superbasic moiety can be generated *in situ* as required, allowing for late-stage tuning of the iminophosphorane pK_{BH+} and improved ease of handling. Indeed, Dixon and co-workers were the first to measure the pK_{BH+} of triaryl-iminophosphoranes and thus to recognize their potential as superbasic motifs (**Figure 11**).[128]

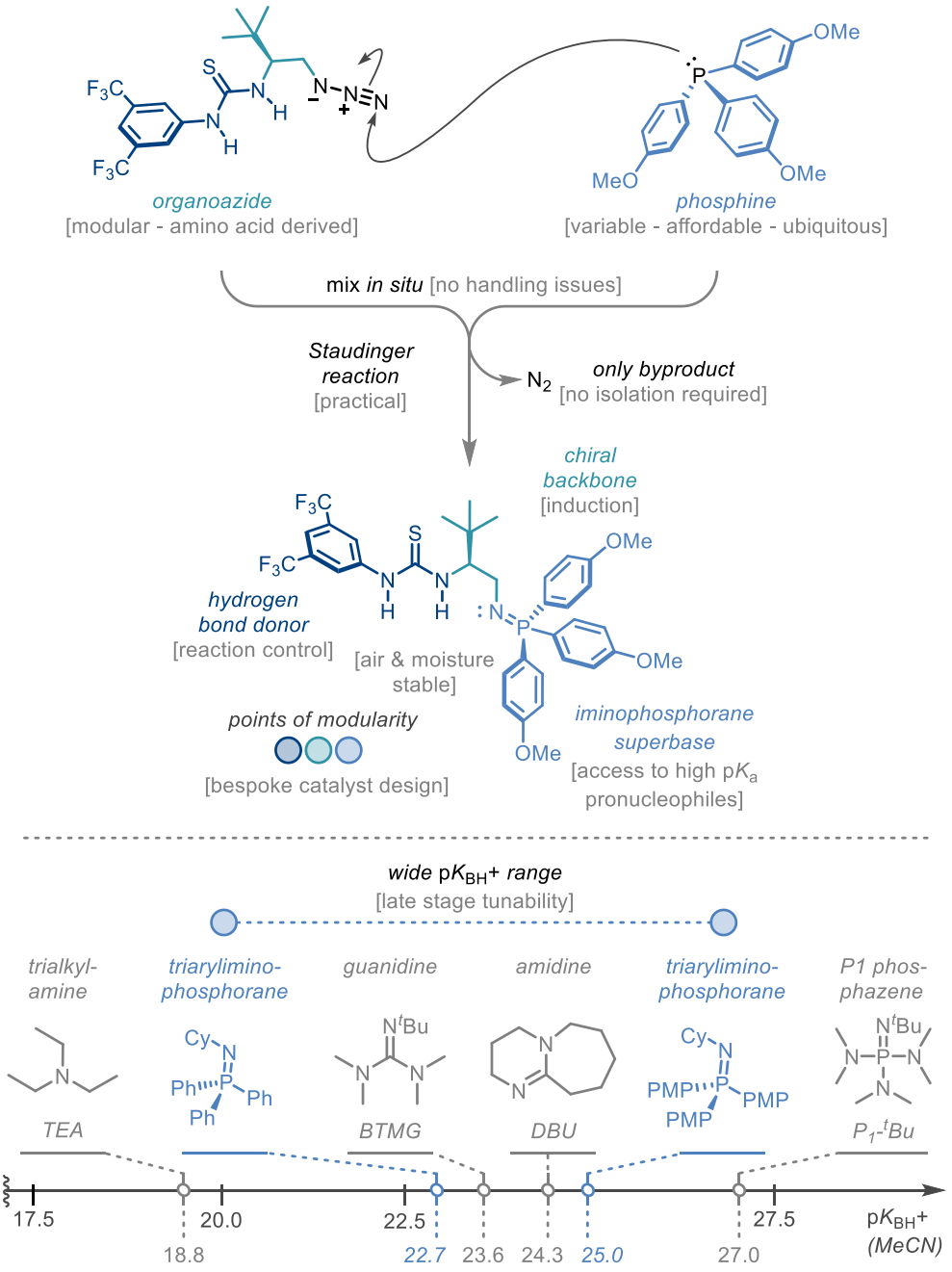
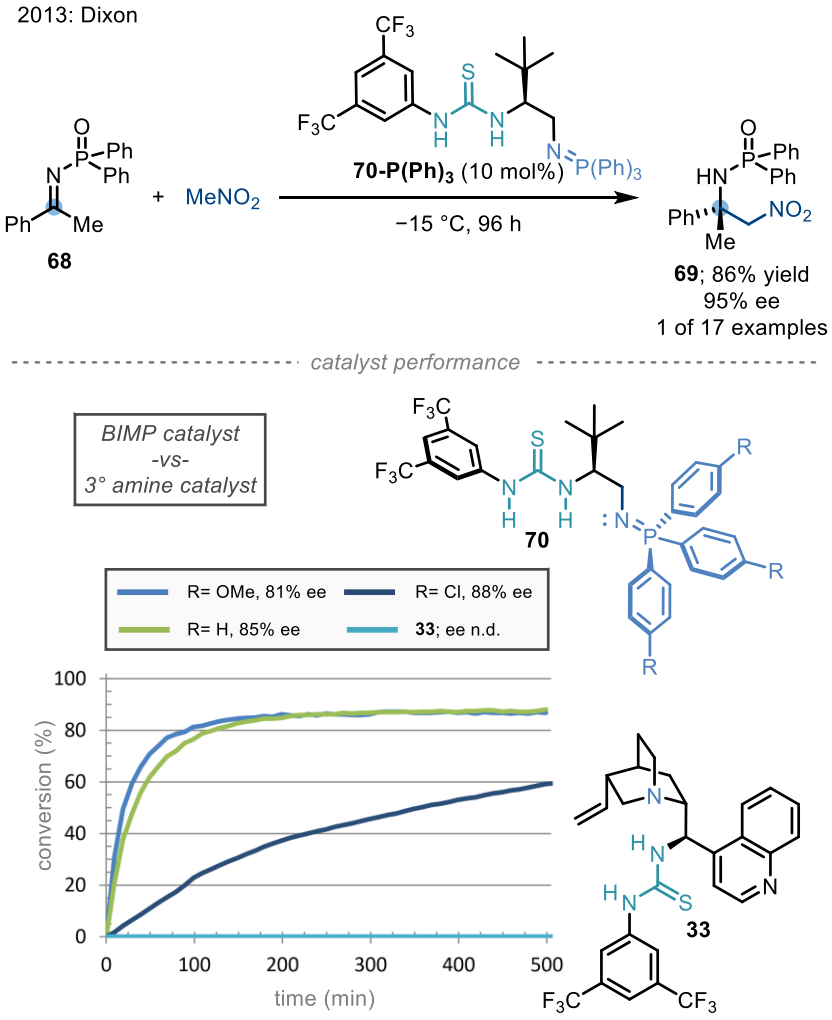


Figure 11. Representative formation of a bifunctional iminophosphorane catalyst and salient catalyst features.

While late-stage generation of the iminophosphorane superbase allows for maximum tunability, BIMP organocatalysts were also found to be both air and moisture stable and could be stored for over 2 years at −20 °C without any appreciable loss in activity.[129]

Through its highly modular design incorporating a variable H-bond donor group, chiral amino acid-derived scaffold and triarylphosphine-derived iminophosphorane superbase, the BIMP catalyst class has enabled exceptional performance in enantioselective Brønsted base catalysis.



Scheme 13. Dixon's BIMP catalysed enantioselective nitro-Mannich reaction to N-DPP protected ketimines and rate comparison between the BIMP catalysts and a *Cinchona* based tertiary amine catalyst.

In 2013, the use of bifunctional iminophosphoranes as catalysts was first demonstrated in the enantioselective addition of nitromethane to poorly reactive *N*-DPP ketimines (**68**) to afford enantioenriched amine products such as **69**.[128] Following the synthesis of a small library of BIMP catalysts, **70-P(Ph)$_3$** was found to be the optimal catalytic system for this reaction, vastly outperforming *Cinchona*-based catalyst **33**. The late-stage tunability of the catalyst was also demonstrated with P(*p*-Cl-C_6H_4)$_3$ derived BIMP catalyst performing at an appreciably lower rate compared to its PPh_3 and P(PMP)$_3$

derived counterparts. Finally, a decagram scale reaction was performed using only 1 mol% of **70-P(Ph)$_3$** to obtain 8.3 g of enantiopure protected β-nitroamine **69** (**Scheme 13**).

Following this seminal publication, the Dixon group, together with elegant contributions by Johnson, employed this newly developed class of catalysts in a wide array of 1,2-addition and 1,4-addition reactions demonstrating the adaptability of the BIMP catalyst system. These include: a phospha-Mannich reaction to N-DPP protected ketimines,[130] an enantioselective direct aldol addition of aryl ketones to α-fluorinated ketones,[131] an enantioselective Pudovik addition – phospha-Brook rearrangement cascade,[132] an asymmetric conjugate addition to enone diesters using nitroalkanes[133] or alkyl thiols[134] and the ring opening polymerization of lactones[135,136] and lactides (**Figure 12**).[137]

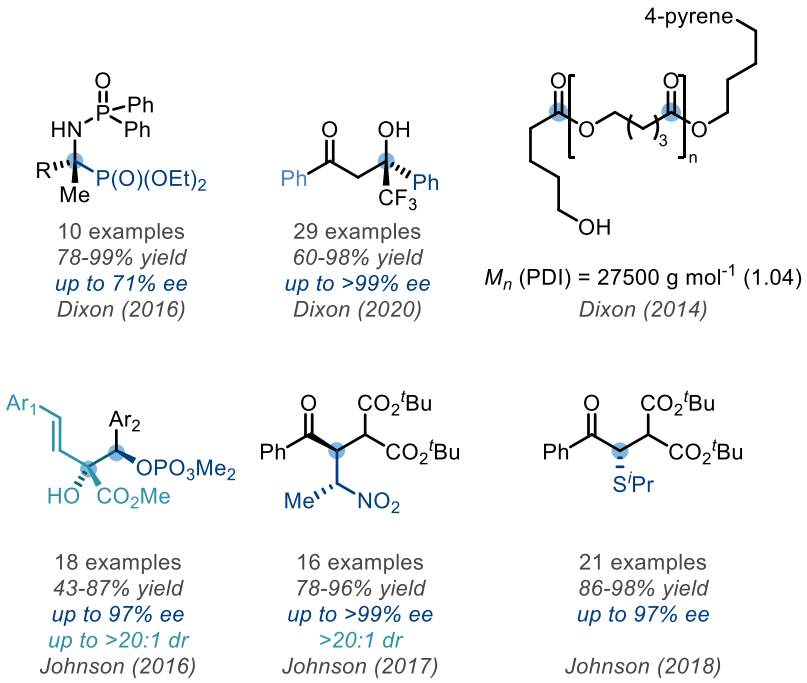


Figure 12. Overview of reactions catalysed by 1st generation BIMP catalysts.

An immobilized version of the BIMP catalyst **70** was also disclosed by Dixon in 2014.[138] The immobilised catalyst (**PS-70**) was easily obtained by combining the chiral azide (**70-N$_3$**) component with commercially available polystyrene supported PPh_3 thus elegantly generating the superbasic moiety, concomitantly with the immobilisation of the catalyst on a heterogeneous support (**Figure 13A**). The effectiveness and recyclability of **PS-70** was demonstrated in enantioselective nitro-Mannich and Michael-addition to nitro-styrene reactions. Additionally, **PS-70** was recycled and reused up to 11 times in the nitro-Mannich

reaction of ketimines without any notable loss in activity and selectivity (**Figure 13B**). This report also represents the only example of a solid-supported superbase catalyst to be used in multiple enantioselective reactions.[139]

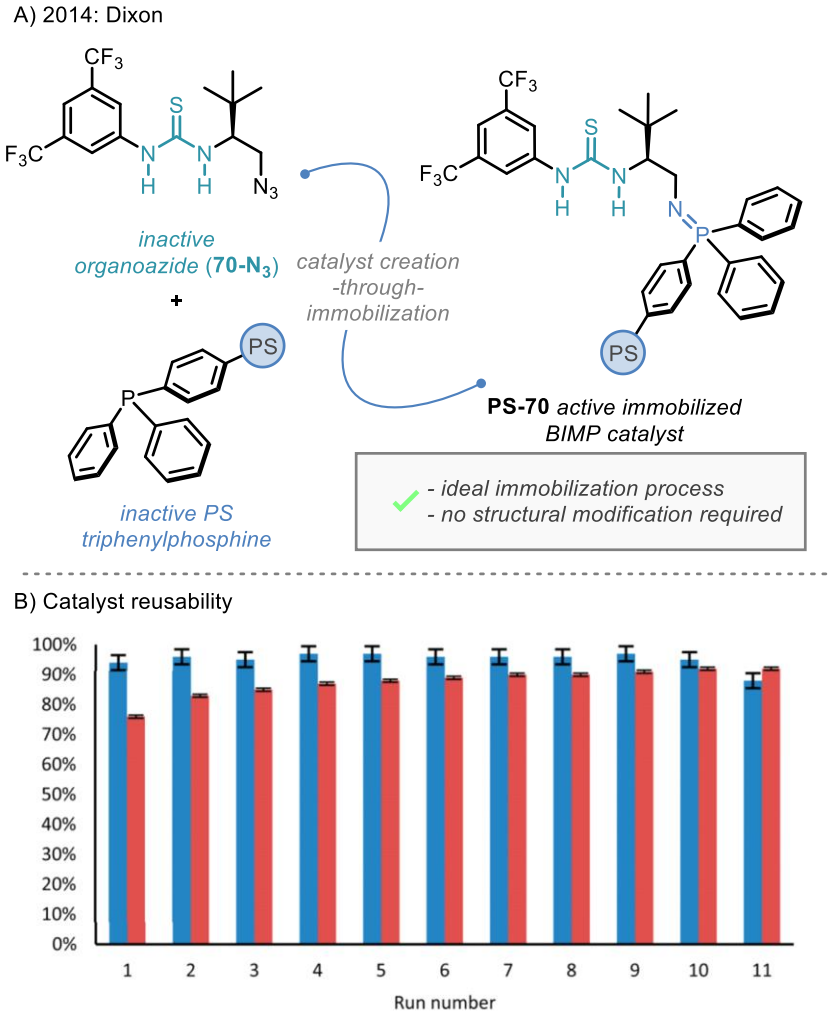
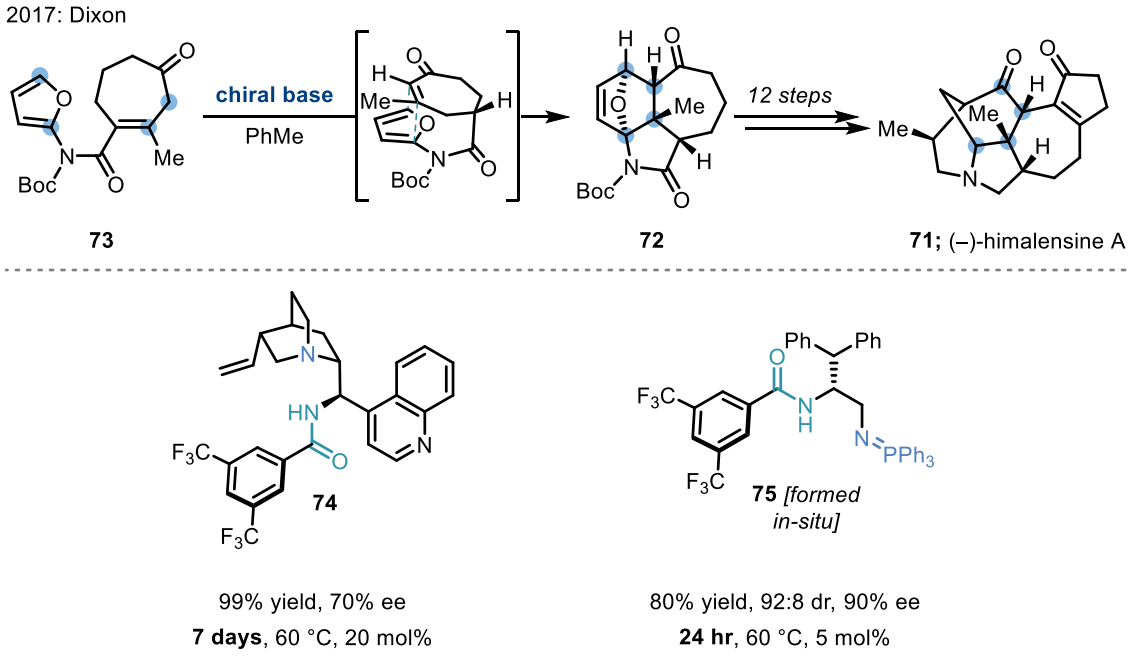


Figure 13. A) Simultaneous BIMP catalyst generation and immobilisation. B) Catalyst reusability over 11 runs in the nitro-Mannich reaction of ketimines. Blue= starting material conversion; Red= ee.

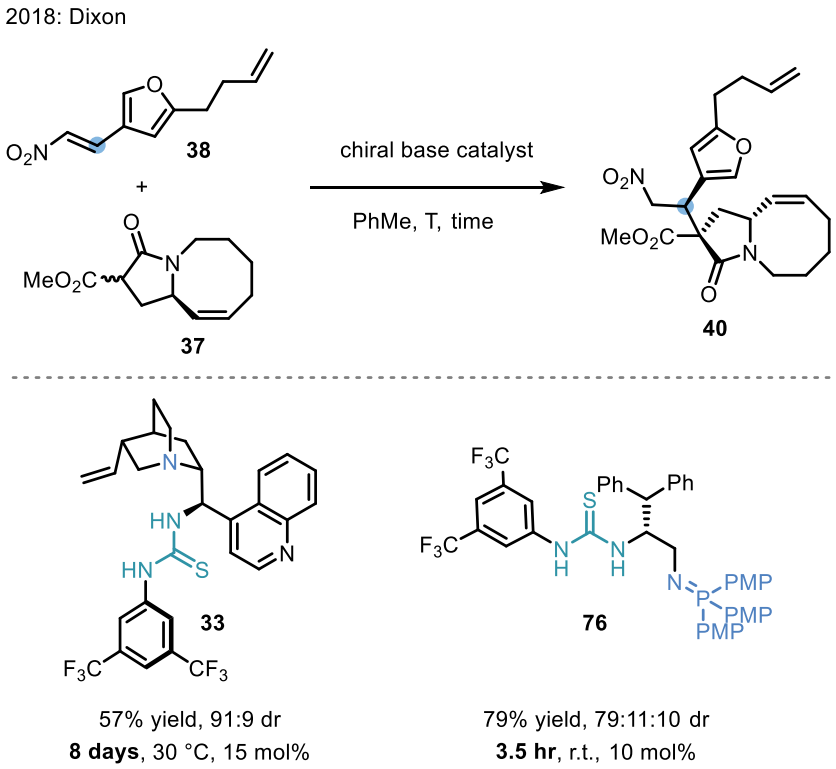
The first generation of BIMP catalysts were also first employed in the total synthesis of alkaloid natural product (−)-himalensine A (**71**) by Dixon in 2017.[140] The synthetic route included a novel base catalysed enantioselective prototropic shift / intramolecular Diels−Alder cycloaddition of furan (IMDAF) cascade reaction as the key step that rapidly constructed the ACD tricyclic ring system **72** from achiral starting material **73**. *Cinchona*-derived chiral bases (**74**) were evaluated in a thorough screening process, which revealed that, despite these Brønsted bases imparted good levels of enantiocontrol, they only provided

modest reactivity, resulting in extended reaction times (7-11 days) and therefore impeding the development of an efficient multi-gram scale process. Identifying the low basicity of tertiary amine catalysts as the main issue, the authors turned to BIMP catalysis which drastically increased the speed of the reaction and, following a short optimization, the enantioselective prototropic shift / IMDAF cascade reaction could be conducted on multi-gram scale providing excellent yield, ee and dr of the desired product using a benzamide derived BIMP catalyst (**75**) with only 5 mol% catalyst loading in 24 hours. Remarkably, no pre-formation of the catalyst was required; the phosphine and azide were added directly to the reaction mixture to generate the active catalyst *in-situ* (**Scheme 14**).



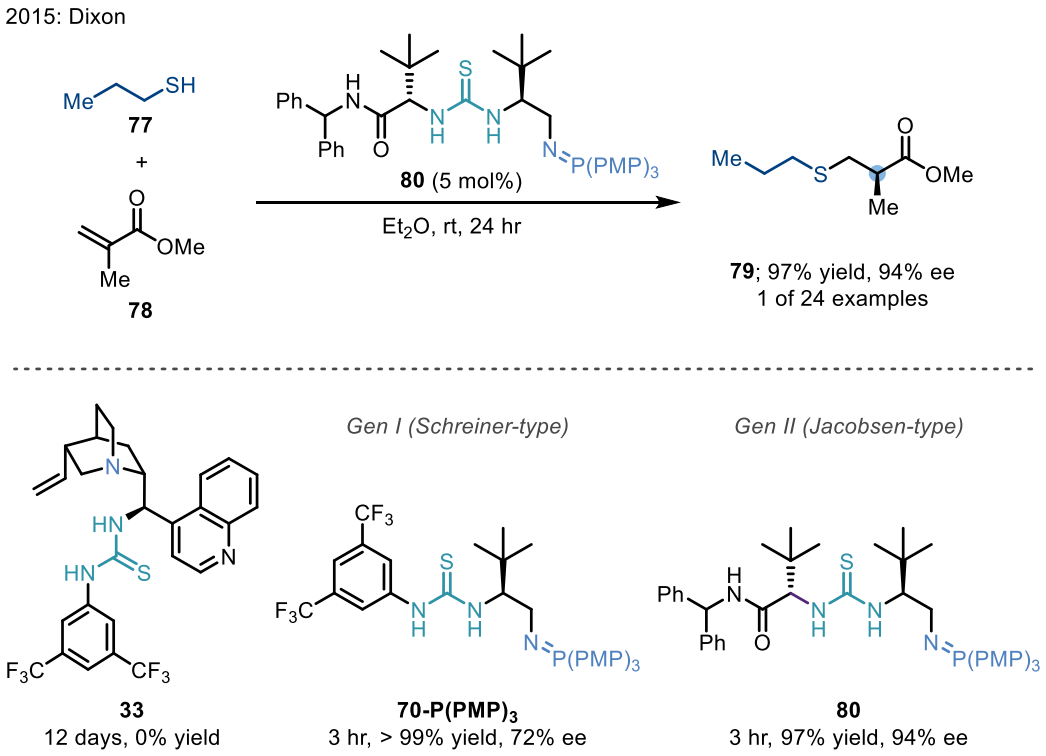
Scheme 14. Dixon's BIMP catalyzed enantioselective prototropic shift / IMDAF cascade *en route* to (−)-himalensine A.

The superior performance of BIMP catalysts compared to bifunctional catalysts based on *Cinchona* alkaloids within the context of complex natural product synthesis was further demonstrated by Dixon in 2018.[141] Once again the group focused on the diastereoselective synthesis of intermediate **40** *en route* to (−)-nakadomarin A as previously mentioned in **Scheme 7**. While 15 mol% of *Cinchona* catalyst **33** was required to promote the addition of **37** to **38** in 57% yield over 8 days, use of BIMP catalyst **76** resulted in higher yields at lower catalyst loading (10 mol%) in only 3.5 hours, albeit with slightly diminished diastereoselectivity (**Scheme 15**).



Scheme 15. BIMP catalysed enantio- and diastereoselective Michael additions towards (−)-nakadomarin A with comparison to the previously utilised *Cinchona*-derived catalyst.

In 2015, while trying to find an optimal catalyst structure to catalyse the first highly enantioselective sulfa-Michael addition of alkyl thiols (**77**) to unactivated α-substituted acrylate esters (**78**), the Dixon group disclosed the first major modification of the BIMP catalyst structure.[142] While BIMP catalyst **70-P(PMP)$_3$** bearing a single stereocentre vastly outperformed *Cinchona* catalyst **33** and provided quantitative yield of product **79** in only 3.5 hours, the enantiomeric ratio was moderate at 84:14. Further modifications of **70-P(PMP)$_3$** did not lead to any improvements in enantioselectivity until a second stereocentre was introduced to flank the thiourea in a manner reminiscent of Jacobsen's catalyst (**17**).[60] Catalyst **80** bearing two stereocentres retained high levels of activity while improving the ee to 94%. The scalability of the reaction was later demonstrated on decagram scale with only 0.05 mol% catalyst (48.0 mg) required to catalyse the reaction on 100 mmol (20.0 g) of **78** to obtain product **79** in 85% yield and 90% ee (**Scheme 16**).



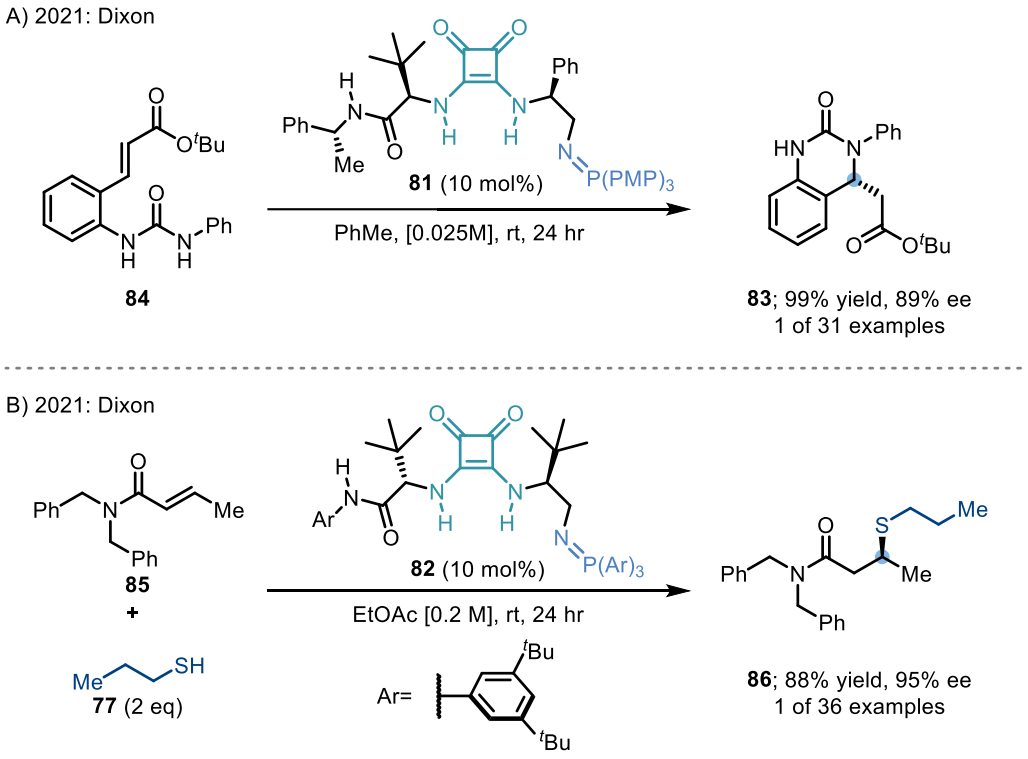
Scheme 16. BIMP catalysed enantioselective SMA to α-substituted acrylate esters and catalyst evolution with selected examples.

The second generation BIMP family was later employed to high effect in the enantioselective SMA to β-substituted acrylate esters[143] and the synthesis of enantioenriched cyclohexenones *via* enantioselective prototopic shift,[144] building upon the reaction previously developed during the total synthesis of (−)-himalensine A.

Most recently, over the course of this DPhil, Dixon also disclosed novel 3rd generation BIMP catalysts containing a squaramide H-bond donor group in place of a thiourea (**81** and **82**). These new catalysts were employed in an enantioselective synthesis of hydroquinazolines such as **83** *via* intramolecular aza-Michael reaction to α,β-unsaturated esters (**84**) (**Scheme 17A**)[145] and to the first metal free conjugate addition to unactivated α,β-unsaturated amides (**85**)[ii] affording enantioenriched Michael addition products such as **86** (**Scheme 17B**).[146] In both reports, the newly developed squaramide-based BIMP catalysts (**81** and **82**) provided substantially higher enantioselectivities than previously developed catalysts

[ii] This work was conducted by Mr Daniel Rozsar (PhD student) and myself but will not be discussed further within the context of this thesis.

bearing urea, thiourea and amide H-bond donors. The observed increase in enantioselectivity has been attributed (*via* DFT calculations) to increased attractive interactions between the substrates and catalyst as well as a lowering of Pauli repulsion.[147] Catalyst loadings of 2 mol% were achieved in both reactions on decagram scale demonstrating their practicality.



Scheme 17. BIMP catalysed synthesis of hydroquinazolines (A) and enantioselective sulfa-Michael addition to unactivated α,β-unsaturated amides (B).

1.5 Conclusion and Thesis Aims

Considering the remarkable tunability, modularity, and adaptability of the BIMP catalyst system, we firmly believe that our group's work to date has only just begun to reveal all the opportunities that this uniquely versatile catalyst platform can provide. By varying the azide scaffold and judiciously selecting the phosphine component, endless permutations of BIMP catalysts are obtainable, and when this is considered alongside Mayr's nucleophilicity and electrophilicity parameters[148–150]– which allow straightforward predictions of reactivity between two potential coupling partners – the stark reality of the plethora of yet unrealized reactivity for this catalyst family and in the field of enantioselective Brønsted base catalysis is laid bare.

To this end **Chapter 2** will focus on the development of a novel enantioselective sulfa-Michael addition employing alkenyl-benzimidazoles as electrophiles.[151] The work conducted in this chapter represents a rare example of organocatalysed enantioselective addition to alkenyl heterocycles for the rapid generation of 3-D drug-like scaffolds.

Chapter 3 will introduce approaches to enantioselective P(V) synthesis, highlighting the strengths and shortcomings of current methods to then focus on the development of an unprecedented enantioselective nucleophilic desymmetrisation of phosphonate esters. The unique ability of a novel ureidopeptide BIMP catalyst to promote this reaction enantioselectively will be demonstrated against a wide array of other BIMPs as well as chinchona alkaloid and phase transfer catalysts. The downstream utility of the desymmetrised product will be demonstrated in the synthesis of numerous attractive nucleoside containing compounds.

Finally, **Chapter 4** will disclose an improved enantioselective nucleophilic desymmetrisation of P(V) containing species. *Via* a superior BIMP catalyst scaffold and a thiazolidinone leaving group on the P(V) electrophiles, higher enantioselectivities, lower catalyst loadings and improved nucleophile scope were obtained.

Detailed experimental procedures and spectroscopical data for synthesised compounds will be reported in **Chapter 5**.

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Chapter 2 : Enantioselective sulfa-Michael addition to alkenyl *N*-heterocycles[i]

2.1 Introduction

2.1.1 Enantioselective sulfa-Michael additions

Enantioselective Michael additions to electron-poor alkenes are amongst the most established reactions to build up chiral molecular complexity (with perfect atom economy)[1] and have been widely investigated.[2–8] Among these, reactions involving thiol nucleophiles are well studied owing to the high nucleophilicity and synthetic utility of the sulphur moiety.[9,10] The oxidation state of the sulphur moiety can be readily manipulated or used as a handle for the introduction of various other functional groups present in a multitude of biologically relevant compounds.

As described in **Chapter 1**, asymmetric sulfa-Michael additions (SMA) were amongst the first enantioselective transformations to be explored with organocatalysts. Since the seminal report from Hiemstra and Wynberg,[11] a multitude of metal free enantioselective SMAs have been developed, although these are typically reliant on highly activated electrophiles such as enals, enones and activated ester derivatives.[12]

As discussed in the previous chapter, the Dixon group has contributed substantially to the field by developing novel BIMP catalysed SMA reactions to traditionally unreactive electrophiles such as unactivated α- or β- substituted α,β-unsaturated esters and amides, which, at the time of their publication, was unprecedented with any form of catalysis.[13]

[i] The work in this chapter was conducted in collaboration with Dr Geffroy Sorin. All results are included for completeness.

2.1.2 Enantioselective 1,4-additions to alkenyl *N*-heterocycles

While 1,4-additions are normally performed with alkenes activated by a carbonyl, nitrile, nitro, sulfonyl, or phosphonyl moiety, imines have also been used.[14] The electronic homology between α,β-unsaturated imine and the C=N moiety of an alkenyl azaarene results in a similar reactivity (**Figure 1**). Indeed, the conjugate addition of Grignard reagents to 2-alkenylquinolines, was demonstrated as far back as 1933.[15]

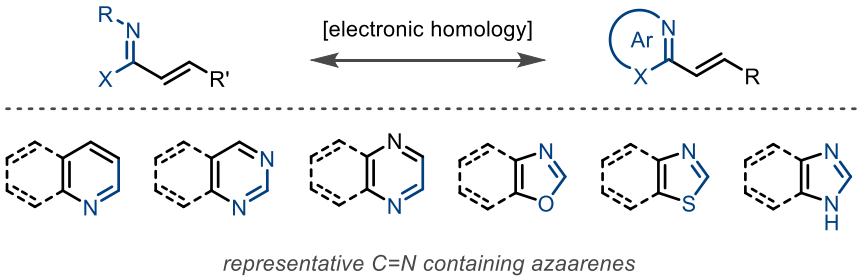
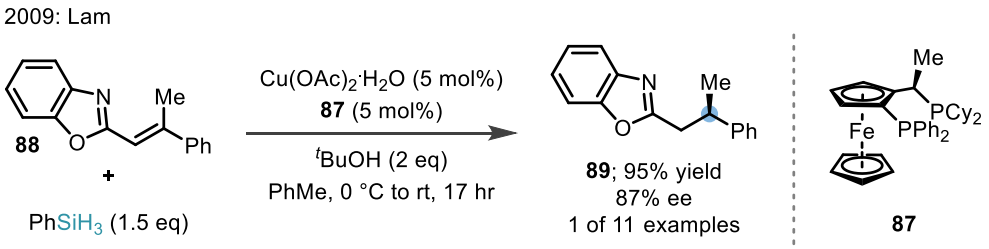


Figure 1. Electronic homology between α,β-unsaturated imine and alkenyl azaarenes (top). Representative C=N containing heterocycles (bottom).

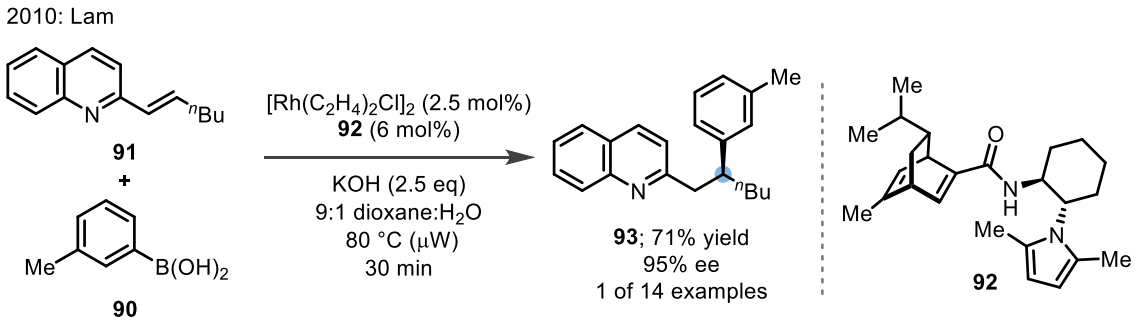
Since then, a multitude of non-enantioselective protocols have been disclosed, involving vinyl-azaarenes as substrates. Additions of nitrogen-, oxygen-, sulphur-, and carbon-centred nucleophiles to such systems are known and have been extensively reviewed in the literature.[16] Additions to β-substituted alkenyl azaarenes are much rarer, potentially due to the greater steric hindrance and hence lower reactivity of these substrates. Nonetheless multiple reactions have been developed using nitrogen-and carbon-centred nucleophiles.[17]

Notwithstanding some early approaches from Houpis, either with chiral auxiliaries[17] or with chiral bisphosphine ligands (albeit with very modest enantiocontrol),[18] asymmetric additions to alkenyl azaarenes remained largely underdeveloped. This paradigm changed in the late 2000's with a seminal publication by Lam which disclosed the enantioselective reduction of 2-alkenylheteroarenes mediated by *in-situ* generated Cu−H species bound by chiral bisphosphine ligands (**Scheme 1**).[19] In this report (*R*,*S*)-JosiPhos ligand **87** was found to be optimal to promote the conjugate reduction of substrates such as **88** to enantioenriched heterocycle **89** using $PhSiH_3$ as the hydride source. A wide range of heterocycles were tolerated including pyridines, pyrazenes, benzothiazoles and quinolines. The scope of this reaction was later extended to azaarenes incorporating β-B(Pin) substituents by Yun and co-workers.[20]



Scheme 1. Lam's asymmetric Cu-H mediated reduction of 2-alkenylheteroarenes.

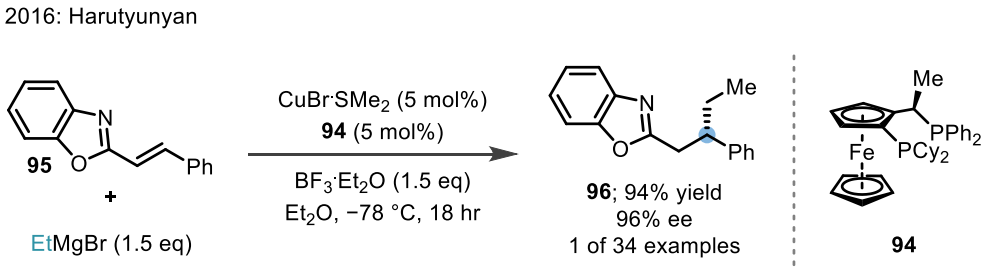
The field was further advanced by Lam the following year by establishing a Rh-catalysed asymmetric 1,4-addition of arylboronic acids to alkenylheteroarenes employing chiral diene ligands (**Scheme 2**).[21] As a representative example, boronic acid **90** was added to 2-alkenylquinoline **91** in the presence of a Rh source and chiral diene ligand **92** to afford product **93** in 71% yield and 95% ee. Notably, the reaction took place in only 30 minutes, employing microwave irradiation to heat the reaction. Once again, the reaction was found to be broad in scope with multiple valuable heteroaromatic motifs, bearing both β-alkyl and β-aryl substituents being tolerated. Alkenyl MIDA boronates[21] were also found to be competent nucleophiles in this reaction but with diminished enantioselectivity. An elegant domino process to synthesise aza-dihydrodibenzoxepines was later disclosed by Lautens who combined Lam's method with a Pd-catalysed C-O coupling, and employing a similar chiral diene ligand.[22]



Scheme 2. Lam's enantioselective Rh-catalysed arylation of alkenylazaarenes with arylboronic acids.

Following these early publications, a wide array of enantioselective transition-metal catalysed conjugate additions have been reported and reviewed in the literature.[17] Amongst the most standout contributions in recent years is Harutyunyan's enantioselective conjugate addition of Grignard reagents to alkenyl-substituted aromatic N-heterocycles disclosed in 2016 (**Scheme 3**).[23]

The method involves the *in-situ* generation of a chiral organocuprate species bearing ligand **94**, which, in the presence of super-stoichiometric Lewis acid, was found to add smoothly to unsaturated azaarenes such as **95** to afford corresponding enantioenriched product **96**. As with previously highlighted methods, a wide range of heterocycles including pyrimidines, triazines, oxazoles and quinolines were tolerated. This methodology was later extended to pyridines, showing remarkable functional group tolerance even with sensitive groups such as aryl bromides, esters and nitriles.[24] Oestreich subsequently demonstrated the use of silicon-centred Grignard reagents in a complementary reaction employing very similar reaction conditions and the same Josiphos ligand (**94**) as Harutyunyan.[25] Unfortunately, in this case, only benzoxazoles bearing aromatic β-substituents afforded products with high levels of enantioselectivity.



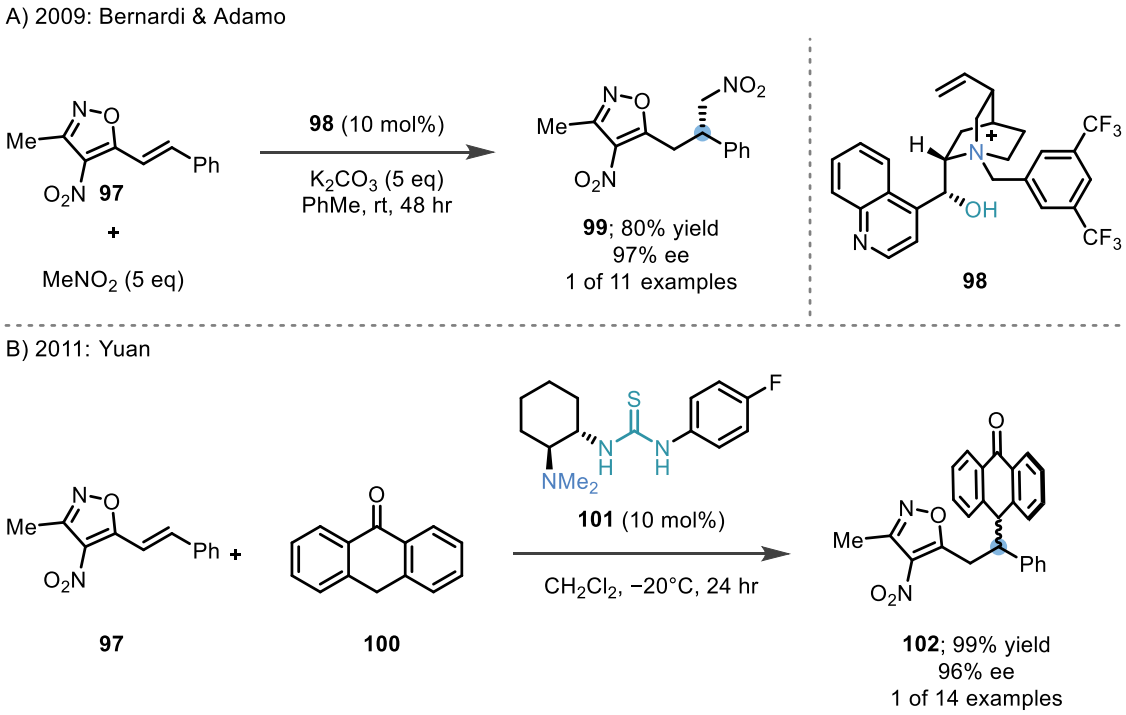
Scheme 3. Harutyunyan's enantioselective asymmetric addition of Grignard reagents to alkenyl-substituted azaarenes.

While collectively these methods have allowed for the direct enantioselective synthesis of a variety of valuable heterocycle-containing products they are not without limitations. Complementary methods which would not require the use of organometallic reagents, expensive/toxic transition metals and cryogenic temperatures would be highly desirable both to expand the scope for these types of Michael-additions, also making them more environmentally sustainable. To that end only a handful of organocatalytic asymmetric 1,4-additions to alkenyl substituted azaarenes had been reported prior to the commencement of the work reported in this chapter.

2.1.3 Organocatalytic asymmetric conjugate additions to alkenyl *N*-heterocycles

The first organocatalytic asymmetric conjugate addition to alkenyl azaarenes was reported by Bernardi and Adamo in 2009. This was, at the time, the first (and only) example of highly enantioselective addition of carbon-centred nucleophiles to alkenylazaarenes, predating Lam's enantioselective Rh-catalysed

arylation by almost a year (**Scheme 4A**).[26] The reaction involved the enantioselective addition of nitromethane to 4- NO_2-5-styrylisoxazoles (**97**) utilizing K_2CO_3 in the presence of cinchonidine derived phase transfer catalyst **98** to afford enantioenriched Michael adducts such as **99**. The 4-NO_2-5-styrylisoxazole served as a masked carboxylic acid which could be readily obtained by heating the product to 100 °C in THF in the presence of 1M NaOH. The resulting acid could then be further manipulated to afford γ-amino acids upon reduction of the nitro group.

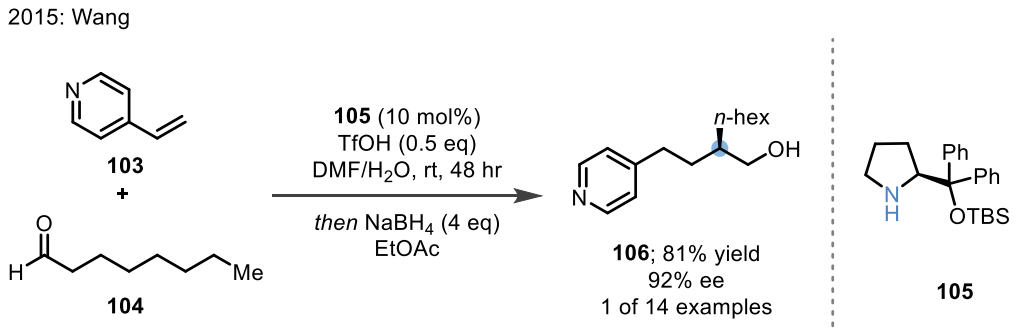


Scheme 4. A) Bernardi and Adamo's catalytic enantioselective 1,4-addition of nitromethane to 4-nitro-5-styrylisoxazoles. B) Yuan's enantioselective addition of anthrones to 4-nitro-5-alkenyl-isoxazoles.

This class of substrates was also later utilized by Yuan which employed anthrone (**100**) as nucleophile, this time catalysed by Takemoto catalyst derivative **101** to afford carba-Michael product **102** in 99% yield and 96% ee (**Scheme 4B**).[27] While both methods delivered the corresponding Michael adducts with high levels of enantioselectivity, the bespoke nature of the heterocyclic motif inherently limits their usefulness. Furthermore, the presence of a strongly electron withdrawing NO_2 group on the heteroaromatic ring was required to increase the electrophilicity of the substrate in order for the reaction to proceed.[28]

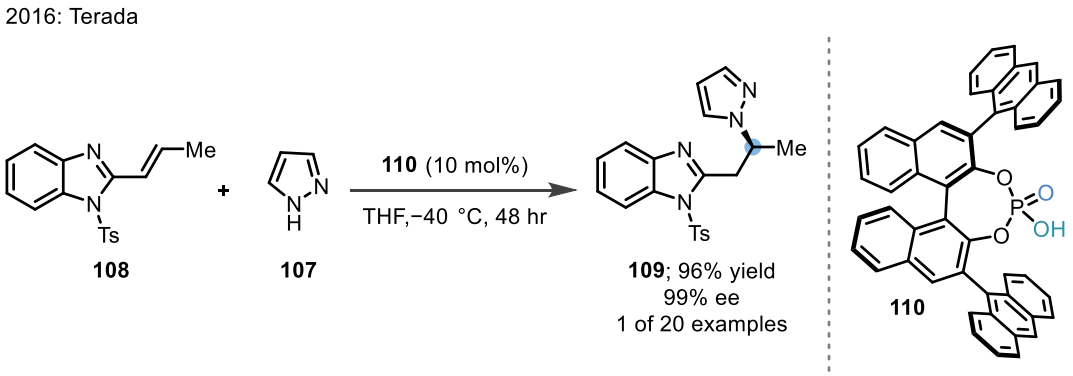
In 2015, Wang demonstrated the first example of organocatalysed enantioselective addition to unactivated azaarenes in the form of 4-vinyl pyridines (**Scheme 5**).[29] The authors coupled 4-vinyl

pyridine **103** to aliphatic aldehydes such as **104** utilising diphenylprolinol *tert*-butyldimethylsilyl (TBS) ether catalyst **105** in combination with TfOH, which served as a co-catalyst protonating the basic pyridine nitrogen atom, thus increasing substrate electrophilicity. The resulting aldehyde product was reduced to the corresponding enantioenriched alcohol product **106** with $NaBH_4$ to avoid racemisation of the newly formed stereocentre. The use of 2-vinyl pyridine as substrate resulted in only 24% yield albeit with 85% ee. No reaction was observed by the authors when using 2- and 4-vinylpyrimidines and 2-vinylpyrazine as substrates.



Scheme 5. Wang's organocatalytic enantioselective direct addition of aldehydes to 4-vinylpyridines.

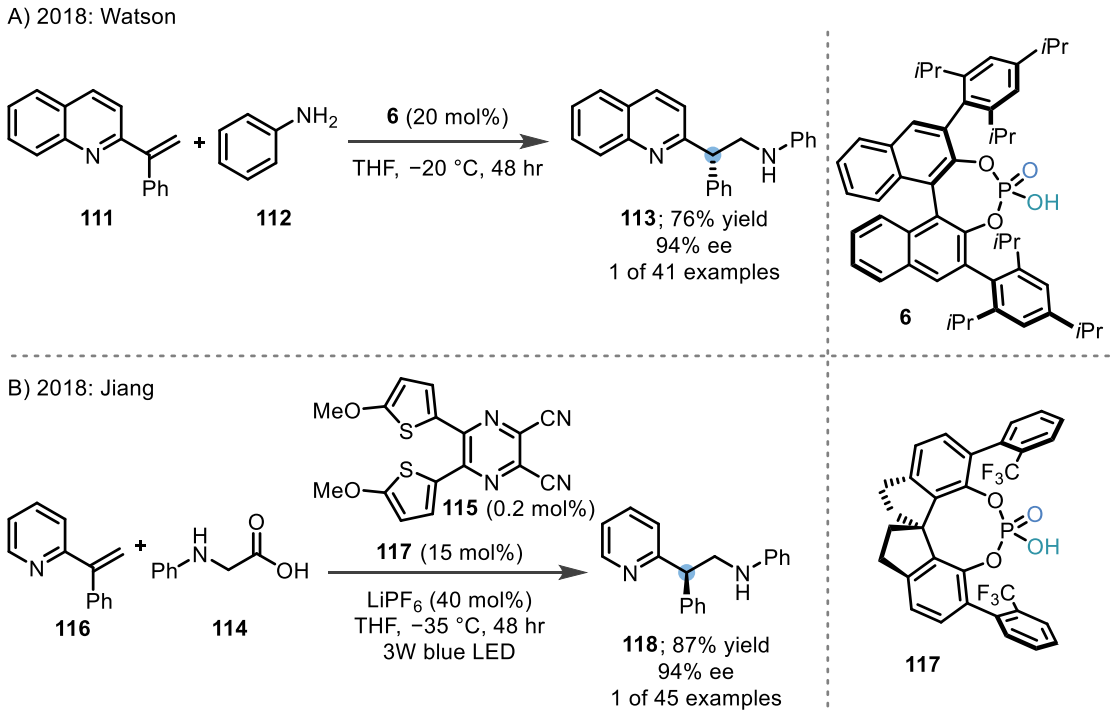
Terada was the first to employ chiral phosphoric acids (CPAs) in enantioselective conjugate additions to azaarenes. [30] Their use was initially demonstrated in the enantioselective aza-Michael addition of pyrazoles (**107**) and indazoles to *N*-protected alkenyl benzimidazoles (**108**), affording enantioenriched azaarene **109** (**Scheme 6**).[31] The authors promoted the enantioselective coupling of the two components employing 9-anthracenyl substituted CPA **110**. A range of different β- substituents were well tolerated as well as variations to the substitution pattern on the nucleophile. Utilising alkenyl imidazoles as electrophiles resulted in diminished yields and enantioselectivities which the authors associated with decreased electronic stabilisation during the transient dearomatisation of the heterocyclic ring upon C−N bond formation. The authors later employed the same catalyst to promote enantioselective C−P bond formation between benzimidazoles and secondary phosphine oxides.[32]



Scheme 6. Terada's CPA catalysed asymmetric aza Michael- addition of pyrazoles to *N*-protected alkenyl benzimidazoles.

A complementary approach was disclosed by Watson in 2018.[33] The authors reported the use of 20 mol% CPA **6** to promote the enantioselective Michael-addition between α-Ph-substituted vinyl quinoline **111** and aniline **112** to afford enantioenriched heterocyclic building blocks such as **113** in high yield and enantioselectivity (**Scheme 7A**). In contrast to Terada's reports in which facial selectivity during C−N bond formation is the enantiodeterming step, here the absolute configuration of the product was determined by enantioselective reprotonation.[34–37] The methodology tolerated a wide array of azaheterocycles as well as both primary and secondary anilines as nucleophiles.

Almost contemporaneously, Jiang reported an alternative protocol leading to similar α-chiral azaaryl ethylamines.[38] The authors cleverly employed *N*-phenyl glycine (**114**) as an α-amino radical precursor which, upon visible light irradiation in the presence of 0.2 mol% of organic photocatalyst DPZ (**115**), generates an α-amino radical *via* loss of CO_2. The *in-situ* generated α-amino radical was found to readily add into α-substituted vinyl-pyridine **116** which could then undergo enantioselective protonation enabled by 15 mol% of SPINOL derived CPA **117**, affording enantioenriched secondary amines such as **118** (**Scheme 7B**). Both vinyl pyridines and quinolines were well tolerated, complementing Watson's method in which the use of pyridines as substrates led to only modest enantioselectivities. Jiang later extended this work to the enantioselective synthesis of all-carbon stereocentres α to azaarenes[39] by employing *N*-aryl cyclopropylamines as nucleophiles and a C_2-symmetric imidodiphosphoric (IDP) acid catalyst pioneered by List.[33]



Scheme 7. A) Watsons's asymmetric synthesis of α -chiral azaheteroaryl ethylamines by enantioselective protonation. B) Jiang's enantioselective conjugate addition−protonation of *N*-aryl glycines to α-branched 2-vinylazaarenes *via* cooperative photoredox and chiral phosphoric acid catalysis.

2.1.4 Aim of the project

Recognising the potential of enantioselective conjugate additions to alkenyl azaarenes to deliver densely functionalised heteroaromatic containing motifs and given our expertise in asymmetric sulfa-Michael addition reactions we were eager to explore the possibility of combining these two reaction types. Additionally, this would represent the first example of an enantioselective sulfa-Michael addition to alkenyl *N*-heterocycles, allowing for the synthesis of appealing enantioenriched thioethers bearing azaarene moieties.

Having already demonstrated the ability of BIMPs to activate high pK_a alkyl thiols and also control their enantiofacial addition to α,β-unsaturated esters, we believed they would be the ideal catalytic platform for this task. We envisioned the BIMP catalyst would promote the enantioselective addition of the thiol to the alkenyl azaarene and the resulting dearomatized aza-enolate could then undergo protonation from the catalyst restarting the catalytic cycle (**Figure 2A**).

Benzimidazoles are highly prevalent and biologically important motifs present in multiple marketed drug molecules such as etonitazene (**119**), bendamustine (**120**), and esomeprazole (**121**). [40–43] Due their low occurrence in asymmetric methodology compared to other heterocycle classes we deemed alkenyl benzimidazoles as ideal electrophiles for the development of our new protocol. This would also represent the first base catalysed enantioselective 1,4-addition to this family of azaarenes (**Figure 2B**).[44]

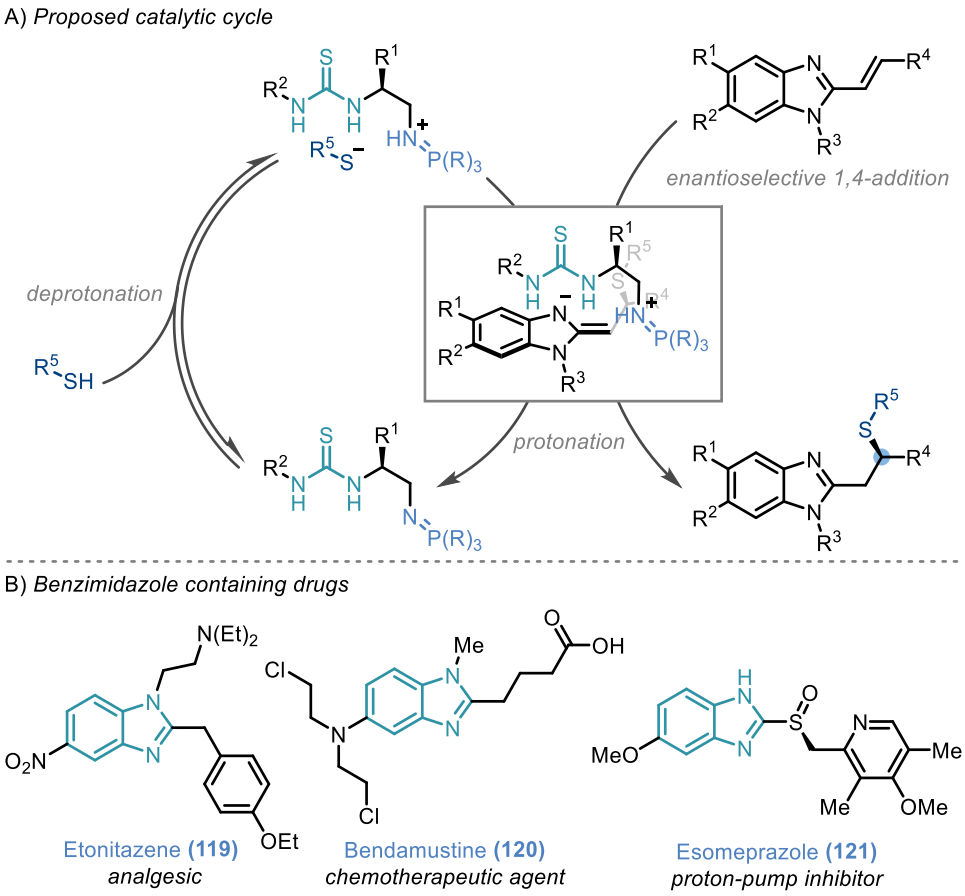
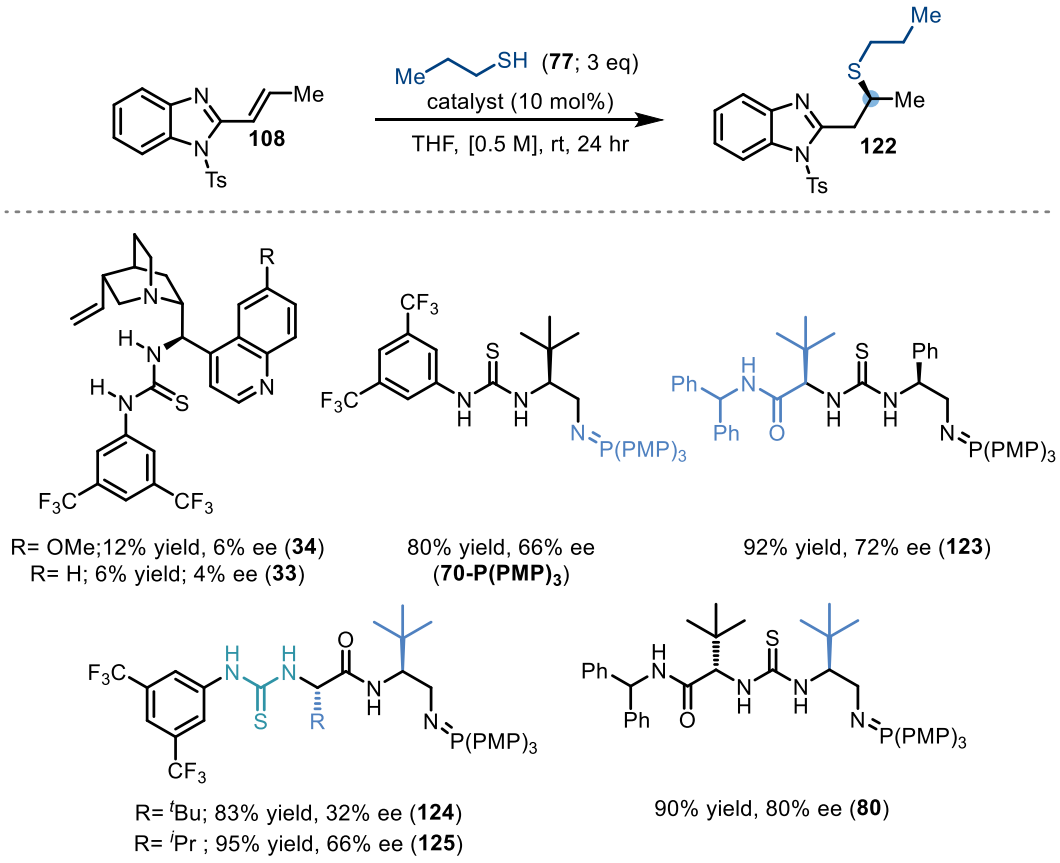


Figure 2. A) Proposed catalytic cycle for the BIMP catalysed asymmetric sulfa-Michael addition to alkenyl benzimidazoles. B) Representative benzimidazole containing drugs.

2.2 Reaction Development: Discovery and Optimisation

2.2.1 Reaction optimisation

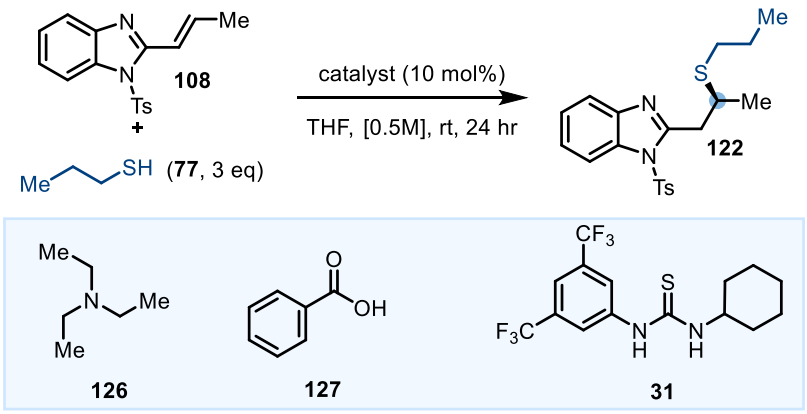
We selected readily prepared[31] (*E*)-2-propenyl-1-tosyl-benzimidazole (**108**) and 1-propane thiol (**77**) as the model electrophile and nucleophile for reaction optimisation. We began by assessing a selection of bifunctional Brønsted base / H-bond donor catalysts using 3 eq of thiol at 0.5 M concentration in THF at rt for 24 hours affording SMA product **122** (**Scheme 8**).



Scheme 8. Initial catalyst screen. Salient features for each catalyst are highlighted for clarity.

Cinchona derived catalysts **34** and **33** only provided **122** in very poor yield and enantioselectivity. We therefore investigated the more basic and more active BIMP catalysts in this reaction and were very pleased to find that 1st generation BIMP catalyst **70-P(PMP)$_3$** bearing one stereocentre and a P(PMP)$_3$ derived iminophosphorane provided desired product **122** in 80% yield and 66% ee. Having established catalyst-enabled reactivity and stereocontrol we then proceeded to investigate second generation catalyst **123** which provided **122** in improved yield and ee at 92% and 72% respectively. Shifting the thiourea

moiety further away from the iminophosphorane (**124** and **125**) showed no improvement in enantiocontrol over **123**. We therefore focused on exploring catalysts built around the same chiral scaffold as **123**. Catalyst **80**[45] bearing *t*Bu groups at both stereocentres in the (*S*,*S*) configuration afforded **122** in 90% yield and 80% ee. At this point the phosphine component of BIMP catalyst **80** was evaluated, however, $P(PMP)_3$ was found to be optimal, with other aryl and alkyl phosphines giving poorer yields and/or levels of enantiocontrol.



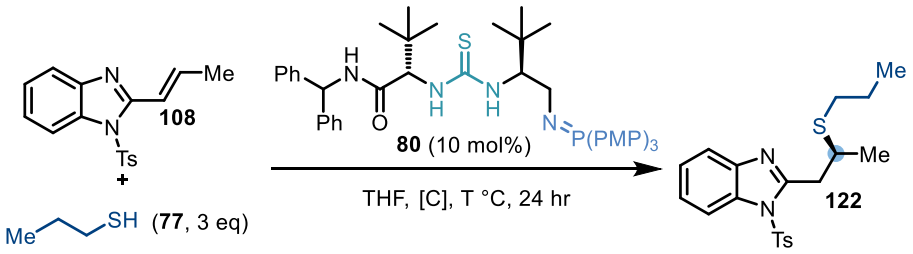
Entry	Basified Thiol[a]	Catalyst	Yield (%)[b]
1	No	-	24
2	Yes	-	12
3	Yes	**126**	trace
4	Yes	**127**	89
5	Yes	**31**	33

Table 1. Control experiments. [a]Thiol was basified by allowing it to stand over K_2CO_3 for 24 h. [b] Isolated Yield.

We then performed preliminary control experiments to try and identify possible background reactivity (**Table 1**). Interestingly, we found that performing the reaction in absence of catalyst **80** resulted in isolation of **122** in 24% yield after 24 hours (*entry 1*). We attributed this background reactivity to possible traces of acid present in commercially available propane thiol. Indeed, when letting the thiol stand over K_2CO_3 for 24 hours prior to use the yield of **122** decreased to 12% (*entry 2*) and finally only trace product was obtained when using Et_3N (**126**) as catalyst (*entry 3*). To confirm that trace acid may lead to higher background reactivity, benzoic acid (**127**) was used as catalyst leading to 89% isolated yield of the desired

product (*entry 4*). A similar increase in yield was observed when using acidic H-bond donor catalyst **31** (*entry 5*). We therefore continued the optimisation by modulating reaction conditions to supress the existing background reactivity.

Having obtained high levels of reactivity and 80% ee, we used catalyst **80** to fine tune the reaction conditions. First, concentration and temperature effects were investigated (**Table 2**). Diluting the reaction two-fold (*entry 2*) or four-fold (*entry 3*) marginally improved the ee to 82%. Cooling the reaction to 12 °C (*entry 4*) had no effect on enantiocontrol while cooling to −15 °C (*entry 5*) increased the ee to 86% while maintaining high product yield. Interestingly, cooling the reaction further to −40 °C (*entry 6*) caused **122** to be isolated with a diminished ee of 64%, possibly due to unproductive catalyst aggregation.[46–51]

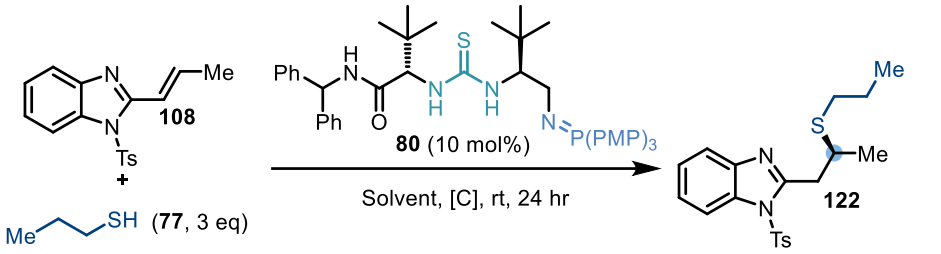


Entry	[C]	T (°C)	Yield (%)[a]	ee (%)[b]
1	0.5 M	rt	90	80
2	0.25 M	rt	86	82
3	0.125 M	rt	86	82
4	0.5 M	12	83	80
5	0.5 M	−15	83	84
6	0.5 M	−40	93	64

Table 2. Temperature and concentration effects. [a] Isolated Yield. [b] Determined by HPLC analysis on a chiral stationary phase.

Having established that diluting and cooling the reaction led to an increase in enantiocontrol we then turned our attention to solvent effects (**Table 3**). TBME and 2-MeTHF (*entries 1,2*) performed similarly to THF. More polar solvents (*entries 3-5*) resulted in either lower enantioselectivity (1,4-dioxane and MeCN) or lower yield (CH_2Cl_2). Using PhMe as solvent also resulted in decreased ee (*entry 6*). Diluting the reaction to 0.06 M in 2-MeTHF resulted in similar er but decreased the yield to 55% (*entry 7*). Utilising

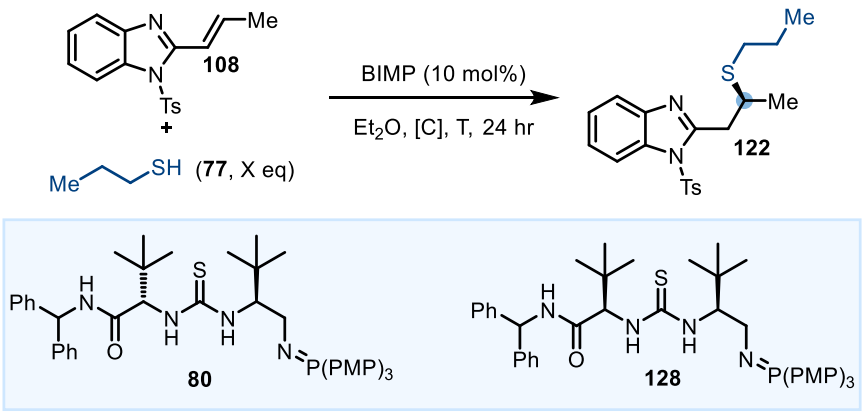
Et_2O at the same concentration however, maintained excellent yield and improved the enantioselectivity to 86% (*entry 8*).



Entry	Solvent	[C]	Yield (%)[a]	ee (%)[b]
1	TBME	0.5 M	80	82
2	2-MeTHF	0.5 M	80	82
3	1,4-dioxane	0.5 M	79	78
4	CH_2Cl_2	0.5 M	70	82
5	MeCN	0.5 M	81	45
6	PhMe	0.5 M	92	78
7	2-MeTHF	0.06 M	55	82
8	Et_2O	0.06 M	**92**	**86**

Table 3. Solvent effects. [a] Isolated Yield. [b] Determined by HPLC analysis on a chiral stationary phase.

Finally, the equivalents of nucleophile used were examined and then combined with favourable factors from previous screens in a bid to find possible synergies (**Table 4**). Lowering the equivalents of thiol to 2 (*entry 1*) and then to 1.2 (*entry 2*) improved er while having little effect on yield. When this was combined with the diluted conditions (0.06 M) from the optimisation table above, as well as lower temperature (0 °C), product **122** was obtained in 93% yield and 88% ee, establishing the optimal reaction conditions (*entry 3*). In a bid to further improve enantiocontrol, diastereoisomeric catalyst **128**,[45] bearing the two ^{t}Bu substituents in the (*R*,*S*) configuration was evaluated under the optimised conditions. Pleasingly, this catalyst was found to have superior performance to **80**, affording the desired product in 98% yield and 90% ee (*entry 4*). Using basified or non-basified thiol gave the same results under the conditions showed in *entry 4,* indicating that background reactivity was indeed suppressed under the optimal reaction conditions.



Entry	Equivalents	[C]	T °C	BIMP	Yield (%)[a]	ee (%)[b]
1	2.0	0.25 M	rt	**80**	92	82
2	1.2	0.25 M	rt	**80**	94	86
3	1.2	0.06 M	0	**80**	93	88
4	1.2	0.06 M	0	**128**	**98**	**90**

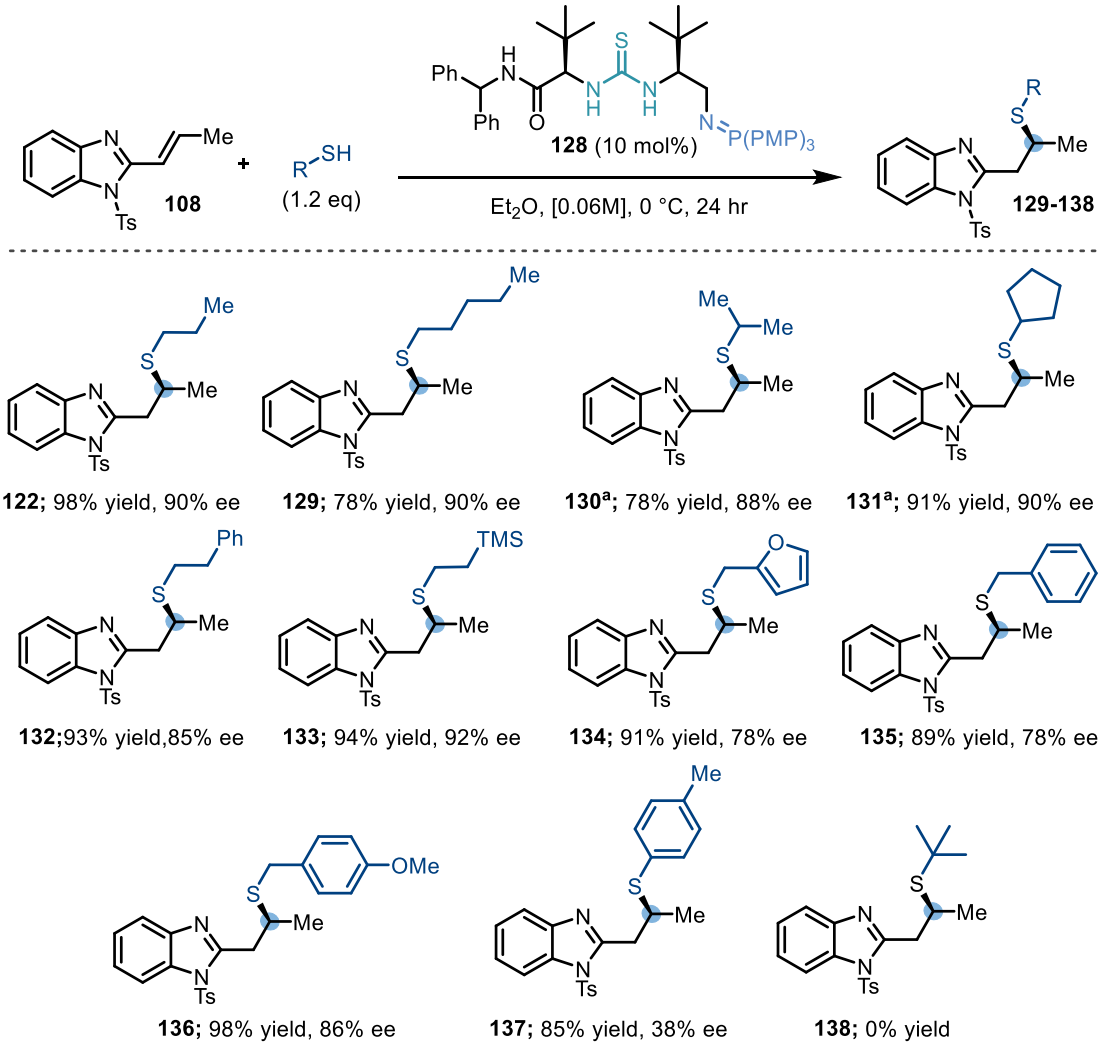
Table 4. Reaction fine-tuning. [a] Isolated Yield. [b] Determined by HPLC analysis on a chiral stationary phase.

2.3 Scope of the Reaction

2.3.1 Scope of the reaction with regards to the thiol nucleophile

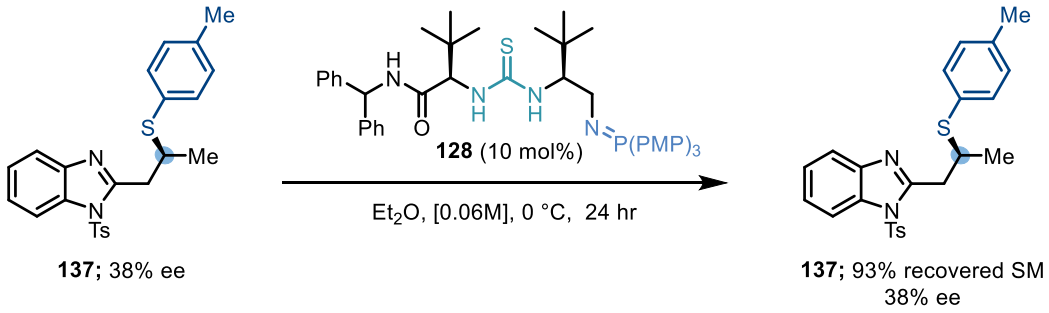
With the optimised reaction conditions in hand, we proceeded to investigate the scope and limitations of the nucleophilic thiol component (**Scheme 9**) using **108** as the model acceptor for this scope. Initially, the steric and electronic properties of the thiol nucleophile were varied. Higher order linear *n*-pentyl thiol was well tolerated affording **129** in 78% yield and 90% ee. Secondary thiols reacted sluggishly under the optimised conditions; however, this issue was easily circumvented by conducting the reaction at room temperature. Doing so afforded products **130** and **131** in good to excellent yield with 88 and 90% ee respectively. The introduction of a phenyl ring on the alkyl chain was well tolerated providing **132** in 93% yield and good ee. Appending a silyl group to the thiol nucleophile also showed no detrimental effect providing **133** in 94% yield and 92% ee. Both benzylic and heterobenzylic thiols provided corresponding Michael adducts **134-136** in high yields and good enantioselectivity, the latter being slightly diminished compared to that observed with alkyl thiols. Unfortunately, when using 4-methylthiophenol as nucleophile, product **137** was only obtained in a modest 38% ee. Similarly, when using *t*BuSH as

nucleophile **138** was not obtained, even when performing the reaction at 40 °C, most probably due to its increased steric bulk.



Scheme 9. Thiol scope. [a] Reaction carried out at 22 °C.

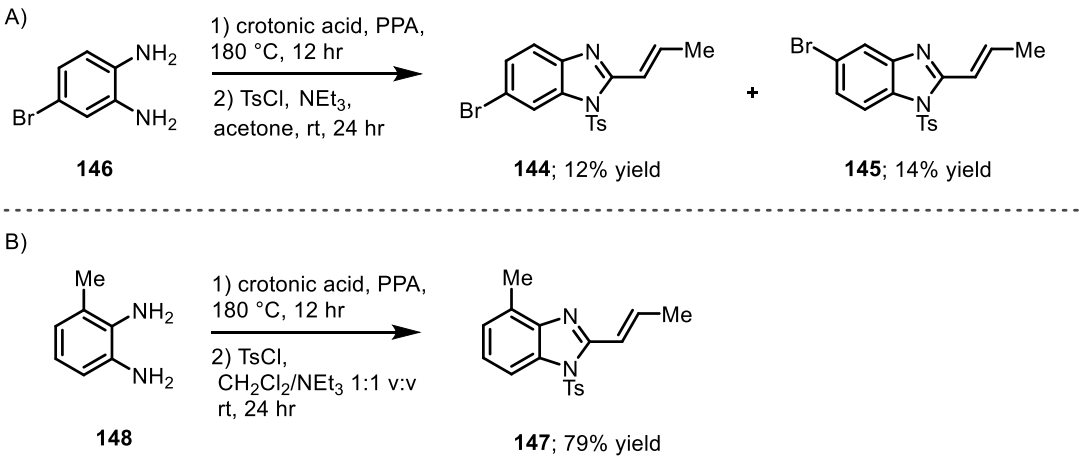
To assess whether the low er obtained when using 4-Me-thiophenol as nucleophile was due to the reaction being reversible as a consequence of the lower pK_a of aromatic thiols (p$K_a \approx 10.0$ in DMSO)[52] **137** was resubmitted to the reaction conditions. After 24 hrs **137** was recovered, however upon analysis by chiral HPLC no racemisation was observed (**Scheme 10**). This indicated that the reaction was non-reversible, and that the low er was possibly due to either structural differences in the nucleophile or having a higher concentration of deprotonated nucleophile present in solution, possibly leading to increased background reactivity.



Scheme 10. Reaction reversibility study with compound **137**.

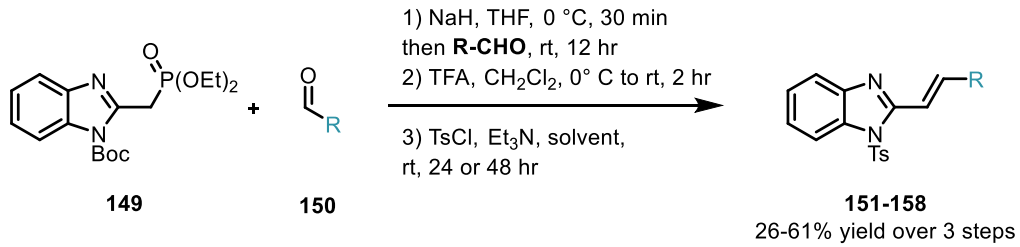
2.3.2 Scope of the reaction with regards to the alkenyl benzimidazole component

Following the investigation of the scope with respect to thiol component of the reaction we turned our attention towards the alkenyl benzimidazole electrophile. Known benzimidazoles **139**-**143** were prepared by Dr. Geoffroy Sorin according to the procedure by Terada *et. al.*.[31] Brominated benzimidazoles **144** and **145** were obtained by the same procedure *via* condensation of brominated diamine **146** and crotonic acid in neat PPA at 180 °C. The resulting crude product was then treated with TsCl and Et_3N in acetone at rt for 24 hours. The two regioisomers were partially separable by silica gel chromatography, affording **144** in 12% yield and **145** in 14% yield over two steps (**Scheme 11A**). The corresponding 4-Me substrate **147** was obtained by a similar procedure from diamine **148** in 79% yield as a single regioisomer which was assigned by NOE (**Scheme 11B**, see **Chapter 5** for more details).



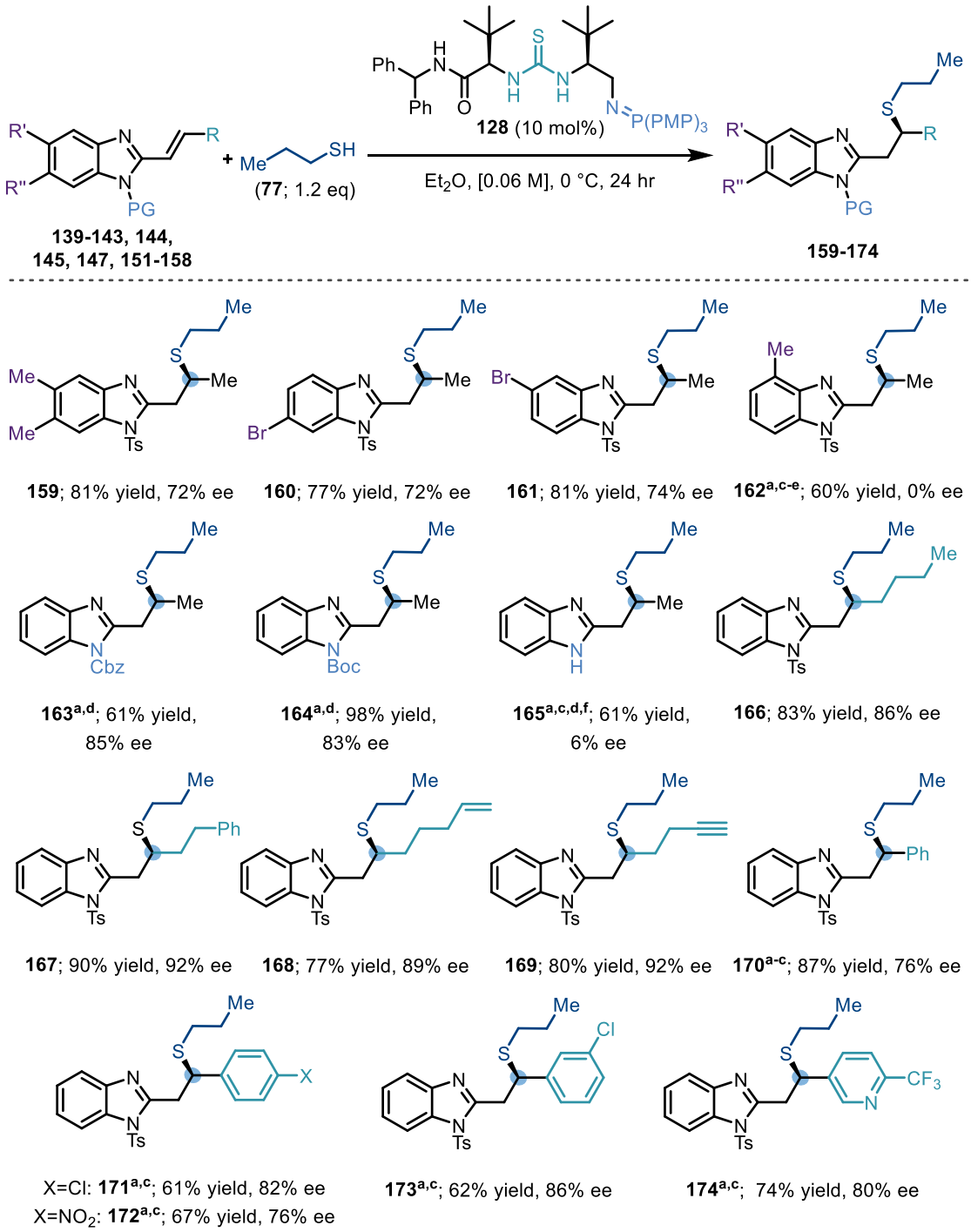
Scheme 11. A) Synthesis of regioisomeric brominated benzimidazoles **144** and **145**. B) Synthesis of substrate **147**.

For studying variations on the alkene substituent, substrates were prepared by HWE olefination between Boc-protected benzimidazole phosphonate ester **149** (see **Chapter 5** for more details) and commercially available aldehydes (**150**). The *N*-Boc group was then cleaved using TFA and subsequently replaced with a tosyl group as illustrated for previous examples (**Scheme 12**). Yields over three steps were found to be moderate to good (**151**-**158**) (see **Chapter 5** for details on individual substrates).



Scheme 12. General synthesis for benzimidazoles with variations at the alkene substituent. Solvent= CH_2Cl_2, acetone or DMF depending on the substrate (see **Chapter 5** for more details).

With a wide variety of alkenyl benzimidazoles in hand we proceeded to investigate the scope and limitations of the electrophilic component (**Scheme 13**). Variations to the phenyl backbone did not affect reactivity, although a slight reduction in enantioselectivity was observed. Disubstitution at the 5- and 6- positions with Me groups afforded corresponding adduct **159** in 81% yield and 72% ee. Alternating monosubstitution between C5 and C6 did not have a large effect, with bromine containing substrates affording the corresponding Michael adducts (**160**, **161**) in greater than 75% yield and 72% ee allowing for potential further functionalization at both positions. Unfortunately, when the benzimidazole ring was substituted with a methyl group at the 4-position (**147**) the sulfa-Michael reaction failed to proceed under the optimised reaction conditions. When the reaction was performed at 0.125 M concentration in THF, rt and with 3 equivalents of *n*-propane thiol (**77**), the corresponding sulfa-Michael product **162** was obtained in 60% yield and 0% ee. This we believe, is due to the steric bulk of the Me group preventing constructive binding of the H-bond donor moiety of the catalyst with the Lewis basic benzimidazole nitrogen and is supported by computational studies (see section **2.4**).



Scheme 13. Benzimidazole scope. [a] Reaction carried out at rt. [b] Reaction carried out using catalyst **80**. [c] Reaction carried out in THF. [d] Reaction carried out using 3 eq of thiol. [e] Reaction carried out at 0.125 M. [f] Reaction carried out at 0.5 M.

We were pleased to find that high enantioselectivities were largely maintained when the nitrogen protecting group was changed from *N*-Ts to *N*-Cbz (**163**) or *N*-Boc (**164**), however in these cases reactivity was found to diminish. This decrease in reactivity was overcome by conducting the reaction at

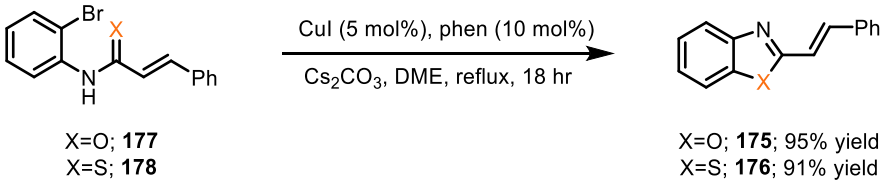
room temperature using 3 equivalents of *n*-propanethiol. The sulfa-Michael reaction however, failed to proceed under the optimised reaction conditions when using unprotected benzimidazole **143**. When the reaction was run at 0.5 M concentration, rt and with 3 equivalents of *n*-propane thiol, **165** was obtained in 61% yield but only 6% ee. This is unsurprising as both nitrogen atoms on substrate **143** are equivalent, and as such, provided no electronic bias for the catalyst to bind one over the other, selectively. The thiol can thus consequently approach the benzimidazole from either the top or bottom face leading to almost racemic product. This observation was found to be in agreement with DFT studies which will be discussed in more detail in section **2.4**. The decrease in yield can be attributed to the lack of an electron withdrawing group, which would stabilise the negative charge built up upon dearomatisation of the benzimidazole ring.

Having varied the substitution pattern on the benzimidazole, we proceeded to investigate the scope with respect to substituents on the alkenyl moiety. The introduction of higher order linear alkyl chains (**150**), bearing aromatic (**151**), alkene (**152**) and alkyne (**153**) substituents, was well-tolerated with all Michael additions with *n*-propyl thiol providing the corresponding products (**166**-**169**) in excellent yield and enantioselectivity. When the alkene moiety was substituted with an aromatic group, the solvent was switched to THF and reactions were run at rt due to the decreased solubility and reactivity of the substrates. When a phenyl substituent was introduced on the alkenyl moiety (**154**), catalyst **128** provided Michael adduct **170** with only a moderate 54% ee, however this was enhanced to 76% when using diastereomeric catalyst **80**. Introducing electron withdrawing groups at either the *para* (**155**,**156**) or *meta* (**157**) positions of the phenyl ring afforded the corresponding products **171**-**173** in good yield and enantioselectivity; in these cases, however, BIMP catalyst **128** proved superior to **80.** Finally, when the phenyl ring was exchanged with a CF_3 substituted 3-pyridyl moiety (**158**) corresponding adduct **174** was smoothly obtained in 74% yield and 80% ee.

2.3.3 Heterocycle variation

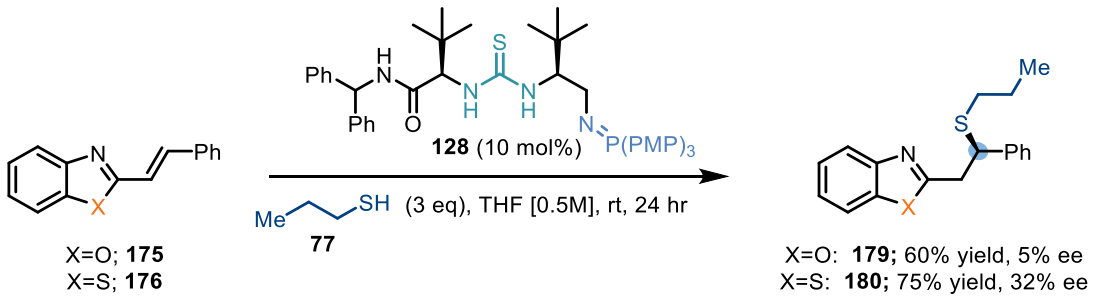
Having demonstrated the scope for this reaction on β-substituted alkenyl benzimidazoles we were interested in exploring the compatibility of the developed protocol to other alkenyl azaarenes. To this end, phenyl-substituted alkenyl benzoxazole (**175**) and benzothiazole (**176**) were synthesized from the

corresponding *ortho*-halobenzanilides (**177**, **178**) under Cu catalysis as reported by Batey[53] in 95% and 91% yield respectively (**Scheme 14**).



Scheme 14. Synthesis of Ph-substituted alkenyl benzoxazole and benzothiazole substrates.

The newly synthesised heterocyclic acceptors (**175** and **176**) were submitted to the optimised reaction conditions (**Scheme 15**) but unfortunately, the sulfa-Michael addition did not proceed. By increasing the temperature and concentration (rt, 0.5 M) and using 3 equivalents of *n*-propane thiol moderate yields of products **179** and **180** were obtained. The enantiomeric excess of the products, however, was found to be 5% for the benzoxazole (**179**) and only 32% for the benzothiazole (**180**) derived substrates. These results further support the hypothesis that a strong electronic and/or steric bias must exist between the two heteroatoms present in the azaarene for the BIMP catalyst to effectively bind to the substrate, so that the nucleophile may attack preferentially from one face of the alkene. This is particularly supported by the case of the benzothiazole derived substrate (**180**), where a moderate 32% ee is observed, contrasting with the complete lack of enantioselectivity which is obtained when using either the unprotected alkenyl benzimidazole (**165**) or benzoxazole (**179**) as substrates.



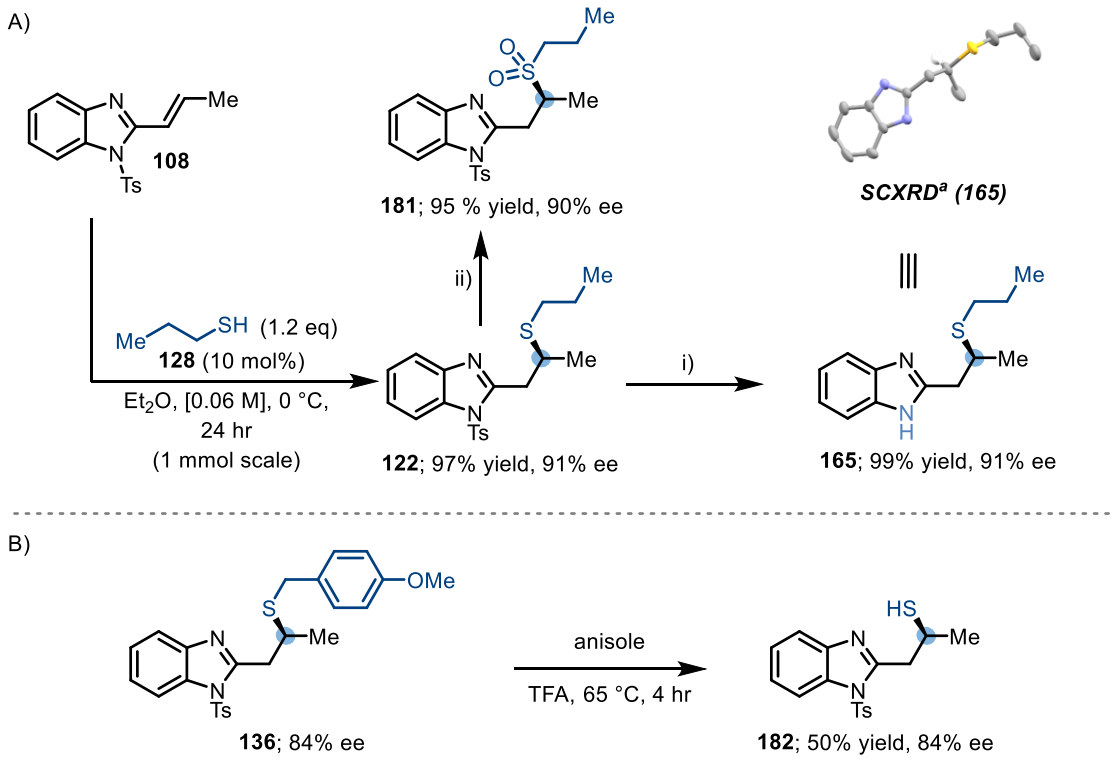
Scheme 15. Enantioselective SMA on benzoxazole and benzothiazole derived substrates.

Given the sensitivity of the reaction to variations in the nature of the heterocycle, we opted not to investigate this variable further, aware that it represents a current limitation of this methodology. We are

confident however, that with a re-optimisation of the catalyst scaffold, a suitable BIMP could be found which would be better matched to other alkenyl-azaarene classes.

2.3.4 Reaction scale up and derivatisation

After establishing the scope and limitations for the newly developed enantioselective SMA we wished to demonstrate its scalability, and to showcase possible product derivatisations (**Scheme 16**).



Scheme 16. A) Scale up (to 1 mmol) and derivatisation of compound **122** and determination of absolute configuration of **165** by single crystal X-Ray analysis [a](some H-atoms omitted for clarity). i) 5 M aq. HCl, 40 °C, THF, 10 hr. ii) *m*-CPBA, CH_2Cl_2, rt, 4 hr. B) Deprotection of Michael adduct **136** to obtain free thiol **182**.

We were pleased to find that increasing the reaction scale 10-fold (1.00 mmol) under the optimised conditions afforded **122** in equal yield and er. Unfortunately, attempts to decrease the catalyst loading led to lower isolated yields of the product. The *N*-Ts group on **122** was easily removed with HCl (5 M aq.), giving the corresponding deprotected product **165** in quantitative yield. Pleasingly, **165** was found to be highly crystalline and was thus recrystallised to enantiopurity by slow evaporation from a solvent mixture of CH_2Cl_2 and hexane. A suitable crystal was then submitted for X-ray diffraction analysis to

determine the absolute stereochemical configuration of model sulfa-Michael product **122.** The stereochemical descriptor for the carbon bearing the newly attached thioether was found to be (*S*) when using catalyst **128**. The stereochemical configuration of all other products was assigned by analogy. We were also pleased to find that, upon treatment of **122** with *m*-CPBA, sulfone **181** was obtained in 95% yield with no loss of optical purity (**Scheme 16A**). Finally, the PMB group on compound **136** was removed in 50% yield upon treatment with anisole and TFA to obtain the free thiol **182** (**Scheme 16B**).

2.4 Computational Studies

To probe the origins of selectivity and to elucidate the possible transition state for the reaction computational studies were conducted in their entirety by Dr Jesus Diaz and Prof Robert Paton. Density functional theory (DFT) was used to investigate the origins of enantioselectivity, performing calculations at the wB97XD/6-31G(d) level of theory (**Figure 3**).[ii] Two substrate activation modes are possible (A vs. B) and either could in principle lead to the formation of the major observed enantiomer (**Figure 3A**). Calculations considered PPh_3-derived catalyst **128-P(Ph)$_3$** with the PMP-groups of **128** modelled by Ph-groups for simplicity. The most stable conformation of the most enantioselective catalyst **128-P(Ph)$_3$** has substituents on either side of the thiourea, oriented with a hydrogen atom towards sulphur: other rotamers are disfavoured. This creates a pocket with the iminophosphorane positioned above the thiourea (**Figure 3B**). Computationally, the interaction of the thiolate nucleophile with the protonated iminophosphorane and the benzimidazole with the thiourea (mode A) was energetically favoured by 4-5 kcal/mol over the alternative (mode B) in which the thiourea binds the nucleophile and the benzimidazole is bound to the protonated iminophosphorane. This mode of activation is consistent the observed sense of enantioselectivity, and with earlier mechanistic proposals of Takemoto. Recent theoretical studies by Grayson and Houk have emphasized the importance of activation mode B in sulfa-Michael reactions promoted by *Cinchona*-derived catalysts.[54–56] Present results suggest that both activation modes may be operative, depending on catalyst and substrate, as originally hypothesized by Soós and Pápai.[57]

[ii] Calculations were performed with Gaussian 09 rev. D.01: Frisch, M. J. *et al.* Gaussian, Inc.: Wallingford, CT, 2013. All calculations were performed with an SMD model of diethyl ether. Full details are given in **Chapter 5**.

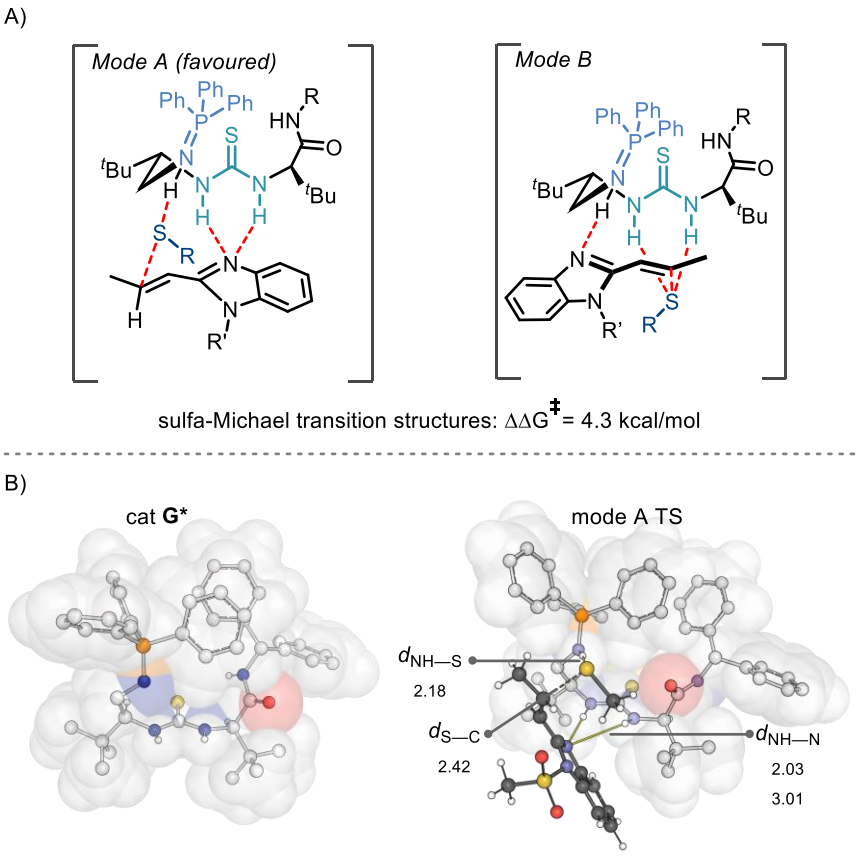


Figure 3. A) Possible modes of substrate activation leading to the major enantiomer. B) SMD-wB97XD/6-31G(d) computed structure of catalyst **128-P(Ph)$_3$** and the most favourable transition structure leading to the major enantiomer.

2.5 Conclusion

In summary, this chapter describes the first enantioselective sulfa-Michael addition of alkyl thiols to alkenyl benzimidazoles. Excellent yields and good enantioselectivities were achieved across a broad range of alkyl thiol and alkenyl benzimidazole reaction partners using a second generation BIMP superbase. This work further demonstrates the versatility and high activity of the BIMP catalyst family, as well as expanding its use in methodology for the synthesis of biologically relevant chiral benzimidazole derivatives. DFT studies were subsequently conducted in collaboration with Prof Paton to elucidate the origin of enantioselectivity. Unfortunately, the developed protocol could not be extended to other classes of alkenyl azaarenes but nonetheless represents the first example of an enantioselective addition of sulphur-based nucleophiles to this class of versatile and medicinally attractive electrophiles.

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Chapter 3 : Enantioselective Nucleophilic Desymmetrisation of Phosphonate Esters

3.1 Introduction to P(V) chemistry

3.1.1 Importance of P(V) containing molecules

Compounds containing one or more phosphorous atoms in the P(V) oxidation state are important to chemistry, biology and medicine (**Figure 1**).[1] These include marketed antiviral drugs such as such as Tenofovir alafenamide (**183**) and Remdesivir (**184**), the latter an effective treatment for Ebola[2] which has currently also been approved for use against SARS-CoV-2.[3] Other relevant compounds include Fosinopril (**185**), used in the treatment of hypertension and WHO essential medicines listed chemotherapy agent Cyclophosphamide (**186**).[4] In addition to being common APIs, P(V) containing compounds are also highly relevant motifs in agrochemistry. A representative example is Dow herbicide Zytron (**187**). From a synthetic perspective chiral P(V) and P(III) compounds have also been extensively used as ligands in enantioselective transition metal catalysis.[5–7]

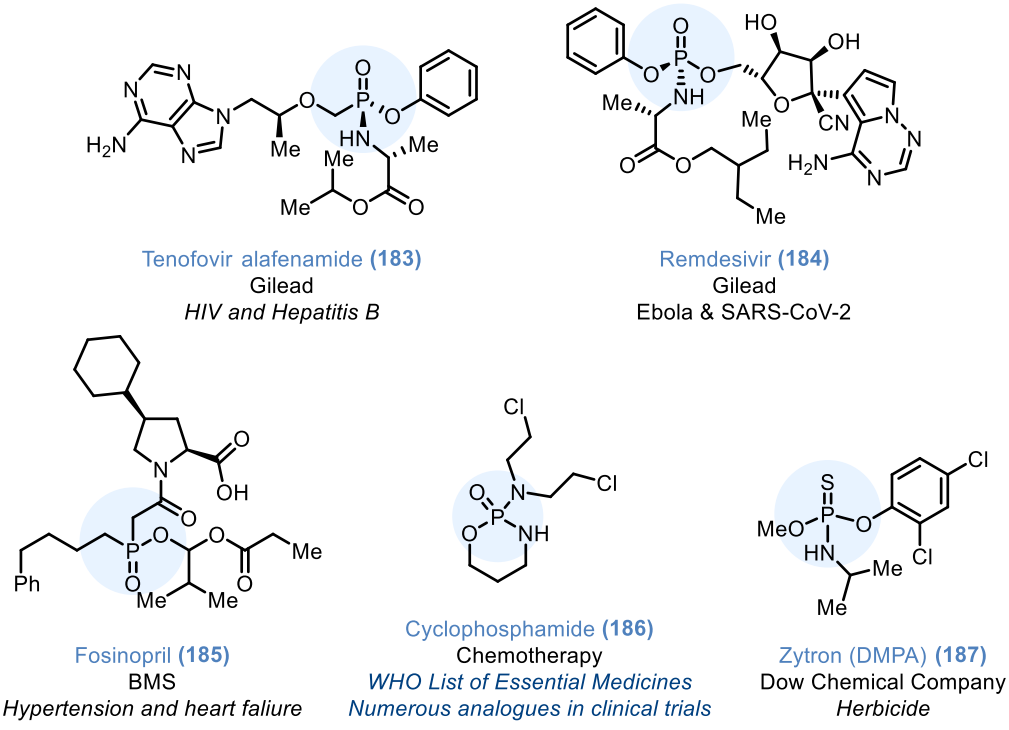


Figure 1. Representative pharmaceuticals and agrochemicals containing a stereogenic P(V) centre.

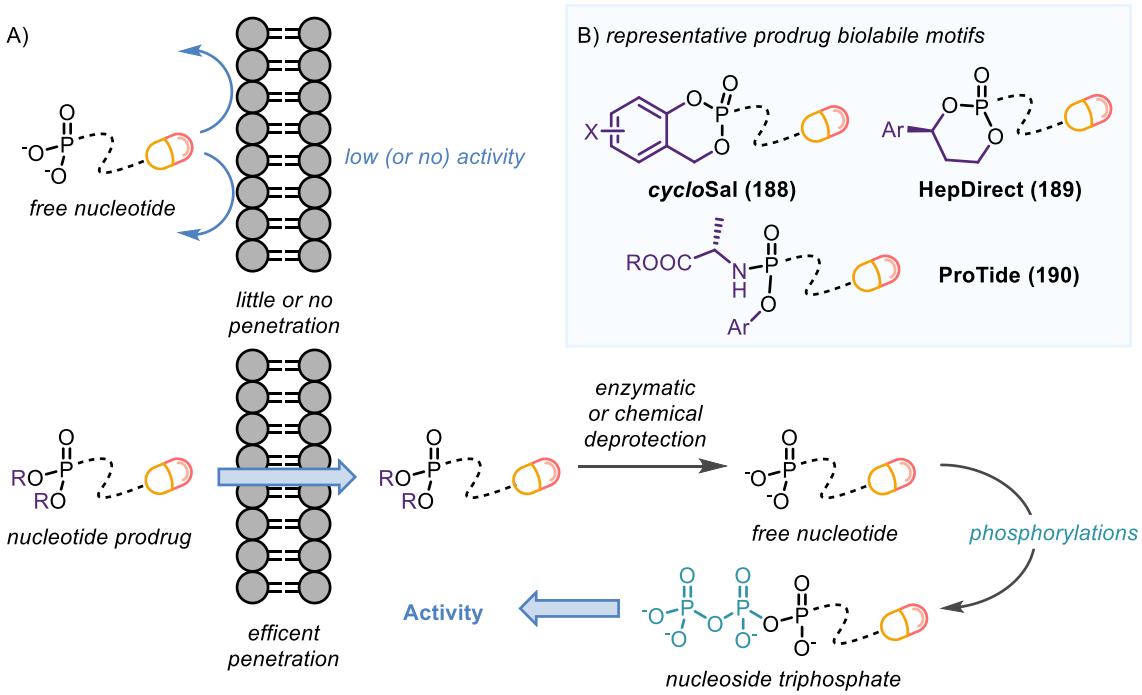


Figure 2. A) Mechanism of activation for nucleoside phosphate and phosphonate prodrugs. B) Representative prodrug motifs.

Due to their poor chemical stability and high polarity, which prevents them from passing across cell membranes, nucleoside triphosphates cannot be considered viable drug candidates. Because of this P(V) based antivirals are often prodrugs, meaning they are structurally modified within the body to reveal the active compound (**Figure 2**). These nucleoside analogues rely on cellular kinases to undergo sequential phosphate group addition to form the corresponding therapeutically active nucleoside triphosphate. Due to the first phosphorylation being identified as the limiting step within the nucleoside analogue phosphate activation process, medicinal chemists have strived to prepare stable (protected) monophosphate nucleosides capable of being delivered intracellularly. These nucleoside monophosphate prodrugs are designed to efficiently cross the biological barriers and reach the targeted cells or tissues. Once inside the cell, these biolabile protecting groups are then degraded enzymatically, releasing the free nucleoside analogue in the active monophosphate form, which can exert its therapeutical effect downstream (**Figure 2A**).[8] Multiple prodrug "masking groups" have been disclosed utilising different motifs which have proved effective to deliver monophosphate nucleoside analogues across cell membranes, amongst these are the *cyclo*Sal (**188**),[9] HepDirect (**189**)[10] and ProTide (**190**)[11] technologies (**Figure 2B**).

Due to their widespread nature and societal importance, new and improved methods for the efficient synthesis of P(V) containing compounds, especially in an enantioselective fashion, remain essential.

3.1.2 Approaches to enantiopure P(V) containing compounds

Synthetic approaches to enantiopure P(V) compounds can be subdivided into five categories (**Figure 3**). These approaches have been extensively reviewed in the literature, [12–17] with salient examples being discussed in more detail in sections **3.1.3** to **3.1.7**.

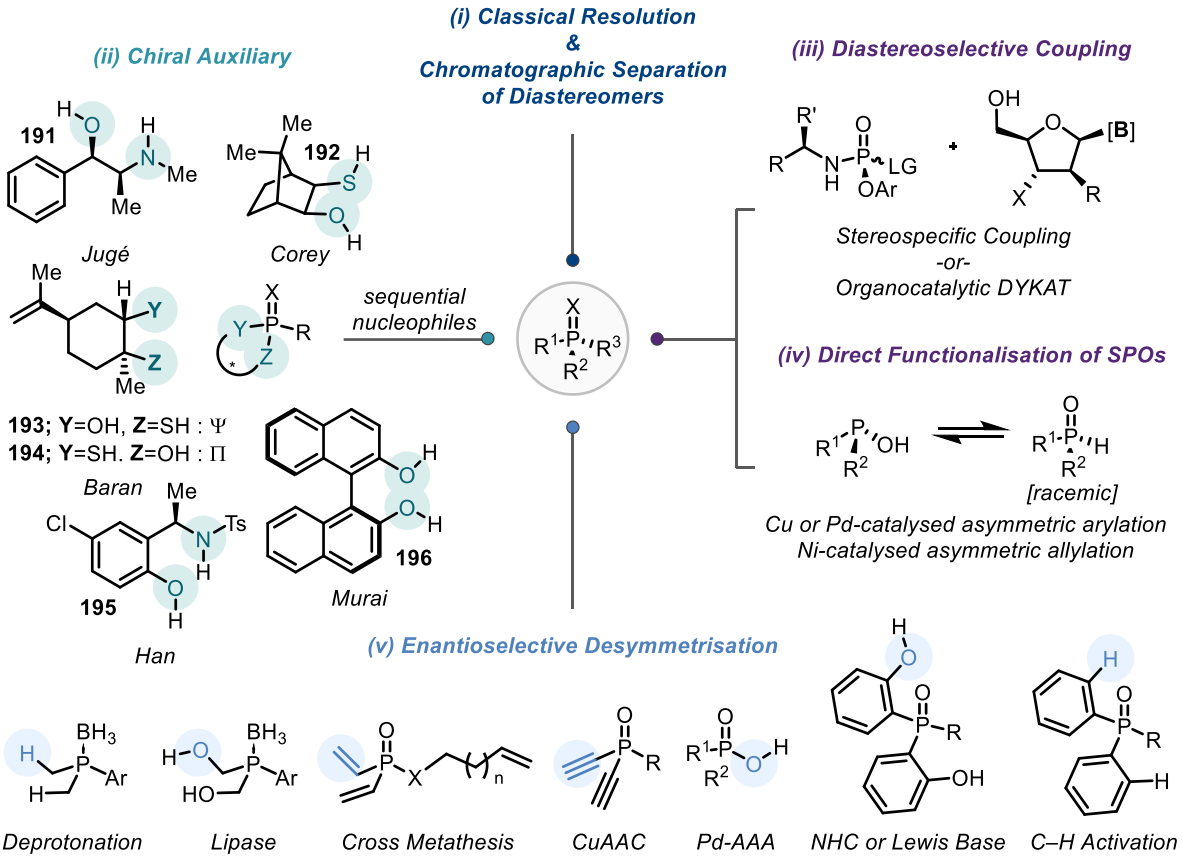


Figure 3. Overview of synthetic approaches to enantioenriched P(V) compounds.

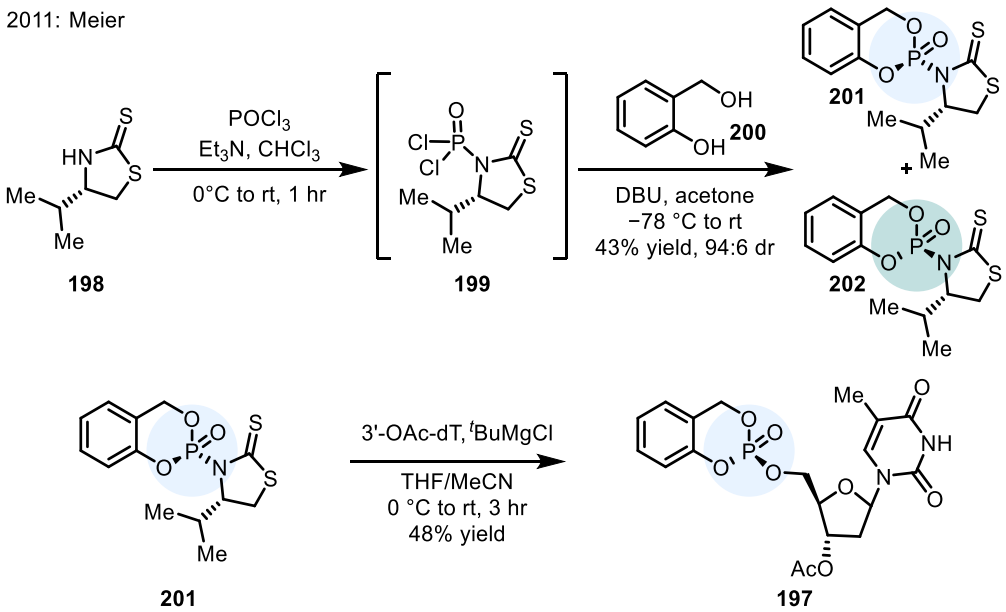
The first approach is classical resolution and/or separation of diastereomers or enantiomers by chromatography (**Figure 3**, **i**). A second approach revolves around the use of labile chiral auxiliaries (**191**-**196**) which can be displaced by sequential diastereoselective nucleophilic additions to afford enantioenriched P(V) species (**Figure 3**, **ii**). Thirdly, a racemic and electrophilic P(V) compound bearing a single leaving group (and often possessing a chiral sidechain) can be coupled diastereoselectively (and catalytically) to a chiral nucleophile (**Figure 3**, **iii**). A subsequent approach involves the direct

functionalisation of secondary phosphine oxides (SPO) by means of a metal catalyst bearing chiral ligands to obtain tertiary phosphine oxides. Notably, however, to date this approach has been widely limited to the synthesis of all carbon substituted phosphine oxides (**Figure 3**, **iv**). The final strategy is enantioselective desymmetrisation by which prochiral groups attached to a phosphorous centre are differentiated by a chiral catalyst (**Figure 3**, **v**). Multiple reactions have been developed using this strategy however none involve chemistry occurring at the P atom directly but rather generate the P stereocentre indirectly (*via* manipulation of enantiotopic side chains) inherently limiting their scope.

Although new and promising catalytic protocols are beginning to arise for the synthesis of racemic P(V) compounds[18,19] new strategic approaches for the stereoselective synthesis of compounds containing P-stereogenic centres are limited, with catalytic enantioselective approaches remaining largely underdeveloped.

3.1.3 Synthesis of enantioenriched P(V) compounds by separation or resolution

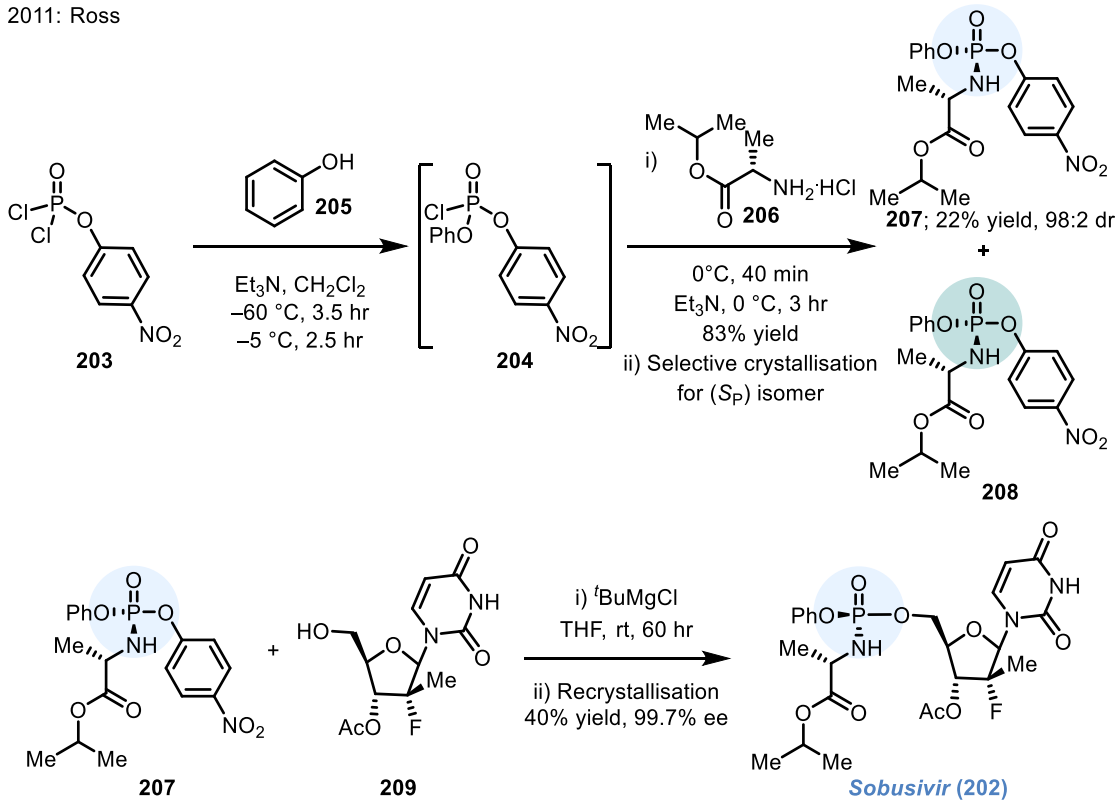
Since its introduction by Mislow in 1967 employing menthyl phosphinates,[20,21] by far the most common approach chemists use to access enantiopure P(V) compounds has been by chromatographic separation of diastereomers.[12,13,22] A modern example of this approach within the context of medicinal chemistry[8] can be seen in the synthesis of prodrug **197** by Meier in 2011 (**Scheme 1**).[23–25]



Scheme 1. Synthesis of diastereomerically pure monophosphate prodrug **197**.

