

Linear Allylic Halides in Metal-Catalysed Asymmetric Substitutions



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A thesis submitted for the degree of
Doctor of Philosophy
Trinity 2018

Declaration

This thesis describes work carried out in the Chemistry Research Laboratory, University of Oxford, between October 2014 and June 2018 under the supervision of Prof. Stephen P. Fletcher. This thesis is a result of my own work, except when otherwise stated, and has not been submitted for any other degree at this or any other university.

Nisha Mistry

Abstract

This thesis describes the use of linear allylic halides in transition metal catalysed asymmetric reactions.

In the first chapter we report the development of a copper-catalysed *hetero*-asymmetric allylic alkylation reaction of ester-containing allylic bromides. Despite the synthesis of a number of phosphoramidite ligands based on a bis-phenol backbone, we achieve only a 44% yield and 73% ee in this challenging reaction. Application of our reaction conditions to other linear allylic halides that do not bear the ester group resulted in only moderate results.

In the second chapter we describe new phosphoramidite ligands based on (*S,S*)-*trans*-cyclohexanediol and (*R,R*)-(+)-1,2-diphenyl-1,2-ethanediol. The ligands were examined in 3 different copper-catalysed asymmetric reactions and enantioselectivity of up to 89% ee was observed. Using the *meso*-diols with a chiral non-racemic amine gave diastereomeric ligands bearing achirotopic stereogenic phosphorus atoms, which were characterised with the assistance of X-ray crystallography and VT NMR studies.

In the last chapter we discuss the development of a rhodium-catalysed asymmetric carboxylation of ester-containing allylic bromides to form stereogenic carbon centres bearing two different carboxylates. The method uses common carboxylic acids as nucleophiles to form new C-O bonds in high yields and excellent enantioselectivities. We also demonstrate that the products can be used to form other chiral acetal derivatives, including valuable γ -butenolides, in subsequent RCM reactions.

The ease of synthesis and stability of the products suggests that a broad range of new chemical species may be accessible by developing strategies to form stereogenic carbon centres featuring different combinations of multiple heteroatoms. We have begun to demonstrate this by using this method for the formation of *O,N*-aminals.

Acknowledgments

First and foremost, I would like to thank my supervisor Steve. Thank you for being so supportive throughout my DPhil, for all your guidance through my challenging projects and for knowing when to give me a kick in the right direction and when to let me abandon ship and go home early! It has been an absolute pleasure to be a member of the Fletcher group and I will take so much away from this experience.

To the Fletcher group: Mireia and Chus, I could not have asked for two better people to spend these years working next to. You are incredible people, brilliant chemists and have brought so much joy and laughter to my time in Oxford. I have learnt so much from you, thank you for always being there for me. To Thomas and Philipp, thank you for all the fun times we had. I will always remember (or remember that I don't remember) all of our fun pub trips, bowling, karaoke, dinners and dancing. To the rest of the Fletcher group, past and present: Manu, Zhenbo, Sarah, Nod, Diego, Reece, Elias, Lucy and everyone else, thank you for being such a fabulous bunch of people and all the fun we had.

To Chus, Sarah, Reece, Lucy and Philipp, thank you for proof reading this thesis, I really appreciate all the time you put in and feedback you gave me.

To all my friends at Oriel College, my housemates, my fellow committee members, thank you all for all the great times and great laughs.

To my Mum, Dad and Sheena, thank you for your love, support and always encouraging me. Thank you Dad for checking all my stereochemistry, thank you Mum for proof reading my whole thesis! I wouldn't have been able to do this without you and I hope I will always make you proud.

Finally to Keshav, my better half. My time at Oxford has been so much more incredible than I ever imagined, because I met you. I cannot believe I have been so lucky to find someone who loves me as much as you do. Thank you for all your love and support.

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Å	Ångstrom
AAA	asymmetric allylic alkylation
Ac	acetyl
ACA	asymmetric conjugate addition
acac	acetylacetone
<i>anti</i>	opposite
aq.	aqueous
ATR	attenuated total reflection
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Boc	<i>tert</i> -butyloxycarbonyl
Bu	butyl
Bz	benzoyl
C	Celsius
c	concentration
calcd.	calculated
Cl-MeO-BIPHEP	(5,5'-Dichloro-6,6'-dimethoxy-1,1'-biphenyl)-2,2'-diyl-bis(diphenylphosphine)
COD	1,3-cyclooctadiene
COE	cyclooctene
COSY	correlation spectroscopy
Cp	cyclopentadienyl
d	doublet (NMR)
DCE	dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DEPT	Distortionless enhancement by polarization transfer spectroscopy
DIB	diacetoxyiodobenzene
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine, Hünig's base
DME	1,2-dimethoxyethane
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DTBM-SEGPBOS	5,5'-Bis[di(3,5-di- <i>tert</i> -butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
DYKAT	dynamic kinetic asymmetric transformation
ee	enantiomeric excess
<i>E</i>	entgegen

EI	electron impact ionisation
eq.	equivalents
ESI	electron impact ionisation
Et	ethyl
<i>et al.</i>	<i>et alia</i> (Latin) and others
g	grams
GC	gas chromatography
<i>gem</i>	geminal
<i>h</i> -AAA	<i>hetero</i> -asymmetric allylic alkylation
hal.	halide
HPLC	high performance liquid chromatography
hr(s)	hour(s)
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
<i>i</i> -	iso
IR	infrared
<i>J</i>	coupling constant (NMR)
K	kelvin
K _a	acid dissociation constant
<i>L</i>	levorotatory
LRMS	low resolution mass spectrometry
m.p.	melting point
M	molar
Me	methyl
mg	milligrams
MHz	mega Hertz
min(s)	minute(s)
mL	millilitres
mm	millimetres
mmol	millimoles
Ms	mesylate
MS	molecular sieves
MTBAP	methyltributylammonium permanganate
MTBE	methyl <i>tert</i> -butyl ether
n	generic integer
n.d.	not determined
nap	naphthyl
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NHC	<i>N</i> -heterocyclic carbene
nm	nanometers
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Ns	nitrobenzenesulfonyl

Nu	nucleophile
<i>o</i>	<i>ortho</i>
o/n	overnight
<i>p</i>	<i>para</i>
ppm	parts per million
Ph	phenyl
pK _a	logarithmic acid dissociation constant
Pr	propyl
<i>p</i> -TSA	<i>para</i> -toluene sulfonic acid
R	any group
<i>R</i>	rectus
RCM	ring closing metathesis
r.t.	room temperature
<i>S</i>	sinister
s	seconds
sat.	saturated
SFC	supercritical fluid chromatography
S _N 2	bimolecular nucleophilic substitution
S _N 2'	bimolecular nucleophilic substitution with allylic rearrangement
SM	starting material
sp ²	orbital hybridisation: 33% s and 67% p character
sp ³	orbital hybridisation: 25% s and 75% p character
<i>t</i> - or <i>tert</i> -	tertiary
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TBHP	<i>tert</i> -butyl hydroperoxide
TC	thiophene-2-carboxylate
THF	tetrahydrofuran
Tf or triflate	trifluoromethanesulfonate
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Tol	tolyl
t _R	retention time
Ts	tosyl
UV	ultraviolet
μL	microliters
VT	variable temperature
Xylyl-P-PHOS	2,2',6,6'-Tetramethoxy-4,4'-bis(di(3,5-xylyl)phosphino)-3,3'-bipyridine
<i>Z</i>	<i>zusammen</i>
δ	chemical shift (NMR)
λ	wavelength (HPLC/SFC)
ν	wavenumber (IR)

Contents

Declaration	i
Abstract	iii
Acknowledgements	v
Abbreviations	vii
1 Introduction	1
1.1 Asymmetric metal-catalysed reactions	1
1.2 Asymmetric allylic alkylation reactions	1
1.2.1 Copper-catalysed asymmetric allylic alkylations	4
1.2.2 Copper-catalysed asymmetric allylic alkylations using alkylzirconium reagents	9
1.3 Tandem reactions	11
1.4 Project aim	13
2 Studies towards a copper-catalysed asymmetric allylic alkylation	15
2.1 Tandem reactions initiated by asymmetric allylic alkylations	15
2.2 Hydrozirconation reactions with dienes	16
2.3 Studies towards functionalised allylic alcohols	18
2.3.1 Reaction development	20
2.3.2 Phosphoramidite ligands based on the bis-phenol backbone	25
2.3.3 Design and synthesis of 2 nd generation ligands	28
2.4 Asymmetric allylic alkylations of linear substrates using alkylzirconium reagents	38
2.5 Asymmetric allylic alkylations with α -halo acetates and benzoates	43
2.6 Conclusions	49

3 Phosphoramidite ligands based on simple 1,2-diols	51
3.1 Examination of new ligands in asymmetric metal-catalysed reactions	53
3.2 Phosphoramidites with achirotopic stereogenic P-atoms	57
3.3 Conclusions	63
4 Rhodium-catalysed asymmetric allylic substitutions	65
4.1 Asymmetric substitutions using boronic acids	65
4.2 Chiral acetals and their derivatives	67
4.3 Stereocontrolled synthesis of <i>geminal</i> -dicarboxylates	69
4.3.1 Reaction development	70
4.3.2 Reaction scope	84
4.4 Catalytic asymmetric synthesis of <i>O,N</i> -aminals	90
4.5 Conclusions and future work	94
5 Experimental	96
5.1 General methods	96
5.2 General experimental procedures	99
5.3 Experimental procedures	105
6 References	280

1 Introduction

1.1 Asymmetric metal-catalysed reactions

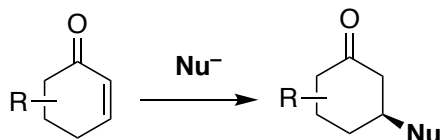
Asymmetric metal-catalysed reactions are powerful tools, fundamental for accessing materials, fragrances and biologically relevant molecules such as pharmaceuticals and natural products. Single-enantiomer compounds are typically generated *via* one of the following strategies: 1) asymmetry is introduced to a prochiral substrate; 2) a catalyst preferentially reacts with one enantiomer of a racemic starting material (the starting material undergoes a resolution); 3) chiral pool synthesis, starting from readily available chiral compounds such as monosaccharides and amino acids.^{1,2}

The use of metal complexes in asymmetric catalysis dates back to the 1950's starting with asymmetric hydrogenations.³ This was shortly followed by asymmetric oxidations; it is therefore unsurprising that the most thoroughly developed transition metal-catalysed reactions are those involving the transfer of either oxygen, such as in epoxidation or dihydroxylation reactions, or molecular hydrogen.⁴ Cyclopropanations and the Diels-Alder reaction were the first examples of asymmetric C-C bond forming reactions. This was followed by the development of the Aldol reaction which enabled additions of non-stabilised nucleophiles into carbonyls.³

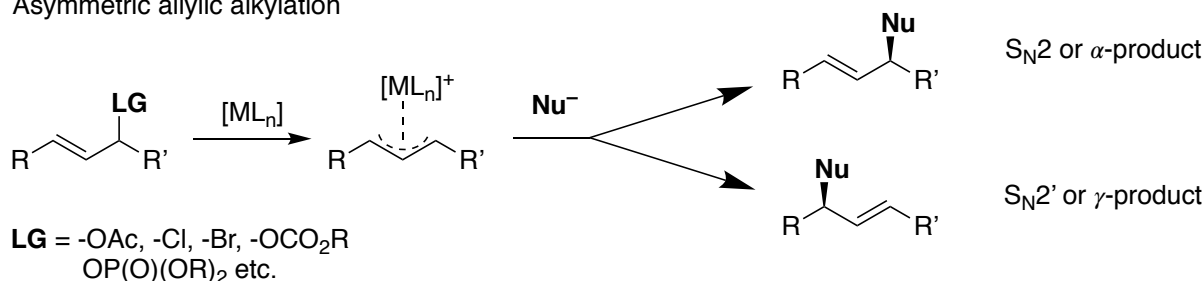
1.2 Asymmetric allylic alkylation reactions

The prochiral approach for the generation of chiral compounds is exemplified by two common approaches: asymmetric conjugate addition (ACA) and asymmetric allylic alkylation (AAA) reactions; this thesis deals with the latter.

Asymmetric conjugate addition

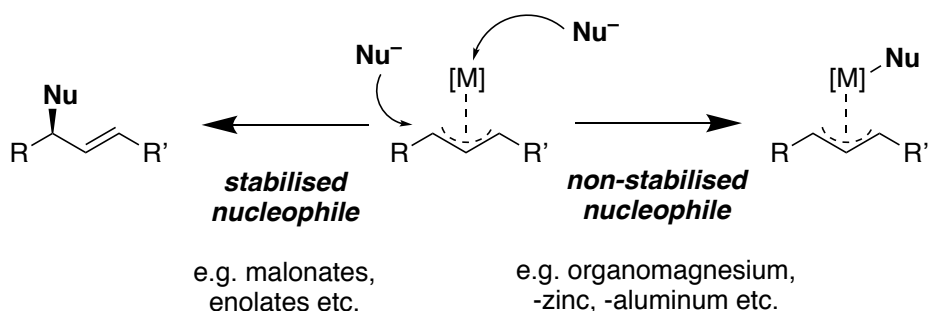


Asymmetric allylic alkylation



Scheme 1.1 Addition to a prochiral starting material by an ACA reaction (top) and AAA (bottom).
AAA reactions may proceed via S_N2 or S_N2' substitution.

Asymmetric allylic alkylations (also known as asymmetric allylic substitutions) have proved to be some of the most versatile metal-catalysed reactions. This type of reaction has been studied with a wide range of transition metals including Cu, Pd, Rh, W, Mo, Ir, Ni, Ru, Pt and Fe.⁴ AAA reactions differ from other methods of asymmetric induction in two important ways: the number of mechanisms for determining the enantioselectivity and the diverse bond types that can be formed. In addition, AAA reactions are able to convert very different starting materials, either chiral racemic, *meso*, or achiral, into enantiomerically pure products.⁵ Another key feature of AAA reactions is their regioselectivity; the reactions may proceed either by an S_N2 or S_N2' substitution (Scheme 1.1).⁶

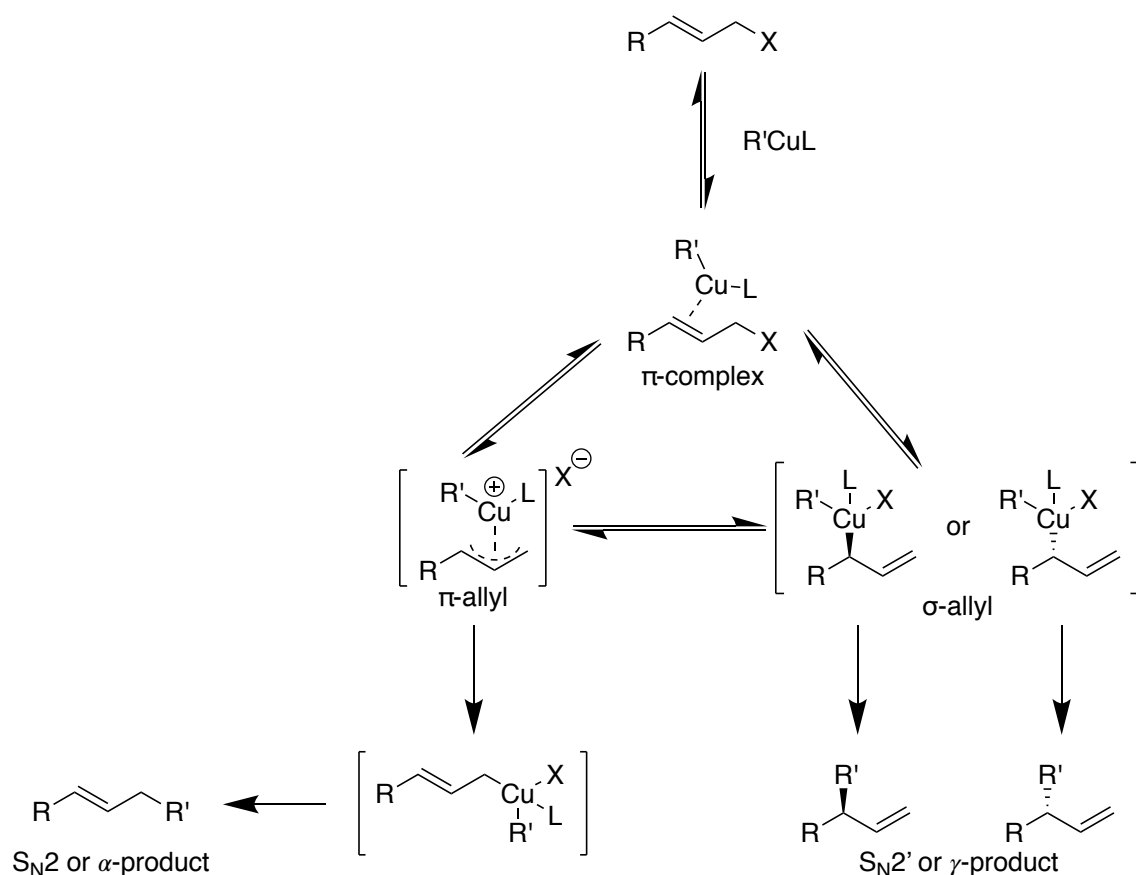


Scheme 1.2 Stabilised and non-stabilised nucleophiles react *via* different mechanisms.

AAA reactions can be divided into two general reaction classes depending on the nature of the nucleophile. “Hard” or “non-stabilised” nucleophiles, which are derived from conjugate

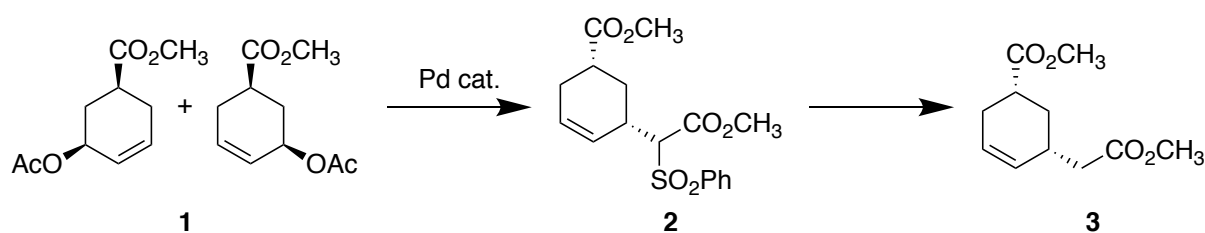
acids with a $pK_a > 25$, attach to the metal catalyst and then undergo a reductive elimination to form the desired product. Grignard reagents, alkylzinc halides and hydride donors such as hydridoborates, hydridostannes and formates are all classed as “non-stabilised” nucleophiles. In contrast, the bond breaking and bond making events for “soft” or “stabilised” nucleophiles, which are derived from conjugate acids with a $pK_a < 25$, occur outside the coordination sphere of the metal.⁴

The typical catalytic cycle for an AAA reaction involves the following steps: olefin complexation, ionisation of a leaving group and then nucleophilic addition and decomplexation.⁵ These reactions proceed through a π -allyl or σ -allyl metal complex, which forms after loss of the leaving group from the substrate (Scheme 1.3). The most common leaving groups in AAA reactions are acetate, halide (usually chloro- or bromo-), phosphate or carbonate groups.⁷



Scheme 1.3 Typical catalytic cycle for a Cu-catalysed AAA using a non-stabilised nucleophile.

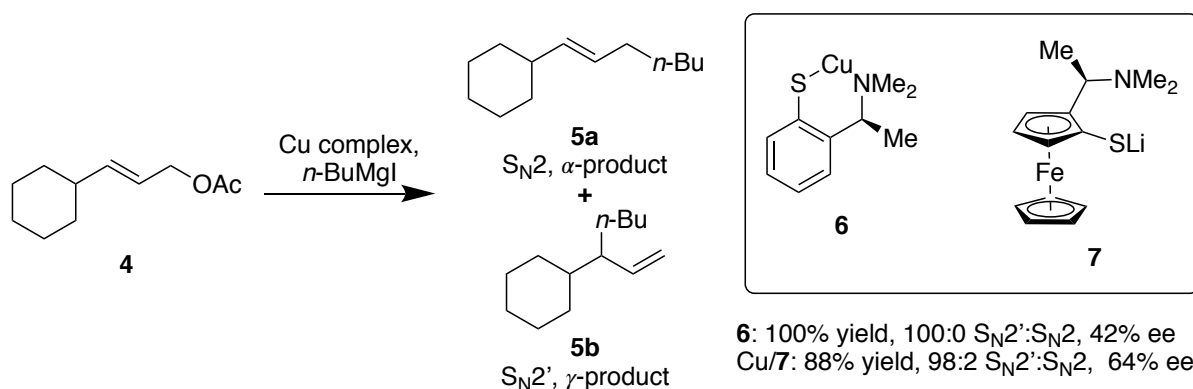
Trost and co-workers demonstrated the first AAA reaction with a stabilised nucleophile in 1977 (Scheme 1.4).⁸ Following this work, almost all investigations into AAA reactions until the late 1990's used palladium. As a result, palladium-catalysed substitution reactions using soft nucleophiles are now well understood. Here we will not discuss palladium-catalysed AAA reactions; Trost,^{4,5} Zhang,⁹ and Bruneau,¹⁰ among others, have written comprehensive reviews on this chemistry.



Scheme 1.4 The first AAA reaction by Trost and co-workers.

1.2.1 Copper-catalysed asymmetric allylic alkylations

The majority of palladium catalysed reactions require soft nucleophiles such as malonate carbanions in order to achieve high stereo- and regiocontrol.¹¹ The advantage of using copper is that it allows the use of hard nucleophiles including Grignard and organozinc reagents. Copper salts are also generally cheaper than palladium salts. The first report of an asymmetric allylic substitution catalysed by copper was by Bäckvall, van Koten and co-workers in 1995.¹² Here they used a chiral arenethiolatocopper(I) complex to catalyse the asymmetric allylic substitution of an allylic acetate with a butylmagnesium reagent.



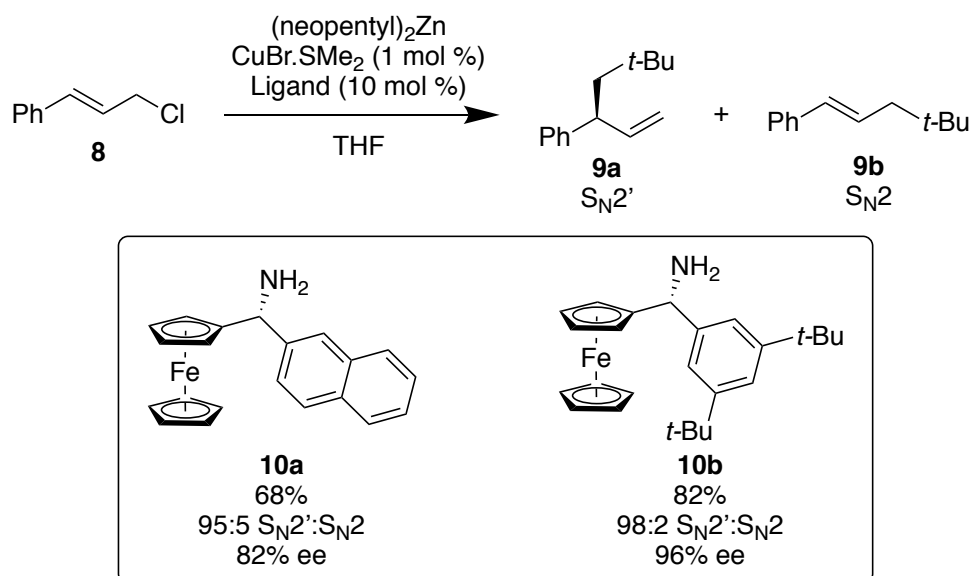
Scheme 1.5 The first Cu-catalysed AAA by Bäckvall and co-workers.

In this reaction the enantiomeric excess of the product is heavily dependent on multiple factors: the coordinating ability of the leaving group in the allylic substrate, the temperature at which the reaction is carried out, the method by which the substrate is added to the reaction and the Grignard reagent. In this initial work, they achieved 42% ee using ligand **6**. More recently, the same group reported a new ligand, **7**, for this reaction, however the highest ee was still only 64% (Scheme 1.5).^{13,14}

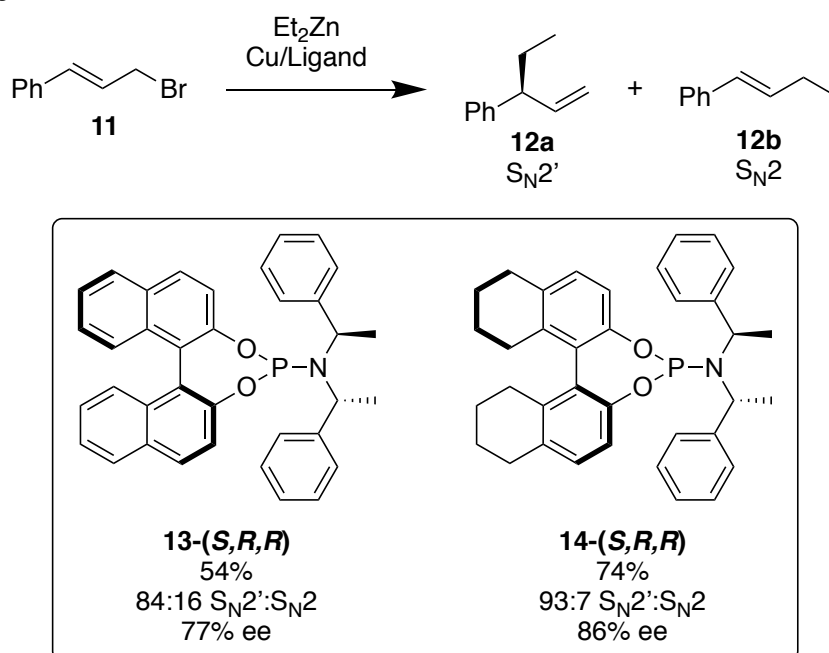
In 1999, Dübner and Knochel used dialkylzinc reagents as an alkyl source in asymmetric allylic substitution reactions.^{15,16} High enantioselectivities were achieved with high ratios of ligand to copper, very low temperatures and bulky alkyl groups on zinc. The product was initially obtained with 82% ee when using ferrocene ligand **10a**, but a later developed ligand **10b** gave an improved result of 96% ee (Scheme 1.6, top).

The use of linear alkylzinc reagents remained challenging until the work of Feringa and co-workers established the use of phosphoramidite ligands. In 2001, they first reported the regio- and enantioselective alkylation of cinnamyl bromide using diethylzinc. Using copper and phosphoramidite ligand **13-(S,R,R)** ee's of up to 77% were achieved.¹⁷ In 2004 this was improved to 86% ee using new ligand **14-(S,R,R)**, which has a partially hydrogenated binol backbone (Scheme 1.6, bottom).¹⁸

Dübner and Knochel 1999:



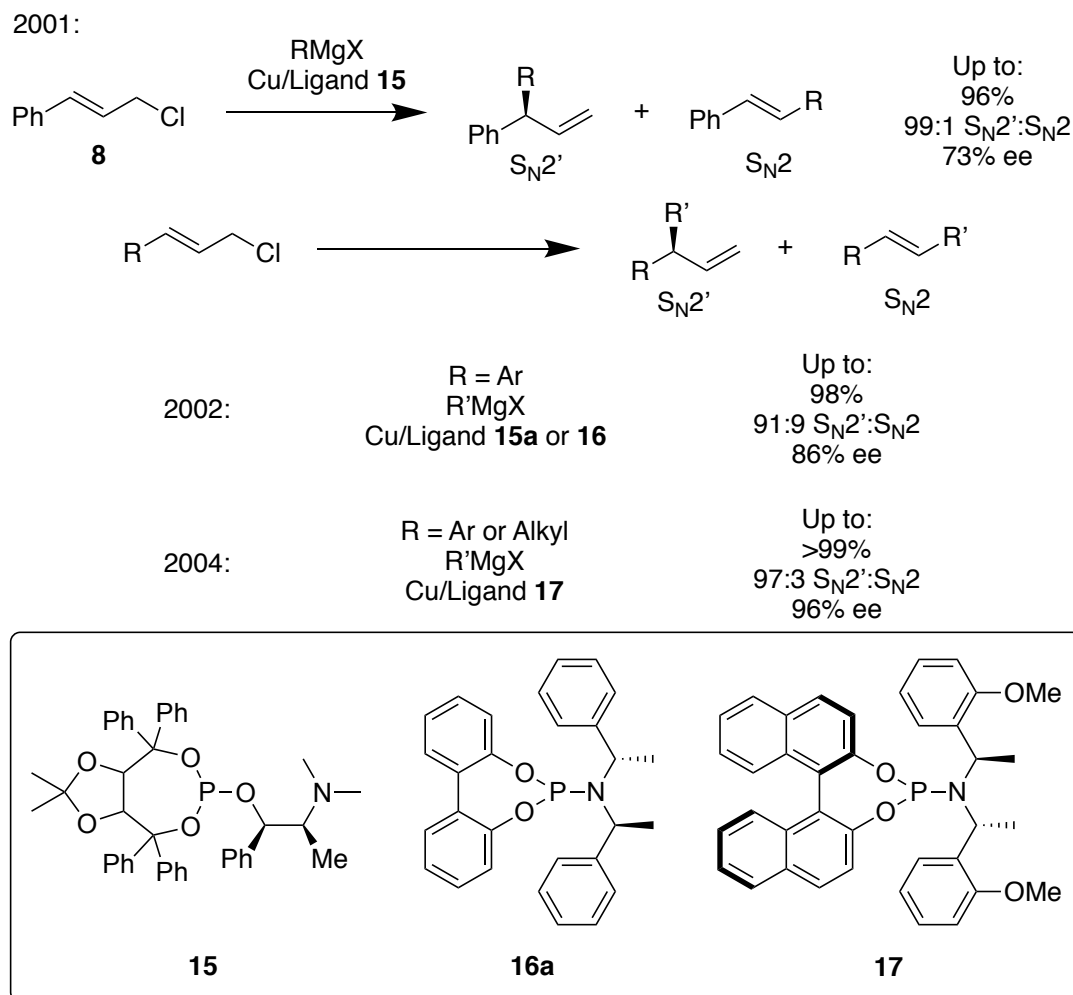
Feringa 2001:



Scheme 1.6 AAA reactions using alkylzinc reagents.

Around the same time, Alexakis and co-workers developed a similar system in which Grignard reagents can be used as the nucleophile. Using the TADDOL-derived ligand **15**, ee's of up to 73% were achieved.¹⁹ The ee was improved to 86% using ligand **16a** and the scope of the reaction could also be broadened to include different aryl and alkyl group on the allyl chloride, without having to further optimise the conditions.²⁰ A range of different

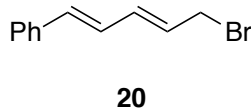
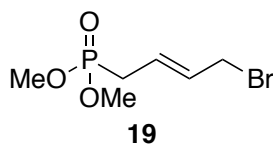
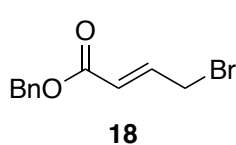
Grignard reagents including those with a terminal olefin were examined. Subsequent tandem reactions to form 5-membered rings, which can be carried out *in situ* were described. Further improvements were made by employing ligand **17**, with the reaction now providing ee's of up to 96%.^{21,22}



Scheme 1.7 AAA using Grignard reagents, developed by Alexakis.

In recent years, the scope of electrophiles that can undergo AAA reactions with Grignards has been expanded to those bearing synthetically useful functional groups such as esters, phosphonates and phosphine oxides, alkenes and alkynes by the groups of both Feringa^{23–25} and Alexakis,²⁶ among others (Figure 1.1).

Feringa 2010–2013:



Alexakis 2012:

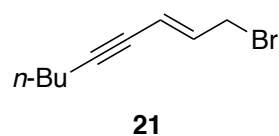


Figure 1.1 Expanded scope for copper-catalysed AAA reactions.

Spiro phosphoramidites and phosphite ligands (Figure 1.2) were applied to asymmetric allylic substitution reactions by Zhou and co-workers.²⁷ However using a range of allyl bromides and diethyl- or diisopropylzinc reagents only moderate yields, regioselectivities and ee's were achieved.

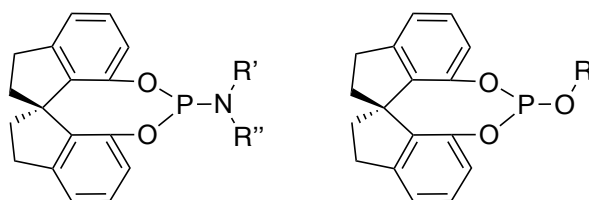
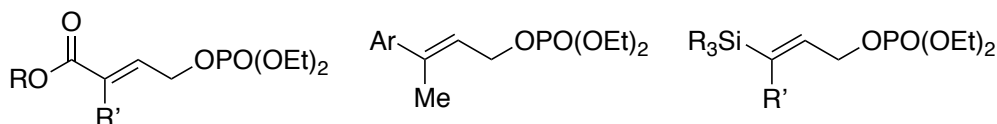


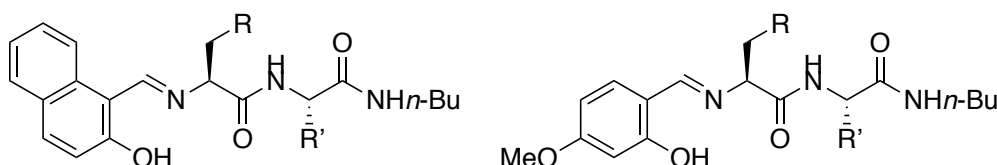
Figure 1.2 Representative structures of spiro phosphoramidite and phosphite ligands.

Hoveyda and co-workers developed chiral peptide-based ligands for the asymmetric allylic substitution of allylic esters that have phosphate leaving groups.^{28–31} Using alkyl zinc reagents ee's of up to 97% were obtained with copper and ligands such as those shown in Figure 1.3. By using the types of allylic phosphates, also shown in Figure 1.3, it was possible to access all-carbon quaternary centres and silicon-substituted stereogenic centres.

Substrates:



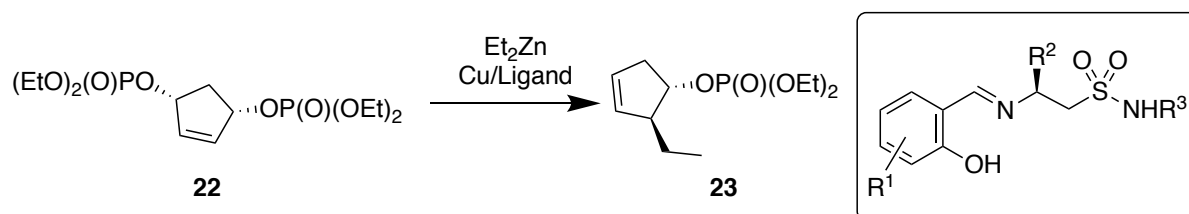
Ligands:



R, R' = Alkyl

Figure 1.3 Allylic phosphate and chiral peptide-based ligands developed by Hoveyda and co-workers.

Piarulli, Gennari and co-workers developed a new family of chiral *Schiff*-base ligands (Scheme 1.8), which they applied in the desymmetrisation reaction of *meso* cyclic allylic phosphates, achieving ee's of up to 88%.^{32,33}



Scheme 1.8 Desymmetrisation of *meso* cyclic allylic phosphates with *Schiff*-base ligands.

Other types of ligands that have been previously used in copper-catalysed asymmetric substitutions³⁴ include, but are not limited to, NHC ligands³⁵ (Okamoto³⁶ and Hoveyda³⁷), secondary amines (Woodward³⁸) and bidentate phosphate ligands (Ohmiya³⁹) (Figure 1.4). The NHC ligands are often used in copper-catalysed AAA reactions with organoaluminium or organoboron reagents.⁴⁰

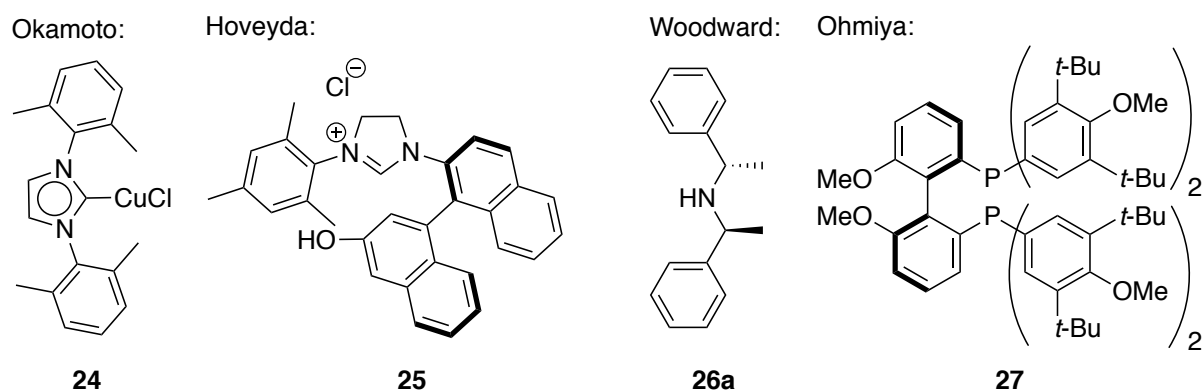


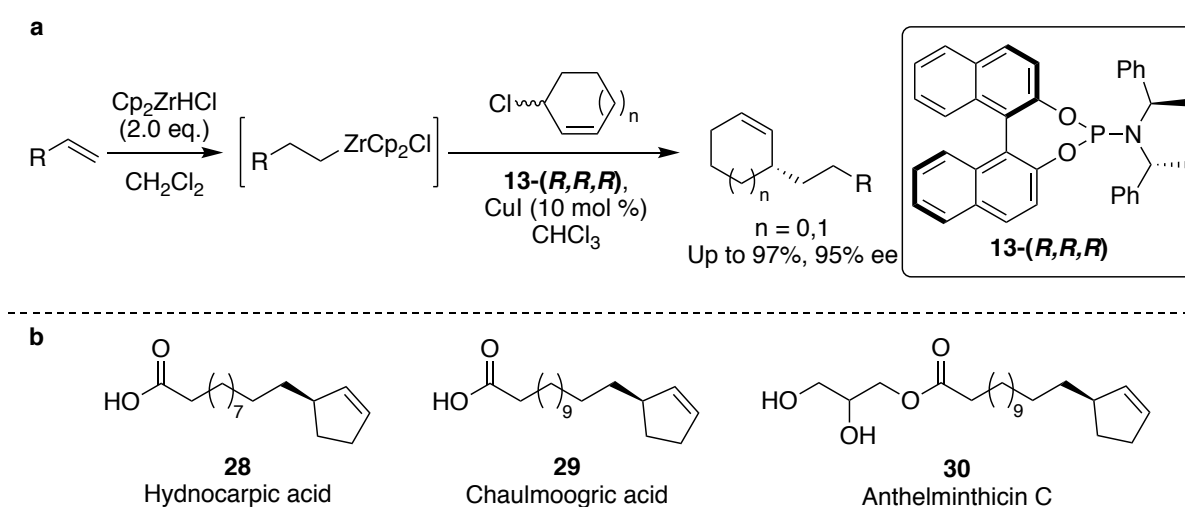
Figure 1.4 Other chiral ligands for AAA reactions.

1.2.2 Copper-catalysed asymmetric allylic alkylations using alkylzirconium

In recent years our group has developed highly enantioselective conjugate addition reactions using alkylzirconium reagents as nucleophiles.^{41–46} In contrast to traditional non-stabilised

nucleophiles (Grignard, alkylzinc and alkylaluminum reagents), which require cryogenic temperatures, these alkylzirconium reagents undergo enantioselective additions at ambient temperatures.

In 2015, our group reported the copper-catalysed AAA reaction of racemic allyl chlorides with alkylzirconocenes to obtain highly enantioenriched products via a dynamic kinetic asymmetric transformation (DYKAT) (Scheme 1.9a).⁴⁷ DYKAT reactions have been developed such that a resolution is coupled with racemisation of the starting material, allowing for a greater than 50% yield to be achieved. The DYKAT reaction developed by our group uses a chiral copper-phosphoramidite complex and allows addition of alkylzirconium species formed *in-situ* from alkenes and the Schwartz reagent (Cp_2ZrHCl).⁴⁸ A diverse variety of alkenes, ranging from simple gaseous alkenes to more functionalised alkenes containing halogens, alkynes and preformed stereogenic centres, among others, are all well tolerated in the reaction. The reaction is also compatible with the 5-membered allyl chloride. The synthetic utility of the method was demonstrated by the synthesis of biologically active natural products hydnocarpic acid (**28**), chaulmoogric acid (**29**) and anthelminthicin C (**30**, Scheme 1.9b).

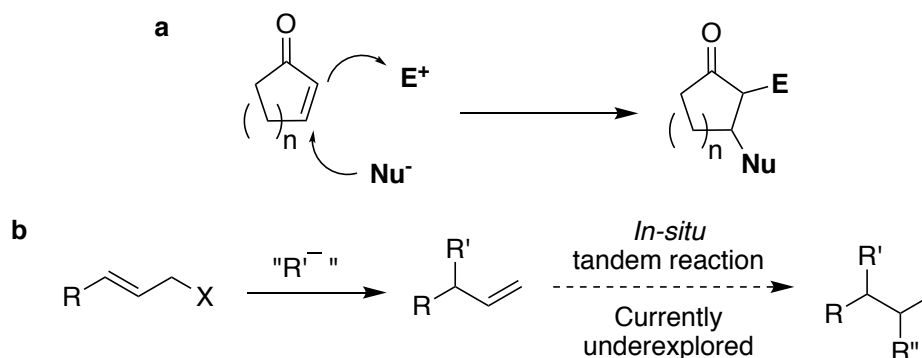


Scheme 1.9 a Cu-catalysed AAA of racemic allyl chlorides with alkylzirconocenes. **b** Natural products hydnocarpic acid (**28**), chaulmoogric acid (**29**) and anthelminthicin C (**30**) can be synthesised using this AAA reaction.

1.3 Tandem reactions

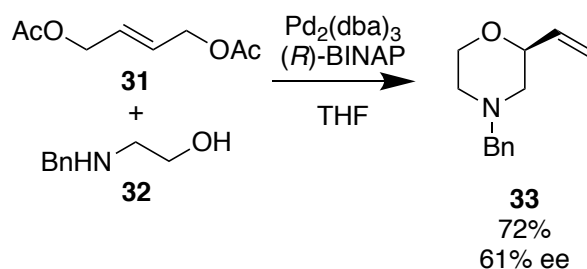
Multicomponent tandem reactions in catalysis have been broadly studied. Defined as “one-pot” processes, regardless of their mechanistic nature, these reactions can either combine three or more substrates simultaneously, or involve the sequential addition of substrates without changing the solvent.⁴⁹ Asymmetric tandem transformations are appealing strategies as they enable the rapid increase in molecular complexity from simple starting materials, in an efficient and usually economical fashion.

Tandem reactions that are initiated by conjugate additions on α,β -unsaturated carbonyl compounds have been well studied.^{50–53} The metal enolate resulting from the 1,4-addition of an organometallic such as a Grignard or organozinc reagent, can undergo electrophilic trapping (Scheme 1.10a). Common methods for trapping these enolates include a subsequent alkylation reaction or aldol condensation.



Scheme 1.10 **a** Typical tandem reactions initiated by 1,4-additions. **b** *In-situ* tandem reactions for AAA are currently underexplored.

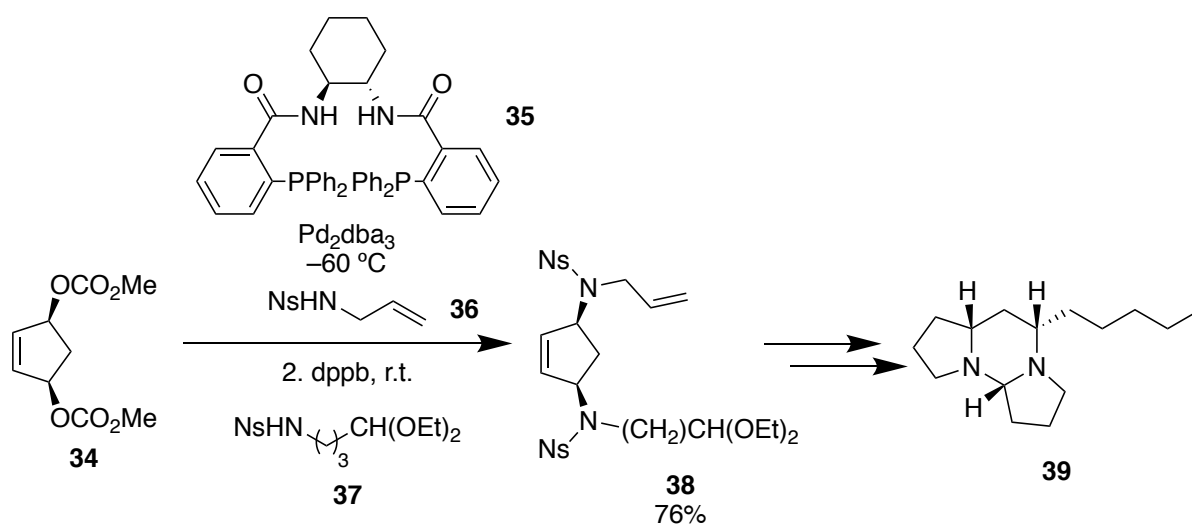
Currently, tandem reactions initiated by asymmetric allylic alkylations are far less studied (Figure 1.10b).^{54,55} In 1993 Hayashi described a palladium-catalysed asymmetric reaction to form morpholines and piperazines with ee's of up to 61% (Scheme 1.11).⁵⁶



Scheme 1.11 Primary work on tandem reactions initiated by AAA by Hayashi.

The groups of Sinou and Achiwa demonstrated small improvements in ee and some increase in scope by the preparation of substituted dioxanes.^{57–59} Muzart and co-workers demonstrated a diastereoselective synthesis of vinylmorpholines using enantiopure aminoalcohols as nucleophiles.⁶⁰ In 2004, Ito and Katsuki reported that using 2-(phosphinophenyl)pyridine as a chiral ligand, they could achieve enantioselectivities of up to 86% in their similar reaction involving 1,2-*hetero*-functionalised compounds as nucleophiles.⁶¹

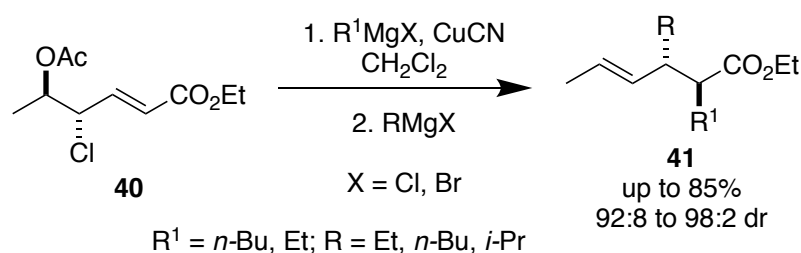
Blechert demonstrated the enantioselective synthesis of tetraopenerines by palladium- and ruthenium-catalysed domino reactions.⁶² Chiral dicarbonate **34**, undergoes sequential tandem allylation reactions with two different primary amines. This is followed by a ruthenium-catalysed tandem ring-opening and ring-closing metathesis process that gives tetraopenerine **39** (Scheme 1.12).



Scheme 1.12 Synthesis of chiral tetraopenerines by Blechert.

All of the above examples use palladium as the transition metal catalyst. There are even fewer examples of copper-catalysed tandem processes initiated by AAA reactions. Alexakis and co-workers reported a one-pot tandem allylation-metathesis reaction using their copper-catalysed AAA reaction shown in Scheme 1.7 followed by a ring-closing metathesis reaction using Grubbs 1st Generation ruthenium catalyst.²⁰

In 2008, Dieter and co-workers reported the first example of two sequential allylic substitution reactions through a copper-mediated process.⁶³ Starting from α,β -enoates such as **40**, their method allows for the synthesis of γ,δ -enoates such as **41**, in good yields and high diastereoselectivities.

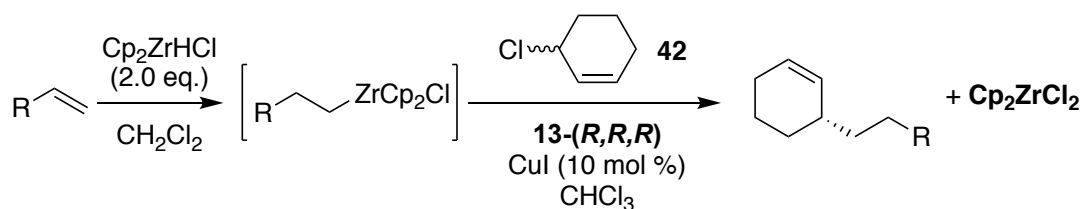


Scheme 1.13 The first example of two sequential AAA reactions.

Given the apparent lack of research in this area we hoped that we could develop a tandem reaction using our copper-catalysed AAA reactions.

1.4 Project aim

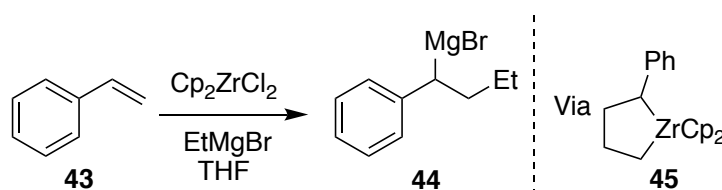
As discussed earlier in the chapter, our group has developed a new copper-catalysed AAA using racemic allyl chlorides to obtain highly enantioenriched products *via* a dynamic kinetic asymmetric transformation (DYKAT).⁴⁷ A known by-product of this reaction is zirconocene dichloride (Cp_2ZrCl_2) and we envisaged that this zirconium salt, generated in the AAA reaction, could be used to promote subsequent tandem reactions.



Scheme 1.14 Cp_2ZrCl_2 is generated as a by-product in the AAA of racemic allyl chlorides.

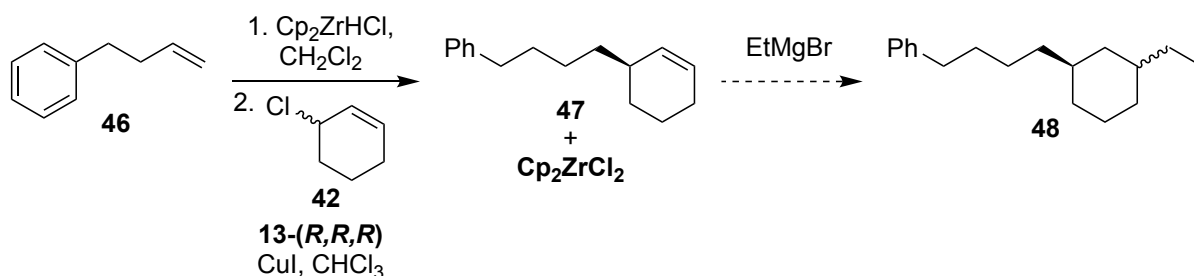
We wished to develop a reaction for the efficient formation of multiple C-C bonds in one step, so that complex compounds could be prepared in a straightforward way. More importantly, this strategy would demonstrate that it is possible to design processes where the by-products or ‘waste’ from a chemical reaction can be used in a second high-value process.

It has previously been shown by Negishi and co-workers that in the presence of Cp_2ZrCl_2 alkenes can undergo zirconium-catalysed addition of Grignard reagents.⁶⁴ The reaction gives 1-aryl-substituted butylmagnesium bromide intermediates, which can then be used in subsequent reactions.



Scheme 1.15 Cp_2ZrCl_2 can be used for the addition of Grignard reagents to alkenes.

The aim of this project was to use the Cp_2ZrCl_2 formed in our AAA reaction to do a subsequent reaction using Grignard reagents, to form a second C-C bond. We were interested to see how the presence of the other reagents, including the copper catalyst, would affect this second reaction.

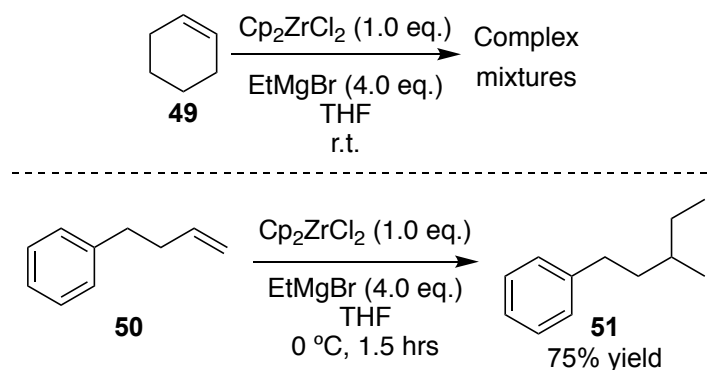


Scheme 1.16 Proposed reaction scheme for a tandem reaction initiated with an AAA reaction.

2 Studies towards a copper-catalysed asymmetric allylic alkylation

2.1 Studies towards tandem reactions initiated by asymmetric allylic alkylations

Our investigations began by testing what would be the second part of the tandem reaction using a simple alkene as a model substrate. Using the method developed by Negishi,⁶⁴ addition of a Grignard reagent to an alkene using zirconocene dichloride was initially carried out on cyclohexene, as this was considered to be a simple model of the AAA product. Unfortunately, only complex mixtures of aliphatic substances were observed by crude ¹H NMR spectroscopy and due to the volatile nature of the products none were isolated or identified.

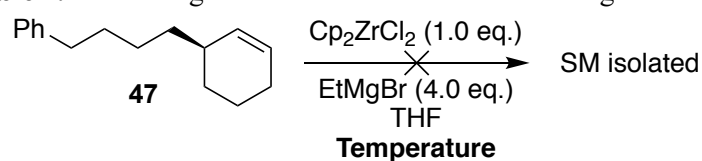


Scheme 2.1 Reaction of cyclohexene (**49**) and 4-phenyl-1-butene (**50**) with Cp_2ZrCl_2 and EtMgBr .

We quickly moved to using 4-phenyl-1-butene (**50**) as our model substrate. While still a simple substrate, it contains a phenyl ring, which acted as a handle for isolation and purification. Again, starting with Negishi's conditions, branched product **51** was obtained in a promising 75% yield. None of the corresponding linear product was observed. When these reaction conditions were then applied to AAA product **47**, no reaction was observed using many variations of the reaction conditions, including refluxing overnight (Table 1, entries 3

and 4). Under all sets of conditions, the majority of the starting material was recovered. The lack of reactivity could perhaps be attributed to the fact that the alkene in the AAA product is not terminal. Despite these negative results one tandem reaction was attempted, however the only product observed was the AAA product, **47**. At this juncture, we decided to attempt a different strategy for developing a new tandem AAA reaction.

Table 2.1 Screening conditions for the addition of Grignards to **47**.

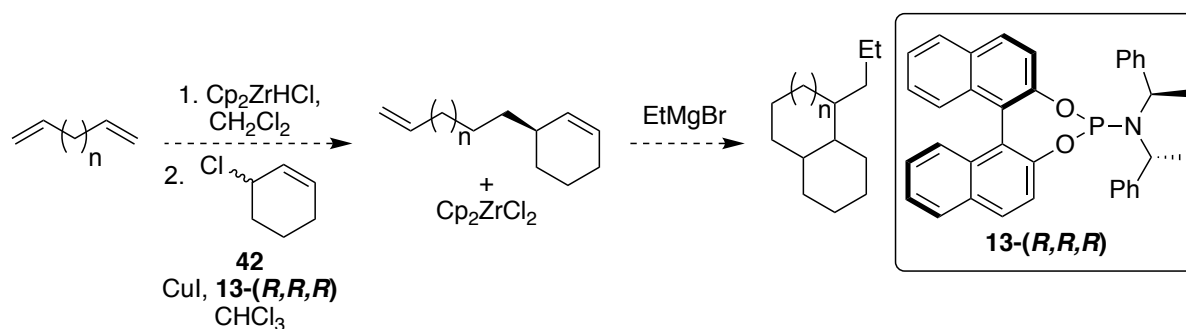


Entry	Temperature (°C)	Reaction Time (hrs) ^[a]	Solvent
1	−20 to 0 ^[b]	5.5	THF
2	r.t.	4	THF
3	reflux	o/n	THF
4	r.t then reflux ^[c]	o/n	2:1 CHCl ₃ :CH ₂ Cl ₂

SM – starting material, r.t. – room temperature, o/n – overnight. [a] Reaction time after the addition of the alkene. [b] −20 °C for 2.5 hours, then warmed to 0 °C over 3 hours. [c] r.t. for 6 hours then reflux o/n.

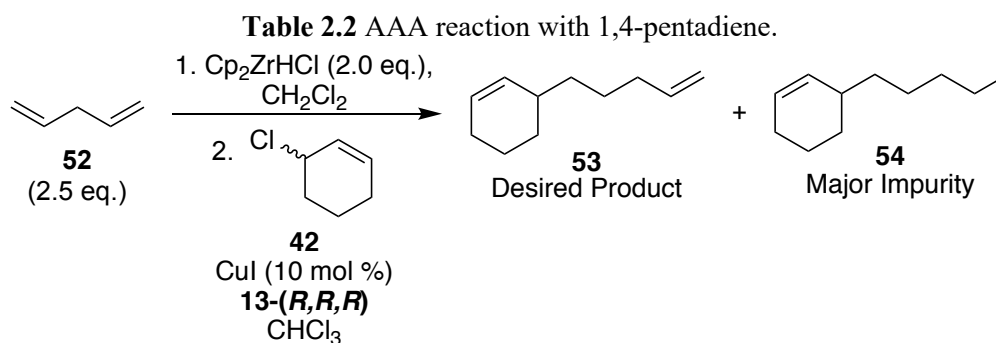
2.2 Hydrozirconation reactions using dienes

Based on our observations and the work of Negishi,⁶⁴ we hypothesised that it may be possible to develop a tandem reaction by using a diene as the nucleophile in the AAA reaction. The product of this reaction would have two alkenes, one of which would be terminal, and it was envisaged that the zirconocene dichloride formed in the reaction in the presence of a Grignard reagent, would promote a cyclisation reaction (Scheme 2.2).



Scheme 2.2 Proposed reaction for the AAA of allyl chloride **42** with a diene.

The allylic alkylation reaction with 1,4-pentadiene (**52**) proved more challenging than the simpler alkenes previously described by the group.^{41,47} In addition to the desired product (**53**), a major impurity (**54**) was also obtained.



Entry	Temperature (°C)	Reaction Time (hrs)	Equivalents of reagents (53:Cp ₂ ZrHCl:42)	Ratio of Products 53:54
1	r.t.	24	1:2:1	1:1.5
2	r.t.	1	2.5:2:1	1:0.3 ^[a]
3	r.t.	3	2.5:2:1	1:0.35
4	r.t.	20	2.5:2:1	1:0.6
5	r.t.	72	2.5:2:1	1:0.7
6	r.t.	17	1:1:1	1:65
7	0	4	2.5:2:1	1:0.3
8	40	18	2.5:2:1	1:1

[a] Allyl chloride starting material also observed.

Many different reaction conditions were tested in order to investigate if it was possible to reduce or eliminate the formation of by-product **54**. Unfortunately, no such conditions were found and the by-product was always observed. As an added complication, the similarities in structure and polarity of products **53** and **54** meant it was not possible to separate them by column chromatography. When the AAA reaction was subjected to the subsequent reaction

with EtMgBr, no cyclised product was obtained and product **53** was recovered unchanged. Once again, there was no evidence of any tandem reactions occurring and since no appropriate reaction conditions could be found to hinder the formation of **54**, no further work was carried out on this project.

2.3 Studies towards functionalised allylic alcohols

Feringa and co-workers, following their work on cinnamyl bromide and related substrates (see Chapter 1), reported a copper-catalysed AAA showing that substrates with oxygen or nitrogen functionalities in the starting materials also work well (Figure 2.1). In this work, chiral primary alcohols and amines can also be obtained in high enantiomeric purity.⁶⁵

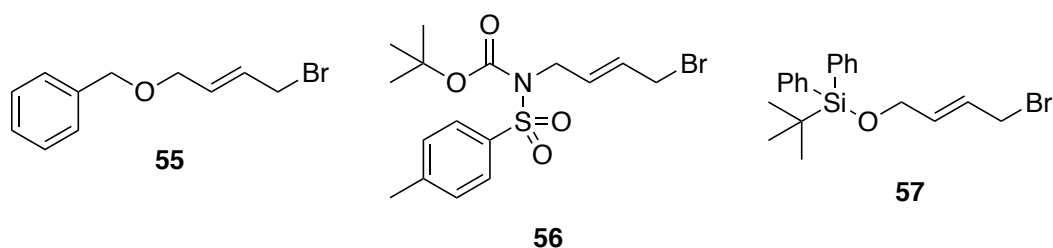
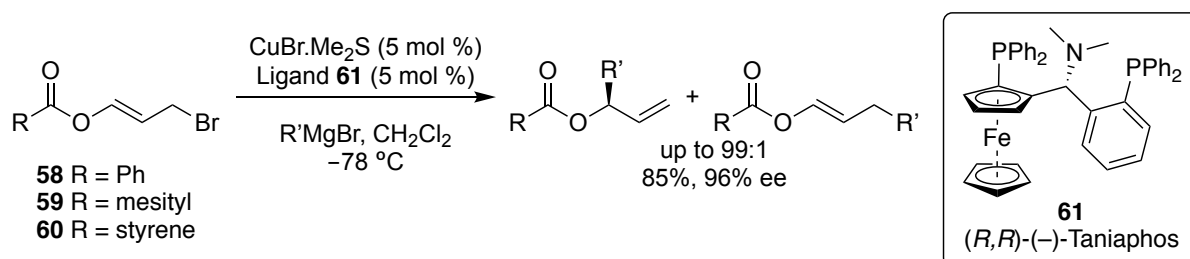


Figure 2.1 A range of allylic substrates containing functional groups are compatible in AAA reactions.

Based on this work they hypothesised that it could be possible to add organometallic reagents to allylic substrates that bear a heteroatom at the γ -position, in a so-called *hetero*-AAA reaction (*h*-AAA). Indeed, using 3-bromopropenyl esters **58-60** it was possible to add a variety of Grignard reagents ranging from simple alkyl groups to those containing functional groups, which allow for further transformations, in good yields and with excellent regio- and enantioselectivities (Scheme 2.3).^{66,67} The system described by the Feringa group has some limitations in that sp^2 - and sp^3 -hybridised Grignard reagents and sterically hindered nucleophiles or electrophiles are not tolerated by the ferrocenyl-based catalyst.⁶⁸ *h*-AAA

reactions with substrates containing boron⁶⁹ and silicon³¹ at the γ -position have also been reported.



Scheme 2.3 Copper-catalysed asymmetric synthesis of chiral allylic esters by Feringa and co-workers.

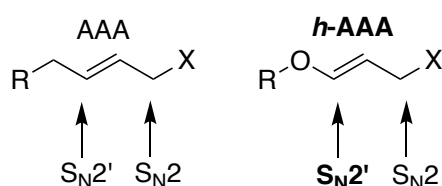
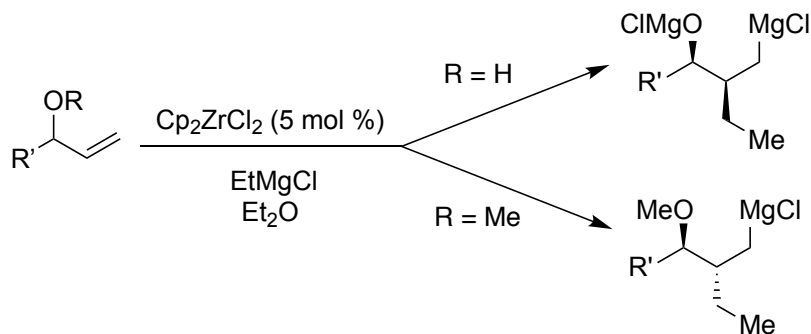


Figure 2.2 The possible reaction pathways for AAA and *h*-AAA reactions.

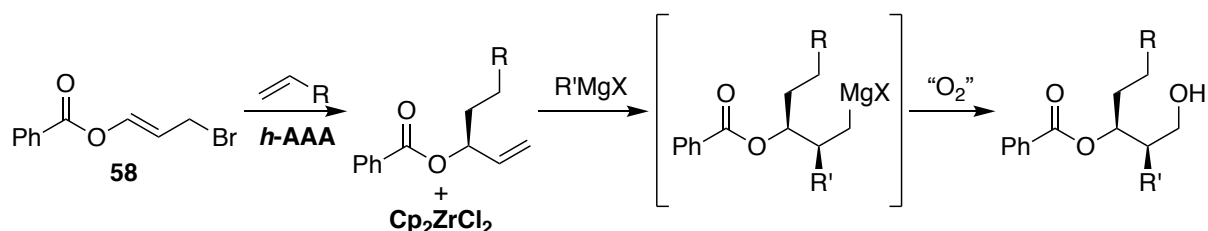
We thought it was feasible that the reaction conditions developed by our group for the AAA on racemic allyl halides could also be applicable to a *h*-AAA reaction. Ideally the reaction would proceed via an $\text{S}_{\text{N}}2'$ mechanism (Figure 2.2) to give the desired product, a hydroxylated alkene, with high levels of enantiomeric excess (Scheme 2.5).

In the early 1990's, Hoveyda reported that Cp_2ZrCl_2 is an efficient catalyst for the addition of Grignard reagents to hydroxylated alkene derivatives.^{70–72} High levels of stereocontrol can be achieved by tuning the substituent on the heteroatom.



Scheme 2.4 The addition of Grignard reagents to hydroxylated alkenes.

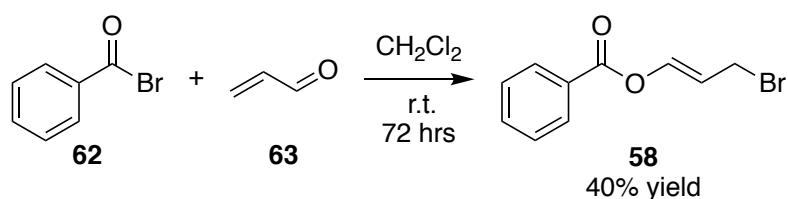
Therefore, the products obtained from our new *h*-AAA reaction could possibly undergo a tandem reaction with the zirconocene dichloride formed *in situ*, on the addition of a Grignard reagent.



Scheme 2.5 Proposed reaction to form hydroxylated alkenes through a *h*-AAA and their subsequent reaction with a Grignard to give highly functionalised chiral products.

2.3.1 Reaction development

Allylic bromide **58** was easily synthesised using literature methods (Scheme 2.6).⁷³ After several recrystallisations, the product was obtained in 40% yield.



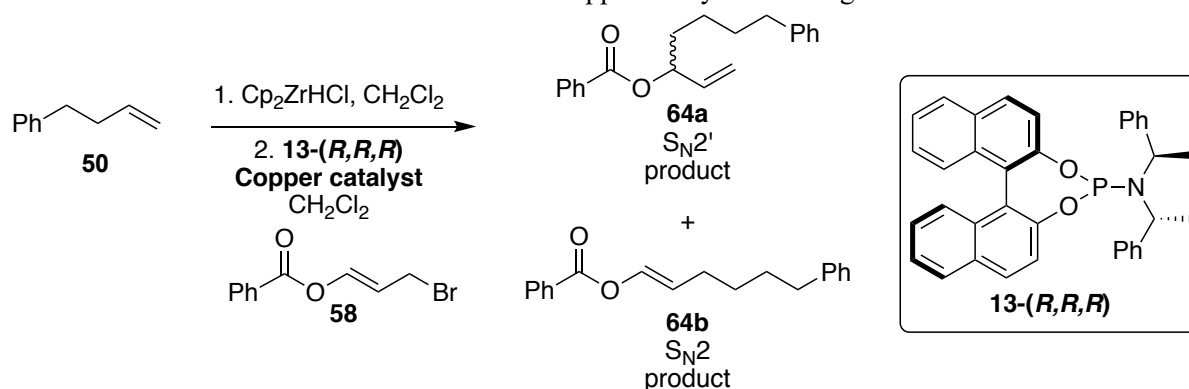
Scheme 2.6 The synthesis of allylic bromide **58**.

We started investigating this new AAA reaction by using the previously optimised conditions for racemic allyl halides⁴⁷ but unfortunately under these conditions there was very poor regioselectivity for the S_N2' product (Table 2.3, entry 1).

We began optimising the reaction by screening copper counterions, with all other reaction components kept constant. All screening reactions were carried out in dichloromethane rather than using chloroform to form the copper-ligand complex, for practical reasons as well as to reduce the number of variables in the reaction during screening. Generally, yields for this reaction were low with only moderate regioselectivity for the S_N2' product over the S_N2 product. The ee's for this reaction were poor with many of the counterions giving racemic or

near racemic mixtures. CuPF_6 and $\text{Cu}(\text{MeCN})_4\text{PF}_6$ (Table 2.3, entries 11 and 17, obtained *in situ* by exchange with the corresponding silver salts) were chosen as the catalysts with which to continue the screening as they gave workable yields albeit with poor ee's.

Table 2.3 Initial copper catalyst screening.

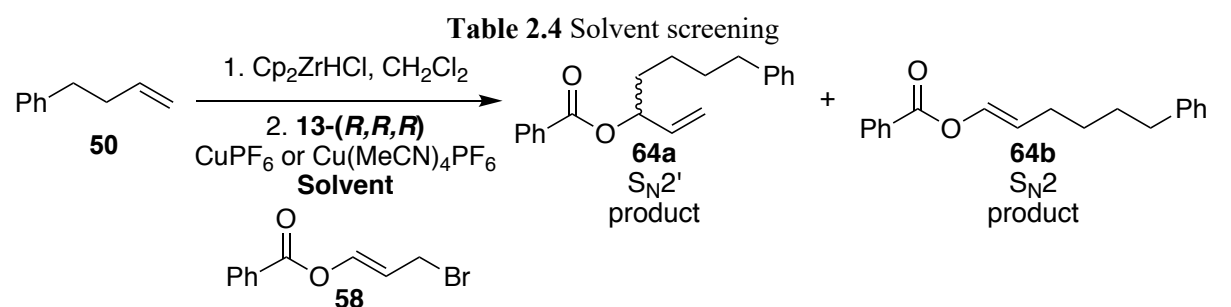


Entry	Copper Catalyst ^[a]	Yield $\text{S}_{\text{N}}2'$ (%) ^[b]	Yield $\text{S}_{\text{N}}2$ (%) ^[b]	ee of 64a (%) ^[c]
1 ^[d]	CuI	3	37	22
2	CuCl	21	16	-3
3	CuBr.SMe ₂	6	31	4
4	CuTC	25	21	-8
5	CuSCN	-	-	-
6	Cu(OTf) ₂	17	48	10
7	CuOAc	-	-	-
8	Cu(OAc) ₂	21	25	racemic
9	CuCl, AgOTs	19	31	-5
10	CuCl, AgOMs	30	48	racemic
11	CuCl, AgPF₆	30	29	-13
12	CuCl, AgSbF ₆	24	32	racemic
13	CuCl, AgBF ₄	29	35	-9
14	CuCl, AgOTf	11	20	-7
15	CuCl, AgNTf ₂	2	30	13
16	CuCl, AgClO ₄	14	20	-16
17	Cu(MeCN)₄PF₆	23	53	-10
18	Cu(MeCN) ₄ BF ₄	19	23	-7
19	Cu(MeCN) ₄ OTf	14	21	racemic

Conditions: 2.5 eq. of **50**, 2.0 eq. of Cp_2ZrHCl , 0.1 eq. of ligand **13-(R,R)**, 0.1 eq. of copper salt and 1.0 eq. of **58** in CH_2Cl_2 at room temperature. [a] Where the copper catalyst is formed *in situ* by transmetalation with a silver salt, 0.1 eq. of CuCl and 0.11 eq. of the corresponding silver salt were used. [b] Isolated yield, the two isomers were separable by column chromatography. [c] ee of $\text{S}_{\text{N}}2'$ product, determined by HPLC using a chiral non-racemic stationary phase. [d] Cu-ligand complex was formed in CHCl_3 as per the conditions for the racemic cyclic allyl halide.

We next moved to examining solvents for the reaction. In these reactions, the hydrozirconation of the alkene, 4-phenyl-1-butene (**50**), is always carried out in CH_2Cl_2 to

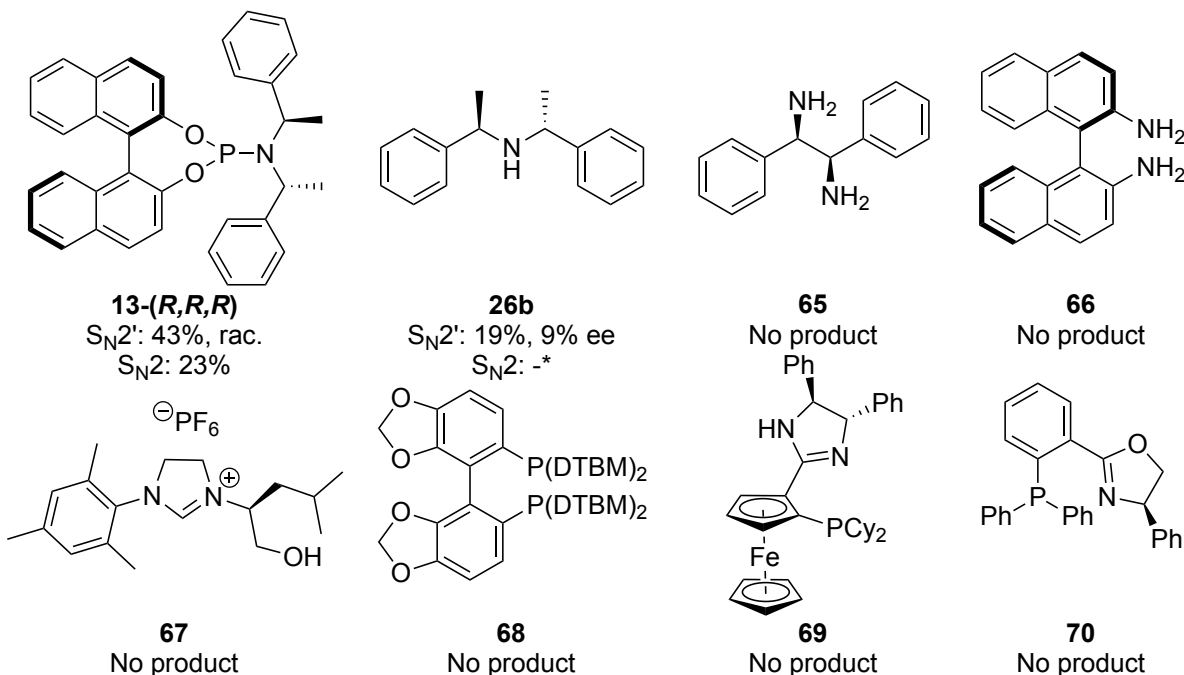
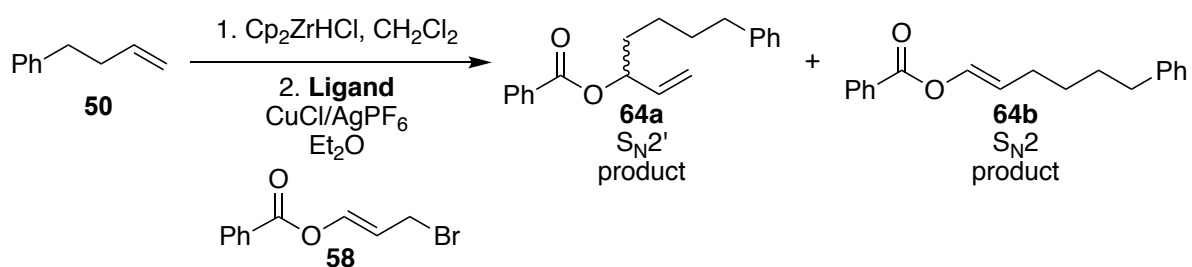
ensure solubility of the hydrozirconated alkene, however the solvent in which the Cu-ligand complex is formed can be varied. A range of solvents were screened with both CuPF₆ and Cu(MeCN)₄PF₆. With the latter however, no products were isolated using any solvent other than CH₂Cl₂. Ethereal solvents such as Et₂O and MTBE, although detrimental to the ee, showed an improved yield and regioselectivity for the S_N2' product (Table 2.4, entries 2 and 3).



Entry	Copper Catalyst ^[a]	Solvent	Yield S _N 2' (%) ^[b]	Yield S _N 2 (%) ^[b]	ee of 64a (%) ^[c]
1	CuCl, AgPF ₆	CH ₂ Cl ₂	30	29	-13
2	CuCl, AgPF₆	Et₂O	46	23	racemic
3	CuCl, AgPF ₆	MTBE	45	17	racemic
4	CuCl, AgPF ₆	THF	37	28	6
5	CuCl, AgPF ₆	1,4-Dioxane	12	60	racemic
6	Cu(MeCN) ₄ PF ₆	CH ₂ Cl ₂	23	53	-10
7	Cu(MeCN) ₄ PF ₆	Et ₂ O	-	-	-
8	Cu(MeCN) ₄ PF ₆	TBME	-	-	-

[a] Where the copper catalyst is formed *in situ* by transmetalation with a silver salt, 0.1 eq. of CuCl and 0.11 eq. of the corresponding silver salt were used. [b] All yields are isolated yields. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase

Since Et₂O gave the best yield of the desired S_N2' product, it was chosen as the solvent in which to screen ligands, even though with ligand **13-(R,R,R)** the product was racemic. We started by exploring different classes of chiral ligand (Figure 2.3). This included chiral amines (**26b**, **65**, **66**) ferrocene derived ligands (**69**), diphosphine ligands such as SegPhos derivatives (**68**), Phox ligands (**70**) and chiral *N*-heterocyclic carbene ligands (**67**).



Scheme 2.7 Ligands of different classes were screened in our *h*-AAA. *Complex mixture of products.

Since all of these other ligand classes (with the exception of amine **26b**) afforded none of the desired product, we decided to continue using phosphoramidite ligands for this reaction. The Feringa ligand⁵¹ (**13-(R,R,R)**) however only gave a racemic product, and so we began making variations to both the amine and backbone of the phosphoramidite scaffold.

The spiro and TADDOL based backbones (**71-74**) for phosphoramidites were quickly ruled out for this reaction. The BINOL derived ligands also proved to be poor for this reaction, giving products with very low ee's (**75-80**); however the bis-phenol derived backbones showed more promising ee's of up to 25% (**14-(S,S,S)** and **16b**). Also examined was Simplephos ligand, **81**. Although not technically a phosphoramidite ligand, its structure

clearly bears resemblance to the other ligands we were investigating. Unfortunately, the ligand performed very poorly in our reaction.

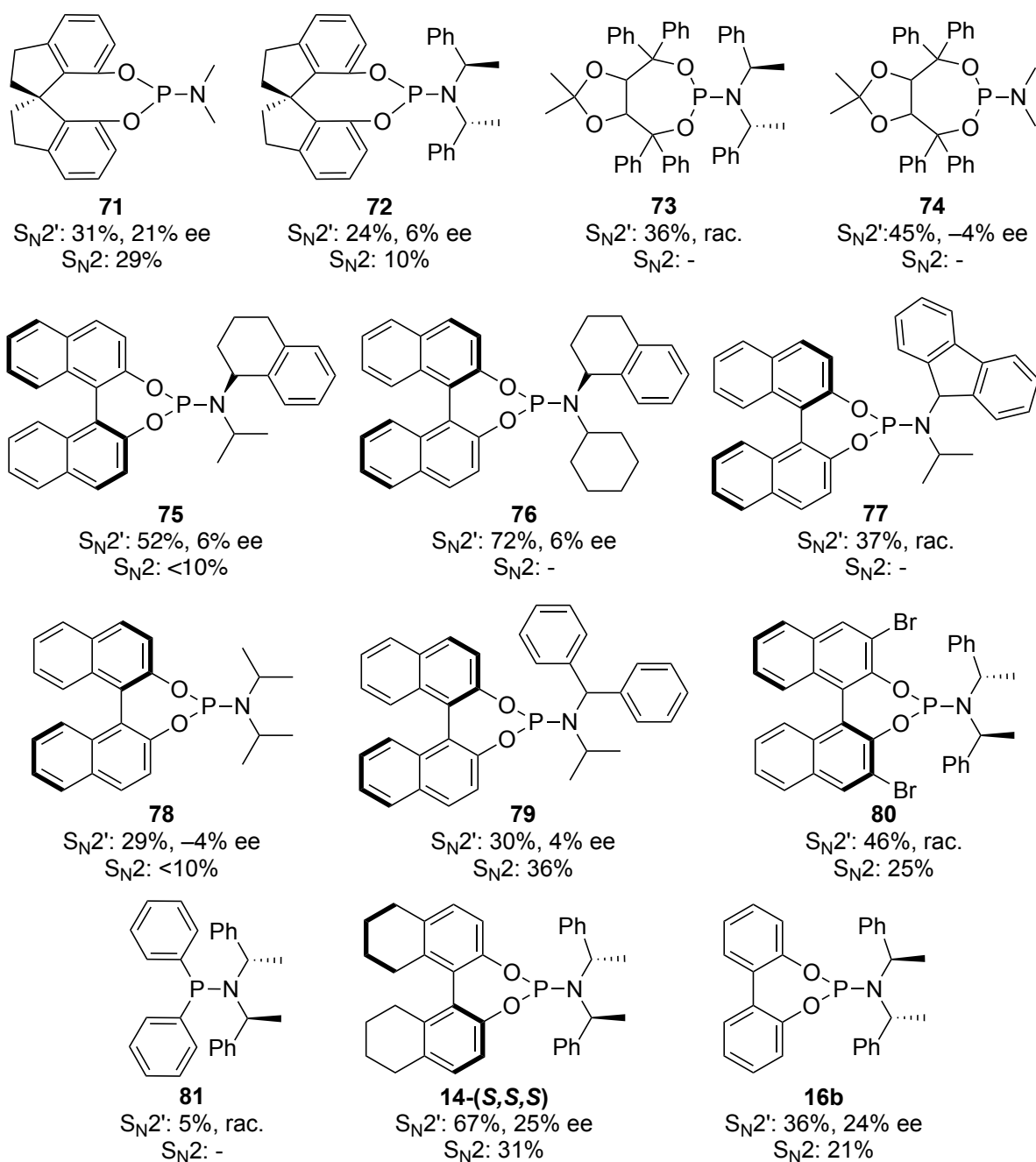
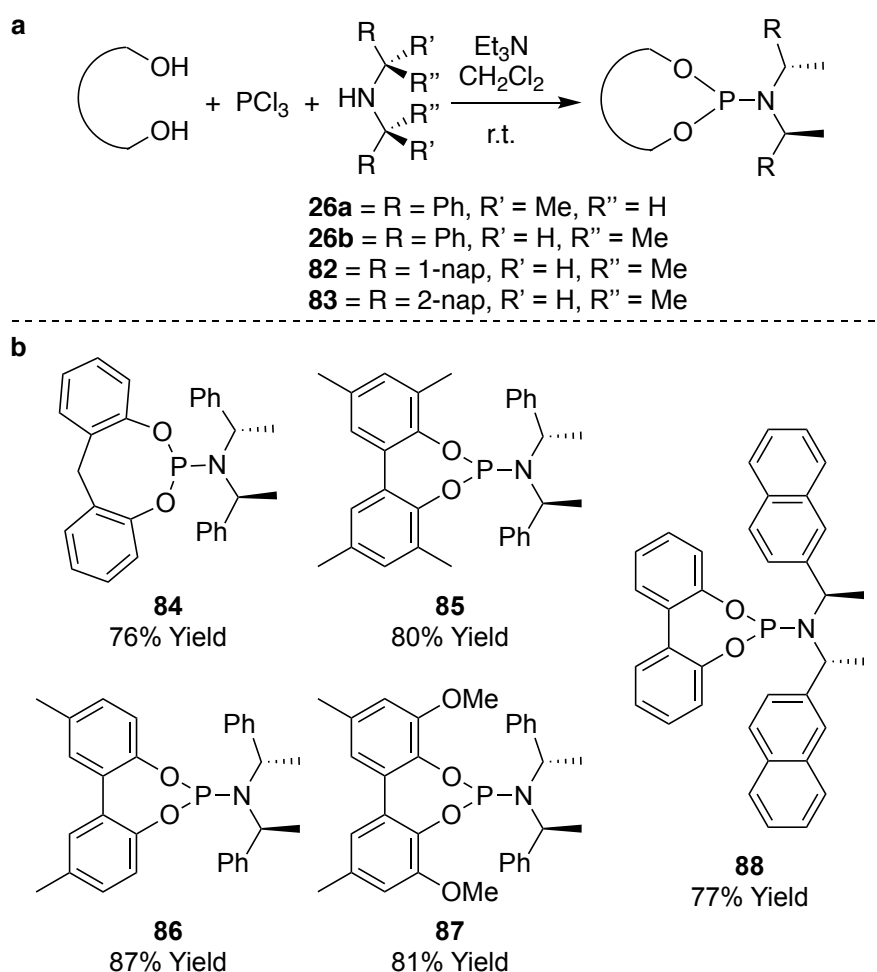


Figure 2.3 Initial phosphoramidite screening.

2.3.2 Phosphoramidite ligands based on the bis-phenol backbone

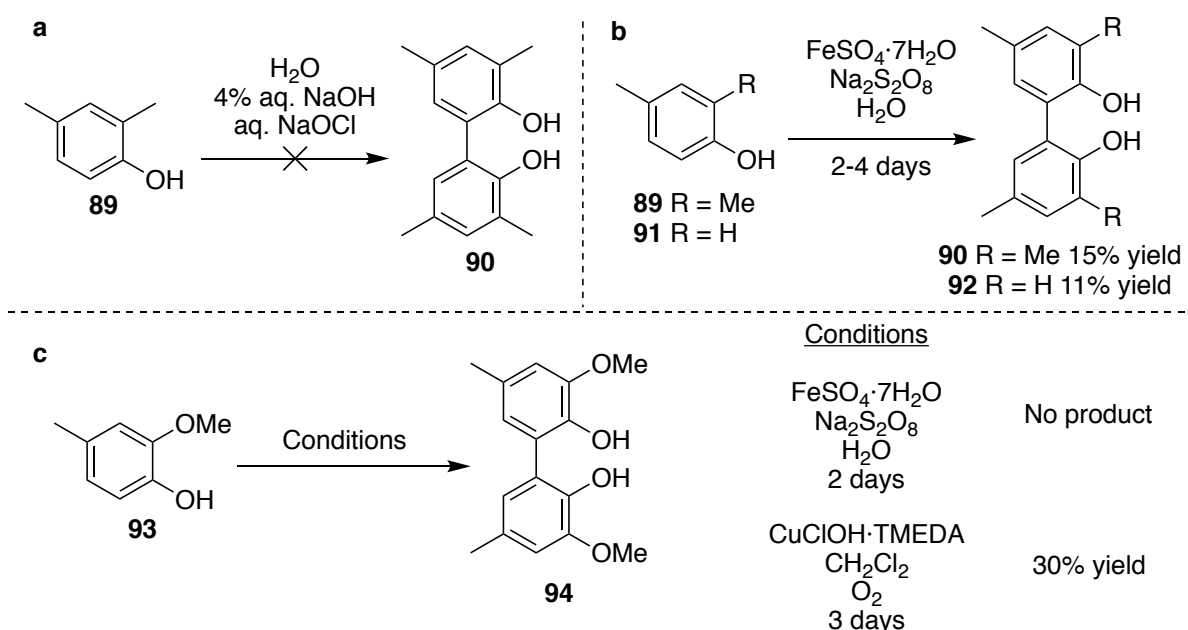
All of the ligands previously screened had been commercially available or had been supplied by the Fletcher group (see Chapter 5 for details). Based on our above findings we now wanted to screen derivatives of the bis-phenol ligand **16b**, to see if the ee's could be further improved. New ligands were designed and synthesised according to the methods used previously by the group (Scheme 2.8a).⁷⁴



Scheme 2.8 a General synthesis for phosphoramidite ligands. **b** Phosphoramidite ligands based on a bis-phenol backbone.

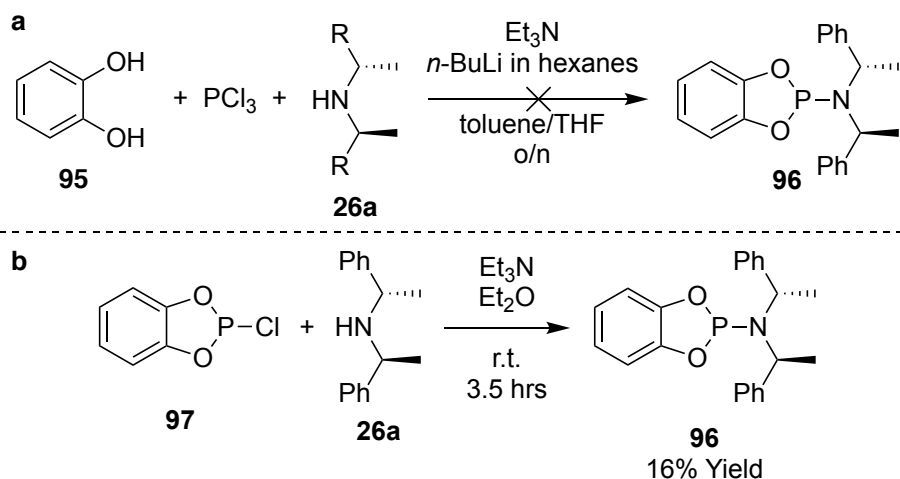
The diol backbones for ligands **84** and **88** were commercially available, but in all other cases the bis-phenol backbones were synthesised before making the subsequent ligands (Scheme 2.8b). This was achieved using a range of literature methods. We started by investigating an aqueous base mediated coupling, however no product was observed using this method

(Scheme 2.10a).⁷⁵ We then tried an iron sulphate mediated coupling,⁷⁶ and though this method did work for synthesising backbones **90** and **92**, the yields were very poor (Scheme 2.9b).

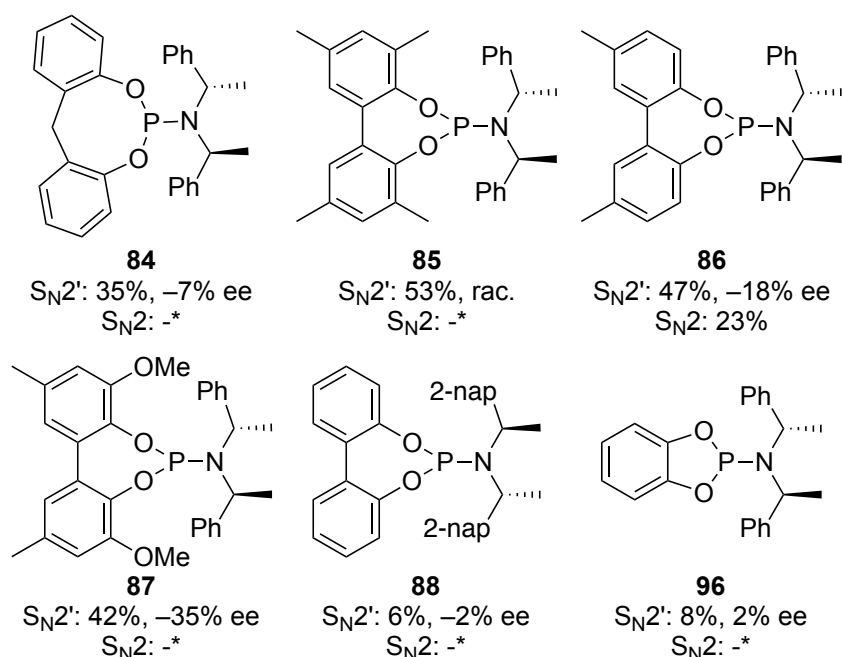
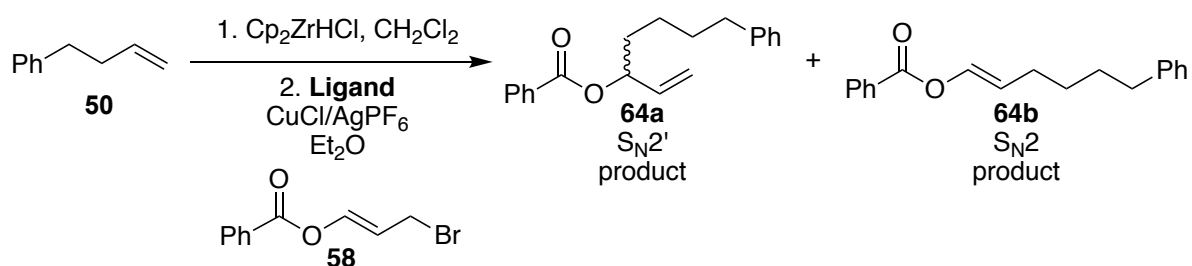


Scheme 2.9 **a** Aqueous base mediated coupling did not give any product. **b** An iron sulphate mediated coupling to give backbones **90** and **92**. **c** A Cu-mediated coupling gave backbone **94**.

This iron sulphate-mediated coupling did not work for backbone **94**, instead we decided to use a copper-mediated method described by Alexakis and co-workers in which they achieve a 52% yield.⁷⁶ In our laboratory, we only achieved a 30% yield of the desired backbone (Scheme 2.9c) from which the corresponding ligand was synthesised in 81% yield (Scheme 2.8b). The catechol-derived ligand **96** was also of interest; however attempts to make this ligand using catechol (**95**) and a literature known method (similar to that used for the other ligands) failed (Scheme 2.10a).⁷⁷ Instead the commercially available 1,2-phenylene phosphorochloridite (**97**) was reacted with amine **26a** directly to give the desired ligand (Scheme 2.10b).⁷⁸



Scheme 2.10 a Attempts to synthesise ligand **96** using catechol directly. **b** Using phosphorochloridite **97**, we were able to synthesise the desired ligand.



Scheme 2.11 The 1st generation ligands were tested in the *h*-AAA reaction. *Complex mixtures of side products and starting material isolated.

These 1st generation ligands were tested in the *h*-AAA reaction. Ligand **87** showed an improved ee of 35% compared to the original ligand **13-(R,R,R)**. Interestingly, the very

similar ligand, **85**, which only differed in a methyl versus methoxy group in the 2- and 2'-positions of bis-phenyl backbone, gave a completely racemic product.

At this point, we decided to retest a small number of copper catalysts. Selecting the two best ligands (**86** and **87**) we rescreened three copper counterions that had previously showed some enantioselectivity, namely CuOTf, CuOTs, and CuBF₄ (Table 2.5). We were pleased to find that when using ligand **87** with CuOTf rather than CuPF₆ we saw a marked improvement in ee from 35 to 73% (Table 2.5, entry 4).

Table 2.5 Rescreening selected copper catalysts.