In their synthesis, the authors coupled chiral auxiliary **198** with $POCl_3$ affording dichloride intermediate **199** which was subsequently combined directly with salicyl alcohol (**200**) in the presence of DBU to afford diastereoisomeric compounds **201** and **202** in a 94:6 ratio. The two compounds were separated by chromatography and desired diastereoisomer **201** was then selected to undergo nucleophilic substitution (S_N2@P) with 3'-OAc-dT in the presence of ^{t}BuMgCl affording the final prodrug **197** in 48% with smooth and predictable inversion at the phosphorous stereocentre.

A complementary method relies on the resolution of diastereomers *via* selective crystallisation. This approach can be exemplified by the work of Ross *et al.* in 2011 on the synthesis of Sobusivir (**202**) (**Scheme 2**).[26] Commercially available nitrophenyl dichlorophosphate **203** was converted to the corresponding phosphorochloridate (**204**) with phenol (**205**) and then subsequently with *L*-alanine isopropyl ester hydrochloride (**206**) to afford a diastereoisomeric mixture of phosphoramidates **207** and **208** in 83% yield. The authors were then able to selectively crystallise the S_P diasteromer **207** in 22% yield and 98:2 dr. **207** was then coupled to nucleoside **209** in the presence of ^{t}BuMgCl to afford final product **202** with inversion of configuration in 40% yield and 99.7% ee after recrystallisation from CH_2Cl_2.



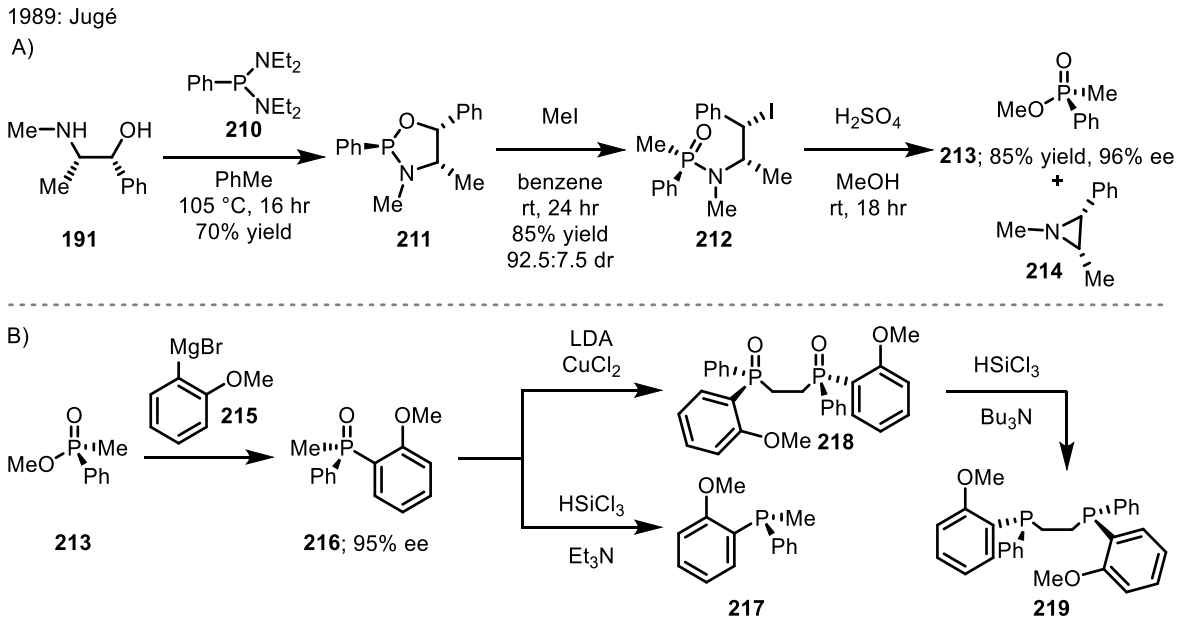
Scheme 2. Synthesis of Sobusivir (**202**) by selective crystallisation.

While both syntheses described above allow for the synthesis of the target prodrug compounds with very high levels of enantiopurity, this approach is inherently limited. Overall, the extremely high prevalence of resolutions and chromatographic separation of diastereoisomers present in the literature for the synthesis of P(V) containing drug compounds limits production and highlights the need for novel catalytic, enantioselective methods towards these highly important motifs in atom- and waste-economical strategies.

3.1.4 Synthesis of enantioenriched P(V) compounds by displacement of chiral auxiliaries

A longstanding alternative approach to the synthesis of enantioenriched compounds bearing a P stereocentre has been the development of electrophilic phosphorous sources bearing chiral auxiliaries as leaving groups which can be displaced by sequential nucleophilic additions in a diastereomeric fashion. An early proponent of this manifold was Jugé, who, as far back as 1989, employed ephedrine (**191**) as an auxiliary for the synthesis of enantioenriched phosphinates, phosphine oxides and phosphines (**Scheme 3**).[27] The authors coupled **191** with P(III) species **210** to obtain P-containing heterocyclic compound **211** in 70% yield. Upon treatment with MeI, **211** was found to undergo a diastereoselective Michaelis-Arbuzov rearrangement to afford compound **212** in 85% yield and 92.5:7.5 dr. The auxiliary was then cleaved with acidic MeOH to give methyl phenyl phosphinate **213** with inversion of configuration at P in 96% ee as well as aziridine **214** which could be recycled back to the ephedrine auxiliary (**Scheme 3A**). Subsequently, **213** underwent nucleophilic substitution with Grignard reagent **215** to afford phosphine oxide **216** in 95% ee, again with inversion of configuration. This product was in turn used for the synthesis of (+)-PAMP (**217**), (−)-DIPAMPO (**218**) and (−)-DIPAMP (**219**) as described by Knowles with inversion of configuration (**Scheme 3B**).[28]

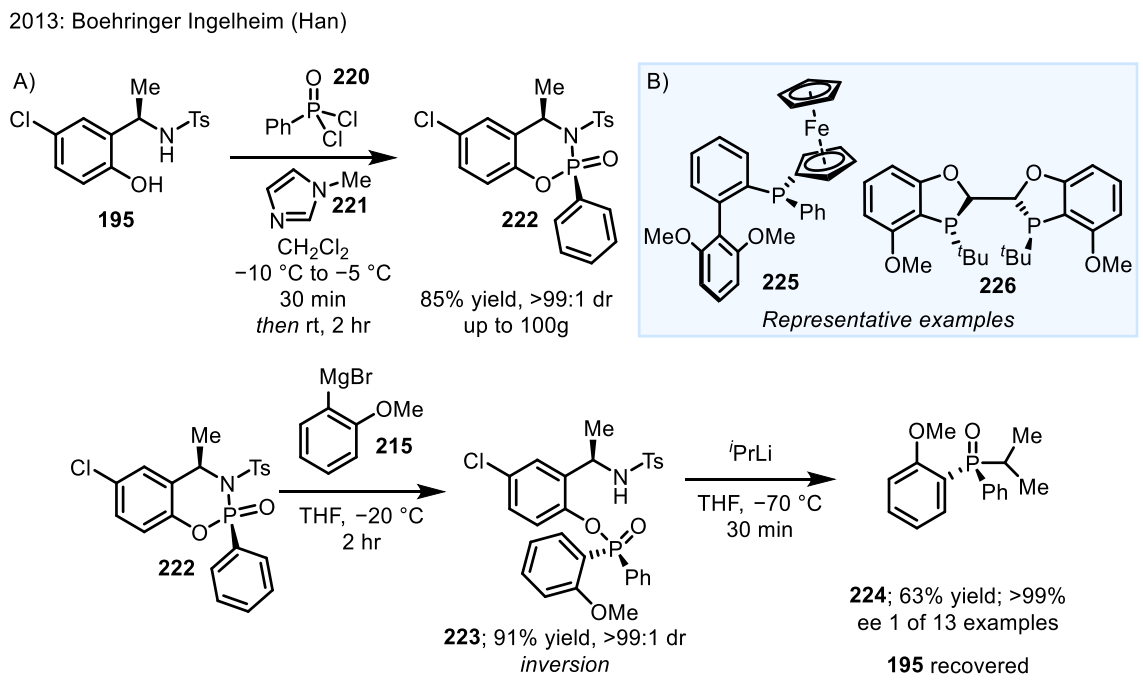
Alternatively, the BH_3 adduct of **211** was also treated directly with an organolithium reagent to form a P–C bond, circumventing the Michaelis-Arbuzov rearrangement and thus expanding the scope of the reaction.[29] Shortly following Jugé's seminal work, Corey reported the use of a camphor based chiral auxiliary (**192**) for the synthesis of two *P*-chiral phosphines in extremely high optical purity.[30]



Scheme 3. Jugé's asymmetric synthesis of phosphinates, phosphine oxides and phosphines.

Following advancements from J. M. Brown,[31] Buono[32] and Riera & Verdaguer[33,34] a considerable improvement to Jugé's method was achieved by chemists at Boehringer Ingelheim in 2013 (**Scheme 3**).[35] After various attempts to improve Jugè's ephedrine auxiliary the authors rationally designed auxiliary **195**. By introducing electron withdrawing substituents on the N and O substituents of the auxiliary, **195** was predicted to be displaced more easily by incoming organometallic nucleophiles allowing for a wider scope. **195** was treated with phenylphosphonic dichloride (**220**), which in the presence of 1-Me-imidazole (**221**) in CH_2Cl_2 afforded diasteromerically pure **222** in 85% yield on up to 100 g scale. The chiral auxiliary on **222** could then be displaced predictably by sequential substitution with organometallic nucleophiles, undergoing P–N bond cleavage for the first addition and P–O bond cleavage for the second. The configuration of the P stereocentre was inverted upon each addition. As an example **222**, was treated with Grignard reagent **215** in THF at –20 °C for 2 hours affording intermediate **223** in 91% yield and >99:1 dr. A subsequent substitution with ^{i}PrLi in THF afforded P chiral phosphine oxide **224** in 63% yield and >99% ee, with auxiliary **195** being recovered (**Scheme 4A**). The authors also elegantly demonstrated the utility of this protocol by synthesising novel P-chiral Buchwald-type phosphines (i.e. **225**),[36–38] intermediates towards bidentate P-chiral ligands, and MeO-BIBOP (**226**) which was previously disclosed by Boehringer Ingelheim as an effective ligand for large-scale Rh-catalysed asymmetric

hydrogenation of *N*-acetyl enamides (**Scheme 4B**).[39] This method was later extended to the synthesis of P-stereogenic phosphinamides.[40]

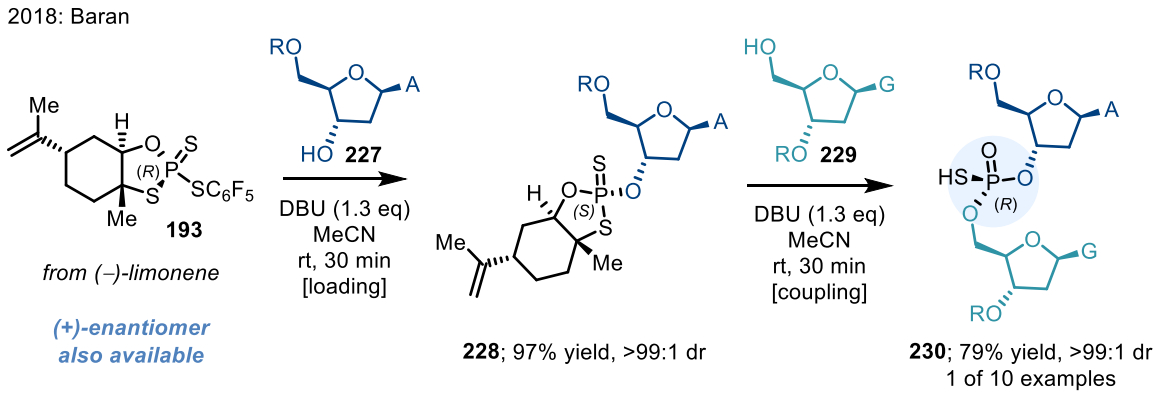


Scheme 4. Boehringer Ingelheim's asymmetric synthesis of phosphine oxides and phosphines.

While this method allows for the streamlined synthesis of a multitude of all carbon substituted P(V) and P(III) compounds, they do not include N, O and S centred nucleophiles which would allow for the synthesis of medicinally relevant P(V) containing drugs. To this end, Murai developed the use of BINOL (**196**) as a chiral auxiliary for phosphorous centres.[41–44] In a series of publications the authors described the ability of this species to undergo axis-to-centre chirality transfer to access various enantioenriched phosphinates and phosphonothioates. Unfortunately, while conceptually intriguing, yields and enantioselectivities vary widely between different nucleophiles and phosphorous substituents limiting the applicability of this method.

A truly unified chiral auxiliary approach was disclosed by Baran in 2018[45] (while the work discussed in this chapter had already begun) and later expanded on by the same group in 2020 and 2021 (**Scheme 5**).[46] After an extensive screening of chiral backbones and aromatic leaving groups (−)-limonene oxide derived reagent **193** (known as PSI or Ψ) was found by the authors to be highly effective for chirality transfer as well as being chemically robust and economical, as to attract potential use in industry.[47]

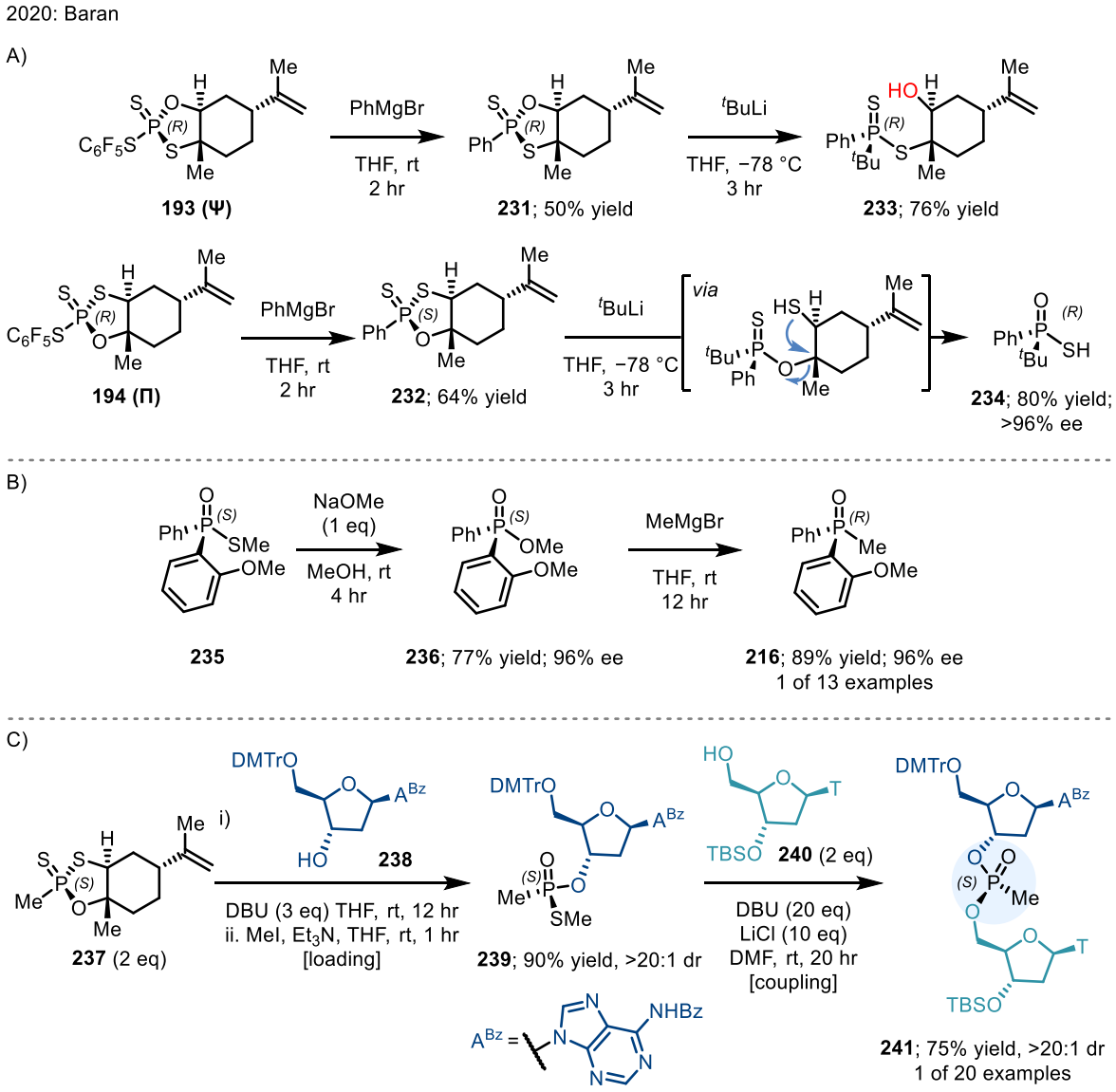
Indeed, this was demonstrated by a 90 g synthesis of the reagent which is found to be both crystalline and bench stable. 5' O-TBDPS protected nucleosides bearing unprotected bases such as **227** are then "loaded" using DBU in MeCN affording intermediate **228** in 97% yield as a single diastereomer with inversion of configuration. A second nucleoside such as **229** could then be coupled using the same conditions to afford phosphorothiodinucleotide **230** in 79% yield and >99:1 dr. The authors demonstrate the generality of this approach by synthesising multiple dinucleotides bearing different DNA bases with no erosion of diastereoselectivity. Most impressively, the Ψ reagent is then used for the synthesis of biologically important cyclic dinucleotides[48] as well as in solid-phase oligonucleotide synthesis to afford a pentamer oligothionucleotide as a single enantiomerically pure diastereoisomer. This represents a drastic improvement over conventional solid-phase oligonucleotide synthesis where previously, for the same synthetic sequence, 16 diastereomers of the target oligonucleotide were obtained. The Ψ reagent was also later used to great effect by the Baran group in the synthetic elaboration of native DNA[49], stereocontrolled oligonucleotide synthesis[50] and for late stage phosphorous incorporation in the synthesis of Tagetitoxin.[51]



Scheme 5. Baran's chiral phosphorothioate synthesis. R=TBDPS.

Later, the authors revealed that when the Ψ reagent was submitted to sequential nucleophilic additions with organometallic reagents, P–O bond cleavage resulted over auxiliary association. This issue was resolved by developing a novel reagent (**194**, PI or Π), which employs a regioisomeric *trans*-limonene oxide-based auxiliary (**Scheme 6A**).[46] By treating both (−)-Ψ (**193**) and (−)-Π (**194**) with PhMgBr, regioisomeric products **231** and **232** were obtained in similarly modest yield. When these were reacted further intermediates with ^{t}BuLi, (−)-Ψ derived intermediate **231** underwent P–O bond cleavage to afford

233, which could not be further derivatised. (−)-Π derived intermediate **232** on the other hand, smoothly afforded desired product **234** in 80% yield and >96% ee *via* P–C bond formation and intramolecular auxiliary cleavage. Both additions proceeded with retention of the stereochemical configuration at phosphorous.



Scheme 6. A) Comparison in reactivity between Ψ and Π reagents. B) Leaving group installation and final displacement. C) Stereoselective synthesis of synthesis of MPOs.

To forge the final P–C bond, the authors had to manipulate the product following the coupling of the second organometallic reagent to convert the SH moiety into an effective leaving group. This was achieved by means of methylation with MeI in a one-pot protocol following the second nucleophilic

substitution affording **235** and displacement with NaOMe to afford **236** in 77% yield and 96% ee, with other leaving groups leading to racemisation. The OMe group could in turn be replaced by a third organometallic reagent (MeMgBr in this case) and afforded target P-chiral phosphine oxide **216** in 89% yield and 96% ee with net retention over two steps (**Scheme 6B**).

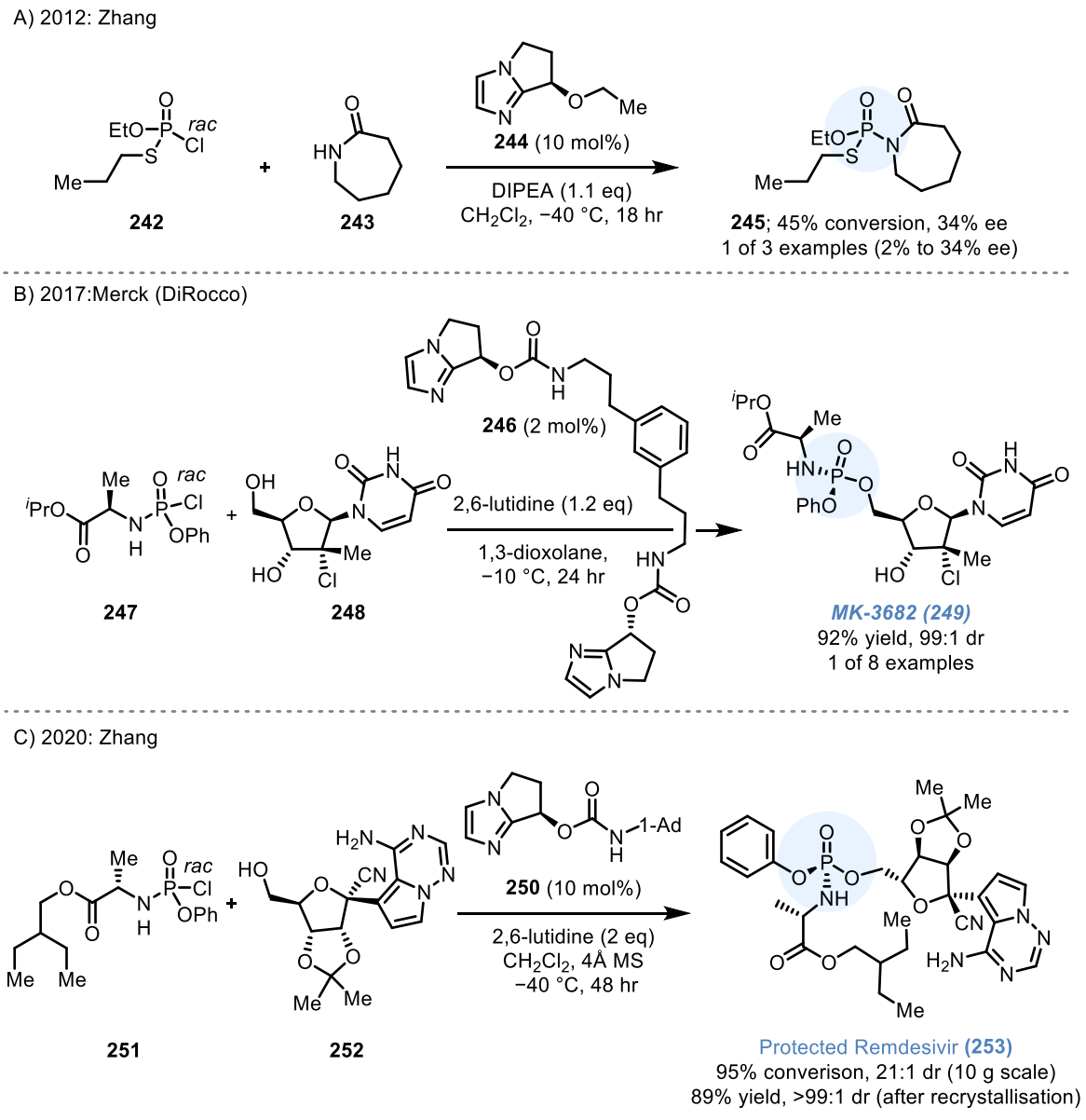
In a final application of the newly disclosed Π reagent, it was employed by the authors in the synthesis of methylphosphonate oligonucleotides (MPOs) which have been demonstrated to possess superior resistance to phosphodiesterase degradation compared to other oligonucleotides (**Scheme 6C**).[52,53] (−)-Π (**194**) was coupled with MeMgBr to deliver methylated intermediate **237**. 5'-ODMTr and NBz protected deoxyguanosine **238** were then "loaded" utilising a combination of 2 equivalents of **237** in the presence of DBU. Following work-up, the resulting SH moiety was subjected to methylation to afford intermediate **239** in 90% yield and >20:1 dr with inversion of configuration. Contrary to the previously described phosphine oxide synthesis, the SMe group could be displaced directly by incoming 3'-OTBS protected thymidine **240** in the presence of 20 eq of DBU and 10 eq of LiCl, affording the desired protected MPO **241** in 75% yield and >20:1 dr, once again with inversion of configuration at phosphorous. Multiple combinations of different nucleosides were demonstrated by the authors for both enantiomers.

3.1.5 Access to P(V) stereogenic compounds *via* catalytic diastereoselective coupling

While substantial progress has been made in the synthesis of enantioenriched phosphorous compounds *via* the use of chiral auxiliaries, these approaches remain inherently wasteful, generating stoichiometric amounts of high molecular weight by-products. As such, catalytic methods to install chirality at phosphorous are highly desirable. While no highly enantioselective[54–56] nucleophilic substitutions at phosphorous currently exist, several elegant diastereoselective reports have recently started to appear.

Most prominent among these is a 2017 report by the Merck process team in Rahway.[57] Their work was based upon a previous report by Zhang in which racemic **242** was coupled to ε-caprolactam (**243**) by means of chiral nucleophilic catalyst **244** affording modestly enantioenriched product **245** in 45% conversion by ^{1}H NMR by means of a dynamic kinetic asymmetric transformation (DYKAT) (**Scheme 7A**).[54] After a thorough investigation into the determination of rate constants the authors elucidated that

the reaction had 2nd order kinetics with respect to the catalyst which led them to design dimeric catalyst **246**. **246** was then employed to couple valuable, biologically relevant building blocks **247** and **248** to afford prodrug MK-3692 (**249**) in an impressive 92% yield and >99:1 dr. The generality of this method was then demonstrated with further examples derived from pharmaceutically important nucleosides (**Scheme 7B**).



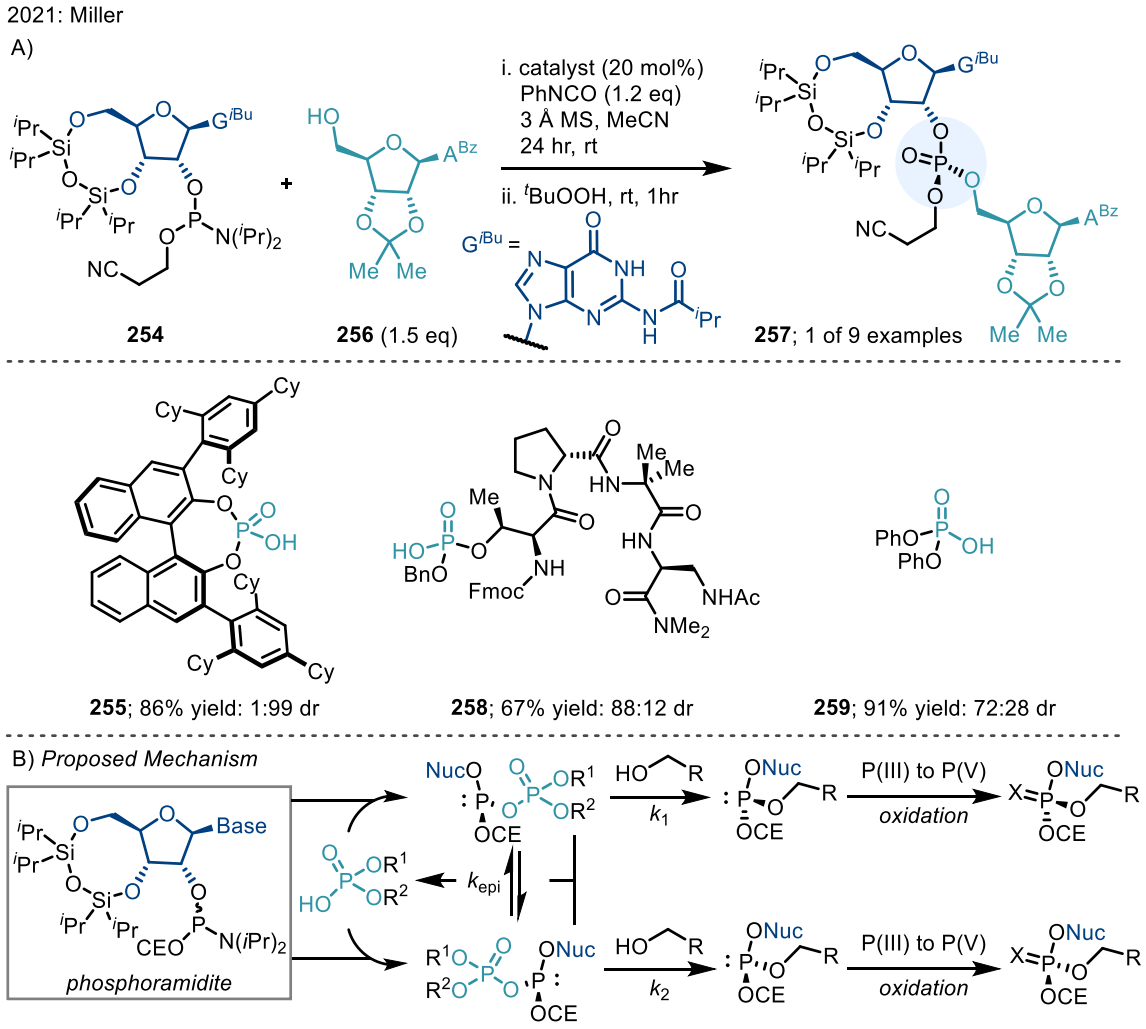
Scheme 7. A) Zhang's modestly enantioselective nucleophilic substitution at phosphorous. B) Merck's highly diastereoselective synthesis of prodrugs. C) Zhang's improved diastereoselective synthesis of Remdesivir.

Following the report from Merck, Zhang disclosed a new monomeric nucleophilic catalyst (**250**) which bears a 1-adamantyl substituted carbamate H-bond donor. The authors demonstrated the utility of this improved catalyst design in the diastereoselective coupling of **251** and **252** to obtain acetal protected Remdesivir (**253**) in 89% yield and >99:1 dr after a single recrystallisation on a 10 g scale (**Scheme 7C**).[58] Remdesivir (**184**) was then be obtained in 73% yield by cleavage of the acetal protecting group with 37% HCl in THF. This report was extremely timely given the prominence of Remdesivir as a treatment for COVID-19 during the 2020 global pandemic and represented a clear step change from previous synthetic routes relying on chromatographic separation[59] or on stereospecific coupling of intermediates obtained by classical resolution *via* recystallisation.[2,60] A very similar catalytic system was later disclosed by Wong and Hung obtaining comparable levels of diastereoselectivity.[61]

Most recently, Miller reported a catalytic, highly diastereoselective and stereodivergent dinucleotide synthesis (**Scheme 8**).[62] The authors exposed phosphoramidite loaded nucleotide **254** (with 1:1 dr at the P centre) to 20 mol% of a phosphoric acid catalyst (**255**) which rapidly racemised the phosphoramidite *via* a mixed valence P(III)-P(V) intermediate, which was subsequently intercepted by the 5'-OH of protected adenosine **256** under a DYKAT regime affording the coupled P(III) product, which was subsequently oxidised with *t*BuOOH in a one-pot protocol to afford corresponding P(V) product **257** (**Scheme 8B**). The authors demonstrated catalyst control by obtaining **257** in 86% yield and 1:99 dr with **255** and then the opposite diastereomer with peptide derived phosphoric catalyst **258** in 67% yield and 88:12 dr. Achiral phosphoric acid **259** delivered the product in 91% yield and 72:28 dr. The PhNCO served as a scavenger for diisopropyl amine formed during the reaction. While the work presented by Miller is highly elegant, it is worth noting that excellent levels of diastereoselectivity are observed only with catalyst **255**, and, while catalyst **258** does offer access to the opposite diastereomer, the levels of dr observed are only marginally better than with achiral phosphoric acid **259**. In addition, both the sugar portion and the base of the nucleoside must be protected. Furthermore, while the authors demonstrated site-selective phosphitylation with catalyst **255** using an unprotected nucleoside, catalyst **258** which is used to obtain the opposite enantiomer preferentially only delivers the desired product in 5% yield.

While collectively these catalytic diastereoselective methods offer a direct route to enantioenriched P(V) compounds, including highly relevant antiviral drugs, they are also reliant on match–mismatch effects

between the catalyst and chiral elements of the nucleophilic and electrophilic coupling partners. As such, complete catalyst control in these reactions is challenging and highlights the need for truly enantioselective methods to obtain both product enantiomers on demand.



Scheme 8. A) Miller's catalytic diastereoselective oligonucleotide synthesis. B) Proposed mechanism. CE= cyanoethyl.

3.1.6 Enantioselective functionalisation of secondary phosphine oxides

Secondary phosphine oxides (SPOs) have recently become prominent feedstock reagents for the synthesis of chiral phosphines by means of direct catalytic enantioselective P–C coupling, averting the need for lengthy multistep syntheses employing chiral auxiliaries. These couplings rely on the equilibrium between the secondary phosphine oxide (**260**) and the corresponding phosphinous acid tautomer (**261**)

which is nucleophilic at phosphorous and can thus bind a transition metal. Both **260** and **261** are configurationally stable (**Figure 4**).[63]

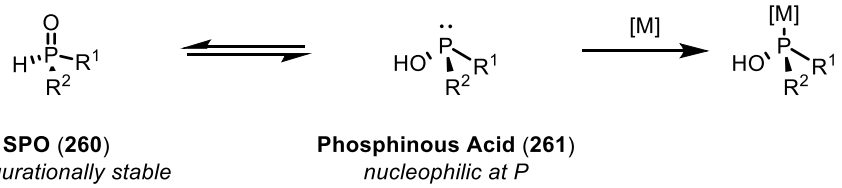
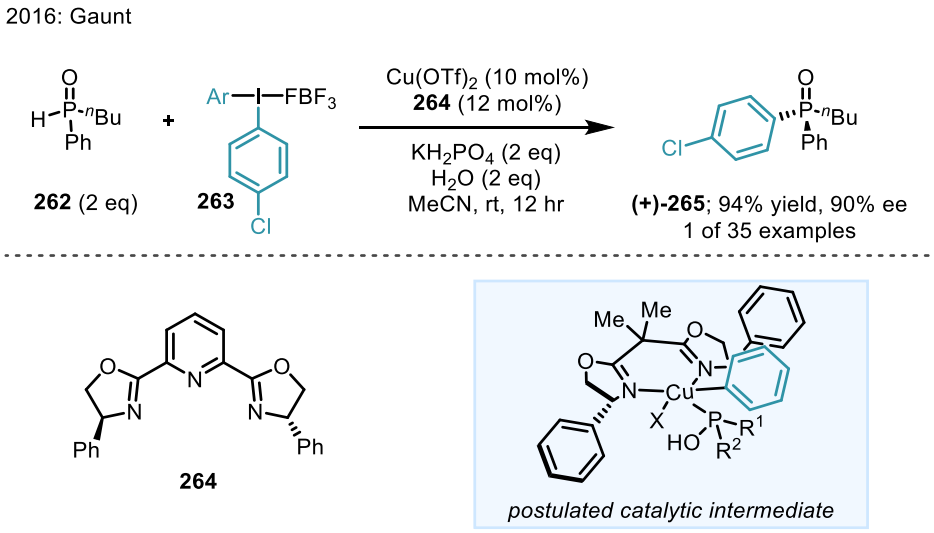


Figure 4. Tautomerisation between SPO and phosphinous acid and subsequent binding to a transition metal.

Following seminal contributions from Glueck,[64] Helmchen,[65] Hayashi,[66] and Bergman & Toste[65] describing enantioselective P–C bond formation with secondary phosphines, Gaunt disclosed a general and highly enantioselective Cu-catalysed approach using SPOs and diaryliodonium salts (**Scheme 9**)[67] based upon a racemic version of the same reaction previously reported by Zhao.[68] The authors employed 2 equivalents of SPO **262** combined with tetrafluoroborate diaryliodonium salt **263** in the presence of 10 mol% $Cu(OTf)_2$ and PyBox ligand **264** to afford enantioenriched tertiary phosphine oxide **265** in 94% yield and 90% ee. The generality of this reaction was shown over 35 examples varying the alkyl substituents on the SPO and the aryl group on the iodonium salt. The utility of the resulting tertiary phosphine oxides was then demonstrated in the synthesis of a chiral phosphines *via* reduction. While the most obvious mechanism for the observed enantioselectivity is a simple kinetic resolution (hence the requirement for 2 equivalents of **262**) the authors observed that the remaining starting material undergoes an oxidation process which converts the remaining SPO into the corresponding phosphinic acid derivative, which then undergoes *O*-arylation to give racemic phosphinate. Further control experiments using 91% ee (−)-**262** and both enantiomers of ligand **264** showed that (−)-**265** was obtained in 68% ee when using the mismatched (*R,R*) enantiomer of **264**, again indicating racemisation of the starting material under the reaction conditions. This led the authors to believe that a possible DYKAT mechanism was at play, and, while some mechanistic questions remain unanswered, the catalytic method developed by Gaunt provides a broadly useful entry point to enantioenriched tertiary phosphine oxides.

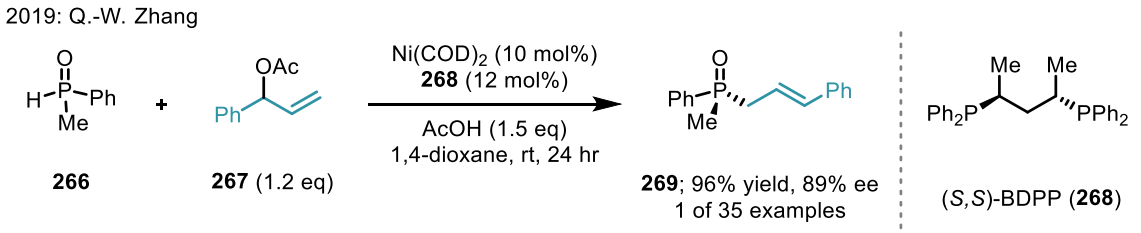


Scheme 9. Gaunt's enantioselective arylation of SPOs. Ar = 4-Cl-C_6H_4

Following the above report, two further developments were disclosed in 2019. The first was an enantioselective[i] Ni-catalysed allylation of SPOs by Q.-W. Zhang (**Scheme 10**)[69] and the second is an enantioselective Pd-catalysed arylation utilising aryl bromides by J. Zhang (**Scheme 11**).[70] Collectively, these two methods complement Gaunt's method by utilising more affordable and readily available electrophilic partners.

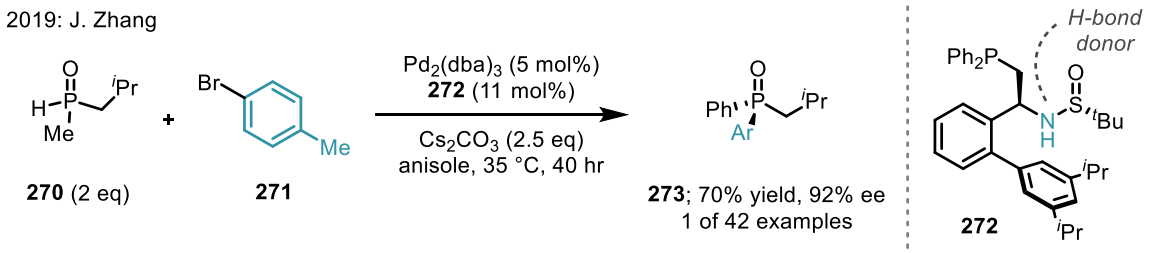
Q.-W. Zhang and co-authors employed 1 equivalent of racemic SPO such as **266** and allylic acetate **267** in the presence of $Ni(COD)_2$ and chiral bis-phosphine ligand **268** and 1.5 eq of AcOH to afford enantioenriched product **269** in 96% yield and 89% ee with exclusively linear selectivity. Multiple variations of the SPO and acetate were tolerated for a total of 35 examples. The authors observed a kinetic resolution when using K_3PO_4 as base and a dynamic kinetic resolution when employing KOAc. While the mechanism remains unclear, the authors proposed that Ni(II) could promote racemisation of the phosphinous acid tautomer of **266** which would then allylate at different rates based on matched/mismatched interactions with the catalyst. Notwithstanding this, the fact that high conversion and ee is obtained when using only 1 eq of SPO indicates that some form of DKR must be involved.

[i] A non-asymmetric version of this reaction was disclosed by Lu in 1987.[141]



Scheme 10. Q.-W. Zhang's enantioselective Ni-catalysed allylation of SPOs.

Building upon a modestly enantioselective approach by Cai,[71] J. Zhang and co-workers employed 2 eq. of SPO **270** which was coupled enantioselectively to aryl bromide **271** by means of $Pd_2(dba)_3$ ligated by bifunctional Xiao-Phos derivative **272** affording tertiary phosphine oxide **273** 70% yield and 92% ee. This method was also applied to the synthesis of DiPAMP ligands demonstrating its utility. From a mechanistic perspective the authors observed a clear kinetic resolution, with recovered excess SPO being enantioenriched and a clear matched/mismatch effect being observed when using 74% ee starting material and opposite enantiomers of the catalyst.



Scheme 11. J. Zhang's enantioselective Pd-catalysed arylation of SPOs. Ar = 4-Me-C_6H_4

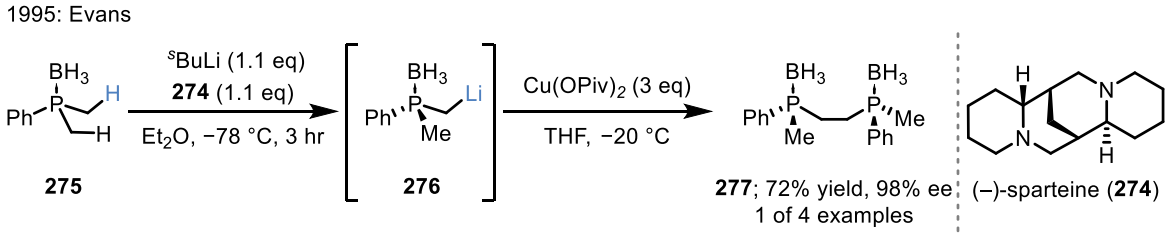
Overall, these methods provide facile and direct access to tertiary phosphine oxides (and therefore phosphines) which can be used as effective ligands in enantioselective catalysis. The main drawback, however, is that only carbon nucleophiles can be employed, and thus these methods cannot be used to access medicinally relevant phosphorous containing compounds which usually contain one or more heteroatom−P bond.

3.1.7 Indirect enantioselective desymmetrisation of P(V) species

The final category of transformations to access enantioenriched P(V) species relies on the desymmetrisation of prochiral groups around a central P atom by means of enantioselective catalysis, thus indirectly generating a P stereocentre.

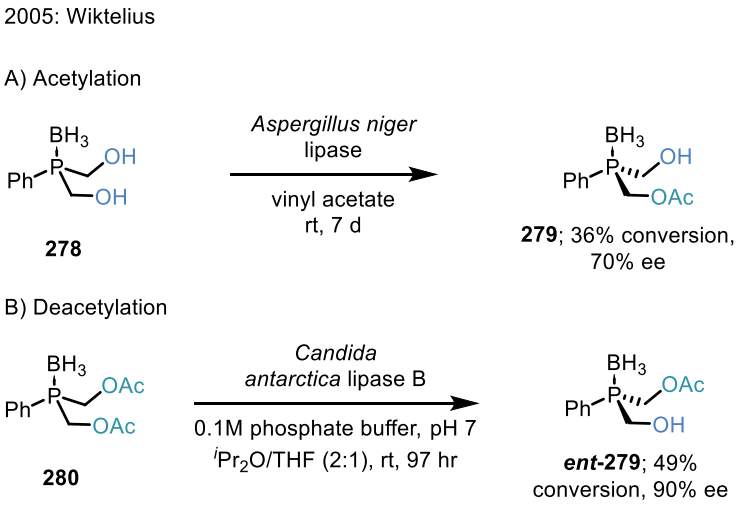
3.1.7.1 Desymmetrisation of BH_3 bound phosphines

Early methodology relied on the desymmetrisation of prochiral methyl groups on BH_3 bound phosphine Lewis adducts. Evans, an early proponent of this approach, employed ^{s}BuLi in combination with (−)-sparteine (**274**) to perform an enantioselective deprotonation of prochiral Me groups on **275** affording chiral lithiated intermediate **276** which could then be homodimerized in the presence of $Cu(OPiv)_2$ to afford BH_3 protected chiral bisphosphine **277** in 72% yield and 98% ee alongside a minor amount of the *meso* dimer which could be easily separated by flash chromatography (**Scheme 12**).[72] The authors also showed that aryldimethylphosphine sulfides could be deprotonated enantioselectively *via* the same method and that both ketones and Me_2SiCl_2 could be used as alternative electrophiles. In 1998, Imamoto disclosed an analogous method for the synthesis of sterically demanding P-chiral bis(trialkylphosphine) ligands.[73] O'Brien later demonstrated that sub-stoichiometric amounts of (−)-sparteine or (+)-sparteine surrogate[74] could be used to obtain similar results,[75] based on the notion that reactivity of ^{n}BuLi or ^{s}BuLi is increased by complexation to (−)-sparteine.[76]



Scheme 12. Evans' (−)-sparteine mediated enantioselective deprotonation of aryldimethylphosphine-boranes.

In a complementary approach, Wiktelius demonstrated a biocatalytic enantioselective desymmetrisation of bis(hydroxymethyl)phenylphosphine-borane (**278**) (**Scheme 13**).[77] In a first instance the authors demonstrated the enantioselective acetylation of prochiral **278** by *Aspergillus niger* lipase in neat vinyl acetate, which afforded product **279** with 36% conversion and 70% ee after 7 days (**Scheme 13A**). Interestingly, the reverse reaction was also possible starting from prochiral diacetylated **280** in the presence of *Candida antarctica* lipase B in a solvent mixture of phosphate buffer and $^{i}Pr_2O$/THF which yielded enantioenriched hydrolysed product *ent*-**279** in 49% conversion and 90% ee (**Scheme 13B**).



Scheme 13. Wiktelius' lipase catalysed enantioselective desymmetrisation by acetylation (A) or deacetylation (B).

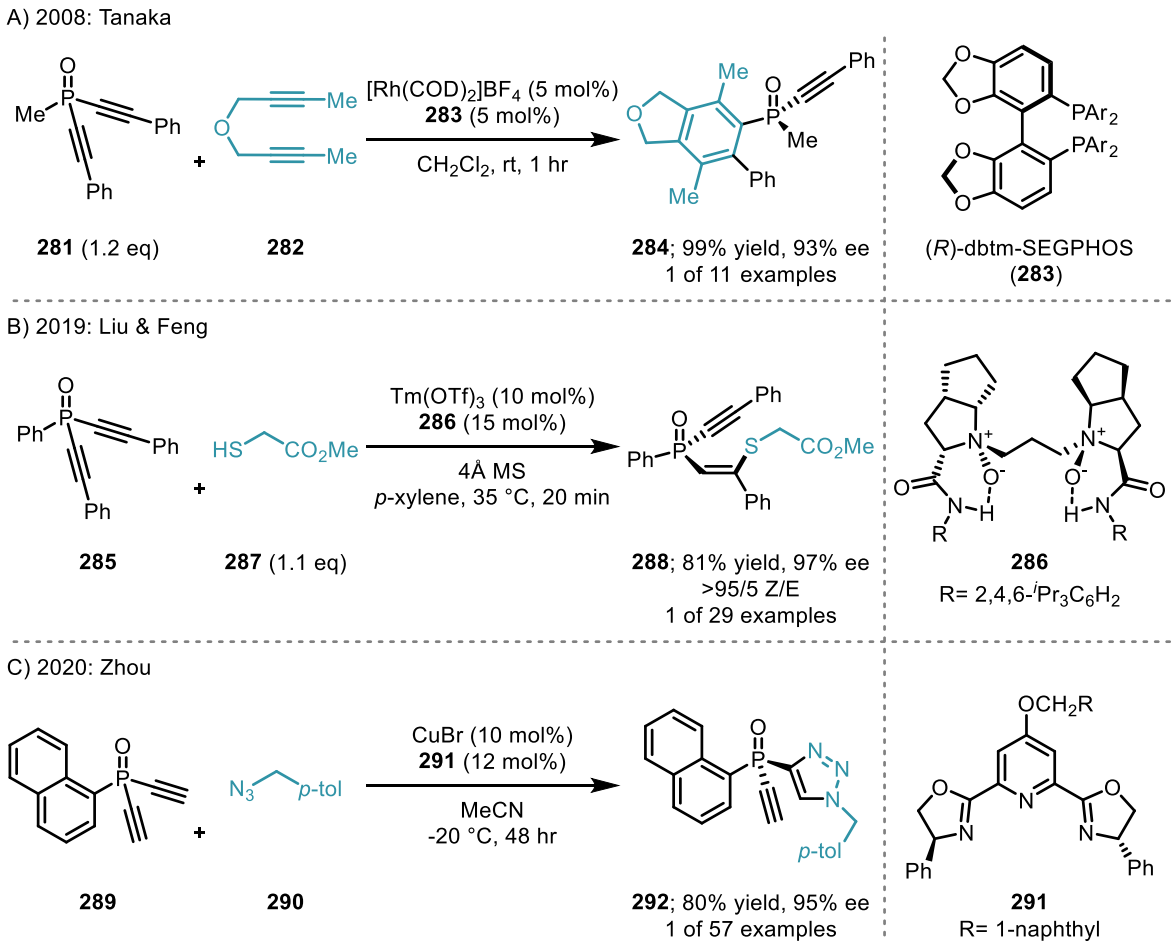
3.1.7.2 Desymmetrisation of bis-alkyne substituted P(V) species

Substrates bearing two identical alkyne substituents have also been used effectively in enantioselective desymmetrisation reactions. In 2008, Tanaka employed symmetrical alkynylphosphine oxides in an enantioselective desymmetrisation *via* a Rh-catalysed [2+2+2] cycloaddition (**Scheme 14A**).[78] The authors employed 1.2 eq of model substrate **281** and with oxygen-tethered diyne **282** in the presence of Rh ligated by (*R*)-dbtm-SEGPHOS (**283**) to afford desymmetrised product **284** in 99% yield and 93% ee.

Liu and Feng employed a similar substrate (**285**) in an enantioselective thulium(III)-**286** catalysed sulfa-Michael addition with thiol **287** to afford product **288** in 81% yield, 97% ee in a >95/5 Z/E ratio (**Scheme 14B**).[79]

Finally in 2020, Zhou reported the desymmetrisation of tertiary phosphine oxides bearing terminal alkynes *via* enantioselective Cu(I)-catalysed azide−alkyne cycloaddition(CuAAC) (**Scheme 14C**).[80] The enantioselective CuAAC between **289** and azide **290** was catalysed by 10% CuBr in the presence of an electron rich PyBox ligand **291** to afford enantioenriched triazole product **292** in 80% yield and 95% ee. The authors then extended this method to the kinetic resolution of racemic alkynylphosphine oxides

bearing three different substituents and subsequently to the desymmetrisation of phosphole oxide-diynes bearing remote alkyne groups for a total of 57 examples.



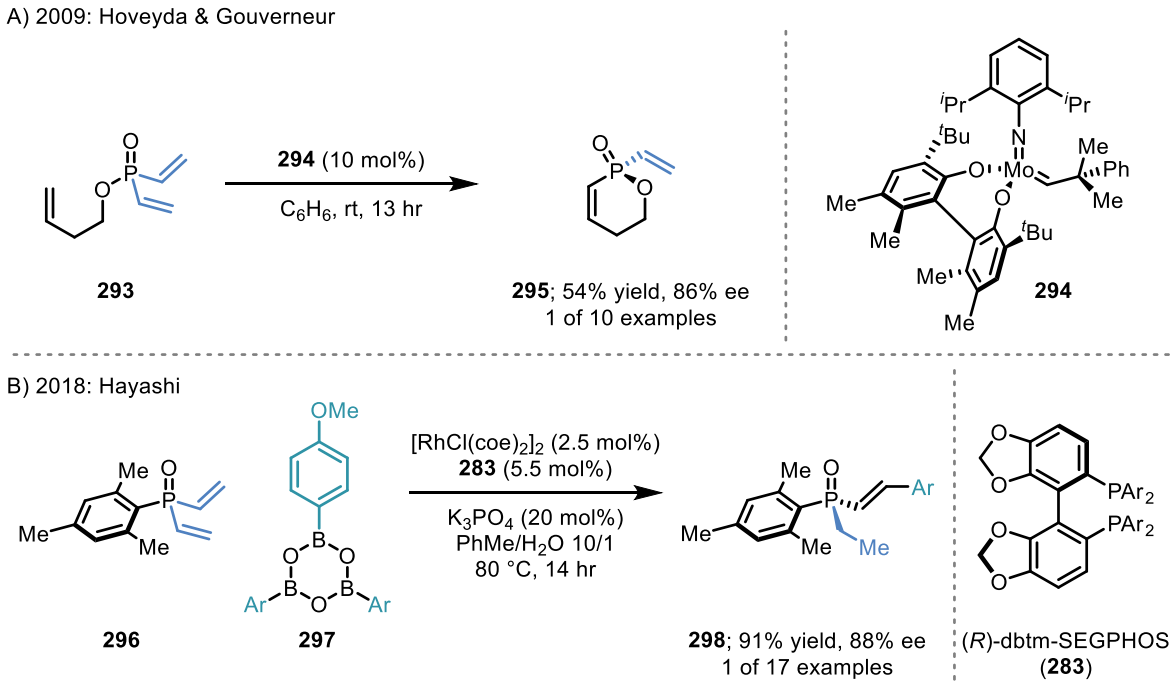
Scheme 14. A) Tanaka's enantioselective Rh-Catalysed [2+2+2]cycloaddition of alkynylphosphine oxides; Ar = 4-MeO-3,5-^{t}Bu$_2$C$_6$H$_2$ B) Liu and Feng's desymmetrisation *via* enantioselective thulium(III)-catalysed sulfa-Michael addition. C) Zhou's desymmetrisation of alkynylphosphine oxides *via* enantioselective Cu(I)-catalysed azide−alkyne cycloaddition(CuAAC).

3.1.7.3 Desymmetrisation of bis-alkene substituted P(V) species

Like their alkynyl counterparts, phosphinates and phosphine oxides bearing prochiral vinyl groups have also been used as substrates for enantioselective desymmetrisation leading to the formation of a phosphorous stereocentre. In 2009, Hoveyda and Gouverneur developed the first asymmetric ring closing metathesis (ARCM) to generate P-stereogenic molecules (**Scheme 15A**).[81] The authors employed divinyl phosphinates (or phosphines) bearing a tethered alkene such as **293** which could then undergo

ARCM in the presence of chiral Mo catalyst **294** to afford enantioenriched cyclic compound **295** in 54% yield and 86% ee. Cyclic phosphinates or phosphine oxides of various ring size were obtained *via* this method, with enantioselectivity appearing to be highly substrate dependant. This issue was partially resolved by using variations of catalyst **294**.

Hayashi later used similar divinylphosphine oxides to perform an enantioselective desymmetrisation *via* rhodium-catalysed selective hydroarylation (**Scheme 15B**).[82] Divinylphosphine oxide **296** was shown to undergo a two-fold transformation (double bond reduction and Heck-type coupling) when reacted with triaryl boroxine **297** in the presence of 2.5 mol% $[RhCl(coe)_2]_2$ and (*R*)-dbtm-SEGPHOS (**283**) to form enantioenriched product **298** in 91% yield and 88% ee. In an alternative approach by Vidal-Ferran, racemic *a,β*-unsaturated phosphine oxides were shown to undergo effective hydrogenative kinetic resolution using a Rh catalyst bearing a chiral mixed phosphine/phosphite bidentate ligand.[83]



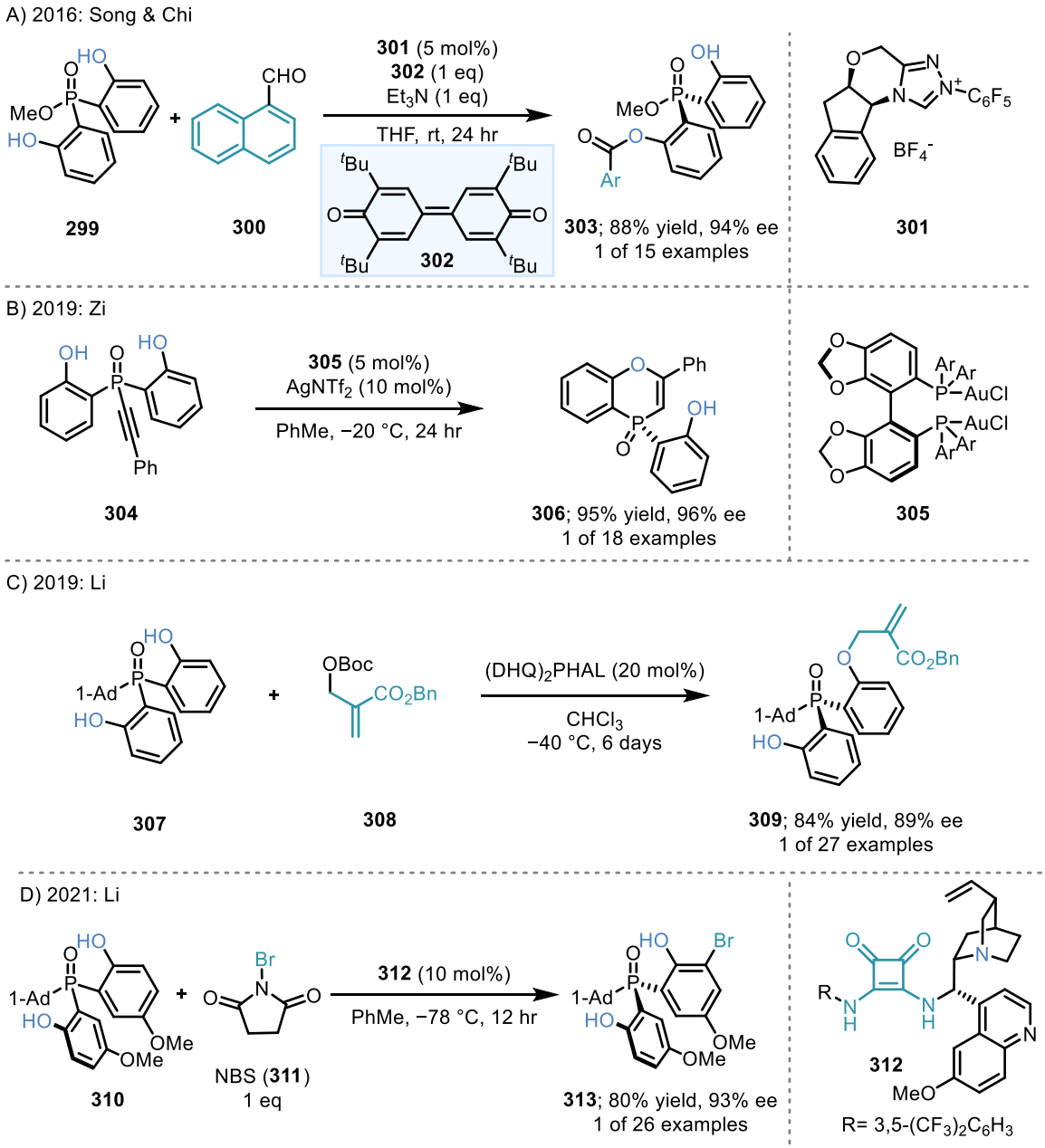
Scheme 15. A) Hoveyda and Gouverneur's enantioselective desymmetrisation *via* Mo-catalysed asymmetric ring closing metathesis. B) Hayashi's enantioselective hydroarylation of divinylphosphine oxides with aryl boroxines; Ar = 4-MeO-3,5-^{t}Bu$_2$C$_6$H$_2$.

3.1.7.4 Desymmetrisation of P-bound bisphenols

A further popular class of substrates for enantioselective desymmetrisation leading to P-stereogenic centres are bisphenols (**Scheme 16**). In 2016, Song and Chi demonstrated that chiral phosphinates could be accessed *via* a N-heterocyclic carbene catalysed desymmetrisation of bisphenols (**Scheme 16A**).[84] The authors employed bis(2-hydroxyphenyl) phosphinate substrate **299** and 1-naphthaldehyde (**300**) as reaction partners which could undergo enantioselective acylation in the presence of 5 mol% chiral NHC precursor **301** and 1 equivalent each of quinone oxidant **302** (introduced as an oxidant by Studer)[85] and Et_3N in THF at rt to afford enantioenriched product **303** in 88% yield and 94% ee. Unfortunately, the enantioselectivity was dramatically decreased when phosphine oxides were used as substrates and only racemic product was observed when the hydroxy group was moved to the 3- or 4- position of the aromatic ring.

In 2019, Zi disclosed an elegant enantio- and regioselective hydroetherification of alkynes *via* gold-catalysed desymmetrisation of prochiral phenols (**Scheme 16B**).[86] Substrate **304** was suggested to undergo an enantioslective 6-*endo*-dig cyclisation in the presence 5 mol% (*S*)-dbtm-SEGPHOS$(AuCl)_2$ (**305**) and 10 mol% $AgNTf_2$ to afford P-stereogenic heterocycle **306** in 95% yield and 96% ee. The authors also employed the same catalyst to promote the desymmetrisation of phosphine oxides bearing two alkyne substituents and one phenol with very high levels of enantiocontrol.

Subsequently, Li and co-workers developed a novel bis-*Cinchona* alkaloid-catalysed highly enantioselective desymmetrisation reaction of prochiral P-containing bisphenol compounds with achiral Morita–Baylis–Hillman (MBH) carbonate agents (**Scheme 16C**).[87] The authors employed phosphine oxide **307** bearing an 1-adamantyl substituent, and combining it with MBH carbonate **308**. Whilst the reaction proceeded slowly in the presence of 20 mol% $(DHQ)_2PHAL$ (hydroquinidine 1,4-phthalazinediyl diether) the desymmetrised product **309** was obtained in 84% yield and 89% ee after 6 days. The scope for this reaction however, appeared to be limited to phosphine oxides bearing a tertiary alkyl substituent, with other functional groups giving decreased selectivity. Similarly, only small variations to the benzyl ester substituent on the MBH carbonate reagent were demonstrated.



Scheme 16. A) Song and Chi's N-heterocyclic carbene-catalysed desymmetrisation of bisphenols. B) Zi's Au catalysed enantio- and regioselective hydroetherification of alkynes; Ar = 4-MeO-3,5-^{t}Bu$_2$C$_6$H$_2$ C) Li's bis-*Cinchona* alkaloid-catalysed enantioselective desymmetrisation of prochiral bisphenols with Morita–Baylis–Hillman carbonate reagents. D) Li's enantioselective bromination of bisphenols.

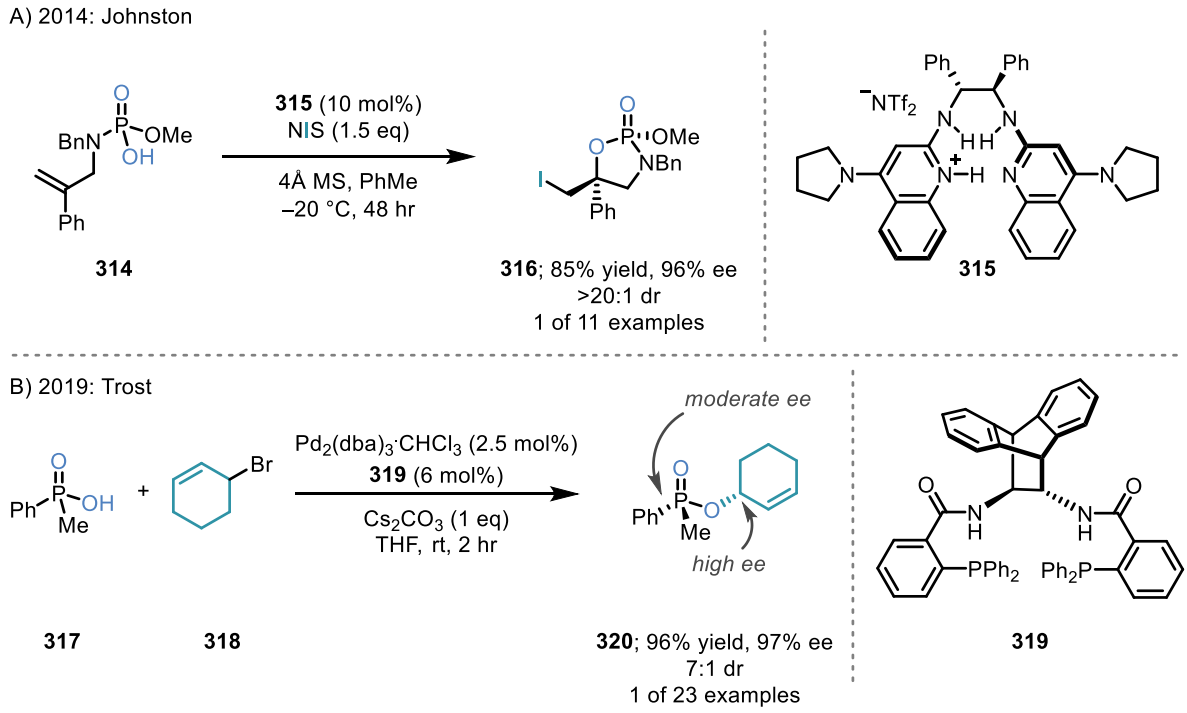
Building upon previous work in organocatalytic atroposelective bromination,[88–91] and seminal contributions in enantioselective brominative desymmetrisation of C-centres by Miller[92] and Yeung,[93] Li recently developed an analogous aromatic bromination reaction to form P-stereogenic centres (**Scheme 16D**).[94] Similarly to their previous work the authors employed 1-Ad-substituted bisphenol **310** and

treated it with 1 equivalent of NBS (**311**) in the presence of chiral bifunctional squaramide catalyst **312** (10 mol%) to afford desymmetrised brominated product **313** in 80% yield and 93% ee. The scope of the reaction was found to be broad with respect to the P substituent and substituents on the phenol rings as well as being applicable to kinetic resolution processes.

3.1.7.5 Desymmetrisation of phosphoramidic and phosphinic acids

While the above transformations focused on prochiral oxygen groups remote from the P-centre, desymmetrisations of oxygen functionalities bound directly to the phosphorous atom have also been achieved. Johnston was the first to develop such a transformation with an enantioselective intramolecular Brønsted acid catalysed phosphoramidic acid addition to alkenes *via* halogenative cyclisation (**Scheme 17A**).[95] Building upon their previous work in enantioselective halocyclisation[96] the authors utilised prochiral substrate **314** which was treated with NIS in the presence of catalyst **315** (comprised of a chiral Brønsted base scaffold protonated with $HNTf_2$) to afford cyclised product **316** in 85% yield, 96% ee and >20:1 dr, setting two stereogenic centres including one at phosphorous. The incorporation of a Brønsted acid co-catalyst was key to achieving high levels of enantioselectivity, with the free base of **315** affording the same product in only 83% ee.

Trost was the first to develop an intermolecular desymmetrisation of phosphinic acids *via* Pd-Catalysed asymmetric allylic alkylation (AAA) (**Scheme 17B**).[97] The authors used phosphinic acid **317** as a model substrate and 3-bromocyclohexene (**318**) as the electrophile to perform the AAA reaction using 2.5 mol% of $Pd_2(dba)_3$ in the presence of Trost ligand **319**. The resulting enantioenriched product **320** was obtained in 96% yield, 97% ee and 7:1 dr. The main drawback of this method was, however, that high enantioselectivity could only be obtained when 3-bromocyclohexene and 3-bromocycloheptene were used as electrophiles. Linear allylating agents resulted in very low levels of enantiomeric excess indicating that **318** acted as a resolving agent where the alkylation proceeded with high ee and the desymmetrisation with good to modest ee. This was also indicated by the varying levels of dr obtained in the scope. Despite this, the cyclohexeneol substituent was demonstrated to be an effective leaving group for nucleophilic substitutions with Grignard reagents which the authors exploited to make (*R*)-PAMPO, a common intermediate for chiral ligands such as (*R*)-CAMP and (*R*)-DIPAMP.



Scheme 17. A) Johnston's enantioselective intramolecular Brønsted acid catalysed halogenative cyclisation. B) Trost's desymmetrisation of phosphinic acids *via* Pd-catalysed AAA.

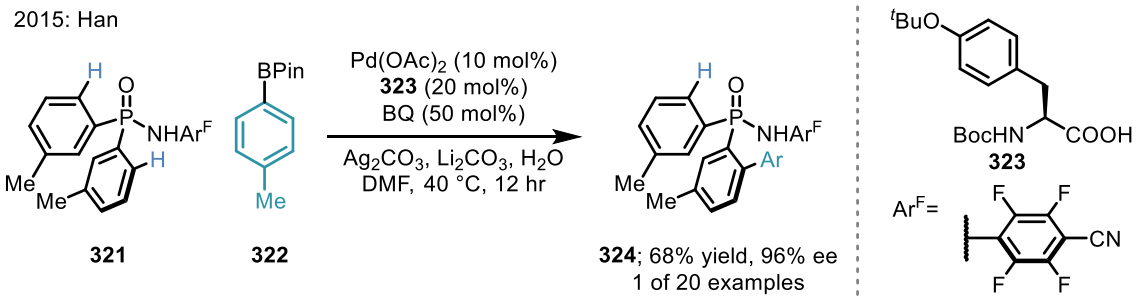
3.1.7.6 Desymmetrisation of P(V) species via enantioselective C–H functionalisation

The final class of desymmetrisation reactions to form P-stereogenic centres revolve around enantioselective C–H functionalisation of prochiral aryl groups. This is by far the most popular form of desymmetrisation at phosphorous and has been recently reviewed in the literature.[14,15] Therefore, only the most important and recent examples will be highlighted.

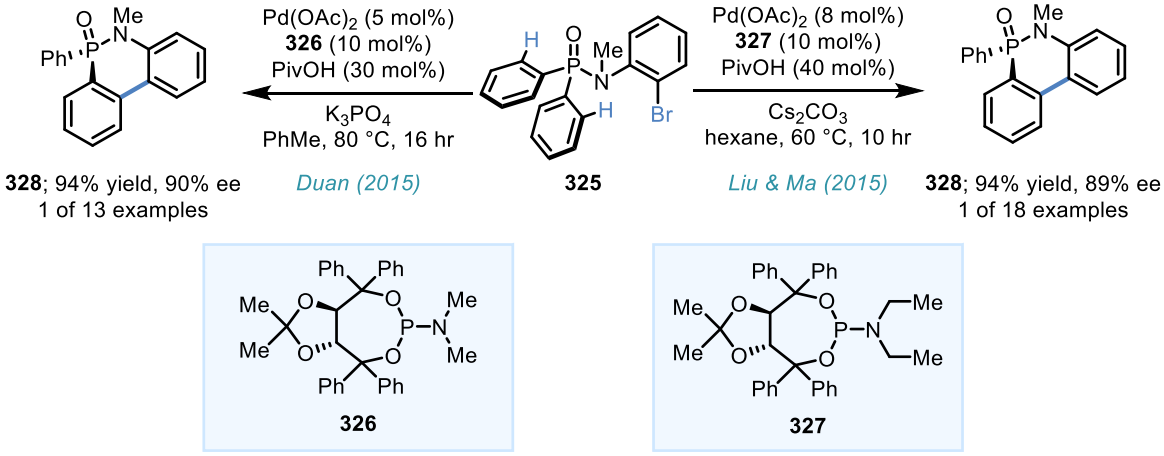
Building upon an analogous non-asymmetric reaction[98] developed by their group, Han disclosed the first enantioselective desymmetrisation of a P(V) species by means of C–H activation (**Scheme 18**).[99] Phosphinamide **321**, bearing two meta substituents and a fluorinated N-substituent[ii] (acting as a directing group for Pd)[100] was used as a model substrate while pinacol boronic ester **322** was used as arylating agent. Boc-protected amino acid **323** was identified as the optimal ligand in the presence of 10 mol% $Pd(OAc)_2$, 50 mol% of benzoquinone, Ag_2CO_3 and Li_2CO_3 to afford enantioenriched C–H arylated product **324** in 68% yield and 96% ee. A wide assortment of aryl groups were tolerated on phosphorous

[ii] An analogous reaction employing C_6F_5 as the *N*-substituent was reported by Han in 2017.[142]

including those possessing *ortho*-substituents as well as unsubstituted phenyl. Due to the high acidity of the N-H bond present in the products, their utility as highly active bifunctional chiral acids was recently demonstrated by the same group for the desymmetrisation of 1,3-diketones by enantioselective reduction.[101]



Scheme 18. Han's enantioselective desymmetrisation of phosphinamides by asymmetric C–H arylation. BQ= benzoquinone.

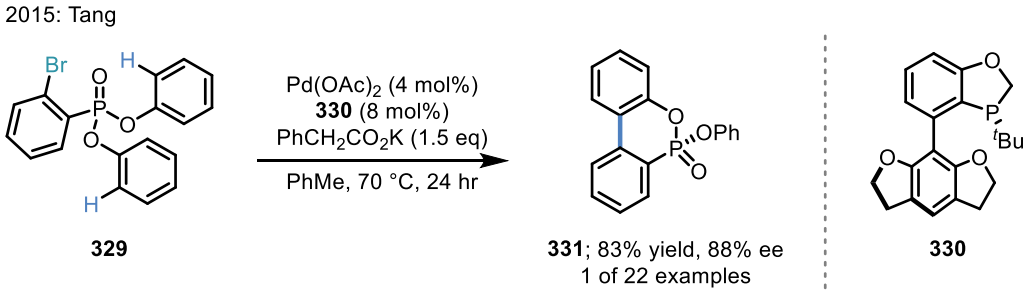


Scheme 19. Duan's (left) and Liu & Ma's (right) intramolecular enantioselective desymmetrisation of phosphinic amides *via* Pd-catalysed C–H arylation using TADDOL ligands.

Following Han's seminal contribution, multiple groups reported highly enantioselective Pd-catalysed intramolecular C–H arylations of phosphinic amides, phosphonates and phosphine oxides. In 2015, the groups of Duan[102] and Liu & Ma[103] almost concomitantly reported an intramolecular Pd-catalysed arylation of phosphinic amides using TADDOL[104] based ligands (**Scheme 19**). The authors employed very similar reaction conditions starting from prochiral substrate **325**, utilising $Pd(OAc)_2$ and 10 mol%

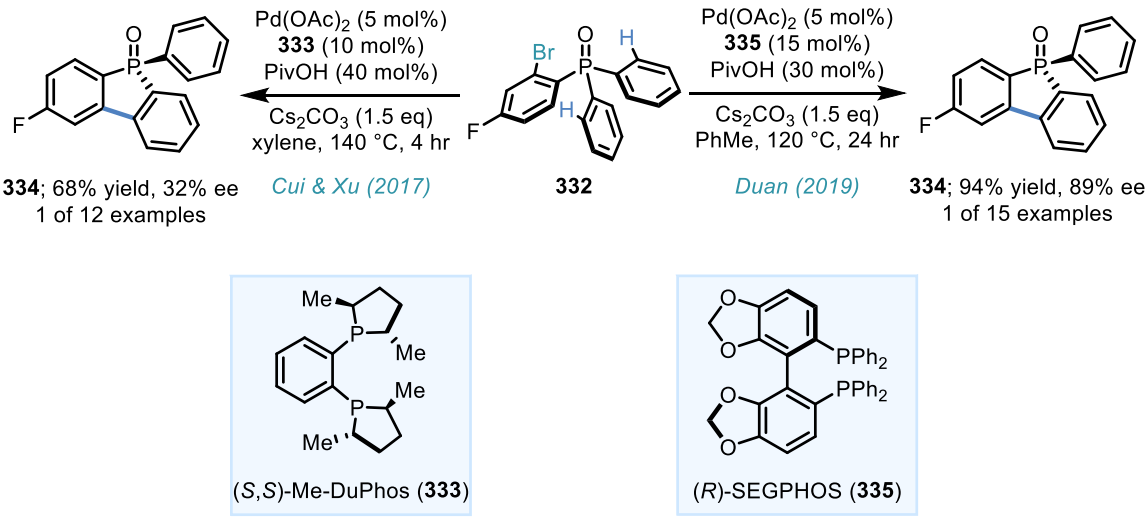
of ligand (**326** for Duan and **327** for Liu & Ma) in the presence of PivOH and either K_3PO_4 or Cs_2CO_3 to obtain enantioenriched P-chiral heterocycle **328** in 94% yield and approximately 90% ee in both cases.

In the same year, Tang disclosed an analogous intramolecular C–H arylation utilising aryl phosphonate esters (**Scheme 20**).[105] Prochiral aryl bromide **329** bearing enantiotropic C–H groups was used as the model substrate in the presence of 4 mol% $Pd(OAc)_2$ and 8 mol% of P-chiral ligand **330** and $PhCH_2CO_2K$ as base to afford enantioenriched product **331** in 83% yield and 88% ee. Both phenyl and naphthyl backbones were tolerated with alongside variations in substituents on either the aryl bromide or the prochiral phenols.



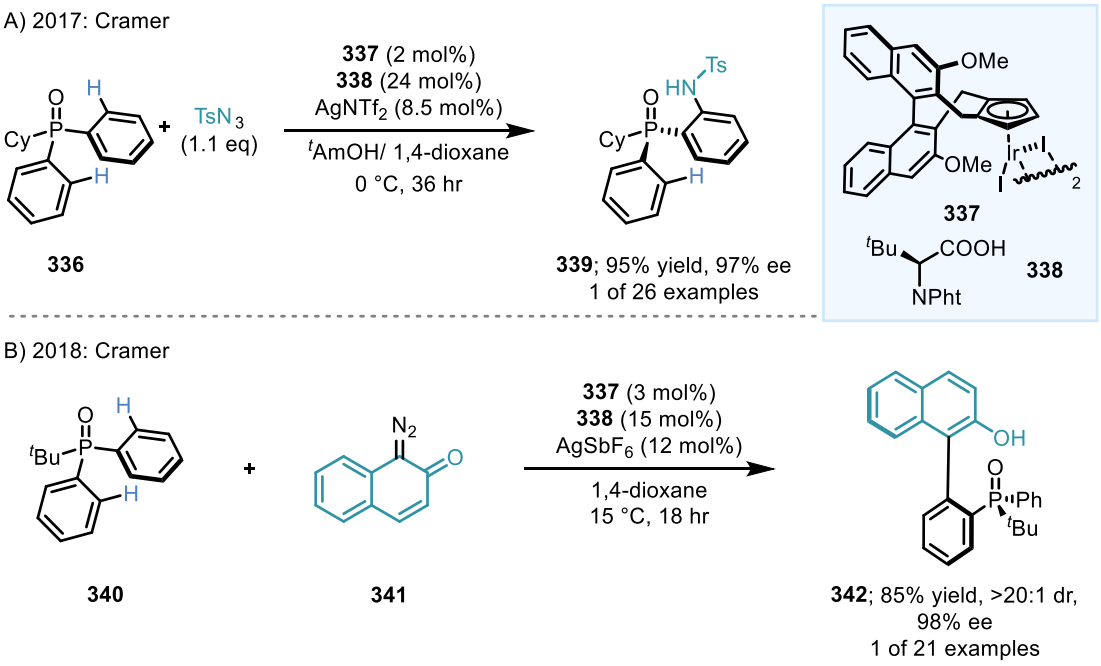
Scheme 20. Tang's enantioselective desymmetrisation of phosphonate esters by asymmetric intramolecular C–H arylation.

As a complementary method to the desymmetrisations of phosphinic amides and phosphonates described above, Cui and Xu developed a novel method for the desymmetrisation of phosphine oxides to afford enantioenriched dibenzophosphole oxides (**Scheme 21**, left).[106] Starting from fluorinated aryl bromide **332** the authors employed 5 mol% $Pd(OAc)_2$, 10 mol% of (*S*,*S*)-Me-DuPhos (**333**), 40 mol% PivOH and Cs_2CO_3 as base to afford enantioenriched product **334** in 68% yield and a very modest 32% ee. Unfortunately, except for a single example, the enantioselectivities reported for most substrates were between 4-75% ee. Duan later improved on of this method by employing (*R*)-SEGPHOS (**335**) as ligand under a similar set of conditions, affording **334** in 94% yield and an improved 89% ee (**Scheme 21**, right).[107] In the same report the authors disclosed an alternative set of conditions utilising $Pd(PCy_3)_2$ and a chiral BINOL-phosphoric acid/amide mixture, which afforded similar products in slightly diminished enantioselectivities.



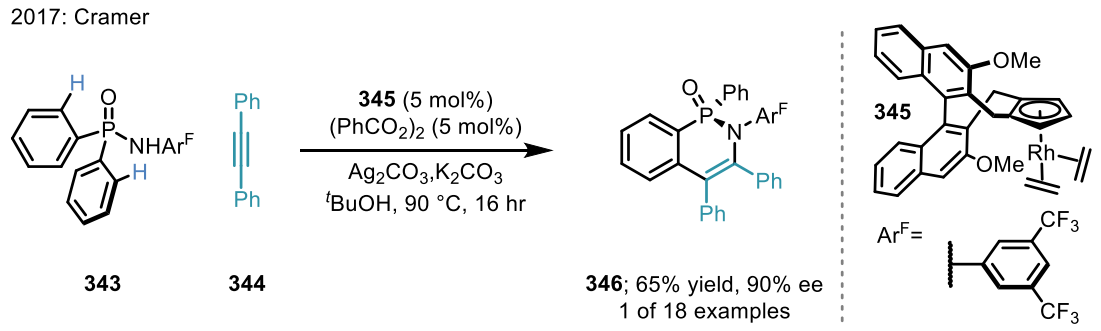
Scheme 21. Cui & Xu's (left) and Duan's (right) intramolecular enantioselective desymmetrisation of phosphine oxides *via* Pd-catalysed C–H arylation.

While Pd has been by far the most employed metal for the desymmetrisation of P(V) species *via* C–H functionalisation, chiral Ir and Rh-based systems have also been used. Building upon a chiral auxiliary approach by Chang,[108] Cramer developed a highly enantioselective $Cp^xIr(III)$[109] catalysed C−H amidation of prochiral phosphine oxides (**Scheme 22A**).[110] The authors employed substrate **336** and 1.1 equivalents of TsN_3 in the presence of 2 mol% of $Cp^xIr(III)$ catalyst **337**, 24 mol% of chirally matched carboxylic acid **338**, and $AgNTf_2$ (which generates the active cationic Ir catalyst) to afford desymmetrised amidated product **339** in an excellent 95% yield and 97% ee. The combination of chiral carboxylic acid and chiral Cp ligand was key to obtain high enantioselectivity, with achiral acids such as PivOH resulting in almost racemic product. The same Ir catalyst/carboxylic acid co-catalytic system was later used again by Cramer for the enantioselective C–H arylation of phosphine oxides (**Scheme 22B**).[111] Here the authors used substrate **340** in combination with diazo compound **341** under a similar set of conditions as their previous report to afford axially and P-chiral products such as **342** in high yields, >20:1 dr and 98% ee. Depending on the substituents on the phosphine oxide or the diazo compound the authors were also able to obtain compounds with either axial or P–chirality (or both) which could hold great promise as ligands for asymmetric catalysis.



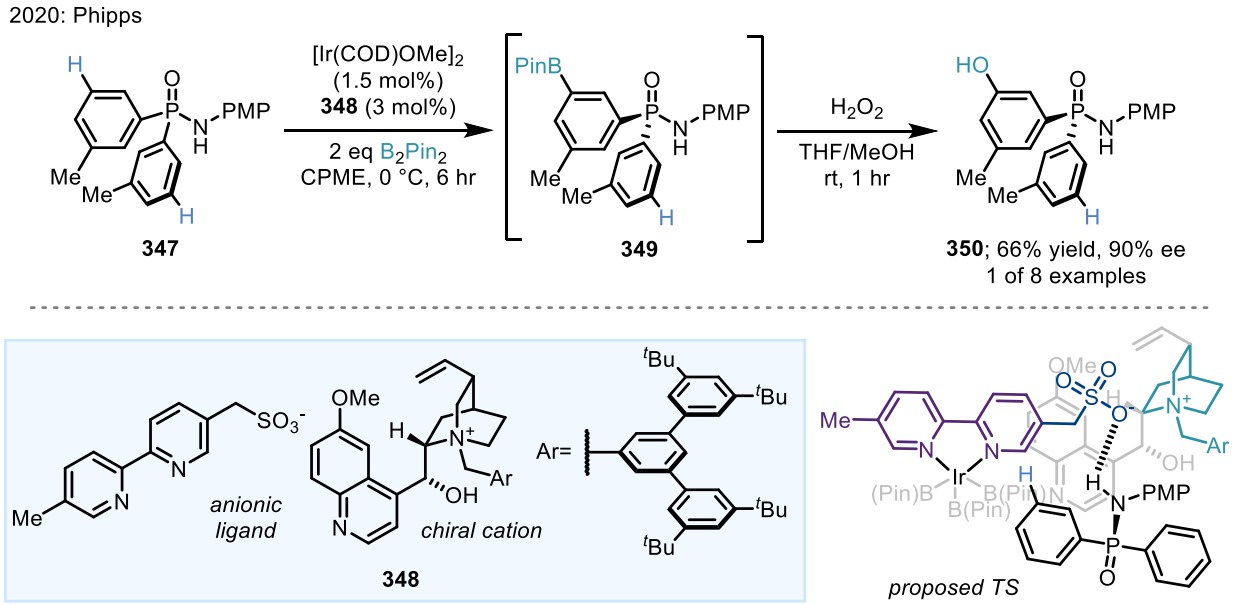
Scheme 22. Cramer's enantioselective Ir catalysed C–H amidation of phosphine oxides (A) and C–H arylation (B).

In a complementary approach to Han,[99] Cramer disclosed a Cp^{x}Rh (III)[112] catalysed enantioselective desymmetrisation of phosphinamides (**Scheme 23**).[113] The authors employed phosphinamide **343** (which bears a fluorinated substituent on nitrogen to act as a directing group for Rh) with internal alkyne **344** in the presence of 5 mol% each of chiral Cp^{x}Rh(III) catalyst **345** and benzoyl peroxide to afford enantioenriched cyclised product **346** in 65% yield and 90% ee. A kinetic resolution variant of this reactions was later developed by the same authors, enabled by a novel trisubstituted chiral Cp^{x}Rh(III) catalyst.[114]



Scheme 23. Cramers's enantioselective desymmetrisation of phosphinamides by asymmetric Rh catalysed C–H activation.

Most recently, Phipps disclosed the first enantioselective desymmetrisation of phosphinamides (and benzhydrylamides) by Ir-catalysed *meta*-selective C–H borylation/oxidation utilizing an elegant chiral counter-cation approach[115] (**Scheme 24**).[116] The authors used *meta*-substituted phosphinamide **347** which underwent C–H borylation with B_2Pin_2 in the presence of 1.5 mol% $[Ir(COD)OMe]_2$ and ligand **348** consisting of an anionic bipyridine ligand and a chiral *Cinchona* derived ammonium countercation to afford enantioenriched borylated product **349** which is then oxidised with H_2O_2 to corresponding phenol product **350** in 66% overall yield and 90% ee. The sulfonate anion on the ligand was postulated to hydrogen-bond to the acidic N–H of the substrate, directing the tethered the Ir catalyst in proximity to the *meta*-position. The strong ionic interaction of the sulfonate anion with the ammonium salt allowed for the chiral scaffold to provide the appropriate chiral environment for enantiofacial discrimination.



Scheme 24. Phipps' enantioselective Ir catalysed C–H borylation of phosphinamides using an anionic ligand with chiral counter-cation.

3.1.7.7 Conclusion

While collectively these methods provide direct access to enantioenriched P(V) species with elegant use of catalysis, they are inherently limited by the requirement of pre-installed prochiral appendages which restricts the scope for these reactions. Despite the authors demonstrating the utility of these compounds in the synthesis of novel ligands or organocatalysts the structural requirements of the substrates which

enable these reactions to proceed with high enantioselectivity impede the widespread use of these protocols in the synthesis of biologically relevant molecules, especially P(chiral) API's.

3.1.8 Aim of the project

In this chapter we will disclose a novel enantioselective desymmetrisation of P(V) species *via* an unprecedented enantioselective nucleophilic substitution of enantiotopic leaving groups (**Figure 5**). We envisioned that *via* judicious choice of leaving group, nucleophile, and catalyst we could obtain the desired enantioenriched species (**351**) in high yield and with excellent enantioselectivity. Our BIMP catalysts, as well as other prevalent catalyst classes will be evaluated in combination with a range of possible leaving groups to achieve the desired results.

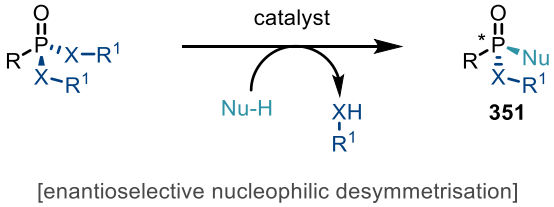


Figure 5. Concept for a novel enantioselective nucleophilic desymmetrisation of P(V) species.

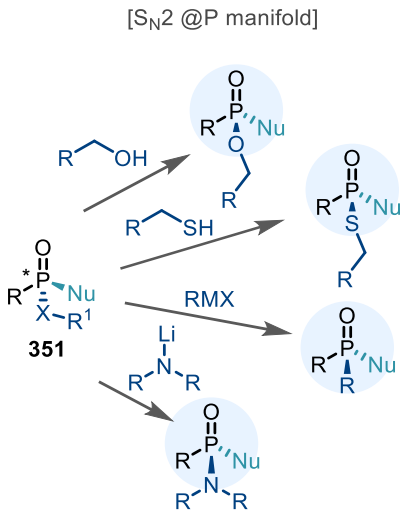


Figure 6. Possible derivatisations of the desymmetrised P(V) product.

Desymmetrised substrate **351** would then still possess another leaving group, perfectly positioned for a second (potentially enantiospecific) nucleophilic substitution reaction enabling diverse downstream derivatisation opportunities (**Figure 6**). This strategy would allow for a wide range of P(V) compounds

to be accessed from a common intermediate, overcoming one of the main limitations of current enantioselective desymmetrisations at phosphorous.

3.2 Reaction Development

3.2.1 Reaction discovery and optimisation

We began our investigation by exploring P(V) species possessing possible leaving groups. Our aim was to design a "tamed" phosphonic dichloride equivalent, replacing the Cl atoms with tuneable leaving groups.[117] The ideal substrate would be air and moisture stable, with low-cost leaving groups of high enough pK_a to allow for catalyst turnover (**Figure 7**).

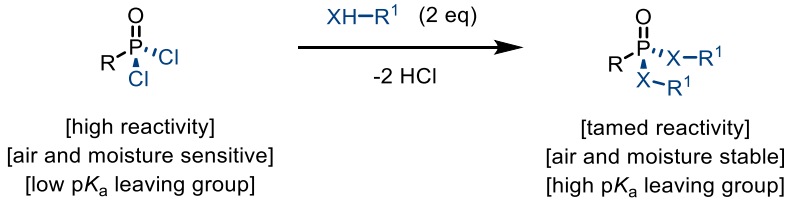
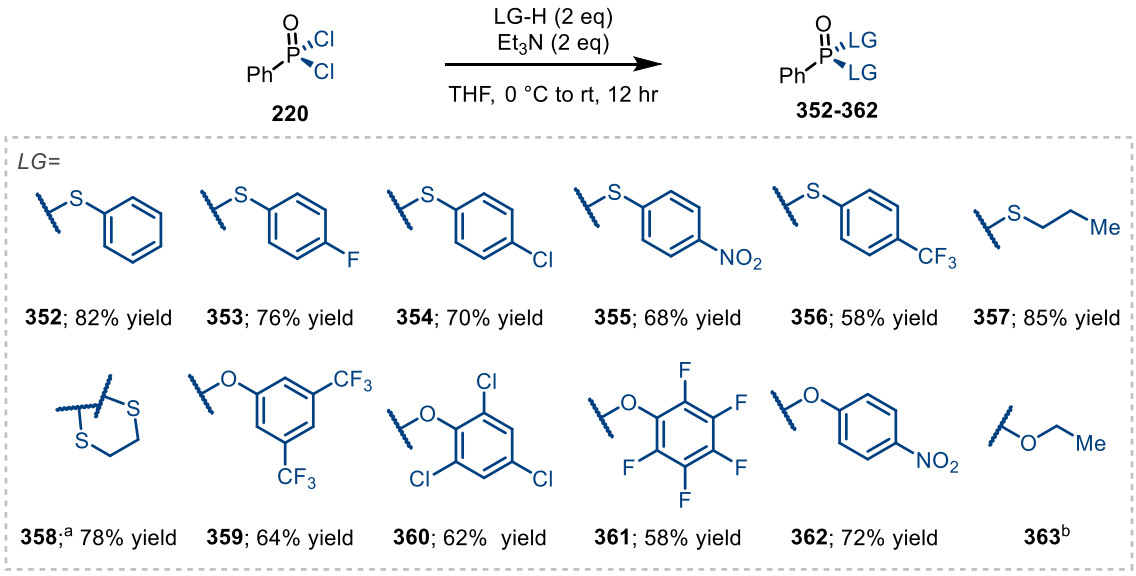


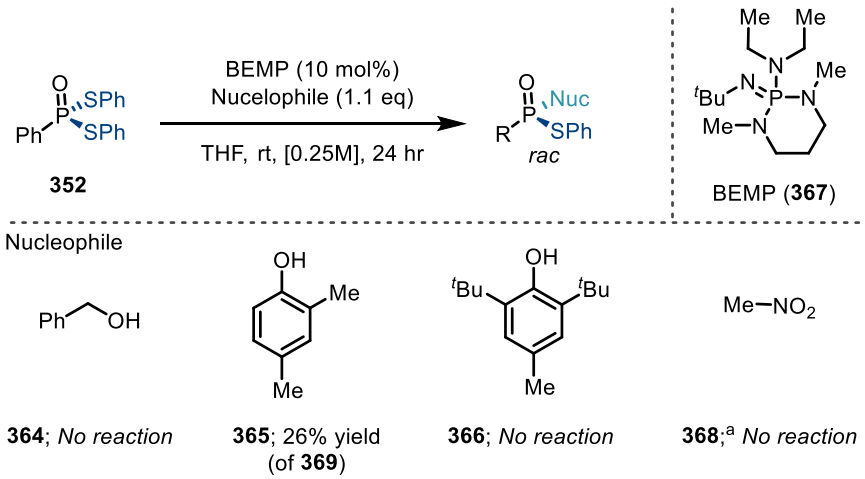
Figure 7. Rationale for electrophile design.

With this aim in mind, a range of phenylphosphonic dichloride (**220**) derivatives were synthesised utilising 2 equivalents of nucleophile and 2 equivalents of triethylamine in THF.[118] Utilising this straightforward method a library of desymmetrisation substrates was obtained in good yields with leaving groups derived from thiophenols (**352**-**356**), thiols (**357**,**358**) and phenols (**359**-**362**), as well as commercially available diethyl phenylphosphonate (**363**) (**Scheme 25**).



Scheme 25. Synthesis of prochiral electrophiles.[a] 1. Eq of nucleophile used. [b] Commercially available.

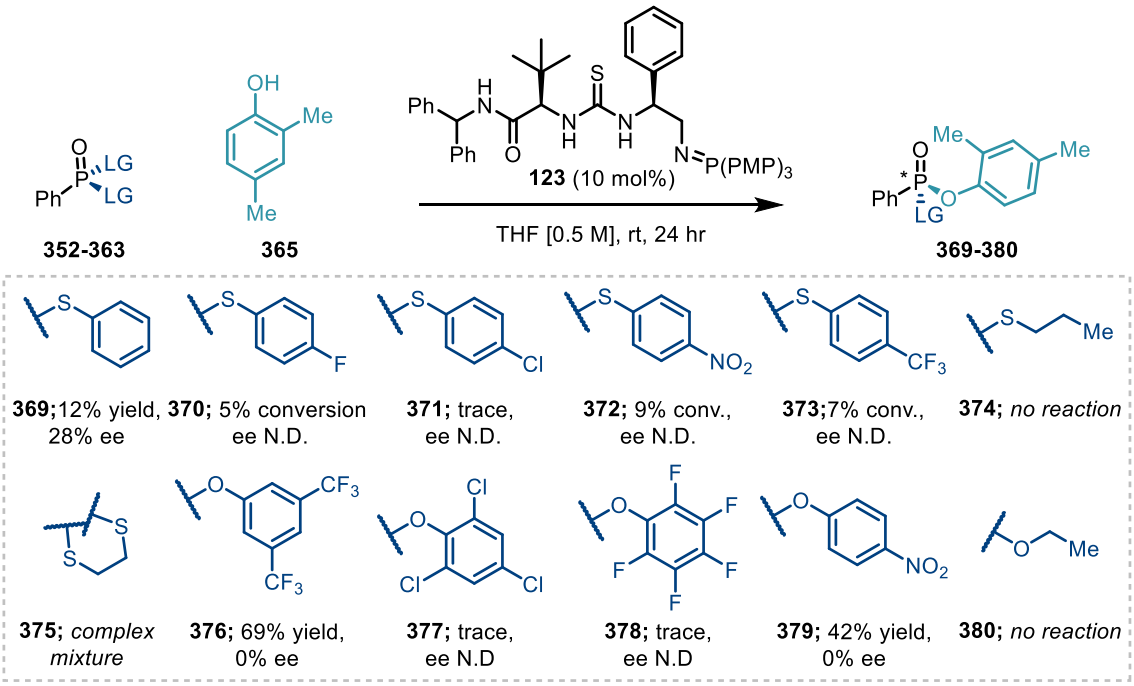
With a library of electrophiles in hand, possible nucleophiles were then explored. We were particularly interested in O-based nucleophiles as chiral at P compounds bearing oxygen substituents are highly prevalent in numerous pharmaceutical and agrochemical APIs. As such, substrate **352** bearing two thiophenol leaving groups was submitted to the reaction conditions with BnOH (**364**), 2,4-dimethyl-phenol (**365**), and 2,6-disubstituted phenol (**366**) in THF using 10 mol% of achiral phosphazene base BEMP (**367**). Nitromethane (**368**) was also evaluated as a potential nucleophile (**Scheme 26**). Amongst these, only product **369** derived from 2,4-dimethyl-phenol (**365**) was obtained in 26% yield, with all other nucleophiles giving no reaction.



Scheme 26. Preliminary nucleophile screen.[a] 1. Eq of BEMP used.

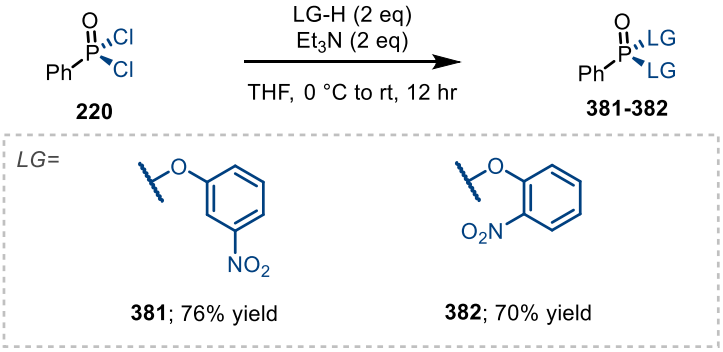
Having identified a 2,4-dimethyl-phenol (**365**) as a nucleophile, the desymmetrisation reaction was assessed across the range of the previously synthesised electrophiles, using 10 mol% of 2nd generation BIMP catalyst **123**,[119] which was readily available in the lab in gram quantities (**Scheme 27**). The crude reaction mixtures were analysed by $^{31}P\{^{1}H\}$ NMR to determine starting material conversion, and the most promising were then isolated and analysed by chiral HPLC to determine the enantiomeric excess of the product against the corresponding racemic sample prepared with BEMP.

352 bearing thiophenol as a leaving group gave product **369** in a poor yield of 12% but a promising ee of 28%. Substrates possessing more electron poor thiophenols (**353**-**356**) afforded the corresponding products (**370**-**373**) in very poor conversion. We attribute the low reactivity of these substrates to the low pK_a of the thiophenol leaving group, which we had previously identified as being acidic enough to fully protonate the BIMP catalyst[120] and thus leading to only one catalyst turnover. Substrate **357**, which possesses an *n*-propane thiol leaving group, led to no reaction while dithiane bearing substrate **358** gave a complex mixture of products. Phenol leaving groups appeared to be more promising, with 3,5-CF_3-phenol bearing substrate **359** affording the corresponding product (**376**) in 69% yield. Unfortunately, however, no enantioselectivity was observed. Polyhalogenated substrates **360** and **361** bearing *ortho*-substituents gave only trace amounts of products **377** and **378**. *para*-Nitrophenol[121] derived substrate **362** proved to be an effective substrate, giving 42% yield of desired product **379**, yet, also in this case no enantioselectivity was observed. Finally, when using commercially available diethyl phosphonate ester **363** no desired product **380** was observed.



Scheme 27. Assessment of potential leaving groups on P(V) using a BIMP catalyst **123**. Isolated yields. Conversion determined by ^{31}P NMR. Enantiomeric excess determined by HPLC using chiral stationary phase.

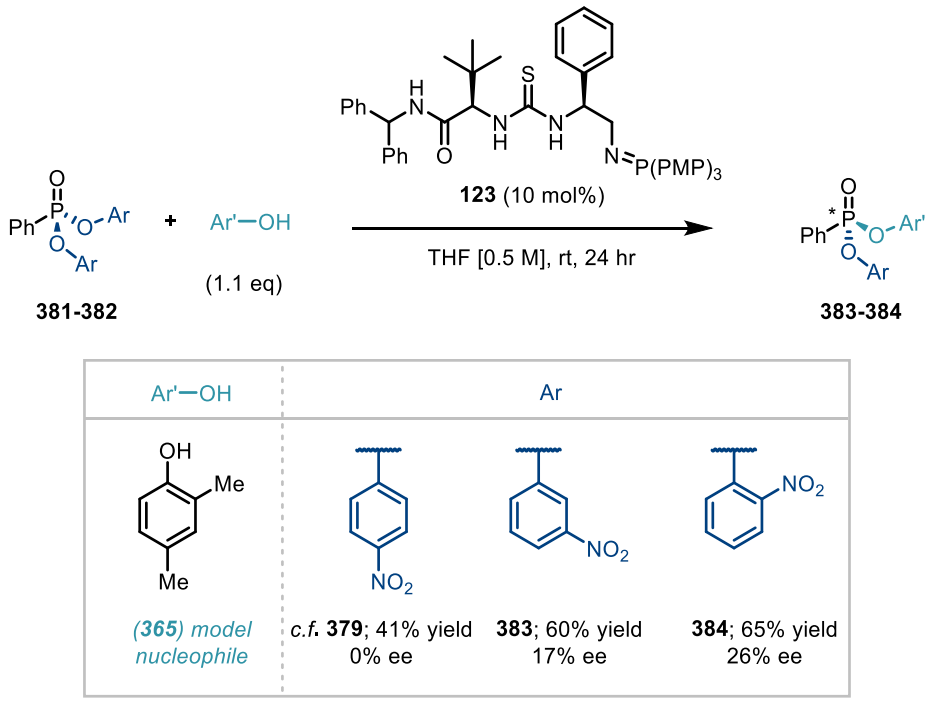
Among the P(V) electrophiles screened, **359** and **362** appeared to be the most promising substrates. As both *meta*-nitrophenol and *ortho*-nitrophenol are low-cost and readily available, corresponding substrates **381** and **382** were synthesized in 76% and 70% yield respectively (**Scheme 28**).



Scheme 28. Synthesis of further nitrophenol derived electrophiles.

The new substrates were submitted to the desymmetrisation reaction under the same conditions as in **Scheme 27** (**Scheme 29**). Pleasingly, *meta*-nitrophenol derived substrate **381** afforded corresponding

product **383** in 60% yield and a non-zero ee of 17%. *ortho*-Nitrophenol derived substrate **382** performed even better, with **384** being obtained in 65% yield and 26% ee.

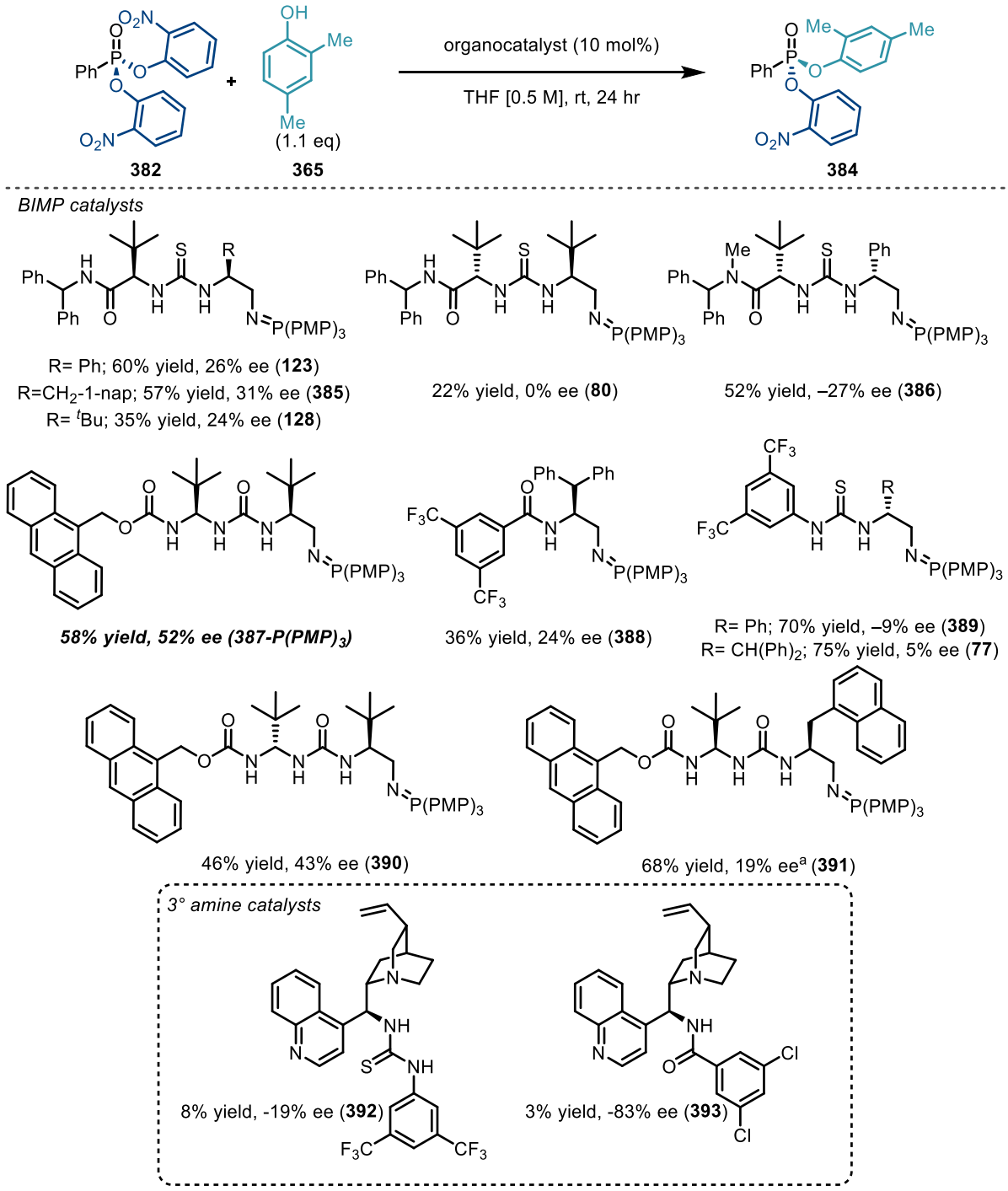


Scheme 29. Screening of nitrophenol derived leaving groups. All yields are isolated yields. Ee determined by HPLC analysis on a chiral stationary phase.

These results encouraged us to perform an extensive catalyst screen using substrate **382** in an attempt to improve both yield and enantioselectivity (**Scheme 30**). *syn*-Configured 2nd generation BIMP catalysts (**385**, **128**) performed similarly giving product **393** in 24-31% ee, while catalyst **80** which bears the two stereocentres in an *anti*-configuration gave **385** as a racemic product. BIMP **386** which does not possess a remote H-bond donor gave a similar ee of 27%. Interestingly, ureidopeptide derived BIMP **387-P(PMP)$_3$**[iii] (inspired by a 3° amine bifunctional catalyst previously reported by Palomo)[122–124] performed well, yielding **384** in 58% yield and 52% ee. Amide derived catalyst **388**[125] performed poorly affording the desired product in only 34% yield and 24% ee. 1st Generation BIMP catalysts **389** and **77** gave **384** in good yields of 70% and 75% respectively but less than 10% ee. Catalysts **390** and **391** were synthesised following the same procedure[126] as **387-P(PMP)$_3$** (see **Chapter 5** for more details). **390**, which bears the

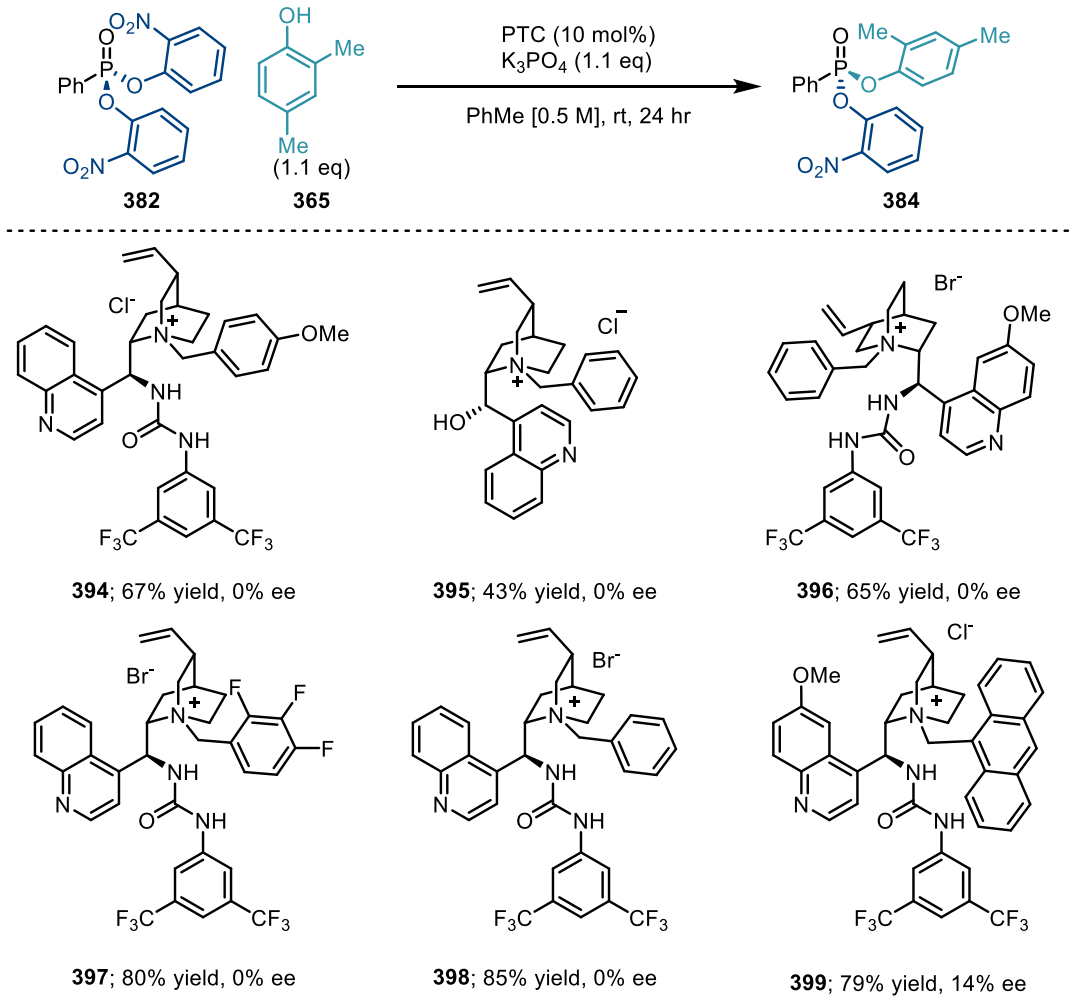
[iii] Catalyst **387** was first synthesised by Dr Alistair J. M. Farley.[126]

two stereocentres flanking the central urea moiety in an *anti*-configuration performed less well than **387-P(PMP)$_3$** affording **384** in 46% yield and 43% ee, demonstrating that the stereocentre proximal to the iminophosphorane is dominant. When **391** was used as catalyst **384** was obtained in 68% yield and 19% ee.



Scheme 30. Screening of organocatalysts using *ortho*-nitrophenol derived substrate **382**.[a] PhF used as solvent. All yields are isolated yields. Ee determined by HPLC analysis on a chiral stationary phase.

At this point two *Cinchona* derived 3° amine bifunctional catalysts were also assessed. Thiourea bearing catalyst **392**[127] gave only 8% yield and 19% ee of the product while amide derived catalyst **393**[125] gave **384** in 3% yield and 83% ee. While the 83% ee obtained with catalyst **393** was impressive, the low yields obtained with both *Cinchona*-derived catalysts indicated that a strong base was required for the desymmetrisation to proceed efficiently.



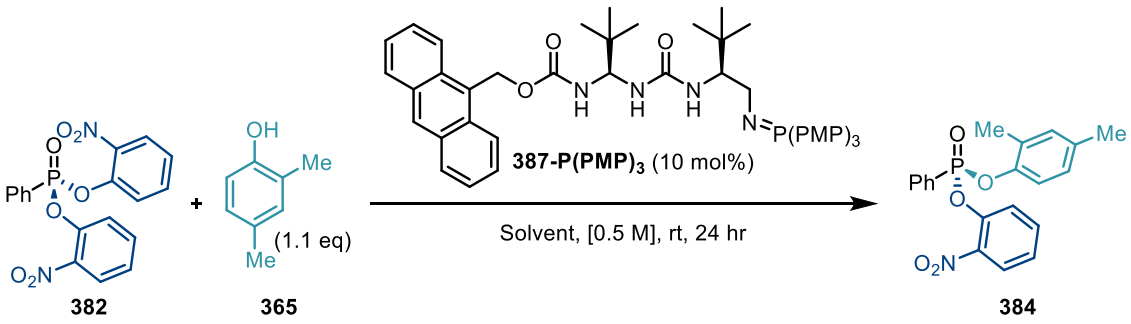
Scheme 31. Screening of chiral phase transfer catalysts. All yields are isolated yields. Ee determined by HPLC analysis on a chiral stationary phase.

As strongly basic conditions appeared to be favourable towards high yields, chiral, *Cinchona* derived phase transfer catalysts[128–132] were also investigated using K_3PO_4 as base and toluene as solvent (**Scheme 31**).[iv] Unfortunately, while all catalysts (**394**-**399**) provided desired product **384** in high yield, only catalyst **399**

[iv] Chiral phase transfer catalysts were synthesised by previous group members and were readily available in our laboratory.[143–146]

bearing an anthracenyl group as the ammonium salt N-substituent afforded any level of enantioselectivity at 14% ee.

Having established that BIMP catalysts provided the best balance of reactivity and enantiocontrol amongst the catalyst classes assessed in the screening the effect of solvent on the reaction was probed using ureidopeptide derived BIMP **387-P(PMP)$_3$** (**Table 1**). Aromatic solvents such as PhMe (*entry 1*) and PhCl (*entry 2*) provided a slight boost in enantioselectivity to 60% and 61% ee respectively. Other ethereal solvents (*entries 3-5*) gave diminished yields and similar enantioselectivity to THF. PhF (*entry 6*) proved to be beneficial as solvent boosting the enantioselectivity to 67% ee. This result prompted us to explore further aromatic solvents (*entries 7-9*), with only 1,2-difluorobenzene (*entry 9*) providing comparable results. More polar aprotic solvents such as MeCN (*entry 10*) resulted in very poor ee. As PhF is far less expensive than 1,2-difluorobenzene further optimisation studies were conducted using PhF as solvent.

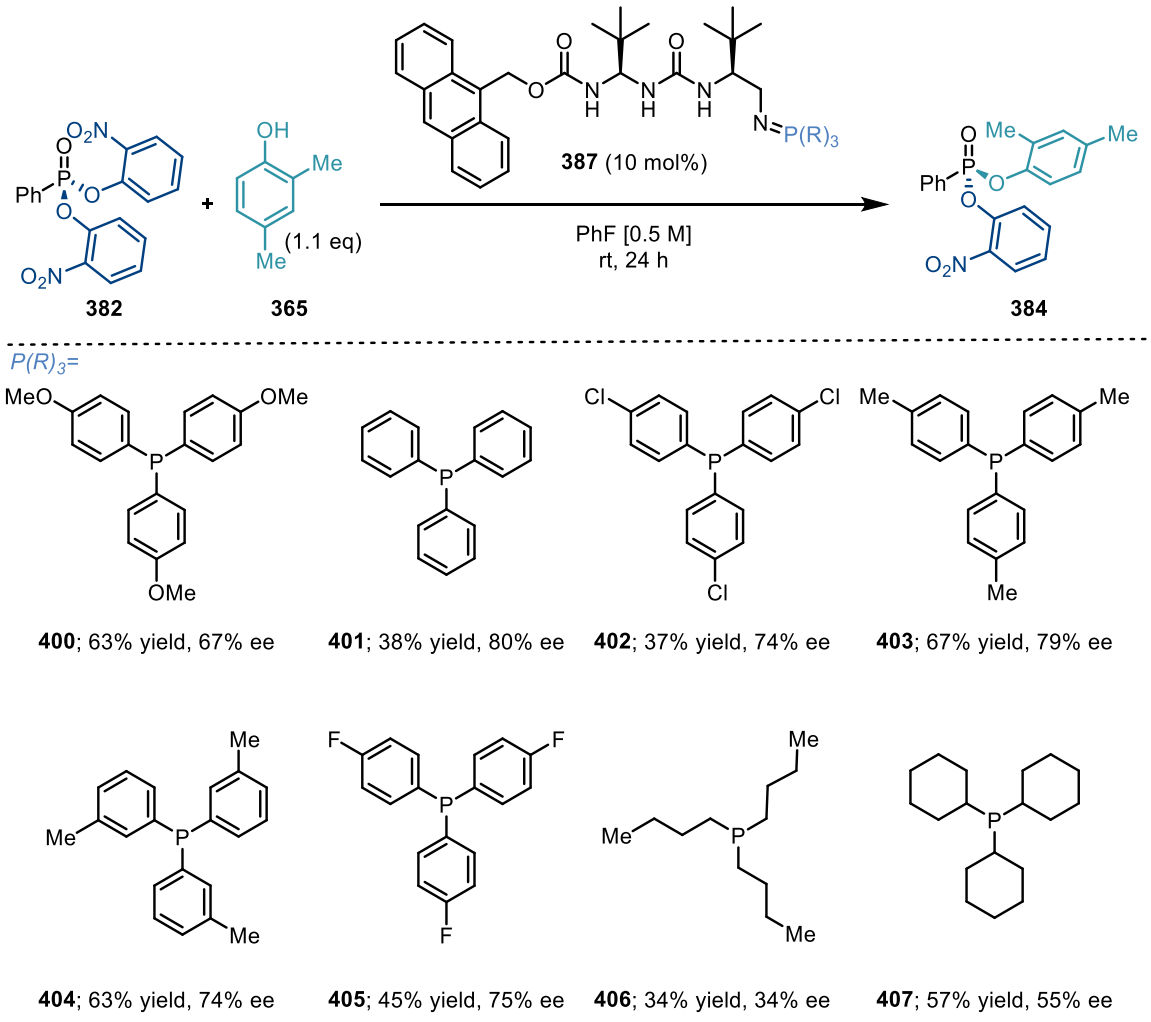


382 **365** **384**

Entry	Solvent	Yield[a] (%)	ee[b] (%)
1	PhMe	52	60
2	PhCl	58	61
3	CPME	60	50
4	1,4 Dioxane	24	44
5	Et_2O	32	59
6	***PhF***	***63***	***67***
7	Mesitylene	60	58
8	1,2-dichlorobenzene	78	61
9	1,2-difluorobenzene	60	67
10	MeCN	53	3

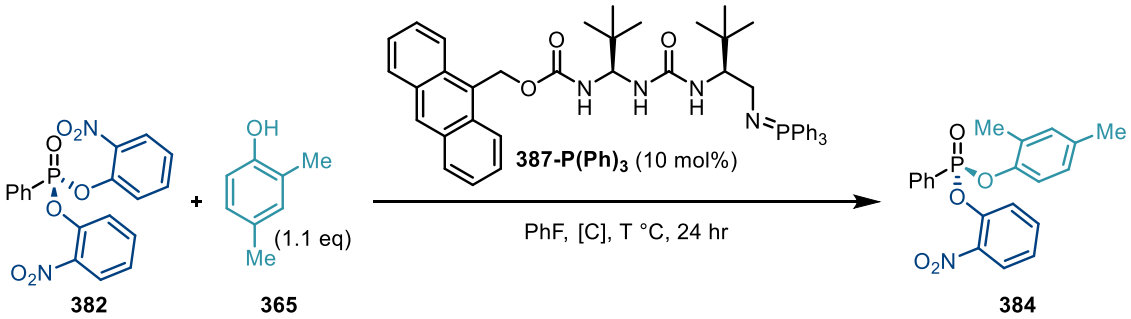
Table 1. Solvent Screen.[a] Isolated yields. [b]Determined by HPLC analysis on a chiral stationary phase.

Next, our attention was turned to the iminophosphorane component of BIMP catalyst **387-P(PMP)$_3$**. Thanks to the modular nature of the BIMP catalyst, varying the electronic and steric parameters of the iminophosphorane is extremely simple and can be achieved by changing the phosphine component used in the Staudinger reaction to generate the catalyst. As such, various phosphines were assessed in the desymmetrisation (**Scheme 32**). Using a PPh_3 (**401**) derived BIMP the yield decreased to 38% but the ee was increased to 80%. Using *para*-Cl triphenylphosphine (**402**) gave similar yield but decreased ee. P(*p*-tol)$_3$ (**403**) boosted the yield back up to 67% and the ee to 79%. Using isomeric P(*m*-tol)$_3$ (**404**) led to a slight decrease in ee while *para*-F-triphenylphosphine (**405**) led to 45% yield and 75% ee. Using alkyl phosphines such as P(^{n}Bu)$_3$ (**406**) and PCy_3 (**407**) did not lead to any improvement in reactivity or enantioselectivity. Both PPh_3 and P(*p*-tol)$_3$ were selected as phosphines to further investigate while tuning reaction parameters such as concentration, temperature, catalyst loading and additives.



Scheme 32. Screening of phosphines to generate the iminophosphorane superbase.

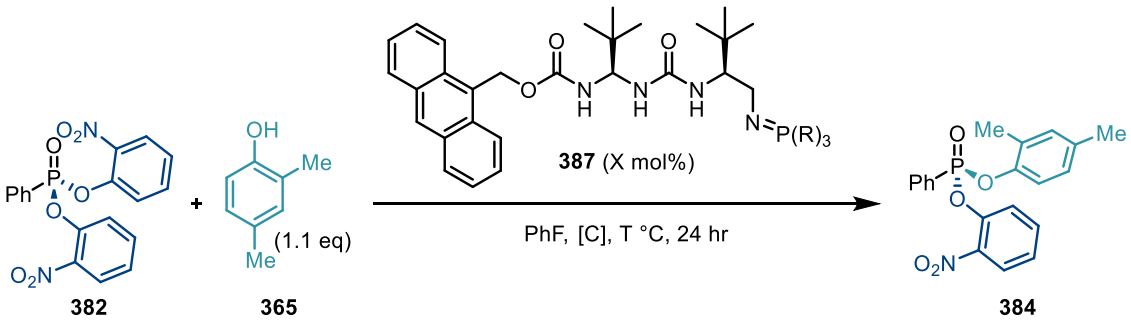
In a bid to improve catalyst turnover, the effects of the addition of solid inorganic base to the reaction were investigated (**Table 2**, *entries 1-2*) and then concentration and temperature effects were explored (*entries 3-5*) using PPh_3 derived BIMP catalyst **387-P(Ph)$_3$**. When adding 1 eq of either Li_2CO_3 (*entry 1*) or $NaHCO_3$ (*entry 2*), both yield and ee remained almost unchanged. Diluting the reaction to 0.06 M (*entry 3*) had a positive effect on both yield and ee. Cooling the reaction to 0 °C (*entry 4*) was also beneficial giving desired product **384** in 41% yield and 87% ee. Cooling and diluting the reaction (*entry 5*) resulted in diminished yield and ee.



Entry	[C]	T (°C)	Additive	Yield[a] (%)	ee[b] (%)
1	0.5 M	rt	Li_2CO_3 (1 eq)	49	81
2	0.5 M	rt	$NaHCO_3$ (1 eq)	48	81
3	0.06 M	rt	-	54	84
4	***0.5 M***	***0***	**-**	***41***	***87***
5	0.06 M	0	-	36	86

Table 2. Miscellaneous conditions screening. [a] Isolated yields. [b] Determined by HPLC analysis on a chiral stationary phase.

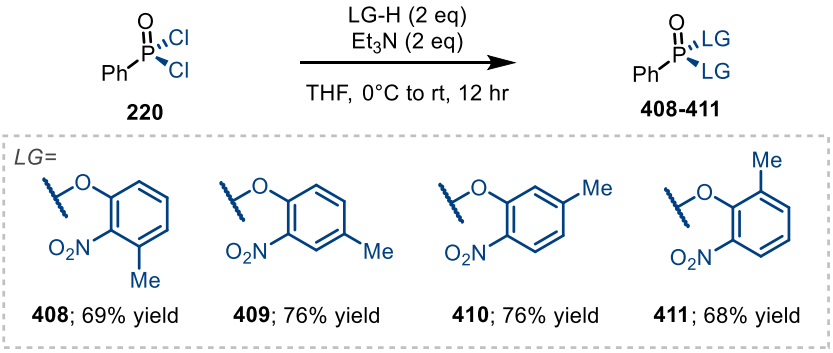
The reaction conditions were fine-tuned by varying reaction temperature, the iminophosphorane substituent and catalyst loading (**Table 3**). Using **387-P(*p*-tol)$_3$** under the current best conditions (*entry 1*) gave a slight boost in yield to 52% but a drop in ee. Cooling to −15 °C (*entry 2*) using the same catalyst resulted in poor yield but a high ee of 90%. Increasing the catalyst loading under the same conditions (*entry 3*) did not improve yield. Using **387-P(Ph)$_3$** at either 10 mol% catalyst loading (*entry 4*) or 15 mol% (entry 5) resulted in poor yield. Finally diluting the reaction to 0.25M at −15 °C with either **387-P(Ph)$_3$** (*entry 6*) or **387-P(*p*-tol)$_3$** (*entry 7*) as phosphine both resulted in 15% yield and 88% ee. The conditions in **Table 2**, *entry 4* were used for further optimisation.



Entry	Cat. Loading	T (°C)	[C]	Phosphine	Yield[a] (%)	ee[b] (%)
1	10 mol%	0	0.5 M	P(*p*-tol)$_3$	52	85
2	10 mol%	−15	0.5 M	P(*p*-tol)$_3$	14	90
3	15 mol%	−15	0.5 M	P(*p*-tol)$_3$	22	89
4	10 mol%	−15	0.5 M	PPh_3	13	88
5	15 mol%	−15	0.5 M	PPh_3	19	88
6	10 mol%	−15	0.25 M	P(*p*-tol)$_3$	16	89
7	10 mol%	−15	0.25 M	PPh_3	15	88

Table 3. Fine-tuning of the reaction conditions. [a] Isolated yields. [b] Determined by HPLC analysis on a chiral stationary phase.

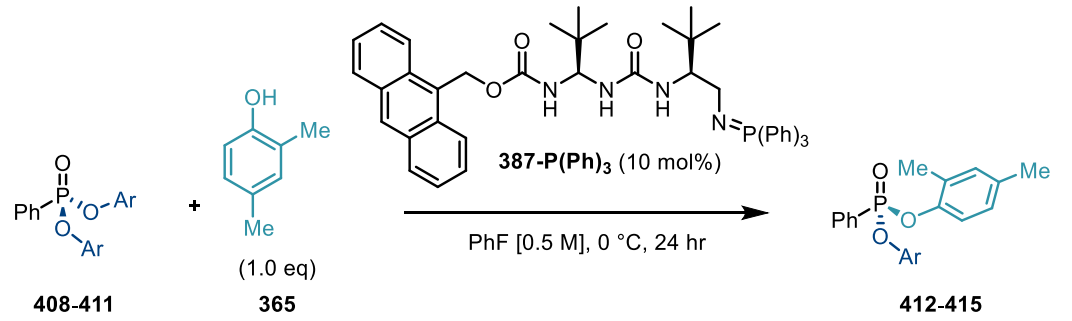
We reasoned that by modulating the leaving group by iteratively methylating at every position of the nitrophenol, higher levels of conversion and enantioselectivity could be achieved. Electrophiles **408**-**411** were therefore synthesised in good yields from the corresponding dichloride **220** (**Scheme 33**).

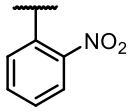
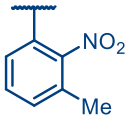
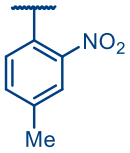
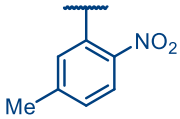
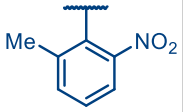


Scheme 33. Synthesis of methyl-nitrophenol derived electrophiles.

Methylation of the leaving group was demonstrated to have a profound effect on yield and enantioselectivity (**Scheme 34**). When **408** (possessing a 3-Me group) was used the corresponding product **412** was only obtained in 5% yield and 50% ee. In contrast, installation of the Me group at the

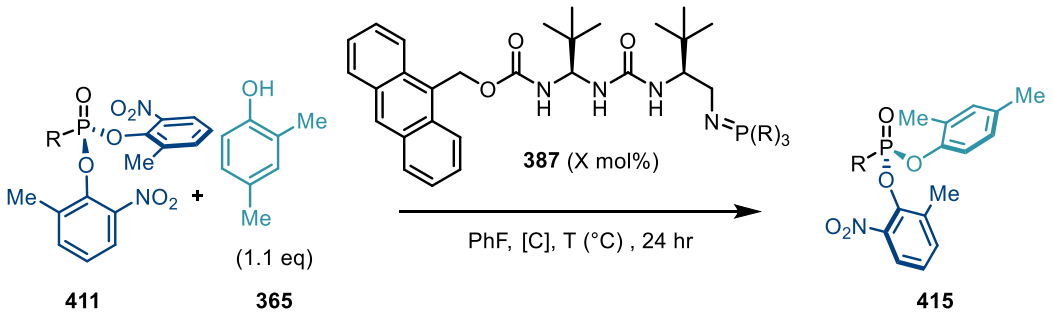
4-position had a positive effect giving **413** in 61% yield and 89% ee. Shifting the Me group further to the 5-position was once again disadvantageous, giving desired product **414** in 34% yield and 67% ee. Finally, when **411**, having the methyl group in the 6-position, was used, **415** was obtained in a low 10% yield but the highest ee observed thus far at 94% ee. We reasoned that the low yield could be due to increased steric hinderance and therefore investigated further reaction conditions in the hope of overcoming this issue.



Initial conditions	Ar			
				
384; 41% yield 87% ee	**412**; 5% yield 50% ee	**413**; 61% yield 89% ee	**414**; 34% yield 67% ee	**415**; 10% yield 94% ee

Scheme 34. Evaluation of methylated nitrophenol leaving groups. All yields are isolated yields. Ee determined by HPLC analysis on a chiral stationary phase.

As reactivity was low at 0 °C (**Table 4**, *entry 1*) the reaction was conducted at room temperature (*entry 2*) which resulted in a considerable increase in yield (42%) and only a minor erosion of ee (92%). Diluting the reaction to 0.25 M (*entry 3*) had no effect. Using BIMP catalyst **387-P(*p*-tol)$_3$** instead of **387-P(Ph)$_3$** (*entry 4*) the yield was improved to 56% maintaining 93% ee. The catalyst loading was then increased to 15 mol% (*entry 5*) giving 66% yield of the desired product with no decrease in enantioselectivity. Increasing the amount of nucleophile **365** to 1.5 equivalents (*entry 6*) had no considerable effect. Further diluting the reaction (*entry 7*) did not improve enantioselectivity and decreased the yield to 59%. Finally, when PhF was dried over 4Å MS, **415** was obtained in 84% yield and 91% ee concluding the optimisation for this reaction.



Entry	Cat. Loading	T (°C)	[C]	Phosphine	Yield[a] (%)	ee[b] (%)
1	10 mol%	0	0.5 M	PPh_3	10	94
2	10 mol%	rt	0.5 M	PPh_3	46	92
3	10 mol%	rt	0.25 M	PPh_3	46	92
4	10 mol%	rt	0.25 M	P(*p*-tol)$_3$	56	93
5	15 mol%	rt	0.25 M	P(*p*-tol)$_3$	66	92.5
6	15 mol% (1.5 eq Nuc)	rt	0.25 M	P(*p*-tol)$_3$	66	92.5
7	15 mol%	rt	0.16 M	P(*p*-tol)$_3$	59	92
8	15 mol% (PhF over 4Å MS)	rt	0.25 M	P(*p*-tol)$_3$	***84***	***91***

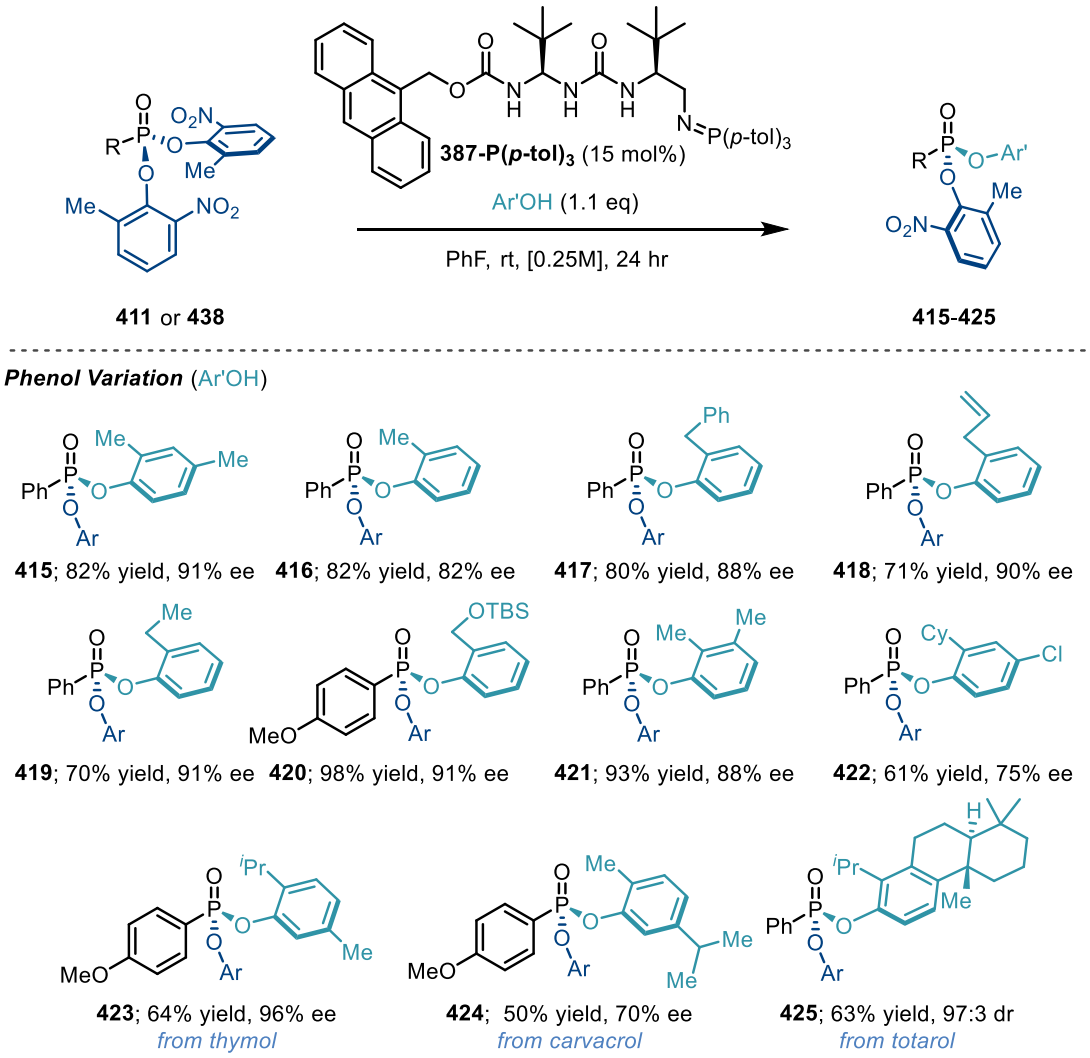
Table 4. Final tuning of the reaction conditions. [a] Isolated yields. [b] Determined by HPLC analysis on a chiral stationary phase.

3.3 Scope of the reaction

3.3.1 Scope of the reaction with regards to the phenol nucleophile

With the optimised reaction conditions in hand, the scope with respect to the phenol nucleophile was examined. The desymmetrisation was found to be highly general with respect to *ortho*-substituted phenol nucleophiles (**Scheme 35**). Products **416**-**419** derived from *ortho*-mono-alkyl-substituted phenols were obtained with high levels of yield and enantioselectivity. Product **420** was obtained in 98% yield and 91% ee from TBS protected salicylic alcohol using substrate **438** bearing a *p*-OMe-C_6H_4 R substituent (see section **3.3.2** for the synthesis) as the analogous Ph compound was inseparable by chiral HPLC. Disubstituted phenols were also well tolerated as nucleophiles, with product **421** being obtained in 93% yield and 88% ee. Using a *para*-Cl substituted phenol afforded product **422** in good yield but a diminished ee of 75%. Products **423**-**425** were obtained from naturally occurring *ortho*-substituted phenols.[133] Thymol derivative **423** was obtained in 64% yield and 96% ee, while its isomer **424** (derived from carvacrol) was obtained in 50% yield and 70% ee. Finally, totarol derived product **425** was obtained in

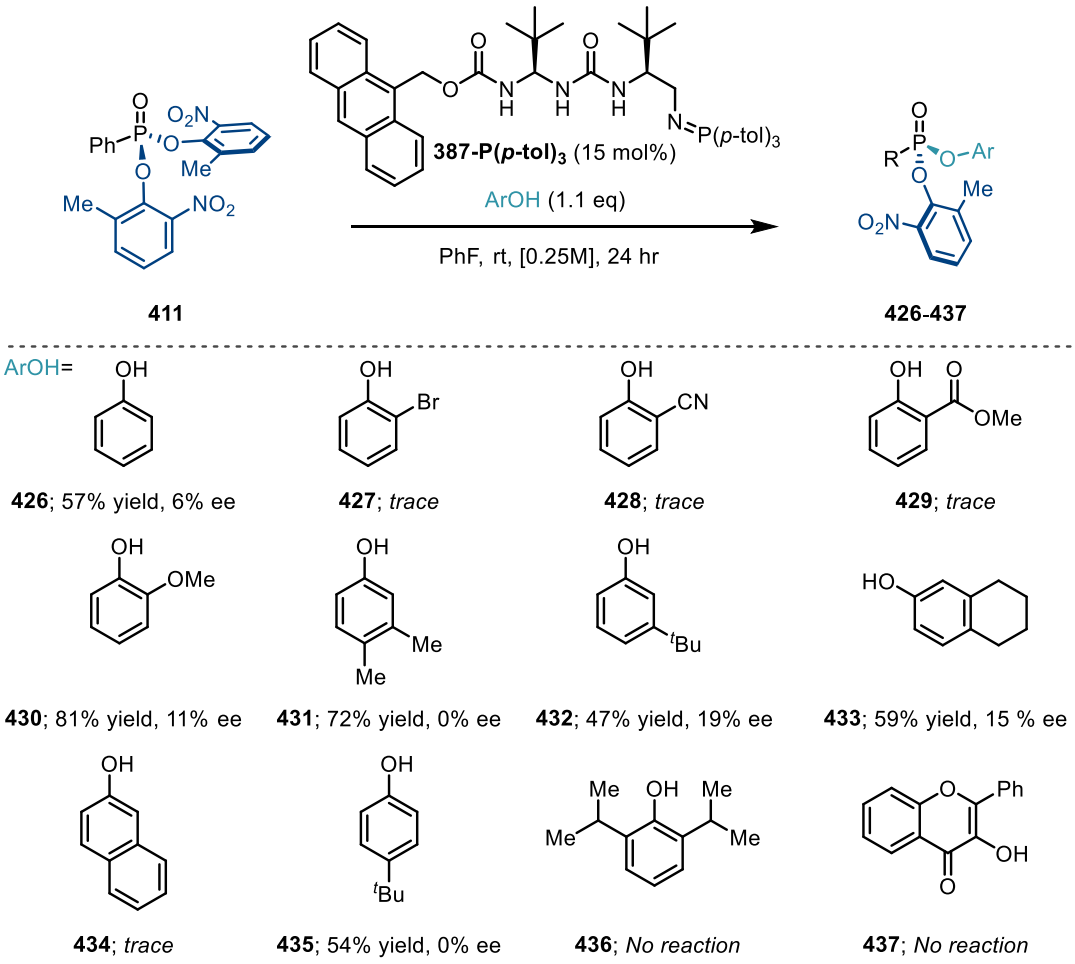
63% yield and 97:3 dr. Importantly when BEMP was used to synthesise a racemic sample of this product (see **Chapter 5**) a 50:50 dr was observed indicating that the desymmetrisation reaction using this nucleophile was fully under catalyst control.



Scheme 35. Scope with respect to the phenol nucleophile. Ar = 2-NO_2-6-Me-C_6H_3. Reactions carried out on 0.1 mmol scale.

Unfortunately, a wide range of phenols were found to be not tolerated as nucleophiles, either due to insufficient reactivity or because their use led to a lack of enantioselectivity (**Scheme 36**). When phenol (**205**) was used as nucleophile, desired product **426** was obtained in 57% yield but only 6% ee. Phenols bearing *ortho*-electron withdrawing groups were particularly unreactive, with only a trace of products **427-429** being observed. Guaiacol was found to be a highly reactive nucleophile, affording desired product **430** in 81% yield but disappointingly, only in 11% ee. Phenols bearing only *meta*-(and *para*-) substituents

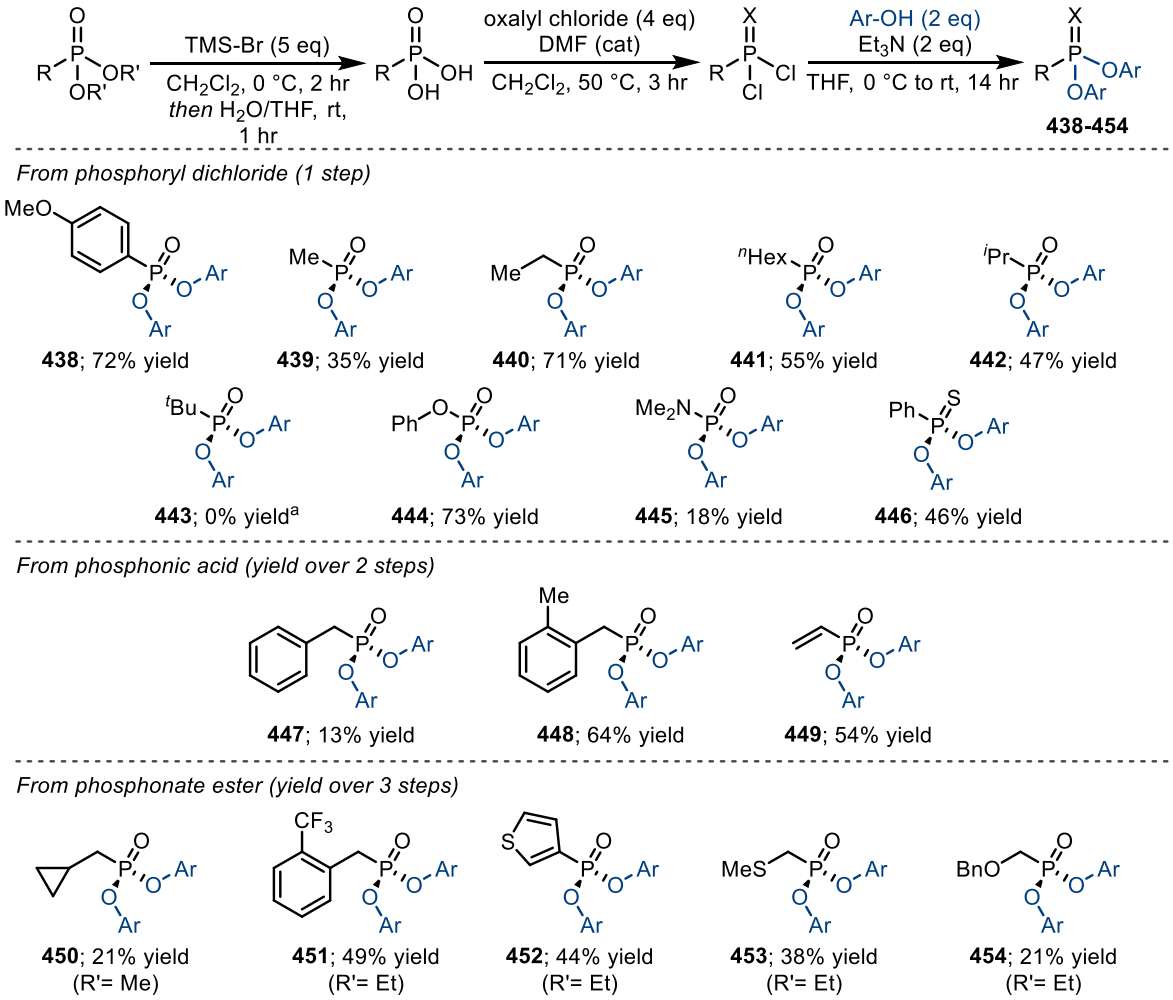
gave desired products (**431-433**) in moderate to good yield but once again with poor ee. When 2-naphthol was used as nucleophile only trace amounts of product **434** were observed. Using *para-tert*-Butyl-substituted phenol afforded **435** in 54% yield with no enantiocontrol. When anaesthetic propofol was used as nucleophile, no formation of desired product **436** was observed. This is most likely due to the severe steric bulk around the hydroxyl moiety. Flavinoid **437** also gave no reaction. From these examples, it was clear that an alkyl *ortho*-substituent was key to obtain high levels of enantioselectivity. This restriction in the nucleophile scope was found to be a strong limitation of the methodology and efforts to overcome it will be presented in **Chapter 4**.



Scheme 36. Unsuccessful phenol nucleophiles. Reactions carried out on 0.1 mmol scale.

3.3.2 Synthesis of substrates[v]

Having established the scope with respect to the nucleophile component, an array of phosphonate esters were synthesised to explore variations in the electrophile. Substrates were either prepared from commercially available phosphonic dichlorides (**Scheme 37A**) or crude dichlorides obtainable from commercially available phosphonic acids in 1-step (**Scheme 37B**) or by a 2-step, 1-pot sequence[134] from commercially available or literature known alkyl phosphonate esters (**Scheme 37C**).



Scheme 37. Electrophile synthesis. [a]Reaction carried out at reflux. Ar = 2-NO_2-6-Me-C_6H_3.

para-MeO-Phenyl derivative **438** was obtained from the corresponding dichloride in 72% yield. Alkyl substituted phosphonates (**439**-**442**) were easily obtained from commercially available dichlorides in 35-71% yield. *t*Bu substituted phosphonate (**443**) was unobtainable using this method even when the

[v] The synthesis of substrates was conducted with contributions by Mr. Naoto Sahara (visiting student). All compounds are included for completeness.

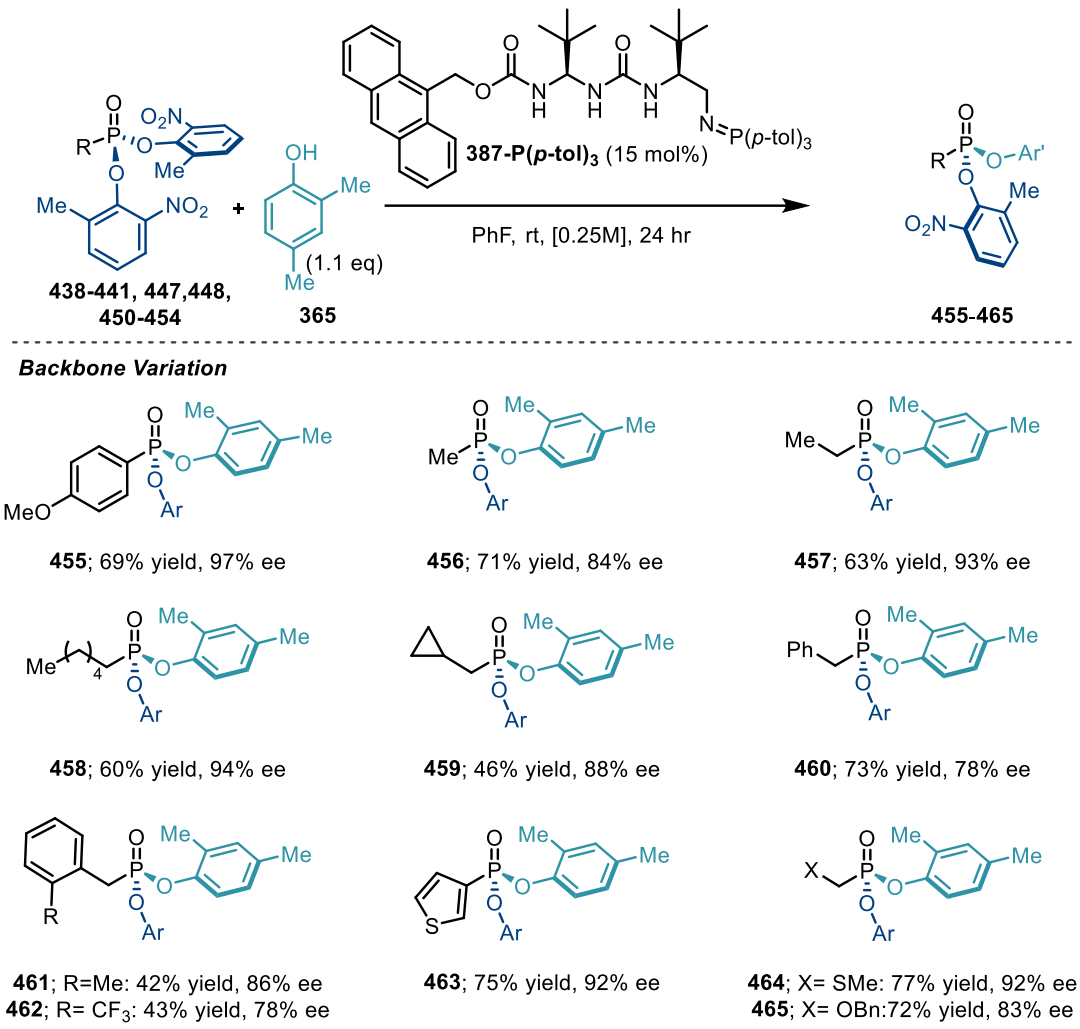
reaction was performed under reflux. Phosphate ester **444** was obtained in 73% yield while phosphoramidate **445** was obtained in 18% yield. Phosphonothioate **446** was obtained in 46% yield from the corresponding phosphonothioic dichloride.

Substrates **447**-**449** were obtained from commercially available phosphonic acids, converted into the corresponding phosphonic dichlorides (used crude) with oxalyl chloride (4 eq) in the presence of catalytic DMF. Benzylic phosphonates **447** and **448** were obtained in 13% and 64% yield respectively over 2 steps while vinyl phosphonate **449** was obtained in 54% yield over 2 steps.

Substrates **450**-**454** were obtained from commercially available or easily prepared phosphonate esters and converted to the corresponding phosphonic acids *via* ester cleavage with 5 eq. of TMS-Br. Upon reaction completion and addition of H_2O, volatiles were removed *in vacuo* to afford the corresponding crude acid. All traces of water were removed *via* azeotropic distillation with toluene. Once dry the resulting phosphonic acids were converted to the corresponding dichlorides and then the desired substrate as described above. Cyclopropyl-appended phosphonate **450** was obtained in 21% yield over 3 steps from the corresponding methyl phosphonate ester. Substrates **451**-**454** were instead derived from the corresponding ethyl phosphonate esters in 21-49% yield over 3 steps.

3.3.3 Scope of the reaction with respect to the phosphonate ester

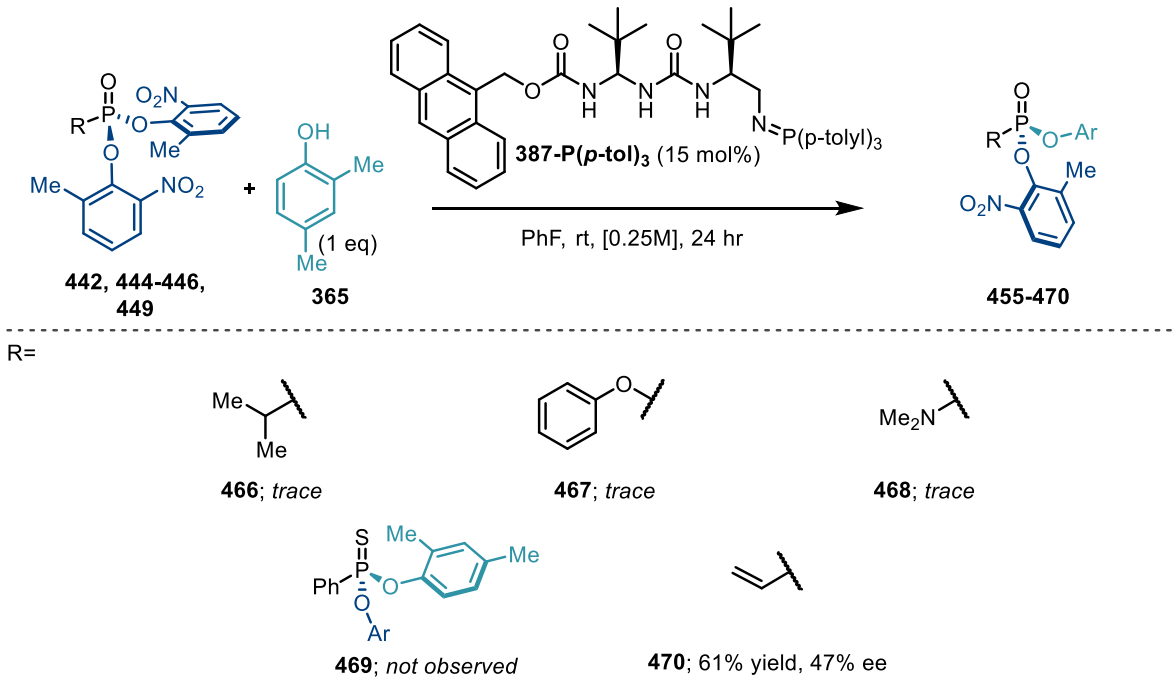
With a library of prochiral phosphonate esters in hand, the scope of the reaction with respect to the electrophilic component was ready to be explored (**Scheme 38**). Product **455**, bearing an electron rich aromatic backbone was obtained in 69% yield and an excellent 97% ee. Multiple aliphatic side-chains were also well tolerated including methyl (**456**, 71% yield, 84% ee), ethyl (**457**, 63% yield, 93% ee), and ^{n}hexyl (**458**, 60% yield, 94% ee). **459**, possessing a β-cyclopropyl substituent, was obtained in 46% yield and 88% ee. Products with benzylic substituents **460**-**462** were obtained in 42-73% yield and 78-86% ee. Heteroaromatic substituents were also well tolerated with thiophene derived product **463** being obtained in 75% yield and 92% ee. β-Heteroatoms were also compatible with this methodology with SMe containing product **464** being obtained in good yield and 92% ee and OBn substituted product **465** being obtained in 72% yield and 83% ee.



Scheme 38. Scope with respect to the phosphonate electrophile. Ar = 2-NO_2-6-Me-C_6H_3. Ar' = 2-4-dimethyl-C_6H_3. Reactions carried out on 0.1 mmol scale.

While multiple different substituents on the electrophile backbone were largely tolerated in the desymmetrisation reaction, others, imparting either strong variations in the electronics or steric bulk of the substrate did not provide sufficient reactivity or enantioselectivity (**Scheme 39**). When ^{i}Pr substituted **442** was submitted to the optimised reaction conditions sluggish reactivity was observed, most probably due to excessive steric hinderance. A similar problem occurred when phosphate ester **444** was used, most likely due to the increased electron richness of the substrate. Unsurprisingly, when even more electron rich phosphoramidate **445** was used as substrate only trace amounts of product **468** were observed. Phosphonothioate **446** gave no conversion to desired product **469** with either BEMP (**367**) or BIMP catalyst **387-P(*p*-tol)$_3$**. Additionally, attempts to obtain this product *via* treatment of **415** with Lawesson's reagent were unsuccessful. Finally, when using **449** as substrate, product **470** was obtained in 61% yield

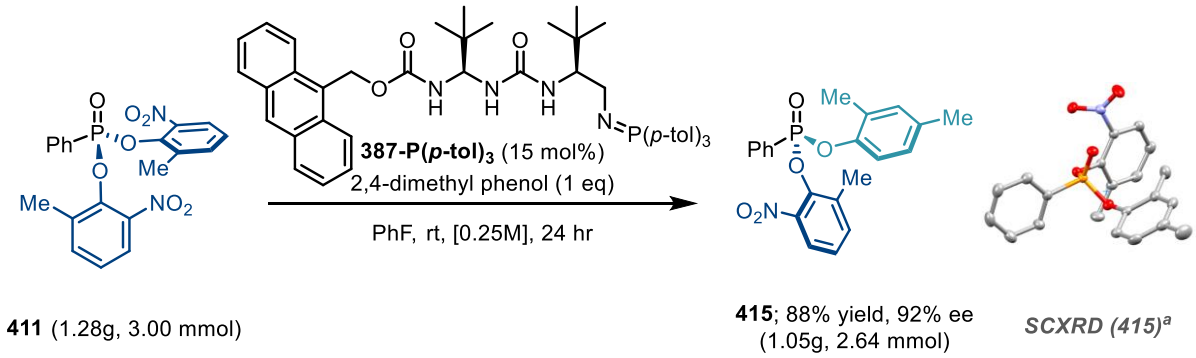
but only 47% ee possibly due to racemisation given vinyl phosphonates can also act as effective Michael acceptors.[135]



Scheme 39. Unsuccessful electrophiles. Ar = 2-4-dimethyl-C_6H_3.

3.3.4 Scale-up and determination of absolute configuration

Having established the scope of the reaction, its scalability was then demonstrated on 3 mmol (1.26 g) scale using model substrate **411** and 2,4-dimethyl phenol affording **415** in 88% yield and 92% ee (**Scheme 40**).



Scheme 40. Gram scale reaction and single crystal X-ray structure of compound **415**.[a]H-Atoms omitted for clarity.

A small amount of **415** was recrystallised to enantiopurity by slow evaporation from CH_2Cl_2/hexane and analysed by X-Ray diffraction allowing for the determination of the absolute stereochemical configuration of the product as (*R*). The stereochemical configuration of all other products was assigned by analogy. The product obtained in this reaction was subsequently used for further derivatisation.

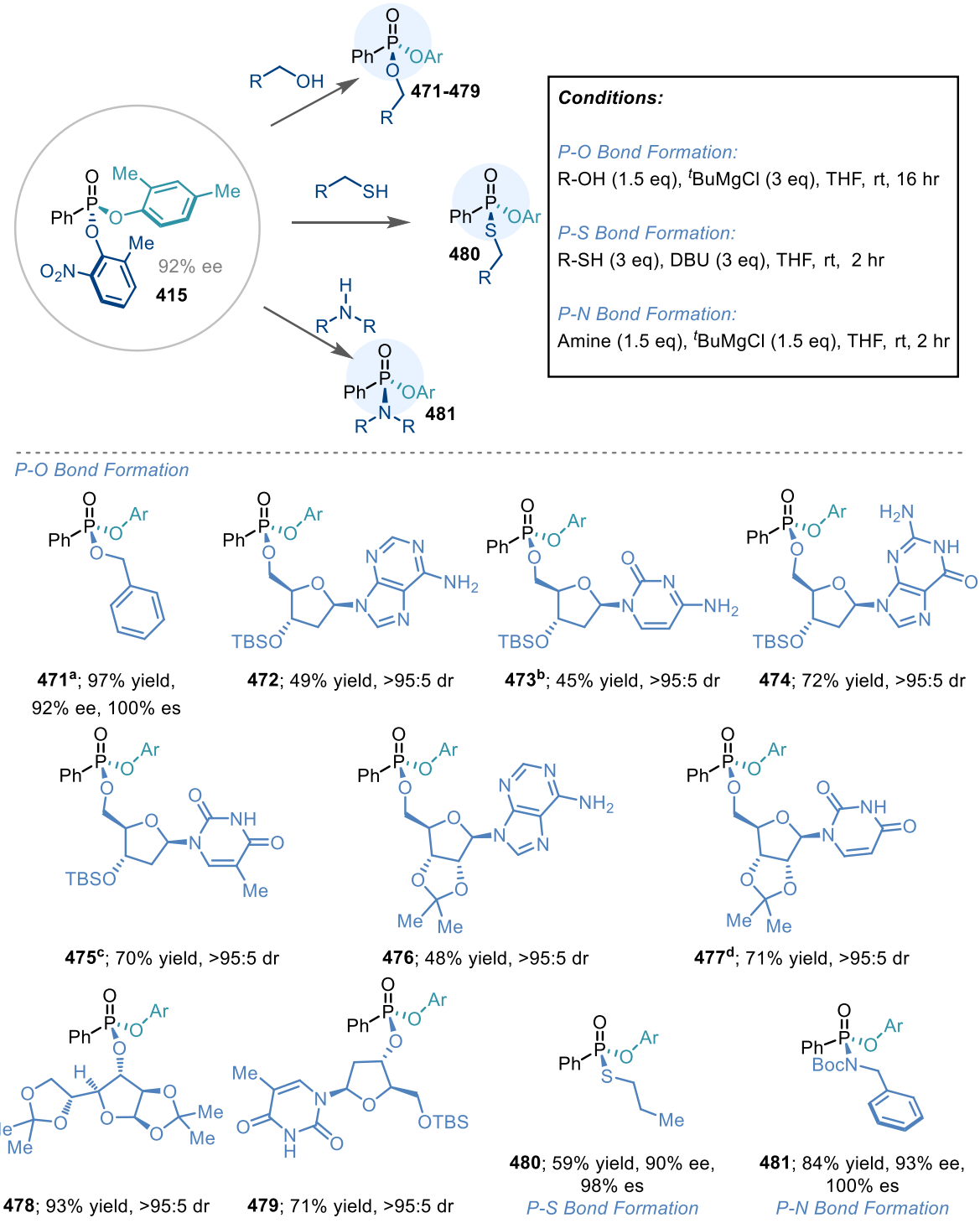
3.4 Reaction Derivatisation[vi]

Next, we turned our attention to displacing the remaining leaving group on **415** with a second nucleophile. Pleasingly, using conditions developed by Merck[136,137] employing a stoichiometric amount of Lewis acid activator, the nitrophenol leaving group could be smoothly displaced by alcohol nucleophiles with no erosion of enantiopurity (**Scheme 41**). We found that ^{t}BuMgCl was optimal to promote the addition of BnOH to **415**, affording **471** in 97% yield in 100% es in 2 hours. Other bases such as DBU or Barton's base resulted in racemisation of the starting material while the use of Me_2AlCl and pyridine gave no reaction. Encouraged by the result with a simple alcohol, 3'-OTBS-protected nucleosides were then used as nucelophiles (**472**-**475**). All silyl-protected DNA nucleosides were tolerated affording the corresponding products (**472**-**475**) in 45-70% yields and all in >95:5 dr. In all cases 1.5 eq of nucleophile, 3 eq of ^{t}BuMgCl and longer reaction times of 16 hr were required to obtain good levels of conversion apart from 3'-OTBS-deoxycytidine which required 4 eq of ^{t}BuMgCl and 48 hr. Next acetal protected RNA nucleosides were used as nucleophiles. Adenosine was well tolerated affording desired phosphonate **476** in 48% yield and >95:5 dr. The displacement also proceeded smoothly with acetal protected uridine affording **477** in 2 hours, 71% yield and >95.5 dr. We were delighted to find that complex secondary alcohols could also be used to displace the nitrophenol leaving group. D-glucose derivative **478** and 5'-OTBS-thymidine derivative **479** were both obtained in high yield and >95:5 dr.

As a control experiment, acetal protected uridine and D-glucose were also submitted to the reaction conditions using racemic **415**. In both cases compounds **478** and **479** were obtained as a 1:1 mixture of

[vi] Derivatisation studies were conducted with contributions from Dr. Heyao Shi and Mr. Naoto Sahara (visiting student). All results are included for completeness.

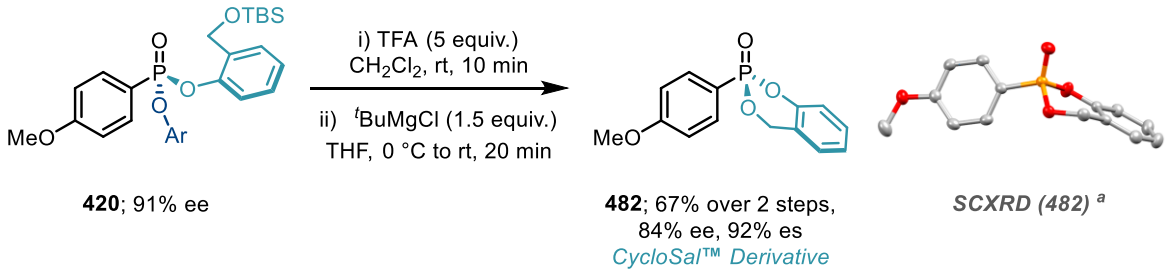
diastereoisomers showing that employing highly enantioenriched **415** is crucial to obtain excellent diastereoselectivity in the second nucleophilic substitution.



Scheme 41. Derivatisation of compound **425**. Ar = 2,4-Me-C_6H_3. Reactions carried out on 0.1 mmol scale.[a] 1.5 eq of nucleophile and ^{t}BuMgCl used, 2 hours. [b] 2.0 eq of nucleophile and 4.0 eq of ^{t}BuMgCl were used, 48 hours.[c] 48 hours. [d] 2 hours.

When using sulphur-based nucleophiles such as using *n*-propane thiol, ^{t}BuMgCl failed to yield the desired product **480**, with **415** undergoing *ispo*-substitution by the thiol at the electron-poor nitrophenol. This issue was overcome by using 3 eq of thiol and 3 eq of DBU to promote the reaction, which afforded the desired product **480** in 59% yield and 98% es. To explore P–N bond formation, N-Boc benzylamine was used as nucleophile. In this case using 1.5 eq each of ^{t}BuMgCl and amine nucleophile smoothly delivered product **481** in 84% yield and 100% es.

Finally, CycloSal™ derivative **482** was obtained in 67% yield and 92% es from substrate **420** by deprotection of the TBS group with TFA in CH_2Cl_2 and then ring closure with 1.5 eq of ^{t}BuMgCl. **482** was also found to be crystalline and was thus recrystallised to enantiopurity by slow evaporation from CH_2Cl_2/hexane and analysed by single crystal X-ray diffraction. The X-ray structure clearly showed that **482** had undergone an inversion of configuration at the P atom when compared to **420**, as is well precedented in the literature for similar nucleophilic substitutions at phosphorous.[44,138–140]

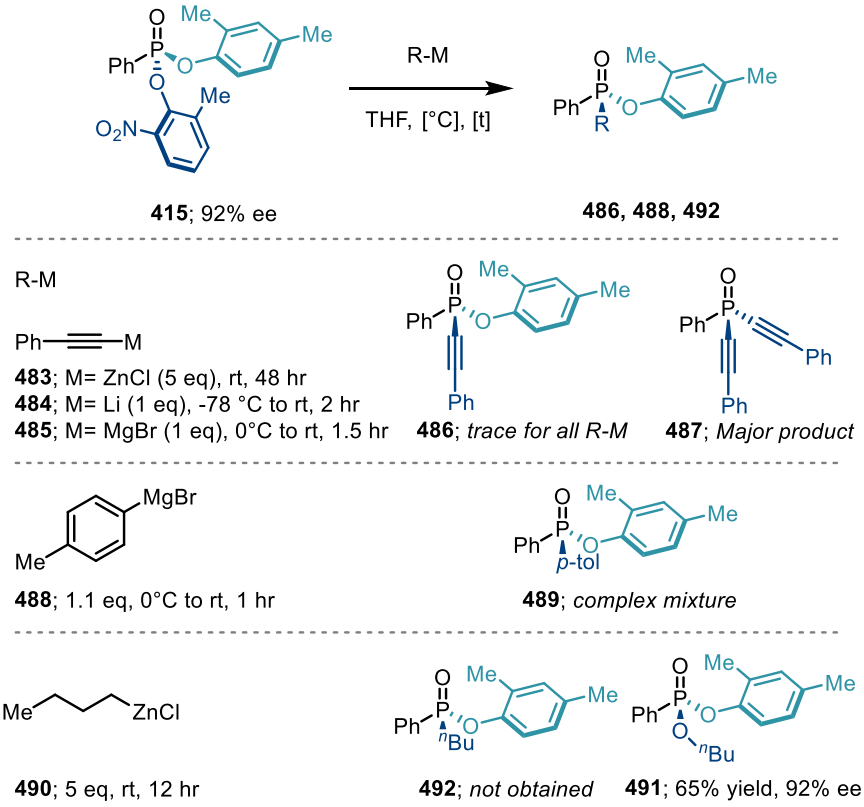


Scheme 39. Synthesis of CycloSal™ derivative **482** and single crystal X-ray structure of compound **482**. [a]H-Atoms omitted for clarity.

Having established reactivity with O-, S- and N-centred nucleophiles, C-centred organometallic nucleophiles were assessed in the second nucleophilic substitution using compound **415** (**Scheme 40**).[vii] Alkynyl nucleophiles (**483**-**485**) failed to afford desired product **486**, with known compound **487** being obtained instead under all conditions assessed. The use of Grignard reagent **488** resulted in a complex mixture being obtained instead of desired compound **489**. Finally, using nucleophile **590** (generated *in-situ* form 5 eq each of $ZnCl_2$ and ^{n}BuLi) delivered *O*-alkylated product **491** in 65% yield and 92% ee instead of desired P-alkylated product **492**. Given the low success obtained with a range of different

[vii] These reactions were conducted by Mr. Naoto Sahara (visiting student) under my supervision and are included for completeness.

carbon nucleophiles we deemed them incompatible with the current system highlighting a limitation of this methodology to be overcome in the future.



Scheme 40. Attempts at P–C bond formation with various carbon nucleophiles.

To gain insight into the mechanism of the reaction and the origin of enantioselectivity the newly developed methodology was investigated using DFT.

3.5 Computational Studies[viii]

Computational analysis of the transition state for the desymmetrisation reaction revealed that several key substrate-catalyst interactions were responsible for stabilising the complex and thus facilitating nucleophilic attack (**Figure 8A**).[ix] *In primis*, second order perturbation analysis was employed to compute the various hydrogen bonding interactions between the urea and carbamate portions of the BIMP catalyst with the P=O oxygen and nitro substituent on the substrate respectively (**Figure 8B**). The

[viii] Computational studies were conducted in their entirety by Miss Tatiana Rogova and Prof. Fernanda Duarte and are included for completeness.
[ix] Computational studies were conducted using substrate **411**, 2,4-dimethylphenol (**365**) as nucleophile and a simplified model of catalyst **387-P(*p*-tol)$_3$**.

energies indicated in the diagram highlight that non-covalent interactions not only bound the substrate within the chiral scaffold of the catalyst, but also contributed significantly to the energetic stabilisation of the complex in the transition state.

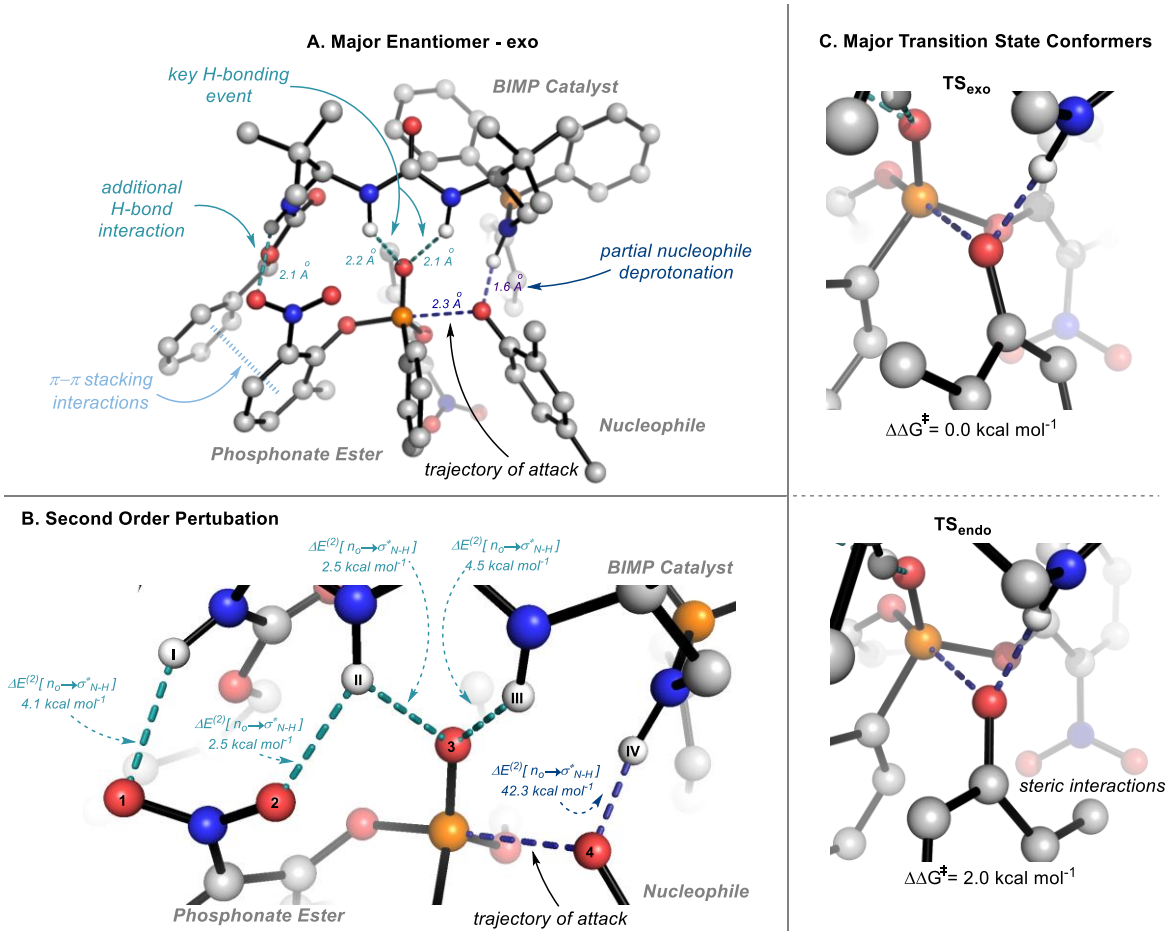


Figure 8.[x] A) Proposed transition state structure for the formation of the major stereoisomer of the P(V) desymmetrised product.[xi] B) Second order perturbation analysis showing all relevant non-covalent interactions and their respective calculated interaction energies (kcal mol^{-1}). C) Close-up comparison of the two possible orientation of the phenol in the transition state and the corresponding relative difference in activation energy.

The same analysis also revealed that the phenol nucleophile was partially deprotonated by the iminophosphorane basic site on the catalyst but remained closely associated to the forming conjugate

[x] Structures were optimized at the SMD(fluorobenzene)-M06-2X/def2TZVP//SMD(fluorobenzene)-M06-2X/def2SVP level of theory.

[xi] *exo* refers to the relative position of the *ortho*-methyl substituent on the phenolic nucleophile, which is pointing away from the BIMP structure catalyst.

acid (O_{Nuc} – H distance of 1.6 Å indicates that full ionisation of the reactant did not occur), thereby generating a more activated nucleophilic species to attack at the phosphorus centre. Furthermore, the vibrational mode associated with the transition state's imaginary frequency further indicated that both the nucleophilic attack and deprotonation events occur concurrently at the activation barrier. Lastly, additional π- π stacking interactions between the exiting nitrophenol leaving group and the anthracenyl group on the BIMP catalyst stabilised the formation of the pentacoordinate intermediate and positioned the ester substituent for subsequent displacement further along the reaction pathway.

The relative position of the *ortho*-methyl substituent on the phenol with respect to the catalyst-substrate complex was also found to influence the activation energy barrier. For example, the *exo* orientation of the methyl group (pointing away from the BIMP catalyst) was found to be 2.0 kcal mol^{-1} lower than the *endo* orientation, wherein the methyl is pointing into the complex cavity. This energetic difference most likely resulted from the minimisation of steric interactions between the various components of the transition state complex in the *exo* conformer. Overall, these combined non-covalent interactions in the activated complex contributed to the facile formation of the desymmetrised P(V) product.

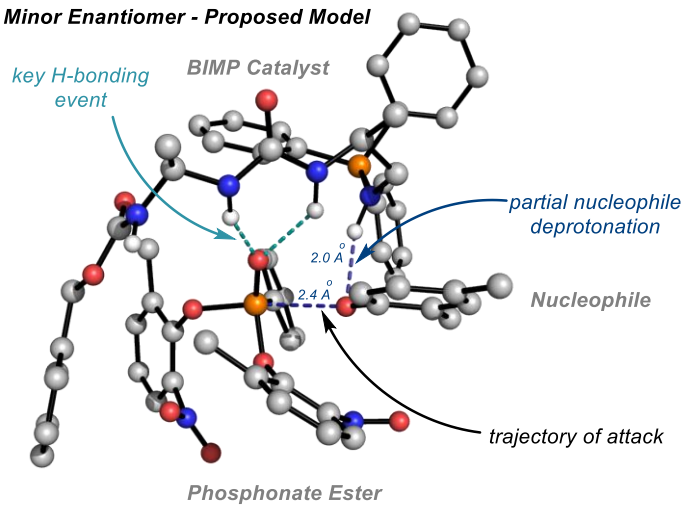


Figure 9. Proposed transition state structure for the formation of the minor stereoisomer of the P(V) desymmetrised product. [xii]

[xii] Geometry was generated using SMD(fluorobenzene)-M06-2X/def2TZVP//SMD(fluorobenzene)-M06-2X/def2SVP level of theory but is yet to be fully optimised.

Further computational analysis is currently ongoing to calculate the energy barrier for the formation of the minor enantiomer complex. It was proposed that an alternative orientation of the prochiral phosphonate ester within the catalyst-reactant complex would result in the formation of the other possible desymmetrised product, however, a real transition state (with one imaginary frequency) for this conformation is yet to be obtained (**Figure 9**). Full evaluation of the transition state structure as well as other relevant intermediates along the reaction coordinate will be obtained in due course.

3.6 Conclusion

In this chapter a novel and unprecedented nucleophilic enantioselective desymmetrisation of P(V) was described. By judicious choice of BIMP catalyst and nitrophenol leaving group, high levels of reactivity and enantioselectivity were observed. The newly established methodology was found to be highly enantioselective and tolerant of a wide range of *ortho*-substituted phenol nucleophiles and phosphonate electrophiles. The products were found to be versatile intermediates to access unsymmetrically substituted phosphonates, phosphonothioates and phosphoramidates with high levels of enantiospecificity and diastereoselectivity (**Figure 10**).

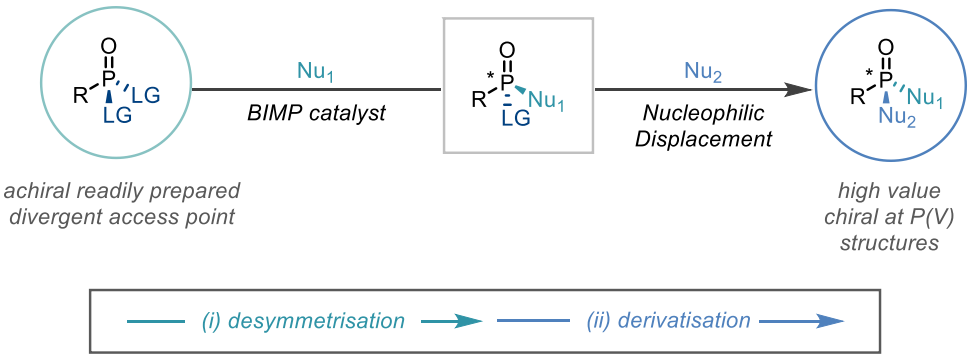


Figure 10. 2-Stage catalytic asymmetric synthesis of P(V) species *via* a desymmetrisation-derivatisation approach.

Chapter 4 will focus on our current efforts to improve on this methodology and address shortcomings in catalyst loading and nucleophile scope as well as expanding the portfolio of possible subsequent derivatisations.

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Chapter 4: 2nd Generation Enantioselective Nucleophilic Desymmetrisation of P(V) Species

4.1 Introduction

4.1.1 Limitations of previous methodology

Despite having established an unprecedented enantioselective nucleophilic desymmetrisation of phosphonate esters (**Chapter 3**) we were also aware of the limitations of the newly developed method (**Figure 1**). The optimal leaving group (**493**), whilst providing high levels of enantioselectivity, also imposed a requirement for high catalyst loading (15 mol%) most probably due to its relatively low pK_a (~12 in DMSO). Additionally, with a cost of 9£/g, it could preclude the application of this methodology on larger scales, especially when similarly priced chiral auxiliaries could be employed to achieve comparable results. Secondly, it was found that only phenols substituted with *ortho*-alkyl substituents were effective nucleophiles for the desymmetrisation. Finally, the resulting product (**415**) could only be further derivatised with O-, S-, and N-centred nucleophiles but not with C-centred nucleophiles. This is an important limitation, as this methodology could not be applied to the synthesis of P-stereogenic phosphinates, phosphine oxides and phosphines.

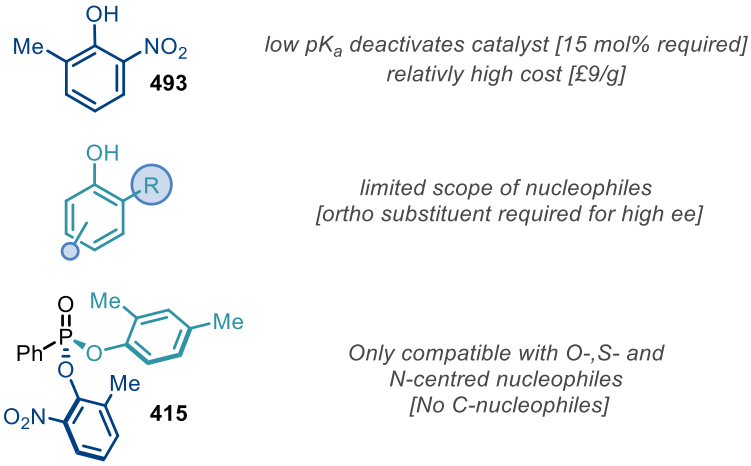


Figure 1. Limitations of the 1st generation enantioselective catalytic nucleophilic desymmetrisation of phosphonate esters.

Taking all these limitations into consideration, we believed they could all be resolved by the judicious replacement of the leaving group.

4.1.2 Aim of the project

In this project new leaving groups for the catalytic enantioselective desymmetrisation of P(V) species were explored. At the outset, we recognised that the novel leaving group would have to enable the same level of reactivity and enantioselectivity as **493**, while also addressing the key limitations listed in section **4.1.1.**

The ideal leaving group would possess a proximal Lewis basic site (which was identified as key to obtain high ee), have a higher pK_a to allow for better catalyst turnover and cost less than **493**. Oxazolidinone (**494**) appeared to be an ideal candidate having a pK_a of 20 in DMSO[1], a cost of only 0.50 £/g and extensive literature precedent as a leaving group for alcohol phosphorylation[2–6] and in P-chiral phosphine synthesis[7–9] (**Figure 2**).

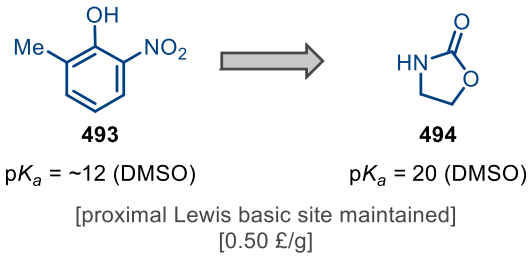


Figure 2. Rationale for switching from a nitrophenol based leaving group to an oxazolidinone based leaving group.

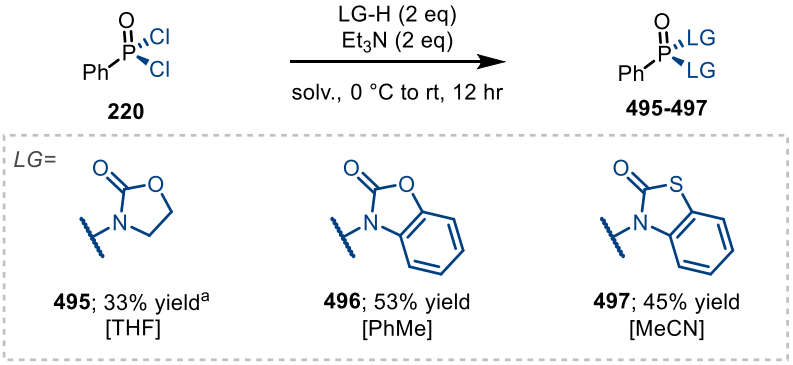
In this chapter, our work on the assessment of oxazolidinone and its isosteres as novel leaving groups in the BIMP catalysed nucleophilic desymmetrisation of P(V) species will be described.

4.2 Reaction Optimisation

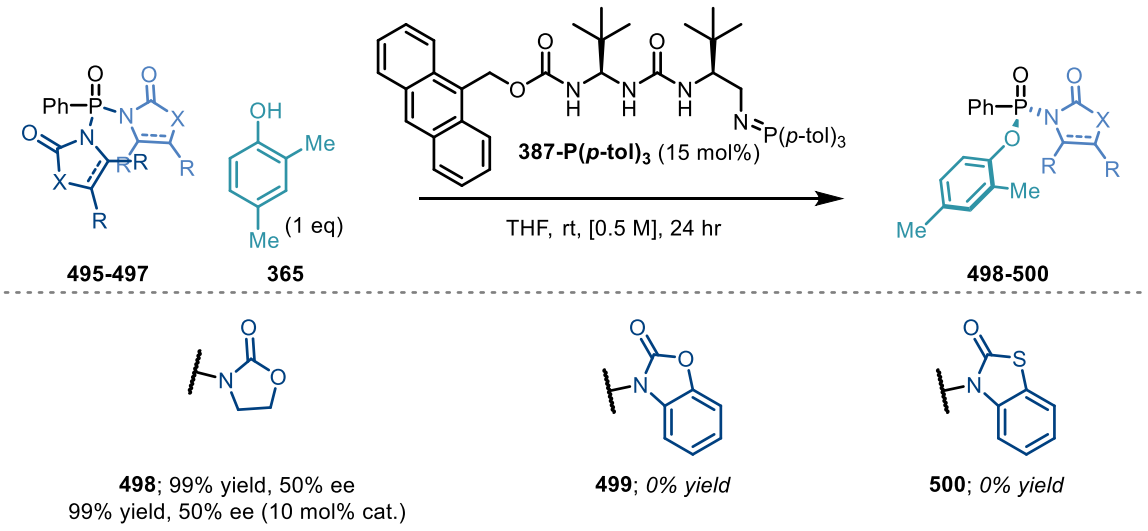
4.2.1 Substrate synthesis and initial desymmetrisation studies.

A range of new P(V) electrophiles were obtained by reacting phenylphosphonyl dichloride (**220**) with N-based nucleophiles (**Scheme 1**) following a procedure from Ueda.[10] Oxazolidinone derived electrophile **495** was obtained in 33% yield after heating at 50 °C in THF, benzoxazolidinone derivative

496 was obtained in 53% yield using toluene and benzothiazolidinone derived **497** was obtained in 45% yield when the reaction was conducted in MeCN. Changes in solvents were required for each substrate due to difference in solubility between the starting materials. All substrates could be easily purified by recrystallisation.



Scheme 1. Synthesis of oxazolidinone based electrophiles. [a] Reaction conducted at 50 °C.

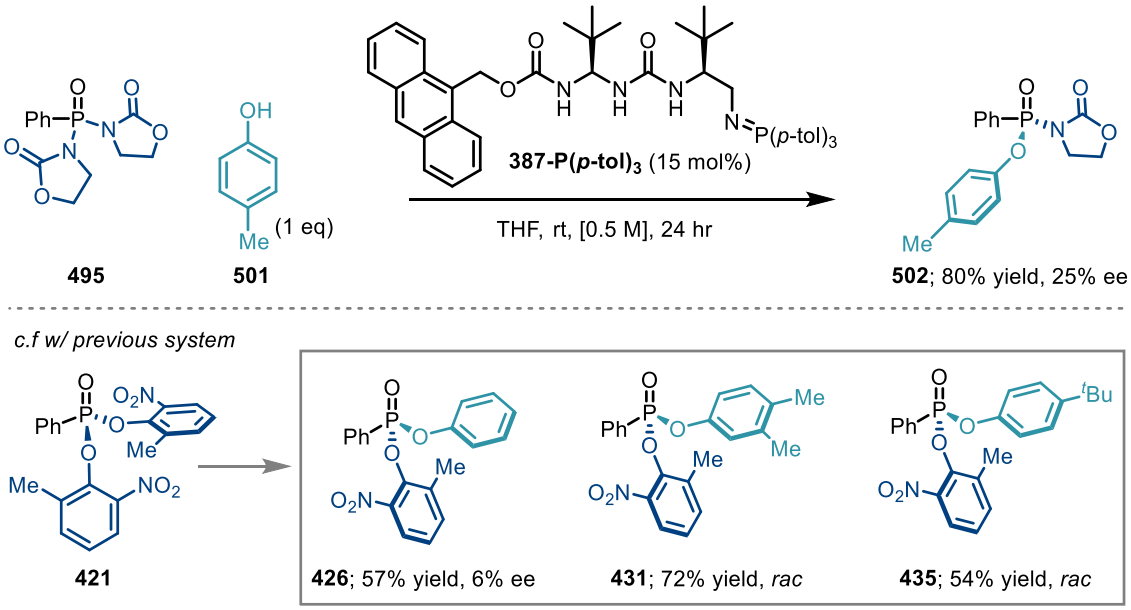


Scheme 2. Preliminary screening of novel leaving groups on P(V). All yields are isolated yields. Ee determined by analysis on a chiral stationary phase.

With a set of new electrophiles in hand their reactivity was probed utilising 2,4-dimethyl phenol (**365**) as nucleophile and the best performing BIMP catalyst (**387-P(*p*-tol)$_3$**) from the previously developed desymmetrisation reaction (**Scheme 2**). Pleasingly, oxazolidinone substrate **495** was smoothly desymmetrised to give product **498** in 99% yield and 50% ee both at 15 and 10 mol% catalyst loading

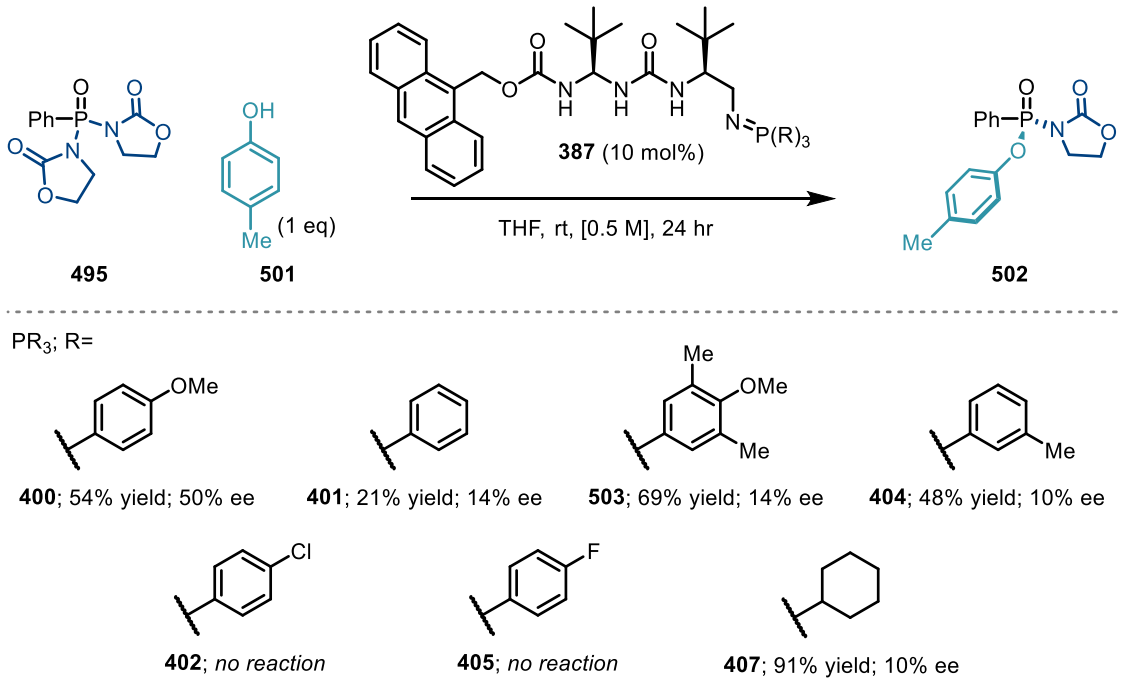
while neither product **499** or **500** was observed when using substrates **496** and **497** most likely due to excessive steric bulk around the central P atom.

The system was then assessed with 4-methyl phenol (**501**) as the nucleophile which pleasingly delivered product **502** in 80% yield and 25% ee (**Scheme 3**), which is considerably greater compared to the previous system in which non *ortho*-substituted nucleophiles afforded racemic products (**426**, **431**, **435**) (see **Chapter 3**).



Scheme 3. Desymmetrisation using 4-Me-phenol as nucleophile and comparison with similar nucleophiles using the previous desymmetrisation protocol. Reactions carried out on 0.1 mmol scale.

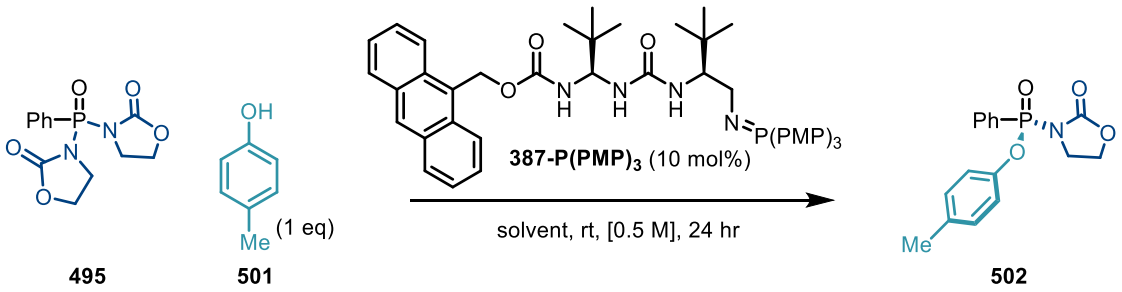
Encouraged by these results, the effects of using different phosphines to form the iminophosphorane from azide **387-N$_3$** were probed while maintaining the catalyst loading at 10 mol% (**Scheme 4**). Using P(PMP)$_3$ (**400**) derived iminophosphorane delivered product **502** in a diminished yield of 54% but improved the ee to 50%. The use of other electron rich or electron neutral phosphines (**401**, **503**, **404**) resulted in lower enantioselectivity. Electron poor phosphines **402** and **405** gave no conversion of starting material **495**, while using PCy$_3$ (**407**) gave an excellent yield of 91% but poor ee (10%). As **387-P(PMP)$_3$** gave the best compromise of reactivity and enantiocontrol it was selected as the go-to catalyst for further optimisation.



Scheme 4. Variation of the iminophosphorane moiety on ureidopeptide catalyst **387**. Reactions carried out on 0.1 mmol scale.

Following the optimisation of the phosphine component, other BIMP catalysts readily available in our laboratory were evaluated in the desymmetrisation reaction, however all of them delivered the desired product with extremely poor levels of enantioselectivity. We therefore proceeded to probe solvent effects using catalyst **387-P(PMP)$_3$** (**Table 1**).

Chlorinated solvents (*entries 1-3*) proved to be effective, delivering **502** in 78-82% yield with the same ee as THF. As substrate **495** was insoluble in PhF (the best solvent in the 1st generation desymmetrisation), the reaction was conducted in a THF:PhF mixture in either 1:1 (*entry 4*) or 1:3 (*entry 5*) ratio however both yield and ee were decreased. Other aromatic solvents (*entries 6-7*) and ethereal solvents (*entries 8-9*) gave poorer yields and enantioselectivities. As CH_2Cl_2 was the cheapest and most available solvent among the chlorinated solvents assessed it was selected to be used in further optimisation.

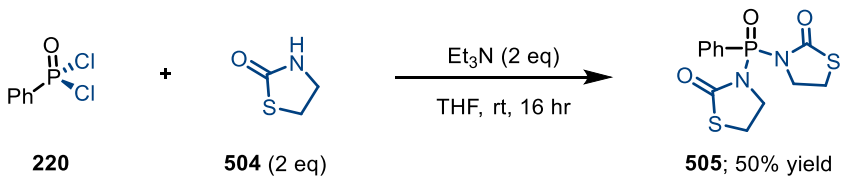


Entry	Solvent	Yield[a] (%)	ee[b] (%)
1	***CH_2Cl_2***	***81***	***50***
2	1,2-dichlorobenzene	78	47
3	DCE	82	50
4	THF:PhF (1:1)	73	33
5	THF:PhF (1:3)	77	38
6	o-Xylene	49	20
7	$PhCF_3$	88	42
8	CPME	81	30
9	MTBE	30	48

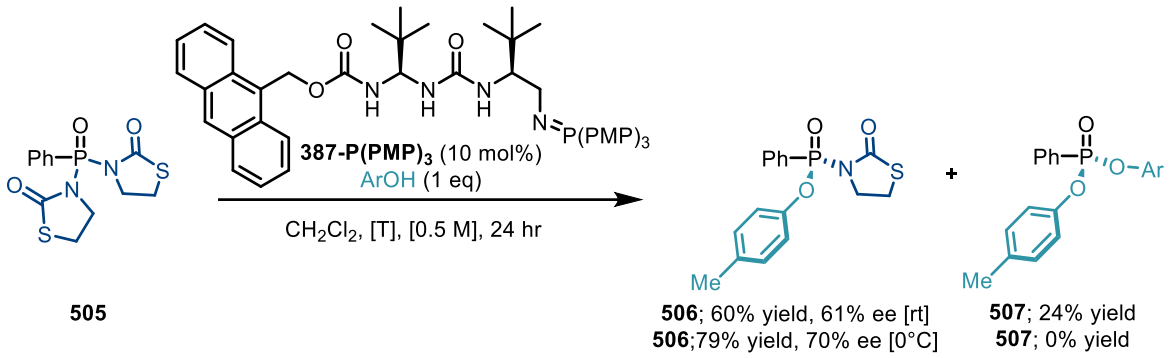
Table 1. Solvent screen. Reactions carried out on 0.1 mmol scale. [a] Isolated yield. [b] Determined by HPLC analysis on a chiral stationary phase.

4.2.2 Use of thiazolidinone leaving groups and final optimisation.

We then considered the use of thiazolidinone (**504**) as a leaving group, following the rationale that subtle electronic changes could positively influence enantioselectivity. Phosphoryl bisthiazolidinone substrate **505** was easily obtained in 50% yield following the previously described synthesis (**Scheme 5**).



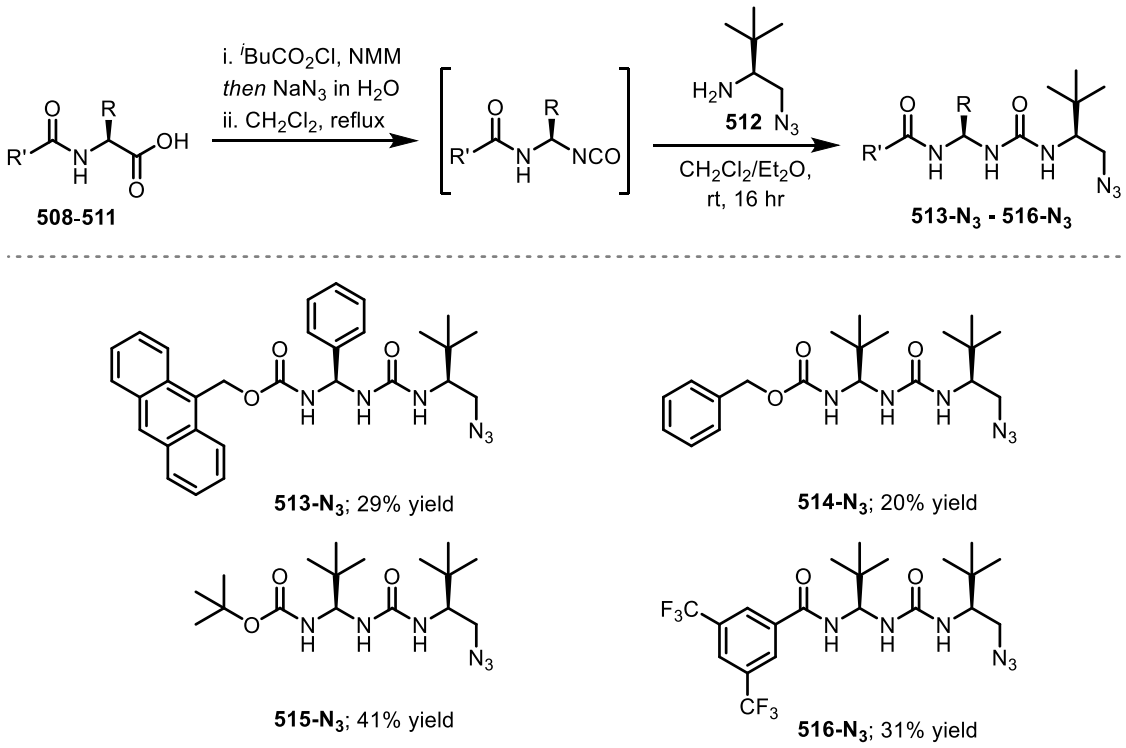
Scheme 5. Synthesis of thiazolidinone derived substrate **505**.



Scheme 6. Evaluation thiazolidinone derived substrate **505** in the BIMP catalysed desymmetrisation. ArOH= 4-Me phenol. Reactions carried out on 0.1 mmol scale.

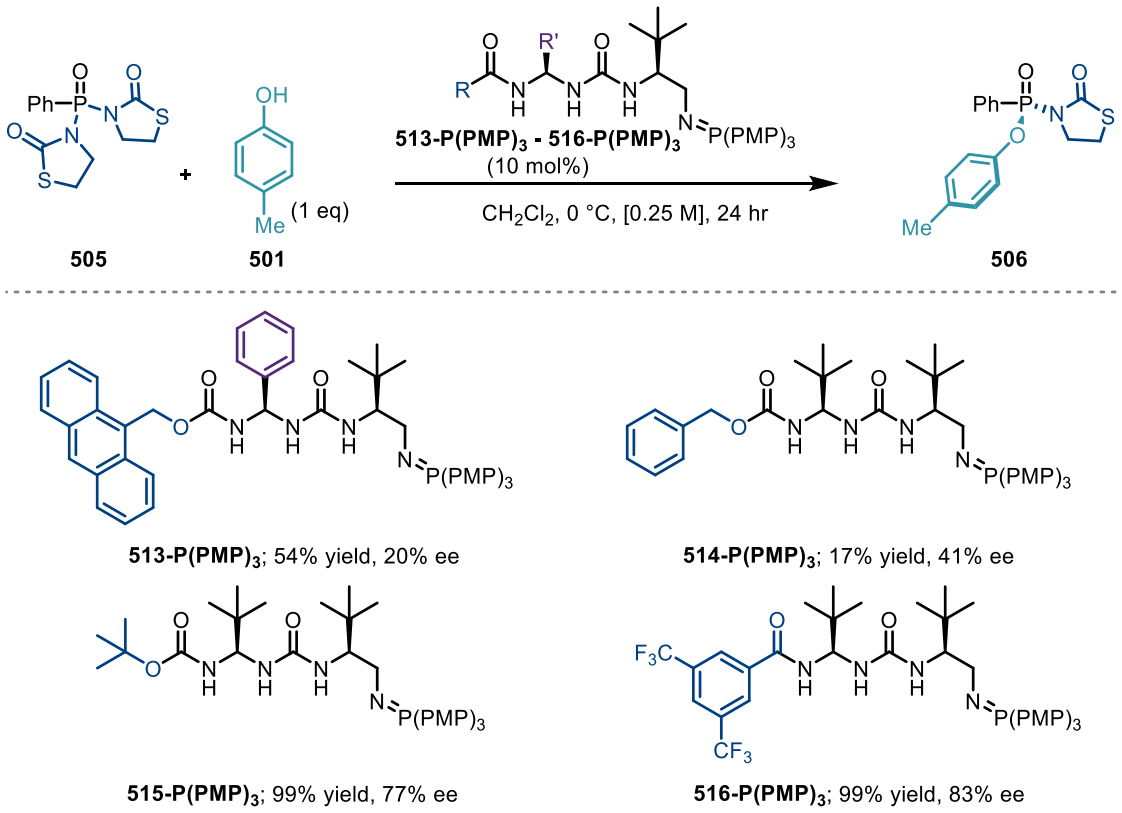
Newly synthesised **505** was assessed in the desymmetrisation reaction under the conditions highlighted in **Table 1** which afforded **506** in 60% yield and 61% ee at room temperature alongside 24% of literature known double addition product **507**.[11,12] This problem was readily solved by conducting the reaction at 0 °C, which resulted in the suppression of the formation of **507** and therefore an an increase to both the yield and ee of **506** to 79% and 70% respectively.

Next, we turned our attention to fine-tuning the catalyst structure. Four novel ureidopeptide BIMP precatalysts were synthesised from commercialy available or readily prepared amino acid building blocks (**Scheme 7**). **508**-**511** were treated with isobutyl chloroformate and *N*-methyl morpholine to form the corresponding mixed anhydrides *in situ* which were then subsequently reacted with NaN_3. The crude acyl azides were extracted with CH_2Cl_2 and dried over $MgSO_4$ and subsequently refluxed in dry CH_2Cl_2 to afford the analogous isocyanates *via* Curtius rearrangement.[13] The crude isocyanates were immediately combined with amino azide **512** and stirred at rt in CH_2Cl_2/Et_2O.[14] Upon removal of solvent the crude catalysts were easily purified by trituration or recrystallisation from EtOAc affording novel ureidopeptide precatalysts **513-N$_3$**-**516-N$_3$** in 20-41% yield over 3 steps.



Scheme 7. Synthesis of novel ureidopeptide BIMP catalyst azide precursors. Yields reported over 3 steps.

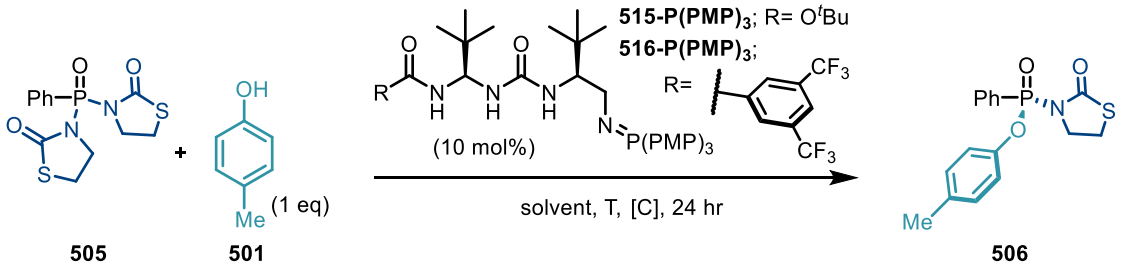
The newly obtained ureidopeptide P(PMP)$_3$ derived BIMP catalysts (**513-P(PMP)$_3$** - **516-P(PMP)$_3$**) were then assessed in the desymmetrisation reaction using thiazolidinone derived substrate **506** in CH_2Cl_2 at 0 °C and 0.25 M concentration (**Scheme 8**). Catalysts **513-P(PMP)$_3$** and **514-P(PMP)$_3$** performed poorly, most certainly due to the low solubility of the corresponding azides and thus incomplete *in-situ* generation of the iminophosphorane moiety when combined with P(PMP)$_3$. Catalyst **515-P(PMP)$_3$**, bearing a distal *N*-Boc group, performed well delivering **506** in quantitative yield and 77% ee. This result was further improved upon when using BIMP **516-P(PMP)$_3$**, which possesses a more acidic amide group on the left-hand side, affording **506** in 99% yield and 83% ee. Both catalysts were selected for further optimisation of the reaction conditions in a bid to improve the ee to over 90%.



Scheme 8. Screening of new ureidopeptide BIMP catalysts (**513-P(PMP)$_3$** - **516-P(PMP)$_3$**) in the enantioselective desymmetrisation reaction. Reactions carried out on 0.1 mmol scale. All yields are isolated yields. Ee determined by HPLC analysis on a chiral stationary phase.

Next, the reaction conditions were fine-tuned using catalyst **515-P(PMP)$_3$** and **516-P(PMP)$_3$** (**Table 2**). Diluting the reaction (*entries 1-2*) had a beneficial effect boosting the yield to 99% and the ee to 81%. Cooling to −20 °C however (*entry 3*) had a detrimental effect giving only 5% yield of desired product **506**. At this point a further solvent evaluation was conducted maintaining the temperature at 0 °C and the concentration at 0.25 M. Out of the five solvents investigated (*entries 4-8*) only EtOAc had a beneficial effect on ee which was boosted to 83%. The yield decreased to 53% however due to incomplete dissolution of the starting material. This was easily overcome by further diluting the reaction mixture to 0.063 M (*entry 9*) which restored the yield to 99% while maintaining the same ee if 83%. Pleasingly, when catalyst **516-P(PMP)$_3$** was used under the same conditions, **506** was obtained in 99% yield and 96% ee giving the final optimised conditions for the second generation enantioselective desymmetrisation at P(V). Lowering the catalyst loading to 5 mol% (*entry 11*) maintained a high level of yield but a lower ee

of 94%. This negative trend continued when the catalyst loading was decreased to 2.5 mol% (*entry 12*) where **506** was obtained in only 90% ee.



Entry	Solvent	Catalyst	T (°C)	[Concentration] (M)	Yield[a] (%)	ee[b] (%)
1	CH_2Cl_2	**515-P(PMP)$_3$**	0	[0.125]	80	77
2	CH_2Cl_2	**515-P(PMP)$_3$**	0	[0.063]	99	81
3	CH_2Cl_2	**515-P(PMP)$_3$**	– 20	[0.25]	5	79
4	DCE	**515-P(PMP)$_3$**	0	[0.25]	71	75
5	MTBE	**515-P(PMP)$_3$**	0	[0.25]	76	78
6	$PhCF_3$	**515-P(PMP)$_3$**	0	[0.25]	19	71
7	PhF	**515-P(PMP)$_3$**	0	[0.25]	67	75
8	EtOAc	**515-P(PMP)$_3$**	0	[0.25]	56	83
9	EtOAc	**515-P(PMP)$_3$**	0	[0.063]	99	83
10	***EtOAc***	**516-P(PMP)$_3$**	***0***	***[0.063]***	***99***	***96***
11	EtOAc	**516-P(PMP)$_3$** (5 mol%)	0	[0.063]	99	94
12	EtOAc	**516-P(PMP)$_3$)** (2.5 mol%)	0	[0.063]	86	90

Table 2. Fine-tuning of the reaction conditions. Reactions performed on 0.1 mmol scale. [a] Isolated yield. [b] Determined by HPLC analysis on a chiral stationary phase.

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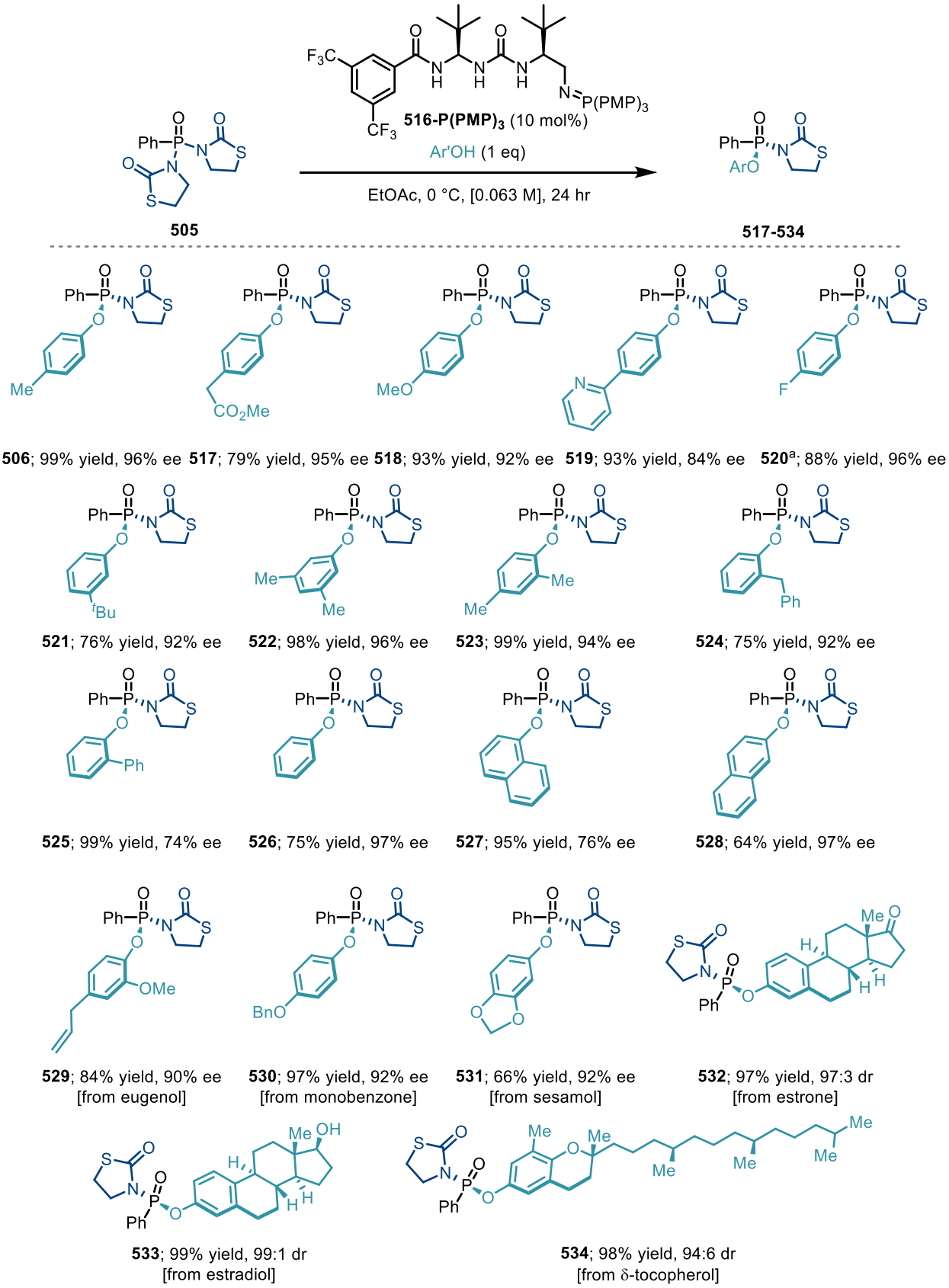
4.3 Scope of the reaction

4.3.1 Scope with regards to the phenol nucleophile

With the optimised conditions in hand, the scope of the desymmetrisation with respect to the phenol nucleophile was then investigated (**Scheme 9**). Pleasingly, and in contrast to the method developed in **Chapter 3**, a wide range of electron donating and withdrawing substituents at the phenol *para*-position were well tolerated providing desired products (**517**-**520**) with high levels of yield and enantioselectivity. Most noticeably, **519**, bearing a 2-pyridyl substituent was obtained in 93% yield and 84% ee. In the case of **520** 2 equivalents of phenol nucleophile were required to obtain 88% yield. **521** and **522** bearing only *meta*-substituents were obtained in 76% and 98% yield, and 92% and 96% ee, respectively.

Alkyl (**523**), benzylic (**524**) and aromatic (**525**) *ortho*-substitents were all tolerated with the desired products being obtained in excellent yields and 74-94% ee. Unsubstituted phenol (**525**) and naphthol nucleophile (**527**-**528**) derived products were obtained in 64-95% yield and 76-97% ee.

Next, we turned our attention to more complex phenol nucleophiles derived from naturally occurring compounds or pharmaceuticals (**529**-**534**). **529** derived from eugenol was obtained in 84% yield and 90% ee. Products **530** and **531** derived from monobenzone and sesamol were obtained in 97% yield and 92% ee, and 66% yield and 92% ee, respectively. Finally, diastereoselective phosphorylations were conducted using structurally complex, enantiomerically pure phenol nucleophiles (**532**-**534**). Estrone derived product **532** was obtained in 97% yield and 97:3 dr while estradiol derived product **533** was obtained in 99% yield and 99:1 dr. **534** was obtained form δ-tocopherol in 98% yield and 94:6 dr. Importantly, when these reactions were conducted using an achiral phosphazene base (BEMP) the resulting dr was always ~1:1 indicating full catalyst control in the diasetereoselective examples (see **Chapter 5** for details).

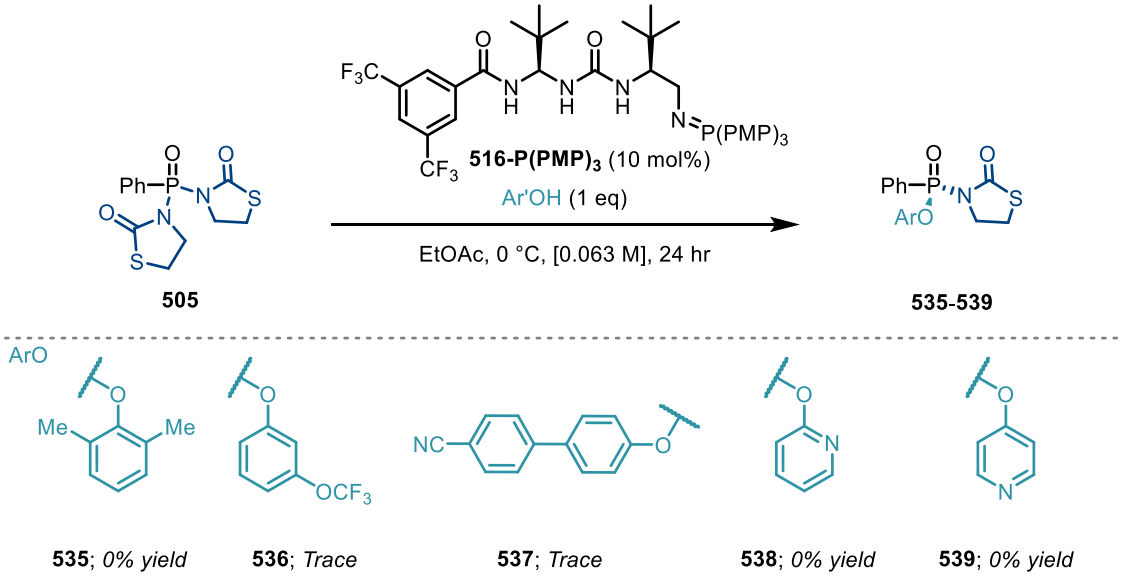


Scheme 9. Phenol scope. [a] 2 eq of phenol nucleophile used. Reactions performed on 0.1 mmol scale.

4.3.2 Unsuccessful nucleophiles

While the nucleophile scope described in this chapter marks a clear improvement from the previously developed enantioselective desymmetrisation (**Chapter 3**) a substantial portion of the phenol nucleophiles assessed proved to be unsuccessful (**Scheme 10**).

Sterically hindered 2,6-dimethyl phenol did not lead to any product (**535**) formation most likely due to unfavorable steric interactions. Similarly, very electron poor nucleophies led to low conversion of **505** to desired products **536** and **537** due to insufficient nucleophilicity. Pyridone nucleophiles also led to no formation of the corresponding phosphorylated products **538** and **539**, either through insufficient nucleophilicity or through strong inhibition of the BIMP catalyst.



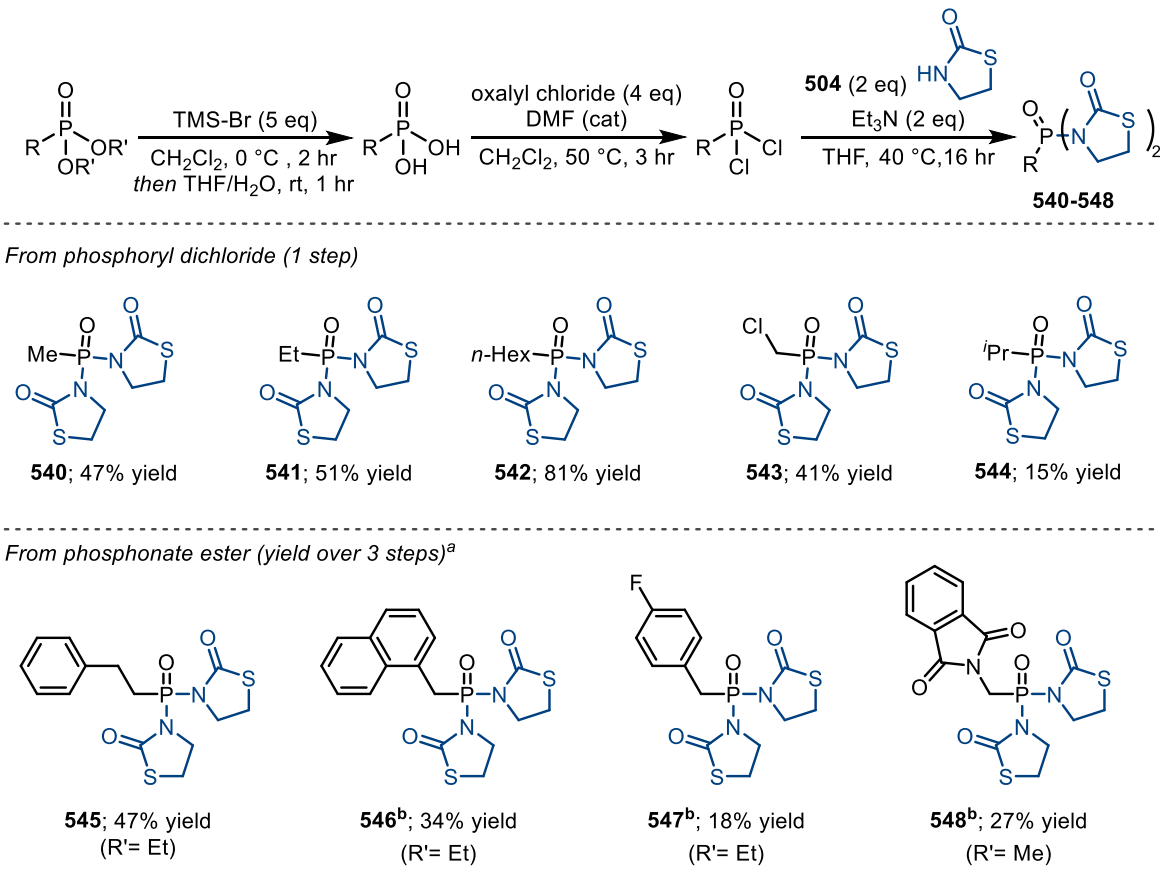
Scheme 10. Unsuccessful nucleophiles. Reactions carried out on 0.1 mmol scale.

4.3.3 Synthesis of P(V) electrophiles

Having established the nucleophile scope for the reaction, a library of novel phosphoryl bisthiazolidinones bearing different alkyl substituents were synthesised (**Scheme 11**).[i] Phosphoryl bisthiazolidinones **540-544** were obtained from the corresponding commercially available phosphoryl dichlorides in moderate to good yield except for **544** which was obtained in 15% yield possibly due to

[i] New P(V) electrophiles were synthesised with ongoing contributions from Mr Thomas Marsh (PhD student) and all results are included for completeness.

the increased steric bulk of the isopropyl group. Electrophiles **545-548** were instead obtained in moderate yield from the corresponding commercially available phoshonate esters in a 3-step, 1-pot procedure consisting of ester cleavage with TMS-Br, hydrolysis with H_2O, chlorination with oxalyl chloride and DMF, and finally coupling with thioazolidione (**504**) in the presence of Et_3N. Solvents and volatile reagents were removed *in vacuo* between each step. It was found that increasing the amount of Et_3N from 2 to 5 equivalents was beneficial to the yield as this excess of base would quench any remaining residual acid from previous steps. The synthesis of further electrophiles is currently ongoing, and results will be disclosed in due course.



Scheme 11. Synthesis of P(V) electrophiles.[a] 5 eq. of Et_3N were used in the final step.[b] Reaction carried out at rt.

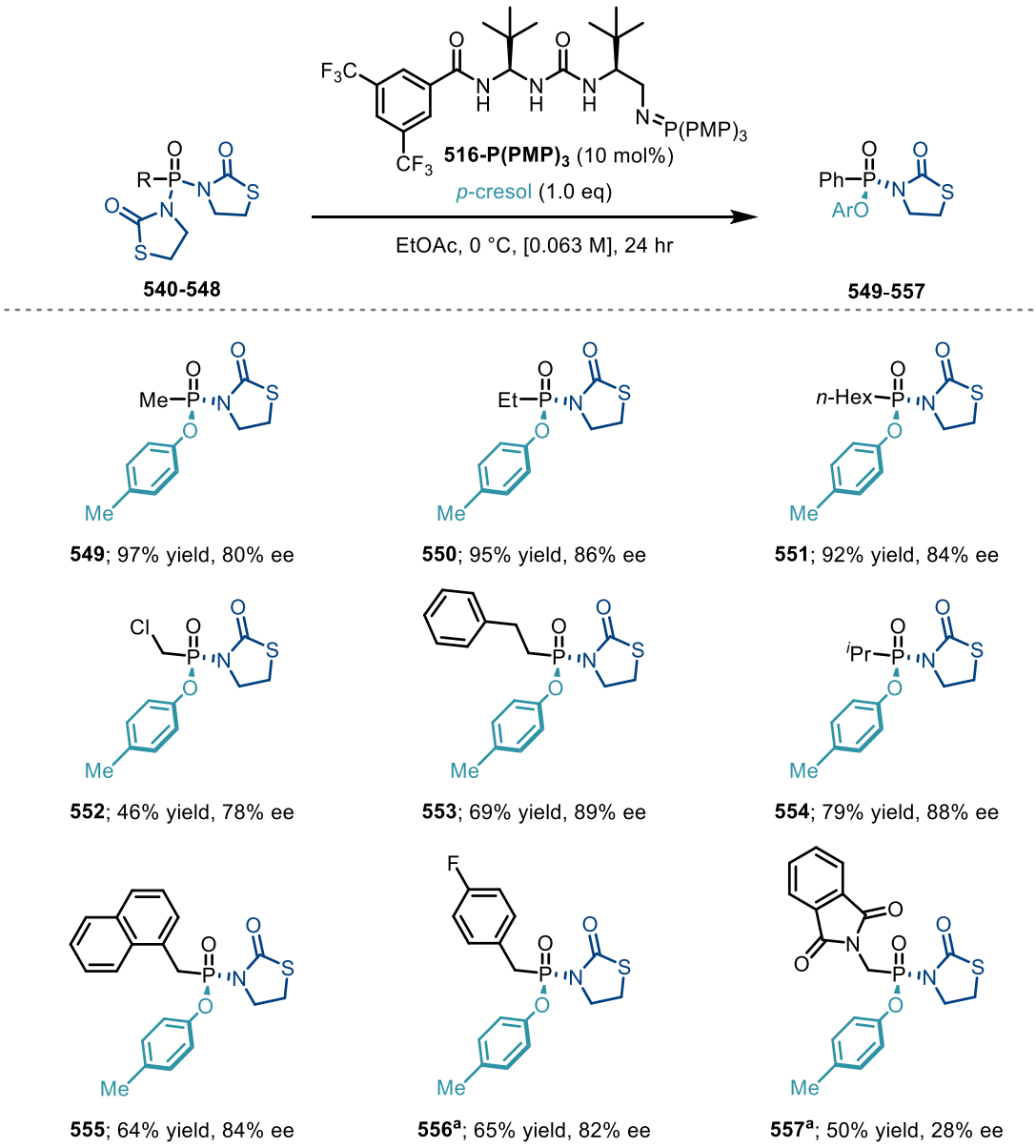
4.3.4 Scope with regards to the P(V) electrophile

With a small library of phosphoryl bisthiazolidinones in hand, the scope of the reaction with respect to the P(V) electrophile was explored.[ii] We were pleased to find that, under the optimised reaction conditions, alkyl substituents were well tolerated. Products **549-551** bearing Me, Et and *n*hexyl substituents respectively, were obtained in 92-97% yield and 80-86% ee. Substrate **543**, containing a chloromethyl group gave corresponding desymmetrised product **552** in 46% yield and 78% ee. The lower yield resulted from a decrease in the reactivity of the substrate rather than the generation of side products. Product **553** bearing a phenylethyl sidechain was obtained in 69% yield and 89% ee.

Pleasingly, hindered substrate **544**, which possesses an isopropyl group was converted to the corresponding desymmetrised product **554** in 79% yield and 89% ee. This was found to contrast with the system disclosed in **Chapter 3**, where the analogous bis(2-NO_2-6-Me-C_6H_3) phosphonate gave very low conversion to the desired product. Substrates **546** and **547** bearing benzylic substituents afforded corresponding products **555** and **556** in 64% and 65% yield, and 84% and 82% ee, respectively. Unfortunately, phthalimide derived product **557** was obtained in 50% yield and 28% ee most probably due to the Lewis basic carbonyl of the phtalimide unproductively interfering with catalyst H-bond donor.

Further efforts to expand the electrophile scope are currently ongoing. Additional substrates containing (hetero)aromatic substituents, as well as side chains derived from drug compounds such as Adefovir (a treatment for Hepatitis B)[15], will be explored and the results will be disclosed in due course.

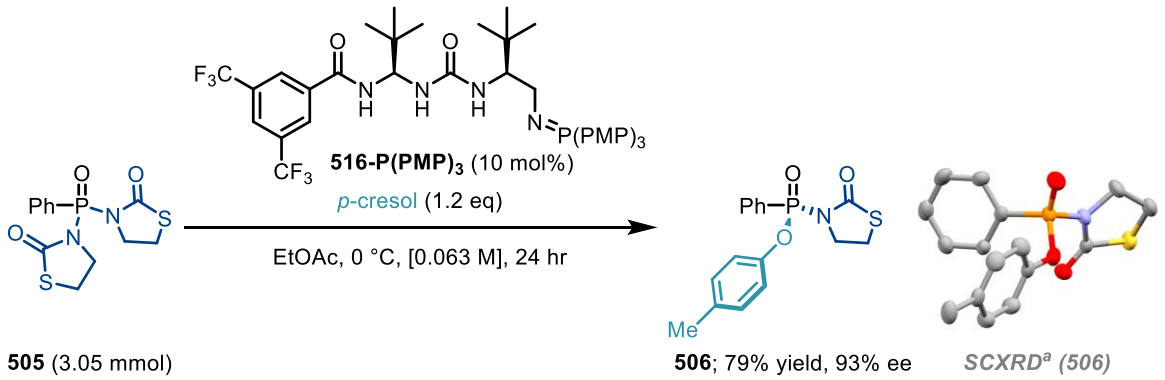
[ii] Scope experiments were conducted with ongoing contributions from Mr Thomas Marsh (PhD student) and all results are included for completeness.



Scheme 12. Electrophile scope. Reactions performed on 0.1 mmol scale.[a] Reactions performed on 0.05 mmol scale.

4.3.5 Reaction scale-up

Having established the scope for the reaction its scalability was demonstrated on 3.05 mmol (1.00 g) scale using model substrate **505** and *p*-cresol affording **506** in a slightly diminished 79% yield and 93% ee (**Scheme 13**).



Scheme 13. Gram scale reaction and single crystal X-ray diffraction of compound **506**.[a]H-Atoms omitted for clarity.

A small amount of **506** was recrystallised to enantiopurity by slow evaporation from CH_2Cl_2/hexane and analysed by single crystal X-Ray diffraction establishing the absolute configuration of the product as (*R*). The stereochemical configuration of all other products was assigned by analogy. The product obtained in this reaction will be used for further derivatisation.

4.4 Conclusion and future work

Future work will focus on completing the product derivatisation to obtain varied enantioenriched P(V) containing molecules. In addition, as previously stated, the scope will be expanded to include further examples bearing aromatic and heteroaromatic substituents on the electrophile backbone.

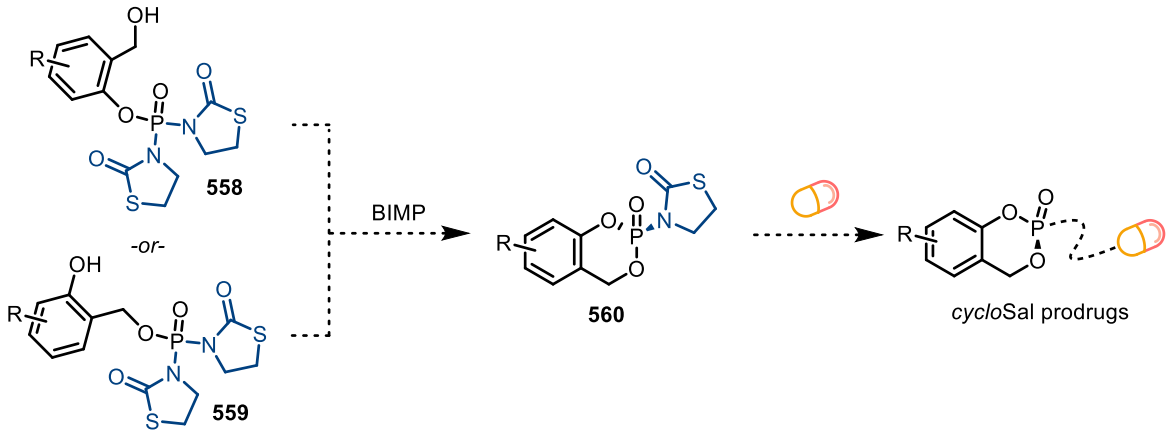


Figure 3. Proposed enantioselective *cyclo*Sal prodrug synthesis.