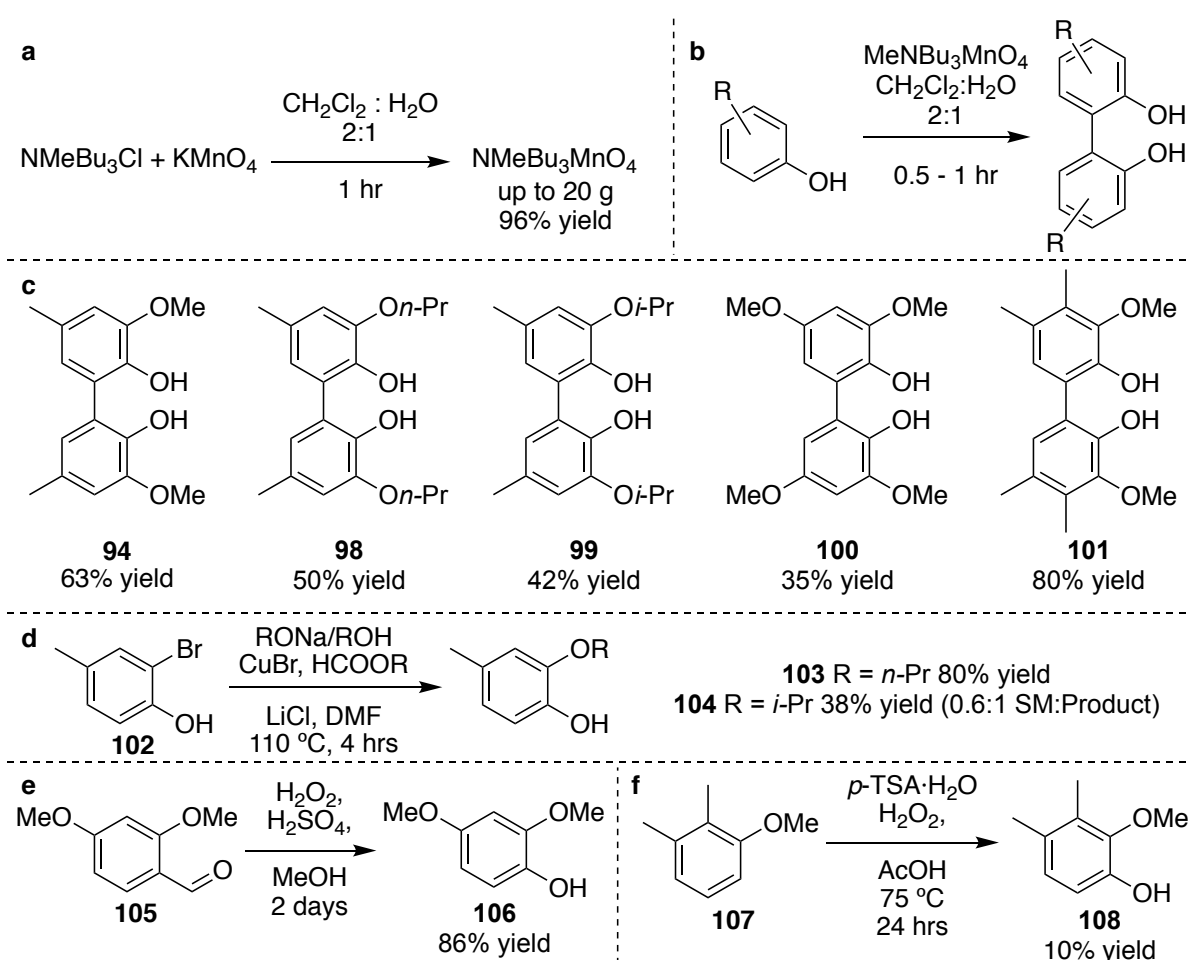
Entry	Ligand	Copper ^[a]	Yield S _N 2' (%) ^[b]	ee (%) ^[c]
1	86	CuCl, AgOTf	26	-34
2	86	CuCl, AgOTs	17	-21
3	86	CuCl, AgBF ₄	42	-16
4	87	CuCl, AgOTf	44	-73
5	87	CuCl, AgOTs	—	—
6	87	CuCl, AgBF ₄	14	-44

[a] Where the copper catalyst is formed *in situ* by transmetalation with a silver salt, 0.1 eq. of CuCl and 0.11 eq. of the corresponding silver salt were used. [b] All yields are isolated yields. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase

2.3.3 Design and synthesis of 2nd generation ligands

With these further optimised conditions in hand, we began designing and synthesising “2nd generation ligands”, based on the bis-phenol backbone. When thinking about the design of new ligands we wished to incorporate methoxy groups into many of the backbones, as this was clearly beneficial to the enantioselectivity of the reaction. This can be seen when comparing ligand **87** with ligands **85** and **86**, in which the methoxy groups in the 2-position

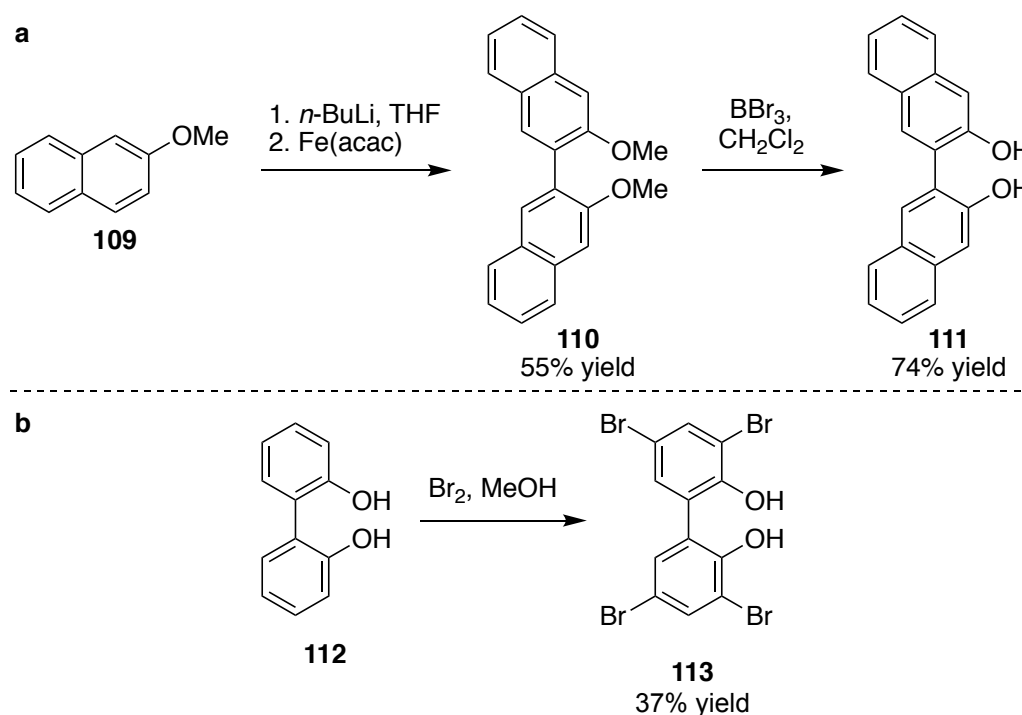
have either been removed entirely or replaced by methyl groups. Both these changes were detrimental to the outcome of the reaction. Many of our target backbones were known in the literature and therefore known synthetic procedures could be applied, as detailed below. In addition to making alterations to the backbone, we also designed some ligands based on the backbone of ligand **87**, but with variations to the amine portion of the ligand. Different amines were synthesised according to previously described literature methods (see Chapter 5).^{41,43,79–81}



Scheme 2.12 **a** Synthesis of MTBAP that could easily be carried out on a large scale. **b** General scheme for the coupling of phenols using MTBAP. **c** Backbones **94**, **98-101** were synthesised using the MTBAP coupling method in good to average yields. **d** Phenols **103** and **104** were synthesised using a Cu-catalysed alkoxylation reaction. **e** Phenol **106** was synthesised by oxidising aldehyde **105**. **f** Phenol **108** was synthesised by oxidation of **107**.

Since we now wanted to make multiple ligands based on backbone **94**, it was important to find a more efficient synthesis. The copper-mediated reaction we used previously gave only a

30% yield, which was not satisfactory. A method by Marques and co-workers describes a coupling of phenols using a manganese complex that is easily synthesised in one step and on a large scale (Scheme 2.12a).^{82,83} The coupling reaction uses methyltributylammonium permanganate (MTBAP) in a mixture of dichloromethane and water, and gave diol **94** in 63% yield – a significant improvement on the previous method. In addition to the improved yield, the reaction was easier to set up and carry out as it did not require a pure oxygen atmosphere and the reaction was complete within 30 minutes rather than 3 days. This manganese coupling proved to be an incredibly robust method for making a range of different backbones (**98-101**) in good to moderate yields (35–80%) (Scheme 2.12c). Phenols **103**, **104**, **106** and **108**, required for making backbones **98-101**, were synthesised according to literature procedures before carrying out the MTBAP coupling reactions (Scheme 2.12d-f).^{84–86}

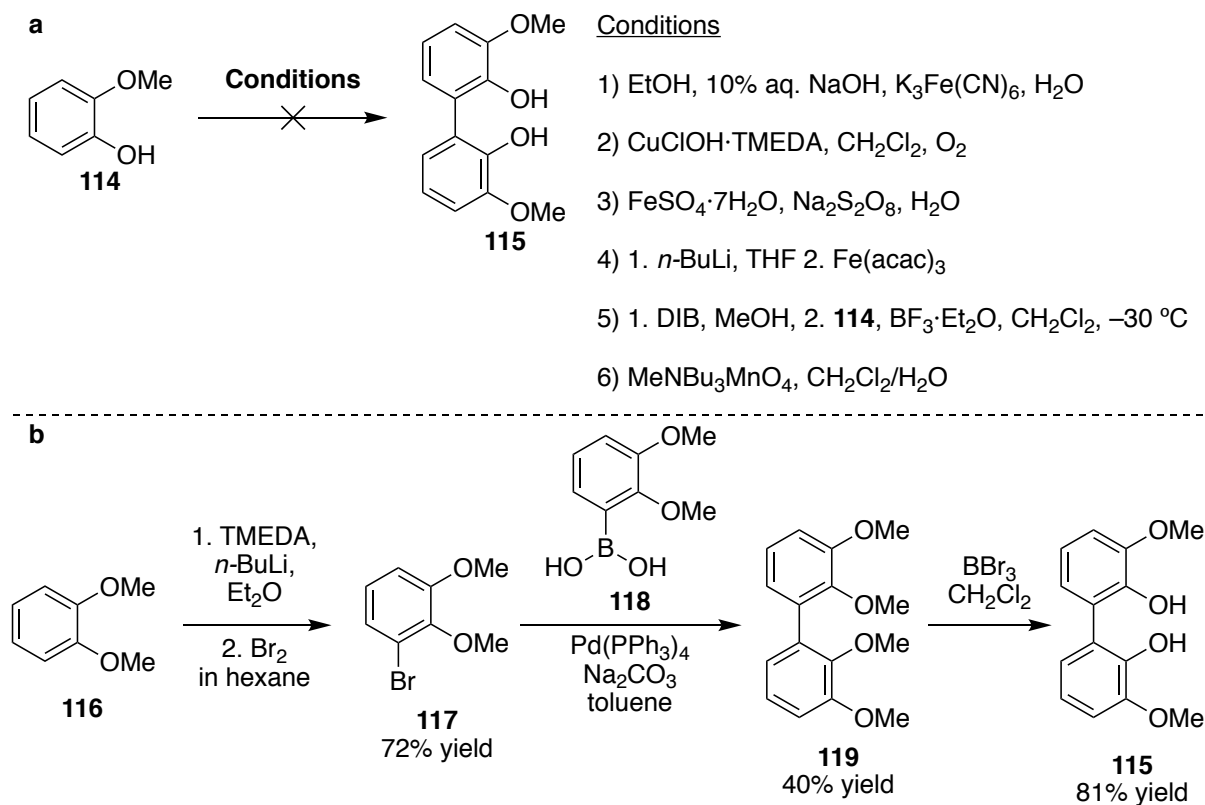


Scheme 2.13 **a** Fe-mediated coupling followed by demethylation gave **111**. **b** Bromination of bis-phenol **112** gave tetrabrominated backbone **113**.

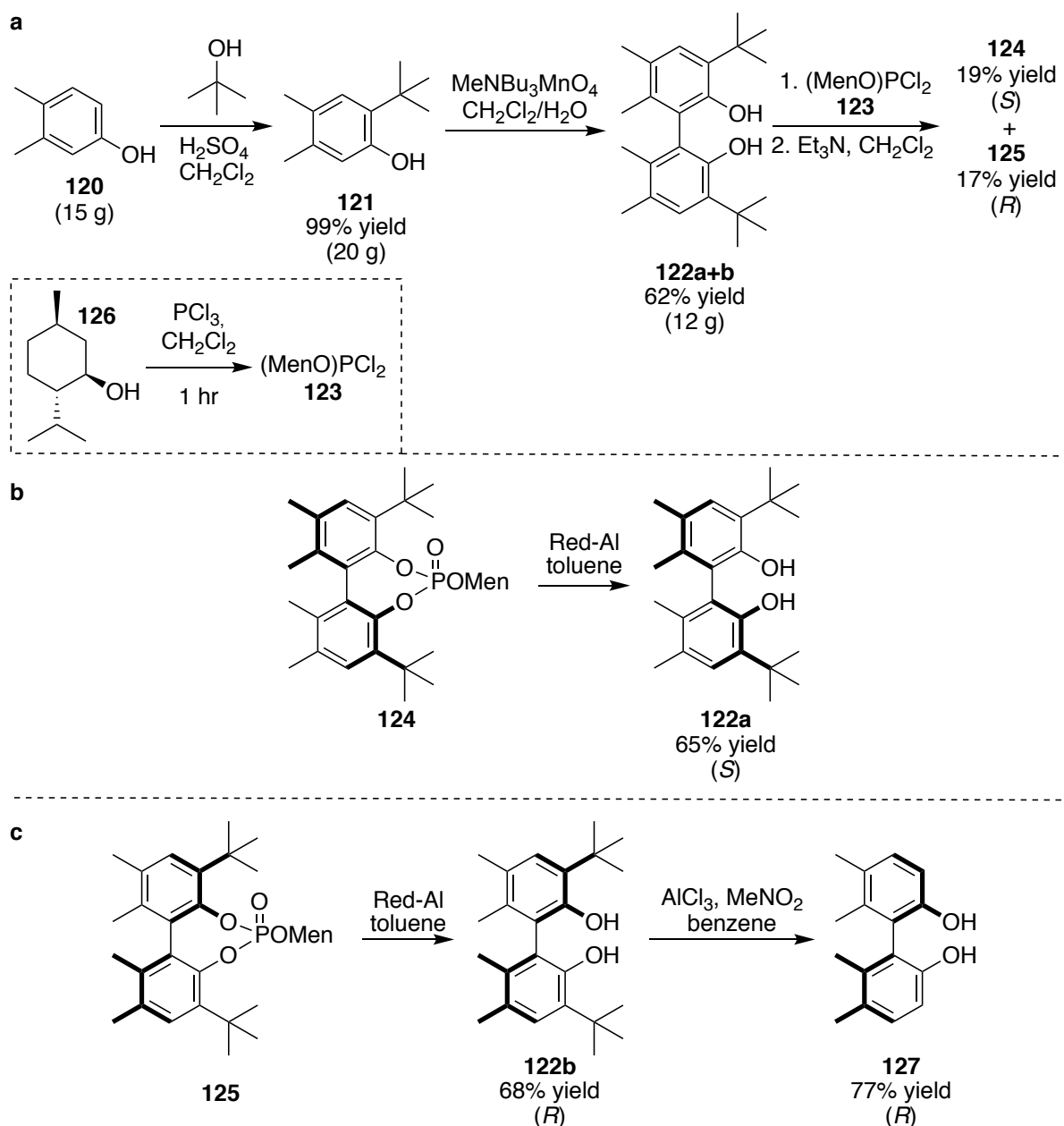
Backbone **111** was synthesised by coupling 2-methoxynaphthalene (**109**) to itself, using Fe(acac)₃, followed by demethylation using BBr₃.^{87,88} Tetrabromo-substituted backbone **113**

was synthesised using known literature procedures, as described by Alexakis and co-workers.⁷⁶

Some backbones proved more challenging to synthesise. Six coupling methods were tested in order to make backbone **115**, unfortunately none gave the desired product. Instead we devised a different route using a Suzuki coupling. The bromide was synthesised from commercial 1,2-dimethoxybenzene (**116**),⁸⁹ which was then used in a Suzuki coupling with boronic acid **118** to give tetramethoxy backbone **119**.⁸³ Using BBr₃, the methoxy groups in the 2- and 2'- positions could be selectively deprotected to give the desired backbone in 81% yield.^{90,91}



Scheme 2.14 **a** Backbone **115** initially proved challenging to synthesise. **b** A Suzuki coupling followed by demethylation gave the desired product.



Scheme 2.15 **a** Synthesis and resolution of bulky phosphate **122**. **b** Reduction of the chiral phosphate group gives the *S*-backbone. **c** Reduction of the chiral phosphate group and subsequent removal of the *t*-Bu groups gives chiral backbone **127**.

All the bis-phenol backbones just described have no fixed stereochemistry – they were flexible. We were interested in synthesising chiral backbone **127**,⁹² in order to probe the effect of having conformational stability in the backbone. To access this backbone in its enantiomerically pure form, it was necessary to carry out a resolution of the racemic diol. A *tert*-butyl group was added to **120** giving phenol **121** in 99% yield on a 15 g scale.⁹³ The MTBAP coupling gave racemic diol **122** in a 62% yield on a 20 g scale. The two enantiomers

of the backbone were separated by reacting the racemic diol with (–)-menthoxy dichlorophosphite (**126**), and recrystallising the two diastereomeric phosphates from different solvent systems. The *S*-diastereomer was recrystallised from acetic acid and the *R*-diastereomer recrystallised from MeOH. Subsequent removal of the menthol unit from each diastereomer using Red-Al returned the now enantiomerically pure backbones **122a** and **b**. Finally, the *tert*-butyl group was removed from the *R*-enantiomer using AlCl₃ and MeNO₂ giving diol **127**.^{94,95}

With the desired diol backbones in hand, the corresponding ligands were synthesised according to Scheme 2.8a in good to moderate yields (Figure 2.4). Unfortunately, we were not able to obtain ligand **136** from the reaction with backbone **122a**.

Upon testing these 2nd generation ligands in the *h*-AAA reaction we were disappointed to find that while some ligands gave very similar results to ligand **87** (44% yield, 73% ee), none of these new ligands made any further improvement on the outcome of the reaction (Table 2.6, entries 4, 7, 13 and 17). Some interesting observations however can be made from these new ligands.

Ligand **134** gave almost identical results to that of ligand **87**, showing that the two methyl groups on the backbone of ligand **87** are not necessary in this reaction (Table 2.6, entry 7, 42% yield, 71% ee). Ligands **128** and **129** (Table 2.6, entries 1 and 2) revealed that other alkoxy groups besides methoxy in the 2- and 2'-positions were detrimental to both the yield (28 and 26% respectively) and ee (51 and 64% respectively). Similarly, ligands **130** (which has a backbone with four methoxy groups) and ligand **131** (which has an additional methyl group in the 3- and 3'-position on the backbone) gave slightly lower ee's than for ligand **87** (Table 2.6, entries 3 and 4, 66 and 67% respectively), however the decrease in yield was more significant (20 and 28% respectively).

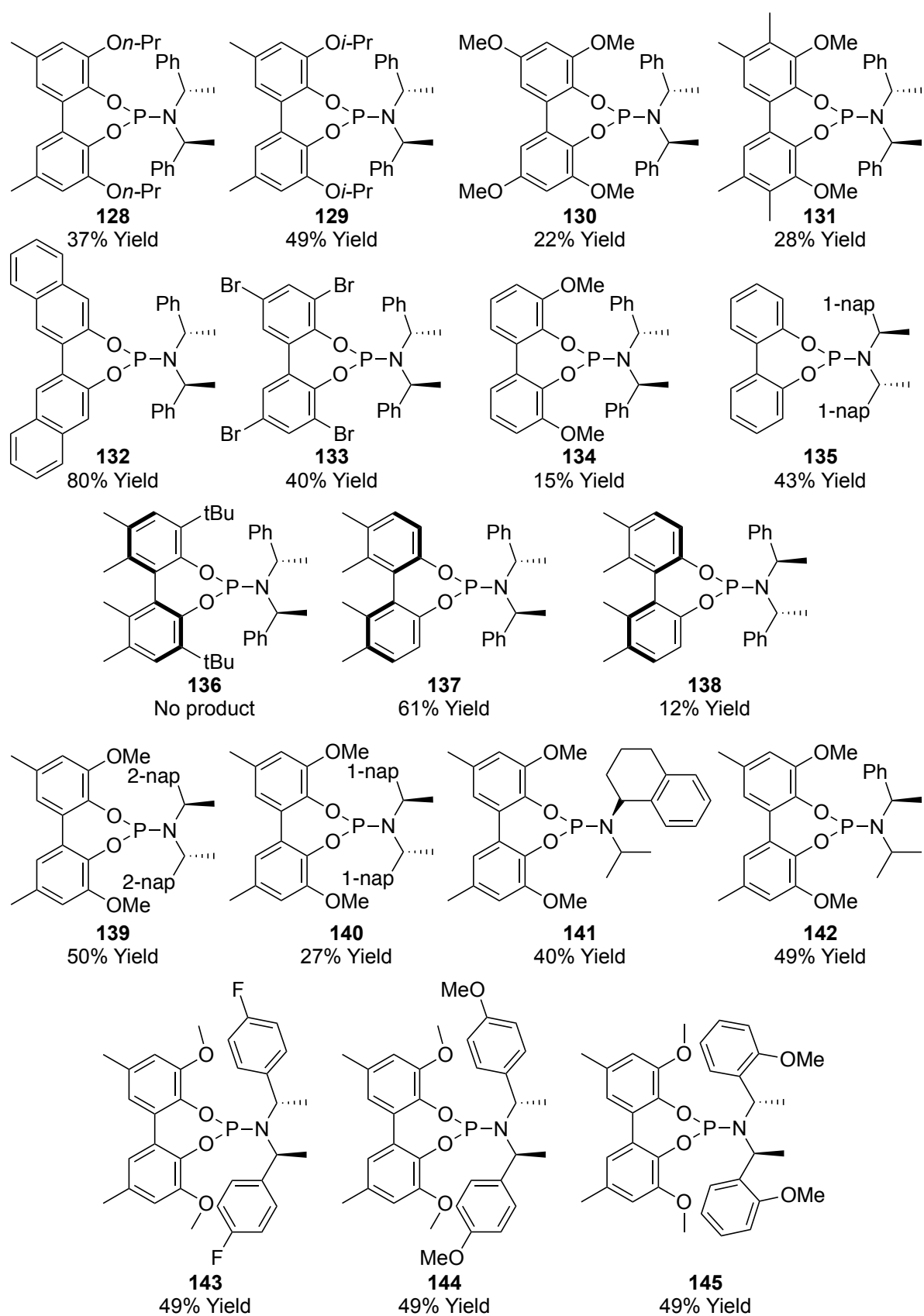
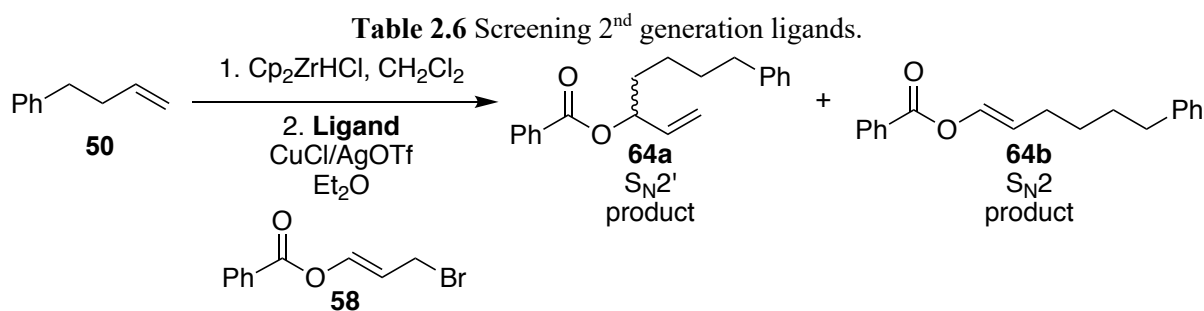


Figure 2.4 2nd Generation phosphoramidite ligands based on the bis-phenol backbone.



Entry	Ligand	Yield S _N 2' (%) ^[a]	Yield S _N 2 (%) ^[a]	ee (%) ^[b]
1	128	28	traces	-51
2	129	26	traces	-64
3	130	20	traces	-66
4	131	28	-	67
5	132	16	-	-23
6	133	6	-	-5
7	134	42	-	-71
8	135	6	-	10
9	137	28	15	-54
10	138	17	10	-47
11	139	39	-	13
12	140	37	6	68
13	141	13	-	5
14	142	21	12	23
15	143	36	-	-48
16	144	35	5	-73
17	145	3	-	12

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase.

Ligands **137** and **138**, which had fixed stereochemistry in the backbone but no methoxy groups showed improved results (up to 54% ee vs. 34% ee) compared to ligand **86** which also had no methoxy groups but a conformationally flexible backbone (Table 2.6, entries 9 and 10).

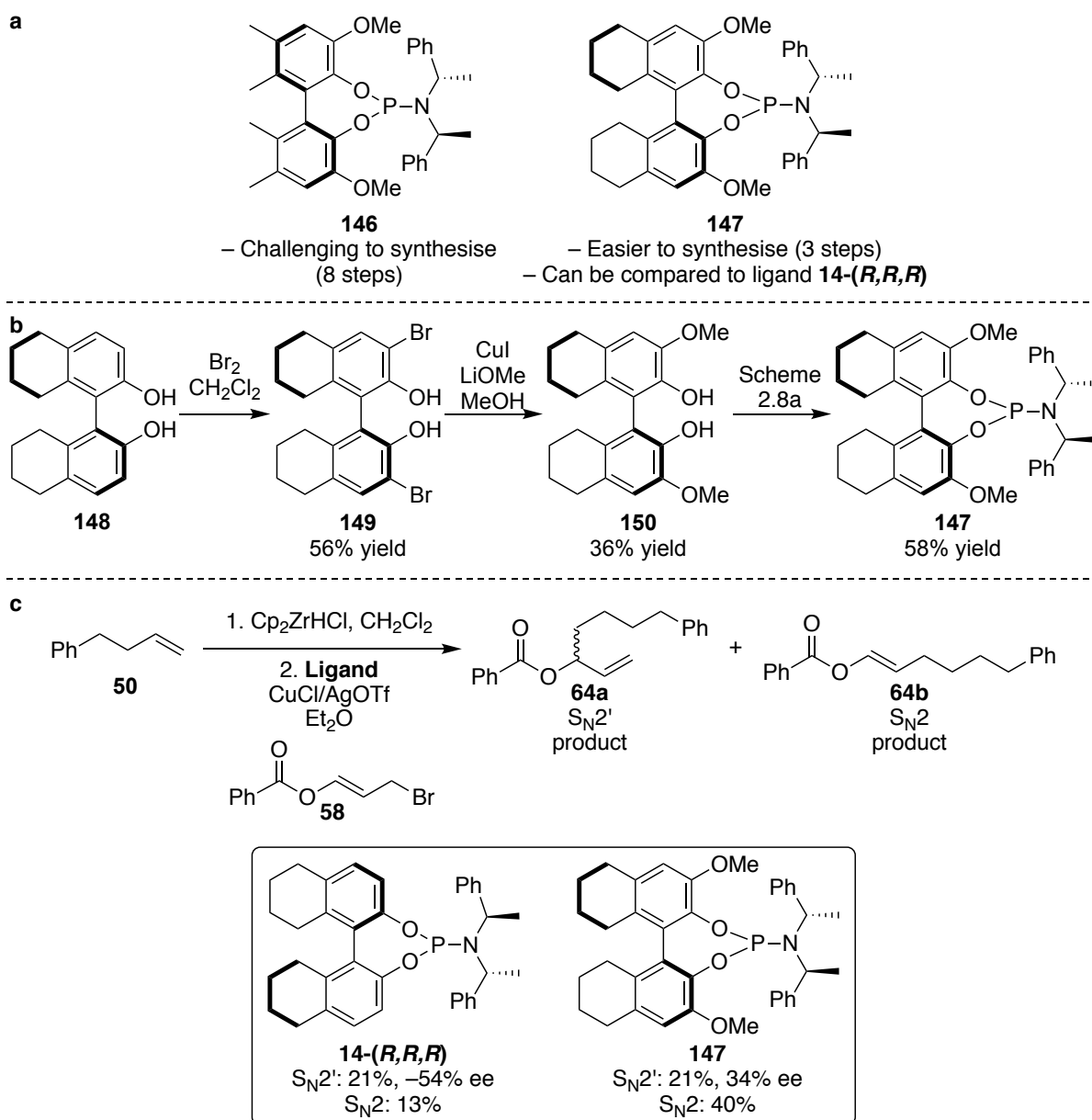
We also looked at making variations in the amine portion of the ligands whilst keeping the backbone the same as in ligand **87**. The bulky naphthyl group was only tolerated in one configuration. When using 1-naphthyl (**140**, Table 2.6, entry 13) the yield and ee was comparable to ligand **87**. However the 2-naphthyl derivative (**139**, Table 2.6, entry 12), whilst giving a comparable yield (39%), only gave a 13% ee. Deviating from the Feringa amine, for example ligands **141** and **142** (Table 2.6, entries 14 and 15) gave very poor results with lower

yields and much lower ee's than for ligand **87**. However, it was possible to add methoxy groups to the 4-position of the phenyl rings on the amines as in **144** (Table 2.6, entry 17), with negligible effect on the yield (35%) and no effect on the ee (73%). Interestingly when the methoxy groups were moved to the 2-position as in ligand **145** (Table 2.6, entry 18), both the yield and ee were severely decreased (3% yield, 12% ee). Lower yields and ee's were also observed when the fluoro group was put in the 4-position as in ligand **143** (36% yield, 48% ee, Table 2.6, entry 16).

Computational studies carried out by Alex Brethomé (Fletcher group), which will not be discussed in any further detail in this thesis, revealed an interaction between one of the methoxy groups in the 2'-position of the backbone of ligand **87** and the copper, in the copper-ligand complex. This observation was consistent with that seen in the ligand screening above. These studies also called into question the benefit of the flexibility in the bis-phenol backbone.

We considered instead that this flexibility was perhaps limiting the ee that could be achieved in this reaction. In order to test this hypothesis, we wished to make ligand **146** (Scheme 2.16a), which has both a fixed conformation in the backbone and methoxy groups in the 2- and 2'-positions. However upon examination of the literature we established that this was going to be challenging, with the best route likely to be a minimum of 8 steps. We therefore decided instead to make ligand **147**, as this would be easier to access in only 3 steps (Scheme 2.16b). If the ee improved with ligand **147** compared to the result with ligand **14-(R,R,R)** we would know that challenging ligand **146** would be worth pursuing.

When we carried out our asymmetric reaction with ligand **14-(R,R,R)** we achieved a 21% yield and 54% ee. Unfortunately with ligand **147**, with which we hoped to see an improved ee, it was in fact decreased to only 34%. At this stage, we concluded that we would not make any more phosphoramidite ligands.

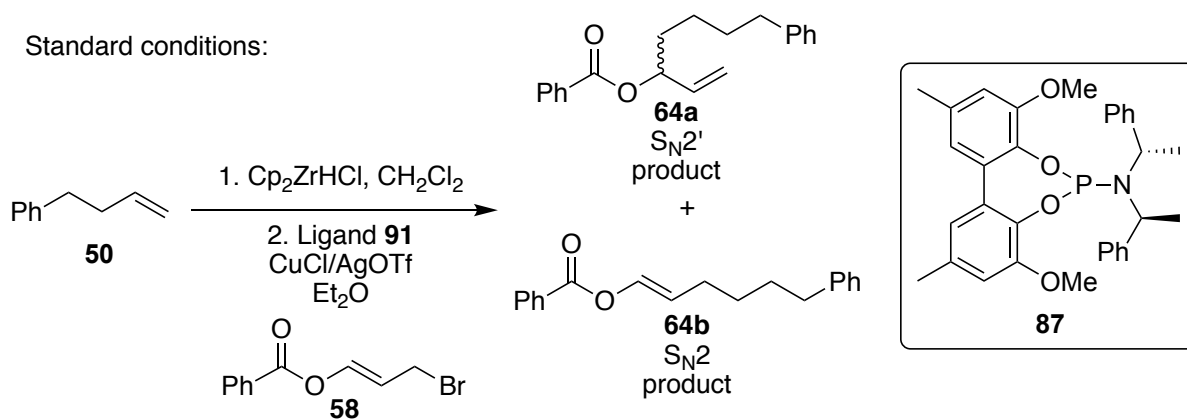


Scheme 2.16 **a** Ligand **146**, with a fixed backbone conformation would be incredibly challenging to synthesise. **b** Synthesis of ligand **147**. **c** Ligand **147** was tested in our reaction and the results compared to ligand **14-(R,R,R)**.

Two final sets of conditions were examined for this *h*-AAA reaction. When changing the solvent from Et₂O to MTBE both the yield and ee decreased. As TMSCl is often used as an additive in AAA and ACA reactions to increase the reactivity of the substrates,^{41,44} we tried using it in our reaction. Although we saw an increase in the yield of the $\text{S}_{\text{N}}2'$ product to 56%, the ee dropped to only 59%. In both cases, the $\text{S}_{\text{N}}2$ product was not isolated. As neither of

these reactions showed any further improvement, we decided to move the project in a different direction.

Table 2.7 Variations from standard conditions.



Entry	Variation from standard conditions	Yield $\text{S}_{\text{N}}2'$ (%) ^[a]	ee (%) ^[b]
1	none	44	−73
2	MTBE instead of Et_2O	27	−63
3	MTBE instead of Et_2O and TMSCl (5.0 eq.)	56	−59

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase.

2.4 Asymmetric allylic alkylations of linear substrates using alkylzirconium reagents

It was clear that this linear *h*-AAA was far more complex and challenging than we had ever envisaged. At this stage we had a system with a low yield, but reasonable ee. We were hopeful that perhaps these conditions could be applied to a different linear system. We note that the conditions which gave good yields and ee's for the cyclic allyl halide substrates did not give the same results for linear substrates, revealing the need to optimise a different system for these substrates.

We first examined cinnamyl-derived substrates **11**, **8**, **152** and **153** as our electrophiles. The synthesis of linear substrate **152** was carried out according to literature procedures.⁹⁶ The Fletcher group provided phosphate **153**. Our initial test reactions revealed that cinnamyl

bromide was likely to be the best choice of electrophile for optimising a new linear AAA reaction, given that the yield, S_N2':S_N2 ratio and ee were all good to moderate at this stage.

Table 2.8 Examination of different linear substrates in an AAA reaction.

151

1. Cp₂ZrHCl, CH₂Cl₂

2. **Electrophile**
Ligand **87**
CuCl/AgOTf
Et₂O

154a
S_N2'
product

+ **154b**
S_N2
product

87

Electrophiles:

11 X = Br

8 X = Cl

152 X = OC(O)CF₃

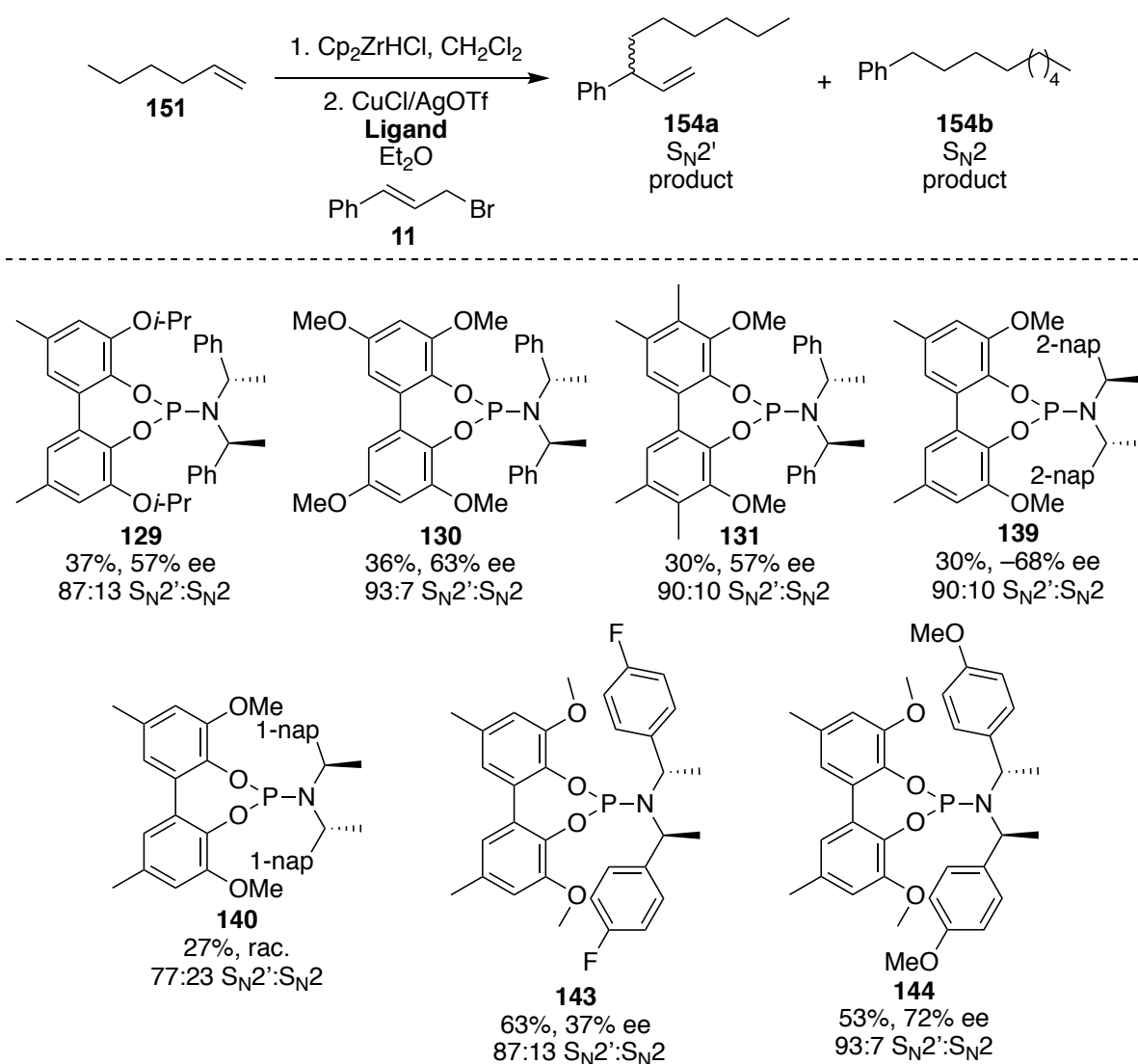
153 X = OP(O)(OEt)₂

Entry	Electrophile	Yield (%) ^[a]	S _N 2':S _N 2	ee (%) ^[b]
1	11	68	91:9	57
2	8	8	69:31	47
3	152	-	-	-
4	153	28	87:13	16

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase after conversion of the product to the corresponding terminal alcohol.

We began by testing some of our most promising ligands from our previous screening, using cinnamyl bromide and hexene. The reaction showed generally good selectivity for the S_N2' product over the S_N2 product and moderate ee's. Ligand **144** gave a lower yield (53% vs. 68% for ligand **87**), however gave a better S_N2':S_N2 ratio (93:7) and higher ee (72% vs. 57%). We also observe some other notable differences between this system and the *h*-AAA system.

The position of the bulky naphthyl groups on the amine appeared to have the opposite effect compared to the *h*-AAA system. Previously the 1-naphthyl amine was preferred over the 2-naphthyl amine, but in this system the opposite is true (Scheme 2.17, **139** and **140**).

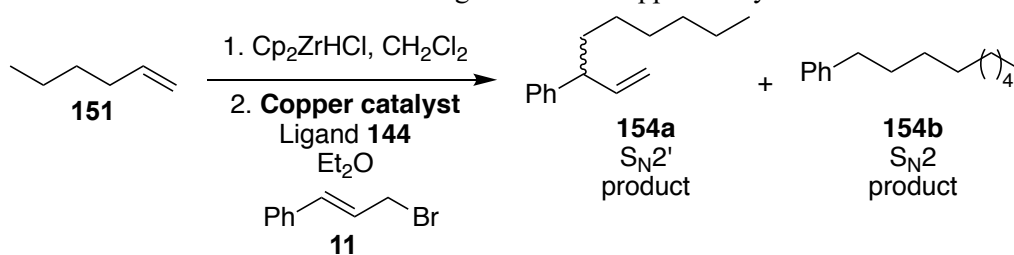


Scheme 2.17 Ligand screening.

A selected number of copper counterions were screened with ligand **144** (Table 2.9). Unfortunately, no improvements were observed. Once again, we failed to optimise the system beyond a moderate yield (53%) and average ee (72%).

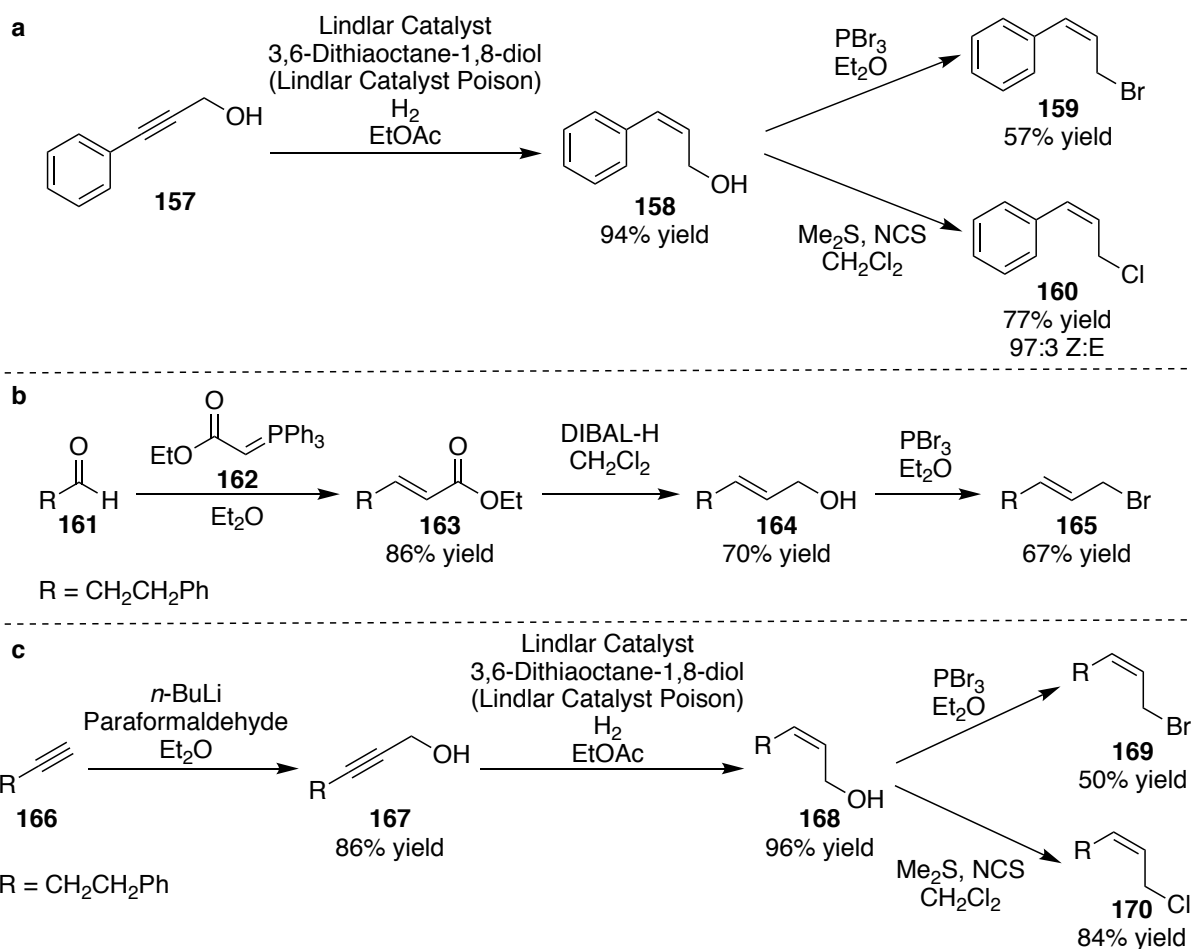
Finally, we decided to examine a range of other *Z* and *E* allylic bromides and chlorides. Here we decided to test the electrophiles in two different systems – the one used for the cyclic system⁴⁷ and the best system we have for the cinnamyl bromide. Crotyl bromide (**155**) and 1,4-dibromo-2-butene (**156**) were commercially available. The allylic halides shown in Scheme 2.18 were synthesised according to literature procedures.^{97–100}

Table 2.9 Screening of selected copper catalysts.



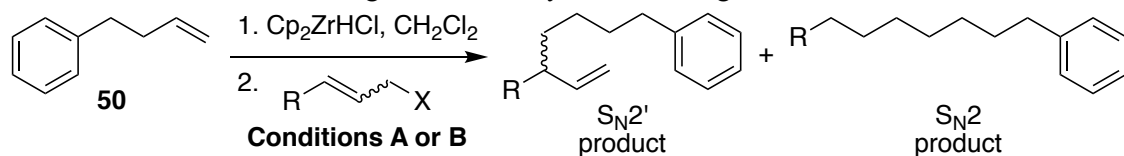
Entry	Copper Catalyst ^[a]	Yield (%) ^[b]	S _N 2':S _N 2	ee (%) ^[c]
1	CuCl, AgOTf	53	93:7	72
2	CuTC	46	85:15	20
3	Cu(OTf) ₂	18	73:27	27
4	CuCl, AgNTf ₂	19	79:21	40
5	CuCl, AgPF ₆	53	83:17	58
6	CuCl, AgBF ₄	37	82:18	60
7	CuCN	35	85:15	20
8	CuCl, AgNO ₂	32	76:24	54

[a] Where the copper catalyst is formed *in situ* by transmetalation with a silver salt, 0.1 eq. of CuCl and 0.11 eq. of the corresponding silver salt were used. [b] All yields are isolated yields. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase after conversion of the product to the corresponding terminal alcohol.



Scheme 2.18 **a** Synthesis of Z allyl halides **159** and **160**. **b** Synthesis of allylic bromide **165**. **c** Synthesis of Z allyl halides **169** and **170**.

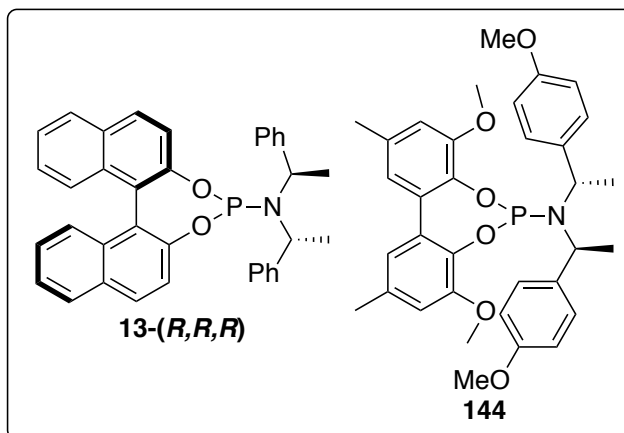
Table 2.10 Screening of *Z* and *E* allyl halides using two sets of conditions.



- 155** (*E*) $R = \text{Me}$, $X = \text{Br}$
156 (*E*) $R = \text{CH}_2\text{Br}$, $X = \text{Br}$
159 (*Z*) $R = \text{Ph}$, $X = \text{Br}$
160 (*Z*) $R = \text{Ph}$, $X = \text{Cl}$
165 (*E*) $R = \text{CH}_2\text{CH}_2\text{Ph}$, $X = \text{Br}$
169 (*Z*) $R = \text{CH}_2\text{CH}_2\text{Ph}$, $X = \text{Br}$
170 (*Z*) $R = \text{CH}_2\text{CH}_2\text{Ph}$, $X = \text{Cl}$

Conditions A: CuCl/AgOTf , Ligand **144**, Et_2O

Conditions B: CuI , Ligand **13-(*R,R,R*)**, CH_2Cl_2



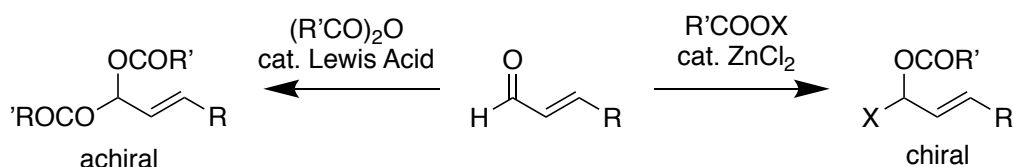
Entry	Substrate	Product	Conditions A/B	Yield (%) ^[a]	$S_N2':S_N2$	ee (%)
1	155		A	53	81:19	−48 ^[b]
2	155	171	B	62	34:66	−12 ^[b]
3	156		A	84	nd	−40 ^[b]
4	156	172	B	79	nd	−16 ^[b]
5	159		A	59	96:4	14
6	159		B	68	81:19	48 ^[b]
7	159		B ^[d]	54	77:23	48 ^[c]
8	159	173	B ^[e]	79	76:24	42 ^[c]
9	160		A	-	-	-
10	160		B	19	85:15	36 ^[c]
11	165		A	62	87:13	−58 ^[c]
12	165		B	74	71:29	−22 ^[c]
13	169		A	40	87:13	46 ^[c]
14	169	174	B	83	82:18	40 ^[c]
15	170		A	70	>99:1	30 ^[c]
16	170		B	75	92:8	28 ^[c]

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase after conversion of the product to the corresponding terminal alcohol. [c] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. [d] CuCl used instead of CuI . [e] CuBr used instead of CuI .

The electrophiles were tested in the two systems as shown in Table 2.10. Unfortunately, none showed improved results compared to cinnamyl bromide. Most electrophiles performed poorly under both sets of conditions, with the *trans* substrates favouring the bis-phenol system and the *cis* substrates favouring the BINOL system as a general rule. While yields of up to 84% (Table 2.10, entry 3) could be achieved, the highest ee was only 58% (Table 2.10, entry 9). At this stage, we concluded this project here.

2.5 Asymmetric allylic alkylations with α -halo acetates and benzoates

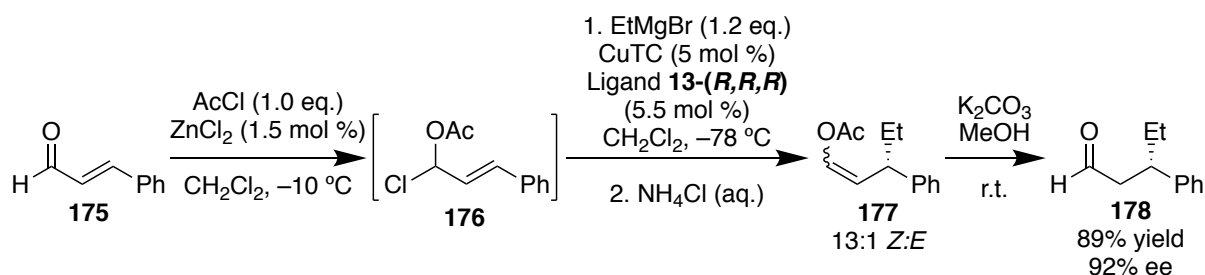
Linear substrates used for asymmetric allylic alkylation reactions are often achiral. As a key example, allylic aldehydes are commonly transformed into achiral, allylic *geminal*-carboxylates. These linear substrates are then applied in palladium-catalysed allylic alkylations.^{101–103} In contrast, the use of racemic linear substrates is far less developed. Aldehydes can be transformed into α -halo acetates by reacting them with an acid halide in the presence of catalytic amounts of zinc chloride.



Scheme 2.19 Aldehydes are commonly transformed into *geminal*-dicarboxylates, which are achiral. Less common is the use of chiral linear allylic substrates in AAA reactions.

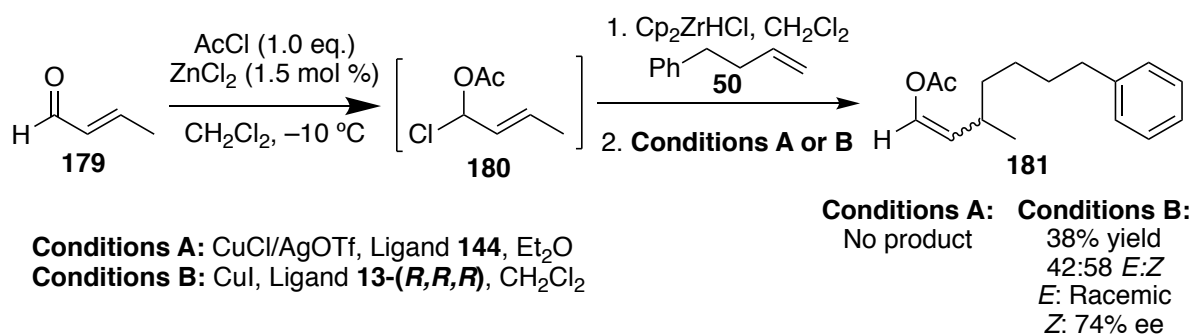
In 2010, Feringa and co-workers demonstrated a copper-catalysed asymmetric allylic alkylation reaction on α -halo acetate (**176**), which was prepared in situ from aldehyde **175**.¹⁰⁴ This intermediate then undergoes an allylic alkylation reaction using CuTC, ligand **13**-(*R,R,R*) and Grignard reagents. The reaction proceeds with good regioselectivity for the $\text{S}_{\text{N}}2'$ product, good selectivity for the *Z* alkene in most cases, good yield and excellent ee's. The

main limitation of this reaction is the use of Grignard reagents, which restricts additions to simple alkyl groups.



Scheme 2.20 Cu-catalysed AAA of α -halo acetates prepared *in situ* from aldehydes.

We hypothesised that it might be possible to use these chiral α -halo acetates as a substrate in our AAA reaction, using alkylzirconium reagents as nucleophiles. We began our investigations by examining the two sets of conditions we were using for our linear substrates (Scheme 2.21). Using conditions **A** we saw no evidence of any product forming. However, under conditions **B** we were pleased to obtain a 38% yield. The ratio of *E:Z* products was near 1:1 and unfortunately the *trans* product was completely racemic. On the other hand, the *cis* product gave a very promising 74% ee.



Scheme 2.21 Two initial reactions to investigate the AAA of α -halo acetates using alkylzirconium reagents.

In these initial reactions we preformed α -halo acetate **180** in a separate flask passing it through a syringe filter under argon before addition to the reaction. As we did not know what the influence would be of the catalytic ZnCl₂ in our AAA reaction, we carried out another reaction using conditions **B** where the solution containing **180** was not filtered before addition to the reaction mixture. Without filtering we saw comparable results (32% yield,

33:67 *E*:*Z*, *E*: 3% ee, *Z*: 71% ee), therefore for purely practical reasons we chose not to filter the solution containing **180** in our subsequent screening. Using conditions **B** as our standard conditions (which were the original conditions for the cyclic allyl chloride system),⁴⁷ we carried out a screening of a small number of phosphoramidite ligands. Ligand **182**, developed by the Fletcher group, has recently been shown to be effective in the ACA of alkylzirconium reagents to linear trisubstituted enones, dienones and ynenones.^{105,106} When we used ligand **182** in this reaction we were pleased to see that the *E*:*Z* ratio improved slightly from ~1:3 to 1:4 and enantioselectivities for both isomers increased from racemic to 33% for the *E* isomer and from 74% to 90% for the *Z* isomer (Table 2.11, entry 5). Upon screening a small number of copper catalysts we established that the reaction was relatively tolerant to halide and thiophene carboxylate anions, with comparable results being obtained; however with CuOTf no product was obtained (Table 2.11, entries 7 – 10). The addition of TMSCl to the reaction gave an increased ee for the *E* isomer from 33% to 59% (Table 2.11, entry 11). We undertook a solvent screen for this reaction and found that the results were either comparable or worse than dichloromethane, with the more noticeable effects being seen in the yield and *E*:*Z* ratios (Table 2.11, entries 12 – 16). We studied the effects of temperature on the reaction, however no improvements in selectivity were observed (Table 2.11, entries 17 – 18).

Despite these screening reactions, no further improvements were observed beyond a 43% yield, 1:4 *E*:*Z* ratio, 59% ee for the *E* isomer and 90% ee for the *Z* isomer for the α -halo acetate formed from acetyl chloride and crotonaldehyde (**180**). We decided at this point to change the substrate to cinnamaldehyde (**175**).

Table 2.11 Screening reaction conditions for the AAA of α -halo acetates using alkylzirconium reagents.

Entry	Copper	Ligand	Solvent	Yield (%) ^[a]	<i>E</i> : <i>Z</i>	ee – <i>E</i> (%) ^[b]	ee – <i>Z</i> (%) ^[b]
1	CuI	13-(<i>S,R,R</i>)	CH ₂ Cl ₂	40	31:69	13	82
2	CuI	13-(<i>R,R,R</i>)	CH ₂ Cl ₂	32	33:67	3	71
3	CuI	79	CH ₂ Cl ₂	30	34:66	4	74
4	CuI	87	CH ₂ Cl ₂	26	39:61	3	26
5	CuI	182	CH ₂ Cl ₂	34	17:83	33	90
6	CuI	183	CH ₂ Cl ₂	27	28:72	12	87
7	CuTC	182	CH ₂ Cl ₂	43	21:79	34	94
8	CuCl	182	CH ₂ Cl ₂	50	22:78	34	94
9	CuBr	182	CH ₂ Cl ₂	28	19:81	27	92
10	CuCl, AgOTf	182	CH ₂ Cl ₂	-	-	-	-
11 ^[c]	CuI	182	CH₂Cl₂	43	19:81	59	90
12 ^[c]	CuI	182	Dioxane	47	26:74	52	89
13 ^[c]	CuI	182	THF	43	28:72	50	85
14 ^[c]	CuI	182	Et ₂ O	29	29:71	50	85
15 ^[c]	CuI	182	CHCl ₃	49	22:78	54	94
16 ^[c]	CuI	182	MTBE	32	25:75	43	88
17 ^[d]	CuI	182	CH ₂ Cl ₂	~5	25:75	36	>99
18 ^[e]	CuI	182	CH ₂ Cl ₂	45	19:81	28	94

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. [c] TMSCl added. [d] Reaction carried out at –10 °C. [e] Reaction carried out at –10 °C and slowly warmed to room temperature.

Table 2.12 Screening reactions using cinnamaldehyde.

Entry	Copper	Yield (%) ^[a]	<i>E</i> : <i>Z</i>	ee – <i>E</i> (%) ^[b]	ee – <i>Z</i> (%) ^[b]
1	CuI	15	56:44	rac.	65
2	CuCl	26	28:72	18	93
3	CuBr	15	29:71	12	80
4	CuTC	19	38:62	13	92
5 ^[c]	CuCl	16	29:71	16	87

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. [c] TMSCl added.

We found that with cinnamaldehyde the *E*:*Z* ratio was slightly worse than with crotonaldehyde, and in addition, the overall yields and ee of the *E*-isomer were significantly lower. Using copper iodide we only achieved a 15% yield, 1:1 *E*:*Z* ratio, a racemic product for the *E*-isomer and only 65% ee for the *Z*-isomer (Table 2.12, entry 1). A screen of copper catalysts revealed that the ee of the *Z*-isomer could be improved to 93% when using CuCl, however the yield and ee of the *E*-isomer were lower than for the crotonaldehyde system (Table 2.12, entry 2). Interestingly, in the reaction with crotonaldehyde the addition of TMSCl improved both the yield and ee of the *E*-isomer, whereas with cinnamaldehyde we saw a decrease in yield and ee of both the *E*- and *Z*-isomers (Table 2.12, entry 5).

At this point, we decided to use crotonaldehyde as our substrate again, but now generate an α -halo benzoate by using benzoyl chloride. We hope that by having a different ester group on the allylic alcohol we could improve our *E*:*Z* selectivity and enantioselectivities. We were pleased to find that with CuI and ligand **182** we obtained a 59% ee for the *E*-isomer and a 89% ee for the *Z*-isomer (Table 2.13, entry 1). Unfortunately, the yield was relatively low at only 29% and the *E*:*Z* ratio was 1:1. Upon screening selected copper catalysts we found that by using CuCl, the yield could be improved to 51%, the ee of the *E*-isomer increased to 74% and the ee of the *Z*-isomer increased to 94% (Table 2.13, entry 3).

Table 2.13 Screening reaction conditions for the AAA of α -halo acetates using alkylzirconium reagents.

Entry	Copper	Ligand	Solvent	Yield (%) ^[a]	<i>E:Z</i>	ee – <i>E</i> (%) ^[b]	ee – <i>Z</i> (%) ^[b]
1	CuI	182	CH ₂ Cl ₂	29	1:1	59	89
2	CuTC	182	CH ₂ Cl ₂	45	43:57	73	93
3	CuCl	182	CH₂Cl₂	51	44:56	74	94
4	CuBr	182	CH ₂ Cl ₂	33	43:57	47	88
5	CuCl, AgOTf	182	CH ₂ Cl ₂	~14	1:1	51	88
6	CuCl	13-(<i>R,R,R</i>)	CH ₂ Cl ₂	22	56:44	29	74
7	CuCl	183	CH ₂ Cl ₂	33	40:60	59	93
8 ^[c]	CuCl	182	CH ₂ Cl ₂	31	46:54	68	94
9	CuCl	182	CHCl ₃	42	43:47	63	95
10	CuCl	182	Et ₂ O	50	52:48	74	94
11	CuCl	182	THF	~31	72:28	8	89
12	CuCl	182	MTBE	30	56:44	72	93
13	CuCl	182	Dioxane	~30	57:43	~79	90

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. [c] TMSCl added.

Unfortunately, regardless of the conditions tried the *E:Z* ratio was generally 1:1, with the exception of changing the solvent to THF. However in this case the yield decreased significantly (Table 2.13, entry 11). Generally, changing the solvent did not show any improvement on the results (Table 2.13, entries 10 – 13) and adding TMSCl was detrimental to the reaction (Table 2.13, entry 8). Neither ligand **13-(*R,R,R*)** nor **183** improved the results of the reaction. Given the poor regioselectivities, generally low yields and despite the high ee's, particularly for the *Z* isomer, no further investigations were carried out on this project.

2.6 Conclusions

We began by investigating a tandem reaction initiated by an asymmetric allylic alkylation of racemic allyl chlorides. We hoped to demonstrate that the by-product of the AAA, Cp_2ZrCl_2 , which comes from the nucleophilic organozirconium species, could be used in a second process – the addition of a Grignard reagent to an alkene. Unfortunately, we quickly realised that this would not be possible using the alkene generated in our reaction.

We investigated the AAA using a diene as the nucleophile, in the hopes that the product of this reaction, which would have a terminal alkene, would then undergo our desired tandem reaction. However, the AAA reaction with 1,4-pentadiene, while giving the desired product, also gave an inseparable side product in which the terminal alkene had been hydrogenated. Regardless, a tandem reaction was attempted, however no reaction occurred upon addition of a Grignard reagent.

We moved our focus to developing a *h*-AAA which we hoped to optimise and then use in subsequent tandem reactions in order to obtain highly functionalised alcohol-containing products. We quickly established that the conditions for the AAA of racemic allyl halides would not be appropriate for this reaction and our investigations led us to designing and synthesising phosphoramidite ligands based on the bis-phenol backbone. The synthesis of 26 ligands has been described in this chapter. Using ligand **87** we could achieve a 44% yield and 73% ee of the desired product. This project was far more challenging than we envisaged, and despite many attempts of further optimisation, no improvements on this result were found.

We moved to applying our conditions to other linear substrates. We examined a range of *cis* and *trans*-allylic bromides. Our best results were achieved using ligand **144** and *trans*-cinnamyl bromide as our electrophile (53% yield, 93:7 $\text{S}_{\text{N}}2':\text{S}_{\text{N}}2$, 72% ee). With other

substrates we were able to obtain yields of up to 84% and excellent $S_N2':S_N2$ ratios of >99:1, however the ee's were not higher than 58%.

Finally, we investigated the AAA with α -halo acetates and benzoates. In this reaction we generally obtained low yields of products and in poor *E:Z* ratios. We did however obtain some excellent ee's of up to 94% with the *Z* isomer. The *E* isomer unfortunately only gave ee's of up to 59%. Despite our attempts at optimising this reaction, including using a different aldehyde, we saw no further improvements.

It is clear to us from these projects that the use of linear substrates in AAA reactions using organozirconium is challenging. Despite our best efforts at optimising these reactions so far, there is still further work that could be done in designing new ligands that may be able to promote good yields and ee's for these reactions.

3 Phosphoramidite ligands based on simple 1,2-diols

Most of this chapter has been published as the following paper: Mistry, N., and Fletcher, S. P., *Adv. Synth. Catal.*, **2016**, 358, 2489–2496.

In chapter 2 we discussed the design and synthesis of many new phosphoramidite ligands. The modular nature of phosphoramidites, the diol-backbone and the amine, allows for libraries that may be finely tuned for enantioselectivity in specific reactions, and this has contributed to the extensive use of these ligands in modern chemistry. Most phosphoramidites use BINOL¹⁰⁷ (A), ‘spiro’ (B) or TADDOL¹⁰⁸ (C) diol backbones which are powerful sources of asymmetry (Figure 3.1).¹⁰⁹ More flexible diols, such as the bisphenol moiety (D), where backbone asymmetry is induced by the amido-unit, are also effective in certain reactions.^{76,110} Generally, BINOL-based phosphoramidites (A) are the most widely used and many modified BINOLs, such as 3,3-disubstituted E¹¹¹ and hydrogenated F,¹¹² have been reported.

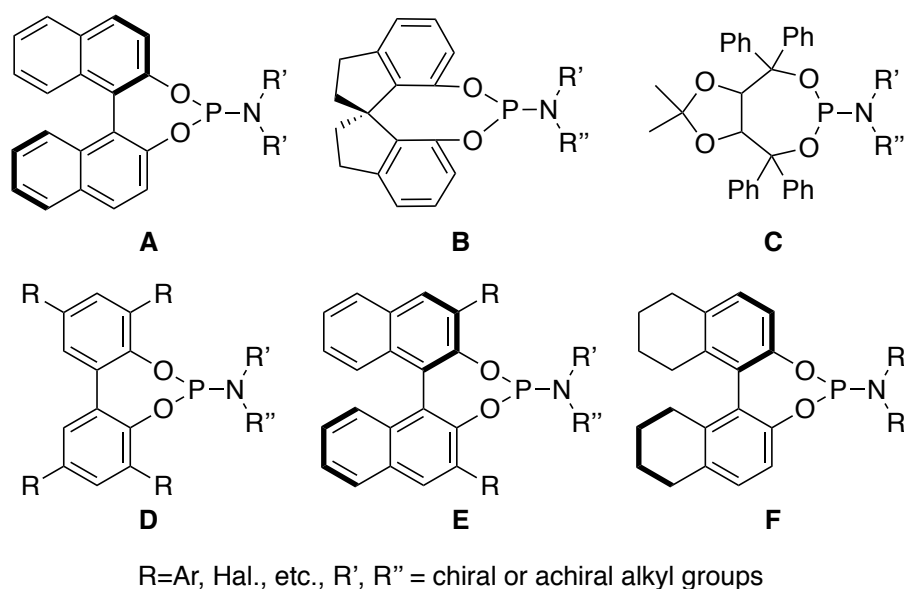
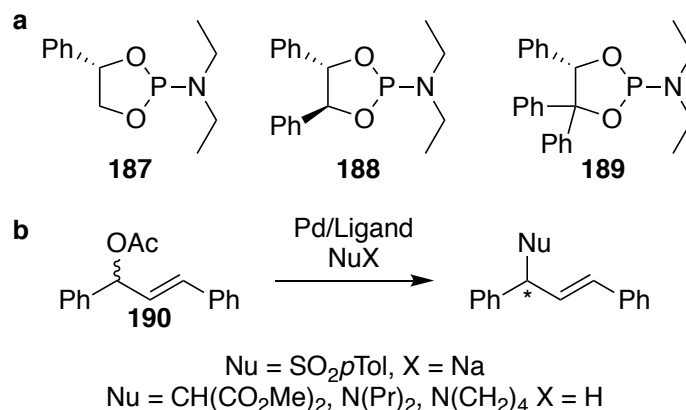


Figure 3.1 Commonly used phosphoramidite ligands: based on BINOL (A), ‘spiro’ (B), TADDOL (C), ‘flexible’ (D) and modified BINOL (E and F) backbones.

Phosphoramidite ligands based on simple diol backbones are almost unreported. To the best of our knowledge, the only relevant use of simple diols was by Gavrilov and co-workers who

described combining chiral 1,2-diols with achiral amines to give ligands such as **187**, **188** and **189** (Scheme 3.1a).^{113,114} In this work they showed that the ligands (**187-189**) can be used to induce enantioselectivity in the palladium-catalysed allylic alkylation, sulfonylation, and amination of (*E*)-1,3-diphenylallyl acetate (**190**), achieving ee's of up to 80% (Scheme 3.1b).



Scheme 3.1 **a** Previously reported phosphoramidites based on simple 1,2-diols by Gavrilov and co-workers. **b** Ligands **187 – 189** can be used in Pd-catalysed asymmetric reactions.

In this chapter, a set of novel phosphoramidite ligands based on simple 1,2-diols are described. We first examined chiral (*S,S*)-trans-cyclohexanediol and (*R,R*)-(+)-1,2-diphenyl-1,2-ethanediol in combination with bis-(1-phenylethyl)amines (**26a** and **b**) to give **191-194**, where **191 + 192** (and **193 + 194**) are diastereomers.

To obtain ligands **195** and **196**, we used (*S,S*)-trans-cyclohexanediol and (*R,R*)-(+)-1,2-diphenyl-1,2-ethanediol in combination with an achiral amine.⁴³ Finally, using *meso cis*-cyclohexanediol and *meso cis*-diphenyl-1,2-ethanediol with a chiral non-racemic amine gave diastereomeric ligands **197 + 198** and **199 + 200** respectively, which bear achirotopic¹¹⁵ stereogenic phosphorus atoms (*vide infra*) (Figure 3.2).

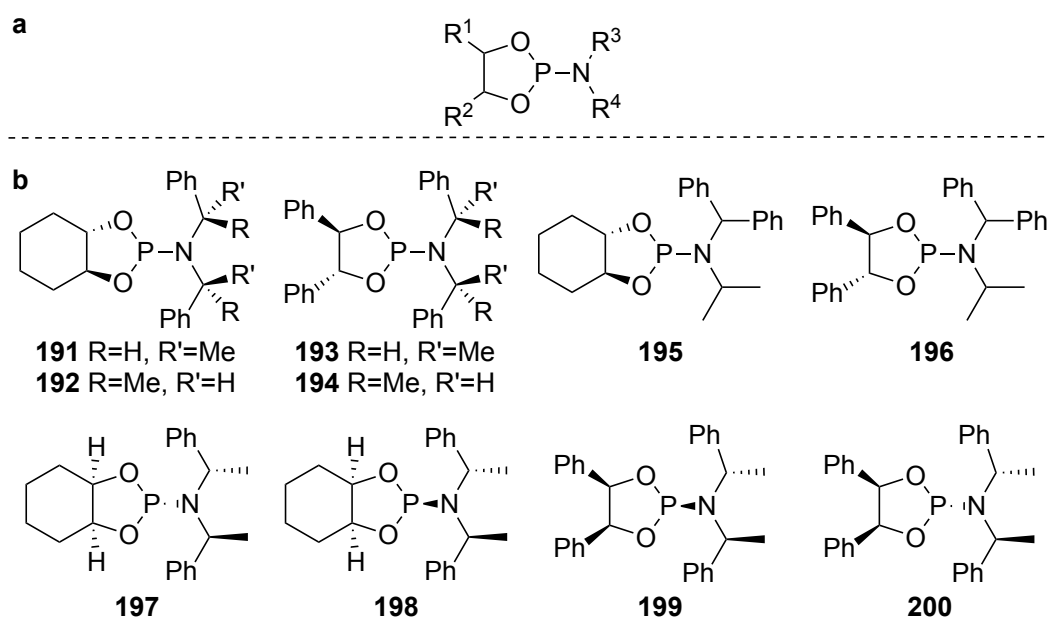


Figure 3.2 **a** Generic phosphoramidite ligand made from a simple diol. **b** New phosphoramidite ligands.

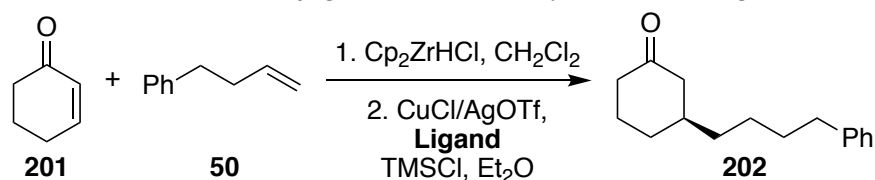
3.1 Examination of new ligands in asymmetric metal-catalysed reactions

In order to examine if these new ligands might be useful, we decided to test them in copper-catalysed asymmetric addition reactions, first examining a hydrometallation–conjugate addition reaction.⁴¹ Compound **202** was obtained in 91% ee using typical BINOL-based phosphoramidite **13-(R,R,R)** (Table 3.1, entry 1), which is far superior to all of the results obtained with the ligands shown in Figure 3.2, where **191** gave the best result of only 56% ee (Table 3.1, entry 2).

The copper-catalysed desymmetrisation of bicycle **203** with AlMe₃, first reported by Alexakis, was then examined (Table 3.2).¹¹⁶ SimplePhos ligands (such as **81**) first described in 2007, as previously mentioned, have obvious similarities to phosphoramidites – phosphinamines have aryl groups directly attached to the phosphorus-atom.¹¹⁷ According to the paper published in 2009, compound **204** can be obtained in 91% ee using ligand **81**, but

we were only able to achieve 83% ee (Table 3.2, entry 1) using the ligand prepared in our laboratory.

Table 3.1 1,4-Conjugate addition of alkylzirconium reagents.



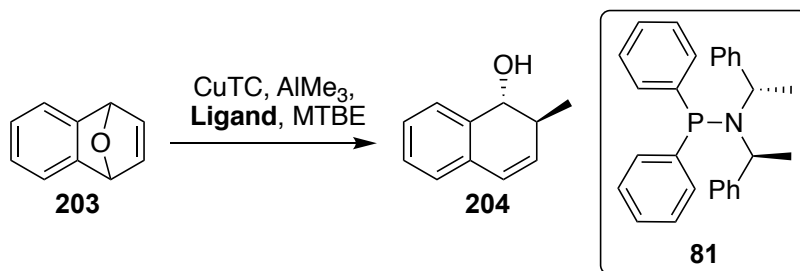
Entry	Ligand	Yield (%) ^[a]	ee (%) ^[b]
1	13-(<i>R,R,R</i>)	47	91
2	191	57	–56
3	192	65	–3
4	193	40	–37
5	194	18	9
6	195	39	–20
7	196	36	–27
8	197+198	64	–19
9	198	30	–14
10	197	36	–12
11	199+200	27	–15

[a] Isolated yield. [b] Determined by HPLC on a chiral non-racemic stationary phase. Negative sign indicates opposite absolute stereochemistry shown in **202**.

Pleasingly, all of the new ligands examined showed high conversion and excellent *anti:syn* ratios. Using ligands **193** and **194** (Table 3.2, entries 4 and 5) which bear a diphenyl backbone, we obtained comparable enantioselectivity to using SimplePhos, with 86% ee and 79% ee observed. Ligand **196**, also bearing the diphenyl backbone, but with an achiral amine, gave the highest observed enantioselectivity (89% ee, Table 3.2, entry 7).

The final reaction investigated was a 1,4-addition with AlMe₃ to form quaternary centres. The synthesis of enantioenriched all carbon quaternary centres is still considered a synthetic challenge,¹¹⁸ and asymmetric conjugate addition can be highly effective in forming these motifs.¹¹⁹

Table 3.2 Desymmetrisation of oxabenzonorbornadienes.



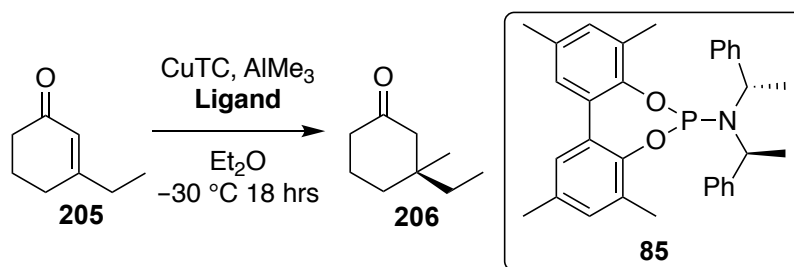
Entry	Ligand	Yield (%) ^[a]	<i>anti:syn</i> ^[b]	ee (%) ^[c]
1	81	96	97:3	83
2	191	79	99:1	17
3	192	93	98:2	-7
4	193	93	99:1	86
5	194	(84)	97:3	79
6	195	(98)	97:3	-8
7	196	75	97:3	89
8	197+198	93	99:1	-19
9	198	98	99:1	-18
10	197	66	97:3	7
11	199+200	99	98:2	Racemic
12	200	58	90:10	45

[a] Isolated yield of *anti* alcohol, Conversion, in parentheses, determined by ^1H NMR spectroscopy.

[b] Determined by ^1H NMR spectroscopy on the crude reaction mixture. [c] Determined by HPLC on a chiral non-racemic stationary phase. Negative sign indicates opposite absolute stereochemistry to that shown in **204**.

Alexakis and co-workers developed the asymmetric addition of AlMe_3 to enone **205**.^{120,121} Ligand **85** gave the best-reported results (94% ee), and similar enantioselectivity was observed in our hands (92% ee, Table 3.3, entry 1). Isolated yields here are generally low because the product is highly volatile. The use of the phosphoramidites seen in Figure 3.2 were generally detrimental to enantioselectivity, with the notable exception of ligand **194** (Table 3.3, entry 5, 81% ee). We saw that matched / mismatched amine and diol stereochemistry is important here. While ligand **194** gave 81% ee, diastereomeric **193** gave only 40% ee (in favour of the opposite enantiomer); here the amine portion of the ligand appears to determine the absolute stereochemistry. The idea that the amine controls the absolute configuration is supported by comparing diastereomeric phosphoramidites **191** and **192** (Table 3.2, entries 2 and 3), and the lack of fixed stereochemistry in the backbone of **85**.

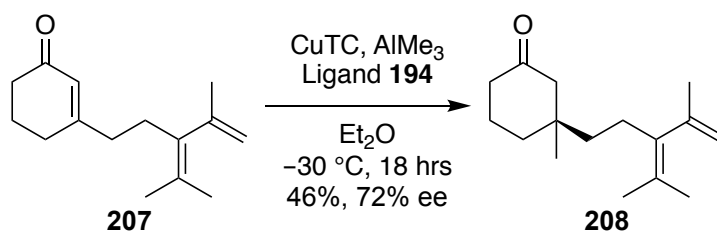
Table 3.3 Asymmetric conjugate addition to form all carbon quaternary centres.



Entry	Ligand	Yield (%) ^[a]	ee (%) ^[b]
1	85	41	92
2	191	9	−52
3	192	29	48
4	193	27	−40
5	194	21	81
6	196	27	33
7	197+198 ^[c]	85	73
8	198	23	−74
9	199+200	32	−48
10	200	83	−64

[a] Isolated yield, the product is highly volatile. [b] Determined by GC on a chiral non-racemic stationary phase. [c] The opposite enantiomer of the ligand mixture, derived from the (*R,R*)-amine, was used in this example.

Forming all-carbon quaternary centres *via* asymmetric catalysis is important because of their presence in natural products.^{118,119,122} A prominent example is by Baran and co-workers, where the asymmetric addition of AlMe_3 to enone **207** sets the absolute stereochemistry in the synthesis of taxadiene.^{123,124} We examined addition to **207** without variation of Alexakis' conditions, but using ligand **194**. We observed 46% yield and a respectable 72% ee and note that this would likely improve if reaction optimisation took place.



Scheme 3.2 Quaternary centre formation from Baran's trisubstituted enone **207**.

All of the above examples use copper catalysis. In order to see if these ligands could be useful in an asymmetric reaction catalysed by a different metal, we investigated an iridium-

catalysed reaction. Hartwig and co-workers developed a regio- and enantioselective allylic amination reaction using an iridium-phosphoramidite complex.¹²⁵ Using $[\text{Ir}(\text{COD})\text{Cl}]_2$ and ligand **13-(R,R,R)**, branched product **210** can be formed from cinnamyl methyl carbonate (**209**) in 84% yield and 95% ee. We obtained a 78% yield and 93% ee using the $[\text{Ir}(\text{COD})\text{Cl}]_2$ synthesised in our laboratory. Using Hartwig's conditions and changing only the ligand, we were disappointed to see that none of our new ligands gave any product in this reaction. Where traces of product were observed, it was racemic (Table 3.4, entries 3 and 4).

Table 3.4 Asymmetric amination of cinnamyl methyl carbonate.

$ \begin{array}{ccc} \text{Ph}-\text{CH}=\text{CH}-\text{CH}_2-\text{OCO}_2\text{Me} & \xrightarrow[\text{THF}]{\begin{array}{c} [\text{Ir}(\text{COD})\text{Cl}]_2 \\ \text{Ligand} \\ \text{Benzylamine} \end{array}} & \text{Ph}-\text{CH}(\text{NHCH}_2\text{Ph})-\text{CH}=\text{CH}_2 \\ \textbf{209} & & \textbf{210} \end{array} $			
Entry	Ligand	Yield ^[a] (%)	ee (%) ^[b]
1	13-(R,R,R)	78	93
2	192	-	-
3	193	2	Racemic
4	194	5	Racemic
5	197	-	-
6	200	-	-

[a] Isolated yield. [b] Determined by HPLC on a chiral non-racemic stationary phase.

3.2 Phosphoramidites with achirotopic stereogenic phosphorus-atoms

Here we will discuss the phosphoramidites based on *meso cis*-1,2-cyclohexanediol (**197** and **198**) and *meso* 1,2-diphenyl-1,2-ethanediol (**199** and **200**) in further detail. The vast majority of phosphoramidite ligands do not possess stereochemistry about the phosphorus atom, although P-chiral phosphoramidites with tetrahedral asymmetry have been synthesised from non-C2-symmetrical diols (Figure 3.3).^{113,126,127} To the best of our knowledge, there are no reports of phosphoramidites with achirotopic stereogenic phosphorous-atoms.

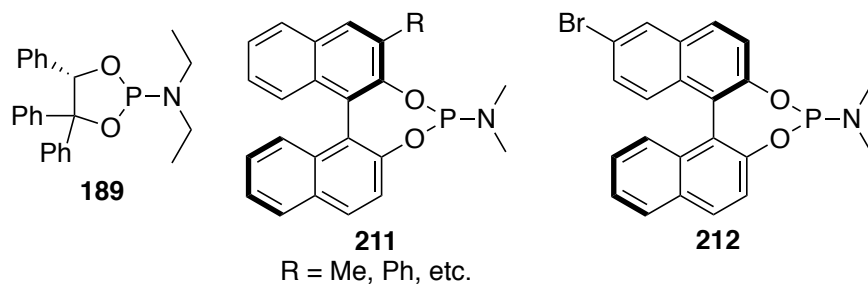


Figure 3.3 P-chiral phosphoramidites with tetrahedral asymmetry.

Ligand synthesis from *meso-cis*-cyclohexanediol and a chiral non-racemic amine gave a mixture of two diastereomeric ligands, which were readily observed by ^{31}P NMR spectroscopy on material that had been purified by flash column chromatography. The diastereoisomers could be separated by HPLC using a chiral non-racemic stationary phase (Figure 3.4a). Semi-preparative conditions [Chiralpak® IC; hexane:*i*-PrOH 99:1; 1 ml/min, λ = 210 nm, t_{R} = 4.29 mins (**197**, minor), t_{R} = 5.96 mins (**198**, major)] allowed us to isolate 104 mg of **198** and 46 mg of **197** over about 9 hours. Heating either **197** or **198** at >70 °C, or any other conditions we examined, did not interconvert ligands **197** and **198**.

X-ray crystallographic structure analysis revealed that **197** and **198** differ in their phosphorus stereochemistry, where the amine group is either in a position that could be described as ‘equatorial’ or ‘exo’ in **197**, or more ‘axial’ or ‘endo’ as in **198** (Figure 3.4b). In minor isomer **197**, which has an ‘equatorial’ amine, the phosphorous lone pair is in an axial-like position, and *vice-versa*.

In each of the X-ray crystallographic structures obtained, only a single cyclohexane conformer was observed, so that the phosphorus has four unique substituents and the P-atoms appear to be tetrahedral asymmetric. Presumably these 3D structures correspond to the lowest energy conformation for each ligand, but different conformations may be favoured in the solid state by packing forces.¹²⁸

In solution, as observed by ^1H NMR spectroscopy, in both the ‘axial’ (**198**) and ‘equatorial’ (**197**) compounds, two additional isomers are present. Based on the VT NMR studies

described below (Figure 3.5), we attribute these isomers to two chair conformations (Figure 3.6a) that rapidly interconvert in solution at room temperature. The isomers are present in roughly equal ratios, so that one conformer does not appear to be favoured over the other.

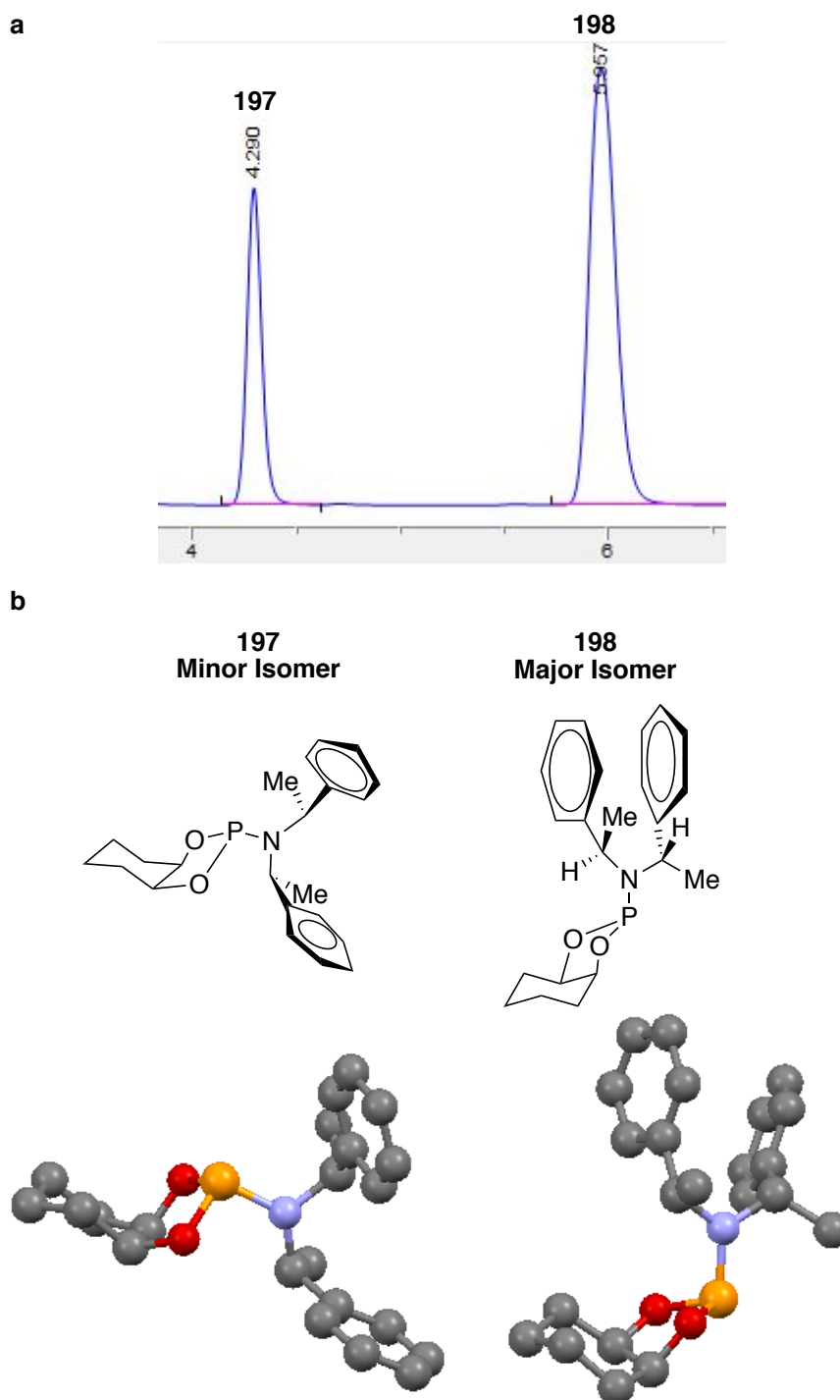


Figure 3.4 **a** HPLC [Chiralpak® IC; hexane:*i*-PrOH 99:1; 1 ml/min, λ = 210 nm, t_R = 4.29 mins (minor), t_R = 5.96 mins (major)] trace showing separation of **197** and **198**. **b** X-ray crystallographic structures of **197** and **198**.

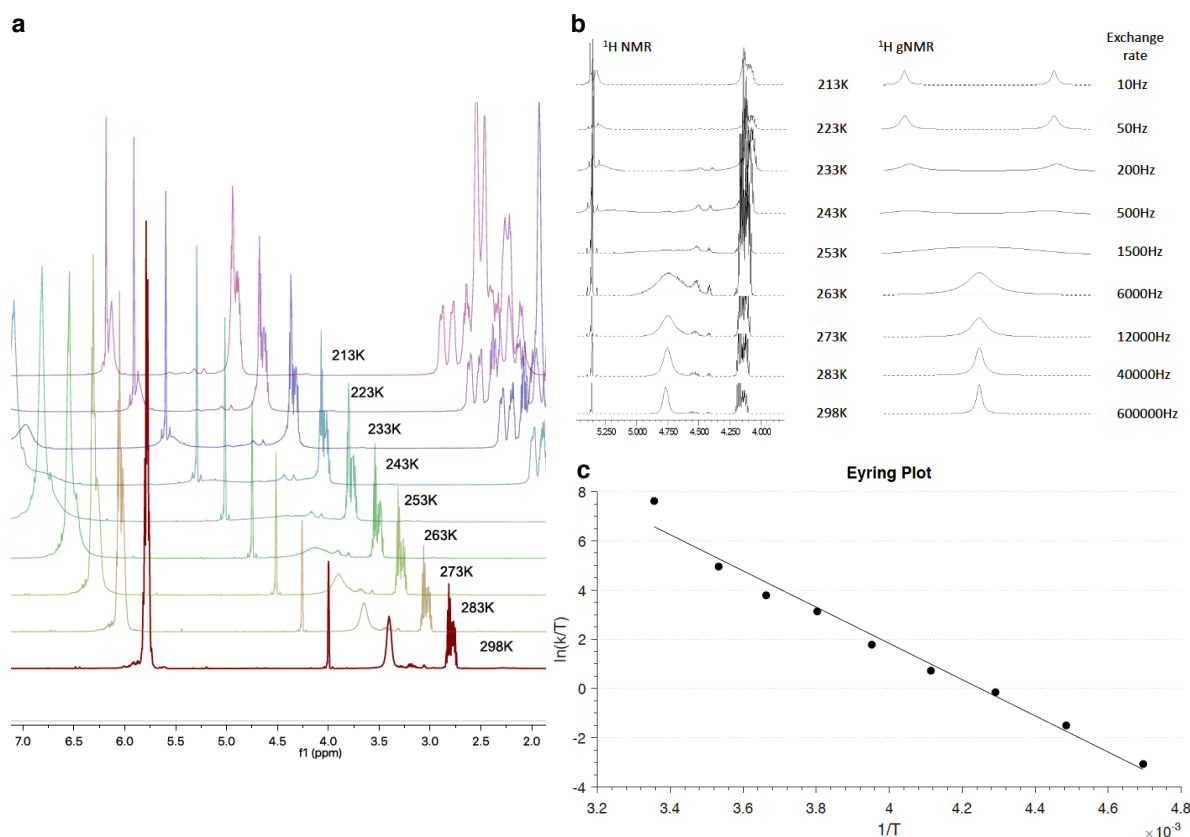


Figure 3.5 a Variable temperature NMR experiments on ligand **198**. Upon cooling to 213 K, the ^1H NMR spectroscopy signals associated with H_a and H_e are well resolved (see Figure 3.6a). **b** Simulated spectra using gNMR. **c** Eyring plot to determine $\Delta H^\ddagger$, $\Delta S^\ddagger$ and $\Delta G^\ddagger$.

Upon cooling ‘axial’ ligand **198**, extensive broadening of ^1H NMR spectroscopy signals for the 2 protons at ~ 3.4 ppm (Figure 3.5a) was observed. Variable temperature NMR experiments allowed us to quantify the energy associated with the isomerisation of **198**, and it is roughly consistent with a cyclohexane ring flip.

Spectra were recorded on a Bruker AVIII HD 500 MHz spectrometer equipped with a VT probe, with a temperature range of -60 $^\circ\text{C}$ to 25 $^\circ\text{C}$, using D_2 -dichloromethane as the solvent. Using the gNMR modelling package to simulate the spectra (Figure 3.5b), we were able to estimate rate constants (k) for exchange at each temperature. k values obtained by the gNMR package have been previously estimated to have a 10% error.¹²⁹ These rate constants, k , were used to construct an Eyring plot (Figure 3.5c), from which $\Delta H^\ddagger$ (61.2 kJ mol $^{-1}$) and $\Delta S^\ddagger$ (62.5 J K $^{-1}$ mol $^{-1}$) were obtained. We note that this $\Delta S^\ddagger$ value is relatively high for a conformational

process¹³⁰ and that this discrepancy may be due to our VT NMR which has an error of ± 2 °C. Nevertheless, these values support chair isomerisation, and inserting the values for $\Delta H^\ddagger$ and $\Delta S^\ddagger$ into the Gibbs free energy equation ($\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$) enabled the barrier to isomerization ($\Delta G^\ddagger = 42.6$ kJ mol⁻¹) to be calculated at room temperature (298 K), consistent with the modelled isomerisation rate of $\sim 600,000$ s⁻¹.

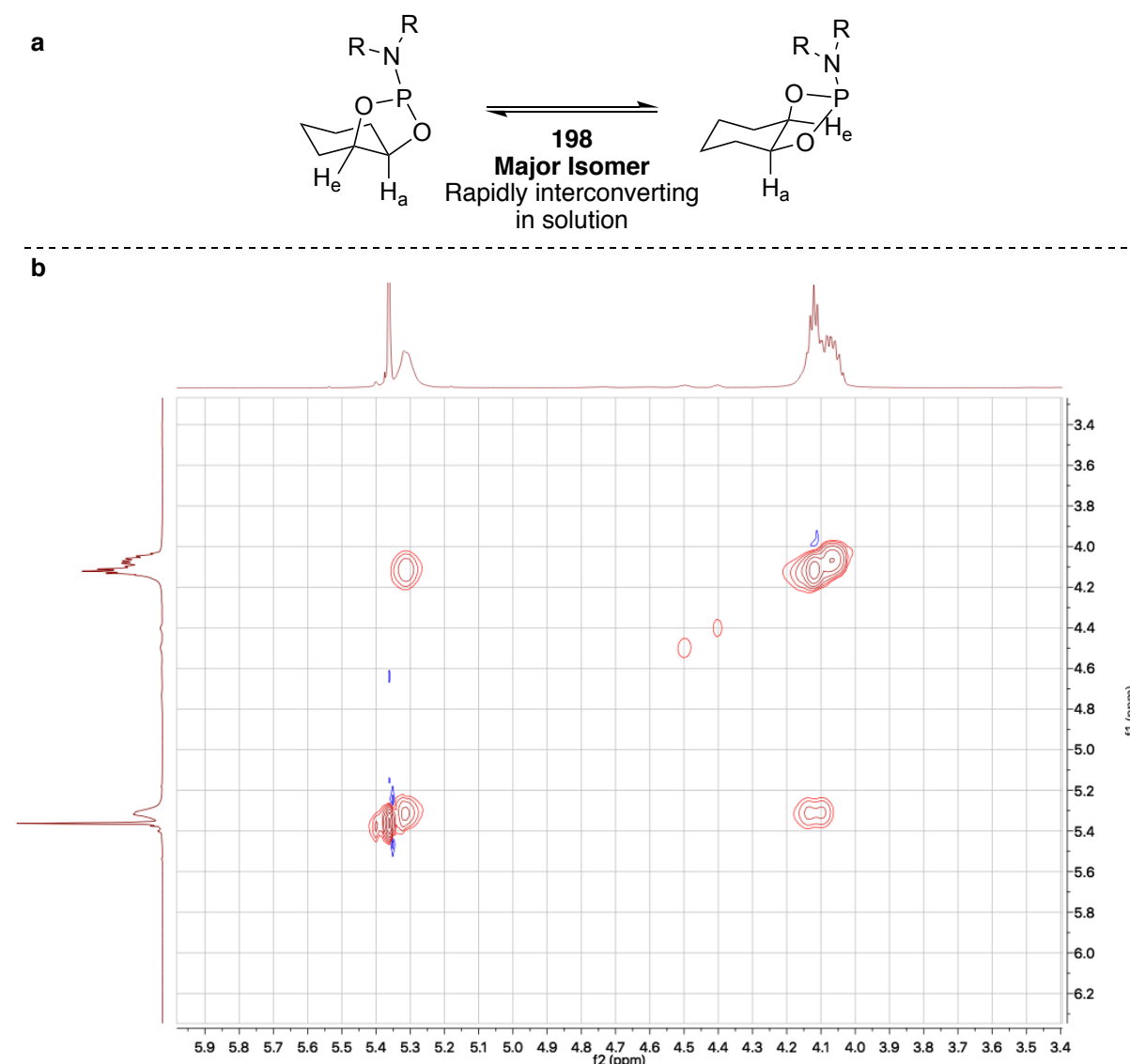


Figure 3.6 a The two chair conformations of **198** rapidly interconvert in solution at room temperature. **b** NOESY NMR experiments carried out at 213 K show that H_a and H_e still interconvert on the NMR timescale at this temperature.

The phosphorus-stereochemistry of **198** is fixed in the solid state so that the P-atom has tetrahedral asymmetry and a single isomer is observed. In solution, at room temperature, the

two oxygen substituents appear to rapidly interconvert by a cyclohexane ring flip (see Figure 3.6a) at $\sim 6 \times 10^5 \text{ s}^{-1}$. NOESY NMR shows rapid exchange on the NMR timescale even at 213 K (Figure 3.6b). A consequence of these solution dynamics is that the P-atoms stereochemistry rapidly inverts from *r*- to *s*-. Atropisomers are often defined as conformers that have a half-life of $>1000 \text{ s}$ at room temperature^{131,132} providing guidance as to how to deal with rapidly equilibrating isomers and suggesting these phosphorus atoms should not be considered chirotopic.

“Achirotopic” is defined by Eliel and Wilen¹³³ as “a point or atom located on a plane or at a centre of symmetry, or at the point where an alternating axis of symmetry intersects its reflection plane”. Structures A and B in Figure 3.7 represent a pair of enantiomers. Carbon 3 in structures A and B, though chirotopic (any point or atom in a chiral molecule is chirotopic) are not stereogenic, as they bear two identical groups. In contrast, carbon 3 in C and D, which are both *meso* structures, differ in configuration at that centre. Since neither C nor D are chiral, these centres are defined as achirotopic stereogenic centres.

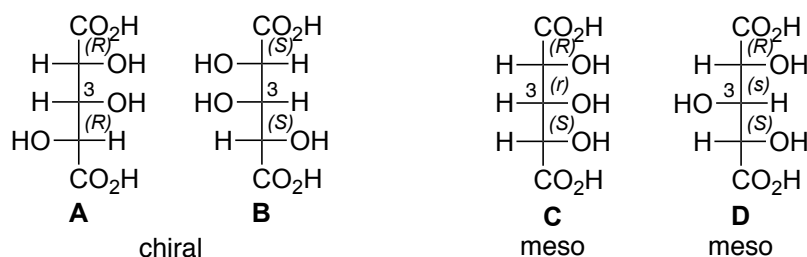


Figure 3.7 Chiral and meso 2,3,4-trihydroxyglutaric acids.

The relative stereochemistry of ligands **197** and **198** needs to be addressed. The isomeric pair differ according to P-stereochemistry, similar to the stereochemical features of double bonds (*cis-trans*), cyclohexane ring substituents (axial-equatorial) or bridged systems (*endo-exo*). Similar to structures C and D (Figure 3.7), here the P-atoms differ in stereochemistry but in solution, are not chirotopic so the centres are best described as achirotopic stereogenic.¹³³ As

the best descriptors for the isomeric pairs seen here have not yet been established, we suggest (arbitrarily), ‘axial’ and ‘equatorial’.

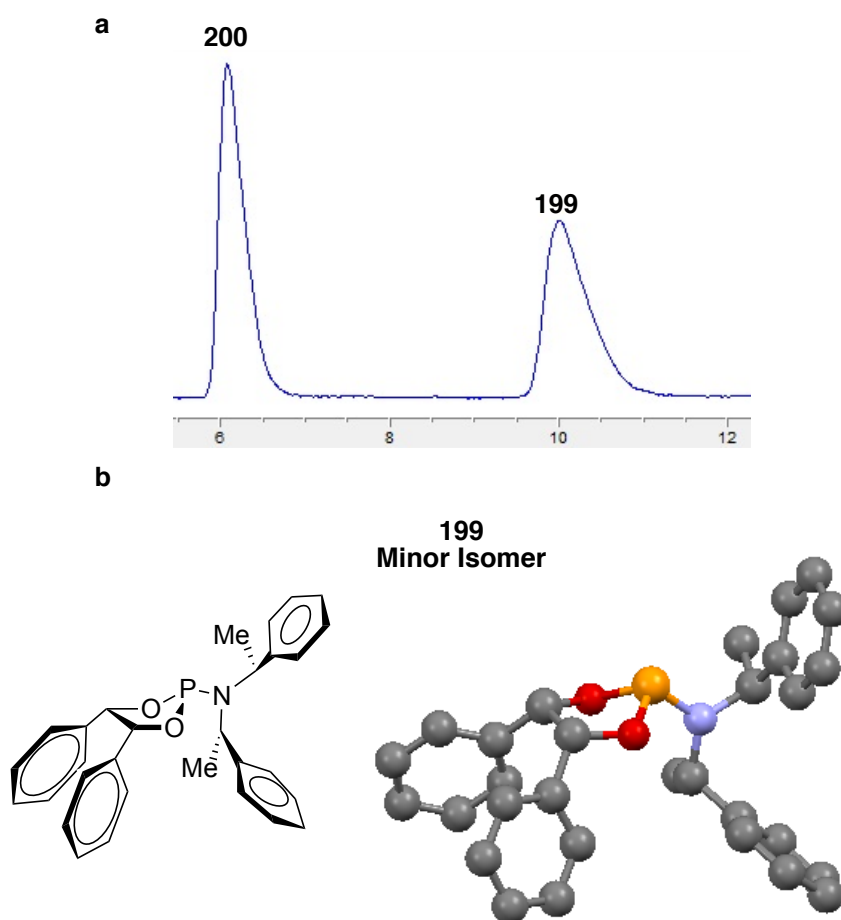


Figure 3.7 **a** HPLC [Chiralpak® IA; hexane:*i*-PrOH 99:1; 1 ml/min, λ = 210 nm, t_R = 6.07 mins (major), t_R = 9.99 mins (minor)] showing separation of *S* and *R*. **b** X-ray crystallographic structure of **199**.

3.3 Conclusions

We have described a set of phosphoramidite ligands based on simple diols and tested them in catalytic asymmetric C-C bond forming reactions. In the case of *meso*-diols we obtained mixtures of P-isomeric ligands. In a 1,4-conjugate addition reaction, best accomplished using BINOL based phosphoramidites, the new ligands were ineffective. However, good results were obtained in two different reactions that required less sterically demanding monodentate

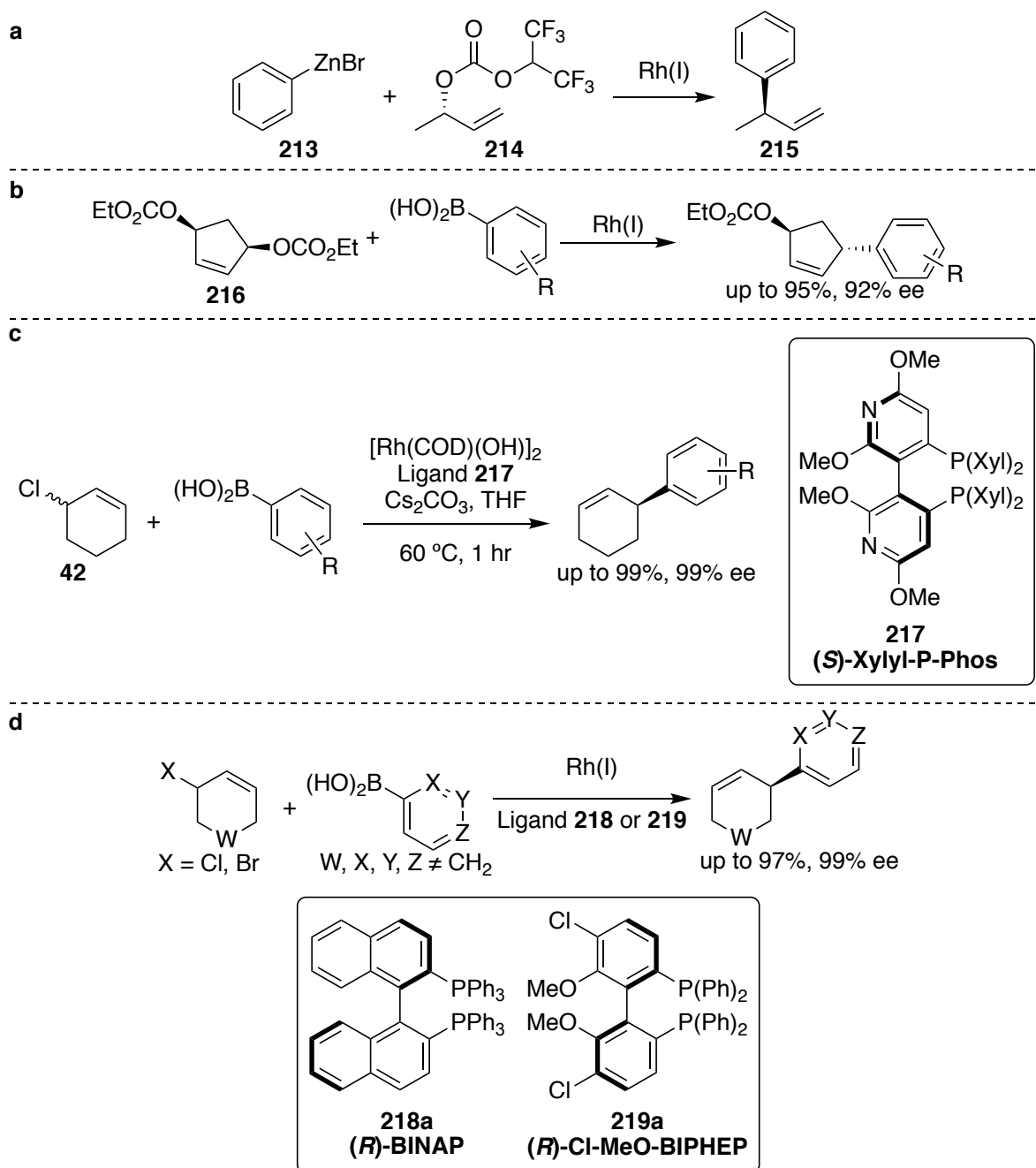
phosphorus-ligands. Comparable ee's with those previously reported (up to 89%) for the addition of AlMe_3 in a ring opening desymmetrisation were achieved. We anticipate that the ligands reported here might be useful in asymmetric reactions where BINOL and TADDOL based phosphoramidites are unable to provide high levels of asymmetry.

4 Rhodium-catalysed asymmetric substitutions

Parts of this chapter have been published as the following paper: Mistry, N., and Fletcher, S. P., *Chem. Sci.*, **2018**, *9*, 6307–6312.

4.1 Asymmetric substitutions using boronic acids

Reactions using rhodium catalysts have been widely studied and it has been well documented that allylic substitutions of chiral substrates using rhodium can be highly selective (Scheme 4.1a).^{134–137} There are currently limited examples of *asymmetric* allylic substitutions of prochiral substrates using rhodium-catalysed processes. Lautens and co-workers described an asymmetric addition of arylboronic acids to prochiral *meso*-allylic diol derivatives and *meso*-bicyclic alkenes (Scheme 4.1b).^{138–140} The Fletcher group have recently made major contributions to this area by demonstrating a novel dynamic kinetic asymmetric allylic arylation reaction of racemic allylic halides using boronic acid nucleophiles, rhodium catalysts and common diphosphine ligands (Scheme 4.1c).¹⁴¹ This asymmetric Suzuki-Miyaura reaction was also applied to the coupling of heterocycles such as pyridyl derivatives, furan, pyrrole and thiophene based substrates among others. (Scheme 4.1d).¹⁴²

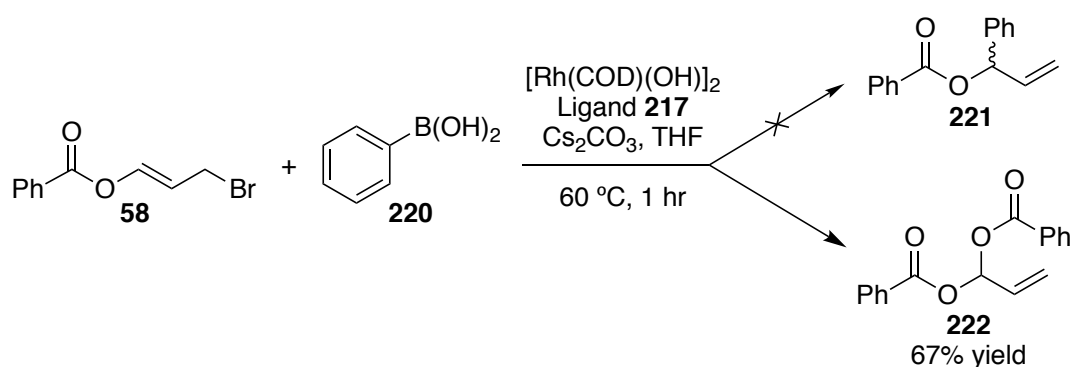


Scheme 4.1 **a** Enantiospecific allylic substitutions are known to be highly selective. **b** Asymmetric addition of arylboronic acids to prochiral substrates. **c** Suzuki-Miyaura cross-coupling of racemic allylic halides using boronic acids. **d** Suzuki-Miyaura cross coupling to form $\text{Csp}^3\text{-Csp}^2$ bonds using heterocycles.

We were interested in expanding our rhodium-catalysed arylation reaction to linear allylic substrates, such as **58**. The products of these reactions would be chiral, protected allylic alcohols which are synthetically useful building blocks. When we carried out the reaction under the conditions as described in scheme 4.1c, we found that the starting material was

completely consumed within 5 minutes. Upon isolating the product, we were surprised to find that none of the desired product (**221**) was formed. Instead, under these conditions, we formed *gem*-dicarboxylate **222**.

We believe that this product was formed through the decomposition of **58** to benzoic acid, which then undergoes a rapid rhodium-catalysed carboxylation to the remaining **58**. Product **222** has a centre bearing two heteroatoms; however in this case the two carboxylate groups are the same and **222** is not chiral.



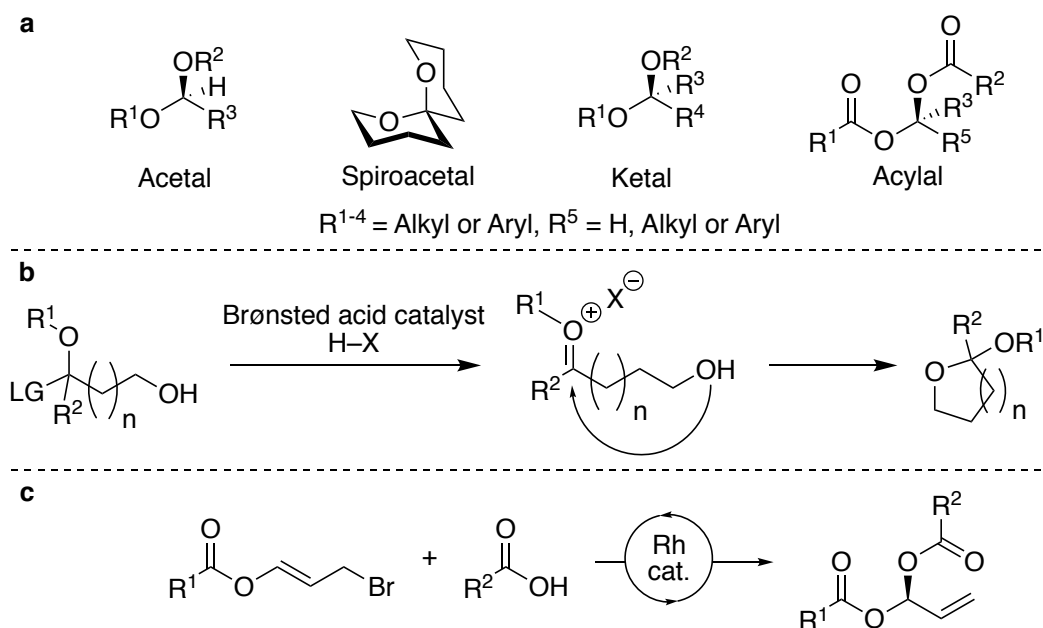
Scheme 4.2 The reaction of linear allylic bromide **58** with a boronic acid gives product **222** rather than the desired **221**.

Based on these observations we anticipated that it might be possible to develop an asymmetric rhodium-catalysed substitution reaction between linear allylic bromide **58** and different carboxylic acids, to form products that contain a stereocentre bearing two heteroatoms.

4.2 Chiral acetals and their derivatives

Stereocentres bearing two heteroatoms, including acetals, spiroacetals and ketals (Scheme 4.3a), are some of the most prevalent structural motifs found in nature. These features are present in virtually all carbohydrate derivatives such as starch and cellulose, and in many small natural products including pheromones, steroids, and polyketides.¹⁴³ The ability to

control the stereochemistry of carbon centres featuring two heteroatoms is also important in the development of pharmaceuticals.^{143,144}



Scheme 4.3 **a** General Structures for *O,O*-Acetals, spiroacetals, ketals and dicarboxylates. **b** Formation of a bis-heteroatom bearing stereogenic centre *via* an oxocarbenium ion intermediate using Brønsted acid catalysis. **c** This work: rhodium-catalysed asymmetric carboxylation of heteroatom containing allyl bromides to form *gem*-dicarboxylates.

For many years, stereocontrolled access to chiral acetal derivatives relied on derivatisation of chiral starting materials,^{145–150} metal mediated desymmetrisations,^{151–153} or kinetic or thermodynamically controlled cyclisation of carbonyl containing chiral-compounds.^{154–159} A recent approach to bis-heteroatom containing stereogenic centres involves catalysis with very sterically hindered chiral Brønsted acids. These reactions are generally envisaged to occur *via* an oxocarbenium ion or imine intermediates (Scheme 4.3b), which then undergo stereoselective addition; although some reactions most likely proceed via single-step asynchronous pathways.¹⁶⁰ This strategy has now been sufficiently developed to allow the asymmetric synthesis of chiral *N,N*-,^{161–164} *N,O*-,¹⁶⁵ *N,S*-,^{166,167} and *O,O*-acetals.^{168–171} Methods for the stereocontrolled formation of analogous linear compounds are less common.^{161,162,165,166}

A variety of rhodium-catalysed asymmetric allylation-type processes (including allylic substitutions), with oxygen, nitrogen and carbon nucleophiles have been used to form allylic alcohols, amines, and tertiary or quaternary carbon stereogenic centres.^{141,172–180} Carboxylic acids may be used as nucleophiles, not only in rhodium-catalysed asymmetric reactions, but also in processes catalysed by iridium,¹⁸¹ palladium,^{182,183} and ruthenium.¹⁸⁴ However, only limited examples of metal-catalysed asymmetric additions to make stereogenic centres bearing two heteroatoms are known, and no rhodium-catalysed processes have been reported.^{159,185–187}

4.3 Stereocontrolled synthesis of *geminal*-dicarboxylates

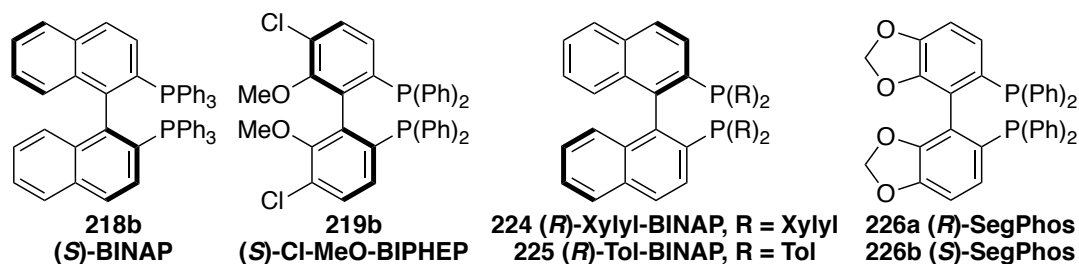
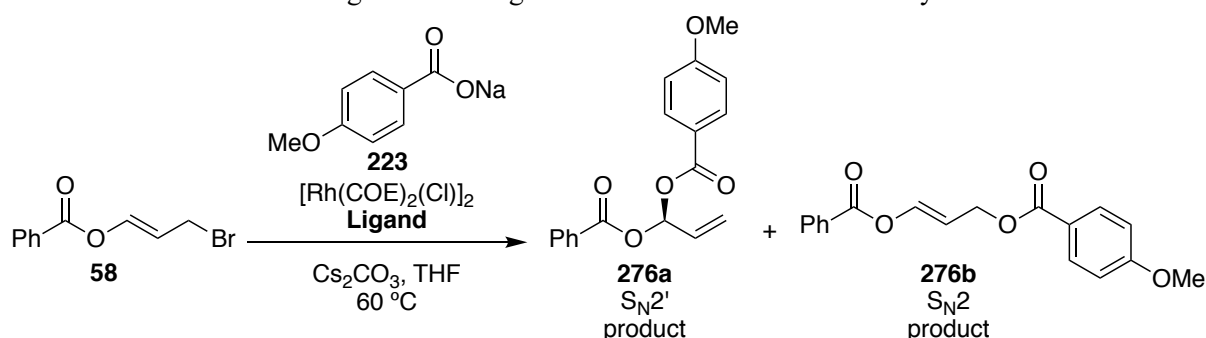
Here we developed the stereocontrolled synthesis of *geminal*-dicarboxylates (acylals) *via* a highly enantioselective rhodium-catalysed carboxylation of allyl bromide derivatives bearing ester groups. These allyl bromides have been used in copper-catalysed additions of Grignard reagents to give allylic esters as described in Chapter 2.⁶⁶ *Geminal*-dicarboxylates are an understudied class of compounds with the exception of the diacetate and dipropionate derivatives, which are often used to protect aldehydes and are important substrates for asymmetric Tsuji-Trost reactions.^{101,188}

Methods for the synthesis of 1,1-diacetates include protic and Lewis acid catalysis,^{189,190} the action of I₂,¹⁹¹ NBS,¹⁹² and various heterogeneous catalysts.¹⁹³ However, none of these methods allow stereocontrol. To the best of our knowledge, the only report of asymmetric induction in *gem*-dicarboxylate formation involved copper-catalysed allylic oxidation of an olefin in 23% yield and 10% ee.¹⁹⁴

4.3.1 Reaction development

We first wanted to test our hypothesis that a carboxylate is the nucleophilic species in the *gem*-dicarboxylate formation described in Scheme 4.2. In order to do this we arbitrarily chose the sodium salt of 4-methoxybenzoic acid as our nucleophile. We were pleased to see that we did in fact form the desired product, **276a**, and could already achieve some low levels of enantioselectivity.

Table 4.1 Initial ligand screening with the sodium salt of 4-methoxybenzoic acid.



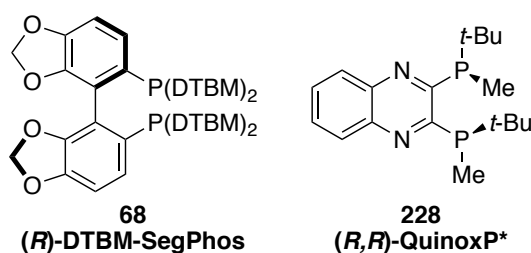
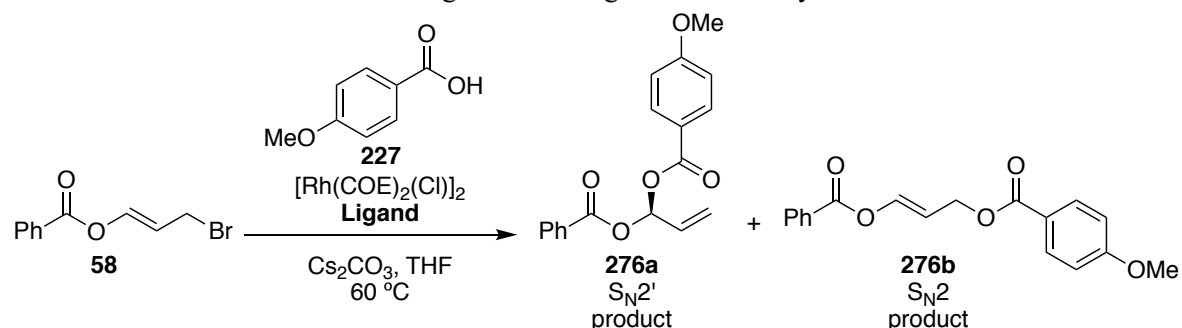
Entry	Ligand	Yield (%) ^[a]	S _N 2':S _N 2 ^[b]	ee (%) ^[c]
1	217	63	65:35	15
2	218b	79	81:19	Racemic
3	219b	99	95:5	Racemic
4	224	59	93:7	−23
5 ^[d]	224	43	99:1	−33
6	225	67	89:11	Racemic
7	226	63	41:59	8

[a] All yields are isolated yields. [b] Determined by ¹H NMR. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase. [d] No base added. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. carboxylate, 2.5 mol % [Rh(COE)₂(Cl)]₂, 6% ligand, 1.0 eq. Cs₂CO₃, 2.0 mL THF, 60 °C.

When using the carboxylic acid directly, rather than the sodium salt, we were pleased to see the reaction proceeded with good yields and promising regioselectivity. Unfortunately the

ee's were disappointingly low, with many of the ligands giving racemic or near racemic product.

Table 4.2 Initial ligand screening with 4-methoxybenzoic acid.

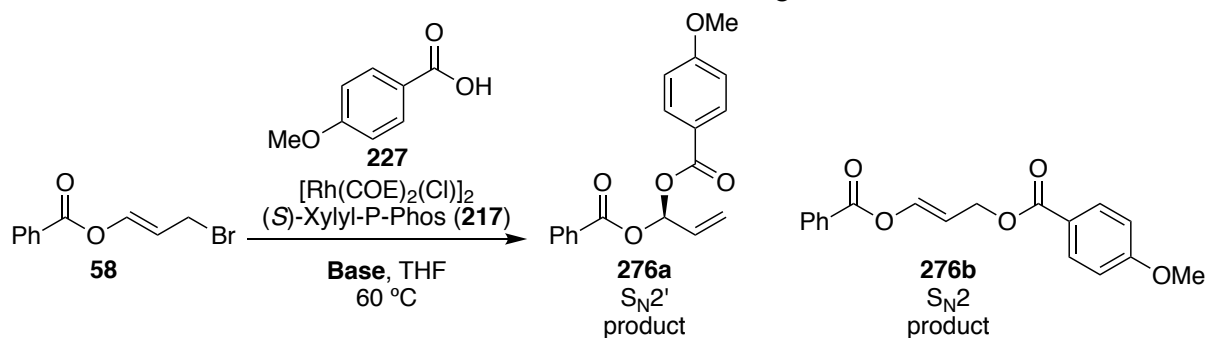


Entry	Ligand	Yield (%) ^[a]	S _N 2':S _N 2 ^[b]	ee (%) ^[c]
1	217	86	73:27	21
2	218	81	84:16	-12
3	219	58	81:19	Racemic
4	224	82	87:13	Racemic
5	225	79	68:32	11
6	226	42	80:20	5
7	68	77	62:38	Racemic
8	228	81	5:95	-5

[a] All yields are isolated yields. [b] Determined by ¹H NMR. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. 4-methoxybenzoic acid, 2.5 mol % $[\text{Rh}(\text{COE})_2(\text{Cl})]_2$, 6% ligand, 1.0 eq. Cs_2CO_3 , 2.0 mL THF, 60 °C.

Taking (*S*)-Xylyl-P-Phos (**217**) as our ligand, we carried out a screen of some different bases. KO*t*-Bu and LiOMe both showed increased ee's of up to 44%. Although LiOMe showed no evidence of the S_N2 product as well as an increased ee, we chose KO*t*-Bu as the base with which to continue screening, as the yield was higher (64% vs. 41%) and the reaction times were shorter (2 hours vs. overnight, Table 4.3, entries 5 and 8).

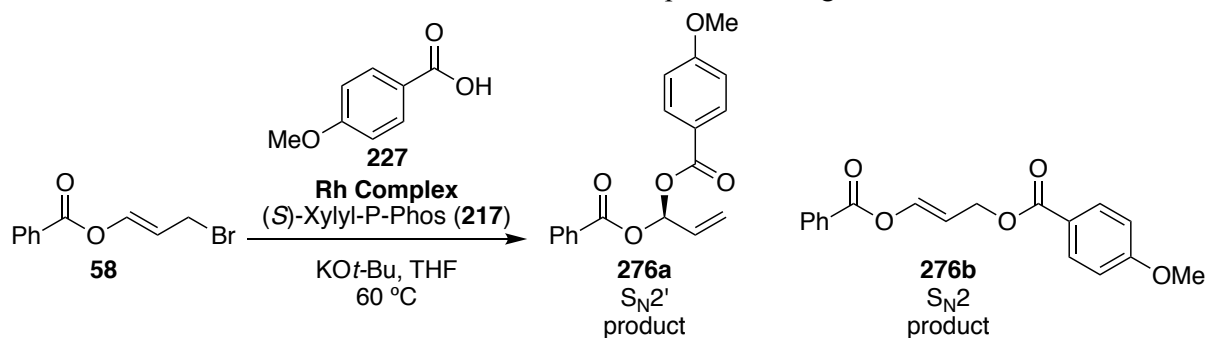
Table 4.3 Initial base screening.



Entry	Base	Reaction Time	Yield (%) ^[a]	$\text{S}_{\text{N}}2':\text{S}_{\text{N}}2$ ^[b]	ee (%) ^[c]
1	Cs_2CO_3	1.5 hrs	86	73:27	21
2	NaOMe	22 hrs	52	>99:1	31
3	Et_3N	20 mins	59	93:7	8
4	NaOAc	22 hrs	57	93:7	15
5	KOt-Bu	2 hrs	64	91:9	40
6^[d]	KOt-Bu	30 mins	38	93:7	37
7	DIPEA	2 hrs	65	93:7	12
8	LiOMe	21 hrs	41	>99:1	41
9^[d]	LiOMe	>21 hrs	39	>99:1	44
10	K_2CO_3	50 mins	97	95:5	28
11	Ag_2CO_3	10 mins	92	80:20	7
12	CsOH	23 hrs	70	41:59	9
13	KOH	23 hrs	35	71:29	26
14	KOMe	20 hrs	54	66:34	15
15	LiOt-Bu	>23 hrs	35	97:3	36
16	Li_2CO_3	>23 hrs	25	89:11	11
17	Na_2CO_3	1 hr 20 mins	~95	98:2	16

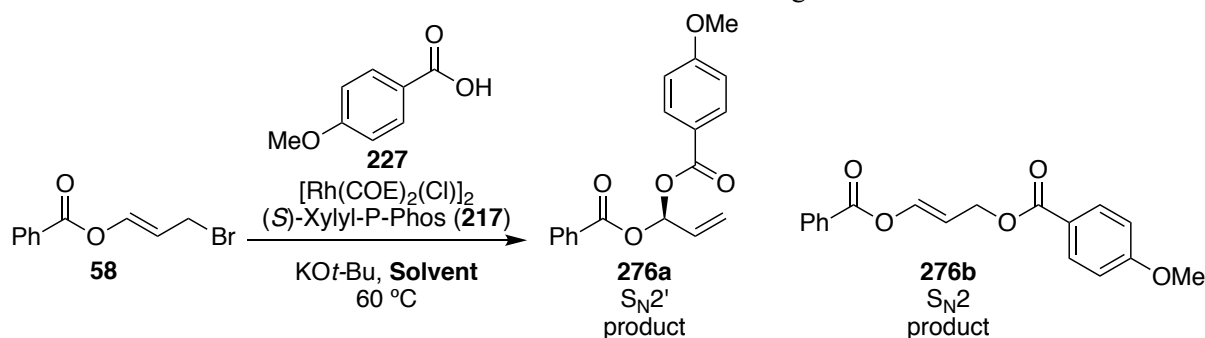
[a] All yields are isolated yields. [b] Determined by ^1H NMR. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase. [d] 2.0 eq. of base rather than 1.0 eq. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. 4-methoxybenzoic acid, 2.5 mol % $[\text{Rh}(\text{COE})_2(\text{Cl})]_2$, 6% (*S*)-Xylyl-P-Phos, 1.0 eq. base, 2.0 mL THF, 60 °C.

Upon screening different rhodium complexes (Table 4.4) and solvents (Table 4.5) we found that there were no improvements on either the $[\text{Rh}(\text{COE})_2(\text{Cl})]_2$ complex or THF solvent so we made no changes at this time.

Table 4.4 Initial Rh complex screening.

Entry	Rhodium Complex	Reaction Time	Yield (%) ^[a]	S _N 2':S _N 2 ^[b]	ee (%) ^[c]
1	[Rh(COE) ₂ (Cl)] ₂	2 hrs	64	91:9	40
2	[Rh(COD)(OH)] ₂	20 hrs	69	60:40	27
3	[Rh(acac)(C ₂ H ₄) ₂]	20 hrs	74	31:69	25
4	[Rh(COD)(MeCN) ₂]BF ₄	20 hrs	42 ^[d]	28:72	8
5	[Rh(COD)(Cl)] ₂	10 mins	77	96:4	26

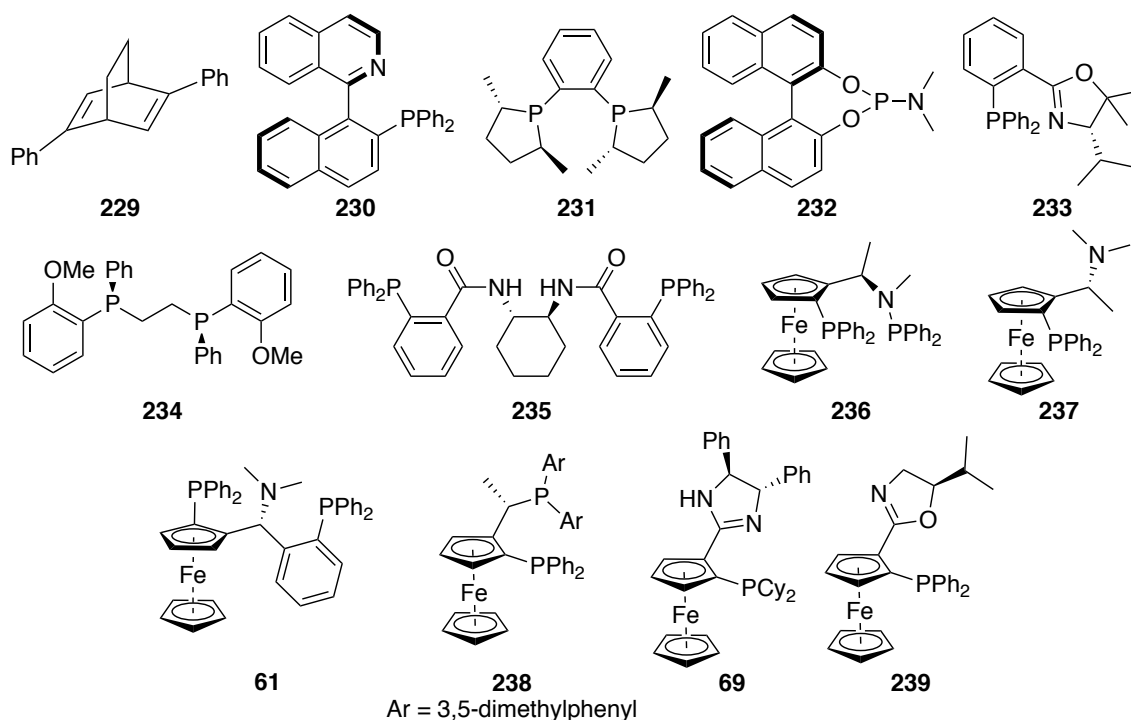
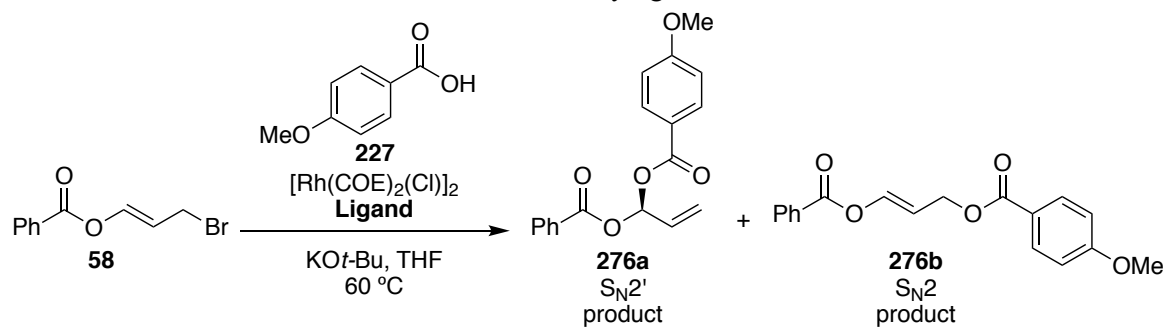
[a] All yields are isolated yields. [b] Determined by ¹H NMR. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase. [d] Yield based on recovered starting material. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. 4-methoxybenzoic acid, 2.5 mol % Rh complex, 6% (S)-Xylyl-P-Phos, 1.0 eq. KO^tBu, 2.0 mL THF.

Table 4.5 Initial solvent screening.

Entry	Solvent	Reaction Time	Yield (%) ^[a]	S _N 2':S _N 2 ^[b]	ee (%) ^[c]
1	THF	2 hrs	64	91:9	40
2	MeCN	17 hrs	31	65:35	-7
3	Toluene	22 hrs	25	76:24	Racemic
4	Hexane	22 hrs	13	39:64	Racemic
5	DCE	22 hrs	6	90:10	13
6	Dioxane	3 hrs	68	97:3	21
7	2-Me-THF	2 hrs	47	90:10	34
8	MTBE	3 hrs	43	92:8	9
9	DME	1 hr	65	96:4	19

[a] All yields are isolated yields. [b] Determined by ¹H NMR. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. 4-methoxybenzoic acid, 2.5 mol % [Rh(COE)₂(Cl)]₂, 6% (S)-Xylyl-P-Phos, 1.0 eq. KO^tBu, 2.0 mL solvent, 60 °C

Table 4.6 Secondary ligand screen.

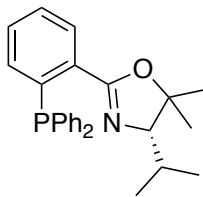
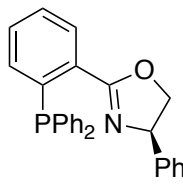
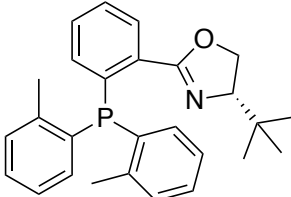
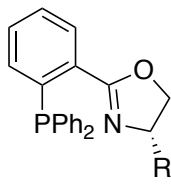


Entry	Ligand	Reaction Time	Yield (%) ^[a]	$\text{S}_{\text{N}}2':\text{S}_{\text{N}}2$	ee (%) ^[b]
1	217	2 hrs	64	91:9	40
2 ^[c]	229	21 hrs	38	89:11	Racemic
3	230	3 hrs	65	93:7	36
4	231	22 hrs	42	37:63	Racemic
5	232	1 hr	43	92:8	Racemic
6	233	1.5 hrs	72	98:2	-38
7	234	2hrs 20 mins	62	65:35	Racemic
8	235	2 hrs	52	79:21	Racemic
9	236	3 hrs	61	88:12	12
10	237	30 mins	78	94:6	29
11	61	6 hrs	61	83:17	14
12	238	6 hrs	64	78:22	12
13	69	1.5 hrs	60	91:9	Racemic
14	239	23 hrs	58	64:36	Racemic

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase. [c] $[\text{Rh}(\text{Cl})(\text{C}_2\text{H}_4)_2]_2$ instead of $[\text{Rh}(\text{COE})_2(\text{Cl})]_2$. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. 4-methoxybenzoic acid, 2.5 mol % $[\text{Rh}(\text{COE})_2(\text{Cl})]_2$, 6% ligand, 1.0 eq. KOt-Bu, 2.0 mL THF, 60 °C.

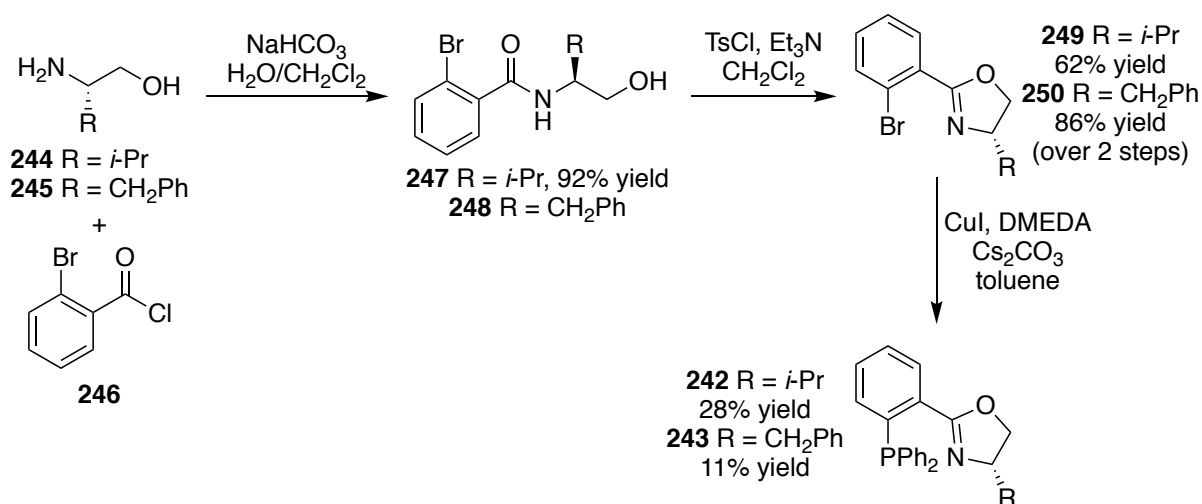
With our choices for the rhodium complex, solvent and base now fixed, we began screening chiral ligands. From our ligand screening we saw that the Phox ligand **233** gave a 72% yield, an excellent S_N2' : S_N2 ratio of 98:2 and 38% ee; the latter comparable to that obtained with (*S*)-xylyl-P-Phos (**217**). Based on this result we decided to investigate these Phox ligands further.

Table 4.7 Phox ligand screening.

				241 R = <i>t</i> -Bu 242 R = <i>i</i> -Pr 243 R = CH ₂ Ph	
233	70	240			
Entry	Ligand	Reaction Time	Yield (%) ^[a]	S _N 2':S _N 2 ^[b]	ee (%) ^[c]
1	233	1.5 hrs	72	98:2	−38
2 ^[d]	233	22 hrs	62	97:3	−24
3 ^[e]	233	>20 hrs	11	87:13	Racemic
4	70	1 hr	65	93:7	Racemic
5	240	2 hrs 45 mins	62	88:12	−7
6	241	2 hrs	51	94:6	−18
7	242	1.5 hrs	49	86:14	−15
8	243	>17 hrs	66	88:12	5

[a] All yields are isolated yields. [b] Determined by ¹H NMR. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase. [d] Room temperature [e] LiOMe rather than KO*t*-Bu. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. 4-methoxybenzoic acid, 2.5 mol % [Rh(COE)₂(Cl)]₂, 6% ligand, 1.0 eq. KO*t*-Bu, 2.0 mL THF, 60 °C.

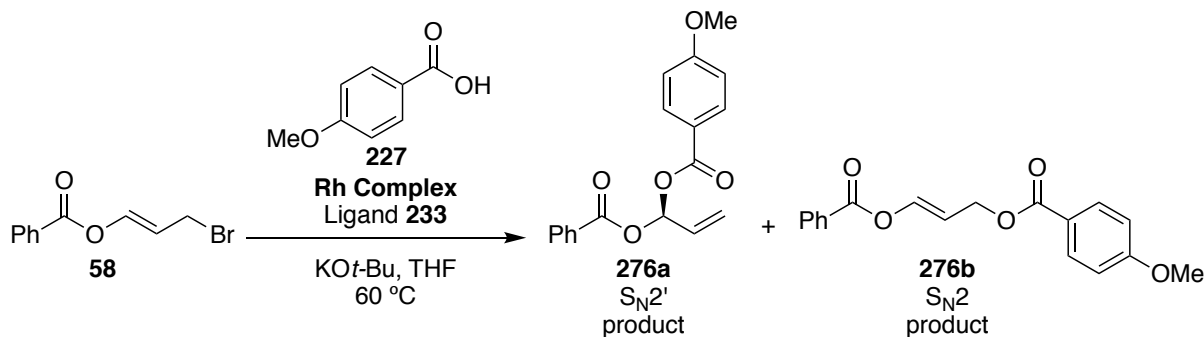
Ligands **70**, **240** and **241** are commercially available and ligands **242** and **243** were synthesised according to the literature methods shown in Scheme 4.4.¹⁹⁵ Unfortunately none of these other Phox ligands showed improved enantioselectivities.



Scheme 4.4 Synthesis of Phox ligands **242** and **243**.

We next screened rhodium complexes with ligand **233**. With the exception of the [Rh(COD)(MeCN)₂]₂BF₄ complex which gave both a lower yield and slightly lower ee than the [Rh(COE)₂(Cl)]₂ complex (Table 4.8, entry 4), all other rhodium complexes gave a racemic product.

Table 4.8 Rhodium complex screening with ligand **233**.



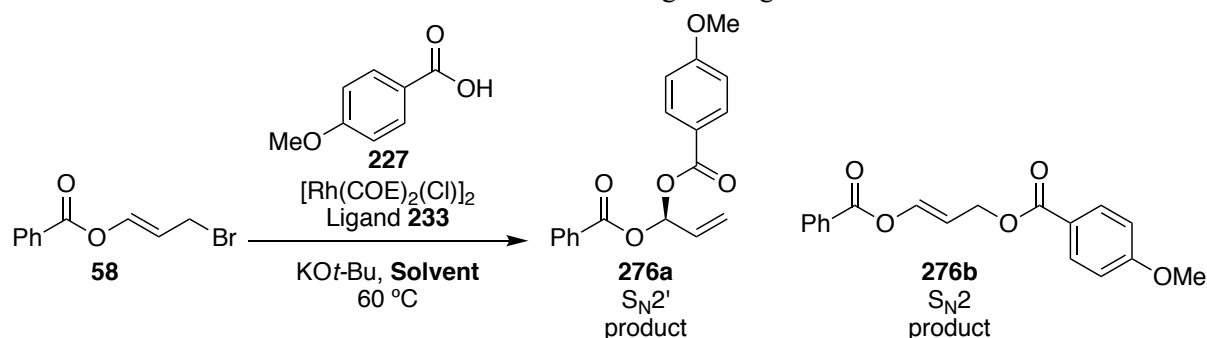
Entry	Rhodium Complex	Reaction Time	Yield (%) ^[a]	S _N 2':S _N 2 ^[b]	ee (%) ^[c]
1	[Rh(COE) ₂ (Cl)] ₂	1.5 hrs	72	98:2	−38
2	[Rh(COD)(OH)] ₂	17 hrs	53	93:7	Racemic
3	[Rh(acac)(C ₂ H ₄) ₂]	17 hrs	34	89:11	Racemic
4	[Rh(COD)(MeCN) ₂] ₂ BF ₄	>17 hrs	50	98:2	−34
5	[Rh(COD)(Cl)] ₂	1.5 hrs	38	92:8	Racemic

[a] All yields are isolated yields. [b] Determined by ¹H NMR. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. 4-methoxybenzoic acid, 2.5 mol % Rh complex, 6% ligand **233**, 1.0 eq. KO*t*-Bu, 2.0 mL THF, 60 °C.

Upon screening solvents (Table 4.9) and bases (Table 4.10) we found that all solvents except THF gave a racemic (or nearly racemic) product. All bases except KO*t*-Bu also gave racemic

product. It became evident that with the Phox ligand the reaction was incredibly sensitive to the other reaction components and we therefore decided that we would be unlikely to optimise this reaction with this ligand any further.

Table 4.9 Solvent screening with ligand **233**.



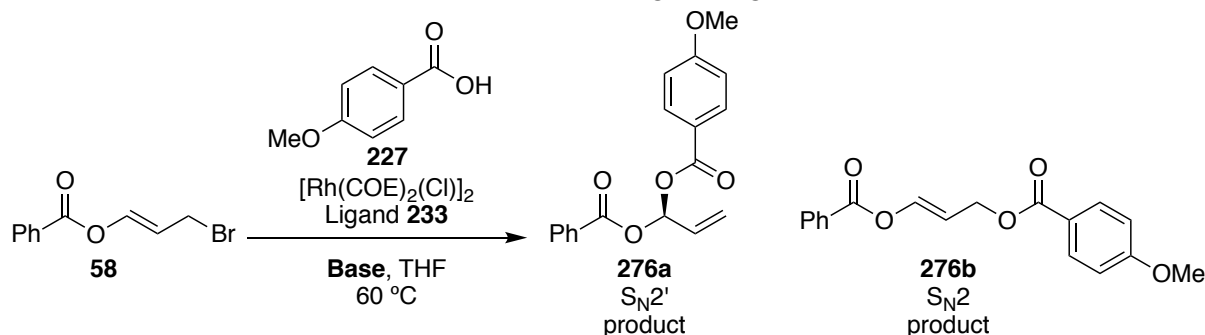
Entry	Solvent	Reaction Time	Yield (%) ^[a]	S _N 2':S _N 2 ^[b]	ee (%) ^[c]
1	THF	1.5 hrs	72	98:2	−38
2	MeCN	19 hrs	29	65:35	Racemic
3	Toluene	19 hrs	38	88:12	Racemic
4	Hexane	>23 hrs	9	69:31	Racemic
5	DCE	>24 hrs	6	95:5	3
6	Dioxane	19 hrs	29	85:15	Racemic
7	2-Me-THF	>21 hrs	29	93:7	Racemic
8	MTBE	>24 hrs	25	87:13	3
9	DME	50 mins	47	92:8	Racemic

[a] All yields are isolated yields. [b] Determined by ¹H NMR. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. 4-methoxybenzoic acid, 2.5 mol % $[\text{Rh}(\text{COE})_2(\text{Cl})]_2$, 6% ligand **233**, 1.0 eq. KOt-Bu, 2.0 mL solvent, 60 °C.

Since 4-methoxybenzoic acid was an arbitrary choice of nucleophile at the beginning of our screening now we chose to screen a number of other nucleophiles under 4 different sets of conditions, A – D (Table 4.11). The following eight nucleophiles were also examined, however no, or very little, product was observed under any conditions – including the racemic reaction: trifluoroacetic acid, phenol, pyrrolidine, indoline, imidazole, pyrrolidinone, dimedone, and 3-Me-pyrazole. Our general observation was that nitrogen nucleophiles do not give any product in these reactions; the exceptions being pyrazole (54% ee, conditions A, Table 4.11, entry 13) and phthalimide (14% ee, conditions B, Table 4.11, entry 10). In terms of the carboxylic acids, those containing alkyl groups such as the pivalic acid and isobutyric

acid showed increased ee's of 49% and 57% ee respectively using conditions C (Table 4.11, entries 7 and 25). Also under conditions C, thiophenol gives the corresponding product in a 55% ee (Table 4.11, entry 34).

Table 4.10 Base screening with ligand **233**.



Entry	Base	Reaction Time	Yield (%) ^[a]	S _N 2':S _N 2 ^[b]	ee (%) ^[c]
1	KOt-Bu	1.5 hrs	72	98:2	-38
2	LiOMe	>20 hrs	18	95:5	Racemic
3	Cs ₂ CO ₃	20 hrs	50	93:7	Racemic
4	NaOMe	>20 hrs	41	99:1	Racemic
5	Et ₃ N	1 hr 45 mins	41	83:17	Racemic
6	NaOAc	>20 hrs	29	97:3	Racemic
7	K ₂ CO ₃	>20 hrs	37	81:19	Racemic
8	Ag ₂ CO ₃	2 hrs	31	71:29	Racemic
9	CsOH	>20 hrs	18	80:20	Racemic
10	KOH	>20 hrs	-	-	-
11	DIPEA	>20 hrs	54	75:25	Racemic
12	KOMe	>20 hrs	36	98:2	Racemic
13	LiOt-Bu	>20 hrs	38	99:1	Racemic
14	Li ₂ CO ₃	>20 hrs	10	94:6	Racemic
15	Na ₂ CO ₃	>20 hrs	38	94:6	Racemic
16	NaOH	>20 hrs	47	96:4	Racemic
17	LiOMe	>20 hrs	18	95:5	Racemic

[a] All yields are isolated yields. [b] Determined by ¹H NMR. [c] Enantiomeric excesses determined by HPLC using a chiral non-racemic stationary phase. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. 4-methoxybenzoic acid, 2.5 mol % [Rh(COE)₂(Cl)]₂, 6% ligand **233**, 1.0 eq. base, 2.0 mL THF, 60 °C.

Table 4.11 Nucleophile screening.

					Ligand	Base
Conditions A					224	Na_2CO_3
Conditions B					217	KO^tBu
Conditions C					217	LiOMe
Conditions D					233	KO^tBu
Entry	Conditions	Nucleophile	Reaction Time	Yield (%) ^[a]	$\text{S}_{\text{N}}2':\text{S}_{\text{N}}2$ ^[b]	ee (%) ^[c]
1	A	Trimethyl-	30 mins	79	>99:1	-18
2	B	benzoic	1.5 hrs	76	87:13	14
3	C	Acid	5 hrs	42	98:2	Racemic
4	D		30 mins	37	85:15	-14
5	A	Pivalic Acid	2 hrs	70	>99:1	Racemic
6	B		3 hrs	86	73:27	-17
7	C		18 hrs	71	>99:1	-49
8	D		4 hrs	40	85:15	-27
9	A	Phthalimide	24 hrs ^[d]	49	1:1	14
10	B		16 hrs	~86	<1:99	21
11	C		22 hrs	~33	40:60	8
12	D		24 hrs ^[d]	traces	—	—
13	A	Pyrazole	1 hr	50	>99:1	-54
14 ^[e]	A		3 hrs	44	>99:1	-52
15	B		1 hr	—	—	—
16	C		1 hr	—	—	—
17	D		18 hrs	—	—	—
18	A	1-Adamantyl-	3 hrs	<30	>99:1	11
19	B	carboxylic acid	3 hrs	~27	72:25	-18
20	C		30 mins	62	>99:1	-56
21 ^[e]	C		22 hrs	60	>99:1	-53
22	D		30 mins	~34	>99:1	-33
23	A	Isobutyric Acid	1.5 hrs	80	>99:1	-13
24	B		1.5 hrs	72	85:15	13
25	C		21 hrs	71	>99:1	57
26 ^[e]	C		22 hrs	56	>99:1	53
27	D		1.5 hrs	50	70:30	16
28	A	Indazole	1.5 hrs	53	>99:1	-41
29	B		21 hrs	—	—	—
30	C		1.5 hrs	7	>99:1	-24
31	D		21 hrs	—	—	—
32	A	Thiophenol	2 hrs	~42	<1:99	—
33	B		2 hrs	50	<1:99	—
34	C		2 hrs	74	50:50	-55
35 ^[e]	C		1 hr	76	39:61	-52
36	D		2 hrs	47	<1:99	—

[a] All yields are isolated yields. [b] Determined by ^1H NMR. [c] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. [d] Some starting material was still remaining after this time. [e] $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ used instead of $[\text{Rh}(\text{COE})_2(\text{Cl})]_2$. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. nucleophile, 2.5 mol % $[\text{Rh}(\text{COE})_2(\text{Cl})]_2$, 6% ligand, 1.0 eq. base, 2.0 mL THF, 60 °C.

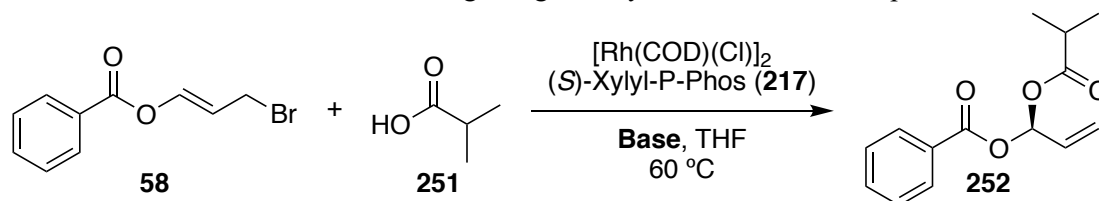
Based on these results, we selected isobutyric acid as the nucleophile to continue optimising the reaction and used conditions C as the starting point. We first screened rhodium complexes and were pleased to find that when using $[\text{Rh}(\text{COD})(\text{Cl})]_2$ the reaction time improved from 21 hours to only 1 hour, with good yields of 70%, excellent regioselectivity for the $\text{S}_{\text{N}}2'$ product (>99:1) and an improved ee (65%) (Table 4.12, entry 6).

Table 4.12 Rhodium complex screening using isobutyric acid as the nucleophile.

Entry	Rhodium Complex	Reaction Time	Yield (%) ^[a]	$\text{S}_{\text{N}}2':\text{S}_{\text{N}}2$ ^[b]	ee (%) ^[c]
1	$[\text{Rh}(\text{COE})_2(\text{Cl})]_2$	21 hrs	71	>99:1	57
2	$[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$	22 hrs	56	>99:1	53
3	$[\text{Rh}(\text{COD})(\text{OH})]_2$	23hrs	74	>99:1	59
4	$[\text{Rh}(\text{COD})(\text{MeCN})_2]\text{BF}_4$	23hrs	67	>99:1	17
5	$[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$	20 hrs	91	>99:1	59
6	$[\text{Rh}(\text{COD})(\text{Cl})]_2$	1 hr	70	>99:1	65

[a] All yields are isolated yields. [b] Determined by ^1H NMR. [c] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. isobutyric acid, 2.5 mol % Rh complex, 6% (*S*)-Xylyl-P-Phos, 1.0 eq. LiOMe, 2.0 mL THF, 60 °C.

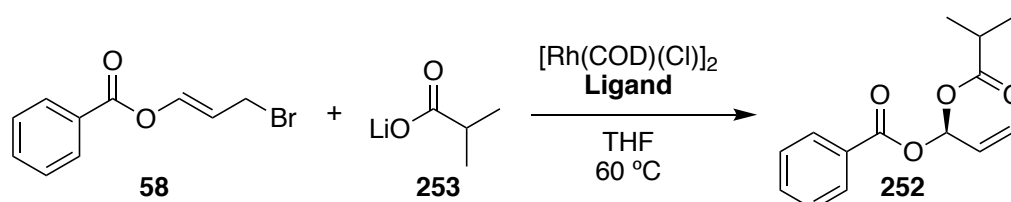
A screening of different bases revealed that the lithium ion must play a key role in affecting the enantioselectivity of the reaction as non-lithium bases showed decreased ee's (Table 4.13, entries 1 and 3-5). Compared to LiOMe, other lithium bases showed similar ee's, although most also showed increased reaction times (Table 4.13, entries 6-11). One exception, LiOt-Bu, showed a decreased reaction time from 1 hour to 30 minutes, and gave a slightly lower yield but comparable ee to LiOMe (Table 4.13, entry 6). Under all the reaction conditions shown in Table 4.13 we observe excellent selectivity for the $\text{S}_{\text{N}}2'$ product and the $\text{S}_{\text{N}}2$ product is no longer observed by ^1H NMR spectroscopy.

Table 4.13 Base screening using isobutyric acid as the nucleophile.

Entry	Base	Reaction Time	Yield (%) ^[a]	ee (%) ^[b]
1	KO ^{<i>t</i>} -Bu	1.5 hrs	72	13
2	LiOMe	21 hrs	71	57
3	Na ₂ CO ₃	1 hr	78	19
4	NaOMe	1 hr	73	26
5	K ₂ CO ₃	1 hr	65	49
6	LiO^{<i>t</i>}-Bu	30 mins	60	63
7	Li ₂ CO ₃	>22 hrs	42	61
8	LiOH	>22 hrs	49	64
9	Li ₂ ZrO ₃	>24 hrs	64	36
10 ^[c]	LiOMe	4.5 hrs	62	59
11 ^[c]	LiOH	>24 hrs	67	60

[a] All yields are isolated yields, none of the linear S_N2 product is observed under any conditions. [b] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. [c] Reaction carried out in the presence of 4 Å Mol. sieves. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. isobutyric acid, 2.5 mol % [Rh(COD)(Cl)]₂, 6% (*S*)-Xylyl-P-Phos, 1.0 eq. base, 2.0 mL THF.

In order to test our hypothesis that the lithium ion is key to the enantioselectivity of this reaction, we carried out two test reactions in which we use the lithium salt of isobutyric acid and no base. With both (*S*)-Xylyl-P-Phos (**217**) and (*R*)-Xylyl-BINAP (**224**) we see a significant increase in ee up to 91% (Table 4.14).

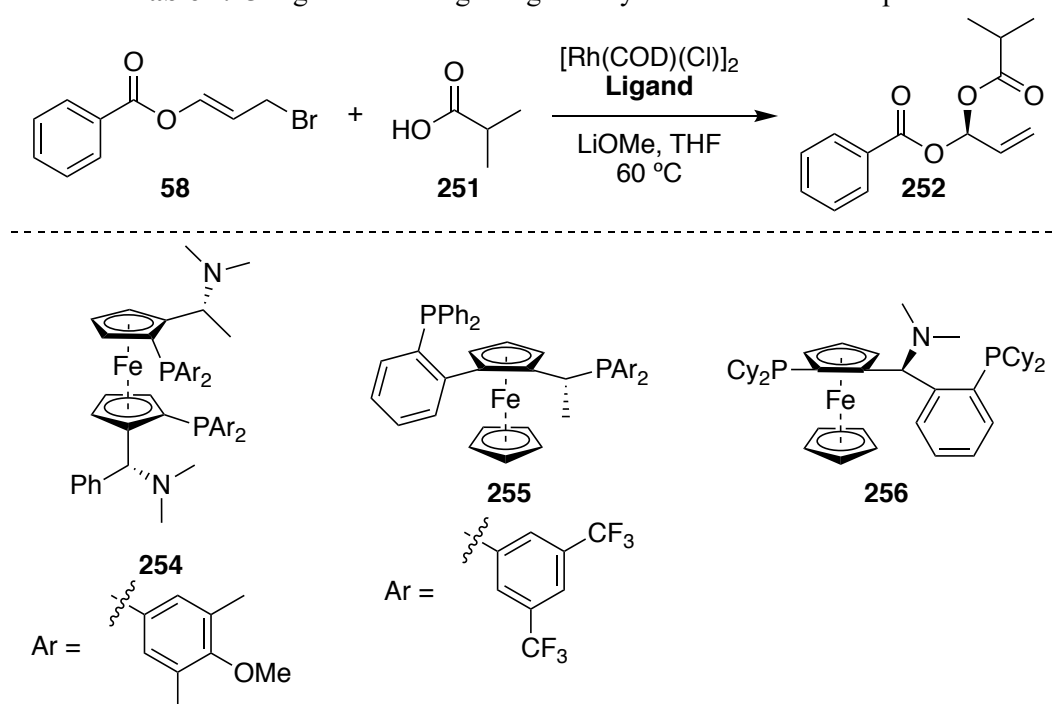
Table 4.14 Test reactions with the lithium salt of isobutyric acid.

Entry	Ligand	Reaction Time	Yield (%) ^[a]	ee (%) ^[b]
1	(<i>S</i>)-Xylyl-P-Phos	3 hrs	59	91
2	(<i>R</i>)-Xylyl-BINAP	20 hrs	42	–85

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. carboxylate, 2.5 mol % [Rh(COD)(Cl)]₂, 6% ligand, 2.0 mL THF, 60 °C.

Encouraged by these results we carried out a limited ligand screening using isobutyric acid. Choosing only ligands that had previously shown some enantioselectivity, we were pleased to find that using the Ugi-amine derived ligand **237**, in 1.5 hours we obtain the desired product in 72% yield and 94% ee (Table 4.15, entry 6). Related ligand **236** gave an increased yield of 87% but lower ee of only 77 % (Table 4.15, entry 5)

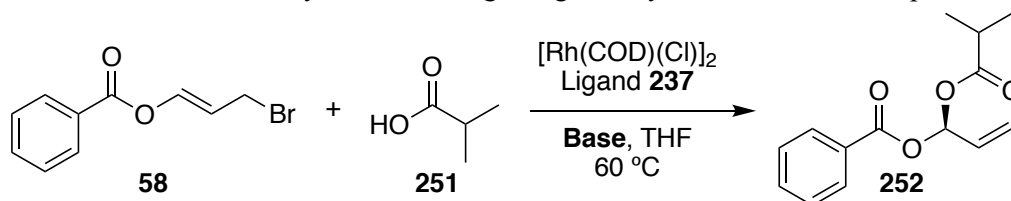
Table 4.15 Ligand screening using isobutyric acid as the nucleophile.



Entry	Ligand	Reaction Time	Yield (%) ^[a]	ee (%) ^[b]
1	217	1 hr	70	65
2 ^[c]	218b	>23 hrs	66	56
3 ^[d]	225	23 hrs	51	-76
4	230	>23 hrs	61	Racemic
5	236	23 hrs	87	-77
6	237	1.5 hrs	72	94
7	238	>21 hrs	69	64
8	254	>21 hrs	34	28
9	255	23 hrs	78	Racemic
10	256	23 hrs	68	Racemic

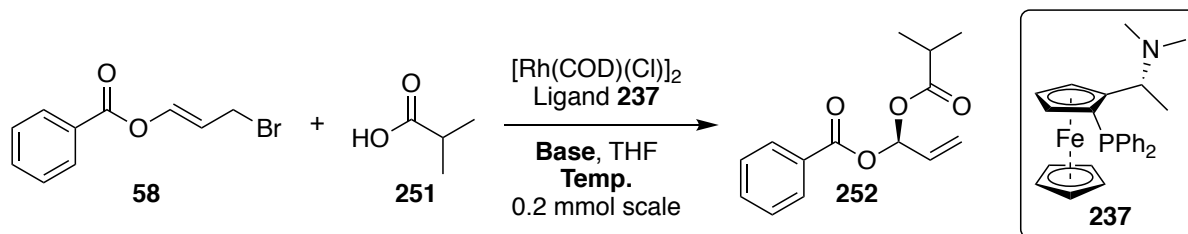
[a] All yields are isolated yields. [b] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. isobutyric acid, 2.5 mol % [Rh(COD)(Cl)]₂, 6% ligand, 1.0 eq. LiOMe, 2.0 mL THF, 60 °C.

Finally, a secondary base screening of lithium bases using ligand **237** showed that LiOt-Bu gave the product in a higher yield of 82% and excellent ee of 98%.

Table 4.16 Secondary base screening using isobutyric acid as the nucleophile.

Entry	Base	Reaction Time	Yield (%) ^[a]	ee (%) ^[b]
1	LiOMe	1.5 hrs	72	94
2	LiOH	>23 hrs	53	92
3	LiOtBu	30 mins	82	98
4	Li ₂ CO ₃	>23 hrs	25	75
5	LiH ₂ PO ₄	>24 hrs	traces	—

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. isobutyric acid, 2.5 mol % $[\text{Rh}(\text{COD})(\text{Cl})]_2$, 6% ligand **237**, 1.0 eq. base, 2.0 mL THF, 60 °C.

Table 4.17 Final optimisations.

Entry	Base	Rhodium (mol %)	Temperature (° C)	Reaction Time	Yield (%) ^[a]	Ee (%) ^[b]
1	LiOMe	2.5	60	1.5 hrs	72	94
2	LiOMe	1.25	40	1 hrs	85	96
3	LiOt-Bu	2.5	60	30 mins	82	98
4	LiOt-Bu	1.25	60	1 hr	83	95
5	LiOt-Bu	1.25	40	1.5 hrs	82	96
6	LiOt-Bu	1.25	r.t.	2 hrs	89	94
7	LiOt-Bu	0	40	o/n ^[c]	—	—
8	none	1.25	40	o/n	—	—
9 ^[d]	LiOt-Bu	1.25	40	o/n	76	racemic
10 ^[e]	LiOt-Bu	1.25	40	50 mins	82	96
11 ^[f]	LiOt-Bu	0.5	40	2 hrs	82	95

[a] All yields are isolated yields. [b] Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase. [c] The reaction was stirred overnight [d] No chiral ligand [e] 1.0 eq. isobutyric acid. [f] Gram-scale reaction, carried out using 0.5 mol % $[\text{Rh}(\text{COD})(\text{Cl})]_2$ and 1.2 mol % ligand. r.t. – room temperature. Typical reaction conditions: 0.2 mmol **58**, 2.0 eq. isobutyric acid, 1.25 mol % $[\text{Rh}(\text{COD})(\text{Cl})]_2$, 3% ligand, 1.0 eq. base, 2.0 mL THF.

Some final optimisations revealed that with both LiOMe and LiOt-Bu, we could carry out the reaction with only 1.25 mol % of the $[\text{Rh}(\text{COD})(\text{Cl})]_2$ (Table 4.17, entries 2 and 4) and at

lower temperatures (Table 4.17, entries 2 and 5) with no detrimental effects on the outcome of the reaction. Room temperature reactions proceed with excellent results but to maintain reaction component solubility, adequate stirring and reasonable reaction times, (particularly when using other nucleophiles), 40 °C appears to be the most suitable temperature (Table 4.17, entry 6). If we removed either the rhodium source or base from the reaction, we obtained no product (Table 4.17, entries 7 and 8) and a reaction without ligand **237** gave a racemic product (Table 4.17, entry 9). The reaction can easily be performed on a gram-scale while simultaneously reducing the amount of rhodium to 0.5 mol % [Rh(COD)(Cl)]₂, and ligand to 1.2 mol % (Table 4.17, entry 11).

4.3.2 Reaction scope

For reaction scope, aliphatic carboxylic acids including bulky *tert*-butyl (**257**) and adamantyl groups (**258**), provided the corresponding products in excellent enantioselectivities (>93% ee), however smaller nucleophiles such as formic and acetic acid, (**260** and **261** respectively) gave lower yields and ee's. In addition to the reduced yield and ee, the reaction with formic acid also gave small amounts of the achiral dibenzoyloxy derivative **222**, this is consistent with our previous observations that under some conditions **58** may decompose to benzoic acid, which then undergoes competitive rhodium-catalysed carboxylation to the remaining **58**. We were not able to separate this by-product from **261**.

This method is compatible with carboxylic acids that contain a terminal alkene (**261**), terminal alkyne (**263**) and an internal alkene (**264**). When racemic ibuprofen is used as a nucleophile, a 1:1 mixture of diastereoisomers is formed (both diastereomers having 94% ee, **265**).

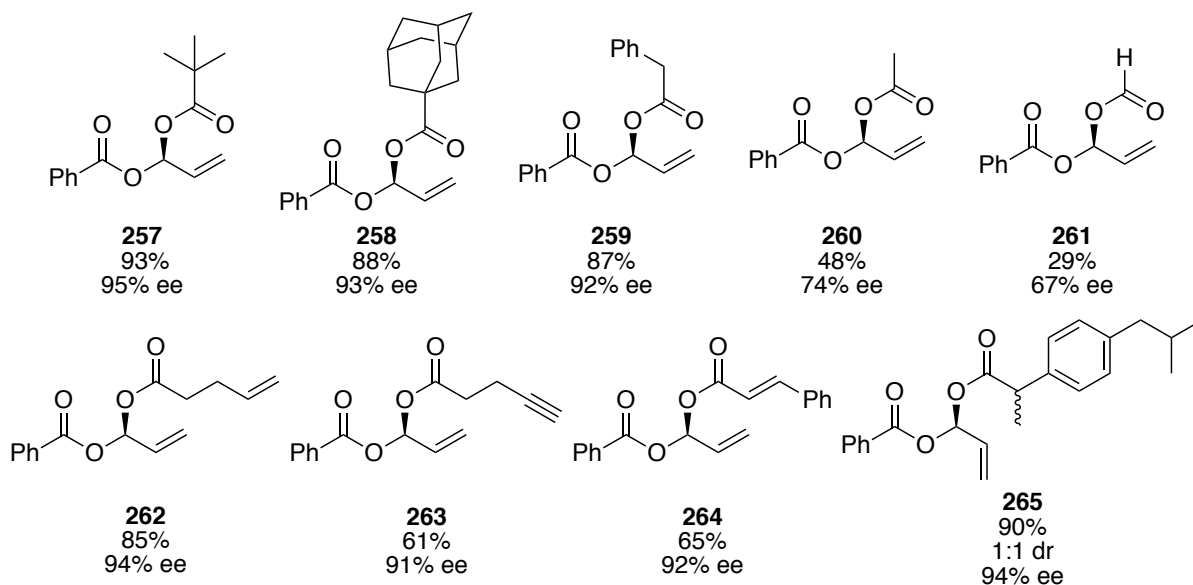


Figure 4.1 Scope of aliphatic carboxylic acids. All reactions were carried out on a 0.4 mmol scale of the electrophile. All yields are isolated yields. Enantiomeric excesses determined by SFC using a chiral non-racemic stationary phase.

Aromatic carboxylic acids generally work well as nucleophiles. 2,4,6-Trimethylbenzoic acid (**266**) and 4,5-dimethoxybenzoic acid (**267**) both gave high yields and ee's over 90%. 4-Chloro- (**273**), 2-chloro- (**270**) and 4-bromobenzoic acid (**274**) also give good ee's. Interestingly the 2-bromo derivative (**271**) was formed in excellent yield (91%) but the ee dropped to only 73%. Increasing the electron withdrawing potential of ring substituents, for example with fluoro (**275**), trifluoromethyl (**277**), nitro (**272** and **278**) or multiple halogens (**268** and **269**) tends to decrease the yield and ee. Curiously 4-methoxybenzoic acid (**276a**) gives only a 34% yield and 83% ee, whereas 4,5-dimethoxybenzoic acid (**267**) gave 88% yield and 93% ee.

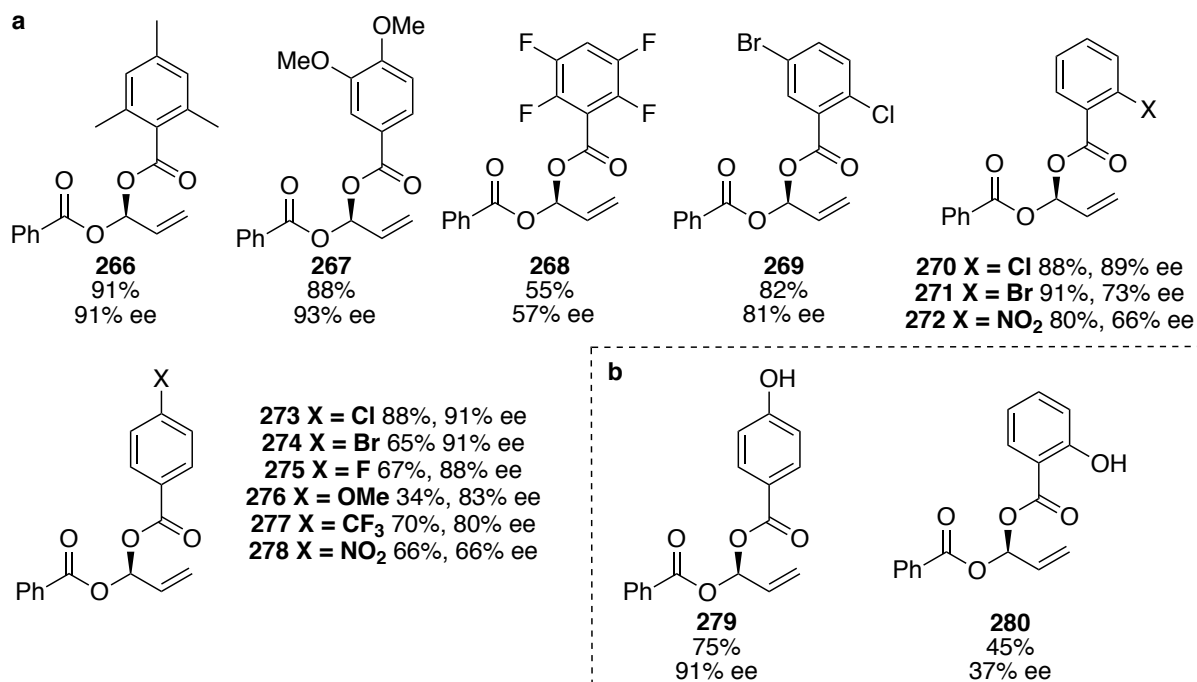


Figure 4.2 **a** Scope of aromatic carboxylic acids. **b** 4-Hydroxybenzoic acid and 2-hydroxybenzoic acid give very different results.

For 4-hydroxybenzoic acid (**279**) we obtained good results (75%, 91% ee) but a hydroxy at the 2-position (**280**) is detrimental (45%, 37% ee), likely due to either chelation of **280** to rhodium during the reaction or hydrogen (or lithium) bonding of the 2-hydroxy group altering the nucleophilicity of the carboxylic acid. A free hydroxyl group in (*R*)-2-hydroxy-2-phenylacetic acid (used as a single enantiomer) entirely suppressed reactivity and no product **281** was observed, but if acetylated (here the single *S*-enantiomer was arbitrarily used) **282** can be obtained (43%, 78% ee).

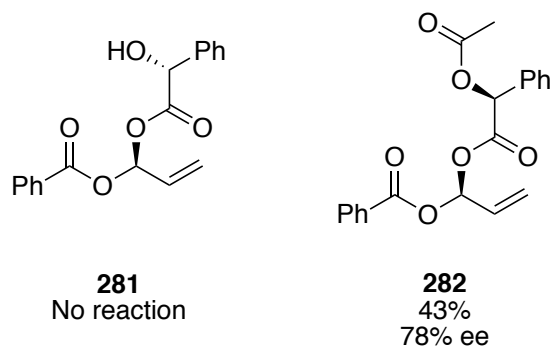


Figure 4.3 Protection of free –OH groups may allow an otherwise problematic reaction to occur.

Substrates containing free amino groups such as enantiomerically pure proline (**283**) and 4-aminobenzoic acid (**285**) give no product, but protected derivatives (single enantiomer Boc-proline and *N,N*-dimethyl-4-aminobenzoic acid) allowed synthesis of **284** and **286** in respectable yield with excellent enantioselectivity (>90% ee). **284** was obtained as a ‘single diastereoisomer’ which exists as a 3:1 mixture of rotamers at room temperature, as observed by NMR spectroscopy (see Chapter 5 for NOESY spectra). Nicotinic acid did not give product **287**, but addition of a chloro group in the 2-position of the pyridyl ring allowed moderate yields and enantioselectivities to be achieved in the formation of **288** and **289**. This observation was consistent with previous rhodium-catalysed asymmetric processes,¹⁴² and overall these experiments suggest that many other carboxylic acid bearing heterocycles and heteroatoms would be compatible with this method if appropriate protecting group strategies are used.

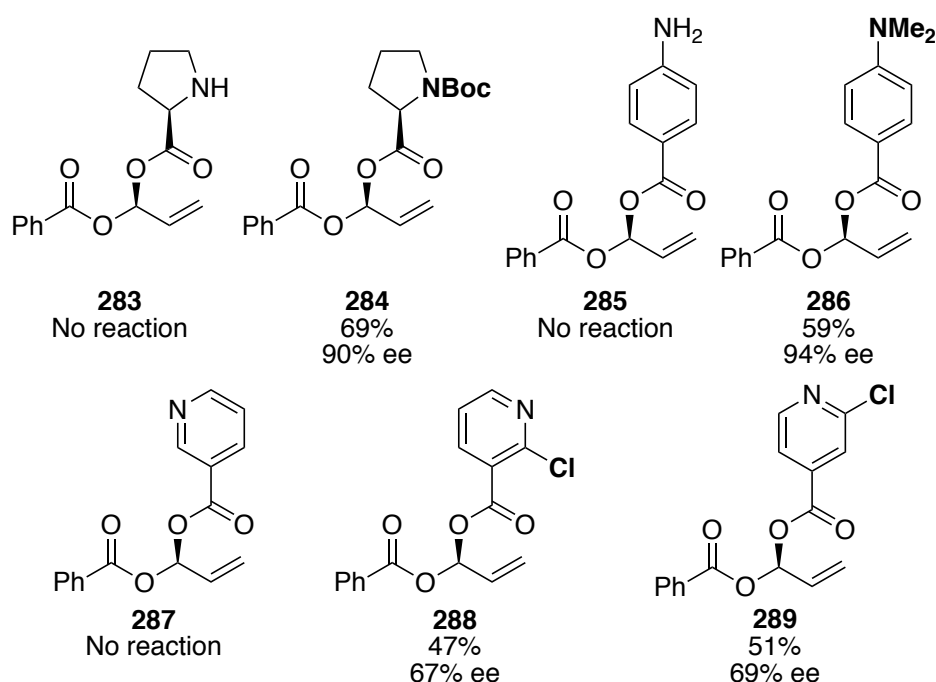


Figure 4.4 Nitrogen-containing and pyridyl substrates.

We then examined different allylic bromides **59** and **60**⁷³ with isobutyric acid which gave **290** and **291** with good yields and excellent ee's. We note that acetic acid in combination with **58**

gave 48% yield and 74% ee however with **60** much better results (**292**, 84%, 92% ee) are observed.

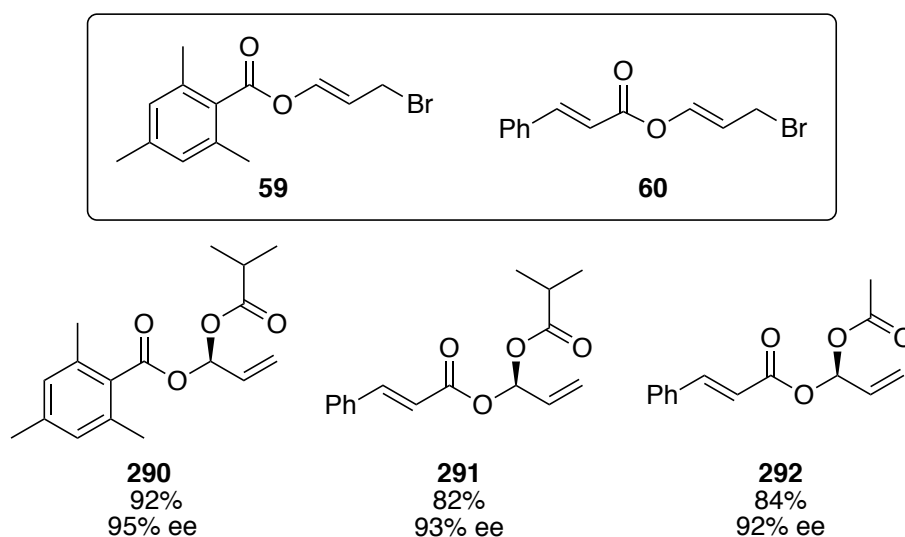
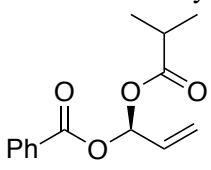


Figure 4.5 Using different carboxylic acid derived electrophiles.

To investigate the stability of the *gem*-dicarboxylates, we subjected **252** to various conditions for 1 hour at room temperature. We found that **252** was remarkably stable to a range of conditions. In aqueous acidic solutions of up to 3 M HCl, there was a negligible loss in the yield and ee of **252** (Table 3, entries 1-2). In aqueous basic solutions of up to 2 M NaOH or KOH we saw some loss of yield, but there was no change in ee (Table 3, entries 1–4). Unsurprisingly, the products were unstable to methanolic basic solutions in combination with potassium salts, and under these conditions complete decomposition was observed (Table 3, entries 5 and 6). Using Na₂CO₃ and MeOH trace decomposition was observed after 1 hour, and complete decomposition occurred overnight.

Table 4.18 Stability of *gem*-dicarboxylates.

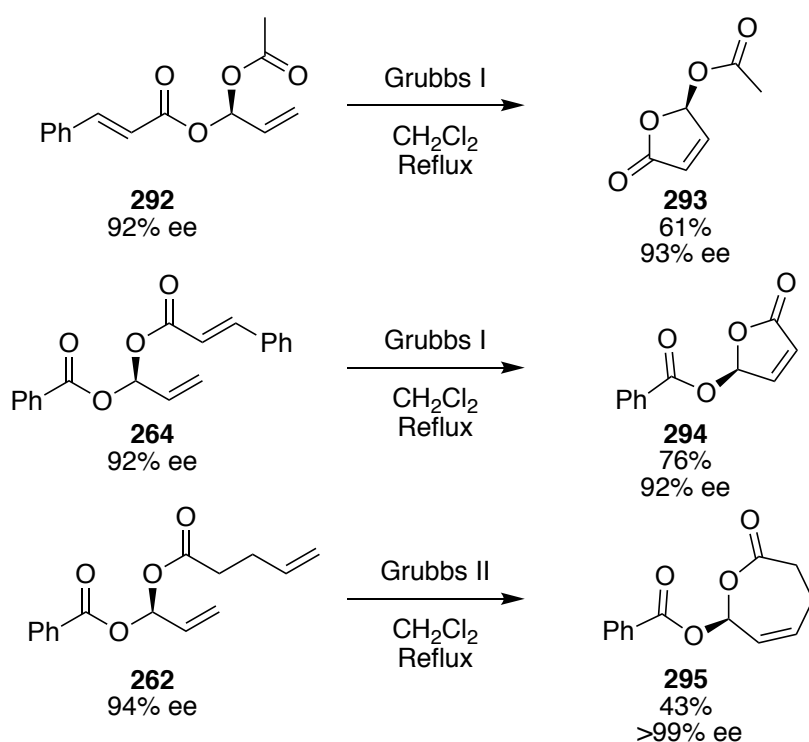


252
95% ee

“Conditions”
1 hr

Entry	Conditions ^[a]	Recovered starting material
1	1 M HCl _(aq.)	88%, 93% ee
2	3 M HCl _(aq.) /THF	quant. 93% ee
3	2 M NaOH _(aq.) /THF	58%, 95% ee
4	2 M KOH _(aq.) /THF	64%, 94% ee
5	1 M KOH _(MeOH)	Decomposed
6	K ₂ CO ₃ /MeOH	Decomposed
7	Na ₂ CO ₃ /MeOH	<72%, 95% ee ^[b]

[a] 25 mg of **252** stirred in 1 mL of a 1:1 mixture of solvents for 1 hour. [b] Complete decomposition observed overnight. (aq.) – aqueous, (MeOH) – methanolic solution.



Scheme 4.5 Derivatization by using ring-closing metathesis of *gem*-dicarboxylates to give lactones. Isolated yields. Enantiomeric excesses determined by SFC.

The *gem*-dicarboxylates shown here have not been previously described in the literature and since there has been no good way to access these chiral compounds before, their chemistry has not yet been explored. In order to demonstrate if the *gem*-dicarboxylates may be useful we briefly examined their conversion to other species using ring-closing metathesis. The

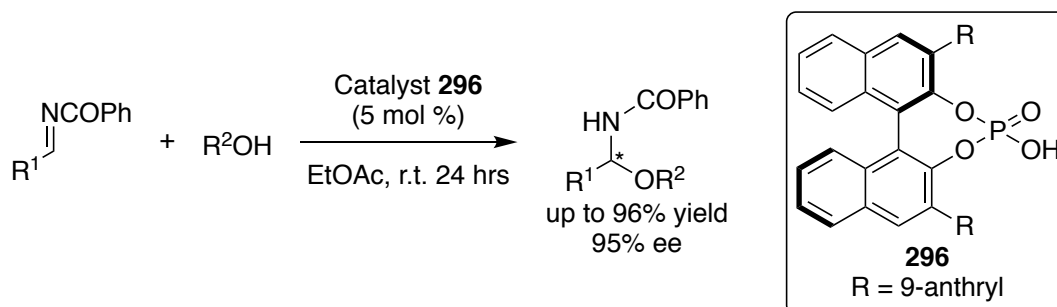
synthesis of cyclic small-ring esters is of considerable interest as they frequently appear in natural products and show important biological activity.¹⁹⁶ Asymmetric γ -butenolides have been widely studied but only acetyl esters in the γ -position have been reported, with asymmetry normally induced using enzymes.^{197–200}

Using the terminal alkene formed during the Rh-catalysed addition, we were able to access 5- and 7-membered lactones. Treatment of **292** and **264** with the 1st generation Grubbs catalyst in refluxing CH₂Cl₂ overnight gave 5-membered lactones **293** and **294**, which have a γ -stereogenic centre. We assign the absolute stereochemistry of all *gem*-dicarboxylate products here, including diastereomeric mixture **265**, and single diastereoisomers **282** and **284**, by comparing the optical rotation of lactone **293** with that quoted in the literature.¹⁹⁸ This is the first asymmetric synthesis of compound **294**.²⁰¹ Using electrophile **60** specifically, the combination of rhodium-catalysed carboxylation followed by RCM has the potential to give access to a range of new chiral γ -butenolides. Attempts to use the Grubbs I catalyst to form a 7-membered ring did not give the desired product **295**, but the 2nd generation Grubbs catalyst gave 43% yield and **295** was obtained as a solid with >99% ee.

4.4 Catalytic asymmetric synthesis of *O,N*-aminals

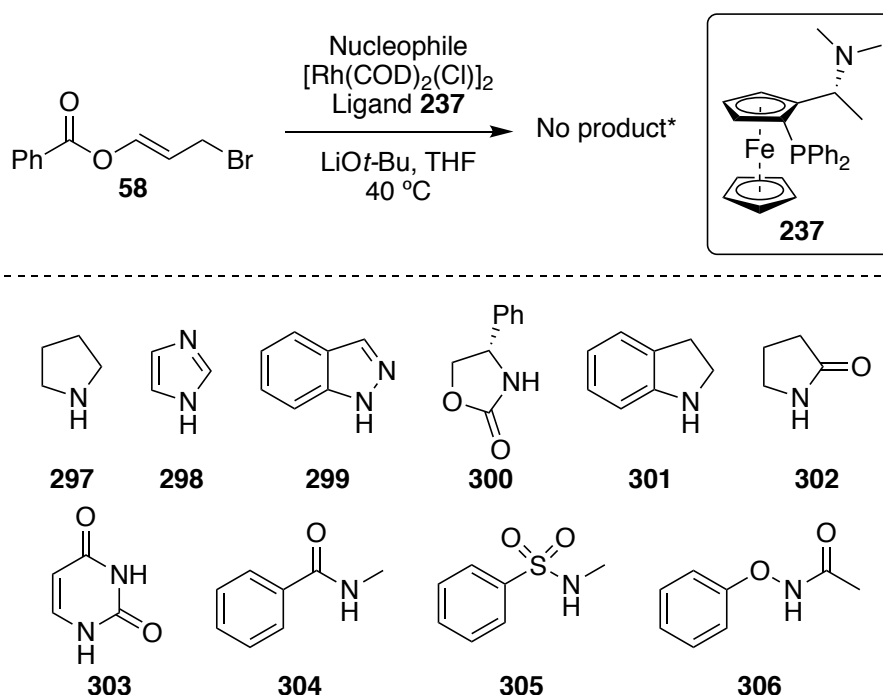
With our optimised conditions in hand, we were interested to see if this methodology could be expanded to other nucleophiles. We were particularly interested in forming *O,N*-aminals as they have been shown to be important in many natural products,^{202,203} pharmaceuticals²⁰⁴ and as a reagent in numerous asymmetric reactions.²⁰⁵ *O,N*-aminals are often useful in synthesis as they are more stable than the corresponding imine and therefore easier to manipulate. Methods for the preparation of *O,N*-aminals include but are not limited to single-electron oxidation processes,^{206,207} Brønstead acid promoted substitutions,²⁰⁸ the

hydrozirconation/acylation of nitriles²⁰⁹ and Lewis acid mediated reactions.²¹⁰ The first synthesis of *O,N*-aminals via asymmetric catalysis was reported by Antilla and co-workers in 2008.¹⁶⁵ The reaction used chiral phosphoric acids to catalyse the addition of alcohols to imines in up to 96% yield and 95% ee (Scheme 4.6).



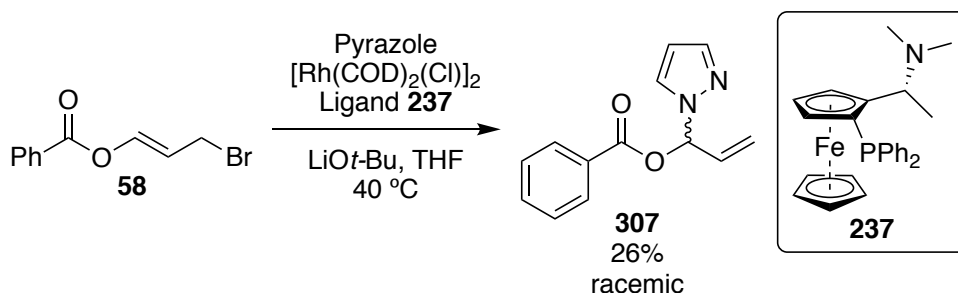
Scheme 4.6 The first catalytic asymmetric synthesis of *O,N*-aminals.

We began by examining a range of different nitrogen nucleophiles in our rhodium-catalysed substitution reaction (Scheme 4.7). Unfortunately none of the nucleophiles **297** – **306** gave any of the desired products. We found that the starting material was either recovered, or completely decomposed depending on the nucleophile used.



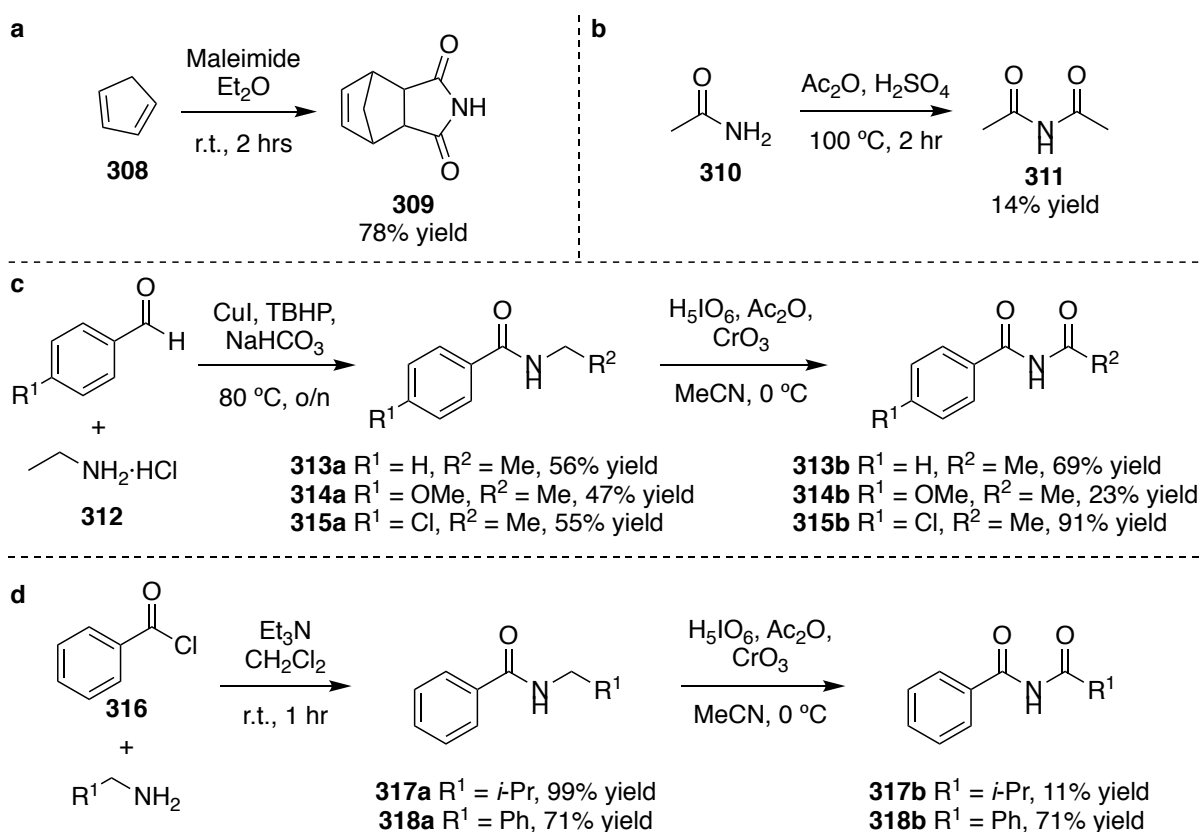
Scheme 4.7 None of the nitrogen nucleophiles **297** – **306** gave any product in the above reaction.

*The starting material was either recovered or complete decomposition was observed with these nucleophiles.



Scheme 4.8 Using pyrazole as the nucleophile only 26% yield and racemic product was obtained.

Under these conditions we found that pyrazole gave only a 26% yield and racemic product, whereas previously during our nucleophile screen, we obtained a 50% yield and 54% ee under conditions A.



Scheme 4.9 Synthesis of different imides. **a** A Diels-Alder reaction of cyclopentadiene gave imide **309**. **b** Reaction of amine **310** with acetic anhydride gave imide **311**. **c** Amide formation from the aldehyde followed by oxidation gave imides **313b-315b**. **d** Amide formation from the acid chloride followed by oxidation gave imides **317b** and **318b**.

We were pleased to find that when using succinimide in our reaction we are able to obtain a 79% yield and 99% ee (**319**, Figure 4.6). Based on this, we were interested to see if other related imide substrates would also be tolerated. Succinimide, maleimide, phthalimide, 1,8-

naphthalimide and 2-benzoxazdione were commercially available. All other imides were synthesised according to the procedures detailed in Scheme 4.9.

Good to average yields and some excellent ee's were obtained with these nucleophiles (Figure 4.6). Using maleimide, we obtained the desired product **320**, in low yield (20%) but excellent ee (96%). Phthalimide (**321**) and 1,8-naphthalimide (**322**) gave reasonable yields (69 and 53% respectively) and excellent ee's (92 and 94% respectively). Imides which have electron donating (**326**) and electron withdrawing (**327**) groups gave low yields and in the case of the electron withdrawing *para*-chloro group, also a low ee (38%). For substrates **326** and **328**, ee's were not obtained as the racemic reactions for these substrates did not give sufficient quantities of pure product. Generally groups bearing a benzoate group did not give good results in this reaction (**328** and **329**). Related substrate benzoxazolone could also be used as a substrate to give **330**, in good yield and excellent ee (92%).

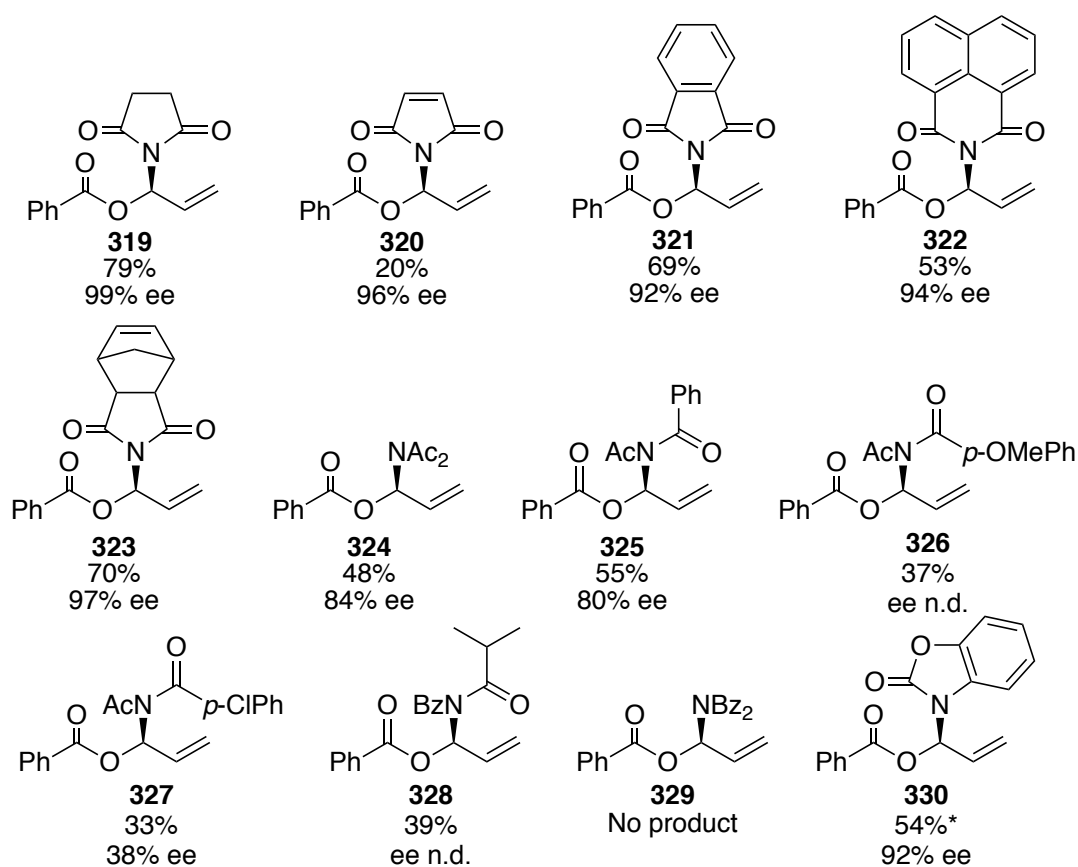


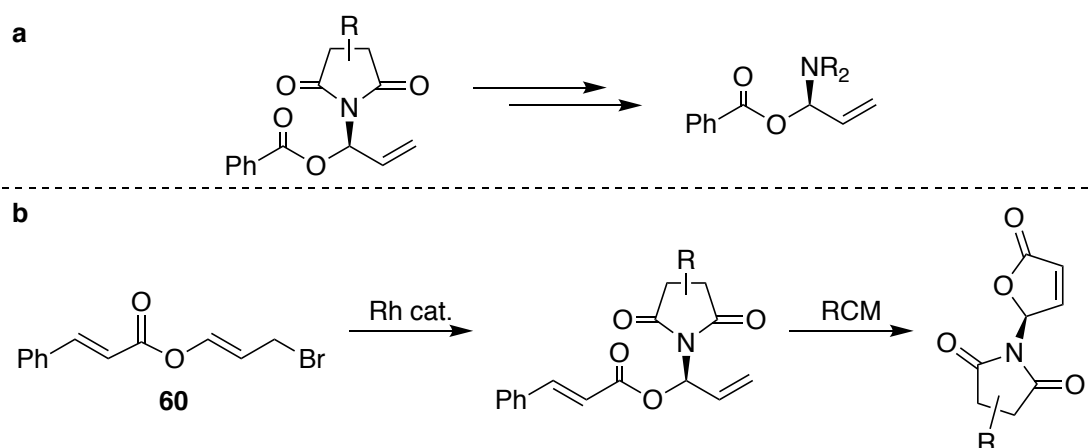
Figure 4.6 Imide substrates generally give good ee's. *The product contains some inseparable impurities.