Following these results, we wish to focus on the synthesis of *cyclo*Sal prodrugs by performing an intramolecular enantioselective desymmetrisation on substrates such as **558** or **559**. This would lead to

common intermediate **560** in which the labile thiazolidinone leaving group could be displaced with multiple pharmaceutically relevant nucleophiles (**Figure 3**). This method would allow for the rapid and divergent synthesis of *cyclo*Sal prodrugs and provide a platform for rapid SAR analysis. Additionally, computational studies are currently ongoing in collaboration with Miss Tatiana Rogova and Prof Fernanda Duarte to elucidate the origin of the increased nucleophile tolerance in this second-generation system compared to the method described in **Chapter 3**.

4.5 References for Chapter 4

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Chapter 5 : Experimental Details

5.1 General Experimental Details

General Techniques: Reactions were carried out under a nitrogen atmosphere unless stated otherwise. Glassware was oven-dried and cooled *in vacuo* 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 unless stated otherwise.

Nomenclature and Numbering: Compounds are named following IUPAC nomenclature as generated by ACD LABS or 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, with the exception of natural products (conventional numbering following biosynthesis).

Solvents and Reagents: Ether refers to diethyl ether; petrol refers to the fraction of petroleum ether that boils between 30 and 40 °C. Where solvent dryness was important, CH_2Cl_2, 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, anisaldehyde, cerium ammonium molybdate, vanillin, or iodine on silica. Purification by flash column chromatography[1] 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 (^{31}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. 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 (νmax) 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 at room temperature employing a chiral stationary phase column specified in the individual experiment and by comparing the samples with the appropriate racemic mixtures.

X-Ray Crystallography: Single crystal X-ray diffraction data were collected using an Enraf–Nonius KCCD diffractometer or an Oxford Diffraction SuperNova diffractometer at 150 K. Crystal structures were solved with SIR92 and refined with CRYSTALS by Dr Heyao Shi (University of Oxford), Dr Amber L. Thompson and Dr Kirsten E. Christensen (University of Oxford Chemical Crystallography department).

Synthesis of Known Compounds: The synthesis of compounds previously reported in the literature are labelled as such. Two relevant pieces of characterisation are given, unless the compound is used without purification in the next step or made by another group member and available in the laboratory. References are given for experimental procedures and data.

Compounds not made myself: Data will be included here if an assignment or an additional piece of information was not present in the original report.

5.2 Experimental Details for Chapter 2

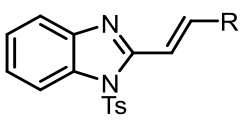
5.2.1 Synthesis of precatalysts and catalysts

Catalysts **34**,[1] **33**,[2] **70-P(PMP)$_3$**[3] and **123**,[4] **124-125**,[5] **80**, **128**[6] were readily available in the lab or prepared by Dr Geoffroy Sorin or Dr Alistair J. M. Farley according to literature procedures.

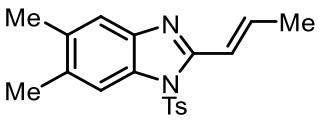
5.2.2 Preparations of *N*-Ts protected alkenyl benzimidazole

Non commercially available aldehydes were prepared by Dr Geoffroy Sorin *via* oxidation of the corresponding alcohol with Dess-Martin Periodinane following the procedure reported by Snowden *et al.*[7]

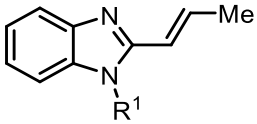
N-Ts benzimidazoles **108**, **139**, **140**, and *N*-Cbz-, *N*-Boc-, and *N*-H benzimidazoles **141-143** were prepared by Dr. Geoffroy Sorin as described by Terada *et al.* [8]



R = Me **108**, Ph **139**

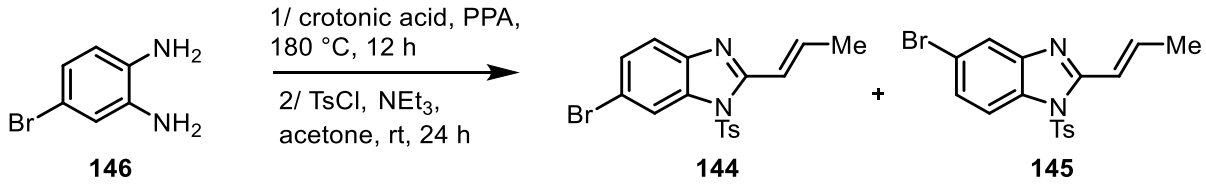


140



R^1 = Cbz **141**, Boc **142,** H **143**

(*E*)-6-bromo-2-(prop-1-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**144**) and (*E*)-5-bromo-2-(prop-1-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**145**)

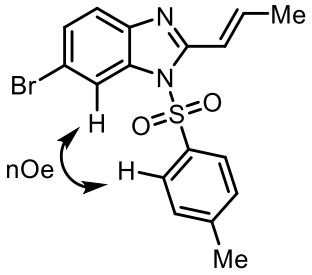


146 **144** **145**

To a mixture of crotonic acid (2.68 g, 30 mmol) in polyphosphoric acid (12.0 g) was added 4-bromo-1,2-diaminobenzene (**146**, 5.61 g, 30 mmol). The reaction was heated at 180 °C for 12 hr. The mixture was cooled down to room temperature and poured carefully onto a saturated solution of $NaHCO_3$. Solid $NaHCO_3$ was added until neutral pH was obtained. The solution was diluted with EtOAc and water then stirred vigorously for 10 min. The aqueous phase was extracted twice with EtOAc and the combined organic phase were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* affording 3.9 g of purple solid.

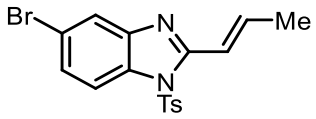
The crude residue (2.0 g, 8.4.00 mmol) was dissolved in acetone (40.0 mL), NEt_3 (1.41 mL, 10.1 mmol) was added then TsCl (1.77 g, 9.3 mmol). The mixture was stirred for 24h at room temperature. The solvent was removed *in vacuo* and the crude was purified by flash chromatography on silica gel (Pentane:EtOAc 9:1). A subsequent trituration of each compound in a mixture of pentane:Et_2O (1:1) afford pure (*E*)-6-bromo-2-(prop-1-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**144**) as a Colourless solid (380 mg, 12% yield) and (*E*)-5-bromo-2-(prop-1-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**145**) as an off-Colourless solid (450 mg, 14% yield).

(*E*)-6-Bromo-2-(prop-1-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**144**)



Mp 160 °C (from EtOAc/Petrol); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 1.8 Hz, 1H, Benzimidazole C<u>H</u>), 7.78 (d, *J* = 8.5 Hz, 2H, Tosyl C<u>H</u>), 7.50 (d, *J* = 8.5 Hz, 1H, Benzimidazole C<u>H</u>), 7.44 (dd, *J* = 8.5, 1.8 Hz, 1H, Benzimidazole C<u>H</u>), 7.30 (d, *J* = 7.8 Hz, 2H, Tosyl C<u>H</u>), 7.20 – 7.14 (m, 1H, ArC<u>H</u>=CHCH$_3$), 7.10 (dq, *J* = 15.3, 6.2 Hz, 1H, ArCH=C<u>H</u>CH$_3$), 2.40 (s, 3H, Tosyl C<u>H</u>$_3$), 2.05 (d, *J* = 5.2 Hz, 3H, ArCH=CHC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.6 (Ar<u>C</u>), 146.3 (Ar<u>C</u>), 141.6 (Ar<u>C</u>), 140.4 (ArCH=<u>C</u>HCH$_3$), 135.2 (Ar<u>C</u>), 133.9 (Ar<u>C</u>), 130.4 (Tosyl <u>C</u>H), 128.5 (Benzimidazole <u>C</u>H), 127.0 (Tosyl <u>C</u>H), 120.9 (Benzimidazole <u>C</u>H), 118.2 (Ar<u>C</u>H=CHCH$_3$), 118.1 (Ar<u>C</u>), 117.0 (Benzimidazole <u>C</u>H), 21.8 (Tosyl <u>C</u>H$_3$), 19.3 (ArCH=CH<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 1642, 1597, 1423, 1378, 1166, 1039, 812, 710, 666; **HRMS** (ESI+): calcd. for $C_{17}H_{16}O_2N_2BrS$ $[M+H]^+$ 391.0109 and 393. 0089, found 391.0113 and 393.0091.

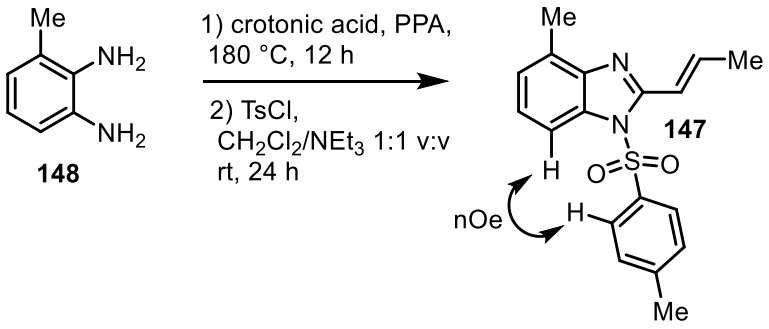
(*E*)-5-Bromo-2-(prop-1-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**145**)



Mp 128 °C (from EtOAc/Petrol); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.8 Hz, 1H, Benzimidazole C<u>H</u>), 7.77 – 7.70 (m, 3H, Benzimidazole C<u>H</u>, Tosyl C<u>H</u>), 7.41 (dd, *J* = 8.8, 1.9 Hz, 1H, Benzimidazole C<u>H</u>), 7.29 – 7.22 (m, 2H, Tosyl C<u>H</u>), 7.21 – 7.12 (m, 1H, ArC<u>H</u>=CHCH$_3$), 7.09 (dq, *J* = 15.3, 5.3 Hz, 1H, ArCH=C<u>H</u>CH$_3$), 2.37 (s, 3H, Tosyl C<u>H$_3$</u>), 2.04 (d, *J* = 5.3 Hz, 3H, ArCH=CHC<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.2 (Ar<u>C</u>), 146.7 (Ar<u>C</u>), 143.9 (Ar<u>C</u>), 140.8 (ArCH=<u>C</u>HCH$_3$), 135.7 (Ar<u>C</u>), 132.0 (Ar<u>C</u>), 130.3 (Tosyl <u>C</u>H), 127.8 5 (Benzimidazole <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 122.7 (Benzimidazole <u>C</u>H), 118.2 (Ar<u>C</u>H=CHCH$_3$), 118.2 (Ar<u>C</u>), 115.7 (Benzimidazole <u>C</u>H), 21.8 (Tosyl <u>C</u>H$_3$), 19.3 (ArCH=CH<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 1644, 1596, 1446, 1379, 1166, 1048, 809, 732, 665; **HRMS** (ESI+): calcd. for $C_{17}H_{16}O_2N_2BrS$ $[M+H]^+$ 391.0109 and 393.0089, found 391.0110 and 393.0089.

5.2.3 Introduction of a 4-Me group (147)

(*E*)-4-methyl-2-(prop-1-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**147**)



To a mixture of crotonic acid (2.68 g, 30.0 mmol) in polyphosphoric acid (12.0 g) was added 3-methylbenzene-1,2-diamine (3.66 g, 30.0 mmol). The reaction was heated at 180 °C for 12 hr. The mixture was cooled down to room temperature and poured carefully onto a saturated solution of $NaHCO_3$. Solid $NaHCO_3$ was added until neutral pH was obtained. The solution was diluted with EtOAc and water then stirred vigorously for 10 min. The aqueous phase was extracted twice with EtOAc and the combined organic phase were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* affording 4.06 g of crude light brown solid.

The crude residue (2.49 g, 14.5 mmol) was dissolved in CH_2Cl_2 (35.0 mL), NEt_3 (35.0 mL) was added then TsCl (3.01 g, 16.0 mmol). The mixture was stirred for 24h at room temperature. The solvent was removed *in vacuo* and the crude was purified by flash chromatography on silica gel (CH_2Cl_2). A subsequent trituration in pentane afforded pure **147** (3.76 g, 11.5 mmol, 79% yield) as a colourless solid.

Mp 178 °C (from CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 1H, Benzimidazole C<u>H</u>), 7.76 (d, *J* = 1.7 Hz, 2H, Tosyl C<u>H</u>), 7.26 – 7.19 (m, 4H, Tosyl C<u>H</u>, Benzimidazole C<u>H</u>), 7.16 – 7.06 (m, 2H C<u>H</u>=C<u>H</u>), 2.59 (s, 3H, Benzimidazole C<u>H</u>$_3$), 2.35 (s, 3H, Tosyl C<u>H</u>$_3$), 2.05 (dd, *J* = 6.8, 1.7 Hz, 3H, CH=CHC<u>H</u>$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.3 (Ar<u>C</u>), 145.7 (Ar<u>C</u>), 141.7 (Ar<u>C</u>), 139.1 (CH=<u>C</u>HMe), 135.5 (Ar<u>C</u>), 132.6 (Ar<u>C</u>), 130.0 (Tosyl <u>C</u>H), 129.9 (Ar<u>C</u>), 126.8 (Tosyl <u>C</u>H), 125.5 (<u>C</u>H=CHMe), 124.6 (Benzimidazole <u>C</u>H), 118.8 (Benzimidazole <u>C</u>H), 111.3 (Benzimidazole <u>C</u>H), 21.6 (Benzimidazole <u>C</u>H$_3$), 19.0 (Tosyl <u>C</u>H$_3$), 16.5 (CH=CH<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2980, 1597, 1517, 1445,

1374, 1339, 1203, 1177, 1161, 1092, 965, 830, 812, 777, 667; **HRMS** (ESI+): calcd. for $C_{18}H_{19}O_2N_2S$ $[M+H]^+$ 327.1162, found 327.1160.

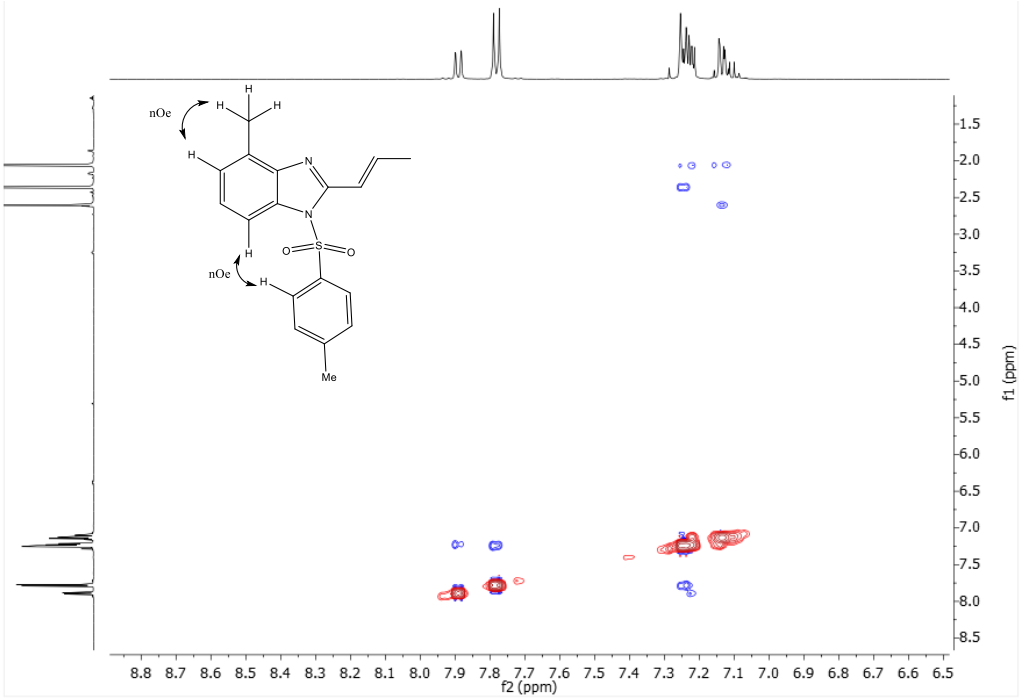
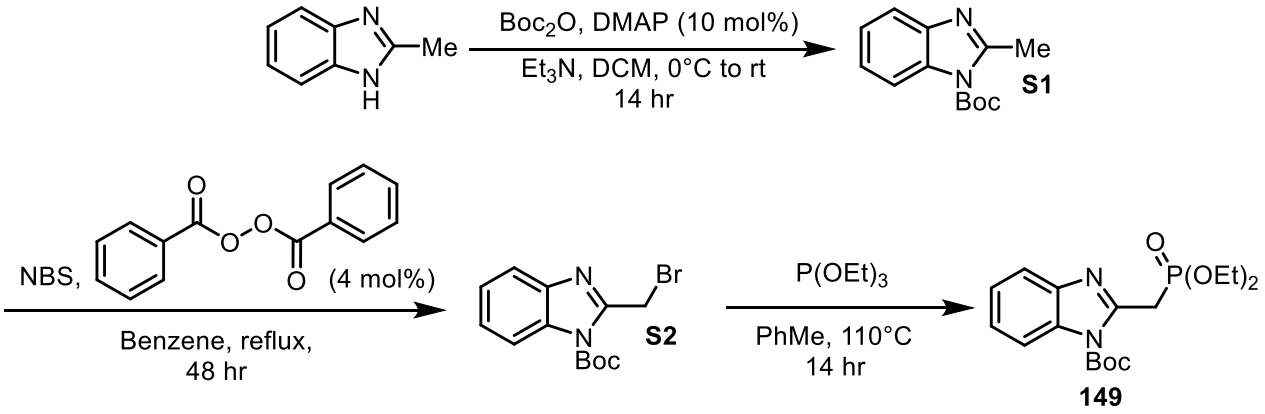


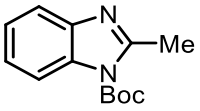
Figure 1. NOESY spectrum for compound **147**.

Other *N*-Ts benzimidazoles Michael acceptors were prepared according the sequence reported below:

tert-butyl 2-((diethoxyphosphoryl)methyl)-1H-benzo[d]imidazole-1-carboxylate (**149**)[8]



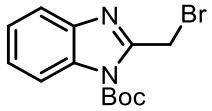
tert-butyl 2-methyl-1H-benzo[d]imidazole-1-carboxylate (**S1**)



2-methyl-1H-benzo[d]imidazole (15.0 g, 113 mmol), and DMAP (1.38 g, 11.2 mmol) were dissolved in CH_2Cl_2 (250.0 mL) and NEt_3 (34.3 mL, 466 mmol) was added. The reaction mixture was then cooled to 0 °C and Boc_2O (49.3 g, 225 mmol) was added. The reaction mixture was then stirred at room temperature for 14 hr and quenched with H_2O (400 mL), extracted with CH_2Cl_2 (2x 400 mL), washed with brine and dried with $MgSO_4$. The organic phase was then concentrated *in vacuo* to 100 mL and cooled to −20 °C to afford **S1** as colourless crystals (22.6 g, 97.2 mmol, 86% yield).

Mp 64 °C (CH_2Cl_2/Pentane); $\mathbf{R_f}$ = 0.7 (CH_2Cl_2:EtOH 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.83 (m, 1H), 7.77 – 7.54 (m, 1H), 7.44 – 7.20 (m, 2H), 2.83 (s, 3H), 1.72 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.6, 137.8, 136.6, 129.5, 123.0, 122.6, 119.4, 115.6, 107.9, 83.6, 28.4, 17.1. Data was consistent with that found in the literature.[8]

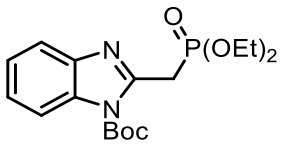
tert-butyl 2-(bromomethyl)-1H-benzo[d]imidazole-1-carboxylate (**S2**)



2-methyl-1H-benzo[d]imidazole (10.4 g, 44.9 mmol), NBS (8.01 g, 45.0 mmol) and benzoyl peroxide (70% in H_2O, 300 mg, 1.23 mmol) were dissolved in benzene (500 mL) and heated to reflux for 48 hr. Solvent was removed *in vacuo* and the resulting crude was purified by flash column chromatography (Pet:EtOAc 9:1 to 3:2) to afford pure **S2** as a pale yellow oil. (4.18 g, 13.4 mmol, 30% yield).

R_f = 0.6 (Petrol:EtOAc 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 2H), 7.76 – 7.68 (m, 2H), 4.95 (s, 2H), 1.75 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.2, 138.0, 136.3, 128.7, 125.6, 123.6, 121.3, 116.3, 112.3, 85.2, 28.5, 28.0; **LRMS** calcd. for $C_{13}H_{15}N_2O_2Na^{79}Br$ $[M+Na]^+$ 333.02, found 333.0. Data was consistent with that found in the literature.[8]

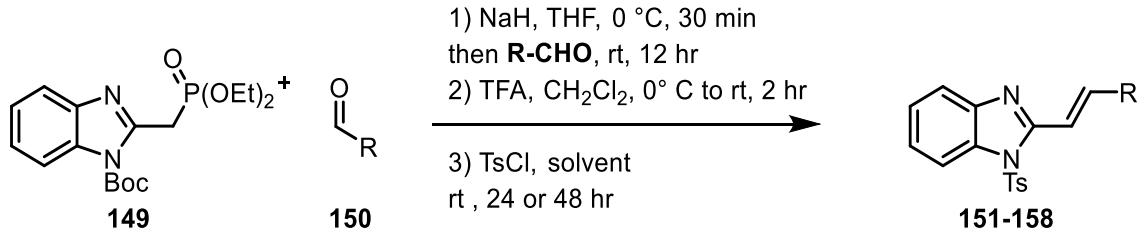
tert-butyl 2-((diethoxyphosphoryl)methyl)-1H-benzo[d]imidazole-1-carboxylate (**149**)



S2 (4.18 g, 13.48 mmol) was dissolved in toluene (135 mL) and $P(OEt)_3$ (3.39 g, 20.4 mmol, 3.50 mL) was added. The reaction mixture was heated to 110 °C for 14 hr. The reaction was then cooled to room temperature and the solvent was removed *in vacuo*. The resulting crude product was purified by by flash column chromatography (Pet:EtOAc 1:1 to 3:7) to afford pure **149** as an orange oil (3.35 g, 9.09 mmol, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.83 (m, 1H), 7.75 – 7.62 (m, 1H), 7.37 – 7.28 (m, 2H), 4.24 – 4.08 (m, 4H), 4.06 (s, 1H), 4.01 (s, 1H), 1.73 (s, 9H), 1.29 (td, *J* = 7.1, 0.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.9, 147.8, 142.2, 133.3, 124.7, 124.3, 119.9, 115.1, 86.1, 62.7 (d, J = 6.5 Hz), 30.7, 29.3, 28.2, 16.5 (d, J = 6.3 Hz); **LRMS** calcd. for $C_{17}H_{25}N_2O_5PNa$ $[M+Na]^+$ 391.14, found 391.2. Data was consistent with that found in the literature.[8]

General procedure I for the synthesis of *N*-Ts precursors (GP I):

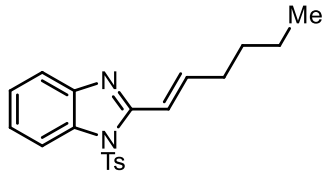


To a solution of *N*-Boc protected benzimidazole **149** (368 mg, 1.00 mmol) in dry THF (12.0 mL) at 0 °C was added portionwise NaH 60% (w/w in oil) (64.0 mg, 1.60 mmol) and stirred under N_2 at 0 °C for 30 min. The corresponding aldehyde (2.00 mmol) was added at 0 °C then the reaction was allowed to warm to room temperature and stirred for 12 hr. The mixture was quenched by adding water and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure.

The residue was taken in dry CH_2Cl_2 (1.00 mL/1.00 mmol) and cooled to 0 °C. TFA (1.00 mL/1.00 mmol) was added and the reaction was stirred at room temperature until TLC shows complete disappearance of the starting material. The mixture was quenched by adding a saturated solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure.

The crude was dissolved in CH_2Cl_2, acetone or DMF (5.00 mL/1.00 mmol), then NEt_3 (2.0 eq) and TsCl (1.2 eq) was added. The mixture was stirred over 48 hr at room temperature then volatiles were removed *in vacuo*. The resulting residue was submitted to a flash chromatography on silica gel or triturated to give the pure product.

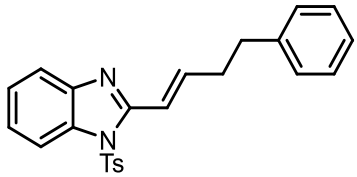
(*E*)-2-(Hex-1-en1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**151**)



151 was synthesized following **GP I** using hexanal (200 mg, 2.00 mmol, 246 μL) as the aldehyde. Acetone was used as a solvent for the *N*-tosylation. Purification by flash chromatography on silica gel (Pentane:Et_2O 8:2) afforded pure **151** as a colourless oil. (156 mg, 0.440 mmol, 50% overall yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.01 (m, 1H, Benzimidazole C<u>H</u>), 7.76 (d, *J* = 8.0 Hz, 2H, Tosyl C<u>H</u>), 7.67 – 7.59 (m, 1H, Benzimidazole C<u>H</u>), 7.36 – 7.28 (m, 2H, Benzimidazole C<u>H</u>), 7.24 (d, *J* = 8.0 Hz, 2H, Tosyl C<u>H</u>), 7.18 (dt, *J* = 15.5, 1.3 Hz, 1H ArC<u>H</u>=CHAlk), 7.07 (dt, *J* = 15.5, 6.9 Hz, 1H, ArCH=C<u>H</u>Alk), 2.40 – 2.32 (s+m, 5H, C<u>H$_2$</u>$CH_2CH_2CH_3$, Tosyl-C<u>H$_3$</u>), 1.58 – 1.48 (m, 2H, CH_2C<u>H$_2$</u>CH_2CH_3), 1.47 – 1.34 (m, 2H, CH_2CH_2C<u>H$_2$</u>CH_3), 0.95 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2CH_2$C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.3 (Ar<u>C</u>), 145.9 (Ar<u>C</u>), 144.8 (ArCH=<u>C</u>HAlk), 142.6 (Ar<u>C</u>), 135.6 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.2 (Tosyl <u>C</u>H), 127.0 (Tosyl <u>C</u>H), 125.1 (Benzimidazole <u>C</u>H), 124.9 (Benzimidazole <u>C</u>H), 119.9 (Benzimidazole <u>C</u>H), 117.3 (Ar<u>C</u>H=CHAlk), 114.0 (Benzimidazole <u>C</u>H), 33.2 (<u>C</u>$H_2CH_2CH_2CH_3$), 30.8 (CH_2<u>C</u>$H_2CH_2CH_3$), 22.4 (CH_2CH_2<u>C</u>H_2CH_3), 21.8 (Tosyl-<u>C</u>H_3), 14.1 ($CH_2CH_2CH_2$<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 2957, 2928, 1640, 1448, 1377, 1169, 1120, 1089, 743, 670; **HRMS** (ESI+): calcd. for $C_{20}H_{23}O_2N_2S$ $[M+H]^+$ 355.1474, found 355.1473.

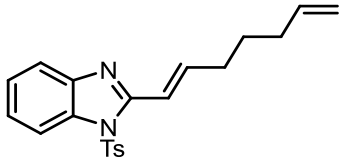
(*E*)-2-(4-Phenylbut-1-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**152**)



152 was synthesized following **GP I** using 3-phenylpropanal (268 mg, 2.00 mmol, 263 μL) as the aldehyde. DMF was used as a solvent for the tosylation. Purification by flash chromatography on silica gel (Pentane:EtOAc 9:1) afforded pure **152** as a yellow solid. (130 mg, 0.322 mmol, 30% overall yield).

Mp 90 °C (from EtOAc/Petrol); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 – 7.98 (m, 1H, Benzimidazole C<u>H</u>), 7.68 (d, *J* = 8.5 Hz, 2H, Tosyl C<u>H</u>), 7.65 – 7.62 (m, 1H, Benzimidazole C<u>H</u>), 7.36 – 7.30 (m, 4H, Benzimidazole C<u>H</u>, Ph-<u>H</u>), 7.28 – 7.24 (m, 3H, Ph-<u>H</u>), 7.23 – 7.19 (m, 3H, Tosyl C<u>H</u>, ArC<u>H</u>=CHAlk), 7.14 (dt, *J* = 15.5, 6.5 Hz, 1H, ArCH=C<u>H</u>Alk), 2.89 (dd, *J* = 8.8, 6.5 Hz, 2H, $CH_2C\underline{H_2}Ph$), 2.75 – 2.68 (m, 2H, $C\underline{H_2}CH_2Ph$), 2.36 (s, 3H, Tosyl $C\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.0 (Ar<u>C</u>), 145.9 (Ar<u>C</u>), 143.3 (ArCH=<u>C</u>HAlk), 142.6 (Ar<u>C</u>), 141.1 (Ar<u>C</u>), 135.4 (Ar<u>C</u>), 133.0 (Ar<u>C</u>), 130.2 (Tosyl <u>C</u>H), 128.6 (Ph-<u>C</u>H), 128.6 (Ph-<u>C</u>H), 126.9 (Tosyl <u>C</u>H), 126.2 (Ph-<u>C</u>H), 125.16 (Benzimidazole <u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 119.9 (Benzimidazole <u>C</u>H), 117.9 (Ar<u>C</u>H=CHAlk), 114.0 (Benzimidazole <u>C</u>H), 34.9 ($CH_2\underline{C}H_2Ph$), 34.9 ($\underline{C}H_2CH_2Ph$), 21.8 (Tosyl-$\underline{C}H_3$); **IR** (film) υ_{max}/cm^{-1}: 3026, 2923, 1641, 1597, 1449, 1377, 1173, 1049, 743, 670; **HRMS** (ESI+): calcd. for $C_{24}H_{23}O_2N_2S$ $[M+H]^+$ 403.1474, found 403.1476.

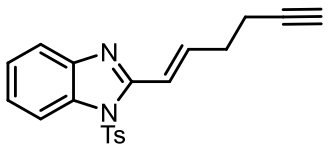
(*E*)-2-(Hepta-1,6-dien-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**153**)



153 was synthesized following **GP I** hex-5-enal (196 mg, 2.00 mmol) as the aldehyde. CH_2Cl_2 was used as a solvent for the *N*-tosylation. Purification by flash chromatography on silica gel (Pentane:EtOAc 9:1) afforded pure **153** as a colourless oil. (310 mg, 0.846 mmol, 44% overall yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.03 (m, 1H, Benzimidazole C<u>H</u>), 7.76 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 7.70 – 7.58 (m, 1H, Benzimidazole C<u>H</u>), 7.39 – 7.29 (m, 2H, Benzimidazole C<u>H</u>), 7.25 (d, *J* = 0.8 Hz, 2H, Tosyl C<u>H</u>), 7.20 (dt, *J* = 15.4, 1.4 Hz, 1H, ArC<u>H</u>=CHAlk), 7.07 (dt, *J* = 15.5, 6.9 Hz, 1H, ArCH=C<u>H</u>Alk), 5.84 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, C<u>H</u>=CH_2), 5.12 – 4.97 (m, 2H, CH=C<u>H_2</u>), 2.45 – 2.38 (m, 2H, ArCH=CHC<u>H_2</u>), 2.36 (s, 3H, Tosyl C<u>H_3</u>), 2.22 – 2.05 (m, 2H, CH_2C<u>H_2</u>CH=CH_2), 1.65 (p, *J* = 7.4 Hz, 2H, C<u>H_2</u>CH_2CH=CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.2 (Ar<u>C</u>), 146.0 (Ar<u>C</u>), 144.3 (ArCH=<u>C</u>HAlk), 142.6 (Ar<u>C</u>), 138.3 (<u>C</u>H=CH_2), 135.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.2 (Tosyl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.2 (Benzimidazole <u>C</u>H), 124.9 (Benzimidazole <u>C</u>H), 119.9 (Benzimidazole <u>C</u>H), 117.6 (Ar<u>C</u>H=CHAlk), 115.2 (CH=<u>C</u>H_2), 114.0 (Benzimidazole <u>C</u>H), 33.4 (CH_2<u>C</u>H_2CH=CH_2), 32.8 (ArCH=CH<u>C</u>H_2), 27.9 (<u>C</u>H_2CH_2CH=CH_2), 21.8 (Tosyl-<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 3076 (CH=CH_2), 2927, 1640, 1448, 1378, 1171, 1049, 919, 744, 670; **HRMS** (ESI+): calcd. for $C_{21}H_{23}O_2N_2S$ $[M+H]^+$ 367.1477, found 367.1474.

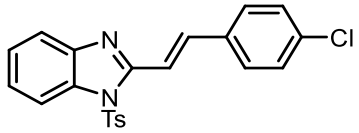
(*E*)-2-(Hex-1-en-5-yn-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**154**)



154 was synthesized following **GP I** using pent-4-ynal (164 mg, 2.00 mmol) as the aldehyde. CH_2Cl_2 was used as a solvent for the *N*-tosylation. Purification by flash chromatography on silica gel (Pentane:EtOAc 8:2) afforded pure **154** as a colourless solid. (170 mg, 0.485 mmol, 26% overall yield).

Mp 104 °C (from EtOAc/Petrol); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 8.01 (m, 1H, Benzimidazole C<u>H</u>), 7.78 (d, *J* = 8.5 Hz, 2H, Tosyl-C<u>H</u>), 7.67 – 7.60 (m, 1H, Benzimidazole C<u>H</u>), 7.35 – 7.27 (m, 3H, Benzimidazole C<u>H</u>, ArC<u>H</u>=CHAlk), 7.23 (d, *J* = 8.5 Hz, 2H, Tosyl-C<u>H</u>), 7.09 (dt, *J* = 15.5, 6.7 Hz, 1H, ArCH=C<u>H</u>Alk), 2.59 (brq, *J* = 6.7 Hz, 2H, C<u>H$_2$</u>CH$_2$CC≡H), 2.44 (td, *J* = 7.1, 2.6 Hz, 2H, CH$_2$C<u>H$_2$</u>CC≡H), 2.34 (s, 3H, Tosyl-C<u>H$_3$</u>), 2.03 (t, *J* =2.6 Hz, 1H, CH$_2$CH$_2$CC≡<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.7 (Ar<u>C</u>), 146.0 (Ar<u>C</u>), 142.5 (Ar<u>C</u>), 141.5 (ArCH=<u>C</u>HAlk), 135.4 (Ar<u>C</u>), 133.0 (Ar<u>C</u>), 130.2 (Tosyl <u>C</u>H), 127.0 (Tosyl <u>C</u>H), 126.9 (Benzimidazole <u>C</u>H), 125.2 (Benzimidazole <u>C</u>H), 125.1 (Benzimidazole <u>C</u>H), 118.6 (Ar<u>C</u>H=CHAlk), 114.0 (Benzimidazole <u>C</u>H), 83.2 (CH$_2$CH$_2$<u>C</u>C≡H), 69.5 (CH$_2$CH$_2$<u>C</u>C≡H), 32.2 (<u>C</u>H$_2$CH$_2$CC≡H), 21.7 (Tosyl-<u>C</u>H$_3$), 18.1 (CH$_2$<u>C</u>H$_2$CC≡H); **IR** (film) υ_{max}/cm^{-1}: 3295 (C≡H), 2920, 1644, 1596, 1448, 1377, 1175, 1049, 744, 669; **HRMS** (ESI+): calcd. for $C_{20}H_{19}O_2N_2S$ $[M+H]^+$ 351.1168, found 351.1159.

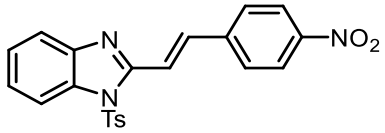
(*E*)-2-(4-Chlorostyryl)-1-tosyl-1*H*-benzo[*d*]imidazole (**155**)



155 was synthesized following **GP I** using 0.68 mmol (250 mg) of *N*-boc protected benzimidazole phosphonate and 4-chlorobenzaldehyde (127 mg, 0.91 mmol) as the aldehyde. CH_2Cl_2:Et_3N 1:1 was used as a solvent for the *N*-tosylation. Purification by flash chromatography on silica gel (pentane to Pentane:EtOAc 4:1) afforded pure **155** as an off-white powder. (168 mg, 0.411 mmol, 61% overall yield).

Mp 168 °C (from EtOAc/Petrol); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 8.02 (m, 1H, Benzimidazole C<u>H</u>), 7.90 (d, *J* = 4.5 Hz, 2H, Tosyl-C<u>H</u>), 7.82 – 7.77 (m, 2H, C<u>H</u>=C<u>H</u>), 7.75 – 7.69 (m, 1H, Benzimidazole C<u>H</u>), 7.64 – 7.58 (m, 2H, Ar-Cl C<u>H</u>), 7.47 – 7.41 (m, 2H, Ar-Cl CH), 7.40 – 7.36 (m, 2H, Benzimidazole C<u>H</u>), 7.25 (d, *J* = 8.1 Hz, 2H, Tosyl-C<u>H</u>), 2.37 (s, 3H, Tosyl-C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.9 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.8 (Ar<u>C</u>), 138.4 (<u>C</u>H=CH), 135.5 (Ar<u>C</u>), 135.4 (Ar<u>C</u>), 134.4 (Ar<u>C</u>), 133.3 (Ar<u>C</u>), 130.3 (Tosyl <u>C</u>H), 129.4 (Ar-Cl <u>C</u>H), 129.0 (Ar-Cl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.5 (Benzimidazole <u>C</u>H), 125.3 (Benzimidazole <u>C</u>H), 120.1 (Benzimidazole <u>C</u>H), 115.1(CH=C<u>H</u>), 114.1 (Benzimidazole <u>C</u>H), 21.8 (Tosyl-<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 3057, 1512, 1490, 1447, 1378, 1344, 1200, 1185, 1168, 1150, 1090, 1051, 1013, 812, 764, 744, 677, 665, 645; **HRMS** (ESI+): calcd. for $C_{22}H_{18}O_2N_2ClS$ $[M+H]^+$ 409.0772, found 409.0770.

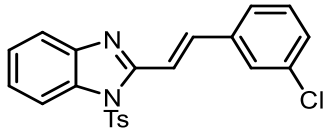
(*E*)-2-(4-Nitrostyryl)-1-tosyl-1*H*-benzo[*d*]imidazole (**156**)



156 was synthesized following **GP I** using 0.60 mmol (220 mg) of *N*-boc protected benzimidazole phosphonate using 4-nitrobenzaldehyde (121 mg, 0.80 mmol) as the aldehyde. CH_2Cl_2:Et_3N 1:1 was used as solvent for the *N*-tosylation. Purification by flash chromatography on silica gel (Pentane:EtOAc 9:1 to Pentane:EtOAc 7:3) afforded pure **156** as a yellow powder. (100 mg, 0.238 mmol, 35% overall yield).

Mp 194 °C (from EtOAc/Petrol); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 – 8.25 (m, 2H, Tosyl-C<u>H</u>), 8.15 – 8.07 (m, 2H, CH=C<u>H</u>, Benzimidazole C<u>H</u>), 7.98 (d, *J* = 15.9 Hz, 1H, C<u>H</u>=CH), 7.83 – 7.77 (m, 4H, Ar-NO_2 C<u>H</u>), 7.77 – 7.70 (m, 1H, Benzimidazole C<u>H</u>), 7.49 – 7.35 (m, 2H, Benzimidazole C<u>H</u>), 7.27 (d, *J* = 7.3 Hz, 2H, Tosyl-C<u>H</u>), 2.38 (s, 3H, Tosyl-C<u>H_3</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.0 (Ar<u>C</u>), 148.1 (Ar<u>C</u>), 146.4 (Ar<u>C</u>), 142.7 (Ar<u>C</u>), 142.1 (Ar<u>C</u>), 136.8 (<u>C</u>H=CH), 135.3 (Ar<u>C</u>), 133.3 (Ar<u>C</u>), 130.4 (Tosyl <u>C</u>H), 128.3 (Ar-NO_2 <u>C</u>H), 126.9 (Ar-NO_2 <u>C</u>H), 125.9 (Benzimidazole <u>C</u>H), 125.7 (Benzimidazole <u>C</u>H), 124.5 (Tosyl <u>C</u>H), 120.4 (Benzimidazole <u>C</u>H), 118.9 (CH=<u>C</u>H), 114.1 (Benzimidazole <u>C</u>H), 21.8 (Tosyl-<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 3078, 1597 (NO_2), 1520, 1377 (NO_2), 1344, 1171, 748, 670; **HRMS** (ESI+): calcd. for $C_{22}H_{18}O_4N_3S$ $[M+H]^+$ 420.1009, found 420.1012.

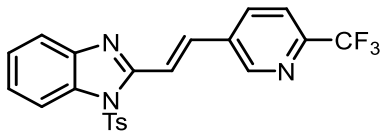
(*E*)-2-(3-Chlorostyryl)-1-tosyl-1*H*-benzo[*d*]imidazole (**157**)



157 was synthesized following **GP I** using 1.09 mmol (400 mg) of *N*-boc protected benzimidazole phosphonate and 3-chlorobenzaldehyde (205 mg, 1.46 mmol). CH_2Cl_2:Et_3N 1:1 was used as a solvent for the *N*-tosylation. Purification by flash chromatography on silica gel (Pentane:EtOAc 8:2) afforded pure **157** as a colourless powder. (186 mg, 0.455 mmol, 42% overall yield).

Mp 126 °C (from EtOAc/Petrol); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 – 8.04 (m, 1H, Benzimidazole C<u>H</u>), 7.92 (d, *J* = 15.9 Hz, 1H, CH=C<u>H</u>), 7.84 (d, *J* = 15.9 Hz, 1H, CH=C<u>H</u>), 7.80 – 7.75 (m, 2H, Tosyl-C<u>H</u>), 7.72 – 7.67 (m, 1H, Benzimidazole C<u>H</u>), 7.62 (q, *J* = 1.4 Hz, 1H, Ar-Cl C<u>H</u>), 7.55 – 7.49 (m, 1H, Benzimidazole C<u>H</u>), 7.41 – 7.32 (m, 4H, Benzimidazole C<u>H</u>, Ar-Cl C<u>H</u>), 7.25 – 7.19 (m, 2H, Tosyl-C<u>H</u>), 2.35 (s, 3H, Tosyl-C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.7 (Ar<u>C</u>), 146.2 (Ar<u>C</u>), 142.8 (Ar<u>C</u>), 138.3 (<u>C</u>H=CH), 137.8 (Ar<u>C</u>), 135.4 (Ar<u>C</u>), 135.1 (Ar<u>C</u>), 133.3 (Ar<u>C</u>), 130.4 (Tosyl <u>C</u>H), 130.3 (Ar-Cl <u>C</u>H), 129.6 (Ar-Cl <u>C</u>H), 127.5 (Ar-Cl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 126.1 (Benzimidazole <u>C</u>H), 125.5 (Benzimidazole <u>C</u>H), 125.4 (Ar-Cl <u>C</u>H), 120.2 (Benzimidazole <u>C</u>H), 116.0 (CH=<u>C</u>H), 114.1 (Benzimidazole <u>C</u>H), 21.8 (Tosyl-<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 3060, 1594, 1511, 1497, 1378, 1343, 1258, 1232, 1201, 1185, 1168, 1150, 1122, 1089, 1052, 782, 764, 744, 702, 690, 671, 645; **HRMS** (ESI+): calcd. for $C_{22}H_{18}O_2N_2ClS$ $[M+H]^+$ 409.0772, found 409.0770.

(*E*)-1-Tosyl-2-(2-(6-(trifluoromethyl)pyridin-3-yl)vinyl)-1*H*-benzo[*d*]imidazole (**158**)

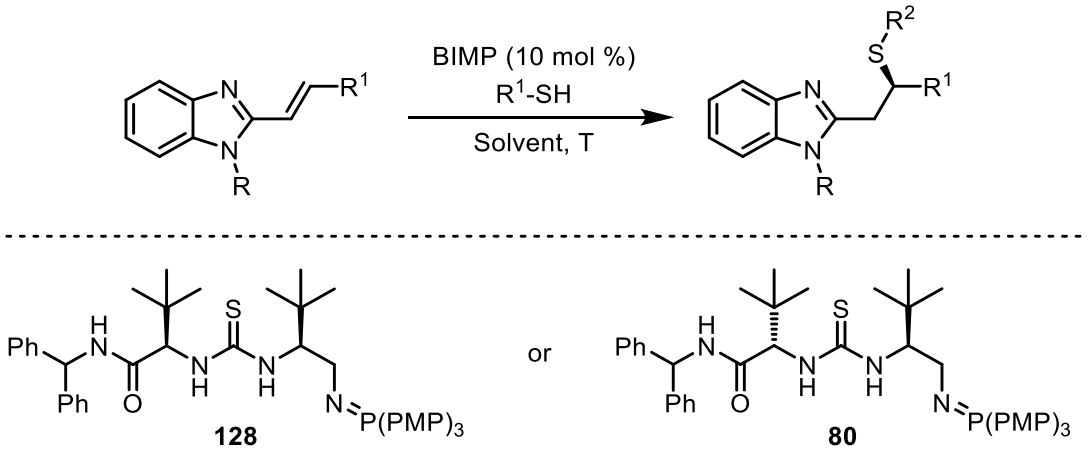


158 was synthesized following **GP I** using 0.68 mmol (250 mg) of *N*-boc protected benzimidazole phosphonate and 6-(trifluoromethyl)nicotinaldehyde (159 mg, 0.91 mmol) as the aldehyde. CH_2Cl_2:Et_3N 1:1 was used as a solvent for the *N*-tosylation. Purification by flash chromatography on silica gel (pentane to Pentane:EtOAc 8:2) afforded pure **158** as an off-white powder. (151 mg, 0.341 mmol 51% overall yield).

Mp 158-160 °C (from EtOAc/Petrol); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 2.1 Hz, 1H, Pyridine C<u>H</u>), 8.16 (dd, *J* = 8.2, 2.2 Hz, 1H, Pyridine C<u>H</u>), 8.13 – 8.06 (m, 2H, Benzimidazole C<u>H</u>, C<u>H</u>=CH), 7.96 (d, *J* = 16.0 Hz, 1H, CH=C<u>H</u>), 7.78 (dd, *J* = 8.3, 4.6 Hz, 3H, Pyridine C<u>H</u>, Tosyl-C<u>H</u>), 7.76 – 7.71 (m, 1H, Benzimidazole C<u>H</u>), 7.47 – 7.37 (m, 2H, Benzimidazole C<u>H</u>), 7.28 (d, *J* = 7.6 Hz, 2H, Tosyl-C<u>H</u>), 2.38 (s, 3H, Tosyl-C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.7 (Ar<u>C</u>), 149.5 (Pyridine <u>C</u>H), 148.3 (q, *J* = 35.2 Hz, <u>C</u>F_3), 146.4 (Ar<u>C</u>), 142.6 (Ar<u>C</u>), 135.3 (Pyridine <u>C</u>H), 135.0 (Ar<u>C</u>), 134.4 (<u>C</u>H=CH), 134.1 (Ar<u>C</u>), 133.3 (Tosyl <u>C</u>H), 130.5 (Pyridine <u>C</u>H), 126.9 (Benzimidazole <u>C</u>H), 126.0 (Benzimidazole <u>C</u>H), 125.7 (Tosyl <u>C</u>H), 120.8 (d, *J* = 2.8 Hz, <u>C</u>CF_3), 120.4 (Benzimidazole <u>C</u>H), 119.1 (CH=<u>C</u>H), 114.1 (Benzimidazole <u>C</u>H), 21.8 (Tosyl-<u>C</u>H_3); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -67.9; **IR** (film) υ_{max}/cm^{-1}: 3062, 1379, 1338, 1171, 1136, 1086, 746, 672; **HRMS** (ESI+): calcd. for $C_{22}H_{17}O_2N_3F_3S$ $[M+H]^+$ 444.0988, found 444.0984.

5.2.4 General Procedures:

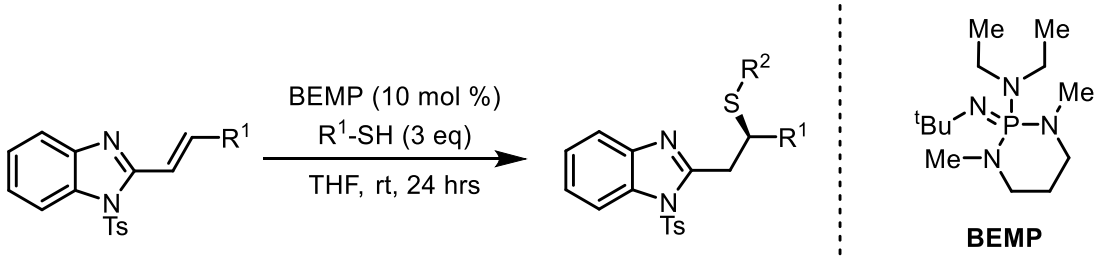
General Procedure for the Thio-1,4 Addition (GP II)



To the corresponding organoazide (0.010 mmol) and tris(4-methoxyphenyl)phosphine (0.010 mmol) under argon atmosphere was added THF (0.20 mL) and the reaction mixture was stirred for 24 hr. The formation of the organocatalysts was monitored by TLC. Upon completion volatiles were removed under a stream of N_2 yielding the expected iminophosphorane which was used without further purification.

To the corresponding Michael acceptor (0.10 mmol) and BIMP organocatalyst (0.01 mmol) under argon atmosphere was added Et_2O (1.60 mL) and thiol (0.12 mmol, 1.2 equivalents) then the reaction was stirred at 0 °C for 24 hr. The reaction mixture was loaded directly onto silica gel and purified by flash column chromatography as specified in the individual experiment to afford pure sulfa-Michael addition product. The two enantiomers were separated by chiral HPLC using conditions specified in the individual experiment.

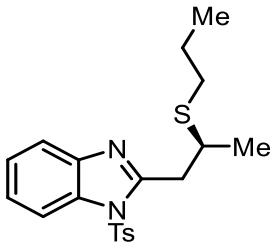
General Procedure for the Synthesis of Racemate 1,4 Addition Products (GP III)



To the corresponding Michael acceptor (0.10 mmol) and 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) (3 μL, 0.010 mmol) under argon was added solvent (0.20 mL) and thiol (0.30 mmol) and the reaction was stirred at room temperature for 24 hr. 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 1,4-addition product. The two enantiomers were separated by chiral HPLC using conditions specified in the individual experiment.

5.2.5 Products: Scope with regards to the thiol nucleophile

(*S*)-2-(2-(Propylthio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**122**)



Compound **122** was synthesized according to **GPII** from **108** (31.2 mg) using catalyst **128** (8.1 mg) and 1-propanethiol (9.1 mg, 11 μL). Clear viscous oil (Petrol:EtOAc 7:3) (38.0 mg, 0.098 mmol, 98% yield, 90% ee).

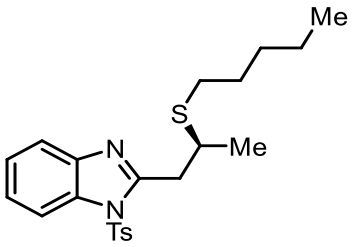
1 mmol scale: To **128** (81.0 mg) in Et_2O (16 mL) at 0 °C was added **108** (312 mg) and 1-propane thiol (91 mg, 110 μL). The reaction was allowed to stir at 0 °C for 24 hr and upon completion of the reaction as judged by TLC the reaction was quenched with 1M aq. AcOH (0.1 mL). Volatiles were removed *in vacuo* and the resulting crude was purified by FCC(Petrol:EtOAc 7:3) affording pure **122** (377 mg, 0.97 mmol, 97% yield, 95.5:4.5 er).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 16.63 min, t (minor) = 18.00 min.

$[\alpha]_D^{25}$ = −2.0 (c = 0.31, $CHCl_3$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.97 (m, 1H, Benzimidazole C<u>H</u>), 7.80 – 7.71 (m, 2H, Tosyl C<u>H</u>), 7.69 – 7.63 (m, 1H, Benzimidazole C<u>H</u>), 7.37 – 7.28 (m, 2H, Benzimidazole C<u>H</u>), 7.27 – 7.18 (m, 2H, Tosyl C<u>H</u>), 3.62 – 3.44 (m, 2H, Ar-C<u>H</u>$_a$H$_b$, C<u>H</u>S), 3.33 – 3.20 (m, 1H, Ar-CH$_a$<u>H</u>$_b$), 2.68 – 2.46 (m, 2H, SC<u>H</u>$_2$CH$_2$CH$_3$), 2.35 (s, 3H, Tosyl C<u>H</u>$_3$), 1.60 (h, *J* = 7.2 Hz, 2H, SCH$_2$C<u>H</u>$_2$CH$_3$), 1.35 – 1.27 (m, 3H, CHC<u>H</u>$_3$), 0.95 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H</u>$_3$); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 152.8 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.1 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.4 (Tosyl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.1 (Benzimidazole <u>C</u>H), 124.9 (Benzimidazole <u>C</u>H), 120.1(Benzimidazole <u>C</u>H), 113.9 (Benzimidazole <u>C</u>H), 38.5 (<u>C</u>HS), 37.9 (Benzimidazole-<u>C</u>H$_2$), 33.0 (S<u>C</u>H$_2$CH$_2$CH$_3$), 23.3 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.8 (Tosyl <u>C</u>H$_3$), 21.3 (CH<u>C</u>H$_3$), 13.7 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2871, 1596,

1481, 1377, 1173, 1189, 765, 667; **HRMS** (ESI +): calcd. for $C_{20}H_{25}O_2N_2S_2$ $[M+H]^+$ 389.1352, Found 389.1352.

(*S*)-2-(2-(Pentylthio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**129**)

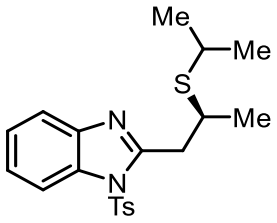


Compound **129** was synthesized according to **GPII** from **108** (31.2 mg) using catalyst **128** (8.1 mg) using pentane-1-thiol (12.5 mg, 15 μL). Clear oil (Petrol:EtOAc 7:3) (32.7 mg, 0.078 mmol, 78% yield, 90% ee)

HPLC Conditions: CHIRALCEL OG, hexane/isopropanol = 97/3, 1 mL/min, λ = 220 nm, t (minor) = 8.48 min, t (major) = 10.33 min.

$[\alpha]_D^{25}$ = −3.7 (c = 0.48, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 7.93 (m, 1H, Benzimidazole C<u>H</u>), 7.82 – 7.71 (m, 2H, Tosyl C<u>H</u>), 7.70 – 7.61 (m, 1H, Benzimidazole C<u>H</u>), 7.39 – 7.29 (m, 2H, Benzimidazole C<u>H</u>), 7.28 – 7.23 (m, 2H, Tosyl C<u>H</u>), 3.66 – 3.42 (m, 2H, Ar-C<u>H</u>$_a$H$_b$, C<u>H</u>S-pentyl), 3.36 – 3.20 (m, 1H, Ar-CH$_a$<u>H</u>$_b$), 2.71 – 2.49 (m, 2H, S-pentylC<u>H</u>$_2$), 2.37 (s, 3H, Tosyl C<u>H</u>$_3$), 1.66 – 1.51 (m, 2H, S-pentyl C<u>H</u>$_2$), 1.41 – 1.20 (m, 7H, CHC<u>H</u>$_3$, S-pentyl C<u>H</u>$_2$C<u>H</u>$_2$), 0.87 (t, *J* = 7.1 Hz, 3H, S-pentyl C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.8 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.1 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.3 (Tosyl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 124.8 (Benzimidazole <u>C</u>H), 120.1(Benzimidazole <u>C</u>H), 113.9 (Benzimidazole <u>C</u>H), 38.5 (<u>C</u>HS-pentyl), 37.9 (Benzimidazole-<u>C</u>H$_2$), 31.3 (S-pentyl <u>C</u>H$_2$), 31.0 (S-pentyl <u>C</u>H$_2$), 29.6 (S-pentyl <u>C</u>H$_2$), 22.4 (S-pentyl <u>C</u>H$_2$), 21.8 (Tosyl <u>C</u>H$_3$), 21.3 (CH<u>C</u>H$_3$), 14.1(S-pentyl <u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2956, 2928, 2859, 1451, 1378, 1172, 1089, 1044, 1014, 745, 703, 667; **HRMS** (ESI +): calcd. for $C_{22}H_{29}O_2N_2S_2$ $[M+H]^+$ 417.1665, Found 417.1663.

(*S*)-2-(2-(Isopropylthio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**130**)

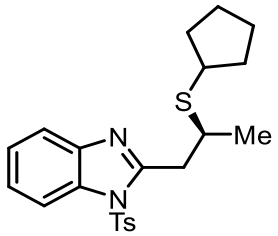


Compound **130** was synthesized according to a modified of **GPII** from **108** (31.2 mg) using catalyst **128** (8.1 mg), propane-2-thiol (9.1 mg, 11 μL) and stirred at room temperature. Clear viscous oil (Petrol:EtOAc 7:3) (29.8 mg, 0.077 mmol, 78% yield, 88% ee)

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 15.60 min, t (minor) = 18.00 min.

$[\alpha]_D^{25}$ = −7.5 (c = 0.58, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 1H, Benzimidazole C<u>H</u>), 7.82 – 7.74 (m, 2H, Tosyl C<u>H</u>), 7.70 – 7.62 (m, 1H, Benzimidazole C<u>H</u>), 7.39 – 7.28 (m, 2H, Benzimidazole C<u>H</u>), 7.26 (dt, *J* = 7.3, 0.8 Hz, 2H, Tosyl C<u>H</u>), 3.66 – 3.55 (m, 1H, C<u>H</u>SCH_3), 3.50 (dd, *J* = 15.4, 5.2 Hz, 1H, Ar-C<u>H_a</u>H_b), 3.34 – 3.24 (m, 1H, Ar-CH_a<u>H_b</u>), 3.04 (p, *J* = 6.7 Hz, 1H, SC<u>H</u>$(CH_3)_2$), 2.36 (s, 3H, Tosyl C<u>H_3</u>), 1.35 – 1.27 (m, 6H, SCH(C<u>H_3</u>$)_2$), 1.24 (d, *J* = 6.7 Hz, 3H, CHC<u>H_3</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.8 (Ar<u>C</u>), 146.1(Ar<u>C</u>), 142.1(Ar<u>C</u>), 135.5(Ar<u>C</u>), 133.1(Ar<u>C</u>), 130.3 (Tosyl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 124.8 (Benzimidazole <u>C</u>H), 120.1 (Benzimidazole <u>C</u>H), 113.9 (Benzimidazole <u>C</u>H), 38.2 (Benzimidazole-<u>C</u>H_2), 37.3 (<u>C</u>HS), 34.5 (S<u>C</u>H$(CH_3)_2$), 24.1 (SCH(<u>C</u>$H_3)_2$), 23.8 (SCH(<u>C</u>$H_3)_2$), 21.8 (Tosyl <u>C</u>H_3), 21.7 (CH<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 2960, 1541, 1337, 1293, 1149, 1089, 745, 667; **HRMS** (ESI +): calcd. for $C_{20}H_{25}O_2N_2S_2$ $[M+H]^+$ 389.1352, Found 389.1352.

(*S*)-2-(2-(Cyclopentylthio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**131**)

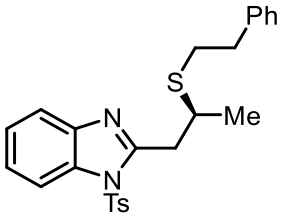


Compound **131** was synthesized according to a modified version of **GPII** from **108** (31.2 mg) using catalyst **128** (8.1 mg), cyclopentanethiol (12.3 mg, 13 μL) and stirred at room temperature. Clear oil (Petrol:EtOAc 7:3) (37.7 mg, 0.091 mmol, 91% yield, 90% ee).

HPLC Conditions: CHIRALCEL OG, hexane/isopropanol = 97/3, 1 mL/min, λ = 220 nm, t (minor) = 10.11 min, t (major) = 11.28 min.

$[\alpha]_D^{25}$ = −6.3 (c = 0.48, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.89 (m, 1H, Benzimidazole C<u>H</u>), 7.76 – 7.67 (m, 2H, Tosyl C<u>H</u>), 7.64 – 7.55 (m, 1H, Benzimidazole C<u>H</u>), 7.31 – 7.22 (m, 2H, Benzimidazole C<u>H</u>), 7.21 – 7.12 (m, 2H, Tosyl C<u>H</u>), 3.60 – 3.44 (m, 2H, Ar-C<u>H$_a$</u>H$_b$, C<u>H</u>SCH), 3.29 – 3.05 (m, 2H, Ar-CH$_a$<u>H$_b$</u>, CHSC<u>H</u>), 2.30 (s, 3H, Tosyl C<u>H$_3$</u>), 2.12 – 1.77 (m, 2H, Cyclopentyl C<u>H$_2$</u>), 1.74 – 1.34 (m, 6H, Cyclopentyl C<u>H$_2$</u>), 1.26 (d, *J* = 6.7 Hz, 3H, CHC<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.9 (Ar<u>C</u>), 146.1(Ar<u>C</u>), 142.0 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.1 (Tosyl <u>C</u>H), 130.3 (Benzimidazole <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 124.8 (Benzimidazole <u>C</u>H), 120.0 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 43.0 (<u>C</u>HSCH), 38.5(CHS<u>C</u>H), 38.1 (<u>CH_2</u>-Ar), 34.6 (Cyclopentyl <u>CH_2</u>), 34.3 (Cyclopentyl <u>CH_2</u>), 24.9 (Cyclopentyl <u>CH_2</u>), 21.8 (Tosyl <u>CH_3</u>), 21.5 (CH<u>CH_3</u>); **IR** (film) υ_{max}/cm^{-1}: 2957, 2960, 1541, 1377, 1293, 1149, 1089, 745, 667; **HRMS** (ESI +): calcd. for $C_{22}H_{27}O_2N_2S_2$ $[M+H]^+$ 415.1508, Found 415.1507.

2-(2-(Phenethylthio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**132**)

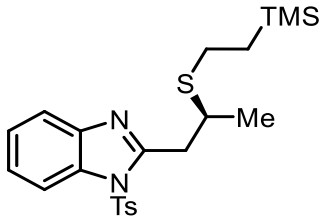


Compound **132** was synthesized according to **GPII** from **108** (31.2 mg) using catalyst **128** (8.1 mg) and 2-phenylethane-1-thiol (16.6 mg, 16 μL). Pale yellow amorphous solid (Petrol:EtOAc 7:3) (42.1 mg, 0.093 mmol, 93% yield, 85% ee)

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 27.01 min, t (major) = 28.93 min.

$[\alpha]_D^{25}$ = +6.9 (c = 0.71, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 8.01 (m, 1H, Benzimidazole C<u>H</u>), 7.78 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 7.73 – 7.66 (m, 1H, Benzimidazole C<u>H</u>), 7.41 – 7.32 (m, 2H, Benzimidazole C<u>H</u>), 7.32 – 7.17 (m, 7H, Tosyl C<u>H</u>, Ph<u>H</u>), 3.70 – 3.51 (m, 2H, Ar-C<u>H$_a$H$_b$</u>, C<u>H</u>S), 3.32 (dd, *J* = 15.2, 8.6 Hz, 1H, Ar-CH$_a$<u>H$_b$</u>), 3.01 – 2.75 (m, 4H, SC<u>H$_2$</u>C<u>H$_2$</u>Ph), 2.38 (s, 3H, Tosyl C<u>H$_3$</u>), 1.38 (d, *J* = 6.7 Hz, 3H, CHC<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.7 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.0 (Ar<u>C</u>), 140.7 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.4 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.8 (Tosyl <u>C</u>H), 126.4 (Ar<u>C</u>H), 125.1 (Benzimidazole <u>C</u>H), 124.9 (Benzimidazole <u>C</u>H), 120.1 (Benzimidazole <u>C</u>H), 113.9 (Benzimidazole <u>C</u>H), 38.7 (<u>C</u>HS), 37.9 (Benzimidazole-<u>C</u>H$_2$), 36.5 (S<u>C</u>H$_2$CH$_2$Ph), 32.4 (SCH$_2$<u>C</u>H$_2$Ph), 21.7 (Tosyl <u>C</u>H$_3$), 21.3 (CH<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2980, 1452, 1378, 1252, 1170, 1045, 668; **HRMS** (ESI +) calcd. for $C_{25}H_{27}O_2N_2S_2$ $[M+H]^+$ 451.1508, Found 451.1505.

(*S*)-1-Tosyl-2-(2-((2-(trimethylsilyl)ethyl)thio)propyl)-1*H*-benzo[*d*]imidazole (**133**)

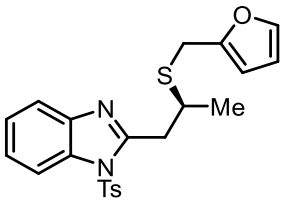


Compound **133** was synthesized according to **GPII** from **108** (31.2 mg) using catalyst **128** (8.1 mg) and 2-(trimethylsilyl)ethane-1-thiol (16.1 mg, 19 μL). Clear oil (Petrol:EtOAc 7:3) (41.3 mg, 0.094 mmol, 94% yield, 92% ee)

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 10.54 min, t (major) = 9.56 min.

$[\alpha]_D^{25}$ =−11.1 (c = 0.82, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 – 7.99 (m, 1H, Benzimidazole C<u>H</u>), 7.84 – 7.77 (m, 2H, Tosyl C<u>H</u>), 7.73 – 7.65 (m, 1H, Benzimidazole C<u>H</u>), 7.41 – 7.32 (m, 2H, Benzimidazole C<u>H</u>), 7.32 – 7.27 (m, 2H, Tosyl C<u>H</u>), 3.69 – 3.50 (m, 2H, SC<u>H</u>, Benzimidazole-<u>H_a</u>H_b), 3.32 (dd, *J* = 15.1, 8.5 Hz, 1H, Benzimidazole-H_a<u>H_b</u>), 2.75 – 2.52 (m, 2H, SC<u>H_2</u>CH_2TMS), 2.40 (s, 3H, Tosyl C<u>H_3</u>), 1.37 (d, *J* = 6.7 Hz, 3H, CHC<u>H_3</u>), 0.99 – 0.77 (m, 2H, SCH_2C<u>H_2</u>TMS), 0.01 (s, 9H, SCH_2CH_2<u>TMS</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.9 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.0 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 130.4 (Tosyl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.1 (Benzimidazole <u>C</u>H), 124.9 (Benzimidazole <u>C</u>H), 120.1 (Benzimidazole <u>C</u>H), 113.9 (Benzimidazole <u>C</u>H), 38.5 (S<u>C</u>H), 38.0 (Benzimidazole-<u>CH_2</u>), 26.7 (S<u>C</u>H_2CH_2TMS), 21.8 (Tosyl <u>C</u>H_3), 21.2 (CH<u>C</u>H_3), 17.4 (SCH_2<u>C</u>H_2TMS), -1.7 Si(<u>C</u>H_3)$_3$; **IR** (film) υ_{max}/cm^{-1}: 2953, 1597, 1542, 1451, 1378, 1248, 1191, 1171, 1149, 1090, 1044, 859, 745, 687, 666; **HRMS** (APCI +) calcd. for $C_{22}H_{31}O_2N_2S_2Si$ $[M+H]^+$ 447.1591, Found 447.1589.

(*S*)-2-(2-((Furan-2-ylmethyl)thio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**134**)

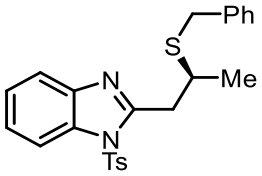


Compound **134** was synthesized according to **GPII** from **108** (31.2 mg) using catalyst **128** (8.1 mg) and furan-2-ylmethanethiol (13.7 mg, 12 μL). Clear oil (Petrol:EtOAc 7:3) (38.7 mg, 0.091 mmol, 91% yield, 78% ee)

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 15.18 min, t (major) = 13.72 min.

$[\alpha]_D^{25}$ = −27.5 (c = 0.83, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 1H, Benzimidazole C<u>H</u>), 7.82 – 7.73 (m, 2H, Tosyl C<u>H</u>), 7.69 – 7.62 (m, 1H, Benzimidazole C<u>H</u>), 7.39 – 7.30 (m, 3H, Benzimidazole C<u>H</u>, Furan C<u>H</u>), 7.29 – 7.22 (m, 2H, Tosyl C<u>H</u>), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H, Furan C<u>H</u>), 6.22 (dd, *J* = 3.2, 0.9 Hz, 1H, Furan C<u>H</u>), 3.90 – 3.77 (m, 2H, Furan-C<u>H$_2$</u>), 3.65 – 3.56 (m, 1H, SC<u>H</u>), 3.55 – 3.46 (m, 1H, Benzimidazole-C<u>H$_a$H$_b$</u>), 3.36 – 3.25 (m, 1H, Benzimidazole-CH$_a$<u>H$_b$</u>), 2.37 (s, 3H, Tosyl C<u>H$_3$</u>), 1.34 (d, *J* = 6.7 Hz, 3H, CHC<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.6 (Ar<u>C</u>), 151.9 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.1 (Furan <u>C</u>H), 142.1 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.4 (Tosyl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.1 (Benzimidazole <u>C</u>H), 124.9 (Benzimidazole <u>C</u>H), 120.1 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 110.6 (Furan <u>C</u>H), 107.5 (Furan <u>C</u>H), 38.9 (S<u>C</u>H), 37.9 (Benzimidazole-<u>C</u>H$_2$), 27.9 (Furan-<u>C</u>H$_2$), 21.8 (Tosyl <u>C</u>H$_3$), 21.1 (CH<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2923, 1596, 1541, 1451, 1376, 1233, 1191, 1170, 1149, 1121, 1089, 1045, 1012, 744, 703, 685, 666, 643; **HRMS** (APCI +) calcd. for $C_{22}H_{23}O_3N_2S_2$ $[M+H]^+$ 427.1144, Found 427.1141.

(*S*)-2-(2-(Benzylthio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**135**)

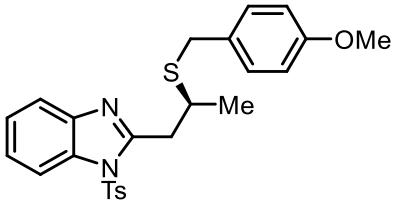


Compound **135** was synthesized according to **GPII** from **108** (31.2 mg) using catalyst **128** (8.1 mg) and phenylmethanethiol (14.9 mg, 14 μL). Clear oil (Petrol:EtOAc 7:3) (41.2 mg, 0.089 mmol, 89% yield, 78% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 24.54 min, t (minor) = 29.98 min.

$[\alpha]_D^{25}$ = −19.5 (c = 0.73, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 1H, Benzimidazole C<u>H</u>), 7.65 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 7.61 – 7.53 (m, 1H, Benzimidazole C<u>H</u>), 7.31 – 7.07 (m, 10H, ArC<u>H</u>), 3.75 (d, *J* = 4.3 Hz, 2H, SC<u>H_2</u>Ph), 3.54 – 3.42 (m, 2H, Benzimidazole-C<u>H_a</u>H_b, C<u>H</u>SCH_2Ph), 3.28 – 3.13 (m, 1H, Benzimidazole-CH_a<u>H_b</u>), 2.28 (s, 3H, Tosyl C<u>H_3</u>), 1.24 (d, *J* = 6.5 Hz, 3H, CHC<u>H_3</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.6 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.0 (Ar<u>C</u>), 138.5 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>H), 130.3 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 126.8 (Tosyl <u>C</u>H), 125.0 (Ar<u>C</u>H), 124.8 (Ar<u>C</u>H), 120.1 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 38.9 (<u>C</u>HSCH_2Ph) ,37.8 (Benzimidazole-<u>C</u>H_2), 35.7 (CHS<u>C</u>H_2Ph), 21.8 (Tosyl <u>C</u>H_3), 21.3 (CH<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 3060, 3028, 2964, 1451, 1376, 1170, 1044, 643; **HRMS** (ESI +) calcd. for $C_{24}H_{25}O_2N_2S_2$ $[M+H]^+$ 437.1352, Found 437.1344.

(*S*)-2-(2-((4-Methoxybenzyl)thio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**136**)

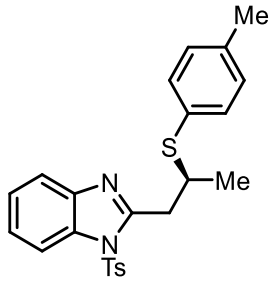


Compound **136** was synthesized according to **GPII** from **108** (31.2 mg) using catalyst **128** (8.1 mg) and (4-methoxyphenyl)methanethiol (18.5 mg, 17 μL). Amorphous colourless solid (Petrol:EtOAc 7:3) (45.5 mg, 0.098 mmol, 98% yield, 86% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (major) = 14.95 min, t (minor) = 18.30 min.

$[\alpha]_D^{25}$ = −19.9 (c = 0.52, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 1H, Benzimidazole C<u>H</u>), 7.80 – 7.71 (m, 2H, Tosyl C<u>H</u>), 7.70 – 7.62 (m, 1H, Benzimidazole C<u>H</u>), 7.40 – 7.29 (m, 2H, Benzimidazole C<u>H</u>), 7.29 – 7.16 (m, 4H, Tosyl C<u>H</u>, PMB C<u>H</u>), 6.85 – 6.76 (m, 2H, PMB C<u>H</u>), 3.78 (d, *J* = 3.4 Hz, 5H, C<u>H_2</u>Ph,OC<u>H_3</u>), 3.60 – 3.47 (m, 2H, Benzimidazole-C<u>H_a</u>H_b, C<u>H</u>SCH_2Ph), 3.36 – 3.20 (m, 1H, Benzimidazole-CH_a<u>H_b</u>), 2.37 (s, 3H, Tosyl C<u>H_3</u>), 1.33 (d, *J* = 6.5 Hz, 3H, CHC<u>H_3</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.6 (Ar<u>C</u>), 152.7 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.1 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.4 (Ar<u>C</u>H), 130.3 (Ar<u>C</u>H), 130.0 (Tosyl <u>C</u>H), 125.1 (Benzimidazole <u>C</u>H), 124.9 (Benzimidazole <u>C</u>H), 120.1 (Benzimidazole <u>C</u>H), 114.0 (PMB <u>C</u>H), 113.9 (Benzimidazole <u>C</u>H), 55.4 (O<u>C</u>H_3), 38.8 (<u>C</u>HSPMB), 37.9 (Benzimidazole-<u>C</u>H_2), 35.1(S<u>C</u>H_2Ph), 21.8 (Tosyl <u>C</u>H_3), 21.3 (CH<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 3023, 1541, 1500, 1451, 1376, 1171, 1013, 884, 668; **HRMS** (ESI+) calcd. for $C_{25}H_{27}O_3N_2S_2$ [M+H]+ 467.1457, Found 467.1454.

(*S*)-2-(2-(*p*-tolylthio)propyl)-1-tosyl-1H-benzo[d]imidazole (**137**)



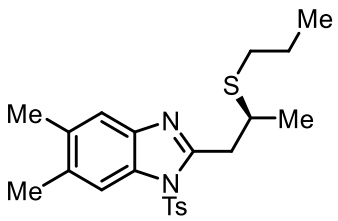
Compound **137** was synthesized according to a modified version of **GPII** from **108** (31.2 mg) using catalyst **128** (8.1 mg) and stirred at 0 °C. Clear Oil (Petrol:EtOAc 7:3) (38.1 mg, 0.085 mmol, 85% yield, 38% ee).

HPLC Conditions: CHIRALCEL AS-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 12.80 min, t (major) = 14.10 min.

$[\alpha]_D^{25}$ = −7.5 (c = 0.39, $CHCl_3$); **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.09 – 7.97 (m, 1H, Benzimidazole C<u>H</u>), 7.70 – 7.62 (m, 3H, Benzimidazole C<u>H</u>, Tosyl C<u>H</u>), 7.45 – 7.39 (m, 2H, ArC<u>H</u>), 7.38 – 7.30 (m, 2H, Benzimidazole C<u>H</u>), 7.26 – 7.16 (m, 2H, Tosyl C<u>H</u>), 7.16 – 7.06 (m, 2H, ArC<u>H</u>), 3.98 (ddd, *J* = 9.2, 6.8, 5.3 Hz, 1H, SC<u>H</u>), 3.45 (dd, *J* = 15.9, 5.3 Hz, 1H, Benzimidazole C<u>H$_a$</u>H$_b$), 3.31 (dd, *J* = 15.9, 9.1 Hz, 1H, Benzimidazole CH$_a$<u>H$_b$</u>), 2.39 (s, 3H, Tosyl C<u>H$_3$</u>), 2.35 (s, 3H, ArC<u>H$_3$</u>), 1.36 (d, *J* = 6.7 Hz, 3H, SCHC<u>H$_3$</u>); **^{13}C NMR** (101 MHz, Chloroform-d) δ 152.6 (Ar<u>C</u>), 146.0 (Ar<u>C</u>), 142.0 (Ar<u>C</u>), 137.6 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.7 (Ar<u>C</u>H), 133.2 (Ar<u>C</u>), 130.3 (Tosyl <u>C</u>H), 129.7 (Ar<u>C</u>H) , 126.8 (Tosyl <u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 124.8 (Benzimidazole <u>C</u>H), 120.0 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 41.8 (S<u>C</u>H), 37.5 (Benzimidazole <u>C</u>H$_2$), 21.8 (Tosyl <u>C</u>H$_3$), 21.3 (Ar<u>C</u>H$_3$), 20.6 (SCH<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2964, 2923, 1597, 1541, 1492, 1451, 1377, 1233, 1190, 1172, 1148, 1121, 1089, 1045, 1015, 811, 745, 686, 666; **HRMS** (APCI +) Mass Calculated for $C_{24}H_{25}O_2N_2S_2$ $[M+H]^+$ 437.1352, Found 437.1348.

5.2.6 Products: Scope with regards to the benzimidazole

(*S*)-2-(2-(Propylthio)hept-6-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**159**)

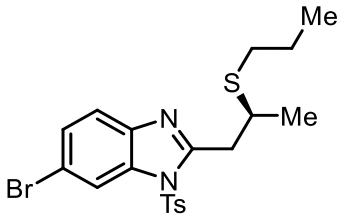


Compound **159** was synthesized according to **GP II** from **140** (34.0 mg) using catalyst **128** (8.1 mg), 1-propanethiol (9.1 mg, 11 μL). Clear oil (Pentane:EtOAc 9:1) (33.7 mg, 0.081 mmol, 81% yield, 72% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 22.89 min, t (major) = 21.24 min.

$[\alpha]_D^{25}$ = −3.5 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (s, 1H, Benzimidazole C<u>H</u>), 7.75 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 7.41 (d, *J* = 0.9 Hz, 1H, Benzimidazole C<u>H</u>), 7.26 (dd, *J* = 8.5, 1.0 Hz, 2H, Tosyl C<u>H</u>), 3.56 – 3.44 (m, 2H, SC<u>H</u>, Benzimidazole C<u>H$_a$</u>H$_b$), 3.27 – 3.18 (m, 1H, Benzimidazole CH$_a$<u>H$_b$</u>), 2.63 – 2.48 (m, 2H, SC<u>H$_2$</u>CH$_2$CH$_3$), 2.38 (s, 3H, Benzimidazole-C<u>H$_3$</u>), 2.37 (s, 3H, Benzimidazole-C<u>H$_3$</u>), 2.32 (s, 3H, Tosyl C<u>H$_3$</u>), 1.67 – 1.53 (m, 2H, SCH$_2$C<u>H$_2$</u>CH$_3$), 1.30 (d, *J* = 6.8 Hz, 3H, CHC<u>H$_3$</u>), 0.97 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.0 (Ar<u>C</u>), 145.9 (Ar<u>C</u>), 140.5 (Ar<u>C</u>), 135.8 (Ar<u>C</u>), 134.3 (Ar<u>C</u>), 133.8 (Ar<u>C</u>), 131.6 (Ar<u>C</u>), 130.3 (Tosyl <u>C</u>H), 126.7 (Tosyl <u>C</u>H), 120.2 (Benzimidazole <u>C</u>H), 114.1 (Benzimidazole <u>C</u>H), 38.5 (S<u>C</u>H), 37.9 (Benzimidazole <u>C</u>H$_2$), 33.0 (S<u>C</u>H$_2$CH$_2$CH$_3$), 23.3 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.7 (Benzimidazole-<u>C</u>H$_3$), 21.2 (CH<u>C</u>H$_3$), 20.8 (Benzimidazole-<u>C</u>H$_3$), 20.3 (Tosyl <u>C</u>H$_3$), 13.7 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2962, 2925, 1596, 1463, 1375, 1230, 1190, 1172, 1090, 1037, 811, 667; **HRMS** (ESI+): calcd. for $C_{22}H_{29}O_2N_2S_2$ $[M+H]^+$ 417.1665, found 417.1663.

(*S*)-6-Bromo-2-(2-(propylthio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**160**)

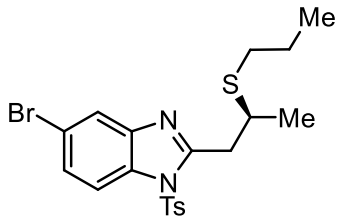


Compound **160** was synthesized according to **GP II** from **144** (39.1 mg) using catalyst **128** (8.1 mg), 1-propanethiol (9.1 mg, 11 μL). Clear oil (Pentane:EtOAc 95:5) (36.0 mg, 0.077 mmol, 77% yield, 72% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 17.65 min, t (major) = 15.93 min.

$[\alpha]_D^{25}$ = −5.9 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 1.8 Hz, 1H, NTsCC<u>H</u>CBr), 7.78 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 7.52 (d, *J* = 8.6 Hz, 1H, CBrCHC<u>H</u>CN), 7.44 (dd, *J* = 8.5, 1.8 Hz, 1H, CBrC<u>H</u>CHCN), 7.31 (d, *J* = 7.8 Hz, 2H, Tosyl C<u>H</u>), 3.57 – 3.41 (m, 2H, SC<u>H</u>, Benzimidazole C<u>H$_a$</u>H$_b$), 3.24 (dd, *J* = 15.4, 8.5 Hz, 1H, Benzimidazole CH$_a$<u>H$_b$</u>), 2.62 – 2.49 (m, 2H, SC<u>H$_2$</u>CH$_2$CH$_3$), 2.40 (s, 3H, Tosyl C<u>H$_3$</u>), 1.61 (h, *J* = 7.3 Hz, 2H, SCH$_2$C<u>H$_2$</u>CH$_3$), 1.32 (d, *J* = 6.5 Hz, 3H, CHC<u>H$_3$</u>), 0.97 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5 (Ar<u>C</u>), 146.5 (Ar<u>C</u>), 141.1 (Ar<u>C</u>), 135.3 (Ar<u>C</u>), 134.1 (Ar<u>C</u>), 130.5 (Tosyl <u>C</u>H), 128.3 (CBr<u>C</u>HCHCN), 127.0 (Tosyl <u>C</u>H), 121.2 (CBrCH<u>C</u>HCN), 118.5 (<u>C</u>Br), 117.0 (NTs<u>C</u>HCBr), 38.4 (S<u>C</u>H), 37.9 (Benzimidazole <u>C</u>H$_2$), 33.0 (S<u>C</u>H$_2$CH$_2$CH$_3$), 23.3 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.9 (Tosyl <u>C</u>H$_3$), 21.4 (CH<u>C</u>H$_3$), 13.7 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2961, 2926, 1730, 1596, 1447, 1424, 1379, 1269, 1191, 1162, 1089, 1037, 939, 813, 708, 664; **HRMS** (ESI+): calcd. for $C_{20}H_{24}O_2N_2BrS_2$ $[M+H]^+$ 467.0457 and 469.0436, found. 467.04565 and 469.0433.

(*S*)-5-Bromo-2-(2-(propylthio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**161**)

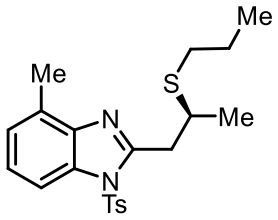


Compound **161** was synthesized according to **GP II** from **145** (39.1 mg) using catalyst **128** (8.1 mg), 1-propanethiol (9.1 mg, 11 μL). Clear oil (Pentane:EtOAc 95:5) (38.8 mg, 0.083 mmol, 81% yield, 68% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 19.17 min, t (major) = 20.44 min.

$[\alpha]_D^{25}$ = −4.4 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.7 Hz, 1H, C<u>H</u>CNTs), 7.80 (d, *J* = 1.9 Hz, 1H, NCC<u>H</u>CBr), 7.75 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 7.45 (dd, *J* = 8.8, 1.9 Hz, 1H, CBrC<u>H</u>CHCNTs), 7.32 – 7.25 (m, 2H, Tosyl C<u>H</u>), 3.57 – 3.43 (m, 2H, SC<u>H</u>, Benzimidazole C<u>H$_a$H$_b$</u>), 3.32 – 3.20 (m, 1H, Benzimidazole CH$_a$<u>H$_b$</u>), 2.64 – 2.47 (m, 2H, SC<u>H$_2$</u>CH$_2$CH$_3$), 2.39 (s, 3H, Tosyl C<u>H$_3$</u>), 1.68 – 1.54 (m, 2H, SCH$_2$C<u>H$_2$</u>CH$_3$), 1.33 (d, *J* = 6.8 Hz, 3H, CHC<u>H$_3$</u>), 0.97 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.1 (Ar<u>C</u>), 146.5 (Ar<u>C</u>), 143.4 (Ar<u>C</u>), 135.3(Ar<u>C</u>), 132.2 (Ar<u>C</u>), 130.5 (Tosyl <u>C</u>H), 128.0 (CBr<u>C</u>HCHCNTs), 126.9 (Tosyl <u>C</u>H), 123.1 (NC<u>C</u>HCBr), 118.0 (CBr), 115.1 (CBrCH<u>C</u>HCNTs), 38.4 (S<u>C</u>H), 37.9 (Benzimidazole <u>C</u>H$_2$), 33.0 (S<u>C</u>H$_2$CH$_2$CH$_3$), 23.3 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.8 (Tosyl <u>C</u>H$_3$), 21.4 (CH<u>C</u>H$_3$), 13.7 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2921, 2926, 1596, 1535, 1448, 1379, 1230, 1172, 1089, 1044, 910, 809, 705, 665; **HRMS** (ESI+): calcd. for $C_{20}H_{24}O_2N_2BrS_2$ $[M+H]^+$ 467.0457 and 469.0436, found 467.0454 and 469.0431.

4-methyl-2-(2-(propylthio)propyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**162**)

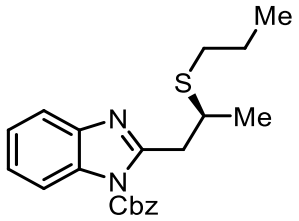


Compound **162** was synthesized according to a modified version of **GPII** from **147** (31.2 mg) using catalyst **128** (8.1 mg), 3 equivalents of 1-propanethiol (22.8 mg, 0.30 mmol, 28 μL) and stirred at room temperature in 0.60 mL of THF. Clear viscous oil (7:3 Petrol:EtOAc) (24.1 mg, 0.060 mmol, 60% yield, 0% ee).

HPLC Condtitions: CHIRALPAK IC, hexane/isopropanol = 99/1, 1 mL/min, λ = 220 nm, t (major) = 16.69 min, t (minor) = 19.91 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dt, *J* = 8.2, 0.9 Hz, 1H, Benzimidazole C<u>H</u>), 7.80 – 7.72 (m, 2H, Tosyl C<u>H</u>), 7.29 – 7.23 (m, 2H, Tosyl C<u>H</u>), 7.21 (d, *J* = 7.9 Hz, 1H, Benzimidazole C<u>H</u>), 7.12 (dt, *J* = 7.5, 1.0 Hz, 1H, Benzimidazole C<u>H</u>), 3.65 – 3.47 (m, 2H, SC<u>H</u>, Benzimidazole C<u>H$_a$</u>H$_b$), 3.34 – 3.22 (m, 1H, Benzimidazole CH$_a$<u>H$_b$</u>), 2.67 – 2.48 (s + m, 5H, Benzimidazole C<u>H$_3$</u>, SC<u>H$_2$</u>CH$_2$CH$_3$), 2.37 (s, 3H, Tosyl C<u>H$_3$</u>), 1.63 (h, *J* = 7.2 Hz, 2H, SCH$_2$C<u>H$_2$</u>CH$_3$), 1.35 (d, *J* = 6.6 Hz, 3H, SCHC<u>H$_3$</u>), 0.97 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.0 (Ar<u>C</u>), 145.9 (Ar<u>C</u>), 141.3 (Ar<u>C</u>), 135.8 (Ar<u>C</u>), 132.9 (Ar<u>C</u>), 130.3 (Tosyl <u>C</u>H), 130.2 (Ar<u>C</u>), 126.9 (Tosyl <u>C</u>H), 125.4 (Benzimidazole <u>C</u>H), 124.8 (Benzimidazole <u>C</u>H), 111.3 (Benzimidazole <u>C</u>H), 38.6 (S<u>C</u>H), 38.1 (Benzimidazole <u>C</u>H$_2$), 33.0 (S<u>C</u>H$_2$CH$_2$CH$_3$), 23.3 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.8 (Benzimidazole <u>C</u>H$_3$), 21.4 (SCH<u>C</u>H$_3$), 16.6 (Tosyl <u>C</u>H$_3$), 13.7 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2962, 2925, 2871, 1374, 1190, 1186, 1103, 1012, 812, 778, 766, 703, 678, 648; **HRMS** (ESI+): calcd. for $C_{21}H_{27}O_2N_2S_2$ $[M+H]^+$ 403.1509, found 403.1506.

Benzyl-2-(2-(propylthio)propyl)-1*H*-benzo[*d*]imidazole-1-carboxylate (**163**)

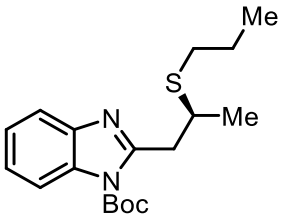


Compound **163** was synthesized according to a modified version of **GPII** from **141** (29.2 mg) using catalyst **128** (8.1 mg), 3 equivalents of 1-propanethiol (22.8 mg, 0.30 mmol, 28 μL) and stirred at room temperature. Clear oil (Petrol:EtOAc 9:1) (22.3 mg, 0.061 mmol, 61% yield, 85% ee).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 97/3, 1 mL/min, λ = 220 nm, t (minor) = 10.23 min, t (major) = 11.45 min.

$[\alpha]_D^{25}$ = +2.0 (c = 0.40, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 1H, Benzimidazole C<u>H</u>), 7.75 – 7.65 (m, 1H, Benzimidazole C<u>H</u>), 7.55 – 7.49 (m, 2H, Ph<u>H</u>), 7.47 – 7.38 (m, 3H, Ph<u>H</u>), 7.35 – 7.25 (m, 2H, Benzimidazole C<u>H</u>), 5.51 (d, *J* = 1.0 Hz, 2H, C<u>H</u>$_2$Ph), 3.63 (dd, *J* = 14.6, 5.3 Hz, 1H, Benzimidazole-C<u>H</u>$_a$H$_b$), 3.47 – 3.36 (m, 1H,C<u>H</u>S), 3.31 (dd, *J* = 14.6, 8.8 Hz, 1H, Benzimidazole-CH$_a$<u>H</u>$_b$), 2.67 – 2.44 (m, 2H, SC<u>H</u>$_2$CH$_2$CH$_3$), 1.59 (h, *J* = 7.4 Hz, 2H, SCH$_2$C<u>H</u>$_2$CH$_3$), 1.34 (d, *J* = 6.7 Hz, 3H, CHC<u>H</u>$_3$), 0.96 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.3 (<u>C</u>(=O)), 150.5 (Ar<u>C</u>), 142.3 (Ar<u>C</u>), 134.3 (Ar<u>C</u>), 132.8 (Ar<u>C</u>), 129.3 (Phenyl <u>C</u>H), 129.1 (Phenyl <u>C</u>H), 129.0 (Phenyl <u>C</u>H), 124.8 (Benzimidazole <u>C</u>H), 124.6 (Benzimidazole <u>C</u>H), 119.9 (Benzimidazole <u>C</u>H), 115.2 (Benzimidazole <u>C</u>H), 69.8 (O<u>C</u>H$_2$Ph), 38.9 (Benzimidazole-<u>C</u>H$_2$), 38.2 (<u>C</u>HS), 32.7 (S<u>C</u>H$_2$CH$_2$CH$_3$), 23.3 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.4 (CH<u>C</u>H$_3$), 13.7 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2964, 1749, 1455, 1385, 1338, 1296, 1258, 1194, 1088, 1081, 746; **HRMS** (ESI +) calcd. for $C_{21}H_{25}O_2N_2S$ $[M+H]^+$ 369.1631, Found 369.1626.

tert-butyl-2-(2-(propylthio)propyl)-1*H*-benzo[*d*]imidazole-1-carboxylate (**164**)

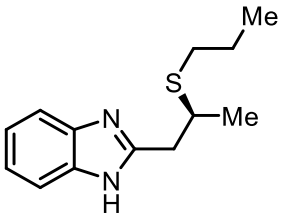


Compound **164** was synthesized according to a modified version of **GPII** from **142** (25.8 mg) using catalyst **128** (8.1 mg), 3 equivalents of 1-propanethiol (22.8 mg, 0.30 mmol, 28 μL) and stirred at room temperature. Clear oil (Pentane:EtOAc 8:2) (32.7 mg, 0.097 mmol, 97% yield, 83% ee)

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 97/3, 1 mL/min, λ = 220 nm, t (major) = 7.30 min, t (minor) = 6.61 min.

$[\alpha]_D^{25}$ = −3.6 (c = 0.43, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.85 (m, 1H, Benzimidazole C<u>H</u>), 7.75 – 7.61 (m, 1H, Benzimidazole C<u>H</u>), 7.35 – 7.27 (m, 2H, Benzimidazole C<u>H</u>), 3.64 (dd, *J* = 14.7, 5.3 Hz, 1H, Benzimidazole-C<u>H</u>$_a$H$_b$), 3.43 (ddd, *J* = 9.0, 6.8, 5.3 Hz, 1H, C<u>H</u>S), 3.30 (dd, *J* = 14.7, 9.0 Hz, 1H, Benzimidazole-CH$_a$<u>H</u>$_b$), 2.66 – 2.46 (m, 2H, SC<u>H</u>$_2$CH$_2$CH$_3$), 1.72 (s, 9H, C(C<u>H</u>$_3$)$_3$), 1.60 (dt, *J* = 14.7, 7.4 Hz, 2H, (SCH$_2$<u>C</u>H$_2$CH$_3$), 1.37 (d, *J* = 6.7 Hz, 3H, CHC<u>H</u>$_3$), 0.97 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$<u>C</u>H$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.4 (<u>C</u>(=O)O), 149.1 (Ar<u>C</u>), 142.2 (Ar<u>C</u>), 137.7 (Ar<u>C</u>), 124.4 (ArC<u>H</u>), 124.2 (ArC<u>H</u>), 119.8 (ArC<u>H</u>), 115.1 (ArC<u>H</u>), 85.7 (O<u>C</u>(CH$_3$)$_3$), 38.9 (Ar-CH$_2$), 38.1 (C<u>H</u>S), 32.6 (S<u>C</u>H$_2$CH$_2$CH$_3$), 28.2 (OC(C<u>H</u>$_3$)$_3$, 23.3(SCH$_2$<u>C</u>H$_2$CH$_3$), 21.3(CH<u>C</u>H$_3$), 13.7 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2970, 1745, 1454, 1341, 1153, 1120, 745; **HRMS** (ESI +) calcd. for $C_{18}H_{27}O_2N_2S$ $[M+H]^+$ 335.1787, Found 335.1787.

(*S*)-2-(2-(propylthio)propyl)-1H-benzo[d]imidazole (**165**)

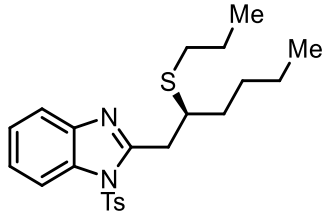


Compound **165** was synthesized according to a modified version of **GPII** from **143** (15.8 mg) using catalyst **128** (8.1 mg), 3 equivalents of 1-propanethiol (22.8 mg, 0.30 mmol, 28 μL) in THF (0.20 mL) and stirred at room temperature. Clear oil (EtOAc) (14.5 mg, 0.061 mmol, 61% yield, 6% ee)

HPLC Conditions: CHIRALCEL OD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 33.17 min, t (major) = 41.12 min.

^{1}H NMR (400 MHz, CD_3OD) δ =7.48 (dd, *J* = 6.1, 3.2 Hz, 2H, Benzimidazole C<u>H</u>), 7.18 (dd, *J* = 6.1, 3.2 Hz, 2H, Benzimidazole C<u>H</u>), 4.87 (s, 1H, N<u>H</u>), 3.34 – 3.23 (m, 1H, SC<u>H</u>), 3.14 (dd, *J* = 14.3, 6.7 Hz, 1H, Benzimidazole-C<u>H$_a$</u>H$_b$), 2.97 (dd, *J* = 14.4, 8.0 Hz, 1H, Benzimidazole-CH$_a$<u>H$_b$</u>), 2.48 (td, *J* = 7.2, 3.5 Hz, 2H, SC<u>H$_2$</u>CH$_2$CH$_3$), 1.55 (h, *J* = 7.3 Hz, 2H, SCH$_2$C<u>H$_2$</u>CH$_3$), 1.27 (d, *J* = 6.8 Hz, 3H, CHC<u>H$_3$</u>), 0.91 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, CD_3OD) δ 152.4 (Ar<u>C</u>), 121.3 (Benzimidazole <u>C</u>H), 113.4 (Benzimidazole <u>C</u>H), 38.2 (S<u>C</u>H), 36.2 (Benzimidazole-<u>C</u>H$_2$), 31.6 (S<u>C</u>H$_2$CH$_2$CH$_3$), 22.1 (SCH$_2$<u>C</u>H$_2$CH$_3$), 19.8 (CH<u>C</u>H$_3$), 11.7 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 3054, 2959, 2869, 1538, 1453, 1437, 1376, 1272, 1026, 742; **HRMS** (ESI+): calcd. for $C_{13}H_{19}N_2S$ $[M+H]^+$ 235.1263, found 235.1263.

(*S*)-2-(2-(Propylthio)hexyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**166**)

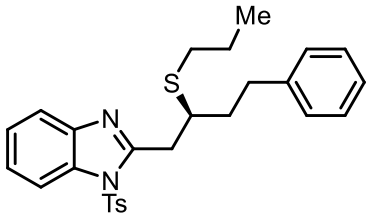


Compound **166** was synthesized according to **GP II** from **151** (35.5 mg) using catalyst **128** (8.1 mg)**,** 1-propanethiol (9.1 mg, 11 μL). Clear oil (Pentane:EtOAc 7:3) (35.7 mg, 0.083 mmol, 83% yield, 86% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 13.39 min, t (major) = 22.26 min.

$[\alpha]_D^{25}$ = −14.9 (c = 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.98 (m, 1H, Benzimidazole C<u>H</u>), 7.78 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 7.70 – 7.64 (m, 1H, Benzimidazole C<u>H</u>), 7.41 – 7.30 (m, 2H, Benzimidazole C<u>H</u>), 7.27 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 3.55 – 3.31 (m, 3H, Benzimidazole-C<u>H_2</u>, SC<u>H</u>), 2.58 – 2.42 (m, 2H,SC<u>H_2</u>CH_2CH_3), 2.38 (s, 3H, Tosyl C<u>H_3</u>), 1.66 – 1.49 (m, 4H, SCH_2C<u>H_2</u>CH_3, C<u>H_2</u>$CH_2CH_2CH_3$), 1.38 – 1.22 (m, 4H, CH_2C<u>H_2</u>C<u>H_2</u>CH_3), 0.93 (t, *J* = 7.3 Hz, 3H, SCH_2CH_2C<u>H_3</u>), 0.86 (t, *J* = 7.2 Hz, 3H, $CH_2CH_2CH_2C$<u>H_3</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.1 (Ar<u>C</u>), 135.7 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 130.3 (Tosyl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 124.8 (Benzimidazole <u>C</u>H), 120.1 (Benzimidazole <u>C</u>H), 113.9 (Benzimidazole <u>C</u>H), 44.3 (S<u>C</u>H), 36.9 (Benzimidazole-<u>$C H_2$</u>), 34.5 (SCH_2<u>C</u>H_2CH_3), 33.1 (S<u>C</u>$H_2CH_2CH_3$), 29.0 (<u>C</u>$H_2CH_2CH_2$), 23.3 (CH_2<u>C</u>H_2CH_2), 22.7 (CH_2CH_2<u>C</u>H_2), 21.8 (Tosyl <u>C</u>H_3), 14.2 (SCH_2CH_2<u>C</u>H_3), 13.7 ($CH_2CH_2CH_2$<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 2958, 2928, 2871, 1451, 1377, 1237, 1189, 1177, 1148, 1120, 1089, 1045, 1014, 812, 765, 745, 703, 666, 623; **HRMS** (ESI+): calcd. for $C_{23}H_{31}O_2N_2S_2$ $[M+H]^+$ 431.1820, found 431.1821.

(*S*)-2-(4-Phenyl-2-(propylthio)butyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**167**)

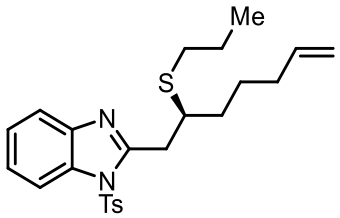


Compound **167** was synthesized according to **GP II** from **152** (40.3 mg) using catalyst **128** (8.1 mg), 1-propanethiol (9.1 mg, 11 μL). Clear oil (Pentane:EtOAc 7:3) (43.3 mg, 0.090 mmol, 90% yield, 92% ee).

HPLC Conditions: CHIRALCEL OG, hexane/isopropanol = 97/3, 1 mL/min, λ = 220 nm, t (minor) = 13.04 min, t (major) = 15.69 min.

$[\alpha]_D^{25}$ = −9.1 (c = 1.12, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 – 8.00 (m, 1H, Benzimidazole C<u>H</u>), 7.84 – 7.76 (m, 2H, Tosyl C<u>H</u>), 7.74 – 7.64 (m, 1H, Benzimidazole C<u>H</u>), 7.43 – 7.32 (m, 2H, Benzimidazole C<u>H</u>), 7.31 – 7.24 (m, 4H, Tosyl C<u>H</u>, PhC<u>H</u>), 7.23 – 7.13 (m, 3H, PhC<u>H</u>), 3.66 – 3.56 (m, 1H, Benzimidazole-C<u>H$_a$</u>H$_b$), 3.55 – 3.35 (m, 2H, Benzimidazole-CH$_a$<u>H$_b$</u>, SC<u>H</u>), 2.95 (ddd, *J* = 13.7, 10.7, 5.0 Hz, 1H, Ph-C<u>H$_a$</u>H$_b$), 2.83 – 2.66 (m, 1H, Ph-C<u>H$_a$</u>H$_b$), 2.66 – 2.48 (m, 2H, SC<u>H$_2$</u>CH$_2$CH$_3$), 2.38 (s, 3H, Tosyl C<u>H$_3$</u>), 2.06 – 1.95 (m, 1H, Ph-CH$_2$CH$_a$C<u>H$_b$</u>), 1.87 (dddd, *J* = 13.9, 10.7, 8.1, 5.0 Hz, 1H, Ph-CH$_2$C<u>H$_a$</u>CH$_b$), 1.68 – 1.59 (m, 2H, SCH$_2$C<u>H$_2$</u>CH$_3$), 0.99 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.8 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.1 (Ar<u>C</u>), 141.9 (Ar<u>C</u>), 135.6 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 130.3 (Ph<u>C</u>H), 128.5 (Tosyl<u>C</u>H), 128.4 (Ph<u>C</u>H), 126.8 (Ph<u>C</u>H), 125.9 (Tosyl<u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 124.8 (Benzimidazole <u>C</u>H), 120.1 (Benzimidazole <u>C</u>H), 113.9 (Benzimidazole <u>C</u>H), 43.9 (S<u>C</u>H), 36.8 (Benzimidazole-<u>C</u>H$_2$), 36.3 (Ph-CH$_2$<u>C</u>H$_2$), 33.1 (Ph-<u>C</u>H$_2$CH$_2$), 33.0 (S<u>C</u>H$_2$CH$_2$CH$_3$), 23.3 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.8 (Tosyl <u>C</u>H$_3$), 13.7(SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 3026, 2960, 2925, 2870, 1597, 1452, 1190, 1176, 1147, 1121, 1089, 1047, 812, 765, 745, 701, 667, 643; **HRMS** (APCI+): calcd. for $C_{27}H_{31}O_2N_2S_2$ $[M+H]^+$ 479.1821, found 479.1816.

(*S*)-2-(2-(Propylthio)hept-6-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**168**)

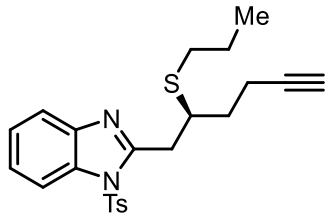


Compound **168** was synthesized according to **GP II** from **153** (36.6 mg) using catalyst **128** (8.1 mg), 1-propanethiol (9.1 mg, 11 μL). Clear oil (Pentane:EtOAc 8:2) (34.1 mg, 0.077 mmol, 77% yield, 89% ee).

HPLC Conditions: CHIRALCEL IB, hexane/isopropanol = 98/2, 1 mL/min, λ = 220 nm, t (minor) = 8.41 min, t (major) = 8.87 min.

$[\alpha]_D^{25}$ = −17.9 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 1H, Benzimidazole C<u>H</u>), 7.77 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 7.69 – 7.64 (m, 1H, Benzimidazole C<u>H</u>), 7.37 – 7.29 (m, 2H, Benzimidazole C<u>H</u>), 7.26 (d, *J* = 8.6 Hz, 2H, Tosyl C<u>H</u>), 5.75 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.96 (dq, *J* = 17.1, 1.6 Hz, 1H, C<u>H</u>=CH_2), 4.90 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H, CH=C<u>H$_{cis}$</u>H$_{trans}$), 3.51 (dd, *J* = 14.0, 5.3 Hz, 1H, CH=CH$_{cis}$<u>H$_{trans}$</u>), 3.45 – 3.39 (m, 1H, Benzimidazole-C<u>H$_a$</u>H$_b$, SC<u>H</u>), 3.36 (dd, *J* = 14.6, 7.7 Hz, 1H, Benzimidazole-CH$_a$<u>H$_b$</u>), 2.59 – 2.41 (m, 2H, SC<u>H$_2$</u>CH_2CH_3), 2.37 (s, 3H, Tosyl C<u>H$_3$</u>), 2.05 – 1.98 (m, 2H, C<u>H$_2$</u>CH=CH_2), 1.72 – 1.47 (m, 6H, SCH_2C<u>H$_2$</u>CH_3, C<u>H$_2$</u>C<u>H$_2$</u>CH_2CH=CH_2), 0.93 (t, *J* = 7.3 Hz, 3H, SCH_2CH_2C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.0 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.1 (Ar<u>C</u>), 138.7 (<u>C</u>H=CH_2), 135.6 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 130.3 (Tosyl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 124.8 (Benzimidazole <u>C</u>H), 120.9 (Benzimidazole <u>C</u>H), 114.7 (CH=<u>C</u>H_2), 113.9 (Benzimidazole <u>C</u>H), 44.1 (S<u>C</u>H), 36.9 (Benzimidazole-<u>C</u>H_2), 34.1 (Alk<u>C</u>H_2), 33.6 (<u>C</u>H_2CH=CH_2), 33.1 (S<u>C</u>$H_2CH_2CH_3$), 26.1 (Alk<u>C</u>H_2), 23.3 (Alk<u>C</u>H_2), 21.8 (Tosyl <u>C</u>H_3), 13.7 (SCH_2CH_2<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 2930, 2859, 1735, 1452, 1378, 1247, 1177, 1089, 1045, 745, 666; **HRMS** (ESI+): calcd. for $C_{24}H_{31}O_2N_2S_2$ $[M+H]^+$ 443.1815, found 443.1821.

(*S*)-2-(2-(Propylthio)hex-5-yn-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**169**)

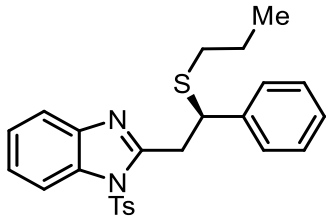


Compound **169** was synthesized according to **GP II** from **154** (35.0 mg) using catalyst **128** (8.1 mg), 1-propanethiol (9.1 mg, 11 μL). Clear oil (Pentane:Et_2O 8:2) (34.1 mg, 0.080 mmol, 80% yield, 92% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 97/3, 1 mL/min, λ = 220 nm, t (minor) = 35.17 min, t (major) = 37.67 min.

$[\alpha]_D^{25}$ = −17.8 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ =8.04 – 7.97 (m, 1H, Benzimidazole C<u>H</u>), 7.78 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 7.69 – 7.65 (m, 1H, Benzimidazole C<u>H</u>), 7.38 – 7.30 (m, 2H, Benzimidazole C<u>H</u>), 7.27 (d, *J*=7.7, 2H, Tosyl C<u>H</u>), 3.56 (dd, *J* = 14.5, 6.2 Hz, 1H, Benzimidazole-C<u>H</u>$_a$H$_b$), 3.53 – 3.46 (m, 1H, SC<u>H</u>), 3.38 (dd, *J* = 14.5, 7.2 Hz, 1H, Benzimidazole-C<u>H</u>$_a$H$_b$), 2.61 – 2.46 (m, 2H, SC<u>H$_2$</u>CH$_2$CH$_3$), 2.45 – 2.34 (m+s, 5H, CH$_2$C<u>H$_2$</u>CC≡H, Tosyl C<u>H$_3$</u>), 2.00 – 1.89 (m, 1H, C<u>H$_a$</u>H$_b$CH$_2$CC≡H), 1.93 (t, *J* = 2.6 Hz, 1H, CH$_2$CH$_2$CC≡<u>H</u>), 1.80 – 1.71 (m, 1H, CH$_a$<u>H$_b$</u>CH$_2$CC≡H), 1.58 (dqd, *J* = 14.7, 7.2, 1.8 Hz, 2H, SCH$_2$C<u>H$_2$</u>CH$_3$), 0.93 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.5 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.1 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 130.4 (Tosyl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.9 (Benzimidazole <u>C</u>H), 124.9 (Benzimidazole <u>C</u>H), 120.2 (Benzimidazole <u>C</u>H), 113.9 (Benzimidazole <u>C</u>H), 83.9 (CH$_a$H$_b$CH$_2$<u>C</u>C≡H), 68.9 (CH$_a$H$_b$CH$_2$<u>C</u><u>C</u>≡H), 43.5 (S<u>C</u>H), 36.9 (Benzimidazole-<u>C</u>H$_2$), 33.5 (<u>C</u>H$_a$H$_b$CH$_2$CC≡H), 33.2 (S<u>C</u>H$_2$CH$_2$CH$_3$), 23.3 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.8 (Tosyl <u>C</u>H$_3$), 16.3 (CH$_a$H$_b$<u>C</u>H$_2$CC≡H), 13.7 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 3298, 3058, 2960, 2923, 2852, 1596, 1540, 1451, 1376, 1189, 1047, 765, 666; **HRMS** (ESI+): calcd. for $C_{23}H_{27}O_2N_2S_2$ $[M+H]^+$ 427.1506, found 427.1508.

(*R*)-2-(2-Phenyl-2-(propylthio)ethyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**170**)

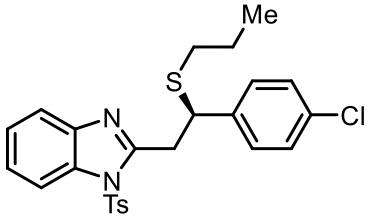


Compound **170** was synthesized according to a modified version of **GPII** from **139** (37.4 mg) using catalyst **80** (8.1 mg), 1-propanethiol (22.8 mg, 11 μL) in THF (1.60 mL) and stirred at room temperature. Amorphous colourless solid (Petrol:EtOAc 7:3) (39.1 mg, 0.087 mmol, 87% yield, 76% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 97/3, 1 mL/min, λ = 220 nm, t (major) = 42.23 min, t (minor) = 62.91 min.

$[\alpha]_D^{25}$ = +5.8 (c = 0.79, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.86 (m, 1H, Benzimidazole C<u>H</u>), 7.72 – 7.65 (m, 2H, Tosyl C<u>H</u>), 7.65 – 7.58 (m, 1H, Benzimidazole C<u>H</u>), 7.43 – 7.36 (m, 2H, Benzimidazole C<u>H</u>), 7.33 – 7.11 (m, 7H, Tosyl C<u>H</u>, Ph<u>H</u>), 4.71 (t, *J* = 7.5 Hz, 1H, SC<u>H</u>), 3.88 – 3.62 (m, 2H, Benzimidazole-CH_2), 2.33 (s, 3H, Tosyl C<u>H</u>$_3$), 2.32 – 2.17 (m, 2H, SC<u>H</u>$_2$$CH_2CH_3$), 1.54 – 1.37 (m, 2H, SCH_2C<u>H</u>$_2CH_3$), 0.83 (t, *J* = 7.3 Hz, 3H, SCH_2CH_2C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.1 (Ar<u>C</u>), 146.0 (Ar<u>C</u>), 142.1 (Ar<u>C</u>), 142.0 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.3 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.0 (Tosyl <u>C</u>H), 127.3 (Ar<u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.0 (Ar<u>C</u>H), 124.8 (Ar<u>C</u>H), 120.2 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 47.6 (S<u>C</u>H), 37.2 (Benzimidazole-<u>C</u>H_2), 33.6 (S<u>C</u>$H_2CH_2CH_3$), 22.7 (SCH_2<u>C</u>H_2CH_3), 21.8 (Tosyl <u>C</u>H_3), 13.6 (SCH_2CH_2<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 2981, 1627, 1597, 1449, 1378, 1378, 1149, 1089, 1051, 669; **HRMS** (ESI +) calcd. for $C_{25}H_{27}O_2N_2S_2$ $[M+H]^+$ 451.1508, Found 451.1505.

(*R*)-2-(2-(4-Chlorophenyl)-2-(propylthio)ethyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**171**)

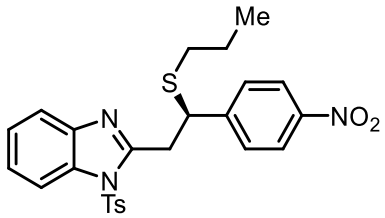


Compound **171** was synthesized according to **GP II** from **155** (40.9 mg) using catalyst **128** (8.1 mg), 1-propanethiol (22.8 mg, 11 µL) in THF (1.60 mL) and stirred at room temperature. Clear oil (Petrol:EtOAc 8:2) (29.6 mg, 0.061 mmol, 61% yield, 82% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 28.80 min, t (major) = 22.55 min.

$[\alpha]_D^{25}$ = +12.3 (c = 0.32, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 1H, Benzimidazole C<u>H</u>), 7.67 (d, *J* = 8.5 Hz, 2H, Tosyl C<u>H</u>), 7.67 – 7.59 (m, 1H, Benzimidazole C<u>H</u>), 7.38 – 7.28 (m, 4H, ArCl C<u>H</u>, Benzimidazole C<u>H</u>), 7.27 – 7.17 (m, 4H, ArCl C<u>H</u>, Tosyl C<u>H</u>), 4.70 (dd, *J* = 8.1, 7.0 Hz, 1H, SC<u>H</u>), 3.70 (qd, *J* = 15.9, 7.5 Hz, 2H, Benzimidazole C<u>H</u>$_3$), 2.38 (s, 3H, Tosyl C<u>H</u>$_3$), 2.31 (td, *J* = 7.8, 6.8 Hz, 2H, SC<u>H</u>$_2$CH$_2$CH$_3$), 1.66 – 1.40 (m, 2H, SCH$_2$C<u>H</u>$_2$CH$_3$), 0.88 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.8 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 142.0 (Ar<u>C</u>), 140.6 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 132.9 (Ar<u>C</u>), 130.4 (Ar <u>C</u>H), 129.5 (ArCl <u>C</u>H), 128.7 (Ar C<u>H</u>), 126.8 (Tosyl <u>C</u>H), 125.1 (Benzimidazole <u>C</u>H), 124.9 (Benzimidazole <u>C</u>H), 120.2 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 46.9 (S<u>C</u>H), 37.2 (Benzimidazole <u>C</u>H$_2$), 33.7 (S<u>C</u>H$_2$CH$_2$CH$_3$), 22.7 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.8 (Tosyl <u>C</u>H$_3$), 13.6 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 3060, 2962, 1594, 1455, 1380, 1189, 1089, 785, 668; **HRMS** (APCI+): calcd. for $C_{25}H_{26}O_2N_2ClS_2$ $[M+H]^+$ 485.1118, found 485.1117.

(*R*)-2-(2-(4-Nitrophenyl)-2-(propylthio)ethyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**172**)

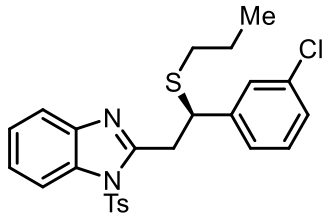


Compound **172** was synthesized according to **GP II** from **156** (41.9 mg) using catalyst **128** (8.1 mg), 1-propanethiol (22.8 mg, 11 μL) in THF (1.60 mL) and stirred at room temperature. Yellow oil (Petrol:EtOAc 8:2) (33.4 mg, 0.067 mmol, 67% yield, 76% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (minor) = 12.69 min, t (major) = 16.93 min.