4.5 Conclusions and future work

We have developed a method to form chiral *gem*-dicarboxylates by rhodium-catalysed asymmetric carboxylation. Many different carboxylic acid nucleophiles can be used to give novel *gem*-dicarboxylates in good yields with high enantioselectivity. The products are remarkably stable to a variety of acidic and basic conditions. We have demonstrated that the products can be used to form other chiral acetal derivatives using the terminal alkene formed in the reaction in subsequent RCM reactions to access novel cyclic products including valuable γ -butenolides. We anticipate that these *gem*-dicarboxylates may have many other potential uses and now that we have described an efficient synthesis, this chemistry can now be explored more fully.

More generally, linear products, chiral by virtue of a stereogenic carbon bearing two differentiated heteroatoms, can be obtained by metal-catalysed asymmetric additions to appropriately substituted electrophiles. The ease of synthesis and stability of the products suggests that a broad range of new chemical species may be accessible by developing strategies to form stereogenic carbon centres featuring different combinations of heteroatoms.

We have begun to demonstrate this by the addition of imides to an ester containing linear allylic bromide to give *O,N*-stereocentres. The scope for this reaction is currently limited and further investigations and synthesis of other imides is required. Further manipulations of the resulting products would be required in order to fully demonstrate the utility of this method. If the imide group on the products could be reduced to amines, these chiral amines would be synthetically useful in further transformations (Scheme 4.10a). Similarly, it should be possible to form cyclic small ring lactones that have stereocentres bearing two different heteroatoms (Scheme 4.10b).²¹¹



Scheme 4.10 **a** Possible reduction of the imide group to a more synthetically useful amine group. **b** Synthesis of cyclic small ring lactones bearing a stereocentre with two different heteroatoms

We can also see from our nucleophile screening that there could be potential to optimise a similar rhodium-catalysed substitution reaction for other nitrogen nucleophiles such as pyrazole. Under conditions A in our nucleophile screening we are already able to achieve a 54% ee. Similarly with thiophenol under conditions C, we are already able to obtain a 74% yield and 55% ee; although in this case we obtain a 1:1 S_N2' : S_N2 ratio. There is the potential here to expand this methodology into the development of reactions to form chiral *O,S*-stereocentres.

There could also be an opportunity to expand this methodology into electrophiles such as the ones shown in Figure 4.7. Electrophile **331** has additional functionality in the second bromide, which could be manipulated in subsequent reactions. Electrophile **333** is a cyclic derivative of **58** and would allow for the formation of quaternary centres.

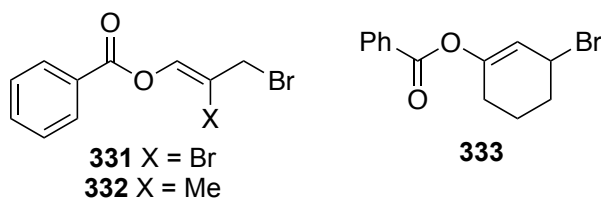


Figure 4.7 Other possible electrophiles

5 Experimentals

5.1 General methods

The reactions were carried out in glassware that was flame-dried under vacuum, in anhydrous solvents with continuous magnetic stirring under an inert argon atmosphere. Cooling to 0 °C was achieved with an ice/water bath and to –78 °C, was achieved with an acetone/dry ice bath. If needed, other temperatures were obtained using a Julabo FT902 immersion cooler. Heating was performed using DrySyn heating blocks.

Thin layer chromatography (TLC) was performed on plates with glass or aluminium backing (Silica Gel 60 F₂₅₄, Merck or Aluminium Oxide N/UV₂₅₄, Macherey–Nagel) and visualised with UV light (254 nm) and aqueous potassium permanganate stain. Column chromatography was performed by using Merck 60 Å silica gel or Acros 60 Å aluminium oxide, neutral and pressure applied with a flow of nitrogen.

Unless otherwise stated, nuclear magnetic resonance (NMR) spectroscopy measurements were carried out at room temperature. ¹H NMR, ¹³C NMR, ¹⁹F NMR, COSY, HSQC, and NOESY experiments were carried out using Bruker AVN-400 (400/100 MHz), DQX-400 (400/100 MHz) or AVC-500 (500/125 MHz) spectrometers.

Chemical shifts (δ) are reported in ppm relative to the residual solvent peak with corresponding coupling constants (J) in Hertz (Hz) and multiplicities (s: singlet, d: doublet, t: triplet, q: quartet, hept: heptet, m: multiplet).

Infrared (IR, neat, thin film) spectroscopy was carried out on a Bruker Tensor 27 FT–IR spectrometer with an internal calibration range of 4000 – 600 cm^{–1}.

Optical rotations ($[\alpha]_{589}^{25}$) were recorded on a Perkin-Elmer 241 polarimeter at 25 °C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{–1} deg/cm² g^{–1} (concentration c given as g/100 mL).

Low-resolution mass spectra (LRMS) were recorded using a Walters LCT premier XE. High Resolution Mass (HRMS) experiments were carried out by the internal service at the University of Oxford. (1) Electrospray ionisation (ESI+) were recorded on a Fisons Platform II. (2) Electron ionisation (EI)/Chemical ionisation (CI): Analyses were performed on an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software. The system was calibrated on the day of the analysis and its mass accuracy with external calibration (as used for these experiments) is better than 5 ppm for 24 hrs following calibration. Source conditions for both EI and CI were adjusted to maximise sensitivity, the reagent gas used in CI was either methane or ammonia (and should be apparent in the metadata associated with the data). (3) Atmospheric pressure chemical ionisation (APCI+): Analyses were performed using a Thermo Exactive mass spectrometer equipped with Waters Acquity liquid chromatography system. Instrument control and data processing were performed using Thermo Xcalibur Software. The system was calibrated on the day of the analysis and its mass accuracy with external calibration (as used for these experiments) is better than 5 ppm for 24 hrs following calibration. The mass spec was operated using the APCI probe and resolution was set to 50,000. APCI source conditions were adjusted to maximise sensitivity. A mixture of 10% water, 89.9% methanol and 0.1% formic acid was used to transport samples to the mass spectrometer at a flow rate of 0.2 mL/min. The values of mass over charge (m/z) indicate the most intense peak.

Melting points (m.p.) were obtained using a Lecia VMTG heated-stage microscope and are uncorrected.

Chiral HPLC separations were achieved using an Agilent 1230 Infinity series normal phase HPLC unit and HP Chemstation software. Chirapak[®] columns (250 × 4.6 mm), fitted with

matching Chiralpak® Guard Cartridges (10 × 4.6 mm), were used as specified in the text. Solvents used were of HPLC grade (Sigma Aldrich); all eluent systems were isocratic. Chiral SFC (supercritical fluid chromatography) separations were conducted on a Waters Acquity UPC2 system using Waters Empower software. Chiralpak® columns (150 × 3 mm, particle size 3 µm) were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn).

X-Ray Crystallography

Low temperature²¹² (150 K) single-crystal X-ray diffraction data were collected using an Oxford Diffraction (Agilent) SuperNova A diffractometer. Raw frame data were reduced using the instrument manufacturer supplied software CrysAlisPro.²¹³ All structures could be solved *ab initio* using SuperFlip,²¹⁴ and full-matrix least-squares refinement was carried out using CRYSTALS.^{215–217} All non-hydrogen atoms were refined using anisotropic displacement ellipsoids, and hydrogen atoms were visible in the difference map. Once the heavy atoms structure was complete, hydrogen atoms were positioned geometrically then refined separately using soft restraints prior to inclusion in the final refinement using a riding model.²¹⁸ All structures have been deposited with the Cambridge Crystallographic Data Centre (reference codes CCDC 1472705-1472707); these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

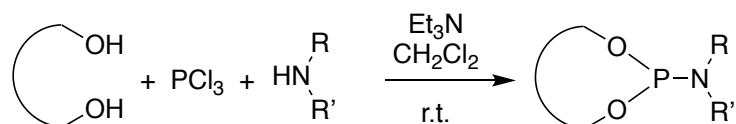
Chemicals

Commercially available reagents were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, Fluorochem and Strem Chemicals and unless otherwise stated were used without further purification. Dry solvents were collected fresh from an mBraun SPS–800 solvent purification system after having passed through anhydrous alumina columns. Deuterated

solvents were purchased from Sigma Aldrich. Pentane (HPLC grade) was used without further purification. The following chiral ligands were provided by the Fletcher group: **13**, **14**, **75**, **76**, **77**, **78**, **79**, **80**, **182**, **183**, **236** and **237**. Amine **82** was provided by the Fletcher group. Phosphate **153** was provided by the Fletcher group. Compound **207** was provided by Patricia Fernandez Rodriguez. Compound **47** was synthesised according to the literature procedures previously detailed by the Fletcher group.⁴⁷

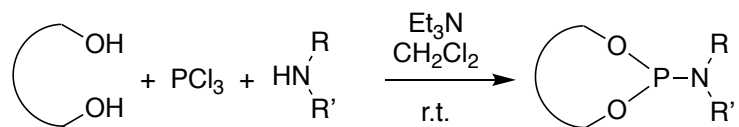
5.2 General experimental procedures

General Procedure 1: phosphoramidite ligand synthesis A



Freshly distilled PCl_3 (1.0 eq.) was added dropwise over about 1 min to a stirred and cooled ($0\text{ }^\circ\text{C}$) solution of Et_3N (8.0 eq.) in CH_2Cl_2 (2.5 mL/0.5 mmol of amine) under an atmosphere of argon. The amine (1.0 eq.) in CH_2Cl_2 (2.5 mL/0.5 mmol of amine), was added to the cooled reaction mixture before stirring was continued for 2 hrs at room temperature. The reaction mixture was then cooled to $0\text{ }^\circ\text{C}$, the diol (1.0 eq.) was added as a solution in CH_2Cl_2 (2.5 mL/0.5 mmol of amine) and stirring continued at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the crude product purified by flash column chromatography to give the pure ligand.

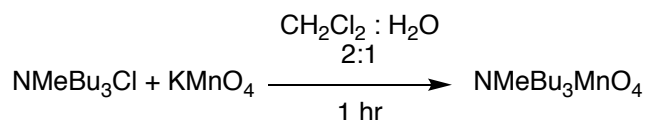
General Procedure 2: phosphoramidite ligand synthesis B



Freshly distilled PCl_3 (1.0 eq.) was added dropwise over about 1 min to a stirred and cooled ($0\text{ }^\circ\text{C}$) solution of Et_3N (8.0 eq.) in CH_2Cl_2 (2.5 mL/0.5 mmol of amine) under an atmosphere of argon. The amine (1.0 eq.) in CH_2Cl_2 (2.5 mL/0.5 mmol of amine), was added to the cooled reaction mixture before stirring was continued for 2 hrs at room temperature. The reaction mixture was then cooled to $0\text{ }^\circ\text{C}$, the diol (1.0 eq.) added as a solid, followed by further CH_2Cl_2 (2.5 mL/0.5 mmol of amine), and stirring continued at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the crude product purified by flash column chromatography to give the pure ligand.

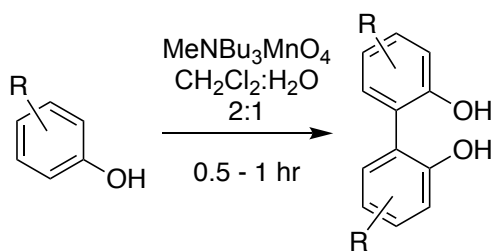
General Procedure 3:

Preparation of MTBAP:



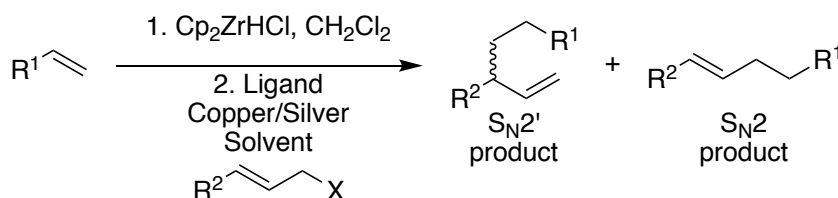
Ammonium chloride (1.0 eq.) was dissolved in CH_2Cl_2 (0.05 M). A solution of KMnO_4 (1.0 eq.) in water (0.025 M) was added to the flask. The reaction was stirred at room temperature for 1 hr. The layers were separated and the aqueous layer washed with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to give a purple solid.

MTBAP coupling:



A solution of the phenol (1.0 eq.) in CH_2Cl_2 (0.09 M) was cooled to 0 °C. Freshly prepared MTBAP was added and the reaction stirred for 15 mins. Water (0.15 M) was added and the formation of a precipitate was observed. The reaction was monitored by TLC and upon consumption of the starting material, the reaction was quenched with 1 M HCl and the aqueous phase extracted with CH_2Cl_2 ($\times 3$). The combined organic phases were washed with brine, dried over MgSO_4 and concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography.

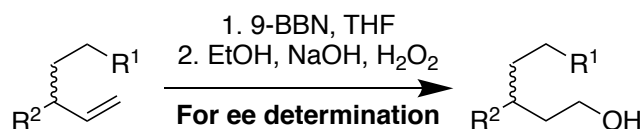
General procedure 4: *h*-AAA and AAA screening reactions:



In a flame dried flask covered in foil to shield from any light, the copper salt (0.04 mmol, 0.1 eq.) and ligand (0.04 mmol, 0.1 eq.) were dissolved in the desired solvent (0.8 mL) under an argon atmosphere and allowed to stir for 1 hr at room temperature. In those reactions involving transmetalation with a silver salt, the silver salt (0.044 mmol, 0.11 eq.) was added to the Cu/ligand mixture and stirred for a further 20 mins. In another flame dried flask also covered in foil to shield from any light, Cp_2ZrHCl (206 mg, 0.8 mmol, 2.0 eq.) was added to a stirred solution of the alkene (1.0 mmol, 2.5 eq.) in CH_2Cl_2 (0.4 mL) at room temperature, under an argon atmosphere. After stirring for 20 mins, the resulting yellow solution turned

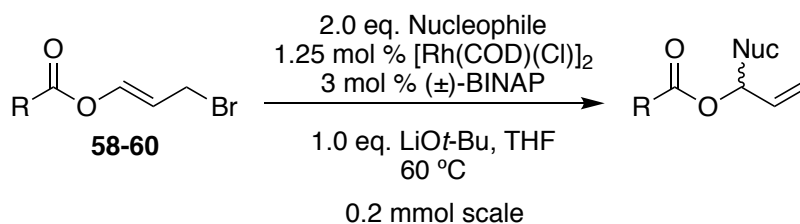
clear. The Cu/ligand(/silver salt) mixture was transferred to the hydrozirconated mixture *via* syringe (filtering through a syringe filter in the cases where a silver salt was used), under an argon atmosphere. The electrophile (0.4 mmol, 1.0 eq.) was added to this mixture as a solution in CH₂Cl₂ (0.2 mL) and the reaction stirred at room temperature overnight. The reaction was diluted with hexane (~3 mL) and quenched with NH₄Cl (1 M aq., ~1.5 mL). The aqueous phase was extracted with hexane (3 × 5 mL), the combined organic phases were washed with NaHCO₃ (5 mL), brine (5 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (SiO₂, 0–1% Et₂O in hexane) to give the desired product.

General procedure 5: derivatisation of selected products to alcohols



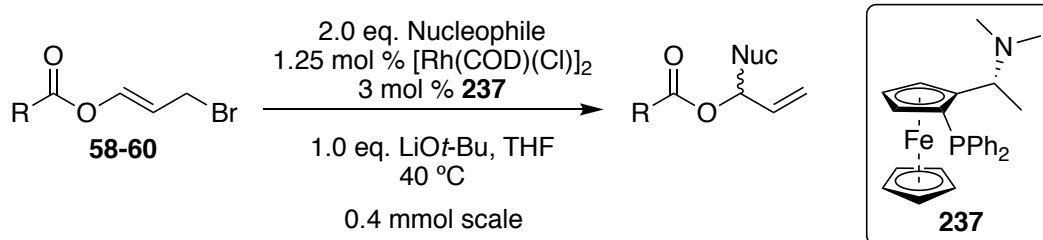
9-BBN (0.5 M in THF, 740 μ L, 0.37 mmol, 3.0 eq.) was added to a solution of the alkene (25 mg, 0.12 mmol, 1.0 eq.) in THF (0.3 mL). The reaction was stirred for 2 hrs at room temperature before the addition of EtOH (0.45 mL), NaOH (6 M, 0.12 mL) and H₂O₂ (30% in water, 0.7 mL). After stirring for 1 hr the reaction was quenched with brine (3 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL), dried over MgSO₄ and concentrated *in vacuo*. The product was purified by filtering over a short pad of silica (0–100% EtOAc in hexane) and used to determine the ee of alkene.

General procedure 7: racemic Rh-catalysed substitution reaction:



In a flame-dried 5 mL round bottomed flask $[\text{Rh}(\text{COD})(\text{Cl})]_2$ (1.2 mg, 0.0025 mmol, 0.0125 eq.), $(\pm)\text{-BINAP}$ (2.6 mg, 0.006 mmol, 0.03 eq.) and LiOt-Bu (16 mg, 0.20 mmol, 1.0 eq.) were stirred in THF (1.0 mL) at 60 °C for 30 min. A solution of the allylic bromide (**58-60**, 0.20 mmol, 1.0 eq.) and the carboxylic acid (0.40 mmol, 2.0 eq.) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred at 60 °C until the reaction was complete by TLC. SiO_2 was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with Et_2O /pentane to afford the products.

General procedure 7: asymmetric Rh-catalysed substitution reaction:

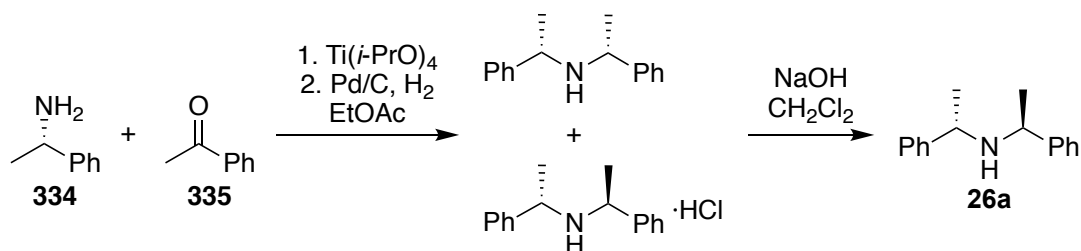


In a flame-dried 10 mL round bottomed flask $[\text{Rh}(\text{COD})(\text{Cl})]_2$ (2.5 mg, 0.005 mmol, 0.0125 eq.), Ligand **237** (5.3 mg, 0.012 mmol, 0.03 eq.) and LiOt-Bu (32 mg, 0.40 mmol, 1.0 eq.) were stirred in THF (2.0 mL) at 60 °C for 30 min. The reaction was cooled to 40 °C then a solution of the allylic bromide (**58-60**, 0.40 mmol, 1.0 eq.) and the carboxylic acid (0.80 mmol, 2.0 eq.) in THF (1.5 mL) was added *via* syringe and the flask rinsed with THF (0.5 mL). The resulting mixture was then stirred at 40 °C until the reaction was complete by TLC. SiO_2 was added and the solvent was then carefully evaporated. The resulting solid was

directly loaded onto a chromatographic column and eluted with Et₂O/pentane to afford the products.

5.3 Experimental procedures

(*S,S*)-Bis(1-phenylethyl)amine (26a)



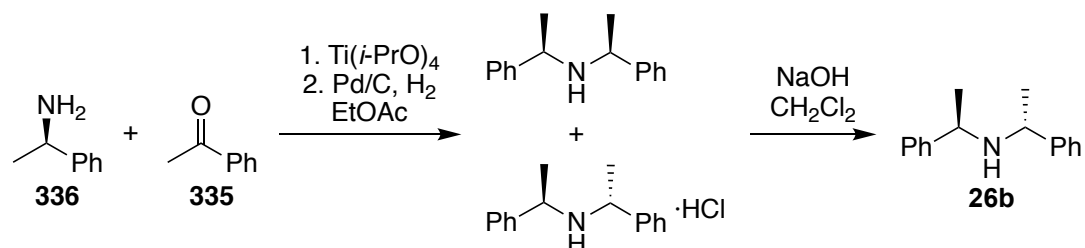
(*S*)-2-Phenylethylamine (13 mL, 100 mmol, 1.0 eq.), acetophenone (12 mL, 100 mmol, 1.0 eq.) and $\text{Ti}(\text{O}i\text{-Pr})_4$ (74 mL, 250 mmol, 2.5 eq.) were stirred at room temperature for 25 mins. Palladium on carbon (1.06 g, 10 mmol, 0.1 eq.) was added and the flask purged with H_2 . The reaction was stirred under H_2 (balloon) for 36 hrs before quenching with EtOAc (100 mL) and 2 M NaOH (60 mL), which formed a grey precipitate. The mixture was filtered over Celite and washed with EtOAc. The filtrate was concentrated to approximately 50 mL *in vacuo* before diluting with 2 M NaOH (100 mL) and extracting with EtOAc ($3 \times \sim 200$ mL). The combined organic phases were dried over MgSO_4 and concentrated *in vacuo*. The oil was diluted with EtOAc (~ 50 mL) and 37% HCl was added to the solution until the amine crashed out as the hydrochloride salt. The white solid was recrystallised from EtOAc with a small amount of EtOH. Brine (150 mL), 2 M NaOH (25 mL) and ca. 12 g NaOH pellets were stirred vigorously for 15 mins before adding to a solution of the amine hydrochloride salt in CH_2Cl_2 (150 mL). The resulting solution was stirred for 1 hr before separating the phases. Brine (75 mL) was added to the aqueous phase before extracting with EtOAc (3×250 mL). The combined organic phases were dried over MgSO_4 and concentrated *in vacuo* to give the pure amine as a colourless oil (14.35 g, 64% yield).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.38 – 7.29 (m, 4H), 7.29 – 7.19 (m, 6H), 3.51 (q, $J = 6.7$ Hz, 2H), 1.27 (s, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 146.0 (2C), 128.5 (4C), 126.9 (2C), 126.8 (4C), 55.2 (2C), 25.1 (2C).

LRMS (ESI) m/z : 226.2 $[\text{M}+\text{H}]^+$

(*R,R*)-Bis(1-phenylethyl)amine (26b)



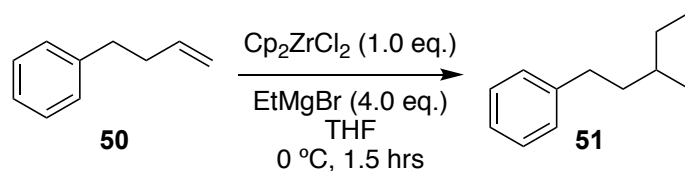
Synthesised from (*R*)-2-Phenylethylamine (13 mL, 100 mmol) according to the same procedure as for **26a**, to give the pure amine as a colourless oil (13.63 g, 60% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.29 (m, 4H), 7.28 – 7.17 (m, 6H), 3.49 (q, J = 6.7 Hz, 2H), 1.27 (d, J = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 145.9 (2C), 128.5 (4C), 126.9 (2C), 126.8 (4C), 55.2 (2C), 25.1 (2C).

LRMS (ESI) m/z : 226.2 $[\text{M}+\text{H}]^+$

(3-Methylpentyl)benzene (51)



Cp_2ZrCl_2 (221 mg, 0.76 mmol, 1.0 eq.) was dissolved in dry THF (3 mL) and cooled to -78 °C before adding EtMgBr (3 M in Et_2O , 1.0 mL, 3.0 mmol, 4.0 eq.) dropwise. The solution was stirred for 1 hr at -78 °C. This was then added to a solution of 4-phenyl-1-butene (114 μL , 0.76 mmol, 1.0 eq.) in THF (1 mL) at 0 °C. The reaction was stirred for 1.5 hrs then

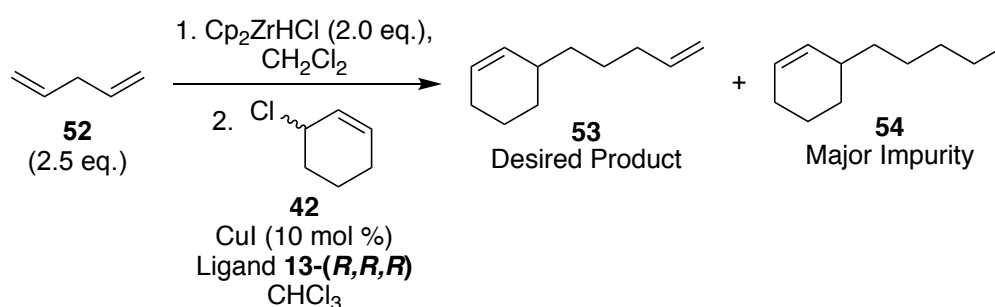
quenched with 2 M HCl (~2 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL), the combined organic phases were washed with saturated NaHCO₃, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 100% hexane) to give a colourless liquid (46 mg, 75% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 2.70 – 2.51 (m, 2H), 1.69 – 1.60 (m, 1H), 1.49 – 1.33 (m, 3H), 1.29 – 1.13 (m, 1H), 0.93 (d, *J* = 6.2 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 143.4, 128.5 (2C), 128.4 (2C), 125.7, 38.7, 34.3, 33.7, 29.5, 19.3, 11.5.

HRMS (ESI) *m/z* calcd. for C₁₂H₁₈ [M]⁺: 162.1409, found: 162.1406.

3-(Pent-4-en-1-yl)cyclohex-1-ene (**53**)



CuI (7.7 mg, 0.04 mmol, 0.1 eq.) and ligand **13-(R,R,R)** (21.6 mg, 0.04 mmol, 0.1 eq.) were dissolved in CHCl₃ (0.8 mL) under an argon atmosphere and allowed to stir for 1 hr at room temperature before cooling to 0 °C. In another flask Cp₂ZrHCl (206 mg, 0.80 mmol, 2.0 eq.) was added to a stirred solution of 1,4-pentadiene (103 μL, 0.10 mmol, 2.5 eq.) in CH₂Cl₂ (0.4 mL) at room temperature, under an argon atmosphere. After stirring for 30 mins, the resulting clear yellow solution was added to the 0 °C Cu/ligand mixture *via* syringe. Allyl chloride (**42**, 50 mg, 0.40 mmol, 1.0 eq.) was added and the reaction stirred at 0 °C for 4 hrs. The reaction was diluted with hexane (3 mL) and quenched with NH₄Cl (1 M aq., ~1.5 mL). The aqueous phase was extracted with hexane (3 × 10 mL), the combined organic phases

were washed with sat. NaHCO_3 (10 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude mixture was obtained as a colourless oil which was analysed by NMR as a 1:0.3 ratio of **53**:**54**. Identification of **54** was by ^1H NMR only.

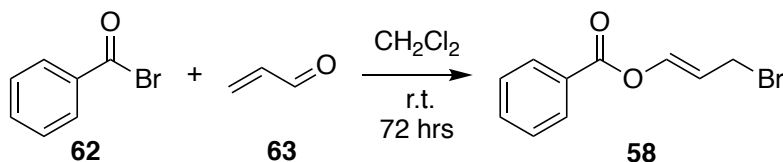
53: ^1H NMR (400 MHz, CDCl_3) δ 5.82 (ddt, $J = 16.9, 10.2, 6.7$ Hz, 1H), 5.69 – 5.54 (m, 2H), 5.04 – 4.91 (m, 2H), 2.09 – 2.01 (m, 3H), 1.99 – 1.93 (m, 2H), 1.82 – 1.66 (m, 2H), 1.54 – 1.39 (m, 2H), 1.37 – 1.15 (m, 4H).

53: ^{13}C NMR (101 MHz, CDCl_3) δ 139.2, 132.3, 126.9, 114.4, 36.0, 35.2, 34.2, 29.2, 26.4, 25.6, 21.7.

54: ^1H NMR (400 MHz, CDCl_3) δ 5.69 – 5.54 (m, 2H), 2.09 – 2.01 (m, 3H), 1.99 – 1.93 (m, 2H), 1.82 – 1.66 (m, 3H), 1.54 – 1.39 (m, 3H), 1.37 – 1.15 (m, 4H), 0.93 – 0.81 (m, 3H).

LRMS – no mass spectra was recorded for this crude mixture.

(*E*)-3-Bromoprop-1-en-1-yl benzoate (**58**)



Prepared according to the procedure of Trombini and Lombardo *et al.*⁷³ Benzoyl bromide and acrolein were freshly distilled. Under an argon atmosphere, acrolein (7.7 mL, 116 mmol, 1.0 eq.) was added to CH_2Cl_2 (115 mL) and the resulting solution cooled to 0 °C. Benzoyl bromide (21.44 g, 116 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 72 hrs. The reaction was concentrated *in vacuo* to give a crude oil. The pure product was recrystallised from pentane to give a white solid (11.31 g, 40% yield)

^1H NMR (400 MHz, CDCl_3) δ 8.13 – 8.07 (m, 2H), 7.72 – 7.65 (m, 1H), 7.62 (td, $J = 7.2, 1.4$ Hz, 1H), 7.48 (dd, $J = 8.4, 7.1$ Hz, 2H), 5.90 (dt, $J = 12.4, 8.4$ Hz, 1H), 4.07 (dd, $J = 8.4, 1.0$ Hz, 2H).

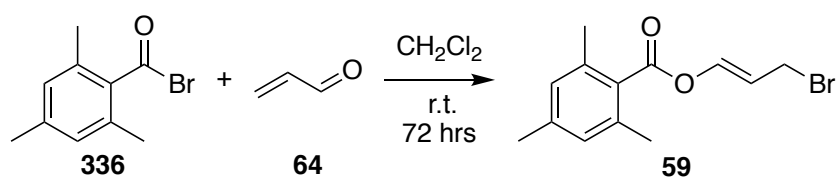
^{13}C NMR (101 MHz, CDCl_3) δ 163.3, 139.6, 134.0, 130.2 (2C), 128.8 (2C), 128.6, 112.0, 28.7.

HRMS (ESI) m/z calcd. for $\text{C}_{10}\text{H}_9\text{BrO}_2$ $[\text{M}]^+$: 239.9786, found: 239.9574.

IR (ATR) ν (cm^{-1} , CHCl_3): 705, 937, 1068, 1160, 1294, 1319, 1732.

m.p.: 72–75 °C.

(E)-3-Bromoprop-1-en-1-yl 2,4,6-trimethylbenzoate (59)



Synthesised using the same procedure as for **58** from the corresponding acid bromide and acrolein, both freshly distilled. The pure product was recrystallised from pentane to give a white solid (1.02 g, 30% yield)

^1H NMR (400 MHz, CDCl_3) δ 7.67 (dt, J = 12.4, 1.1 Hz, 1H), 6.88 (d, J = 1.1 Hz, 2H), 5.79 (dt, J = 12.3, 8.4 Hz, 1H), 4.04 (dd, J = 8.4, 1.0 Hz, 2H), 2.32 (s, 6H), 2.30 (s, 3H).

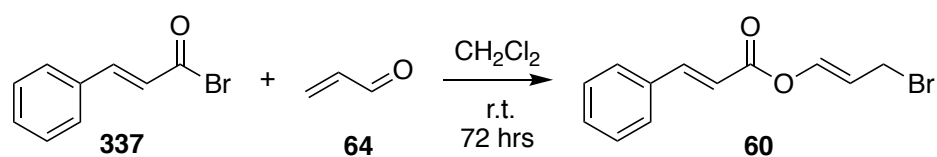
^{13}C NMR (101 MHz, CDCl_3) δ 166.3, 140.4 (2C), 139.2, 136.2 (2C), 128.7 (2C), 111.8, 28.4, 21.2, 20.1 (2C).

HRMS (GCMS with methane as reagent gas) m/z calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{Br}$ $[\text{M}+\text{H}]^+$: 282.0328, found: 283.0320.

IR (ATR) ν (cm^{-1} , CHCl_3): 930, 1166, 1246, 1735, 2360.

m.p.: 84–86 °C.

(*E*)-3-Bromoprop-1-en-1-yl cinnamate (**60**)



Synthesised using the same procedure as for **58** from the corresponding acid bromide and acrolein, both freshly distilled. The pure product was recrystallised from pentane to give a white solid (1.74 g, 46% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, $J = 16.0$ Hz, 1H), 7.63 – 7.50 (m, 3H), 7.48 – 7.36 (m, 3H), 6.45 (d, $J = 16.0$ Hz, 1H), 5.80 (dt, $J = 12.4, 8.4$ Hz, 1H), 4.04 (dd, $J = 8.4, 1.1$ Hz, 2H).

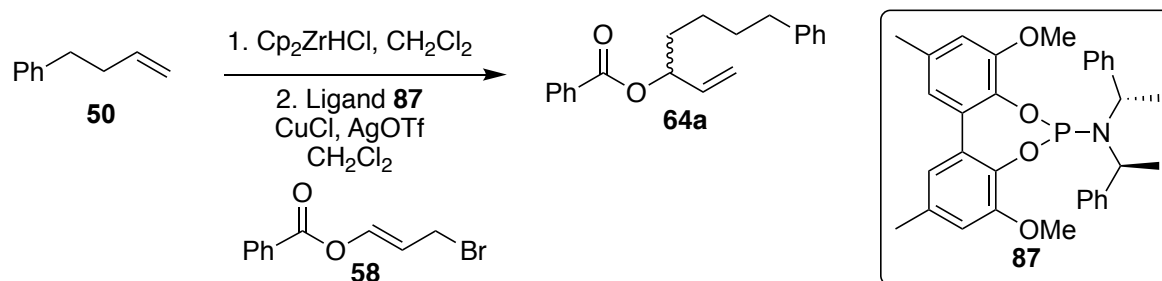
^{13}C NMR (101 MHz, CDCl_3) δ 163.6, 147.5, 139.5, 134.1, 131.1, 129.2 (2C), 128.5 (2C), 116.2, 111.5, 28.9.

HRMS (GCMS with methane as reagent gas) m/z calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{Br}$ $[\text{M}+\text{H}]^+$: 267.0015, found: 267.0011.

IR (ATR) ν (cm^{-1} , CHCl_3): 763, 976, 1139, 1167, 1633, 1728, 2361.

m.p.: 98–100 $^\circ\text{C}$.

7-Phenylhept-1-en-3-yl benzoate (**64a**)



Synthesised according to general procedure 4. The crude mixture was purified by flash column chromatography (SiO_2 , 0–1% Et_2O in hexane) to give the desired product as a yellow oil (52 mg, 44% yield, 73% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.09 – 8.03 (m, 2H), 7.60 – 7.54 (m, 1H), 7.50 – 7.42 (m, 2H), 7.30 – 7.22 (m, 2H), 7.21 – 7.13 (m, 3H), 5.96 – 5.85 (m, 1H), 5.53 – 5.45 (m, 1H), 5.32 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.20 (dt, *J* = 10.5 Hz, 1.3, 1H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.89 – 1.73 (m, 2H), 1.71 – 1.63 (m, 2H), 1.50 – 1.42 (m, 2H).

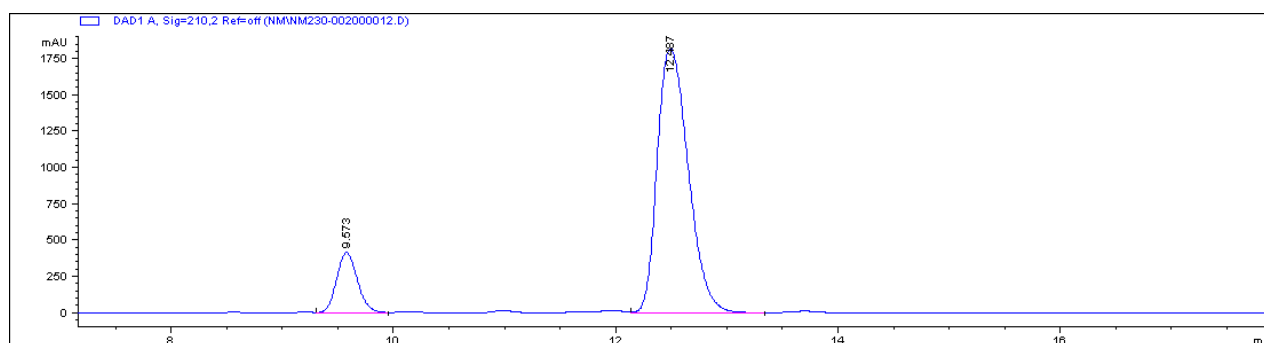
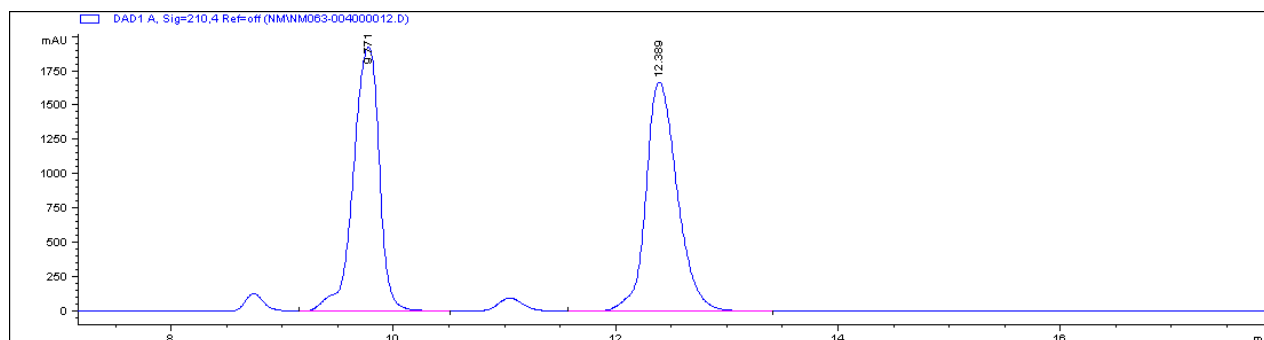
¹³C NMR (101 MHz, CDCl₃) δ 165.9, 142.4, 136.5, 132.9, 130.6, 129.6 (2C), 128.8 (2C), 128.4 (2C), 128.3 (2C), 125.7, 116.7, 75.2, 35.8, 34.2, 31.2, 24.7.

HRMS (CI with methane as reagent gas) *m/z* calcd. for C₂₀H₂₂O₂ [M+H]⁺: 295.1693, found: 295.1704.

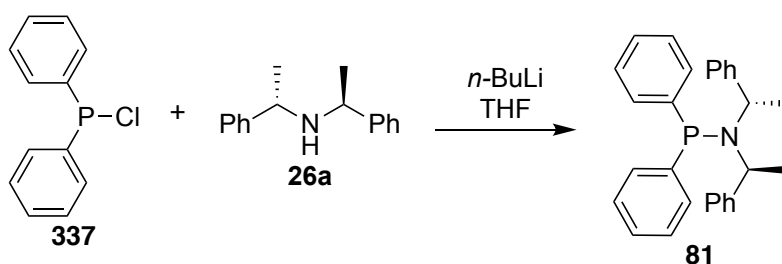
[α]_D²⁵ = −11 (c = 1.0 in CHCl₃, 73% ee).

IR (ATR) ν (cm^{−1}, CHCl₃): 712, 1112, 1270, 1718, 2936.

The enantiomeric excess was determined by HPLC [Chiralpak® IC; hexane:*i*-PrOH 99.4:0.6; 1.0 mL/min, λ=210 nm, minor enantiomer *t*_R = 9.57 mins, major enantiomer *t*_R = 12.49 mins].



1,1-Diphenyl-*N,N*-bis(*S*)-1-phenylethyl)phosphinamine (81)



According to the procedure of Alexakis *et al.*,¹¹⁷ *n*-BuLi (2.5 M in hexanes, 890 μ L, 2.2 mmol, 1.0 eq.) was added to a solution of (*S,S*)-bis(1-phenylethyl)amine (500 mg, 2.2 mmol, 1.0 eq.) in THF (15 mL) at -78 $^{\circ}$ C. The reaction was warmed slowly to room temperature and stirred for 4 additional hrs. Freshly distilled chlorodiphenylphosphine (410 μ L, 2.2 mmol, 1.0 eq.) was added at -78 $^{\circ}$ C. The dry ice/acetone bath was removed and the reaction stirred at room temperature overnight. The reaction mixture was concentrated and the crude product purified by column chromatography (Alumina, 100% toluene) to give **81** as a white solid (85 mg, 9% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.79 – 7.73 (m, 2H), 7.46 – 7.40 (m, 3H), 7.25 – 7.13 (m, 9H), 7.13 – 7.07 (m, 2H), 6.98 – 6.90 (m, 4H), 4.53 (dd, J = 12.6, 6.8 Hz, 2H), 1.50 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 144.4, 140.0, 139.7, 139.3, 133.9, 133.7, 132.6, 132.4, 128.9, 128.5, 128.4, 128.3 (2C), 128.2 (2C), 128.0, 128.0 (3C), 127.9, 127.8, 126.8 (2C), 56.4, 56.3, 21.8, 21.7.

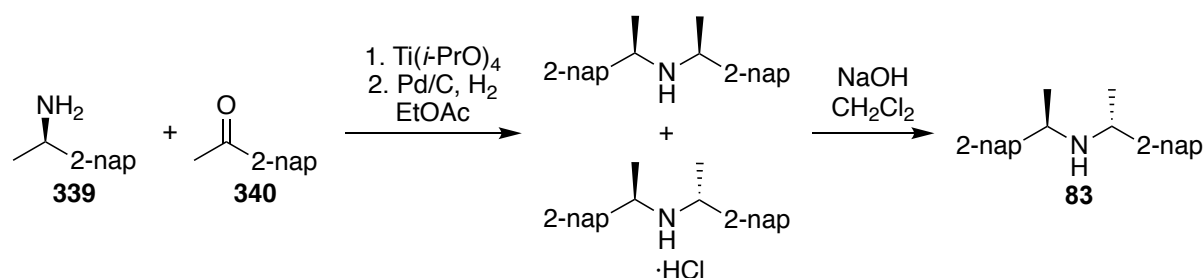
^{31}P NMR (162 MHz, CDCl_3) δ 42.02.

$[\alpha]_{589}^{25} = -244$ (c = 1.0 in CHCl_3).

LRMS (ESI) m/z : 410.2 $[\text{M}+\text{H}]^+$

IR (ATR) ν (cm^{-1} , CHCl_3): 698, 743, 918, 1089, 1118, 1434, 2968.

(*R,R*)-Bis(1-(naphthalen-2-yl)ethyl)amine (83)



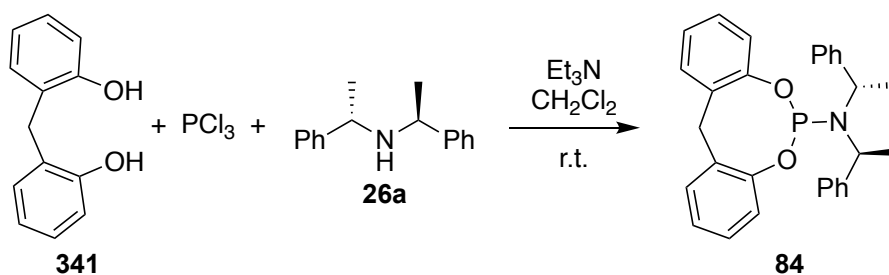
Synthesised from (*R*)-(+)-1-(2-naphthyl)ethylamine (5.0 g, 29 mmol, 1.0 eq.) and 2-acetylnaphthylene (4.97 g, 29 mmol, 1.0 eq.) according to the same procedure as for **26a**, to give the pure amine as a white solid (6.46 g, 68% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.5 Hz, 4H), 7.83 – 7.78 (m, 2H), 7.58 (s, 2H), 7.55 – 7.38 (m, 6H), 3.70 (q, *J* = 6.7 Hz, 2H), 1.69 (s, 1H), 1.37 (d, *J* = 6.7 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 143.3 (2C), 133.6 (2C), 133.0 (2C), 128.4 (2C), 127.9 (2C), 127.8 (2C), 126.1 (2C), 125.6 (4C), 125.0 (2C), 55.4 (2C), 25.1 (2C).

LRMS (ESI) *m/z*: 326.2 [M+H]⁺

***N,N*-Bis((*S*)-1-phenylethyl)-12*H*-dibenzo[*d,g*][1,3,2]dioxaphosphocin-6-amine (84)**



According to the procedure of Mikami *et al.*,²¹⁹ freshly distilled PCl₃ (380 μL, 4.4 mmol, 1.0 eq.) was added dropwise to a solution of Et₃N (5.0 mL, 36 mmol, 8.0 eq.) and CH₂Cl₂ (5 mL) at 0 °C under an atmosphere of argon. Amine **26a** (1.0 g, 4.4 mmol, 1.0 eq.) was added to the reaction as a solution in CH₂Cl₂ (5 mL), before stirring at room temperature for 3 hrs. The reaction was cooled to 0 °C and *bis*(2-hydroxyphenyl)methane (880 mg, 4.4 mmol, 1.0 eq.) was added as a solution in CH₂Cl₂ (5 mL), followed by stirring at room temperature

overnight. The reaction mixture was quenched with water (30 mL) and extracted with CH₂Cl₂ (3 × 75 mL). The combined organic layers were dried over K₂CO₃ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 82:17:1 hexane:CH₂Cl₂:Et₃N) to give the pure product as a foamy white solid (1.52 g, 76% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.29 (m, 2H), 7.25 – 7.22 (m, 4H), 7.22 – 7.12 (m, 7H), 7.12 – 6.96 (m, 4H), 6.69 (d, *J* = 7.9 Hz, 1H), 4.92 (dq, *J* = 11.9, 7.1 Hz, 2H), 4.45 (dd, *J* = 12.8, 3.1 Hz, 1H), 3.55 (d, *J* = 12.8 Hz, 1H), 1.84 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 152.2, 152.1, 151.9, 151.8, 143.5, 143.5, 135.6 (t, *J* = 3.4 Hz, 2C), 130.0, 129.8, 128.2, 128.2, 128.1 (d, *J* = 1.4 Hz), 128.1 (d, *J* = 1.3 Hz), 128.0 (4C), 126.8 – 126.7 (m, 2C), 124.6 (d, *J* = 1.3 Hz), 124.5 (d, *J* = 1.5 Hz), 123.2 (d, *J* = 3.1 Hz), 123.0 (d, *J* = 3.3 Hz), 53.2, 53.1, 34.2, 22.3, 22.2.

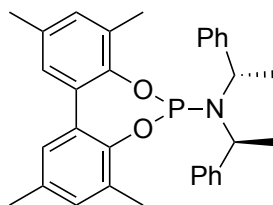
³¹P NMR (162 MHz, CDCl₃) δ 141.89.

[α]_D²⁵ = −83 (c = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₂₉H₂₈NO₂P [M]⁺: 454.1930, found: 454.1930.

IR (ATR) ν (cm^{−1}, CHCl₃): 682, 764, 864, 1233, 1486, 2359.

2,4,8,10-Tetramethyl-*N,N*-bis((*S*)-1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (85)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A. The crude product was purified by flash column chromatography (SiO₂, 82:17:1 hexane:CH₂Cl₂:Et₃N) to give the pure ligand as a foamy white solid (672 mg, 80% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.16 – 6.97 (m, 14H), 4.68 (d, *J* = 10.6 Hz, 2H), 2.46 (s, 3H), 2.33 (d, *J* = 5.5 Hz, 6H), 2.08 (s, 3H), 1.69 (d, *J* = 7.2 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 148.1, 148.0, 147.2, 147.2, 137.6, 133.4, 132.7, 131.4, 131.4, 131.2, 131.0, 130.4, 130.4, 129.4, 128.3, 128.2, 128.1 (2C), 127.8 (4C), 126.7 (2C), 52.6, 52.5, 21.0, 20.9, 17.5 (2C), 16.5 (2C).

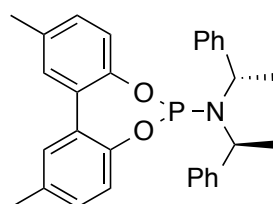
³¹P NMR (162 MHz, CDCl₃) δ 142.07.

[α]²⁵₅₈₉ = −233 (*c* = 1.0 in CHCl₃).

LRMS (ESI) *m/z*: 496.2 [M+H]⁺

IR (ATR) *v* (cm^{−1}, CHCl₃): 697, 856, 1124, 1217, 1478, 2971.

2,10-Dimethyl-*N,N*-bis((*S*)-1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine
(86)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A. The crude product was purified by flash column chromatography (SiO₂, 82:17:1 hexane:CH₂Cl₂:Et₃N) to give the pure product as a foamy white solid (731 mg, 87% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, *J* = 2.2 Hz, 2H), 7.19 – 7.07 (m, 14H), 4.59 (dq, *J* = 11.2, 7.1 Hz, 2H), 2.38 (s, 6H), 1.73 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 149.9, 149.8, 149.0 (2C), 143.2, 143.2, 134.1, 133.4, 131.0, 130.4, 130.3, 129.8, 129.6, 128.1, 128.1 (2C), 127.8 (4C), 126.7 (2C), 122.3, 121.8, 52.8, 52.6, 22.4, 22.3, 21.0, 21.0.

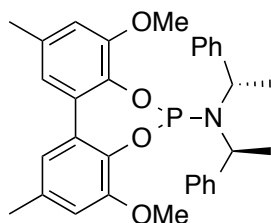
³¹P NMR (162 MHz, CDCl₃) δ 145.25.

[α]²⁵₅₈₉ = −231 (*c* = 1.0 in CHCl₃).

HRMS (ESI) m/z calcd. for $C_{30}H_{30}NO_2P$ $[M]^+$: 468.2087, found: 468.2090.

IR (ATR) ν (cm^{-1} , $CHCl_3$): 697, 849, 967, 1116, 1493, 2971, 3028.

4,8-Dimethoxy-2,10-dimethyl-*N,N*-bis((*S*)-1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (87)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A. The crude product was purified by flash column chromatography (SiO_2 , 72:27:1 hexane: CH_2Cl_2 : Et_3N) to give the pure product as a foamy white solid (311 mg, 81% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 4H), 7.14 – 7.02 (m, 6H), 6.88 – 6.83 (m, 2H), 6.75 (dd, J = 5.8, 1.9 Hz, 2H), 4.61 (dd, J = 10.9, 7.1 Hz, 2H), 3.91 (s, 3H), 3.77 (s, 3H), 2.37 (dd, J = 1.9, 0.9 Hz, 6H), 1.73 (d, J = 7.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 151.9, 151.4, 143.5, 133.9, 133.9, 133.1, 132.0, 132.0, 130.7, 130.7, 128.1, 128.1, 127.6 (4C), 126.4 (2C), 123.0, 121.9, 113.2, 112.3, 100.1, 56.5, 55.8, 53.1, 53.0, 22.2, 22.1, 21.6, 21.6.

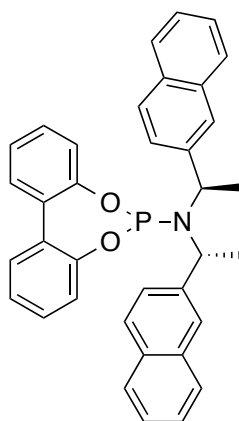
^{31}P NMR (162 MHz, $CDCl_3$) δ 145.38.

$[\alpha]^{25}_{589} = -217$ (c = 1.0 in $CHCl_3$).

HRMS (ESI) m/z calcd. for $C_{32}H_{35}NO_4P$ $[M+H]^+$: 528.2298, found: 528.2296.

IR (ATR) ν (cm^{-1} , $CHCl_3$): 756, 860, 1139, 1414, 1456, 2968.

***N,N*-Bis((*R*)-1-(naphthalen-2-yl)ethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (**88**)**



Freshly distilled PCl_3 (130 μL , 1.5 mmol, 1.0 eq.) was added dropwise over 5 mins to a solution of Et_3N (1.0 mL, 7.5 mmol, 5.0 eq.) in THF (2.5 mL) at 0 °C under an atmosphere of argon. Amine **83** (500 mg, 1.5 mmol, 1.0 eq.) was added to the reaction as a solution in THF (1.0 mL), before stirring at room temperature for 3.5 hrs. The reaction was cooled to 0 °C and 2,2'-biphenol (280 mg, 1.5 mmol, 1.0 eq.) was added as a solution in THF (0.5 mL), followed by stirring at room temperature overnight. The reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 $\times$ 20 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 80:19:1 hexane: CH_2Cl_2 : Et_3N) to give the pure product as a foamy white solid (620 mg, 77% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.69 (dd, $J = 7.7, 1.8$ Hz, 2H), 7.55 – 7.47 (m, 6H), 7.45 – 7.34 (m, 8H), 7.30 (s, 3H), 7.25 – 7.20 (m, 2H), 7.16 – 7.11 (m, 1H), 4.77 (dd, $J = 11.5, 6.9$ Hz, 2H), 1.88 (d, $J = 7.1$ Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 152.1, 152.0, 151.2 (2C), 140.5, 140.5, 133.1, 132.5, 130.2, 130.0, 129.3, 129.1, 128.0 (2C), 127.5 (2C), 127.4 (2C), 127.2, 127.2, 126.2, 126.2, 125.8 (2C), 125.7 (2C), 124.8, 124.8, 124.2, 122.7, 122.7, 122.2, 53.0, 52.9, 22.4, 22.3.

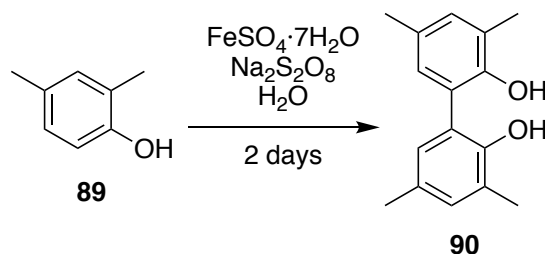
^{31}P NMR (162 MHz, CDCl_3) δ 145.99.

$[\alpha]_{\text{D}}^{25} = +412$ ($c = 1.0$ in CHCl_3).

HRMS (ESI) m/z calcd. for $C_{36}H_{30}NO_2PNa$ $[M+Na]^+$: 562.1906, found: 562.1903.

IR (ATR) ν (cm^{-1} , $CHCl_3$): 749, 887, 1120, 1247, 1434, 2362, 3057.

3,3',5,5'-Tetramethyl-[1,1'-biphenyl]-2,2'-diol (90)



According to literature procedures,⁷⁵ 2,4-dimethylphenol (6.0 mL, 50 mmol, 1.0 eq.) was added to a solution of $FeSO_4 \cdot 7H_2O$ (0.70 g, 2.5 mmol, 0.05 eq.) in water (75 mL). A solution of $Na_2S_2O_8$ (11.9 g, 50 mmol, 1.0 eq.) in water (50 mL) was then added slowly over 2 hrs. The reaction mixture was stirred at room temperature for 2 days before the suspension was extracted with EtOAc ($3 \times \sim 100$ mL); the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The red-brown powder was purified by Kugelrohr distillation (57 mbar, 225 °C) followed by recrystallisation in cyclohexane to give a white solid (892 mg, 15% yield)

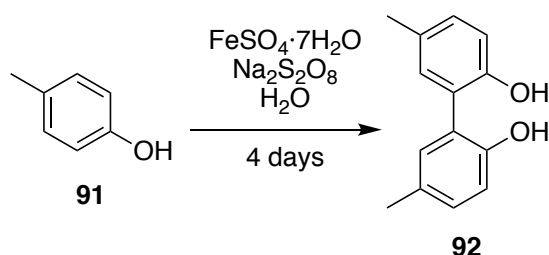
^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, $J = 2.1$ Hz, 2H), 6.86 (d, $J = 2.1$ Hz, 2H), 5.05 (s, 2H), 2.28 (d, $J = 1.5$ Hz, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3 (2C), 132.2 (2C), 130.2 (2C), 128.6 (2C), 125.3 (2C), 122.3 (2C), 20.6 (2C), 16.3 (2C).

HRMS (ESI) m/z calcd. for $C_{16}H_{18}O_2$ $[M]^+$: 265.1199, found: 265.1200.

IR (ATR) ν (cm^{-1} , $CHCl_3$): 793, 858, 1121, 1192, 1479, 2916, 3378.

5,5'-Dimethyl-[1,1'-biphenyl]-2,2'-diol (92)



p-Cresol (5.2 mL, 50 mmol, 1.0 eq.) was added to a solution of FeSO₄·7H₂O (0.70 g, 2.5 mmol, 0.05 eq.) in water (75 mL). A solution of Na₂S₂O₈ (11.9 g, 50 mmol, 1.0 eq.) in water (50 mL) was added slowly over 2 hrs. The reaction was stirred at room temperature for 4 days. The suspension was extracted with EtOAc (3 × 250 mL); the combined organic layers were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 30% Et₂O in hexane) to give a red oil that was purified further by flash column chromatography (SiO₂, 100% CH₂Cl₂) giving the pure product as a foamy orange solid (593 mg, 11% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.12 (dd, *J* = 8.3, 2.2 Hz, 2H), 7.06 (d, *J* = 2.2 Hz, 2H), 6.93 (d, *J* = 8.2 Hz, 2H), 5.21 (s, 2H), 2.33 (s, 6H).

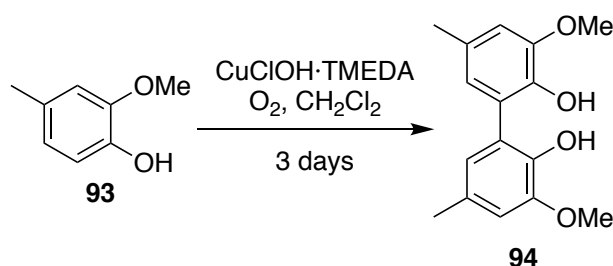
¹³C NMR (101 MHz, CDCl₃) δ 150.8 (2C), 131.6 (2C), 131.0 (2C), 130.6 (2C), 123.4 (2C), 116.6 (2C), 20.6 (2C).

LRMS (ESI) *m/z*: 213.1 [M-H]⁻

IR (ATR) ν (cm⁻¹, CHCl₃): 772, 814, 1115, 1222, 1271, 1497, 3258.

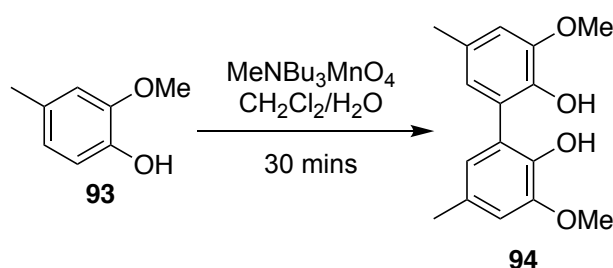
3,3'-Dimethoxy-5,5'-dimethyl-[1,1'-biphenyl]-2,2'-diol (94)

Procedure 1:



2-Methoxy-4-methylphenol (1.0 mL, 7.9 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 (15 mL) and the flask purged with O_2 . $\text{CuClOH}\cdot\text{TMEDA}$ (360 mg, 0.79 mmol, 0.1 eq.) was added and the reaction stirred under a pure O_2 atmosphere for 4 days. The reaction was quenched with 10% aq. HCl (10 mL) and the aqueous phase extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO_4 and concentrated *in vacuo* to give the crude product as a red/brown solid. Purification by flash column chromatography (SiO_2 , 10–50% EtOAc in hexane) gave the pure product as a foamy white solid (329 mg, 30% yield).

Procedure 2:



Synthesised according to general procedure 3: MTBAP coupling. Purification by flash column chromatography (SiO_2 , 100% CH_2Cl_2) gave the pure product as a yellow solid (2.46 g, 63% yield).

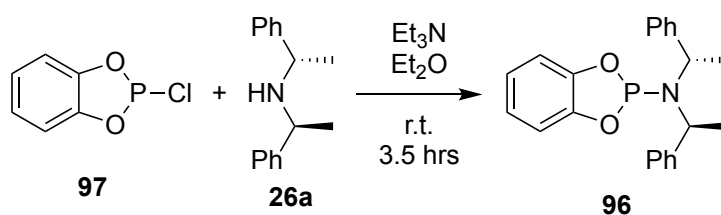
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.75 – 6.70 (m, 4H), 5.97 (s, 2H), 3.91 (s, 6H), 2.33 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 147.2 (2C), 140.4 (2C), 129.8 (2C), 124.5 (2C), 123.6 (2C), 111.4 (2C), 56.2 (2C), 21.3 (2C).

HRMS (ESI) *m/z* calcd. for C₁₆H₁₉O₄ [M+H]⁺: 275.1278, found: 275.1279.

IR (ATR) ν (cm⁻¹, CHCl₃): 836, 1050, 1142, 1256, 1462, 1599, 3392.

***N,N*-Bis((*S*)-1-phenylethyl)benzo[*d*][1,3,2]dioxaphosphol-2-amine (96)**



A solution of amine **26a** (643 mg, 2.9 mmol, 1.0 eq.) in Et₂O (2 mL) was added to a solution of 1,2-phenylene phosphorochloridite (340 μL, 2.9 mmol, 1.0 eq.) and Et₃N (400 μL, 2.9 mmol, 1.0 eq.) in Et₂O (2.0 mL) at 0 °C. The reaction was stirred at room temperature for 3.5 hrs before filtering through Celite and washing with Et₂O and EtOAc. The filtrate was concentrated *in vacuo* and the crude product purified by flash column chromatography (SiO₂, 82:17:1 hexane:CH₂Cl₂:Et₃N) to give the product as a foamy white solid (165 mg, 16% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.15 – 7.08 (m, 6H), 7.07 – 6.97 (m, 6H), 6.90 – 6.82 (m, 2H), 4.29 (dd, *J* = 10.0, 7.1 Hz, 2H), 1.67 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 142.2 (2C), 128.1 (4C), 127.8 (2C), 127.8 (2C), 127.0 (2C), 121.9, 121.9, 111.6 (2C), 100.1 (2C), 53.4, 53.3, 22.6, 22.5.

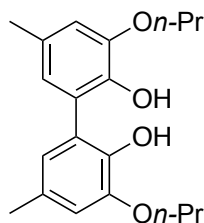
³¹P NMR (162 MHz, CDCl₃) δ 151.84.

[α]_D²⁵ = –375 (c = 1.0 in CHCl₃).

LRMS (ESI) *m/z*: 364.1 [M+H]⁺

IR (ATR) ν (cm⁻¹, CHCl₃): 742, 821, 1077, 1236, 1479, 2972, 3029.

5,5'-Dimethyl-3,3'-dipropoxy-[1,1'-biphenyl]-2,2'-diol (**98**)



Synthesised according to general procedure 3: MTBAP coupling. Purification by flash column chromatography (SiO₂, 0–40% EtOAc in hexane) gave the desired product as a yellow oil (555 mg, 50% yield).

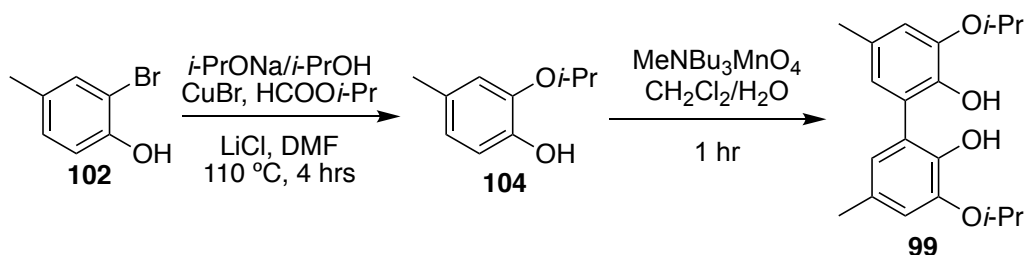
¹H NMR (400 MHz, CDCl₃) δ 6.75 – 6.67 (m, 4H), 5.90 (d, J = 1.0 Hz, 2H), 4.02 (td, J = 6.7, 1.0 Hz, 4H), 2.31 (s, 6H), 1.86 (h, J = 6.6 Hz, 4H), 1.05 (td, J = 7.4, 1.0 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 146.4 (2C), 140.9 (2C), 129.3 (2C), 124.3 (2C), 123.5 (2C), 112.4 (2C), 70.8 (2C), 22.8 (2C), 21.3 (2C), 10.7 (2C).

HRMS (ESI) m/z calcd. for C₂₀H₂₇O₄ [M+H]⁺: 331.1904, found: 331.1901.

IR (ATR) ν (cm⁻¹, CHCl₃): 835, 1139, 1250, 1491, 1597, 2965, 3529.

3,3'-Diisopropoxy-5,5'-dimethyl-[1,1'-biphenyl]-2,2'-diol (**99**)



Phenol **104** was synthesised using the same procedure as for **103**. Purification by flash column chromatography gave a 0.6:1 mixture of starting material (**102**):product (**104**) (38% yield) which was used in the next step without further purification.

Using general procedure 3: MTBAP coupling of phenol **104** and purification by flash column chromatography (SiO₂, 0–20% EtOAc in hexane) gave diol **99** as a yellow oil (263 mg, 42% yield)

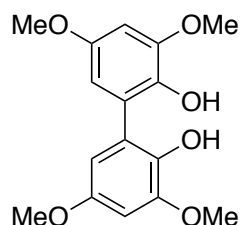
¹H NMR (400 MHz, CDCl₃) δ 6.75 – 6.69 (m, 4H), 5.94 (s, 2H), 4.59 (hept, *J* = 6.1 Hz, 2H), 2.31 (s, 6H), 1.39 (d, *J* = 6.1 Hz, 12H).

¹³C NMR (101 MHz, CDCl₃) δ 145.1 (2C), 141.7 (2C), 129.2 (2C), 124.5 (2C), 123.8 (2C), 114.2 (2C), 72.0 (2C), 22.4 (4C), 21.3 (2C).

HRMS (ESI) *m/z* calcd. for C₂₀H₂₆O₄Na [M+Na]⁺: 353.1723, found: 353.1724.

IR (ATR) ν (cm⁻¹, CHCl₃): 1016, 1134, 1250, 1489, 2976.

3,3',5,5'-Tetramethoxy-[1,1'-biphenyl]-2,2'-diol (100)



Synthesised according to general procedure 3: MTBAP coupling. Purification by flash column chromatography (SiO₂, 0–50% EtOAc in hexane) gave the desired product as an off-white solid (413 mg, 35% yield).

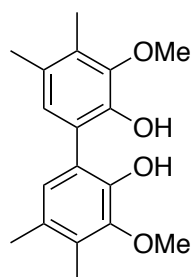
¹H NMR (400 MHz, CDCl₃) δ 6.54 (d, *J* = 2.8 Hz, 2H), 6.46 (d, *J* = 2.8 Hz, 2H), 5.84 (s, 2H), 3.91 (s, 6H), 3.79 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 153.5 (2C), 148.2 (2C), 136.9 (2C), 124.7 (2C), 106.1 (2C), 99.5 (2C), 56.3 (2C), 55.9 (2C).

HRMS (ESI) *m/z* calcd. for C₁₆H₁₈O₆Na [M+Na]⁺: 329.0996, found: 329.0993.

IR (ATR) ν (cm⁻¹, CHCl₃): 1153, 1201, 1463, 1608, 3418.

3,3'-Dimethoxy-4,4',5,5'-tetramethyl-[1,1'-biphenyl]-2,2'-diol (101)



Synthesised according to general procedure 3: MTBAP coupling. Purification by flash column chromatography (SiO₂, 0–20% EtOAc in hexane) gave the desired product (315 mg, 80% yield).

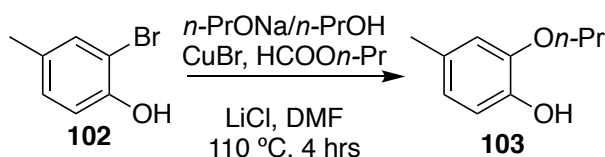
¹H NMR (400 MHz, CDCl₃) δ 6.89 (s, 2H), 6.14 (s, 2H), 3.84 (s, 6H), 2.24 (s, 12H).

¹³C NMR (101 MHz, CDCl₃) δ 146.2 (2C), 144.0 (2C), 129.6 (2C), 129.3 (2C), 127.3 (2C), 122.5 (2C), 60.9 (2C), 19.7 (2C), 12.6 (2C).

HRMS (ESI) *m/z* calcd. for C₁₈H₂₃O₄ [M+H]⁺: 303.1591, found: 303.1592.

IR (ATR) ν (cm⁻¹, CHCl₃): 1025, 1087, 1465, 1686, 1930.

4-Methyl-2-propoxyphenol (103)



Using the modified procedure by Pan and Ji *et al.*,⁸⁴ a sealed pressure tube was charged with a solution of *n*-PrONa in *n*-PrOH [freshly prepared from metallic Na (414 mg, 18 mmol, 2.0 eq.) and *n*-PrOH (18 mL)], LiCl (378 mg, 9.0 mmol, 1.0 eq.), 2-bromo-4-methylphenol (1.68 g, 9.0 mmol, 1.0 eq.), CuBr (25.7 mg, 1.8 mmol, 0.2 eq.), and HCOOn-Pr (880 μL, 9.0 mmol, 1.0 eq.). The mixture was stirred in the sealed tube for 20 mins at room temperature, and then it was heated at 110 °C for 5 hrs. The mixture was stirred open to the air for 30 mins at room temperature, then water (5.0 mL) and Et₂O (5.0 mL) were added and

stirring was continued for 10 mins. The solution was transferred to a separating funnel and the solution extracted with Et₂O (3 × 50 mL). The combined organic layers were dried with MgSO₄, and then concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂, 0–3% EtOAc in Hexane) to give the desired product as a white solid (1.2 g, 80% yield).

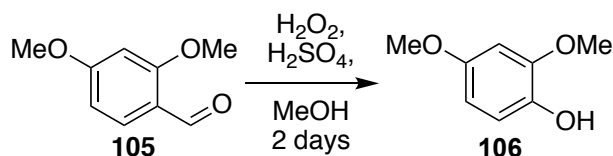
¹H NMR (400 MHz, CDCl₃) δ 6.81 (d, *J* = 7.8 Hz, 1H), 6.70 – 6.61 (m, 2H), 5.49 (s, 1H), 3.98 (t, *J* = 6.6 Hz, 2H), 2.28 (s, 3H), 1.84 (dtd, *J* = 13.9, 7.4, 6.5 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 145.8, 143.6, 129.7, 121.5, 114.1, 112.7, 70.5, 22.8, 21.2, 10.7.

HRMS (CI with ammonia as reagent gas) *m/z* calcd. for C₁₀H₁₈NO₂ [M+NH₄]⁺: 184.1332, found: 184.1332.

IR (ATR) ν (cm⁻¹, CHCl₃): 809, 1121, 1268, 1512, 2966, 3542.

2,4-Dimethoxyphenol (106)



Sulphuric acid (0.5 mL) was added dropwise to a solution of 2,4-dimethoxybenzaldehyde (1.5 g, 9.0 mmol) and H₂O₂ (30% in water, 1.5 mL) in methanol (15 mL). The mixture was stirred for 22 hrs at room temperature. The solution was concentrated *in vacuo* until only ~3 mL remained and the solution was partitioned between dichloromethane and water. The aqueous phase was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic phases were washed with water (3 × 30 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 100% CHCl₃) to give the desired product as an orange oil (1.20 g, 86% yield).

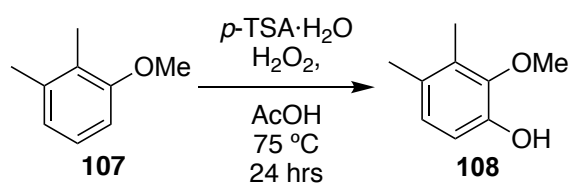
¹H NMR (400 MHz, CDCl₃) δ 6.83 (d, *J* = 8.6 Hz, 1H), 6.49 (d, *J* = 2.7 Hz, 1H), 6.39 (dd, *J* = 8.7, 2.8 Hz, 1H), 5.23 (s, 1H), 3.86 (s, 3H), 3.76 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 153.7, 147.2, 139.9, 114.2, 104.4, 99.6, 56.0, 55.9.

HRMS (EI) *m/z* calcd. for C₈H₁₀O₃ [M]⁺: 154.0630, found: 154.0623.

IR (ATR) *v* (cm⁻¹, CHCl₃): 793, 1032, 1153, 1205, 1510, 2941, 3431.

2-Methoxy-3,4-dimethylphenol (108)



2,3-Dimethylanisole (4.0 g, 29 mmol, 1.0 eq.) and glacial acetic acid (30 mL) were added to a round bottom flask fitted with a reflux condenser. *p*-TSA·H₂O (559 mg, 2.9 mmol, 0.1 eq.) and H₂O₂ (30% in water, 5.0 mL, 88 mmol, 3.0 eq.) were added and the reaction stirred at 75 °C for 24 hrs. The reaction was cooled to room temperature, diluted with EtOAc (100 mL). The organic phase was washed with sat. aq. NaHCO₃ (4 × 75 mL), then the combined aqueous phases were washed with EtOAc (100 mL). The organic layers were combined, washed with brine (75 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (SiO₂, 100% CH₂Cl₂) to give a brown oil (451 mg, 10% yield).

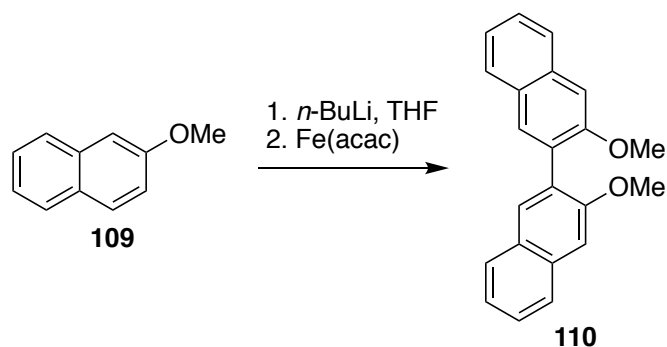
¹H NMR (400 MHz, CDCl₃) δ 6.81 (d, *J* = 8.2 Hz, 1H), 6.75 – 6.69 (m, 1H), 5.50 (s, 1H), 3.76 (s, 4H), 2.19 (d, *J* = 3.6 Hz, 7H).

¹³C NMR (101 MHz, CDCl₃) δ 146.8, 145.5, 136.4, 129.4, 125.7, 112.3, 61.0, 19.5, 12.3.

HRMS (CI with ammonia as reagent gas) *m/z* calcd. for C₉H₁₆NO₂ [M+NH₄]⁺: 170.1176, found: 170.1177.

IR (ATR) *v* (cm⁻¹, CHCl₃): 1082, 1282, 1467, 1763, 2920, 3382.

3,3'-Dimethoxy-2,2'-binaphthalene (110)



2-Methoxynaphthalene (5.0 g, 32 mmol, 1.0 eq.) was dissolved in THF (125 mL) and cooled to 0 °C, before adding *n*-BuLi (1.6 M in hexanes, 22 mL, 35 mmol, 1.1 eq.). The resulting orange solution was stirred at 0 °C for 2 hrs. Fe(acac)₃ (12.4 g, 35 mmol, 1.1 eq.) was added and the reaction allowed to stir at room temperature overnight. The reaction mixture was filtered over Celite and washed with hexane (100 mL) and CHCl₃ (100 mL). The filtrate was concentrated *in vacuo* to give a red solid, which was purified by flash column chromatography (SiO₂, 0–40% CHCl₃ in hexane) to give a foamy white solid (2.75 g, 55% yield).

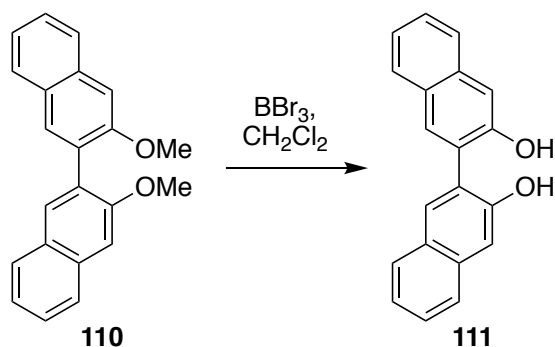
¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.76 (m, 6H), 7.48 (td, *J* = 8.1, 6.9, 1.2 Hz, 2H), 7.37 (td, *J* = 8.1, 6.9, 1.2 Hz, 2H), 7.25 (d, *J* = 4.5 Hz, 2H), 3.90 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 156.4 (2C), 134.5 (2C), 130.4 (2C), 130.0 (2C), 128.8 (2C), 127.8 (2C) 126.6 (2C), 126.4 (2C), 123.9 (2C), 105.5 (2C), 55.8 (2C).

HRMS (ESI) *m/z* calcd. for C₂₂H₁₉O₂ [M+H]⁺: 315.1380, found: 315.1379.

IR (ATR) ν (cm⁻¹, CHCl₃): 747, 862, 1037, 1169, 1215, 1465, 1630, 2954.

[2,2'-Binaphthalene]-3,3'-diol (111**)**



3,3'-Dimethoxy-2,2'-binaphthalene (**110**, 2.5 g, 7.7 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. BBr_3 (1 M in CH_2Cl_2 , 18 mL, 18 mmol, 2.2 eq.) was added and the ice/water bath removed. The reaction was stirred at room temperature for 1 hr before pouring into ice water (50 mL) and extracting with EtOAc (3×75 mL). The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 20% EtOAc in hexane) to give the pure product as a foamy white solid (1.69 g, 74% yield).

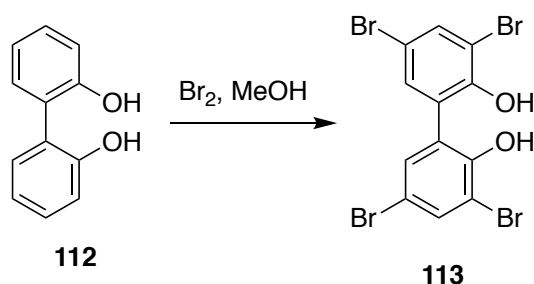
^1H NMR (400 MHz, CDCl_3) δ 7.88 (s, 2H), 7.85 – 7.80 (m, 2H), 7.80 – 7.75 (m, 2H), 7.50 (td, $J = 8.1, 6.8, 1.2$ Hz, 2H), 7.43 (s, 2H), 7.40 (td, $J = 8.1, 6.8, 1.2$ Hz, 2H), 5.72 (s, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 156.3 (2C), 134.4 (2C), 130.3 (2C), 129.9 (2C), 128.7 (2C), 127.7 (2C), 126.5 (2C), 126.3 (2C), 123.8 (2C), 105.4 (2C), 55.7 (2C).

HRMS (ESI) m/z calcd. for $\text{C}_{20}\text{H}_{13}\text{O}_2$ $[\text{M}-\text{H}]^-$: 285.0921, found: 285.0918.

IR (ATR) ν (cm^{-1} , CHCl_3): 745, 867, 1163, 1215, 1459, 1632, 3296 .

3,3',5,5'-Tetrabromo-[1,1'-biphenyl]-2,2'-diol (113)



2,2'-Biphenol (2.0 g, 11 mmol, 1.0 eq.) was dissolved in MeOH (~150 mL). Bromine (2.8 mL, 54 mmol, 5.0 eq.) was added, the colourless solution turned orange and the formation of a precipitate was observed. After stirring at room temperature for 2 hrs the reaction mixture was filtered through a sintered funnel and washed with small quantities of MeOH (10 mL), aqueous saturated NaHCO₃ solution (10 mL), aqueous saturated Na₂SO₄ solution (10 mL) and water (10 mL). The resulting white solid was dissolved in acetone (40 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude material was recrystallised from acetone to give the desired product as a white solid (2.0 g, 37% yield).

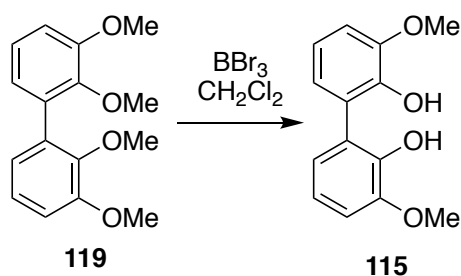
¹H NMR (400 MHz, DMSO-*d*₆) δ 7.62 (d, *J* = 2.5, 2H), 7.29 (d, *J* = 2.5, 2H) (*OH* protons not observed).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 154.8 (2C), 133.2 (2C), 132.1 (2C), 129.2 (2C), 113.8 (2C), 107.7 (2C).

HRMS (ESI) *m/z* calcd. for C₁₂H₅O₂Br₄ [M-H]⁻: 496.7029, found: 496.7030.

IR (ATR) ν (cm⁻¹, CHCl₃): 687, 858, 1222, 1456, 2359.

3,3'-Dimethoxy-[1,1'-biphenyl]-2,2'-diol (**115**)



BBr₃ (0.99 mL, 0.99 mmol, 0.66 eq.) was added dropwise to a solution of **119** (400 mg, 1.5 mmol, 1.0 eq.) in CH₂Cl₂ (4.0 mL), at -78 °C, over ~10 mins. After 20 mins the cold bath was removed and the reaction stirred at room temperature for 24 hrs. The crude reaction was poured into ice water (20 mL), stirred for 30 mins, saturated with NaCl and extracted with CH₂Cl₂ (3 × 50 mL). The organic phases were combined, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 100% CH₂Cl₂) to give the desired product as a white solid (301 mg, 81% yield).

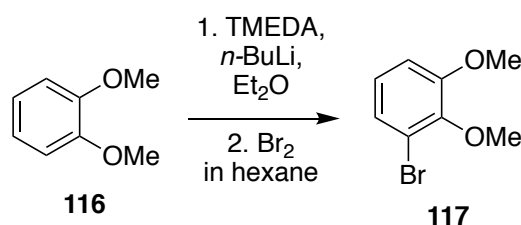
¹H NMR (400 MHz, CDCl₃) δ 6.98 – 6.89 (m, 6H), 6.08 (s, 2H), 3.94 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 147.4 (2C), 142.9 (2C), 124.6 (2C), 123.6 (2C), 120.2 (2C), 110.4 (2C), 56.2 (2C).

HRMS (ESI) *m/z* calcd. for C₁₄H₁₅O₄ [M+H]⁺: 247.0964, found: 247.0968.

IR (ATR) ν (cm⁻¹, CHCl₃): 767, 1027, 1221, 1463, 2360, 3503.

1-Bromo-2,3-dimethoxybenzene (**117**)



n-BuLi (1.6 M in hexanes, 11 mL, 18 mmol, 1.0 eq.) was added to a solution of TMEDA (2.7 mL, 18 mmol, 1.0 eq.) in Et₂O (50 mL) and the resulting mixture stirred for 10 mins at

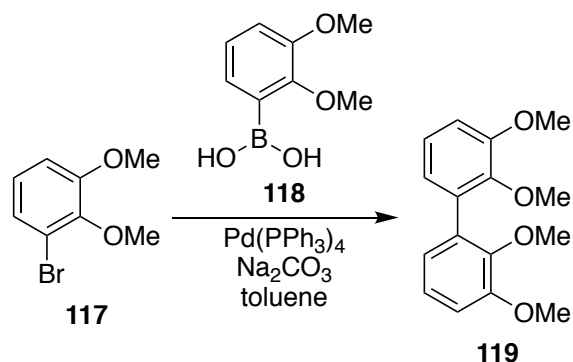
room temperature. 1,2-Dimethoxybenzene (2.5 g, 18 mmol, 1.0 eq.) was added, the solution turned yellow and after 5 mins a precipitate formed. After stirring at room temperature for 2 hrs, the reaction was cooled to $-78\text{ }^{\circ}\text{C}$. Bromine (0.93 mL, 18 mmol, 1.0 eq.) was added to the reaction as a solution in hexane (5.0 mL). After 30 mins, the dry ice/acetone bath was removed and the reaction was allowed to warm to room temperature and stirred for 21 hrs. The reaction was quenched with a saturated solution of Na_2SO_4 (~10 mL) and the aqueous phase extracted with EtOAc ($3 \times 50\text{ mL}$). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 0–10% EtOAc in hexane) to give the desired product as a yellow oil (2.62 g, 67% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.13 (dd, $J = 8.0, 1.5\text{ Hz}$, 1H), 6.93 (t, $J = 8.1\text{ Hz}$, 1H), 6.86 (dd, $J = 8.3, 1.5\text{ Hz}$, 1H), 3.86 (d, $J = 3.3\text{ Hz}$, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 154.1, 146.7, 125.1, 124.9, 117.9, 111.8, 60.7, 56.2.

HRMS (CI with ammonia as reagent gas) m/z calcd. for $\text{C}_8\text{H}_{13}\text{BrNO}_2$ $[\text{M}+\text{NH}_4]^+$: 234.0124, found: 234.0126.

2,2',3,3'-Tetramethoxy-1,1'-biphenyl (**119**)



According to the procedure by Albrecht,⁸³ 3-bromoveratrole (**117**, 800 mg, 3.7 mmol, 1.0 eq.) and $\text{Pd}(\text{PPh}_3)_4$ (258 mg, 0.22 mmol, 0.06 eq.) were dissolved in toluene (20 mL) and successively 2 M aq. Na_2CO_3 solution (4.8 mL) and 2,3-dimethoxyphenylboronic acid (**118**,

691 mg, 3.8 mmol, 1.02 eq.) in EtOH (5.0 mL) were added. After refluxing at 90 °C overnight the mixture was cooled to room temperature, washed with saturated aq. Na₂CO₃ (10 mL) solution, and the aqueous phase extracted with Et₂O (3 × 30 mL). The combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂, 100% CH₂Cl₂) to give the desired product as a white solid (409 mg, 40% yield).

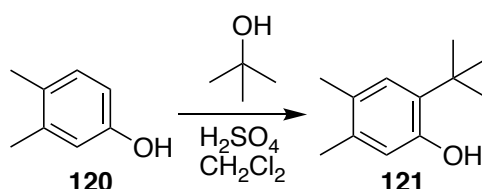
¹H NMR (400 MHz, CDCl₃) δ 7.08 (dd, *J* = 8.2, 7.6 Hz, 2H), 6.94 (dd, *J* = 8.2, 1.6 Hz, 2H), 6.87 (dd, *J* = 7.6, 1.6 Hz, 2H), 3.91 (s, 6H), 3.65 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 152.9 (2C), 147.0 (2C), 133.0 (2C), 123.5 (2C), 123.4 (2C), 111.7 (2C), 60.8 (2C), 56.0 (2C).

HRMS (CI with ammonia as reagent gas) *m/z* calcd. for C₁₆H₁₉O₄ [M+H]⁺: 275.1278, found: 274.1205.

IR (ATR) ν (cm⁻¹, CHCl₃): 751, 1031, 1261, 1465, 2937.

2-(*tert*-Butyl)-4,5-dimethylphenol (**121**)



t-Butyl alcohol (9.55 g, 129 mmol, 1.05 eq.) was added to a solution of 3,4-dimethylphenol (15 g, 123 mmol, 1.0 eq.) in dry CH₂Cl₂ (100 mL). Concentrated H₂SO₄ (7.2 mL) was added dropwise at room temperature. The reaction was stirred at room temperature for 1 hr before adding further *t*-butyl alcohol (5.9 mL). After stirring was continued for 1 hr, the reaction was quenched with 2 M aqueous NaOH (40 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 300 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column

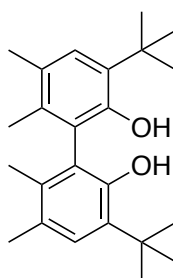
chromatography (SiO₂, 0–10% EtOAc in hexane) to give the desired product as a yellow liquid (21.76 g, 99% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.02 (s, 1H), 6.48 (s, 1H), 4.53 (s, 1H), 2.18 (d, *J* = 6.6 Hz, 6H), 1.40 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 152.0, 135.2, 133.3, 128.5, 128.2, 118.2, 34.2, 29.9 (3C), 19.2, 19.1.

HRMS (CI with ammonia as reagent gas) *m/z* calcd. for C₁₂H₁₈O [M+NH₄]⁺: 196.1696, found: 196.1695.

3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diol (122)



Synthesised according to general procedure 3: MTBAP coupling. Purification by flash column chromatography (SiO₂, 0–5% ETOAc in hexane) gave the desired product (12.2 g, 62% yield)

¹H NMR (400 MHz, CDCl₃) δ 7.13 (s, 2H), 4.80 (s, 2H), 2.26 (s, 6H), 1.83 (s, 6H), 1.40 (s, 18H).

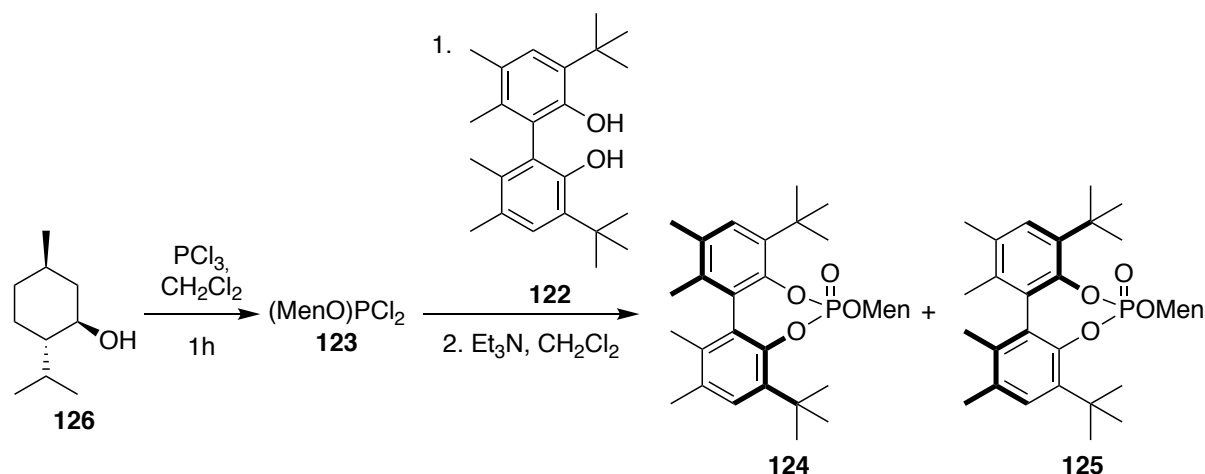
¹³C NMR (101 MHz, CDCl₃) δ 150.5 (2C), 134.3 (2C), 133.5 (2C), 128.9 (2C), 128.2 (2C), 121.1 (2C), 34.6 (2C), 29.7 (6C), 20.2 (2C), 16.1 (2C).

HRMS (EI) *m/z* calcd. for C₂₄H₃₄O₂Na [M+Na]⁺: 377.2451, found: 377.2451.

Resolution of 124 and 125:

(11a*S*)-4,8-di-*tert*-butyl-6-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-1,2,10,11-tetramethyldibenzo[*d,f*][1,3,2]dioxaphosphepine 6-oxide (**124**)

(11a*R*)-4,8-di-*tert*-butyl-6-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-1,2,10,11-tetramethyldibenzo[*d,f*][1,3,2]dioxaphosphepine 6-oxide (**125**)



A solution of (–)-menthol (6.17 g, 40 mmol, 1.0 eq.) in CH_2Cl_2 (14 mL) was added to a 0 °C solution of PCl_3 (5.2 mL, 59 mmol, 1.5 eq.) in CH_2Cl_2 (14 mL) over a period of 5 mins. The ice bath was removed, and after 1 hr at room temperature, the volatile components were removed *in vacuo*. The oil was redissolved in CH_2Cl_2 (35 mL), and a solution of Et_3N (17 mL, 178 mmol, 3.0 eq.) and **122** (14 g, 40 mmol, 1.0 eq.) in CH_2Cl_2 (56 mL) was added over 15 mins. After 3 hrs the reaction mixture was filtered and H_2O_2 (35% in water, 25 mL) was added slowly with stirring (caution! extremely vigorous reaction). The biphasic mixture was stirred rapidly for 1.5 hrs after which the layers were allowed to separate. The organic phase was washed with water (50 mL), brine (60 mL), dried over MgSO_4 concentrated *in vacuo* to give a yellow solid, which was dried under vacuum to afford a mixture of **124** and **125**.

The diastereomeric mixture of phosphates was dissolved in refluxing acetic acid (~80 mL). After 16 hrs white crystals (inorganic impurities) were collected by filtration. The filtrate was concentrated *in vacuo*. The residue was redissolved in refluxing acetic acid (30 mL). After standing for 16 hrs at room temperature a white solid crashed out, was collected by filtration then washed with cold acetic acid (2×50 mL). The solid was then dried *in vacuo* to give **124** (5.64 g, 96% de). This material was recrystallised from refluxing acetic acid to afford **124** (4.38 g, >99% de, corresponding to 19% of the *S* diastereomer).

The liquor from the first crystallisation was concentrated *in vacuo* to give a solid enriched with **125**. This solid was recrystallised from refluxing MeOH (30 mL). After leaving the solution in the freezer overnight, white crystals of **125** were obtained (4.1 g, >99% de, 17% *R* diastereomer).

***S*-Diastereoisomer (124)**

¹H NMR (400 MHz, CDCl₃) δ 7.23 – 7.16 (m, 2H), 4.31 (tdd, $J = 10.8, 8.6, 4.5$ Hz, 1H), 2.29 – 2.19 (m, 6H), 2.22 – 2.14 (m, 1H), 1.83 (s, 3H), 1.79 (s, 3H), 1.77 – 1.68 (m, 1H), 1.68 – 1.55 (m, 2H), 1.50 (s, 9H), 1.44 (s, 9H), 1.38 – 1.21 (m, 2H), 1.04 – 0.89 (m, 2H), 0.87 – 0.76 (m, 10H).

¹³C NMR (101 MHz, CDCl₃) δ 137.6 (2C), 135.3, 135.3, 134.9, 133.4, 133.0, 129.0, 129.0, 128.9, 128.8, 82.2, 82.1, 48.3 (d, $J = 6.1$ Hz), 41.9, 35.1, 34.9, 34.0, 31.7, 31.6 (3C), 31.5 (3C), 25.4, 23.0, 22.0, 21.0, 20.5, 16.8, 16.8, 15.8.

³¹P NMR (162 MHz, CDCl₃) δ –5.64.

$[\alpha]^{25}_{589} = +130$ (c = 1.0 in CHCl₃).

HRMS (GCMS with ammonia as reagent gas) m/z calcd. for C₃₄H₅₂O₄P [M+H]⁺: 555.3598, found: 555.3609.

IR (ATR) ν (cm⁻¹, CHCl₃): 754, 909, 1009, 1224, 1293, 2956.

***R*-Diastereoisomer (125)**

¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, *J* = 8.1 Hz, 2H), 4.25 (tdd, *J* = 10.6, 6.0, 4.5 Hz, 1H), 2.49 – 2.39 (m, 1H), 2.29 – 2.19 (m, 6H), 1.82 (s, 3H), 1.78 (s, 3H), 1.64 – 1.52 (m, 2H), 1.50 (s, 10H), 1.43 (s, 9H), 1.29 – 1.11 (m, 3H), 0.93 (s, 2H), 0.92 – 0.76 (m, 3H), 0.61 (d, *J* = 7.0 Hz, 3H), 0.39 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 137.9, 137.6, 135.2, 134.9, 133.3, 133.0, 129.1, 128.9, 128.8 (2C), 81.1, 81.0, 48.6 (d, *J* = 7.3 Hz), 42.9, 35.1, 35.0, 34.1, 31.8 (3C), 31.7, 31.6 (3C), 24.6, 22.8, 22.0, 21.0, 20.5, 16.7, 16.7, 15.6.

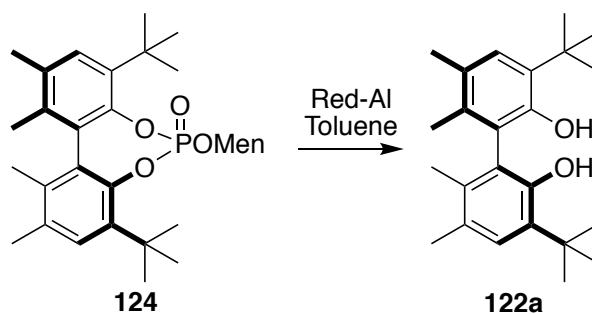
³¹P NMR (162 MHz, CDCl₃) δ –6.12.

[α]_D²⁵ = –191 (c = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₃₄H₅₁O₄PNa [M+Na]⁺: 577.3417, found: 577.3413.

IR (ATR) ν (cm^{–1}, CHCl₃): 754, 911, 1013, 1224, 1299, 1456, 2956.

(*S*)-3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diol (122a)



124 (4.2 g, 7.2 mmol, 1.0 eq.) was dissolved in toluene (50 mL) and cooled to 0 °C. Red-Al (60% in toluene, 5.8 mL, 5.8 mmol, 0.8 eq.) added dropwise over 30 mins. The reaction mixture was stirred at room temperature for 14 hrs and then carefully quenched with water (10 mL) and bleach (50% aq. solution, 10 mL). The slurry was filtered through Celite, and the pad washed with toluene (75 mL). The phases were separated and the organic layer washed with bleach and brine (30 mL each), dried over MgSO₄ and concentrated *in vacuo* to

give a white solid. The crude mixture was purified by column chromatography (SiO₂, 100% hexane) to give the desired product as a white solid (1.65 g, 65% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.13 (s, 2H), 4.80 (d, *J* = 0.6 Hz, 2H), 2.26 (s, 6H), 1.82 (s, 6H), 1.40 (s, 18H).

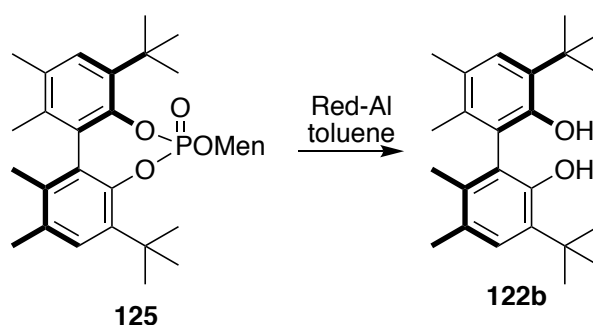
¹³C NMR (101 MHz, CDCl₃) δ 150.5 (2C), 134.3 (2C), 133.5 (2C), 128.9 (2C), 128.2 (2C), 121.1 (2C), 34.6 (2C), 29.7 (6C), 20.2 (2C), 16.1 (2C).

[α]²⁵₅₈₉ = − 68 (c = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₂₄H₃₄O₂Na [M+Na]⁺: 377.2451, found: 377.2449.

IR (ATR) ν (cm^{−1}, CHCl₃): 759, 1043, 1182, 1440, 2957, 3514.

(*R*)-3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diol (122b)



Prepared according to the same procedure as for **122a** to give the desired product as a white solid (1.64 g, 68% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.13 (s, 2H), 4.80 (d, *J* = 0.6 Hz, 2H), 2.26 (s, 6H), 1.40 (s, 18H).

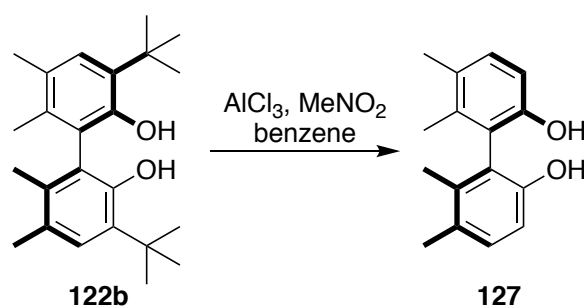
¹³C NMR (101 MHz, CDCl₃) δ 150.5 (2C), 134.3 (2C), 133.5 (2C), 128.9 (2C), 128.2 (2C), 121.1 (2C), 34.6 (2C), 29.7 (6C), 20.2 (2C), 16.1 (2C).

[α]²⁵₅₈₉ = +74 (c = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₂₄H₃₄O₂Na [M+Na]⁺: 377.2451, found: 377.2450.

IR (ATR) ν (cm^{−1}, CHCl₃): 884, 1043, 1182, 1440, 2957, 3514.

(R)-5,5',6,6'-Tetramethyl-[1,1'-biphenyl]-2,2'-diol (127)



In a flame-dried flask, diol **122b** (1.5 g, 4.2 mmol, 1.0 eq.) was dissolved in benzene (22 mL) and cooled to 0 °C. A solution of AlCl₃ (902 mg, 6.8 mmol, 1.6 eq.) in a mixture of MeNO₂ (8.0 mL) and benzene (4.0 mL) was added dropwise over 10 mins. After stirring at 0 °C for 1 hr the reaction was quenched with water and extracted with Et₂O (3 × 50 mL). The combined organic phases were washed with brine (30 mL), dried over MgSO₄ and concentrated *in vacuo*. The pure product was obtained as a white solid after recrystallisation from hexane/CH₂Cl₂ (783 mg, 77% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 4.50 (s, 2H), 2.26 (s, 6H), 1.90 (s, 6H).

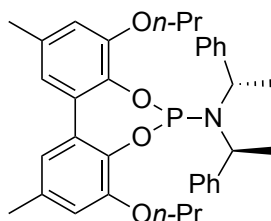
¹³C NMR (101 MHz, CDCl₃) δ 151.9 (2C), 137.1 (2C), 131.5 (2C), 129.4 (2C), 120.3 (2C), 112.8 (2C), 20.0 (2C), 16.5 (2C).

[α]_D²⁵ = +52 (c = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₁₆H₁₉O₂ [M+H]⁺: 243.1380, found: 243.1380.

IR (ATR) ν (cm⁻¹, CHCl₃): 820, 1152, 1181, 1471, 1588, 3466.

2,10-Dimethyl-*N,N*-bis((*S*)-1-phenylethyl)-4,8-dipropoxydibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (128)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (265 mg, 37% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.22 – 7.14 (m, 4H), 7.13 – 7.00 (m, 6H), 6.82 (dd, $J = 14.3$, 1.7 Hz, 2H), 6.74 (dd, $J = 14.4$, 1.8 Hz, 2H), 4.65 (dq, $J = 14.1$, 7.2 Hz, 2H), 4.05 – 3.83 (m, 4H), 2.35 (d, $J = 3.2$ Hz, 6H), 2.01 – 1.85 (m, 2H), 1.82 – 1.70 (m, 8H), 1.13 (t, $J = 7.4$ Hz, 3H), 0.99 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 150.9 (2C), 143.7 (2C), 133.9, 132.9, 132.3, 132.2, 131.1, 131.1, 128.1 (2C), 128.0 (2C), 127.6 (4C), 126.3 (2C), 122.0, 121.7, 114.1, 114.0, 70.7, 70.6, 52.4, 52.3, 23.1, 23.0, 21.6 (2C), 21.5 (2C), 10.9, 10.8.

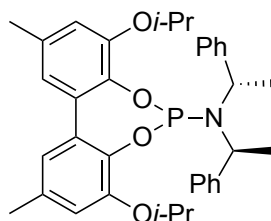
^{31}P NMR (162 MHz, CDCl_3) δ 143.96.

$[\alpha]_{589}^{25} = -227$ ($c = 1.0$ in CHCl_3).

HRMS (ESI) m/z calcd. for $\text{C}_{36}\text{H}_{43}\text{NO}_4\text{P}$ $[\text{M}+\text{H}]^+$: 584.2924, found: 584.2914.

IR (ATR) ν (cm^{-1} , CHCl_3): 697, 859, 1138, 1452, 1590, 2965.

4,8-diisopropoxy-2,10-dimethyl-*N,N*-bis((*S*)-1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (129)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (188 mg, 49% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.24 – 7.15 (m, 4H), 7.14 – 7.04 (m, 6H), 6.87 (dd, J = 10.6, 1.8 Hz, 2H), 6.81 (dd, J = 7.3, 1.8 Hz, 2H), 4.72 – 4.55 (m, 3H), 4.47 (p, J = 6.1 Hz, 1H), 2.36 (d, J = 4.0 Hz, 6H), 1.78 (d, J = 7.2 Hz, 6H), 1.42 (t, J = 5.7 Hz, 6H), 1.26 (t, J = 6.2 Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 150.1 (d, J = 2.5 Hz), 149.5, 143.7, 140.9, 140.2, 133.8, 132.8, 132.7 (d, J = 3.7 Hz), 131.4 (d, J = 3.0 Hz), 129.2, 128.2 (2C), 128.2 (2C), 127.6 (4C), 126.4 (2C), 122.9 (2C), 118.4, 118.1, 72.5, 72.1, 52.5, 52.4, 22.6, 22.5, 22.5, 22.4, 21.5 (2C), 21.4 (2C).

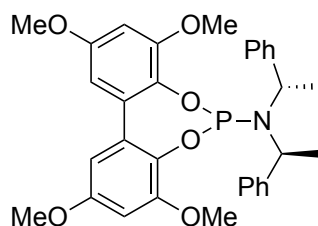
^{31}P NMR (162 MHz, CDCl_3) δ 143.87.

$[\alpha]^{25}_{589} = -238$ (c = 1.0 in CHCl_3).

HRMS (ESI) m/z calcd. for $\text{C}_{36}\text{H}_{43}\text{NO}_4\text{P}$ $[\text{M}+\text{H}]^+$: 584.2924, found: 584.2924.

IR (ATR) ν (cm^{-1} , CHCl_3): 697, 860, 1133, 1382, 1451, 2980, 3658.

2,4,8,10-Tetramethoxy-*N,N*-bis((*S*)-1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (130)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (143 mg, 22% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.24 – 7.17 (m, 4H), 7.17 – 7.02 (m, 6H), 6.56 (s, 2H), 6.54 (d, *J* = 1.6 Hz, 2H), 4.61 (dq, *J* = 10.8, 7.1 Hz, 2H), 3.91 (s, 3H), 3.83 (d, *J* = 3.5 Hz, 6H), 3.77 (s, 3H), 1.73 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 156.4, 155.7, 153.0 (d, *J* = 2.0 Hz), 152.5, 143.5 (2C), 135.6 (d, *J* = 8.4 Hz), 134.8, 132.4, 131.2 (d, *J* = 2.8 Hz), 128.1 (2C), 128.1 (2C), 127.7 (4C), 126.4 (2C), 104.6, 104.4, 100.4, 99.9, 56.5, 55.9, 55.8 (2C), 53.1, 53.0, 22.2, 22.0.

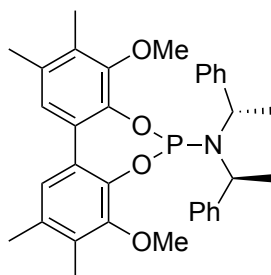
³¹P NMR (162 MHz, CDCl₃) δ 145.60.

[α]²⁵₅₈₉ = −191 (*c* = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₃₂H₃₅NO₆P [M+H]⁺: 560.2197, found: 560.2194.

IR (ATR) ν (cm^{−1}, CHCl₃): 754, 859, 1053, 1200, 1419, 1599, 2970.

4,8-Dimethoxy-2,3,9,10-tetramethyl-*N,N*-bis((*S*)-1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (131)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (204 mg, 28% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.21 – 7.15 (m, 4H), 7.14 – 7.05 (m, 6H), 6.98 (d, $J = 6.2$ Hz, 2H), 4.63 (dq, $J = 11.6, 7.1$ Hz, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 2.29 (d, $J = 3.0$ Hz, 6H), 2.26 (s, 3H), 2.22 (s, 3H), 1.77 (d, $J = 7.1$ Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ (101 MHz, CDCl_3) δ 150.5 (d, $J = 2.5$ Hz, 2C), 150.0, 143.6, 143.1, 133.4, 132.5, 130.4, 129.8, 129.2, 128.5 (d, $J = 2.2$ Hz), 128.4, 128.1 (2C), 128.1 (2C), 127.7 (4C), 126.5 (2C), 125.3, 125.3, 61.1 (d, $J = 4.5$ Hz), 60.4, 52.7, 52.5, 21.6, 21.5, 20.1, 20.0, 12.6, 12.6.

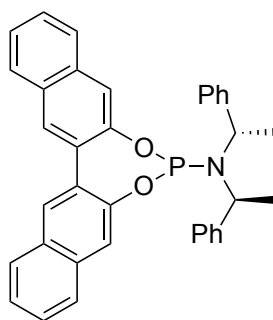
^{31}P NMR (162 MHz, CDCl_3) δ 145.40.

$[\alpha]^{25}_{589} = -227$ ($c = 1.0$ in CHCl_3).

HRMS (ESI) m/z calcd. for $\text{C}_{34}\text{H}_{39}\text{NO}_4\text{P}$ $[\text{M}+\text{H}]^+$: 556.2611, found: 556.2612.

IR (ATR) ν (cm^{-1} , CHCl_3): 697, 766, 868, 1016, 1097, 1398, 1449, 2980.

***N,N*-Bis((*S*)-1-phenylethyl)dinaphtho[2,3-*d*:2',3'-*f*][1,3,2]dioxaphosphepin-7-amine (132)**



Freshly distilled PCl_3 (97 μL , 1.1 mmol, 1.0 eq.) was added dropwise to a solution of Et_3N (1.2 mL, 8.8 mmol, 8.0 eq.) and CH_2Cl_2 (5.0 mL) at 0 $^\circ\text{C}$ under an atmosphere of argon. Amine **26a** (250 mg, 1.1 mmol, 1.0 eq.) was added to the reaction, before stirring at room temperature for 2 hrs. The reaction was cooled to 0 $^\circ\text{C}$ and diol **111** (315 mg, 1.1 mmol, 1.0 eq.) was added, followed by stirring at room temperature overnight. The reaction mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography (Alumina, 100% toluene) to give the pure product as a white foam (433 mg, 80% yield)

^1H NMR (400 MHz, CDCl_3) δ 8.06 (s, 1H), 7.93 – 7.88 (m, 2H), 7.88 – 7.82 (m, 1H), 7.80 – 7.72 (m, 2H), 7.56 (s, 1H), 7.53 – 7.40 (m, 4H), 7.24 – 7.20 (m, 2H), 7.20 – 7.08 (m, 12H), 4.61 (dq, $J = 14.2, 7.0$ Hz, 2H), 2.34 (s, 3H), 1.75 (d, $J = 7.1$ Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 150.0 (d, $J = 7.7$ Hz), 149.3 (d, $J = 2.1$ Hz), 143.1 (d, $J = 1.8$ Hz), 138.0, 134.4 – 134.2 (m), 132.3 (d, $J = 3.3$ Hz), 131.5 (d, $J = 2.2$ Hz), 131.3, 130.9, 129.7 (d, $J = 6.5$ Hz), 129.2 (2C), 128.4 (2C), 128.1 (2C), 128.1 (2C), 127.9 (4C), 127.0, 126.9, 126.8 (2C), 126.7, 126.7, 125.4, 125.3, 119.0 (d, $J = 2.4$ Hz), 118.3, 52.8, 52.7, 22.4 (d, $J = 8.9$ Hz), 21.6.

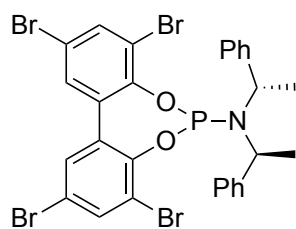
^{31}P NMR (162 MHz, CDCl_3) δ 141.35.

$[\alpha]^{25}_{589} = -315$ ($c = 1.0$ in CHCl_3).

HRMS (ESI) m/z calcd. for $\text{C}_{36}\text{H}_{31}\text{NO}_2\text{P}$ $[\text{M}+\text{H}]^+$: 540.2087, found: 540.2085.

IR (ATR) ν (cm^{-1} , CHCl_3): 696, 749, 1050, 1496, 3057.

2,4,8,10-tetrabromo-*N,N*-bis((*S*)-1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (133)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (303 mg, 40% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.8 (d, *J* = 2.4 Hz, 1H), 7.8 (d, *J* = 2.3 Hz, 1H), 7.5 (d, *J* = 2.3 Hz, 1H), 7.5 (d, *J* = 2.3 Hz, 1H), 7.2 – 7.1 (m, 10H), 4.7 (d, *J* = 9.5 Hz, 2H), 1.8 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 148.7, 147.5 (d, *J* = 1.3 Hz), 136.0 (2C), 135.7 (2C), 132.7 (d, *J* = 3.9 Hz), 131.9 (2C), 131.1 (d, *J* = 2.3 Hz), 129.2, 128.4, 128.0 (6C), 127.0 (2C), 118.6 (d, *J* = 2.3 Hz), 117.7, 117.5, 116.4 – 116.2 (m), 53.2, 53.1, 21.6, 21.4.

³¹P NMR (162 MHz, CDCl₃) δ 147.17.

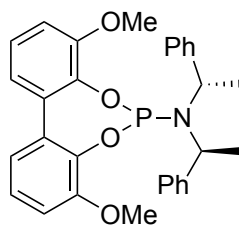
[α]_D²⁵ = −249 (*c* = 1.0 in CHCl₃).

HRMS (GCMS with ammonia as reagent gas) *m/z* calcd. for C₂₈H₂₂NO₂PBr₄ [M+H]⁺: 751.8194, found: 751.8219.

IR (ATR) ν (cm^{−1}, CHCl₃): 697, 744, 1056, 1390, 1448, 3062.

4,8-Dimethoxy-*N,N*-bis((*S*)-1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine

(134)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (79 mg, 15% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.24 – 7.21 (m, 4H), 7.15 – 7.03 (m, 10H), 6.95 (ddd, *J* = 9.6, 7.8, 1.8 Hz, 2H), 4.62 (dd, *J* = 11.0, 7.1 Hz, 2H), 3.94 (s, 3H), 3.80 (s, 3H), 1.74 (d, *J* = 7.2 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 152.4 (2C), 151.8 (2C), 143.4 (d, *J* = 1.4 Hz, 2C), 132.4 (d, *J* = 3.4 Hz, 2C), 128.1 (2C), 128.1 (2C), 127.7 (4C), 126.4 (2C), 124.4, 123.6, 121.9, 121.7, 112.2, 111.4, 56.5, 55.8, 53.1, 53.0, 22.1, 22.0.

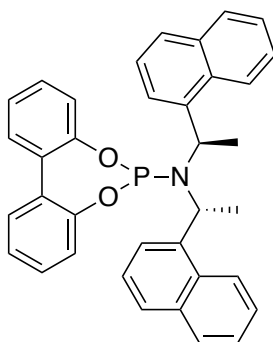
³¹P NMR (162 MHz, CDCl₃) δ 146.29.

[α]_D²⁵ = −225 (*c* = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₃₀H₃₁NO₄P [M+H]⁺: 500.1985, found: 500.1987.

IR (ATR) ν (cm^{−1}, CHCl₃): 698, 760, 875, 1146, 1265, 1455, 2969.

***N,N*-Bis((*R*)-1-(naphthalen-1-yl)ethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (135)**



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (180 mg, 43% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, *J* = 7.9, 2H), 7.58 (dd, *J* = 8.8, 6.9, 4H), 7.50 (d, *J* = 7.2, 2H), 7.45 – 7.36 (m, 2H), 7.34 – 7.21 (m, 11H), 6.82 (t, *J* = 7.7, 2H), 5.54 (t, *J* = 7.1, 2H), 1.80 (d, *J* = 7.1, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 152.0, 151.9, 151.6, 151.6, 138.4 (d, *J* = 2.8 Hz, 2C), 133.1, 131.4 – 131.3 (m), 130.9, 130.4, 130.3, 130.2 – 130.2 (m), 129.4, 129.3, 129.2, 128.5 (2C), 128.4, 127.1 (2C), 125.4 (2C), 125.0 (2C), 124.9, 124.6 (2C), 124.6, 124.2, 123.4, 122.6, 122.5, 50.8, 50.7, 23.2, 23.0.

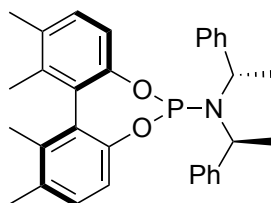
³¹P NMR (162 MHz, CDCl₃) δ 148.86.

[α]²⁵₅₈₉ = −165 (c = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₃₆H₃₁NO₂P [M+H]⁺: 540.2087, found: 540.2085.

IR (ATR) ν (cm^{−1}, CHCl₃): 759, 889, 1058, 1374, 3051.

(11a*R*)-1,2,10,11-Tetramethyl-*N,N*-bis((*S*)-1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (137)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white solid (369 mg, 61% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.17 – 7.05 (m, 12H), 4.45 (dq, *J* = 11.4, 7.1 Hz, 2H), 2.29 (d, *J* = 3.7 Hz, 6H), 2.04 (s, 3H), 1.99 (s, 3H), 1.68 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 149.6, 149.3 (d, *J* = 6.2 Hz), 143.4 (2C), 137.2 (d, *J* = 2.0 Hz), 136.6, 133.4 (d, *J* = 1.9 Hz), 132.0, 130.6 (d, *J* = 4.7 Hz), 129.2, 128.8 (d, *J* = 2.1 Hz), 128.4, 128.1 (2C), 128.1 (2C), 127.8 (4C), 126.6 (2C), 119.0 (d, *J* = 2.9 Hz), 118.7, 52.3, 52.1, 22.2 – 22.1 (m, 2C), 20.4, 20.3, 17.8, 17.5.

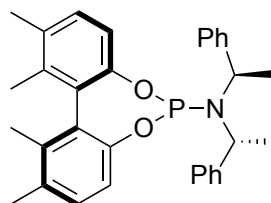
³¹P NMR (162 MHz, CDCl₃) δ 139.33.

[α]_D²⁵ = −252 (c = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₃₂H₃₄NO₂PNa [M+Na]⁺: 518.2219, found: 518.2218.

IR (ATR) ν (cm^{−1}, CHCl₃): 698, 764, 825, 1005, 1229, 1416, 2970.

(11a*R*)-1,2,10,11-tetramethyl-*N,N*-bis((*R*)-1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (138)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B. Flash column chromatography (SiO₂, 90:9:1 hexane:CH₂Cl₂:Et₃N) gave the pure product as a white foam (76 mg, 12% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.21 – 7.11 (m, 11H), 7.07 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.92 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.83 – 6.76 (m, 1H), 4.37 (ddt, *J* = 10.3, 6.9, 3.6 Hz, 2H), 2.32 – 2.27 (m, 3H), 2.22 (d, *J* = 2.4 Hz, 3H), 1.99 (dd, *J* = 20.5, 2.3 Hz, 6H), 1.65 (dt, *J* = 7.1, 2.0 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 149.8, 149.5 (d, *J* = 8.4 Hz), 143.6 (2C), 137.4, 136.5, 133.5 (d, *J* = 2.0 Hz), 131.8, 130.7 (d, *J* = 5.0 Hz), 130.0 (d, *J* = 1.6 Hz), 129.4 (d, *J* = 1.5 Hz), 128.5 (d, *J* = 2.1 Hz), 128.2 (2C), 128.2 (2C), 127.8 (4C), 126.6 (2C), 119.1 (d, *J* = 3.1 Hz), 118.9, 54.6, 54.5, 23.2, 23.1, 20.4, 20.3, 17.8, 17.5.

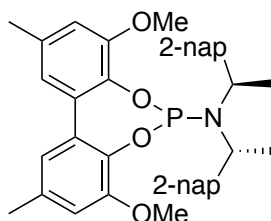
³¹P NMR (162 MHz, CDCl₃) δ 144.96.

[α]_D²⁵ = +129 (c = 1.0 in CHCl₃).

HRMS (GCMS with ammonia as reagent gas) *m/z* calcd. for C₃₂H₃₄NO₂P [M+H]⁺: 496.2400, found: 496.2419.

IR (ATR) ν (cm⁻¹, CHCl₃): 698, 758, 824, 1005, 1245, 1471, 2970.

4,8-Dimethoxy-2,10-dimethyl-*N,N*-bis((*R*)-1-(naphthalen-2-yl)ethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (139)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (461 mg, 50% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.68 – 7.61 (m, 2H), 7.57 – 7.51 (m, 4H), 7.51 – 7.47 (m, 2H), 7.46 – 7.41 (m, 2H), 7.38 – 7.31 (m, 4H), 6.91 – 6.85 (m, 2H), 6.81 – 6.70 (m, 2H), 4.80 (dq, *J* = 10.9, 7.1 Hz, 2H), 3.95 (s, 3H), 3.64 (s, 3H), 2.38 (d, *J* = 8.0 Hz, 6H), 1.88 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 152.0 (d, *J* = 1.9 Hz, 2C), 151.4 (2C), 141.0 (2C), 133.9, 133.2, 133.1 (2C), 132.4 (2C), 131.9 (d, *J* = 3.8 Hz), 130.9 (d, *J* = 2.9 Hz), 128.0 (2C), 127.4 (d, *J* = 2.7 Hz, 2C), 127.3 (2C), 127.1 (2C), 126.2 (d, *J* = 1.9 Hz, 2C), 125.5 (2C), 125.4 (2C), 122.1, 121.9, 113.1, 112.5, 56.3, 55.9, 53.2, 53.1, 22.0, 21.9, 21.6, 21.6.

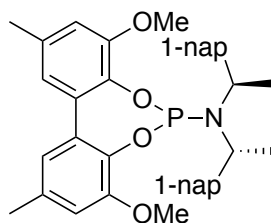
³¹P NMR (162 MHz, CDCl₃) δ 145.40.

[α]_D²⁵ = +374 (c = 1.0 in CHCl₃).

HRMS (CI with ammonia as reagent gas) *m/z* calcd. for C₄₀H₃₈NO₄P [M+H]⁺: 628.2611, found: 628.2606.

IR (ATR) ν (cm⁻¹, CHCl₃): 751, 857, 1139, 1414, 1459, 1592, 2968.

4,8-Dimethoxy-2,10-dimethyl-N,N-bis((R)-1-(naphthalen-1-yl)ethyl)dibenzo[d,f][1,3,2]dioxaphosphepin-6-amine (140)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (249 mg, 27% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.04 (s, 2H), 7.59 – 7.47 (m, 4H), 7.34 – 7.28 (m, 4H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.96 (dd, *J* = 11.8, 1.9 Hz, 2H), 6.84 (t, *J* = 2.3 Hz, 2H), 6.74 (t, *J* = 8.1, 7.3 Hz, 2H), 5.60 – 5.47 (m, 2H), 4.00 (d, *J* = 6.4 Hz, 6H), 2.43 (d, *J* = 5.0 Hz, 6H), 1.77 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 152.1 (2C), 151.6 (2C), 139.4 (d, *J* = 8.5 Hz), 138.8, 138.5, 134.2, 133.2, 133.0 (3C), 132.1 (d, *J* = 3.9 Hz), 130.9 (d, *J* = 9.8 Hz), 128.3 (2C), 126.6 (2C), 125.2 (2C), 124.7 (2C), 124.6 (2C), 124.6 (2C), 123.8 (2C), 122.1, 121.9, 112.6, 112.5, 56.4, 56.0, 50.4, 50.3, 22.4, 22.2, 21.7, 21.6.

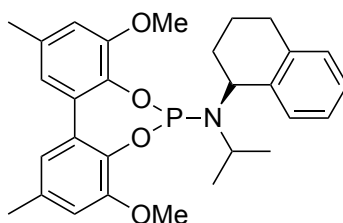
³¹P NMR (162 MHz, CDCl₃) δ 148.31.

[α]_D²⁵ = −152 (c = 1.0 in CHCl₃).

HRMS (CI with ammonia as reagent gas) *m/z* calcd. for C₄₀H₃₉NO₄P [M+H]⁺: 628.2611, found: 628.2592.

IR (ATR) ν (cm^{−1}, CHCl₃): 776, 861, 1052, 1139, 1460, 2966.

(*R*)-*N*-Isopropyl-4,8-dimethoxy-2,10-dimethyl-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (141)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (297 mg, 40% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.26 – 7.18 (m, 1H), 7.15 – 7.09 (m, 1H), 7.06 – 6.99 (m, 1H), 6.86 – 6.79 (m, 2H), 6.72 (dd, *J* = 12.4, 1.9 Hz, 2H), 4.50 (td, *J* = 11.5, 5.1 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.47 (s, 1H), 2.91 – 2.78 (m, 1H), 2.75 – 2.64 (m, 1H), 2.36 (d, *J* = 7.2 Hz, 6H), 2.35 – 2.19 (m, 1H), 2.09 – 1.92 (m, 2H), 1.69 – 1.58 (m, 1H), 1.31 (dd, *J* = 6.7, 3.5 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 151.8, 151.5, 139.1 (d, *J* = 6.8 Hz), 138.8 (d, *J* = 4.8 Hz), 138.3 (2C), 133.5, 133.2, 131.6 (d, *J* = 3.4 Hz), 131.3 (d, *J* = 2.8 Hz), 129.2, 128.7, 126.3, 125.7, 121.9, 121.8, 112.8, 112.4, 56.3, 56.0, 54.0 – 53.6 (m), 46.7 (d, *J* = 11.3 Hz), 33.7 – 33.5 (m), 30.0, 25.6 – 25.2 (m), 24.0 – 23.7 (m), 22.8, 21.6 (d, *J* = 1.0 Hz, 2C).

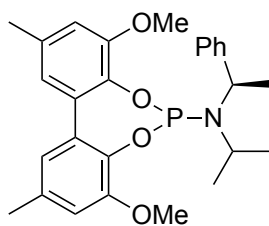
³¹P NMR (162 MHz, CDCl₃) δ 150.88.

[α]_D²⁵ = –81 (c = 1.0 in CHCl₃).

HRMS (GCMS with ammonia as reagent gas) *m/z* calcd. for C₂₉H₃₅NO₄P [M+H]⁺: 492.2298, found: 429.2300.

IR (ATR) ν (cm^{–1}, CHCl₃): 762, 857, 1052, 1139, 1459, 2932.

(*R*)-*N*-Isopropyl-4,8-dimethoxy-2,10-dimethyl-*N*-(1-phenylethyl)dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (142)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A, from backbone **94** and amine **351**. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (343 mg, 49% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.62 (dq, *J* = 6.6, 1.0 Hz, 2H), 7.33 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.25 – 7.14 (m, 1H), 6.86 (dd, *J* = 3.6, 1.9 Hz, 2H), 6.74 (dd, *J* = 6.9, 1.9 Hz, 2H), 4.72 – 4.60 (m, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.58 – 3.44 (m, 1H), 2.41 – 2.37 (m, 6H), 1.69 (d, *J* = 7.0 Hz, 3H), 1.30 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 151.9, 151.5, 145.5, 139.1 (d, *J* = 7.1 Hz), 138.8 (d, *J* = 4.5 Hz), 133.6, 133.2, 131.7 (d, *J* = 3.1 Hz), 131.2 (d, *J* = 2.7 Hz), 128.0 (2C), 127.6 (d, *J* = 2.4 Hz, 2C), 126.4, 121.9, 121.8, 112.7, 112.5, 56.2, 56.0, 52.1 (d, *J* = 14.0 Hz), 46.3 (d, *J* = 10.1 Hz), 24.4 (d, *J* = 6.5 Hz), 23.9 (d, *J* = 7.1 Hz), 22.9 (d, *J* = 15.1 Hz), 21.6 (2C).

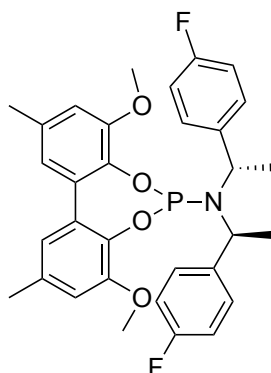
³¹P NMR (162 MHz, CDCl₃) δ 148.47.

[α]_D²⁵ = +126 (c = 1.0 in CHCl₃).

HRMS (GCMS with ammonia as reagent gas) *m/z* calcd. for C₂₇H₃₃NO₄P [M+H]⁺: 466.2142, found: 466.2149.

IR (ATR) ν (cm⁻¹, CHCl₃): 758, 858, 1139, 1459, 1590, 2968.

***N,N*-Bis((*S*)-1-(4-fluorophenyl)ethyl)-4,8-dimethoxy-2,10-dimethyldibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (143)**



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B, from backbone **94** and amine **354**. Flash column chromatography (SiO₂, 80:19:1 hexane:CH₂Cl₂:Et₃N) gave the pure product as a white foam (861 mg, 85% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.19 – 7.11 (m, 4H), 6.90 – 6.83 (m, 2H), 6.83 – 6.73 (m, 6H), 4.56 (dq, *J* = 10.5, 7.2, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 2.38 (s, 6H), 1.71 (d, *J* = 7.1, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 162.8 (2C), 160.4 (2C), 151.9, 151.3, 139.3, 139.0 (d, *J* = 9.5 Hz), 134.2, 133.2, 132.0 (d, *J* = 3.7 Hz), 130.6 (d, *J* = 3.2 Hz), 129.7, 129.6, 129.6, 129.6, 122.0, 121.8, 114.4 (2C), 114.2 (2C), 112.9, 112.4, 56.3, 55.8, 52.4, 52.3, 22.3 – 22.0 (m, 2C), 21.6, 21.5.

³¹P NMR (162 MHz, CDCl₃) δ 144.03.

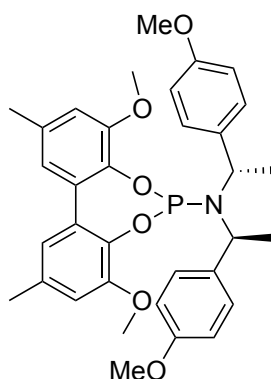
¹⁹F NMR (376 MHz, CDCl₃) δ –116.98.

[α]_D²⁵ = –203 (c = 1.0 in CHCl₃).

HRMS (CI with methane as reagent gas) *m/z* calcd. for C₃₂H₃₃F₂NO₄P [M+H]⁺: 564.2110, found: 654.2104.

IR (ATR) ν (cm^{–1}, CHCl₃): 758, 834, 1139, 1223, 1460, 2980.

4,8-Dimethoxy-*N,N*-bis((*S*)-1-(4-methoxyphenyl)ethyl)-2,10-dimethyldibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (144)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B, from backbone **94** and amine **357**. Flash column chromatography (SiO₂, 60:39:1 hexane:CH₂Cl₂:Et₃N) gave the pure product as a white foam (830 mg, 78% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 8.6 Hz, 4H), 6.90 – 6.82 (m, 2H), 6.74 (dd, *J* = 7.0, 1.9 Hz, 2H), 6.71 – 6.64 (m, 4H), 4.55 (dq, *J* = 10.8, 7.1 Hz, 2H), 3.90 (s, 3H), 3.77 (s, 3H), 3.75 (s, 6H), 2.41 – 2.34 (m, 6H), 1.71 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 158.1 (2C), 151.9 (d, *J* = 1.7 Hz), 151.4, 139.2 (d, *J* = 8.5 Hz), 138.5 (d, *J* = 2.5 Hz), 135.9 (2C), 133.8, 133.0, 132.0 (d, *J* = 3.7 Hz), 130.8 (d, *J* = 2.2 Hz), 129.3 (2C), 129.3 (2C), 122.0, 121.9, 113.1, 113.0 (4C), 112.3, 56.5 (d, *J* = 2.2 Hz), 55.8 (d, *J* = 1.8 Hz), 55.3, 55.3, 52.2, 52.1, 22.2, 22.1, 21.6, 21.5.

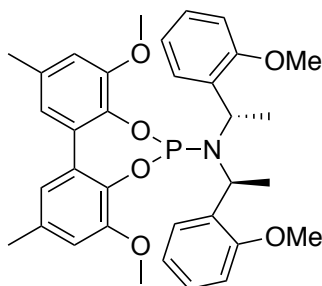
³¹P NMR (162 MHz, CDCl₃) δ 146.08.

[α]²⁵₅₈₉ = −233 (c = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₃₄H₃₉NO₆P [M+H]⁺: 588.2510, found: 588.2510.

IR (ATR) ν (cm^{−1}, CHCl₃): 832, 1139, 1248, 1460, 1512, 2981.

4,8-Dimethoxy-*N,N*-bis((*S*)-1-(2-methoxyphenyl)ethyl)-2,10-dimethyldibenzo[*d,f*][1,3,2]dioxaphosphepin-6-amine (145)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B, from backbone **94** and amine **360**. Flash column chromatography (Alumina, 100% Toluene) gave the pure product as a white foam (137 mg, 27% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.59 (m, 2H), 6.98 – 6.89 (m, 2H), 6.88 (d, *J* = 9.6 Hz, 2H), 6.79 – 6.73 (m, 2H), 6.71 (t, *J* = 7.2 Hz, 2H), 6.41 (d, *J* = 8.0 Hz, 2H), 4.98 (p, *J* = 7.4 Hz, 2H), 3.91 (d, *J* = 6.2 Hz, 6H), 3.62 (s, 6H), 2.39 (d, *J* = 3.7 Hz, 6H), 1.54 (d, *J* = 7.6 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 156.3 (2C), 151.9, 151.6, 139.5, 139.4, 139.1 (d, *J* = 2.9 Hz), 133.4 (d, *J* = 1.2 Hz), 132.9 (d, *J* = 1.0 Hz), 132.7, 132.1 (d, *J* = 3.6 Hz), 131.0 (d, *J* = 2.9 Hz), 127.9, 127.8, 127.1 (2C), 121.9 (2C), 119.5 (2C), 112.5, 112.3, 109.1 (2C), 56.2, 55.9, 54.7 (2C), 49.6, 49.5, 21.8 – 21.4 (m, 4C).

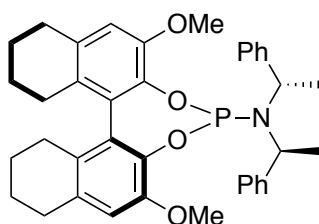
³¹P NMR (162 MHz, CDCl₃) δ 151.35.

[α]_D²⁵ = +4 (c = 1.0 in CHCl₃).

HRMS (GCMS with ammonia as reagent gas) *m/z* calcd. for C₃₄H₃₉NO₆P [M+H]⁺: 588.2510, found: 588.2511.

IR (ATR) ν (cm⁻¹, CHCl₃): 772, 956, 1140, 1383, 1462, 2981.

(11b*S*)-2,6-Dimethoxy-*N,N*-bis((*S*)-1-phenylethyl)-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (147)



Synthesised according to general procedure 1: phosphoramidite ligand synthesis A. Flash column chromatography (SiO₂, 80:19:1 hexane:CH₂Cl₂:Et₃N) gave the pure product as a white foam (198 mg, 58% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.26 – 7.21 (m, 4H), 7.18 – 7.06 (m, 6H), 6.70 (s, 1H), 6.48 (s, 1H), 4.38 (dq, *J* = 10.5, 7.1 Hz, 2H), 3.91 (s, 3H), 3.60 (s, 3H), 2.87 – 2.46 (m, 6H), 2.24 – 2.16 (m, 1H), 2.14 – 2.05 (m, 1H), 1.79 – 1.70 (m, 6H), 1.66 (d, *J* = 7.1 Hz, 6H), 1.58 – 1.41 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 149.8, 149.7, 148.9 (2C), 143.8 (2C), 133.8 (2C), 131.8 (2C), 131.0, 131.0, 128.3 (2C), 128.3 (2C), 127.6 (4C), 126.4 (2C), 112.9, 111.3, 56.6, 55.1, 54.9, 54.8, 29.9, 29.7, 27.5, 27.1, 23.4, 23.3, 23.2, 23.2, 23.1, 23.0.

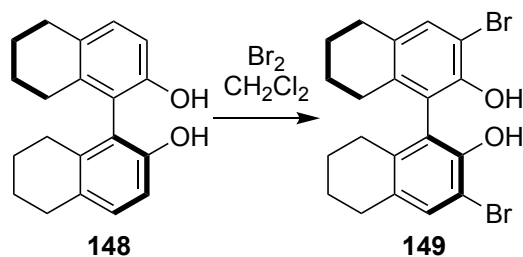
³¹P NMR (162 MHz, CDCl₃) δ 146.67.

[α]²⁵₅₈₉ = −17 (*c* = 1.0 in CHCl₃).

LRMS (ESI) *m/z*: 608.3 [M+H]⁺

IR (ATR) ν (cm^{−1}, CHCl₃): 758, 843, 1106, 1458, 2980.

(S)-3,3'-Dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (149)



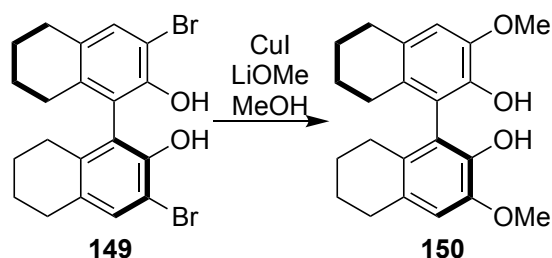
(S)-(-)-5,5',6,6',7,7',8,8'-Octahydro-1,1'-2-naphthol (1.0 g, 3.4 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (25 mL) and the solution cooled to -30 °C. Bromine (390 μL, 7.7 mmol, 2.25 eq.) was added as a solution in CH₂Cl₂ (5.0 mL). The reaction was stirred at -30 °C for 1.5 hrs before quenching with sat. aq. Na₂S₂O₃ (40 mL) and slowly warming to room temperature. The mixture was extracted with CH₂Cl₂ (2 × 50 mL). The combined organic phases were washed with sat. aq. NaHCO₃ (50 mL), brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 0–20% EtOAc in hexane) to give the pure product as a yellow foam (893 mg, 56% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.28 (s, 2H), 5.10 (s, 2H), 2.77 – 2.70 (m, 4H), 2.35 – 2.22 (m, 2H), 2.15 – 2.05 (m, 2H), 1.79 – 1.58 (m, 8H).

¹³C NMR (101 MHz, CDCl₃) δ 147.3 (2C), 136.9 (2C), 132.7 (2C), 131.7 (2C), 122.3 (2C), 107.3 (2C), 29.2 (2C), 27.1 (2C), 22.9 (2C), 22.9 (2C).

LRMS (ESI) *m/z*: 449.0 [M-H]⁻

(S)-3,3'-Dimethoxy-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (150)



LiOMe (375 mg, 9.9 mmol, 6.0 eq.) and MeOH (10 mL) were added to a high-pressure boiling tube. Copper iodide (625 mg, 3.3 mmol, 2.0 eq.) was added, followed by **149** (740 mg, 1.6 mmol, 1.0 eq.) as a solution in MeOH (5.0 mL). The tube was sealed and heated to 120 °C. The reaction was stirred for 3 days after which time further copper iodide (312 mg, 1.6 mmol, 1.0 eq.) was added and reaction stirred for a further 2 days at 150 °C. The reaction was cooled, quenched with 1M HCl (5.0 mL) and the aqueous phase extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 0–25% EtOAc in pentane) to give the pure product as a white foam (211 mg, 36% yield).

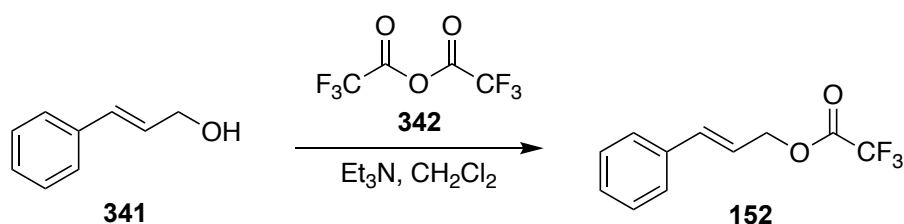
¹H NMR (400 MHz, CDCl₃) δ 6.63 (s, 2H), 5.23 (s, 2H), 3.88 (s, 6H), 2.75 (t, *J* = 6.2 Hz, 5H), 2.32 (ddd, *J* = 16.6, 7.0, 5.3 Hz, 3H), 2.16 – 2.02 (m, 2H), 1.80 – 1.57 (m, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 144.6 (2C), 140.5 (2C), 128.5 (2C), 128.2 (2C), 111.1 (2C), 100.0 (2C), 55.8 (2C), 29.8 (2C), 26.4 (2C), 23.3 (2C), 23.2 (2C).

LRMS (ESI) *m/z*: 377.2 [M+Na]⁺

IR (ATR) ν (cm⁻¹, CHCl₃): 755, 835, 1113, 1252, 1483, 2928.

Cinnamyl 2,2,2-trifluoroacetate (152)



Cinnamyl alcohol (1.0 g, 7.5 mmol, 1.0 eq.), Et₃N (2.1 mL, 15 mmol, 2.0 eq.) and CH₂Cl₂ (35 mL) were cooled to 0 °C. Trifluoroacetic anhydride (1.4 mL, 9.7 mmol, 1.3 eq.) was added dropwise over 5 mins. The reaction was warmed to room temperature. After 2 hrs, the reaction was quenched by pouring over 1 M HCl (30 mL). The organic phase was washed with water (2 × 30 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 0–5% EtOAc in hexane) to give the pure product as a colourless oil (761 mg, 44% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.39 (m, 2H), 7.39 – 7.26 (m, 3H), 6.77 (d, *J* = 15.8 Hz, 1H), 6.30 (dt, *J* = 15.9, 6.8 Hz, 1H), 4.99 (dd, *J* = 6.8, 1.2 Hz, 2H).

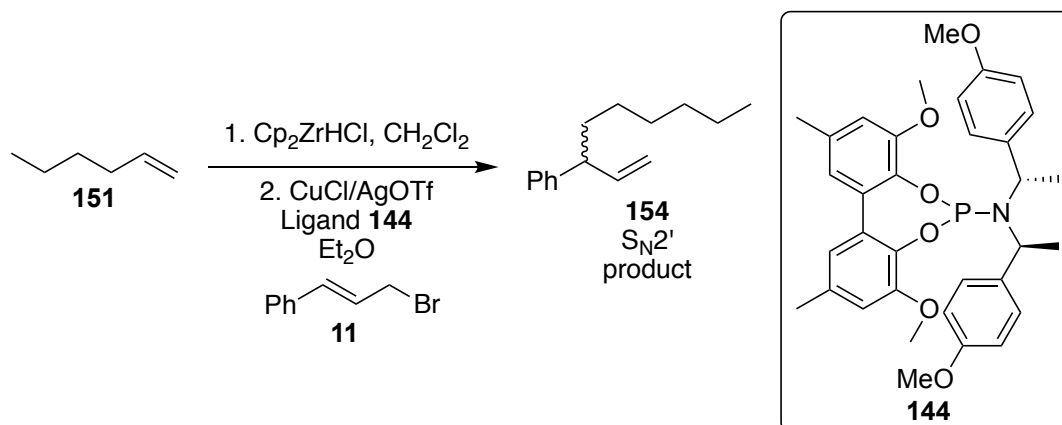
¹³C NMR (101 MHz, CDCl₃) δ 157.8 – 157.5 (m), 137.2 (2C), 135.6, 128.9 (3C), 127.0 (2C), 120.2, 68.7.

¹⁹F NMR (376 MHz, CDCl₃) δ –74.96.

HRMS (GCMS with methane as reagent gas) *m/z* calcd. for C₁₁H₁₀O₂F₃ [M+H]⁺: 231.0627, found: 231.0638.

IR (ATR) ν (cm^{–1}, CHCl₃): 731, 967, 1143, 1782, 2981.

Non-1-en-3-ylbenzene (154)



Synthesised according to general procedure 4. The crude mixture was purified by flash column chromatography (SiO_2 , 100% hexane) to give the desired product as a colourless oil (43 mg, 53% yield, 93:7 $\text{S}_{\text{N}}2'$: $\text{S}_{\text{N}}2$, 72% ee)

^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.27 (m, 2H), 7.23 – 7.18 (m, 3H), 6.03 – 5.90 (m, 1H), 5.04 (dd, $J = 5.9, 1.3$ Hz, 1H), 5.00 (d, $J = 1.1$ Hz, 1H), 3.24 (q, $J = 7.5$ Hz, 1H), 1.71 (q, $J = 6.2$ Hz, 2H), 1.35 – 1.21 (m, 8H), 0.88 (dt, $J = 9.5, 3.9$ Hz, 3H).

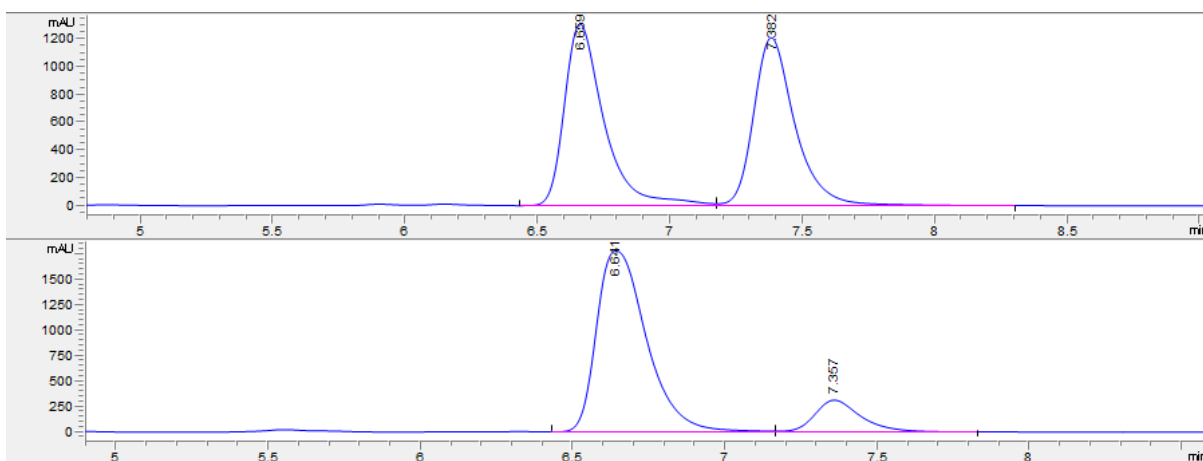
^{13}C NMR (101 MHz, CDCl_3) δ 144.8, 142.7, 128.5 (2C), 127.7 (2C), 126.2, 113.9, 50.1, 35.6, 31.9, 29.4, 27.6, 22.8, 14.2.

$[\alpha]_{589}^{25} = -20$ ($c = 0.8$ in CHCl_3 , 72% ee)

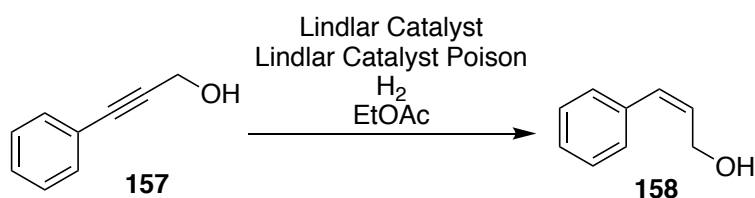
LRMS (ESI) m/z : 201.0 $[\text{M}+\text{H}]^+$

IR (ATR) ν (cm^{-1} , CHCl_3): 699, 757, 912, 1453, 2856, 2927.

The enantiomeric excess was determined by HPLC analysis of the crude alcohol derived from **154** (general procedure 5) [Chiralpak® IB; hexane:*i*-PrOH 95:5; 1.0 mL/min, $\lambda=210$ nm, major enantiomer $t_R = 6.64$ mins, minor enantiomer $t_R = 7.36$ mins].



(*Z*)-3-Phenylprop-2-en-1-ol (**158**)



3-Phenyl-2-propyn-1-ol (**157**, 4.0 g, 30 mmol, 1.0 eq.) was dissolved in EtOAc (40 mL, dried over 3 Å MS overnight). Hydrogen gas was bubbled through the solution for 20 minutes. Lindlar catalyst (1.55 g) and Lindlar catalyst poison (40 mg) were added to the reaction, before stirring under an atmosphere of hydrogen gas for 36 hrs. The reaction mixture was filtered over a pad of Celite, washing with EtOAc, before concentrating *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 15–40% EtOAc in hexane) and unreacted starting material subjected to the reaction conditions for a second time. The pure product was obtained as a pale yellow oil (3.8 g, 94% yield).

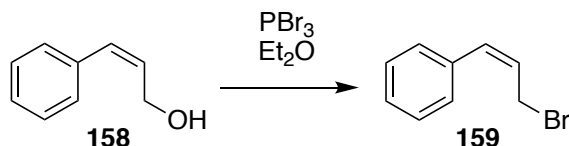
¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.30 (m, 2H), 7.30 – 7.24 (m, 1H), 7.24 – 7.17 (m, 2H), 6.58 (dt, *J* = 11.7, 1.8 Hz, 1H), 5.88 (dt, *J* = 11.7, 6.4 Hz, 1H), 4.45 (dd, *J* = 6.4, 1.7 Hz, 2H), 1.57 (s, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 136.6, 131.3, 131.2, 128.9 (2C), 128.4 (2C), 127.4, 59.9.

HRMS (GCMS with methane as reagent gas) m/z calcd. for $C_9H_{11}O$ $[M+H]^+$: 135.0804, found: 135.7504.

IR (ATR) ν (cm^{-1} , $CHCl_3$): 691, 756, 1031, 1490, 2981, 3319.

(Z)-(3-Bromoprop-1-en-1-yl)benzene (169)



Under an argon atmosphere, a solution of (Z)-3-phenylprop-2-en-1-ol (**158**, 500 mg, 3.7 mmol, 1.0 eq.) in Et₂O (30 mL) was cooled to 0 °C. PBr₃ (140 μ L, 1.5 mmol, 0.4 eq.) was added dropwise over 5 mins. The ice bath was removed and the reaction stirred at room temperature for 30 mins. CH₂Cl₂ (30 mL) and sat. aq. NaHCO₃ (20 mL) were added and the phases separated. The organic phase was washed with brine (30 mL), dried over MgSO₄ and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO₂, 100% hexane) to give the pure product as a pale yellow oil (419 mg, 57% yield).

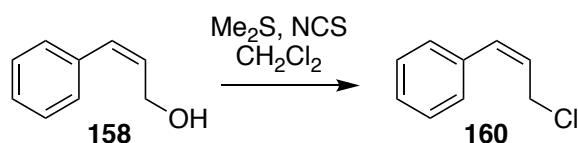
¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.35 (m, 3H), 7.35 – 7.25 (m, 2H), 6.61 (d, J = 11.2 Hz, 1H), 5.99 (dt, J = 11.2, 8.7 Hz, 1H), 4.17 (dd, J = 8.7, 0.9 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 135.7, 133.6, 128.8 (2C), 128.7 (2C), 127.8, 127.1, 29.1.

HRMS (GCMS with methane as reagent gas) m/z calcd. for $C_9H_{10}Br$ $[M+H]^+$: 196.9960, found: 196.9952.

IR (ATR) ν (cm^{-1} , $CHCl_3$): 698, 772, 1206, 1495, 2981.

(Z)-(3-Chloroprop-1-en-1-yl)benzene (160)



Under an argon atmosphere, a solution of *N*-chlorosuccinimide (1.2 g, 9.0 mmol, 1.2 eq.) in CH_2Cl_2 (50 mL) was cooled to 0 °C. Dimethyl sulphide (770 μL , 10 mmol, 1.4 eq.) was added and the mixture cooled to –20 °C. A solution of (Z)-3-phenylprop-2-en-1-ol (**158**, 1.0 g, 7.5 mmol, 1.0 eq.) in CH_2Cl_2 (25 mL) was added and reaction mixture was warmed to 0 °C. After stirring for 2.5 hrs at 0 °C the reaction was poured over ice. The aqueous phase was extracted with CH_2Cl_2 (3 $\times$ 50 mL). The combined organic phases were dried over MgSO_4 and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2 , 100% hexane) to give the pure product as a colourless oil (874 mg, 77% yield, 97:3 *Z:E*).

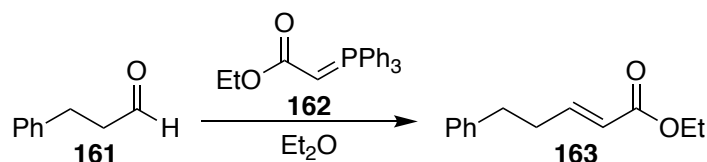
^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.34 (m, 2H), 7.39 – 7.25 (m, 3H), 6.67 (d, J = 11.3 Hz, 1H), 5.91 (dt, J = 11.3, 8.1 Hz, 1H), 4.28 (dd, J = 8.1, 1.1 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 135.8, 133.6, 128.9 (2C), 128.6 (2C), 127.8, 127.1, 41.0.

HRMS (GCMS with methane as reagent gas) m/z calcd. for $\text{C}_9\text{H}_{10}\text{Cl}$ $[\text{M}+\text{H}]^+$: 153.0466, found: 153.0393.

IR (ATR) ν (cm^{-1} , CHCl_3): 699, 774, 1155, 1256, 1383, 2981.

(E)-Ethyl-5-phenylpent-2-enoate (163)



A solution of ethyl(triphenylphosphoranylidene) acetate (**162**, 4.67 g, 13 mmol, 1.2 eq.) dissolved in CH_2Cl_2 (11 mL) was added dropwise, over 15 mins, to a solution of freshly

distilled 3-phenylpropanal (**161**, 1.5 mL, 11 mmol 1.0 eq.) in CH₂Cl₂ (14 mL). The reaction was stirred at room temperature for 2 hrs, before pouring into a separating funnel containing brine (20 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (20 mL). The combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. The crude was purified by column chromatography (SiO₂, 0–10% EtOAc in hexane) to give the pure product as a colourless oil (1.96 g, 86% yield).

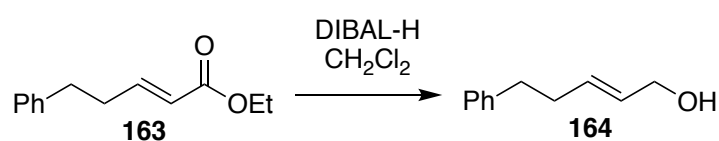
¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.24 (m, 2H), 7.24 – 7.15 (m, 3H), 7.01 (dt, *J* = 15.7, 6.8 Hz, 1H), 5.85 (d, *J* = 15.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.78 (dd, *J* = 8.9, 6.7 Hz, 2H), 2.58 – 2.47 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 166.7, 148.2, 141.0, 128.6 (2C), 128.5 (2C), 126.3, 122.0, 60.4, 34.5, 34.0, 14.4.

HRMS (GCMS with methane as reagent gas) *m/z* calcd. for C₁₃H₁₇O₂ [M+H]⁺: 205.1223, found: 205.1226.

IR (ATR) ν (cm⁻¹, CHCl₃): 699, 1149, 1266, 1718, 2980.

(*E*)-5-Phenylpent-2-en-1-ol (**164**)



DIBAL-H (1 M in CH₂Cl₂, 7.7 mL, 2.1 eq.) was added to a solution of ethyl (*E*)-5-phenylpent-2-enoate (**163**, 750 mg, 3.7 mmol, 1.0 eq.) in CH₂Cl₂ (10mL) at –78 °C, over 10 mins. The reaction was stirred for 50 mins before quenching with MeOH (0.3 mL). The reaction was warmed to room temperature and saturated aq. potassium sodium tartrate (15 mL) and EtOAc (30 mL) were added before stirring vigorously for 45 mins. The phases were separated and the aqueous phase extracted with EtOAc (2 × 30 mL). The organic phases were combined, washed with saturated aq. potassium sodium tartrate (15 mL), water

(15 mL), brine (15 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2 , 20–30% EtOAc in hexane) to give the pure product as a colourless oil (417 mg, 70% yield).

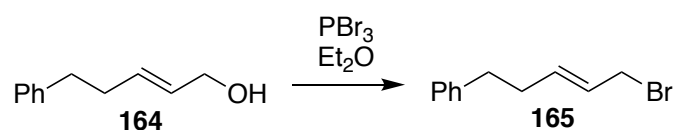
^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.24 (m, 2H), 7.24 – 7.16 (m, 3H), 5.80 – 5.63 (m, 2H), 4.11 – 4.04 (m, 2H), 2.78 – 2.66 (m, 2H), 2.45 – 2.33 (m, 2H), 1.38 (s, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 141.7, 132.3, 129.6, 128.4 (2C), 128.3 (2C), 125.9, 63.7, 35.6, 34.0.

HRMS (ESI) m/z calcd. for $\text{C}_{11}\text{H}_{14}\text{ONa}$ $[\text{M}+\text{Na}]^+$: 185.0937, found: 185.0939.

IR (ATR) ν (cm^{-1} , CHCl_3): 699, 697, 1082, 1382, 2361, 2981, 3321.

(*E*)-(5-Bromopent-3-en-1-yl)benzene (**165**)



Under an argon atmosphere, a solution of (*E*)-5-phenylpent-2-en-1-ol (**164**, 400 mg, 2.5 mmol, 1.0 eq.) in Et_2O (3 mL) was cooled to 0 °C. PBr_3 (120 μL , 1.2 mmol, 0.5 eq.) was added dropwise over 5 mins. The ice bath was removed and the reaction stirred at room temperature for 1 hr. The reaction was quenched by pouring into a separating funnel containing ice-water (3 mL). The aqueous phase was extracted with Et_2O (3×7 mL). The combined organic phases were washed with water (5 mL), sat. aq. NaHCO_3 (5 mL), brine (5 mL), dried over MgSO_4 and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2 , 100% hexane) to give the pure product as a colourless oil (368 mg, 67% yield).

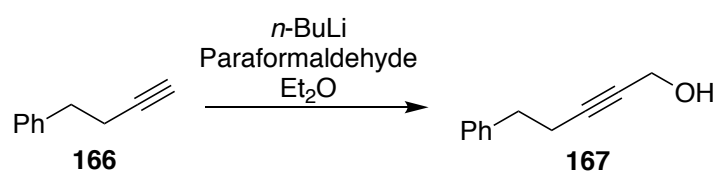
^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.25 (m, 2H), 7.24 – 7.14 (m, 3H), 5.88 – 5.65 (m, 2H), 3.94 (d, $J = 7.2$ Hz, 2H), 2.71 (t, $J = 7.8$ Hz, 2H), 2.40 (q, $J = 7.1$ Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 141.5, 135.6, 128.5 (2C), 128.5 (2C), 127.1, 126.1, 35.3, 33.9, 33.5.

HRMS (CI with methane as reagent gas) *m/z* calcd. for C₁₁H₁₄Br [M+H]⁺: 225.0273, found: 225.0262.

IR (ATR) ν (cm⁻¹, CHCl₃): 699, 965, 1204, 1453, 2360, 2981.

5-Phenylpent-2-yn-1-ol (**167**)



n-BuLi (1.4 M in hexane, 9.1 mL, 13 mmol, 1.1 eq.) was added dropwise to a solution of 4-phenyl-1-butyne (**166**, 1.5 g, 12 mmol, 1.0 eq.) in Et₂O (22.5 mL) at -10 °C. The reaction was stirred for 1 hr before adding a suspension of paraformaldehyde (0.81 g) in THF (22.5 mL). The flask containing the paraformaldehyde was rinsed with THF (5 mL) and the washing added to the reaction mixture. The resulting solution was stirred at -10 °C for 1 hr, after which the cooling bath was removed and the flask fitted with a reflux condenser. The reaction was heated at 80 °C for 2 hrs before cooling to room temperature and quenching with saturated aq. NH₄Cl (20 mL). The aqueous phase was extracted with EtOAc (2 × 40 mL). The combined organic phases for washed with distilled water (20 mL), brine (20 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude was purified by flash column chromatography (SiO₂, 25% EtOAc in hexane) to give the pure product as a yellow oil (1.59 g, 86% yield).

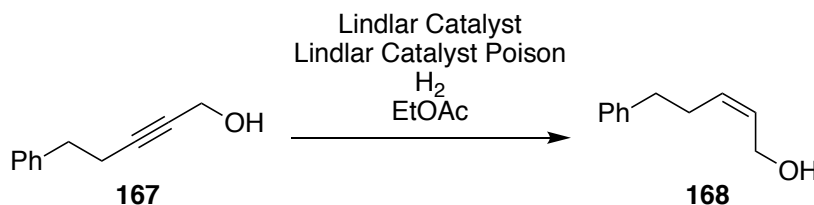
¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.22 (m, 4H), 7.21 (q, *J* = 1.6 Hz, 1H), 4.23 (dt, *J* = 6.0, 2.1 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.52 (tt, *J* = 7.5, 2.2 Hz, 2H), 1.68 – 1.55 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 140.6, 128.5 (4C), 126.5, 85.9, 79.2, 51.5, 35.1, 21.0.

HRMS (CI with ammonia as reagent gas) m/z calcd. for $C_{11}H_{16}NO$ $[M+NH_4]^+$: 178.1226, found: 178.1230.

IR (ATR) ν (cm^{-1} , $CHCl_3$): 699, 1012, 1134, 1383, 2981, 3331.

(Z)-5-Phenylpent-2-en-1-ol (168)



5-Phenylpent-2-yn-1-ol (**167**, 1.59 g, 9.9 mmol, 1.0 eq.) was dissolved in EtOAc (40 mL, dried over 3 Å MS overnight). Hydrogen gas was bubbled through the solution for 20 mins. Lindlar catalyst (1.0 g) and Lindlar catalyst poison (30 mg) were added to the reaction, before stirring under an atmosphere of hydrogen gas overnight. The reaction mixture was filtered over a pad of Celite and washed with EtOAc, before concentrating *in vacuo*. The crude was purified by flash column chromatography (SiO_2 , 25% EtOAc in hexane) to give the pure product as a slightly yellow oil (1.55 g, 96% yield).

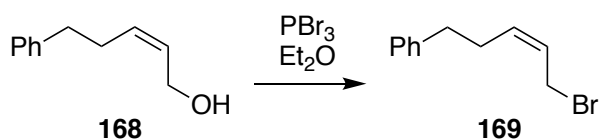
^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 5H), 5.67 – 5.51 (m, 2H), 4.05 – 3.97 (m, 2H), 2.70 (t, $J = 7.4$ Hz, 2H), 2.47 – 2.35 (m, 2H), 0.98 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 131.7, 129.4, 128.7 (2C), 128.4 (2C), 126.1, 58.5, 35.8, 29.4.

HRMS (CI with ammonia as reagent gas) m/z calcd. for $C_{11}H_{18}NO$ $[M+NH_4]^+$: 180.1383, found: 180.1385.

IR (ATR) ν (cm^{-1} , $CHCl_3$): 699, 1028, 1383, 1454, 2981.

(Z)-(5-Bromopent-3-en-1-yl)benzene (169)



Under an argon atmosphere, a solution of (Z)-5-phenylpent-2-en-1-ol (**168**, 700 mg, 4.3 mmol, 1.0 eq.) in Et₂O (3.0 mL) was cooled to 0 °C. PBr₃ (160 μL, 1.7 mmol, 0.4 eq.) was added dropwise over 5 mins. The ice bath was removed and the reaction stirred at room temperature for 25 mins. Et₂O (40 mL) and sat. aq. NaHCO₃ (30 mL) were added and the phases separated. The aqueous phase was extracted with Et₂O (40 mL). The combined organic phases were washed with brine (40 mL), dried over MgSO₄ and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO₂, 100% hexane) to give the pure product as a colourless oil (481 mg, 50% yield).

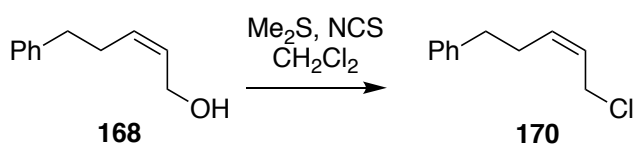
¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.27 (m, 2H), 7.21 (td, *J* = 6.5, 1.7 Hz, 3H), 5.81 – 5.71 (m, 1H), 5.69 – 5.59 (m, 1H), 3.90 (d, *J* = 8.2 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.47 (qd, *J* = 7.6, 1.4 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 141.3, 134.7, 128.6 (2C), 128.5 (2C), 126.2, 126.1, 35.3, 28.9, 27.2.

HRMS (CI with ammonia as reagent gas) *m/z* calcd. for C₁₁H₁₇NBr [M+NH₄]⁺: 242.0539, found: 242.0534.

IR (ATR) ν (cm⁻¹, CHCl₃): 772, 954, 1152, 1383, 2981.

(Z)-(5-Chloropent-3-en-1-yl)benzene (170)



Under an argon atmosphere, a solution of *N*-chlorosuccinimide (695 mg, 5.2 mmol, 1.2 eq.) in CH₂Cl₂ (35 mL) was cooled to 0 °C. Dimethyl sulphide (440 μL, 6.0 mmol, 1.4 eq.) was

added and the mixture cooled to $-78\text{ }^{\circ}\text{C}$. A solution of (*Z*)-5-phenylpent-2-en-1-ol (**168**, 700 mg, 4.3 mmol, 1.0 eq.) in CH_2Cl_2 (15 mL) was added and reaction mixture was warmed to $0\text{ }^{\circ}\text{C}$. After stirring for 2 hrs at $0\text{ }^{\circ}\text{C}$ the reaction was poured over ice. The aqueous phase was extracted with CH_2Cl_2 ($3 \times 35\text{ mL}$). The combined organic phases were dried over MgSO_4 and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2 , 100% hexane) to give the pure product as a colourless oil (655 mg, 84% yield).

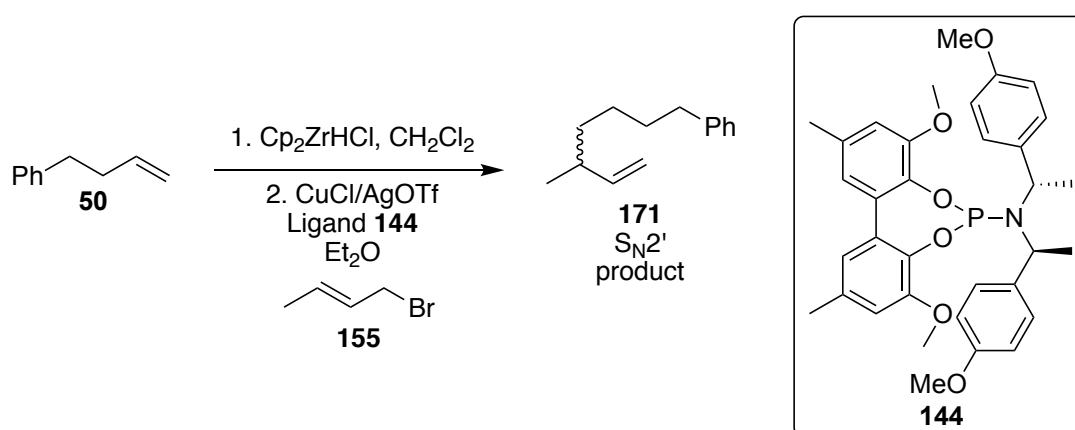
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.33 – 7.27 (m, 1H), 7.24 – 7.17 (m, 1H), 5.73 – 5.61 (m, 1H), 3.99 (d, $J = 6.6\text{ Hz}$, 1H), 2.72 (t, $J = 7.6\text{ Hz}$, 1H), 2.50 – 2.41 (m, 1H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 141.3, 134.2, 128.6 (2C), 128.5 (2C), 126.2, 126.1, 39.5, 35.6, 29.1.

HRMS (CI with ammonia as reagent gas) m/z calcd. for $\text{C}_{11}\text{H}_{17}\text{NCl}$ $[\text{M}+\text{NH}_4]^+$: 198.1044, found: 198.1052.

IR (ATR) ν (cm^{-1} , CHCl_3): 699, 744, 1251, 1383, 1454, 2981.

(5-Methylhept-6-en-1-yl)benzene (**171**)



Synthesised according to general procedure 4. The crude mixture was purified by flash column chromatography (SiO_2 , 100% hexane) to give the desired product as a colourless oil (42.6 mg, 53% yield, 81:19 $\text{S}_{\text{N}}2'$: $\text{S}_{\text{N}}2$, 48% ee).

^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.27 (m, 1H), 7.24 – 7.17 (m, 1H), 5.73 – 5.61 (m, 1H), 3.99 (d, $J = 6.6$ Hz, 1H), 2.72 (t, $J = 7.6$ Hz, 1H), 2.50 – 2.41 (m, 1H).

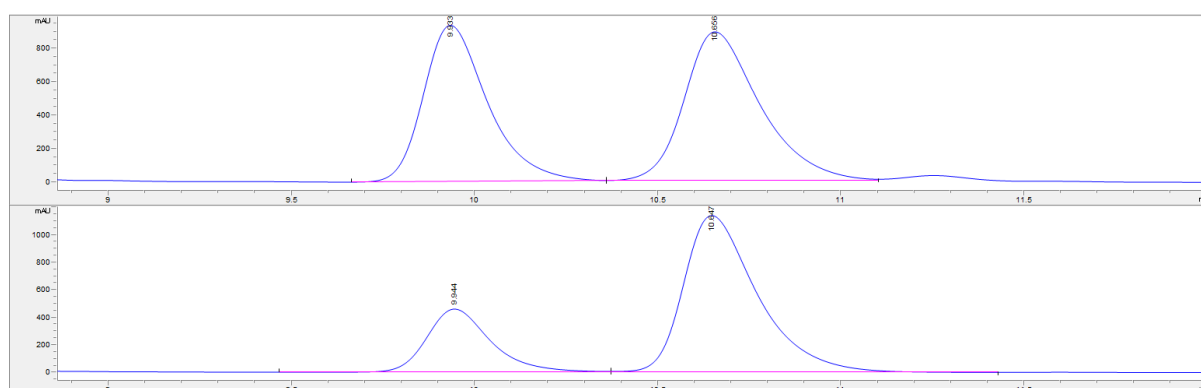
^{13}C NMR (101 MHz, CDCl_3) δ 145.0, 143.0, 128.5 (2C), 128.4 (2C), 125.7, 112.5, 37.8, 36.6, 36.1, 31.8, 27.1, 20.3.

$[\alpha]_{589}^{25} = +45.9$ ($c = 0.17$ in CHCl_3 , 48% ee).

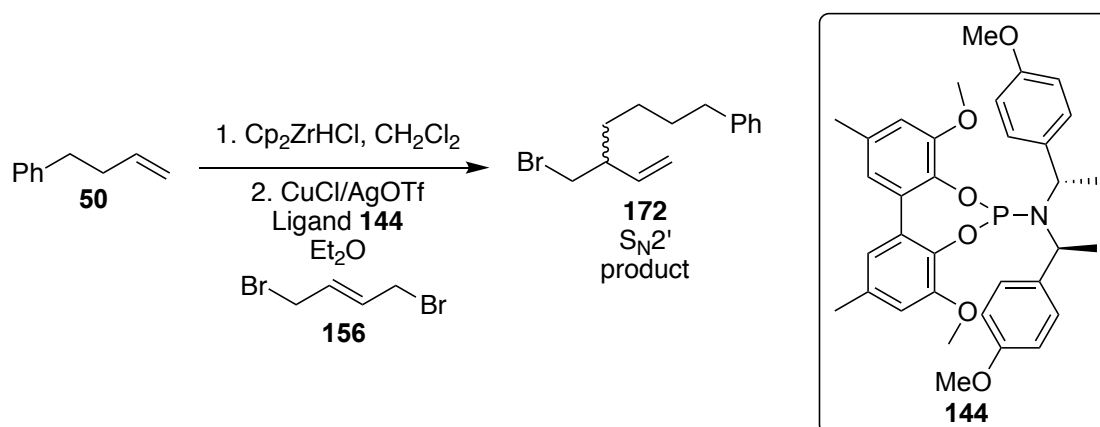
HRMS (GCMS using methane as reagent gas) m/z calcd. for $\text{C}_{14}\text{H}_{21}$ $[\text{M}+\text{H}]^+$: 189.1638, found: 189.1638.

IR (ATR) ν (cm^{-1} , CHCl_3): 773, 910, 1220, 2361, 2929.

The enantiomeric excess was determined by HPLC analysis of the crude alcohol derived from **171** (general procedure 5) [Chiralpak® IB; hexane:*i*-PrOH 98:2; 1.0 mL/min, $\lambda=210$ nm, minor enantiomer $t_R = 9.94$ mins, major enantiomer $t_R = 10.65$ mins].



(5-(Bromomethyl)hept-6-en-1-yl)benzene (172)



Synthesised according to general procedure 4. The crude mixture was purified by flash column chromatography (SiO_2 , 100% hexane) to give the desired product as a colourless oil (88.7 mg, 84% yield, 40% ee).

^1H NMR (400 MHz, CDCl_3) δ 7.32 – 7.25 (m, 2H), 7.22 – 7.14 (m, 3H), 5.61 (ddd, $J = 17.1$, 10.4, 8.3 Hz, 1H), 5.14 – 5.05 (m, 2H), 3.37 (dd, $J = 6.1$, 0.9 Hz, 2H), 2.65 – 2.56 (m, 2H), 2.41 – 2.30 (m, 1H), 2.17 (s, 2H), 1.70 – 1.56 (m, 2H), 1.45 – 1.26 (m, 2H).

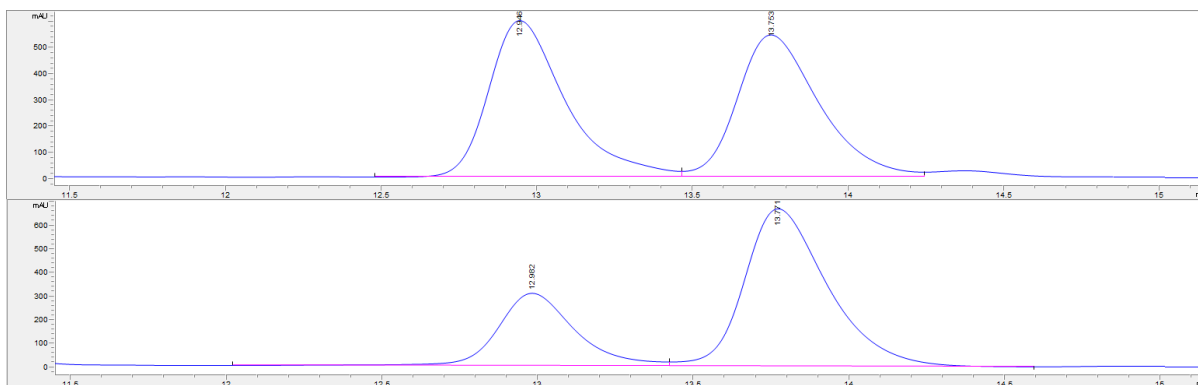
^{13}C NMR (101 MHz, CDCl_3) δ 142.7, 139.7, 128.5 (2C), 128.4 (2C), 125.8, 116.9, 45.6, 38.4, 35.9, 32.9, 31.5, 26.6.

$[\alpha]^{25}_{589} = -9$ ($c = 1.0$ in CHCl_3 , 40% ee).

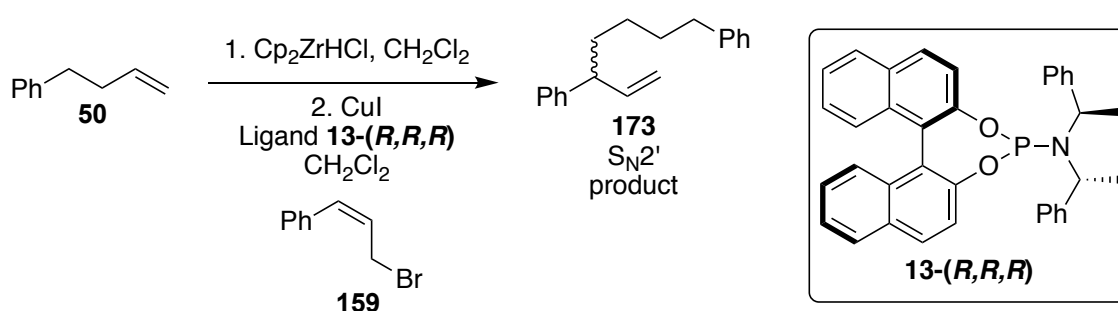
HRMS (GCMS with methane as reagent gas) m/z calcd. for $\text{C}_{14}\text{H}_{20}\text{Br}$ $[\text{M}+\text{H}]^+$: 267.0743, found: 267.0722.

IR (ATR) ν (cm^{-1} , CHCl_3): 698, 746, 919, 1454, 1496, 2931.

The enantiomeric excess was determined by HPLC analysis of the crude alcohol derived from **172** (general procedure 5) [Chiralpak® IB; hexane:*i*-PrOH 97:3; 1.0 mL/min, $\lambda=210$ nm, minor enantiomer $t_R = 12.98$ mins, major enantiomer $t_R = 13.77$ mins].



Hept-6-ene-1,5-diylidibenzene (173)



Synthesised according to general procedure 4. The crude mixture was purified by flash column chromatography (SiO_2 , 100% hexane) to give the desired product as a colourless oil (68.2 mg, 68% yield, 81:19 $\text{S}_{\text{N}}2'$: $\text{S}_{\text{N}}2$, 48% ee).

^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.22 (m, 4H), 7.24 – 7.12 (m, 6H), 5.95 (ddd, $J = 17.5$, 9.8, 7.6 Hz, 1H), 5.07 – 5.00 (m, 1H), 5.00 (q, $J = 1.4$ Hz, 1H), 3.24 (q, $J = 7.5$ Hz, 1H), 2.62 – 2.53 (m, 2H), 1.79 – 1.71 (m, 2H), 1.68 – 1.58 (m, 2H), 1.45 – 1.21 (m, 2H).

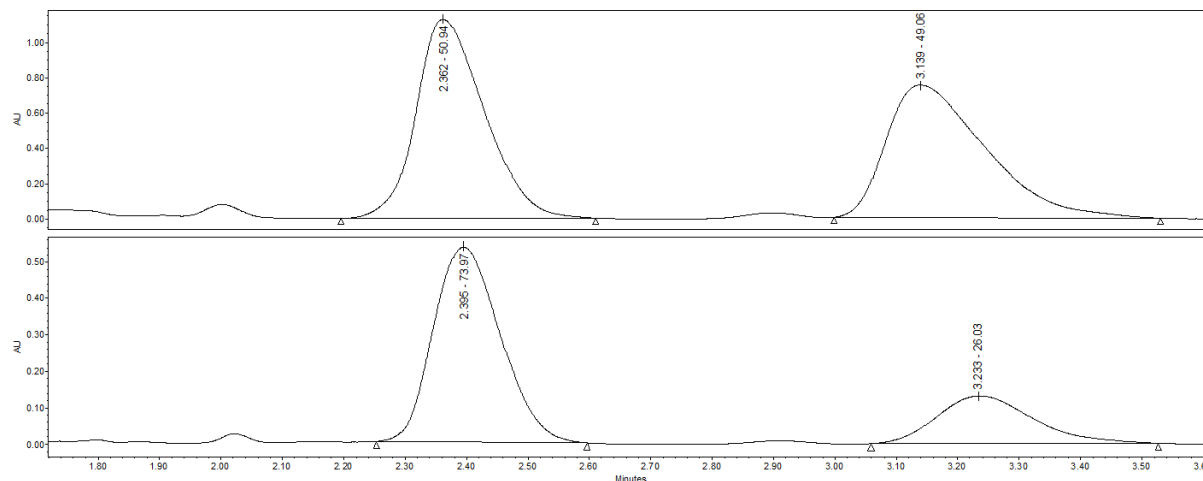
^{13}C NMR (101 MHz, CDCl_3) δ 144.7, 142.9, 142.5, 128.6 (2C), 128.5 (2C), 128.4 (2C), 127.7 (2C), 126.3, 125.7, 114.1, 50.0, 36.0, 35.4, 31.6, 27.4.

$[\alpha]_{\text{D}}^{25} = +8$ ($c = 1.0$ in CHCl_3 , 48% ee).

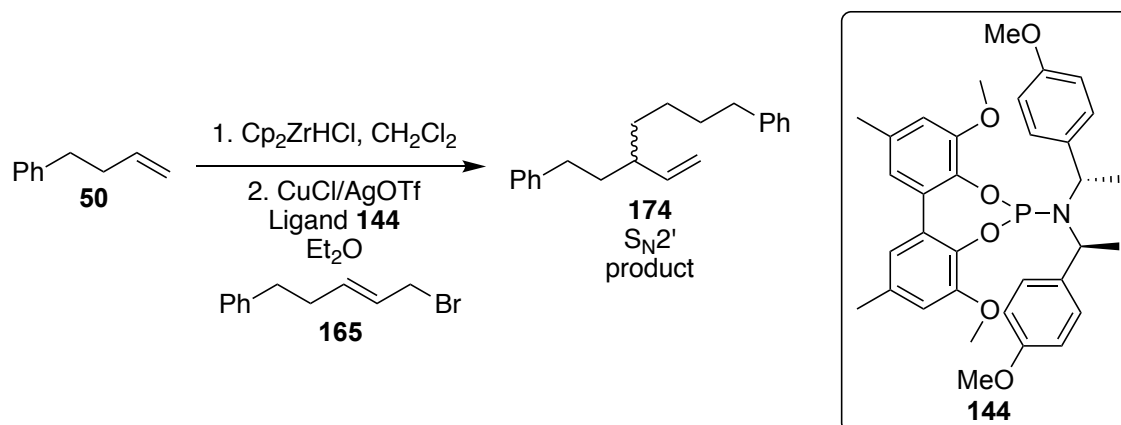
HRMS (EI) m/z calcd. for $\text{C}_{19}\text{H}_{23}$ $[\text{M}+\text{H}]^+$: 251.1794, found: 250.1756.

IR (ATR) ν (cm^{-1} , CHCl_3): 698, 747, 912, 1452, 1494.

The enantiomeric excess of 48% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; CO₂:MeOH 99:1; 1.5 mL/min; λ=210 nm; major enantiomer t_R = 2.39 mins, minor enantiomer t_R = 3.23 mins].



(3-Vinylheptane-1,7-diyl)dibenzene (**174**)



Synthesised according to general procedure 4. The crude mixture was purified by flash column chromatography (SiO₂, 0–5% Et₂O in hexane) to give the desired product as a colourless oil (68.8 mg, 62% yield, 87:13 *S_N2'*:*S_N2*, 58% ee).

¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.24 (m, 4H), 7.24 – 7.14 (m, 6H), 5.58 (ddd, *J* = 17.0, 10.3, 8.9 Hz, 1H), 5.10 – 4.95 (m, 2H), 2.71 – 2.56 (m, 4H), 2.56 – 2.45 (m, 1H), 2.05 – 1.93 (m, 1H), 1.75 – 1.52 (m, 3H), 1.46 – 1.24 (m, 3H).

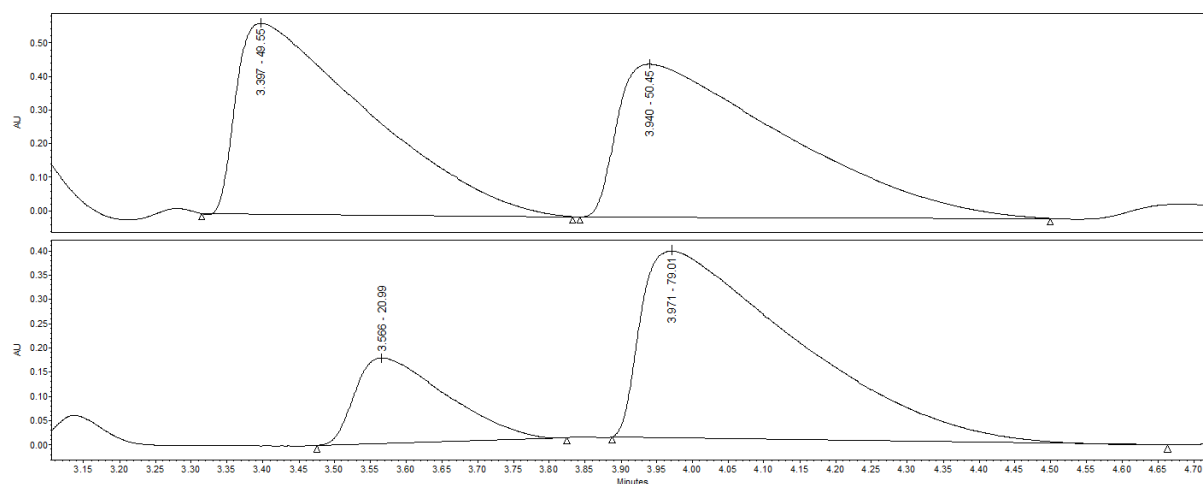
^{13}C NMR (101 MHz, CDCl_3) δ 143.1, 143.0 (2C), 128.5 (2C), 128.5 (2C), 128.4 (2C), 128.4 (2C), 125.7 (2C), 114.9, 43.8, 37.0, 36.1, 35.0, 33.7, 31.7, 27.0.

$[\alpha]^{25}_{589} = -1$ ($c = 1.0$ in CHCl_3 , 58% ee).

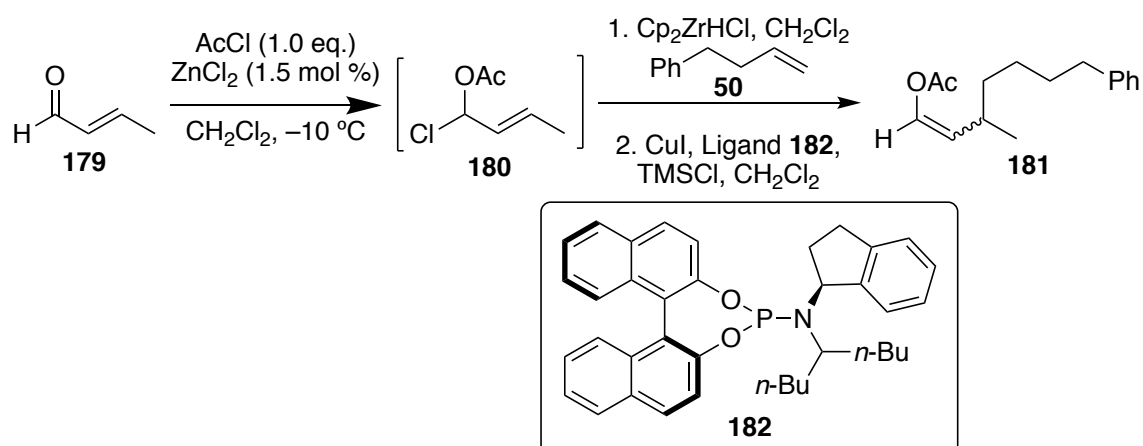
LRMS (ESI) m/z : 279.0 $[\text{M}+\text{H}]^+$

IR (ATR) ν (cm^{-1} , CHCl_3): 698, 746, 911, 1454, 1496, 2928.

The enantiomeric excess of 58% was determined by SFC [Chiralpak® ID; 1500 psi, 30 °C; CO_2 :MeOH 99.5:0.5; 1.5 mL/min; $\lambda=210$ nm; minor enantiomer $t_R = 3.57$ mins, major enantiomer $t_R = 3.97$ mins].



3-methyl-7-phenylhept-1-en-1-yl acetate (**181**)



CuI (7.7 mg, 0.04 mmol, 0.1 eq.) and ligand **182** (23.5 mg, 0.04 mmol, 0.1 eq.) were dissolved in the Et₂O (0.8 mL) under an argon atmosphere and allowed to stir for 1 hr at room temperature. In another flask Cp₂ZrHCl (206 mg, 0.80 mmol, 2.0 eq.) was added to a stirred solution of 4-phenyl-1-butene (150 µL, 1.00 mmol, 2.5 eq.) in CH₂Cl₂ (0.4 mL) at room temperature, under an argon atmosphere. After stirring for 20 mins, the resulting yellow solution turned clear. In a third flask crotonaldehyde (33 µL, 0.40 mmol, 1.0 eq.) was added to a solution of acetyl chloride (29 µL, 0.40 mmol, 1.0 eq.) and freshly fused ZnCl₂ (0.8 mg, 0.006 mmol, 0.015 eq.) in CH₂Cl₂ (0.8 mL) and stirred for 20 mins. The hydrozirconated mixture was first transferred into to the Cu/ligand mixture via syringe, followed by the solution of preformed enol acetate **180**. The reaction stirred at room temperature overnight before diluting with hexane (~3 mL) and quenching with NH₄Cl (1 M aq., ~1.5 mL). The aqueous phase was extracted with Et₂O (3 × 10 mL), the combined organic phases dried over MgSO₄ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (SiO₂, 0–5% Et₂O in pentane) to give the desired product as a colourless oil (42.1 mg, 43% yield, 19:81 *E:Z*, *E*: 59% ee, *Z*: 90% ee).

***E* Isomer:**

¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.27 (m, 2H), 7.21 – 7.13 (m, 3H), 7.06 (dd, *J* = 12.5, 1.0 Hz, 1H), 5.30 (dd, *J* = 12.5, 8.7 Hz, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.12 (s, 3H), 1.67 – 1.54 (m, 3H), 1.42 – 1.23 (m, 4H), 1.01 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 168.4, 142.9, 134.6, 128.5 (2C), 128.4 (2C), 125.7, 120.9, 37.1, 36.1, 32.5, 31.7, 27.1, 21.1, 20.9.

***Z* Isomer:**

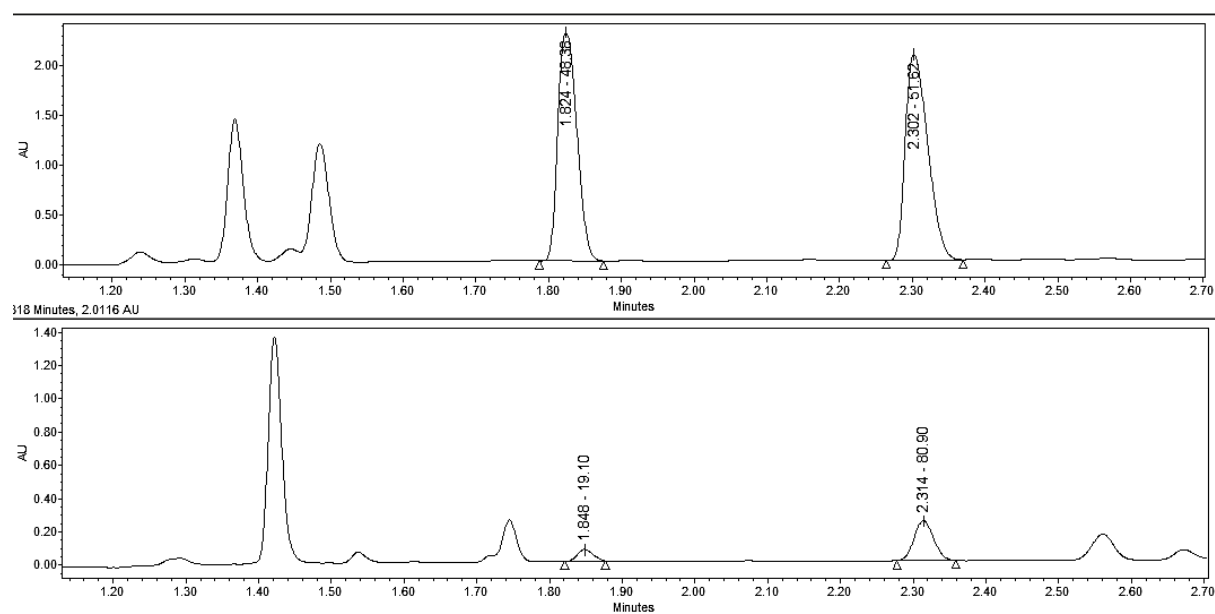
¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.24 (m, 2H), 7.24 – 7.15 (m, 3H), 6.98 (dd, *J* = 6.4, 0.9 Hz, 1H), 4.67 (dd, *J* = 9.8, 6.4 Hz, 1H), 2.65 – 2.57 (m, 2H), 2.13 (s, 3H), 1.68 – 1.58 (m, 3H), 1.43 – 1.23 (m, 4H), 0.99 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 168.3, 142.9, 133.1, 128.5 (2C), 128.4 (2C), 125.7, 120.4, 37.1, 36.1, 31.6, 29.6, 27.2, 21.1, 20.9.

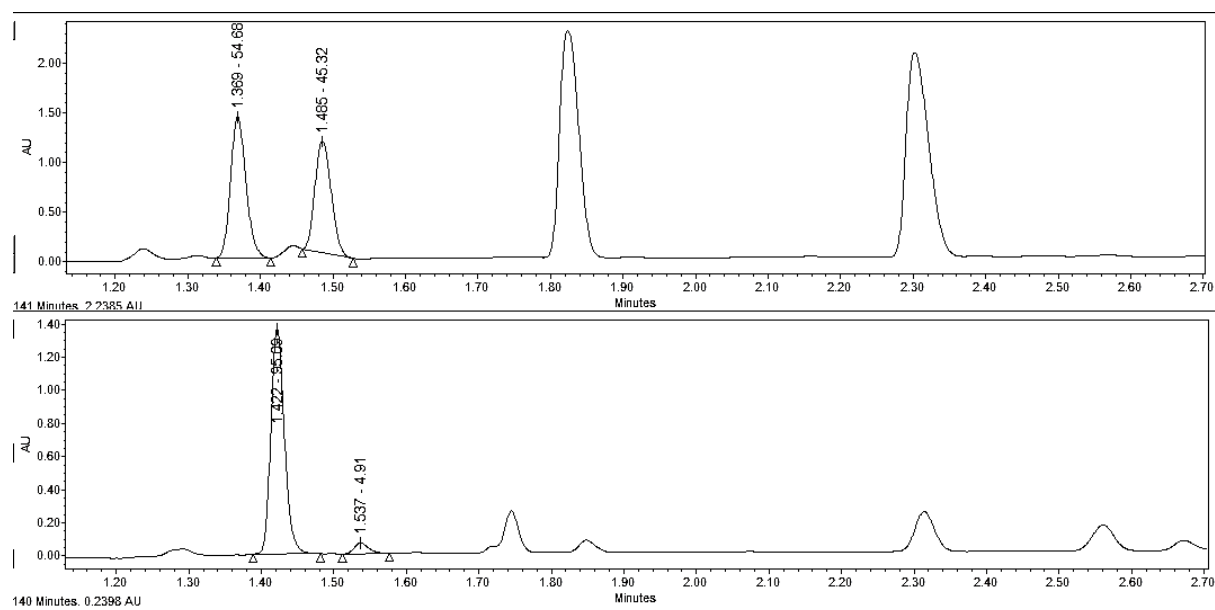
LRMS (ESI) *m/z*: 269.2 [M+Na]⁺

The enantiomeric excess of 59% (*E*) and 90% (*Z*) was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1% to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=210 nm; *E*: minor enantiomer *t_R* = 1.85 mins, major enantiomer *t_R* = 2.31 mins; *Z*: major enantiomer *t_R* = 1.42 mins, minor enantiomer *t_R* = 1.54 mins].