$[\alpha]_D^{25}$ = +15.7 (c = 1.21, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 – 8.08 (m, 2H, $ArNO_2$ C<u>H</u>), 8.01 – 7.95 (m, 1H, Benzimidazole C<u>H</u>), 7.76 – 7.70 (m, 2H, Tosyl C<u>H</u>), 7.67 – 7.61 (m, 1H, Benzimidazole C<u>H</u>), 7.60 – 7.55 (m, 2H, $ArNO_2$ C<u>H</u>), 7.34 (ddd, *J* = 7.0, 5.0, 1.7 Hz, 2H, Benzimidazole C<u>H</u>), 7.28 (dd, *J* = 8.9, 1.0 Hz, 2H, Tosyl C<u>H</u>), 4.83 (dd, *J* = 8.4, 6.8 Hz, 1H, SC<u>H</u>), 3.84 – 3.67 (m, 2H, Benzimidazole C<u>H</u>$_2$), 2.39 (s, 3H, Tosyl C<u>H</u>$_3$), 2.38 – 2.23 (m, 2H, SC<u>H</u>$_2$$CH_2CH_3$), 1.65 – 1.41 (m, 2H, SCH_2C<u>H</u>$_2$$CH_3$), 0.91 (t, *J* = 7.3 Hz, 3H, SCH_2CH_2C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.1 (Ar<u>C</u>), 149.8 (Ar<u>C</u>), 147.1 (Ar<u>C</u>), 146.3 (Ar<u>C</u>), 141.8 (Ar<u>C</u>), 135.4 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.4 (Tosyl <u>C</u>H), 129.0 ($ArNO_2$ <u>C</u>H), 126.8 (Tosyl <u>C</u>H), 125.3 (Benzimidazole <u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 123.8 ($ArNO_2$ <u>C</u>H), 120.2 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 46.9 (S<u>C</u>H), 36.8 (Benzimidazole <u>C</u>H$_2$), 33.8 (S<u>C</u>H$_2$$CH_2CH_3$), 22.6 ($SCH_2$<u>C</u>H$_2$$CH_3$), 21.8 (Tosyl <u>C</u>H$_3$), 13.5 ($SCH_2CH_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2962, 2929, 1596, 1519 (NO_2), 1451, 1371, 1349 (NO_2), 1189, 1049, 745, 668; **HRMS** (APCI+): calcd. for $C_{25}H_{26}O_4N_3S_2$ $[M+H]^+$ 496.1359, found 496.1356.

(*R*)-2-(2-(3-Chlorophenyl)-2-(propylthio)ethyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**173**)

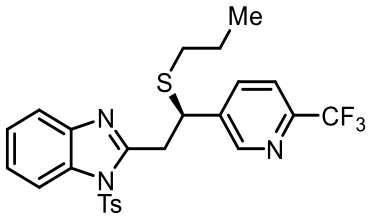


Compound **173** was synthesized according to **GP II** from **157** (40.1 mg) using catalyst **128** (8.1 mg), 1-propanethiol (22.8 mg, 11 μL) in THF (1.60 mL) and stirred at room temperature. Clear oil (Petrol:EtOAc 7:3) (29.9 mg, 0.062 mmol, 62% yield, 86% ee).

HPLC Conditions: CHIRALPAK AD-H hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (minor) =17.19 min, t (major) = 11.32 min.

$[\alpha]_D^{25}$ = +17.1 (c = 0.66, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 1H, Benzimidazole C<u>H</u>), 7.75 – 7.69 (m, 2H, Tosyl C<u>H</u>), 7.67 – 7.61 (m, 1H Benzimidazole C<u>H</u>), 7.42 – 7.38 (m, 1H, ArCl C<u>H</u>), 7.34 – 7.28 (m, 3H, Benzimidazole C<u>H</u>, ArCl C<u>H</u>), 7.25 (m, 2H, Tosyl C<u>H</u>), 7.22 – 7.10 (m, 2H, ArCl C<u>H</u>), 4.70 (t, *J* = 7.5 Hz, 1H, SC<u>H</u>), 3.71 (t, *J* = 7.6 Hz, 2H, Benzimidazole C<u>H</u>$_2$), 2.37 (s, 3H, Tosyl C<u>H</u>$_3$), 2.34 – 2.20 (m, 2H, SC<u>H</u>$_2$CH$_2$CH$_3$), 1.55 – 1.44 (m, 2H, SCH$_2$C<u>H</u>$_2$CH$_3$), 0.87 (t, *J* = 7.5 Hz, 3H, SCH$_2$CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.7 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 144.3 (Ar<u>C</u>), 142.0 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 134.4 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 130.4 (Tosyl <u>C</u>H), 129.8 (ArCl <u>C</u>H), 128.1 (ArCl <u>C</u>H), 127.6 (ArCl <u>C</u>H), 126.8 (Tosyl <u>C</u>H), 126.4 (ArCl <u>C</u>H), 125.1 (Benzimidazole <u>C</u>H), 124.8 (Benzimidazole <u>C</u>H), 120.2 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 47.0 (S<u>C</u>H), 37.1 (Benzimidazole <u>C</u>H$_2$), 33.7 (S<u>C</u>H$_2$CH$_2$CH$_3$), 22.6 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.8 (Tosyl <u>C</u>H$_3$), 13.6 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 3058, 2961, 1596, 1452, 1377, 1189, 1089, 1048, 765, 668; **HRMS** (APCI+): calcd. for $C_{25}H_{26}O_2N_2ClS_2$ $[M+H]^+$ 485.1118, found 485.1118.

(*R*)-2-(2-(Propylthio)-2-(6-(trifluoromethyl)pyridin-3-yl)ethyl)-1-tosyl-1*H*-benzo[*d*]imidazole (**174**)



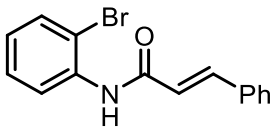
Compound **174** was synthesized according to **GP II** from **158** (44.3 mg) using catalyst **128** (8.1 mg), 1-propanethiol (22.8 mg, 11 μL) in THF (1.60 mL) and stirred at room temperature. Clear oil (Petrol:EtOAc 4:2) (38.4 mg, 0.074 mmol, 74% yield, 80% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = gradient 995/005 to 70/30, 1 mL/min, λ = 220 nm, t (minor) = 41.05 min, t (major) = 42.29 min.

$[\alpha]_D^{25}$ = +13.2 (c = 0.54, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.1 Hz, 1H, Pyridine C<u>H</u>), 7.99 (ddd, *J* = 7.9, 1.9, 1.0 Hz, 2H, Pyridine C<u>H</u>, Benzimidazole C<u>H</u>), 7.75 – 7.68 (m, 2H, Tosyl C<u>H</u>), 7.66 – 7.59 (m, 2H, Pyridine C<u>H</u>, Benzimidazole C<u>H</u>), 7.35 (ddd, *J* = 7.0, 4.8, 1.7 Hz, 2H, Benzimidazole C<u>H</u>), 7.28 (dd, *J* = 8.6, 1.0 Hz, 2H, Tosyl C<u>H</u>), 4.83 (dd, *J* = 8.3, 6.8 Hz, 1H, SC<u>H</u>), 3.78 (dd, *J* = 7.6, 4.0 Hz, 2H, Benzimidazole-C<u>H</u>$_2$), 2.40 (s, 3H, Tosyl C<u>H</u>$_3$), 2.39 – 2.26 (m, 2H, SC<u>H</u>$_2$CH$_2$CH$_3$), 1.65 – 1.47 (m, 2H, SCH$_2$C<u>H</u>$_2$CH$_3$), 0.93 (t, *J* = 7.4 Hz, 3H, SCH$_2$CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.8 (Ar<u>C</u>), 150.1 (Pyridine <u>C</u>H), 147.0 (q, *J* = 34.6 Hz, <u>C</u>F$_3$), 146.4 (Ar<u>C</u>), 141.8 (Ar<u>C</u>), 141.3 (Ar<u>C</u>), 136.8 (Pyridine <u>C</u>H), 135.4 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.5 (Tosyl <u>C</u>H), 126.7 (Tosyl <u>C</u>H), 125.4 (Benzimidazole <u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 120.4 (d, *J* = 2.6 Hz, Pyridine <u>C</u>H), 120.2 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 44.3 (S<u>C</u>H), 36.8 (Benzimidazole <u>C</u>H$_2$), 33.8 (S<u>C</u>H$_2$CH$_2$CH$_3$), 22.6 (SCH$_2$<u>C</u>H$_2$CH$_3$), 21.8 (Tosyl <u>C</u>H$_3$), 13.5 (SCH$_2$CH$_2$<u>C</u>H$_3$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -67.8; **IR** (film) υ_{max}/cm^{-1}: 3057, 2963, 2931, 1452, 1378, 1337, 1174, 1137, 1088, 1051, 745, 669; **HRMS** (APCI+): calcd. for $C_{25}H_{25}O_2N_3F_3S_2$ $[M+H]^+$ 520.1334, found 520.1333.

5.2.7 Heterocycle variation

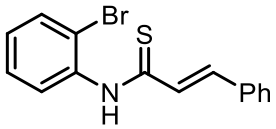
N-(2-bromophenyl)cinnamamide (**177**)



A procedure[9] from the literature was modified as follows. *o*-bromoanilline (5.00 g, 3.27 ml, 29.0 mmol) and cinnamoyl chloride (5.33 g, 32.0 mmol) were dissolved in dry THF (60.0 mL) and stirred at room temperature for 12 hr. The crude was diluted with EtOAc (100 mL) and washed with 5% aq. $NaHCO_3$ (3x 100 mL), then brine (1 x 75.0 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield crude compound **177** as a colourless solid (6.65 g, 22.0 mmol, 76% yield) which was used for subsequent steps without any further purification.

Mp 148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.3 Hz, 1H), 7.89 – 7.71 (m, 2H), 7.57 (td, *J* = 7.6, 2.9 Hz, 3H), 7.47 – 7.30 (m, 4H), 7.00 (td, *J* = 7.8, 1.6 Hz, 1H), 6.60 (d, *J* = 15.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.0, 143.2, 136.0, 134.6, 132.4, 130.3, 129.1, 128.6, 128.2, 125.3, 122.1, 120.7, 113.7. Data matches that found in the literature[9]

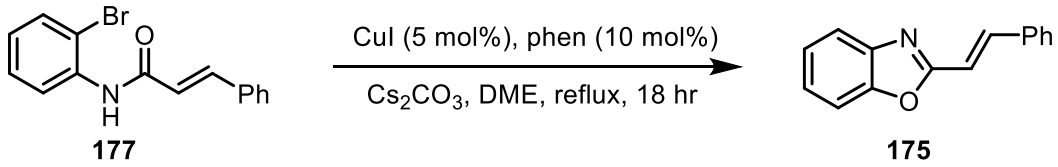
(*E*)-*N*-(2-bromophenyl)-3-phenylprop-2-enethioamide (**178**)



A procedure[9] from the literature was modified as follows. N-(2-bromophenyl)cinnamamide (3.00 g, 9.28 mmol) and Lawsson's reagent (4.81 g, 11.9 mmol) were dissolved in THF (45.0 mL) and heated at 70 °C for 18 hr. The reaction mixture was concentrated *in vacuo* and the resulting crude was purified by flash column chromatography (Petrol: EtOAc 4:1) affording **178** as a bright orange powder (1.68 g, 5.27 mmol, 57% yield).

Mp 114-116 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.98 (s, 1H, NH), 8.02 – 7.81 (m, 1H, (C=S)CH=CHPh)), 7.66 (dd, *J* = 8.1, 1.4 Hz, 1H, ArCH), 7.56 (dt, *J* = 7.1, 3.3 Hz, 2H, ArCH), 7.45 – 7.32 (m, 4H, ArCH) 7.17 (td, *J* = 7.8, 1.6 Hz, 1H, ArCH), 7.01 (d, *J* = 15.2 Hz, 1H, (C=S)CH=CHPh); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.7 (C=S), 142.0 (C(S)CHCHPh), 136.6 (ArC), 134.9 (ArC), 133.1 (ArCH), 130.4 (ArCH), 129.1 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 128.0 (C(S)CHCHPh), 127.8 (ArCH), 126.5 (ArCH), 122.4 (ArC); **IR** (film) υ_{max}/cm^{-1}: 3189, 3058, 2971, 1631(C=S), 1514, 1169, 969, 753; **HRMS** (ESI +) calcd. for $C_{15}H_{13}NBrS$ $[M+H]^+$ 317.9947, Found 317.9949.

(*E*)-2-styrylbenzo[d]oxazole (**175**)

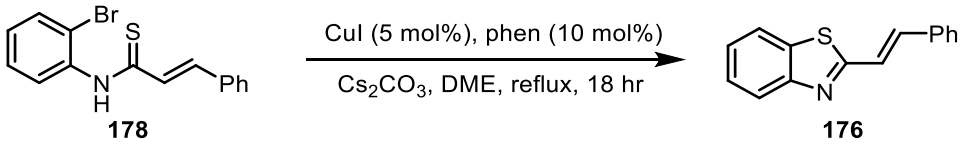


177 **175**

A procedure[9] from the literature was modified as follows. **177** (2.00 g, 6.61 mmol), CuI (63.0 mg, 0.33 mmol), Cs_2CO_3 (3.23 g, 9.89 mmol) and phenanthroline (119.0 mg, 0.66 mmol) were dissolved in DME (51.0 mL) and heated 85 °C for 18 hr. The reaction mixture was diluted with CH_2Cl_2 (30.0 mL) and H_2O (30.0 ml). The aqueous phase was extracted with CH_2Cl_2 (3x 60.0 mL) and the combined organic phases were washed with brine (50.0 mL) and dried of anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (Petrol: EtOAc 9:1) affording the title compound (**175**) as a colourless solid (1.38 g, 95% yield).

Mp 72-74 °C (lit 79-80 °C)[10]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 16.4 Hz, 1H), 7.75 – 7.69 (m, 1H), 7.64 – 7.56 (m, 2H), 7.55 – 7.50 (m, 1H), 7.45 – 7.30 (m, 6H), 7.08 (d, *J* = 16.3 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9, 150.5, 142.3, 139.5, 135.2, 129.9, 129.1, 127.7, 125.3, 124.6, 119.97, 114.0, 110.4; **LRMS** (ESI+) expected: 222.09 found: 222.0 $[M+H]^+$. Data was consistent with that found in the literature.[10]

(*E*)-2-styrylbenzothiazole (**176**)

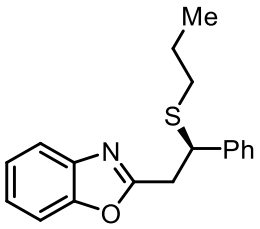


178 **176**

A procedure[9] from the literature was modified as follows. **178** (1.5 g, 4.73 mmol), CuI (52.0 mg, 0.237 mmol), Cs_2CO_3 (2.31 g, 7.10 mmol) and phenanthroline (85.0 mg, 0.473 mmol) were dissolved in DME (36.0 mL) and heated 85 °C for 18 hr. The reaction mixture was diluted with CH_2Cl_2 (40.0 mL) and H_2O (40.0 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 40.0 mL) and the combined organic phases were washed with brine (40.0 mL) and dried of anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (Petrol: EtOAc 9:1) affording **176** as a pale-yellow solid (1.02 g, 91% yield).

Mp 104-106 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 1H), 7.86 (ddd, *J* = 8.0, 1.3, 0.6 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.53 (d, *J* = 16.3 Hz, 1H), 7.48 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.44 – 7.34 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.1, 154.0, 137.8, 135.5, 134.5, 129.6, 129.1, 127.5, 126.4, 125.5, 123.1, 122.2, 121.6; **LRMS** (ESI+) expected: 238.07 found: 238.0 $[M+H]^+$. Data was consistent with that found in the literature.[10]

2-(2-phenyl-2-(propylthio)ethyl)benzo[d]oxazole (**179**)

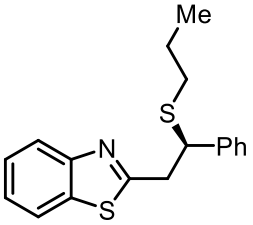


Compound **179** was synthesized according to a modified version of **GP II** from **175** (22.2 mg) using catalyst **128** (8.1 mg), 3 equivalents of propane thiol (57.0 mg, 27.5 μL, 0.30 mmol) in THF (1.60 mL) and stirred at room temperature. Clear oil (Petrol:EtOAc 9:1) (17.7 mg, 0.060 mmol, 60% yield, 52.5:47.5 er).

HPLC Conditions: CHIRALCEL OJ, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (minor) = 9.73 min, t (major) = 14.51 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.60 (m, 1H, Benzoxazole C<u>H</u>), 7.46 – 7.40 (m, 1H, Benzoxazole C<u>H</u>), 7.39 – 7.34 (m, 2H, Benzoxazole C<u>H</u>), 7.33 – 7.17 (m, 5, Ph<u>H</u>), 4.48 (t, *J* = 7.9 Hz, 1H, C<u>H</u>S), 3.59 – 3.33 (m, 2H Benzoxazole-C<u>H</u>$_2$), 2.43 – 2.20 (m, 2H, SC<u>H</u>$_2$$CH_2CH_3$), 1.62 – 1.36 (m, 2H, SCH_2C<u>H</u>$_2CH_3$), 0.85 (t, *J* = 7.3 Hz, 3H, SCH_2CH_2C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.1 (N<u>C</u>O), 150.7 (Ar<u>C</u>), 141.2 (Ar<u>C</u>), 141.2 (Ar<u>C</u>), 128.6 (Phenyl <u>C</u>H), 127.6 (ArC<u>H</u>), 127.6 (ArC<u>H</u>), 124.7 (Phenyl <u>C</u>H), 124.2 (Phenyl <u>C</u>H), 119.8 (Benzoxazole <u>C</u>H), 110.4 (Benzoxazole <u>C</u>H), 47.2 (<u>C</u>HS), 36.3 (Benzoxazole-<u>C</u>H$_2$), 33.5 (S<u>C</u>$H_2CH_2CH_3$), 22.6 (SCH_2<u>C</u>H_2CH_3), 13.6 (SCH_2CH_2<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 2980, 1615, 1570, 1492, 1379, 1242, 1142, 1076, 956, 746, 699, 669; **HRMS** (ESI +) calcd. for $C_{18}H_{20}ONS$ $[M+H]^+$ 298.1260, Found 298.1259.

2-(2-phenyl-2-(propylthio)ethyl)benzo[d]thiazole (**180**)

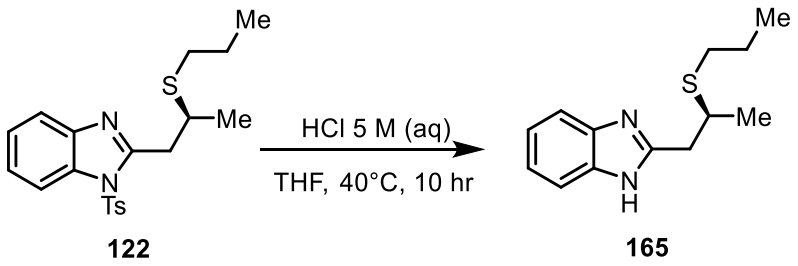


Compound **180** was synthesized according to a modified version of **GP II** using **176** (23.8 mg) catalyst **128**, 3 equivalents of propane thiol (57.0 mg, 27.5 μL, 0.30 mmol) in THF (1.60 mL) and stirred at room temperature. Pale yellow amorphous solid (Petrol:EtOAc 9:1) (22.2 mg, 0.075 mmol, 75% yield, 66:33 er).

HPLC Conditions: CHIRALCEL OD-H, hexane/isopropanol = 98/2, 1 mL/min, λ = 220 nm, t (minor) = 9.81 min, t (major) = 12.20 min.

$[\alpha]_D^{25}$ = +5.9 (c = 0.37, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (dt, *J* = 8.1, 0.9 Hz, 1H, Benzothiazole-C<u>H</u>), 7.73 (dt, *J* = 8.0, 0.9 Hz, 1H, Benzothiazole-C<u>H</u>), 7.43 – 7.15 (m, 7H, Benzothiazole-C<u>H</u>, Ph<u>H</u>), 4.34 (dd, *J* = 8.2, 7.2 Hz, 1H, C<u>H</u>S), 3.79 – 3.34 (m, 2H, Benzothiazole-C<u>H$_2$</u>), 2.29 (qdd, *J* = 12.6, 7.8, 6.7 Hz, 2H, SC<u>H$_2$</u>CH_2CH_3), 1.60 – 1.41 (m, 2H, SCH_2C<u>H$_2$</u>CH_3), 0.84 (t, *J* = 7.3 Hz, 3H, SCH_2CH_2C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.5 (N<u>C</u>S), 153.1 (Ar<u>C</u>), 141.3(Ar<u>C</u>), 135.4 (Ar<u>C</u>), 128.7 (ArC<u>H</u>), 128.0 (ArC<u>H</u>), 127.6 (ArC<u>H</u>), 126.0 (ArC<u>H</u>), 124.9 (ArC<u>H</u>), 122.8 (Benzothiazole <u>C</u>H), 121.6 (Benzothiazole <u>C</u>H), 49.2 (<u>C</u>HS), 41.4 (Benzothiazole-<u>C</u>H$_2$), 33.6 (S<u>C</u>$H_2CH_2CH_3$), 22.7 (SCH_2<u>C</u>H_2CH_3), 13.6 (SCH_2CH_2<u>C</u>H_3); **IR** (film) υ_{max}/cm^{-1}: 2980, 1508, 1455, 1438 ,1380, 1243, 1075, 955, 759; **HRMS** (ESI +) calcd. for $C_{18}H_{20}NS_2$ $[M+H]^+$ 314.1032, found 314.1030.

5.2.8 Cleavage of *N*-Ts group (165)



122 **165**

To a solution of **122** (50.0 mg, 0.129 mmol) in THF (1.00 mL) was added 5 M aq. HCl (1.00 mL). The mixture was stirred at 40 °C for 10 hr. The reaction was quenched with a solution of saturated $NaHCO_3$, and the aqueous phase extracted twice with EtOAc (5 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography with pure EtOAc affording product **165** as a colourless solid (30.2 mg, 0.129 mmol, 100% yield and 95.5:4.5 er).

HPLC Conditions: CHIRALCEL OD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 33.17 min, t (major) = 41.12 min.

$[\alpha]_D^{25}$ = −38.9 (c = 0.4, $CHCl_3$); **Mp**: 94 °C (from EtOAc); **^{1}H NMR** (400 MHz, CD_3OD) δ =7.48 (dd, *J* = 6.1, 3.2 Hz, 2H, Benzimidazole C<u>H</u>), 7.18 (dd, *J* = 6.1, 3.2 Hz, 2H, Benzimidazole C<u>H</u>), 4.87 (s, 1H, N<u>H</u>), 3.34 – 3.23 (m, 1H, SC<u>H</u>), 3.14 (dd, *J* = 14.3, 6.7 Hz, 1H, Benzimidazole-C<u>H$_a$</u>H$_b$), 2.97 (dd, *J* = 14.4, 8.0 Hz, 1H, Benzimidazole-CH$_a$<u>H$_b$</u>), 2.48 (td, *J* = 7.2, 3.5 Hz, 2H, SC<u>H$_2$</u>CH$_2$CH$_3$), 1.55 (h, *J* = 7.3 Hz, 2H, SCH$_2$C<u>H$_2$</u>CH$_3$), 1.27 (d, *J* = 6.8 Hz, 3H, CHC<u>H$_3$</u>), 0.91 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, CD_3OD) δ 152.4 (Ar<u>C</u>), 121.3 (Benzimidazole <u>C</u>H), 113.4 (Benzimidazole <u>C</u>H), 38.2 (S<u>C</u>H), 36.2 (Benzimidazole-<u>C</u>H$_2$), 31.6 (S<u>C</u>H$_2$CH$_2$CH$_3$), 22.1 (SCH$_2$<u>C</u>H$_2$CH$_3$), 19.8 (CH<u>C</u>H$_3$), 11.7 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 3054, 2959, 2869, 1538, 1453, 1437, 1376, 1272, 1026, 742; **HRMS** (ESI+): calcd. for $C_{13}H_{19}N_2S$ $[M+H]^+$ 235.1263, found 235.1263.

5.2.8.1 Single crystal X-ray diffraction data for compound ***165***

CCDC:1833189

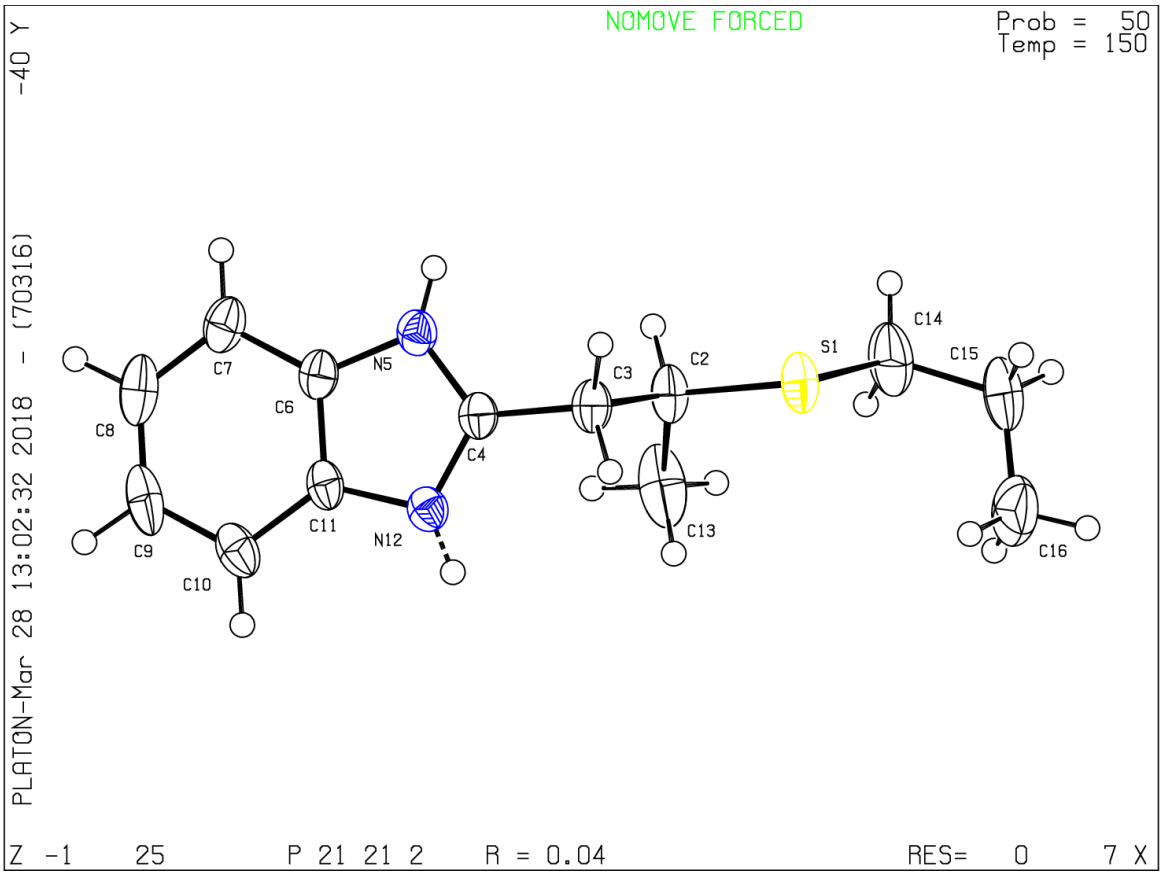


Table 1

Experimental details

Crystal data	
Chemical formula	$C_{13}H_{18}N_2S$
M_r	234.37
Crystal system, space group	*Ortho*rhombic, $P2_12_12$
Temperature (K)	150
a, *b*, *c* (Å)	20.7206 (4), 9.8606 (2), 6.3486 (1)
V (Å^3)	1297.13 (4)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	2.00
Crystal size (mm)	0.20 × 0.20 × 0.15

Data collection	
Diffractometer	Unknown
Absorption correction	Multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	0.42, 0.74
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	26964, 2686, 2630
R_{int}	0.047
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.630
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.037, 0.108, 0.99
No. of reflections	2686
No. of parameters	155
No. of restraints	8
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\varrho_{max}$, $\Delta\varrho_{min}$ (e Å^{-3})	0.33, −0.34
Absolute structure	Flack (1983), 1104 Friedel-pairs
Absolute structure parameter	0.01 (2)

Computer programs: USER DEFINED DATA COLLECTION, USER DEFINED *CELL* REFINEMENT, USER DEFINED DATA REDUCTION, *SIR92* (Altomare *et al.*, 1994), *CRYSTALS*(Betteridge *et al.*, 2003), *CAMERON* (Watkin *et al.*, 1996).

Table 2

Selected geometric parameters (Å, º)

S1—C2	1.8212 (16)	C6—C11	1.394 (2)
S1—C14	1.821 (2)	C7—C8	1.377 (3)
C2—C3	1.538 (2)	C8—C9	1.388 (3)
C2—C13	1.511 (3)	C9—C10	1.383 (3)
C3—C4	1.490 (2)	C10—C11	1.398 (3)

C4—N5	1.332 (2)	C11—N12	1.389 (3)
C4—N12	1.338 (2)	C14—C15	1.527 (3)
N5—C6	1.390 (3)	C15—C16	1.491 (4)
C6—C7	1.398 (3)		
C2—S1—C14	104.02 (9)	C7—C6—C11	121.5 (2)
S1—C2—C3	104.10 (10)	C6—C7—C8	116.6 (2)
S1—C2—C13	113.04 (15)	C7—C8—C9	122.2 (3)
C3—C2—C13	112.10 (18)	C8—C9—C10	121.7 (3)
C2—C3—C4	113.54 (13)	C9—C10—C11	116.8 (2)
C3—C4—N5	123.70 (19)	C10—C11—C6	121.2 (2)
C3—C4—N12	123.28 (18)	C10—C11—N12	131.34 (19)
N5—C4—N12	113.02 (13)	C6—C11—N12	107.46 (18)
C4—N5—C6	106.14 (15)	C11—N12—C4	105.98 (15)
N5—C6—C7	131.08 (18)	S1—C14—C15	109.75 (16)
N5—C6—C11	107.40 (18)	C14—C15—C16	114.3 (2)

Table 3

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5—H51···N5^{i}	0.85	1.98	2.792 (3)	161 (2)
N12—H121···N12^{ii}	0.86	1.98	2.801 (3)	162 (5)

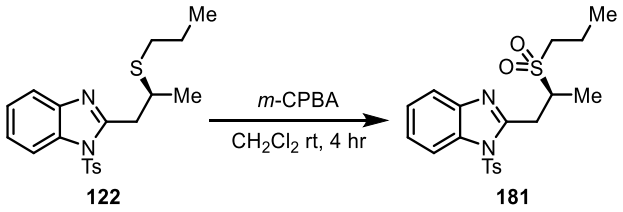
Symmetry codes: (i) −*x*+1, −*y*+1, *z*; (ii) −*x*+1, −*y*, *z*.

Alert level C

PLAT250_ALERT_2_C Large U3/U1 Ratio for Average U(i,j) Tensor .. 2.6 Note

This alert is due to disorder in the structure.

5.2.9 Oxidation of sulfur (181)



122 **181**

To a solution of **122** (40.0 mg, 0.103 mmol) in CH_2Cl_2 (1.00 mL) at room temperature was added *m*-CPBA (77% in water) (53.0 mg, 0.236 mmol). The mixture was stirred for 4 hr. The reaction was diluted with CH_2Cl_2 (5.0 mL) and quenched with a solution of saturated $Na_2S_2O_3$. The organic layer was washed with a solution of saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Et_2O:Pentane 6:4) affording the pure compound **181** as a colourless oil (41.1 mg, 0.098 mmol, 95% yield and 95:5 er).

HPLC Conditions: CHIRALPAK AD-H, hexane/ isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (minor) = 37.12 min, t (major) = 49.98 min.

$[\alpha]_D^{25}$ = −1.8 (c = 1.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 8.01 (m, 1H, Benzimidazole C<u>H</u>), 7.82 (d, *J* = 8.4 Hz, 2H, Tosyl C<u>H</u>), 7.68 – 7.62 (m, 1H, Benzimidazole C<u>H</u>), 7.41 – 7.32 (m, 2H, Benzimidazole C<u>H</u>), 7.30 (d, *J* = 7.8 Hz, 2H, Tosyl C<u>H</u>), 3.97 (dqd, *J* = 9.6, 6.9, 3.8 Hz, 1H, SC<u>H</u>), 3.86 (dd, *J* = 16.5, 3.8 Hz, 1H, Benzimidazole-C<u>H$_a$</u>H$_b$), 3.37 (dd, *J* = 16.5, 9.6 Hz, 1H, Benzimidazole-CH$_a$<u>H$_b$</u>), 3.06 – 2.92 (m, 2H, SC<u>H$_2$</u>CH$_2$CH$_3$), 2.38 (s, 3H, Tosyl C<u>H$_3$</u>), 2.01 – 1.84 (m, 2H, SCH$_2$C<u>H$_2$</u>CH$_3$), 1.47 (d, *J* = 6.9 Hz, 3H, CHC<u>H$_3$</u>), 1.07 (t, *J* = 7.5 Hz, 3H, SCH$_2$CH$_2$C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.6 (Ar<u>C</u>), 146.5 (Ar<u>C</u>), 141.8 (Ar<u>C</u>), 135.1 (Ar<u>C</u>), 133.3 (Ar<u>C</u>), 130.6 (Tosyl <u>C</u>H), 127.0 (Tosyl <u>C</u>H), 125.5 (Benzimidazole <u>C</u>H), 125.0 (Benzimidazole <u>C</u>H), 120.1 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 55.3 (S<u>C</u>H), 52.4 (S<u>C</u>H$_2$CH$_2$CH$_3$), 30.0 (Benzimidazole-<u>C</u>H$_2$), 21.8 (Tosyl <u>C</u>H$_3$), 15.6 (SCH$_2$<u>C</u>H$_2$CH$_3$), 13.6 (CH<u>C</u>H$_3$), 13.4 (SCH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2971, 1596, 1541; 1452, 1376, 1292, 1170, 1122, 1088, 746, 668; **HRMS** (ESI+): calcd. for $C_{20}H_{25}O_4N_2S_2$ $[M+H]^+$ 421.1250, found 421.1240.

5.2.10 Removal of *para*-methoxybenzyl group (182)



136 **182**

A procedure from the literature[11] was modified as follows. To a solution of **136** (45.0 mg, 0.095 mmol, 91:9 er) in TFA (621 μL) was added anisole (72 μL, 0.66 mmol) and was stirred at 65 °C for 4 hr. Volatiles were then removed under a stream of N_2 and the resulting crude was dissolved in Et_2O (1.60 mL) and passed through a plug of K_2CO_3. The resulting solution was loaded directly onto silica gel (Petrol:EtOAc 7:3) to afford pure **182** as a clear oil (16.1 mg, 0.048 mmol, 50% yield, 91:9 er).

HPLC Conditions: CHIRALPAK AD-H, hexane/ isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 19.00 min, t (major) = 22.53 min.

$[\alpha]_D^{25}$ = +3.9 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.98 (m, 1H, Benzimidazole C<u>H</u>), 7.82 – 7.77 (m, 2H, Tosyl C<u>H</u>), 7.71 – 7.65 (m, 1H, Benzimidazole C<u>H</u>), 7.39 – 7.31 (m, 2H, Benzimidazole C<u>H</u>), 7.30 – 7.27 (m, 2H, Tosyl C<u>H</u>), 3.79 – 3.68 (m, 1H, SC<u>H</u>), 3.51 – 3.37 (m, 2H, Benzimidazole-C<u>H</u>$_2$), 2.38 (s, 3H, Tosyl C<u>H</u>$_3$), 2.04 (dd, *J* = 6.5, 0.5 Hz, 1H, S<u>H</u>), 1.47 (dd, *J* = 6.5, 0.5 Hz, 3H, CHC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.6 (Ar<u>C</u>), 146.2 (Ar<u>C</u>), 142.1 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.4 (Tosyl <u>C</u>H), 126.9 (Tosyl <u>C</u>H), 125.2 (Benzimidazole <u>C</u>H), 124.9 (Benzimidazole <u>C</u>H), 120.2 (Benzimidazole <u>C</u>H), 113.8 (Benzimidazole <u>C</u>H), 41.5 (S<u>C</u>H), 33.5 (Benzimidazole-<u>C</u>H$_2$), 24.7 (Tosyl <u>C</u>H$_3$), 21.8 (CH<u>C</u>H$_3$); **IR** (film) υ_{max}/cm^{-1}: 2968, 2923, 1452, 1378, 1254, 1232, 1170, 1089, 1048, 746, 668; **HRMS** (APCI+): calcd. for $C_{17}H_{19}O_2N_2S_2$ $[M+H]^+$ 347.0883, found 347.0880.

5.2.11 Computational methods for chapter 2

The range-separated dispersion-corrected ωB97X-D density functional[12,13] was used with the 6-31G(d) basis set to optimize geometries. Vibrational frequency calculations were carried out to confirm that stationary points were either minima or first-order saddle points on the potential energy surface, and to obtain thermal corrections to Gibbs free energies at 298.15 K (80 °C). Quasi-harmonic (QHA) corrections were applied to the computed vibrational entropies using a frequency cut-off value of 100.0 cm^{-1}, adopting the model proposed by Grimme.[14] This was automated by the *GoodVibes* program.[i] Vibrational frequency calculations were carried out to confirm that stationary points were either minima or first-order saddle points on the potential energy surface, and to obtain thermal corrections to Gibbs free energies at 353.15 K (80 °C). Quasi-harmonic (QHA) corrections were applied to the computed vibrational entropies using a frequency cut-off value of 100.0 cm^{-1}, adopting the model proposed by Grimme.[14] This was automated by the *GoodVibes* program.[ii] Solvent effects were considered using the integral equation formalism variant of the polarizable continuum model (IEF-PCM)[15–19] with the SMD solvation model (solvent=ethanol).[20] Density functional theory (DFT) calculations were carried out in *Gaussian 09*.[iii]

[i] GoodVibes, version 2.0.1, I. Funes-Ardoiz, R. S. Paton, http://doi.org/10.5281/zenodo.595246 (accessed 13 April 2018).

[ii] GoodVibes, version 2.0.1, I. Funes-Ardoiz, R. S. Paton, http://doi.org/10.5281/zenodo.595246 (accessed 13 April 2018).

[iii] Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian, Inc., Wallingford CT, 2009

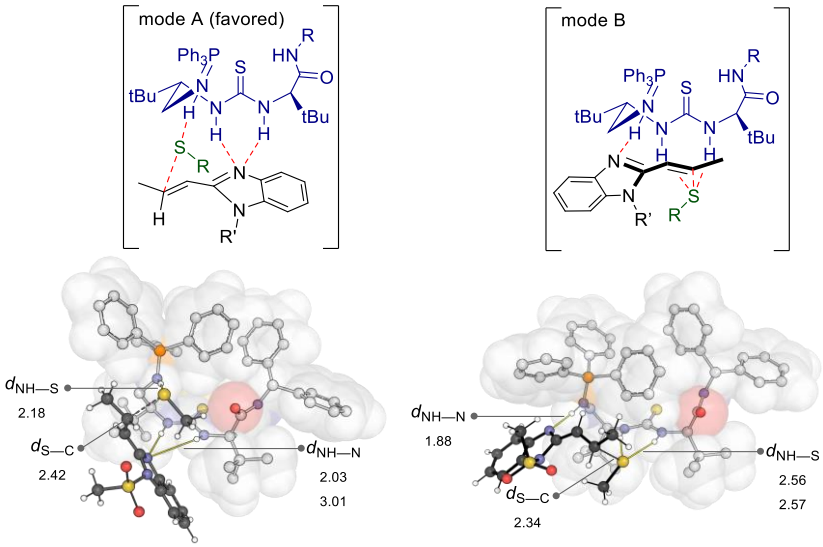


Figure 2. Comparison of 'mode A' and 'mode B' transition structures leading the major enantiomeric product. Mode A is favoured by several kcal/mol using either wB97XD or M06-2X functionals.

Cartesian Coordinates (xyz format):

136

mode A TS (E = -4263.576613 H)

C -1.126728 -2.730766 0.944321

N -0.007387 -1.837566 1.158652

H 0.780734 -1.945485 0.532640

C -0.070408 -0.683240 1.868412

S -1.499399 -0.202053 2.666146

N 1.079709 0.015110 1.905089

H 1.931533 -0.424272 1.534365

C 1.218856 1.383877 2.378892

H 0.209980 1.712905 2.639152

H 1.177054 1.803527 -0.799539

C 1.723846 2.243898 1.210007

N 0.799005 2.236325 0.074436

H 2.670389 1.846266 0.837006

P -0.253350 3.458853 -0.207747

C 0.566197 4.936354 -0.852937

C 1.793344 4.765370 -1.501702

C -0.010260 6.208858 -0.765937

C 2.439858 5.863106 -2.059835

H 2.236992 3.776224 -1.580900

C 0.640958 7.301169 -1.328736

H -0.960717 6.350653 -0.259584

C 1.864760 7.128364 -1.972947

H 3.391805 5.726403 -2.563381

H 0.193429 8.287805 -1.260857

H 2.369937 7.984361 -2.410275

C -1.085940 3.897989 1.326436

C -0.542886 4.844802 2.203309

C -2.248565 3.204474 1.672516

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136

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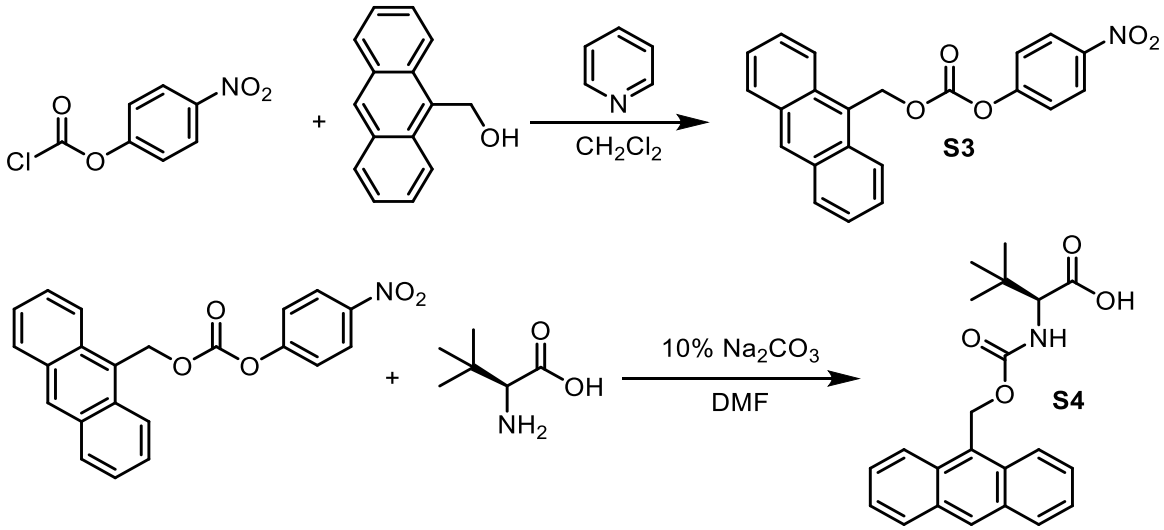
5.3 Experimental Details for Chapter 3

5.3.1 Synthesis of pre-catalysts and catalysts:

5.3.1.1 Synthesis of novel ureidopeptide BIMP catalysts

(*S*)-2-(((anthracen-9-ylmethoxy)carbonyl)amino)-3,3-dimethylbutanoic acid (**S4**)



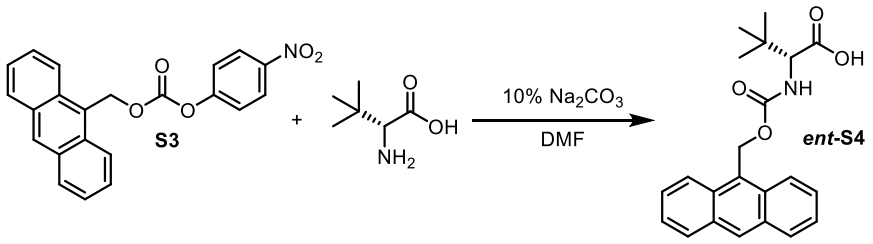
According to a literature procedure,[21] to a solution of 4-nitrophenylchloroformate (2.2 g, 11 mmol, 1.1 eq) in CH_2Cl_2 (14.0 mL) at room temperature was added pyridine (0.90 mL, 11 mmol, 1.1 eq) dropwise. The slurry was cooled to 0 °C and 9-anthracenemethanol (2.08 g, 10 mmol, 1.0 eq) was added portion wise. The reaction mixture was then allowed to warm to room temperature and stirring maintained for 18 hr. The reaction mixture was diluted with CH_2Cl_2 (40.0 mL) and washed with 1 M HCl (20.0 mL), water (20.0 mL) and brine (20.0 mL) and dried ($MgSO_4$). The volatiles were removed *in vacuo* to afford **S3** as a yellow solid in 60% yield (2.23 g) which was used without further purification.

To a stirred solution of L-*tert*-Leucine (0.66 g, 5.0 mmol, 1.0 eq) in 10% aqueous Na_2CO_3 (13.0 mL) and DMF (10.0 mL) at 0 °C was slowly added the 4-nitrophenylcarbonate (1.87 g, 5.0 mmol, 1.0 eq) in DMF (15.0 mL). After stirring for one hour at this temperature, the reaction mixture was allowed to warm to room temperature for 18 hr, diluted by the addition of H_2O (50.0 mL) and extracted with Et_2O (3 x 20.0 mL). The aqueous layer was cooled in an ice bath and acidified to pH 1 by the addition of concentrated

HCl and then extracted with EtOAc (3 x 25.0 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to EtOAc] afforded **S4** as a pale-yellow solid in 60% yield (1.08 g, 6.6 mmol).

Mp 153 – 154 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.00 (s, 9 H), 4.27 (d, *J* = 10.0 Hz, 1 H), 5.31 (d, *J* = 10.0 Hz, 1 H), 6.13 (d, *J* = 12.5 Hz, 1 H), 6.20 (d, *J* = 12.5 Hz, 1 H), 7.44 - 7.61 (m, 4 H), 8.01 (d, *J* = 8.5 Hz, 2 hr), 8.37 (d, *J* = 8.5 Hz, 2 hr), 8.49 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.6, 34.7, 59.8, 62.4, 124.1, 125.2, 126.4, 126.8, 129.2, 129.3, 131.2, 131.5, 156.6, 176.4. Data was in agreement with the litrature.[21,22]

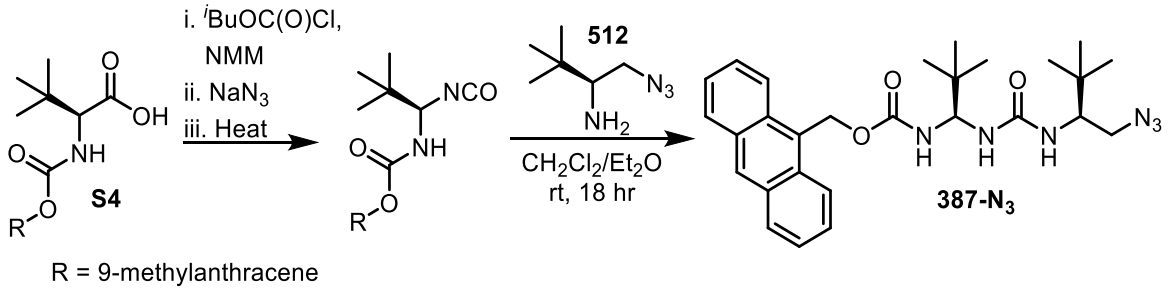
(*R*)-2-(((anthracen-9-ylmethoxy)carbonyl)amino)-3,3-dimethylbutanoic acid (*ent*-**S4**)



To a stirred solution of *R-tert*-Leucine (0.52 g, 4.00 mmol, 1.0 eq) in 10% aqueous Na_2CO_3 (10.40 mL) and DMF (8.0 mL) at 0 °C was slowly added the 4-nitrophenylcarbonate (**S3**, 1.50 g, 4.00 mmol, 1.0 eq) in DMF (10.0 mL). After stirring for one hour at this temperature, the reaction mixture was allowed to warm to room temperature for 18 hr, diluted by the addition of H_2O (50.0 mL) and extracted with Et_2O (3 x 20.0 mL). The aqueous layer was cooled in an ice bath and acidified to pH 1 by the addition of concentrated HCl and then extracted with EtOAc (3 x 25.0 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to EtOAc] afforded *ent*-**S4** as a pale-yellow solid in 32% yield (474 mg, 13.0 mmol).

Analytical data matched compound **S4** and was in agreement with the literature.[21,22]

Anthracen-9-ylmethyl [(1*S*)-1-({[(2*S*)-1-azido-3,3-dimethylbutan-2-yl]carbamoyl}amino)-2,2-dimethylpropyl]carbamate (**387-N_3**)



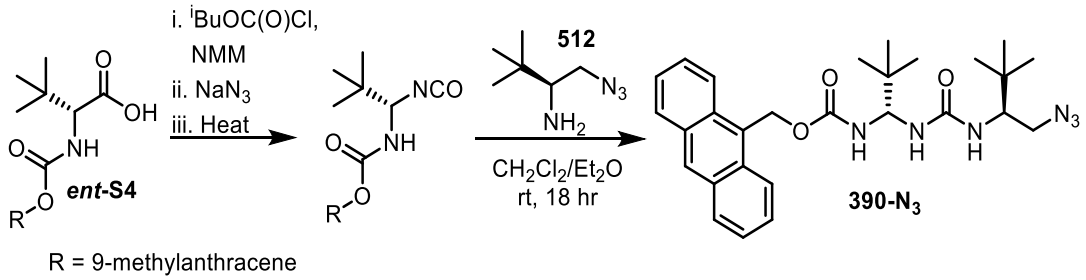
According to a modified literature procedure,[22] to a solution of **S4** (365 mg, 1.00 mmol, 1.0 eq) in THF (4.00 mL) at −20 °C were added sequentially isobutyl chloroformate (130 μL, 1.00 mmol, 1.0 eq) and *N*-methylmorpholine (110 μL, 1.00 mmol, 1.0 eq) and stirring was maintained for 20 min. To the reaction mixture was added sodium azide (98.0 mg, 1.50 mmol, 1.5 eq) in H_2O (1.00 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 hr and then the reaction mixture was cooled to room temperature and the crude amino azide (**512**,[iv] 156 mg, 1.00 mmol, 1.0 eq) as a solution in Et_2O (4.00 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 hr and then the volatiles removed *in vacuo*. The crude was triturated in toluene at 100 °C, cooled to room temperature, filtered, and washed with pentane to obtain **387-N_3** as a colourless solid in 40% yield (200 mg, 0.40 mmol). Data was consistent with that found in the literature.[22]

$[\alpha]_D^{25}$ = +20.8 (c = 0.91, $CHCl_3$); **Mp** 268 – 270 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.39 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 8.3 Hz, 2H), 7.57 (dt, *J* = 21.4, 7.1 Hz, 4H), 7.36 (d, *J* = 9.2 Hz, 1H), 6.08 (dq, *J* = 34.3, 12.3, 10.8 Hz, 4H), 5.26 (t, *J* = 9.5 Hz, 1H), 3.60 (dt, *J* = 9.7, 4.8 Hz, 1H), 3.43 (dd, *J* = 12.8, 3.6 Hz, 1H), 3.17 (dd, *J* = 12.7, 8.8 Hz, 1H), 0.84 (d, *J* = 5.6 Hz, 18H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 156.9, 155.7, 130.9, 130.5, 128.9, 128.5, 127.4, 126.5, 125.2, 124.2, 64.8, 57.8, 56.7,

[iv] *N*-Boc **512** is synthesized regularly and in large quantities by various group members. It is deprotected and free-based *in-situ* prior to being added to the iso(thio)cyante according to literature procedures.[22,31,32]

51.9, 36.2, 34.3, 26.4, 25.3; **IR** ν_{max}/cm^{-1}: 3658, 3376, 2977, 2887, 2172, 1667, 1385, 1259, 1004; **HRMS** (ESI+): calcd. for $C_{28}H_{36}N_6NaO_3$ $[M+Na]^+$ 527.2741, found 527.2742.

anthracen-9-ylmethyl ((*R*)-1-(3-((*S*)-1-azido-3,3-dimethylbutan-2-yl)ureido)-2,2-dimethylpropyl)carbamate (**390-N$_3$**)

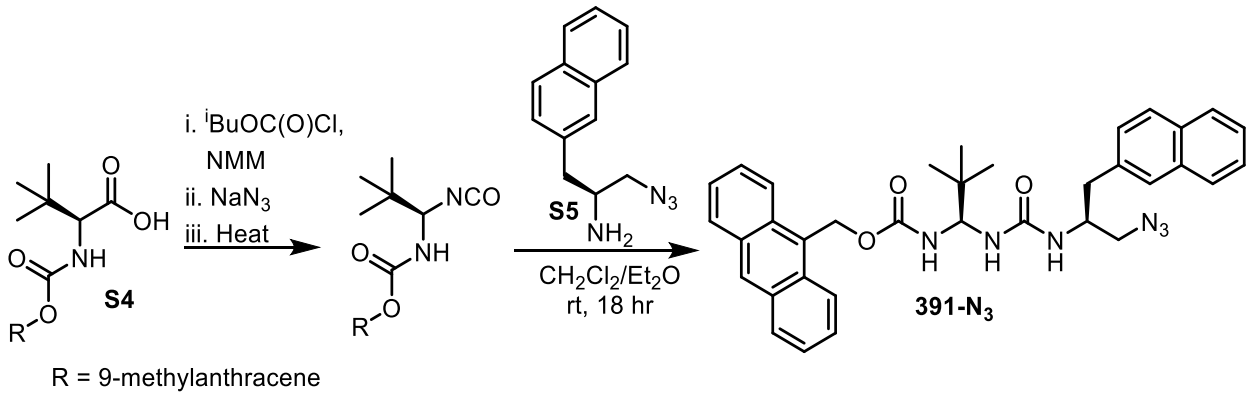


According to a modified literature procedure,[22] to a solution of ***ent*-S4** (365 mg, 1.00 mmol, 1.0 eq) in THF (4.00 mL) at −20 °C were added sequentially isobutyl chloroformate (130 μL, 1.00 mmol, 1.0 eq) and *N*-methylmorpholine (110 μL, 1.00 mmol, 1.0 eq) and stirring was maintained for 20 min. To the reaction mixture was added sodium azide (98.0 mg, 1.50 mmol, 1.5 eq) in H_2O (1.00 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 hr and then the reaction mixture was cooled to room temperature and the crude amino azide (156 mg, 1.00 mmol, 1.0 eq) as a solution in Et_2O (4.00 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 hr and then the volatiles removed *in vacuo*. The crude was triturated in toluene at 100 °C, cooled to room temperature, filtered, and washed with pentane to obtain **390-N$_3$** as a colourless solid in 29% yield (148 mg, 0.29 mmol).

$[\alpha]_D^{25}$ = −5.67 (c = 0.90, DMSO); **Mp** decomp >240 °C (toluene); **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.53 (s, 1H, ArC<u>H</u>), 8.39 (dd, *J* = 8.8, 1.1 Hz, 2H, ArC<u>H</u>), 8.05 (dq, *J* = 8.4, 0.8 Hz, 2H, ArC<u>H</u>), 7.58 (ddd, *J* = 8.9, 6.5, 1.4 Hz, 2H, ArC<u>H</u>), 7.50 (ddd, *J* = 7.8, 6.6, 1.1 Hz, 2H, ArC<u>H</u>), 6.25 – 5.99 (m, 2H, C<u>H</u>$_2$-anthracenyl), 5.36 – 5.26 (m, 2H, 2x N<u>H</u>), 4.88 (m, 2H, N<u>H</u> + NHC<u>H</u>NH), 3.76 (td, *J* = 9.7, 3.3 Hz, 1H, C<u>H</u>CH$_2$N$_3$), 3.24 (dd, *J* = 12.6, 3.3 Hz, 1H, CH$_a$<u>H</u>$_b$N$_3$), 2.83 (dd, *J* = 12.6, 9.7 Hz, 1H, C<u>H</u>$_a$H$_b$N$_3$), 0.97

(s, 9H, C(C<u>H</u>$_3$)$_3$), 0.93 (s, 9H, C(C<u>H</u>$_3$)$_3$). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 158.0 (carbamate <u>C</u>), 157.6 (urea <u>C</u>), 132.0 (Ar<u>C</u>), 131.6 (Ar<u>C</u>), 130.6 (Ar<u>C</u>) 129.8(Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 125.7(Ar<u>C</u>H), 124.7 (Ar<u>C</u>H), 67.4 (NH<u>C</u>HNH), 60.5 (<u>C</u>H$_2$-anthracenyl), 58.6 (<u>C</u>HCH$_2$N$_3$), 52.4 (<u>C</u>H$_2$N$_3$), 35.6 (<u>C</u>(CH$_3$)$_3$), 34.6 (<u>C</u>(CH$_3$)$_3$), 26.9 (C(<u>C</u>H$_3$)$_3$), 25.9 (C(<u>C</u>H$_3$)$_3$); **IR** ν_{max}/cm^{-1}: 2980, 2160, 2047, 2033, 1667 (C=O), 1534, 1241, 731; **HRMS** (ESI+): calcd. for $C_{28}H_{36}N_6NaO_3$ $[M+Na]^+$ 527.2741, found 527.2739.

<u>anthracen-9-ylmethyl ((S)-1-(3-((S)-1-azido-3-(naphthalen-2-yl)propan-2-yl)ureido)-2,2-dimethylpropyl)carbamate (**391-N$_3$**)</u>



According to a modified literature procedure,[22] to a solution of **S4** (365 mg, 1.00 mmol, 1.0 eq) in THF (4.00 mL) at −20 °C were added sequentially isobutyl chloroformate (130 μL, 1.00 mmol, 1.0 eq) and *N*-methylmorpholine (110 μL, 1.00 mmol, 1.0 eq) and stirring was maintained for 20 min. To the reaction mixture was added sodium azide (98.0 mg, 1.50 mmol, 1.5 eq) in H_2O (1.00 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 5.0 mL. The reaction mixture was heated to reflux for 2 hr and then the reaction mixture was cooled to room temperature and the crude amino azide **S5**[v] (226 mg, 1.00 mmol, 1.0 eq) as a solution in Et_2O (4.00 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 hr and then the volatiles removed *in vacuo*. The crude was recrystallised from hot

[v] Crude amino azide **S5** was obtained from the corresponding *N*-Boc **S5** prepared by Mr Jonathan Golec according to literature procedure.[24]

toluene/Et_2O, cooled to room temperature, filtered, and washed with pentane to obtain **391-N_3** as a colourless solid in 53% yield (313 mg, 0.53 mmol).

$[\alpha]_D^{25}$ = −19.67 (c = 0.87, DMSO); **Mp** decomp. >240 °C (toluene/Et_2O); **^{1}H NMR** (400 MHz, DMSO d_6) δ 8.34 (s, 1H, ArC<u>H</u>), 8.29 (d, *J* = 8.9 Hz, 2H, ArC<u>H</u>), 8.14 (d, *J* = 8.3 Hz, 1H, ArC<u>H</u>), 7.89 (d, *J* = 8.4 Hz, 2H, ArC<u>H</u>), 7.82 (dd, *J* = 8.0, 1.5 Hz, 1H, ArC<u>H</u>), 7.72 (d, *J* = 8.2 Hz, 1H, ArC<u>H</u>), 7.56 – 7.42 (m, 4H, ArC<u>H</u>), 7.41 – 7.28 (m, 3H, ArC<u>H</u>), 7.28 – 7.10 (m, 2H, ArC<u>H</u>), 6.17 – 5.91 (m, 2H, C<u>H</u>$_2$-anthracenyl), 5.39 (s, 1H, N<u>H</u>), 4.99 (m, 2H, N<u>H</u>+ NHC<u>H</u>NH), 4.24 (s, 1H, C<u>H</u>CH$_2$-N_3), 3.36 (dd, *J* = 12.4, 3.9 Hz, 1H, CH$_a$<u>H$_b$</u>-napthalene), 3.26 – 3.09 (m, 2H, C<u>H$_a$</u>H$_b$-napthalene+C<u>H$_a$</u>H$_b$N$_3$), 2.97 (dd, *J* = 14.0, 8.6 Hz, 1H, CH$_a$<u>H$_b$</u>N$_3$), 0.93 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 134.5 (Ar<u>C</u>), 134.4 (Ar<u>C</u>), 132.6 (Ar<u>C</u>), 131.8 (Ar<u>C</u>), 131.4 (Ar<u>C</u>), 129.6 (Ar<u>C</u>), 129.5(Ar<u>C</u>H), 129.2(Ar<u>C</u>H), 128.0(Ar<u>C</u>H), 127.9(Ar<u>C</u>H), 127.1(Ar<u>C</u>H), 126.8(Ar<u>C</u>H), 126.2(Ar<u>C</u>H), 125.9(Ar<u>C</u>H), 125.6(Ar<u>C</u>H), 124.5(Ar<u>C</u>H), 124.5(Ar<u>C</u>H), 66.4 (NH<u>C</u>HNH), 60.2 (<u>C</u>H$_2$-anthracenyl), 54.3(<u>C</u>H$_2$-napthalene), 51.1(<u>C</u>HCH$_2$N$_3$), 36.2 (<u>C</u>H$_2$N$_3$), 35.8 (<u>C</u>(CH$_3$)$_3$), 25.8 (C(<u>C</u>H$_3$)$_3$) (carbamate <u>C</u> and urea <u>C</u> not visible); **IR** ν_{max}/cm^{-1}: 3374, 3242, 2980, 1663 (C=O), 1534 (C=O), 1260, 778, 730; **HRMS** (ESI+): calcd. for $C_{35}H_{37}N_6O_3$ $[M+H]^+$ 589.2922, found 589.2912.

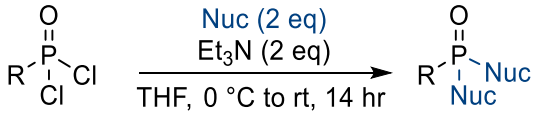
5.3.1.2 Synthesis of other catalysts tested during optimisation

All other known BIMP (**77**, **80**, **123**, **128**, **385**, **386, 388**, **389**), 3° amine (**392**, **393**) or phase transfer catalysts (**394-399**) were readily available in our laboratories at the time of the study, synthesized by past and current group members (including myself) according to literature procedures.[1–6,23,24] A small sample of phase transfer catalyst **397** was generously provided by the Smith group.

5.3.2 Substrate Synthesis:

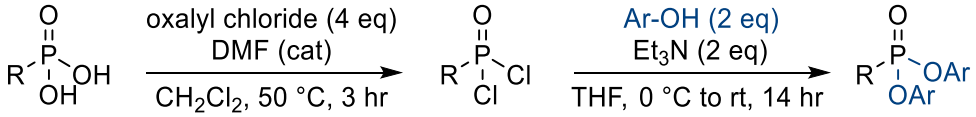
5.3.2.1 General Procedure IV: synthesis of P(V) desymmetrisation substrates

General Procedure **IV-A**: Substrate synthesis from phosphoryl dichloride:



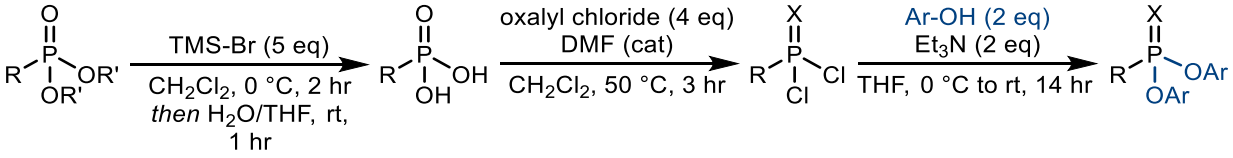
According to a modified literature procedure.[25] The corresponding phosphonic dichloride (4.00 mmol) and the corresponding nucleophile (8.00 mmol) were dissolved in THF (40.0 mL) and cooled to 0 °C. Et_3N (800 mg, 8 mmol, 1.10.0 mL) was added dropwise resulting in the formation of a colourless precipitate. The reaction mixture was then allowed to warm to room temperature and stirred for 14 hr. The reaction mixture was filtered, and the solvent was removed *in vacuo*. The resulting crude was dissolved in CH_2Cl_2 (40.0 mL) and was washed sequentially with 1M aq. NaOH (15.0 mL), brine (15.0 mL), 1M aq. HCl(15.0 mL) and 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 FCC as described in the individual experiment and subsequently triturated with pentane to afford the pure phosphonate ester.

General Procedure **IV-B**: Substrate synthesis from phosphonic acid:



According to a modified literature procedure.[26] The corresponding phosphonic acid (4.00 mmol) was dissolved in CH_2Cl_2 (8.00 mL) and a catalytic amount of DMF (0.10.0 mL) was added. The solution was heated to 50 °C and oxalyl chloride (1.36 mL, 16.0 mmol) 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 **IV-A**.

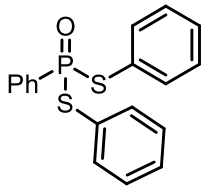
General Procedure **IV-C**: Substrate synthesis from alkyl phosphonate ester:



According to a modified literature procedure.[25] The corresponding alkyl phosphonate ester (4.00 mmol) was dissolved in CH_2Cl_2 (32.0 mL) and cooled to 0 °C then TMS-Br was added (5.28 mL, 20 mmol) and the solution was stirred for a further 2 hr. Volatiles were removed *in vacuo* and the crude was stirred in THF (13.6 mL) and H_2O (0.136 mL) 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 converted to the desired phosphonate ester following General Procedure **IV-B**.

5.3.2.2 Synthesis of starting materials

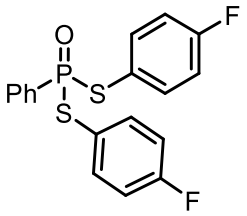
S,S-diphenyl phenylphosphonodithioate (**352**)



352 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and thiophenol (881 mg, 8.00 mmol, 0.822 mL) was used as nucleophile. Colourless solid (1.17 g, 3.42 mmol, 86% yield).

Mp 52 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 – 7.66 (m, 2H, ArC<u>H</u>), 7.46 – 7.36 (m, 5H ArC<u>H</u>), 7.35 – 7.28 (m, 2H, ArC<u>H</u>), 7.28 – 7.22 (m, 2H, ArC<u>H</u>), 7.21 – 7.16 (m, 4H, ArC<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.8 (d, *J* = 4.3 Hz, Ar<u>C</u>H), 133.9 (<u>C</u>P, other doublet peak beneath Ar<u>C</u>H) 132.8 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 131.8 (d, *J* = 10.8 Hz, Ar<u>C</u>H), 129.5 (d, *J* = 2.8 Hz, Ar<u>C</u>H), 129.4 (d, *J* = 2.3 Hz, Ar<u>C</u>H), 128.5 (d, *J* = 14.4 Hz, Ar<u>C</u>H), 126.4 (d, *J* = 6.0 Hz, <u>C</u>S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 49.69; **IR** (film) υ_{max}/cm^{-1}: 3058, 1577, 1477, 1439, 1214 (P=O), 1101, 1069, 744, 712, 688; **HRMS** (ESI+): calcd. for $C_{18}H_{16}OPS_2$ 343.03747 $[M+H]^+$, found 343.03741.

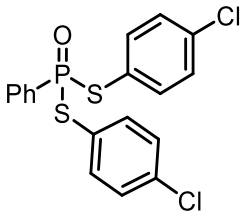
S,S-bis(4-fluorophenyl) phenylphosphonodithioate (**353**)



353 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 4-fluorothiophenol (1.03 g, 8.00 mmol, 0.852 mL) was used as nucleophile. Colourless solid (1.15 g, 3.04.00 mmol, 76% yield).

Mp 56 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$)δ 7.82 – 7.74 (m, 2H, phenyl ArCH), 7.56 – 7.49 (m, 1H, phenyl ArCH), 7.47 – 7.37 (m, 6H, 4x thiophenol + 2x phenyl ArCH), 7.03 – 6.90 (m, 4H, thiophenol ArCH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8 (dd, *J* = 250.7, 3.1 Hz, CF), 137.9 (dd, *J* = 8.7, 4.0 Hz, thiophenol ArCH), 133.1 (d, *J* = 3.4 Hz, phenyl ArCH), 133.0 (d, *J* = 108.0 Hz, CP), 131.7 (d, *J* = 10.9 Hz, phenyl ArCH), 128.7 (d, *J* = 14.4 Hz, phenyl ArCH), 121.3 (dd, *J* = 6.1, 3.4 Hz CS), 116.7 (dd, *J* = 22.2, 2.4 Hz, thiophenol ArCH); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 49.36 (t, *J* = 5.4 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –110.79 (ddt, *J* = 14.4, 8.8, 5.6 Hz); **IR** (film) υ_{max}/cm^{-1}: 3061, 1587, 1488, 1227 (P=O), 1157, 1104, 830, 691, 629; **HRMS** (ESI+): calcd. for $C_{18}H_{14}OF_2PS_2$ 379.01863 $[M+H]^+$, found 379.01868.

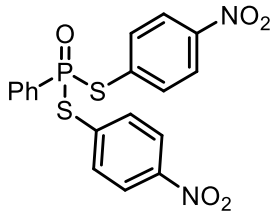
S,S-bis(4-chlorophenyl) phenylphosphonodithioate (**354**)



354 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 4-chlorothiophenol (1.16 g, 8.00 mmol) was used as nucleophile. Colourless solid (1.18 g, 2.87 mmol, 72% yield).

Mp 62 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 2H, phenyl ArC<u>H</u>), 7.59 – 7.51 (m, 1H, phenyl ArC<u>H</u>), 7.49 – 7.42 (m, 2H, phenyl ArC<u>H</u>), 7.41 – 7.36 (m, 4H, thiophenol ArC<u>H</u>), 7.28 – 7.23 (m, 4H, thiophenol ArC<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.9 (d, *J* = 4.2 Hz, thiophenol Ar<u>C</u>H), 136.3 (d, *J* = 3.4 Hz, <u>C</u>Cl), 133.2 (d, *J* = 3.3 Hz, phenyl Ar<u>C</u>H), 132.9 (d, *J* = 108.4 Hz, <u>C</u>P), 131.7 (d, *J* = 11.1 Hz, phenyl Ar<u>C</u>H), 129.6 (d, *J* = 2.3 Hz, thiophenol Ar<u>C</u>H), 128.8 (d, *J* = 14.4 Hz, phenyl Ar<u>C</u>H), 124.6 (d, *J* = 6.2 Hz, <u>C</u>S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 48.83; **IR** (film) υ_{max}/cm^{-1}: 3058, 1571, 1474, 1438, 1390, 1215 (P=O), 1084, 1013, 819,746, 690; **HRMS** (ESI+): calcd. for $C_{18}H_{14}O^{35}Cl_2PS_2$ 410.95952, found 410.95947.

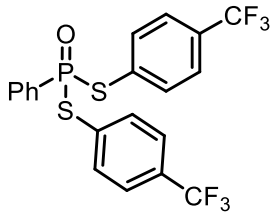
S,S-bis(4-nitrophenyl) phenylphosphonodithioate (**355**)



355 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 4-nitrothiophenol (1.24 g, 8.00 mmol) was used as nucleophile. Pale yellow solid (1.16 g, 2.68 mmol, 67% yield).

Mp 52 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 8.09 (m, 4H, thiophenol ArC<u>H</u>), 7.91 – 7.81 (m, 2H, phenyl ArC<u>H</u>), 7.72 – 7.65 (m, 4H, thiophenol ArC<u>H</u>), 7.64 – 7.57 (m, 1H, phenyl ArC<u>H</u>), 7.50 (ddd, *J* = 8.7, 6.9, 4.9 Hz, 2H, phenyl ArC<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.6 (<u>C</u>NO_2), 135.9 (d, *J* = 4.6 Hz, thiophenol Ar<u>C</u>H), 134.8 (d, *J* = 6.0 Hz, phenyl Ar<u>C</u>H), 134.0 (d, *J* = 3.5 Hz, <u>C</u>S), 132.2 (d, *J* = 110.4 Hz, <u>C</u>P), 131.7 (d, *J* = 11.3 Hz, phenyl Ar<u>C</u>H), 129.2 (d, *J* = 14.8 Hz, phenyl Ar<u>C</u>H), 124.3 (d, *J* = 1.8 Hz, thiophenol Ar<u>C</u>H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 47.99; **IR** (film) υ_{max}/cm^{-1}: 3099, 1597, 1576, 1514 (NO_2), 1477, 1438, 1338 (NO_2), 1215 (P=O), 1101, 1013, 960, 851, 742, 713, 689; **HRMS** (ESI+): calcd. for $C_{18}H_{14}O_5N_2PS_2$ 433.00763 $[M+H]^+$, found 433.00775.

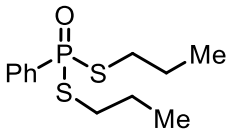
S,S-bis(4-(trifluoromethyl)phenyl) phenylphosphonodithioate (**356**)



356 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 4-trifluoromethylthiophenol (1.43 g, 8.00 mmol, 1.10.0 mL) was used as nucleophile. Colourless wax (1.11 g, 2.32 mmol, 58% yield).

Mp 28 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.79 (m, 2H, phenyl ArC<u>H</u>), 7.63 – 7.56 (m, 5H, 4x thiophenol + phenyl ArC<u>H</u>), 7.56 – 7.51 (m, 4H, thiophenol ArC<u>H</u>), 7.47 (ddd, *J* = 8.6, 6.8, 4.7 Hz, 2H, phenyl ArC<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.7 (d, *J* = 4.3 Hz, thiophenol Ar<u>C</u>H), 133.6 (d, *J* = 3.5 Hz, phenyl Ar<u>C</u>H), 132.7 (d, *J* = 109.9 Hz, <u>C</u>P), 131.9 (d, *J* = 2.8 Hz, phenyl Ar<u>C</u>H), 131.6 (d, *J* = 11.2 Hz, phenyl Ar<u>C</u>H), 131.1 (d, *J* = 6.1 Hz, thiophenol Ar<u>C</u>H), 129.0 (d, *J* = 14.7 Hz, phenyl Ar<u>C</u>H), 126.2 (qd, *J* = 3.9, 2.1 Hz, <u>C</u>CF_3) 123.8 (q, *J* = 272.6 Hz, <u>C</u>F_3); **^{19}F NMR** (376 MHz, $CDCl_3$) δ – 62.97; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 48.42; **IR** (film) υ_{max}/cm^{-1}: 1321, 1217 (P=O), 1167, 1124, 1104, 1088, 1062, 1015, 834, 690; **HRMS** (ESI+): calcd. for $C_{20}H_{14}OF_6PS_2$ 479.01224 $[M+H]^+$, found 479.01199.

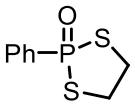
S,S-dipropyl phenylphosphonodithioate (**357**)



357 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and *n*-propane thiol (377 mg, 8.00 mmol, 0.335 mL) was used as nucleophile. Pale yellow oil (846 mg, 3.08 mmol, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.89 (m, 2H, ArC<u>H</u>), 7.59 – 7.44 (m, 3H, ArC<u>H</u>), 2.88 (dt, *J* = 12.7, 7.3 Hz, 4H, $SC\underline{H_2}CH_2CH_3$), 1.68 (h, *J* = 7.3 Hz, 4H, $SCH_2C\underline{H_2}CH_3$), 0.95 (t, *J* = 7.3 Hz, 6H, $SCH_2CH_2C\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.5 (d, *J* = 110.1 Hz, <u>C</u>P), 132.7 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 131.2 (d, *J* = 11.2 Hz, Ar<u>C</u>H), 128.7 (d, *J* = 14.1 Hz, Ar<u>C</u>H), 33.2 (d, *J* = 3.2 Hz, $S\underline{C}H_2CH_2CH_3$), 24.3 (d, *J* = 4.9 Hz, $SCH_2\underline{C}H_2CH_3$), 13.4 ($SCH_2CH_2\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 54.42; **IR** (film) υ_{max}/cm^{-1}: 2963, 2931, 2872, 1437, 1241 (P=O), 1198, 1103, 749, 711, 692; **HRMS** (ESI+): calcd. For $C_{12}H_{20}OPS_2$ 275.06877 $[M+H]^+$, found 275.06873.

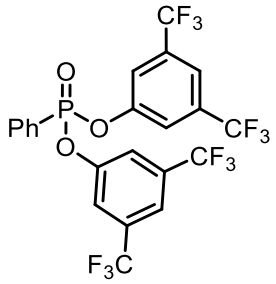
2-phenyl-1,3,2-dithiaphospholane 2-oxide (**358**)



358 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and ethane-1,2-dithiol (376.5 mg, 4.00 mmol, 335 μL) was used as nucleophile. No base wash was performed for this compound. Colourless solid (673 mg, 3.12 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 2H), 7.60 – 7.54 (m, 1H), 7.53 – 7.46 (m, 2H), 3.90 – 3.73 (m, 2H), 3.71 – 3.53 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.9 (d, J = 114.8 Hz), 132.9 (d, J = 3.5 Hz), 132.2 (d, J = 11.9 Hz), 128.7 (d, J = 14.9 Hz), 41.3; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 74.45. Data consistent with the literature.[27]

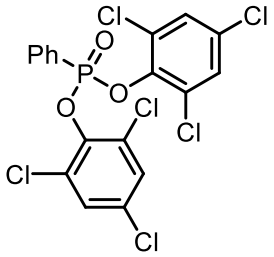
bis(3,5-bis(trifluoromethyl)phenyl) phenylphosphonate (**359**)



359 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 3,5-bis(trifluoromethyl)phenol (1.84 g, 8.00 mmol, 1.22 mL) was used as nucleophile. Colourless wax (1.41 g, 2.42 mmol, 61% yield).

Mp 51 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.98 (m, 2H, PhH), 7.76 – 7.67 (m, 7H, ArCH), 7.64 – 7.58 (m, 2H, ArCH); **^{13}C NMR**(101 MHz, $CDCl_3$) δ 150.7 (d, *J* = 7.3 Hz, CO), 134.8 (d, *J* = 3.3 Hz, ArCH), 133.8 (q, *J* = 34.4 Hz, CF_3), 132.4 (d, *J* = 11.0 Hz, ArCH), 129.5 (d, *J* = 16.3 Hz, ArCH), 124.5 (d, *J* = 194.1 Hz, CP), 124.0 (ArCH), 121.4 (p, *J* = 4.0 Hz, ArCH), 119.6 (q, *J* = 3.9 Hz, CCF_3); **^{19}F NMR** δ (376 MHz, $CDCl_3$) –63.18; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.76; **IR** (film) υ_{max}/cm^{-1}: 3727, 3629, 1462, 1362,1278 (P=O), 1176, 1134, 1007, 894, 699; **HRMS** (ESI+): calcd. for $C_{22}H_{12}O_3F_{12}P$ 583.03270 $[M+H]^+$, 583.03271 found.

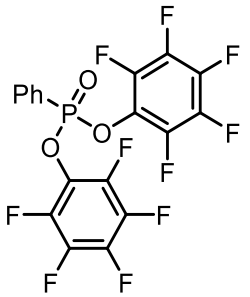
bis(2,4,6-trichlorophenyl) phenylphosphonate (**360**)



360 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 2,4,6-trichlorophenol (1.58 g, 8.00 mmol) was used as nucleophile. Colourless solid (1.21 g, 2.33 mmol, 58% yield).

Mp 135°C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 – 8.07 (m, 2H, phenyl C<u>H</u>), 7.68 – 7.59 (m, 1H, phenyl C<u>H</u>), 7.55 – 7.47 (m, 3H, phenyl C<u>H</u>), 7.30 (d, *J* = 0.7 Hz, 4H, trichlorophenol C<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2 (d, *J* = 10.3 Hz, <u>C</u>Cl), 133.9 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 132.7 (d, *J* = 11.0 Hz, <u>C</u>Cl), 131.3 (d, *J* = 2.4 Hz, <u>C</u>O), 129.4 (d, *J* = 3.7 Hz, Ar<u>C</u>H), 129.0 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 128.5 (d, *J* = 16.7 Hz, Ar<u>C</u>H), 126.4 (d, *J* = 196.7 Hz, <u>C</u>P); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 11.90; **IR** (film) υ_{max}/cm^{-1}: 3066, 1560, 1445, 1386, 1292, 1239 (P=O), 1129, 916, 857, 825 (C-Cl), 732, 693; **HRMS** (ESI+): calcd. for $C_{18}H_{10}O_3{}^{35}Cl_6P$ 514.84932 $[M+H]^+$, found 514.84943.

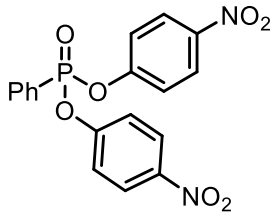
bis(perfluorophenyl) phenylphosphonate (**361**)



361 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and perfluorophenol (1.47 g, 8.00 mmol) was used as nucleophile. Colourless oil (1.14 g, 2.33 mmol, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.02 (m, 2H, PhH), 7.77 (tdd, *J* = 7.1, 2.9, 1.5 Hz, 1H, phenyl para-CH), 7.63 (dddd, *J* = 8.1, 6.4, 5.4, 1.1 Hz, 2H, phenyl H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.7 (m, CF), 140.1 (m, CF), 139.4 (m, CF), 136.9 (CO), 134.9 (d, *J* = 3.5 Hz, ArCH), 132.5 (d, *J* = 11.5 Hz, ArCH), 129.2 (d, *J* = 17.1 Hz, ArCH), 123.7 (d, *J* = 197.1 Hz, CP); **^{31}P NMR** (162 MHz, $CDCl_3$) 17.04; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –151.94- –153.35 (m), –158.07 (td, *J* = 22.0, 4.4 Hz), –161.49 (qt, *J* = 15.6, 7.8 Hz); **IR** (film) υ_{max}/cm^{-1}: 1517, 1480, 1296 (P=O), 1131, 1022, 996, 835, 818, 712, 692; **HRMS** (ESI+): calcd. for $C_{18}H_6O_3F_{10}P$ 490.98894 $[M+H]^+$, found 490.98901.

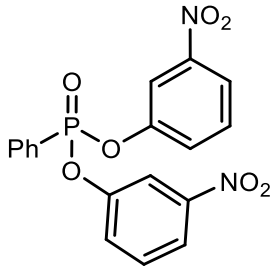
bis(4-nitrophenyl) phenylphosphonate (**362**)



362 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 4-nitrophenol (1.11 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (1.15g, 2.87 mmol, 72% yield).

Mp 76 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 – 8.18 (m, 4H, Nitrophenol C<u>H</u>), 8.05 – 7.91 (m, 2H, Ph<u>H</u>), 7.74 – 7.65 (m, 1H, Ph<u>H</u>), 7.62 – 7.52 (m, 2H, Ph<u>H</u>), 7.42 – 7.33 (m, 4H, Nitrophenol C<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.9 (d, *J* = 7.0 Hz, <u>C</u>NO_2), 145.2 (<u>C</u>O), 134.5 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.4 (d, *J* = 10.8 Hz, Ar<u>C</u>H), 129.3 (d, *J* = 16.2 Hz, Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 124.0 (<u>C</u>P, other peak beneath others), 121.3 (d, *J* = 4.9 Hz, Ar<u>C</u>H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.72; **IR** (film) υ_{max}/cm^{-1}: 3082, 1614, 1590, 1520 (NO_2), 1488, 1345 (NO_2), 1200 (P=O), 1161, 1131, 917, 857, 748, 690; **HRMS** (ESI+): calcd. for $C_{18}H_{13}O_7N_2NaP$ 423.03526 $[M+Na]^+$, found 423.03516.

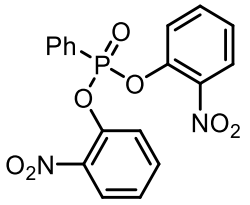
bis(3-nitrophenyl) phenylphosphonate (**381**)



381 was synthesized following GP **IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 3-nitrophenol (1.11 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3 Colourless solid (1.21 g, 3.02 mmol, 76% yield).

Mp 88 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 – 7.95 (m, 6H, ArC<u>H</u>), 7.73 – 7.66 (m, 1H, ArC<u>H</u>), 7.64 – 7.55 (m, 4H, ArC<u>H</u>), 7.55 – 7.48 (m, 2H, ArC<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.5 (d, *J* = 7.2 Hz, <u>C</u>NO_2), 149.1 (<u>C</u>O), 134.4 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.4 (d, *J* = 10.8 Hz, Ar<u>C</u>H), 130.7 (Ar<u>C</u>H), 129.3 (d, *J* = 16.3 Hz, Ar<u>C</u>H), 126.9 (d, *J* = 4.3 Hz, Ar<u>C</u>H), 125.0 (d, *J* = 193.1 Hz, <u>C</u>P), 120.6 (Ar<u>C</u>H), 116.3 (d, *J* = 5.1 Hz, Ar<u>C</u>H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.45; **IR** (film) υ_{max}/cm^{-1}: 3086, 1598, 1524 (NO_2), 1488, 1356 (NO_2), 1224 (P=O), 1164, 1138, 857, 744, 698; **HRMS** (ESI+): calcd. for $C_{18}H_{14}O_7N_2P$ 401.0553 $[M+H]^+$, found 401.0525.

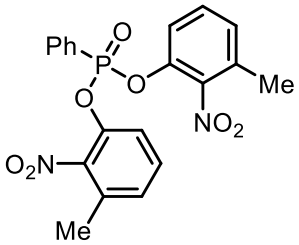
bis(2-nitrophenyl) phenylphosphonate (**382**)



382 was synthesized following GP **IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 2-nitrophenol (1.11 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Pale yellow solid (1.11 g, 2.78 mmol, 70% yield).

Mp 58 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 – 8.05 (m, 2H, phenyl ArC<u>H</u>), 7.94 (dt, *J* = 8.4, 1.2 Hz, 2H, ArC<u>H</u>), 7.71 – 7.65 (m, 1H, phenyl ArC<u>H</u>), 7.61 – 7.48 (m, 6H, ArC<u>H</u>), 7.33 – 7.27 (m, 2H, ArC<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1 (d, *J* = 7.6 Hz, <u>C</u>NO_2), 141.6 (<u>C</u>O), 134.5 (d, *J* = 1.4 Hz, Ar<u>C</u>H), 134.4 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 132.7 (d, *J* = 11.3 Hz, phenyl Ar<u>C</u>H), 129.1 (d, *J* = 16.7 Hz, phenyl Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 125.8 (d, *J* = 1.2 Hz, Ar<u>C</u>H), 124.8 (d, *J* = 196.5 Hz, <u>C</u>P), 123.3 (d, *J* = 3.2 Hz, Ar<u>C</u>H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.90; **IR** (film) υ_{max}/cm^{-1}: 1602, 1526 (NO_2), 1480, 1349 (NO_2), 1264 (P=O), 1213, 1130, 1089, 919, 846, 779, 746; **HRMS** (ESI+): calcd. for $C_{18}H_{14}O_7N_2P$ 401.0553 $[M+H]^+$, found 401.0525.

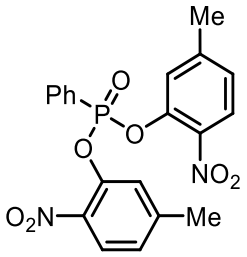
bis(3-methyl-2-nitrophenyl) phenylphosphonate (**408**)



408 was synthesized following **GP IV-A.** Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 3-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (1.18 g, 2.77 mmol, 69% yield).

Mp 82 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.89 (m, 2H, ArC<u>H</u>), 7.70 – 7.62 (m, 1H, ArC<u>H</u>), 7.58 – 7.50 (m, 2H, ArC<u>H</u>), 7.37 (dtd, *J* = 8.4, 1.3, 0.6 Hz, 2H, ArC<u>H</u>), 7.30 (dd, *J* = 8.4, 7.6 Hz, 2H, ArC<u>H</u>), 7.09 (ddt, *J* = 7.5, 1.4, 0.7 Hz, 2H, ArC<u>H</u>), 2.32 (s, 6H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1(<u>C</u>O), 141.6 (d, *J* = 7.1 Hz, <u>C</u>NO_2), 134.4 (d, *J* = 3.4 Hz, Ar<u>C</u>H), 132.6 (d, *J* = 11.2 Hz, Ar<u>C</u>H), 132.3 (<u>C</u>CH_3), 131.1 (Ar<u>C</u>H), 129.1 (d, *J* = 16.6 Hz, Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 124.5 (d, *J* = 195.2 Hz, <u>C</u>P), 119.1 (d, *J* = 3.1 Hz, Ar<u>C</u>H), 17.5 (<u>C</u>H_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.62; **IR** υ_{max}/cm^{-1}: 3320, 2970, 2095, 1641, 1546 (NO_2), 1356 (NO_2), 1276, 1261 (P=O), 1185, 1131, 1055, 695; **HRMS** (ESI+): calcd. for $C_{20}H_{18}O_7N_2P$ 429.0846 $[M+H]^+$, found 429.0848.

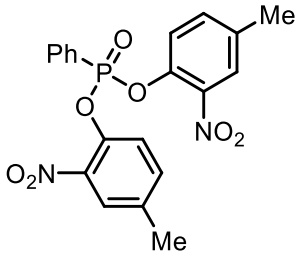
bis(5-methyl-2-nitrophenyl) phenylphosphonate (**409**)



409 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (1.30 g, 3.06 mmol, 76% yield).

Mp 76 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 – 8.04 (m, 2H, PhH), 7.87 (dd, *J* = 8.4, 0.9 Hz, 2H, 2-NO_2-5-Me-phenol CHCH), 7.72 – 7.63 (m, 1H, PhH), 7.61 – 7.52 (m, 2H, PhH), 7.31 (td, *J* = 1.7, 0.8 Hz, 2H, 2-NO_2-5-Me-phenol CH), 7.08 (ddt, *J* = 8.4, 1.7, 0.8 Hz, 2H, 2-NO_2-5-Me-phenol CHCH), 2.37 (s, 6H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.5 (ArC), 143.1 (d, *J* = 7.9 Hz, ArC), 139.2 (CCH_3), 134.3 (d, *J* = 3.3 Hz, ArCH), 132.8 (d, *J* = 11.3 Hz, ArCH), 129.0 (d, *J* = 16.7 Hz, ArCH), 126.4 (ArCH), 126.1 (2-NO_2-5-Me-phenol CHCH), 125.0 (2-NO_2-5-Me-phenol CHCH) (d, *J* = 196.6 Hz, CP), 123.6 (d, *J* = 3.3 Hz, 2-NO_2-5-Me-phenol CH), 21.7 (CH_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.57; **IR** (film) υ_{max}/cm^{-1}: 1591, 1521 (NO_2), 1491, 1345 (NO_2), 1265, 1242 (P=O), 1171, 1129, 1086, 853, 828, 752, 731, 711; **HRMS** (ESI+): calcd. for $C_{20}H_{18}O_7N_2P$ 429.0846 $[M+H]^+$, found 429.0840.

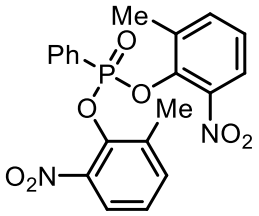
bis(4-methyl-2-nitrophenyl) phenylphosphonate (**410**)



410 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (779.9 mg, 4.00 mmol, 567 μL) was used and 4-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (1.29 g, 3.02 mmol, 76% yield).

Mp 126 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 7.98 (m, 2H, PhH), 7.72 (dd, *J* = 2.0, 1.0 Hz, 2H, PhH), 7.68 – 7.62 (m, 1H, PhH), 7.58 – 7.50 (m, 2H, 2-NO_2-4-Me-phenol CH), 7.37 (dd, *J* = 8.4, 1.5 Hz, 2H, 2-NO_2-4-Me-phenol CHCH), 7.34 – 7.28 (m, 2H, 2-NO_2-4-Me-phenol CHCH), 2.36 (d, *J* = 0.9 Hz, 6H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.1 (d, *J* = 6.2 Hz, ArC), 140.8 (d, *J* = 7.8 Hz, ArC), 136.2 (d, *J* = 1.4 Hz, CCH_3), 135.1 (d, *J* = 1.6 Hz, 2-NO_2-4-Me-phenol CHCH), 134.2 (d, *J* = 3.4 Hz, ArCH), 132.7 (d, *J* = 11.2 Hz, ArCH), 129.0 (d, *J* = 16.6 Hz, ArCH), 126.1 (NO_2-4-Me-phenol CH), 124.9 (d, *J* = 196.0 Hz, CP), 123.0 (d, *J* = 3.2 Hz, 2-NO_2-4-Me-phenol CHCH), 20.7 (CH_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.98; **IR** (film) υ_{max}/cm^{-1}: 1531 (NO_2), 1496, 1351 (NO_2), 1232 (P=O), 1205, 1130, 1086, 936, 901, 808; **HRMS** (ESI+): calcd. for $C_{20}H_{18}O_7N_2P$ 429.0846 $[M+H]^+$, found 429.0838.

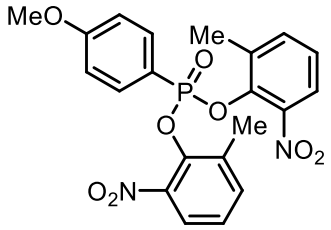
bis(2-methyl-6-nitrophenyl) phenylphosphonate (**411**)



411 was synthesized following **GP IV-A**. Phenylphosphonic dichloride (780.0 mg, 4.00 mmol, 567 μL) was used and 6-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (1.17 g, 2.73 mmol, 68% yield).

Mp 168 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.95 (m, 2H, phenyl ArC<u>H</u>), 7.68 (dd, *J* = 8.1, 1.7 Hz, 3H, 1x phenyl ArC<u>H</u> + 2x nitrophenol ArC<u>H</u>), 7.41 (ddt, *J* = 7.6, 1.6, 0.8 Hz, 2H, phenyl ArC<u>H</u>), 7.19 (td, *J* = 7.9, 1.2 Hz, 2H, nitrophenol ArC<u>H</u>), 7.07 – 6.98 (m, 2H, nitrophenol ArC<u>H</u>), 2.18 (s, 6H, C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6 (Ar<u>C</u>), 140.9 (d, *J* = 9.9 Hz, Ar<u>C</u>), 136.0 (d, *J* = 1.8 Hz, nitrophenol ArC<u>H</u>), 134.2 (d, *J* = 3.7 Hz, phenyl ArC<u>H</u>), 134.2 (d, *J* = 3.3 Hz, Ar<u>C</u>), 132.9 (d, *J* = 11.1 Hz, phenyl ArC<u>H</u>), 129.0 (d, *J* = 16.4 Hz, phenyl ArC<u>H</u>), 125.7 (d, *J* = 195.9 Hz, <u>C</u>P), 125.6 (d, *J* = 1.8 Hz, nitrophenol ArC<u>H</u>), 123.4 (d, *J* = 1.7 Hz, nitrophenol ArC<u>H</u>), 17.2 (<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.01; **IR** (film) υ_{max}/cm^{-1}: 1532 (NO_2), 1471, 1357 (NO_2), 1275, 1213 (P=O), 1178, 1152, 1130, 1092, 933, 803; 751, 694; **HRMS** (ESI+): calcd. for $C_{20}H_{18}O_7N_2P$ 429.0846 $[M+H]^+$, found 429.0842.

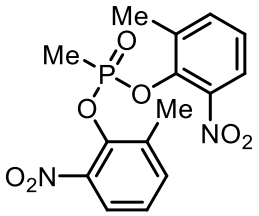
bis(2-methyl-6-nitrophenyl) (4-methoxyphenyl)phosphonate (**438**)



438 was synthesized following **GP IV-A**. 4-methoxyphenyl phosphonic dichloride (900.0 mg, 4.00 mmol, 635 μL) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 6:4. Colourless solid (1.33 g, 2.90 mmol, 72% yield).

Mp 127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.95 (m, 2H, *p*-$OMeC_6H_4$-H), 7.68 (dd, *J* = 8.1, 1.7 Hz, 2H, phenyl ArCH), 7.41 (ddt, *J* = 7.6, 1.6, 0.8 Hz, 2H, phenyl ArCH), 7.19 (td, *J* = 7.9, 1.2 Hz, 2H, phenyl ArCH), 7.07 – 6.98 (m, 2H, *p*-$OMeC_6H_4$-H), 3.89 (s, 3H, OCH_3), 2.18 (s, 6H, $ArCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.3 (d, *J* = 3.6 Hz, COMe), 143.7 (d, *J* = 3.2 Hz, ArC), 141.0 (d, *J* = 9.9 Hz, ArC), 135.9 (d, *J* = 1.8 Hz, ArCH), 135.1 (d, *J* = 13.0 Hz, ArCH), 134.3 (d, *J* = 3.8 Hz, ArC), 125.4 (d, *J* = 1.9 Hz, ArCH), 123.3 (d, *J* = 1.7 Hz, ArCH), 116.5 (d, *J* = 204.5 Hz, CP), 114.5 (d, *J* = 17.8 Hz), 55.6 (OCH_3), 17.2 (CH_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 14.12; **IR** (film) υ_{max}/cm^{-1}:1598, 1531 (NO_2), 1471, 1357 (NO_2), 1260, 1213 (P=O), 1179, 1157, 1129, 1092, 906, 804, 756; **HRMS** (ESI+): calcd. for $C_{21}H_{20}N_2O_8P$ 459.0952 $[M+H]^+$, found 459.0945.

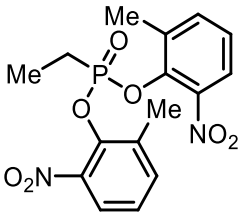
bis(2-methyl-6-nitrophenyl) methylphosphonate (**439**)



439 was synthesized following **GP IV-A**. Methylphosphonic dichloride (532 mg, 4.00 mmol, 362 μL) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (520.0 mg, 1.42 mmol, 35% yield).

Mp 138 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.1, 1.7 Hz, 2H, ArC<u>H</u>), 7.50 (ddt, *J* = 7.7, 1.7, 0.8 Hz, 2H, ArC<u>H</u>), 7.24 (td, *J* = 7.9, 1.2 Hz, 2H, ArC<u>H</u>), 2.40 (d, *J* = 0.9 Hz, 6H, ArC<u>H</u>$_3$), 1.98 (d, *J* = 18.0 Hz, 3H, C<u>H</u>$_3$P); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.0 (Ar<u>C</u>), 141.2 (d, *J* = 9.8 Hz, Ar<u>C</u>), 136.3 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 134.0 (d, *J* = 3.5 Hz, Ar<u>C</u>), 125.5 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 123.6 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 17.2 (Ar<u>C</u>H$_3$), 13.1 (d, *J* = 143.8 Hz, <u>C</u>H$_3$P); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 26.75; **IR** (film) υ_{max}/cm^{-1}: 1598, 1531 (NO_2), 1471, 1357 (NO_2), 1314, 1269 (P=O), 1214, 1180, 1158, 1093, 925, 803, 752; **HRMS** (ESI+) calcd. for $C_{15}H_{16}N_2O_7P$ 367.0690 $[M+H]^+$, found 367.0702.

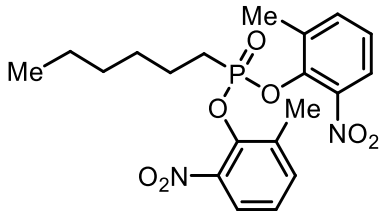
bis(2-methyl-6-nitrophenyl) ethylphosphonate (**440**)



440 was synthesized following **GP IV-A**. Ethylphosphonic dichloride (588 mg, 4.00 mmol, 427 μL) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (1.08 g, 2.84 mmol, 71% yield).

Mp 126 °C (pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.2, 1.7 Hz, 2H, ArC<u>H</u>), 7.45 (ddt, *J* = 7.6, 1.7, 0.8 Hz, 2H, ArC<u>H</u>), 7.20 (td, *J* = 7.9, 1.2 Hz, 2H, ArC<u>H</u>), 2.35 (d, *J* = 0.9 Hz, 6H, ArC<u>H</u>$_3$), 2.21 (dq, *J* = 18.4, 7.6 Hz, 2H, C<u>H</u>$_2$CH$_3$), 1.39 (dt, *J* = 22.4, 7.6 Hz, 3H, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (Ar<u>C</u>), 141.1 (d, *J* = 10.5 Hz, Ar<u>C</u>), 136.1 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 134.0 (d, *J* = 3.6 Hz, Ar<u>C</u>), 125.4 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 123.5 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 21.0 (d, *J* = 140.1 Hz, <u>C</u>H$_2$P), 17.1 (Ar<u>C</u>H$_3$), 6.7 (d, *J* = 7.6 Hz, CH$_2$CH$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 29.73; **IR** (film) υ_{max}/cm^{-1}: 2981, 1532 (NO_2), 1472, 1356 (NO_2), 1266 (P=O), 1213, 1179, 924, 909, 804, 773, 747; **HRMS** (ESI+) calcd. for $C_{16}H_{18}N_2O_7P$ 381.0846 $[M+H]^+$, found 381.0838.

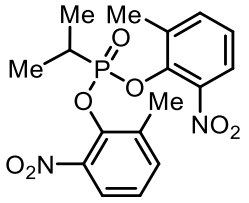
bis(2-methyl-6-nitrophenyl) hexylphosphonate (**441**)



441 was synthesized following **GP IV-A**. Hexylphosphonic dichloride (812.0 mg, 4.00 mmol, 685 μL) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (955 mg, 2.19 mmol, 55% yield).

Mp 80 °C (pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.1, 1.7 Hz, 2H, ArC<u>H</u>), 7.45 (ddt, *J* = 7.7, 1.7, 0.8 Hz, 2H, ArC<u>H</u>), 7.20 (td, *J* = 7.9, 1.1 Hz, 2H, ArC<u>H</u>), 2.34 (s, 6H, C<u>H</u>$_3$), 2.25 – 2.11 (m, 2H, C<u>H</u>$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.87 – 1.72 (m, 2H, CH$_2$C<u>H</u>$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.46 (p, *J* = 7.2 Hz, 2H, CH$_2$CH$_2$C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 1.36 – 1.27 (m, 4H, CH$_2$CH$_2$CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 0.92 – 0.85 (m, 3H, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (d, *J* = 3.4 Hz, Ar<u>C</u>), 141.1 (d, *J* = 10.5 Hz, Ar<u>C</u>), 136.0 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 133.9 (d, *J* = 3.6 Hz, Ar<u>C</u>), 125.4 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 123.4 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 31.3 (d, *J* = 1.4 Hz, CH$_2$CH$_2$CH$_2$<u>C</u>H$_2$CH$_2$CH$_3$), 30.4 (d, *J* = 18.4 Hz, CH$_2$<u>C</u>H$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 27.7 (d, *J* = 137.0 Hz, <u>C</u>H$_2$P), 22.5 (CH$_2$CH$_2$<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$), 22.4 (CH$_2$CH$_2$CH$_2$CH$_2$<u>C</u>H$_2$CH$_3$) (d, *J* = 6.1 Hz, Ar<u>C</u>H$_3$), 17.1 (Ar<u>C</u>H$_3$), 14.1 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 28.68; **IR** (film) υ_{max}/cm^{-1}: 2926, 1532 (NO_2), 1470, 1356 (NO_2), 1275, 1214 (P=O), 1179, 1093, 1092, 906, 802, 752; **HRMS** (ESI+) calcd. for $C_{20}H_{26}N_2O_7P$ 437.1472 $[M+H]^+$, found 437.1461.

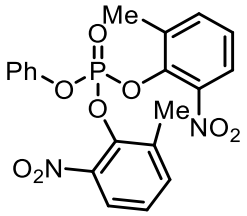
bis(2-methyl-6-nitrophenyl) isopropylphosphonate (**442**)



442 was synthesized following **GP IV-A**. Isopropylphosphonic dichloride (643 mg, 4.00 mmol, 501 μL) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (741 mg, 1.88 mmol, 47% yield).

Mp 138 °C (pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.1, 1.7 Hz, 2H, ArC<u>H</u>), 7.44 (ddt, *J* = 7.7, 1.7, 0.8 Hz, 2H, ArC<u>H</u>), 7.19 (td, *J* = 7.9, 1.1 Hz, 2H, ArC<u>H</u>), 2.42 – 2.35 (m, 1H, C<u>H</u>CH_3), 2.34 – 2.33 (m, 6H, ArC<u>H</u>$_3$), 1.42 (dd, *J* = 20.8, 7.1 Hz, 6H CHC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6 (Ar<u>C</u>), 141.2 (d, *J* = 11.2 Hz, Ar<u>C</u>), 135.9 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 133.8 (d, *J* = 3.6 Hz, Ar<u>C</u>), 125.3 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 123.3 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 28.2 (d, *J* = 138.1 Hz C<u>H</u>P), 17.2 (ArC<u>H</u>$_3$), 16.4 (d, *J* = 5.5 Hz, C<u>H</u>CH_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 31.54; **IR** υ_{max}/cm^{-1}: 3318, 2970, 2095, 1640, 1532 (NO_2), 1355 (NO_2), 1262 (P=O), 1179, 1092, 934, 906, 756, 696; **HRMS** (ESI+) calcd. for $C_{17}H_{20}N_2O_7P$ 395.1003 $[M+H]^+$, found 395.1008.

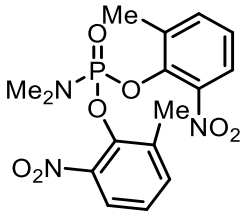
bis(2-methyl-6-nitrophenyl) phenyl phosphate (**444**)



444 was synthesized following **GP IV-A**. Phenyl dichlorophosphate (843 mg, 597 μL, 4.00 mmol) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (1.30 g, 2.92 mmol, 73% yield).

Mp 42 °C (pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.2, 1.7 Hz, 2H, ArC<u>H</u>), 7.50 (ddt, *J* = 7.7, 1.7, 0.9 Hz, 2H, ArC<u>H</u>), 7.36 – 7.23 (m, 4H, ArC<u>H</u>), 7.21 – 7.15 (m, 3H, ArC<u>H</u>), 2.47 (d, *J* = 1.2 Hz, 6H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 13C NMR (101 MHz, $CDCl_3$) δ 150.4 (d, *J* = 7.1 Hz, Ar<u>C</u>), 142.9 (d, *J* = 3.6 Hz, Ar<u>C</u>), 140.8 (d, *J* = 8.5 Hz, Ar<u>C</u>H), 136.3 (d, *J* = 1.9 Hz, Ar<u>C</u>), 134.1 (d, *J* = 4.1 Hz, Ar<u>C</u>H), 129.9 (Ar<u>C</u>H), 126.1 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 123.6 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 119.7 (d, *J* = 5.2 Hz, Ar<u>C</u>H), 16.9 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ -18.46; **IR** υ_{max}/cm^{-1}: 2980, 1528 (NO_2), 1355 (NO_2), 1177 (P=O), 1157, 969, 952, 766; **HRMS** (ESI+) calcd. for $C_{20}H_{18}N_2O_8P$ 445.0795 $[M+H]^+$, found 445.0795.

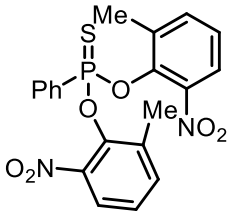
bis(2-methyl-6-nitrophenyl) dimethylphosphoramidate (**445**)



445 was synthesized following **GP IV-A**. *N,N*-Dimethylphosphoramic dichloride (648 mg, 475 μL, 4.00 mmol) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless oil (281 mg, 0.72 mmol, 18% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.69 (m, 2H, ArC<u>H</u>), 7.50 (ddq, *J* = 7.7, 1.6, 0.7 Hz, 2H, ArC<u>H</u>), 7.32 – 7.19 (m, 1H, ArC<u>H</u>), 2.91 (s, 3H, NC<u>H</u>$_3$), 2.87 (s, 3H, NC<u>H</u>$_3$), 2.54 – 2.50 (s, 6H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5 (Ar<u>C</u>), 140.3 (d, *J* = 9.4 Hz, Ar<u>C</u>), 136.4 (d, *J* = 2.3 Hz, Ar<u>C</u>H), 134.6 (d, *J* = 4.0 Hz, Ar<u>C</u>), 126.1 (d, *J* = 2.5 Hz, Ar<u>C</u>H), 123.5 (d, *J* = 2.1 Hz, Ar<u>C</u>H), 37.0 (d, *J* = 3.6 Hz, N(<u>C</u>H$_3$)$_2$), 17.8 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.61; **IR** (film) υ_{max}/cm^{-1}: 2981, 1533 (NO_2), 1471, 1356 (NO_2), 1314, 1266 (P=O), 1186, 997, 804, 765, 745; **HRMS** (ESI+) calcd. for $C_{16}H_{18}N_3NaO_7P$ 418.0780 $[M+Na]^+$, found 418.0783.

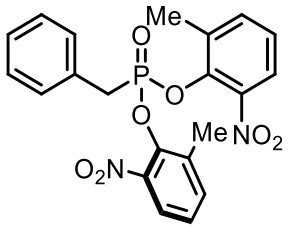
O,O-bis(2-methyl-6-nitrophenyl) phenylphosphonothioate (**446**)



446 was synthesized following **GP IV-A**. Phenylphosphonothioic dichloride (844 mg, 602 μL, 4.00 mmol) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane to Pentane:EtOAc 9:1. Colourless solid (818 mg, 1.84 mmol, 46% yield).

Mp 46 °C (pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 – 8.10 (m, 2H, PhH), 7.79 (dd, *J* = 8.1, 1.7 Hz, 2H, ArCH), 7.70 – 7.64 (m, 2H, ArCH), 7.62 – 7.56 (m, 2H, ArCH), 7.52 (ddd, *J* = 7.7, 1.8, 1.0 Hz, 2H,m ArCH), 7.32 – 7.23 (m, 2H, ArCH), 2.46 (d, *J* = 1.5 Hz, 6H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.5 (ArC), 141.7 (d, *J* = 12.0 Hz, ArC), 136.4 (d, *J* = 2.6 Hz, ArCH), 135.9 (d, *J* = 141.4 Hz, CP), 135.0 (d, *J* = 4.4 Hz, ArCH), 133.7 (d, *J* = 3.6 Hz, ArCH), 130.6 (d, *J* = 13.8 Hz, ArCH), 128.8 (d, *J* = 17.2 Hz, ArCH), 126.1 (d, *J* = 2.8 Hz, ArCH), 123.6 (d, *J* = 2.4 Hz, ArCH), 18.7 (CH_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 88.72; **IR** υ_{max}/cm^{-1}: 2981, 1530 (NO_2), 1348 (NO_2), 1176 (P=S), 902, 771, 738, 687, 689; **HRMS** (ESI+) calcd. for $C_{20}H_{18}N_2O_6PS$ 445.0618 $[M+H]^+$, found 445.0620.

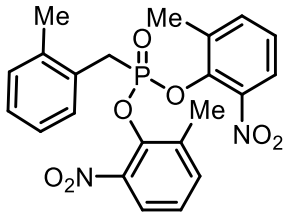
bis(2-methyl-6-nitrophenyl) benzylphosphonate (**447**)



447 was synthesized following **GP IV-B**. Benzylphosphonic acid (441 mg, 2.56 mmol) was used and 5-methyl-2-nitrophenol (784 mg, 5.12 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 1:1. Colourless solid (144 mg, 0.320 mmol, 13% yield).

Mp 125 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.2, 1.7 Hz, 2H, ArC<u>H</u>), 7.41 (dddd, *J* = 7.4, 4.7, 2.1, 1.1 Hz, 4H, ArC<u>H</u>), 7.33 – 7.25 (m, 3H, ArC<u>H</u>), 7.20 (td, *J* = 7.9, 1.1 Hz, 2H, ArC<u>H</u>), 3.65 (d, *J* = 22.0 Hz, 2H, C<u>H</u>$_2$P), 2.21 (s, 6H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1 (Ar<u>C</u>), 141.2 (d, *J* = 10.7 Hz, Ar<u>C</u>), 136.1 (d, *J* = 1.6 Hz, Ar<u>C</u>), 134.0 (d, *J* = 3.5 Hz, Ar<u>C</u>H), 130.2 (d, *J* = 7.7 Hz, Ar<u>C</u>H), 129.5 (d, *J* = 9.9 Hz, Ar<u>C</u>), 128.8 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 127.6 (d, *J* = 3.9 Hz, Ar<u>C</u>H), 125.5 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 123.4 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 35.1 (d, *J* = 136.7 Hz, <u>C</u>H_2P), 17.0 (Ar<u>C</u>H_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.20; **IR** (film) υ_{max}/cm^{-1}: 1532 (NO_2), 1356 (NO_2), 1277, 1213 (P=O), 1158, 926; **HRMS** (ESI+) calcd. for $C_{21}H_{19}N_2NaO_7P$ 465.0828 $[M+Na]^+$, found 465.0822.

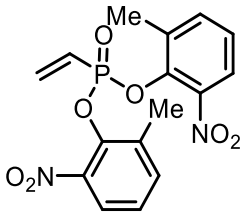
bis(2-methyl-6-nitrophenyl) (2-methylbenzyl)phosphonate (**448**)



448 was synthesized following **GP IV-B**. 2-Methylbenzyl phosphonic acid (745 mg, 4.00 mmol) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (1.17 g, 2.56 mmol, 64% yield).

Mp 126° C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.2, 1.7 Hz, 2H, ArC<u>H</u>), 7.45 – 7.38 (m, 2H, ArC<u>H</u>), 7.23 – 7.17 (m, 4H, ArC<u>H</u>), 7.17 – 7.11 (m, 1H, ArC<u>H</u>), 3.63 (d, *J* = 22.1 Hz, 2H, C<u>H</u>$_2$P), 2.45 (d, *J* = 1.9 Hz, 3H, Benzyl C<u>H</u>$_3$), 2.16 (s, 6H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2 (Ar<u>C</u>), 141.1 (d, *J* = 10.9 Hz, Ar<u>C</u>), 137.6 (d, *J* = 8.1 Hz, Ar<u>C</u>), 136.2 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 134.1 (d, *J* = 3.6 Hz, Ar<u>C</u>), 131.1 (d, *J* = 6.1 Hz, Ar<u>C</u>H), 130.8 (d, *J* = 3.5 Hz, Ar<u>C</u>H), 128.2 (d, *J* = 10.3 Hz, Ar<u>C</u>), 127.8 (d, *J* = 4.1 Hz, Ar<u>C</u>H), 126.3 (d, *J* = 3.8 Hz, Ar<u>C</u>H), 125.5 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 123.4 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 32.3 (d, *J* = 136.9 Hz, <u>C</u>H$_2$P), 20.1 (Benzyl <u>C</u>H$_3$), 16.9 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.72; **IR** (film) υ_{max}/cm^{-1}: 1531 (NO_2), 1470, 1356 (NO_2), 1277, 1213 (P=O), 1179, 1158, 1092, 924, 803, 750; **HRMS** (ESI+) calcd. for $C_{22}H_{22}N_2O_7P$ 457.1159 $[M+H]^+$, found 457.1162.

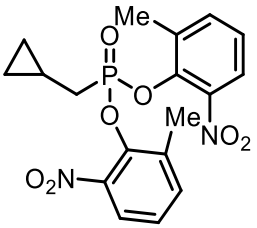
bis(2-methyl-6-nitrophenyl) vinylphosphonate (**449**)



449 was synthesized following **GP IV-B**. Vinylphosphonic acid (432 mg, 309 μL 4.00 mmol) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 6:4. Colourless solid (819 mg, 2.16 mmol, 54% yield).

Mp 118°C (pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.2, 1.7 Hz, 2H, ArC<u>H</u>), 7.47 (ddt, *J* = 7.7, 1.7, 0.8 Hz, 2H, ArC<u>H</u>), 7.22 (td, *J* = 7.9, 1.2 Hz, 2H, ArC<u>H</u>), 6.61 – 6.36 (m, 3H <u>H</u>$_2$C=C<u>H</u>P), 2.39 (s, 6H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1 (Ar<u>C</u>), 141.0 (d, *J* = 9.5 Hz, Ar<u>C</u>), 140.5 (d, *J* = 3.3 Hz, H$_2$<u>C</u>=CHP), 136.2 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 134.2 (d, *J* = 3.6 Hz, Ar<u>C</u>), 125.6 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 124.3 (d, *J* = 187.2 Hz, <u>C</u>P), 123.5 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 17.3 (ArC<u>H</u>$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 11.83; **IR** υ_{max}/cm^{-1}: 2981, 2160, 1528 (NO_2), 1352 (NO_2), 1233 (P=O), 1176, 1157, 936, 920, 801, 753, 670; **HRMS** (ESI+) calcd. for $C_{16}H_{16}N_2O_7P$ 379.0690 $[M+H]^+$, found 379.0687.

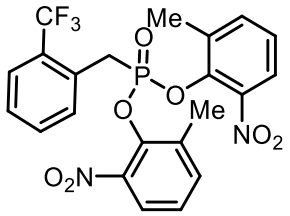
bis(2-methyl-6-nitrophenyl) (cyclopropylmethyl)phosphonate (**450**)



450 was synthesized following **GP IV-C**. Diethyl (cyclopropylmethyl)phosphonate (754 μL, 4.00 mmol) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 2:1. Colourless solid (339 mg, 0.835 mmol, 21% yield).

Mp 97 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.64 (dd, *J* = 8.2, 1.7 Hz, 2H, ArC<u>H</u>), 7.39 (ddt, *J* = 7.6, 1.7, 0.7 Hz, 2H, ArC<u>H</u>), 7.13 (td, *J* = 7.9, 1.1 Hz, 2H, ArC<u>H</u>), 2.29 (d, *J* = 0.9 Hz, 6H, ArC<u>H</u>$_3$), 2.08 (dd, *J* = 17.5, 7.0 Hz, 2H, C<u>H</u>$_2$P), 2.06 (d, *J* = 7.1 Hz, 1H, cyclopropane C<u>H</u>), 0.68 – 0.53 (m, 2H, cyclopropane C<u>H</u>$_2$), 0.39 – 0.22 (m, 2H, cyclopropane C<u>H</u>$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2 (Ar<u>C</u>), 141.0 (d, *J* = 10.4 Hz, Ar<u>C</u>), 135.9 (Ar<u>C</u>H), 133.9 (d, *J* = 3.4 Hz, Ar<u>C</u>), 125.2 (Ar<u>C</u>H), 123.3 (Ar<u>C</u>H), 32.6 (d, *J* = 136.9 Hz, <u>C</u>H$_2$P), 17.1 (Ar<u>C</u>H$_3$), 5.7 (d, *J* = 10.4 Hz, cyclopropane <u>C</u>H), 4.2 (d, *J* = 5.9 Hz, cyclopropane <u>C</u>H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 26.54; **IR** (film) υ_{max}/cm^{-1}: 1533 (NO_2), 1471, 1357 (NO_2), 1281, 1213 (P=O), 1179, 1158,1092, 924, 803; **HRMS** (ESI+) calcd. for $C_{18}H_{19}N_2NaO_7P$ 429.0828 $[M+Na]^+$, found 429.0820.

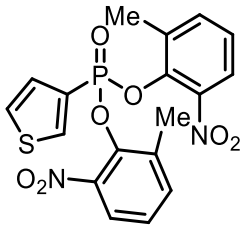
bis(2-methyl-6-nitrophenyl) (2-(trifluoromethyl)benzyl)phosphonate (**451**)



451 was synthesized following **GP IV-C**. diethyl (2-(trifluoromethyl)benzyl)phosphonate (1.18 g, 4.00 mmol, 971 μL) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (1.00 g, 1.97 mmol, 49% yield).

Mp 114°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.2, 1.7 Hz, 2H, ArC<u>H</u>), 7.66 – 7.59 (m, 2H, ArC<u>H</u>), 7.57 – 7.51 (m, 1H, ArC<u>H</u>), 7.48 – 7.37 (m, 3H, ArC<u>H</u>), 7.21 (td, *J* = 7.9, 1.1 Hz, 2H, ArC<u>H</u>), 3.72 (d, *J* = 22.3 Hz, 2H, C<u>H</u>$_2$P), 2.20 (s, 6H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.0 (Ar<u>C</u>), 141.1 (d, *J* = 10.7 Hz, Ar<u>C</u>), 136.3 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 133.9 (d, *J* = 3.6 Hz, Ar<u>C</u>H), 133.7 (d, *J* = 7.2 Hz, Ar<u>C</u>), 131.9 – 130.6 (m, <u>C</u>F$_3$), 130.8 (d, *J* = 9.6 Hz, Ar<u>C</u>), 129.3 (d, *J* = 3.1 Hz, Ar<u>C</u>H), 126.8 (dd, *J* = 7.9, 3.9 Hz, Ar<u>C</u>H), 125.7 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 124.6 (t, *J* = 3.8 Hz, Ar<u>C</u>H), 124.0 (d, *J* = 272.5 Hz, Ar<u>C</u>), 123.5 (d, *J* = 1.3 Hz, Ar<u>C</u>H), 34.9 (d, *J* = 137.7 Hz, <u>C</u>H$_2$P), 17.0 (Ar<u>C</u>H$_3$); **^{19}F NMR** (377 MHz, $CDCl_3$) δ - 62.66; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 19.83; **IR** (film) υ_{max}/cm^{-1}: 2981, 1532 (NO_2), 1356 (NO_2), 1330, 1278, 1226 (P=O), 1213, 1159, 1125, 1092, 1075, 926, 887, 803, 766, 751, 702; **HRMS** (ESI+) calcd. for $C_{22}H_{19}F_3N_2O_7P$ 511.0876 $[M+H]^+$, found 511.0872.

bis(2-methyl-6-nitrophenyl) thiophen-3-ylphosphonate (**452**)

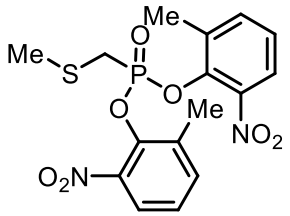


452 was synthesized following **GP IV-C**. Diethyl (thiophen-3-yl)phosphonate[vi] (848 mg, 3.28 mmol) was used and 5-methyl-2-nitrophenol (918 mg, 6.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 1:1. Colourless solid (845 mg, 1.94.00 mmol, 44% yield).

Mp 178 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (ddd, *J* = 8.9, 2.9, 1.2 Hz, 1H, thiophene C<u>H</u>), 7.67 – 7.53 (m, 3H, ArC<u>H</u>), 7.46 (ddd, *J* = 5.1, 4.0, 2.9 Hz, 1H, thiophene C<u>H</u>), 7.37 (ddt, *J* = 7.6, 1.7, 0.8 Hz, 2H, ArC<u>H</u>), 7.14 (td, *J* = 7.9, 1.3 Hz, 2H, ArC<u>H</u>), 2.14 (s, 6H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4 (d, *J* = 2.8 Hz, Ar<u>C</u>), 140.8 (d, *J* = 9.6 Hz, Ar<u>C</u>), 138.9 (d, *J* = 20.7 Hz, ArC<u>H</u>), 135.9, 134.1 (d, *J* = 3.4 Hz, Ar<u>C</u>), 129.7 (d, *J* = 18.4 Hz, thiophene <u>C</u>H), 127.9 (d, *J* = 21.8 Hz, thiophene <u>C</u>H), 126.2 (d, *J* = 209 Hz, <u>C</u>P), 125.5 (ArC<u>H</u>), 123.3 (d, *J* = 1.3 Hz, Ar<u>C</u>H), 16.9 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 6.09; **IR** (film) υ_{max}/cm^{-1}: 1532 (NO_2), 1357 (NO_2), 1276 (P=O), 1178, 1090, 943,924, 770; **HRMS** (ESI+) calcd. for $C_{18}H_{16}N_2O_7PS$ 435.0416 $[M+H]^+$, found 435.010.

[vi] Diethyl (thiophen-3-yl)phosphonate was prepared by Mr. Naoto Sahara according to literature procedures[33]

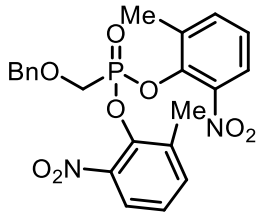
bis(2-methyl-6-nitrophenyl) ((methylthio)methyl)phosphonate (**453**)



453 was synthesized following **GP IV-C**. Diethyl ((methylthio)methyl)phosphonate (792 mg, 4.00 mmol, 0.701 mL) was used and 5-methyl-2-nitrophenol (1.22 g, 8.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 7:3. Colourless solid (627 mg, 1.52 mmol, 38% yield).

Mp 122 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.1, 1.7 Hz, 2H, ArC<u>H</u>), 7.48 (ddt, *J* = 7.7, 1.7, 0.8 Hz, 2H, ArC<u>H</u>), 7.21 (td, *J* = 7.9, 1.1 Hz, 2H, ArC<u>H</u>), 3.21 (d, *J* = 12.0 Hz, 2H, C<u>H</u>$_2$P), 2.43 – 2.37 (m, 6H, ArC<u>H</u>$_3$), 2.31 (d, *J* = 1.5 Hz, 3H, SC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.7 (Ar<u>C</u>), 141.6 (d, *J* = 10.9 Hz, Ar<u>C</u>), 136.3 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 134.0 (d, *J* = 3.7 Hz, Ar<u>C</u>), 125.5 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 123.6 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 29.1 (d, *J* = 150.6 Hz, <u>C</u>H$_2$P), 17.6 (d, *J* = 1.5 Hz, S<u>C</u>H$_3$), 17.2 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 17.81; **IR** (film) υ_{max}/cm^{-1}: 1530 (NO_2), 1470, 1354 (NO_2), 1277, 1213, 1178, 1158, 1092, 926, 804, 749; **HRMS** (ESI+) calcd. for $C_{16}H_{18}N_2O_7PS$ 413.0567 $[M+H]^+$, found 413.0581.

bis(2-methyl-6-nitrophenyl) ((benzyloxy)methyl)phosphonate (**454**)

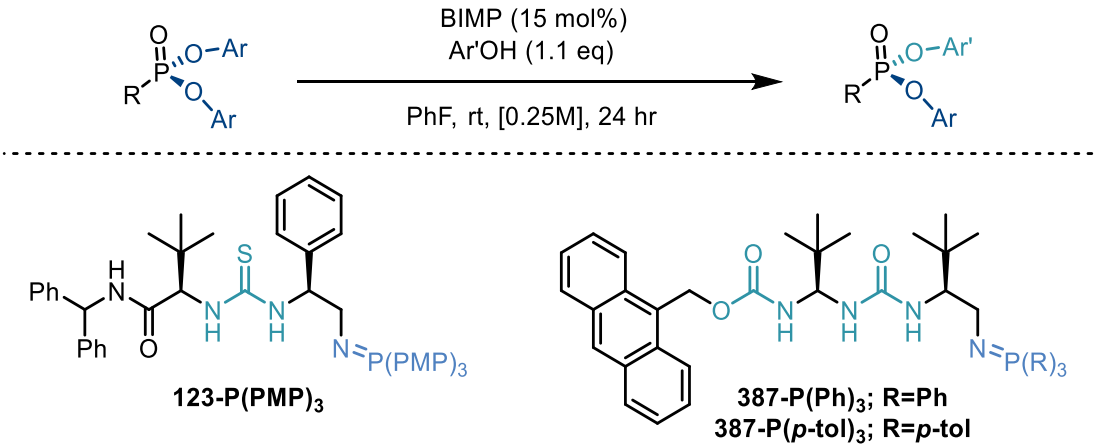


454 was synthesized following **GP IV-C**. Diethyl ((benzyloxy)methyl)phosphonate[vii] (848 mg, 3.28 mmol) was used and 5-methyl-2-nitrophenol (918 mg, 6.00 mmol) was used as nucleophile. FCC Pentane:EtOAc 9:1 to 1:1. Colourless solid (325 mg, 0.687 mmol, 21% yield).

Mp 120 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.1, 1.7 Hz, 2H, ArC<u>H</u>), 7.46 (ddt, *J* = 7.7, 1.7, 0.8 Hz, 2H, ArC<u>H</u>), 7.38 – 7.27 (m, 3H, ArC<u>H</u>), 7.25 – 7.15 (m, 4H, ArC<u>H</u>), 4.64 (s, 2H, C<u>H</u>$_2$O), 4.25 (d, *J* = 7.0 Hz, 2H, C<u>H</u>$_2$P), 2.41 (s, 6H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.6 (Ar<u>C</u>), 141.2 (d, *J* = 10.4 Hz, Ar<u>C</u>), 136.3 (Ar<u>C</u>), 136.2 (Ar<u>C</u>H), 134.0 (d, *J* = 3.3 Hz, Ar<u>C</u>), 128.4 (Ar<u>C</u>H), 128.2(Ar<u>C</u>H), 128.1(Ar<u>C</u>H), 125.4(Ar<u>C</u>H), 123.4 (Ar<u>C</u>H), 75.2 (d, *J* = 11.3 Hz, <u>C</u>H$_2$O), 64.9 (d, *J* = 167.7 Hz, <u>C</u>H$_2$P), 15.39 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.72; **IR** (film) υ_{max}/cm^{-1}: 1532 (NO_2), 1461, 1354 (NO_2), 1321, 1244,1213, 1093, 926, 743; **HRMS** (ESI+) calcd. for $C_{22}H_{22}N_2O_8P$ 473.1140 $[M+H]^+$, found 473.1108.

[vii] Diethyl ((benzyloxy)methyl)phosphonate was synthesized by Mr. Naoto Sahara according to literature procedures.[34]

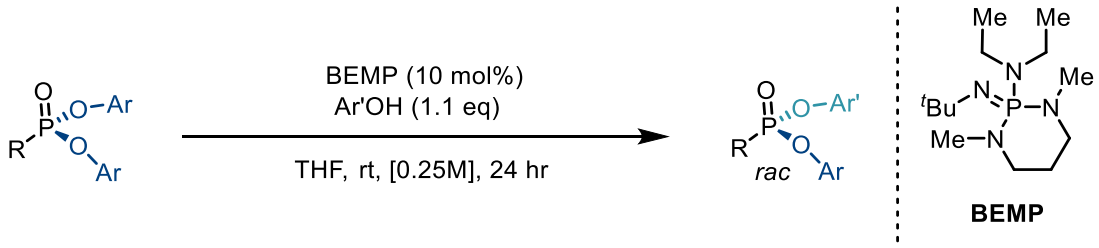
5.3.3 General Procedure V: enantioselective desymmetrisation of phosphonate esters



To the corresponding organoazide **387-N_3** (0.015 mmol) and P(*p*-tol)$_3$ (0.015 mmol) under argon atmosphere was added THF (0.40 mL) and the reaction mixture was stirred for 24 hr. The formation of the organocatalysts was monitored by TLC. Upon completion volatiles were removed under a stream of N_2 yielding the expected iminophosphorane which was used without further purification.

To the corresponding phosphonate (0.10 mmol) and BIMP organocatalyst (0.015 mmol) under argon atmosphere was added PhF (0.40 mL) and phenol (0.11 mmol, 1.1 equivalents) then the reaction was stirred at room temperature for 24 hr. 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.

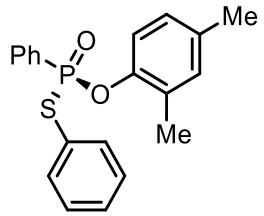
5.3.4 General Procedure VI: racemic desymmetrisation of phosphonate esters



To the corresponding phosphonate (0.10 mmol) and 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) (4.5 μL, 0.015 mmol) under argon was added THF (0.40 mL) and the corresponding phenol (0.11 mmol) and the reaction was stirred at room temperature for 24 hr. 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.

5.3.5 Products: Leaving group variation

O-(2,4-dimethylphenyl) S-phenyl (*R*)-phenylphosphonothioate (**369**)

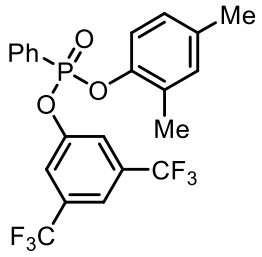


369 was synthesized following **GP V. 352** (34.2 mg, 0.10 mmol) was used as electrophile, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **123-P(PMP)$_3$** (8.25 mg, 0.01 mmol) as catalyst in THF (0.20 mL). Pentane:EtOAc 7:3. Colourless oil (4.2 mg, 0.012 mmol, 12% yield, 28% ee).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol =85/15, 1 mL/min, λ = 220 nm, t (major) = 15.11 min, t (minor) = 31.08 min

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.75 (m, 2H, ArC<u>H</u>), 7.59 – 7.50 (m, 1H, ArC<u>H</u>), 7.47 – 7.35 (m, 3H, ArC<u>H</u>), 7.32 – 7.23 (m, 1H, ArC<u>H</u>), 7.25 – 7.13 (m, 4H, ArC<u>H</u>), 7.01 (d, *J* = 2.4 Hz, 1H, ArC<u>H</u>), 6.96 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 2.31 – 2.28 (m, 3H, ArC<u>H</u>$_3$), 2.18 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.5 (Ar<u>C</u>), 147.4 (Ar<u>C</u>), 135.9 (d, *J* = 4.3 Hz, Ar<u>C</u>H), 134.7(Ar<u>C</u>), 132.9 (d, *J* = 3.4 Hz, Ar<u>C</u>H), 132.1 (Ar<u>C</u>H), 131.8 (d, *J* = 10.7 Hz, Ar<u>C</u>H), 131.8 (d, *J* = 151.4 Hz, <u>C</u>P), 129.3 (Ar<u>C</u>H), 129.3 (d, *J* = 2.4 Hz, Ar<u>C</u>H), 129.0 (Ar<u>C</u>), 128.5 (d, *J* = 15.1 Hz, Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 120.5 (d, *J* = 3.7 Hz, Ar<u>C</u>H), 20.9 (Ar<u>C</u>H$_3$), 16.8 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 38.49; **IR** (film) υ_{max}/cm^{-1}: 3059, 2192, 1496, 1440, 1243 (P=O), 1196, 1116, 943, 899, 747, 719, 692; **HRMS** (ESI+): calcd. for $C_{20}H_{20}O_2PS$ 355.09161 $[M+H]^+$, found 355.09152.

3,5-bis(trifluoromethyl)phenyl (2,4-dimethylphenyl) phenylphosphonate (**376**)

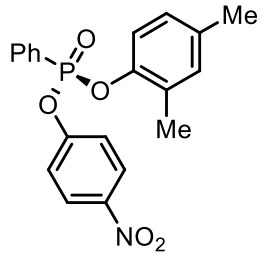


376 was synthesized following **GP V. 361** (55.0 mg, 0.10 mmol) was used as electrophile, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **123-P(PMP)$_3$** (8.25 mg, 0.01 mmol) as catalyst in THF (0.20 mL). Pentane:EtOAc 9:1. Colourless oil (32.6 mg, 0.069 mmol, 69% yield, 0% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol =99/1 1 mL/min, λ = 220 nm, t (1) = 13.31 min, t (2) = 13.86 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.95 (m, 2H, ArC<u>H</u>), 7.72 – 7.64 (m, 2H, ArC<u>H</u>), 7.63 – 7.53 (m, 4H, ArC<u>H</u>), 7.20 (s, 1H, ArC<u>H</u>), 7.11 (dd, *J* = 8.2, 1.5 Hz, 1H, ArC<u>H</u>), 7.03 – 6.98 (m, 1H, ArC<u>H</u>), 6.91 (dd, *J* = 8.3, 2.2 Hz, 1H, ArC<u>H</u>), 2.26 (s, 3H, ArC<u>H</u>$_3$), 2.22 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6 (Ar<u>C</u>), 151.1 (Ar<u>C</u>), 146.4 (Ar<u>C</u>), 135.6(Ar<u>C</u>), 134.1 (Ar<u>C</u>H), 133.4 (d, *J* = 34.2 Hz, <u>C</u>F$_3$), 132.5(Ar<u>C</u>H), 132.2 (d, *J* = 10.5 Hz, Ar<u>C</u>H), 129.2 (d, *J* = 16.2 Hz, Ar<u>C</u>H), 127.8 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 126.0 (d, *J* = 195.0 Hz, <u>C</u>P), 124.1 (Ar<u>C</u>), 121.6 (Ar<u>C</u>H), 120.2 (d, *J* = 2.8 Hz, (Ar<u>C</u>H), 119.1 (Ar<u>C</u>H), 116.0 (Ar<u>C</u>H), 20.8 (Ar<u>C</u>H$_3$), 16.6 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.70; **^{19}F NMR** δ (376 MHz, $CDCl_3$) -63.14 (d, *J* = 25.1 Hz); **IR** (film) υ_{max}/cm^{-1}: 1368, 1277 (P=O), 1176, 1131, 968, 894, 695; **HRMS** (ESI+): calcd. for $C_{22}H_{18}O_3F_6P$ 475.08923 $[M+H]^+$, found 475.08908.

2,4-dimethylphenyl (4-nitrophenyl) (*R*)-phenylphosphonate (**379**)

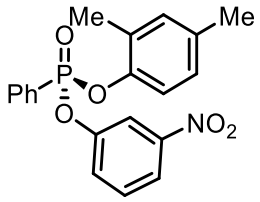


379 was synthesized following **GP V**. **362** (40.0 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **123-P(PMP)$_3$** (8.25 mg, 0.01 mmol) as catalyst in THF (0.20 mL). Pentane:EtOAc 7:3. Colourless oil (15.4 mg, 0.041 mmol, 41% yield, 0% ee).

HPLC Conditions: CHIRALPAK IB, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (1) = 11.76 min, t (2) = 12.78 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.13 (m, 2H, nitrophenol C<u>H</u>), 8.01 – 7.94 (m, 2H, ArC<u>H</u>), 7.69 – 7.61 (m, 1H, ArC<u>H</u>), 7.54 (ddd, *J* = 8.7, 6.9, 4.8 Hz, 2H, ArC<u>H</u>), 7.35 – 7.30 (m, 2H, nitrophenol C<u>H</u>), 7.13 (dd, *J* = 8.3, 1.5 Hz, 1H, ArC<u>H</u>), 7.00 (t, *J* = 1.6 Hz, 1H, ArC<u>H</u>), 6.92 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 2.27 (s, 3H, ArC<u>H</u>$_3$), 2.22 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5 (d, *J* = 7.1 Hz, Ar<u>C</u>), 146.6 (d, *J* = 8.6 Hz, Ar<u>C</u>), 144.8 (Ar<u>C</u>), 135.2 (d, *J* = 1.6 Hz, Ar<u>C</u>), 133.8 (d, *J* = 3.2 Hz, (Ar<u>C</u>H), 132.3 (Ar<u>C</u>), 132.3 (d, *J* = 10.6 Hz, (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 129.0 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 126.5 (d, *J* = 193.8 Hz, <u>C</u>P), 125.7 (nitrophenol <u>C</u>H), 121.3 (d, *J* = 4.8 Hz, nitrophenol <u>C</u>H), 120.2 (d, *J* = 2.8 Hz, Ar<u>C</u>H), 20.8 (Ar<u>C</u>H$_3$), 16.6 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.03; **IR** (film) υ_{max}/cm^{-1}: 2923, 1591, 1521 (NO_2), 1491, 1346 (NO_2), 1251, 1223 (P=O), 1193, 1130 ,1115, 953, 918, 749; **HRMS** (ESI+): calcd. for $C_{20}H_{19}O_5NP$ 384.09954 $[M+H]^+$, found 384.09943.

2,4-dimethylphenyl (3-nitrophenyl) (*R*)-phenylphosphonate (**383**)

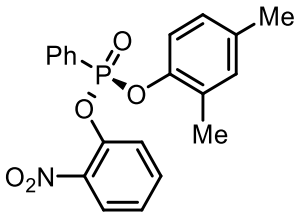


383 was synthesized following **GP V**. **381** (40.0 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **123-P(PMP)$_3$** (8.25 mg, 0.01 mmol) as catalyst in THF (0.20 mL). Pentane:EtOAc 7:3. Colourless oil (23.0 mg, 0.060 mmol, 60% yield, 17% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (minor) = 19.82 min, t (major) = 22.32 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.96 (m, 3H, ArC<u>H</u>), 7.94 (td, *J* = 2.2, 1.3 Hz, 1H, ArC<u>H</u>), 7.75 – 7.50 (m, 6H, ArC<u>H</u>), 7.46 (t, *J* = 8.2 Hz, 1H, ArC<u>H</u>), 7.31 (t, *J* = 8.2 Hz, 1H, ArC<u>H</u>), 7.10 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 2H, ArC<u>H</u>), 6.99 (dd, *J* = 2.4, 1.2 Hz, 1H, ArC<u>H</u>), 6.91 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 2.25 (d, *J* = 1.1 Hz, 3H, ArC<u>H</u>$_3$), 2.22 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.7 (d, *J* = 7.4 Hz, Ar<u>C</u>), 149.1 (d, *J* = 21.0 Hz, Ar<u>C</u>), 146.4 (d, *J* = 8.8 Hz, Ar<u>C</u>), 135.5 (d, *J* = 1.6 Hz, Ar<u>C</u>), 134.1 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 132.5 (Ar<u>C</u>H), 132.2 (d, *J* = 10.6 Hz, Ar<u>C</u>H), 130.6 (Ar<u>C</u>H), 130.1 (Ar<u>C</u>H), 129.2 (d, *J* = 16.1 Hz, Ar<u>C</u>H), 129.2 (d, *J* = 5.5 Hz, Ar<u>C</u>), 127.8 (d, *J* = 1.6 Hz), 127.1 (d, *J* = 4.0 Hz, Ar<u>C</u>H), 125.9 (d, *J* = 194.5 Hz, <u>C</u>P), 122.1 (Ar<u>C</u>H), 120.4 (Ar<u>C</u>H), 120.1 (d, *J* = 2.8 Hz, Ar<u>C</u>H), 116.4 (d, *J* = 4.9 Hz, Ar<u>C</u>H), 115.2 (Ar<u>C</u>H), 110.6 (Ar<u>C</u>H), 20.8 (Ar<u>C</u>H$_3$), 16.6 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.71; **IR** (film) υ_{max}/cm^{-1}: 2922, 1613, 1528 (NO_2), 1491, 1344 (NO_2), 1258, 1236 (P=O), 1186, 1134 ,1115, 912, 764; **HRMS** (ESI+): calcd. for $C_{20}H_{19}O_5NP$ 384.09954 $[M+H]^+$, found 384.09951.

2,4-dimethylphenyl (2-nitrophenyl) (*R*)-phenylphosphonate (**384**)

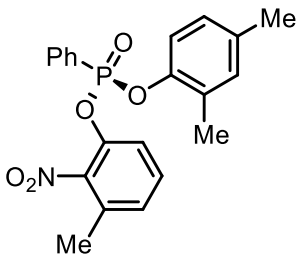


382 was synthesized following **GP V**. **382** (40.0 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(Ph)$_3$** (7.8 mg, 0.01 mmol) as catalyst in PhF (0.40 mL) at 0 °C. Pentane:EtOAc 7:3. Colourless oil (15.7 mg, 0.041 mmol, 41% yield, 87% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (major) = 19.87 min, t (minor) = 24.11 min.

[α]$_D^{25}$ = +20.9 (c = 0.56, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (ddt, *J* = 14.3, 6.9, 1.4 Hz, 2H, ArC<u>H</u>), 7.90 (dt, *J* = 8.2, 1.2 Hz, 1H, ArC<u>H</u>), 7.65 (tt, *J* = 7.4, 1.5 Hz, 2H, ArC<u>H</u>), 7.57 – 7.48 (m, 3H, ArC<u>H</u>), 7.31 – 7.22 (m, 1H, ArC<u>H</u>), 7.10 (dd, *J* = 8.2, 1.5 Hz, 1H, ArC<u>H</u>), 6.97 (d, *J* = 2.2 Hz, 1H, ArC<u>H</u>), 6.89 (dd, *J* = 8.3, 2.2 Hz, 1H, ArC<u>H</u>), 2.25 (s, 3H, ArC<u>H</u>$_3$), 2.16 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.7 (d, *J* = 8.5 Hz, Ar<u>C</u>), 143.6 (d, *J* = 7.2 Hz, Ar<u>C</u>), 135.1 (d, *J* = 1.6 Hz. Ar<u>C</u>), 134.4 (Ar<u>C</u>H), 133.8 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 132.6(d, *J* = 10.8 Hz, Ar<u>C</u>H), 132.3 (Ar<u>C</u>H), 129.3 (Ar<u>C</u>), 128.9 (d, *J* = 16.1 Hz, Ar<u>C</u>H), 128.2 (d, *J* = 220.6 Hz, <u>C</u>P), 127.6 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 125.3 (Ar<u>C</u>H), 125.2 (Ar<u>C</u>H), 123.5 (d, *J* = 3.1 Hz, Ar<u>C</u>H), 120.2 (d, *J* = 2.7 Hz, Ar<u>C</u>H), 20.8 (Ar<u>C</u>H$_3$), 16.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.88; **IR** (film) υ_{max}/cm^{-1}: 2924, 1663, 1531 (NO_2), 1495, 1352 (NO_2), 1276, 1231 (P=O), 1194, 1131, 1117, 951, 921, 750, 694; **HRMS** (ESI+): calcd. for $C_{20}H_{19}O_5NP$ 384.09954 $[M+H]^+$, found 384.09949.

2,4-dimethylphenyl (3-methyl-2-nitrophenyl) (*R*)-phenylphosphonate (**412**)

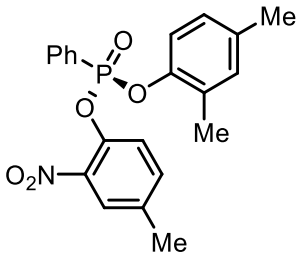


412 was synthesized following **GP V**. **408** (42.6 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(Ph)$_3$** (7.8 mg, 0.01 mmol) as catalyst in PhF (0.40 mL) at 0 °C. Pentane:EtOAc 7:3. Colourless oil (1.9 mg, 0.005 mmol, 5% yield, 50% ee).

HPLC Conditions: CHIRALPAK IB, hexane/isopropanol = 95/5, 1 mL/min, λ = 240 nm, t (major) = 10.47 min, t (minor) = 11.36 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.88 (m, 2H, ArC<u>H</u>), 7.67 – 7.58 (m, 1H, ArC<u>H</u>), 7.55 – 7.48 (m, 2H, ArC<u>H</u>), 7.46 (dtd, *J* = 8.4, 1.2, 0.6 Hz, 1H, ArC<u>H</u>), 7.30 – 7.22 (m, 1H, ArC<u>H</u>), 7.08 (dd, *J* = 8.3, 1.5 Hz, 1H, ArC<u>H</u>), 7.03 (ddt, *J* = 7.7, 1.4, 0.7 Hz, 1H, ArC<u>H</u>), 6.98 – 6.94 (m, 1H, ArC<u>H</u>), 6.90 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 2.30 (s, 3H, ArC<u>H</u>), 2.25 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>), 2.16 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.5 (d, *J* = 8.7 Hz, Ar<u>C</u>), 142.1 (Ar<u>C</u>), 135.2 (Ar<u>C</u>), 135.1 (Ar<u>C</u>), 133.8 (d, *J* = 3.2 Hz, (Ar<u>C</u>H), 132.5 (d, *J* = 10.7 Hz, (Ar<u>C</u>H)), 132.2 (Ar<u>C</u>H), 131.8 (Ar<u>C</u>), 131.0 (Ar<u>C</u>H), 129.4 (Ar<u>C</u>H), 128.9 (d, *J* = 16.2 Hz, Ar<u>C</u>H), 128.2 (d, *J* = 246.7 Hz, <u>C</u>P), 127.6 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 127.1 (Ar<u>C</u>H), 120.3 (d, *J* = 2.5 Hz, Ar<u>C</u>H), 119.1 (d, *J* = 2.8 Hz, Ar<u>C</u>H), 20.8 (Ar<u>C</u>H$_3$), 17.4 (Ar<u>C</u>H$_3$), 16.4 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.55; **IR** (film) υ_{max}/cm^{-1}: 2928, 1535 (NO_2), 1489, 1350 (NO_2), 1278, 1228 (P=O), 1201, 1118, 937, 899, 595; **HRMS** (ESI+): calcd. for $C_{21}H_{21}NO_5P$ 398.1152 $[M+H]^+$, found 398.1147.

2,4-dimethylphenyl (4-methyl-2-nitrophenyl (*R*)-phenylphosphonate (**413**)

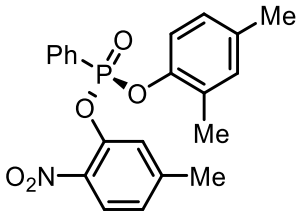


413 was synthesized following **GP V**. **409** (42.6 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **B1 387-P(Ph)$_3$** (7.8 mg, 0.01 mmol) as catalyst in PhF (0.40 mL) at 0 °C. Pentane:EtOAc 7:3. Colourless oil (24.2 mg, 0.061 mmol, 61% yield, 89% ee).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = gradient 98/2 to 70/30 over 40 min, 1 mL/min, λ = 220 nm, t (major) = 17.79 min, t (minor) = 16.50 min

[α]$_D^{25}$ = +26.0 (c = 0.66, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 7.98 (m, 2H, ArC<u>H</u>), 7.69 (dt, *J* = 2.1, 0.9 Hz, 1H), 7.66 – 7.59 (m, 1H, ArC<u>H</u>), 7.55 – 7.47 (m, 3H, ArC<u>H</u>), 7.31 (ddd, *J* = 8.5, 2.3, 0.8 Hz, 1H, ArC<u>H</u>), 7.09 (dd, *J* = 8.2, 1.5 Hz, 1H, ArC<u>H</u>), 6.98 – 6.93 (m, 1H, ArC<u>H</u>), 6.88 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 2.36 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 2.24 (d, *J* = 1.0 Hz, 3H, ArC<u>H</u>$_3$), 2.15 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.7 (d, *J* = 8.4 Hz, Ar<u>C</u>), 141.3 (d, *J* = 7.2 Hz, Ar<u>C</u>), 135.7 (Ar<u>C</u>), 135.0, 133.7 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.6 (Ar<u>C</u>H), 132.5 (Ar<u>C</u>H), 132.2 (Ar<u>C</u>H), 129.3 (d, *J* = 5.6 Hz, Ar<u>C</u>), 128.9 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 127.6 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 126.2 (d, *J* = 194.5 Hz, <u>C</u>P), 125.9 (Ar<u>C</u>H), 123.2 (d, *J* = 3.1 Hz, Ar<u>C</u>H), 120.2 (d, *J* = 2.8 Hz, Ar<u>C</u>H), 20.8 (Ar<u>C</u>H$_3$), 20.7 (Ar<u>C</u>H$_3$), 16.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.91; **IR** (film) υ_{max}/cm^{-1}: 2924, 1534 (NO_2), 1496, 1353 (NO_2), 1276, 1240 (P=O), 1194, 1131, 1118, 937, 899; **HRMS** (ESI+): calcd. for $C_{21}H_{21}NO_5P$ 398.1152 $[M+H]^+$, found 398.1145.

2,4-dimethylphenyl (5-methyl-2-nitrophenyl) (*R*)-phenylphosphonate (**414**)

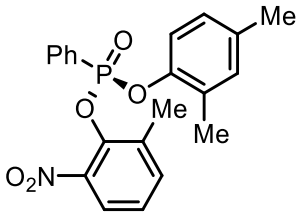


414 was synthesized following **GP V**. **410** (42.6 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **B1 387-P(Ph)$_3$** (7.8 mg, 0.01 mmol) as catalyst in PhF (0.40 mL) at 0 °C. Pentane:EtOAc 7:3. Colourless oil (14.7 mg, 0.034 mmol, 34% yield, 67% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (major) = 38.75 min, t (minor) = 40.59 min

[α]$_D^{25}$ = +28.8 (c = 0.16, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 – 8.01 (m, 2H, ArC<u>H</u>), 7.83 (dd, *J* = 8.4, 0.9 Hz, 1H, ArC<u>H</u>), 7.67 – 7.58 (m, 1H, ArC<u>H</u>), 7.52 (tdd, *J* = 8.3, 4.9, 0.8 Hz, 2H, ArC<u>H</u>), 7.42 (td, *J* = 1.7, 0.9 Hz, 1H, ArC<u>H</u>), 7.09 (dd, *J* = 8.3, 1.5 Hz, 1H, ArC<u>H</u>), 7.04 (ddt, *J* = 8.3, 1.7, 0.8 Hz, 1H, ArC<u>H</u>), 6.97 – 6.93 (m, 1H, ArC<u>H</u>), 6.88 (dd, *J* = 8.2, 2.3 Hz, 1H, ArC<u>H</u>), 2.37 (s, 3H, ArC<u>H</u>$_3$), 2.24 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 2.15 (s, 3H, ArC<u>H</u>$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.7 (d, *J* = 8.4 Hz, Ar<u>C</u>), 146.48 (Ar<u>C</u>), 143.5 (d, *J* = 7.6 Hz, Ar<u>C</u>), 139.2 (Ar<u>C</u>), 135.0 (d, *J* = 1.6 Hz, Ar<u>C</u>), 133.7 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.7 (Ar<u>C</u>H), 132.5 (Ar<u>C</u>H), 132.2 (Ar<u>C</u>H), 129.3 (d, *J* = 5.4 Hz, Ar<u>C</u>), 128.9 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 127.5 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 126.2 (d, *J* = 195.2 Hz, <u>C</u>P), 123.9 (d, *J* = 3.0 Hz, Ar<u>C</u>H), 120.2 (d, *J* = 2.8 Hz, Ar<u>C</u>H), 21.7 (Ar<u>C</u>H$_3$), 20.8 (Ar<u>C</u>H$_3$), 16.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.80; **IR** (film) υ_{max}/cm^{-1}: 1596, 1524 (NO_2), 1497, 1348 (NO_2), 1263 (P=O), 1198, 1131, 1118, 592; **HRMS** (ESI+): calcd. for $C_{21}H_{21}NO_5P$ 398.1152 $[M+H]^+$, found 398.1148.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) (*R*)-phenylphosphonate (**415**)



415 was synthesized following **GP V**. **411** (42.6 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless (33.0 mg, 0.084 mmol, 84% yield, 91% ee).

3 mmol scale: **411** (1.28 g, 3 mmol) with **387-P(*p*-tol)$_3$** (351 mg, 0.45 mmol) and ,4-dimethylphenol (338 μL, 3.30 mmol) in PhF (12.0 mL). Colourless solid (1.05 g, 2.64 mmol, 88% yield, 92% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (major) = 17.17 min, t (minor) = 28.28 min

Mp 62 °C; **$[\alpha]_D^{25}$** = -15.9 (c = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.98 (m, 2H, ArC<u>H</u>), 7.71 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.68 – 7.61 (m, 1H, ArC<u>H</u>), 7.56 – 7.50 (m, 2H, ArC<u>H</u>), 7.47 (ddt, *J* = 7.7, 1.6, 0.8 Hz, 1H, ArC<u>H</u>), 7.22 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 6.93 – 6.85 (m, 2H, ArC<u>H</u>), 6.79 (dd, *J* = 8.4, 2.2 Hz, 1H, ArC<u>H</u>), 2.44 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 2.22 – 2.18 (m, 3H, ArC<u>H</u>$_3$), 2.05 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.8 (d, *J* = 7.2 Hz, Ar<u>C</u>), 143.8 (Ar<u>C</u>), 141.0 (d, *J* = 10.1 Hz, Ar<u>C</u>), 136.0 (d, *J* = 1.9 Hz, Ar<u>C</u>), 134.8 (d, *J* = 1.5 Hz, Ar<u>C</u>), 134.6 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 133.6 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 132.6 (d, *J* = 10.8 Hz, Ar<u>C</u>H), 132.2 (Ar<u>C</u>H), 129.1 (d, *J* = 5.6 Hz, Ar<u>C</u>), 128.8 (d, *J* = 16.2 Hz, Ar<u>C</u>H), 127.4 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 126.6 (d, *J* = 194.3 Hz, <u>C</u>P), 125.4 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 123.3 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 119.9 (d, *J* = 2.7 Hz, Ar<u>C</u>H), 20.7 (Ar<u>C</u>H$_3$), 17.5 (Ar<u>C</u>H$_3$), 16.4 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.30; **IR** (film) υ_{max}/cm^{-1}: 1533 (NO_2), 1497, 1356 (NO_2), 1272, 1220 (P=O), 1197, 1181, 1130, 1117, 910, 803, 768, 749, 694; **HRMS** (ESI+): calcd. for $C_{21}H_{21}NO_5P$ 398.1152 $[M+H]^+$, found 398.1140.

5.3.5.1 Single crystal X-ray diffraction data for compound ***415***

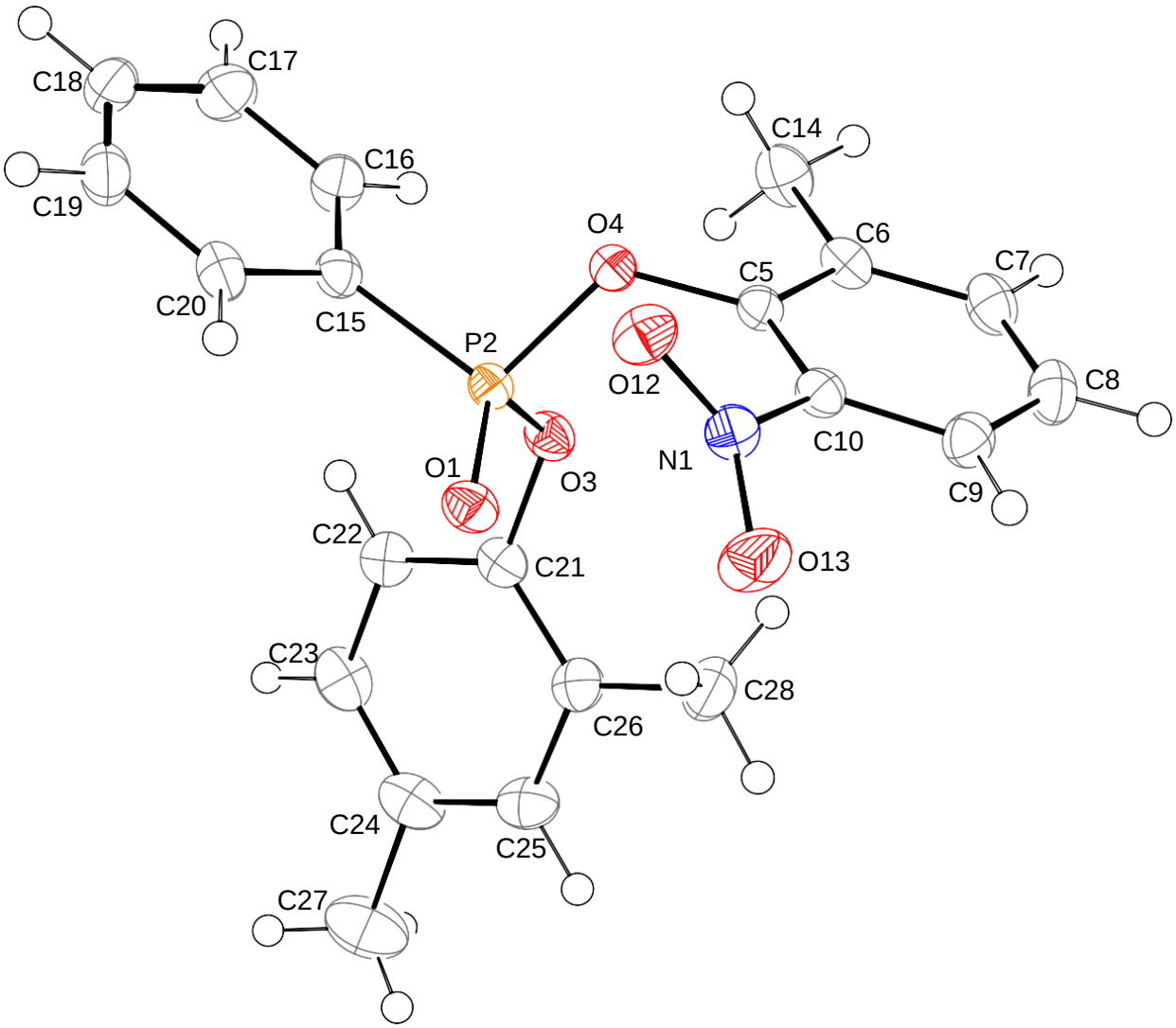


Table 1. Crystal data and structure refinement for **415**.

Identification code	**415**	
Empirical formula	C21 H20 N O5 P	
Formula weight	397.37	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.85800(10) Å	□ = 90°.
	b = 10.65460(10) Å	□ = 102.0500(14)°.
	c = 12.0478(2) Å	□ = 90°.
Volume	986.46(2) $Å^3$	
Z	2	
Density (calculated)	1.338 Mg/m^3	
Absorption coefficient	1.515 mm^{-1}	
F(000)	416	
Crystal size	0.10 x 0.05 x 0.02 mm^3	
Theta range for data collection	3.752 to 76.371°.	
Index ranges	-9<=h<=9, -13<=k<=13, -15<=l<=14	
Reflections collected	21118	
Independent reflections	4101 [R(int) = 0.042]	
Completeness to theta = 76.371°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.97 and 0.86	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4101 / 1 / 254	
Goodness-of-fit on F^2	1.0009	
Final R indices [I>2sigma(I)]	R1 = 0.0257, wR2 = 0.0668	
R indices (all data)	R1 = 0.0263, wR2 = 0.0674	
Absolute structure parameter	0.000(7)	
Largest diff. peak and hole	0.05 and -0.05 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 7381. U(eq) is defined as one third of the trace of the *ortho*gonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3081(1)	5294(1)	8446(1)	25
P(2)	1579(1)	4491(1)	8021(1)	18
O(3)	618(1)	4786(1)	6739(1)	23
O(4)	-32(1)	4643(1)	8632(1)	20
C(5)	-944(2)	5771(1)	8571(1)	19
C(6)	-2611(2)	5803(1)	7896(1)	23
C(7)	-3520(2)	6940(2)	7817(1)	28
C(8)	-2774(2)	8011(2)	8360(1)	30
C(9)	-1116(2)	7972(1)	9034(1)	25
C(10)	-232(2)	6838(1)	9157(1)	20
N(11)	1435(2)	6796(1)	9979(1)	23
O(12)	1762(1)	5873(1)	10585(1)	28
O(13)	2372(1)	7721(1)	10045(1)	38
C(14)	-3397(2)	4644(2)	7284(1)	31
C(15)	1946(2)	2847(1)	8143(1)	21
C(16)	735(2)	1997(1)	7554(1)	29
C(17)	990(2)	724(2)	7722(2)	35
C(18)	2451(2)	293(2)	8491(2)	35
C(19)	3663(2)	1128(2)	9073(1)	32
C(20)	3423(2)	2410(2)	8897(1)	26
C(21)	1624(2)	5118(1)	5948(1)	22
C(22)	2201(2)	4178(1)	5329(1)	26
C(23)	3181(2)	4496(2)	4531(1)	32
C(24)	3566(2)	5745(2)	4350(1)	33
C(25)	2943(2)	6662(2)	4983(1)	30
C(26)	1961(2)	6382(1)	5788(1)	25
C(27)	4605(3)	6103(2)	3476(2)	51
C(28)	1327(2)	7395(2)	6474(1)	35

Table 3. Bond lengths [Å] and angles [°] for 7381.

O(1)-P(2)	1.4613(10)	C(21)-C(26)	1.3936(19)
P(2)-O(3)	1.6023(9)	C(22)-C(23)	1.393(2)
P(2)-O(4)	1.5999(9)	C(22)-H(221)	0.945
P(2)-C(15)	1.7762(14)	C(23)-C(24)	1.392(3)
O(3)-C(21)	1.4049(16)	C(23)-H(231)	0.950
O(4)-C(5)	1.3935(15)	C(24)-C(25)	1.390(2)
C(5)-C(6)	1.3905(17)	C(24)-C(27)	1.510(2)
C(5)-C(10)	1.3923(18)	C(25)-C(26)	1.393(2)
C(6)-C(7)	1.399(2)	C(25)-H(251)	0.960
C(6)-C(14)	1.5038(19)	C(26)-C(28)	1.505(2)
C(7)-C(8)	1.383(2)	C(27)-H(271)	0.947
C(7)-H(71)	0.953	C(27)-H(272)	0.981
C(8)-C(9)	1.385(2)	C(27)-H(273)	0.966
C(8)-H(81)	v0.957	C(28)-H(283)	0.959
C(9)-C(10)	1.3859(18)	C(28)-H(282)	0.967
C(9)-H(91)	0.975	C(28)-H(281)	0.967
C(10)-N(11)	1.4684(16)		
N(11)-O(12)	1.2200(16)	O(1)-P(2)-O(3)	113.96(5)
N(11)-O(13)	1.2231(16)	O(1)-P(2)-O(4)	116.02(5)
C(14)-H(141)	0.935	O(3)-P(2)-O(4)	99.49(5)
C(14)-H(142)	0.937	O(1)-P(2)-C(15)	116.30(6)
C(14)-H(143)	0.933	O(3)-P(2)-C(15)	108.00(5)
C(15)-C(16)	1.3960(19)	O(4)-P(2)-C(15)	101.07(5)
C(15)-C(20)	1.3963(18)	P(2)-O(3)-C(21)	119.01(8)
C(16)-C(17)	1.379(2)	P(2)-O(4)-C(5)	120.71(8)
C(16)-H(161)	0.930	O(4)-C(5)-C(6)	117.62(11)
C(17)-C(18)	1.394(2)	O(4)-C(5)-C(10)	121.96(11)
C(17)-H(171)	0.954	C(6)-C(5)-C(10)	120.42(12)
C(18)-C(19)	1.383(2)	C(5)-C(6)-C(7)	117.79(13)
C(18)-H(181)	0.933	C(5)-C(6)-C(14)	120.45(12)
C(19)-C(20)	1.389(2)	C(7)-C(6)-C(14)	121.76(12)
C(19)-H(191)	0.943	C(6)-C(7)-C(8)	121.48(12)
C(20)-H(201)	0.938	C(6)-C(7)-H(71)	117.3
C(21)-C(22)	1.3807(19)	C(8)-C(7)-H(71)	121.2

C(7)-C(8)-C(9)	120.41(13)	C(15)-C(20)-C(19)	119.69(14)
C(7)-C(8)-H(81)	120.2	C(15)-C(20)-H(201)	119.0
C(9)-C(8)-H(81)	119.3	C(19)-C(20)-H(201)	121.3
C(8)-C(9)-C(10)	118.59(13)	O(3)-C(21)-C(22)	118.60(12)
C(8)-C(9)-H(91)	122.3	O(3)-C(21)-C(26)	119.11(12)
C(10)-C(9)-H(91)	119.1	C(22)-C(21)-C(26)	122.26(13)
C(5)-C(10)-C(9)	121.18(12)	C(21)-C(22)-C(23)	119.16(14)
C(5)-C(10)-N(11)	121.68(12)	C(21)-C(22)-H(221)	118.4
C(9)-C(10)-N(11)	117.05(12)	C(23)-C(22)-H(221)	122.4
C(10)-N(11)-O(12)	118.35(11)	C(22)-C(23)-C(24)	120.70(14)
C(10)-N(11)-O(13)	117.38(12)	C(22)-C(23)-H(231)	120.3
O(12)-N(11)-O(13)	124.18(12)	C(24)-C(23)-H(231)	119.0
C(6)-C(14)-H(141)	112.1	C(23)-C(24)-C(25)	118.23(14)
C(6)-C(14)-H(142)	107.0	C(23)-C(24)-C(27)	121.23(16)
H(141)-C(14)-H(142)	107.8	C(25)-C(24)-C(27)	120.53(17)
C(6)-C(14)-H(143)	113.1	C(24)-C(25)-C(26)	122.79(14)
H(141)-C(14)-H(143)	108.8	C(24)-C(25)-H(251)	118.9
H(142)-C(14)-H(143)	107.8	C(26)-C(25)-H(251)	118.3
P(2)-C(15)-C(16)	121.07(10)	C(21)-C(26)-C(25)	116.84(14)
P(2)-C(15)-C(20)	118.80(10)	C(21)-C(26)-C(28)	121.54(13)
C(16)-C(15)-C(20)	120.00(13)	C(25)-C(26)-C(28)	121.61(14)
C(15)-C(16)-C(17)	120.05(14)	C(24)-C(27)-H(271)	111.0
C(15)-C(16)-H(161)	119.7	C(24)-C(27)-H(272)	109.8
C(17)-C(16)-H(161)	120.2	H(271)-C(27)-H(272)	108.1
C(16)-C(17)-C(18)	119.72(15)	C(24)-C(27)-H(273)	111.0
C(16)-C(17)-H(171)	120.4	H(271)-C(27)-H(273)	107.9
C(18)-C(17)-H(171)	119.8	H(272)-C(27)-H(273)	109.0
C(17)-C(18)-C(19)	120.65(14)	C(26)-C(28)-H(283)	109.8
C(17)-C(18)-H(181)	119.8	C(26)-C(28)-H(282)	108.3
C(19)-C(18)-H(181)	119.5	H(283)-C(28)-H(282)	109.9
C(18)-C(19)-C(20)	119.87(14)	C(26)-C(28)-H(281)	110.8
C(18)-C(19)-H(191)	119.7	H(283)-C(28)-H(281)	108.8
C(20)-C(19)-H(191)	120.5	H(282)-C(28)-H(281)	109.2

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 7381. 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)	21(1)	28(1)	26(1)	-3(1)	5(1)	-4(1)
P(2)	16(1)	20(1)	19(1)	-1(1)	3(1)	0(1)
O(3)	20(1)	29(1)	22(1)	2(1)	4(1)	0(1)
O(4)	20(1)	19(1)	23(1)	-1(1)	6(1)	0(1)
C(5)	20(1)	21(1)	18(1)	0(1)	6(1)	1(1)
C(6)	20(1)	30(1)	21(1)	-2(1)	5(1)	-1(1)
C(7)	22(1)	36(1)	25(1)	1(1)	3(1)	6(1)
C(8)	31(1)	31(1)	27(1)	3(1)	6(1)	11(1)
C(9)	29(1)	23(1)	23(1)	-1(1)	8(1)	2(1)
C(10)	20(1)	24(1)	18(1)	0(1)	5(1)	0(1)
N(11)	23(1)	23(1)	23(1)	-3(1)	3(1)	-2(1)
O(12)	31(1)	28(1)	23(1)	4(1)	0(1)	-1(1)
O(13)	30(1)	27(1)	51(1)	1(1)	-5(1)	-9(1)
C(14)	22(1)	37(1)	33(1)	-9(1)	1(1)	-3(1)
C(15)	22(1)	23(1)	19(1)	-1(1)	7(1)	2(1)
C(16)	27(1)	26(1)	31(1)	-2(1)	2(1)	0(1)
C(17)	37(1)	26(1)	44(1)	-4(1)	11(1)	-5(1)
C(18)	42(1)	25(1)	43(1)	7(1)	19(1)	7(1)
C(19)	31(1)	35(1)	31(1)	8(1)	11(1)	12(1)
C(20)	22(1)	32(1)	25(1)	0(1)	5(1)	5(1)
C(21)	19(1)	29(1)	17(1)	1(1)	1(1)	0(1)
C(22)	27(1)	29(1)	22(1)	-2(1)	2(1)	0(1)
C(23)	33(1)	43(1)	22(1)	-7(1)	7(1)	3(1)
C(24)	29(1)	50(1)	20(1)	2(1)	4(1)	-5(1)
C(25)	31(1)	35(1)	23(1)	7(1)	2(1)	-4(1)
C(26)	24(1)	28(1)	22(1)	3(1)	0(1)	2(1)
C(27)	50(1)	74(1)	34(1)	1(1)	19(1)	-13(1)
C(28)	41(1)	27(1)	37(1)	3(1)	9(1)	7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 7381.

	x	y	z	U(eq)
H(71)	-4677	6947	7377	35
H(81)	-3420	8778	8301	36
H(91)	-550	8712	9419	30
H(141)	-4584	4742	6975	48
H(142)	-3277	3998	7822	49
H(143)	-2839	4391	6709	48
H(161)	-233	2292	7038	36
H(171)	176	138	7312	42
H(181)	2622	-567	8607	41
H(191)	4647	821	9589	38
H(201)	4245	2992	9267	31
H(221)	1961	3336	5489	29
H(231)	3601	3860	4104	40
H(251)	3201	7526	4864	36
H(271)	5142	6895	3644	77
H(272)	5521	5480	3470	77
H(273)	3868	6150	2727	78
H(283)	1485	8201	6158	52
H(282)	1994	7346	7245	52
H(281)	108	7283	6477	53

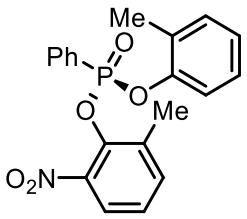
Table 6. Hydrogen bonds for 7381 [Å and °].

D-H..A	d(D-H)	d(H..A)	d(D..A)	<(DHA)
C(9)-H(91)..O(4)#1	0.97	2.50	3.292(2)	138
C(9)-H(91)..O(12)#1	0.97	2.49	3.182(2)	128
C(18)-H(181)..O(13)#2	0.93	2.55	3.327(2)	141

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

5.3.6 Products: Scope with respect to the phenol nucleophile

2-methyl-6-nitrophenyl *o*-tolyl (*R*)-phenylphosphonate (**416**)

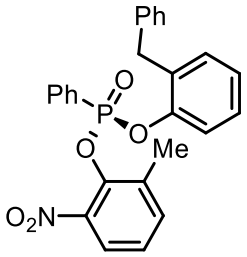


416 was synthesized following **GP V**. **411** (42.6 mg, 0.10 mmol) was used as phosphonate, 2-methylphenol (11.9 mg, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (31.4 mg, 0.082 mmol, 82% yield, 82% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (major) = 11.03 min, t (minor) = 14.71 min.

[α]$_D^{25}$ = −3.3 (c = 0.58, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) 8.08 – 8.00 (m, 2H,v), 7.72 (dd, *J* = 8.2, 1.7 Hz, 1H, ArC<u>H</u>), 7.69 – 7.60 (m, 1H, ArC<u>H</u>), 7.58 – 7.51 (m, 2H, ArC<u>H</u>), 7.48 (ddt, *J* = 7.6, 1.7, 0.8 Hz, 1H, ArC<u>H</u>), 7.23 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 7.13 – 7.08 (m, 1H, ArC<u>H</u>), 7.04 – 6.96 (m, 3H, ArC<u>H</u>), 2.44 (s, 3H, ArC<u>H</u>$_3$), 2.11 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.0 (d, *J* = 7.2 Hz, Ar<u>C</u>), 143.9 (Ar<u>C</u>), 141.0 (d, *J* = 10.3 Hz, Ar<u>C</u>), 136.0 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 134.6 (d, *J* = 3.5 Hz, Ar<u>C</u>), 133.7 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.6 (d, *J* = 10.9 Hz, Ar<u>C</u>H), 131.6 (Ar<u>C</u>H), 129.6 (d, *J* = 5.6 Hz, Ar<u>C</u>), 128.9 (Ar<u>C</u>H), 127.0 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 126.5 (d, *J* = 194.7 Hz, <u>C</u>P), 125.5 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 125.3 (Ar<u>C</u>H), 123.4 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 120.2 (d, *J* = 2.7 Hz, Ar<u>C</u>H), 17.5 (Ar<u>C</u>H$_3$), 16.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.18; **IR** (film) υ_{max}/cm^{-1}: 1534 (NO_2), 1492, 1357 (NO_2), 1272, 1218 (P=O), 1172, 1130, 1111, 926, 865, 750; **HRMS** (ESI+): calcd. for $C_{20}H_{19}NO_5P$ 384.0995 $[M+H]^+$, found 384.0983.

2-benzylphenyl (2-methyl-6-nitrophenyl) *(R)*-phenylphosphonate (**417**)

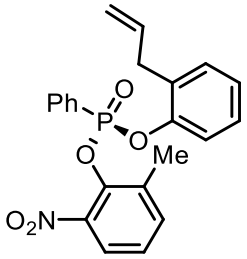


417 was synthesized following **GP V**. **411** (42.6 mg, 0.10 mmol) was used as phosphonate, 2-benzylphenol (20.1 mg, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (37.5 mg, 0.080 mmol, 80% yield, 88% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (major) = 22.55 min, t (minor) = 19.94 min.

[α]$_D^{25}$ =−10.9 (c = 0.67, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.84 (m, 2H, ArC<u>H</u>), 7.69 (dd, *J* = 8.2, 1.7 Hz, 1H, ArC<u>H</u>), 7.65 – 7.58 (m, 1H, ArC<u>H</u>), 7.50 – 7.40 (m, 3H, ArC<u>H</u>), 7.25 – 7.16 (m, 4H, ArC<u>H</u>), 7.15 – 7.10 (m, 1H, ArC<u>H</u>), 7.08 – 6.98 (m, 5H, ArC<u>H</u>), 3.93 – 3.85 (m, 2H, benzyl C<u>H</u>$_2$), 2.34 (d, *J* = 1.0 Hz, 3H, $ArCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.7 (d, *J* = 7.1 Hz, Ar<u>C</u>), 143.6 (Ar<u>C</u>), 141.0 (d, *J* = 9.9 Hz, Ar<u>C</u>), 139.8 (Ar<u>C</u>), 136.0 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 134.5 (d, *J* = 3.4 Hz, Ar<u>C</u>), 133.6 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.4 (d, *J* = 11.0 Hz, Ar<u>C</u>), 132.1 (d, *J* = 6.1 Hz, Ar<u>C</u>H), 131.4 (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 128.8 (d, *J* = 16.3 Hz, Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 126.3 (d, *J* = 194.7 Hz, <u>C</u>P), 126.2 (Ar<u>C</u>H), 125.4 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 123.4 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 120.2 (d, *J* = 2.8 Hz, Ar<u>C</u>H), 35.7 (benzyl <u>C</u>H$_2$), 17.4 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.24; **IR** (film) υ_{max}/cm^{-1}: 1534 (NO_2), 1490, 1452, 1357 (NO_2), 1273, 1215 (P=O), 1171, 1130, 1093, 926, 751; **HRMS** (ESI+): calcd. for $C_{26}H_{23}NO_5P$ 460.1308 $[M+H]^+$, found 460.1314.

2-allylphenyl (2-methyl-6-nitrophenyl) *(R)*-phenylphosphonate (**418**)

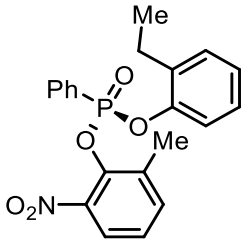


418 was synthesized following **GP V**. **411** (42.6 mg, 0.10 mmol) was used as phosphonate, 2-allylphenol (14.6 mg, 14.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (29.8 mg, 0.071 mmol, 71% yield, 90% ee).

HPLC Conditions: CHIRALPAK IB, hexane/isopropanol = 95/05, 1 mL/min, λ = 220 nm, t (major) = 13.13 min, t (minor) = 12.78 min.

[α]$_D^{25}$ = −8.4 (c = 0.63, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.98 (m, 2H, ArC<u>H</u>), 7.72 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.69 – 7.63 (m, 1H, ArC<u>H</u>), 7.58 – 7.50 (m, 2H, ArC<u>H</u>), 7.47 (ddt, *J* = 7.7, 1.6, 0.8 Hz, 1H, ArC<u>H</u>), 7.23 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 7.17 – 7.10 (m, 1H, ArC<u>H</u>), 7.08 – 7.02 (m, 3H, ArC<u>H</u>), 5.79 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H, C<u>H</u>=CH_aH_b), 4.99 (dq, *J* = 10.1, 1.5 Hz, 1H, CH=CH_a<u>H_b</u>), 4.93 (dq, *J* = 17.0, 1.7 Hz, 1H, CH=C<u>H_a</u>H_b), 3.27 (dt, *J* = 6.5, 1.6 Hz, 2H, Allyl C<u>H_2</u>), 2.42 (d, *J* = 0.9 Hz, 3H, ArC<u>H_3</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.5 (d, *J* = 7.4 Hz, Ar<u>C</u>), 143.7 (Ar<u>C</u>), 141.1 (d, *J* = 10.1 Hz. Ar<u>C</u>), 136.1 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 135.9 (<u>C</u>H=CH_2), 134.6 (d, *J* = 3.5 Hz, Ar<u>C</u>), 133.7 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 132.5 (d, *J* = 10.9 Hz, Ar<u>C</u>H), 131.3 (d, *J* = 6.0 Hz, Ar<u>C</u>), 130.7 (Ar<u>C</u>H), 128.9 (d, *J* = 16.3 Hz, Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 126.5 (d, *J* = 182.9 Hz, <u>C</u>P), 125.5 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 123.4 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 120.4 (d, *J* = 2.7 Hz, Ar<u>C</u>H), 116.4 (CH=<u>C</u>H_2), 34.0 (Allyl <u>C</u>H_2), 17.5 (Ar<u>C</u>H_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.16; **IR** (film) υ_{max}/cm^{-1}: 1535 (NO_2), 1489, 1357 (NO_2), 1272, 1212 (P=O), 1170, 1130, 925, 750; **HRMS** (ESI+): calcd. for $C_{22}H_{21}NO_5P$ 410.1152 $[M+H]^+$, found 410.1144.

2-ethylphenyl (2-methyl-6-nitrophenyl) *(R)*-phenylphosphonate (**419**)

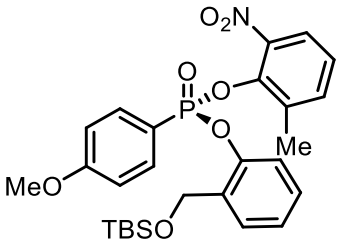


419 was synthesized following **GP V. 411** (42.6 mg, 0.10 mmol) was used as phosphonate, 2-ethylphenol (13.4 mg, 13.0 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (29.9 mg, 0.070 mmol, 70% yield, 91% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (major) = 13.02 min, t (minor) = 13.88 min.

[α]$_D^{25}$ = −5.9 (c = 0.72, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 – 7.98 (m, 2H, ArC<u>H</u>), 7.73 (dt, *J* = 8.3, 1.1 Hz, 1H, ArC<u>H</u>), 7.66 (tdd, *J* = 6.9, 2.9, 1.4 Hz, 1H, ArC<u>H</u>), 7.59 – 7.52 (m, 2H,v), 7.48 (ddt, *J* = 7.6, 1.6, 0.8 Hz, 1H, ArC<u>H</u>), 7.23 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 7.18 – 7.13 (m, 1H, ArC<u>H</u>), 7.08 – 6.98 (m, 3H, ArC<u>H</u>), 2.50 (qd, *J* = 7.5, 2.0 Hz, 2H, C<u>H</u>$_2$CH$_3$), 2.43 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 1.06 (t, *J* = 7.6 Hz, 3H, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.5 (d, *J* = 7.3 Hz, Ar<u>C</u>), 143.8 (Ar<u>C</u>), 141.1 (d, *J* = 10.0 Hz, Ar<u>C</u>), 136.1 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 135.2 (d, *J* = 5.8 Hz, Ar<u>C</u>), 134.6 (d, *J* = 3.5 Hz, Ar<u>C</u>), 133.7 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.6 (Ar<u>C</u>H), 132.5 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 128.9 (d, *J* = 16.3 Hz, Ar<u>C</u>H), 127.0 (d, *J* = 1.4 Hz, Ar<u>C</u>H), 126.5 (d, *J* = 195.0 Hz, <u>C</u>P), 125.4 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 123.4 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 120.3 (d, *J* = 2.7 Hz, Ar<u>C</u>H), 23.1 (<u>C</u>H$_2$CH$_3$), 17.5 (Ar<u>C</u>H$_3$), 14.2 (CH$_2$<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.08; **IR** (film) υ_{max}/cm^{-1}: 1534 (NO_2), 1490, 1357 (NO_2), 1273, 1213 (P=O), 1179, 1159, 1130, 1117, 925, 751; **HRMS** (ESI+): calcd. for $C_{21}H_{21}NO_5P$ 398.1152 $[M+H]^+$, found 398.1140.

2-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl (2-methyl-6-nitrophenyl) (*R*)-(4-methoxyphenyl)phosphonate (**420**)



420 was synthesized following **GP V**. **438** (45.8 mg, 0.10 mmol) was used as phosphonate, 2-(((*tert*-butyldimethylsilyl)oxy)methyl)phenol[viii] (28.0 mg, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless Oil (53.4 mg, 0.098 mmol, 98% yield, 91% ee).

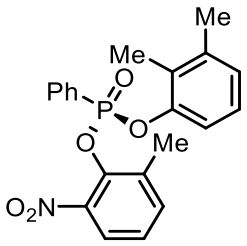
HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (major) = 8.63 min, t (minor) = 9.40 min.

[α]$_D^{25}$ = − 7.2 (c = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.89 (m, 2H, ArC<u>H</u>), 7.72 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.51 – 7.45 (m, 2H, ArC<u>H</u>), 7.23 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 7.11 (tt, *J* = 7.4, 1.1 Hz, 1H, ArC<u>H</u>), 7.07 – 6.99 (m, 3H, ArC<u>H</u>), 6.97 (dt, *J* = 8.0, 1.3 Hz, 1H, ArC<u>H</u>), 4.69 (d, *J* = 14.6 Hz, 1H, $CH_a\underline{H}_bOTBS$), 4.51 (d, *J* = 14.6 Hz, 1H $C\underline{H}_aH_bOTBS$), 3.87 (s, 3H, $OC\underline{H}_3$), 2.46 (d, *J* = 1.0 Hz, 3H, $ArC\underline{H}_3$), 0.92 (s, 9H, TBS $C(C\underline{H}_3)_3$), 0.05 (s, 6H, TBS $C\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.0 (d, *J* = 3.6 Hz, <u>C</u>OMe), 146.8 (d, *J* = 6.9 Hz, Ar<u>C</u>), 143.9 (Ar<u>C</u>), 141.0 (d, *J* = 10.2 Hz, Ar<u>C</u>), 136.0 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 134.8 (Ar<u>C</u>), 134.6 (Ar<u>C</u>H), 133.1 (d, *J* = 5.6 Hz, Ar<u>C</u>H), 127.6 (ArC), 127.3 (Ar<u>C</u>H), 125.5 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 125.3 (Ar<u>C</u>H), 123.3 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 119.7 (d, *J* = 2.8 Hz, Ar<u>C</u>H), 117.1 (d, *J* = 202.5 Hz, <u>C</u>P), 114.5 (d, *J* = 17.4 Hz, Ar<u>C</u>H), 59.8 ($\underline{C}H_2OTBS$), 55.6 ($OC\underline{H}_3$), 26.1 ($SiC(\underline{C}H_3)_3$), 18.5 ($Si\underline{C}(CH_3)_3$), 17.6 ($ArCH_3$), -5.3 ($SiC\underline{H}_3$), -5.3 ($SiC\underline{H}_3$); **^{31}P NMR** (162 MHz $CDCl_3$) δ 14.26; **IR** (film) υ_{max}/cm^{-1}: 2929, 2856, 1599, 1535 (NO_2), 1456, 1357 (NO_2), 1257, 1213 (P=O), 1173,

[viii] 2-(((tert-butyldimethylsilyl)oxy)methyl)phenol was prepared by Dr. Heyao Shi according to literature procedures.[35]

1129, 1077, 921, 835, 805, 764, 736; **HRMS** (ESI+): calcd. for $C_{27}H_{34}NO_7PSi$ 544.1915 $[M+H]^+$, found 544.1913.

2,3-dimethylphenyl (2-methyl-6-nitrophenyl) (*R*)-phenylphosphonate (**421**)

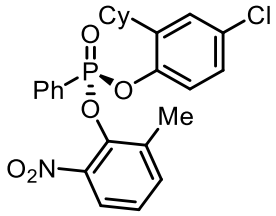


421 was synthesized following **GP V**. **411** (42.6 mg, 0.10 mmol) was used as phosphonate, 2,3-dimethylphenol (13.4 mg, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (36.8 mg, 0.093 mmol, 93% yield, 88% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (major) = 11.98 min, t (minor) = 13.86 min.

$[\alpha]_D^{25}$ = −8.4 (c = 0.77, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.96 (m, 2H, ArC<u>H</u>), 7.72 (dd, *J* = 8.2, 1.7 Hz, 1H, ArC<u>H</u>), 7.68 – 7.63 (m, 1H, ArC<u>H</u>), 7.58 – 7.50 (m, 2H, ArC<u>H</u>), 7.48 (ddt, *J* = 7.6, 1.6, 0.7 Hz, 1H, ArC<u>H</u>), 7.23 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 6.94 – 6.79 (m, 3H, ArC<u>H</u>), 2.44 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 2.21 (s, 3H, ArC<u>H</u>$_3$), 2.01 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.8 (d, *J* = 7.2 Hz, Ar<u>C</u>), 143.8 (Ar<u>C</u>), 141.1 (d, *J* = 10.2 Hz, Ar<u>C</u>), 138.9 (Ar<u>C</u>), 136.0 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 134.6 (d, *J* = 3.3 Hz, Ar<u>C</u>), 133.6 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.1 (d, *J* = 5.8 Hz, Ar<u>C</u>H), 126.8 (Ar<u>C</u>), 126.5 (d, *J* = 194.5 Hz, <u>C</u>P), 126.1 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 125.4 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 123.3 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 117.8 (d, *J* = 2.7 Hz, Ar<u>C</u>H), 20.3 (ArC<u>H</u>$_3$), 17.5 (ArC<u>H</u>$_3$), 12.5 (ArC<u>H</u>$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.14; **IR** (film) υ_{max}/cm^{-1}: 1534 (NO_2), 1469, 1357 (NO_2), 1274, 1232, 1218 (P=O), 1182, 1131, 1064, 926, 804, 750; **HRMS** (ESI+): calcd. for $C_{21}H_{21}NO_5P$ 398.1152 $[M+H]^+$, found 398.1143.

4-chloro-2-cyclohexylphenyl (2-methyl-6-nitrophenyl) (*R*)-phenylphosphonate (**422**)

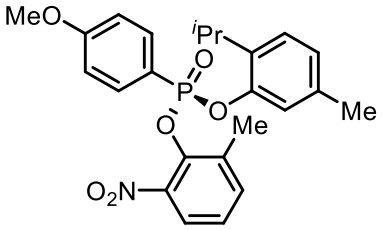


422 was synthesized following **GP V**. **411** (43.4 mg, 0.10 mmol) was used as phosphonate, 4-chloro-2-cyclohexylphenol (23.0 mg, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (29.8 mg, 0.061 mmol, 61% yield, 75% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (major) = 10.61 min, t (minor) = 12.47 min.

[α]$_D^{25}$ = −1.6 (c = 0.38, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$ δ 8.01 – 7.90 (m, 2H, ArC<u>H</u>), 7.69 – 7.54 (m, 2H, ArC<u>H</u>), 7.53 – 7.39 (m, 3H, ArC<u>H</u>), 7.23 – 7.14 (m, 1H, ArC<u>H</u>), 7.05 (dd, *J* = 2.5, 1.0 Hz, 1H, ArC<u>H</u>), 6.92 – 6.79 (m, 2H, ArC<u>H</u>), 2.59 – 2.47 (m, 1H Cyclohexyl-C<u>H</u>), 2.39 (s, 3H, $ArCH_3$), 1.76 – 1.65 (m, 2H, Cyclohexyl-C<u>H</u>$_2$), 1.63 – 1.54 (m, 2H, Cyclohexyl-C<u>H</u>$_2$), 1.37 – 0.85 (m, 6H, Cyclohexyl-C<u>H</u>$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.9 (d, *J* = 7.4 Hz, Ar<u>C</u>), 143.7 (d, *J* = 3.1 Hz, Ar<u>C</u>), 140.9 (d, *J* = 5.8 Hz, Ar<u>C</u>), 140.7 (d, *J* = 10.4 Hz, Ar<u>C</u>), 135.9 (Ar<u>C</u>H), 134.5 (d, *J* = 3.3 Hz, Ar<u>C</u>), 133.7 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.40 (d, *J* = 11.0 Hz, Ar<u>C</u>H), 130.80 (Ar<u>C</u>), 128.8 (d, *J* = 16.1 Hz, Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 126.5 (Ar<u>C</u>H), 125.9 (d, *J* = 195 Hz, <u>C</u>P), 125.5 (Ar<u>C</u>H), 123.3 (Ar<u>C</u>H), 121.8 (d, *J* = 2.5 Hz, Ar<u>C</u>H), 36.9 (Cyclohexyl-<u>C</u>H$_2$), 33.3 (d, *J* = 8.4 Hz, Cyclohexyl-<u>C</u>H$_2$), 26.6 (Cyclohexyl-<u>C</u>H$_2$), 26.0 (Cyclohexyl-<u>C</u>H), 17.4 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.23; **IR** (film) υ_{max}/cm^{-1}:2927, 2159, 1535 (NO_2), 1481, 1357 (NO_2), 1277, 1213 (P=O), 1167, 1130, 1105, 928; **HRMS** (ESI+): calcd. for $C_{25}H_{26}ClNO_5P$ 486.1237 $[M+H]^+$, found 486.1231.

2-isopropyl-5-methylphenyl (2-methyl-6-nitrophenyl) (*R*)-(4-methoxyphenyl)phosphonate (**423**)

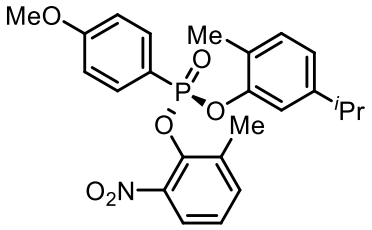


423 was synthesized following **GP V**. **438** (45.8 mg, 0.10 mmol) was used as phosphonate, 2-isopropyl-5-methylphenol (16.5 mg, 0.11 mmol) was used as nucleophile and **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (29.0 mg, 0.064 mmol, 64% yield, 96% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (major) = 9.75 min, t (minor) = 11.28 min.

$[\alpha]_D^{25}$ = − 31.9 (c = 0.48, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.90 (m, 2H, *p*-OMe-ArC<u>H</u>), 7.70 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.47 (ddt, *J* = 7.7, 1.7, 0.8 Hz, 1H, ArC<u>H</u>), 7.21 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 7.09 – 7.05 (m, 1H, ArC<u>H</u>), 7.04 – 6.98 (m, 2H, *p*-OMe-ArC<u>H</u>), 6.88 (t, *J* = 3.5 Hz, 2H, ArC<u>H</u>), 3.88 (s, 3H, OC<u>H</u>$_3$), 3.05 (p, *J* = 6.9 Hz, 1H, C<u>H</u>$(CH_3)_2$), 2.44 (d, *J* = 1.0 Hz, 3H, ArC<u>H</u>$_3$), 2.17 (s, 3H, ArC<u>H</u>$_3$), 1.05 (dd, *J* = 49.8, 6.9 Hz, 6H, CH(C<u>H</u>$_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9 (d, *J* = 3.6 Hz, <u>C</u>OMe), 147.6 (d, *J* = 7.3 Hz, Ar<u>C</u>), 143.9 (Ar<u>C</u>), 141.3 (d, *J* = 10.2 Hz, Ar<u>C</u>), 136.7 (Ar<u>C</u>), 136.5 (d, *J* = 5.9 Hz, Ar<u>C</u>), 135.9 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 134.7 (d, *J* = 2.0 Hz *p*-OMe-Ar<u>C</u>H), 134.6 (Ar<u>C</u>), 126.6(Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 125.3 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 123.3 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 120.8 (d, *J* = 2.6 Hz, Ar<u>C</u>H), 117.5 (d, *J* = 203.2 Hz, <u>C</u>P), 114.4 (d, *J* = 17.3 Hz, *p*-OMe-Ar<u>C</u>H), 55.6 (O<u>C</u>H$_3$), 26.4 (<u>C</u>H$(CH_3)_a(CH_3)_b$), 23.3 (CH$(CH_3)_a$(<u>C</u>H$_3)_b$), 23.2 (CH(<u>C</u>H$_3)_a(CH_3)_b$), 21.0 (Ar<u>C</u>H$_3$), 17.6 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.88; **IR** (film) υ_{max}/cm^{-1}: 2965, 1599, 1535 (NO_2), 1506, 1357 (NO_2), 1259, 1219 (P=O), 1181, 1130, 1087, 924, 911; **HRMS** (ESI+): calcd. for $C_{24}H_{27}NO_6P$ 456.1571 $[M+H]^+$, found 456.1562.

5-isopropyl-2-methylphenyl (2-methyl-6-nitrophenyl) (*R*)- (4-methoxyphenyl)phosphonate (**424**)

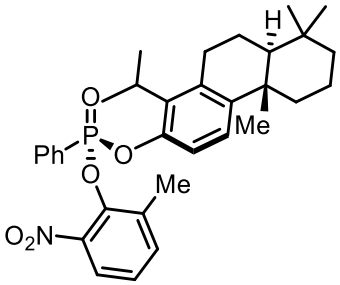


424 was synthesized following **GP V**. **438** (45.8 mg, 0.10 mmol) was used as phosphonate, 5-isopropyl-2-methylphenol (16.9 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (22.7 mg, 0.05 mmol, 50% yield, 70% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (major) = 9.40 min, t (minor) = 10.67 min.

[α]$_D^{25}$ = − 14.7(c = 0.21, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.91 (m, 2H, ArC<u>H</u>), 7.70 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.47 (ddt, *J* = 7.7, 1.6, 0.7 Hz, 1H, ArC<u>H</u>), 7.21 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 7.02 (m, 3H, ArC<u>H</u>), 6.91 – 6.83 (m, 2H, ArC<u>H</u>), 3.88 (s, 3H, OC<u>H</u>$_3$), 2.72 (p, *J* = 6.9 Hz, 1H, C<u>H</u>$(CH_3)_2$), 2.44 (d, *J* = 1.0 Hz, 3H, ArC<u>H</u>$_3$), 2.09 (s, 3H, ArC<u>H</u>$_3$), 1.09 (dd, *J* = 6.9, 1.3 Hz, 6H, CH(C<u>H</u>$_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7 (d, *J* = 3.5 Hz, <u>C</u>OMe), 148.9 (d, *J* = 7.2 Hz, Ar<u>C</u>), 148.1 (Ar<u>C</u>), 141.1 (d, *J* = 10.2 Hz, Ar<u>C</u>), 135.8 (d, *J* = 1.9 Hz, Ar<u>C</u>), 134.6 (Ar<u>C</u>), 134.5 (Ar<u>C</u>H), 131.1 (Ar<u>C</u>H), 126.5 (d, *J* = 5.8 Hz, Ar<u>C</u>H), 125.1 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 123.2 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 123.0 (Ar<u>C</u>H), 118.2 (d, *J* = 2.9 Hz, Ar<u>C</u>H), 117.4 (d, *J* = 203.0 Hz, <u>C</u>P), 114.3 (Ar<u>C</u>H), 114.2 (Ar<u>C</u>H), 55.4 (O<u>C</u>H$_3$), 33.5 (<u>C</u>H$(CH_3)_a(CH_3)_b$), 23.8 (CH$(CH_3)_a$(<u>C</u>H$_3)_b$), 23.7 (CH(<u>C</u>H$_3)_a(CH_3)_b$), 17.4 (Ar<u>C</u>H$_3$), 16.0 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 14.18; **IR** (film) υ_{max}/cm^{-1}:1599, 1532 (NO_2), 1506, 1358 (NO_2), 1259 (P=O), 1131, 924; **HRMS** (ESI+): calcd. for $C_{24}H_{27}NO_6P$ 456.1571 $[M+H]^+$, found 456.1565.

(8a*S*)-1-isopropyl-4b,8,8-trimethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthren-2-yl (2-methyl-6-nitrophenyl) (*R*)-phenylphosphonate (**425**)

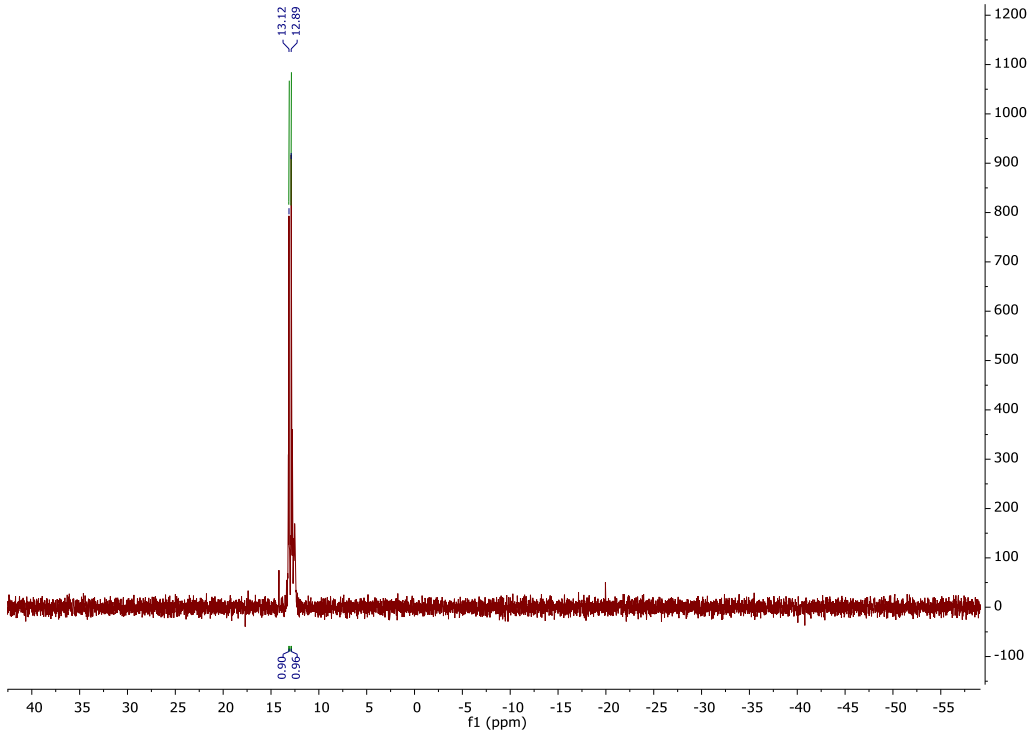


425 was synthesized following **GP V**. **411** (43.4 mg, 0.10 mmol) was used as phosphonate, totarol (31.5 mg, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless Oil (35.4 mg, 0.063 mmol, 63% yield, 97:3 dr).

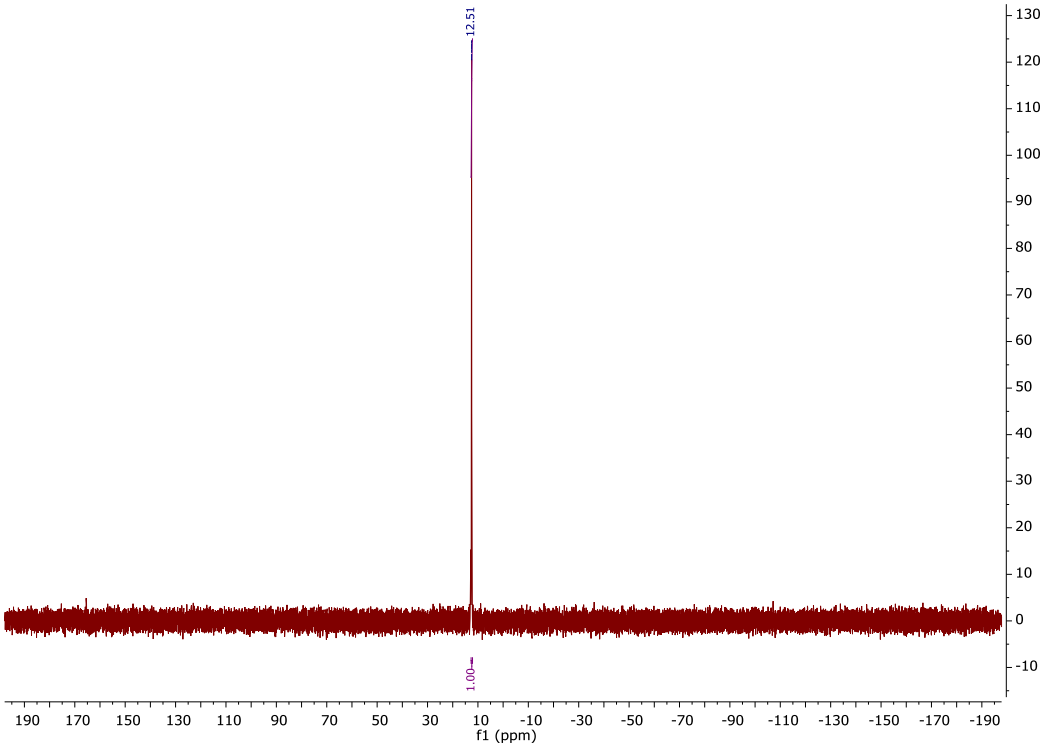
[α]$_D^{25}$ = − 20.2 (c = 0.65, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (ddt, *J* = 14.4, 6.9, 1.4 Hz, 2H), 7.68 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.62 (dq, *J* = 6.9, 1.7 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.45 (s, 1H), 7.19 (td, *J* = 7.9, 1.2 Hz, 1H), 6.92 (d, *J* = 4.4 Hz, 2H), 3.29 (dq, *J* = 14.7, 7.4, 6.0 Hz, 1H, totarol benzylic C$\underline{H}_a$H$_b$), 2.93 (ddd, *J* = 17.2, 6.6, 1.7 Hz, 1H, totarol benzylic C$\underline{H}_a$H$_b$), 2.73 (ddd, *J* = 17.7, 11.2, 7.8 Hz, 1H, totarol CH_2), 2.34 (d, *J* = 3.4 Hz, 3H, ArC$\underline{H}_3$), 2.19 – 2.09 (m, 1H, totarol C$\underline{H}_2$), 1.88 (dd, *J* = 13.4, 7.7 Hz, 1H, $CH_3C\underline{H}CH_3$), 1.77 – 1.52 (m, 3H, totarol C$\underline{H}_3$), 1.44 (dtd, *J* = 13.2, 3.3, 1.3 Hz, 1H, totarol C$\underline{H}$), 1.36 – 1.19 (m, 4H, totarol C$\underline{H}_2$), 1.17 (d, *J* = 7.1 Hz, 3H, $CH_3CHC\underline{H}_3$), 1.13 (s, 3H, $CH_3CHC\underline{H}_3$), 0.92 (s, 3H, totarol gem-C$\underline{H}_3$), 0.90 (s, 3H, totarol gem-C$\underline{H}_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.4 (Ar$\underline{C}$), 143.6 (Ar$\underline{C}$), 141.4 (d, *J* = 9.1 Hz, Ar$\underline{C}$), 136.0 (d, *J* = 1.8 Hz), 135.1 (Ar$\underline{C}$), 134.5 (d, *J* = 3.3 Hz, Ar$\underline{C}$), 133.4 (d, *J* = 3.3 Hz, Ar$\underline{C}$), 132.5 (Ar$\underline{C}$H), 132.4 (Ar$\underline{C}$H), 128.8 (Ar$\underline{C}$), 128.7 (Ar$\underline{C}$H), 127.1 (d, *J* = 195.1 Hz, $\underline{C}$P), 125.2 (Ar$\underline{C}$H), 123.4 (d, *J* = 1.5 Hz, Ar$\underline{C}$H), 123.3 (Ar$\underline{C}$H), 117.7 (d, *J* = 2.9 Hz, Ar$\underline{C}$H), 53.6 (totarol C$\underline{H}$), 49.4 (totarol $\underline{C}$H(CH$_3$)$_2$), 41.6 (totarol $\underline{C}$H$_2$), 39.4 (totarol $\underline{C}$H$_2$), 38.1 ($\underline{C}$H(CH$_3$)$_2$), 33.4 (benzylic totarol $\underline{C}$H$_2$), 33.3 (totarol $\underline{C}$H$_2$), 28.9 (totarol $\underline{C}$H$_2$), 25.1 ($\underline{C}$H(CH$_3$)), 20.7 (totarol gem-$\underline{C}$H$_3$), 20.7 (totarol gem-$\underline{C}$H$_3$), 19.5 (CH($\underline{C}$H$_3$)), 19.4 (CH($\underline{C}$H$_3$)), 17.6 (Ar$\underline{C}$H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.51; **IR** (film) υ_{max}/cm^{-1}:2927, 1536 (NO_2), 1471, 1440, 1357 (NO_2), 1275, 1219 (P=O), 1197, 1179,

1129, 982, 923, 804, 766, 740, 644; **HRMS** (ESI+): calcd. for $C_{33}H_{41}NO_5P$ 562.2717 $[M+H]^+$, found 562.2715.

^{31}P NMR (rac):

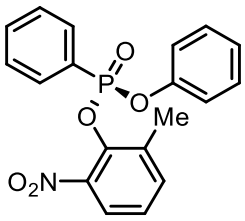


^{31}P NMR (enantioenriched):



5.3.7 Products: Phenol scope (unsuccessful examples)

2-methyl-6-nitrophenyl phenyl (*R*)-phenylphosphonate (**426**)

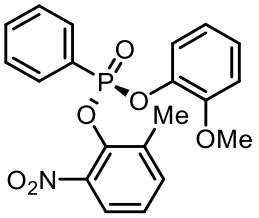


426 was synthesized following **GP V**. **411** (43.4 mg, 0.10 mmol) was used as phosphonate, phenol (10.4 mg, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (22.3 mg, 0.057 mmol, 57% yield, 6% ee).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (minor) = 11.04 min, t (major) = 13.27 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.00 (m, 2H, ArC<u>H</u>), 7.74 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.68 – 7.63 (m, 1H, ArC<u>H</u>), 7.58 – 7.51 (m, 2H, ArC<u>H</u>), 7.48 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H, ArC<u>H</u>), 7.24 – 7.18 (m, 3H, ArC<u>H</u>), 7.11 – 7.02 (m, 3H, ArC<u>H</u>), 2.46 (d, *J* = 1.0 Hz, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.3 (m, Ar<u>C</u>), 143.8 (m, Ar<u>C</u>), 140.8 (m, Ar<u>C</u>), 136.1 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 134.6 (Ar<u>C</u>), 133.8 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.7 (d, *J* = 11.0 Hz, phenyl Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 128.9 (d, *J* = 16.2 Hz, phenyl Ar<u>C</u>H), 125.9 (d, *J* = 194.1 Hz, <u>C</u>P), 125.5 (Ar<u>C</u>H), 125.2 (Ar<u>C</u>H), 123.4 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 120.2 (d, *J* = 4.8 Hz, Ar<u>C</u>H), 17.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.06; **IR** (film) υ_{max}/cm^{-1}:1533 (NO_2), 1357 (NO_2), 1276 (P=O), 1130, 924, 769, 749; **HRMS** (ESI+): calcd. for $C_{19}H_{17}NO_5P$ 370.0839 $[M+H]^+$, found 370.0840.

2-methoxyphenyl (2-methyl-6-nitrophenyl) (*S*)-phenylphosphonate (**430**)

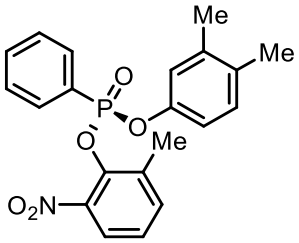


430 was synthesized following **GP V**. **411** (43.4 mg, 0.10 mmol) was used as phosphonate, Guaiacol (12.3 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (32.3 mg, 0.081 mmol, 81% yield, 11% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 mL/min, λ = 220 nm, t (major) = 11.29 min, t (minor) = 24.46 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.06 (m, 2H, ArC<u>H</u>), 7.82 – 7.75 (m, 1H, ArC<u>H</u>), 7.67 – 7.62 (m, 1H, ArC<u>H</u>), 7.58 – 7.52 (m, 2H, ArC<u>H</u>), 7.49 (ddt, *J* = 7.7, 1.6, 0.7 Hz, 1H, ArC<u>H</u>), 7.28 – 7.16 (m, 1H, ArC<u>H</u>), 7.03 (dddd, *J* = 8.4, 7.5, 1.6, 1.0 Hz, 1H, ArC<u>H</u>), 6.95 – 6.91 (m, 1H, ArC<u>H</u>), 6.83 – 6.69 (m, 2H, ArC<u>H</u>), 3.55 (s, 3H, OC<u>H</u>$_3$), 2.50 (d, *J* = 1.0 Hz, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.4 (Ar<u>C</u>), 143.8 (m, Ar<u>C</u>), 141.0 (m, Ar<u>C</u>), 139.7 (d, *J* = 7.9 Hz, Ar<u>C</u>), 135.8 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 134.7 (d, *J* = 3.6 Hz, Ar<u>C</u>), 133.2 (d, *J* = 3.4 Hz, Ar<u>C</u>H), 132.4 (d, *J* = 11.0 Hz, phenyl Ar<u>C</u>H), 128.4 (d, *J* = 16.6 Hz, phenyl Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 125.4 (d, *J* = 196.1 Hz, <u>C</u>P), 125.2 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 123.2 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 121.3 (d, *J* = 3.6 Hz, Ar<u>C</u>H), 120.8 (Ar<u>C</u>H), 112.7 (Ar<u>C</u>H), 55.5 (O<u>C</u>H$_3$), 17.4 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 14.07; **IR** (film) υ_{max}/cm^{-1}: 1534 (NO_2), 1502, 1357 (NO_2); **HRMS** (ESI+): calcd. for $C_{20}H_{19}NO_6P$ 400.0945 $[M+H]^+$, found 400.0946.

3,4-dimethylphenyl (2-methyl-6-nitrophenyl)-phenylphosphonate (**431**)

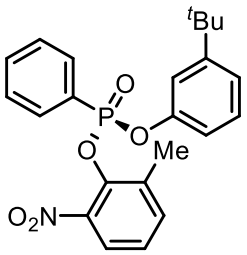


431 was synthesized following **GP V**. **411** (43.4 mg, 0.10 mmol) was used as phosphonate, 3,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (29.3 mg, 0.072 mmol, 72% yield, 0% ee).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (1) = 9.05 min, t (2) = 10.51 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.97 (m, 2H, ArC<u>H</u>), 7.73 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.68 – 7.59 (m, 1H, ArC<u>H</u>), 7.57 – 7.50 (m, 2H, ArC<u>H</u>), 7.47 (ddd, *J* = 7.7, 1.7, 0.8 Hz, 1H, ArC<u>H</u>), 7.22 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 6.93 (d, *J* = 8.2 Hz, 1H, ArC<u>H</u>), 6.87 – 6.81 (m, 1H, ArC<u>H</u>), 6.75 (dq, *J* = 8.2, 1.1 Hz, 1H, ArC<u>H</u>), 2.46 (s, 3H, ArC<u>H</u>$_3$), 2.13 (m, 6H, 2x Nucleophile ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.2 (d, *J* = 6.7 Hz, Ar<u>C</u>), 143.9 (Ar<u>C</u>), 141.0 (d, *J* = 10.4 Hz, Ar<u>C</u>), 138.3 (Ar<u>C</u>), 136.0 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 134.6 (d, *J* = 3.2 Hz, Ar<u>C</u>), 133.7 (d, *J* = 3.2 Hz), 133.5 (Ar<u>C</u>), 132.7 (d, *J* = 10.8 Hz, phenyl Ar<u>C</u>H), 130.5 (Ar<u>C</u>H), 128.8 (d, *J* = 16.2 Hz, phenyl Ar<u>C</u>H), 126.1 (d, *J* = 193.6 Hz, <u>C</u>P), 125.4 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 123.3 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 121.1 (d, *J* = 4.8 Hz, Ar<u>C</u>H), 117.1 (d, *J* = 4.7 Hz, Ar<u>C</u>H), 19.9 (Nucleophile Ar<u>C</u>H$_3$), 19.1 (Nucleophile Ar<u>C</u>H$_3$), 17.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.09; **IR** (film) υ_{max}/cm^{-1}: 2970, 1534 (NO_2), 1357 (NO_2), 1271 (P=O), 1152, 965, 925, 748; **HRMS** (ESI+): calcd. for $C_{21}H_{21}NO_5P$ 398.1152 $[M+H]^+$, found 398.1146.

3-(*tert*-butyl)phenyl (2-methyl-6-nitrophenyl) (*R*)-phenylphosphonate (**432**)

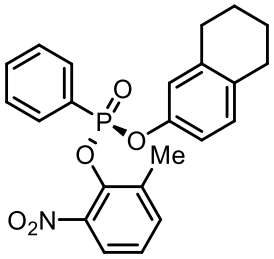


432 was synthesized following **GP V**. **411** (43.4 mg, 0.10 mmol) was used as phosphonate, 3-(*tert*-butyl)phenol (16.5 mg, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (20.2 mg, 0.047 mmol, 47% yield, 19% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 8.48 min, t (major) = 10.94 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.96 (m, 2H, ArC<u>H</u>), 7.74 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.67 – 7.59 (m, 1H, ArC<u>H</u>), 7.57 – 7.50 (m, 2H, ArC<u>H</u>), 7.47 (ddt, *J* = 7.7, 1.6, 0.8 Hz, 1H, ArC<u>H</u>), 7.23 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 7.17 – 7.06 (m, 2H, ArC<u>H</u>), 7.03 (dt, *J* = 2.7, 1.5 Hz, 1H, ArC<u>H</u>), 6.87 (ddt, *J* = 7.8, 2.6, 1.3 Hz, 1H, ArC<u>H</u>), 2.46 (d, *J* = 1.0 Hz, 3H, ArC<u>H</u>$_3$), 1.20 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5 (Ar<u>C</u>), 150.3 (d, *J* = 6.7 Hz, Ar<u>C</u>), 143.8 (Ar<u>C</u>), 141.0 (d, *J* = 10.4 Hz, phenyl Ar<u>C</u>), 136.0 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 134.7 (d, *J* = 3.5 Hz, Ar<u>C</u>), 133.7 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 132.7 (d, *J* = 10.9 Hz, phenyl Ar<u>C</u>H), 129.3 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 126.2 (d, *J* = 194.2 Hz, <u>C</u>P), 125.5 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 123.3 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 122.1, 117.3 (d, *J* = 4.9 Hz, Ar<u>C</u>H), 117.0 (d, *J* = 4.6 Hz, Ar<u>C</u>H), 34.8 (<u>C</u>(CH$_3$)$_3$), 31.2 (C(<u>C</u>H$_3$)$_3$), 17.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.99; **IR** (film) υ_{max}/cm^{-1}: 2964, 1534 (NO_2), 1357 (NO_2), 1267 (P=O), 1180, 1130, 960, 924, 802, 749, 695; **HRMS** (ESI+): calcd. for $C_{23}H_{25}NO_5P$ 426.1465 $[M+H]^+$, found 426.1464.

2-methyl-6-nitrophenyl (5,6,7,8-tetrahydronaphthalen-2-yl) (*R*)-phenylphosphonate (**433**)

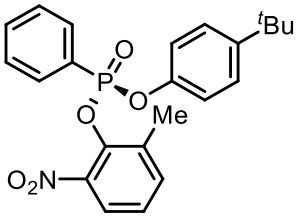


433 was synthesized following **GP V**. **411** (43.4 mg, 0.10 mmol) was used as phosphonate, 5,6,7,8-tetrahydronaphthalen-2-ol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (24.9 mg, 0.059 mmol, 59% yield, 15% ee).

HPLC Conditions: CHIRALPAK IB, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (minor) = 11.11 min, t (major) = 12.89 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.96 (m, 2H, ArC<u>H</u>), 7.73 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.68 – 7.60 (m, 1H, ArC<u>H</u>), 7.56 – 7.51 (m, 2H, ArC<u>H</u>), 7.47 (ddt, *J* = 7.6, 1.6, 0.8 Hz, 1H, ArC<u>H</u>), 7.22 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 6.87 (d, *J* = 8.1 Hz, 1H, ArC<u>H</u>), 6.76 – 6.68 (m, 2H, ArC<u>H</u>), 2.67 – 2.57 (m, 4H, C<u>H$_2$</u>CH$_2$CH$_2$C<u>H$_2$</u>), 2.47 (s, 3H, ArC<u>H$_3$</u>), 1.70 (p, *J* = 3.2 Hz, 4H, CH$_2$C<u>H$_2$</u>C<u>H$_2$</u>CH$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.9 (Ar<u>C</u>), 143.9 (Ar<u>C</u>), 140.9 (m, Ar<u>C</u>), 138.9 (Ar<u>C</u>), 136.0 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 134.7 (Ar<u>C</u>), 134.1 (Ar<u>C</u>), 133.7 (Ar<u>C</u>H), 132.7 (d, *J* = 11.0 Hz, phenyl Ar<u>C</u>H), 130.2 (Ar<u>C</u>H), 128.9 (d, *J* = 16.2 Hz, phenyl Ar<u>C</u>H), 126.2 (d, *J* = 194.0 Hz, <u>C</u>P), 125.4 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 123.3 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 120.2 (d, *J* = 4.6 Hz, Ar<u>C</u>H), 117.2 (d, *J* = 4.8 Hz, Ar<u>C</u>H), 29.5 (Benzylic <u>C</u>H$_2$), 28.8 (Benzylic <u>C</u>H$_2$), 23.2 (<u>C</u>H$_2$), 22.9 (<u>C</u>H$_2$), 17.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.08; **IR** (film) υ_{max}/cm^{-1}:2930, 1534 (NO_2), 1496, 1357 (NO_2), 1273 (P=O), 1216, 1147, 1131, 960, 925, 749; **HRMS** (ESI+): calcd. for $C_{23}H_{23}NO_5P$ 424.1308 $[M+H]^+$, found 424.1308.

4-(*tert*-butyl)phenyl (2-methyl-6-nitrophenyl)phenylphosphonate (**435**)



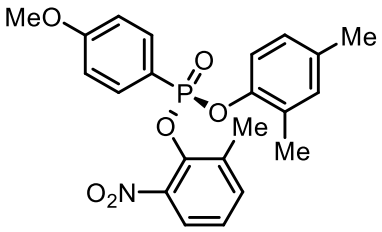
435 was synthesized following **GP V**. **411** (43.4 mg, 0.10 mmol) was used as phosphonate, 4-(*tert*-butyl)phenol (16.5 mg, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (23.4 mg, 0.054 mmol, 54% yield, 0% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (1) = 10.33 min, t (2) = 18.55 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 7.96 (m, 2H, ArC<u>H</u>), 7.77 – 7.70 (m, 1H, ArC<u>H</u>), 7.69 – 7.61 (m, 1H, ArC<u>H</u>), 7.58 – 7.51 (m, 2H, ArC<u>H</u>), 7.48 (ddt, *J* = 7.6, 1.6, 0.8 Hz, 1H, ArC<u>H</u>), 7.25 – 7.19 (m, 3H, 4-(*tert*-butyl)phenyl C<u>H</u> + ArC<u>H</u>), 7.00 – 6.91 (m, 2H, 4-(*tert*-butyl)phenyl C<u>H</u>), 2.47 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 1.22 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.0 (Ar<u>C</u>), 148.0 (Ar<u>C</u>), 143.9 (Ar<u>C</u>), 140.9 (d, *J* = 10.6 Hz, Ar<u>C</u>), 136.0 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 134.7 (d, *J* = 3.5 Hz, Ar<u>C</u>), 133.7 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.7 (d, *J* = 10.9 Hz, phenyl Ar<u>C</u>H), 128.9 (d, *J* = 16.3 Hz, phenyl Ar<u>C</u>H), 126.7 (4-(*tert*-butyl)phenyl <u>C</u>H), 126.2 (d, *J* = 194.0 Hz, <u>C</u>P), 125.5 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 123.3 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 119.5 (d, *J* = 4.7 Hz, 4-(*tert*-butyl)phenyl <u>C</u>H), 34.4 (<u>C</u>(CH$_3$)$_3$), 31.4 (C(<u>C</u>H$_3$)$_3$), 17.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.17; **IR** (film) υ_{max}/cm^{-1}: 2964, 1534 (NO_2), 1509, 1357 (NO_2), 1272 (P=O), 1207, 1173, 1130, 925, 749; **HRMS** (ESI+): calcd. for $C_{23}H_{25}NO_5P$ 426.1465 $[M+H]^+$, found 426.1464.

5.3.8 Products: Scope with respect to the P(V) electrophile

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) *(R)*- (4-methoxyphenyl)phosphonate (**455**)

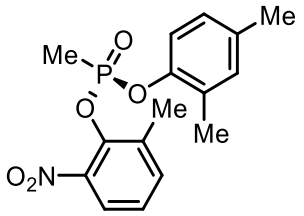


455 was synthesized following **GP V**. **438** (45.8 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (29.4 mg, 0.069 mmol, 69% yield, 97% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 mL/min, λ = 220 nm, t (major) = 11.73 min, t (minor) = 21.94 min.

[α]$_D^{25}$ = −15.5 (c = 0.65, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.90 (m, 2H, ArC<u>H</u>), 7.73 – 7.68 (m, 1H, ArC<u>H</u>), 7.47 (ddt, *J* = 7.7, 1.6, 0.7 Hz, 1H, ArC<u>H</u>), 7.22 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 7.02 (ddd, *J* = 8.7, 4.2, 2.3 Hz, 2H, ArC<u>H</u>), 6.92 – 6.85 (m, 2H, ArC<u>H</u>), 6.79 (dd, *J* = 8.4, 2.3 Hz, 1H, ArC<u>H</u>), 3.88 (s, 3H, OC<u>H</u>$_3$), 2.45 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 2.24 – 2.14 (m, 3H, ArC<u>H</u>$_3$), 2.05 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9 (d, *J* = 3.5 Hz, OCH_3), 146.9 (d, *J* = 7.0 Hz, Ar<u>C</u>), 144.0 (Ar<u>C</u>), 141.2 (d, *J* = 10.0 Hz, Ar<u>C</u>), 136.0 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 135.1 (d, *J* = 13.2 Hz, Ar<u>C</u>H), 134.7 (d, *J* = 12.3 Hz, Ar<u>C</u>), 134.7 (d, *J* = 3.3 Hz, Ar<u>C</u>), 132.1 (Ar<u>C</u>H), 129.2 (d, *J* = 5.6 Hz, Ar<u>C</u>), 127.4 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 125.3 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 123.3 (Ar<u>C</u>H), 123.3 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 117.5 (d, *J* = 202.5 Hz, <u>C</u>P), 114.4 (d, *J* = 17.2 Hz, Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 55.5 (O<u>C</u>H$_3$), 20.7 (Ar<u>C</u>H$_3$), 17.6 (Ar<u>C</u>H$_3$), 16.4 (Ar<u>C</u>H$_3$);**^{31}P NMR** (162 MHz, $CDCl_3$) δ 14.32; **IR** (film) υ_{max}/cm^{-1}:1599, 1534 (NO_2), 1404, 1358 (NO_2), 1259 (P=O), 1181, 1130, 923, 908, 765; **HRMS** (ESI+): calcd. for $C_{22}H_{23}NO_6P$ 428.1258 $[M+H]^+$, found 428.1255.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) *(R)*-methylphosphonate (**456**)

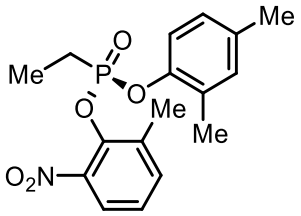


456 was synthesized following **GP V**. **439** (36.6 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (23.7 mg, 0.071 mmol, 71% yield, 84% ee).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (major) = 8.93 min, t (minor) = 11.15 min.

$[\alpha]_D^{25}$ =−55.0 (c = 0.76, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 – 7.71 (m, 1H, ArC<u>H</u>), 7.47 (ddt, *J* = 7.7, 1.7, 0.8 Hz, 1H, ArC<u>H</u>), 7.21 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 7.05 – 6.98 (m, 2H, ArC<u>H</u>), 6.89 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 2.41 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 2.26 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 2.20 (s, 3H, ArC<u>H</u>$_3$), 1.90 (d, *J* = 17.8 Hz, 3H, C<u>H</u>$_3$P); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.8 (d, *J* = 7.6 Hz, Ar<u>C</u>), 143.1 (Ar<u>C</u>), 141.6 (d, *J* = 10.3 Hz, Ar<u>C</u>), 136.3 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 135.0 (Ar<u>C</u>), 134.3 (d, *J* = 3.2 Hz, Ar<u>C</u>), 132.3 (Ar<u>C</u>H), 128.9 (d, *J* = 5.7 Hz, Ar<u>C</u>), 127.7 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 125.3 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 123.5 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 119.8 (d, *J* = 2.5 Hz, Ar<u>C</u>H), 20.8 (Ar<u>C</u>H$_3$), 17.4 (Ar<u>C</u>H$_3$), 16.4 (Ar<u>C</u>H$_3$), 12.3 (d, *J* = 144.2 Hz, <u>C</u>H$_3$P);**^{31}P NMR** (162 MHz, $CDCl_3$) δ 26.08; **IR** (film) υ_{max}/cm^{-1}: 1535 (NO_2), 1356 (NO_2), 1268, 1223 (P=O), 1199, 1183, 1119, 920; **HRMS** (ESI+): calcd. for $C_{16}H_{19}NO_5P$ 336.0995 $[M+H]^+$, found 336.0991.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) *(R)*-ethylphosphonate (**457**)

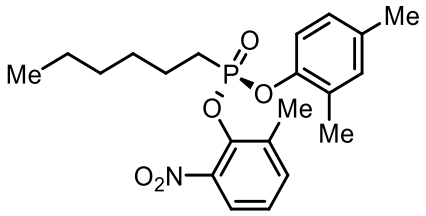


457 was synthesized following **GP V**. **440** (38.0 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (22.4 mg, 0.063 mmol, 63% yield, 93% ee).

HPLC Conditions: CHIRALPAK AS-H, hexane/isopropanol =90/10, 1 mL/min, λ = 220 nm, t (major) = 6.75 min, t (minor) = 7.39 min.

[α]$_D^{25}$ = −69.2 (c = 0.52, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.44 (ddt, *J* = 7.8, 1.7, 0.8 Hz, 1H, ArC<u>H</u>), 7.20 (td, *J* = 7.9, 1.2 Hz, 1H, ArC<u>H</u>), 7.01 (dd, *J* = 8.4, 1.2 Hz, 1H, ArC<u>H</u>), 6.98 – 6.94 (m, 1H, ArC<u>H</u>), 6.84 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 2.38 (s, 3H, ArC<u>H</u>$_3$), 2.27 – 2.22 (m, 4H, ArC<u>H</u>$_3$ + ½ $CH_3C\underline{H}_2P$), 2.21 – 2.13 (m, 4H, ArC<u>H</u>$_3$ + ½ $CH_3C\underline{H}_2P$), 1.37 (dt, *J* = 21.8, 7.7 Hz, 3H, C<u>H</u>$_3CH_2P$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.0 (d, *J* = 8.1 Hz, Ar<u>C</u>), 143.5 (Ar<u>C</u>), 141.3 (d, *J* = 10.7 Hz, Ar<u>C</u>), 136.1 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 134.7 (Ar<u>C</u>), 134.4 (d, *J* = 3.2 Hz), 132.2 (Ar<u>C</u>), 128.6 (d, *J* = 6.0 Hz, Ar<u>C</u>), 127.6 (Ar<u>C</u>H), 125.2 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 123.4 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 119.5 (d, *J* = 2.4 Hz, Ar<u>C</u>H), 20.7 (Ar<u>C</u>H$_3$), 20.1 (d, *J* = 141.3 Hz, $CH_3\underline{C}H_2P$), 17.3(Ar<u>C</u>H$_3$), 16.4, (Ar<u>C</u>H$_3$), 6.8 (d, *J* = 7.6 Hz, <u>C</u>H$_3CH_2P$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 29.03; **IR** (film) υ_{max}/cm^{-1}: 1535 (NO_2), 1357 (NO_2), 1183 (P=O), 924, 909, 775; **HRMS** (ESI+): calcd. for $C_{17}H_{21}NO_5P$ 350.1152 $[M+H]^+$, found 350.1151.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) *(R)*-hexylphosphonate (**458**)

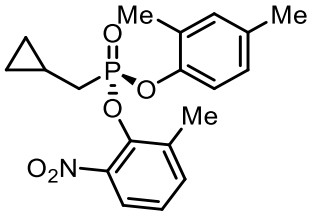


458 was synthesized following **GP V**. **441** (43.6 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (24.2 mg, 0.060 mmol, 60% yield, 94% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (major) = 12.43 min, t (minor) = 15.35 min.

$[\alpha]_D^{25}$ = −51.5 (c = 0.79, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.44 (ddt, *J* = 7.6, 1.6, 0.7 Hz, 1H, ArC<u>H</u>), 7.19 (td, *J* = 7.9, 1.2 Hz, 1H, ArC<u>H</u>), 7.00 (dd, *J* = 8.3, 1.2 Hz, 1H, ArC<u>H</u>), 6.97 – 6.94 (m, 1H, ArC<u>H</u>), 6.84 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 2.38 (s, 3H, ArC<u>H</u>$_3$), 2.25 – 2.23 (m, 3H, ArC<u>H</u>$_3$), 2.21 – 2.10 (m, 5H, ArC<u>H</u>$_3$ + PC<u>H</u>$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.80 (dddd, *J* = 15.2, 11.6, 7.7, 5.9 Hz, 2H, PCH$_2$C<u>H</u>$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.45 (p, *J* = 7.3 Hz, 2H, PCH$_2$CH$_2$C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 1.31 (ddt, *J* = 7.2, 5.0, 2.7 Hz, 4H, PCH$_2$CH$_2$CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 0.93 – 0.85 (m, 3H, PCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.1 (d, *J* = 8.2 Hz, Ar<u>C</u>), 143.4 (Ar<u>C</u>), 141.4 (d, *J* = 10.9 Hz, Ar<u>C</u>), 136.1 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 134.6 (Ar<u>C</u>), 134.4 (d, *J* = 3.2 Hz, Ar<u>C</u>), 132.2 (Ar<u>C</u>H), 128.6 (d, *J* = 6.1 Hz, Ar<u>C</u>), 127.6 (Ar<u>C</u>H), 125.2 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 123.4 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 119.5 (d, *J* = 2.4 Hz, Ar<u>C</u>H), 31.3 (d, *J* = 1.3 Hz, PCH$_2$CH$_2$CH$_2$<u>C</u>H$_2$<u>C</u>H$_2$CH$_3$), 30.3 (d, *J* = 18.2 Hz, PCH$_2$<u>C</u>H$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 26.8 (d, *J* = 138.5 Hz, P<u>C</u>H$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 22.5 (PCH$_2$CH$_2$<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$), 22.4 (PCH$_2$CH$_2$CH$_2$CH$_2$<u>C</u>H$_2$CH$_3$), 20.7 (PCH$_2$CH$_2$CH$_2$<u>C</u>H$_2$CH$_2$CH$_3$) (Ar<u>C</u>H$_3$), 17.3 (Ar<u>C</u>H$_3$), 16.4 (Ar<u>C</u>H$_3$), 14.1 (PCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 28.03; **IR** (film) υ_{max}/cm^{-1}: 2928, 1536 (NO_2), 1356 (NO_2), 1199 (P=O), 1120, 948, 924, 909, 804, 760; **HRMS** (ESI+): calcd. for $C_{21}H_{29}NO_5P$ 406.1778 $[M+H]^+$, found 406.1776.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) (*R*)-(cyclopropylmethyl)phosphonate (**459**)

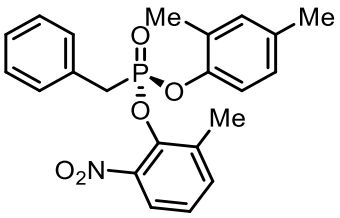


459 was synthesized following **GP V**. **450** (40.6 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (17.1 mg, 0.046 mmol, 46% yield, 88% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (major) = 13.06 min, t (minor) = 14.53 min.