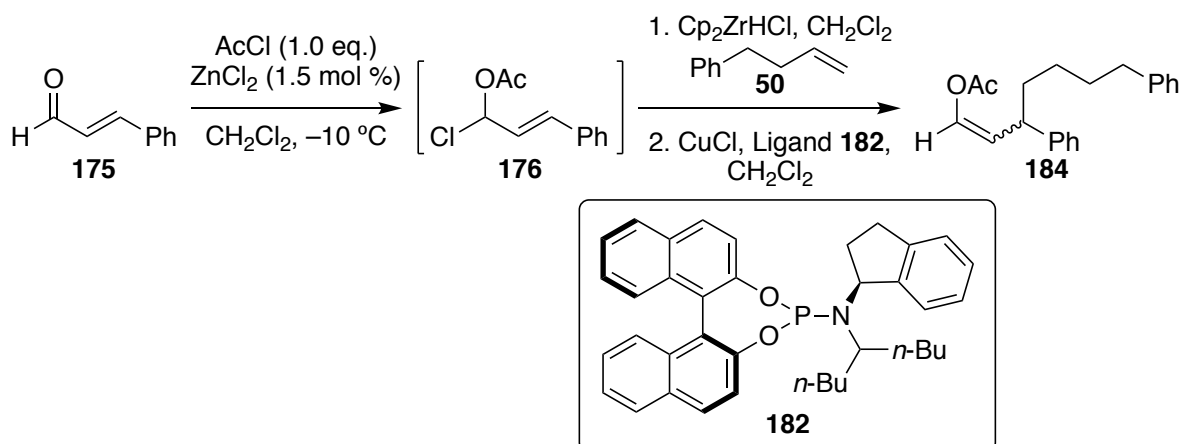
***E* Isomer:**



***Z* Isomer:**



3,7-Diphenylhept-1-en-1-yl acetate (**184**)



Synthesised according to the same procedure as for **181**. The crude mixture was purified by flash column chromatography (SiO₂, 0–5% Et₂O in pentane) to give the desired product as a colourless oil (31.9 mg, 26% yield, 28:72 *E*:*Z*, *E*: 18% ee, *Z*: 93% ee).

E Isomer:

¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.18 (m, 5H), 7.07 (d, *J* = 0.7 Hz, 6H), 5.52 (dd, *J* = 12.5, 8.9 Hz, 1H), 3.17 (q, *J* = 7.8 Hz, 1H), 2.58 – 2.47 (m, 2H), 2.04 (s, 3H), 1.74 – 1.62 (m, 1H), 1.62 – 1.51 (m, 2H), 1.42 – 1.13 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 168.3, 144.4, 142.7, 135.5, 128.7 (2C), 128.5 (2C), 128.4 (2C), 127.5 (2C), 126.5, 125.8, 118.8, 44.3, 36.0, 35.9, 31.5, 27.3, 20.9.

Z Isomer:

¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.18 (m, 4H), 7.18 – 7.06 (m, 6H), 7.02 (dd, *J* = 6.4, 0.9 Hz, 1H), 4.97 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.80 – 3.71 (m, 1H), 2.57 – 2.49 (m, 2H), 2.07 (s, 3H), 1.77 – 1.51 (m, 4H), 1.40 – 1.18 (m, 2H).

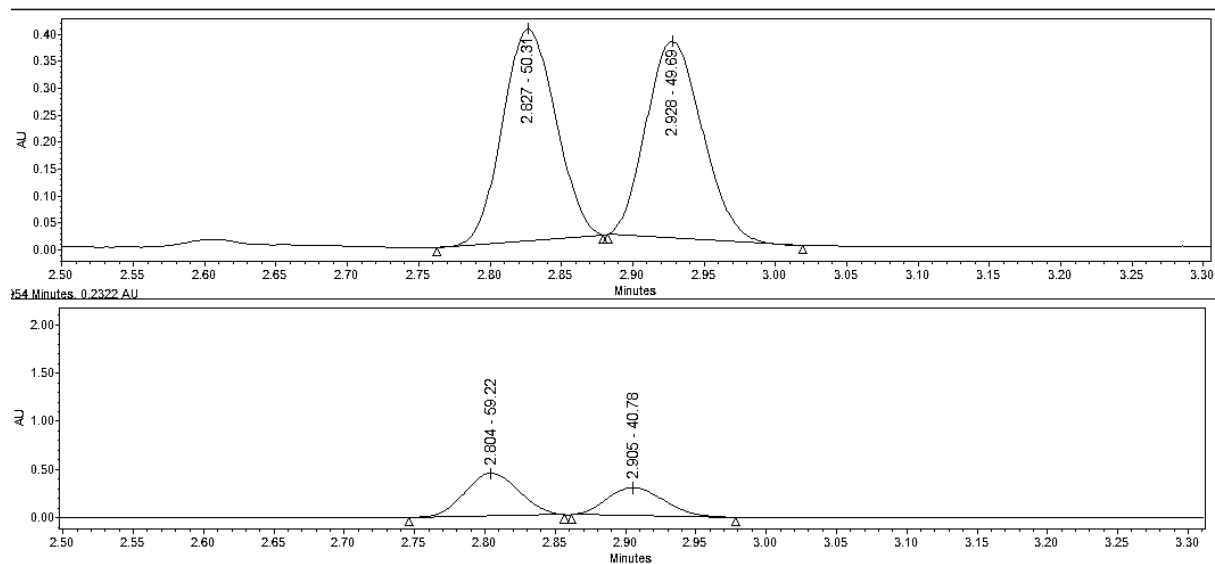
¹³C NMR (101 MHz, CDCl₃) δ 168.0, 144.8, 142.8, 133.7, 128.6 (2C), 128.5 (2C), 128.4 (2C), 127.3 (2C), 126.3, 125.8, 117.7, 41.0, 36.4, 36.0, 31.5, 27.2, 20.9.

LRMS (ESI) *m/z*: 269.2 [M+Na]⁺

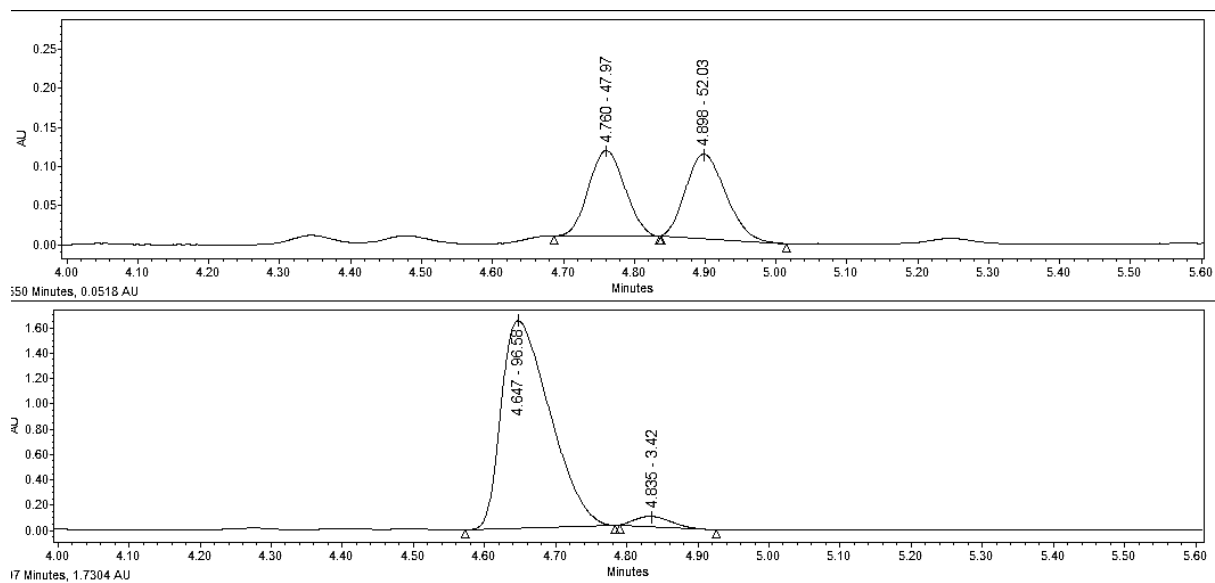
The enantiomeric excess of 18% (*E*) and 93% (*Z*) was determined by SFC [Chiralpak® IF; 1500 psi, 30 °C; 1% to 5% MeOH in 7 mins; flow: 1 mL/min; λ=215 nm; *E*: major

enantiomer $t_R = 2.80$ mins, minor enantiomer $t_R = 2.91$ mins; Z: major enantiomer $t_R = 4.65$ mins, minor enantiomer $t_R = 4.83$ mins].

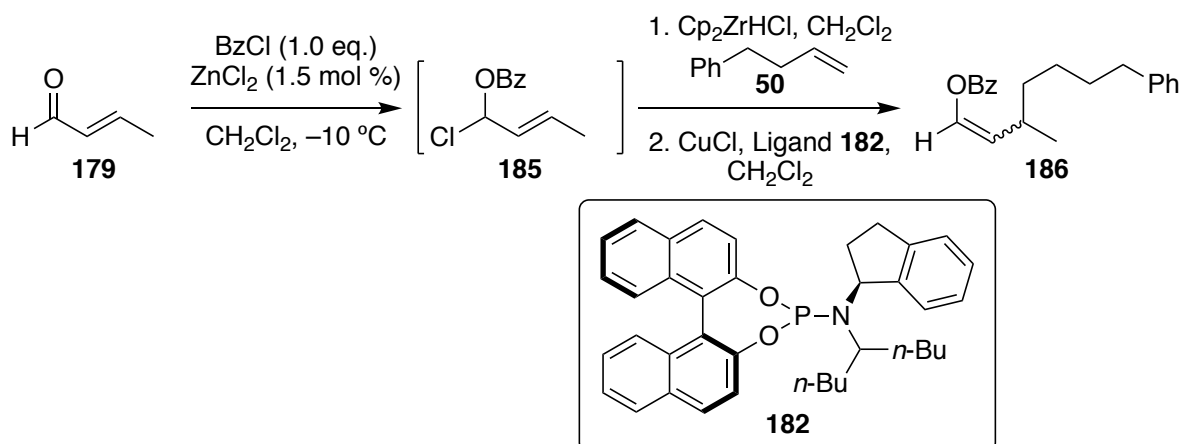
***E* Isomer:**



***Z* Isomer:**



3-Methyl-7-phenylhept-1-en-1-yl benzoate (**186**)



Synthesised according to the same procedure as for **181**. The crude mixture was purified by flash column chromatography (SiO_2 , 0–5% Et_2O in pentane) to give the desired product as a colourless oil (62.3 mg, 51% yield, 44:56 *E*:*Z*, *E*: 74% ee, *Z*: 94% ee).

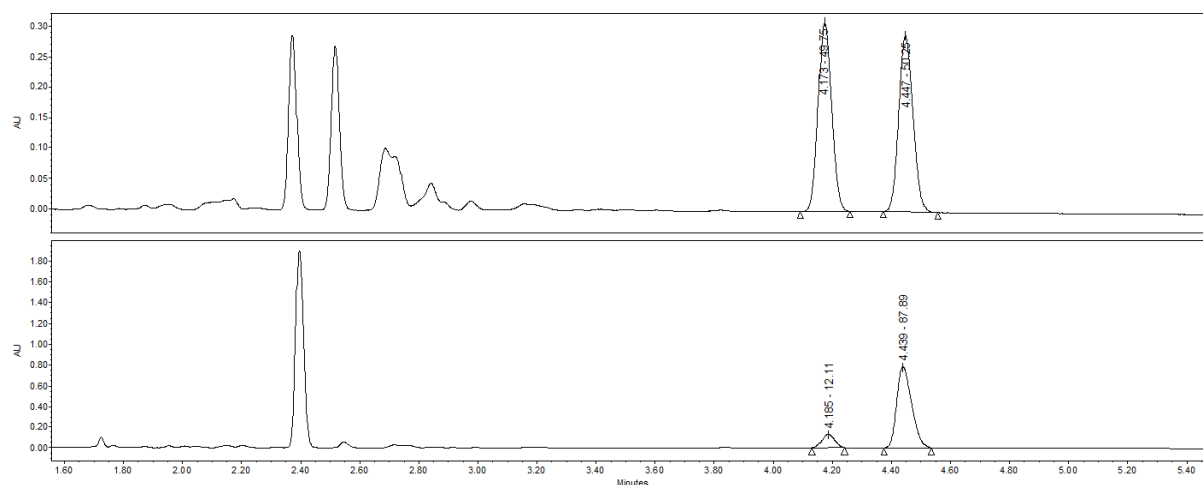
^1H NMR (400 MHz, CDCl_3) δ 8.07 – 7.98 (m, 4H), 7.57 – 7.48 (m, 2H), 7.43 – 7.37 (m, 4H), 7.25 – 7.03 (m, 12H), 5.42 (*E*, dd, J = 12.4, 8.7 Hz, 1H), 4.73 (*Z*, dd, J = 9.7, 6.4 Hz, 1H), 2.83 – 2.72 (*Z*, m, 1H), 2.60 – 2.48 (m, 4H), 2.24 – 2.06 (*E*, m, 1H), 1.62 – 1.49 (m, 6H), 1.43 – 1.16 (m, 6H), 0.99 (*E*, d, J = 6.7 Hz, 3H), 0.98 (*Z*, d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 164.0, 163.7, 142.9 (2C), 134.8, 133.5, 133.5, 133.4, 130.0 (6C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.5 (2C), 128.3 (2C), 125.7 (2C), 125.7 (2C), 121.5, 120.9, 37.2, 37.1, 36.1, 36.1, 32.7, 31.7, 31.7, 29.9, 27.3, 27.1, 21.2, 21.1.

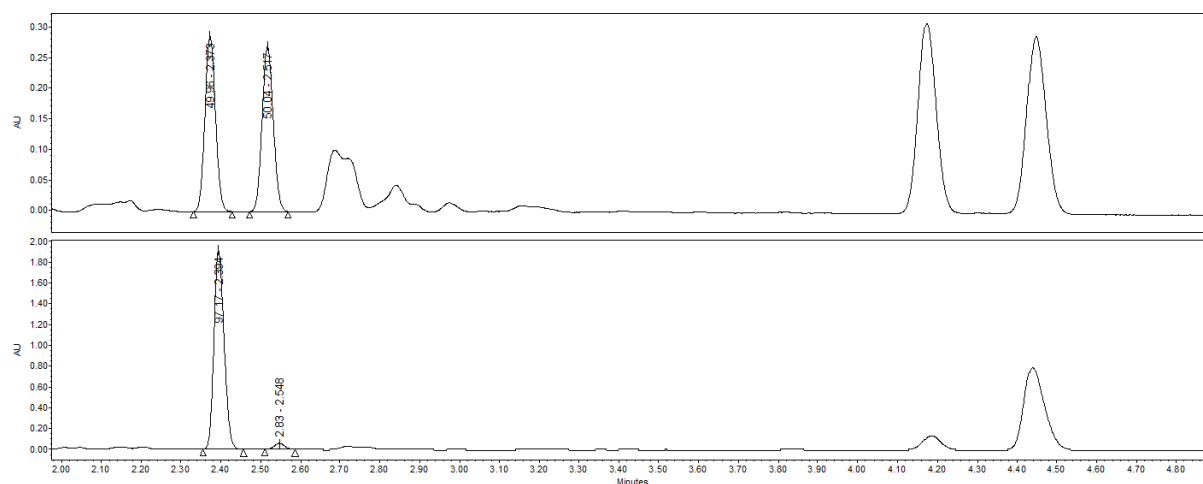
LRMS (ESI) m/z : 331.2 $[\text{M}+\text{Na}]^+$

The enantiomeric excess of 74% (*E*) and 94% (*Z*) was determined by SFC [Chiralpak® IG; 1500 psi, 30 $^\circ\text{C}$; 1% to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =230 nm; *E*: minor enantiomer t_R = 4.19 mins, major enantiomer t_R = 4.44 mins; *Z*: major enantiomer t_R = 2.39 mins, minor enantiomer t_R = 2.55 mins].

***E* Isomer:**

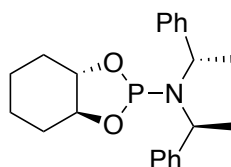


***Z* Isomer:**



(3*aS*,7*aS*)-*N,N*-Bis((*S*)-1-phenylethyl)hexahydrobenzo[*d*][1,3,2]dioxaphosphol-2-amine

(191)



Freshly distilled PCl_3 (97 μL , 1.1 mmol, 1.0 eq.) was added dropwise over about 1 min to a stirred and cooled (0 $^\circ\text{C}$) solution of Et_3N (1.2 mL, 8.8 mmol, 8.0 eq.) in CH_2Cl_2 (2.5 mL) under an argon atmosphere. (*S,S*)-*Bis*(1-phenylethyl)amine (250 mg, 1.1 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL) was added to the cooled reaction mixture before stirring was continued for

2 hrs at room temperature. The reaction mixture was then cooled to 0 °C and (*S,S*)-*trans*-cyclohexanediol (128 mg, 1.1 mmol, 1.0 eq.) was added and stirring was then continued at room temperature overnight. The reaction mixture was concentrated in vacuo. The crude product was taken up in toluene (~10 mL) and filtered over a short pad of alumina, washing with more toluene. The filtrate was concentrated *in vacuo* and the residue purified by flash column chromatography (Alumina, 100% toluene) to give pure **191** as a white solid (68 mg, 17% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.15 – 7.04 (m, 10H), 4.55 – 4.46 (m, 2H), 3.64 (ddd, *J* = 12.0, 9.0, 3.8 Hz, 1H), 3.45 (ddd, *J* = 12.0, 9.0, 3.8 Hz, 1H), 2.29 – 2.19 (m, 2H), 1.86 – 1.76 (m, 2H), 1.67 (d, *J* = 7.1 Hz, 6H), 1.62 – 1.53 (m, 1H), 1.44 – 1.23 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 143.4, 143.4, 128.0 (2C), 128.0 (2C), 127.9 (4C), 126.6 (2C), 80.8 (d, *J* = 2.0 Hz), 78.9 (d, *J* = 6.0 Hz), 53.8, 53.7, 30.9 (d, *J* = 6.2 Hz), 30.2 (d, *J* = 5.0 Hz), 24.3, 24.1, 22.7, 22.6.

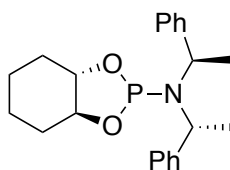
³¹P NMR (162 MHz, CDCl₃) δ 144.70.

[α]²⁵₅₈₉ = –194 (c = 1.0 in CHCl₃).

HRMS (CI with ammonia as the reagent gas) *m/z* calcd. for C₂₂H₂₉NO₂P [M+H]⁺: 370.1930, found: 370.1950.

IR (ATR) ν (cm⁻¹, CHCl₃): 696, 766, 1029, 1097, 2943, 3025.

(3a*S*,7a*S*)-*N,N*-Bis((*R*)-1-phenylethyl)hexahydrobenzo[*d*][1,3,2]dioxaphosphol-2-amine
(192)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white crystalline solid (67 mg, 17% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.16 – 7.03 (m, 10H), 4.65 – 4.54 (m, 2H), 3.54 – 3.37 (m, 2H), 2.31 – 2.19 (m, 2H), 1.87 – 1.78 (m, 2H), 1.71 (d, *J* = 7.2 Hz, 6H), 1.68 – 1.59 (m, 1H), 1.49 – 1.27 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 143.3 (2C), 127.9 (2C), 127.9 (2C), 127.9 (4C), 126.6 (2C), 81.1 (d, *J* = 2.8 Hz), 78.4 (d, *J* = 5.9 Hz), 52.8, 52.7, 30.9 (d, *J* = 5.5 Hz), 30.1 (d, *J* = 4.7 Hz), 24.3, 24.1, 22.5, 22.4.

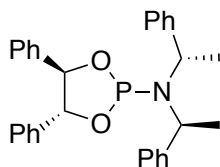
³¹P NMR (162 MHz, CDCl₃) δ 142.66.

[α]²⁵₅₈₉ = +220 (c = 1.0 in CHCl₃).

HRMS (CI with methane as the reagent gas) *m/z* calcd. for C₂₂H₂₉NO₂P [M+H]⁺: 370.1930, found: 370.1934.

IR (ATR) ν (cm⁻¹, CHCl₃): 696, 765, 1030, 1449, 2938, 3028.

(4*R*,5*R*)-4,5-Diphenyl-*N,N*-bis((*S*)-1-phenylethyl)-1,3,2-dioxaphospholan-2-amine (193)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (319 mg, 62% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.31 (m, 3H), 7.27 – 7.22 (m, 6H), 7.21 – 7.11 (m, 11H), 4.90 (d, *J* = 1.0 Hz, 2H), 4.86 – 4.74 (m, 2H), 1.79 (d, *J* = 7.2 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 143.0 (2C), 137.8 (d, *J* = 8.0 Hz), 136.1 (d, *J* = 8.0 Hz), 128.6 – 128.3 (m, 4C), 128.0 – 127.7 (m, 8C), 127.4 – 127.0 (m, 2C), 126.9 – 126.4 (m, 6C), 84.9 (d, *J* = 2.9 Hz), 82.6 (d, *J* = 5.8 Hz), 52.6, 52.5, 22.8 – 21.9 (m, 2C).

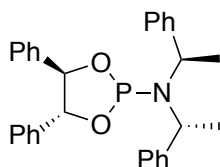
³¹P NMR (162 MHz, CDCl₃) δ 148.37.

[α]_D²⁵ = −189 (c = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₃₀H₃₁NO₂P [M+H]⁺: 468.2087, found: 468.2088.

IR (ATR) ν (cm^{−1}, CHCl₃): 697, 720, 996, 1205, 1451, 2971.

(4*R*,5*R*)-4,5-Diphenyl-*N,N*-bis((*R*)-1-phenylethyl)-1,3,2-dioxaphospholan-2-amine (194)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white foam (372 mg, 36% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.27 (m, 6H), 7.25 – 7.19 (m, 4H), 7.16 – 7.06 (m, 10H), 4.99 (d, *J* = 8.7 Hz, 1H), 4.91 (d, *J* = 8.7 Hz, 1H), 4.79 – 4.67 (m, 2H), 1.82 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 143.0 (2C), 138.1 (d, *J* = 8.0 Hz), 136.5 (d, *J* = 5.0 Hz), 128.5 (2C), 128.4, 128.4, 128.0 – 127.7 (m, 10C), 127.4 (2C), 126.6 (2C), 126.4 (2C), 84.6 (d, *J* = 4.1 Hz), 82.9 (d, *J* = 6.3 Hz), 53.1, 53.0, 22.9 – 22.6 (m, 2C).

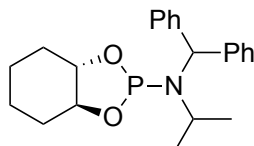
³¹P NMR (162 MHz, CDCl₃) δ 149.43.

[α]_D²⁵ = +191 (c = 1.0 in CHCl₃).

HRMS (CI with methane as the reagent gas) *m/z* calcd. for C₃₀H₃₁NO₂P [M+H]⁺: 468.2087, found: 468.2093.

IR (ATR) ν (cm⁻¹, CHCl₃): 697, 782, 1008, 1205, 1305, 2841, 3030.

(3a*S*,7a*S*)-*N*-Benzhydryl-*N*-isopropylhexahydrobenzo[*d*][1,3,2]dioxaphosphol-2-amine (195)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B using amine **362**. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white crystalline solid (55 mg, 14% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.29 (m, 8H), 7.29 – 7.21 (m, 2H), 5.79 (d, *J* = 12.2 Hz, 1H), 3.82 (hept, *J* = 6.7 Hz, 1H), 3.47 – 3.38 (m, 1H), 3.37 – 3.28 (m, 1H), 2.28 – 2.21 (m, 1H), 2.19 – 2.11 (m, 1H), 1.85 – 1.70 (m, 2H), 1.67 – 1.53 (m, 1H), 1.35 – 1.27 (m, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 143.4 (d, *J* = 3.4 Hz), 143.3 (d, *J* = 4.7 Hz), 129.3, 129.2, 129.0, 129.0, 128.3 (d, *J* = 1.0 Hz, 4C), 126.9, 126.9, 81.0 (d, *J* = 2.5 Hz), 78.5 (d, *J* = 6.1

Hz), 61.1, 60.9, 47.1, 47.1, 30.8 (d, $J = 5.7$ Hz), 30.1 (d, $J = 4.5$ Hz), 24.2 (d, $J = 12.4$ Hz), 24.1 – 23.9 (m).

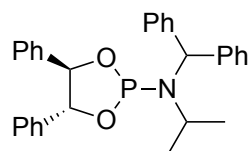
^{31}P NMR (162 MHz, CDCl_3) δ 145.05.

$[\alpha]^{25}_{589} = +13$ ($c = 1.0$ in CHCl_3).

HRMS (CI with methane as the reagent gas) m/z calcd. for $\text{C}_{22}\text{H}_{29}\text{NO}_2\text{P}$ $[\text{M}+\text{H}]^+$: 370.1930, found: 370.1939.

IR (ATR) ν (cm^{-1} , CHCl_3): 698, 775, 1018, 1200, 1307, 2937, 3027.

(4*R*,5*R*)-*N*-Benzhydryl-*N*-isopropyl-4,5-diphenyl-1,3,2-dioxaphospholan-2-amine (196)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B, using amine **362**. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white crystalline solid (276 mg, 54% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.29 (m, 12H), 7.29 – 7.23 (m, 3H), 7.23 – 7.16 (m, 3H), 7.11 – 7.05 (m, 2H), 5.90 (d, $J = 13.3$ Hz, 1H), 4.90 – 4.77 (m, 2H), 4.09 (h, $J = 6.6$ Hz, 1H), 1.36 (d, $J = 6.7$ Hz, 3H), 1.15 (d, $J = 6.7$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 143.4 (d, $J = 4.3$ Hz), 143.2 (d, $J = 3.6$ Hz), 138.1 (d, $J = 8.0$ Hz), 136.7 (d, $J = 4.5$ Hz), 129.1, 129.1, 128.8, 128.8, 128.5 (2C), 128.4 (2C), 128.4, 128.3 (2C), 128.3 (2C), 128.2, 127.4 (2C), 127.0, 126.9, 126.3 (2C), 84.6 (d, $J = 4.6$ Hz), 83.1 (d, $J = 6.3$ Hz), 60.6 (d, $J = 17.5$ Hz), 46.8 (d, $J = 3.5$ Hz), 24.0 – 23.4 (m, 2C).

^{31}P NMR (162 MHz, CDCl_3) δ 151.52.

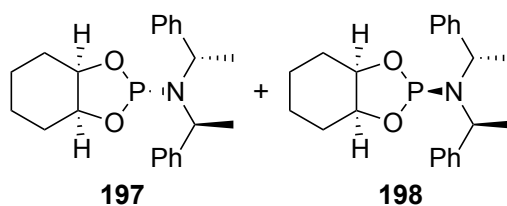
$[\alpha]^{25}_{589} = -5$ ($c = 1.0$ in CHCl_3).

HRMS (ESI) m/z calcd. for $\text{C}_{30}\text{H}_{31}\text{NO}_2\text{P}$ $[\text{M}+\text{H}]^+$: 468.2087, found: 468.2085.

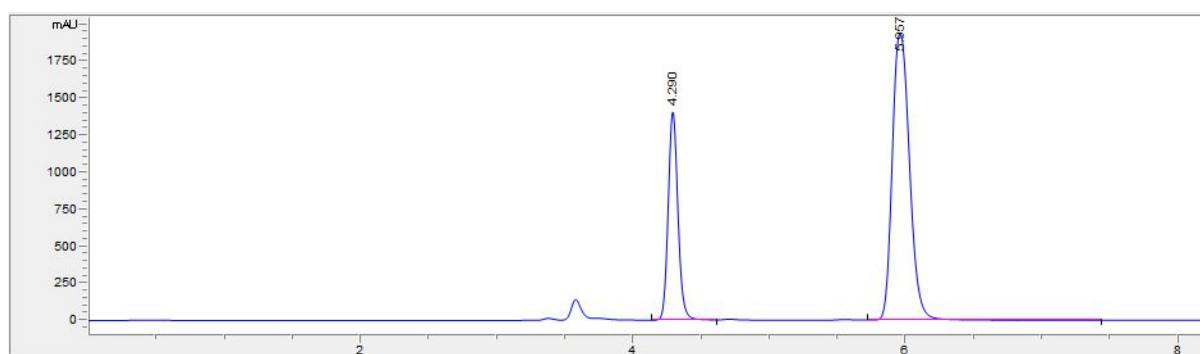
IR (ATR) ν (cm^{-1} , CHCl_3): 698, 790, 1001, 1159, 1453, 2969, 3030.

(3a*R*,7a*S*)-*N,N*-Bis((*S*)-1-phenylethyl)hexahydrobenzo[*d*][1,3,2]dioxaphosphol-2-amine

(197 + 198)



Freshly distilled PCl_3 (97 μL , 1.1 mmol, 1.0 eq.) was added dropwise over about 1 min to a stirred and cooled (0 $^\circ\text{C}$) solution of Et_3N (1.2 mL, 8.8 mmol, 8.0 eq.) in CH_2Cl_2 (2.5 mL) under an argon atmosphere. (*S,S*)-Bis(1-phenylethyl)amine (250 mg, 1.1 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL) was added to the cooled reaction mixture as a solution, before stirring was continued for 2 hrs at room temperature. The reaction mixture was then cooled to 0 $^\circ\text{C}$ and *cis*-1,2-cyclohexanediol (128 mg, 1.1 mmol, 1.0 eq.) was added, and stirring was then continued at room temperature overnight. The reaction mixture was concentrated *in vacuo*. The crude product was taken up in toluene (~10 mL), filtered over a short pad of alumina and washed with more toluene (30 mL). The filtrate was concentrated *in vacuo* and the two isomers separated by chiral preparative HPLC [Chiralpak® IC; hexane:*i*-PrOH 99:1; 1 mL/min, λ =210 nm, minor t_R = 4.29 mins, major t_R = 5.96 mins].



Minor Isomer (197): white solid (45.8 mg, 6% yield)

^1H NMR (400 MHz, CDCl_3) δ 7.15 – 7.01 (m, 10H), 4.56 – 4.43 (m, 3H), 4.37 (dt, $J = 4.8$, 2.4 Hz, 1H), 2.04 – 1.94 (m, 1H), 1.93 – 1.70 (m, 3H), 1.67 (d, $J = 7.2$ Hz, 6H), 1.63 – 1.56 (m, 1H), 1.55 – 1.47 (m, 1H), 1.35 (ddt, $J = 10.7$, 7.1, 3.7 Hz, 1H), 1.28 – 1.17 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 143.4 (2C), 127.9 (2C), 127.9 (2C), 127.9 (4C), 126.5 (2C), 74.7 (d, $J = 6.9$), 73.6 (d, $J = 7.1$), 52.9, 52.8, 29.7 (d, $J = 3.7$), 29.4 (d, $J = 5.3$), 22.6, 22.5, 21.6, 20.6.

^{31}P NMR (162 MHz, CDCl_3) δ 143.82.

$[\alpha]_{589}^{25} = -139$ ($c = 1.0$ in CHCl_3).

HRMS (GCMS with ammonia as the reagent gas) m/z calcd. for $\text{C}_{22}\text{H}_{29}\text{NO}_2\text{P}$ $[\text{M}+\text{H}]^+$: 370.1930, found: 370.1934.

IR (ATR) ν (cm^{-1} , CHCl_3): 698, 755, 986, 1125, 1449, 2935.

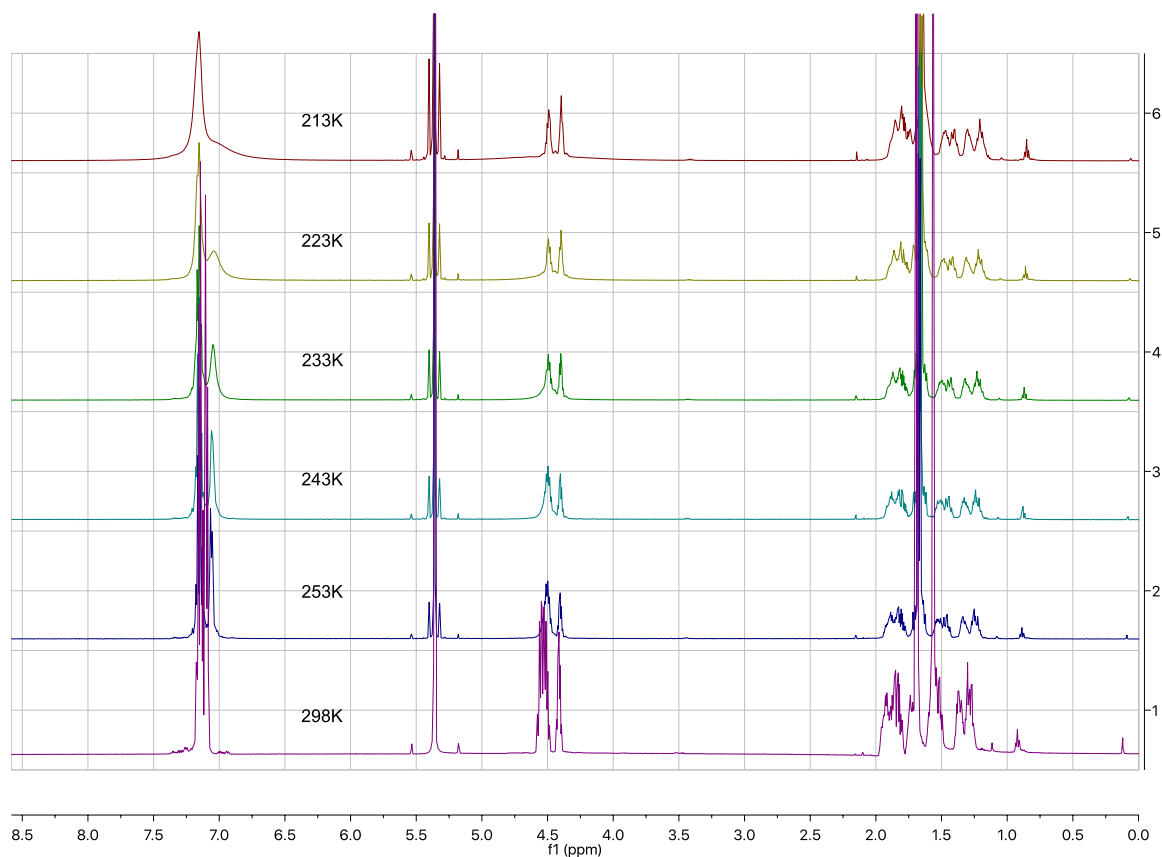
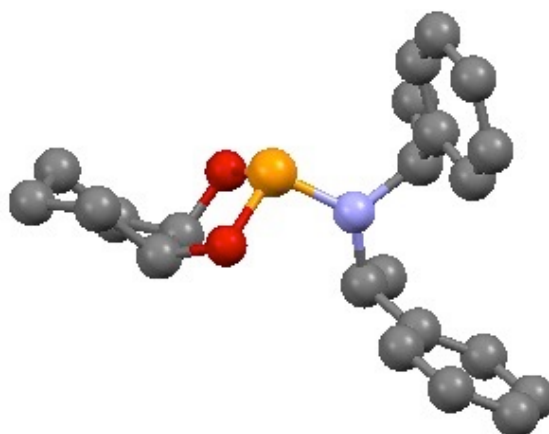


Figure 5.1 VT NMR for **197**

Table 5.1 X-Ray Crystal Structure for (197)



Formula	C ₂₂ H ₂₈ N ₁₀ O ₂ P ₁
mol weight	369.44
Crystal system	monoclinic
T [K]	150
Space group	P 21
a [Å]	6.7383(1)
b [Å]	8.7443(2)
c [Å]	16.9390(3)
α [°]	90
β [°]	92.2747(18)
γ [°]	90
V [Å³]	997.29(3)
Z	2
D_{calc} [g cm⁻³]	1.230
F(0 0 0)	396
μ [mm⁻¹]	1.335
Crystal size [mm]	0.06 * 0.12 * 0.18
Colour, shape	Clear pale colourless, block
R_{int}	2.69
θ_{min}, θ_{max} [deg]	5.226 - 76.343
Total refl. (before merge)	20372
Data (I > 3.0/sigma(I))	4126, 1, 236
[reflections, restraints, parameters]	
S (=GooF)	0.999
Min. and max. Resd. Dens., [e/Å³]	-0.16
	0.15
Threshold Expression	I > 2sigma(I)
R₁	0.0263
wR₂	0.0677
Flack	(-)-0.019(13)

Major Isomer (198): white solid (104 mg, 13% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.16 – 7.03 (m, 10H), 4.72 (s, 2H), 4.20 – 4.07 (m, 2H), 1.95 (dt, $J = 21.2, 5.1$ Hz, 2H), 1.86 (dq, $J = 11.8, 4.3$ Hz, 2H), 1.70 (d, $J = 7.2$ Hz, 6H), 1.63 – 1.51 (m, 2H), 1.42 – 1.29 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 143.4 (2C), 128.0 (2C), 128.0 (2C), 127.9 (4C), 126.6 (2C), 71.9, 71.8, 52.1, 52.0, 30.1 (d, $J = 2.2$), 30.1 (d, $J = 3.1$), 22.5 – 22.3 (m, 2C), 21.8, 21.4.

^{31}P NMR (162 MHz, CDCl_3) δ 150.25.

$[\alpha]_{589}^{25} = -235$ ($c = 1.0$ in CHCl_3).

HRMS (CI with methane as the reagent gas) m/z calcd. for $\text{C}_{22}\text{H}_{29}\text{NO}_2\text{P}$ $[\text{M}+\text{H}]^+$: 370.1930, found: 370.1940.

IR (ATR) ν (cm^{-1} , CHCl_3): 698, 770, 989, 1126, 1450, 2935.

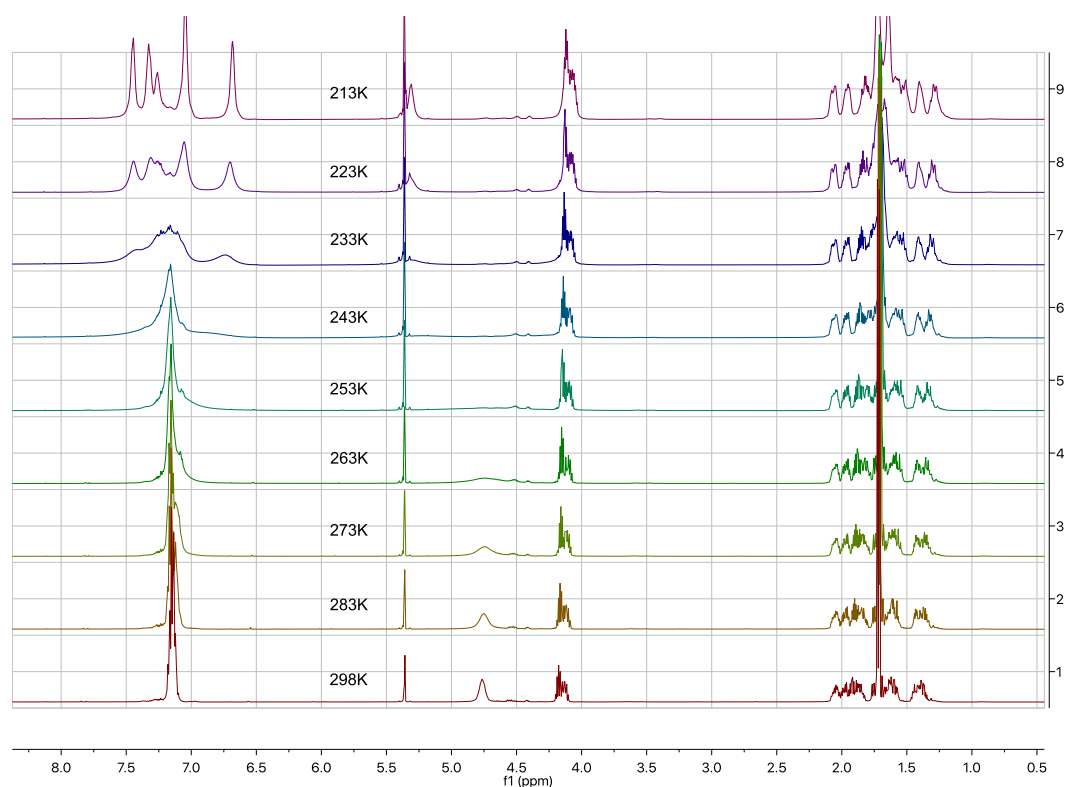


Figure 5.2 VT NMR for **198**

NOESY NMR for **198** at 213 K

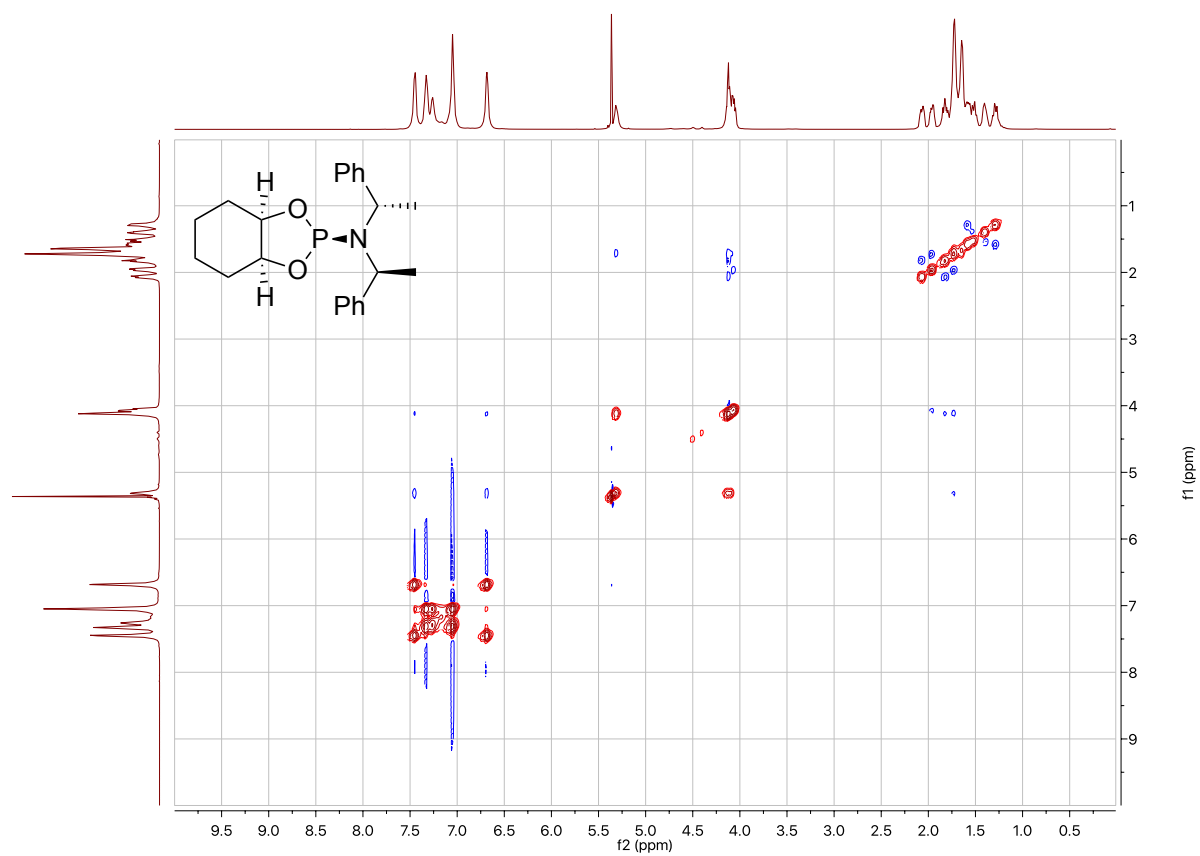
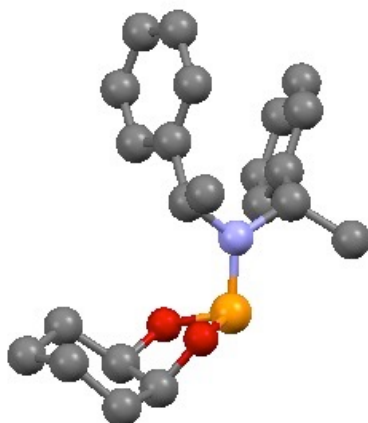


Figure 5.3 NOESY NMR for **198** at 213 K

Table 5.2 X-Ray Crystal Structure for (198)



Formula	C ₂₂ H ₂₈ N ₁ O ₂ P ₁
mol weight	369.44
Crystal system	monoclinic
T [K]	150
Space group	P 21
a [Å]	6.6591(2)
b [Å]	18.0087(5)
c [Å]	8.2314(3)
α [°]	90
β [°]	95.729(3)
γ [°]	90
V [Å³]	982.19(5)
Z	2
D_{calc} [g cm⁻³]	1.249
F(0 0 0)	396
μ [mm⁻¹]	1.356
Crystal size [mm]	0.02 * 0.11 * 0.20
Colour, shape	Clear pale colourless, prism
R_{int}	3.42
θ_{min}, θ_{max} [deg]	4.911 - 74.785
Total refl. (before merge)	9071
Data (I > 3.0/sigma(I))	3695, 1, 236
[reflections, restraints, parameters]	
S (=GooF)	1.001
Min. and max. Resd. Dens., [e/Å³]	-0.26
	0.43
Threshold Expression	I > 2sigma(I)
R₁	0.0335
wR₂	0.0878
Flack	(-)0.010(15)

gNMR Studies for (198)

Using the gNMR modelling package to simulate the spectra corresponding to the axial and equatorial protons which allowed us to estimate rate constants (k) for exchange at each temperature.

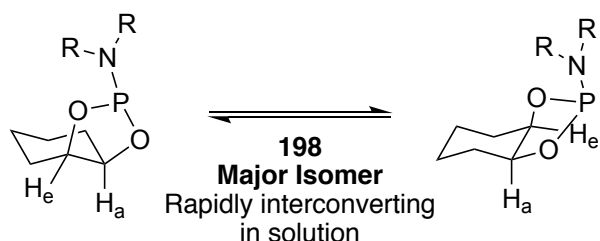


Figure 5.4 The two chair conformations of **198** rapidly interconvert in solution at room temperature.

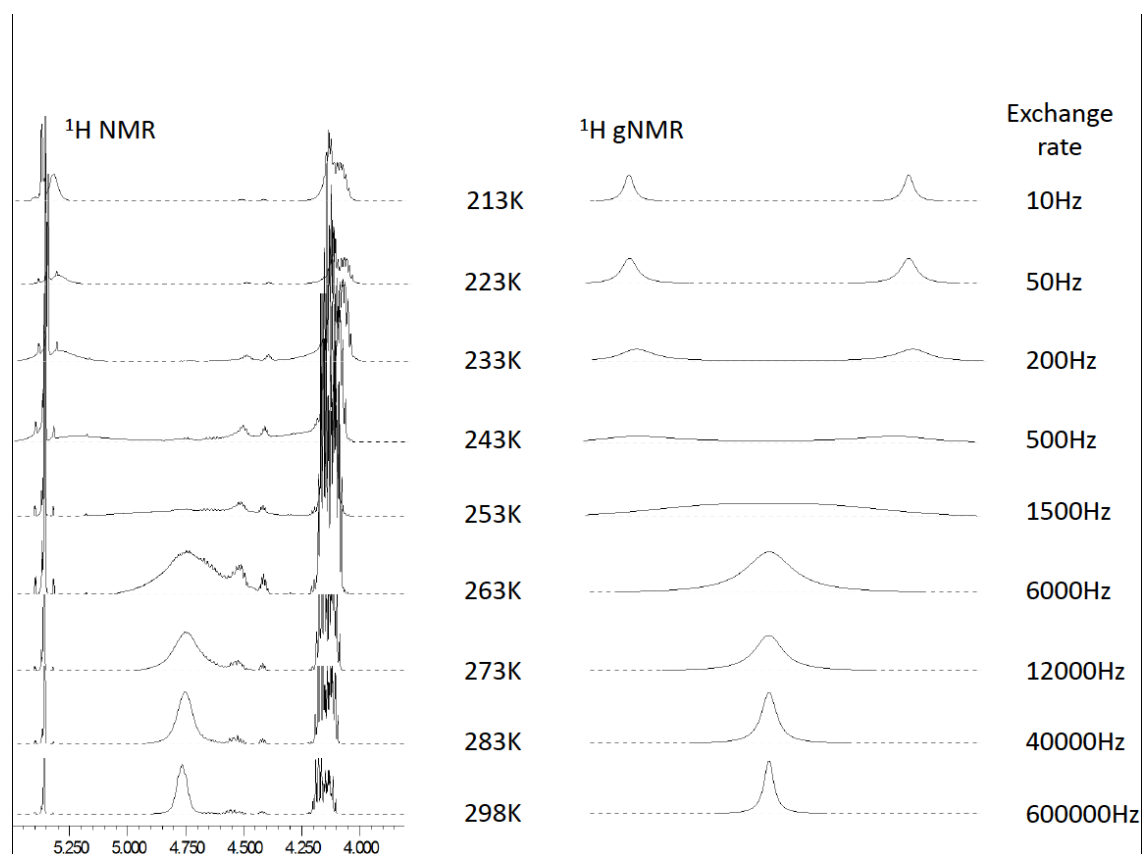
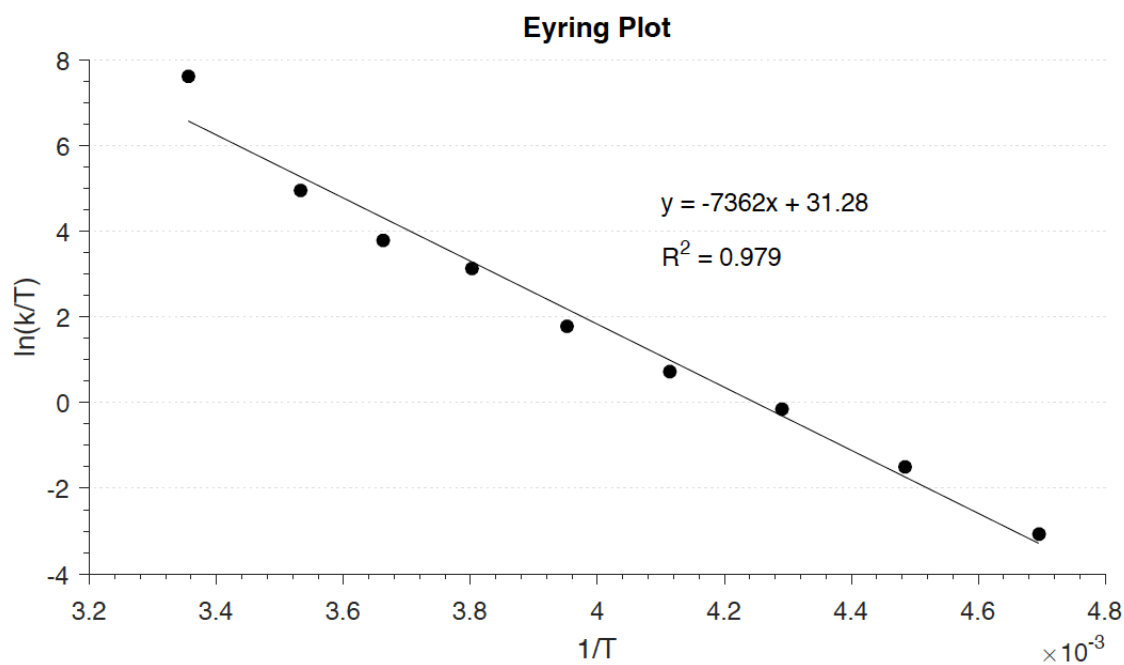


Figure 5.6 gNMR modelling for the axial and equatorial protons of **198**

These rate constants, k , were used to construct an Eyring plot (Figure 5.7), from which $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were obtained. Inserting the values for $\Delta H^\ddagger$ and $\Delta S^\ddagger$ into the Gibbs free energy equation ($\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$) enabled the barrier to isomerisation to be calculated at room temperature (298 K), corresponding to a rate of $\sim 600,000 \text{ s}^{-1}$.

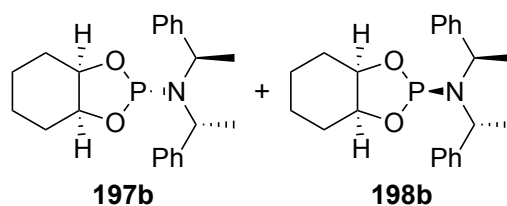
Table 5.3 Eyring plot values

$\ln(k/T)$	$1/T$
-3.058707073	0.004694836
-1.495148766	0.004484305
-0.152721087	0.004291845
0.721546655	0.004115226
1.779830898	0.003952569
3.127360716	0.003802281
3.783190134	0.003663004
4.951187835	0.003533569
7.607591448	0.003355705

**Figure 5.7** Eyring plot**Table 5.4** Thermodynamic values for **198**

Ligand 198	
$\Delta H^\ddagger$ (J mol ⁻¹)	0.000831
$\Delta S^\ddagger$ (J K ⁻¹ mol ⁻¹)	-197.4
$\Delta G^\ddagger$ (kJ mol ⁻¹)	58.83

(3a*R*,7a*S*)-*N,N*-Bis((*R*)-1-phenylethyl)hexahydrobenzo[*d*][1,3,2]dioxaphosphol-2-amine
(197b + 198b)



Synthesised according to general procedure 2: phosphoramidite ligand synthesis B. Flash column chromatography (Alumina, 100% toluene) gave the pure product as a white solid (82.3 mg, 10% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.19 – 7.00 (m, 15H), 4.72 (s, 2H, major), 4.49 (dtd, *J* = 15.6, 6.6, 6.1, 2.3 Hz, 1.5H, minor), 4.37 (dd, *J* = 4.7, 3.1 Hz, 0.5H, minor), 4.20 – 4.08 (m, 2H, major), 2.07 – 1.93 (m, 3H), 1.93 – 1.78 (m, 3H), 1.70 (d, *J* = 7.2 Hz, 6H, major), 1.68 (d, *J* = 7.1 Hz, 3H, minor), 1.63 – 1.49 (m, 3H), 1.44 – 1.29 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 145.1 – 142.1 (m, 4C), 128.0 (major, 2C), 127.9 (minor, 2C), 127.9 (4C), 127.8 (2C), 126.6 (major, 2C), 126.5 (minor, 2C), 74.7 (d, *J* = 6.9 Hz, minor), 73.6 (d, *J* = 7.2 Hz, minor), 71.9 (major), 71.8 (major), 52.9 (minor), 52.8 (minor), 52.1 (major), 51.9 (major), 30.1 (d, *J* = 1.5 Hz, major), 30.1 (d, *J* = 3.3 Hz, major), 29.7 (d, *J* = 3.2 Hz, minor), 29.4 (d, *J* = 4.6 Hz, minor), 22.6, 22.5, 21.8 (major), 21.6 (minor), 21.4 (major), 20.6 (minor).

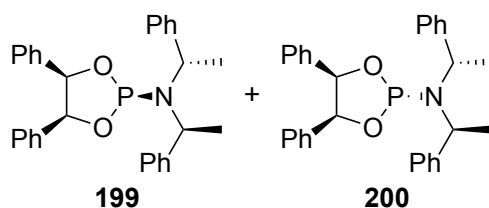
³¹P NMR (162 MHz, CDCl₃) δ 150.24 (major), 143.80 (minor).

[α]_D²⁵₅₈₉ = +209 (*c* = 1.0 in CHCl₃).

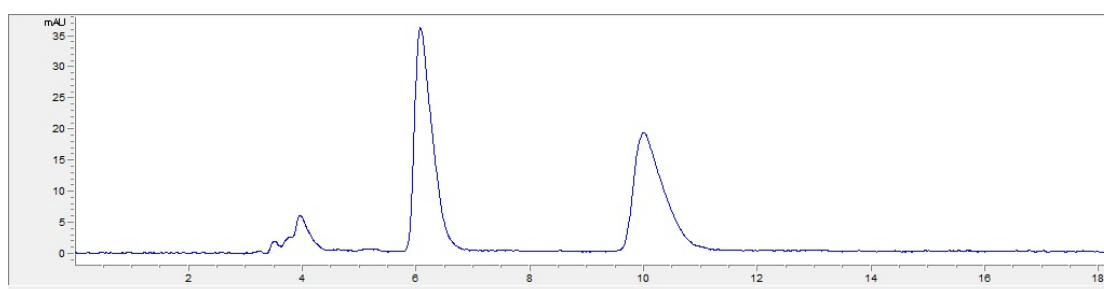
HRMS (ESI) *m/z* calcd. for C₂₂H₂₉NO₂P [M+H]⁺: 370.1930, found: 370.1928.

IR (ATR) ν (cm⁻¹, CHCl₃): 698, 769, 988, 1126, 1450, 2936.

(4*S*,5*R*)-4,5-Diphenyl-*N,N*-bis((*S*)-1-phenylethyl)-1,3,2-dioxaphospholan-2-amine (199 + 200)



Freshly distilled PCl_3 (190 μL , 2.2 mmol, 1.0 eq.) was added dropwise over about 1 min to a stirred and cooled (0 $^\circ\text{C}$) solution of Et_3N (2.5 mL, 18 mmol, 8.0 eq.) in CH_2Cl_2 (5.0 mL) under an atmosphere of argon. (*R,R*)-bis(1-phenylethyl)amine (500 mg, 2.2 mmol, 1.0 eq.) in CH_2Cl_2 (3.0 mL), was added to the cooled reaction mixture as a solution, before stirring was continued for 2 hrs at room temperature. The reaction mixture was then cooled to 0 $^\circ\text{C}$ and *meso*-1,2-diphenyl-1,2-ethanediol (471 mg, 2.2 mmol, 1.0 eq.) was added and stirring was then continued at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the crude product purified by flash column chromatography (Alumina, 100% toluene) to give the mixture of isomers as a white solid. The two isomers were separated by chiral preparative HPLC [Chiralpak® IA; hexane:*i*-PrOH 99:1; 1 mL/min, $\lambda=210$ nm, major $t_R = 6.07$ mins, minor $t_R = 9.99$ mins].



Minor Isomer (199): white solid (20 mg, 2% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.21 – 7.07 (m, 12H), 7.09 – 7.00 (m, 8H), 5.57 – 5.48 (m, 2H), 4.85 (s, 2H), 1.77 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 138.6, 138.6, 138.1, 138.1, 128.0 (2C), 128.0 (2C), 127.9 (6C), 127.7 (2C), 127.5 (2C), 127.5, 127.3, 127.2 (2C), 126.7 (2C), 77.7 (d, *J* = 5.3), 77.4, 52.0, 51.9, 22.8, 22.7.

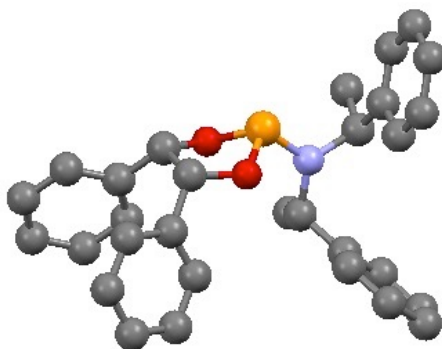
³¹P NMR (162 MHz, CDCl₃) δ 149.02.

[α]²⁵₅₈₉ = −293 (c = 1.0 in CHCl₃).

HRMS (CI with ammonia as the reagent gas) *m/z* calcd. for C₃₀H₃₁NO₂P [M+H]⁺: 468.2087, found: 468.2091.

IR (ATR) ν (cm^{−1}, CHCl₃): 697, 783, 1010, 1451, 2971, 3029.

Table 5.5 X-Ray Crystal Structure for (199)



Formula	C ₃₀ H ₃₀ N ₁ O ₂ P ₁
mol weight	467.55
Crystal system	orthorhombic
T [K]	150
Space group	P 2 ₁ 2 ₁ 2 ₁
a [Å]	8.1656(1)
b [Å]	11.4001(1)
c [Å]	27.1674(2)
α [°]	90
β [°]	90
γ [°]	90
V [Å³]	2528.98(4)
Z	4
D_{calc} [g cm⁻³]	1.228
F(0 0 0)	992
μ [mm⁻¹]	1.167
Crystal size [mm]	0.12 * 0.16 * 0.18
Colour, shape	Clear pale colourless, block
R_{int}	2.49
θ_{min}, θ_{max} [deg]	3.253 - 76.025
Total refl. (before merge)	52486
Data (I>-3.0/sigma(I))	5265, 0, 308
[reflections, restraints, parameters]	
S (=GooF)	1.002
Min. and max. Resd. Dens., [e/Å³]	-0.23 0.14
Threshold Expression	I>2sigma(I)
R₁	0.0245
wR₂	0.0642
Flack	0.007(12)

Major Isomer (200): white solid (80 mg, 8% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.19 – 7.09 (m, 10H), 7.09 – 7.03 (m, 6H), 6.99 – 6.90 (m, 4H), 5.83 (dd, *J* = 6.5, 4.0 Hz, 1H), 5.63 (dd, *J* = 6.5, 1.8 Hz, 1H), 4.66 (dq, *J* = 9.5, 7.2 Hz, 2H), 1.78 (d, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 143.3 – 143.1 (m, 2C), 137.7 (d, *J* = 3.7 Hz), 137.5 (d, *J* = 4.8 Hz), 128.0 (4C), 128.0 (6C), 127.8 (2C), 127.8 (2C), 127.5 – 127.5 (m), 127.1, 127.0, 127.0 – 126.9 (m), 126.7 (2C), 82.8 (d, *J* = 8.7 Hz), 81.8 (d, *J* = 8.3 Hz), 53.4, 53.3, 22.7, 22.6.

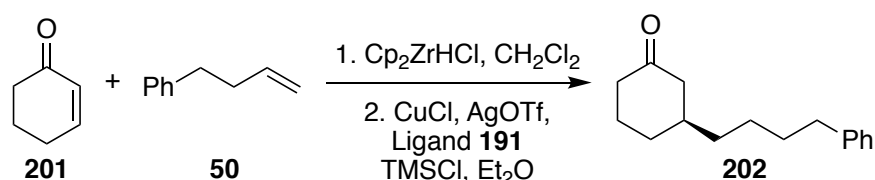
³¹P NMR (162 MHz, CDCl₃) δ 145.81.

[α]_D²⁵₅₈₉ = –152 (*c* = 1.0 in CHCl₃).

HRMS (CI with ammonia as the reagent gas) *m/z* calcd. for C₃₀H₃₁NO₂P [M+H]⁺: 468.2087, found: 468.2078.

IR (ATR) *v* (cm^{–1}, CHCl₃): 698, 778, 1008, 1452, 2971, 3030.

(S)-3-(4-Phenylbutyl)cyclohexan-1-one (202)



In a flame dried flask covered in foil to shield from any light, CuCl (3.8 mg, 0.04 mmol, 0.1 eq.) and ligand **191** (14.8 mg, 0.04 mmol, 0.1 eq.) were dissolved in Et₂O (2.0 mL) under an argon atmosphere and allowed to stir for 1 hr at room temperature. AgOTf (11.3 mg, 0.044 mmol, 0.11 eq.) was added and the reaction stirred for a further 15 mins. In another flask Cp₂ZrHCl (206 mg, 0.8 mmol, 2.0 eq.) was added to a stirred solution of 4-phenyl-1-butene (150 μL, 1.0 mmol, 2.5 eq.) in CH₂Cl₂ (0.4 mL) at room temperature, under an argon atmosphere. After stirring for 15 mins, the resulting yellow solution turned clear. The

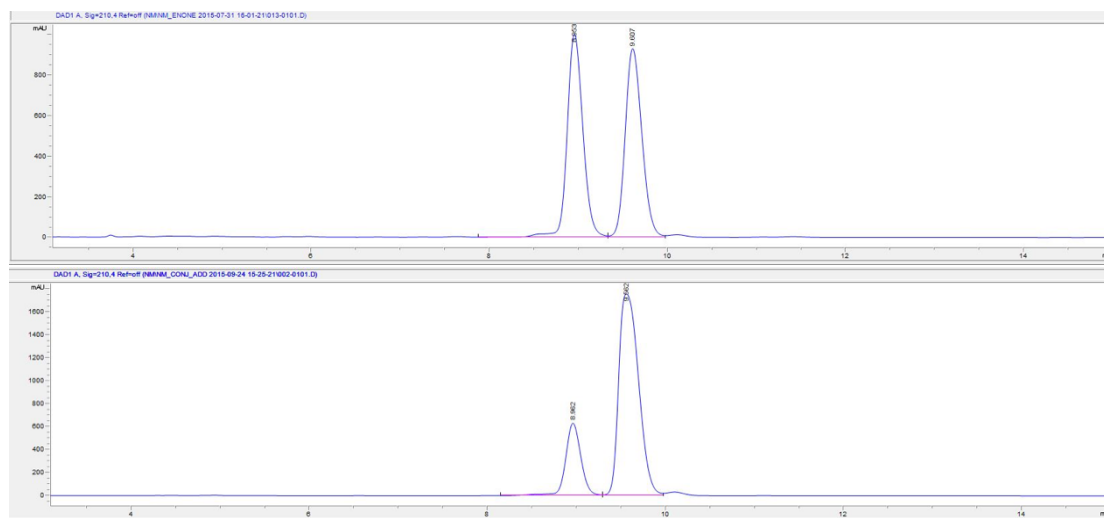
Cu/ligand/silver salt mixture was transferred into the hydrozirconated mixture via syringe, filtering through a syringe filter, under an argon atmosphere. Cyclohexenone (39 μ L, 0.4 mmol, 1.0 eq.) was added, followed by TMSCl (250 μ L, 2.0 mmol, 5.0 eq.) and the reaction stirred at room temperature overnight. Upon completion the reaction was diluted with Et₂O (2 mL), quenched with 1 M NH₄Cl (2 mL) then extracted with more Et₂O (3 $\times$ 10 mL). The combined organic phases were washed with sat. NaHCO₃ (5 mL), brine (5 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography (SiO₂, 5% EtOAc in hexane) to give the pure product as a pale yellow oil (51.8 mg, 57% yield, 56% ee).

¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, J = 7.8 Hz, 2H), 7.23 – 7.12 (m, 3H), 2.66 – 2.56 (m, 2H), 2.45 – 2.19 (m, 3H), 2.08 – 1.93 (m, 2H), 1.88 (ddq, J = 11.6, 3.8, 1.9 Hz, 1H), 1.80 – 1.71 (m, 1H), 1.68 – 1.53 (m, 3H), 1.43 – 1.21 (m, 5H).

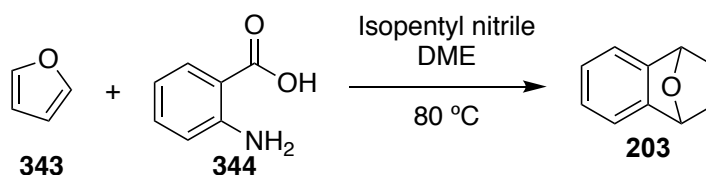
¹³C NMR (101 MHz, CDCl₃) δ 212.1, 142.5, 128.4 (2C), 128.3 (2C), 125.7, 48.2, 41.5, 39.1, 36.5, 35.9, 31.5, 31.3, 26.3, 25.3.

LRMS (ESI) m/z : 253.1 [M+Na]⁺

The enantiomeric excess of 56% was determined by HPLC [Chiralpak® IC; hexane:*i*-PrOH 95:5; 1.5 mL/min, λ =210 nm, *S* enantiomer t_R = 9.07 mins, *R* enantiomer t_R = 9.77 mins].



1,4-Dihydro-1,4-epoxynaphthalene (203)



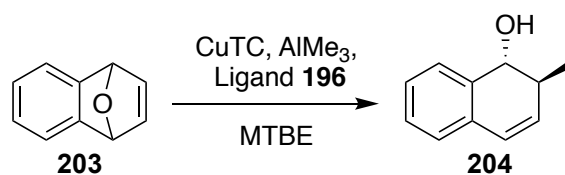
Behind a blast shield, furan (9.0 mL, 124 mmol, 6.2 eq.) and dimethoxyethane (10 mL) were added to a flame-dried flask with stirring, and the mixture heated to reflux (~60 °C). Isopentyl nitrile (4.0 mL, 30 mmol, 1.5 eq.) in dimethoxyethane (10 mL) was added to dropping funnel A. Anthranilic acid (2.75 g, 20 mmol, 1.0 eq.) in dimethoxyethane (10 mL) was added to dropping funnel B. Slow addition from both dropping funnels simultaneously, over 3 hrs, saw the evolution of gas and the initially colourless solution eventually turned red. After the addition of all the reagents, the temperature of the reaction mixture was increased to 80 °C for 2 additional hrs. The reaction mixture was quenched with NaOH (2% aq. solution, 25 mL), partitioned, and the aqueous phase extracted with CHCl₃ (4 × 20 mL). The combined organic layers were washed with water (20 mL), dried over MgSO₄ and concentrated *in vacuo* to give an orange residue. The crude product was purified by column chromatography (SiO₂, 0–20% EtOAc in hexane) then crystallised from petroleum ether (40–60) to give the pure product as yellow crystals (1.57 g, 54% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.25 (dd, *J* = 5.1, 3.1 Hz, 2H), 7.03 (d, *J* = 1.0 Hz, 2H), 6.97 (dd, *J* = 5.1, 3.0 Hz, 2H), 5.72 (s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 149.1 (2C), 143.2 (2C), 125.1 (2C), 120.4 (2C), 82.5 (2C).

HRMS (GCMS with ammonia as the reagent gas) *m/z* calcd. for C₁₀H₉O [M+H]⁺: 145.0648, found: 145.0651.

(1*R*,2*S*)-2-methyl-1,2-dihydronaphthalen-1-ol (204)



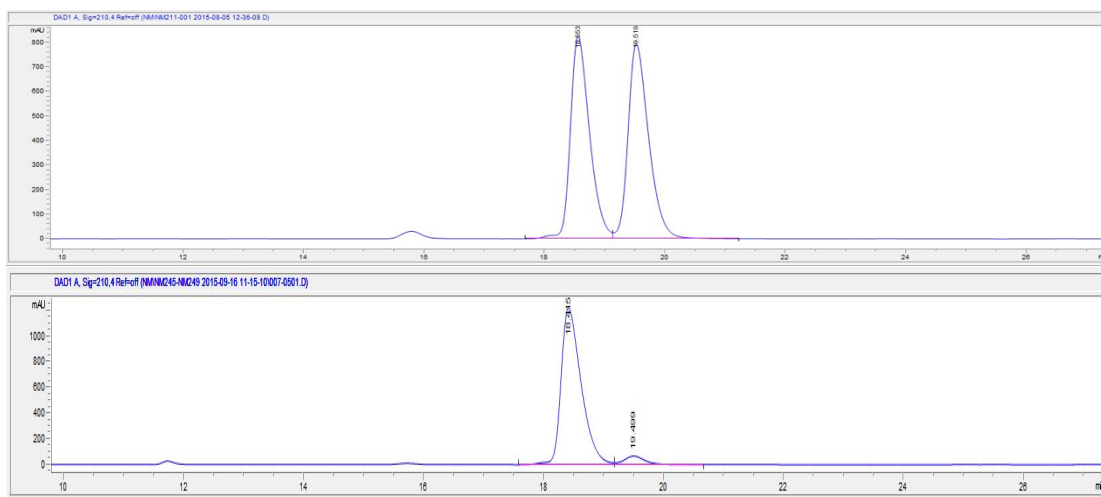
According to the literature procedure by Alexakis *et al.*,¹¹⁶ in a flame dried flask, CuTC (2.9 mg, 0.015 mmol, 0.03 eq.) and ligand **196** (7 mg, 0.015 mmol, 0.03 eq.) were stirred in methyl *tert*-butyl ether (3 ml) for 40 mins at room temperature. AlMe₃ (2.0 M in heptane, 300 μ L, 0.6 mmol, 1.2 eq.) was added dropwise over 10 mins and then 1,4-dihydro-1,4-epoxynaphthalene (72 mg, 0.5 mmol, 1.0 eq.) was added and the reaction stirred overnight. Upon completion, the reaction was quenched with water (2 mL) and 1 M aq. HCl (1 mL). The aqueous phase was extracted with CH₂Cl₂ (3 $\times$ 5 mL). The combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂, 0–15% EtOAc in hexane) to give the desired product as a white solid (74.4 mg, 75% yield, 97:3 *anti:syn*, 89% ee).

¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, *J* = 6.7, 2.1 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.11 (dd, *J* = 6.6, 2.1 Hz, 1H), 6.46 (dd, *J* = 9.6, 1.5 Hz, 1H), 5.94 (dd, *J* = 9.6, 4.4 Hz, 1H), 4.48 (t, *J* = 6.5 Hz, 1H), 2.64 (dddd, *J* = 7.4, 5.9, 4.4, 1.5 Hz, 1H), 1.72 (d, *J* = 7.1 Hz, 1H), 1.07 (d, *J* = 7.2 Hz, 3H).

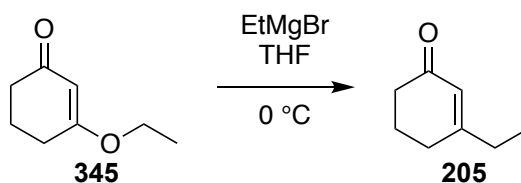
¹³C NMR (101 MHz, CDCl₃) δ 135.9, 132.5, 132.5, 128.5, 127.8, 127.4, 126.5, 125.9, 74.3, 37.6, 17.2.

LRMS (ESI) *m/z*: 183.2 [M+Na]⁺

The enantiomeric excess of 89% was determined by HPLC [Chiralpak® IB; hexane:*i*-PrOH 99.2:0.8; 1 mL/min, λ =210 nm, 1*R*,2*S* enantiomer *t_R* = 18.55 mins, 1*S*,2*R* enantiomer *t_R* = 19.52 mins].



3-Ethylcyclohex-2-en-1-one (205)



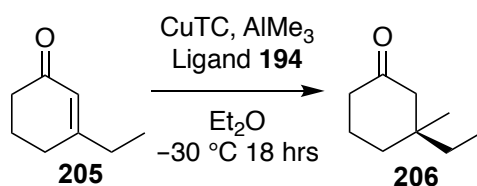
According to the literature procedure by Alexakis *et al.*,¹²⁰ in a flame dried flask, EtMgBr (3 M in Et₂O, 9.52 mL, 29 mmol, 2.0 eq.) was cooled to 0 °C. 3-Ethoxy-2-cyclohexenone (2.1 mL, 14 mmol, 1.0 eq.) in THF (10 mL) was added dropwise over 10 mins. Once the addition was complete the reaction was stirred at room temperature overnight. The reaction was cooled to 0 °C and quenched very slowly over ~15 mins with H₂SO₄ (5% aq. solution, 5 mL). The aqueous phase was extracted with Et₂O (3 × 30 mL), and the combined organic layers washed with sat. NaHCO₃ (15 mL), brine (15 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by Kugelrohr distillation under reduced pressure (48 mbar, 220 °C) to give the pure product (1.71 g, 96% yield).

¹H NMR (400 MHz, CDCl₃) δ 5.87 (s, 1H), 2.38 – 2.32 (m, 2H), 2.31 – 2.25 (m, 2H), 2.25 – 2.19 (m, 2H), 1.98 (p, *J* = 6.3 Hz, 2H), 1.09 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 200.2, 168.0, 124.7, 37.5, 31.0, 29.8, 22.9, 11.4.

LRMS (ESI) *m/z*: 125.1 [M+H]⁺

(S)-3-Ethyl-3-methylcyclohexan-1-one (206)



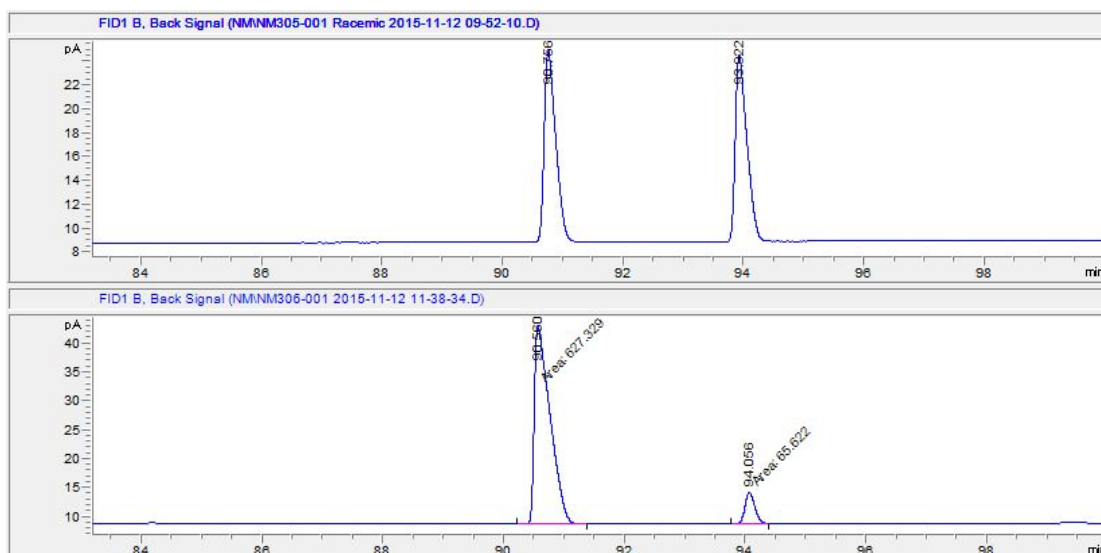
According to literature procedures,¹²⁰ in a flame dried flask, CuTC (1.9 mg, 0.01 mmol, 0.02 eq.) and ligand **194** (9.3 mg, 0.02 mmol, 0.04 eq.) were stirred in Et₂O (1 ml) for 30 mins at room temperature. The solution was cooled to -30 °C. AlMe₃ (2 M in hexanes, 500 µL, 1.0 mmol, 2.0 eq.) was added dropwise while ensuring the internal reaction temperature did not rise above -30 °C. The reaction was stirred for a further 5 mins before 3-ethylcyclohex-2-enone (62 mg, 0.5 mmol, 1.0 eq.) was added over 1 min as a solution in Et₂O (0.25 mL). The reaction was stirred at -30 °C overnight. Upon completion (TLC control), the reaction was quenched with MeOH (2 mL) at -30 °C before warming to room temperature. 2 M HCl (3 mL) was added and the aqueous phase extracted with Et₂O (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂, 0–10% Et₂O in hexane) to give the pure product as a yellow oil (18.5 mg, 21% yield, 81% ee).

¹H NMR (400 MHz, CDCl₃) δ 2.27 (t, *J* = 6.9 Hz, 2H), 2.20 – 2.06 (m, 2H), 1.89 – 1.81 (m, 2H), 1.66 – 1.48 (m, 2H), 1.31 (q, *J* = 8.1, 6.5 Hz, 2H), 0.89 (s, 3H), 0.83 (t, *J* = 7.5 Hz, 3H).

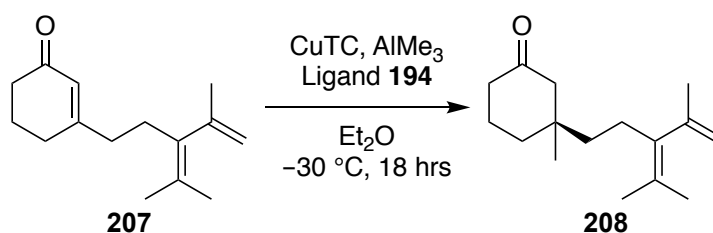
¹³C NMR (101 MHz, CDCl₃) δ 212.6, 53.4, 41.1, 38.7, 35.4, 34.0, 24.4, 22.1, 7.8.

LRMS (ESI) *m/z*: 141.1 [M+H]⁺

The enantiomeric excess was determined by GC using a chiral non-racemic stationary phase [Gamme DEX 225 50-30-1-120-10, *R* enantiomer *t_R* = 90.56 mins, *S* enantiomer *t_R* = 94.06 min].



(*R*)-3-Methyl-3-(4-methyl-3-(prop-1-en-2-yl)pent-3-en-1-yl)cyclohexan-1-one (208)



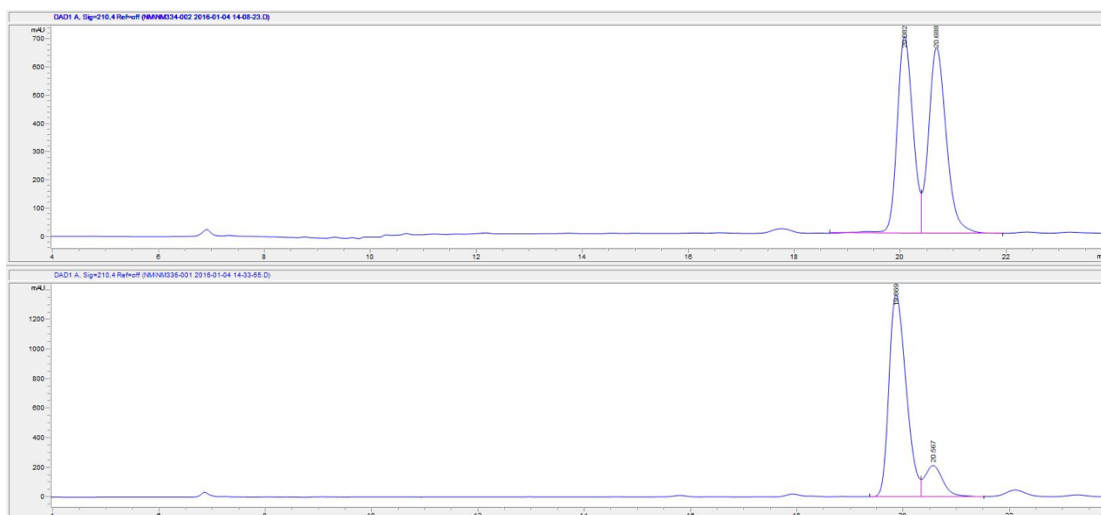
In a flame-dried flask, covered in foil to shield from light, CuTC (1.1 mg, 0.006 mmol, 0.02 eq.) and ligand **194** (5.2 mg, 0.011, 0.4 eq.) were stirred in Et₂O (0.6 ml) for 30 mins at room temperature. The solution was cooled to -78 °C and then 3-(4-methyl-3-(prop-1-en-2-yl)pent-3-en-1-yl)cyclohex-2-en-1-one (**204**, 60 mg, 0.28 mmol, 1.0 eq.) was added as a solution in Et₂O (0.6 mL). AlMe₃ (2 M in hexanes, 195 μL, 0.39 mmol, 1.4 eq.) was then added dropwise and the reaction was stirred at -30 °C for 24 hrs. The reaction was diluted with Et₂O (1 mL), quenched with 2 M HCl (2 mL) then extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂, 0–5% EtOAc in hexane) to give the pure product as a yellow oil (30.2 mg, 46% yield, 72% ee).

¹H NMR (400 MHz, CDCl₃) δ 4.90 (dd, *J* = 2.8, 1.5 Hz, 1H), 4.52 (dd, *J* = 2.7, 1.1 Hz, 1H), 2.27 (t, *J* = 6.7 Hz, 2H), 2.23 – 2.08 (m, 2H), 2.06 – 1.96 (m, 2H), 1.90 – 1.82 (m, 2H), 1.74 (t, *J* = 1.2 Hz, 3H), 1.64 (d, *J* = 1.9 Hz, 6H), 1.58 (s, 2H), 1.27 (ddd, *J* = 9.8, 8.3, 3.4 Hz, 2H), 0.93 (s, 3H).

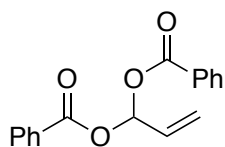
¹³C NMR (101 MHz, CDCl₃) δ 212.3, 146.4, 136.2, 125.0, 113.2, 53.7, 41.1, 40.0, 38.5, 35.7, 25.0, 24.8, 22.7, 22.2, 21.8, 19.5.

LRMS (ESI) *m/z*: 257.2 [M+Na]⁺

The enantiomeric excess was determined by HPLC [Chiralpak® IC; hexane:*i*-PrOH 99.4:0.6; 0.5 mL/min, λ=210 nm, *t_R* = 19.87 min (R enantiomer), *t_R* = 20.57 min (S enantiomer)].



Prop-2-ene-1,1-diyl dibenzoate (222)



In a flame-dried 5 mL round bottomed flask [Rh(COD)(OH)]₂ (4.6 mg, 0.01 mmol, 0.025 eq.), (*S*)-Xylyl-P-Phos (18.2 mg, 0.024 mmol, 0.06 eq.) and Cs₂CO₃ (130.3 mg, 0.40 mmol, 1.00 eq.) were stirred in THF (2.0 mL) at 60 °C for 30 min. A solution of allylic bromide **58** (96.4 mg, 0.40 mmol, 1.0 eq.) and phenyl boronic acid (97.5 mg, 0.40 mmol,

2.00 eq.) in THF (1.5 mL) was added *via* syringe and the flask rinsed with THF (0.5 mL). The resulting mixture was then stirred at 60 °C until no allyl bromide was remaining by TLC. SiO₂ was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with 0–5% Et₂O in pentane to afford the product (38 mg, 67% yield).

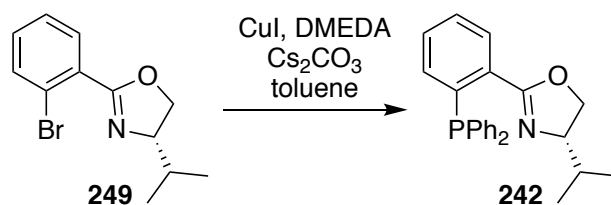
¹H NMR (400 MHz, CDCl₃) δ 8.15 – 8.05 (m, 4H), 7.68 (dt, *J* = 5.4, 1.1, 1H), 7.64 – 7.54 (m, 2H), 7.54 – 7.40 (m, 4H), 6.17 (ddd, *J* = 17.3, 10.6, 5.5, 1H), 5.76 (dt, *J* = 17.3, 1.0, 1H), 5.52 (dt, *J* = 10.6, 1.0, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 164.5 (2C), 133.7 (2C), 131.5 (2C), 130.2 (4C), 129.3, 128.6 (4C), 121.0, 90.2.

HRMS (ESI) *m/z* calcd. for C₁₇H₁₄O₄Na [M+Na]⁺: 305.0784, found: 305.0784.

IR (ATR) *v* (cm⁻¹, CHCl₃): 708, 951, 1060, 1245, 1738.

(*S*)-2-(2-(Diphenylphosphanyl)phenyl)-4-isopropyl-4,5-dihydrooxazole (242)



A mixture of CuI (44 mg, 0.2 mmol, 0.125 eq.), diphenylphosphine (610 μL, 3.5 mmol, 1.9 eq.) and *N,N'*-dimethylethylenediamine (180 μL, 1.6 mmol, 0.875 eq.) in toluene (8.0 mL) was stirred for 20 mins at room temperature. A mixture of phenyloxazoline **249** (500 mg, 1.9 mmol, 1.0 eq.) and Cs₂CO₃ (2.29 g, 7.0 mmol, 3.75 eq.) in toluene (8.0 mL) was added, the flask sealed and heated to 110 °C. After 6 hrs, the reaction mixture was allowed to cool to room temperature, filtered, and the filter cake washed with CH₂Cl₂ (50 mL). The filtrate was concentrated *in vacuo* and the residue purified by flash column chromatography (SiO₂, 0-20% Et₂O in hexane) to give the pure product as a white solid (449 mg, 64% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.90 (ddd, *J* = 7.6, 3.6, 1.5 Hz, 1H), 7.40 – 7.24 (m, 12H), 6.87 (ddd, *J* = 7.8, 4.1, 1.3 Hz, 1H), 4.20 – 4.08 (m, 1H), 3.92 – 3.79 (m, 2H), 1.55 – 1.42 (m, 1H), 0.81 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 163.1, 139.1, 138.4, 138.1, 134.6, 134.4 (2H), 134.0, 133.8, 132.1, 132.0, 130.5, 130.0, 128.7, 128.6, 128.5, 128.5, 128.4, 128.1, 73.3, 70.2, 32.9, 19.1, 18.5.

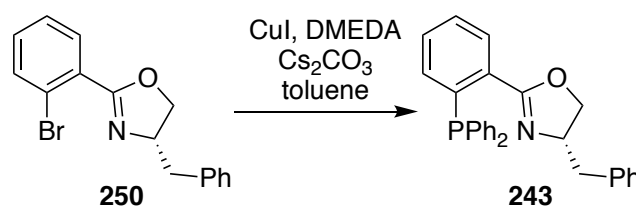
³¹P NMR (162 MHz, CDCl₃) δ –5.52.

[α]_D²⁵ = –52 (*c* = 1.0 in CHCl₃).

LRMS (ESI) *m/z*: 374.2 [M+H]⁺

IR (ATR) ν (cm^{–1}, CHCl₃): 697, 743, 1089, 1434, 1651, 2360, 2956.

(*S*)-4-Benzyl-2-(2-(diphenylphosphaneyl)phenyl)-4,5-dihydrooxazole (243)



Synthesised according to the same procedure as for ligand **242**. Purification by flash column chromatography (SiO₂, 0–20% Et₂O in hexane) to give the pure product as a white foam (376 mg, 48% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.87 (ddd, *J* = 7.6, 3.5, 1.5 Hz, 1H), 7.38 – 7.31 (m, 11H), 7.29 – 7.22 (m, 3H), 7.22 – 7.16 (m, 1H), 7.11 – 7.03 (m, 2H), 6.86 (ddd, *J* = 7.7, 4.3, 1.4 Hz, 1H), 4.43 – 4.29 (m, 1H), 4.03 (dd, *J* = 9.3, 8.4 Hz, 1H), 3.77 (dd, *J* = 8.4, 7.5 Hz, 1H), 2.92 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.10 (dd, *J* = 13.8, 9.3 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 164.0, 138.9, 138.3, 138.1 (d, *J* = 3.2 Hz), 138.0, 134.7, 134.5, 134.1, 133.9, 133.7 (d, *J* = 2.4 Hz), 131.8, 130.7, 130.1 (d, *J* = 3.1 Hz), 129.2 (2C), 128.9, 128.7, 128.7, 128.6 (2C), 128.6 (2C), 128.5, 128.1, 126.4, 71.6, 68.1, 41.3.

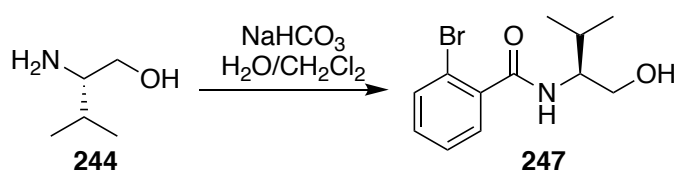
^{31}P NMR (162 MHz, CDCl_3) δ -4.69.

$[\alpha]^{25}_{589}$ = +29 (c = 1.0 in CHCl_3).

HRMS (CI with methane as reagent gas) m/z calcd. for $\text{C}_{28}\text{H}_{25}\text{NOP}$ $[\text{M}+\text{H}]^+$: 422.1668, found: 422.1678.

IR (ATR) ν (cm^{-1} , CHCl_3): 698, 743, 964, 1209, 1311, 1724.

(S)-2-Bromo-N-(1-hydroxy-3-methylbutan-2-yl)benzamide (247)



A solution of Na_2CO_3 (1.2 g, 15 mmol, 3.0 eq.) in water (12 mL) was added to a solution of (S)-valinol (500 mg, 4.9 mmol, 1.0 eq.) in CH_2Cl_2 (16 mL). The biphasic mixture was vigorously stirred as 2-bromobenzoyl chloride (1.2 g, 5.6 mmol, 1.15 eq.) was added dropwise over 10 mins. The reaction was stirred for 16 hrs at room temperature after which the layers were separated, and the aqueous layer extracted with CH_2Cl_2 (2×10 mL). The combined organics were treated with KOH (1 M methanolic solution, 2.5 mL) and the solution stirred for 15 mins. After neutralising with 3 M HCl, water (10 mL) was added, the layers separated and the aqueous layer extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude was purified by flash column chromatography (SiO_2 , 100% acetone) to give the pure product as a white solid (1.36 g, 92% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.61 – 7.52 (m, 2H), 7.41 – 7.33 (m, 1H), 7.29 (dd, J = 7.8, 1.8 Hz, 1H), 6.18 (d, J = 8.4 Hz, 1H), 4.04 – 3.95 (m, 1H), 3.82 (qd, J = 11.2, 4.6 Hz, 2H), 2.17 (s, 1H), 2.00 (h, J = 6.8 Hz, 1H), 1.04 (dd, J = 6.8, 2.4 Hz, 6H).

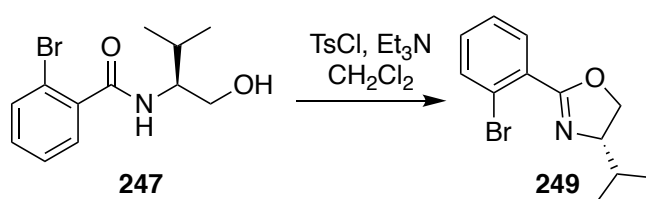
^{13}C NMR (101 MHz, CDCl_3) δ 168.6, 138.0, 133.5, 131.5, 129.8, 127.8, 119.3, 63.9, 57.9, 29.3, 19.8, 19.1.

$[\alpha]^{25}_{589} = -20$ ($c = 1.0$ in CHCl_3).

HRMS (ESI) m/z calcd. for $\text{C}_{12}\text{H}_{15}\text{NO}_2\text{Br}$ $[\text{M}-\text{H}]^-$: 284.0292, found: 284.0290.

IR (ATR) ν (cm^{-1} , CHCl_3): 749, 955, 1072, 1155, 1387, 1639, 2980, 3272.

(S)-2-(2-Bromophenyl)-4-isopropyl-4,5-dihydrooxazole (249)



A solution of amide **247** (1.2 g, 4.2 mmol, 1.0 eq.), *p*-toluenesulfonyl chloride (1.05 g, 5.5 mmol, 1.3 eq.), triethylamine (2.9 mL, 21 mmol, 5.0 eq.) in CH_2Cl_2 (30 mL) in a round bottom flask equipped with a reflux condenser was heated at 55 °C for 20 hrs. Water (4.4 mL) was added and heating continued at 75 °C for 2.5 hrs. The reaction mixture was cooled, the layers separated and the aqueous layer extracted with CH_2Cl_2 (2×5 mL). The combined organics were dried over MgSO_4 , concentrated *in vacuo*, and the residue purified by flash column chromatography (SiO_2 , 10–15% EtOAc in hexane) to give the pure product as a pale yellow oil (691 mg, 62% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.64 (ddd, $J = 14.2, 7.8, 1.6$ Hz, 2H), 7.38 – 7.24 (m, 2H), 4.47 – 4.38 (m, 1H), 4.20 – 4.08 (m, 2H), 1.97 – 1.85 (m, 1H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J = 6.8$ Hz, 3H).

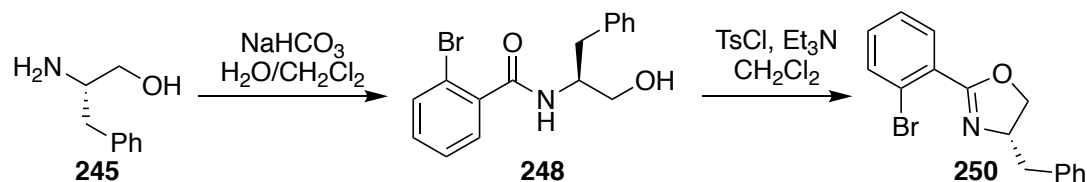
^{13}C NMR (101 MHz, CDCl_3) δ 163.0, 133.8, 131.6, 131.4, 130.3, 127.2, 121.9, 73.1, 70.5, 32.8, 18.9, 18.4.

$[\alpha]^{25}_{589} = -57$ ($c = 1.0$ in CHCl_3).

HRMS (GCMS with ammonia as reagent gas) m/z calcd. for $C_{12}H_{15}NOBr$ $[M+H]^+$: 268.0332, found: 268.0332

IR (ATR) ν (cm^{-1} , $CHCl_3$): 763, 1026, 1094, 1352, 1653, 2958

(S)-4-Benzyl-2-(2-bromophenyl)-4,5-dihydrooxazole (250)



Amine **248** was synthesised according to the same procedure as for amide **247** from *L*-phenylalaninol (500 mg, 3.3 mmol, 1.0 eq.). The crude was purified by flash column chromatography (SiO_2 , 100% acetone) to give the product as a white solid, which was used in the next step without further purification.

Phenyloxazoline **250** was synthesised according to the same procedure as for **249**. Purification by flash column chromatography (SiO_2 , 10–15% EtOAc in hexane) gave the desired product as a yellow oil (896 mg, 86% yield, over two steps).

^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.61 (m, 2H), 7.39 – 7.19 (m, 7H), 4.71 – 4.58 (m, 1H), 4.38 (dd, $J = 9.4, 8.5$, 1H), 4.18 (dd, $J = 8.5, 7.3$, 1H), 3.25 (dd, $J = 13.7, 5.3$, 1H), 2.81 (dd, $J = 13.7, 8.4$, 1H).

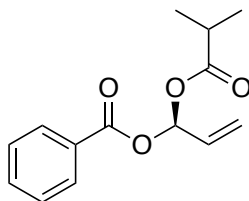
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 137.9, 133.9, 131.8, 131.4, 130.0, 129.5 (2C), 128.7 (2C), 127.2, 126.7, 122.0, 72.0, 68.3, 41.7.

$[\alpha]^{25}_{589} = -12$ ($c = 1.0$ in $CHCl_3$).

LRMS (ESI) m/z : 316.0 $[M+H]^+$

IR (ATR) ν (cm^{-1} , $CHCl_3$): 701, 1023, 1097, 1355, 1650, 2360, 3027.

(+)-(R)-1-(Isobutyryloxy)allyl benzoate (252)



Synthesised according to general procedure 7. Reaction time: 1.5 hrs. Flash column chromatography (SiO₂, 0–5% Et₂O in pentane) gave the product as a colourless oil (81.4 mg, 82% yield, 96% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.13 – 8.02 (m, 2H), 7.65 – 7.54 (m, 1H), 7.50 – 7.44 (m, 2H), 7.44 – 7.39 (m, 1H), 6.04 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1H), 5.65 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.46 (dt, *J* = 10.6, 1.0 Hz, 1H), 2.61 (hept, *J* = 7.0 Hz, 1H), 1.20 (d, *J* = 7.0 Hz, 6H).