[α]$_D^{25}$ = −76.17 (c = 0.34, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.1, 1.6 Hz, 1H, ArC<u>H</u>), 7.48 – 7.41 (m, 1H, ArC<u>H</u>), 7.20 (td, *J* = 7.9, 1.2 Hz, 1H, ArC<u>H</u>), 7.06 (dd, *J* = 8.2, 1.1 Hz, 1H, ArC<u>H</u>), 6.99 – 6.94 (m, 1H, ArC<u>H</u>), 6.84 (dd, *J* = 8.4, 2.3 Hz, 1H, ArC<u>H</u>), 2.39 (s, 3H, ArC<u>H</u>$_3$), 2.24 (s, 3H, ArC<u>H</u>$_3$), 2.18 (s, 4H, ArC<u>H</u>$_3$ + ½ C<u>H</u>$_2$P), 2.20 – 2.11 (m, 1H, ½ C<u>H</u>$_2$P), 1.19 – 1.04 (m, 1H, cyclopropane C<u>H</u>), 0.72 – 0.59 (m, 2H, cyclopropane C<u>H</u>$_2$), 0.40 – 0.26 (m, 2H, cyclopropane C<u>H</u>$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.1 (d, *J* = 8.0 Hz, Ar<u>C</u>), 143.5 – 142.8 (m, Ar<u>C</u>), 141.3 (d, *J* = 11.2 Hz, Ar<u>C</u>), 136.0, 134.4 (Ar<u>C</u>), 134.2 (d, *J* = 3.2 Hz, Ar<u>C</u>), 132.0 (Ar<u>C</u>H), 128.4 (d, *J* = 6.6 Hz, Ar<u>C</u>), 127.4 (Ar<u>C</u>H), 125.0 (Ar<u>C</u>H), 123.3 (Ar<u>C</u>H), 119.2 (d, *J* = 2.9 Hz, Ar<u>C</u>H), 31.8 (d, *J* = 138.9 Hz, <u>C</u>H$_2$P), 20.6 (Ar<u>C</u>H$_3$), 17.2 (Ar<u>C</u>H$_3$), 16.3 (Ar<u>C</u>H$_3$), 5.6 (dd, *J* = 10.4, 3.0 Hz, cyclopropane <u>C</u>H$_2$), 4.3 (d, *J* = 5.6 Hz, cyclopropane <u>C</u>H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 26.12; **IR** (film) υ_{max}/cm^{-1}:1535 (NO_2), 1498, 1356 (NO_2), 1279, 1222 (P=O), 1199, 1182, 1119, 923, 799, 762; **HRMS** (ESI+): calcd. for $C_{19}H_{23}NO_5P$ 376.1314 $[M+H]^+$, found 376.1308.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) (*R*)-benzylphosphonate (**460**)

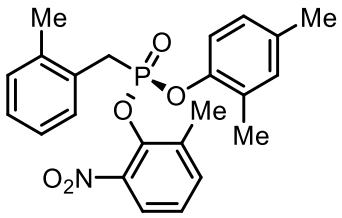


460 was synthesized following **GP V**. **447** (44.2 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (30.1 mg, 0.073 mmol, 73% yield, 82% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 mL/min, λ = 220 nm, t (minor) = 12.86 min, t (major) = 15.61 min.

$[\alpha]_D^{25}$ = −84.76 (c = 0.21, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.45 – 7.38 (m, 1H, ArC<u>H</u>), 7.40 – 7.23 (m, 5H, ArC<u>H</u>), 7.20 (td, *J* = 7.9, 1.2 Hz, 1H, ArC<u>H</u>), 6.96 – 6.87 (m, 2H, ArC<u>H</u>), 6.79 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 3.72 – 3.54 (m, 2H, C<u>H</u>$_2$P), 2.23 (s, 3H, ArC<u>H</u>$_3$), 2.21 (s, 3H, ArC<u>H</u>$_3$), 1.93 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.0 (d, *J* = 8.4 Hz, Ar<u>C</u>), 143.1 (Ar<u>C</u>), 141.4 (d, *J* = 11.0 Hz, Ar<u>C</u>), 136.1 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 134.5 (Ar<u>C</u>), 134.2 (d, *J* = 3.4 Hz, Ar<u>C</u>), 132.0 (Ar<u>C</u>), 130.2 (d, *J* = 7.2 Hz, Ar<u>C</u>H), 130.1 (d, *J* = 10.1 Hz, Ar<u>C</u>H), 128.6 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 128.6 (Ar<u>C</u>), 127.3, 127.3 (Ar<u>C</u>), 125.1 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 123.4 (d, *J* = 1.3 Hz, Ar<u>C</u>H), 119.0 (d, *J* = 2.4 Hz, Ar<u>C</u>H), 34.1 (d, *J* = 137.7 Hz, <u>C</u>H$_2$P), 20.6 (Ar<u>C</u>H$_3$), 17.0 (Ar<u>C</u>H$_3$), 16.0 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.15; **IR** (film) υ_{max}/cm^{-1}:2160, 1534 (NO_2), 1356 (NO_2), 1276, 1221 (P=O), 923; **HRMS** (ESI+): calcd. for $C_{22}H_{22}NNaO_5P$ 434.1133 $[M+Na]^+$, found 434.1127.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) *(R)*-(2-methylbenzyl)phosphonate (**461**)

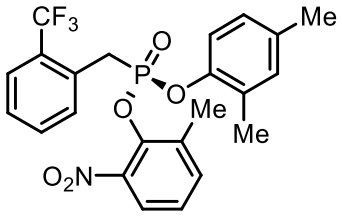


461 was synthesized following **GP V**. **448** (45.6 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (17.7 mg, 0.042 mmol, 42% yield, 86% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (major) = 15.19 min, t (minor) = 22.72 min.

$[\alpha]_D^{25}$ = −42.3 (c = 0.23, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.44 – 7.35 (m, 2H, ArC<u>H</u>), 7.22 – 7.10 (m, 4H, ArC<u>H</u>), 6.91 – 6.88 (m, 1H, ArC<u>H</u>), 6.82 (dd, *J* = 8.3, 1.2 Hz, 1H, ArC<u>H</u>), 6.75 (dd, *J* = 8.4, 2.3 Hz, 1H, ArC<u>H</u>), 3.66 (d, *J* = 22.3 Hz, 2H, C<u>H</u>$_2$P), 2.41 (d, *J* = 1.9 Hz, 3H, ArC<u>H</u>$_3$), 2.22 – 2.20 (m, 3H, ArC<u>H</u>$_3$), 2.20 – 2.17 (m, 3H, ArC<u>H</u>$_3$), 1.94 (s, 3H, PhC<u>H</u>$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.1 (d, *J* = 9.0 Hz, Ar<u>C</u>), 143.3 (d, *J* = 3.7 Hz, Ar<u>C</u>), 141.4 (d, *J* = 11.4 Hz, Ar<u>C</u>), 137.6 (d, *J* = 7.7 Hz, Ar<u>C</u>), 136.2 (d, *J* = 1.8 Hz), 134.6 (Ar<u>C</u>), 134.4 (d, *J* = 3.2 Hz, Ar<u>C</u>), 132.1 (Ar<u>C</u>H), 131.1 (d, *J* = 6.0 Hz, Ar<u>C</u>H), 130.8 (d, *J* = 3.6 Hz, Ar<u>C</u>H), 128.8 (d, *J* = 10.1 Hz, Ar<u>C</u>), 128.7 (d, *J* = 6.4 Hz, Ar<u>C</u>), 127.7 (d, *J* = 4.1 Hz), 127.5 (Ar<u>C</u>H), 126.3 (d, *J* = 3.8 Hz, Ar<u>C</u>H), 125.2 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 123.5 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 119.2 (d, *J* = 2.5 Hz, Ar<u>C</u>H), 31.6 (d, *J* = 138.5 Hz, <u>C</u>H$_2$P), 20.7 (Ar<u>C</u>H$_3$), 20.1 (Ar<u>C</u>H$_3$), 17.0 (Ar<u>C</u>H$_3$), 16.1 (Ph<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.57; **IR** (film) υ_{max}/cm^{-1}: 1535 (NO_2), 1497, 1356 (NO_2), 1275, 1223 (P=O), 1198, 951, 912; **HRMS** (ESI+): calcd. for $C_{23}H_{25}NO_5P$ 426.1465 $[M+H]^+$, found 426.1461.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) *(R)*- (2-(trifluoromethyl)benzyl)phosphonate (**462**)

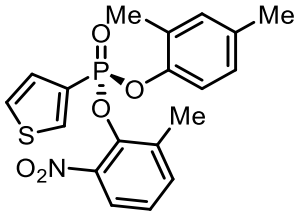


462 was synthesized following **GP V**. **451** (51.0 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (20.6 mg, 0.043 mmol, 43% yield, 78% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (major) = 14.84 min, t (minor) = 12.87 min.

[α]$_D^{25}$ = −61.0 (c = 0.66, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.2, 1.7 Hz, 1H, ArC<u>H</u>), 7.60 (d, *J* = 7.7 Hz, 1H, ArC<u>H</u>), 7.57 – 7.48 (m, 2H, ArC<u>H</u>), 7.48 – 7.39 (m, 2H, ArC<u>H</u>), 7.21 (td, *J* = 7.9, 1.2 Hz, 1H, ArC<u>H</u>), 6.99 (dd, *J* = 8.3, 1.2 Hz, 1H, ArC<u>H</u>), 6.91 (dd, *J* = 2.2, 1.1 Hz, 1H, ArC<u>H</u>), 6.81 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 3.78 – 3.62 (m, 2H, C<u>H</u>$_2$P), 2.23 (s, 3H, ArC<u>H</u>$_3$), 2.21 (s, 3H, ArC<u>H</u>$_3$), 1.91 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.9 (d, *J* = 8.4 Hz, Ar<u>C</u>), 143.0 (d, *J* = 3.7 Hz, Ar<u>C</u>), 141.4 (d, *J* = 10.9 Hz, Ar<u>C</u>), 136.4 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 134.9 (Ar<u>C</u>), 134.2 (d, *J* = 3.2 Hz, Ar<u>C</u>), 133.7 (d, *J* = 6.7 Hz, Ar<u>C</u>H), 132.3, 131.5 (d, *J* = 9.9 Hz, Ar<u>C</u>H), 131.1 (dd, *J* = 32.6, 3.1 Hz,<u>C</u>CF_3), 129.3 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 128.6 (d, *J* = 6.8 Hz, Ar<u>C</u>), 127.6, 127.0 – 126.6 (m, Ar<u>C</u>H), 125.4 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 124.4 (t, *J* = 3.8 Hz, Ar<u>C</u>H), 124.0 (q, *J* = 272.4 Hz, CF_3), 123.6 (d, *J* = 1.8 Hz), 118.9 (d, *J* = 2.6 Hz), 34.0 (d, *J* = 138.1 Hz, <u>C</u>H$_2$P), 20.7 (Ar<u>C</u>H$_3$), 17.0 (Ar<u>C</u>H$_3$), 16.1 (Ar<u>C</u>H$_3$); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.74; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 19.65; **IR** (film) υ_{max}/cm^{-1}: 1536 (NO_2), 1356, 1331 (NO_2), 1122, 952, 915; **HRMS** (ESI+): calcd. for $C_{23}H_{21}F_3NO_5P$ 480.1181 $[M+H]^+$, found 480.1178.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) (*R*)-thiophen-3-ylphosphonate (**463**)

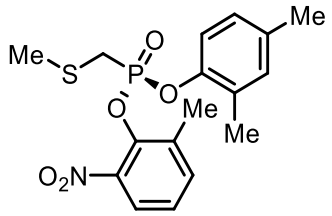


463 was synthesized following **GP V**. **452** (43.4 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (30.3 mg, 0.075 mmol, 75% yield, 92% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30 1 mL/min, λ = 220 nm, t (major) = 10.70 min, t (minor) = 15.49 min.

$[\alpha]_D^{25}$ = −1.93 (c = 0.62, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (ddd, *J* = 8.7, 2.9, 1.2 Hz, 1H, ArC<u>H</u>), 7.71 (dd, *J* = 8.1, 1.7 Hz, 1H, ArC<u>H</u>), 7.55 (ddd, *J* = 5.1, 4.0, 1.2 Hz, 1H, ArC<u>H</u>), 7.53 – 7.44 (m, 2H, ArC<u>H</u>), 7.22 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 6.95 – 6.85 (m, 2H, ArC<u>H</u>), 6.82 (dd, *J* = 8.4, 2.2 Hz, 1H, ArC<u>H</u>), 2.44 (s, 3H, ArC<u>H</u>$_3$), 2.22 (s, 3H, ArC<u>H</u>$_3$), 2.06 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.7 (d, *J* = 7.4 Hz, Ar<u>C</u>), 143.8 (Ar<u>C</u>), 141.0 (d, *J* = 9.8 Hz, Ar<u>C</u>), 137.9 (d, *J* = 19.9 Hz, Ar<u>C</u>H), 136.1 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 134.9 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 134.6 (d, *J* = 3.5 Hz, Ar<u>C</u>), 132.2 (Ar<u>C</u>), 129.4, 129.1 (d, *J* = 5.6 Hz, Ar<u>C</u>H), 127.7 (d, *J* = 21.2 Hz, Ar<u>C</u>H), 127.5 (Ar<u>C</u>), 127.3 (d, *J* = 205.4 Hz, <u>C</u>P), 125.5 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 123.3 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 120.0 (d, *J* = 2.6 Hz, Ar<u>C</u>H), 20.8 (Ar<u>C</u>H$_3$), 17.5 (Ar<u>C</u>H$_3$), 16.4 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 6.71; **IR** (film) υ_{max}/cm^{-1}:1534 (NO_2), 1496, 1356 (NO_2), 1272, 1221 (P=O), 1196, 1181, 1176, 1090, 931, 913, 801, 764, 736, 631; **HRMS** (ESI+): calcd. for $C_{19}H_{19}NO_5PS$ 404.0722 $[M+H]^+$, found 404.0715.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) *(R)*-((methylthio)methyl)phosphonate (**464**)

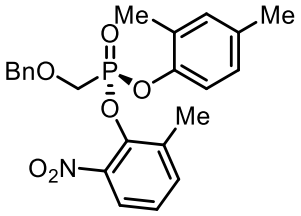


464 was synthesized following **GP V**. **453** (41.2 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (29.2 mg, 0.077 mmol, 77% yield, 92% ee).

HPLC Conditions: CHIRALPAK IB, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (major) = 11.58 min, t (minor) = 11.16 min.

[α]$_D^{25}$ = −41.0 (c = 0.73, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 1H, ArC<u>H</u>), 7.46 (ddt, *J* = 7.7, 1.8, 0.8 Hz, 1H, ArC<u>H</u>), 7.21 (td, *J* = 7.9, 1.2 Hz, 1H, ArC<u>H</u>), 7.10 (dd, *J* = 8.3, 1.2 Hz, 1H, ArC<u>H</u>), 6.99 – 6.95 (m, 1H, ArC<u>H</u>), 6.90 – 6.84 (m, 1H, ArC<u>H</u>), 3.14 (d, *J* = 12.3 Hz, 2H, C<u>H</u>$_2$P), 2.39 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 2.33 (d, *J* = 1.5 Hz, 3H, SC<u>H</u>$_3$), 2.25 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 2.20 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.1 (d, *J* = 8.6 Hz, Ar<u>C</u>), 143.0 (Ar<u>C</u>), 141.6 (d, *J* = 10.9 Hz, Ar<u>C</u>), 136.4 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 134.9 (Ar<u>C</u>), 134.3 (d, *J* = 3.3 Hz, Ar<u>C</u>), 132.2 (Ar<u>C</u>H), 128.8 (d, *J* = 6.1 Hz, Ar<u>C</u>), 127.6 (Ar<u>C</u>H), 125.4 (d, *J* = 1.8 Hz, Ar<u>C</u>H), 123.6 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 119.5 (d, *J* = 2.4 Hz, Ar<u>C</u>H), 28.2 (d, *J* = 150.4 Hz, <u>C</u>H$_2$P), 20.8 (Ar<u>C</u>H$_3$), 17.6 (d, *J* = 2.2 Hz, S<u>C</u>H)), 17.3 (Ar<u>C</u>H$_3$), 16.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 18.97; **IR** (film) υ_{max}/cm^{-1}: 1534 (NO_2), 1497, 1355 (NO_2), 1274, 1222 (P=O), 1199, 1181, 1116, 951, 928, 912; **HRMS** (ESI+): $C_{17}H_{21}NO_5PS$ 382.0873 $[M+H]^+$, found 382.0881.

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) (*R*)-((benzyloxy)methyl)phosphonate (**465**)



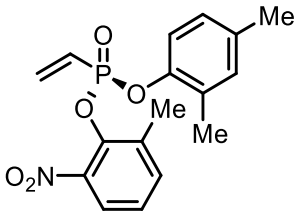
465 was synthesized following **GP V**. **454** (47.2 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** 11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (31.8 mg, 0.072 mmol, 72% yield, 83% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (major) = 25.09 min, t (minor) = 35.82 min.

[α]$_D^{25}$ = −21.9 (c = 1.20, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.2, 1.5 Hz, 1H, ArC<u>H</u>), 7.42 – 7.34 (m, 1H, ArC<u>H</u>), 7.31 – 7.07 (m, 6H, ArC<u>H</u>), 7.03 (d, *J* = 8.3 Hz, 1H, ArC<u>H</u>), 6.89 (s, 1H, ArC<u>H</u>), 6.79 (dd, *J* = 8.3, 2.1 Hz, 1H, ArC<u>H</u>), 4.63 – 4.52 (m, 2H, C<u>H</u>$_2$O), 4.17 – 3.99 (m, 2H, C<u>H</u>$_2$P), 2.35 (s, 3H, ArC<u>H</u>$_3$), 2.19 (s, 3H, ArC<u>H</u>$_3$), 2.08 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) 146.7 (d, *J* = 8.0 Hz, Ar<u>C</u>), 142.9 (Ar<u>C</u>), 141.3 (d, *J* = 10.5 Hz, Ar<u>C</u>), 136.5 (Ar<u>C</u>H), 136.2 (Ar<u>C</u>H), 134.9 (Ar<u>C</u>), 134.2 (d, *J* = 3.2 Hz, Ar<u>C</u>), 132.1 (Ar<u>C</u>H), 129.0 (d, *J* = 5.6 Hz, Ar<u>C</u>), 128.4 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>), 127.4(Ar<u>C</u>H), 125.3 (Ar<u>C</u>H), 123.5 (Ar<u>C</u>H), 119.7 (d, *J* = 2.4 Hz, Ar<u>C</u>H), 75.2 (d, *J* = 12.7 Hz, <u>C</u>H$_2$O), 63.8 (d, *J* = 166.2 Hz, <u>C</u>H$_2$P), 20.7 (Ar<u>C</u>H$_3$), 17.3 (Ar<u>C</u>H$_3$), 16.2 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.26; **IR** (film) υ_{max}/cm^{-1}:1535 (NO_2), 1497, 1355 (NO_2), 1264 (P=O), 1197, 1117, 928, 804, 753; **HRMS** (ESI+): calcd. for $C_{23}H_{24}NNaO_6P$ 464.1239 $[M+Na]^+$, found 464.1231.

5.3.9 Products: P(V) electrophile scope (unsuccessful examples)

2,4-dimethylphenyl (2-methyl-6-nitrophenyl) (*R*)-vinylphosphonate (**470**)



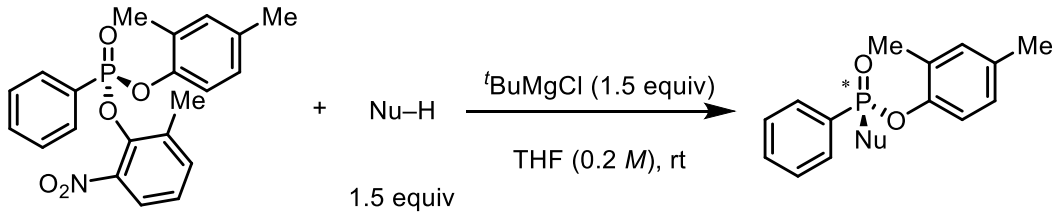
470 was synthesized following **GP V**. **449** (37.8 mg, 0.10 mmol) was used as phosphonate, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile used as nucleophile and **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in PhF (0.40 mL) at room temperature. Pentane:EtOAc 7:3. Colourless oil (21.1 mg, 0.061 mmol, 61% yield, 47% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 220 nm, t (minor) = 12.70 min, t (major) = 14.44 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.2, 1.7 Hz, 1H, ArC<u>H</u>), 7.47 (ddt, *J* = 7.7, 1.6, 0.8 Hz, 1H, ArC<u>H</u>), 7.21 (td, *J* = 7.9, 1.3 Hz, 1H, ArC<u>H</u>), 7.05 (dd, *J* = 8.3, 1.4 Hz, 1H, ArC<u>H</u>), 7.00 – 6.96 (m, 1H, ArC<u>H</u>), 6.89 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 6.61 – 6.17 (m, 3H, PC<u>H</u>=C<u>H</u>$_2$), 2.44 (d, *J* = 0.9 Hz, 3H, ArC<u>H</u>$_3$), 2.25 (d, *J* = 1.0 Hz, 3H, ArC<u>H</u>$_3$), 2.16 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.6 (d, *J* = 7.4 Hz, Ar<u>C</u>), 143.2 (Ar<u>C</u>), 141.3 (d, *J* = 9.6 Hz, Ar<u>C</u>), 139.3 (d, *J* = 2.8 Hz, <u>C</u>H$_2$=CHP), 136.2 (d, *J* = 2.0 Hz, Ar<u>C</u>H), 135.0 (Ar<u>C</u>), 134.6 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.2 (Ar<u>C</u>), 129.1 (d, *J* = 5.5 Hz, Ar<u>C</u>H), 127.6 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 125.4 (d, *J* = 1.9 Hz, Ar<u>C</u>H), 124.7 (d, *J* = 186.7 Hz, CH$_2$=<u>C</u>HP), 123.4 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 120.1 (d, *J* = 2.7 Hz, Ar<u>C</u>H), 20.8 (Ar<u>C</u>H$_3$), 17.6 (Ar<u>C</u>H$_3$), 16.4 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 11.63; **IR** (film) υ_{max}/cm^{-1}: 2980, 1536 (NO_2), 1497, 1356 (NO_2), 1249, 1221 (P=O), 1197, 1182, 1119, 987, 928, 911; **HRMS** (ESI+): $C_{17}H_{19}NO_5P$ 348.0995 $[M+H]^+$, found 348.0995.

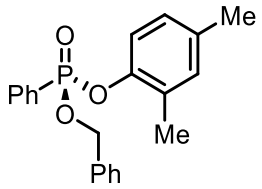
5.3.10 Products: Derivatisation

5.3.10.1 General Procedure VII: second nucleophilic displacement



To a solution of nucleophile in THF was added *t*BuMgCl under argon at 0 °C. After 20 min, phosphonate **415** (0.10 mmol, 92% ee) was added, and the reaction mixture was stirred at room temperature for the time specified in the individual experiment. The resulting mixture was loaded directly onto silica gel and purified by flash column chromatography as specified in the individual experiment to afford pure product. The two enantiomers were separated by chiral HPLC using conditions specified in the individual experiment and compared to a racemic sample obtained by using ***rac*-415** as substrate.

benzyl (2,4-dimethylphenyl) (*R*)-phenylphosphonate (**471**)

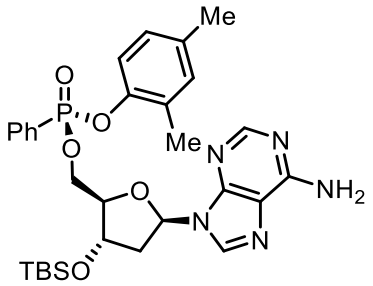


471 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, benzyl alcohol (16.0 μL, 0.150 mmol) was used as nucleophile and *t*-BuMgCl (2 *M* in Et_2O, 75.0 μL, 0.150 mmol) as base in THF (0.50 mL) at room temperature for 2 hr. Pentane:EtOAc 7:3. Colourless oil (24.2 mg, 0.063 mmol, 63% yield, 92% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 mL/min, λ = 220 nm, t (major) = 11.04 min, t (minor) = 17.81 min.

$[\alpha]_D^{25}$ = −8.0 (c = 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.77 (m, 2H, ArC<u>H</u>), 7.56 – 7.46 (m, 1H, ArC<u>H</u>), 7.49 – 7.35 (m, 2H, ArC<u>H</u>), 7.35 – 7.18 (m, 2H, ArC<u>H</u>), 7.05 (dd, *J* = 8.3, 1.4 Hz, 1H, ArC<u>H</u>), 6.92 – 6.86 (m, 1H, ArC<u>H</u>), 6.82 (dd, *J* = 8.3, 2.2 Hz, 1H, ArC<u>H</u>), 5.19 – 5.04 (m, 2H, PhC<u>H</u>$_2$), 2.20 (s, 3H, ArC<u>H</u>$_3$), 2.13 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.9 (d, *J* = 8.0 Hz, Ar<u>C</u>), 136.0 (d, *J* = 7.1 Hz, Ar<u>C</u>), 134.3 (Ar<u>C</u>), 132.7 (d, *J* = 3.1 Hz, Ar<u>C</u>H), 131.9 (d, *J* = 10.3 Hz, Ar<u>C</u>H), 131.9 (Ar<u>C</u>H), 129.1 (d, *J* = 5.3 Hz, Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.34 (d, *J* = 8.9 Hz, Ar<u>C</u>H), 128.0 (d, *J* = 192 Hz, <u>C</u>P), 127.9 (Ar<u>C</u>H), 120.2 (d, *J* = 2.5 Hz, Ar<u>C</u>H), 68.1 (d, *J* = 5.6 Hz, PhC<u>H</u>$_2$), 20.7 (Ar<u>C</u>H$_3$), 16.5 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 15.76; **IR** (film) υ_{max}/cm^{-1}: 1497, 1439, 1256, 1201 (P=O), 1130, 1009, 947, 907; **HRMS** (ESI+): calcd. for $C_{21}H_{21}NaO_3P$ 375.1126 $[M+Na]^+$, found 375.1121.

((2*R*,3*S*,5*R*)-5-(6-amino-9H-purin-9-yl)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)methyl (2,4-dimethylphenyl) (*R*)-phenylphosphonate (**472**)



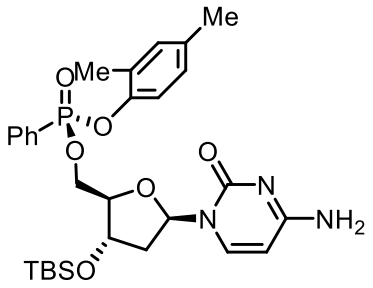
26 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, 3'-OTBS – deoxyadenosine[ix] (54.8 mg, 0.150 mmol) was used as nucleophile and *t*-BuMgCl (2 *M* in Et_2O, 150 μL, 0.30 mmol) as base in THF (0.50 mL) at room temperature for 16 hr. CH_2Cl_2:MeOH 95:5. Colourless oil (29.2 mg, 0.048 mmol, 49% yield, >95:5 dr).

$[\alpha]_D^{25}$ = −14.9 (c = 0.18, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.38 (s, 1H, NC<u>H</u>N), 8.22 – 8.12 (m, 2H, ArC<u>H</u>), 7.95 (s, 1H, ArC<u>H</u>), 7.80 (s, 1H, ArC<u>H</u>), 7.58 – 7.52 (m, 1H, ArC<u>H</u>), 7.50 – 7.43 (m, 2H, ArC<u>H</u>), 7.21 (dd, *J* = 8.2, 1.3 Hz, 1H, ArC<u>H</u>), 6.97 (d, *J* = 2.0 Hz, 1H, ArC<u>H</u>), 6.84 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 6.23 (dd, *J* = 9.6, 5.4 Hz, 1H, OC<u>H</u>-Het), 6.00 (s, 1H, N<u>H</u>), 4.66 (d, *J* = 4.8 Hz, 1H, $POCH_2C\underline{H}O$), 3.98 – 3.87 (m, 1H, $POCH_aC\underline{H}_b$), 3.76 – 3.66 (m, 2H, $POCH_aC\underline{H}_b$), 2.92 (ddd, *J* = 13.0, 9.6, 5.0 Hz, 1H, C<u>H</u>OTBS), 2.35 (s, 3H, ArC<u>H_3</u>), 2.24 (s, 3H, ArC<u>H_3</u>), 2.22 (s, 1H, TBS-OCHC<u>H_a</u>CH_b), 2.17 (dd, *J* = 13.0, 5.5 Hz, 1H, $TBSOCHCH_aC\underline{H}_b$), 0.92 (s, 9H, $SiC(C\underline{H}_3)_3$), 0.10 (s, 6H, $SiC\underline{H}_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.1 (Ar<u>C</u>H), 151.6 (Ar<u>C</u>), 149.5 (Ar<u>C</u>), 146.8 (d, *J* = 8.6 Hz, Ar<u>C</u>), 142.3 (Ar<u>C</u>H), 134.6 (Ar<u>C</u>), 132.9 (d, *J* = 3.0 Hz, Ar<u>C</u>H), 132.6 (d, *J* = 11.0 Hz, Ar<u>C</u>H), 132.3 (Ar<u>C</u>H), 129.5 (d, *J* = 5.8 Hz, Ar<u>C</u>), 129.3 (d, *J* = 182.3 Hz, <u>C</u>P), 128.4 (d, *J* = 15.8 Hz, Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 120.0 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 90.6 (C<u>H</u>OTBS), 88.1 (O<u>C</u>H-Het), 74.2 ($POCH_2\underline{C}HO$), 63.5 ($PO\underline{C}H_2$), 41.5 ($TBSOCH\underline{C}H_2$), 25.9 ($SiC(\underline{C}H_3)_3$), 20.8 (Ar<u>C</u>H_3), 18.2 ($Si\underline{C}(CH_3)_3$), 16.9 (Ar<u>C</u>H_3), -4.6 ($Si\underline{C}H_3$), -4.6 ($Si\underline{C}H_3$); **^{31}P NMR** (202 MHz, $CDCl_3$) δ 12.79; **IR** (film) υ_{max}/cm^{-1}: 2927, 2856, 1606, 1584, 1462, 1439,

[ix] 3'-OTBS –deoxyadenosine was prepared by Dr. Heyao Shi according to literature procedures.[36]

1252, 1220 (P=O), 1123, 1101, 1063, 1025, 950, 909, 835, 734; **HRMS** (ESI+): calcd. for $C_{30}H_{41}N_5O_5PSi$ 610.2609 $[M+H]^+$, found 610.2608.

((2*R*,3*S*,5*R*)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)methyl (2,4-dimethylphenyl) (*R*)-phenylphosphonate (**473**)

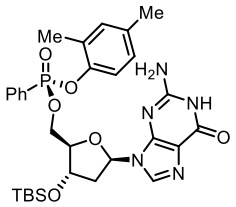


473 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, 3'-OTBS – deoxycytidine[x] (68.3 mg, 0.20 mmol) was used as nucleophile and *t*-BuMgCl (2 *M* in Et_2O, 200 μL, 0.40 mmol) as base in THF (0.50 mL) at room temperature for 48 h. CH_2Cl_2:MeOH 95:5. Colourless oil (28.1 mg, 0.048 mmol, 48% yield, >95:5 dr).

$[\alpha]_D^{25}$ = +57.0 (c = 0.45, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (ddt, *J* = 13.8, 6.9, 1.4 Hz, 2H, ArC<u>H</u>), 7.64 – 7.57 (m, 1H, ArC<u>H</u>), 7.54 – 7.46 (m, 3H, ArC<u>H</u>), 7.08 (dd, *J* = 8.3, 1.4 Hz, 1H, ArC<u>H</u>), 6.96 – 6.94 (m, 1H, ArC<u>H</u>), 6.86 (dd, *J* = 8.2, 2.3 Hz, 1H, ArC<u>H</u>), 6.20 (t, *J* = 6.3 Hz, 1H, OC<u>H</u>-Het), 5.58 (d, *J* = 7.5 Hz, 1H, cytidine ArC<u>H</u>), 4.42 – 4.19 (m, 3H, POC<u>H</u>$_2$ + POCH$_2$C<u>H</u>O), 4.02 (dd, *J* = 3.8, 1.9 Hz, 1H, C<u>H</u>OTBS), 2.34 (ddd, *J* = 13.5, 6.2, 4.1 Hz, 1H, TBSOCHCH$_a$C<u>H</u>$_b$), 2.23 (s, 3H, ArC<u>H</u>$_3$), 2.20 (s, 3H, ArC<u>H</u>$_3$), 1.91 (dt, *J* = 13.3, 6.5 Hz, 1H, TBSOCHC<u>H</u>$_a$CH$_b$), 0.84 (s, 9H, SiC(C<u>H</u>$_3$)$_3$), 0.02 (s, 3H, SiC<u>H</u>$_3$), 0.00 (s, 3H, SiC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.4 (<u>C</u>-NH$_2$), 155.6 (C=O), 146.8 (d, *J* = 7.5 Hz, Ar<u>C</u>), 140.7 (Ar<u>C</u>H), 134.8 (Ar<u>C</u>), 133.4 (d, *J* = 3.1 Hz, Ar<u>C</u>H), 132.2 (Ar<u>C</u>H), 131.9(d, *J* = 10.1 Hz, Ar<u>C</u>H), 129.0 (d, *J* = 15.7 Hz, Ar<u>C</u>H), 129.0 (d, *J* = 5.7 Hz, Ar<u>C</u>), 127.6, 127.3 (d, *J* = 191.8 Hz, CP), 120.0 (d, *J* = 2.5 Hz, Ar<u>C</u>H), 94.6 (cytidine ArC<u>H</u>), 86.4 (O<u>C</u>H-Het), 85.4 (d, *J* = 7.9 Hz, C<u>H</u>OTBS), 71.5 (POCH$_2$<u>C</u>HO), 65.3 (PO<u>C</u>H$_2$), 41.8 (TBSOCH<u>C</u>H$_2$), 25.8 (SiC(<u>C</u>H$_3$)$_3$), 20.8 (Ar<u>C</u>H$_3$), 18.0 (Si<u>C</u>(CH$_3$)$_3$), 16.7 (Ar<u>C</u>H$_3$), -4.6 (Si<u>C</u>H$_3$), -4.9 (Si<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 15.97 (major), 15.91 (minor); **IR** (film) υ_{max}/cm^{-1}: 2928, 1648 (C=O), 1496, 1251, 1200 (P=O), 1118, 1024, 948, 909, 935, 781, 696; **HRMS** (ESI+): calcd. for $C_{29}H_{41}N_3O_6PSi$ 586.2497 $[M+H]^+$, found 586.2491.

[x] 3'-OTBS – deoxycytidine was prepared by Dr. Heyao Shi according to literature procedures.[37]

((2*R*,3*S*,5*R*)-5-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)methyl (2,4-dimethylphenyl) (*R*)-phenylphosphonate (**474**)

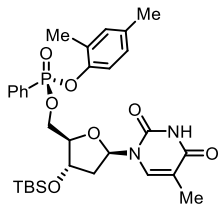


474 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, 3'-OTBS - deoxyguanosine[xi] (57.2 mg, 0.150 mmol) was used as nucleophile and *t*-BuMgCl (2 *M* in Et_2O, 150 μL, 0.30 mmol) as base in THF (0.50 mL) at room temperature for 16 hr. CH_2Cl_2:MeOH 9:1. Colourless oil (45.0 mg, 0.072 mmol, 72% yield, >95:5 dr).

$[\alpha]_D^{25}$ = +34.9 (c = 0.45, DMSO); **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.66 (s, 1H, NH), 7.83 (s, 1H, ArCH), 7.79 (ddd, *J* = 13.6, 8.1, 1.4 Hz, 2H, ArCH), 7.68 (td, *J* = 7.4, 1.4 Hz, 1H, ArCH), 7.55 (td, *J* = 7.6, 4.4 Hz, 2H, ArCH), 7.01 (d, *J* = 2.1 Hz, 1H, ArCH), 6.99 (dd, *J* = 8.3, 1.2 Hz, 1H, ArCH), 6.87 (dd, *J* = 8.4, 2.2 Hz, 1H, ArCH), 6.48 (s, 2H, NH_2), 6.12 (dd, *J* = 7.6, 6.3 Hz, 1H, OCH-Het), 4.52 (dt, *J* = 6.1, 3.2 Hz, 1H, $POCH_2CH$), 4.29 (ddd, *J* = 11.6, 6.9, 4.9 Hz, 1H, $POCH_aCH_b$), 4.17 (ddd, *J* = 11.5, 6.7, 5.4 Hz, 1H, $POCH_aCH_b$), 3.98 (td, *J* = 5.1, 2.9 Hz, 1H, CHOTBS), 2.63 (ddd, *J* = 13.4, 7.7, 5.9 Hz, 1H, TBS-$OCHCH_aCH_b$), 2.23 (ddd, *J* = 13.5, 6.4, 3.5 Hz, 1H, TBS-$OCHCH_aCH_b$), 2.19 (s, 3H, $ArCH_3$), 2.11 (s, 3H, $ArCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 156.7 (C=O), 153.7 (ArC), 150.9 (ArC), 146.4 (d, *J* = 7.6 Hz, ArC), 135.2 (ArCH), 134.0 (ArC), 133.3 (d, *J* = 3.1 Hz, ArCH), 131.9 (ArCH), 131.5 (d, *J* = 10.2 Hz, ArCH), 128.9 (d, *J* = 15.2 Hz, ArCH), 128.6 (d, *J* = 5.3 Hz, ArCH), 127.3 (ArC), 127.0 (d, *J* = 189.6 Hz, CP), 119.6 (d, *J* = 2.7 Hz, ArCH), 116.7 (ArC), 84.9 (d, *J* = 7.2 Hz, CHOTBS), 82.5 (OCH-Het), 72.1 ($POCH_2CHO$), 65.5 (d, *J* = 5.7 Hz, $POCH_2$), 38.8 ($TBSOCHCH_2$), 25.6 ($SiC(CH_3)_3$), 20.2 ($ArCH_3$), 17.6 ($SiC(CH_3)_3$), 16.1 ($ArCH_3$), -4.9 ($SiCH_3$), -5.1 ($SiCH_3$); **^{31}P NMR** (202 MHz, DMSO-d_6) δ 15.57; **IR** (film) υ_{max}/cm^{-1}: 2863, 1592, 1498, 1423, 1267, 1213 (P=O), 1128, 1112, 1058, 1022, 962, 913, 848, 744; **HRMS** (ESI+): calcd. for $C_{30}H_{41}N_5O_6PSi$ 626.2558 $[M+H]^+$, found 626.2551.

[xi] 3'-OTBS – deoxyguanosine was prepared by Dr. Heyao Shi according to literature procedures.[38]

((2*R*,3*S*,5*R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl (2,4-dimethylphenyl) (*R*)-phenylphosphonate (**475**)

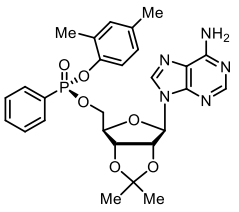


475 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, 3'-OTBS – thymidine[xii] (53.5 mg, 0.150 mmol) was used as nucleophile and *t*-BuMgCl (2 *M* in Et_2O, 150 μL, 0.30 mmol) as base in THF (0.50 mL) at room temperature for 48 h. CH_2Cl_2:MeOH 95:5. Colourless oil (42.0 mg, 0.070 mmol, 70% yield, >95:5 dr).

$[\alpha]_D^{25}$ = +23.4 (c = 0.86, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.63 (s, 1H, NH), 7.88 (ddt, *J* = 13.8, 6.9, 1.4 Hz, 2H, ArCH), 7.66 – 7.60 (m, 1H, ArCH), 7.53 – 7.47 (m, 2H, ArCH), 7.34 (q, *J* = 1.2 Hz, 1H, ArCH), 7.07 (dd, *J* = 8.3, 1.5 Hz, 1H, ArCH), 6.99 – 6.92 (m, 1H, ArCH), 6.86 (dd, *J* = 8.3, 2.3 Hz, 1H, ArCH), 6.30 (dd, *J* = 7.9, 5.8 Hz, 1H, ArCH), 4.42 (dt, *J* = 5.9, 2.8 Hz, 1H, OCH-Het), 4.34 – 4.30 (m, 2H, $POCH_2$), 4.06 (td, *J* = 3.0, 2.0 Hz, 1H, CHOTBS), 2.28 – 2.15 (m, 7H, 2x $ArCH_3$ + TBS-$OCHCH_aCH_b$), 1.94 (ddd, *J* = 13.7, 7.9, 6.2 Hz, 1H, TBS-$OCHCH_aCH_b$), 1.72 (d, *J* = 1.2 Hz, 3H, thymidine CH_3), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8 (C=O), 150.4 (C=O), 146.8 (d, *J* = 7.5 Hz, ArCH), 135.3 (ArC), 134.8 (ArC), 133.4 (d, *J* = 3.1 Hz, ArCH), 132.2 (ArCH), 131.9 (d, *J* = 10.4 Hz, ArCH), 129.0 (ArC), 128.9 (ArCH), 127.6 (ArCH), 127.2 (d, *J* = 190.9 Hz, CP), 119.9 (d, *J* = 2.5 Hz), 111.3 (ArC), 85.7 (d, *J* = 7.8 Hz, CHOTBS), 85.1 (OCH-Het), 72.1 ($POCH_2CHO$), 65.6 (d, *J* = 5.6 Hz, $POCH_2$), 41.0 (TBSOCHCH_2), 25.6($SiC(CH_3)_3$), 20.8 ($ArCH_3$), 18.0 ($SiC(CH_3)_3$), 16.7 ($ArCH_3$), 12.4, (thymidine CH_3), -4.6 ($SiCH_3$), -4.8 ($SiCH_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.04; **IR** (film) υ_{max}/cm^{-1}: 2928, 2856, 1688 (C=O), 1498, 1470, 1440, 1251 (P=O), 1149, 1131, 1117, 1086, 1033, 950, 910, 834, 780, 754, 696; **HRMS** (ESI+): calcd. for $C_{30}H_{42}N_2O_7PSi$ 601.2493 $[M+H]^+$, found 601.2490.

[xii] 3'-OTBS – thymidine was prepared by Dr. Heyao Shi according to literature procedures.[37]

((3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl (2,4-dimethylphenyl) (*R*)-phenylphosphonate (**476**)

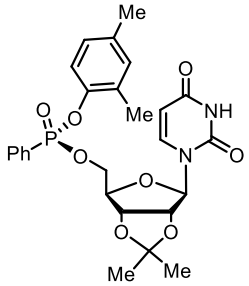


476 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, 2',3'-isopropylideneadenosine[xiii] (45.0 mg, 0.150 mmol) was used as nucleophile and *t*-BuMgCl (2 *M* in Et_2O, 150 μL, 0.30 mmol) as base in THF (0.50 mL) at room temperature for 16 hr. CH_2Cl_2:MeOH 95:5. Colourless oil (26.4 mg, 0.048 mmol, 48% yield, >95:5 dr).

$[\alpha]_D^{25}$ = −53.6 (c = 1.00, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 12.3 Hz, 2H, ArC<u>H</u>), 8.18 – 8.06 (m, 3H), 7.58 – 7.49 (m, 1H, ArC<u>H</u>), 7.46 (dtd, *J* = 8.8, 4.5, 2.6 Hz, 2H, ArC<u>H</u>), 7.19 (dd, *J* = 8.4, 1.4 Hz, 1H, ArC<u>H</u>), 7.00 – 6.86 (m, 1H, ArC<u>H</u>), 6.81 (dd, *J* = 8.3, 2.3 Hz, 1H, ArC<u>H</u>), 5.90 (d, *J* = 4.4 Hz, 1H, OCH_2CHO), 5.85 – 5.72 (m, 1H, NC<u>H</u>N), 5.09 (dd, *J* = 5.9, 4.4 Hz, 1H, OC<u>H</u>CHO), 5.04 (dd, *J* = 5.8, 1.3 Hz, 1H, OCHC<u>H</u>O), 4.51 (q, *J* = 1.7 Hz, 1H, OC<u>H</u>-Het), 3.90 (dt, *J* = 12.6, 2.0 Hz, 1H, $POCH_aCH_b$), 3.75 (ddd, *J* = 12.4, 10.0, 2.1 Hz, 1H, $POCH_aCH_b$), 2.34 (s, 3H, ArCH_3), 2.22 (s, 3H, ArCH_3), 1.63 (s, 3H, acetal CH_3), 1.36 (s, 3H, acetal CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.0 (Ar<u>C</u>H), 151.8 (Ar<u>C</u>), 146.8 (d, *J* = 8.8 Hz, Ar<u>C</u>), 142.5 (Ar<u>C</u>H), 134.5 (Ar<u>C</u>), 132.8 (d, *J* = 3.1 Hz, Ar<u>C</u>), 132.5 (d, *J* = 11.0 Hz, Ar<u>C</u>H), 129.5 (d, *J* = 6.1 Hz, ArC), 129.4 (d, *J* = 183.2 Hz, <u>C</u>P), 128.4 (d, *J* = 15.7 Hz, Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 119.9 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 114.2 (ArC<u>H</u>), 94.1 (O<u>C</u>H-Het), 83.7 (O<u>C</u>HCHO), 81.8 (OCH<u>C</u>HO), 63.3 ($PO\underline{C}H_2$), 27.7 (acetal <u>C</u>H_3), 25.4 (acetal <u>C</u>H_3), 20.8 (Ar<u>C</u>H_3), 16.9 (Ar<u>C</u>H_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.93; **IR** (film) υ_{max}/cm^{-1}: 2924, 1606, 1586, 1498, 1461, 1440, 1383, 1203 (P=O), 1154, 1118, 1082, 1036, 951, 911, 706, 694, 695; **HRMS** (ESI+): calcd. for $C_{27}H_{30}N_5O_6P$ 552.2006 $[M+H]^+$, found 552.2007.

[xiii] 2',3'-isopropylideneadenosine was prepared by Mr. Naoto Sahara according to literature procedures.[39]

2,4-dimethylphenyl (((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl) (*R*)-phenylphosphonate (**477**)

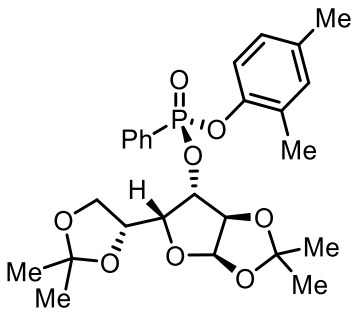


477 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, 2',3'-isopropylideneuridine[xiv] (31.0 mg, 0.150 mmol) was used as nucleophile and *t*-BuMgCl (2 *M* in Et_2O, 150 μL, 0.30 mmol) as base in THF (0.50 mL) at room temperature for 2 hr. CH_2Cl_2:Acetone 10:1 to 5:1. Colourless oil (37.7 mg, 0.071 mmol, 71% yield, >95:5 dr).

$[\alpha]_D^{25}$ = +4.49 (c = 1.27, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.36 (s, 1H, NH), 7.87 (dd, *J* = 13.8, 6.8 Hz, 2H), 7.65 – 7.55 (m, 1H), 7.54 – 7.44 (m, 2H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.95 (s, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 5.78 (d, *J* = 2.8 Hz, 1H, OCH-Het), 5.51 (d, *J* = 8.1 Hz, 1H, uracil ArCH), 4.79 (dd, *J* = 6.5, 2.3 Hz, 1H, $POCH_aCH_b$), 4.67 (dd, *J* = 6.5, 2.8 Hz, 1H, $POCH_aCH_b$), 4.37 (m, 3H, $POCH_2CH$ + OCHCHO), 2.23 (s, 3H, $ArCH_3$), 2.19 (s, 3H, $ArCH_3$), 1.55 (s, 3H, acetal CH_3), 1.32 (s, 3H, acetal CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) 163.3 (C=O), 150.0 (C=O), 146.7 (d, *J* = 7.9 Hz, ArC), 140.9 (ArC), 134.7 (ArCH), 133.3 (d, *J* = 3.1 Hz, ArCH), 132.1 (ArCH), 131.9 (d, *J* = 10.3 Hz, ArCH), 128.8 (d, *J* = 5.7 Hz, ArC), 128.8 (d, *J* = 15.5 Hz, ArCH), 127.5 (ArCH), 127.0 (d, *J* = 192 Hz, CP), 119.8 (d, *J* = 2.7 Hz, ArCH), 114.6 (ArCH), 102.5 (uracil ArCH), 93.0 (OCH-Het), 84.9 (d, *J* = 7.2 Hz, OCHCHO), 84.4 (OCHCHO), 80.5 ($POCH_2CH$), 65.9 (d, *J* = 4.6 Hz, $POCH_2$), 27.1 (acetal CH_3), 25.2 (acetal CH_3), 20.7 ($ArCH_3$), 16.6 ($ArCH_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.09 (minor), 15.94 (major); **IR** (film) υ_{max}/cm^{-1}: 2897, 1693 (C=O), 1498, 1456, 1381, 1253 (P=O), 1201, 1118, 1068, 949, 909, 754, 696; **HRMS** (ESI+): calcd. for $C_{26}H_{30}N_2O_8P$ 529.1740 $[M+H]^+$, found 529.1733.

[xiv] 2',3'-isopropylideneuridine was prepared by Mr. Naoto Sahara according to literature procedures.[40]

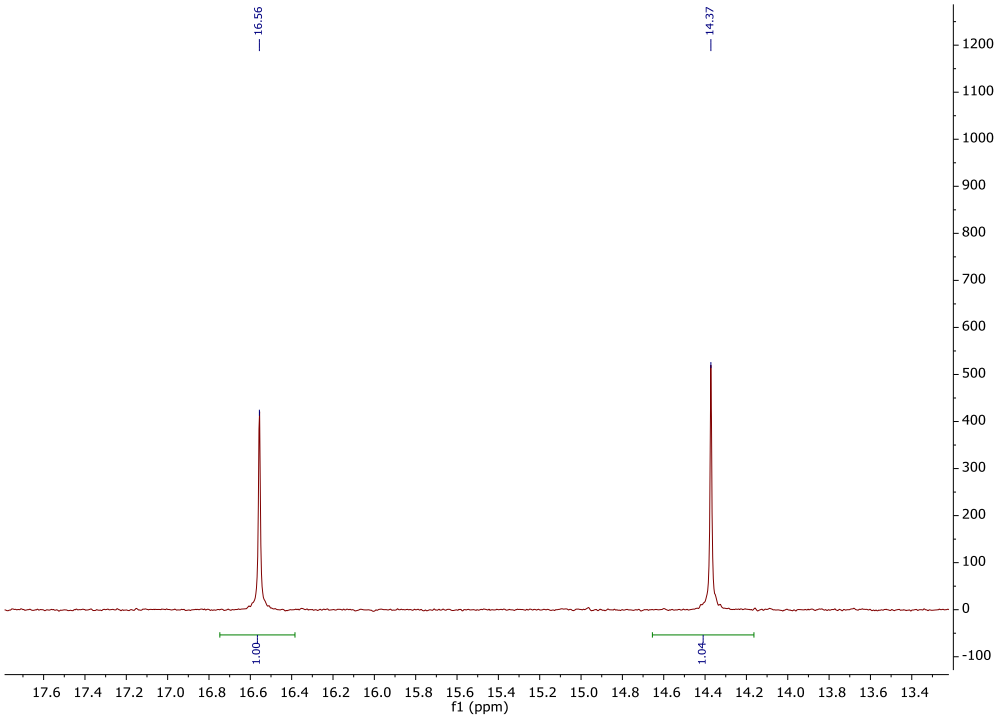
(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl (2,4-dimethylphenyl) phenylphosphonate (**479**)



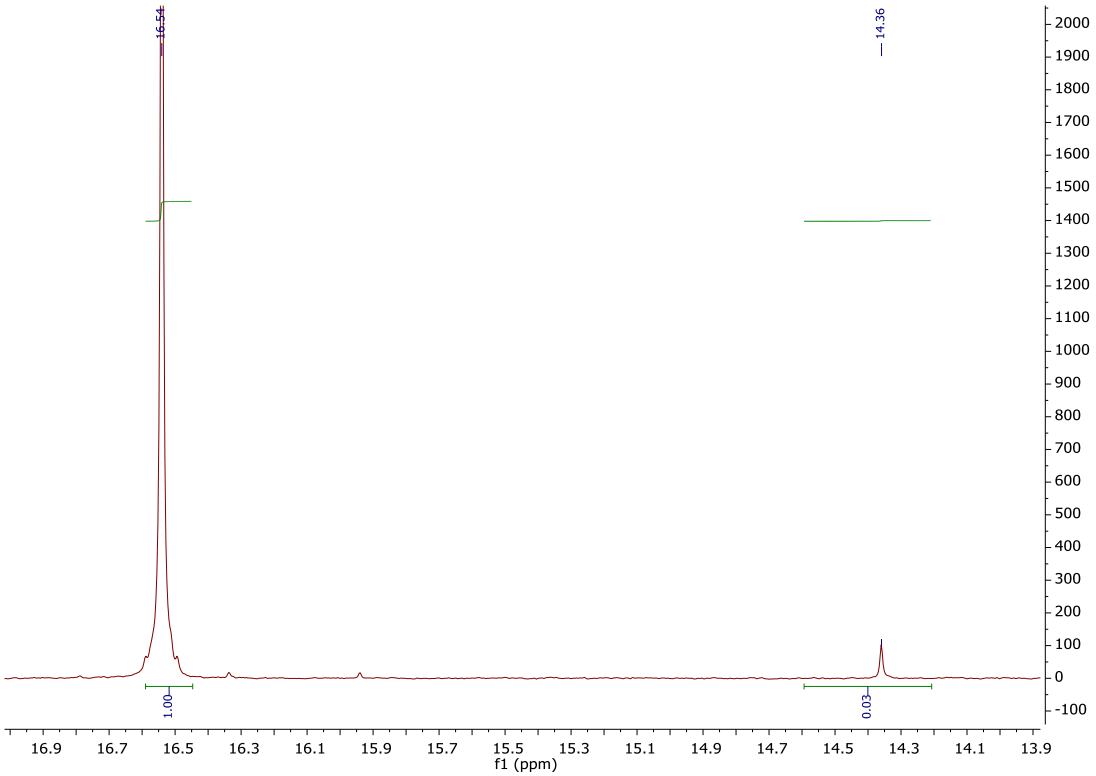
478 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, diacetone D-glucose (39.0 mg, 0.150 mmol) was used as nucleophile and *t*-BuMgCl (2 *M* in Et_2O, 75.0 μL, 0.150 mmol) as base in THF (0.50 mL) at room temperature for 24 hr. Pentane:EtOAc 7:3. Colourless oil (48.9 mg, 0.096 mmol, 96% yield, >95:5 dr).

$[\alpha]_D^{25}$ = −50.8 (c = 0.43, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.82 (m, 2H, ArC<u>H</u>), 7.57 – 7.45 (m, 1H, ArC<u>H</u>), 7.47 – 7.35 (m, 2H, ArC<u>H</u>), 7.10 (dd, *J* = 8.2, 1.5 Hz, 1H, ArC<u>H</u>), 6.93 (t, *J* = 1.5 Hz, 1H, ArC<u>H</u>), 6.87 (dd, *J* = 8.3, 2.2 Hz, 1H, ArC<u>H</u>), 5.62 (d, *J* = 3.5 Hz, 1H, OC<u>H</u>O), 4.77 (dd, *J* = 7.3, 2.6 Hz, 1H, POC<u>H</u>), 4.32 (d, *J* = 3.5 Hz, 1H, OC<u>H</u>), 4.08 – 3.97 (m, 2H, $OCH_2C\underline{H}C\underline{H}$), 3.94 (dd, *J* = 8.5, 5.9 Hz, 1H, $OCH_a\underline{H}_b$), 3.83 (dd, *J* = 8.5, 5.3 Hz, 1H, $OC\underline{H}_aH_b$), 2.20 (s, 3H, ArC$\underline{H}_3$), 2.17 (s, 3H, ArC$\underline{H}_3$), 1.37 (s, 3H, acetal C$\underline{H}_3$), 1.23 (s, 3H, acetal C$\underline{H}_3$), 1.12 (s, 3H, acetal C$\underline{H}_3$), 1.08 (s, 3H, acetal C$\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.5 (d, *J* = 8.7 Hz, Ar<u>C</u>), 134.9 (d, *J* = 1.3 Hz, Ar<u>C</u>), 133.0 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.2 (d, *J* = 10.3 Hz, Ar<u>C</u>H), 132.0 (Ar<u>C</u>H), 129.5 (d, *J* = 5.0 Hz, Ar<u>C</u>), 128.4 (d, *J* = 15.6 Hz, Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 127.0 (d, *J* = 193.92 Hz, <u>C</u>P), 120.8 (d, *J* = 2.9 Hz, Ar<u>C</u>H), 112.2 (O<u>C</u>O), 109.2 (O<u>C</u>O), 105.1 (OC<u>H</u>O), 83.6 (POCHCH), 80.7 (d, *J* = 8.5 Hz, POC<u>H</u>), 78.9 (d, *J* = 5.0 Hz, OC<u>H</u>), 77.2 ($OCH_2CHC\underline{H}$), 72.1 ($OCH_2C\underline{H}CH$), 67.43 ($OC\underline{H}_2$), 26.7 (acetal <u>C</u>H_3), 26.6 (acetal <u>C</u>H_3), 26.0 (acetal <u>C</u>H_3), 25.0 (acetal <u>C</u>H_3), 20.6 (Ar<u>C</u>H_3), 16.5 (Ar<u>C</u>H_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.54 (major), 14.36 (minor); **IR** (film) υ_{max}/cm^{-1}:1498, 1440, 1373, 1262, 1201 (P=O), 1164, 1131, 1075, 1021, 949, 904, 842, 751, 695; **HRMS** (ESI+): calcd. for $C_{26}H_{33}NaO_8P$ 527.1811 $[M+Na]^+$, found 527.1803.

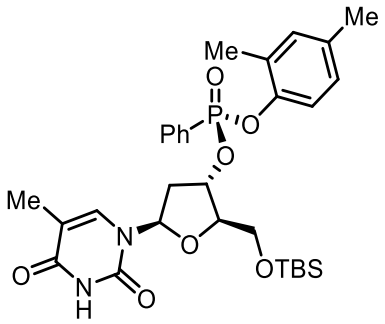
^{31}P NMR (rac):



^{31}P NMR (enantioenriched):



(2*R*,3*S*,5*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl (2,4-dimethylphenyl) (*R*)-phenylphosphonate (**479**)



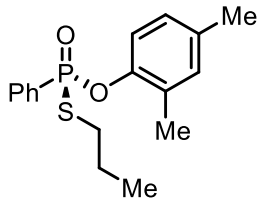
479 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, 5'-OTBS – thymidine[xv] (53.5 mg, 0.150 mmol) was used as nucleophile and *t*-BuMgCl (2 *M* in Et_2O, 150 μL, 0.30 mmol) as base in THF (0.50 mL) at room temperature for 16 hr. CH_2Cl_2:MeOH 95:5. Colourless oil (42.6 mg, 0.071 mmol, 71% yield, >95:5 dr).

$[\alpha]_D^{25}$ = −5.3 (c = 0.95, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.44 (s, 1H, NH), 7.90 (ddt, *J* = 13.9, 6.9, 1.4 Hz, 2H, ArCH), 7.63 – 7.56 (m, 1H, ArCH), 7.54 – 7.47 (m, 2H, ArCH), 7.45 (d, *J* = 1.4 Hz, 1H, ArCH), 7.13 (dd, *J* = 8.2, 1.5 Hz, 1H, ArCH), 6.97 (d, *J* = 2.4 Hz, 1H, ArCH), 6.90 (dd, *J* = 8.3, 2.3 Hz, 1H, ArCH), 6.37 (dd, *J* = 9.1, 5.2 Hz, 1H, OCH-Het), 5.19 – 5.02 (m, 1H, POCH), 4.14 (q, *J* = 1.9 Hz, 1H, $TBSOCH_2CH$), 3.80 (dd, *J* = 11.5, 2.0 Hz, 1H, CH_aH_bOTBS), 3.69 (dd, *J* = 11.5, 2.2 Hz, 1H, CH_aH_bOTBS), 2.49 – 2.35 (m, 1H, $POCHCH_aH_b$), 2.25 (s, 3H, $ArCH_3$), 2.22 (s, 3H, $ArCH_3$), 2.02 (dddd, *J* = 13.7, 9.2, 5.8, 1.5 Hz, 1H, $POCHCH_aH_b$), 1.89 (d, *J* = 1.3 Hz, 3H, thymidine CH_3), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9 (C=O), 150.6 (C=O), 146.5 (d, *J* = 8.4 Hz, ArC), 135.0, 134.8 (ArC), 133.2 (d, *J* = 3.1 Hz, ArCH), 132.2 (ArCH), 131.9 (d, *J* = 10.3 Hz, ArCH), 129.3 (d, *J* = 5.3 Hz, ArC), 128.8 (d, *J* = 15.6 Hz, ArCH), 127.6 (d, *J* = 192.6 Hz, CP), 127.5 (d, *J* = 1.7 Hz, ArCH), 120.4 (d, *J* = 2.7 Hz, ArCH), 111.3 (thymidine CCH_3), 86.3 (d, *J* = 3.6 Hz, $TBSOCH_2CH$), 84.6 (OCH-Het), 77.6 (d, *J* = 5.5 Hz, POCH), 63.2 (CH_2OTBS), 39.6 (d, *J* = 5.2 Hz, $POCHCH_2$), 26.0 ($SiC(CH_3)_3$), 20.7 ($ArCH_3$), 18.4 ($SiC(CH_3)_3$), 16.6 ($ArCH_3$), 12.6 (thymidine CH_3), -5.4 ($SiCH_3$), -5.4 ($SiCH_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 15.93; **IR** (film) υ_{max}/cm^{-1}: 2929, 1687 (C=O), 1497,

[xv] 5'-OTBS – thymidine was prepared by Dr. Heyao Shi according to literature procedures.[41]

1496, 1262 (P=O), 1198, 1130, 1071, 1009, 974, 950, 908, 832, 781, 733, 697, 625; **HRMS** (ESI+): calcd. for $C_{30}H_{42}N_2O_7PSi$ 601.2493 $[M+H]^+$, found 601.2488.

O-(2,4-dimethylphenyl) S-propyl (*S*)-phenylphosphonothioate (**480**)

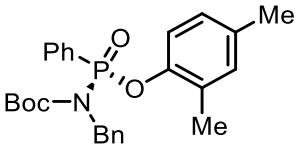


480 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, 1-propanethiol (28.0 μL, 0.30 mmol) was used as nucleophile and DBU (45.0 μL, 0.30 mmol) as base in THF (0.50 mL) at room temperature for 2 hr. Pentane:EtOAc 8:2. Colourless oil (19.2 mg, 0.06 mmol, 60% yield, 90% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 23.18 min, t (minor) = 25.89 min.

$[\alpha]_D^{25}$ = −41.8 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.98 – 7.86 (m, 2H, ArC<u>H</u>), 7.56 – 7.46 (m, 1H, ArC<u>H</u>), 7.50 – 7.37 (m, 2H, ArC<u>H</u>), 7.23 (dd, *J* = 8.2, 1.6 Hz, 1H, ArC<u>H</u>), 6.97 – 6.91 (m, 1H, ArC<u>H</u>), 6.91 – 6.82 (m, 1H, ArC<u>H</u>), 2.69 (dtd, *J* = 12.5, 7.2, 5.2 Hz, 2H, SC<u>H</u>$_2$CH$_2$CH$_3$), 2.21 (s, 3H, ArC<u>H</u>$_3$), 2.20 (s, 3H, ArC<u>H</u>$_3$), 1.47 (h, *J* = 7.4 Hz, 2H, SCH$_2$C<u>H</u>$_2$CH$_3$), 0.79 (t, *J* = 7.3 Hz, 3H, SCH$_2$CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.1 (d, *J* = 10.1 Hz, Ar<u>C</u>) 134.6 (Ar<u>C</u>), 133.0 (d, *J* = 153 Hz, <u>C</u>P), 132.7 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 132.3 (Ar<u>C</u>H), 132.0 (Ar<u>C</u>H), 131.3 (d, *J* = 10.7 Hz, Ar<u>C</u>H), 129.2 (d, *J* = 5.5 Hz, Ar<u>C</u>), 128.6 (d, *J* = 15.0 Hz, Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 120.7 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 32.6 (d, *J* = 2.5 Hz, S<u>C</u>H$_2$CH$_2$CH$_3$), 24.1 (d, *J* = 5.3 Hz, SCH$_2$<u>C</u>H$_2$CH$_3$), 20.7(Ar<u>C</u>H$_3$), 16.8 (Ar<u>C</u>H$_3$), 13.1 (SCH$_2$CH$_2$CH$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 42.82; **IR** (film) υ_{max}/cm^{-1}:1495, 1438, 1280, 1195 (P=O), 1149, 1114, 941, 895, 816, 720, 694; **HRMS** (ESI+): calcd. for $C_{17}H_{22}O_2PS$ 321.1078 $[M+H]^+$, found 321.1073.

tert-butyl (*S*)-benzyl((2,4-dimethylphenoxy)(phenyl)phosphoryl)carbamate (**481**)

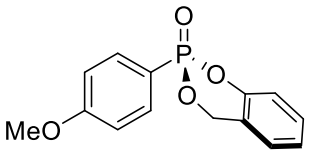


481 was synthesized following **GP VII**. **415** (39.7 mg, 0.10 mmol, 92% ee) was used as phosphonate, *tert*-butyl benzylcarbamate (42.6 mg, 0.150 mmol) was used as nucleophile and *t*-BuMgCl (2 *M* in Et_2O, 75 μL, 0.15.0 mmol) as base in THF (0.50 mL) at room temperature for 2 hr. Pentane:EtOAc 8:2. Colourless oil (36.9 mg, 0.084 mmol, 84% yield, 93% ee).

HPLC Conditions: CHIRALPAK OD-H, hexane/isopropanol = 99/1, 1 mL/min, λ = 220 nm, t (major) = 23.61, t (minor) = 31.84 min.

$[\alpha]_D^{25}$ = −47.1 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$ 7.72 – 7.60 (m, 2H, ArC<u>H</u>), 7.49 – 7.39 (m, 1H, ArC<u>H</u>), 7.39 – 7.28 (m, 4H, ArC<u>H</u>), 7.23 – 7.13 (m, 3H, ArC<u>H</u>), 6.96 – 6.88 (m, 2H, ArC<u>H</u>), 6.77 (dd, *J* = 8.3, 2.2 Hz, 1H, ArC<u>H</u>), 4.89 – 4.74 (m, 2H, PhC<u>H_2</u>), 2.20 (s, 3H, ArC<u>H_3</u>) 2.17 (s, 3H, ArC<u>H_3</u>), 1.11 (s, 9H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5 (d, *J* = 6.4 Hz, Ar<u>C</u>), 146.5 (d, *J* = 8.8 Hz, Ar<u>C</u>), 138.6, 134.4 (Ar<u>C</u>), 132.1 (Ar<u>C</u>H), 132.0 (Ar<u>C</u>H), 131.2 (d, *J* = 10.6 Hz, Ar<u>C</u>H), 131.0 (d, *J* = 193 Hz, <u>C</u>P), 129.4 (d, *J* = 5.5 Hz, Ar<u>C</u>), 128.9 (Ar<u>C</u>H), 128.22 (Ar<u>C</u>H), 128.17 (d, *J* = 15.9 Hz, Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 127.3(Ar<u>C</u>H), 120.1 (d, *J* = 3.2 Hz, Ar<u>C</u>H), 83.0 (PhC<u>H_2</u>N), 48.5 (d, *J* = 2.1 Hz, <u>C</u>(CH$_3$)$_3$), 27.8 C(<u>C</u>H_3)$_3$, 20.7 (Ar<u>C</u>H_3), 16.7 (Ar<u>C</u>H_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.08; **IR** (film) υ_{max}/cm^{-1}: 1717 (C=O), 1497, 1439, 1368, 1292, 1249 (P=O), 1199, 1157, 1125, 1092, 1062, 945, 906, 853, 814, 739, 695; **HRMS** (ESI+): calcd. for $C_{26}H_{30}NNaO_4P$ 474.1810 $[M+Na]^+$, found 474.1805.

(*R*)-2-(4-methoxyphenyl)-4H-benzo[d][1,3,2]dioxaphosphinine 2-oxide (**482**)



420 (55.6 mg, 0.10 mmol, 91% ee) was dissolved in CH_2Cl_2 (900 μL) and TFA (38.3 μL, 57.0 mg, 0.50 mmol) was added dropwise and the reaction was stirred at room temperature for 10 min. The solution was passed through a short plug of $NaHCO_3$ and $MgSO_4$ and evaporated to dryness. The crude deprotected compound was dissolved in THF (1.00 mL) and cooled to 0 °C after which and *t*-BuMgCl (2 *M* in Et_2O, 75 μL, 0.15.0 mmol) was added dropwise and the reaction was stirred at room temperature for 20 min. Upon completion by TLC the reaction solution was loaded directly onto silica gel for silica gel chromatography. Pentane:EtOAc 1:1. Colourless Oil (18.5 mg, 0.067 mmol, 67% yield, 84% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 220 nm, t (major) = 17.54 min, t (minor) = 20.01 min.

$[\alpha]_D^{25}$ = −17.5 (c = 0.82, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.52 (m, 2H, ArC<u>H</u>), 7.26 (tdd, *J* = 8.1, 4.3, 1.9 Hz, 1H, ArC<u>H</u>), 7.12 – 7.02 (m, 2H, ArC<u>H</u>), 7.02 – 6.96 (m, 1H, ArC<u>H</u>), 6.92 – 6.82 (m, 2H, ArC<u>H</u>), 5.48 (ddd, *J* = 13.8, 9.3, 1.0 Hz, 1H, $OCH_aC\underline{H}_bAr$), 5.08 (dd, *J* = 18.7, 13.8 Hz, 1H, $OC\underline{H}_aCH_bAr$), 3.77 (s, 3H, $OC\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7 (d, *J* = 3.6 Hz, <u>C</u>OCH_3), 150.7 (d, *J* = 7.6 Hz, Ar<u>C</u>), 134.3 (Ar<u>C</u>H), 134.1 (Ar<u>C</u>H), 130.1 (Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 122.9 (d, *J* = 8.7 Hz, Ar<u>C</u>), 118.8 (d, *J* = 7.2 Hz, Ar<u>C</u>H), 117.5 (d, *J* = 202.3 Hz, <u>C</u>P), 114.4 (d, *J* = 17.1 Hz, Ar<u>C</u>H), 66.4 (d, *J* = 6.8 Hz, O<u>C</u>H_2Ar), 55.5 (O<u>C</u>H_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 14.01; **IR** (film) υ_{max}/cm^{-1}: 2933, 1598, 1505, 1488, 1459, 1253 (P=O), 1191, 1130, 1106, 1015, 1987, 911, 826, 797, 758, 729; **HRMS** (ESI+): calcd. for $C_{14}H_{13}O_4P$ 277.0624 $[M+H]^+$, found 277.0624.

5.3.10.2 Single crystal X-ray diffraction data for compound ***482***

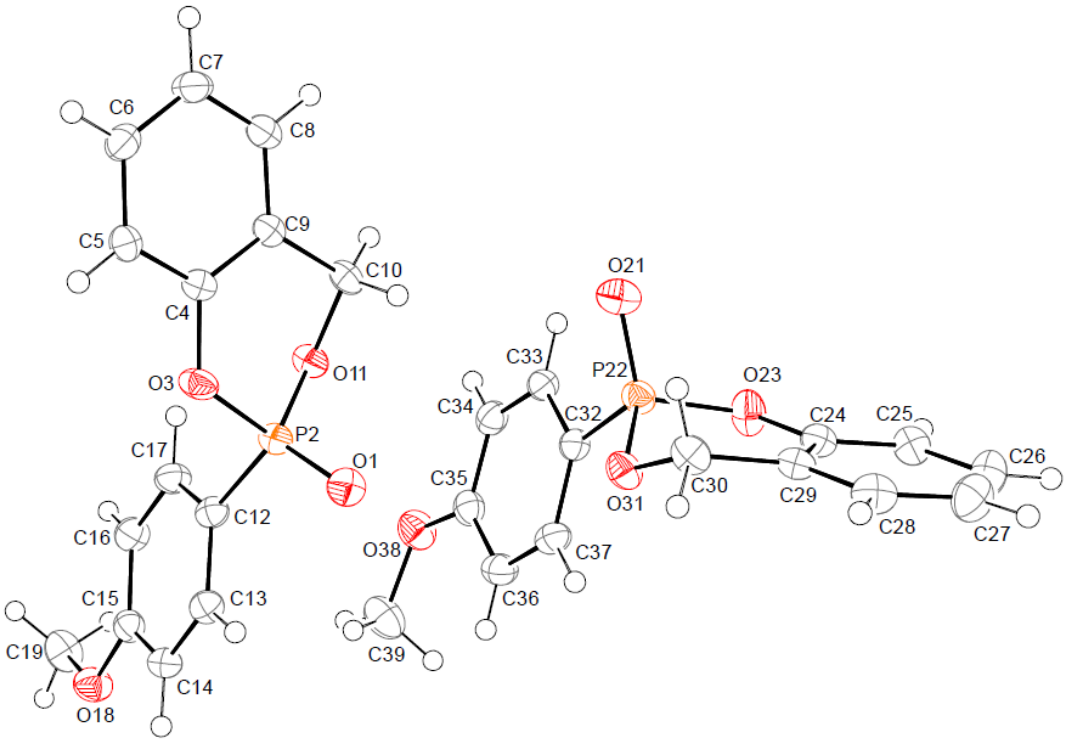


Table 1. Crystal data and structure refinement for **482**.

Identification code	**482**	
Empirical formula	C14 H13 O4 P	
Formula weight	276.23	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 15.0390(3) Å	□ = 90°.
	b = 5.80870(10) Å	□ = 115.683(2)°.
	c = 15.9467(3) Å	□ = 90°.
Volume	1255.43(5) $Å^3$	
Z	4	
Density (calculated)	1.461 Mg/m^3	
Absorption coefficient	2.027 mm^{-1}	
F(000)	575.997	
Crystal size	0.23 x 0.20 x 0.19 mm^3	
Theta range for data collection	3.261 to 75.971°.	
Index ranges	-18<=h<=18, -7<=k<=7, -17<=l<=20	
Reflections collected	17317	
Independent reflections	5177 [R(int) = 0.024]	
Completeness to theta = 75.971°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.68 and 0.64	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5171 / 1 / 344	
Goodness-of-fit on F^2	1.0165	
Final R indices [I>2sigma(I)]	R1 = 0.0284, wR2 = 0.0781	
R indices (all data)	R1 = 0.0288, wR2 = 0.0785	
Absolute structure parameter	0	
Largest diff. peak and hole	0.23 and -0.24 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 7379. U(eq) is defined as one third of the trace of the *ortho*gonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7111(1)	5000(2)	3052(1)	29
P(2)	6966(1)	6380(1)	3751(1)	22
O(3)	7806(1)	5812(2)	4780(1)	28
C(4)	8596(1)	7284(3)	5261(1)	21
C(5)	9259(1)	6609(3)	6148(1)	24
C(6)	10056(1)	8028(3)	6655(1)	28
C(7)	10171(1)	10111(3)	6283(1)	31
C(8)	9506(1)	10757(3)	5398(1)	26
C(9)	8716(1)	9334(3)	4865(1)	21
C(10)	8012(1)	9943(3)	3881(1)	24
O(11)	7031(1)	9082(2)	3689(1)	25
C(12)	5812(1)	5961(3)	3784(1)	23
C(13)	5276(1)	3948(3)	3410(1)	25
C(14)	4347(1)	3663(3)	3370(1)	27
C(15)	3938(1)	5376(3)	3703(1)	25
C(16)	4473(1)	7376(3)	4100(1)	28
C(17)	5404(1)	7642(3)	4134(1)	28
O(18)	3012(1)	4955(2)	3617(1)	32
C(19)	2533(1)	6739(4)	3889(1)	35
O(21)	8886(1)	9140(2)	1769(1)	33
P(22)	8040(1)	7898(1)	1076(1)	24
O(23)	7867(1)	8545(2)	34(1)	32
C(24)	8260(1)	7218(3)	-450(1)	24
C(25)	8118(1)	8010(3)	-1318(1)	28
C(26)	8501(1)	6748(4)	-1827(1)	35
C(27)	9014(2)	4707(4)	-1473(1)	36
C(28)	9129(1)	3928(3)	-611(1)	31
C(29)	8767(1)	5173(3)	-82(1)	24
C(30)	8938(1)	4371(3)	872(1)	28
O(31)	8144(1)	5188(2)	1090(1)	27
C(32)	6902(1)	8428(3)	1114(1)	23

(33)	6778(1)	10513(3)	1488(1)	25
(34)	5917(1)	10932(3)	1576(1)	27
(35)	5186(1)	9247(3)	1317(1)	26
(36)	5293(1)	7182(3)	924(1)	28
(37)	6152(1)	6790(3)	826(1)	26
'(38)	4392(1)	9775(3)	1479(1)	35
(39)	3673(1)	8013(4)	1317(2)	39

Table 3. Bond lengths [Å] and angles [°] for 7379.

O(1)-P(2)	1.4625(13)	O(21)-P(22)	1.4640(14)
P(2)-O(3)	1.6130(12)	P(22)-O(23)	1.6123(13)
P(2)-O(11)	1.5781(12)	P(22)-O(31)	1.5816(13)
P(2)-C(12)	1.7761(17)	P(22)-C(32)	1.7649(17)
O(3)-C(4)	1.3934(19)	O(23)-C(24)	1.391(2)
C(4)-C(5)	1.388(2)	C(24)-C(25)	1.384(2)
C(4)-C(9)	1.396(2)	C(24)-C(29)	1.396(2)
C(5)-C(6)	1.389(2)	C(25)-C(26)	1.390(3)
C(5)-H(51)	0.923	C(25)-H(251)	0.931
C(6)-C(7)	1.391(3)	C(26)-C(27)	1.393(3)
C(6)-H(61)	0.935	C(26)-H(261)	0.922
C(7)-C(8)	1.382(3)	C(27)-C(28)	1.385(3)
C(7)-H(71)	0.963	C(27)-H(271)	0.927
C(8)-C(9)	1.393(2)	C(28)-C(29)	1.390(3)
C(8)-H(81)	0.958	C(28)-H(281)	0.946
C(9)-C(10)	1.506(2)	C(29)-C(30)	1.501(2)
C(10)-O(11)	1.4588(19)	C(30)-O(31)	1.461(2)
C(10)-H(102)	0.960	C(30)-H(302)	0.983
C(10)-H(101)	0.985	C(30)-H(301)	0.956
C(12)-C(13)	1.399(2)	C(32)-C(33)	1.398(2)
C(12)-C(17)	1.393(2)	C(32)-C(37)	1.392(2)
C(13)-C(14)	1.381(2)	C(33)-C(34)	1.382(2)
C(13)-H(131)	0.948	C(33)-H(331)	0.931
C(14)-C(15)	1.390(3)	C(34)-C(35)	1.394(3)
C(14)-H(141)	0.935	C(34)-H(341)	0.913
C(15)-C(16)	1.399(2)	C(35)-C(36)	1.395(3)
C(15)-O(18)	1.360(2)	C(35)-O(38)	1.362(2)
C(16)-C(17)	1.385(2)	C(36)-C(37)	1.387(2)
C(16)-H(161)	0.930	C(36)-H(361)	0.915
C(17)-H(171)	0.947	C(37)-H(371)	0.963
O(18)-C(19)	1.433(2)	O(38)-C(39)	1.428(3)
C(19)-H(192)	0.980	C(39)-H(392)	0.977
C(19)-H(191)	0.964	C(39)-H(391)	0.996
C(19)-H(193)	0.985	C(39)-H(393)	0.950

O(1)-P(2)-O(3)	110.73(7)
O(1)-P(2)-O(11)	117.64(8)
O(3)-P(2)-O(11)	102.98(7)
O(1)-P(2)-C(12)	114.67(8)
O(3)-P(2)-C(12)	106.55(7)
O(11)-P(2)-C(12)	103.07(7)
P(2)-O(3)-C(4)	122.61(10)
O(3)-C(4)-C(5)	116.87(14)
O(3)-C(4)-C(9)	121.44(14)
C(5)-C(4)-C(9)	121.68(15)
C(4)-C(5)-C(6)	118.90(15)
C(4)-C(5)-H(51)	120.3
C(6)-C(5)-H(51)	120.8
C(5)-C(6)-C(7)	120.22(15)
C(5)-C(6)-H(61)	119.1
C(7)-C(6)-H(61)	120.7
C(6)-C(7)-C(8)	120.18(16)
C(6)-C(7)-H(71)	118.7
C(8)-C(7)-H(71)	121.2
C(7)-C(8)-C(9)	120.70(16)
C(7)-C(8)-H(81)	120.2
C(9)-C(8)-H(81)	119.0
C(4)-C(9)-C(8)	118.25(15)
C(4)-C(9)-C(10)	120.07(14)
C(8)-C(9)-C(10)	121.67(15)
C(9)-C(10)-O(11)	109.17(13)
C(9)-C(10)-H(102)	110.5
O(11)-C(10)-H(102)	107.6
C(9)-C(10)-H(101)	111.3
O(11)-C(10)-H(101)	108.0
H(102)-C(10)-H(101)	110.1
C(10)-O(11)-P(2)	114.34(10)
P(2)-C(12)-C(13)	119.44(12)
P(2)-C(12)-C(17)	121.52(13)
C(13)-C(12)-C(17)	118.97(15)
C(12)-C(13)-C(14)	120.26(16)
C(12)-C(13)-H(131)	118.8
C(14)-C(13)-H(131)	120.9
C(13)-C(14)-C(15)	120.23(16)
C(13)-C(14)-H(141)	122.1
C(15)-C(14)-H(141)	117.6
C(14)-C(15)-C(16)	120.23(15)
C(14)-C(15)-O(18)	115.84(16)
C(16)-C(15)-O(18)	123.93(16)
C(15)-C(16)-C(17)	118.97(16)
C(15)-C(16)-H(161)	121.1
C(17)-C(16)-H(161)	120.0
C(12)-C(17)-C(16)	121.30(16)
C(12)-C(17)-H(171)	117.8
C(16)-C(17)-H(171)	120.9
C(15)-O(18)-C(19)	117.81(15)
O(18)-C(19)-H(192)	109.7
O(18)-C(19)-H(191)	110.8
H(192)-C(19)-H(191)	108.4
O(18)-C(19)-H(193)	111.6
H(192)-C(19)-H(193)	107.6
H(191)-C(19)-H(193)	108.5
O(21)-P(22)-O(23)	111.26(8)
O(21)-P(22)-O(31)	115.58(8)
O(23)-P(22)-O(31)	102.53(7)
O(21)-P(22)-C(32)	115.29(8)
O(23)-P(22)-C(32)	105.59(7)
O(31)-P(22)-C(32)	105.36(7)
P(22)-O(23)-C(24)	121.71(11)
O(23)-C(24)-C(25)	116.88(15)
O(23)-C(24)-C(29)	121.58(15)
C(25)-C(24)-C(29)	121.53(16)
C(24)-C(25)-C(26)	119.01(17)
C(24)-C(25)-H(251)	119.1
C(26)-C(25)-H(251)	121.8
C(25)-C(26)-C(27)	120.61(17)

C(25)-C(26)-H(261)	120.1	C(32)-C(33)-H(331)	122.6
C(27)-C(26)-H(261)	119.3	C(34)-C(33)-H(331)	117.4
C(26)-C(27)-C(28)	119.24(17)	C(33)-C(34)-C(35)	119.97(16)
C(26)-C(27)-H(271)	118.5	C(33)-C(34)-H(341)	120.8
C(28)-C(27)-H(271)	122.2	C(35)-C(34)-H(341)	119.2
C(27)-C(28)-C(29)	121.33(17)	C(34)-C(35)-C(36)	120.46(16)
C(27)-C(28)-H(281)	119.8	C(34)-C(35)-O(38)	115.45(16)
C(29)-C(28)-H(281)	118.9	C(36)-C(35)-O(38)	124.09(17)
C(24)-C(29)-C(28)	118.24(16)	C(35)-C(36)-C(37)	119.13(16)
C(24)-C(29)-C(30)	120.86(15)	C(35)-C(36)-H(361)	121.0
C(28)-C(29)-C(30)	120.88(15)	C(37)-C(36)-H(361)	119.9
C(29)-C(30)-O(31)	109.97(13)	C(32)-C(37)-C(36)	120.77(16)
C(29)-C(30)-H(302)	109.5	C(32)-C(37)-H(371)	119.6
O(31)-C(30)-H(302)	108.1	C(36)-C(37)-H(371)	119.6
C(29)-C(30)-H(301)	111.3	C(35)-O(38)-C(39)	117.47(16)
O(31)-C(30)-H(301)	105.7	O(38)-C(39)-H(392)	108.3
H(302)-C(30)-H(301)	112.2	O(38)-C(39)-H(391)	111.4
C(30)-O(31)-P(22)	113.97(11)	H(392)-C(39)-H(391)	110.9
P(22)-C(32)-C(33)	118.44(13)	O(38)-C(39)-H(393)	107.7
P(22)-C(32)-C(37)	121.87(13)	H(392)-C(39)-H(393)	109.9
C(33)-C(32)-C(37)	119.61(16)	H(391)-C(39)-H(393)	108.6
C(32)-C(33)-C(34)	119.99(16)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 7379. 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)	27(1)	30(1)	32(1)	0(1)	14(1)	2(1)
P(2)	19(1)	20(1)	24(1)	2(1)	8(1)	1(1)
O(3)	25(1)	21(1)	30(1)	6(1)	5(1)	-4(1)
C(4)	20(1)	19(1)	26(1)	-1(1)	11(1)	1(1)
C(5)	25(1)	23(1)	24(1)	3(1)	12(1)	2(1)
C(6)	26(1)	33(1)	22(1)	-2(1)	8(1)	0(1)
C(7)	28(1)	32(1)	31(1)	-9(1)	12(1)	-9(1)
C(8)	26(1)	22(1)	32(1)	-2(1)	16(1)	-2(1)
C(9)	21(1)	20(1)	26(1)	0(1)	13(1)	2(1)
C(10)	23(1)	20(1)	30(1)	6(1)	13(1)	1(1)
O(11)	20(1)	22(1)	29(1)	6(1)	8(1)	2(1)
C(12)	22(1)	22(1)	22(1)	0(1)	7(1)	1(1)
C(13)	26(1)	24(1)	26(1)	0(1)	11(1)	1(1)
C(14)	27(1)	25(1)	28(1)	-3(1)	11(1)	-6(1)
C(15)	23(1)	28(1)	24(1)	2(1)	10(1)	-1(1)
C(16)	30(1)	25(1)	31(1)	-3(1)	16(1)	2(1)
C(17)	29(1)	23(1)	30(1)	-5(1)	12(1)	-3(1)
O(18)	26(1)	35(1)	39(1)	-5(1)	17(1)	-3(1)
C(19)	30(1)	37(1)	46(1)	5(1)	23(1)	7(1)
O(21)	28(1)	30(1)	40(1)	-3(1)	13(1)	-3(1)
P(22)	26(1)	20(1)	26(1)	1(1)	12(1)	-1(1)
O(23)	47(1)	22(1)	35(1)	7(1)	26(1)	10(1)
C(24)	23(1)	22(1)	29(1)	-1(1)	13(1)	-1(1)
C(25)	25(1)	30(1)	29(1)	4(1)	11(1)	3(1)
C(26)	34(1)	44(1)	29(1)	1(1)	16(1)	5(1)
C(27)	34(1)	41(1)	37(1)	-4(1)	19(1)	7(1)
C(28)	22(1)	30(1)	38(1)	0(1)	11(1)	5(1)
C(29)	21(1)	21(1)	28(1)	0(1)	9(1)	-3(1)
C(30)	28(1)	22(1)	33(1)	4(1)	14(1)	4(1)
O(31)	30(1)	22(1)	31(1)	5(1)	16(1)	1(1)
C(32)	26(1)	24(1)	20(1)	1(1)	9(1)	-2(1)

C(33)	29(1)	23(1)	22(1)	0(1)	10(1)	-4(1)
C(34)	33(1)	24(1)	24(1)	-1(1)	13(1)	1(1)
C(35)	26(1)	29(1)	24(1)	5(1)	11(1)	2(1)
C(36)	25(1)	27(1)	28(1)	0(1)	8(1)	-3(1)
C(37)	28(1)	23(1)	25(1)	-3(1)	9(1)	-2(1)
O(38)	32(1)	36(1)	43(1)	1(1)	22(1)	2(1)
C(39)	29(1)	41(1)	49(1)	12(1)	18(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 7379.

	x	y	z	U(eq)	
(51)	9171	5234	6393	28	
(61)	10504	7577	7252	32	
(71)	10727	11070	6650	38	
(81)	9587	12187	5140	31	
(102)	8212	9224	3447	28	
(101)	7966	11622	3786	30	
(131)	5554	2810	3167	31	
(141)	3967	2349	3113	33	
(161)	4213	8520	4336	34	
(171)	5783	8979	4397	33	
(192)	1860	6261	3757	53	
(191)	2496	8139	3551	53	
(193)	2882	7069	4560	52	
(251)	7786	9395	-1537	32	
(261)	8404	7238	-2410	42	
(271)	9274	3924	-1823	43	
(281)	9459	2522	-374	38	
(302)	8939	2680	887	33	
(301)	9531	5012	1340	32	
(331)	7251	11674	1675	30	
(341)	5828	12286	1820	34	
(361)	4809	6083	739	32	
(371)	6240	5351	571	31	
(392)	3190	8578	1526	59	
(391)	3345	7566	648	57	
(393)	4005	6706	1673	58	

Table 6. Hydrogen bonds for 7379 [Å and °].

D-H..A	d(D-H)	d(H..A)	d(D..A)	<(DHA)
(6)-H(61)..O(21)#1	93	2.45	3.237(3)	141
(10)-H(101)..O(1)#2	98	2.36	3.265(3)	152
(30)-H(302)..O(21)#3	98	2.51	3.374(3)	146

Symmetry transformations used to generate equivalent atoms:

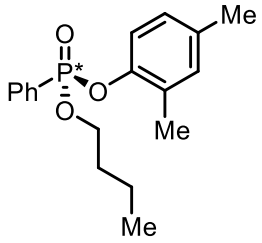
#1 -x+2,y-1/2,-z+1

#2 x,y+1,z

#3 x,y-1,z

5.3.11 Derivatisation (unsuccessful examples)

butyl (2,4-dimethylphenyl) phenylphosphonate (**491**)



To a solution of $ZnCl_2$ (1 *M* in Et_2O, 500 μL, 0.500 mmol) in THF (500 μL) was added ^{n}BuLi (2.5 *M* in hexane, 200 μL, 0.500 mmol) under argon at 0 °C and allowed to warm rt. After 30 min, **415** (39.7 mg, 0.10 mmol, 92% ee) was added and the reaction mixture was stirred at room temperature for 12 hr. The resulting mixture was loaded directly onto silica gel and purified by flash column chromatography to afford pure **491**. Pentane:EtOAc 7:3. Colourless oil (21.1 mg, 0.07 mmol, 70% yield, 91% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol= 85/15, 1 mL/min, λ = 220 nm, t (major) = 8.03 min, t (minor) = 8.96 min.

$[\alpha]_D^{25}$ = +10.1 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 2H, ArC<u>H</u>), 7.54 – 7.45 (m, 1H, ArC<u>H</u>), 7.45 – 7.34 (m, 2H, ArC<u>H</u>), 7.02 (dd, *J* = 8.2, 1.4 Hz, 1H, ArC<u>H</u>), 6.91 – 6.85 (m, 1H, ArC<u>H</u>), 6.85 – 6.77 (m, 1H), 4.16 – 3.99 (m, 2H, C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 2.18 (s, 3H, ArC<u>H</u>$_3$), 2.13 (s, 3H, ArC<u>H</u>$_3$), 1.65 – 1.53 (m, 2H, CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 1.38 – 1.24 (m, 2H, CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 0.82 (t, *J* = 7.4 Hz, 3H, CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.9 (d, *J* = 7.9 Hz, Ar<u>C</u>), 134.2 (Ar<u>C</u>), 132.6 (d, *J* = 3.1 Hz, Ar<u>C</u>H), 131.9 (Ar<u>C</u>H), 131.8 (d, *J* = 2.9 Hz, Ar<u>C</u>H), 129.2 (<u>C</u>P, other peak beneath other signal), 129.1 (d, *J* = 5.5 Hz, Ar<u>C</u>), 128.5 (d, *J* = 15.1 Hz, Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 120.1 (d, *J* = 2.9 Hz, Ar<u>C</u>H), 66.5 (d, *J* = 5.7 Hz, <u>C</u>H$_2$CH$_2$CH$_2$CH$_3$), 32.4 (d, *J* = 6.4 Hz, CH$_2$<u>C</u>H$_2$CH$_2$CH$_3$), 20.6 (Ar<u>C</u>H$_3$), 18.7 (CH$_2$CH$_2$<u>C</u>H$_2$CH$_3$), 16.5 (Ar<u>C</u>H$_3$), 13.5 (CH$_2$CH$_2$CH$_2$<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 15.27; **IR** (film) υ_{max}/cm^{-1}:1498, 1440, 1258, 1202 (P=O), 1130, 1060, 1024, 981, 946, 908, 818, 737, 718, 695; **HRMS** (ESI+): calcd. for $C_{18}H_{24}O_3P$ 318.1385 $[M+H]^+$, found 318.1381.

5.3.12 Computational methods for chapter 3

5.3.12.1 Computational method

Calculations were performed using Gaussian 16 A.03.[xvi] Geometry optimisations of all structures were carried out with the *para*-generalized gradient (GGA) M06-2X functional in combination with the def2SVP basis set.[28,29] The effect of PhF solvent was evaluated using the SMD implicit solvent model.[20] Harmonic vibrational frequencies at the same level of theory were calculated to characterize stationary points as transition state (TS) structures and to calculate the zero-point vibrational energy and thermal corrections. Free energies were evaluated at 25 °C and have been corrected to a standard liquid state of 1 mol/L. In all cases, vibrational entropies were obtained using a quasi-harmonic approximation, treating vibrational modes below 100 cm^{-1} as free rotors and as rigid rotors above this cut off, as first proposed by Grimme[14] and implemented in Python.[xvii] Single point energies were evaluated at the SMD(fluorobenzene)-M06-2X/def2TZVP level of theory. Second order perturbation theory analysis of the Fock matrix from NBO (v3.1) was used to quantify $\Delta E^{(2)}$ energies for *O* lone pair donation to each N-H bond. Molecular graphics were generated with *PyMol 4.50.5*.

[xvi] Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.

[xvii] Funes-Ardoiz, I; Paton, R. S. GoodVibes v2.0.2 DOI: 10.5281/zenodo.595246.

5.3.12.2 Second order perturbation analysis

Table 1. Delocalisation Energy ($\Delta E^{(2)}$) of the relevant oxygen lone pairs for the transition state structure **TS-exo** into the indicated σ^* N-H bonds on the BIMP catalyst (see **Figure 8B** in **Chapter 3**). Calculated at the NBO/SMD(fluorobenzene)-M06-2X/def2TZVP level of theory.

Interaction	***$\Delta E^{(2)}$ [$n_O \rightarrow \sigma^*_{N\text{-}H}$]/ kcal mol^{-1}***
$n_{O1} \rightarrow \sigma^*_{N\text{-}H(I)}$	4.1
$n_{O2} \rightarrow \sigma^*_{N\text{-}H(II)}$	2.5
$n_{O3} \rightarrow \sigma^*_{N\text{-}H(II)}$	2.5
$n_{O3} \rightarrow \sigma^*_{N\text{-}H(III)}$	4.5
$n_{O4} \rightarrow \sigma^*_{N\text{-}H(IV)}$	42.3

5.3.12.3 absolute energies

Table 2. Absolute energies for species in the proposed formation of the desired racemic desymmetrized phosphonate ester. Units are given in Hartrees. **E_{el}**: absolute electronic energies, **ZPE**: zero-point energy correction, **H**: enthalpy and **qh-G(T)**: quasi-harmonic Gibbs energy (calculated at the SMD(fluorobenzene)-**M06-2X/def2SVP** level of theory). **E_{el}^{high}** corresponds to the single point energies, which were calculated at the SMD(fluorobenzene)-**M06-2X/def2TZVP** level of theory. Thermochemistry was evaluated at 298.15 K and 1M.

Structure	***E***	***ZPE***	***H***	***G(T)***	***qh-G(T)***	***E_{el}^{high}***	***TS Freq***
TS-exo	-4393.81884	1.307808	-4392.428980	-4392.626787	-4392.608008	-4398.215810	-142.8
TS-endo	-4393.81678	1.308169	-4392.426569	-4392.624003	-4392.605430	-4398.213114	-139.1

5.3.12.4 xyz coordinates

TS1-exo

C -0.821429 4.44595 0.139999

N 0.003087 3.440854 0.788414

H -0.473895 2.591675 1.082679

C 1.363476 3.398904 0.658085

N 1.946768 2.31482 1.285929

H 1.368318 1.470757 1.304423

C 3.385531 2.123947 1.243742

H 3.765029 2.571358 0.30466

H 2.180768 -0.669722 0.4513

C 3.654403 0.615011 1.23574

N 3.031884 -0.106356 0.134105

H 3.223823 0.17106 2.143467

P 3.626548 -0.144498 -1.380695

C 2.966041 -1.627007 -2.166405

C 2.625358 -2.725828 -1.369523

C 2.852451 -1.695459 -3.561045

C 2.176333 -3.899573 -1.975698

H 2.702527 -2.666338 -0.281958

C 2.410201 -2.874428 -4.156011

H 3.100386 -0.831833 -4.181729

C 2.076798 -3.976075 -3.364623

H 1.896352 -4.755667 -1.358033

H 2.319854 -2.931369 -5.241848

H 1.727707 -4.897809 -3.833582

C 5.434364 -0.239228 -1.322695

C 6.083587 -1.47474 -1.427786

C 6.17242 0.926352 -1.072247

C 7.46954 -1.539771 -1.288067

H 5.512803 -2.385448 -1.621561

C 7.555779 0.851559 -0.925686

H 5.667051 1.892487 -0.989147

C 8.203077 -0.38045 -1.035744

H 7.976672 -2.501473 -1.376572

H 8.127911 1.758536 -0.724412

H 9.287225 -0.436531 -0.924456

C 3.210618 1.295799 -2.389796

C 2.015999 1.973539 -2.122882

C 4.030679 1.690634 -3.459144

C 1.640532 3.046845 -2.932065

H 1.372182 1.663191 -1.292878

C 3.648678 2.764473 -4.257739

H 4.96457 1.163407 -3.666921

C 2.454365 3.440207 -3.992438

H 4.285084 3.076714 -5.087181

H 2.158895 4.283056 -4.619976

H 4.737946 0.425405 1.261767

H 0.697099 3.550368 -2.722634

H -0.293038 4.786383 -0.764935

C -1.095938 5.685473 1.036961

C 4.141318 2.825546 2.417961

O 1.138266 -1.337651 1.451437

C 1.317077 -2.444956 2.144605

C 1.712885 -2.41447 3.514967

C 1.100143 -3.72058 1.576815

C 1.814292 -3.608435 4.231038

C 1.208782 -4.897142 2.314597

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H 0.999167 -5.852386 1.823917

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C -0.817593 -1.716848 -2.64467

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C -1.100281 -2.296141 -3.886788

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H -1.613146 -4.066032 -5.019483

O -2.487821 -0.402418 -0.097862

O -0.192017 0.552105 0.287149

O 2.002249 4.267465 0.079922

N -2.081949 3.850673 -0.244152

C -2.195621 2.965822 -1.2605

O -3.390832 2.335415 -1.203048

O -1.379426 2.768439 -2.131185

C -3.706463 1.48121 -2.291938

H -3.491466 2.001917 -3.238574

H -2.838116 3.859876 0.435416

C -3.730199 -0.463239 0.433856

C -4.271443 0.524735 1.278577

C -4.596547 -1.497658 0.018713

C -5.568242 0.455085 1.789038

C -5.89026 -1.560096 0.536608

C -6.372745 -0.615845 1.443787

H -5.921306 1.254546 2.438883

H -6.538552 -2.375322 0.208452

H -7.383816 -0.69656 1.84324

C -1.414818 -1.143385 2.268767

C -2.120175 -2.318276 2.528509

C -1.060183 -0.282931 3.311697

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C -1.425749 -0.596695 4.616672

C -2.130388 -1.773904 4.883249

H -3.017059 -3.556852 4.046649

H -1.150286 0.074631 5.431844

H -2.407747 -2.021649 5.909432

O -0.673899 -2.074152 -0.236645

N -1.132043 -4.82233 -0.533516

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O -1.83429 -4.590349 0.419947

H -2.380226 -2.993284 1.714503

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N -3.53672 1.742223 1.575843

O -2.334259 1.689843 1.668905

O -4.178055 2.767646 1.704202

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H 0.838539 -6.171753 5.241999

H 1.574745 -7.019262 3.866855

H 2.59888 -6.174572 5.050635

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H -1.040009 0.390483 -2.098824
H 0.571712 -0.26674 -1.935901
H -0.082252 0.071789 -3.563893
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H -3.602307 -2.013439 -1.819533
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H 3.150678 -0.939472 4.169579
H 1.599414 -0.269748 3.626413
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H 6.071578 1.838381 2.012405
H 5.845363 3.400765 1.179179
H 6.187147 3.35547 2.922517
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H 4.285774 2.692404 4.581554
H 2.81177 1.953215 3.909871
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H 0.930642 5.766731 1.855782

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H 0.02964 7.303901 1.926907

C -1.712533 5.257847 2.373042

H -1.909742 6.145454 2.993408

H -2.665186 4.719145 2.256044

H -1.022296 4.601893 2.923646

C -2.03688 6.640521 0.295455

H -3.040585 6.212184 0.162299

H -2.142065 7.579025 0.86056

H -1.637948 6.888813 -0.701079

TS1-endo

C -0.828502 4.404766 -0.024497

N 0.020581 3.414918 0.615139

H -0.443539 2.574679 0.953227

C 1.375926 3.373539 0.440236

N 1.984294 2.312755 1.082987

H 1.404534 1.473957 1.168833

C 3.420688 2.120539 0.997626

H 3.767573 2.552998 0.03946

H 2.149753 -0.643944 0.340262

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N 3.001503 -0.138306 -0.030383

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P 3.525666 -0.271569 -1.567686

C 2.833458 -1.799556 -2.229644

C 2.457218 -2.820639 -1.348685

C 2.729809 -1.978385 -3.61539

C 1.987343 -4.028609 -1.865232

H 2.506913 -2.667728 -0.268107

C 2.264414 -3.190559 -4.118757

H 3.004094 -1.174314 -4.301503

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H 1.530717 -5.164746 -3.639445

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C 6.096379 0.802138 -1.513656

C 7.346925 -1.695602 -1.395814

H 5.366843 -2.540362 -1.540597

C 7.4827 0.720904 -1.398679

H 5.61034 1.779996 -1.559888

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H 7.8355 -2.669867 -1.352245

H 8.075844 1.635377 -1.352842

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C 1.921801 1.84598 -2.326844

C 3.821598 1.413981 -3.786127

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H 1.328461 1.602467 -1.439264

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H 4.722477 0.845271 -4.027363

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H 3.997786 2.693993 -5.508506

H 1.953062 4.002691 -4.960416

H 4.783553 0.436079 0.937954

H 0.61244 3.432126 -2.923453

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C 4.209783 2.845003 2.134506

O 1.126596 -1.356529 1.431779

C 1.519839 -1.907925 2.565289

C 1.554021 -3.318984 2.75684

C 1.932912 -1.108375 3.656194

C 1.988937 -3.840799 3.977443

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P -0.919445 -0.736579 0.64306

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C -1.276301 -2.418462 -3.801621

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H -1.749983 -5.637724 -2.815485

H -1.876595 -4.197361 -4.876036

O -2.487951 -0.490991 -0.034158

O -0.19641 0.50222 0.250997

O 1.99194 4.223492 -0.188393

N -2.10053 3.800024 -0.351799

C -2.239966 2.879929 -1.333294

O -3.428943 2.246275 -1.217598

O -1.448518 2.656934 -2.220455

C -3.768386 1.342134 -2.257615

H -3.569817 1.81486 -3.232471

H -2.831299 3.821378 0.354775

C -3.714366 -0.514885 0.530156

C -4.226985 0.505003 1.356997

C -4.605313 -1.552797 0.174516

C -5.505793 0.45714 1.91499

C -5.879209 -1.593714 0.740447

C -6.325376 -0.621187 1.636728

H -5.83273 1.280134 2.548949

H -6.54194 -2.415265 0.460304

H -7.320778 -0.685657 2.076384

C -1.382993 -1.122479 2.330418

C -2.078717 -2.29248 2.637924

C -1.037501 -0.21777 3.338334

C -2.436075 -2.553558 3.961253

C -1.409435 -0.478412 4.654326

C -2.10561 -1.647206 4.967508

H -2.975729 -3.470698 4.202366

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O -0.657842 -2.140638 -0.181221

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N -3.487648 1.734967 1.580728
O -2.282314 1.692634 1.624165
O -4.129197 2.762135 1.698612
C 2.860237 -3.657684 6.346814
H 2.054781 -4.239749 6.82171
H 3.705845 -4.345792 6.191442
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H -0.180014 -0.075091 -3.572008
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H -3.474798 -3.297933 -0.357906
H -5.049033 -3.155497 -1.177206
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H 0.313592 -4.908379 1.952522
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H 1.896537 -0.024079 3.529652
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C -6.097542 1.574024 -1.259235
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C -7.435427 1.175723 -1.20035
H -5.725082 2.359136 -0.599176
C -7.026951 -0.47694 -2.908631
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H -8.112418 1.666884 -0.498381
H -7.38436 -1.280963 -3.554802
H -8.949785 -0.15732 -1.971744
C 3.919815 2.209685 3.499293
H 4.321999 1.18913 3.587123
H 4.375959 2.813114 4.29926
H 2.834315 2.173462 3.683542

C 5.712814 2.778953 1.834862

H 6.10683 1.752098 1.856787

H 5.935755 3.214727 0.847358

H 6.271427 3.357853 2.586505

C 3.802904 4.320924 2.201089

H 3.942782 4.822638 1.234533

H 2.74433 4.425803 2.481998

H 4.407261 4.834978 2.964961

C -1.642581 5.262192 2.220877

H -1.818588 6.162238 2.829606

H -2.598226 4.721031 2.148071

H -0.932704 4.617773 2.760099

C 0.253006 6.393907 1.070513

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H -3.049226 6.167412 0.038643

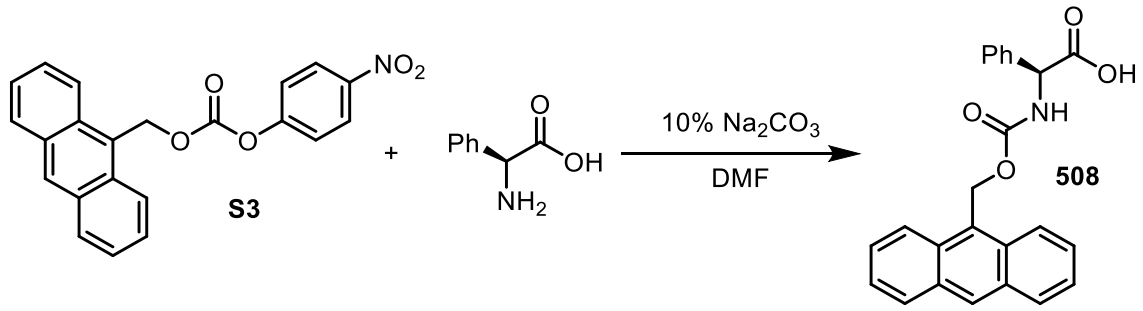
H -2.130621 7.550068 0.677163

H -1.679434 6.829132 -0.886853

5.4 Experimental Details for Chapter 4

5.4.1 Synthesis of pre-catalysts and catalysts:

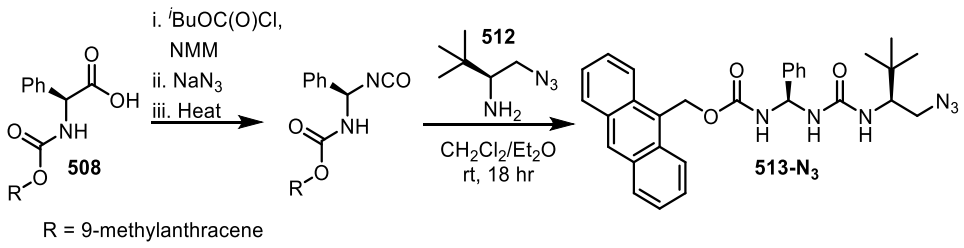
(*S*)-2-(((anthracen-9-ylmethoxy)carbonyl)amino)-2-phenylacetic acid (**508**)



To a stirred solution of *S*-phenyl glycine (605 mg, 5.0 mmol, 1.0 eq) in 10% aqueous Na_2CO_3 (10.40 mL) and DMF (8.0 mL) at 0 °C was slowly added the 4-nitrophenylcarbonate (150 g, 4.00 mmol, 1.0 eq) in DMF (12.0 mL). After stirring for one hour at this temperature, the reaction mixture was warmed to room temperature for 18 hr, diluted by the addition of H_2O (50.0 mL) and extracted with Et_2O (3 x 20.0 mL). The aqueous layer was cooled in an ice bath and acidified to pH 1 by the addition of concentrated HCl and then extracted with EtOAc (3 x 25.0 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography 9:1 to 1:1 Pet:EtOAc afforded the **508** as a pale-yellow solid in 60% yield (481 mg, 1.25 mmol, 31% yield).

$[\alpha]_D^{25}$ = +20.3 (c = 0.48, $CHCl_3$); **Mp** 115 °C (pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 13.2 Hz, 1H, ArC<u>H</u>), 8.34 (d, *J* = 8.8 Hz, 1H, ArC<u>H</u>), 8.19 – 8.12 (m, 1H, ArC<u>H</u>), 8.08 (s, 1H, ArC<u>H</u>), 8.02 (d, *J* = 7.7 Hz, 2H, ArC<u>H</u>), 7.63 – 7.30 (m, 5H, ArC<u>H</u>), 7.11 (s, 2H, ArC<u>H</u>), 6.94 – 6.79 (m, 1H, ArC<u>H</u>), 6.17 (m, 2H, C<u>H</u>$_2$-anthracenyl), 5.82 – 5.69 (m, 1H, N<u>H</u>), 5.43 (d, *J* = 7.1 Hz, 1H, C<u>H</u>Ph); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 183.4 (<u>C</u>=O), 173.4 (<u>C</u>=O), 163.1 (Ar<u>C</u>), 161.5 (Ar<u>C</u>), 155.9 (Ar<u>C</u>), 136.2 (Ar<u>C</u>), 134.3 (Ar<u>C</u>H), 131.5 (Ar<u>C</u>), 131.2 (Ar<u>C</u>H), 129.4 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 125.3 (Ar<u>C</u>H), 124.1 (Ar<u>C</u>H), 59.9 (benzylic <u>C</u>H$_3$), 58.0 (NH<u>C</u>HCOOH); **IR** ν_{max}/cm^{-1}: 2980, 1686 (C=O), 1643 (C=O) 1515, 1334, 1285, 1251, 728, 694; **HRMS** (ESI+): calcd. for $C_{24}H_{19}NO_4Na$ $[M+Na]^+$ 408.1206, found 408.1207.

anthracen-9-ylmethyl ((*S*)-(3-((*S*)-1-azido-3,3-dimethylbutan-2-yl)ureido)(phenyl)methyl)carbamate (**513-N_3**)

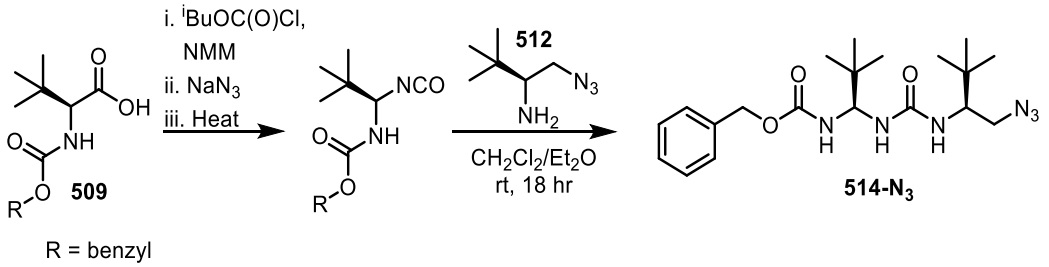


According to a modified literature procedure,[22] to a solution of **508** (385 mg, 1.00 mmol, 1.0 eq) in THF (4.00 mL) at −20 °C were added sequentially isobutyl chloroformate (130 μL, 1.00 mmol, 1.0 eq) and *N*-methylmorpholine (110 μL, 1.00 mmol, 1.0 eq) and stirring was maintained for 20 min. To the reaction mixture was added sodium azide (98.0 mg, 1.50 mmol, 1.5 eq) in H_2O (1.00 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 5.0 mL. The reaction mixture was heated to reflux for 2 hr and then the reaction mixture was cooled to room temperature and the crude amino azide (156 mg, 1.00 mmol, 1.0 eq) as a solution in Et_2O (4.00 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 hr and then the volatiles removed *in vacuo*. The crude was triturated in toluene at 100 °C, cooled to room temperature, filtered, and washed with pentane to obtain **513-N_3** as a colourless solid in 29% yield (153 mg, 0.29 mmol).

$[\alpha]_D^{25}$ = + 3.8 (c = 0.84, DMSO); **Mp** 180 °C (toluene); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.69 (s, 1H, ArC<u>H</u>), 8.39 (dd, *J* = 8.6, 4.2 Hz, 2H, ArC<u>H</u>), 8.19 – 8.06 (m, 3H, ArC<u>H</u>+ N<u>H</u>), 7.64 – 7.48 (m, 5H, ArC<u>H</u>+ N<u>H</u>), 7.30 (dd, *J* = 23.2, 5.8 Hz, 6H, ArC<u>H</u> +N<u>H</u>), 6.15 – 6.00 (m, 2H, C<u>H</u>$_2$-anthracenyl), 3.61 (tt, *J* = 6.9, 3.1 Hz, 1H, C<u>H</u>Ph), 3.42 (ddd, *J* = 18.6, 12.7, 3.5 Hz, 1H, $CH_aC\underline{H}_bN_3$), 3.16 (ddd, *J* = 16.3, 12.7, 9.2 Hz, 1H, $C\underline{H}_aCH_bN_3$), 0.85 (d, *J* = 4.3 Hz, 9H, C($C\underline{H}_3$)$_3$); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 156.7 (C=O), 155.3 (C=O), 141.8 (Ar<u>C</u>), 130.9 (Ar<u>C</u>H), 130.4 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>), 128.2 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>), 127.3 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>), 126.6 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>), 125.8 (Ar<u>C</u>H), 125.2 (Ar<u>C</u>H), 124.1 (Ar<u>C</u>H), 56.9 (<u>C</u>HPh), 51.8 (<u>C</u>H$_2$-anthracenyl), 51.7 (<u>C</u>H-*t*-Bu), 34.2, (<u>C</u>H$_2$N$_3$), 33.9

(C(CH$_3$)$_3$, 26.4 (C(CH$_3$)$_3$; **IR** ν_{max}/cm^{-1}: 3312, 2981, 1688 (C=O), 1642 (C=O), 1518, 1496, 1251, 1061, 1027, 729, 696; **HRMS** (ESI+): calcd. for $C_{30}H_{33}N_6O_3$ $[M+H]^+$ 525.2609, found 525.2610.

benzyl ((*S*)-1-(3-((*S*)-1-azido-3,3-dimethylbutan-2-yl)ureido)-2,2-dimethylpropyl)carbamate (**514-N$_3$**)

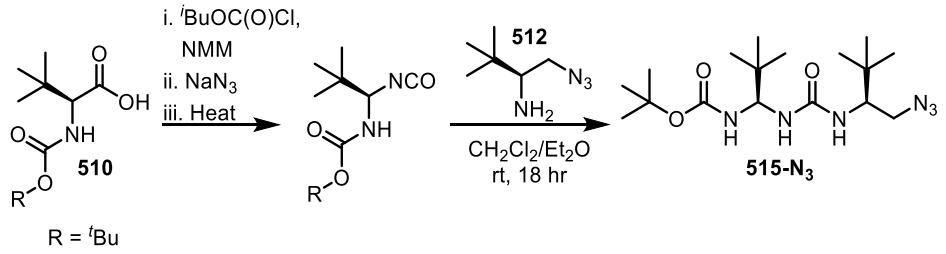


According to a modified literature procedure,[22] to a solution of CBZ-*S*-*tert*-leucine (**509**, 265 mg, 1.00 mmol, 1.0 eq) in THF (4.00 mL) at −20 °C were added sequentially isobutyl chloroformate (130 μL, 1.00 mmol, 1.0 eq) and *N*-methylmorpholine (110 μL, 1.00 mmol, 1.0 eq) and stirring was maintained for 20 min. To the reaction mixture was added sodium azide (98.0 mg, 1.50 mmol, 1.5 eq) in H_2O (1.00 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 hr and then the reaction mixture was cooled to room temperature and the crude amino azide (156 mg, 1.00 mmol, 1.0 eq) as a solution in Et_2O (4.00 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 hr and then the volatiles removed *in vacuo*. The crude was triturated in toluene at 100 °C, cooled to room temperature, filtered, and washed with pentane to obtain **514-N$_3$** as a colourless solid in 20% yield (101 mg, 0.20 mmol).