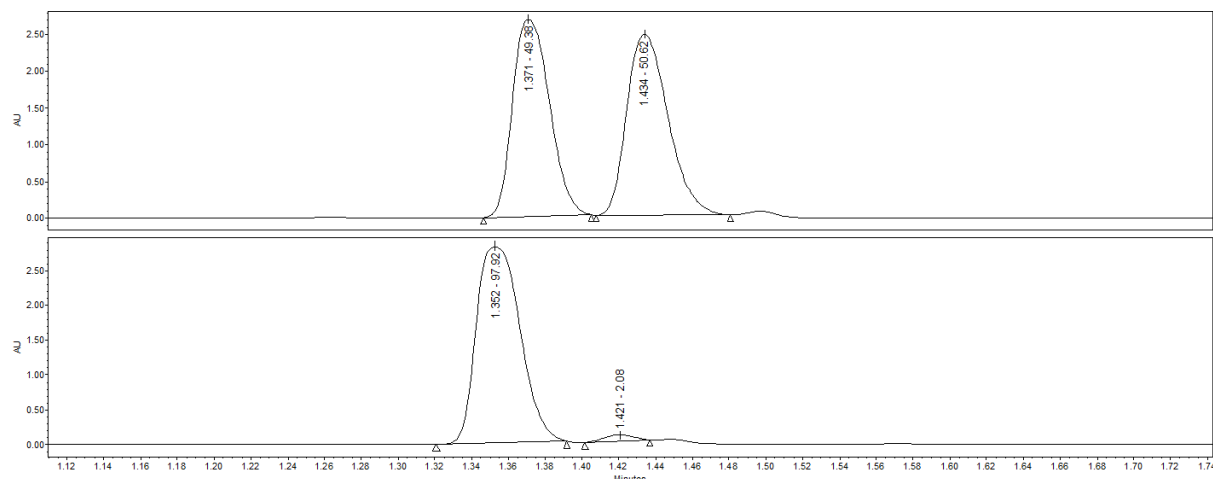
¹³C NMR (101 MHz, CDCl₃) δ 175.0, 164.5, 133.6, 131.6, 130.1 (2C), 129.4, 128.6 (2C), 120.6, 89.7, 34.1, 18.8 (2C).

[α]_D²⁵ = +10 (c = 1.0 in CHCl₃, 96% ee).

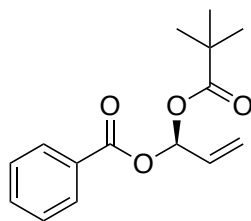
HRMS (ESI) *m/z* calcd. for C₁₄H₁₆O₄Na [M+Na]⁺: 271.0941, found: 271.0940.

IR (ATR) ν (cm⁻¹, CHCl₃): 711, 957, 1084, 1265, 1749, 2977.

The enantiomeric excess of 96% was determined by SFC [Chiralpak® ID; 1500 psi, 30 °C; 1% to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=225 nm; major enantiomer *t*_R = 1.35 mins, minor enantiomer *t*_R = 1.42 mins].



(+)-(S)-1-(Pivaloyloxy)allyl benzoate (257)



Synthesised according to general procedure 7. Reaction time: 1 hr. Flash column chromatography (SiO₂, 0–5% Et₂O in pentane) gave the product as a yellow oil (97.3 mg, 93% yield, 95% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.06 – 7.95 (m, 2H), 7.56 – 7.47 (m, 1H), 7.43 – 7.34 (m, 2H), 7.39 – 7.28 (m, 1H), 5.97 (ddd, *J* = 17.3, 10.6, 5.3 Hz, 1H), 5.57 (dt, *J* = 17.3, 1.1 Hz, 1H), 5.38 (dt, *J* = 10.6, 1.0 Hz, 1H), 1.16 (s, 9H), 1.29 – 1.08 (m, 2H).

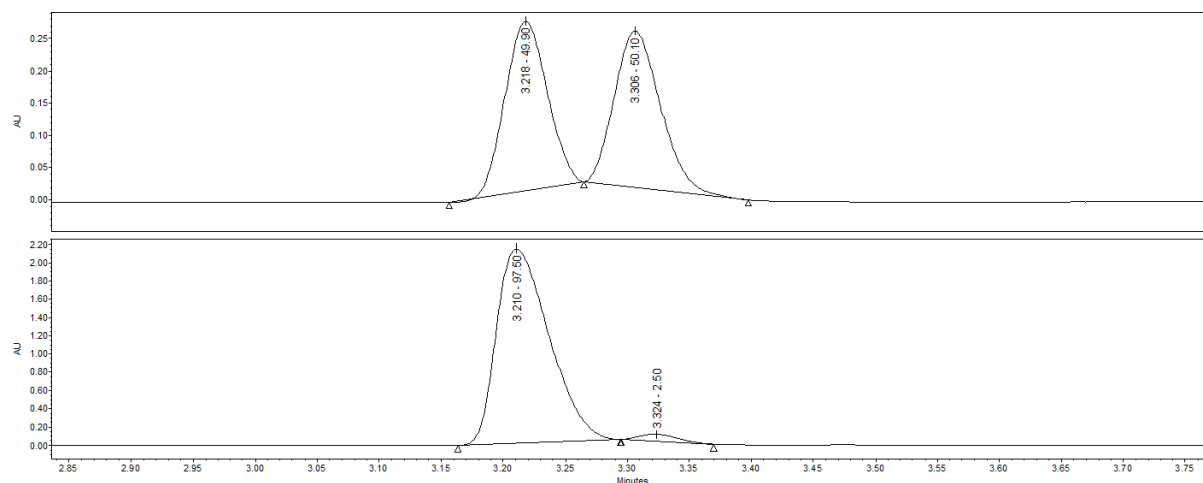
¹³C NMR (101 MHz, CDCl₃) δ 176.4, 164.5, 133.6, 131.6, 130.0 (2C), 129.4, 128.6 (2C), 120.5, 89.7, 39.0, 27.0 (3C).

[α]_D²⁵ = +7 (c = 1.0 in CHCl₃, 95% ee).

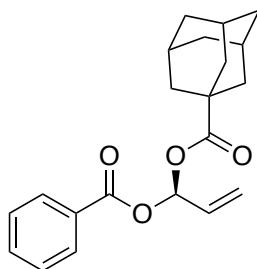
HRMS (ESI) *m/z* calcd. for C₁₅H₁₈O₄Na [M+Na]⁺: 285.1098, found: 285.1099.

IR (ATR) ν (cm⁻¹, CHCl₃): 711, 968, 1087, 1263, 1746, 2976.

The enantiomeric excess of 95% was determined by SFC [Chiralpak® ID; 1500 psi, 30 °C; 0 to 5% MeOH in 5 mins; flow: 1 mL/min; λ=225 nm; major enantiomer *t*_R = 3.21 mins, minor enantiomer *t*_R = 3.32 mins].



(+)-(S)-1-(Benzoyloxy)allyl (3S,5S,7S)-adamantane-1-carboxylate (258)



Synthesised according to general procedure 7. Reaction time: 1 hr. Flash column chromatography (SiO₂, 0–5% Et₂O in pentane) gave the product as a colourless oil (119.5 mg, 88% yield, 93% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.09 – 8.03 (m, 2H), 7.62 – 7.55 (m, 1H), 7.49 – 7.42 (m, 2H), 7.38 (dt, *J* = 5.2, 1.1 Hz, 1H), 6.03 (ddd, *J* = 17.3, 10.6, 5.2 Hz, 1H), 5.64 (dt, *J* = 17.3, 1.1 Hz, 1H), 5.44 (dt, *J* = 10.6, 1.1 Hz, 1H), 2.06 – 1.98 (m, 3H), 1.95 – 1.91 (m, 6H), 1.79 – 1.64 (m, 6H).

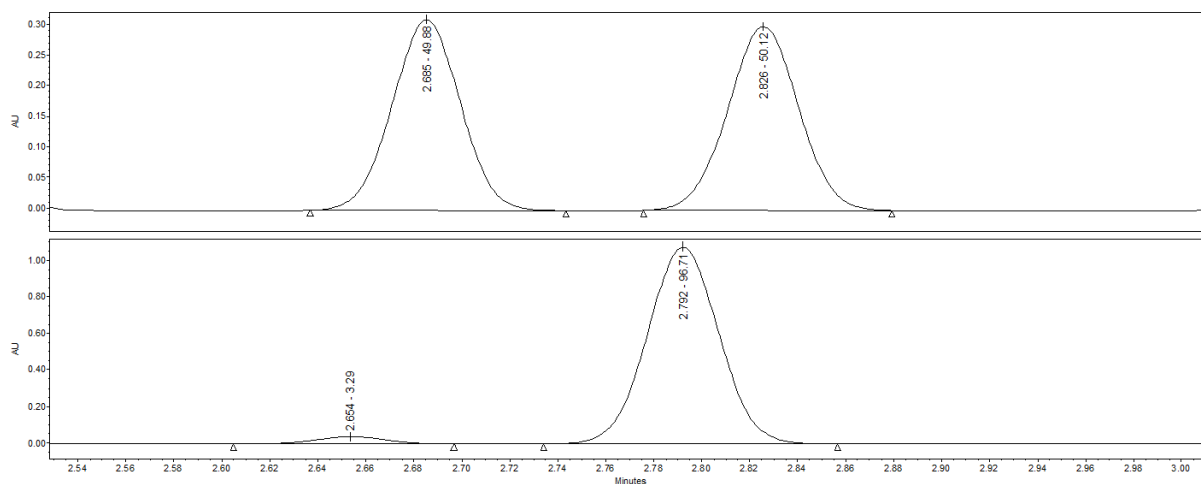
¹³C NMR (101 MHz, CDCl₃) δ 175.4, 164.5, 133.6, 131.7, 130.1 (2C), 129.4, 128.6 (2C), 120.4, 89.5, 40.9, 38.6 (3C), 36.5 (3C), 27.9 (3C).

[α]²⁵₅₈₉ = +1 (*c* = 1.0 in CHCl₃, 93% ee).

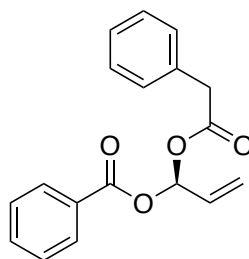
HRMS (ESI) *m/z* calcd. for C₂₁H₂₄O₄Na [M+Na]⁺: 363.1567, found: 363.1564.

IR (ATR) ν (cm⁻¹, CHCl₃): 711, 952, 1053, 1265, 1744, 2907.

The enantiomeric excess of 93% was determined by SFC [Chiralpak® IC; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=230 nm; minor enantiomer *t*_R = 2.65 mins, major enantiomer *t*_R = 2.79 mins].



(+)-(*R*)-1-(2-Phenylacetoxy)allyl benzoate (259)



Synthesised according to general procedure 7. Reaction time: 2 hrs. Flash column chromatography (SiO₂, 0–10% Et₂O in pentane) gave the product as a colourless oil (105.5 mg, 87% yield, 92% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.07 – 8.00 (m, 2H), 7.62 – 7.55 (m, 1H), 7.49 – 7.44 (m, 2H), 7.42 (dt, *J* = 5.5, 1.0 Hz, 1H), 7.36 – 7.25 (m, 5H), 6.02 (ddd, *J* = 17.3, 10.5, 5.4 Hz, 1H), 5.61 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.44 (dt, *J* = 10.6, 0.9 Hz, 1H), 3.70 (s, 2H).

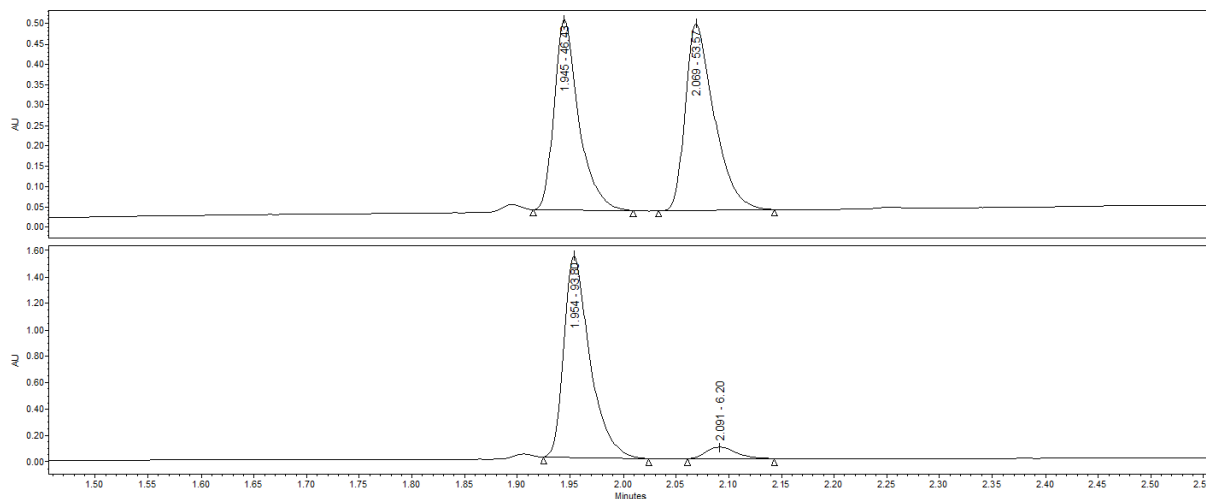
¹³C NMR (101 MHz, CDCl₃) δ 169.5, 164.4, 133.7, 133.3, 131.3, 130.1 (2C), 129.4 (2C), 129.2, 128.7 (2C), 128.6 (2C), 127.4, 120.9, 90.0, 41.2.

[α]_D²⁵ = +13 (c = 1.0 in CHCl₃ 92% ee).

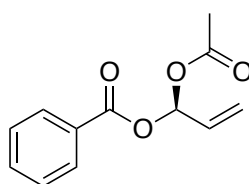
HRMS (ESI) *m/z* calcd. for C₁₈H₁₆O₄Na [M+Na]⁺: 319.0941, found: 319.0943.

IR (ATR) ν (cm⁻¹, CHCl₃): 711, 965, 1088, 1267, 1733, 1752.

The enantiomeric excess of 92% was determined by SFC [Chiralpak® IB; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =210 nm; major enantiomer t_R = 1.95 mins, minor enantiomer t_R = 2.09 mins].



(+)-(R)-1-Acetoxyallyl benzoate (260)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–10% Et₂O in pentane) gave the product as a colourless oil (42.4 mg, 48% yield, 74% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.13 – 8.03 (m, 2H), 7.64 – 7.54 (m, 1H), 7.49 – 7.43 (m, 2H), 7.41 (dt, J = 5.6, 1.1 Hz, 1H), 6.03 (ddd, J = 17.3, 10.5, 5.5 Hz, 1H), 5.66 (dt, J = 17.3, 1.0 Hz, 1H), 5.46 (dt, J = 10.6, 1.0 Hz, 1H), 2.13 (s, 3H).

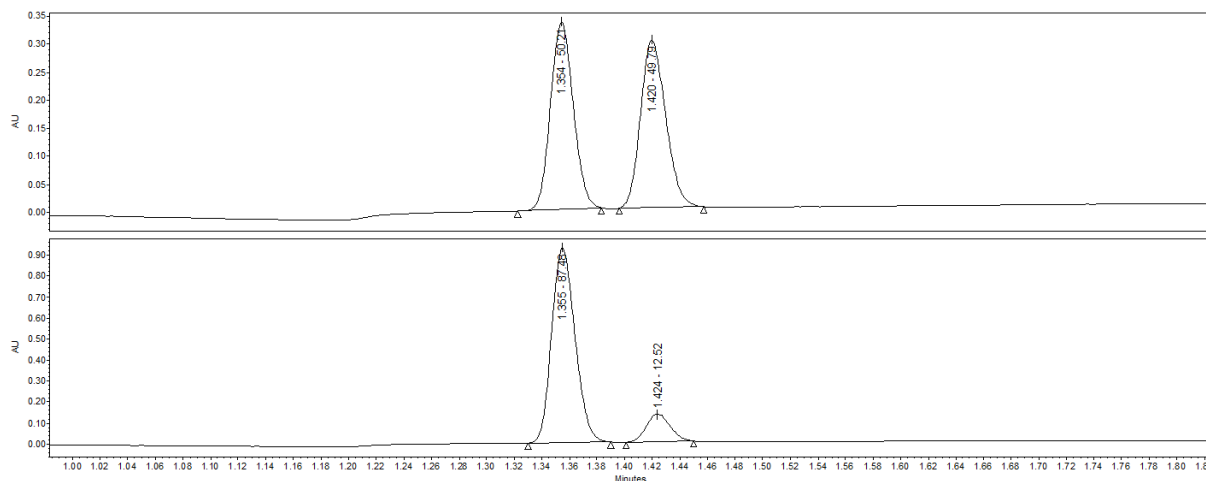
¹³C NMR (101 MHz, CDCl₃) δ 168.8, 164.4, 133.7, 131.4, 130.1 (2C), 129.3, 128.6 (2C), 120.8, 89.7, 21.0.

$[\alpha]^{25}_{589}$ = +11 (c = 1.0 in CHCl₃, 74% ee).

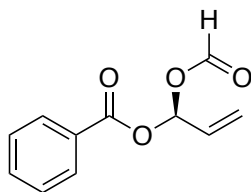
HRMS (ESI) m/z calcd. for C₁₂H₁₂O₄Na [M+Na]⁺: 243.0628, found: 243.0628.

IR (ATR) ν (cm^{-1} , CHCl_3): 711, 956, 1218, 1269, 1734, 1757.

The enantiomeric excess of 74% was determined by SFC [Chiralpak® ID; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =210 nm; major enantiomer t_R = 1.36 mins, minor enantiomer t_R = 1.42 mins].



(+)-(R)-1-(Formyloxy)allyl benzoate (261)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO_2 , 0–5% Et_2O in pentane) gave the product as a colourless oil (29.8 mg, 29% yield, 67% ee).

Note: The reaction with formic acid also gave small amounts of the achiral dibenzoyloxy derivative of **222** and under some conditions **58** may decompose to benzoic acid, which then undergoes competitive rhodium-catalysed carboxylation to the remaining **58**. We were not able to separate this by-product from **261**.

¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, *J* = 0.8 Hz, 1H), 8.11 – 8.04 (m, 2H), 7.64 – 7.57 (m, 1H), 7.50 – 7.44 (m, 3H), 6.06 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.70 (dt, *J* = 17.3, 0.9 Hz, 1H), 5.51 (dt, *J* = 10.6, 0.9 Hz, 1H).

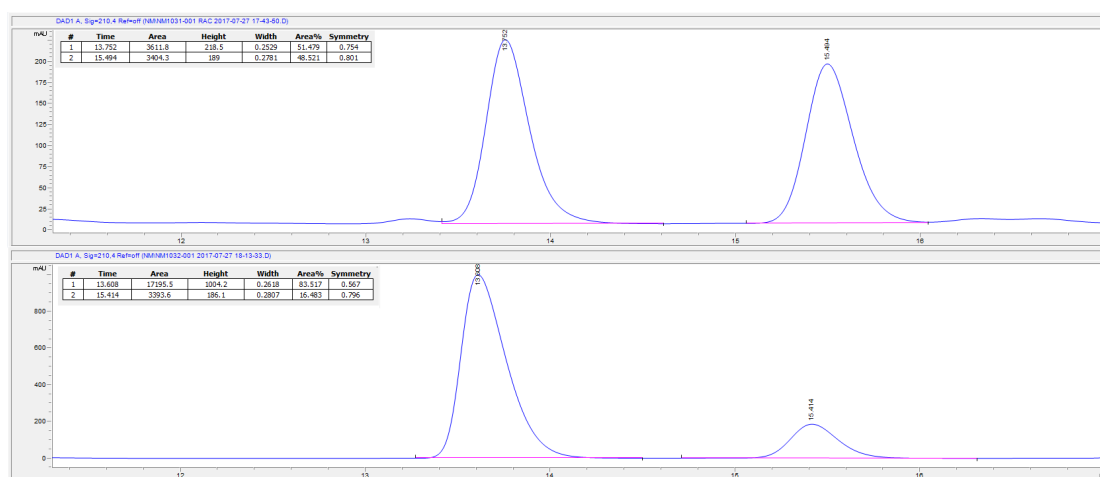
¹³C NMR (101 MHz, CDCl₃) δ 158.8 (2C), 133.9, 130.9, 130.1 (2C), 128.7 (2C), 128.6, 121.5, 89.3.

[α]_D²⁵ = +14 (c = 1.0 in CHCl₃, 67% ee).

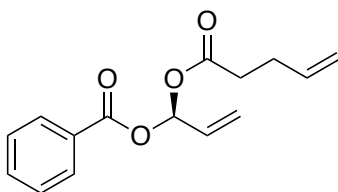
HRMS (GCMS EI) *m/z* calcd. for C₁₁H₁₀O₄P [M]⁺: 206.0574, found: 206.0583.

IR (ATR) ν (cm⁻¹, CHCl₃): 710, 953, 1065, 1085, 1264, 1740 .

The enantiomeric excess of 67% was determined by HPLC [Chiralpak® IC; hexane:*i*-PrOH 99:1; 1.3 mL/min; λ=210 nm; major enantiomer t_R = 13.61 mins, minor enantiomer t_R = 15.41 mins].



(+)-(R)-1-(Pent-4-enoyloxy)allyl benzoate (262)



Synthesised according to general procedure 7. Reaction time: 2.25 hrs. Flash column chromatography (SiO₂, 0–5% Et₂O in pentane) gave the product as a colourless oil (87.9 mg, 85% yield, 94% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.12 – 8.02 (m, 2H), 7.63 – 7.53 (m, 1H), 7.49 – 7.39 (m, 3H), 6.03 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.81 (ddt, *J* = 16.5, 10.2, 6.2 Hz, 1H), 5.65 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.46 (dt, *J* = 10.4, 1.0 Hz, 1H), 5.11 – 4.96 (m, 2H), 2.56 – 2.43 (m, 2H), 2.43 – 2.34 (m, 2H).

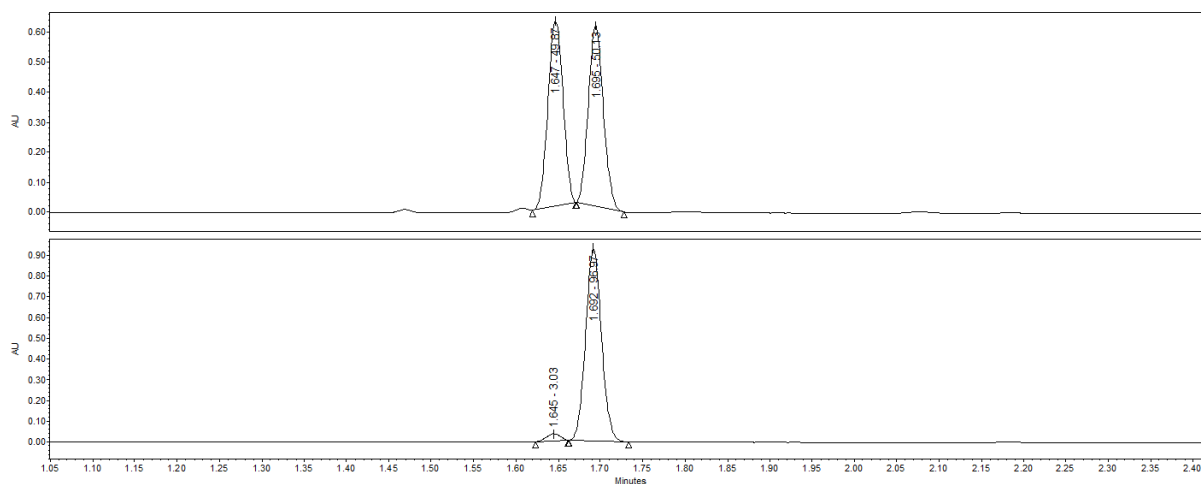
¹³C NMR (101 MHz, CDCl₃) δ 170.8, 164.4, 136.3, 133.6, 131.4, 130.0 (2C), 129.2, 128.5 (2C), 120.7, 115.9, 89.6, 33.4, 28.6.

[α]_D²⁵ = +9 (c = 1.1 in CHCl₃, 94% ee).

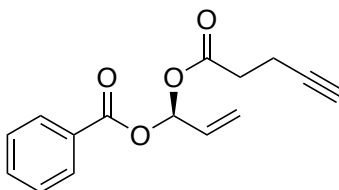
HRMS (ESI) *m/z* calcd. for C₁₅H₁₆O₄Na [M+Na]⁺: 283.0941, found: 283.0942.

IR (ATR) ν (cm⁻¹, CHCl₃): 711, 954, 1086, 1265, 1734, 2981.

The enantiomeric excess of 94% was determined by SFC [Chiralpak® IC; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=220 nm; minor enantiomer *t*_R = 1.65 mins, major enantiomer *t*_R = 1.69 mins].



(+)-(R)-1-(Pent-4-ynoxy)allyl benzoate (263)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–5% Et₂O in pentane) gave the product as a slightly yellow oil (63.1 mg, 61% yield, 91% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.12 – 8.02 (m, 2H), 7.64 – 7.54 (m, 1H), 7.50 – 7.40 (m, 3H), 6.04 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.67 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.47 (dt, *J* = 10.5, 1.0 Hz, 1H), 2.70 – 2.58 (m, 2H), 2.62 – 2.46 (m, 2H), 1.96 (t, *J* = 2.6 Hz, 1H).

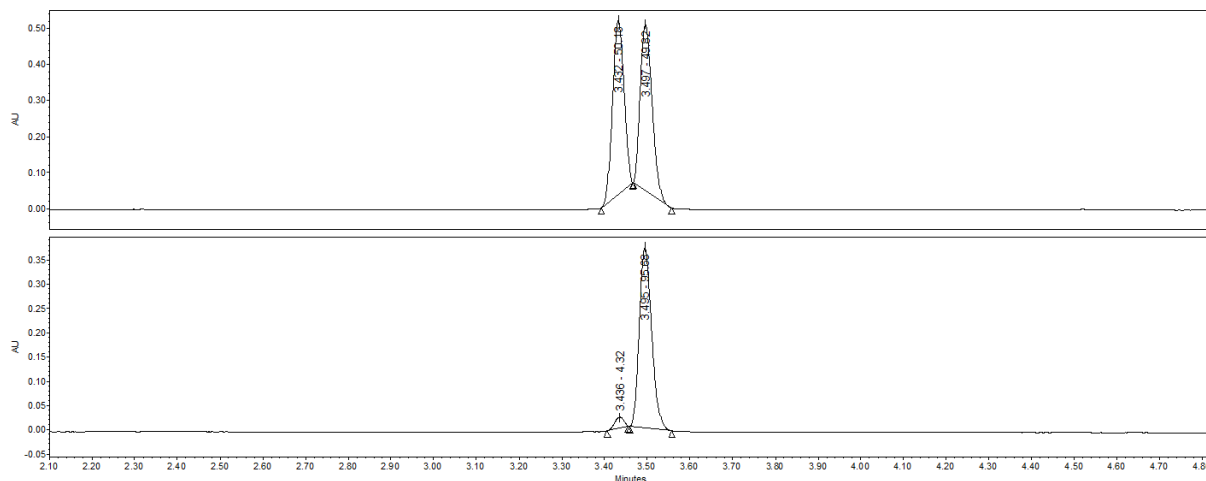
¹³C NMR (101 MHz, CDCl₃) δ 169.6, 164.3, 133.6, 131.1, 130.0 (2C), 129.1, 128.5 (2C), 120.9, 89.7, 82.0, 69.3, 33.2, 14.2.

[α]_D²⁵ = +7 (c = 1.0 in CHCl₃, 91% ee).

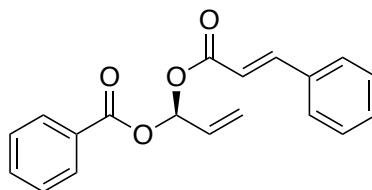
HRMS (ESI) *m/z* calcd. for C₁₅H₁₄O₄Na [M+Na]⁺: 281.0784, found: 281.0784.

IR (ATR) ν (cm⁻¹, CHCl₃): 711, 955, 1089, 1265, 1732.

The enantiomeric excess of 91% was determined by SFC [Chiralpak® IF; 1500 psi, 30 °C; 0 to 10% MeOH in 5 mins; flow: 1.0 mL/min; λ =220 nm; minor enantiomer t_R = 3.44 mins, major enantiomer t_R = 3.50 mins].



(-)-(R)-1-(Cinnamoyloxy)allyl benzoate (264)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–10% Et₂O in pentane) gave the product as a colourless oil (84.7 mg, 65% yield, 92% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.13 – 8.06 (m, 2H), 7.78 (d, J = 16.0 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.55 – 7.50 (m, 2H), 7.49 – 7.43 (m, 2H), 7.41 – 7.37 (m, 3H), 6.47 (d, J = 16.0 Hz, 1H), 6.12 (ddd, J = 17.3, 10.5, 5.4 Hz, 1H), 5.72 (dt, J = 17.3, 1.0 Hz, 1H), 5.50 (dt, J = 10.6, 1.0 Hz, 1H).

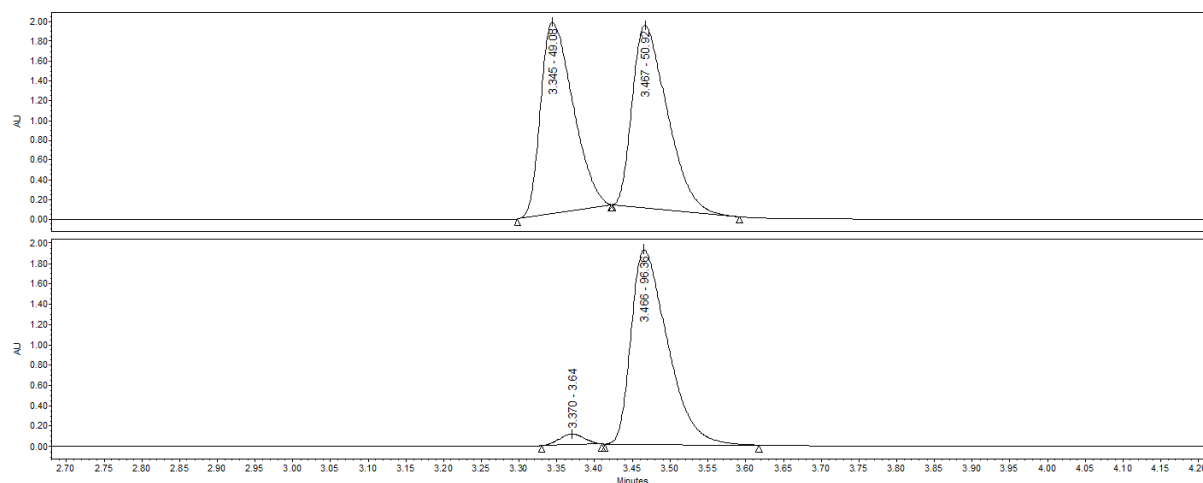
¹³C NMR (101 MHz, CDCl₃) δ 164.7, 164.5, 146.7, 134.2, 133.7, 131.6, 130.8, 130.1 (2C), 129.3, 129.1 (2C), 128.6 (2C), 128.4 (2C), 120.8, 117.0, 89.9.

$[\alpha]^{25}_{589} = -16$ (c = 1.0 in CHCl₃, 92% ee).

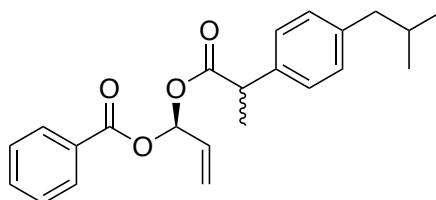
HRMS (ESI) m/z calcd. for $C_{19}H_{16}O_4Na$ $[M+Na]^+$: 331.0941, found: 331.0938.

IR (ATR) ν (cm^{-1} , $CHCl_3$): 709, 962, 1264, 1635, 1734.

The enantiomeric excess of 92% was determined by SFC [Chiralpak® ID; 1500 psi, 30 °C; 1 to 20% MeOH in 5 mins; 1.5 mL/min; $\lambda=215$ nm; minor enantiomer t_R = 3.37 mins, major enantiomer t_R = 3.47 mins].



(-)-(1*R*)-1-((2-(4-Isobutylphenyl)propanoyl)oxy)allyl benzoate (265)



Synthesised according to general procedure 7. Reaction time: 1 hr. Flash column chromatography (SiO_2 , 0–10% Et_2O in pentane) gave the product as a colourless oil (132 mg, 90% yield, 1:1 dr, 94% ee).

^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, J = 8.4, 1.3 Hz, 2H, **D1**), 7.92 (dd, J = 8.4, 1.3 Hz, 2H, **D2**), 7.61 – 7.53 (m, 2H, **D1** and **D2**), 7.48 – 7.37 (m, 6H, **D1** and **D2**), 7.23 – 7.16 (m, 4H, **D1** and **D2**), 7.08 (d, J = 14.2 Hz, 2H, **D1**), 7.06 (d, J = 14.3 Hz, 2H, **D2**), 6.00 (ddd, J = 16.3, 10.0, 5.0 Hz, 1H, **D2**), 5.92 (ddd, 1H, **D1**), 5.60 (dt, J = 17.2, 1.0 Hz, 1H, **D2**), 5.44 (dt, J = 3.2, 0.9 Hz, 1H, **D1**), 5.41 (dt, J = 3.4, 1.0 Hz, 1H, **D1**), 5.33 (dt, J = 10.6, 1.0 Hz, 1H,

D2), 3.80 – 3.75 (m, 1H, **D2**), 3.75 – 3.71 (m, 1H, **D1**), 2.44 (d, $J = 7.2$ Hz, 2H, **D1**), 2.42 (d, $J = 7.2$ Hz, 2H, **D2**), 1.85 (t, $J = 6.7$ Hz, 1H, **D2**), 1.80 (dd, $J = 13.0, 6.3$ Hz, 1H, **D1**), 1.52 (d, $J = 5.0$ Hz, 3H, **D2**), 1.50 (d, $J = 5.1$ Hz, 3H, **D1**), 0.89 (d, $J = 6.6$ Hz, 6H, **D1**), 0.87 (d, $J = 6.6$ Hz, 6H, **D2**).

^{13}C NMR (101 MHz, CDCl_3) δ 172.6 (2C), 164.5 (**D2**), 164.3 (**D1**), 140.8 (**D1**), 140.7 (**D2**), 137.2 (**D1**), 137.1 (**D2**), 133.7 (**D1**), 133.5 (**D2**), 131.4 (**D1**), 131.3 (**D2**), 130.1 (**D1**, 2C), 130.0 (**D2**, 2C), 129.5 (**D1**, 2C), 129.4 (**D2**, 2C), 129.3 (**D1**), 129.3 (**D2**), 128.6 (**D1**, 2C), 128.5 (**D2**, 2C), 127.4 (4C), 120.8 (**D2**), 120.5 (**D1**), 89.8 (**D2**), 89.6 (**D1**), 45.2 (2C), 45.1 (2C), 30.3 (2C), 22.5 (2C), 18.5 (2C), 18.4 (2C).

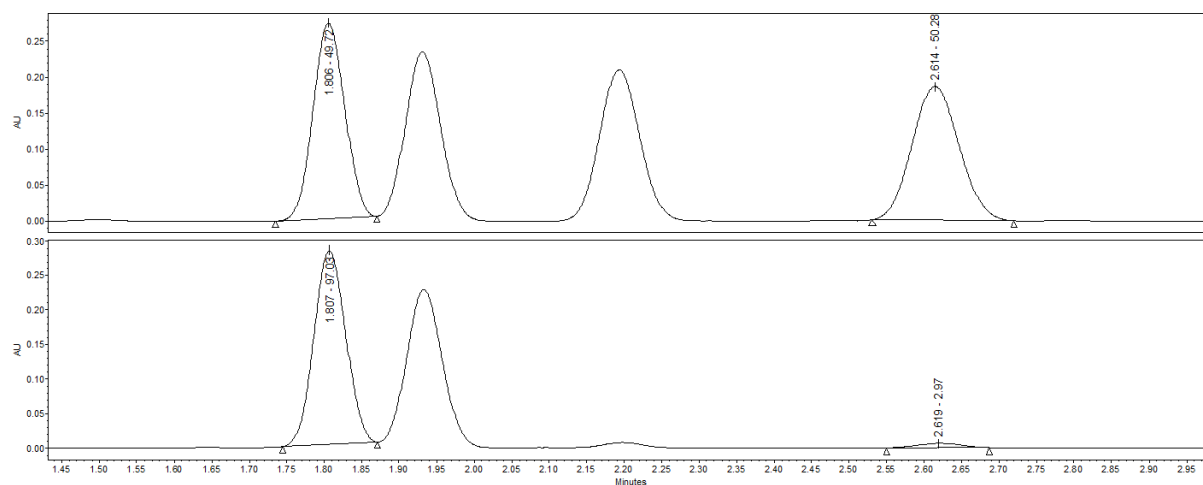
$[\alpha]_{589}^{25} = -17$ ($c = 1.0$ in CHCl_3 , 94% ee).

HRMS (ESI) m/z calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 389.1723, found: 389.1723.

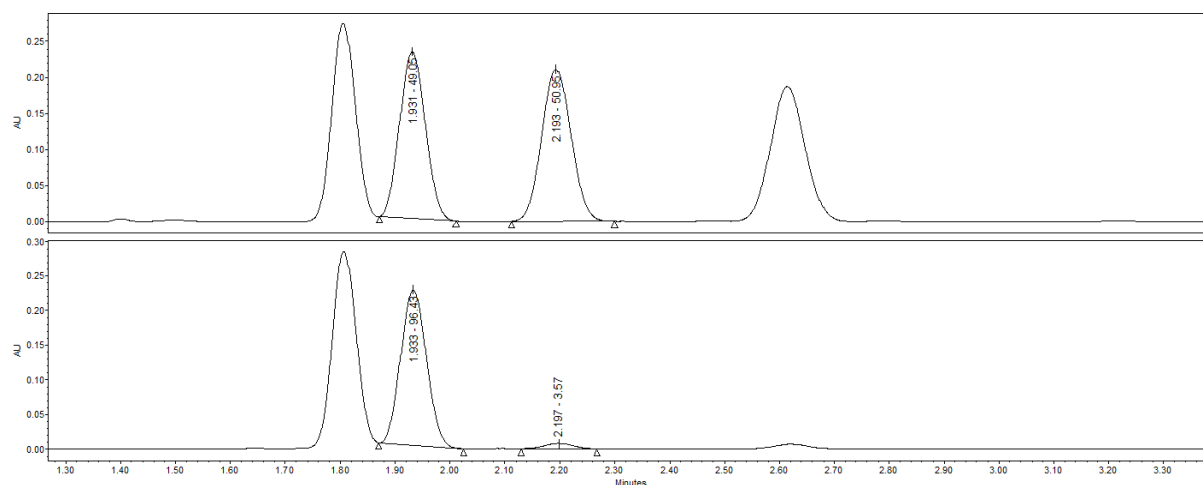
IR (ATR) ν (cm^{-1} , CHCl_3): 711, 951, 1063, 1265, 1749, 2360, 2980.

The enantiomeric excess of 94% was determined by SFC [Chiralpak® IG; 1500 psi; 30 °C; 95:5 CO_2 :MeOH; flow: 1.5 mL/min; $\lambda=220$ nm; **D1** – major enantiomer $t_R = 1.81$ mins, minor enantiomer $t_R = 2.62$ mins; **D2** – major enantiomer $t_R = 1.93$ mins, minor enantiomer $t_R = 2.20$ mins].

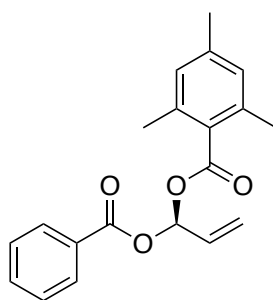
D1:



D2:



(–)-(S)-1-(Benzoyloxy)allyl 2,4,6-trimethylbenzoate (266)



Synthesised according to general procedure 7. Reaction time: 1 hr. Flash column chromatography (SiO₂, 0–5% Et₂O in pentane) gave the product as a colourless oil (117.4 mg, 91% yield, 91% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.12 – 8.04 (m, 2H), 7.69 – 7.62 (m, 1H), 7.65 – 7.55 (m, 1H), 7.51 – 7.41 (m, 2H), 6.85 (s, 2H), 6.13 (ddd, *J* = 17.3, 10.5, 5.8 Hz, 1H), 5.76 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.52 (dt, *J* = 10.5, 0.9 Hz, 1H), 2.32 (s, 6H), 2.27 (s, 3H).

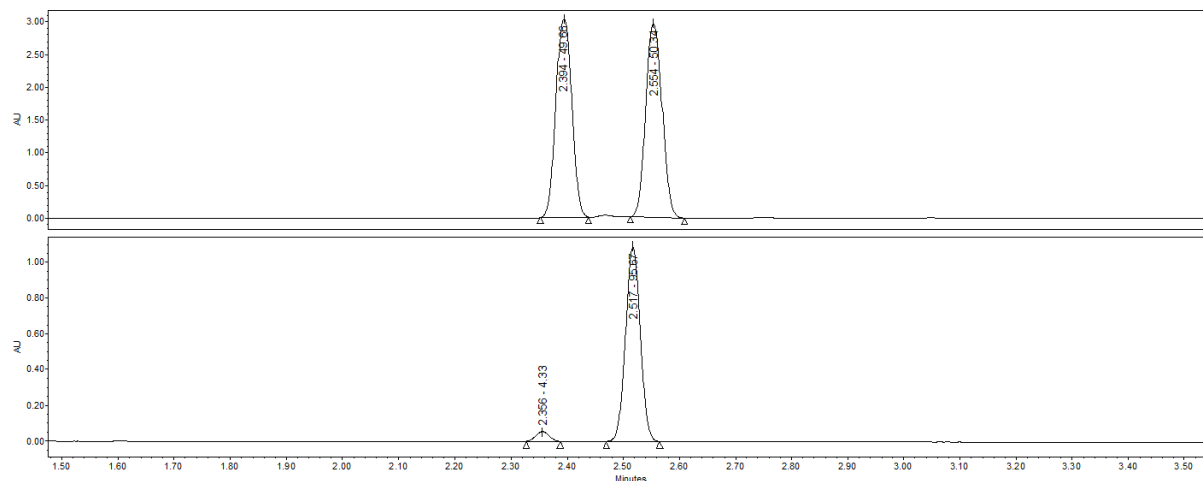
¹³C NMR (101 MHz, CDCl₃) δ 167.8, 164.4, 139.9 (2C), 135.7, 133.7, 131.4, 130.1 (2C), 129.8, 129.3, 128.6 (2C), 128.6 (2C), 121.2, 90.2, 21.3, 19.9 (2C).

[α]_D²⁵₅₈₉ = –40 (c = 1.0 in CHCl₃, 91% ee).

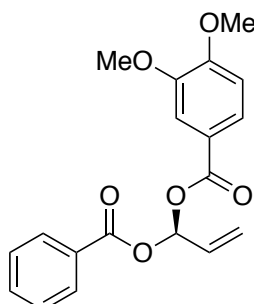
HRMS (ESI) *m/z* calcd. for C₂₀H₂₀O₄Na [M+Na]⁺: 347.1254, found: 347.1253.

IR (ATR) ν (cm^{–1}, CHCl₃): 710, 956, 1054, 1242, 1269, 1741.

The enantiomeric excess of 91% was determined by analytical chiral SFC [Chiralpak® IC; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =225 nm; minor enantiomer t_R = 2.36 mins, major enantiomer t_R = 2.52 mins].



(-)-(S)-1-(Benzoyloxy)allyl 3,4-dimethoxybenzoate (267)



Synthesised according to general procedure 7. Reaction time: 2 hrs. Flash column chromatography (SiO₂, 0–40% Et₂O in pentane) gave the product as a yellow oil (119.8 mg, 88% yield, 93% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.13 – 8.05 (m, 2H), 7.74 (dd, J = 8.5, 2.0 Hz, 1H), 7.66 (dt, J = 5.4, 1.1 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.49 – 7.40 (m, 2H), 6.88 (d, J = 8.5 Hz, 1H), 6.17 (ddd, J = 17.3, 10.6, 5.4 Hz, 1H), 5.74 (dt, J = 17.3, 1.1 Hz, 1H), 5.51 (dt, J = 10.5, 1.0 Hz, 1H), 3.93 (d, J = 6.4 Hz, 6H).

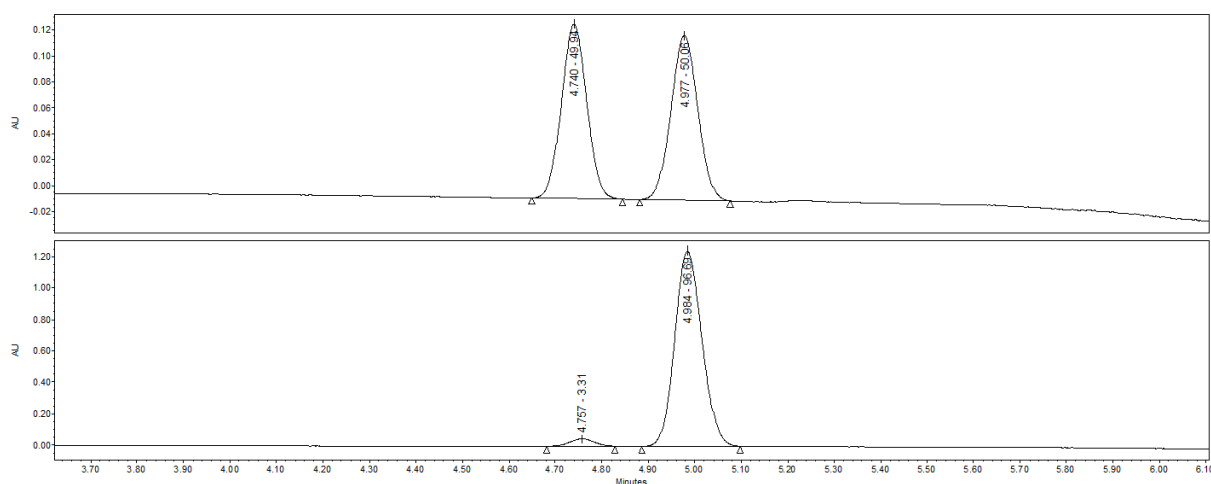
¹³C NMR (101 MHz, CDCl₃) δ 164.5, 164.3, 153.6, 148.8, 133.7, 131.7, 130.1 (2C), 129.3, 128.6 (2C), 124.3, 121.6, 120.8, 112.3, 110.4, 90.1, 56.2, 56.2.

$[\alpha]^{25}_{589} = -8$ ($c = 1.0$ in CHCl_3 , 93% ee).

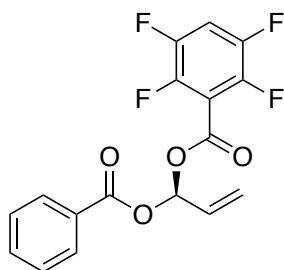
HRMS (ESI) m/z calcd. for $\text{C}_{19}\text{H}_{18}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 365.0996, found: 365.0994.

IR (ATR) ν (cm^{-1} , CHCl_3): 711, 952, 1024, 1267, 1732.

The enantiomeric excess of 93% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; $\lambda=220$ nm; minor enantiomer $t_R = 4.76$ mins, major enantiomer $t_R = 4.98$ mins].



(-)-(S)-1-(Benzoyloxy)allyl 2,3,5,6-tetrafluorobenzoate (268)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO_2 , 0–5% Et_2O in pentane) gave the product as a colourless oil (77.9 mg, 55% yield, 57% ee).

^1H NMR (400 MHz, CDCl_3) δ 8.16 – 8.05 (m, 2H), 7.66 – 7.62 (m, 1H), 7.62 – 7.58 (m, 1H), 7.55 – 7.39 (m, 2H), 7.22 (tt, $J = 9.4, 7.2$ Hz, 1H), 6.14 (ddd, $J = 17.3, 10.5, 5.6$ Hz, 1H), 5.80 (dt, $J = 17.2, 0.9$ Hz, 1H), 5.57 (dt, $J = 10.6, 0.9$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 164.3, 157.6, 147.6 – 147.0 (m), 146.4 – 146.0 (m), 145.0 – 144.6 (m), 143.8 – 143.4 (m), 134.0, 130.5, 130.2 (2C), 128.8, 128.8, 128.7 (2C), 122.0, 109.5 (t, $J = 22.4$ Hz), 90.9.

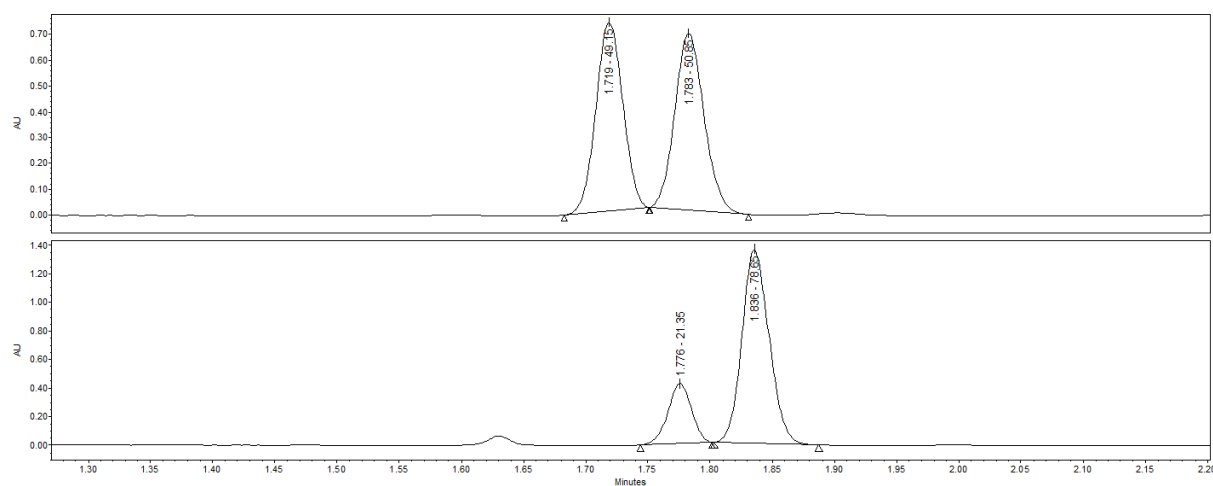
^{19}F NMR (377 MHz, CDCl_3) δ –136.33 – –137.21 (2F, m), –138.34 – –138.82 (2F, m).

$[\alpha]^{25}_{589} = -2$ ($c = 1.0$ in CHCl_3 , 57% ee).

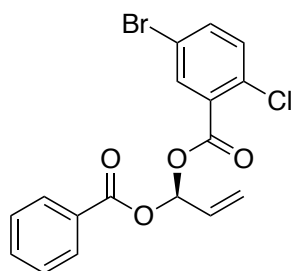
HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{10}\text{O}_4\text{F}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 377.0407, found: 377.0408.

IR (ATR) ν (cm^{-1} , CHCl_3): 711, 953, 1262, 1298, 1503, 1749.

The enantiomeric excess of 57% was determined by SFC [Chiralpak® IE, 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; $\lambda=220$ nm; minor enantiomer $t_R = 1.78$ mins, major enantiomer $t_R = 1.84$ mins].



(-)-(S)-1-(Benzoyloxy)allyl 5-bromo-2-chlorobenzoate (269)



Synthesised according to general procedure 7. Reaction time: 5 hrs. Flash column chromatography (SiO₂, 0–5% Et₂O in pentane) gave the product as a yellow oil (129.1 mg, 82% yield, 81% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.12 – 8.05 (m, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.50 – 7.42 (m, 3H), 6.15 (ddd, *J* = 17.3, 10.6, 5.6 Hz, 1H), 5.77 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.54 (dt, *J* = 10.6, 0.9 Hz, 1H).

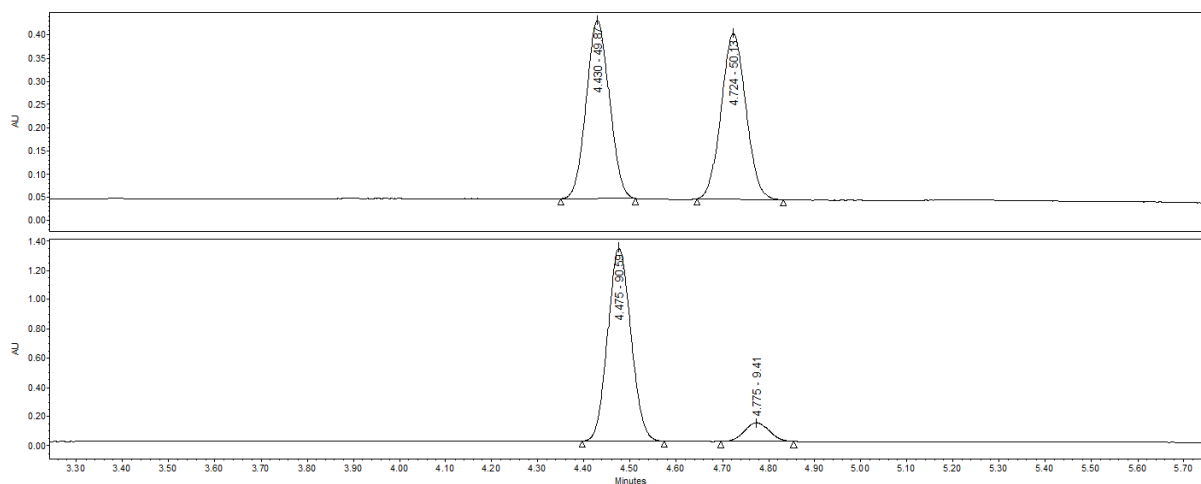
¹³C NMR (101 MHz, CDCl₃) δ 164.4, 162.6, 135.7, 134.2, 133.8, 133.1, 131.0, 130.2 (2C), 129.1, 128.7 (3C), 127.7, 127.3, 121.5, 90.7.

[α]_D²⁵ = –1 (c = 1.0 in CHCl₃, 81% ee).

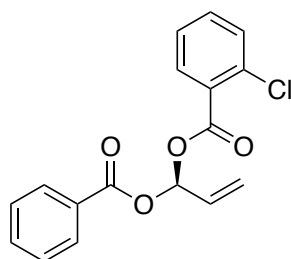
HRMS (ESI) *m/z* calcd. for C₁₇H₁₂O₄BrClNa [M+Na]⁺: 416.9500, found: 416.9501.

IR (ATR) ν (cm^{–1}, CHCl₃): 711, 952, 1083, 1234, 1580, 1742.

The enantiomeric excess of 81% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=210 nm; major enantiomer *t*_R = 4.48 mins, minor enantiomer *t*_R = 4.78 mins].



(+)-(-S)-1-(Benzoyloxy)allyl 2-chlorobenzoate (270)



Synthesised according to general procedure 7. Reaction time: 1.5 hrs. Flash column chromatography (SiO₂, 0–10% Et₂O in pentane) gave the product as a yellow oil (110.9 mg, 88% yield, 89% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.14 – 8.07 (m, 2H), 7.93 – 7.86 (m, 1H), 7.64 (dt, *J* = 5.5, 1.0 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.49 – 7.41 (m, 4H), 7.32 (ddd, *J* = 7.8, 6.6, 2.1 Hz, 1H), 6.16 (ddd, *J* = 17.3, 10.5, 5.6 Hz, 1H), 5.78 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.54 (dt, *J* = 10.6, 1.0 Hz, 1H).

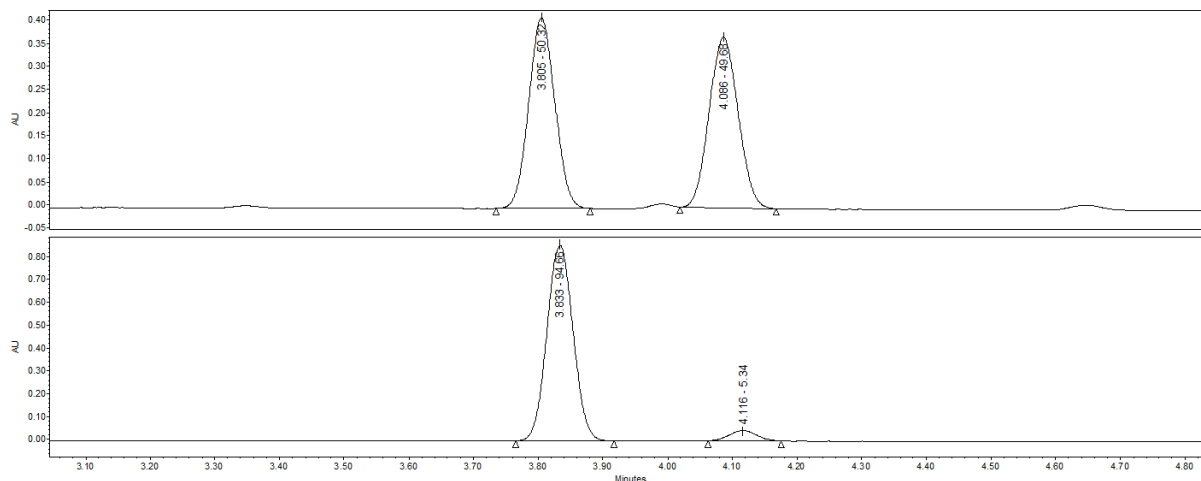
¹³C NMR (101 MHz, CDCl₃) δ 164.5, 163.4, 134.5, 133.8, 133.3, 131.9, 131.4, 131.2, 130.2 (2C), 129.2, 129.0, 128.6 (2C), 126.8, 121.3, 90.6.

[α]_D²⁵ = +3 (c = 1.0 in CHCl₃, 89% ee).

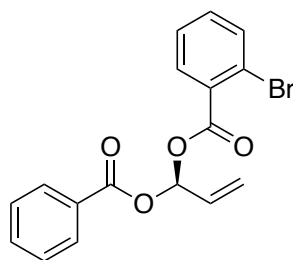
HRMS (ESI) *m/z* calcd. for C₁₇H₁₃O₄ClNa [M+Na]⁺: 339.0395, found: 339.0398.

IR (ATR) ν (cm⁻¹, CHCl₃): 711, 951, 1085, 1940, 1742, 2981.

The enantiomeric excess of 89% was determined by SFC [Chiralpak® IG; 1500 psi; 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =220 nm; major enantiomer t_R = 3.83 mins, minor enantiomer t_R = 4.12 mins].



(+)-(*S*)-1-(Benzoyloxy)allyl 2-bromobenzoate (271)



Synthesised according to general procedure 7. Reaction time: 2.5 hrs. Flash column chromatography (SiO₂, 0–10% Et₂O in pentane) gave the product as a colourless oil (130.5 mg, 91% yield, 73% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.15 – 8.06 (m, 2H), 7.90 – 7.83 (m, 1H), 7.71 – 7.63 (m, 2H), 7.60 (ddt, J = 8.0, 6.9, 1.3 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.40 – 7.31 (m, 2H), 6.17 (ddd, J = 17.3, 10.5, 5.6 Hz, 1H), 5.78 (dt, J = 17.3, 1.0 Hz, 1H), 5.54 (dt, J = 10.6, 0.9 Hz, 1H).

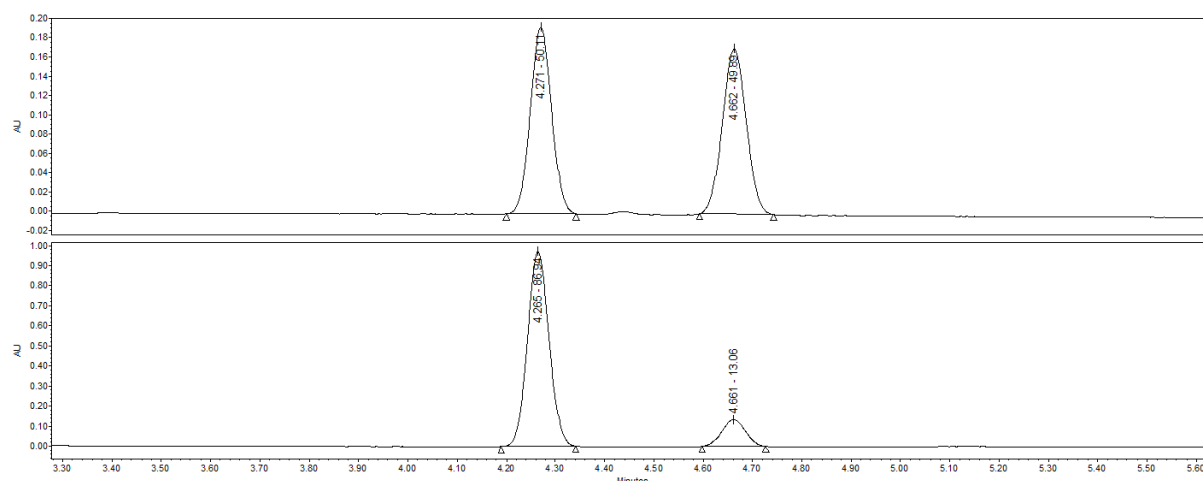
¹³C NMR (101 MHz, CDCl₃) δ 164.5, 163.8, 134.7, 133.8, 133.2, 131.9, 131.2, 131.1, 130.2 (2C), 129.2, 128.6, 127.3 (2C), 122.3, 121.3, 90.7.

$[\alpha]_{589}^{25}$ = +7 (c = 1.0 in CHCl₃, 73% ee).

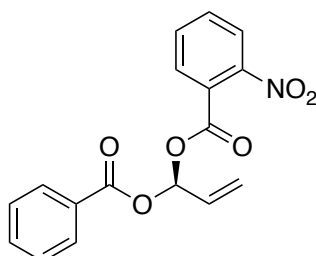
HRMS (APCI) m/z calcd. for $C_{17}H_{13}O_4BrNa$ $[M+Na]^+$: 382.9889, found: 382.9886.

IR (ATR) ν (cm^{-1} , $CHCl_3$): 710, 951, 1081, 1240, 1744.

The enantiomeric excess of 73% was determined by SFC [Chiralpak® IG; 1500 psi; 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =225 nm; major enantiomer t_R = 4.27 mins, minor enantiomer t_R = 4.66 mins].



(-)-(S)-1-(Benzoyloxy)allyl 2-nitrobenzoate (272)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO_2 , 0–25% Et_2O in pentane) gave the product as a colourless oil (105.7 mg, 80% yield, 66% ee).

^1H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.07 (m, 2H), 7.99 – 7.91 (m, 1H), 7.81 – 7.74 (m, 1H), 7.72 – 7.55 (m, 4H), 7.47 (ddt, J = 7.9, 6.6, 1.2 Hz, 2H), 6.11 (ddd, J = 17.3, 10.6, 5.6 Hz, 1H), 5.77 (dt, J = 17.2, 0.9 Hz, 1H), 5.55 (dt, J = 10.5, 0.9 Hz, 1H).

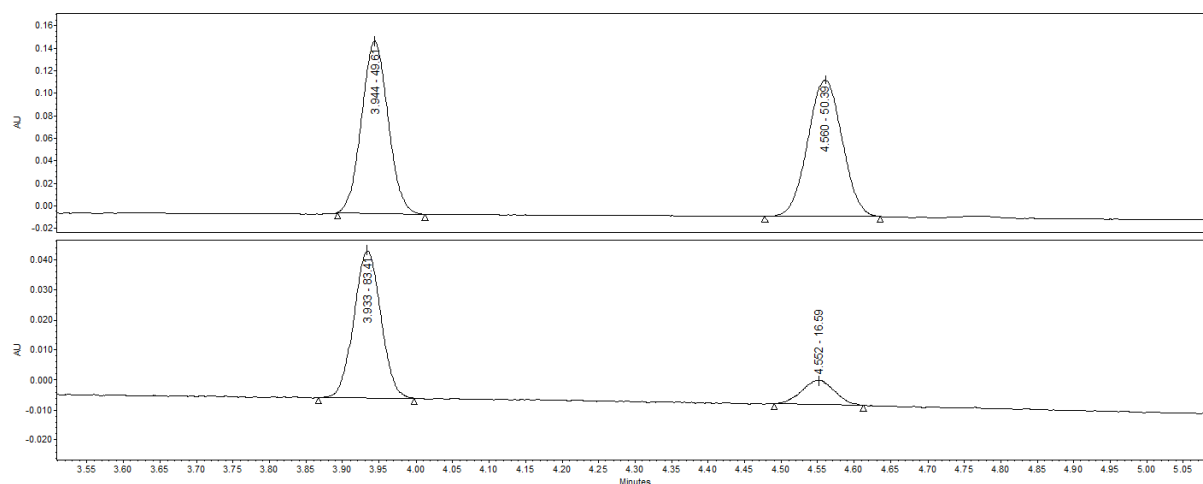
^{13}C NMR (101 MHz, CDCl_3) δ 164.4, 163.5, 148.1, 133.9, 133.2, 132.2, 130.5, 130.2, 130.2 (2C), 129.0, 128.7 (2C), 127.0, 124.2, 121.7, 90.9.

$[\alpha]^{25}_{589} = -25$ ($c = 1.1$ in CHCl_3 , 66% ee).

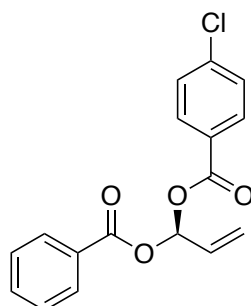
HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{13}\text{O}_6\text{NNa}$ $[\text{M}+\text{Na}]^+$: 350.0635, found: 350.0639.

IR (ATR) ν (cm^{-1} , CHCl_3): 712, 954, 1059, 1246, 1536, 1747.

The enantiomeric excess of 66% was determined by SFC [Chiralpak® IG; 1500 psi; 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; $\lambda=220$ nm; major enantiomer $t_R = 3.96$ mins, minor enantiomer $t_R = 4.62$ mins].



(-)-(S)-1-(Benzoyloxy)allyl 4-chlorobenzoate (273)



Synthesised according to general procedure 7. Reaction time: 5.5 hrs. Flash column chromatography (SiO_2 , 0–5% Et_2O in pentane) gave the product as a colourless oil (111.3 mg, 88% yield, 91% ee).

^1H NMR (400 MHz, CDCl_3) δ 8.13 – 8.07 (m, 2H), 8.06 – 7.98 (m, 2H), 7.65 (dt, $J = 5.5, 1.0$ Hz, 1H), 7.64 – 7.56 (m, 1H), 7.48 – 7.40 (m, 4H), 6.16 (ddd, $J = 17.3, 10.6, 5.5$ Hz, 1H), 5.75 (dt, $J = 17.3, 1.0$ Hz, 1H), 5.53 (dt, $J = 10.6, 0.9$ Hz, 1H).

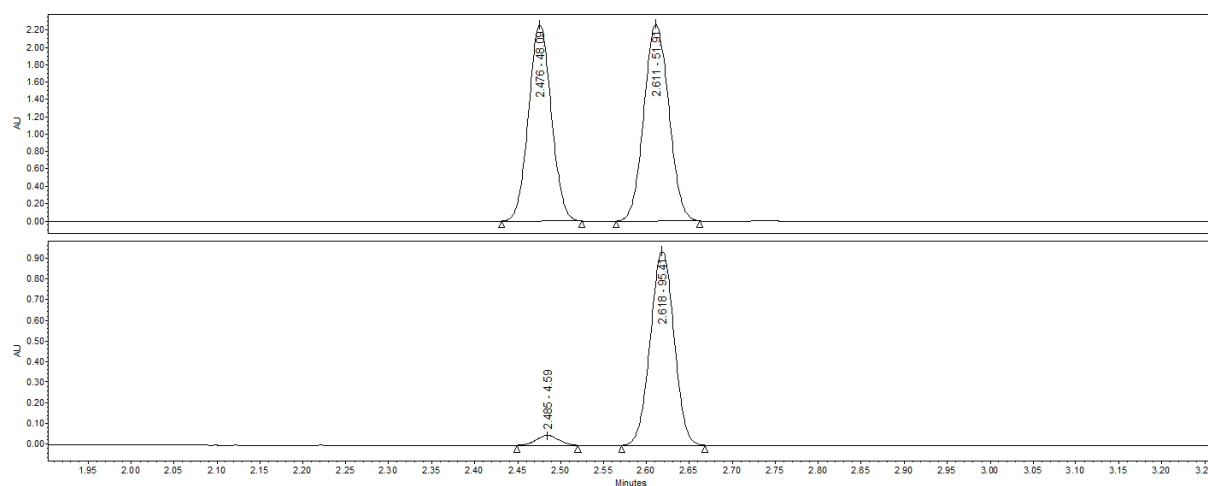
^{13}C NMR (101 MHz, CDCl_3) δ 164.4, 163.7, 140.2, 133.8, 131.5 (2C), 131.4, 130.1 (2C), 129.2, 129.0 (2C), 128.6 (2C), 127.7, 121.2, 90.3.

$[\alpha]^{25}_{589} = -3$ ($c = 1.0$ in CHCl_3 , 91% ee).

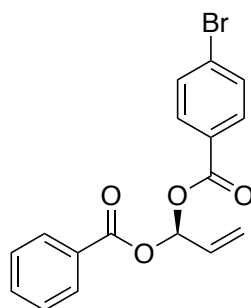
HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{13}\text{O}_4\text{ClNa}$ $[\text{M}+\text{Na}]^+$: 339.0395, found: 339.0395.

IR (ATR) ν (cm^{-1} , CHCl_3): 710, 950, 1062, 1247, 1738, 2981.

The enantiomeric excess of 91% was determined by SFC [Chiralpak® IC; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; $\lambda=235$ nm; minor enantiomer $t_R = 2.49$ mins, major enantiomer $t_R = 2.62$ mins].



(-)-(S)-1-(Benzoyloxy)allyl 4-bromobenzoate (274)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–5% Et₂O in pentane) gave the product as a colourless oil (94.1 mg, 65% yield, 91% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.12 – 8.06 (m, 2H), 7.97 – 7.91 (m, 2H), 7.65 (dt, *J* = 5.5, 1.0 Hz, 1H), 7.62 – 7.56 (m, 3H), 7.49 – 7.42 (m, 2H), 6.16 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1H), 5.75 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.53 (dt, *J* = 10.6, 1.0 Hz, 1H).

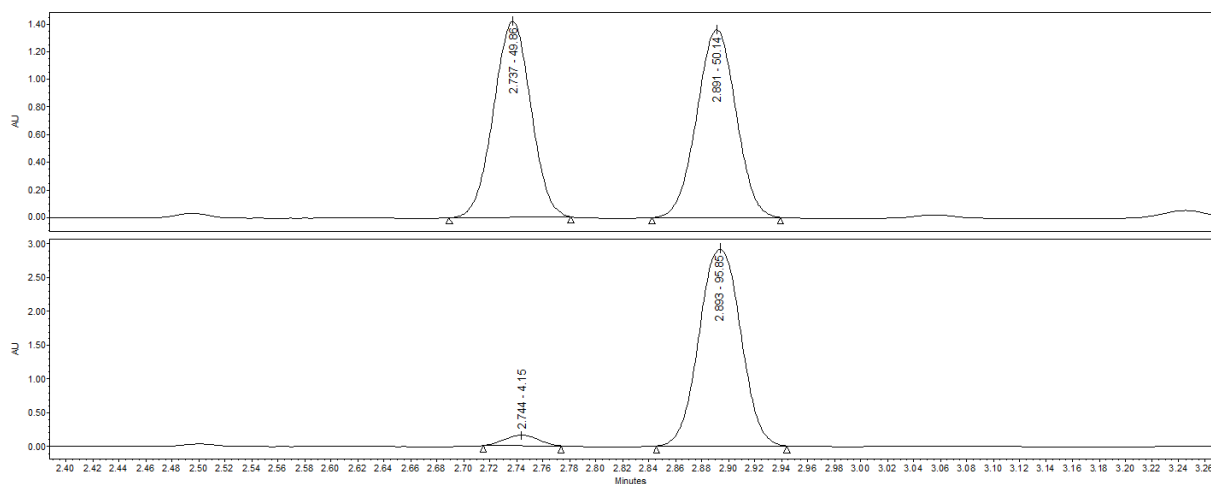
¹³C NMR (101 MHz, CDCl₃) δ 164.4, 163.8, 133.8, 132.0 (2C), 131.6 (2C), 131.3, 130.1 (2C), 129.1, 128.9, 128.6 (2C), 128.2, 121.2, 90.3.

[α]_D²⁵ = −4 (c = 1.0 in CHCl₃, 91% ee).

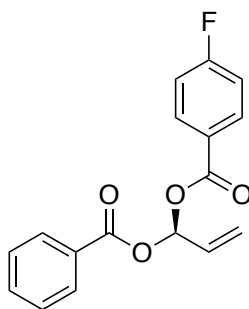
HRMS (ESI) *m/z* calcd. for C₁₇H₁₃O₄BrNa [M+Na]⁺: 382.9889, found: 382.9893.

IR (ATR) ν (cm^{−1}, CHCl₃): 712, 954, 1059, 1246, 1536, 1747.

The enantiomeric excess of 91% was determined by SFC [Chiralpak® IC; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=235 nm; minor enantiomer *t*_R = 2.74 mins, major enantiomer *t*_R = 2.89 mins].



(+)-(-S)-1-(Benzoyloxy)allyl 4-fluorobenzoate (275)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–5% Et₂O in pentane) gave the product as a pale yellow oil (83.3 mg, 67% yield, 88% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.16 – 8.05 (m, 4H), 7.65 (dt, *J* = 5.5, 1.1 Hz, 1H), 7.59 (ddt, *J* = 7.9, 7.0, 1.3 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.17 – 7.07 (m, 2H), 6.16 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1H), 5.75 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.53 (dt, *J* = 10.6, 0.9 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 167.5, 165.0, 164.5, 163.5, 133.8, 132.8, 132.7, 131.4, 130.1 (2C), 129.2, 128.6 (2C), 121.1, 115.9, 115.7, 90.3.

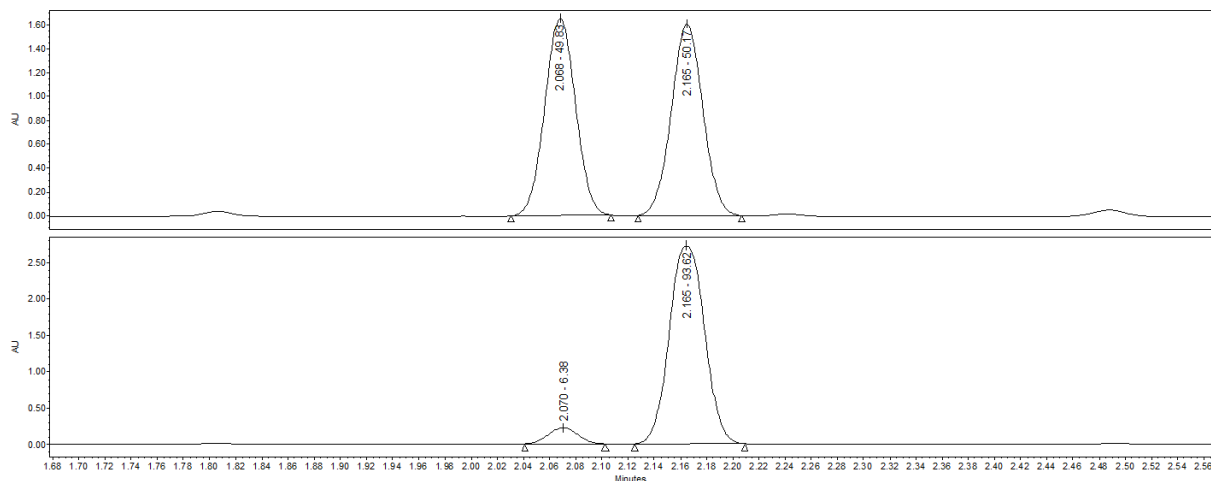
¹⁹F NMR (377 MHz, CDCl₃) δ –104.44.

[α]_D²⁵ = +3 (c = 1.0 in CHCl₃, 88% ee).

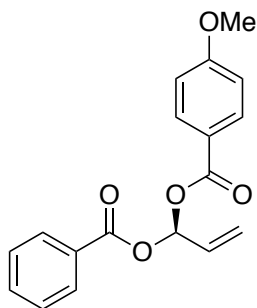
HRMS (GCMS EI) *m/z* calcd. for C₁₇H₁₃O₄F [M]⁺: 300.0792, found: 300.0795.

IR (ATR) ν (cm^{–1}, CHCl₃): 711, 950, 1061, 1246, 1604, 1739.

The enantiomeric excess of 88% was determined by SFC [Chiralpak® IC; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =220 nm; minor enantiomer t_R = 2.07 mins, major enantiomer t_R = 2.16 mins].



(-)-(S)-1-(Benzoyloxy)allyl 4-methoxybenzoate (276)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–10% Et₂O in pentane) gave the product as a colourless oil (42.6 mg, 34% yield, 83% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.13 – 8.07 (m, 2H), 8.06 – 8.02 (m, 2H), 7.66 (dt, J = 5.4, 1.1 Hz, 1H), 7.63 – 7.53 (m, 1H), 7.49 – 7.40 (m, 2H), 6.96 – 6.88 (m, 2H), 6.16 (ddd, J = 17.3, 10.5, 5.4 Hz, 1H), 5.74 (dt, J = 17.3, 1.1 Hz, 1H), 5.50 (dt, J = 10.6, 1.0 Hz, 1H), 3.86 (s, 3H).

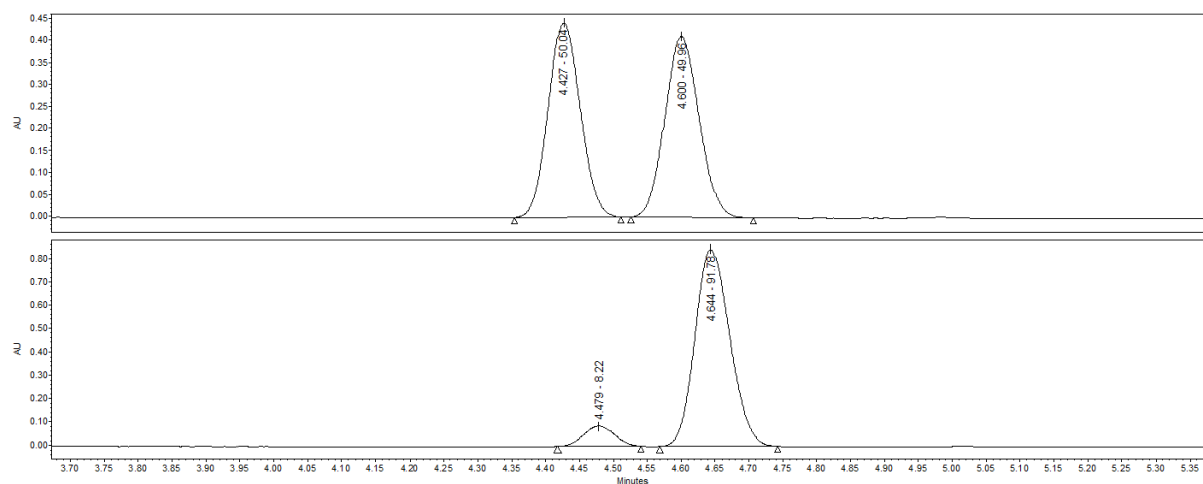
^{13}C NMR (101 MHz, CDCl_3) δ 164.5, 164.2, 164.0, 133.6, 132.3 (2C), 131.8, 130.1 (2C), 129.4, 128.6 (2C), 121.6, 120.7, 113.9 (2C), 90.0, 55.6.

$[\alpha]^{25}_{589} = -7$ ($c = 1.0$ in CHCl_3 , 83% ee).

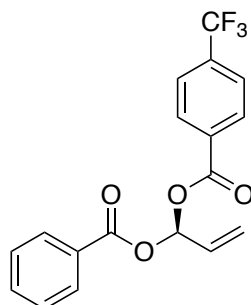
HRMS (GCMS with ammonia as reagent gas) m/z calcd. for $\text{C}_{18}\text{H}_{20}\text{NO}_5$ $[\text{M}+\text{NH}_4]^+$: 330.1336, found: 330.1318.

IR (ATR) ν (cm^{-1} , CHCl_3): 711, 950, 1061, 1249, 1605, 1733, 2980.

The enantiomeric excess of 83% was determined by SFC [Chiralpak[®] IC, 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; $\lambda=250$ nm; minor enantiomer $t_R = 4.48$ mins, major enantiomers $t_R = 4.64$ mins].



(+)-(*S*)-1-(Benzoyloxy)allyl 4-(trifluoromethyl)benzoate (277)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO_2 , 0–5% Et_2O in pentane) gave the product as a colourless oil (98.1 mg, 70% yield, 80% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.23 – 8.17 (m, 2H), 8.11 – 8.07 (m, 2H), 7.75 – 7.69 (m, 2H), 7.69 – 7.67 (m, 1H), 7.63 – 7.57 (m, 1H), 7.50 – 7.43 (m, 2H), 6.17 (ddd, *J* = 17.3, 10.6, 5.6 Hz, 1H), 5.77 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.55 (dt, *J* = 10.6, 0.9 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 164.4, 163.3, 135.1 (q, *J* = 32.7 Hz), 133.9, 132.6 (2C), 131.2, 130.5 (2C), 130.2 (2C), 129.1, 128.7 (2C), 125.6 (q, *J* = 3.7 Hz, 2C), 121.3, 90.5.

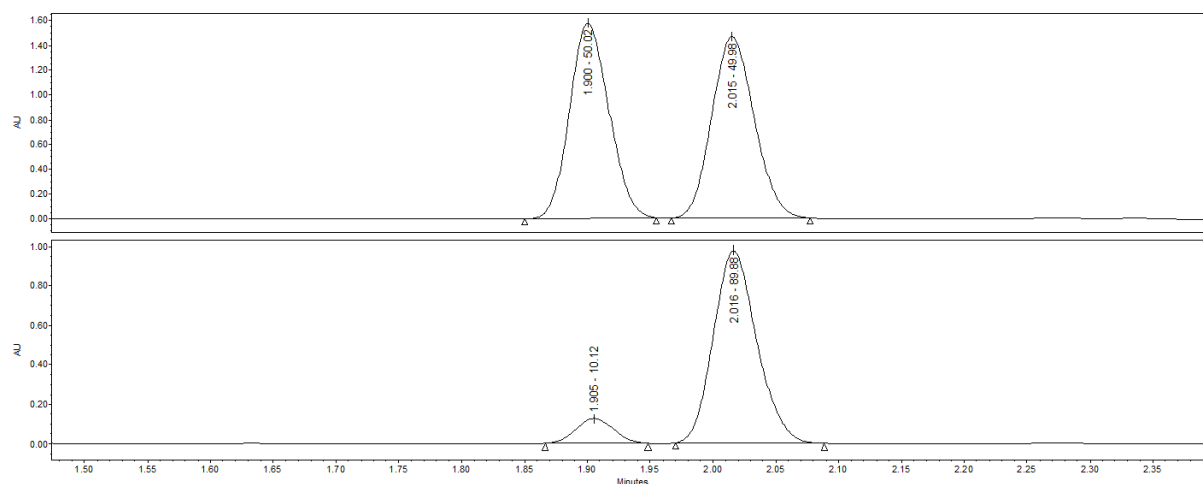
¹⁹F NMR (377 MHz, CDCl₃) δ –63.19.

[α]_D²⁵ = +7 (c = 1.0 in CHCl₃, 80% ee).

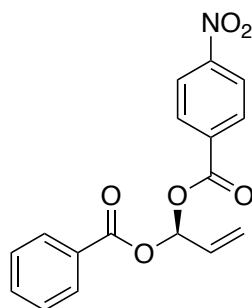
HRMS (ESI) *m/z* calcd. for C₁₈H₁₃O₄F₃Na [M+Na]⁺: 373.0658, found: 373.0658.

IR (ATR) ν (cm⁻¹, CHCl₃): 709, 951, 1066, 1325, 1742.

The enantiomeric excess of 80% was determined by SFC [Chiralpak® IG, 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=220 nm; minor enantiomer *t*_R = 1.91 mins, major enantiomers *t*_R = 2.02 mins].



(+)-(S)-1-(Benzoyloxy)allyl 4-nitrobenzoate (278)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–10% Et₂O in pentane) gave the product as a yellow oil (86.2 mg, 66% yield, 66% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.32 – 8.22 (m, 4H), 8.11 – 8.06 (m, 2H), 7.67 (dt, *J* = 5.7, 1.0 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.50 – 7.44 (m, 2H), 6.18 (ddd, *J* = 17.3, 10.6, 5.7 Hz, 1H), 5.78 (dt, *J* = 17.3, 0.9 Hz, 1H), 5.57 (dt, *J* = 10.5, 0.9 Hz, 1H).

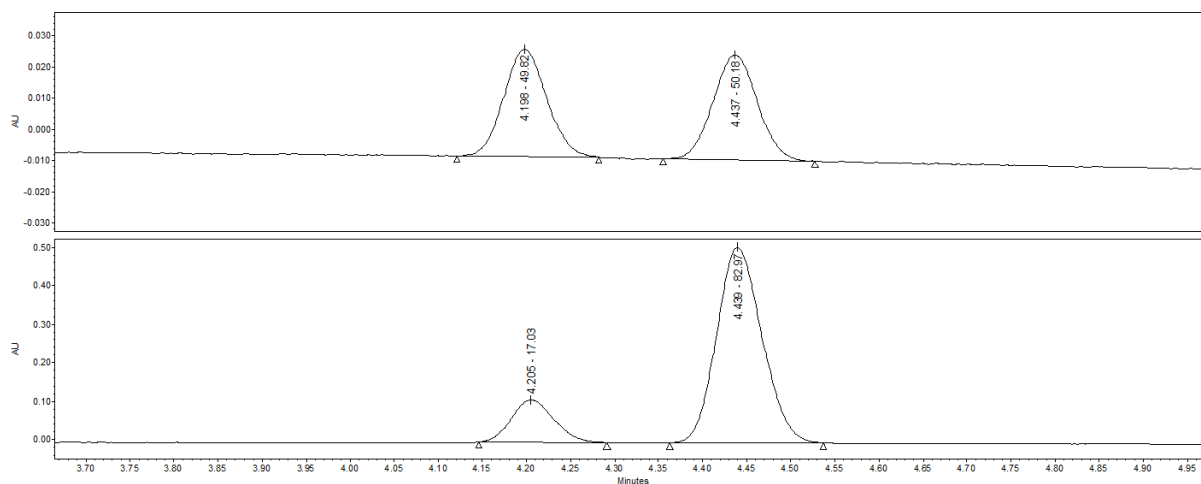
¹³C NMR (101 MHz, CDCl₃) δ 164.4, 162.7, 134.7, 134.0, 131.3 (2C), 131.0, 130.2 (2C), 128.9, 128.7 (2C), 123.8 (2C), 121.7, 100.1, 90.8.

[α]_D²⁵ = +3 (c = 1.0 in CHCl₃, 66% ee).

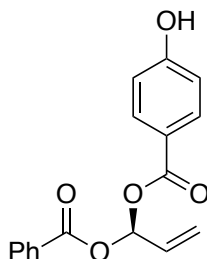
HRMS (ESI) *m/z* calcd. for C₁₇H₁₃O₆NNa [M+Na]⁺: 350.0635, found: 350.0636.

IR (ATR) ν (cm⁻¹, CHCl₃): 711, 953, 1064, 1246, 1527, 1741.

The enantiomeric excess of 66% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=220 nm; minor enantiomer *t*_R = 4.21 mins, major enantiomer *t*_R = 4.44 mins].



(-)-(S)-1-(Benzoyloxy)allyl 4-hydroxybenzoate (279)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–30% Et₂O in pentane) gave the product as a colourless oil (89.8 mg, 75% yield, 91% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.14 – 8.04 (m, 2H), 7.98 (d, *J* = 8.7 Hz, 2H), 7.65 (dt, *J* = 5.4, 1.0 Hz, 1H), 7.58 (ddt, *J* = 7.9, 7.0, 1.3 Hz, 1H), 7.44 (ddt, *J* = 7.8, 6.6, 1.1 Hz, 2H), 6.91 – 6.83 (m, 2H), 6.16 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.97 (s, 1H), 5.74 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.51 (dt, *J* = 10.6, 1.0 Hz, 1H).

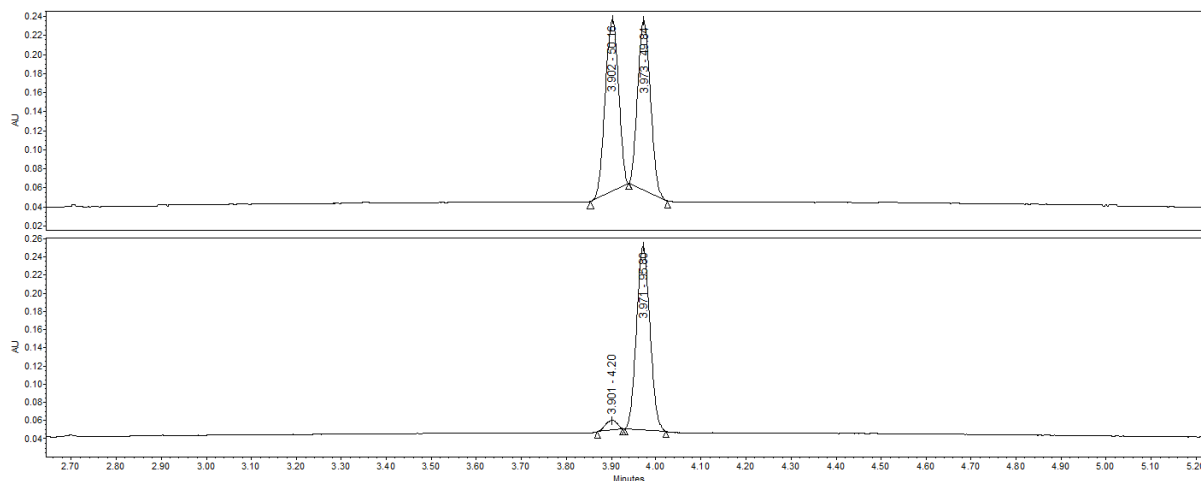
¹³C NMR (101 MHz, CDCl₃) δ 164.8, 164.4, 160.7, 133.8, 132.6 (2C), 131.6, 130.2 (2C), 129.3, 128.6 (2C), 120.9, 121.5, 115.5 (2C), 90.2.

[α]_D²⁵ = −12 (*c* = 1.0 in CHCl₃, 91% ee).

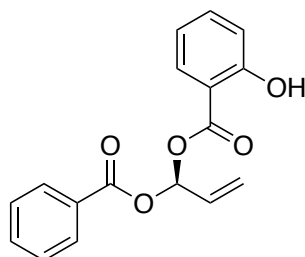
HRMS (ESI) *m/z* calcd. for C₁₇H₁₄O₅Na [M+Na]⁺: 321.0733, found: 321.0735.

IR (ATR) ν (cm^{−1}, CHCl₃): 711, 950, 1063, 1255, 1607, 1732, 3380.

The enantiomeric excess of 91% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =210 nm; major enantiomer t_R = 3.91 mins, minor enantiomer t_R = 3.98 mins].



(+)-(S)-1-(Benzoyloxy)allyl 2-hydroxybenzoate (280)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–10% Et₂O in pentane) gave the product as a colourless oil (54.1 mg, 45% yield, 37% ee).

¹H NMR (400 MHz, CDCl₃) δ 10.47 (s, 1H), 8.17 – 8.06 (m, 2H), 7.89 (dd, J = 8.0, 1.7 Hz, 1H), 7.69 (dt, J = 5.5, 1.0 Hz, 1H), 7.65 – 7.56 (m, 1H), 7.55 – 7.42 (m, 3H), 6.99 (dd, J = 8.5, 1.1 Hz, 1H), 6.89 (ddd, J = 8.3, 7.2, 1.1 Hz, 1H), 6.17 (ddd, J = 17.3, 10.6, 5.5 Hz, 1H), 5.77 (dt, J = 17.3, 0.9 Hz, 1H), 5.56 (dt, J = 10.6, 0.9 Hz, 1H).

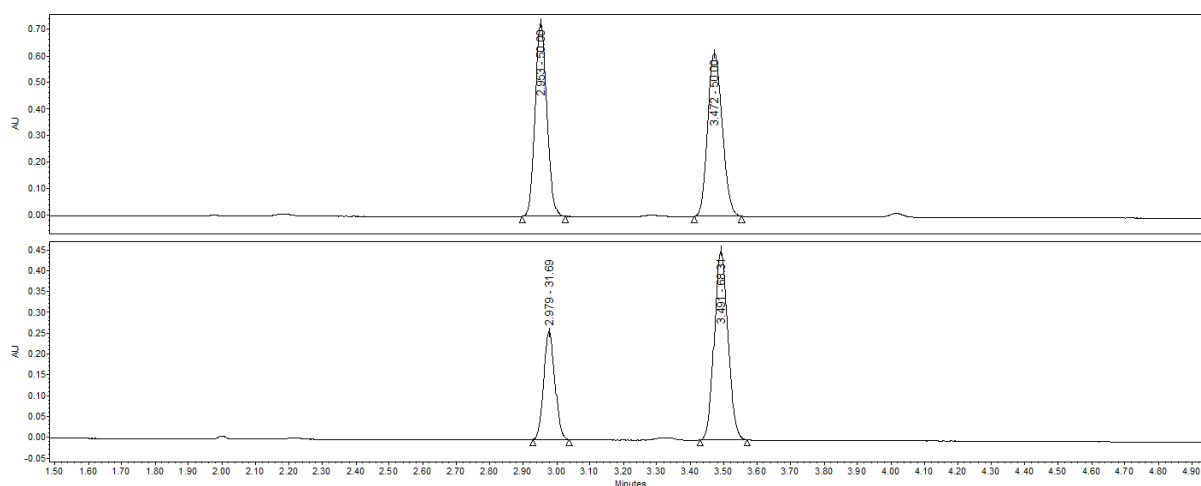
¹³C NMR (101 MHz, CDCl₃) δ 168.1, 164.3, 162.1, 136.4, 133.8, 130.9, 130.1, 130.1 (2C), 128.8, 128.6 (2C), 121.4, 119.3, 117.8, 111.5, 89.9.

$[\alpha]_{589}^{25} = +10$ ($c = 1.1$ in CHCl_3 , 37% ee).

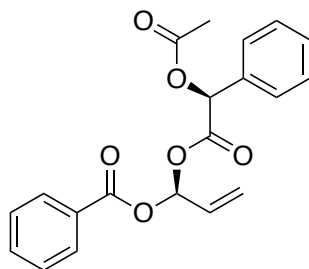
HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 321.0733, found: 321.0734.

IR (ATR) ν (cm^{-1} , CHCl_3): 710, 953, 1062, 1247, 1737, 3230.

The enantiomeric excess of 37% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; $\lambda=220$ nm; minor enantiomer $t_R = 2.98$ mins, major enantiomer $t_R = 3.49$ mins].



(+)-(S,S)-1-(2-Acetoxy-2-phenylacetoxy)allyl benzoate (282)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO_2 , 0–15% Et_2O in pentane) gave the product as a yellow oil (60.7 mg, 43% yield, 78% ee).

^1H NMR (400 MHz, CDCl_3) δ 8.1 – 8.0 (m, 2H), 7.7 – 7.6 (m, 1H), 7.5 – 7.3 (m, 8H), 6.0 (s, 1H), 5.9 (ddd, $J = 17.3, 10.6, 5.2$ Hz, 1H), 5.5 (dd, $J = 17.3, 1.1$ Hz, 1H), 5.4 (dd, $J = 10.6, 1.0$ Hz, 1H), 2.2 (s, 3H).

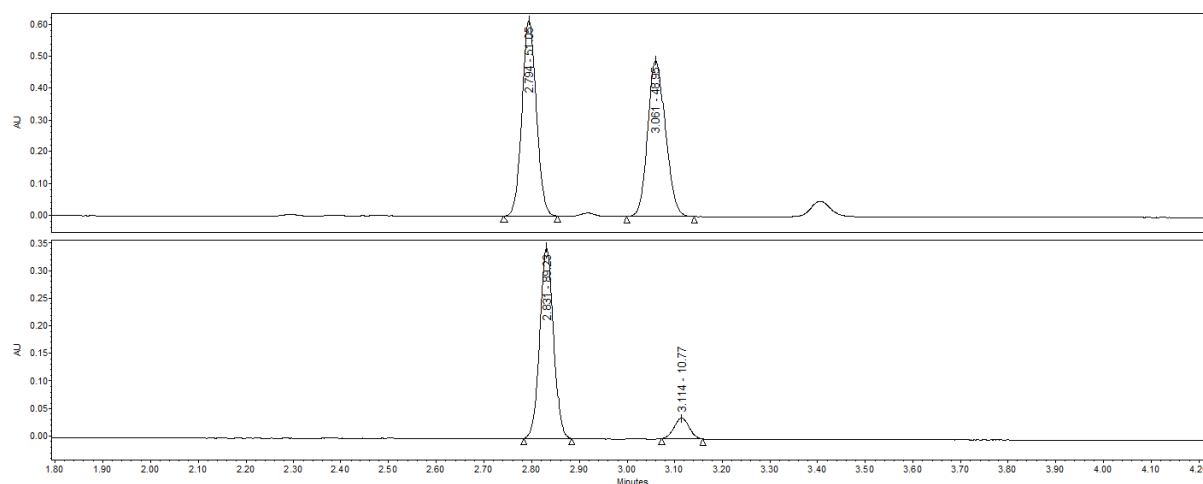
^{13}C NMR (101 MHz, CDCl_3) δ 170.2, 166.9, 164.2, 133.7, 133.4, 130.7, 130.2 (2C), 129.6, 129.0, 129.0 (2C), 128.6 (2C), 127.9 (2C), 121.0, 90.2, 74.3, 20.8.

$[\alpha]^{25}_{589} = +70$ ($c = 1.0$ in CHCl_3 , 78% ee).

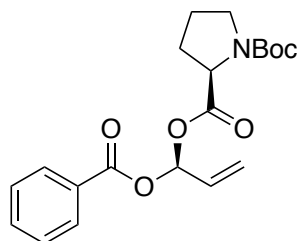
HRMS (ESI) m/z calcd. for $\text{C}_{20}\text{H}_{18}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 377.0996, found: 377.0989

IR (ATR) ν (cm^{-1} , CHCl_3): 711, 957, 1053, 1228, 1740, 2360.

The enantiomeric excess of 78% was determined by SFC [Chiralpak® IE; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; $\lambda=220$ nm; major enantiomer $t_R = 2.83$ mins, minor enantiomer $t_R = 3.11$ mins].