$[\alpha]_D^{25}$ = −11.4 (c = 0.27, DMSO); **Mp** 275 °C (toluene); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.34 – 7.15 (m, 5H, PhH), 6.45 (d, J = 52.5 Hz, 1H, NH), 6.28 – 6.02 (m, 3H, CH_2Ph + NH), 5.04 (s, 1H, NH), 4.22 (m, 1H, NCHN), 3.60 (td, J = 9.2, 3.2 Hz, 1H, CHC(CH$_3$)$_3$), 3.43 – 3.33 (m, 1H, CH$_a$CH$_b$N$_3$), 3.14 (ddd, J = 27.0, 12.7, 9.2 Hz, 1H, CH$_a$CH$_b$N$_3$), 0.88 (s, 9H, C(CH$_3$)$_3$), 0.85 (s, 9H, C(CH$_3$)$_3$); **^{13}C NMR** (151 MHz, DMSO-d_6) δ 157.5 (C=O), 140.7 (ArC), 128.2 (ArCH), 126.9 (ArCH), 126.6 (ArCH), 63.9 (NCHN), 57.2 (CHC(CH$_3$)$_3$), 51.7 (CH$_2$-N$_3$), 42.8 (benzyl CH$_2$), 34.2 (C(CH$_3$)$_3$), 34.0 (C(CH$_3$)$_3$), 26.4

(C(<u>C</u>H$_3$)$_3$), 25.4 (C(<u>C</u>H$_3$)$_3$); **IR** ν_{max}/cm^{-1}: 3314, 2969, 2095, 1638 (C=O), 1550 (C=O), 1244, 729, 697; **HRMS** (ESI+): calcd. for $C_{20}H_{33}N_6O_3$ [M+H]$^+$ 405.2609, found 405.2611.

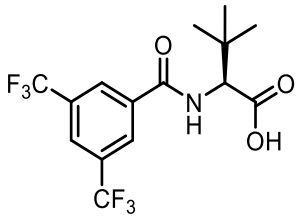
<u>*tert*-butyl ((*S*)-1-(3-((*S*)-1-azido-3,3-dimethylbutan-2-yl)ureido)-2,2-dimethylpropyl)carbamate (**515-N$_3$**)</u>



According to a modified literature procedure,[22] to a solution of Boc-*S*-*tert*-leucine (**510**, 231 mg, 1.00 mmol, 1.0 eq) in THF (4.00 mL) at −20 °C were added sequentially isobutyl chloroformate (130 μL, 1.00 mmol, 1.0 eq) and *N*-methylmorpholine (110 μL, 1.00 mmol, 1.0 eq) and stirring was maintained for 20 min. To the reaction mixture was added sodium azide (98.0 mg, 1.50 mmol, 1.5 eq) in H_2O (1.00 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 hr and then the reaction mixture was cooled to room temperature and the crude amino azide (156 mg, 1.00 mmol, 1.0 eq) as a solution in Et_2O (4.00 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 hr and then the volatiles removed *in vacuo*. The crude was recrystallized from EtOAc, filtered, and washed with pentane to obtain **515-N$_3$** as a colourless solid in 41% yield (113 mg, 0.41 mmol).

[α]$_D^{25}$ = − 49.2 (c = 0.94, $CHCl_3$); **Mp** 206 °C (EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.21 (d, *J* = 9.4 Hz, 1H, N<u>H</u>), 4.98 (d, *J* = 10.0 Hz, 1H, N<u>H</u>), 4.91 – 4.72 (m, 2H, NC<u>H</u>N + N<u>H</u>), 3.93 (td, *J* = 9.1, 3.4 Hz, 1H, C<u>H</u>C(CH$_3$)), 3.42 (dd, *J* = 12.6, 3.5 Hz, 1H, CH$_a$C<u>H</u>$_b$N$_3$), 3.26 (dd, *J* = 12.6, 8.9 Hz, 1H, C<u>H</u>$_a$CH$_b$N$_3$), 1.45 (s, 9H, C(C<u>H</u>$_3$)$_3$), 1.00 (s, 9H, C(C<u>H</u>$_3$)$_3$), 0.96 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.0 (C=O), 156.3 (C=O), 80.9 (Boc-<u>C</u>O), 66.5 (NC<u>H</u>N), 58.5 (<u>C</u>HC(CH$_3$)$_3$), 52.6 (<u>C</u>H$_2$), 35.4 (<u>C</u>(CH$_3$)$_3$), 34.3 (<u>C</u>(CH$_3$)$_3$), 28.6(Boc-C(<u>C</u>H$_3$)$_3$), 26.8(C(<u>C</u>H$_3$)$_3$), 25.7(C(<u>C</u>H$_3$)$_3$); **IR** ν_{max}/cm^{-1}: 2969, 2086, 1633 (C=O), 1558 (C=O), 1246, 739, 701, 697; **HRMS** (ESI+): calcd. for $C_{17}H_{35}N_6O_3$ [M+H]$^+$ 371.2765, found 371.2769.

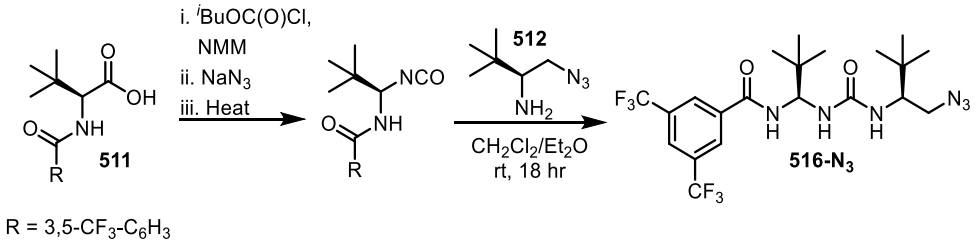
(*S*)-2-(3,5-bis(trifluoromethyl)benzamido)-3,3-dimethylbutanoic acid (**511**)



To a vigorously stirred solution of (*S*)-*tert*-leucine (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 (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 2x 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 which was further purified by FCC (CH_2Cl_2 to 9:1 CH_2Cl_2:MeOH) to afford pure **511** in 44% yield (2.51 g, 6.70 mmol)

$[\alpha]_D^{25}$ = +20.0 (c = 0.63, $CHCl_3$); **Mp** 62 °C (pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.63 (s, 1H, COO<u>H</u>), 8.22 (s, 2H, *ortho*-ArC<u>H</u>), 8.01 (s, 1H, *para*-ArC<u>H</u>), 7.02 (s, 1H, N<u>H</u>), 4.75 (d, *J* = 9.1 Hz, 1H, C<u>H</u>C(CH_3)), 1.10 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4 (C=O), 165.4 (C=O), 136.0 (Ar<u>C</u>), 132.5 (q, *J* = 33.4 Hz, <u>C</u>F_3), 125.7 (Ar<u>C</u>), 124.3 (d, *J* = 4.8 Hz, *ortho*-Ar<u>C</u>H), 121.6 (d, *J* = 4.6 Hz, *para*-Ar<u>C</u>H), 35.1 (<u>C</u>(CH_3)$_3$), 26.8 (C(<u>C</u>H$_3$)$_3$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.03; **IR** ν_{max}/cm^{-1}: 3314, 2970, 2695, 1640 (C=O), 1546, 1277, 1132, 670, 682; **HRMS** (ESI+): calcd. for $C_{15}H_{16}NO_3F_6$ $[M+H]^+$ 372.1029, found 372.1028.

N-((*R*)-1-(3-((*S*)-1-azido-3,3-dimethylbutan-2-yl)ureido)-2,2-dimethylpropyl)-3,5-bis(trifluoromethyl)benzamide (**516-N_3**)



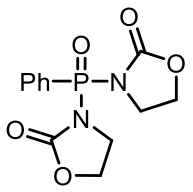
According to a modified literature procedure,[22] to a solution of **511** (371 mg, 1.00 mmol, 1.0 eq) in THF (4.00 mL) at −20 °C were added sequentially isobutyl chloroformate (130 μL, 1.00 mmol, 1.0 eq) and *N*-methylmorpholine (110 μL, 1.00 mmol, 1.0 eq) and stirring was maintained for 20 min. To the reaction mixture was added sodium azide (98.0 mg, 1.50 mmol, 1.5 eq) in H_2O (1.00 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 hr and then the reaction mixture was cooled to room temperature and the crude amino azide (156 mg, 1.00 mmol, 1.0 eq) as a solution in Et_2O (4.00 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 hr and then the volatiles removed *in vacuo*. The crude was recrystallised from hot EtOAc, cooled to room temperature, filtered, and washed with pentane to obtain **516-N_3** as a colourless solid in 31% yield (246 mg, 0.31 mmol).

$[\alpha]_D^{25}$ = −2.00 (c = 0.95, DMSO); **Mp** 248 °C (EtOAc); **^{1}H NMR** (400 MHz, DMSO-d_6) 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, $CH_aCH_bN_3$), 3.22 – 3.10 (m, 1H, $CH_aCH_bN_3$), 0.95 (s, 9H, C(CH_3)$_3$), 0.86 (s, 9H, C(CH_3)$_3$; **^{13}C NMR** (101 MHz, DMSO-d_6) 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.

5.4.2 Synthesis of substrates for optimisation

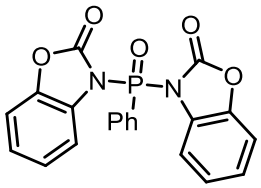
3,3'-(phenylphosphoryl)bis(oxazolidin-2-one) (**495**)



According to a modified literature procedure,[30] oxazolidinone (2.61 g, 15.0 mmol) was dissolved in THF (12.0 mL) and cooled to 0 °C. Et_3N (8.40 mL, 30 mmol) was then added followed by the dropwise addition of phenylphosphoryl dichloride (2.13 mL, 15.0 mmol) in 12.0 mL THF. The resulting solution was allowed to warm to room temperature and then heated to 50 °C for 16 hr. The resulting suspension was poured over ice cold water (100 mL) and extracted with CH_2Cl_2 (3 x 50.0 mL). The combined organic phases were washed with H_2O (30.0 mL) and then brine (30.0 mL), dried over $MgSO_4$, filtered, and reduced *in vacuo* to give the crude product which was purified by recrystallisation from toluene affording **495** in 33% yield (1.47 g, 5.01 mmol).

Mp 148 °C (from toluene); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 – 8.05 (m, 2H, ArC<u>H</u>), 7.70 – 7.63 (m, 1H, *para*-Ph-C<u>H</u>), 7.60 – 7.50 (m, 2H, ArC<u>H</u>), 4.54 – 4.35 (m, 4H, $NCH_2C\underline{H}_2O$), 3.94 (tdd, *J* = 9.0, 6.8, 2.1 Hz, 2H, $NC\underline{H}_2CH_2O$), 3.80 (td, *J* = 8.9, 6.9 Hz, 2H, $NC\underline{H}_2CH_2O$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.5 (d, *J* = 6.2 Hz, <u>C</u>=O), 134.3 (d, *J* = 3.2 Hz, *para*-Ph-<u>C</u>H), 132.5 (d, *J* = 11.5 Hz, Ar<u>C</u>H), 129.2 (d, *J* = 15.4 Hz, Ar<u>C</u>H), 126.5 (d, *J* = 166.9 Hz, <u>C</u>P), 64.4 (d, *J* = 8.8 Hz, $NCH_2\underline{C}H_2O$), 45.1 (d, *J* = 4.5 Hz, $N\underline{C}H_2CH_2O$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 10.51; **IR** υ_{max}/cm^{-1}: 3319, 2969, 2095, 1641 (C=O), 1546, 1275, 1260, 1230 (P=O), 1185, 1130, 1055, 695; **HRMS** (ESI+): calcd. for $C_{12}H_{14}O_5N_2P$ 297.0635 $[M+H]^+$, found 297.0635.

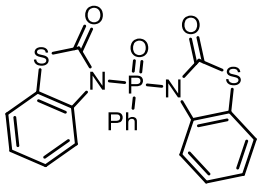
3,3'-(phenylphosphoryl)bis(benzo[d]oxazol-2(3H)-one) (**496**)



According to a modified literature procedure,[30] benzoxazolidinone (5.53 g, 15.0 mmol) was dissolved in toluene (12.0 mL) and cooled to 0 °C. Et_3N (8.40 mL, 30 mmol) was then added followed by the dropwise addition of phenylphosphoryl dichloride (2.13 mL, 15.0 mmol) in 12.0 mL toluene. The resulting solution warmed to room temperature and stirred for 16 hr. The resulting suspension was poured over ice cold water (200 mL) resulting in the precipitation of the crude product which was filtered and washed with H_2O (2 x 100 mL), cold EtOH (50.0 mL) and then pentane (50.0 mL). Recrystallisation from toluene affording the pure **496** in 53% yield (5.57 g, 7.95 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (ddt, *J* = 15.6, 7.0, 1.4 Hz, 2H), 7.86 – 7.75 (m, 1H), 7.65 (ddd, *J* = 8.8, 7.2, 4.9 Hz, 2H), 7.39 – 7.33 (m, 2H), 7.28 – 7.20 (m, 4H), 7.14 (ddd, *J* = 7.9, 7.1, 1.9 Hz, 2H).;**^{13}C NMR** (101 MHz, $CDCl_3$) δ 13C NMR (101 MHz, CDCl3) δ 152.1 (d, *J* = 5.8 Hz), 143.6 (d, *J* = 10.0 Hz), 135.5 (d, *J* = 3.4 Hz), 133.4 (d, *J* = 12.4 Hz), 130.4 – 127.9 (m), 124.7, 124.6 (d, *J* = 166.4 Hz), 113.7, 110.6; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 8.05. Data was consistent with that presented in the literature.[30]

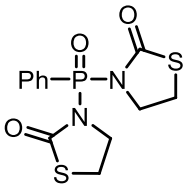
3,3'-(phenylphosphoryl)bis(benzo[d]thiazol-2(3H)-one)(**497**)



According to a literature procedure,[30] benzothioazolidinone (5.53 g, 15.0 mmol) was dissolved in MeCN (12.0 mL) and cooled to 0 °C. Et_3N (8.40 mL, 30 mmol) was then added followed by the dropwise addition of phenylphosphoryl dichloride (2.13 mL, 15.0 mmol) in 12.0 mL MeCN. The resulting solution warmed to room temperature and stirred for 16 hr. The resulting suspension was poured over ice cold water (200 mL) resulting in the precipitation of the crude product which was filtered and washed with H_2O (2 x 100 mL), cold EtOH (50.0 mL) and then pentane (50.0 mL). Recrystallisation from toluene affording the pure **497** in 45% yield (3.15 g, 6.75 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 15.7, 7.7 Hz, 2H), 7.93 – 7.82 (m, 2H), 7.77 – 7.65 (m, 1H), 7.55 (td, *J* = 7.6, 4.8 Hz, 2H), 7.39 (p, *J* = 4.7 Hz, 2H), 7.22 (dt, *J* = 6.1, 3.7 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.2, 135.9 (d, *J* = 5.8 Hz), 134.7 (d, *J* = 3.5 Hz), 133.1 (d, *J* = 12.5 Hz), 128.9 (d, *J* = 16.7 Hz), 126.9, 126.6 (d, *J* = 163.9 Hz), 125.2, 123.9 (d, *J* = 9.6 Hz), 122.6, 115.9; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 10.89. Data was consistent with that presented in the literature.[30]

3,3'-(phenylphosphoryl)bis(oxazolidin-2-one)(**505**)

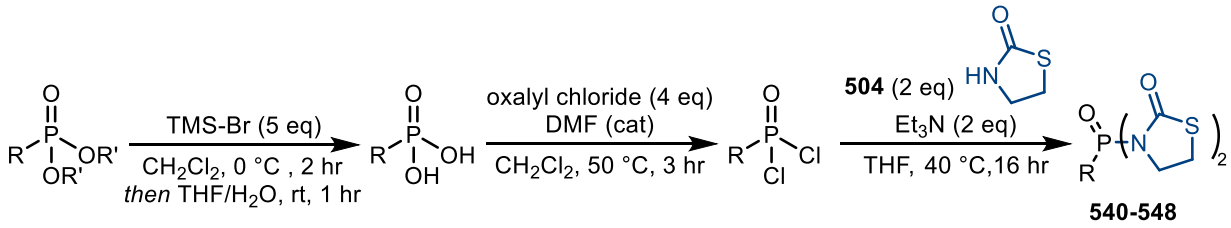


According to a modified literature procedure,[30] benzothioazolidinone (5.53 g, 15.0 mmol) was dissolved in THF (12.0 mL) and cooled to 0 °C. Et_3N (8.40 mL, 30.0 mmol) was then added followed by the dropwise addition of phenylphosphoryl dichloride (2.13 mL, 15.0 mmol) in 12.0 mL THF. The resulting solution warmed to room temperature 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 (20.0 mL), filtered, washed with cold EtOH (10.0 mL) and then pentane (50.0 mL). Recrystallisation from toluene affording the pure **505** in 50% yield (2.46 g, 7.50 mmol).

Mp 160 °C (from toluene); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (dt, *J* = 14.1, 6.7 Hz, 2H, ArC<u>H</u>), 7.66 – 7.59 (m, 1H, *para*-PhC<u>H</u>), 7.53 (dp, *J* = 7.8, 3.7 Hz, 2H, ArC<u>H</u>), 4.04 – 3.81 (m, 4H, NC<u>H$_2$</u>CH$_2$S), 3.44 – 3.25 (m, 4H, NCH$_2$C<u>H$_2$</u>S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8 (C=O), 134.0 (d, *J* = 3.2 Hz, *para*-Ph-<u>C</u>H), 132.3 (d, *J* = 11.5 Hz, ArC<u>H</u>), 129.1 (d, *J* = 15.5 Hz, ArC<u>H</u>), 127.9 (d, *J* = 162.9 Hz, <u>C</u>P), 49.1 (d, *J* = 6.0 Hz, N<u>C</u>H$_2$CH$_2$S), 29.3 (d, *J* = 8.9 Hz, NCH$_2$<u>C</u>H$_2$S); **^{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 $C_{12}H_{13}O_3N_2NaPS2$ 350.9997 $[M+Na]^+$, found 350.9998.

5.4.3 Synthesis of P(V) electrophiles

5.4.3.1 General Procedure VIII: Synthesis of P(V) electrophiles



General Procedure VIII-A: Substrate synthesis from phosphoryl dichloride

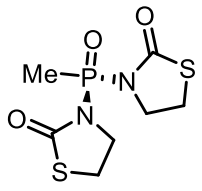
The corresponding phosphonic dichloride (1 eq) and 1,3-thiazolidin-2-one (2 eq) were dissolved in THF and cooled to 0 °C. Et_3N (2 eq) was added dropwise resulting in the formation of a Colourless precipitate. The reaction mixture was then allowed to warm to room temperature or 40 °C (as specified in 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 VIII-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 VII-B**.

5.4.3.2 P(V) electrophiles

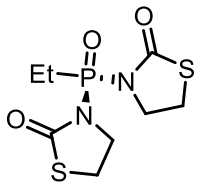
Bis(1,3-thiazolidin-2-one) methylphosphonate (**540**)



540 was synthesised following **General Procedure VIII-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. Colourless solid (0.34 g, 1.30 mmol, 17% yield).

Mp 170 °C (from pentane); **^{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, $C\underline{H_3}P$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.3 ($\underline{C}$=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, $\underline{C}H_3P$); **^{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.

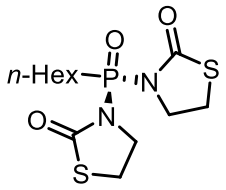
Bis(1,3-thiazolidin-2-one) ethylphosphonate (**541**)



541 was synthesised following **General Procedure VIII-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. Colourless solid (0.91 g, 3.20 mmol, 43% yield).

Mp 142 °C; (from pentane); **^{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 ($\underline{C}$=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.

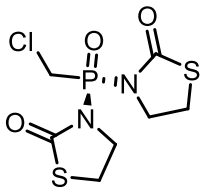
Bis(1,3-thiazolidin-2-one) hexylphosphonate (**542**)



542 was synthesised following **General Procedure VIII-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. Colourless solid (0.28 g, 0.76 mmol, 80% yield).

Mp 60 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.07 – 3.99 (m, 4H, CH_3CH_2), 3.47 – 3.33 (m, 4H, $CH_3CH_2CH_2$, $CH_3CH_2CH_2$), 2.40 – 2.24 (m, 2H, CH_2CH_2P), 1.73 – 1.58 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.50 – 1.37 (m, 2H, CH_2P), 1.36 – 1.23 (m, 4H, NCH_2CH_2S), 0.96 – 0.81 (m, 3H, NCH_2CH_2S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.1 (C=O), 47.9 (d, J = 4.3 Hz, NCH_2CH_2S), 31.2 (CH_3CH_2), 30.1 (d, J = 18.2 Hz, CH_2CH_2P), 29.1 (d, J = 7.9 Hz, NCH_2CH_2S), 27.8 (d, J = 108.1 Hz, CH_2P), 22.4 ($CH_3CH_2CH_2$), 20.8 (d, J = 5.0 Hz, $CH_2CH_2CH_2P$), 14.0 (CH_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.

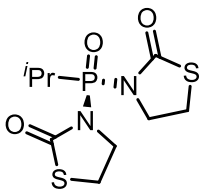
Bis(1,3-thiazolidin-2-one) chloromethylphosphonate (**543**)



543 was synthesised following **General Procedure VIII-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. Colourless solid (0.49 g, 1.60 mmol, 41% yield).

Mp 160 °C (pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.25 (d, *J* = 8.1 Hz, 2H, $ClC\underline{H_2}P$), 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, $\underline{C}$=O), 47.6 (d, *J* = 4.0 Hz, $N\underline{C}H_2\underline{C}H_2S$), 36.8 (d, *J* = 121.7 Hz, $NCH_2\underline{C}H_2S$), 29.4 (d, *J* = 8.1 Hz, $Cl\underline{C}H_2P$); **^{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.

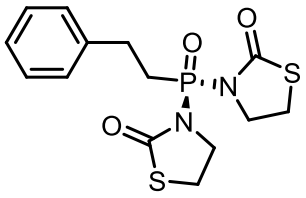
Bis(1,3-thiazolidin-2-one) isopropylphosphonate (**544**)



544 was synthesised following **General Procedure VIII-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. Colourless solid (0.17 g, 0.59 mmol, 15% yield).

Mp 130 °C (pentane); **^{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 (<u>C</u>=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.

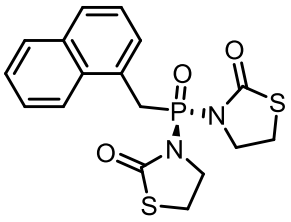
Bis(1,3-thiazolidin-2-one) phenylethylphosphonate (**545**)



545 was synthesised according to **General Procedure VIII-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:MeOH, off-white solid (0.33 g, 0.94 mmol, 47% yield).

Mp 204 °C(from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 4H, Ar<u>H</u>), 4.01 – 3.84 (m, 4H, NC<u>H$_2$</u>CH_2S), 3.39 – 3.18 (m, 4H, NCH_2C<u>H$_2$</u>S), 3.10 – 2.96 (m, 2H, ArC<u>H$_2$</u>), 2.79 – 2.63 (m, 2H, $ArCH_2$C<u>H$_2$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (<u>C</u>=O), 139.4 (d, *J* = 14.6 Hz, Ar<u>C</u>CH_2), 128.8 (Ar<u>CH</u>), 128.3 (Ar<u>C</u>H) 126.8 (Ar<u>C</u>H), 47.6 (d, *J* = 4.3 Hz, N<u>C</u>H_2CH_2S), 29.2 (d, *J* = 107.7 Hz, <u>C</u>H_2P), 28.9 (d, *J* = 8.1 Hz, NCH_2<u>C</u>H_2S), 27.2 (d, *J* = 4.6 Hz, Ar<u>C</u>H_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.

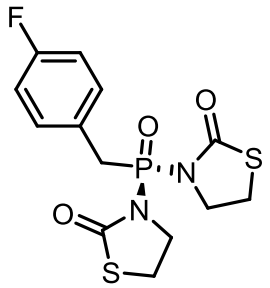
Bis(1,3-thiazolidin-2-one) (1-naphthylmethyl)phosphonate (**546**)



546 was synthesised according to **General Procedure VIII-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 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 8.5, 1.2 Hz, 1H, ArC<u>H</u>), 7.89 – 7.78 (m, 2H, ArC<u>H</u>), 7.64 – 7.55 (m, 1H, ArC<u>H</u>), 7.56 – 7.42 (m, 3H, ArC<u>H</u>), 4.31 (d, *J* = 19.2 Hz, 2H, C<u>H</u>$_2$P), 3.90 – 3.52 (m, 4H, NC<u>H</u>$_2$CH$_2$S), 3.33 – 2.98 (m, 4H, NCH$_2$C<u>H</u>$_2$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.34 (d, *J* = 1.7 Hz, <u>C</u>=O), 133.91 (d, *J* = 3.4 Hz, Ar<u>C</u>), 132.41 (d, *J* = 5.3 Hz, Ar<u>C</u>), 129.19 (d, *J* = 8.1 Hz. Ar<u>C</u>H), 128.7 (d, J = 4.8 Hz, Ar<u>C</u>H) 128.6 (s, Ar<u>C</u>H), 126.76 (Ar<u>C</u>), 126.18 (Ar<u>C</u>H), 125.46 (d, *J* = 11.0 Hz, Ar<u>C</u>H), 125.33 (d, *J* = 4.7 Hz, Ar<u>C</u>H), 124.33 (d, *J* = 2.1 Hz, Ar<u>C</u>H), 47.68 (d, *J* = 3.9 Hz, N<u>C</u>H$_2$CH$_2$S), 32.09 (d, *J* = 103.9 Hz, <u>C</u>H$_2$P), 28.94 (d, *J* = 7.8 Hz, NCH$_2$<u>C</u>H$_2$S); **^{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.

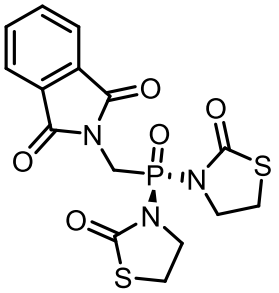
Bis(1,3-thiazolidin-2-one) phthalimidomethylphosphonate (**547**)



547 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 °C (from pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H, ArC<u>H</u>), 7.10 – 7.02 (m, 2H, ArC<u>H</u>), 3.94 – 3.63 (m, 4H, NC<u>H$_2$</u>CH$_2$S), 3.83 – 3.73 (m, 2H, C<u>H$_2$</u>P), 3.41 – 3.12 (m, 4H, NCH$_2$C<u>H$_2$</u>S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (<u>C</u>=O), 162.4 (d, *J* = 251.5 Hz, Ar<u>C</u>F), 132.0 – 131.7 (m, Ar<u>C</u>H), 124.5 – 124.9 (m, Ar<u>C</u>CH$_2$) 115.9 (dd, *J* = 21.7, 3.5 Hz, Ar<u>C</u>H), 47.7 (d, *J* = 3.8 Hz, N<u>C</u>H$_2$CH$_2$S), 34.3 (d, *J* = 104.1 Hz, <u>C</u>H$_2$P), 29.1 (d, *J* = 7.9 Hz, NCH$_2$<u>C</u>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.

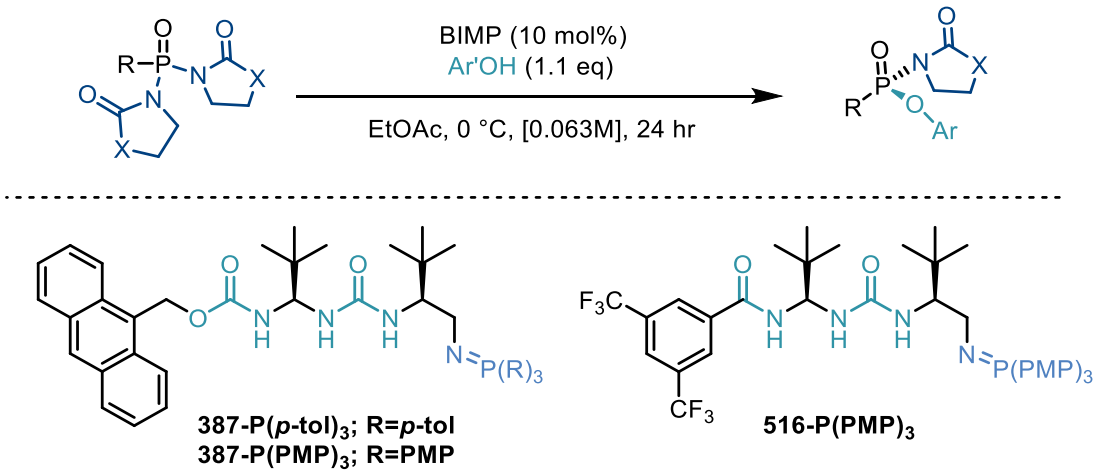
Bis(1,3-thiazolidin-2-one) phthalimidomethylphosphonate (**548**)



548 was synthesised according to **General Procedure VIII-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-Colourless solid (0.17 g, 0.41 mmol, 27% yield).

Mp 208 °C (from pentane); **^{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, NCH_2CH_2S), 3.52 – 3.38 (m, 4H, NCH_2CH_2S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8 (d, *J* = 2.0 Hz, C=O thiazolidinone), 167.4 (C=O phtalimide), 134.6 (ArCH), 131.95 (ArC), 123.9 (ArCH), 47.9 (d, *J* = 4.7 Hz, NCH_2CH_2S), 36.1 (d, *J* = 122.4 Hz, CH_2P), 29.6 (d, *J* = 8.3 Hz, NCH_2CH_2S); **^{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.

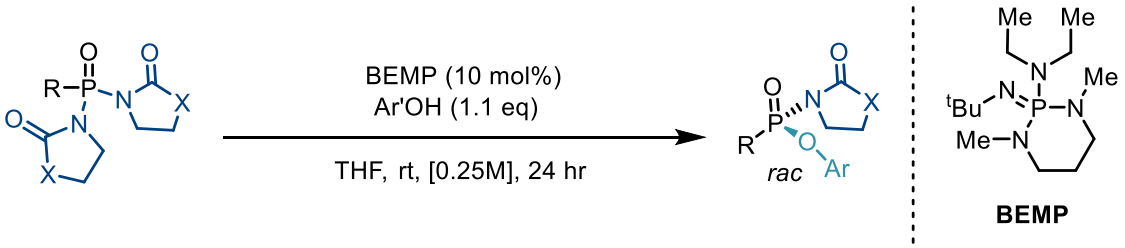
5.4.4 General Procedure IX: enantioselective desymmetrisation of P(V) electrophiles



To the corresponding organoazide **516-N_3** (5.0 mg, 0.01 mmol) and $P(PMP)_3$ (3.5 mg, 0.01 mmol) under argon atmosphere was added THF (0.40 mL) and the reaction mixture was stirred for 24 hr. The formation of the organocatalysts was monitored by TLC. Upon completion volatiles were removed under a stream of N_2 yielding the expected iminophosphorane which was used without further purification.

To the corresponding P(V) electrophile (0.10 mmol) and BIMP organocatalyst (0.010 mmol) under argon atmosphere were added phenol (0.10 mmol, 1.0 equivalents) and EtOAc (1.60 mL) then the reaction was stirred at 0 °C for 24 hr. 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 P(V) product. The two enantiomers were separated by chiral HPLC using conditions specified in the individual experiment.

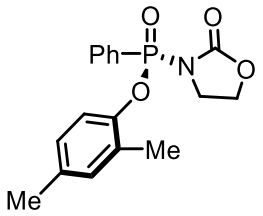
5.4.5 General Procedure X: racemic desymmetrisation of P(V) electrophiles



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 (0.40 mL) and the corresponding phenol (0.11 mmol) and the reaction was stirred at room temperature for 24 hr. 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 P(V) product. The two enantiomers were separated by chiral HPLC using conditions specified in the individual experiment.

5.4.6 Products: Leaving group optimisation

2,4-dimethylphenyl-(*R*)-(2-oxooxazolidin-3-yl)(phenyl)phosphinate (**498**)

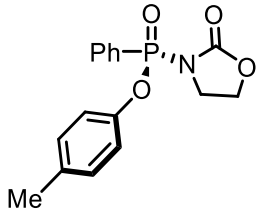


498 was synthesized following **GP IX**. **495** (29.6 mg, 0.10 mmol) was used as electrophile, 2,4-dimethylphenol (12.4 μL, 0.11 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (7.8 mg, 0.010 mmol) as catalyst in THF (0.40 mL) at room temperature. $CHCl_3$:MeOH 98:2. Colourless oil (33.0 mg, 0.099 mmol, 99% yield, 50% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 13.03 min, t (major) = 22.40 min

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.02 (m, 2H, ArC<u>H</u>), 7.67 – 7.56 (m, 1H, ArC<u>H</u>), 7.55 – 7.43 (m, 2H, ArC<u>H</u>), 7.29 (dd, *J* = 8.2, 1.4 Hz, 1H, ArC<u>H</u>), 7.02 (q, *J* = 1.2 Hz, 1H, ArC<u>H</u>), 6.91 (dd, *J* = 8.4, 2.4 Hz, 1H, ArC<u>H</u>), 4.36 – 4.22 (m, 2H, $NCH_2C\underline{H}_2O$), 4.07 – 3.89 (m, 2H, $NC\underline{H}_2CH_2O$), 2.36 (s, 3H, $ArC\underline{H}_3$), 2.27 (s, 3H, $ArC\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$)δ 155.5 (d, *J* = 8.2 Hz, <u>C</u>=O), 146.9 (d, *J* = 9.1 Hz, Ar<u>C</u>O), 134.9 (Ar<u>C</u>), 133.6 (d, *J* = 3.2 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 10.5 Hz, phenyl Ar<u>C</u>H), 132.3 (phenol Ar<u>C</u>H), 129.9 – 129.3 (m, Ar<u>C</u>), 128.6 (d, *J* = 15.9 Hz, phenyl Ar<u>C</u>H), 127.5 (phenol Ar<u>C</u>H), 127.3 (d, *J* = 184.6 Hz, <u>C</u>P), 119.2 (d, *J* = 3.3 Hz, phenol Ar<u>C</u>H), 64.0 (d, *J* = 7.9 Hz, $NCH_2\underline{C}H_2O$ 2), 45.1 (d, *J* = 3.4 Hz, $N\underline{C}H_2CH_2O$), 20.8 ($Ar\underline{C}H_3$), 16.6 ($Ar\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 11.78; **IR** (film) υ_{max}/cm^{-1}: 1766 (C=O), 1498, 1388, 1259 (P=O), 1194, 1152, 1178, 952, 912, 768, 695; **HRMS** (ESI+): calcd. for $C_{17}H_{18}O_4NNaP$ 354.0866 $[M+Na]^+$, found 354.0866.

p-tolyl-(*R*)-(2-oxooxazolidin-3-yl)(phenyl)phosphinate (**502**)

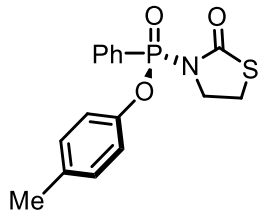


502 was synthesized following **GP IX**. **495** (29.4 mg, 0.10 mmol) was used as electrophile, 4-methylphenol (10.4 mg, 0.10 mmol) was used as nucleophile and BIMP **387-P(*p*-tol)$_3$** (11.7 mg, 0.015 mmol) as catalyst in THF (0.40 mL) at room temperature. Pentane:EtOAc 6:4. Colourless oil (27.0 mg, 0.085 mmol, 85% yield, 25% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 13.37 min, t (major) = 17.19 min

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.05 (m, 2H, phenyl ArC<u>H</u>), 7.65 – 7.57 (m, 1H, phenyl ArC<u>H</u>), 7.55 – 7.45 (m, 2H, phenyl ArC<u>H</u>), 7.29 – 7.20 (m, 2H, phenol ArC<u>H</u>), 7.18 – 7.09 (m, 2H, phenol ArC<u>H</u>), 4.27 (dtd, *J* = 19.4, 8.7, 7.0 Hz, 2H, NCH$_2$C<u>H</u>$_2$O), 4.02 – 3.69 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 2.32 (d, *J* = 1.0 Hz, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.6 (d, *J* = 8.1 Hz, C=O), 147.6 (d, *J* = 9.4 Hz, Ar<u>C</u>O), 135.4 (d, *J* = 1.7 Hz, Ar<u>C</u>), 133.6 (d, *J* = 3.2 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 11.0 Hz, phenyl Ar<u>C</u>H), 130.5 (d, *J* = 1.2 Hz, phenol Ar<u>C</u>H), 128.6 (d, *J* = 15.9 Hz, phenyl Ar<u>C</u>H), 127.0 (d, *J* = 184.2 Hz, <u>C</u>P), 120.7 (d, *J* = 4.6 Hz, phenol Ar<u>C</u>H), 63.9 (d, *J* = 7.9 Hz, NCH$_2$<u>C</u>H$_2$O), 44.9 (d, *J* = 3.4 Hz, N<u>C</u>H$_2$CH$_2$O), 20.9 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.21; **IR** (film) υ_{max}/cm^{-1}:2981, 2160 ,1764 (C=O), 1505, 1387, 1261 (P=O), 1195, 1164, 1150, 1128, 930, 767, 695; **HRMS** (ESI+): calcd. for $C_{16}H_{16}O_4NNaP$ 340.0709 $[M+Na]^+$, found 340.0710.

p-tolyl-(*R*)-(2-oxooxazolidin-3-yl)(phenyl)phosphinate (**506**)



506 was synthesized following **GP IX**. **505** (32.8 mg, 0.10 mmol) was used as electrophile, 4-methylphenol (10.4 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Pentane:EtOAc 6:4. Colourless oil (33.2 mg, 0.099 mmol, 99% yield, 96% ee).

3.05 mmol scale: BIMP **516-P(PMP)$_3$** (259 mg, 0.31 mmol) and **505** (1.00 g, 3.05 mmol) were used as electrophile was dissolved EtOAc (48.0 mL) and cooled to 0 °C, then 4-methylphenol (320 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 (Pentane:EtOAc 6:4. Colourless Oil (825 mg, 2.32 mmol, 79% yield, 93% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 11.79 min, t (major) = 16.69 min.

[α]$_D^{25}$ = +148.9 (c = 0.47, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 7.99 (m, 2H, phenyl ArC<u>H</u>), 7.66 – 7.56 (m, 1H, phenyl ArC<u>H</u>), 7.56 – 7.43 (m, 2H, phenyl ArC<u>H</u>), 7.22 – 7.17 (m, 2H, phenol ArC<u>H</u>), 7.16 – 7.11 (m, 2H, phenol ArC<u>H</u>), 4.01 (ddtd, *J* = 43.6, 10.9, 7.1, 1.2 Hz, 2H, NC<u>H</u>$_2$CH$_2$S), 3.33 – 3.11 (m, 2H, NCH$_2$C<u>H</u>$_2$S), 2.32 (d, *J* = 1.0 Hz, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (<u>C</u>=O), 147.5 (d, *J* = 9.6 Hz, Ar<u>C</u>O), 135.4 (d, *J* = 1.7 Hz, Ar<u>C</u>), 133.5 (d, *J* = 3.2 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 11.1 Hz, phenyl Ar<u>C</u>H), 130.4 (d, *J* = 1.3 Hz, phenol Ar<u>C</u>H), 128.5 (d, *J* = 16.0 Hz, phenyl Ar<u>C</u>H), 127.3 (d, *J* = 183.3 Hz, <u>C</u>P), 120.7 (d, *J* = 4.5 Hz, phenol Ar<u>C</u>H), 48.7 (d, *J* = 4.6 Hz, N<u>C</u>H$_2$CH$_2$S), 29.1 (d, *J* = 7.8 Hz, NCH$_2$<u>C</u>H$_2$S), 20.9 (Ar<u>C</u>H$_3$); **^{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.

5.4.6.1 Single crystal X-ray diffraction data for compound 506

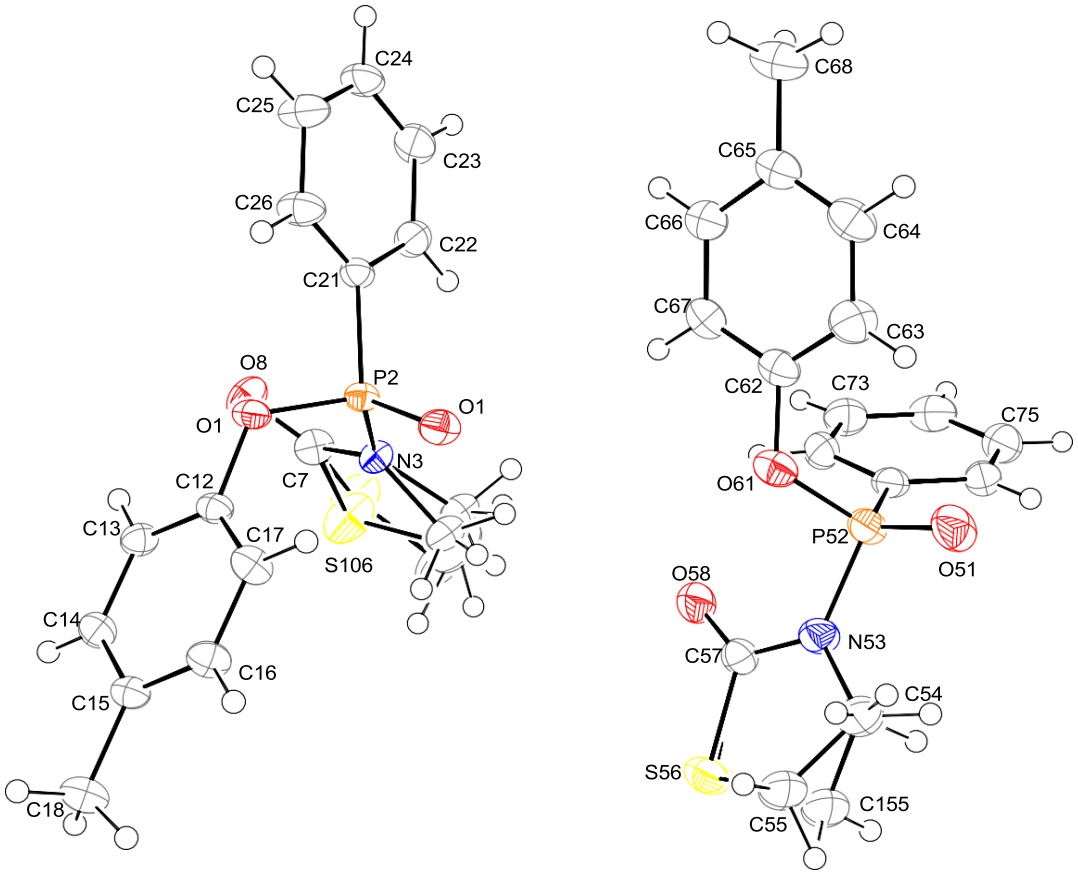


Table 1. Crystal data and structure refinement for **506**.

Identification code	**506**	
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 anisotropicdisplacement 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

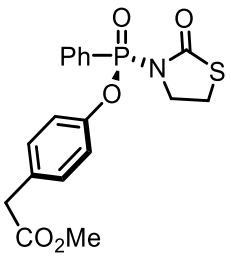
Table 6. Hydrogen bonds for 7420 [Å and °].

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

5.4.7 Products: Scope with respect to the phenol nucleophile

methyl-2-(4-(((*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphoryl)oxy)phenyl)acetate (**517**)

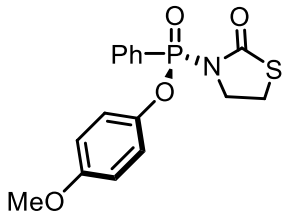


517 was synthesized following **GP IX**. **505** (32.8 mg, 0.10 mmol) was used as electrophile, 4-methylphenol (16.6 μL, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Pentane:EtOAc 1:1. Colourless oil (29.0 mg, 0.079 mmol, 79% yield, 95% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 22.13 min, t (major) = 30.87 min.

[α]$_D^{25}$ = +134.0 (c = 0.10, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 – 8.01 (m, 2H, phenyl ArC<u>H</u>), 7.65 – 7.57 (m, 1H, phenyl ArC<u>H</u>), 7.54 – 7.46 (m, 2H, phenyl ArC<u>H</u>), 7.28 (d, *J* = 1.2 Hz, 4H, phenol ArC<u>H</u>), 4.16 – 3.94 (m, 2H, C<u>H</u>$_2$COOMe), 3.69 (s, 3H, ester C<u>H</u>$_3$), 3.64 – 3.59 (m, 2H, NC<u>H</u>$_2$CH$_2$S), 3.34 – 3.17 (m, 2H, NCH$_2$C<u>H</u>$_2$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3 (<u>C</u>=O), 171.9 (<u>C</u>=O), 148.9 (d, *J* = 9.4 Hz, Ar<u>C</u>O), 133.5 (d, *J* = 3.2 Hz, phenyl Ar<u>C</u>H), 132.5 (d, *J* = 11.2 Hz, phenyl Ar<u>C</u>H), 131.5 (Ar<u>C</u>), 130.9 (phenol Ar<u>C</u>H), 128.6 (phenyl Ar<u>C</u>H), 127.2 (d, *J* = 183.5 Hz, <u>C</u>P), 121.1 (d, *J* = 4.5 Hz, phenol Ar<u>C</u>H), 52.2 (ester <u>C</u>H$_3$), 48.7 (d, *J* = 4.5 Hz, N<u>C</u>H$_2$CH$_2$S), 40.5 (<u>C</u>H$_2$COOMe), 29.1 (d, *J* = 7.7 Hz, NCH$_2$<u>C</u>H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.86; **IR** (film) υ_{max}/cm^{-1}: 1742 (C=O ester), 1689 (C=O thiazolidinone), 1505, 1238 (P=O), 1128, 940, 678; **HRMS** (ESI+): calcd. for $C_{18}H_{18}O_5NNaPS$ 414.0536 $[M+Na]^+$, found 414.0535.

4-methoxyphenyl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**518**)

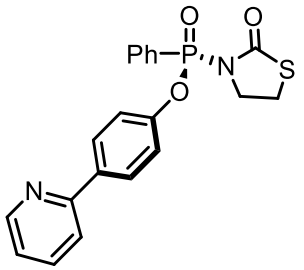


518 was synthesized following **GP IX**. **505** (32.8 mg, 0.10 mmol) was used as electrophile, 4-OMe-phenol (12.4 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (32.4 mg, 0.093 mmol, 93% yield, 92% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 16.42 min, t (major) = 21.72 min.

$[\alpha]_D^{25}$ = +129.2 (c = 0.38, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 – 8.02 (m, 2H, phenyl ArC<u>H</u>), 7.68 – 7.57 (m, 1H, phenyl ArC<u>H</u>), 7.57 – 7.46 (m, 2H, phenyl ArC<u>H</u>), 7.31 – 7.22 (m, 2H, phenol ArC<u>H</u>), 6.94 – 6.79 (m, 2H, phenol ArC<u>H</u>), 4.23 – 3.90 (m, 2H, NC<u>H</u>$_2$CH$_2$S), 3.80 (s, 3H, OC<u>H</u>$_3$), 3.35 – 3.14 (m, 2H, NCH$_2$C<u>H</u>$_2$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (<u>C</u>=O), 157.2 <u>C</u>OMe), 143.2 (d, *J* = 9.6 Hz, Ar<u>C</u>O), 133.4 (d, *J* = 3.3 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 11.1 Hz, phenyl Ar<u>C</u>H), 128.5 (d, *J* = 15.9 Hz, phenyl Ar<u>C</u>H), 127.3 (d, *J* = 183.1 Hz, <u>C</u>P), 121.9 (d, *J* = 4.3 Hz, phenol Ar<u>C</u>H), 114.9 (d, *J* = 1.4 Hz, phenol Ar<u>C</u>H), 55.7 (O<u>C</u>H$_3$), 48.7 (d, *J* = 4.5 Hz, N<u>C</u>H$_2$CH$_2$S), 29.1 (d, *J* = 7.8 Hz, NCH$_2$<u>C</u>H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.08; **IR** (film) υ_{max}/cm^{-1}: 1689 (C=O), 1504, 1256 (P=O), 1195, 1128, 1032, 939, 835, 729, 696; **HRMS** (ESI+): calcd. for $C_{16}H_{17}O_4NPS$ 350.0610 $[M+H]^+$, found 350.0611.

4-(pyridin-2-yl)phenyl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**519**)

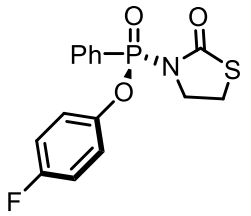


519 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, 4-(pyridin-2-yl)phenol (17.1 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. $CHCl_3$:MeOH 9:1. Colourless oil (36.8 mg, 0.093 mmol, 93% yield, 84% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 mL/min, λ = 240 nm, t (minor) = 19.70 min, t (minor) = 23.10 min.

$[\alpha]_D^{25}$ = +54.4 (c = 0.62, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1H NMR (400 MHz, CDCl3) δ 8.68 (ddt, *J* = 4.9, 1.8, 0.8 Hz, 1H, ArC<u>H</u>), 8.11 (ddt, *J* = 14.4, 7.0, 1.4 Hz, 2H, ArC<u>H</u>), 8.04 – 7.99 (m, 2H, phenol ArC<u>H</u>), 7.80 – 7.57 (m, 4H, ArC<u>H</u>), 7.56 – 7.49 (m, 2H, phenol ArC<u>H</u>), 7.48 – 7.42 (m, 2H, NC<u>H</u>$_2$CH$_2$S), 4.06 (dddd, *J* = 34.7, 10.9, 7.1, 1.1 Hz, 2H, NCH$_2$C<u>H</u>$_2$S), 3.33 – 3.16 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (<u>C</u>=O), 156.5 (Ar<u>C</u>), 150.6 (d, *J* = 9.3 Hz, Ar<u>C</u>), 149.8 (d, *J* = 7.1 Hz, Ar<u>C</u>O), 137.0 (Ar<u>C</u>H), 133.6 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 132.6 (d, *J* = 11.2 Hz, Ar<u>C</u>H), 128.6 (d, *J* = 3.2 Hz, phenol Ar<u>C</u>H), 128.5 (d, *J* = 2.1 Hz, Ar<u>C</u>H), 127.2 (d, *J* = 183.3 Hz, <u>C</u>P), 122.4 (Ar<u>C</u>H), 121.4 (d, *J* = 4.7 Hz, Ar<u>C</u>H), 121.0 (d, *J* = 4.7 Hz, Ar<u>C</u>H), 120.5 (phenol Ar<u>C</u>H), 48.8 (d, *J* = 4.5 Hz, N<u>C</u>H$_2$CH$_2$S), 29.1 (d, *J* = 7.9 Hz, NCH$_2$<u>C</u>H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.99; **IR** (film) υ_{max}/cm^{-1}:1680 (C=O), 1467, 1218 (P=O), 1129, 933, 784, 694; **HRMS** (ESI+): calcd. for $C_{20}H_{18}O_3N_2PS$ 397.0770 $[M+H]^+$, found 397.0771.

4-fluorophenyl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**520**)

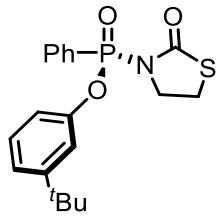


520 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, 4-fluorophenol (22.4 mg, 0.20 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (26.7 mg, 0.088 mmol, 88% yield, 96% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 12.69 min, t (minor) = 13.88 min.

[α]$_D^{25}$ = +152.9 (c = 0.18, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 8.01 (m, 2H, phenyl ArC<u>H</u>), 7.67 – 7.60 (m, 1H, phenyl ArC<u>H</u>), 7.56 – 7.48 (m, 2H, phenol ArC<u>H</u>), 7.34 – 7.27 (m, 2H, phenyl ArC<u>H</u>), 7.11 – 7.00 (m, 2H, phenol ArC<u>H</u>), 4.02 (ddtd, *J* = 43.2, 11.0, 7.0, 1.2 Hz, 2H, NC<u>H</u>$_2$CH$_2$S), 3.35 – 3.16 (m, 2H, NCH$_2$C<u>H</u>$_2$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.2 (<u>C</u>=O), 160.3 (d, *J* = 244.4 Hz, <u>C</u>F), 145.6 (<u>C</u>O), 133.7 (d, *J* = 3.3 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 11.2 Hz, phenyl Ar<u>C</u>H), 128.6 (d, *J* = 16.1 Hz, phenol Ar<u>C</u>H), 127.0 (d, *J* = 183.2 Hz, <u>C</u>P), 122.5 (dd, *J* = 8.5, 4.5 Hz, phenyl Ar<u>C</u>H), 117.5 – 116.0 (m, phenol Ar<u>C</u>H), 48.7 (d, *J* = 4.6 Hz, N<u>C</u>H$_2$CH$_2$S), 29.1 (d, *J* = 7.9 Hz, NCH$_2$<u>C</u>H$_2$S); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -116.82 (d, *J* = 2.5 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.37 (d, *J* = 2.4 Hz); **IR** (film) υ_{max}/cm^{-1}: 1689 (C=O), 1501, 1257 (P=O), 1189, 1128, 940, 841, 695; **HRMS** (ESI+): calcd. for $C_{15}H_{13}O_3NFNaPS$ 360.0230 $[M+Na]^+$, found 360.0230.

3-(*tert*-butyl)phenyl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**521**)

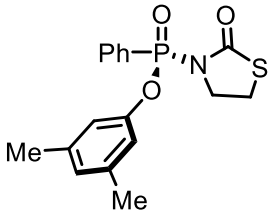


521 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, 3-*tert*-butylphenol (15.0 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (28.5 mg, 0.076 mmol, 76% yield, 92% ee).

HPLC Conditions: CHIRALPAK IB, hexane/isopropanol = 90/10, 1 mL/min, λ = 240 nm, t (major) = 8.78 min, t (minor) = 10.58 min.

$[\alpha]_D^{25}$ = +132.4 (c = 0.27, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 – 8.01 (m, 2H, phenyl ArC<u>H</u>), 7.64 – 7.58 (m, 1H, phenyl ArC<u>H</u>), 7.56 – 7.46 (m, 2H, phenyl ArC<u>H</u>), 7.37 – 7.21 (m, 3H, phenol ArC<u>H</u>), 7.16 (ddt, *J* = 7.8, 2.4, 1.5 Hz, 1H, phenol ArC<u>H</u>), 4.23 – 3.81 (m, 2H, NC<u>H</u>$_2$CH$_2$S), 3.31 – 3.06 (m, 2H, NCH$_2$C<u>H</u>$_2$S), 1.31 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.0 (C=O), 153.8 (Ar<u>C</u>O), 149.7 (d, *J* = 9.6 Hz, Ar<u>C</u>), 133.4 (d, *J* = 3.3 Hz, phenyl Ar<u>C</u>H), 132.7 (d, *J* = 10.9 Hz, phenyl Ar<u>C</u>H), 129.4 (d, *J* = 1.4 Hz, phenol Ar<u>C</u>H), 128.5 (d, *J* = 15.9 Hz, phenyl Ar<u>C</u>H), 127.4 (d, *J* = 183.4 Hz, <u>C</u>P), 122.7 (d, *J* = 1.6 Hz, phenol Ar<u>C</u>H), 118.3 (d, *J* = 4.6 Hz, phenol Ar<u>C</u>H), 118.1 (d, *J* = 4.1 Hz, phenol Ar<u>C</u>H), 48.8 (d, *J* = 4.5 Hz, N<u>C</u>H$_2$CH$_2$S), 35.0 (<u>C</u>(CH$_3$)$_3$), 31.3 (C(<u>C</u>H$_3$)$_3$), 29.1 (d, *J* = 7.7 Hz, NCH$_2$<u>C</u>H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.73; **IR** (film) υ_{max}/cm^{-1}: 2962, 1691 (P=O), 1581, 1486, 1440, 1258 (P=O), 1190, 1128, 856, 795, 728, 693; **HRMS** (ESI+): calcd. for $C_{19}H_{23}O_3NPS$ 376.1131 $[M+H]^+$, found 376.1131.

3,5-dimethylphenyl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**522**)

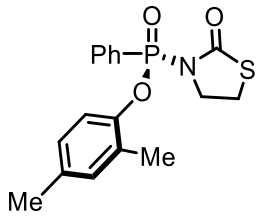


522 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, 3,5-dimethylphenol (12.2 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (34.0 mg, 0.098 mmol, 98% yield, 96% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 mL/min, λ = 240 nm, t (major) = 11.69 min, t (minor) = 12.94 min.

[α]$_D^{25}$ = +150.1 (c = 0.28, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1H NMR (400 MHz, CDCl3) δ 8.06 (ddt, *J* = 14.4, 7.0, 1.4 Hz, 2H, phenyl ArC<u>H</u>), 7.65 – 7.56 (m, 1H, phenyl ArC<u>H</u>), 7.50 (ddd, *J* = 8.5, 6.9, 4.7 Hz, 2H, phenyl ArC<u>H</u>), 6.94 (s, 2H, phenol *ortho*-C<u>H</u>), 6.88 – 6.78 (m, 1H, phenol *para*-C<u>H</u>), 4.04 (ddtd, *J* = 37.9, 11.0, 7.1, 1.2 Hz, 2H, NC<u>H</u>$_2$CH$_2$S), 3.34 – 3.07 (m, 2H, NCH$_2$C<u>H</u>$_2$S), 2.30 (s, 6H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (<u>C</u>=O), 149.7 (d, *J* = 9.4 Hz, Ar<u>C</u>O), 139.8 (Ar<u>C</u>), 133.4 (d, *J* = 3.3 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 11.1 Hz, phenyl Ar<u>C</u>H), 128.5 (d, *J* = 15.9 Hz, phenyl Ar<u>C</u>H), 127.5 (d, *J* = 183.6 Hz, <u>C</u>P), 127.4 (d, *J* = 1.5 Hz, phenol *ortho*-<u>C</u>H), 118.4 (d, *J* = 4.7 Hz, phenol *ortho*-<u>C</u>H), 48.8 (d, *J* = 4.5 Hz, N<u>C</u>H$_2$CH$_2$S), 29.1 (d, *J* = 7.8 Hz, NCH$_2$<u>C</u>H$_2$S), 21.4 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.35; **IR** (film) υ_{max}/cm^{-1}:2160, 1690 (C=O), 1591, 1440, 1290, 1255 (P=O), 1034, 966, 855, 727, 612; **HRMS** (ESI+): calcd. for $C_{17}H_{19}O_3NPS$ 348.0818 $[M+H]^+$, found 348.0819.

2,4-dimethylphenyl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**523**)

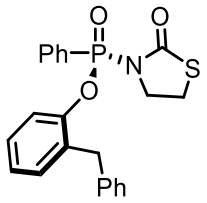


523 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, 2,4-dimethylphenol (12.4 μL, 0.10 mmol) was used as nucleophile and **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (34.4 mg, 0.099 mmol, 99% yield, 94% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 11.22 min, t (major) = 16.28 min.

[α]$_D^{25}$ = +114.9 (c = 0.33, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 – 7.99 (m, 2H, phenyl Ar<u>C</u>H), 7.67 – 7.58 (m, 1H, phenyl Ar<u>C</u>H), 7.56 – 7.41 (m, 2H, phenyl Ar<u>C</u>H), 7.30 – 7.22 (m, 1H, phenol Ar<u>C</u>H), 7.03 (dd, *J* = 2.3, 1.1 Hz, 1H, phenol Ar<u>C</u>H), 6.94 (dd, *J* = 8.3, 2.2 Hz, 1H, phenol Ar<u>C</u>H), 4.25 – 4.01 (m, 2H, N<u>C</u>H$_2$CH$_2$S), 3.34 – 3.16 (m, 2H, NCH$_2$<u>C</u>H$_2$S), 2.36 (s, 3H, ArC<u>H</u>$_3$), 2.28 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.0 (<u>C</u>=O), 146.8 (d, *J* = 9.3 Hz, Ar<u>C</u>O), 134.9 (Ar<u>C</u>), 133.4 (d, *J* = 3.3 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 4.0 Hz, phenyl Ar<u>C</u>H), 132.4 (phenol Ar<u>C</u>H), 129.6 (d, *J* = 6.1 Hz, Ar<u>C</u>), 128.5 (phenyl Ar<u>C</u>H), 127.8 (d, *J* = 183.6 Hz, <u>C</u>P), 127.5 (phenol Ar<u>C</u>H), 119.3 (d, *J* = 3.5 Hz, phenol Ar<u>C</u>H), 48.8 (d, *J* = 4.6 Hz, N<u>C</u>H$_2$CH$_2$S), 29.2 (d, *J* = 7.7 Hz, NCH$_2$<u>C</u>H$_2$S), 20.8 (Ar<u>C</u>H$_3$), 16.7 (Ar<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 11.93; **IR** (film) υ_{max}/cm^{-1}: 2968, 2924, 1689 (C=O), 1498, 1410, 1254 (P=O), 1223, 1199, 1144, 1127, 1105, 952, 913, 728, 697; **HRMS** (ESI+): calcd. for $C_{17}H_{19}O_3NPS$ 348.0818 $[M+H]^+$, found 348.0818.

2-benzylphenyl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**524**)

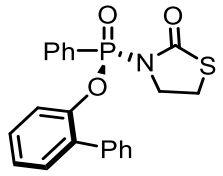


524 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, 2-benzylphenol (18.4 mg, 0.10 mmol) was used as nucleophile and **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (30.7 mg, 0.075 mmol, 75% yield, 84% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 15.30 min, t (major) = 20.93 min.

$[\alpha]_D^{25}$ = +52.3 (c = 0.34, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8 1H NMR (400 MHz, CDCl3) δ 8.03 – 7.93 (m, 2H, backbone phenyl ArC<u>H</u>), 7.64 – 7.56 (m, 1H, backbone phenyl ArC<u>H</u>), 7.47 (dddd, *J* = 9.5, 8.3, 3.6, 1.5 Hz, 3H, ArC<u>H</u> + backbone phenyl ArC<u>H</u>), 7.31 – 7.23 (m, 2H, ArC<u>H</u>), 7.19 (tdd, *J* = 7.9, 3.1, 1.4 Hz, 3H, ArC<u>H</u>), 7.15 – 7.07 (m, 2H, ArC<u>H</u>), 4.18 (d, *J* = 1.8 Hz, 2H, ArC<u>H</u>$_2$Ar), 4.15 – 4.03 (m, 2H, NC<u>H</u>$_2$CH$_2$S), 3.29 (qt, *J* = 11.0, 7.0 Hz, 2H, NCH$_2$C<u>H</u>$_2$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.0 (<u>C</u>=O), 148.7 (d, *J* = 9.2 Hz, Ar<u>C</u>O), 139.9 (Ar<u>C</u>), 133.3 (d, *J* = 3.5 Hz), 132.6 (d, *J* = 6.6 Hz, Ar<u>C</u>), 132.3 (d, *J* = 11.2 Hz, Ar<u>C</u>H), 131.6 (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 128.5 (d, *J* = 16.0 Hz, Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 127.6 (d, *J* = 183.4 Hz, <u>C</u>P), 125.4 (Ar<u>C</u>H), 119.5 (Ar<u>C</u>H), 48.6 (d, *J* = 4.7 Hz, N<u>C</u>H$_2$CH$_2$S), 35.9 (Ar<u>C</u>H$_2$Ar), 29.1 (d, *J* = 7.9 Hz, NCH$_2$<u>C</u>H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.30; **IR** (film) υ_{max}/cm^{-1}:1690 (C=O), 1489, 1451, 1257 (P=O), 1221, 1127, 948, 728, 693; **HRMS** (ESI+): calcd. for $C_{21}H_{19}O_3NPS$ 396.0818 $[M+H]^+$, found 396.0818.

[1,1'-biphenyl]-2-yl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**525**)

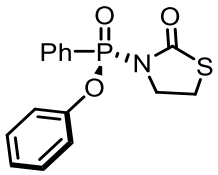


525 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, [1,1'-biphenyl]-2-ol (18.4 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (39.1 mg, 0.099 mmol, 99% yield, 74% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 13.70 min, t (major) = 16.13 min.

[α]$_D^{25}$ = +5.0 (c = 0.46, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 – 7.67 (m, 2H, backbone phenyl ArC<u>H</u>), 7.52 (dq, *J* = 7.6, 1.7 Hz, 3H, ArC<u>H</u>), 7.47 – 7.29 (m, 8H, ArC<u>H</u>), 7.29 – 7.20 (m, 1H), 3.96 (ddtd, *J* = 44.1, 10.9, 7.0, 1.1 Hz, 2H, NC<u>H</u>$_2$CH$_2$S), 3.31 – 3.15 (m, 2H, NCH$_2$C<u>H</u>$_2$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.7 (<u>C</u>=O), 147.4 (d, *J* = 9.0 Hz, Ar<u>C</u>O), 137.5 (Ar<u>C</u>), 134.2 (d, *J* = 6.4 Hz, Ar<u>C</u>H), 133.2 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 132.3 (d, *J* = 11.5 Hz, Ar<u>C</u>H), 131.7 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>), 128.4 (d, *J* = 16.0 Hz, Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 127.7 (d, *J* = 183.1 Hz, <u>C</u>P), 127.6 (Ar<u>C</u>H), 125.5 (Ar<u>C</u>H), 120.2 (d, *J* = 3.7 Hz, Ar<u>C</u>H), 48.4 (d, *J* = 4.5 Hz, N<u>C</u>H$_2$CH$_2$S), 29.1 (d, *J* = 8.0 Hz, NCH$_2$<u>C</u>H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.45; **IR** (film) υ_{max}/cm^{-1}:1690 (C=O), 1479, 1435, 1254 (P=O), 1199, 1107, 931, 731, 757, 727, 964; **HRMS** (ESI+): calcd. for $C_{21}H_{19}O_3NPS$ 396.0818 $[M+H]^+$, found 396.0818.

phenyl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate **526**

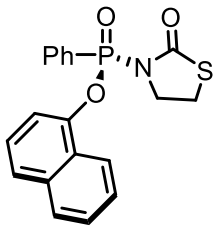


526 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, phenol (9.4 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (23.9 mg, 0.075 mmol, 75% yield, 97% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 11.51 min, t (major) = 13.48 min.

[α]$_D^{25}$ = +158.0 (c = 0.33, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 7.98 (m, 2H, phenyl ArC<u>H</u>), 7.68 – 7.56 (m, 1H, phenyl ArC<u>H</u>), 7.55 – 7.47 (m, 2H, phenyl ArC<u>H</u>), 7.41 – 7.30 (m, 4H, phenol ArC<u>H</u>), 7.24 – 7.16 (m, 1H, phenol ArC<u>H</u>), 4.10 – 3.94 (m, 2H, NC<u>H</u>$_2$CH$_2$S), 3.34 – 3.10 (m, 2H, NCH$_2$C<u>H</u>$_2$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.9 (<u>C</u>=O), 149.7 (d, *J* = 9.3 Hz, Ar<u>C</u>O), 133.4 (phenyl Ar<u>C</u>H), 132.5 (d, *J* = 11.1 Hz, phenol Ar<u>C</u>H), 129.9 (phenyl Ar<u>C</u>H), 128.44 (d, *J* = 15.9 Hz, phenyl Ar<u>C</u>H) 127.2 (d, *J* = 183.2 Hz, <u>C</u>P), 125.7 (phenol Ar<u>C</u>H), 120.9 (d, *J* = 4.6 Hz, phenol Ar<u>C</u>H), 48.6 (d, *J* = 4.6 Hz, N<u>C</u>H$_2$CH$_2$S), 29.0 (d, *J* = 7.9 Hz, NCH$_2$<u>C</u>H$_2$S). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.79; **IR** (film) υ_{max}/cm^{-1}: 1689 (C=O), 1591, 1488, 1440, 1256 (P=O), 1199, 1128, 934, 771, 612; **HRMS** (ESI+): calcd. for $C_{15}H_{15}O_3NPS$ 320.0505 $[M+H]^+$, found 320.0506.

naphthalen-1-yl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**527**)

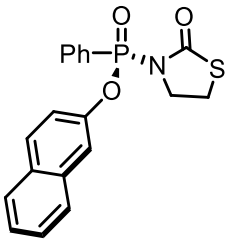


527 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, 1-naphthol (14.4 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C Toluene:MeOH 95:5. Colourless oil (35.1 mg, 0.095 mmol, 95% yield, 76% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 14.80 min, t (major) = 19.07 min.

$[\alpha]_D^{25}$ = +80.7 (c = 0.56, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (dt, *J* = 8.9, 1.0 Hz, 1H, naphthol ArC<u>H</u>), 8.21 – 8.07 (m, 2H, phenyl ArC<u>H</u>), 7.87 – 7.82 (m, 1H, naphthol ArC<u>H</u>), 7.69 – 7.64 (m, 1H, naphthol ArC<u>H</u>), 7.63 – 7.45 (m, 6H, ArC<u>H</u>), 7.38 (t, *J* = 8.0 Hz, 1H, naphthol ArC<u>H</u>), 4.23 – 4.01 (m, 2H, NC<u>H$_2$</u>CH$_2$S), 3.34 – 3.18 (m, 2H, NCH$_2$C<u>H$_2$</u>S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3 (<u>C</u>=O), 146.4 (d, *J* = 9.0 Hz, Ar<u>C</u>O), 135.0 (Ar<u>C</u>), 133.6 (ArC<u>H</u>), 133.6 (ArC<u>H</u>), 132.5 (d, *J* = 11.3 Hz, phenyl Ar<u>C</u>H), 128.7 (ArC<u>H</u>), 127.7 (naphthtol ArC<u>H</u>), 127.5 (d, *J* = 172.2 Hz, <u>C</u>P), 126.9 (d, *J* = 24.3 Hz, phenyl Ar<u>C</u>H), 126.6 (d, *J* = 3.6 Hz, Ar<u>C</u>), 125.5 (d, *J* = 1.8 Hz, naphthtol ArC<u>H</u>), 122.3 (naphthtol ArC<u>H</u>), 115.4 (ArC<u>H</u>), 115.3 (ArC<u>H</u>), 48.7 (d, *J* = 5.1 Hz, N<u>C</u>H$_2$CH$_2$S), 29.2 (d, *J* = 8.0 Hz, NCH$_2$<u>C</u>H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.04; **IR** (film) υ_{max}/cm^{-1}: 3060, 2989, 1690 (C=O), 1596, 1440, 1391, 1256 (P=O), 1225, 1126, 1082, 1044, 926, 772, 727; **HRMS** (ESI+): calcd. for $C_{18}H_{17}O_3NPS$ 370.0661 $[M+H]^+$, found 370.0659.

naphthalen-2-yl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**528**)

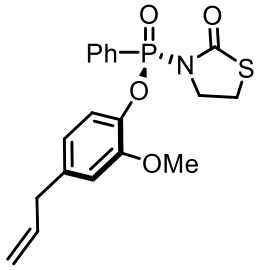


528 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, 2-naphthol (14.4 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (23.6 mg, 0.064 mmol, 64% yield, 96% ee).

HPLC Conditions: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (minor) = 17.22 min, t (major) = 30.14 min.

[α]$_D^{25}$ = +141.5 (c = 0.13, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 – 8.08 (m, 2H, phenyl ArC<u>H</u>), 7.88 – 7.79 (m, 4H, ArC<u>H</u>), 7.67 – 7.59 (m, 1H, ArC<u>H</u>), 7.57 – 7.41 (m, 5H, ArC<u>H</u>), 4.18 – 3.90 (m, 2H, NC<u>H</u>$_2$CH$_2$S), 3.20 (ddt, *J* = 44.6, 11.0, 7.1 Hz, 2H, NCH$_2$C<u>H</u>$_2$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.2 (<u>C</u>=O), 147.5 (d, *J* = 9.7 Hz, <u>C</u>O), 134.0 (Ar<u>C</u>), 133.6 (d, *J* = 3.3 Hz, Ar<u>C</u>H), 132.6 (d, *J* = 11.1 Hz, phenyl Ar<u>C</u>H), 131.4 (Ar<u>C</u>), 130.2 (ArC<u>H</u>), 128.6 (d, *J* = 15.9 Hz, phenyl Ar<u>C</u>H), 127.8 (d, *J* = 7.4 Hz, Ar<u>C</u>H), 127.3 (d, *J* = 183.1 Hz, <u>C</u>P), 126.9 (ArC<u>H</u>), 125.9 (ArC<u>H</u>), 120.75 (d, *J* = 4.5 Hz, ArC<u>H</u>), 120.7 (naphthtol ArC<u>H</u>), 117.8 (naphthtol ArC<u>H</u>), 117.7 (naphthtol ArC<u>H</u>), 48.8 (d, *J* = 4.7 Hz, N<u>C</u>H$_2$CH$_2$S), 29.1 (d, *J* = 7.8 Hz NCH$_2$<u>C</u>H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.00; **IR** (film) υ_{max}/cm^{-1}:3058, 1684 (C=O), 1598, 1464, 1440, 1257 (P=O), 1210, 1127, 970, 863, 727, 694; **HRMS** (ESI+): calcd. for $C_{18}H_{17}O_3NPS$ 370.0661 $[M+H]^+$, found 370.0662.

4-allyl-2-methoxyphenyl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**529**)

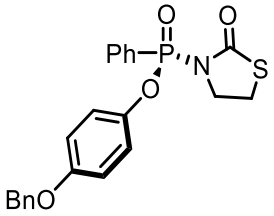


529 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, eugenol (16.1 μL, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (32.7 mg, 0.084 mmol, 84% yield, 90% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 mL/min, λ = 240 nm, t (minor) = 12.00 min, t (major) = 21.25 min.

$[\alpha]_D^{25}$ = +81.4 (c = 0.32, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 – 8.01 (m, 2H, ArC<u>H</u>), 7.63 – 7.55 (m, 1H, ArC<u>H</u>), 7.52 – 7.43 (m, 2H, phenyl ArC<u>H</u>), 7.18 (dd, *J* = 8.2, 1.7 Hz, 1H, eugenol ArC<u>H</u>), 6.77 (d, *J* = 2.0 Hz, 1H, eugenol ArC<u>H</u>), 6.71 (dd, *J* = 8.2, 2.0 Hz, 1H, eugenol ArC<u>H</u>), 5.93 (ddt, *J* = 17.5, 9.6, 6.7 Hz, 1H, <u>H</u>C=CH_2), 5.14 – 5.01 (m, 2H, HC=C<u>H</u>$_2$), 4.20 – 4.03 (m, 2H, NC<u>H</u>$_2$$CH_2$S), 3.84 (s, 3H, OC<u>H</u>$_3$), 3.37 – 3.25 (m, 4H, NCH_2C<u>H</u>$_2$S + allyl C<u>H</u>$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.0 (<u>C</u>=O), 150.8 (d, *J* = 4.3 Hz, Ar<u>C</u>O), 138.5 (d, *J* = 1.7 Hz, Ar<u>C</u>), 137.2 (d, *J* = 9.5 Hz, Ar<u>C</u>), 137.1 (H<u>C</u>=CH_2), 133.2 (d, *J* = 3.4 Hz, phenyl Ar<u>C</u>H), 132.4 (d, *J* = 11.2 Hz, phenyl Ar<u>C</u>H), 128.4 (d, *J* = 15.9 Hz, phenyl Ar<u>C</u>H), 128.0 (d, *J* = 182.8 Hz, <u>C</u>P), 121.9 (d, *J* = 3.7 Hz, eugenol Ar<u>C</u>H), 120.9 (d, *J* = 1.7 Hz, eugenol Ar<u>C</u>H), 116.3 (HC=<u>C</u>H_2), 113.4 (eugenol Ar<u>C</u>H), 56.3 (O<u>C</u>H_3), 48.6 (d, *J* = 4.3 Hz, N<u>C</u>H_2CH_2S), 40.0 (allyl <u>C</u>H_2), 29.2 (d, *J* = 8.0 Hz, NCH_2<u>C</u>H_2S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.11; **IR** (film) υ_{max}/cm^{-1}: 1690 (C=O), 1509, 1259 (P=O), 1205, 1127, 927, 693; **HRMS** (ESI+): calcd. for $C_{19}H_{21}O_4NPS$ 390.0923 $[M+H]^+$, found 390.0923.

4-(benzyloxy)phenyl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**530**)

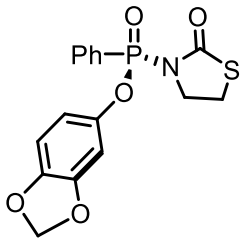


530 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, 4-(benzyloxy)phenol (20.0 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (41.3 mg, 0.097 mmol, 97% yield, 92% ee).

HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 mL/min, λ = 240 nm, t (minor) = 18.53 min, t (major) = 22.27 min.

$[\alpha]_D^{25}$ = +139.5 (c = 0.86, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (ddt, *J* = 14.4, 7.0, 1.4 Hz, 2H, phenyl ArC<u>H</u>), 7.68 – 7.57 (m, 1H, phenyl ArC<u>H</u>), 7.52 (ddd, *J* = 8.6, 6.9, 4.7 Hz, 2H, phenyl ArC<u>H</u>), 7.46 – 7.32 (m, 5H, ArC<u>H</u>), 7.29 – 7.21 (m, 2H, ArC<u>H</u>), 6.99 – 6.91 (m, 2H, ArC<u>H</u>), 5.05 (s, 2H, benzyl C<u>H</u>$_2$), 4.18 – 3.89 (m, 2H, NC<u>H</u>$_2$CH$_2$S), 3.24 (ddt, *J* = 34.1, 11.0, 7.0 Hz, 2H, NCH$_2$C<u>H</u>$_2$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (C=O), 156.5 (Ar<u>C</u>), 143.4 (d, *J* = 9.7 Hz, Ar<u>C</u>O), 136.8 (Ar<u>C</u>), 133.5 (d, *J* = 3.3 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 11.1 Hz, phenyl Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.5 (d, *J* = 15.9 Hz, phenyl Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 127.3 (d, *J* = 182.8 Hz, <u>C</u>P), 122.0 (d, *J* = 4.3 Hz, Ar<u>C</u>H), 116.0, 70.6 (benzyl <u>C</u>H$_2$), 48.8 (d, *J* = 4.5 Hz N<u>C</u>H$_2$CH$_2$S), 29.1 (d, *J* = 7.8 Hz, NCH$_2$<u>C</u>H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.14; **IR** (film) υ_{max}/cm^{-1}: 1689 (C=O), 1502, 1255 (P=O), 1192, 1127, 939, 834, 729, 694; **HRMS** (ESI+): calcd. for $C_{22}H_{21}O_4NPS$ 426.0923 $[M+H]^+$, found 426.0923.

benzo[d][1,3]dioxol-5-yl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**531**)

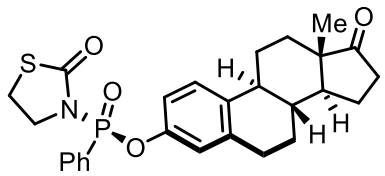


531 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, sesamol (13.8 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (24.0 mg, 0.066 mmol, 66% yield, 92% ee).

HPLC Conditions: CHIRALPAK IB, hexane/isopropanol = 85/15, 1 mL/min, λ = 240 nm, t (major) = 15.42 min, t (minor) = 18.56 min.

[α]$_D^{25}$ = +135.7 (c = 0.45, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 – 8.01 (m, 2H, phenyl ArC<u>H</u>), 7.67 – 7.57 (m, 1H, phenyl ArC<u>H</u>), 7.55 – 7.47 (m, 2H, phenyl ArC<u>H</u>), 6.87 (dd, *J* = 2.4, 1.4 Hz, 1H, sesamol ArC<u>H</u>), 6.81 (ddd, *J* = 8.4, 2.4, 1.8 Hz, 1H, sesamol ArC<u>H</u>), 6.75 (d, *J* = 8.5 Hz, 1H, sesamol ArC<u>H</u>), 5.98 (s, 2H, OC<u>H</u>$_2$O), 4.04 (ddtd, *J* = 36.5, 11.0, 7.1, 1.2 Hz, 2H, NC<u>H</u>$_2$CH$_2$S), 3.36 – 3.14 (m, 2H, NCH$_2$C<u>H</u>$_2$S); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.2 (C=O), 148.3 (Ar<u>C</u>O), 145.4 (Ar<u>C</u>), 143.9 (Ar<u>C</u>), 133.6 (d, *J* = 3.3 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 11.1 Hz, phenyl Ar<u>C</u>H), 128.6 (d, *J* = 16.1 Hz, phenyl Ar<u>C</u>H), 127.1 (d, *J* = 183.2 Hz, <u>C</u>P), 113.4 (d, *J* = 4.8 Hz, sesamol Ar<u>C</u>H), 108.3 (d, *J* = 1.6 Hz, sesamol Ar<u>C</u>H), 103.4 (d, *J* = 4.4 Hz, sesamol Ar<u>C</u>H), 101.9 (O<u>C</u>H$_2$O), 48.8 (d, *J* = 4.5 Hz, N<u>C</u>H$_2$CH$_2$S), 29.2 (d, *J* = 7.8 Hz, NCH$_2$<u>C</u>H$_2$S); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.23; **IR** (film) υ_{max}/cm^{-1}: 2926, 1687 (C=O), 1482, 1247 (P=O), 1171, 1128, 1035, 958, 879, 693; **HRMS** (ESI+): calcd. for $C_{16}H_{15}O_5NPS$ 364.0403 $[M+H]^+$, found 364.0408.

(8*R*,9*S*,13*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**532**)



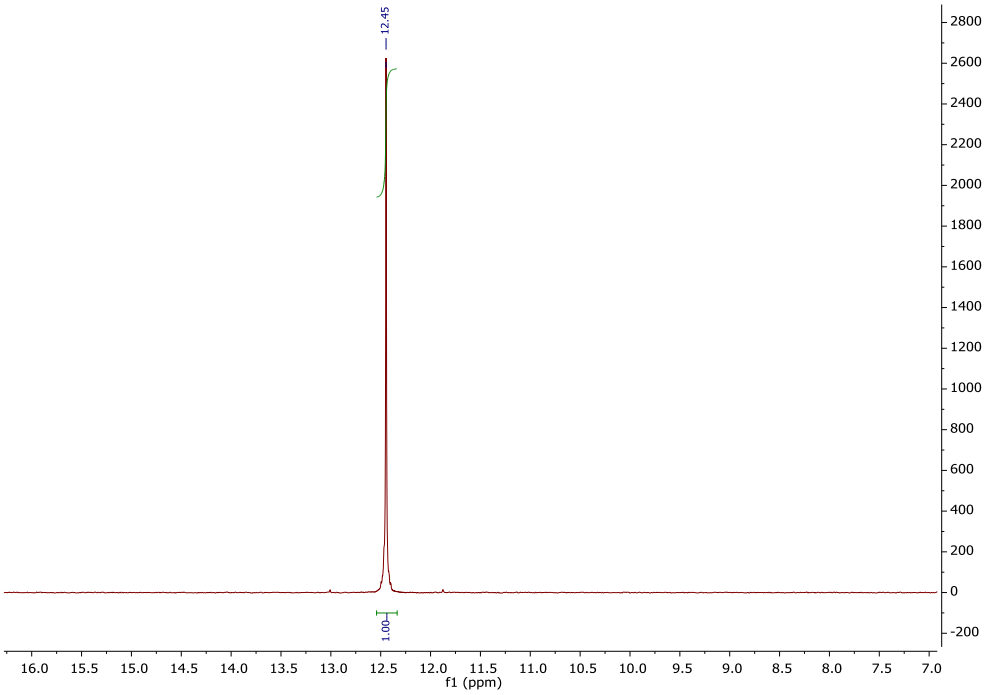
532 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, estrone (27.0 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (48.1 mg, 0.097 mmol, 97% yield, 97:3 dr).

HPLC Conditions: CHIRALPAK IB, hexane/isopropanol = 70:30 IB, 1 mL/min, λ = 240 nm, t (major) = 16.40 min, t (minor) = 23.90 min.

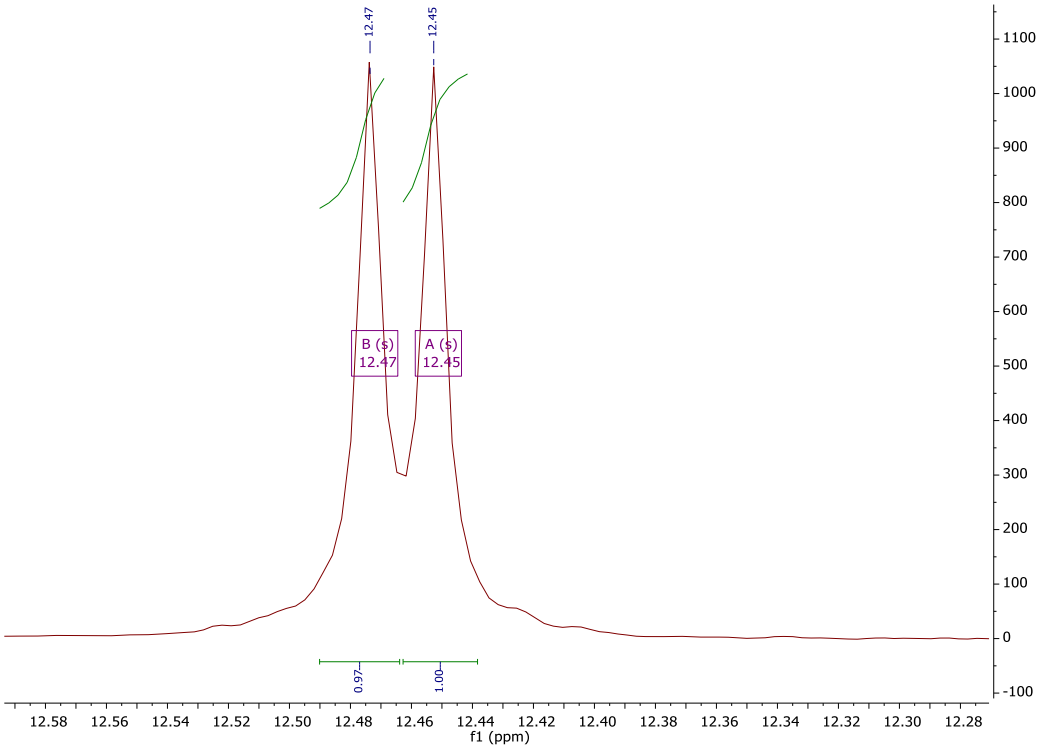
[α]$_D^{25}$ = +149.2 (c = 0.65, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 7.99 (m, 2H, phenyl ArC<u>H</u>), 7.65 – 7.56 (m, 1H, phenyl ArC<u>H</u>), 7.50 (tdd, *J* = 8.2, 4.6, 0.8 Hz, 2H, phenyl ArC<u>H</u>), 7.27 – 7.21 (m, 1H, estrone ArC<u>H</u>), 7.09 (ddd, *J* = 8.5, 2.7, 1.4 Hz, 1H, estrone ArC<u>H</u>), 7.04 (dd, *J* = 2.7, 1.4 Hz, 1H, estrone ArC<u>H</u>), 4.16 – 3.96 (m, 2H, NC<u>H$_2$</u>CH$_2$S), 3.26 (qt, *J* = 11.0, 7.1 Hz, 2H, NCH$_2$C<u>H$_2$</u>S), 2.90 (dd, *J* = 9.0, 4.3 Hz, 2H, C(O)C<u>H$_2$</u>), 2.57 – 2.47 (m, 1H, ½ estrone C<u>H$_2$</u>), 2.44 – 2.23 (m, 3H, estrone C<u>H$_2$</u> + estrone C<u>H</u>), 2.20 – 1.92 (m, 4H, estrone C<u>H$_2$</u> + estrone C<u>H</u>), 1.75 – 1.38 (m, 6H, estrone C<u>H$_2$</u> + estrone C<u>H</u>), 0.91 (s, 3H, estrone C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.8 (<u>C</u>=O, ketone), 174.0 (<u>C</u>=O, thiazolidinone), 147.7 (d, *J* = 9.5 Hz, Ar<u>C</u>O), 138.6 (Ar<u>C</u>), 137.3 (d, *J* = 1.5 Hz, Ar<u>C</u>), 133.4 (d, *J* = 3.4 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 11.1 Hz, phenyl Ar<u>C</u>H), 129.2 (Ar<u>C</u>), 128.5 (d, *J* = 15.9 Hz, phenyl Ar<u>C</u>H), 127.5 (d, *J* = 175.7 Hz, <u>C</u>P), 126.8 (estrone Ar<u>C</u>H), 120.9 (d, *J* = 4.7 Hz, estrone Ar<u>C</u>H), 118.0 (d, *J* = 4.5 Hz, estrone Ar<u>C</u>H), 50.6 (estrone <u>C</u>H), 48.7 (d, *J* = 4.5 Hz, N<u>C</u>H$_2$CH$_2$S), 48.1 (estrone <u>C</u>CH$_3$), 44.2 (estrone <u>C</u>H$_2$), 38.1 (estrone <u>C</u>H), 36.0 (estrone <u>C</u>H$_2$), 31.7 (estrone <u>C</u>H$_2$), 29.5 (estrone <u>C</u>H$_2$), 29.1 (d, *J* = 7.8 Hz, NCH$_2$<u>C</u>H$_2$S), 26.4 (estrone <u>C</u>H$_2$), 25.9 (estrone <u>C</u>H$_2$), 21.7 (estrone <u>C</u>H$_3$), 14.0 (estrone <u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.45; **IR** (film) υ_{max}/cm^{-1}: 2932, 1736 (C=O ketone),

1690 (C=O thiazolidinone), 1492, 1440, 1257, 1223 (P=O), 822, 752, 693; **HRMS** (ESI+): calcd. for $C_{27}H_{31}O_4NPS$ 496.1706 $[M+H]^+$, found 496.1707.

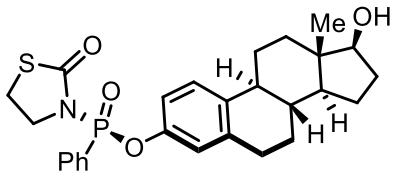
^{31}P NMR 532 (enantioenriched):



^{31}P NMR 532 (racemic):



(8*R*,9*S*,13*S*,17*S*)-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**533**)

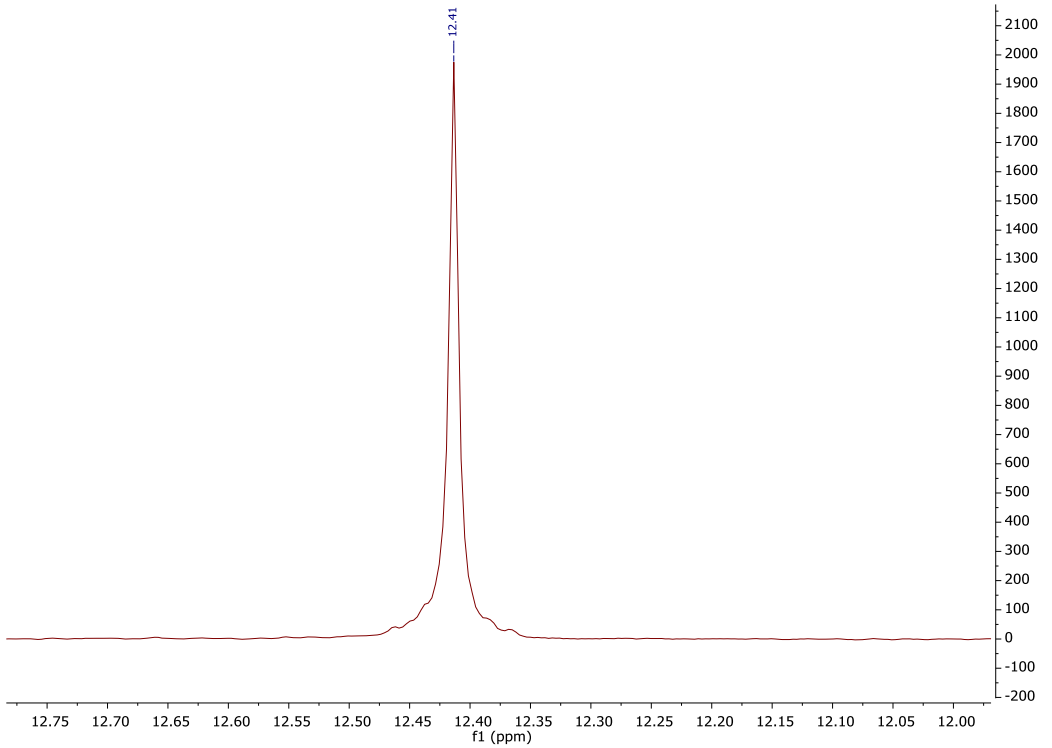


533 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, estradiol (27.2 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. $CHCl_3$:MeCN 9:1. Colourless oil (49.3 mg, 0.099 mmol, 99% yield, 99:1 dr).

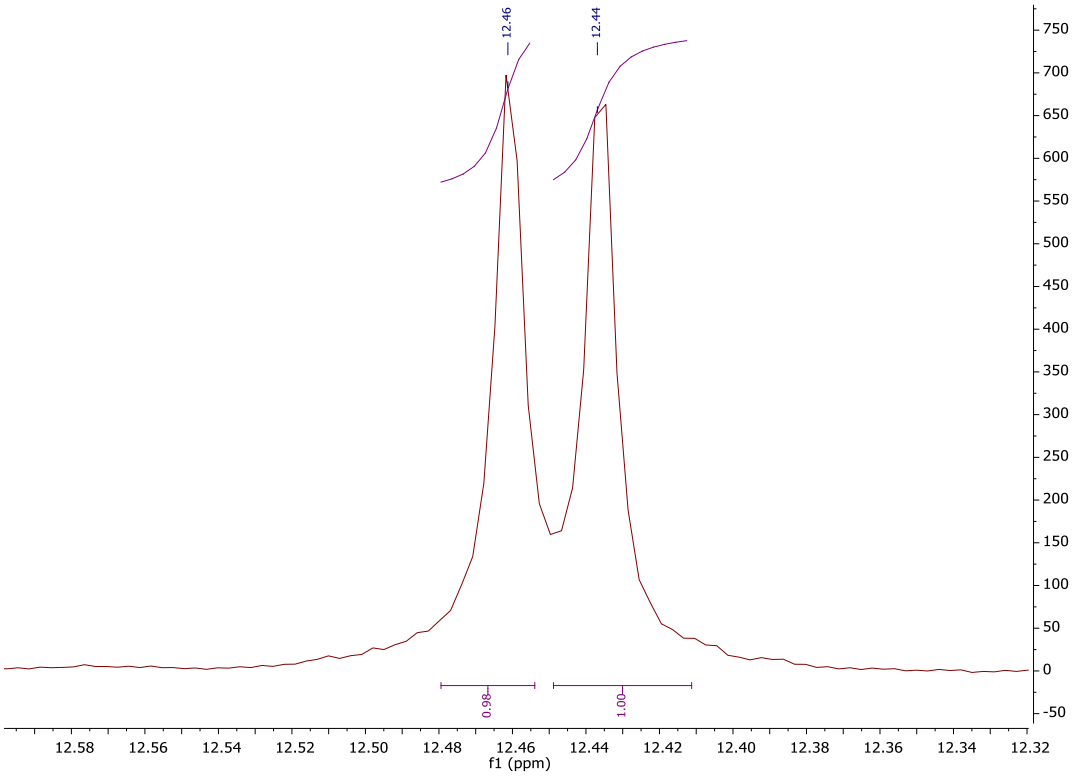
HPLC Conditions: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 mL/min, λ = 240 nm, t (major) = 36.73 min, t (minor) = 49.50 min.

$[\alpha]_D^{25}$ = +106.9 (c = 0.74, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 – 8.03 (m, 2H, phenyl ArC<u>H</u>), 7.65 – 7.56 (m, 1H, phenyl ArC<u>H</u>), 7.55 – 7.46 (m, 2H, phenyl ArC<u>H</u>), 7.26 – 7.23 (m, 1H, estradiol ArC<u>H</u>), 7.08 (ddd, *J* = 8.7, 2.7, 1.4 Hz, 1H, estradiol ArC<u>H</u>), 7.03 (dd, *J* = 2.7, 1.4 Hz, 1H, estradiol ArC<u>H</u>), 4.06 (ddtd, *J* = 30.2, 10.9, 7.0, 1.1 Hz, 2H, NC<u>H$_2$</u>CH$_2$S), 3.73 (t, *J* = 8.5 Hz, 1H, C<u>H</u>OH), 3.26 (qt, *J* = 11.0, 7.1 Hz, 2H, NCH$_2$C<u>H$_2$</u>S), 2.86 (dt, *J* = 8.7, 3.9 Hz, 2H, estradiol benzylic C<u>H$_2$</u>), 2.33 – 2.06 (m, 3H, estradiol C<u>H</u> + C<u>H$_2$</u>), 2.00 – 1.79 (m, 2H, estradiol C<u>H$_2$</u>), 1.70 (dddd, *J* = 12.3, 9.8, 7.0, 3.1 Hz, 1H, ½ estradiol C<u>H$_2$</u>), 1.61 – 1.09 (m, 6H, estradiol C<u>H</u> + C<u>H$_2$</u>), 0.79 (s, 3H, estradiol C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (<u>C</u>=O), 147.5 (d, *J* = 9.5 Hz, Ar<u>C</u>O), 138.9 (Ar<u>C</u>), 137.9 (Ar<u>C</u>) 133.4 (d, *J* = 3.2 Hz, Phenyl Ar<u>C</u>H), 132.6 (d, *J* = 11.1 Hz, Phenyl Ar<u>C</u>H), 128.5 (d, *J* = 15.9 Hz, Phenyl Ar<u>C</u>H), 127.5 (d, *J* = 174.5 Hz, <u>C</u>P), 126.8 (estradiol Ar<u>C</u>H), 120.9 (d, *J* = 4.6 Hz, estradiol Ar<u>C</u>H), 117.9 (d, *J* = 4.4 Hz, estradiol Ar<u>C</u>H), 81.9 (<u>C</u>HOH), 50.2 (estradiol <u>C</u>H), 48.8 (d, *J* = 4.6 Hz, N<u>C</u>H$_2$CH$_2$S), 44.2 (estradiol <u>C</u>H), 43.1 (<u>C</u>CH$_3$), 38.6 (estradiol <u>C</u>H), 36.8 (estradiol <u>C</u>H$_2$), 30.7 (estradiol <u>C</u>H$_2$), 29.7 (estradiol <u>C</u>H$_2$), 29.1 (d, *J* = 7.7 Hz, NCH$_2$<u>C</u>H$_2$S), 27.1 (estradiol <u>C</u>H$_2$), 26.3 (estradiol <u>C</u>H$_2$), 23.3 (estradiol <u>C</u>H$_2$), 11.2 (estradiol <u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.41; **IR** (film) υ_{max}/cm^{-1}:2926, 1688 (C=O), 1492, 1440, 1224 (P=O), 1129, 970, 693; **HRMS** (ESI+): calcd. for $C_{27}H_{33}O_4NPS$ 498.1862 $[M+H]^+$, found 498.1862.

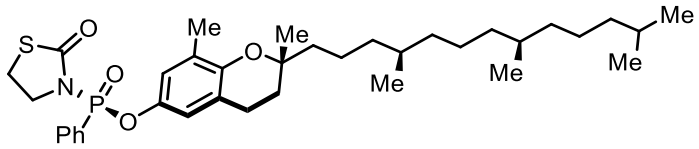
^{31}P NMR 533 (enantioenriched):



^{31}P NMR 533 (racemic):



(*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl-(*R*)-(2-oxothiazolidin-3-yl)(phenyl)phosphinate (**534**)



534 was synthesized following **GP IX**. **505** (32.6 mg, 0.10 mmol) was used as electrophile, δ-tocopherol (40.2 mg, 0.10 mmol) was used as nucleophile and BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL) at 0 °C. Toluene:MeOH 95:5. Colourless oil (61.5 mg, 0.098 mmol, 98% yield, 94:6 dr (determined by chiral HPLC)).

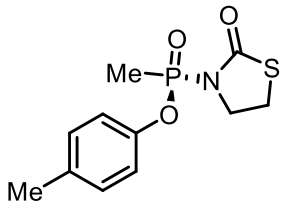
HPLC Conditions: CHIRALPAK IB, hexane/isopropanol = 90/10, 1 mL/min, λ = 240 nm, t (major) = 7.78 min, t (minor) = 9.34 min.

[α]$_D^{25}$ = +83.2 (c = 0.85, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 – 8.00 (m, 2H, ArC<u>H</u>), 7.64 – 7.55 (m, 1H), 7.54 – 7.45 (m, 2H, phenyl ArC<u>H</u>), 6.93 – 6.90 (m, 1H, δ-tocopherol ArC<u>H</u>), 6.87 (dd, *J* = 2.9, 1.6 Hz, 1H, δ-tocopherol ArC<u>H</u>), 4.03 (ddtd, *J* = 37.3, 11.0, 7.0, 1.2 Hz, 2H, NC<u>H$_2$</u>CH$_2$S), 3.24 (ddt, *J* = 29.9, 10.9, 7.0 Hz, 2H, NCH$_2$C<u>H$_2$</u>S), 2.73 (q, *J* = 6.5 Hz, 2H, δ-tocopherol ArC<u>H$_2$</u>CH$_2$ (ring)), 2.15 (s, 3H, δ-tocopherol ArC<u>H$_3$</u>), 1.76 (ddq, *J* = 20.1, 13.4, 6.9 Hz, 2H, δ-tocopherol ArCH$_2$C<u>H$_2$</u> (ring)), 1.53 (qdd, *J* = 13.3, 7.1, 3.2 Hz, 3H, δ-tocopherol C<u>H</u> + C<u>H$_2$</u>), 1.46 – 0.98 (m, 14H, δ-tocopherol C<u>H</u> + C<u>H$_2$</u> + CC<u>H$_3$</u>), 0.90 – 0.81 (m, 12H, δ-tocopherol C<u>H$_3$</u> (iPr and alkyl chain)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (<u>C</u>=O), 149.7 (Ar<u>C</u>), 141.6 (d, *J* = 9.6 Hz, Ar<u>C</u>O), 133.3 (d, *J* = 3.3 Hz, phenyl Ar<u>C</u>H), 132.6 (d, *J* = 10.9 Hz, phenyl Ar<u>C</u>H), 128.4 (d, *J* = 15.8 Hz, phenyl Ar<u>C</u>H), 127.8 (Ar<u>C</u>), 127.7 (d, *J* = 183.3 Hz, <u>C</u>P), 121.6 (Ar<u>C</u>), 120.7 (d, *J* = 4.3 Hz, δ-tocopherol Ar<u>C</u>H), 118.6 (d, *J* = 4.3 Hz, δ-tocopherol Ar<u>C</u>H), 48.8 (d, *J* = 4.3 Hz, N<u>C</u>H$_2$CH$_2$S), 40.3 (δ-tocopherol <u>C</u>H$_2$), 39.5 (δ-tocopherol <u>C</u>H$_2$), 37.6 (δ-tocopherol <u>C</u>H$_2$), 37.6 (δ-tocopherol <u>C</u>H$_2$), 37.4 (δ-tocopherol <u>C</u>H$_2$), 32.9 (δ-tocopherol <u>C</u>H), 32.8 (δ-tocopherol <u>C</u>H), 31.2 (δ-tocopherol ArCH$_2$<u>C</u>H$_2$ (ring)), 29.1 (d, *J* = 7.6 Hz, NCH$_2$<u>C</u>H$_2$S), 28.1 (δ-tocopherol <u>C</u>H$_2$), 24.9 (δ-tocopherol <u>C</u>H$_2$), 24.6 (δ-tocopherol <u>C</u>H$_2$), 24.2 (δ-tocopherol C<u>C</u>H$_3$), 22.8 (δ-tocopherol <u>C</u>H), 22.8 (δ-tocopherol <u>C</u>H$_3$), 22.6 (δ-tocopherol <u>C</u>H$_3$), 21.1 (δ-tocopherol Ar<u>C</u>H$_2$CH$_2$

(ring)), 19.9 (δ-tocopherol $\underline{C}H_3$), 19.8 (δ-tocopherol $\underline{C}H_3$), 16.2 (δ-tocopherol Ar$\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.45; **IR** (film) υ_{max}/cm^{-1}: 2926, 1692 (C=O), 1474, 1258 (P=O), 1128, 1008, 878, 727, 693; **HRMS** (ESI+): calcd. for $C_{36}H_{55}O_4NPS$ 628.3584 $[M+H]^+$, found 628.3580.

5.4.8 Products: Scope with respect to the P(V) electrophile

4-methylphenyl-(1,3-thiazolidin-2-one)-(*R*)-methylphosphonate (**549**)

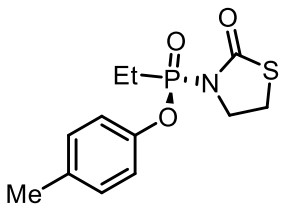


549 was synthesised following **General Procedure IX**. **540** (26.6 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL). CH_2Cl_2:acetone 95:5, colourless oil (26.4 mg, 0.097 mmol, 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.

$[\alpha]_D^{25}$ = +92.6 (c = 0.33, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.05 (m, 4H, ArC$\underline{H}$), 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, ArC$\underline{H}_3$), 1.97 (d, *J* = 17.9 Hz, 3H, C$\underline{H}_3$P); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.8 ($\underline{C}$=O), 147.3 (d, *J* = 9.8 Hz, Ar$\underline{C}$O), 135.4 (d, *J* = 1.9 Hz, Ar$\underline{C}$CH$_3$), 130.4 (d, *J* = 1.7 Hz, Ar$\underline{C}$H), 120.6 (d, *J* = 4.1 Hz, Ar$\underline{C}$H), 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 (Ar$\underline{C}$H$_3$), 13.2 (d, *J* = 131.6 Hz, $\underline{C}$H$_3$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.

4-methylphenyl-(1,3-thiazolidin-2-one)-(*R*)-ethylphosphonate (**550**)

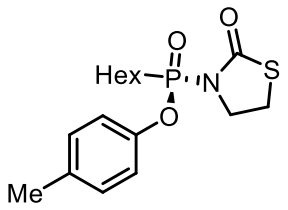


550 was synthesised following **General Procedure IX**. **541** (28.0 mg, 0.1 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) as catalyst in EtOAc (1.60 mL). CH_2Cl_2:acetone 95:5, colourless oil (27.2 mg, 0.095 mmol, 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.

$[\alpha]_D^{25}$ = +28.9 (c = 0.07, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.05 (m, 4H, ArC<u>H</u>), 4.05 – 3.71 (m, 2H, NC<u>H$_2$</u>CH$_2$S), 3.36 – 3.04 (m, 2H, NCH$_2$C<u>H$_2$</u>S), 2.41 – 2.22 (m, 5H, ArC<u>H$_3$</u>, CH$_3$C<u>H$_2$</u>), 1.34 – 1.21 (m, 3H, C<u>H$_3$</u>CH$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.67 (<u>C</u>=O), 147.39 (d, *J* = 10.4 Hz, Ar<u>C</u>O), 135.20 (Ar<u>C</u>CH$_3$), 130.30 (d, *J* = 1.7 Hz, Ar<u>C</u>H), 120.64 (d, *J* = 4.1 Hz, Ar<u>C</u>H), 48.48 (d, *J* = 3.5 Hz, N<u>C</u>H$_2$CH$_2$S), 29.11 (d, *J* = 7.1 Hz, NCH$_2$<u>C</u>H$_2$S), 20.78 (Ar<u>C</u>H$_3$), 19.9 (d, *J* = 128.3 Hz, CH$_3$<u>C</u>H$_2$P), 5.5 (d, *J* = 6.0 Hz, <u>C</u>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.

4-methylphenyl-(1,3-thiazolidin-2-one)-(*R*)-hexylphosphonate (**551**)

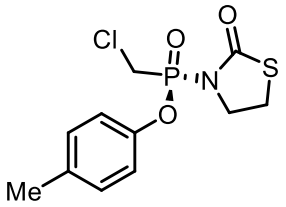


551 was synthesised following **General Procedure IX**. **542** (32.2 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). CH_2Cl_2:acetone 95:5, colourless oil (30.0 mg, 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.

$[\alpha]_D^{25}$ = +56.8 (c = 0.36, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 – 7.04 (m, 4H, ArH), 4.03 – 3.71 (m, 2H, NCH$_2$CH$_2$S), 3.32 – 3.04 (m, 2H, NCH$_2$CH$_2$S), 2.39 – 2.21 (m, 5H, ArCH$_3$, CH$_2$CH$_2$P), 1.83 – 1.57 (m, 2H, CH$_2$CH$_2$CH$_2$P), 1.49 – 1.38 (m, 2H, CH$_2$CH$_2$P), 1.36 – 1.26 (m, 4H, CH$_3$CH$_2$CH$_2$, CH$_3$CH$_2$CH$_2$), 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, ArCCH$_3$), 130.4 (d, *J* = 1.6 Hz, ArCH), 120.8 (d, *J* = 4.1 Hz, ArCH), 48.5 (d, *J* = 3.5 Hz, NCH$_2$CH$_2$S), 31.3 (CH$_3$CH$_2$), 30.2 (d, *J* = 17.8 Hz, CH$_2$CH$_2$P), 29.2 (d, *J* = 7.1 Hz, NCH$_2$CH$_2$S), 26.7 (d, *J* = 126.0 Hz, CH$_2$CH$_2$P), 22.5 (d, *J* = 4.8 Hz, CH$_3$CH$_2$CH$_2$), 21.5 (d, *J* = 4.7 Hz, CH$_2$CH$_2$CH$_2$P), 20.9 (ArCH$_3$), 14.1 (d, *J* = 6.6 Hz, CH$_3$CH$_2$); **^{31}P NMR** (162 MHz, $CDCl_3$) 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.

4-methylphenyl-(1,3-thiazolidin-2-one)-(*R*)-chloromethylphosphonate (**552**)

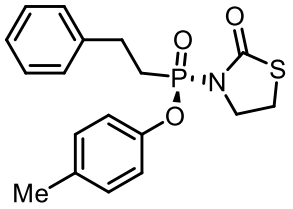


552 was synthesised following **General Procedure IX**. **543** (30.7 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). CH_2Cl_2:acetone 95:5, Colourless solid (14.1 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, Ar<u>H</u>), 4.17 – 3.83 (m, 4H, NC<u>H</u>$_2$CH$_2$S, ClC<u>H</u>$_2$P), 3.33 – 3.12 (m, 2H, NCH$_2$C<u>H</u>$_2$S), 2.26 (s, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9 (<u>C</u>=O), 146.9 (d, *J* = 10.0 Hz, Ar<u>C</u>O), 135.7 (d, *J* = 1.8 Hz, Ar<u>C</u>CH$_3$), 130.4 (d, *J* = 1.5 Hz, Ar<u>C</u>H), 120.3 (d, *J* = 4.3 Hz, Ar<u>C</u>H), 48.7 (d, *J* = 3.7 Hz, N<u>C</u>H$_2$CH$_2$S), 34.3 (d, *J* = 147.5 Hz, Cl<u>C</u>H$_2$P), 29.2 (d, *J* = 7.7 Hz, NCH$_2$<u>C</u>H$_2$S), 20.7 (Ar<u>C</u>H$_3$); **^{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 $C_{11}H_{14}O_3N^{35}ClPS$ 306.0115 $[M+H]^+$, found 306.0117.

4-methylphenyl-(1,3-thiazolidin-2-one)-(*R*)-(phenylethyl)phosphonate (**553**)

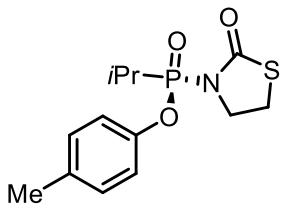


553 was synthesised following **General Procedure IX**. **545** (35.6 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, BIMP **516-P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (0.80 mL). CH_2Cl_2:acetone 95:5, colourless oil (25.1 mg, 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.

$[\alpha]_D^{25}$ = +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, NCH_2CH_2S), 3.12 – 2.84 (m, 4H, NCH_2CH_2S, $ArCH_2CH_2P$), 2.80 – 2.39 (m, 2H, $ArCH_2CH_2P$), 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, $ArCCH_2CH_2P$), 135.2 (d, *J* = 1.8 Hz, $ArCCH_3$), 130.2 (d, *J* = 1.6 Hz, phenol ArCH), 128.6 (phenyl ArCH), 128.2 (phenyl ArCH), 126.5 (phenyl ArCH), 120.6 (d, *J* = 4.1 Hz, phenol ArCH), 48.0 (d, *J* = 3.8 Hz, NCH_2CH_2S), 28.7 (d, *J* = 7.4 Hz, $ArCH_2CH_2P$), 27.7 (d, *J* = 126.0 Hz, $ArCH_2CH_2P$), 27.7 (d, *J* = 3.9 Hz, NCH_2CH_2S), 20.7 ($ArCH_3$); **^{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.

4-methylphenyl-(1,3-thiazolidin-2-one)-(*R*)-isopropylphosphonate (**554**)

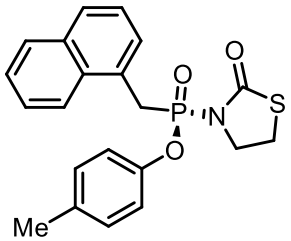


554 was synthesised following **General Procedure IX**. **544** (29.4 mg, 0.1 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.1 mmol) was used as nucleophile, BIMP **516-(P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). CH_2Cl_2:acetone 95:5, colourless oil (23.6 mg, 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.

$[\alpha]_D^{25}$ = +35.5 (c = 0.54, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.04 (m, 4H, Ar<u>H</u>), 3.98 – 3.73 (m, 2H, NC<u>H</u>$_2$CH$_2$S), 3.30 – 3.04 (m, 2H, NCH$_2$C<u>H</u>$_2$S), 2.87 – 2.69 (m, 1H, C<u>H</u>(CH$_3$)$_2$), 2.32 (s, 3H, ArC<u>H</u>$_3$), 1.45 – 1.17 (m, 6H, CH(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.7 (C=O), 147.7 (d, *J* = 11.5 Hz, Ar<u>C</u>O), 135.2 (d, *J* = 1.7 Hz, Ar<u>C</u>CH$_3$), 130.4 (d, *J* = 1.6 Hz, Ar<u>C</u>H), 120.7 (d, *J* = 4.1 Hz, Ar<u>C</u>H), 49.0 (d, *J* = 3.1 Hz, N<u>C</u>H$_2$CH$_2$S), 29.4 (d, *J* = 6.6 Hz, NCH$_2$<u>C</u>H$_2$S), 26.1 (d, *J* = 127.0 Hz, <u>C</u>H(CH$_3$)$_2$), 20.9 (Ar<u>C</u>H$_3$), 15.2 (d, *J* = 2.6 Hz, CH(<u>C</u>H$_3$)$_2$), 14.9 (d, *J* = 5.5 Hz, CH(<u>C</u>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.

4-methylphenyl-(1,3-thiazolidin-2-one)-(*R*)-(1-naphthylmethyl)phosphonate (**555**)

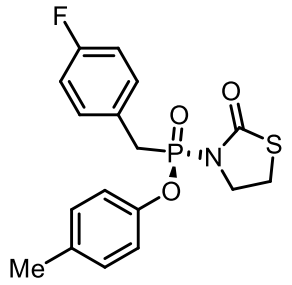


555 was synthesised following **General Procedure IX. 546** (39.0 mg, 0.10 mmol) was used as phosphonate, 4-methylphenol (10.8 mg, 0.10 mmol) was used as nucleophile, BIMP **516-(P(PMP)$_3$** (8.5 mg, 0.01 mmol) was used as catalyst in EtOAc (1.60 mL). CH_2Cl_2:acetone 95:5, colourless oil (25.2 mg, 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, NCH_2CH_2S), 3.03 – 2.82 (m, 2H, NCH_2CH_2S), 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, phenol 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, phenol ArCH), 124.5 (d, *J* = 2.2 Hz, ArCH), 120.5 (d, *J* = 4.4 Hz, ArCH), 48.6 (d, *J* = 3.5 Hz, NCH_2CH_2S), 31.0 (d, *J* = 125.2 Hz, CH_2P), 29.0 (d, *J* = 7.1 Hz, NCH_2CH_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.

4-methylphenyl-(1,3-thiazolidin-2-one)-(*R*)-(4-fluorobenzyl)phosphonate (**556**)

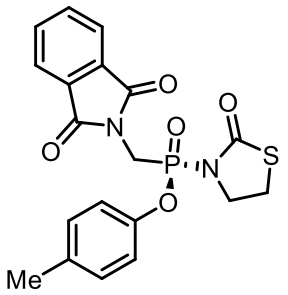


556 was synthesised following **General Procedure IX**. **547** (20.0 mg, 0.056 mmol) was used as phosphonate, 4-methylphenol (5.6 mg, 0.056 mmol) was used as nucleophile, BIMP **516-(P(PMP)$_3$** (4.3 mg, 0.005 mmol) was used as catalyst in EtOAc (0.80 mL). CH_2Cl_2:acetone 95:5, colourless oil (13.2 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, $CDCl_3$) 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.

4-methylphenyl-(1,3-thiazolidin-2-one)-(*R*)-(pthalamidomethyl)phosphonate (**557**)



557 was synthesised following **General Procedure IX**. **548** (21.0 mg, 0.05 mmol) was used as phosphonate, 4-methylphenol (5.4 mg, 0.05 mmol) was used as nucleophile, BIMP **516-(P(PMP)$_3$** (4.3 mg, 0.005 mmol) was used as catalyst in EtOAc (0.80 mL). 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, $CDCl_3$) δ 7.93 – 7.72 (m, 4H, Ar<u>H</u>), 7.13 (d, *J* = 1.1 Hz, 4H, Ar<u>H</u>), 4.67 – 4.50 (m, 2H, C<u>H</u>$_2$P), 4.06 – 3.75 (m, 2H, NC<u>H</u>$_2$CH$_2$S), 3.44 – 3.13 (m, 2H, NCH$_2$C<u>H</u>$_2$S), 2.32 (d, *J* = 1.1 Hz, 3H, ArC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6 (<u>C</u>=O phtalimide), 167.4 (<u>C</u>=O thioazolidinone), 147.3 (d, *J* = 10.5 Hz, Ar<u>C</u>O), 135.7 (d, *J* = 1.6 Hz, Ar<u>C</u>CH$_3$), 134.4 (Ar<u>C</u>H), 132.1 (Ar<u>C</u>), 130.5 (Ar<u>C</u>H), 123.8 (Ar<u>C</u>H), 120.6 (d, *J* = 4.5 Hz, Ar<u>C</u>H), 48.0 (d, *J* = 4.7 Hz, N<u>C</u>H$_2$CH$_2$S), 34.5 (d, *J* = 146.1 Hz, <u>C</u>H$_2$P), 29.5 (d, *J* = 7.7 Hz, NH$_2$<u>C</u>H$_2$S), 20.9 (Ar<u>C</u>H$_3$); **^{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.

5.5 References for Chapter 5

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