(-)-2-((*S,R*)-1-(Benzoyloxy)allyl)-1-(*tert*-butyl)-(pyrrolidine-1,2-dicarboxylate (284)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO_2 , 0–30% Et_2O in pentane) gave the product as a yellow oil (103.6 mg, 69% yield, 90% ee). The product is obtained as ~2:1 ratio of rotamers, as confirmed by NOESY NMR (see Figure 5.8), NMR assignments below are for the major rotamer.

¹H NMR Major Rotamer (400 MHz, CDCl₃) δ 8.10 – 8.02 (m, 2H), 7.64 – 7.55 (m, 1H), 7.49 – 7.40 (m, 3H), 6.03 (ddd, *J* = 17.2, 10.6, 5.7 Hz, 1H), 5.67 (d, *J* = 17.2 Hz, 1H), 5.47 (d, *J* = 10.5 Hz, 1H), 4.29 (dd, *J* = 8.7, 4.0 Hz, 1H), 3.57 – 3.40 (m, 2H), 2.31 – 2.16 (m, 1H), 2.07 – 1.97 (m, 1H), 1.97 – 1.79 (m, 2H), 1.43 (s, 3H), 1.37 (s, 6H).

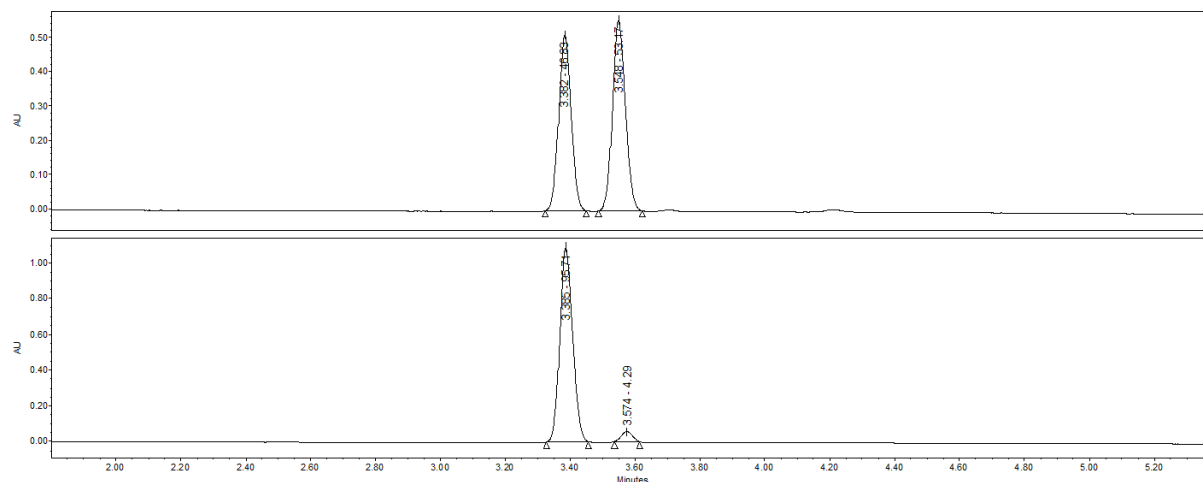
¹³C NMR Major Rotamer (101 MHz, CDCl₃) δ 171.0, 164.3, 153.8, 133.8, 131.2, 130.0 (2C), 129.1, 128.6 (2C), 121.2, 90.1, 59.2, 46.4, 31.0, 28.5, 28.4 (3C), 23.6.

[α]²⁵₅₈₉ = −54 (c = 1.0 in CHCl₃, 90% ee).

HRMS (ESI) *m/z* calcd. for C₂₀H₂₅NO₆Na [M+Na]⁺: 398.1574, found: 398.1573.

IR (ATR) ν (cm^{−1}, CHCl₃): 712, 956, 1160, 1395, 1700, 2360, 2980.

The enantiomeric excess of 90% was determined by SFC [Chiralpak® IE; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=220 nm; major enantiomer *t*_R = 3.39 mins, minor enantiomer *t*_R = 3.57 mins].



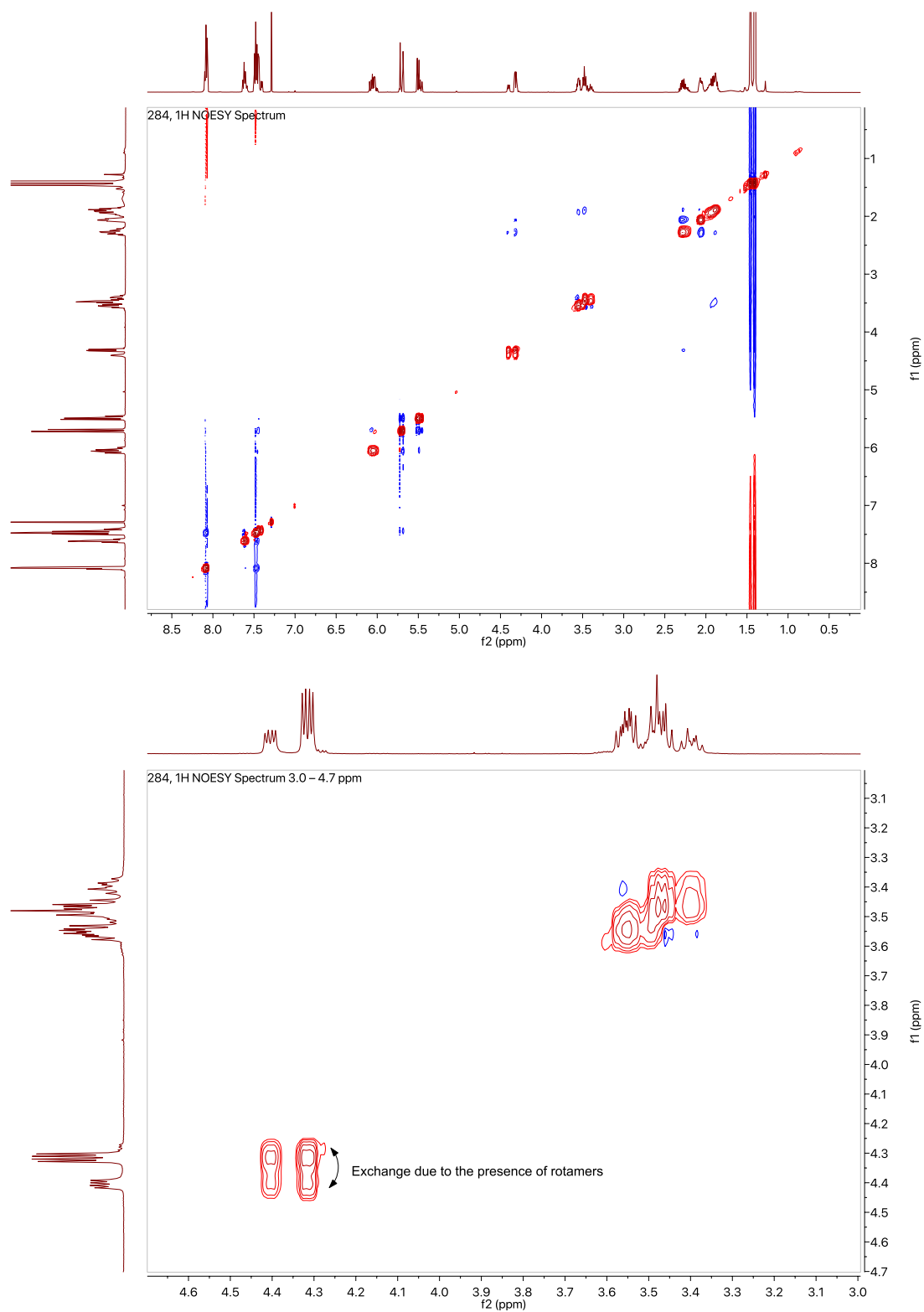
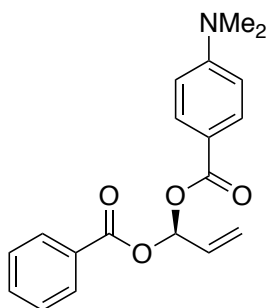


Figure 5.8 NOESY Spectrum for **284** (top). Zoomed in from 3.00 – 4.70 ppm (bottom).

(-)-(S)-1-(Benzoyloxy)allyl 4-(dimethylamino)benzoate (286)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–30% Et₂O in pentane) gave the product as a yellow oil (76.7 mg, 59% yield, 94% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.17 – 8.07 (m, 2H), 8.02 – 7.93 (m, 2H), 7.68 (dt, *J* = 5.3, 1.1 Hz, 1H), 7.64 – 7.54 (m, 1H), 7.51 – 7.41 (m, 2H), 6.70 – 6.62 (m, 2H), 6.19 (ddd, *J* = 17.3, 10.6, 5.3 Hz, 1H), 5.75 (dt, *J* = 17.3, 1.1 Hz, 1H), 5.51 (dt, *J* = 10.6, 1.0 Hz, 1H), 3.07 (s, 6H).

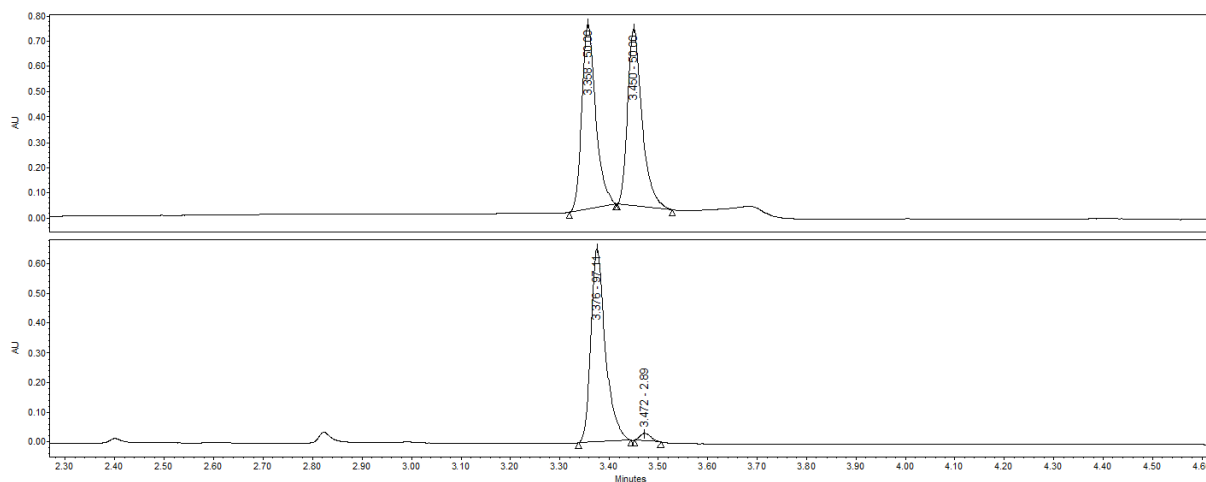
¹³C NMR (101 MHz, CDCl₃) δ 164.6, 164.4, 153.7, 133.4, 132.0, 131.8 (2C), 130.0 (2C), 129.5, 128.4 (2C), 120.2, 115.5, 110.7 (2C), 89.6, 40.1.

[α]_D²⁵ = –45 (c = 1.0 in CHCl₃, 94% ee).

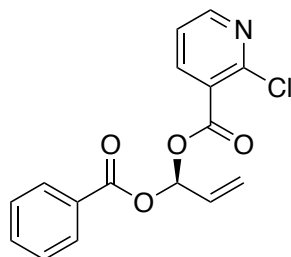
HRMS (ESI) *m/z* calcd. for C₁₉H₁₉NO₄Na [M+Na]⁺: 348.1206, found: 348.1204.

IR (ATR) ν (cm⁻¹, CHCl₃): 711, 946, 1060, 1259, 1605, 1731, 2360, 2981.

The enantiomeric excess of 94% was determined by SFC [Chiralpak® IB; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=220 nm; major enantiomer *t*_R = 3.38 mins, minor enantiomer *t*_R = 3.47 mins].



(+)-(S)-1-(Benzoyloxy)allyl 2-chloronicotinate (288)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–30% Et₂O in pentane) gave the product as a colourless oil (59.3 mg, 47% yield, 67% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.53 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.21 (dd, *J* = 7.7, 2.0 Hz, 1H), 8.14 – 8.05 (m, 2H), 7.66 – 7.61 (m, 1H), 7.61 – 7.57 (m, 1H), 7.51 – 7.41 (m, 2H), 7.33 (dd, *J* = 7.7, 4.8 Hz, 1H), 6.16 (ddd, *J* = 17.3, 10.6, 5.7 Hz, 1H), 5.78 (dt, *J* = 17.3, 0.9 Hz, 1H), 5.56 (dt, *J* = 10.6, 0.9 Hz, 1H).

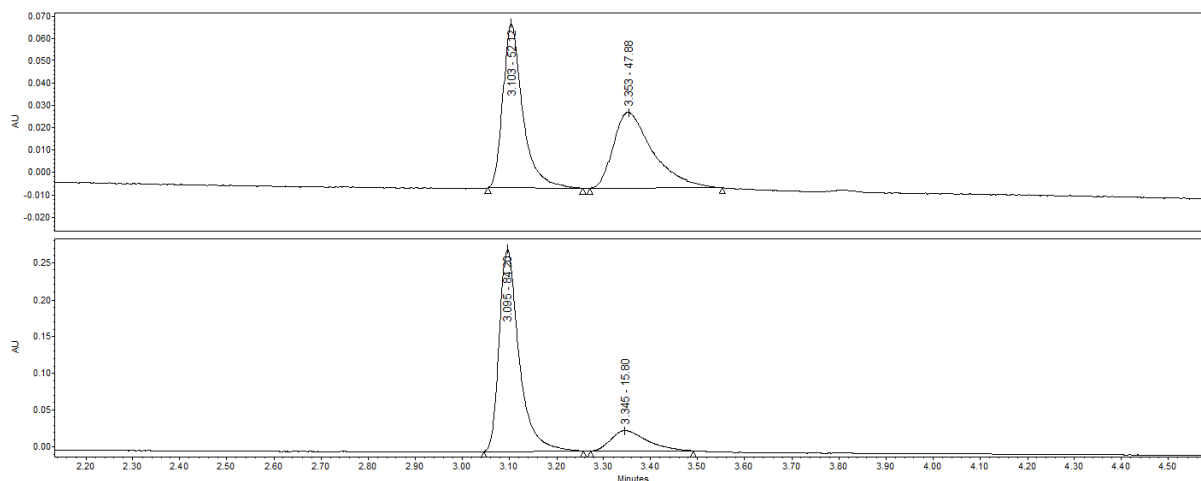
¹³C NMR (101 MHz, CDCl₃) δ 164.4, 162.3, 152.5, 150.5, 140.8, 133.9, 130.8, 130.1 (2C), 128.9, 128.7 (2C), 126.0, 122.2, 121.7, 90.9.

[α]_D²⁵ = +4 (c = 1.04 in CHCl₃, 67% ee).

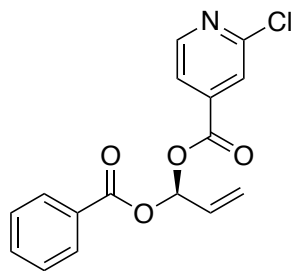
HRMS (ESI) *m/z* calcd. for C₁₆H₁₂O₄NCINa [M+Na]⁺: 340.0347, found: 340.0348.

IR (ATR) ν (cm⁻¹, CHCl₃): 711, 953, 1043, 1261, 1406, 1738.

The enantiomeric excess of 67% was determined by SFC [Chiralpak® ID; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =220 nm; major enantiomer t_R = 3.10 mins, minor enantiomer t_R = 3.35 mins].



(+)-(*S*)-1-(Benzoyloxy)allyl 2-chloroisonicotinate (289)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–30% Et₂O in pentane) gave the product as an orange oil (65.2 mg, 51% yield, 69% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.55 (dd, J = 5.1, 0.8 Hz, 1H), 8.13 – 8.04 (m, 2H), 7.93 – 7.87 (m, 1H), 7.80 (dd, J = 5.1, 1.4 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.61 – 7.58 (m, 1H), 7.51 – 7.42 (m, 2H), 6.15 (ddd, J = 17.3, 10.6, 5.7 Hz, 1H), 5.77 (dt, J = 17.2, 0.9 Hz, 1H), 5.57 (dt, J = 10.6, 0.9 Hz, 1H).

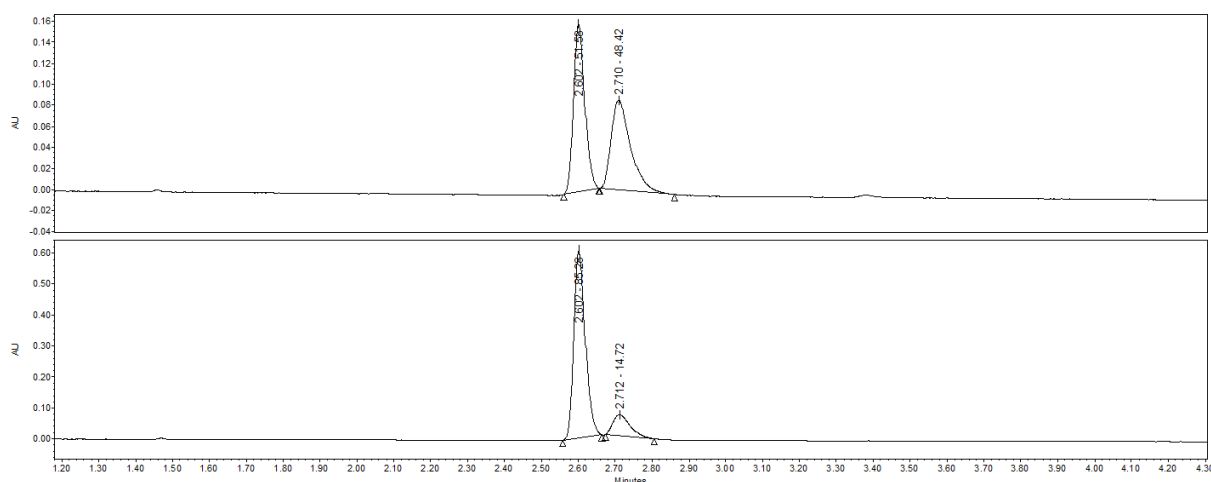
¹³C NMR (101 MHz, CDCl₃) δ 164.3, 161.9, 152.6, 150.7, 139.5, 134.0, 130.7, 130.1 (2C), 128.7, 128.7 (2C), 124.3, 121.9 (2C), 90.9.

$[\alpha]^{25}_{589} = +7$ ($c = 1.0$ in CHCl_3 , 69% ee).

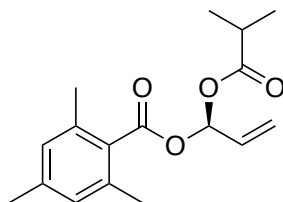
HRMS (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{12}\text{O}_4\text{NCINa}$ $[\text{M}+\text{Na}]^+$: 340.0347, found: 340.0348.

IR (ATR) ν (cm^{-1} , CHCl_3): 711, 954, 1081, 1245, 1370, 1743.

The enantiomeric excess of 69% was determined by SFC [Chiralpak® ID; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; $\lambda=220$ nm; major enantiomer $t_R = 2.60$ mins, minor enantiomer $t_R = 2.71$ mins].



(+)-(R)-1-(Isobutyryloxy)allyl 2,4,6-trimethylbenzoate (290)



Synthesised according to general procedure 7. Reaction time: 50 mins. Flash column chromatography (SiO_2 , 0–10% Et_2O in pentane) gave the product as a colourless oil (107.0 mg, 92% yield, 95% ee).

^1H NMR (400 MHz, CDCl_3) δ 7.40 (dt, $J = 5.7, 1.0$ Hz, 1H), 6.88 – 6.82 (m, 2H), 6.00 (ddd, $J = 17.3, 10.5, 5.8$ Hz, 1H), 5.66 (dt, $J = 17.3, 1.0$ Hz, 1H), 5.45 (dt, $J = 10.6, 1.0$ Hz, 1H), 2.61 (hept, $J = 7.0$ Hz, 1H), 2.30 (s, 6H), 2.28 (s, 3H), 1.21 (d, $J = 7.0$ Hz, 6H).

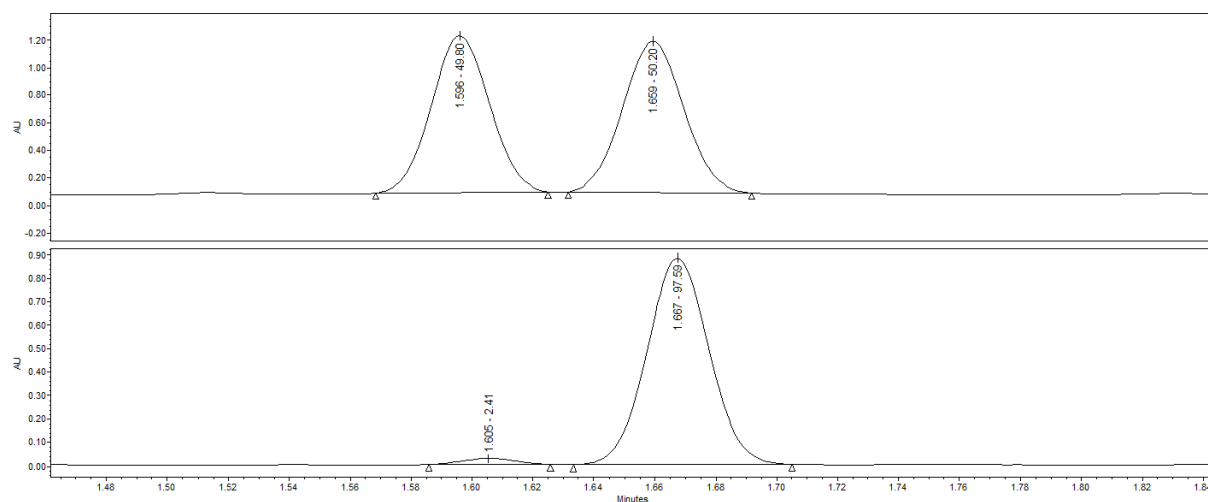
^{13}C NMR (101 MHz, CDCl_3) δ 174.8, 167.8, 139.9, 135.6 (2C), 131.5, 129.9, 128.6 (2C), 120.9, 89.6, 34.1, 21.3, 19.9 (2C), 18.9, 18.8.

$[\alpha]^{25}_{589}$ = +24 (c = 1.0 in CHCl_3 , 95% ee).

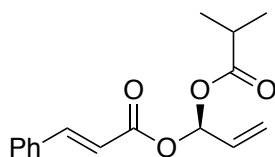
HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 313.1410, found: 313.1410.

IR (ATR) ν (cm^{-1} , CHCl_3): 958, 1061, 1258, 1753, 2360.

The enantiomeric excess of 95% was determined by SFC [Chiralpak® IC; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =215 nm; minor enantiomer t_R = 1.61 mins, major enantiomer t_R = 1.67 mins].



(+)-(S)-1-(Isobutyryloxy)allyl cinnamate (**291**)



Synthesised according to general procedure 7. Reaction time: 30 mins. Flash column chromatography (SiO_2 , 0–5% Et_2O in pentane) gave the product as a pale yellow oil (90.2 mg, 82% yield, 93% ee).

^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, J = 16.0 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.43 – 7.35 (m, 3H), 7.29 (dt, J = 5.4, 1.0 Hz, 1H), 6.44 (d, J = 16.0 Hz, 1H), 5.99 (ddd, J = 17.3, 10.6,

5.4 Hz, 1H), 5.62 (dt, $J = 17.3, 1.0$ Hz, 1H), 5.44 (dt, $J = 10.6, 1.0$ Hz, 1H), 2.61 (hept, $J = 7.0$ Hz, 1H), 1.20 (d, $J = 7.0$ Hz, 6H).

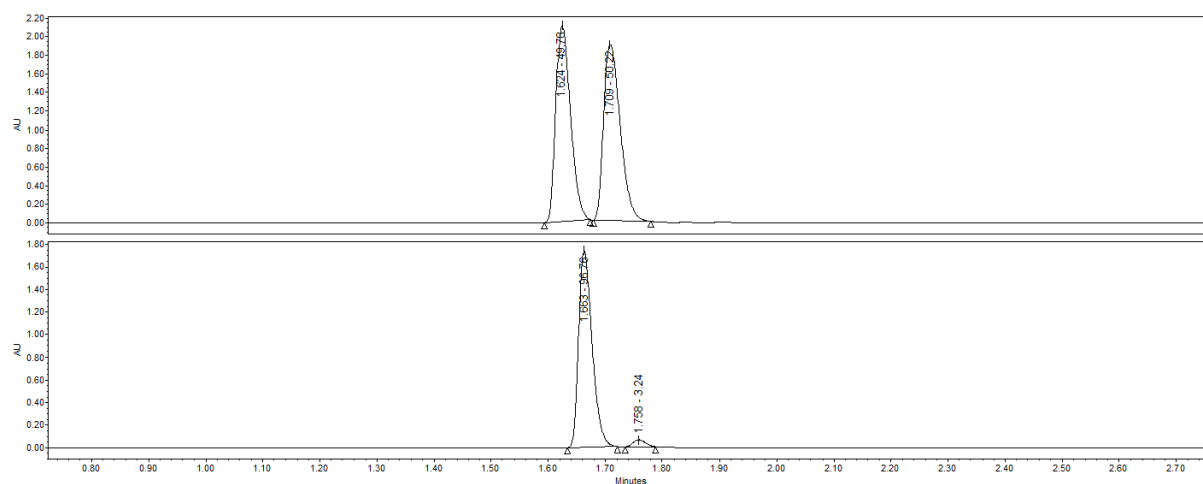
^{13}C NMR (101 MHz, CDCl_3) δ 174.9, 164.7, 146.5, 134.3, 131.6, 130.8, 129.1 (2C), 128.4 (2C), 120.5, 117.1, 89.3, 34.1, 18.8, 18.8.

$[\alpha]^{25}_{589} = +20$ ($c = 1.0$ in CHCl_3 , 93% ee).

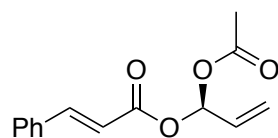
HRMS (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{18}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 297.1097, found: 297.1098.

IR (ATR) ν (cm^{-1} , CHCl_3): 768, 963, 1127, 1636, 1747, 2360.

The enantiomeric excess of 93% was determined by SFC [Chiralpak® IA; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; $\lambda=275$ nm; major enantiomer $t_R = 1.66$ mins, minor enantiomer $t_R = 1.76$ mins].



(+)-(R)-1-Acetoxyallyl cinnamate (292)



Synthesised according to general procedure 7. Reaction time: 1.5 hrs. Flash column chromatography (SiO_2 , 0–10% Et_2O in pentane) gave the product as a yellow oil (82.7 mg, 84% yield, 92% ee).

¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.45 – 7.36 (m, 3H), 7.30 (dt, *J* = 5.5, 1.0 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.62 (dt, *J* = 17.3, 1.0 Hz, 1H), 5.44 (dt, *J* = 10.5, 1.0 Hz, 1H), 2.13 (s, 3H).

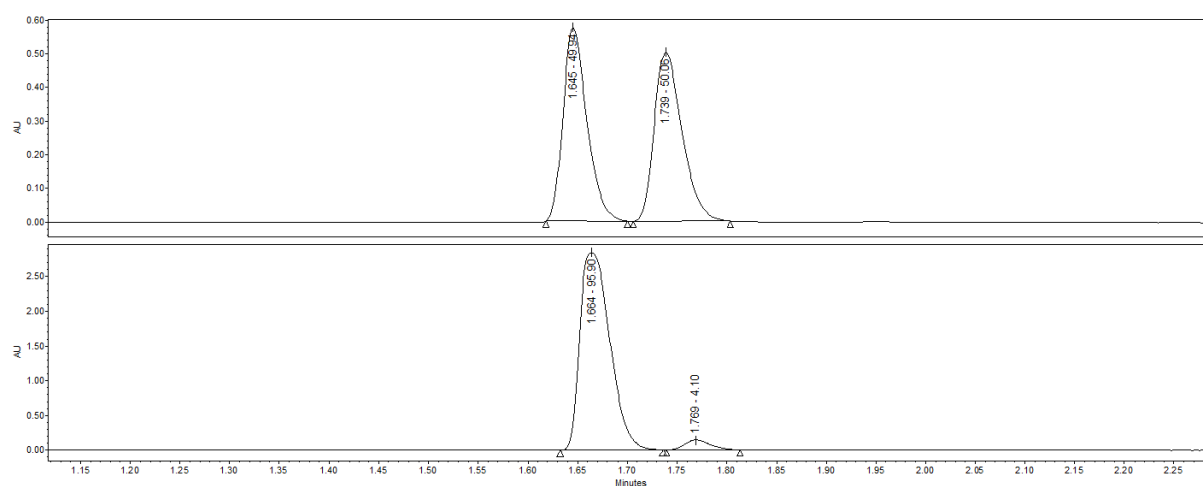
¹³C NMR (101 MHz, CDCl₃) δ 168.8, 164.7, 146.7, 134.2, 131.5, 130.8, 129.1 (2C), 128.4 (2C), 120.7, 117.0, 89.4, 21.0.

[α]²⁵₅₈₉ = +23 (c = 1.0 in CHCl₃, 92% ee).

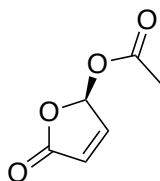
HRMS (ESI) *m/z* calcd. for C₁₄H₁₄O₄Na [M+Na]⁺: 269.0784, found: 269.0785.

IR (ATR) ν (cm⁻¹, CHCl₃): 768, 965, 1150, 1222, 1636, 1756.

The enantiomeric excess of 92% was determined by SFC [Chiralpak® IA; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=275 nm; major enantiomer *t*_R = 1.66 mins, minor enantiomer *t*_R = 1.77 mins].



(+)-(R)-5-Oxo-2,5-dihydrofuran-2-yl acetate (293**)**



(*R*)-1-Acetoxyallyl cinnamate (**292**, 57 mg, 0.23 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (46 mL) and the resulting solution, degassed by bubbling through argon for 30 mins. Grubbs I catalyst (19 mg, 0.023 mmol, 0.1 eq.) was added, the flask fitted with a reflux condenser and the reaction stirred at 50 °C for 24 hrs. SiO₂ was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with 0–50% Et₂O in pentane to afford the product as a brown oil (19.8 mg, 61% yield, 93% ee). Absolute stereochemistry was assigned by comparison with the literature.¹⁹⁸

¹H NMR (400 MHz, CDCl₃) δ 7.32 (dd, *J* = 5.6, 1.3 Hz, 1H), 7.00 (t, *J* = 1.3 Hz, 1H), 6.32 (dd, *J* = 5.7, 1.2 Hz, 1H), 2.17 (s, 3H).

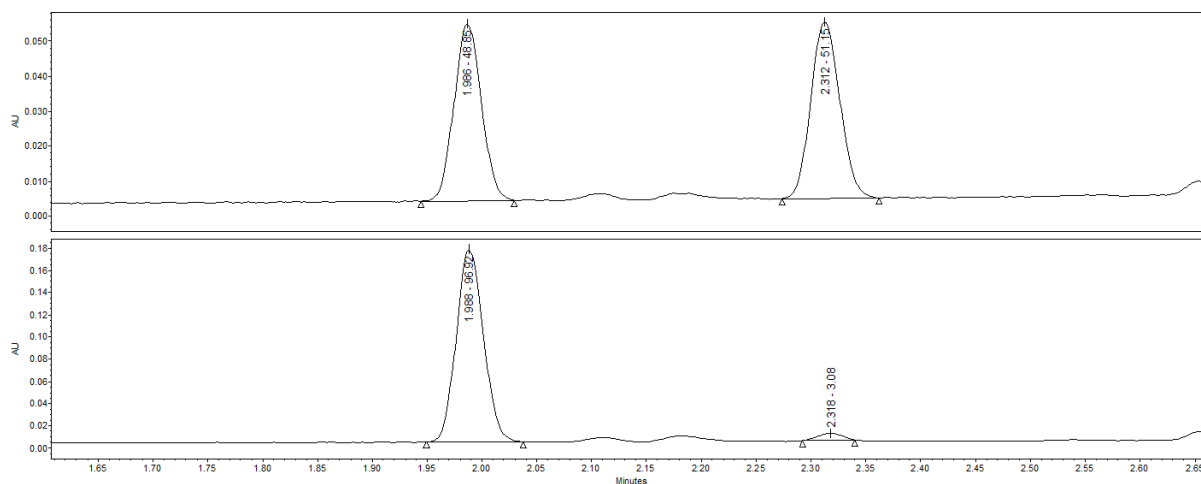
¹³C NMR (101 MHz, CDCl₃) δ 169.7, 169.0, 149.8, 125.4, 93.9, 20.8.

[α]_D²⁵ = +21 (c = 1.0 in CHCl₃, 93% ee).

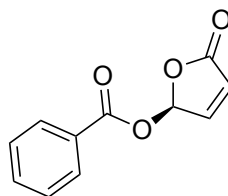
HRMS (ESI) *m/z* calcd. for C₆H₇O₄ [M+H]⁺: 143.0339, found: 143.0340.

IR (ATR) ν (cm⁻¹, CHCl₃): 820, 880, 1023, 1086, 1212, 1791.

The enantiomeric excess of 93% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=215 nm; major enantiomer t_R = 1.99 mins, minor enantiomer t_R = 2.32 mins].



(+)-(R)-5-Oxo-2,5-dihydrofuran-2-yl benzoate (294)



(*R*)-1-(Cinnamoyloxy)allyl benzoate (**264**, 80 mg, 0.26 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (52 mL) and the resulting solution, degassed by bubbling through argon for 30 mins. Grubbs I catalyst (21.3 mg, 0.026 mmol, 0.1 eq.) was added, the flask fitted with a reflux condenser and the reaction stirred at 50 °C for 24 hrs. SiO₂ was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with 0–40% Et₂O in pentane to afford the product as an off-white solid (40.4 mg, 76% yield, 92% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.09 – 8.01 (m, 2H), 7.67 – 7.58 (m, 1H), 7.52 – 7.41 (m, 3H), 7.25 (t, *J* = 1.3 Hz, 1H), 6.39 (dd, *J* = 5.7, 1.2 Hz, 1H).

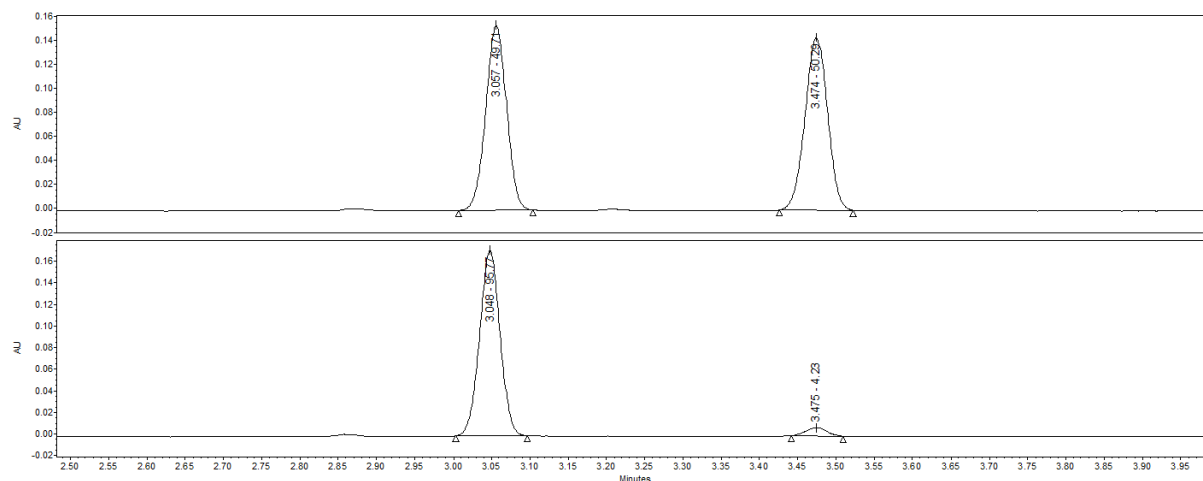
¹³C NMR (101 MHz, CDCl₃) δ 169.8, 164.7, 149.9, 134.3, 130.3 (2C), 128.8 (2C), 128.3, 125.5, 94.6.

[α]_D²⁵ = +110 (c = 1.0 in CHCl₃, 92% ee).

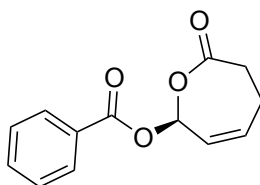
HRMS (ESI) *m/z* calcd. for C₁₁H₈O₄Na [M+Na]⁺: 227.0315, found: 227.0316.

IR (ATR) ν (cm^{-1} , CHCl_3): 718, 891, 1084, 1252, 1736, 1795.

The enantiomeric excess of 92% was determined by SFC [Chiralpak® IC; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =235 nm; major enantiomer t_R = 3.04 mins, minor enantiomer t_R = 3.48 mins].



(-)-(R)-5-Oxo-2,5-dihydrofuran-2-yl benzoate (295)



(*R*)-1-(Pent-4-enoyloxy)allyl benzoate (**262**, 47.5 mg, 0.18 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (36 mL) and the resulting solution, degassed by bubbling through argon for 45 mins. Grubbs II catalyst (15.5 mg, 0.018 mmol, 0.1 eq.) was added, the flask fitted with a reflux condenser and the reaction stirred at 50 °C for 24 hrs. SiO_2 was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with 0–40% Et_2O in pentane to afford the product as an off-white solid (43% yield, >99% ee). Most trace impurities were removed by trituration in hexane. No change in ee was observed before and after trituration.

¹H NMR (400 MHz, CDCl₃) δ 8.13 – 8.08 (m, 2H), 7.64 – 7.59 (m, 1H), 7.47 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.35 (dd, *J* = 7.6, 0.5 Hz, 1H), 6.13 – 6.04 (m, 1H), 5.83 (ddt, *J* = 15.6, 7.6, 1.3 Hz, 1H), 2.70 – 2.56 (m, 1H), 2.54 – 2.43 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 169.5, 164.4, 135.7, 133.8, 130.1 (2C), 129.3, 128.7 (2C), 125.7, 91.0, 33.0, 27.8.

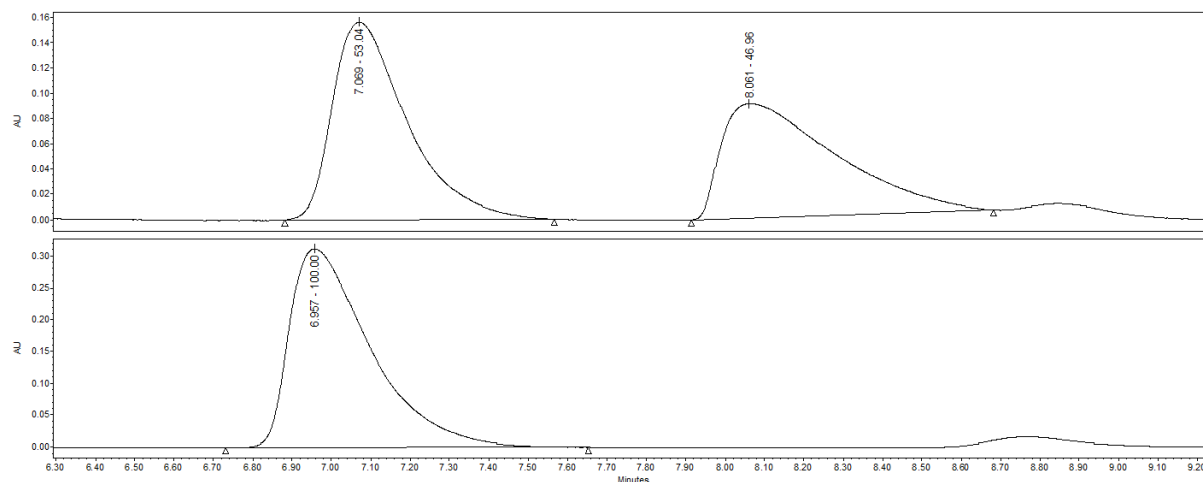
[α]_D²⁵ = −4 (c = 1.0 in CHCl₃, >99% ee).

HRMS (ESI) *m/z* calcd. for C₁₃H₁₂O₄Na [M+Na]⁺: 255.0628, found: 255.0628.

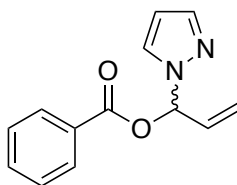
IR (ATR) ν (cm^{−1}, CHCl₃): 711, 957, 1065, 1269, 1747.

m.p.: 183–186 °C

The enantiomeric excess of >99% was determined by SFC [Chiralpak® IB; 1500 psi, 30 °C; 97:3 CO₂:MeOH; flow: 1.5 mL/min; λ=225 nm; major enantiomer *t*_R = 6.96 mins, minor enantiomer not observed].



1-(1*H*-Pyrazol-1-yl)allyl benzoate (307)



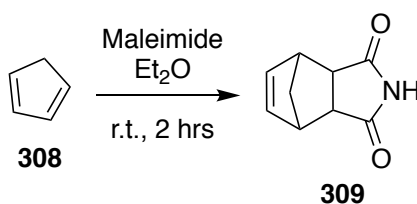
Synthesised according to general procedure 7. Reaction time: 5 mins. Flash column chromatography (SiO₂, 20% Et₂O in pentane) gave the product as a yellow oil (23.3 mg, 26% yield, racemic).

¹H NMR (400 MHz, CDCl₃) δ 8.13 – 8.03 (m, 2H), 7.74 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.67 – 7.53 (m, 2H), 7.49 – 7.38 (m, 3H), 6.41 (ddd, *J* = 17.2, 10.6, 5.2 Hz, 1H), 6.32 (dd, *J* = 2.5, 1.8 Hz, 1H), 5.65 (ddd, *J* = 17.2, 1.5, 0.7 Hz, 1H), 5.55 (ddd, *J* = 10.6, 1.4, 0.7 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 165.1, 141.1, 133.8, 131.5, 130.1 (2C), 130.0, 129.1, 128.6 (2C), 120.2, 106.7, 81.8.

LRMS (ESI) *m/z*: 251.0 [M+Na]⁺

Bicyclo<2.2.1>-5-hepten-2,3-dicarbonimide (309)



Freshly cracked cyclopentadiene (2.8 mL, 33.3 mmol, 1.01 eq.) was added to a solution of maleimide (3.2 g, 33.0 mmol, 1.0 eq.) in Et₂O (80 mL), forming a white precipitate. The reaction was stirred for 2 hrs at room temperature. The white solid was filtered and dried under a stream of N₂ before recrystallising from 2:1 Et₂O:MeOH to give the pure product as white crystals (4.18 g, 78% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.82 (s, 1H), 6.20 (t, *J* = 1.8 Hz, 2H), 3.38 (dq, *J* = 3.4, 1.7 Hz, 2H), 3.31 (dd, *J* = 3.1, 1.6 Hz, 2H), 1.75 (d, *J* = 8.8 Hz, 1H), 1.52 (d, *J* = 8.8 Hz, 1H).

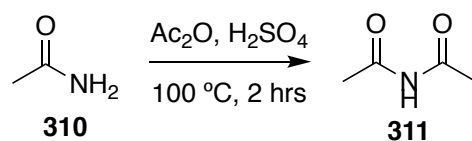
^{13}C NMR (101 MHz, CDCl_3) δ 177.8 (2C), 134.7 (2C), 52.4, 47.5 (2C), 45.1 (2C).

HRMS (APCI) m/z calcd. for $\text{C}_9\text{H}_8\text{O}_2\text{N}$ $[\text{M}-\text{H}]^-$: 162.0561, found: 162.0561.

IR (ATR) ν (cm^{-1} , CHCl_3): 630, 735, 1190, 1699, 3063.

m.p.: 179–180 °C

N-Acetylacetamide (311)



Acetamide (5.0 g, 85 mmol, 1.0 eq.), acetic anhydride (8.8 mL, 93 mmol, 1.1 eq.) and concentrated H_2SO_4 (0.5 mL) were added to a round bottom flask fitted with a reflux condenser and heated at 100 °C for 1 hr. The reaction was quenched with sat. aq. NaHCO_3 (40 mL) and more solid NaHCO_3 was added until the evolution of gas was no longer observed. Water (~30 mL) was added to redissolve the salts, and the aqueous phase was extracted with CH_2Cl_2 (3×60 mL). The combined organic phases were washed with brine (40 mL), dried over MgSO_4 and concentrated *in vacuo* to give the pure product as a white solid (1.18 g, 14% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.98 (s, 1H), 2.31 (s, 6H).

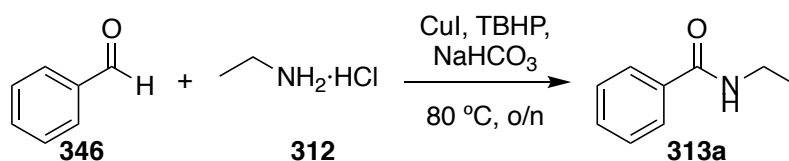
^{13}C NMR (101 MHz, CDCl_3) δ 171.8 (2C), 25.1 (2C).

HRMS (APCI) m/z calcd. for $\text{C}_4\text{H}_8\text{O}_2\text{N}$ $[\text{M}+\text{H}]^+$: 102.0550, found: 102.0549.

IR (ATR) ν (cm^{-1} , CHCl_3): 647, 1029, 1219, 1306, 1504, 1687, 3216.

m.p.: 75–77 °C

***N*-Ethylbenzamide (313a)**



Ethylamine hydrochloride (3.48 g, 43 mmol, 1.5 eq.), CuI (269 mg, 1.4 mmol, 0.05 eq.) and NaHCO₃ (2.62 g, 31 mmol, 1.1 eq.) were added to a flame-dried flask, under an argon atmosphere. Benzaldehyde (2.9 mL, 28 mmol, 1.0 eq.) was added via syringe and the mixture cooled to 0 °C. *t*-Butyl hydroperoxide (5.5 M in decane, 5.7 mL, 31 mmol, 1.1 eq.) was added slowly to the cooled reaction. The reaction was very slowly warmed to room temperature over 1 hr, until the evolution of gas was no longer observed. The flask was fitted with a condenser, heated to 80 °C and stirred overnight. The reaction mixture was diluted with CH₂Cl₂ (50 mL) and water (50 mL). The organic phase was extracted with water (30 mL). The aqueous phases were extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phases were washed with water (30 mL), brine (30 mL) dried over MgSO₄ and concentrated *in vacuo* onto SiO₂. Purification by flash column chromatography (SiO₂, 0–40% EtOAc in pentane) to give a yellow solid (2.36 g, 56% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.80 – 7.72 (m, 2H), 7.51 – 7.45 (m, 1H), 7.45 – 7.36 (m, 2H), 6.27 (s, 1H), 3.48 (qd, *J* = 7.2, 5.6 Hz, 2H), 1.24 (t, *J* = 7.3 Hz, 3H).

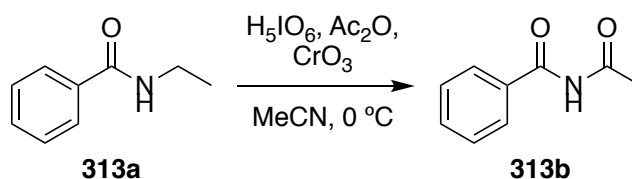
¹³C NMR (101 MHz, CDCl₃) δ 167.6, 134.9, 131.4, 128.6 (2C), 126.9 (2C), 35.0, 15.0.

LRMS (ESI) *m/z*: 150.0 [M+H]⁺

IR (ATR) ν (cm⁻¹, CHCl₃): 694, 1309, 1541, 1637, 3307.

m.p.: 67–69 °C

***N*-Acetylbenzamide (313b)**



H_5IO_6 (18.4 g, 81 mmol, 6.0 eq.) and CrO_3 (67.1 mg, 0.67 mmol, 0.05 eq.) were dissolved in MeCN (190 mL) and stirred at room temperature for 30 mins. Acetic anhydride (3.8 mL, 40 mmol, 3.0 eq.) was added and the reaction cooled to $0\text{ }^\circ\text{C}$. Amide **313a** (2 g, 13 mmol, 1.0 eq.) was added and the reaction stirred for 1 hr at $0\text{ }^\circ\text{C}$. The reaction mixture was poured into ice-water (200 mL) before extracting the aqueous with EtOAc ($2 \times 200\text{ mL}$). The combined organic phases were washed with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (200 mL), brine (200 mL) and dried over MgSO_4 . SiO_2 was added and the solvent carefully evaporated. The resulting solid was purified by flash column chromatography (SiO_2 , 50% EtOAc in pentane) to give the pure product as a white solid (1.52 g, 69% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.96 (s, 1H), 7.88 – 7.77 (m, 2H), 7.54 (t, $J = 7.4\text{ Hz}$, 1H), 7.43 (t, $J = 7.6\text{ Hz}$, 2H), 2.55 (s, 3H).

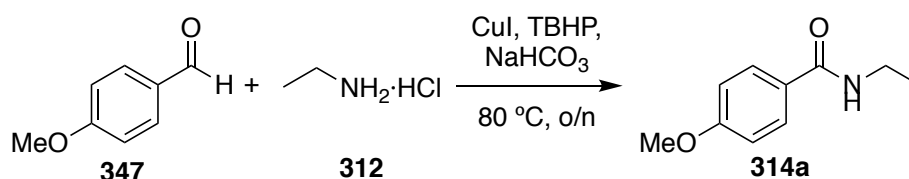
^{13}C NMR (101 MHz, CDCl_3) δ 173.8, 165.9, 133.4, 132.8, 129.1 (2C), 127.9 (2C), 25.7.

LRMS (ESI) m/z : 162.1 $[\text{M}-\text{H}]^-$

IR (ATR) ν (cm^{-1} , CHCl_3): 703, 1021, 1288, 1372, 1669, 3295.

m.p.: 115–118 $^\circ\text{C}$

***N*-Ethyl-4-methoxybenzamide (314a)**



Synthesised according to the same procedure as for **313a**. Purification by flash column chromatography (SiO₂, 60% EtOAc in pentane) gave the product as a white solid (1.69 g, 47% yield).

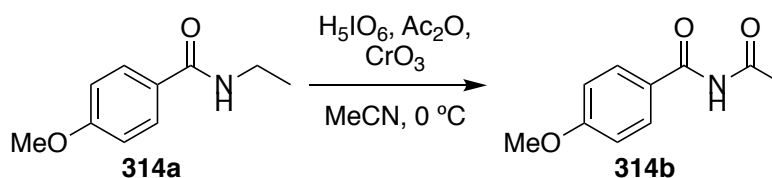
¹H NMR (400 MHz, CDCl₃) δ 7.77 – 7.69 (m, 2H), 6.94 – 6.86 (m, 2H), 6.11 (s, 1H), 3.83 (s, 3H), 3.53 – 3.41 (m, 2H), 1.23 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 167.1, 162.1, 128.7 (2C), 127.2, 113.8 (2C), 55.5, 35.0, 15.1.

LRMS (ESI) *m/z*: 202.0 [M+Na]⁺

IR (ATR) *v* (cm⁻¹, CHCl₃): 845, 1180, 1253, 1504, 1606, 3321.

***N*-Acetyl-4-methoxybenzamide (314b)**



Synthesised according to the same procedure as for **313b**. Purification by flash column chromatography (SiO₂, 0–30% EtOAc in pentane) gave the product as a white solid (196.1 g, 23% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.66 (s, 1H), 7.88 – 7.79 (m, 2H), 7.00 – 6.95 (m, 2H), 3.88 (s, 3H), 2.60 (s, 3H).

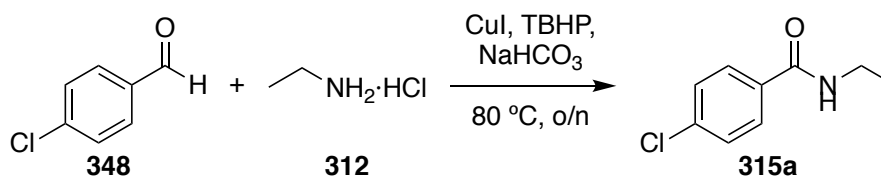
¹³C NMR (101 MHz, CDCl₃) δ 173.6, 165.1, 163.8, 129.9 (2C), 124.9, 114.4 (2C), 55.7, 25.6.

LRMS (ESI) *m/z*: 216.0 [M+Na]⁺

IR (ATR) ν (cm^{-1} , CHCl_3): 756, 1026, 1257, 1609, 1682, 3235.

m.p.: 114–116 °C

4-Chloro-N-ethylbenzamide (**315a**)



Synthesised according to the same procedure as for **313a**. Purification by flash column chromatography (SiO_2 , 0–40% EtOAc in pentane) gave the product as a white solid (1.42 g, 55% yield).

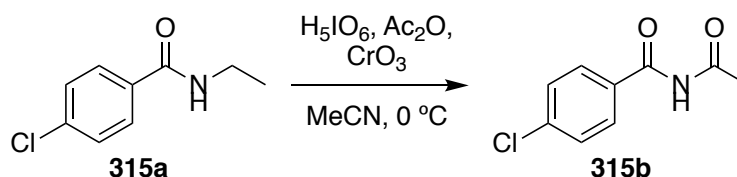
^1H NMR (400 MHz, CDCl_3) δ 7.75 – 7.66 (m, 2H), 7.44 – 7.37 (m, 2H), 6.05 (s, 1H), 3.49 (qd, $J = 7.3, 5.6$ Hz, 2H), 1.25 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 166.5, 137.7, 133.3, 128.9 (2C), 128.4 (2C), 35.2, 15.0.

LRMS (ESI) m/z : 184.0 $[\text{M}+\text{H}]^+$

IR (ATR) ν (cm^{-1} , CHCl_3): 844, 1092, 1541, 1633, 3301.

N-Acetyl-4-chlorobenzamide (**315b**)



Synthesised according to the same procedure as for **313b**. Purification by flash column chromatography (SiO_2 , 0–40% EtOAc in pentane) gave the product as a white solid (1.18 g, 91% yield).

^1H NMR (400 MHz, CDCl_3) δ 9.44 (s, 1H), 7.92 – 7.82 (m, 2H), 7.54 – 7.43 (m, 2H), 2.59 (s, 3H).

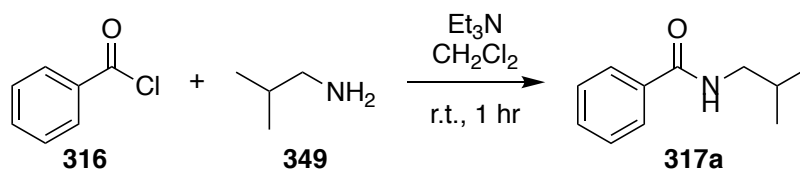
¹³C NMR (101 MHz, CDCl₃) δ 174.3, 165.1, 139.8, 131.1, 129.5 (2C), 129.3 (2C), 25.8.

LRMS (ESI) *m/z*: 196.0 [M-H]⁻

IR (ATR) ν (cm⁻¹, CHCl₃): 745, 1011, 1243, 1463, 1687, 3262.

m.p.: 140–143 °C.

***N*-Isobutylbenzamide (317a)**



Benzoyl chloride (1.7 mL, 14 mmol, 1.0 eq.) was added dropwise to a solution of isobutylamine (1.7 mL, 17 mmol, 1.2 eq.) and Et₃N (2.4 mL, 17 mmol, 1.2 eq.) in CH₂Cl₂ (25 mL) and stirred at room temperature for 1 hr. The mixture was diluted with CH₂Cl₂ (50 mL), washed with 1 M HCl (2 × 40 mL). The organic layer was filtered over a plug of SiO₂ and washed with 10% EtOAc in CH₂Cl₂. The eluent was dried over MgSO₄ and concentrated *in vacuo* to give a white solid (2.50 g, 99% yield).

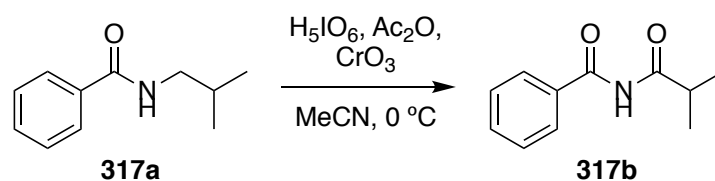
¹H NMR (400 MHz, CDCl₃) δ 7.80 – 7.73 (m, 2H), 7.53 – 7.46 (m, 1H), 7.46 – 7.39 (m, 2H), 6.19 (s, 1H), 3.29 (dd, *J* = 6.8, 6.0 Hz, 2H), 1.90 (hept, *J* = 6.8 Hz, 1H), 0.98 (d, *J* = 6.6 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 167.7, 135.1, 131.4, 128.7 (2C), 127.0 (2C), 47.5, 28.8, 20.3 (2C).

LRMS (ESI) *m/z*: 178.2 [M+H]⁺

IR (ATR) ν (cm⁻¹, CHCl₃): 695, 1291, 1542, 1638, 2960, 3311.

N-Isobutyrylbenzamide (**317b**)



Synthesised according to the same procedure as for **313b**. Purification by flash column chromatography (SiO_2 , 0–30% EtOAc in pentane) gave the product as a white solid (244.2 g, 11% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.67 (s, 1H), 7.87 (d, $J = 7.5$ Hz, 2H), 7.60 (t, $J = 7.3$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 2H), 3.66 (h, $J = 6.7$ Hz, 1H), 1.26 (d, $J = 6.7$ Hz, 6H).

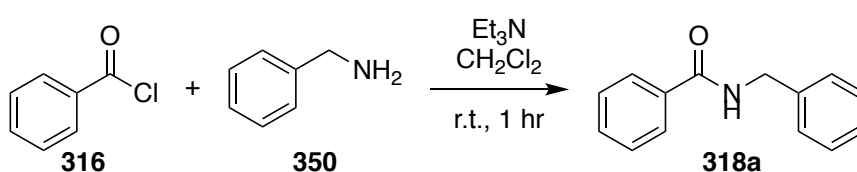
^{13}C NMR (101 MHz, CDCl_3) δ 180.1, 165.2, 133.1, 128.9 (2C), 127.7 (2C), 77.4, 34.9, 18.8 (2C).

LRMS (ESI) m/z : 214.0 $[\text{M}+\text{Na}]^+$

IR (ATR) ν (cm^{-1} , CHCl_3): 707, 1148, 1270, 1486, 1721, 3264.

m.p.: 146–148 $^\circ\text{C}$.

N-Benzylbenzamide (**318a**)



Synthesised according to the same procedure as for amide **317a** to give a white solid (2.12 g, 71% yield).

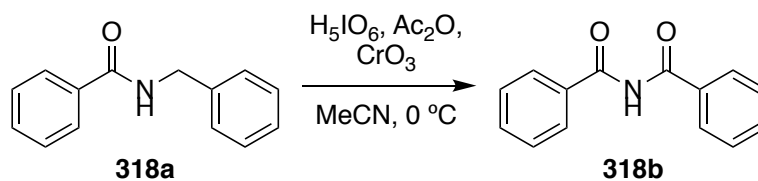
^1H NMR (400 MHz, CDCl_3) δ 7.84 – 7.75 (m, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.40 (m, 2H), 7.40 – 7.35 (m, 4H), 7.35 – 7.28 (m, 1H), 6.45 (s, 1H), 4.65 (d, $J = 5.7$ Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 167.5, 138.4, 134.6, 131.7, 129.0 (2C), 128.7 (2C), 128.1 (2C), 127.8, 127.1 (2C), 44.3.

LRMS (ESI) m/z : 234.0 $[M+Na]^+$

IR (ATR) ν (cm^{-1} , CHCl_3): 693, 1259, 1543, 1640, 3319.

***N*-Benzoylbenzamide (318b)**



Synthesised according to the same procedure as for **313b**. Purification by flash column chromatography (SiO_2 , 0–60% EtOAc in pentane) gave the product as a white solid (1.52 g, 71% yield).

^1H NMR (400 MHz, CDCl_3) δ 9.03 (s, 1H), 7.87 (dd, $J = 8.3, 1.2$ Hz, 4H), 7.64 – 7.57 (m, 2H), 7.53 – 7.46 (m, 4H).

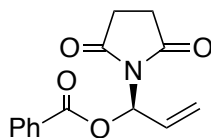
^{13}C NMR (101 MHz, CDCl_3) δ 166.6 (2C), 133.5 (2C), 133.2 (2C), 129.0 (4C), 128.1 (4C).

LRMS (ESI) m/z : 248.0 $[M+Na]^+$

IR (ATR) ν (cm^{-1} , CHCl_3): 709, 1225, 1475, 1501, 1703, 3246.

m.p.: 148–150 $^\circ\text{C}$.

(-)-(R)-1-(2,5-Dioxopyrrolidin-1-yl)allyl benzoate (319)



Synthesised according to general procedure 7. Reaction time: 1 hr. Flash column chromatography (SiO₂, 0–60% Et₂O in pentane) gave the product as a yellow solid (82.1 mg, 79% yield, 99% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.10 – 8.03 (m, 2H), 7.62 – 7.53 (m, 1H), 7.48 – 7.40 (m, 2H), 7.10 (dt, J = 7.0, 1.0 Hz, 1H), 6.46 (ddd, J = 17.4, 10.4, 7.0 Hz, 1H), 5.60 (dt, J = 17.4, 0.9 Hz, 1H), 5.44 (dt, J = 10.4, 0.9 Hz, 1H), 2.74 (s, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 175.2 (2C), 164.7, 133.7, 130.5, 130.2 (2C), 129.2, 128.6 (2C), 121.3, 75.2, 28.2 (2C).

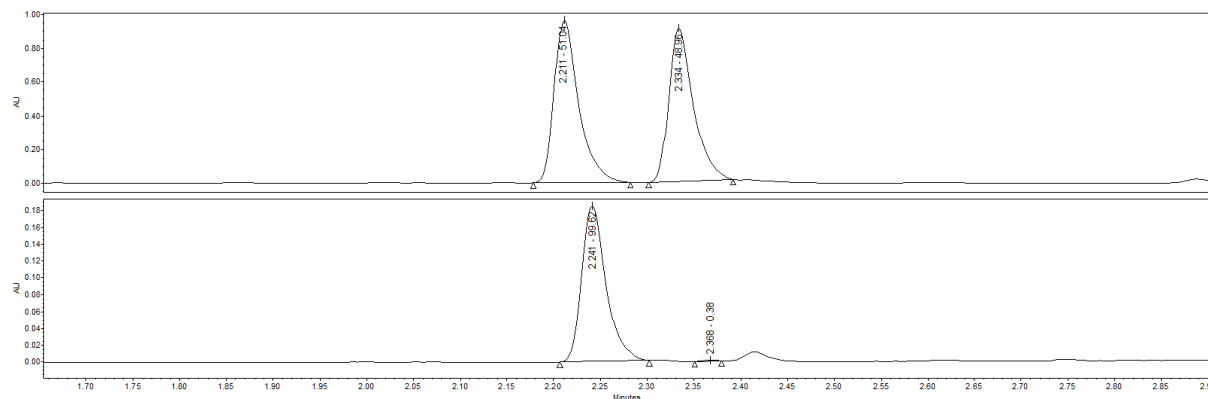
$[\alpha]^{25}_{589} = -32$ (c = 1.0 in CHCl₃).

HRMS (ESI) m/z calcd. for C₁₄H₁₃O₄N [M+Na]⁺: 282.0737, found: 282.0736.

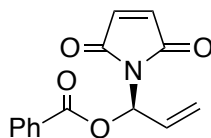
IR (ATR) ν (cm⁻¹, CHCl₃): 712, 1094, 1253, 1381, 1730.

mp: 118–121°C.

The enantiomeric excess of 99% was determined by SFC [Chiralpak® IB; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ =220 nm; major enantiomer t_R = 2.24 mins, minor enantiomer t_R = 2.42 mins].



(-)-(R)-1-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)allyl benzoate (320)



Synthesised according to general procedure 7. Reaction time: overnight. Flash column chromatography (SiO₂, 0–40% Et₂O in pentane) gave the product as a yellow oil (21.5 mg, 20% yield, 96% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.06 (dt, J = 8.4, 1.5 Hz, 2H), 7.62 – 7.54 (m, 1H), 7.48 – 7.40 (m, 2H), 7.10 (dt, J = 6.6, 1.1 Hz, 1H), 6.75 (s, 2H), 6.43 (ddd, J = 17.1, 10.5, 6.7 Hz, 1H), 5.58 (dt, J = 17.2, 0.9 Hz, 1H), 5.44 (dt, J = 10.4, 0.9 Hz, 1H).

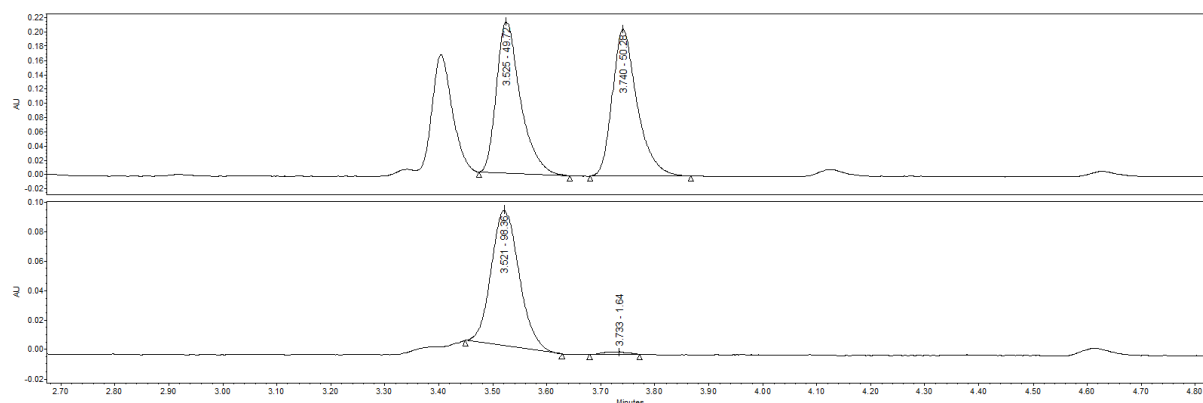
¹³C NMR (101 MHz, CDCl₃) δ 168.7 (2C), 164.7, 134.7 (2C), 133.7, 130.8, 130.1, 129.2 (2C), 128.6 (2C), 120.8, 74.3.

$[\alpha]^{25}_{589} = -45$ (c = 1.0 in CHCl₃).

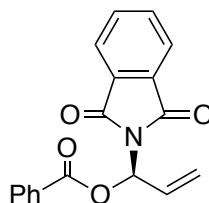
HRMS (APCI) m/z calcd. for C₁₄H₁₁NO₄ [M+H]⁺: 258.0761, found: 258.0762.

IR (ATR) ν (cm⁻¹, CHCl₃): 696, 1091, 1259, 1380, 1726.

The enantiomeric excess of 96% was determined by SFC [Chiralpak® IB; 1500 psi, 30 °C; 1 to 10% MeOH in 6 mins; flow: 0.9 mL/min; λ =220 nm; major enantiomer t_R = 3.52 mins, minor enantiomer t_R = 3.73 mins].



(-)-(R)-1-(1,3-Dioxoisindolin-2-yl)allyl benzoate (321)



Synthesised according to general procedure 7. Reaction time: 1 hr. Flash column chromatography (SiO₂, 0–30% Et₂O in pentane) gave the product as a yellow oil (84.7 mg, 69% yield, 92% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.12 – 8.05 (m, 2H), 7.92 – 7.87 (m, 2H), 7.78 – 7.73 (m, 2H), 7.60 – 7.53 (m, 1H), 7.46 – 7.39 (m, 2H), 7.31 (dt, *J* = 6.7, 1.1 Hz, 1H), 6.56 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.64 (d, *J* = 17.2 Hz, 1H), 5.47 (d, *J* = 10.4 Hz, 1H).

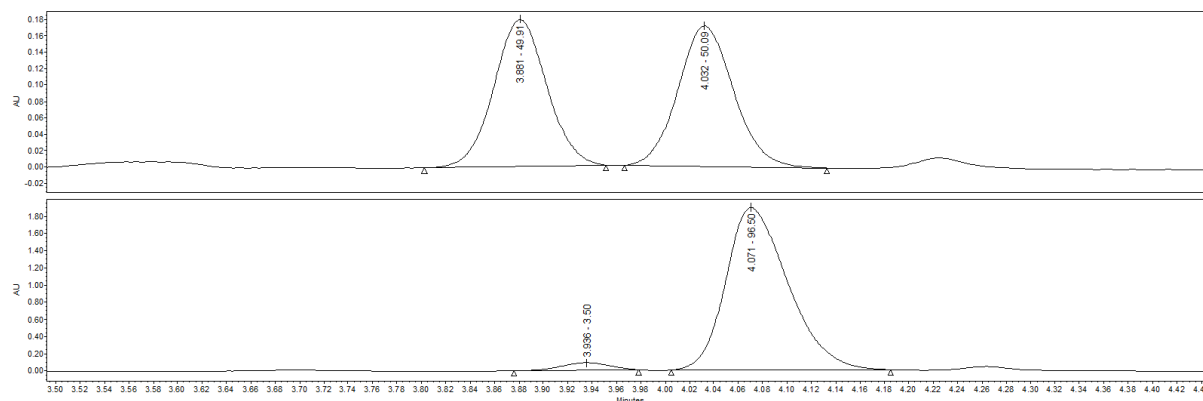
¹³C NMR (101 MHz, CDCl₃) δ 166.5 (2C), 164.8, 134.6 (2C), 133.6, 131.8 (2C), 131.1, 130.2 (2C), 129.3, 128.6 (2C), 124.0 (2C), 120.8, 74.8.

[α]_D²⁵ = –2 (c = 1.0 in CHCl₃, 92% ee).

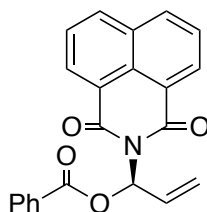
HRMS (ESI) *m/z* calcd. for C₁₈H₁₃O₄NNa [M+Na]⁺: 330.0737, found: 330.0737.

IR (ATR) ν (cm^{–1}, CHCl₃): 712, 1090, 1260, 1380, 1732, 2981.

The enantiomeric excess of 92% was determined by SFC [Chiralpak® IE; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=220 nm; minor enantiomer *t*_R = 3.94 mins, major enantiomer *t*_R = 4.07 mins].



(+)-(R)-1-(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)allyl benzoate (322)



Synthesised according to general procedure 7. Reaction time: 1 hr. Flash column chromatography (SiO₂, 0–40% Et₂O in pentane) gave the product as an off-white solid (76.2 mg, 53% yield, 94% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.64 (d, *J* = 7.3 Hz, 2H), 8.21 (dd, *J* = 7.3, 3.2 Hz, 3H), 8.14 – 8.09 (m, 2H), 7.77 (q, *J* = 8.3 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 6.69 (ddd, *J* = 16.9, 10.5, 6.1 Hz, 1H), 5.65 (d, *J* = 17.5 Hz, 1H), 5.44 (d, *J* = 10.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 165.1, 163.4 (2C), 134.4 (2C), 133.5, 133.1, 131.8 (2C), 131.7, 130.2 (2C), 129.6, 128.6, 128.5 (2C), 127.1 (2C), 122.6 (2C), 119.6, 76.6.

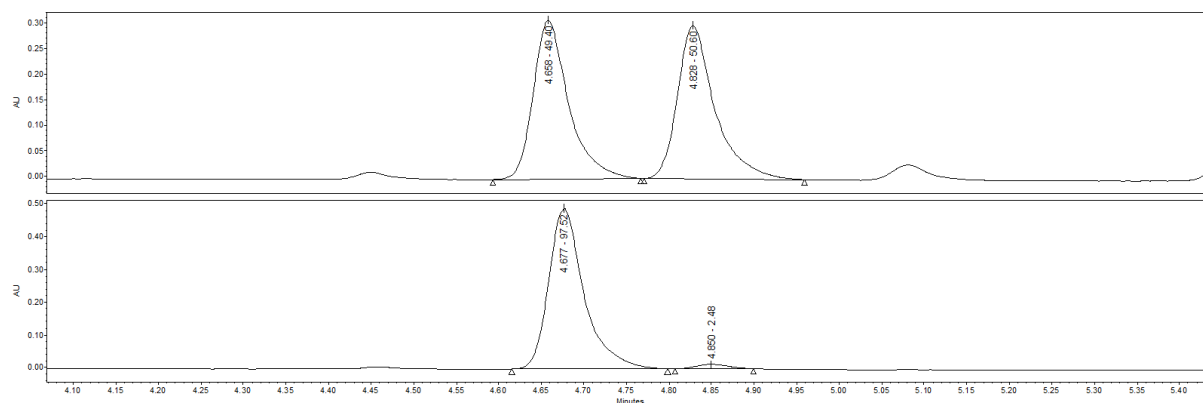
[α]_D²⁵ = +21 (c = 1.0 in CHCl₃, 94% ee).

HRMS (ESI) *m/z* calcd. for C₂₂H₁₅O₄NNa [M+Na]⁺: 380.0893, found: 380.0892.

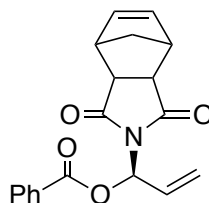
IR (ATR) ν (cm⁻¹, CHCl₃): 778, 1093, 1267, 1674, 1726, 2980.

m.p.: 180–183 °C.

The enantiomeric excess of 94% was determined by SFC [Chiralpak® IB; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=225 nm; major enantiomer *t*_R = 4.67 mins, minor enantiomer *t*_R = 4.85 mins].



(-)-(1*R*)-1-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-4,7-methanoisindol-2-yl)allyl benzoate (323)



Synthesised according to general procedure 7. Reaction time: 3 hrs. Flash column chromatography (SiO₂, 0–40% Et₂O in pentane) gave the product as a yellow solid (91.0 mg, 70% yield, 97% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.10 – 7.99 (m, 2H), 7.62 – 7.54 (m, 1H), 7.49 – 7.40 (m, 2H), 6.93 (dt, *J* = 6.8, 1.1 Hz, 1H), 6.34 (ddd, *J* = 17.2, 10.5, 6.8 Hz, 1H), 6.01 (ddd, *J* = 39.9, 5.7, 3.2 Hz, 2H), 5.51 (dt, *J* = 17.4, 1.0 Hz, 1H), 5.37 (dt, *J* = 10.4, 1.0 Hz, 1H), 3.46 – 3.35 (m, 2H), 3.32 – 3.20 (m, 2H), 1.68 (dt, *J* = 8.8, 1.6 Hz, 1H), 1.50 (d, *J* = 8.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 175.9, 175.8, 164.6, 134.7, 134.3, 133.6, 130.7, 130.1 (2C), 129.3, 128.6 (2C), 120.7, 74.8, 52.1, 45.8, 45.6, 45.5, 45.5.

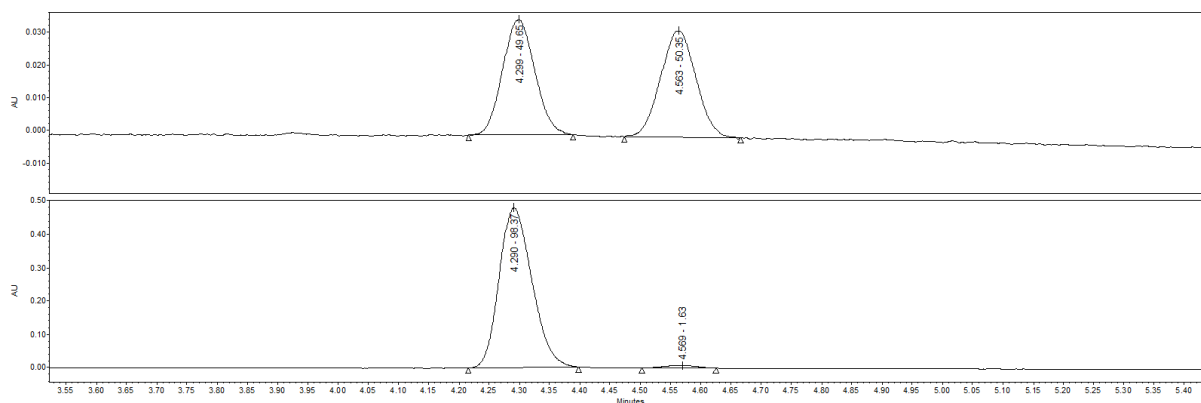
[α]²⁵₅₈₉ = –32 (*c* = 1.0 in CHCl₃, 97% ee).

HRMS (ESI) *m/z* calcd. for C₁₉H₁₇O₄NNa [M+Na]⁺: 346.1050, found: 346.1052.

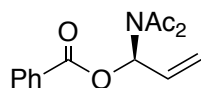
IR (ATR) ν (cm^{–1}, CHCl₃): 713, 1261, 1711, 1730, 2981.

m.p.: 88–89 °C.

The enantiomeric excess of 97% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=220 nm; major enantiomer *t*_R = 4.290 mins, minor enantiomer *t*_R = 4.569 mins].



(-)-(R)-1-(N-Acetylacetamido)allyl benzoate (324)



Synthesised according to general procedure 7. Reaction time: 1 hr. Flash column chromatography (SiO₂, 0–20% Et₂O in pentane) gave the product as a yellow oil (50.0 mg, 48% yield, 84% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.07 (dt, *J* = 8.6, 1.5 Hz, 2H), 7.65 – 7.58 (m, 2H), 7.53 – 7.44 (m, 2H), 6.16 (ddd, *J* = 17.4, 10.8, 3.5 Hz, 1H), 5.51 – 5.41 (m, 2H), 2.48 (s, 6H).

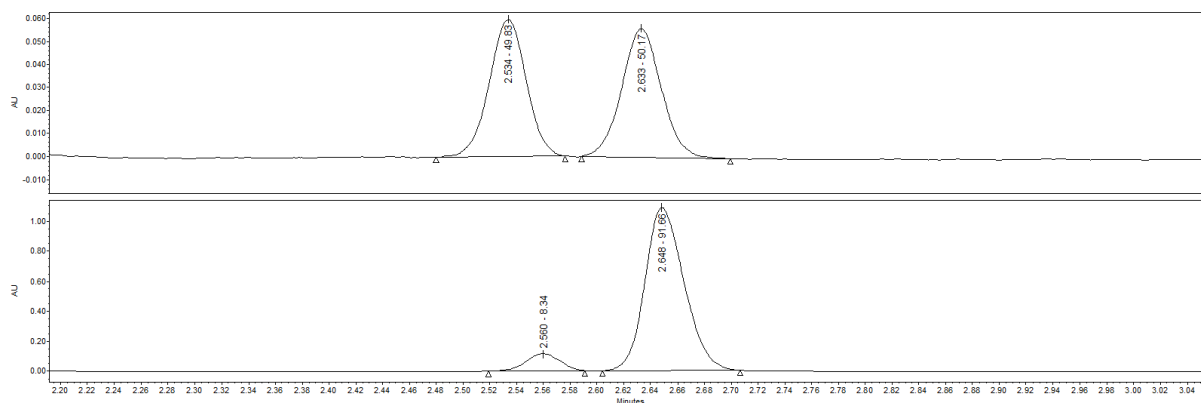
¹³C NMR (101 MHz, CDCl₃) δ 173.5 (2C), 164.8, 133.9, 133.7, 130.0 (2C), 129.0, 128.8 (2C), 118.7, 77.4, 26.8 (2C).

[α]_D²⁵ = −17 (*c* = 1.0 in CHCl₃, 84% ee).

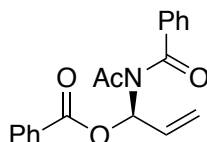
HRMS (APCI) *m/z* calcd. for C₁₄H₁₆O₄N [M+H]⁺: 262.1074, found: 262.1075.

IR (ATR) ν (cm^{−1}, CHCl₃): 712, 1068, 1089, 1244, 1718.

The enantiomeric excess of 84% was determined by SFC [Chiralpak® IE; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=220 nm; minor enantiomer *t*_R = 2.56 mins, major enantiomer *t*_R = 2.65 mins].



(-)-(R)-1-(N-Acetylbenzamido)allyl benzoate (325)



Synthesised according to general procedure 7. Reaction time: 1.5 hrs. Flash column chromatography (SiO₂, 0–20% Et₂O in pentane) gave the product as a yellow oil (71.1 mg, 55% yield, 80% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.07 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.74 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.63 – 7.54 (m, 2H), 7.51 – 7.41 (m, 4H), 7.23 (dt, *J* = 5.5, 1.5 Hz, 1H), 6.31 (ddd, *J* = 17.4, 10.6, 5.4 Hz, 1H), 5.52 (ddd, *J* = 17.4, 1.5, 0.7 Hz, 1H), 5.41 (ddd, *J* = 10.6, 1.5, 0.7 Hz, 1H), 2.17 (s, 3H).

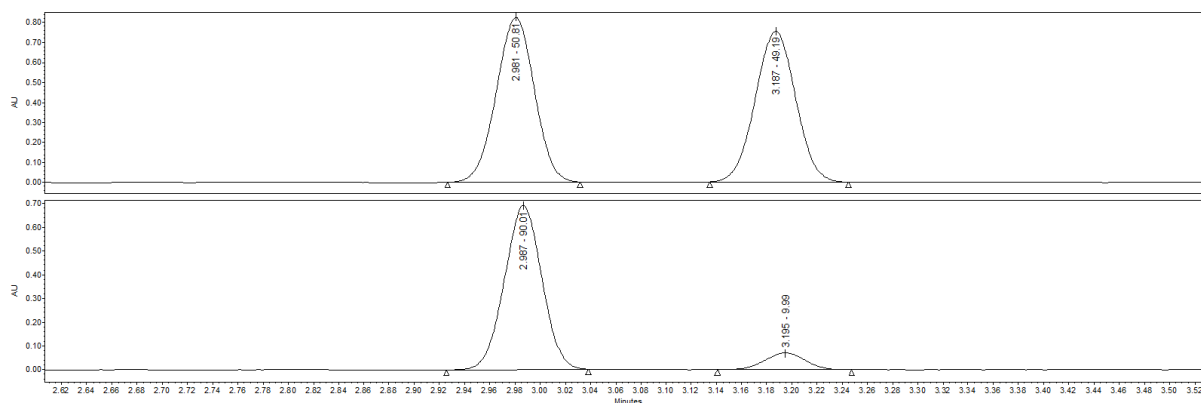
¹³C NMR (101 MHz, CDCl₃) δ 173.8, 172.2, 165.4, 135.4, 133.7, 133.4, 132.4 (2C), 130.1 (2C), 129.3 (2C), 129.0 (2C), 128.7 (2C), 119.9, 80.2, 26.2.

[α]_D²⁵ = −39 (c = 1.0 in CHCl₃, 80% ee).

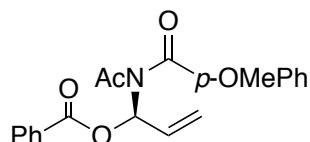
HRMS (APCI) *m/z* calcd. for C₁₉H₁₈O₄N [M+H]⁺: 324.1230, found: 324.1234.

IR (ATR) ν (cm^{−1}, CHCl₃): 712, 1090, 1248, 1722, 2981.

The enantiomeric excess of 80% was determined by SFC [Chiralpak® IC; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=220 nm; major enantiomer *t*_R = 2.99 mins, minor enantiomer *t*_R = 3.20 mins].



(*R*)-1-(*N*-Acetyl-4-methoxybenzamido)allyl benzoate (326)



Synthesised according to general procedure 7. Reaction time: 40 mins. Flash column chromatography (SiO₂, 0–40% Et₂O in pentane) gave the product as a yellow oil (52.2 mg, 37% yield, ee n.d.).

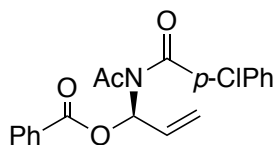
¹H NMR (400 MHz, CDCl₃) δ 8.09 – 8.02 (m, 2H), 7.80 – 7.73 (m, 2H), 7.63 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 7.28 (dt, *J* = 5.5, 1.4 Hz, 1H), 6.98 – 6.91 (m, 2H), 6.28 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.52 (ddd, *J* = 17.2, 1.3, 0.7 Hz, 1H), 5.38 (ddd, *J* = 10.6, 1.5, 0.9 Hz, 1H), 3.87 (s, 3H), 2.12 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 173.0, 171.8, 165.3, 164.2, 133.6, 132.5, 132.1 (2C), 130.1 (2C), 129.5, 128.6 (2C), 127.5, 119.8, 114.4 (2C), 80.1, 55.7, 25.8.

HRMS (ESI) *m/z* calcd. for C₂₀H₁₉O₅NNa [M+Na]⁺: 376.1155, found: 376.1155

IR (ATR) ν (cm⁻¹, CHCl₃): 713, 1170, 1253, 1719, 2361, 2981.

(-)-(R)-1-(N-Acetyl-4-chlorobenzamido)allyl benzoate (327)



Synthesised according to general procedure 7. Reaction time: 2 hrs. Purification: 0–25% Et₂O in pentane. Yellow oil (47.6 mg, 33% yield, 38% ee).

¹H NMR (400 MHz, CDCl₃) δ 8.10 – 8.03 (m, 2H), 7.69 – 7.63 (m, 2H), 7.60 (tt, *J* = 7.0, 1.3 Hz, 1H), 7.51 – 7.41 (m, 4H), 7.19 (dt, *J* = 5.1, 1.5 Hz, 1H), 6.29 (ddd, *J* = 17.2, 10.6, 5.2 Hz, 1H), 5.53 (dd, *J* = 17.3, 1.0 Hz, 1H), 5.42 (dd, *J* = 10.6, 1.1 Hz, 1H), 2.22 (s, 3H).

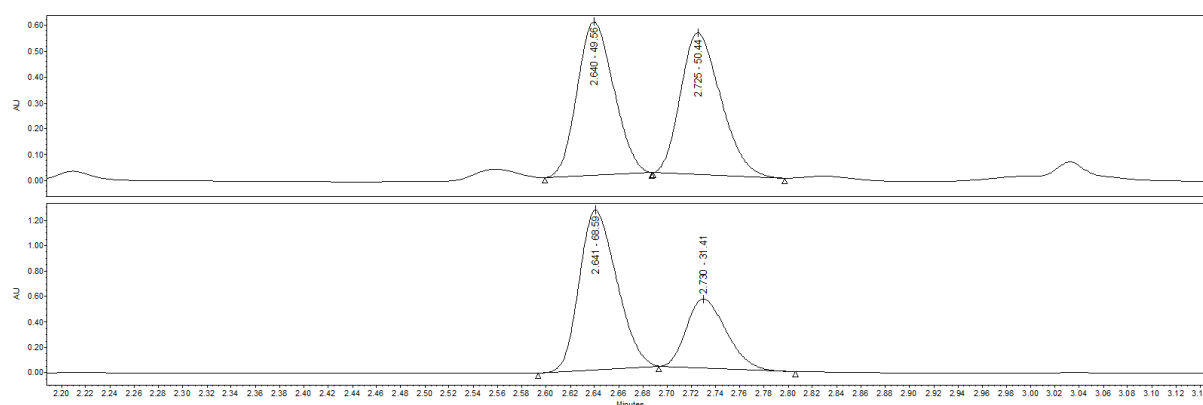
¹³C NMR (101 MHz, CDCl₃) δ 172.9, 172.2, 165.4, 139.7, 133.8, 133.7, 132.4, 130.6 (2C), 130.1 (2C), 129.3 (2C), 129.2, 128.7 (2C), 120.0, 80.2, 26.0.

[α]_D²⁵₅₈₉ = –13 (*c* = 1.0 in CHCl₃, 38% ee).

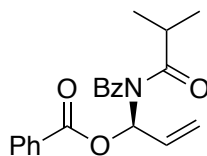
HRMS (ESI) *m/z* calcd. for C₁₉H₁₆O₄NCINa [M+Na]⁺: 380.0660, found: 380.0660.

IR (ATR) ν (cm^{–1}, CHCl₃): 713, 1090, 1247, 1723, 2980.

The enantiomeric excess of 38% was determined by SFC [Chiralpak® ID; 1500 psi, 30 °C; 1 to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ=220 nm; major enantiomer *t*_R = 2.64 mins, minor enantiomer *t*_R = 2.73 mins].



(*R*)-1-(*N*-Isobutyrylbenzamido)allyl benzoate (328)



Synthesised according to general procedure 7. Reaction time: 2 hrs. Flash column chromatography (SiO₂, 0–15% Et₂O in pentane) gave the product as a yellow oil (40.6 mg, 29% yield, ee n.d.).

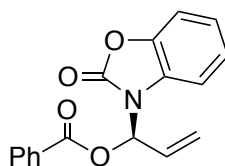
¹H NMR (400 MHz, CDCl₃) δ 8.07 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.72 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.63 – 7.54 (m, 2H), 7.51 – 7.41 (m, 4H), 7.31 (dt, *J* = 5.5, 1.5 Hz, 1H), 6.28 (ddd, *J* = 17.4, 10.6, 5.4 Hz, 1H), 5.54 (ddd, *J* = 17.2, 1.5, 0.7 Hz, 1H), 5.40 (ddd, *J* = 10.6, 1.5, 0.7 Hz, 1H), 2.68 (p, *J* = 6.7 Hz, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 180.6, 173.7, 165.3, 135.7, 133.6, 133.3, 132.7, 130.1 (2C), 129.5, 129.2 (2C), 129.0 (2C), 128.6 (2C), 119.7, 80.1, 37.0, 20.2, 18.6.

HRMS (ESI) *m/z* calcd. for C₂₁H₂₁O₄NNa [M+Na]⁺: 374.1363, found: 374.1365.

IR (ATR) ν (cm⁻¹, CHCl₃): 712, 1086, 1259, 1725, 2360, 2980.

(-)-(*R*)-1-(2-Oxobenzo[*d*]oxazol-3(2*H*)-yl)allyl benzoate (330)



Synthesised according to general procedure 7. Reaction time: 6.5 hrs. Flash column chromatography (SiO₂, 0–20% Et₂O in pentane) gave the product as a yellow oil (64.5 mg, 54% yield, 92% ee). The product contains inseparable by-products.

¹H NMR (400 MHz, CDCl₃) δ 8.08 – 8.03 (m, 2H), 7.62 – 7.56 (m, 1H), 7.48 – 7.42 (m, 3H), 7.33 – 7.29 (m, 1H), 7.24 – 7.11 (m, 3H), 6.27 (ddd, *J* = 17.2, 10.6, 4.5 Hz, 1H), 5.68 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.58 (dd, *J* = 10.6, 1.7 Hz, 1H).

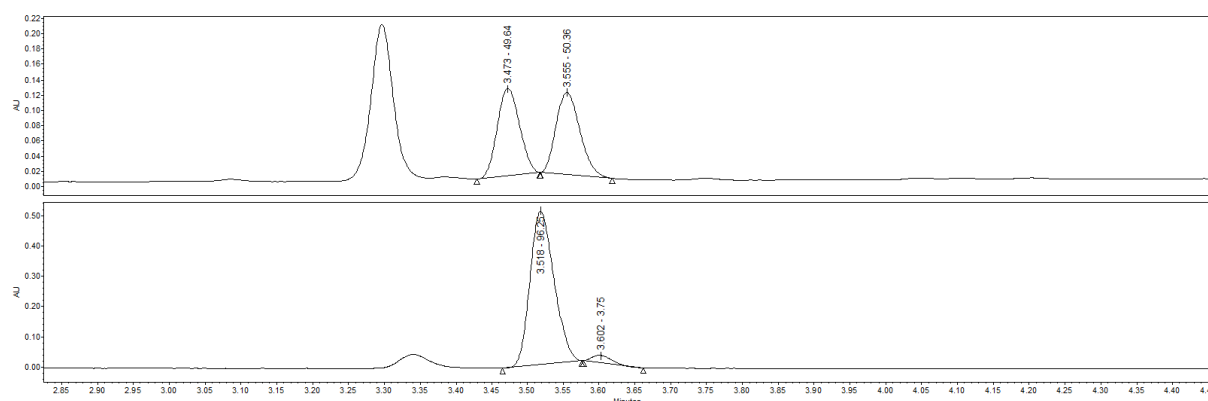
^{13}C NMR (101 MHz, CDCl_3) δ 164.4, 152.9, 142.8, 134.0, 130.3, 130.1 (2C), 128.8 (2C), 124.7, 124.1, 123.3, 121.0, 111.3, 110.9, 110.5, 77.0.

$[\alpha]^{25}_{589} = -23$ ($c = 1.0$ in CHCl_3 , 92% ee).

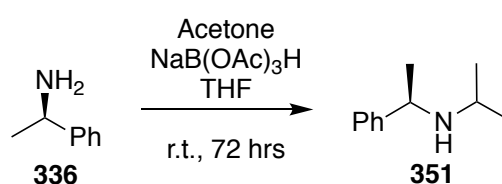
HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{13}\text{O}_4\text{NNa}$ $[\text{M}+\text{Na}]^+$: 318.0737, found: 318.0736.

IR (ATR) ν (cm^{-1} , CHCl_3): 712, 1251, 1483, 1782, 2981.

The enantiomeric excess of 92% was determined by SFC [Chiralpak® ID; 1500 psi, 30 °C; 1 to 20% MeOH in 5 mins; flow: 1.5 mL/min; $\lambda=215$ nm; major enantiomer $t_R = 3.52$ mins, minor enantiomer $t_R = 3.61$ mins].



(*R*)-*N*-(1-Phenylethyl)propan-2-amine



Acetone (1.8 mL, 25 mmol, 2.0 eq.) and $\text{NaB}(\text{OAc})_3\text{H}$ (3.82 g, 18 mmol, 1.5 eq.) were added to a solution of *R*-(+)-1-Phenylethylamine in THF (5.5 mL). The reaction was stirred at room temperature for 72 hrs, before diluting with Et_2O (40 mL) and quenching with a saturated solution of NaHCO_3 (40 mL). The aqueous phase was extracted with (3×100 mL) and the combined organic phases concentrated in vacuo to 1/3 of the volume. 2 M HCl (20 mL) was added and the solution diluted with Et_2O (20 mL). The organic phase was extracted with 2 M HCl (3×30 mL). CH_2Cl_2 (30 mL) was added and the mixture basified with 2 M NaOH until

~ pH 14. The aqueous phase was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic phases were dried over MgSO₄ and concentrated in vacuo to give a colourless oil (1.95 g, 97% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.26 (m, 4H), 7.25 – 7.20 (m, 1H), 3.89 (q, *J* = 6.6 Hz, 1H), 2.62 (hept, *J* = 6.3 Hz, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.1 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H).

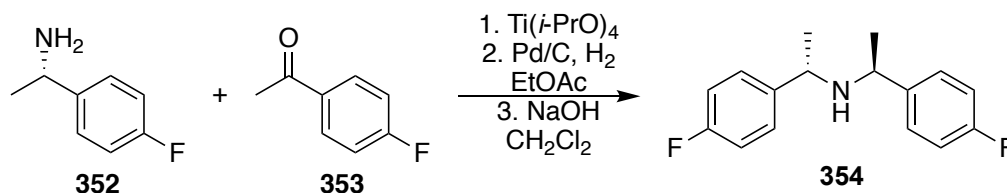
¹³C NMR (101 MHz, CDCl₃) δ 146.0, 128.2 (2C), 126.5, 126.3 (2C), 54.9, 45.3, 24.7, 23.9, 22.0.

[α]_D²⁵ = +59 (c = 1.0 in CHCl₃).

LRMS (ESI) *m/z*: 164.2 [M+H]⁺

IR (ATR) ν (cm⁻¹, CHCl₃): 668, 773, 1219, 2339, 2360.

(*S,S*)-Bis(1-(4-fluorophenyl)ethyl)amine (**355**)



Synthesised from *S*-(-)-1-(4-fluorophenyl)ethylamine (2.0 g, 14 mmol, 1.0 eq.) and 4'-fluoroacetophenone (1.7 mL, 14 mmol, 1.0 eq.) according to the same procedure as for **26a**, to give the pure amine as a colourless oil (1.85 g, 49% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.23 – 7.13 (m, 4H), 7.08 – 6.99 (m, 4H), 3.48 (q, *J* = 6.7, 2H), 1.27 (d, *J* = 6.7, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 163.1, 160.7, 141.4, 141.4, 128.2 (2C), 128.1 (2C), 115.4 (2C), 115.2 (2C), 54.5 (2C), 25.2 (2C).

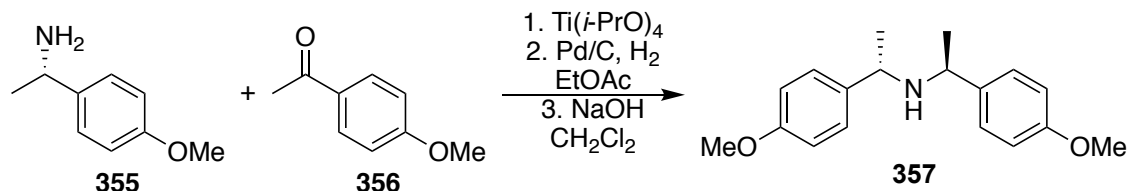
¹⁹F NMR (376 MHz, CDCl₃) δ -116.31.

[α]_D²⁵ = -126 (c = 1.0 in CHCl₃).

HRMS (ESI) *m/z* calcd. for C₁₆H₁₈NF₂ [M+H]⁺: 262.1402, found: 262.1399.

IR (ATR) ν (cm⁻¹, CHCl₃): 834, 954, 1155, 1222, 1603, 2980.

(*S,S*)-Bis(1-(4-methoxyphenyl)ethyl)amine (358)



Synthesised from (*S*)-4-methoxy- α -methylbenzylamine (2.0 g, 13 mmol, 1.0 eq.) and acetanisole (2.0 g, 13 mmol, 1.0 eq.) according to the same procedure as for **26a**, to give the pure amine as a white solid (1.38 g, 37% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.17 – 7.09 (m, 4H), 6.92 – 6.83 (m, 4H), 3.82 (s, 6H), 3.45 (q, *J* = 6.7 Hz, 2H), 1.24 (d, *J* = 6.7 Hz, 6H).

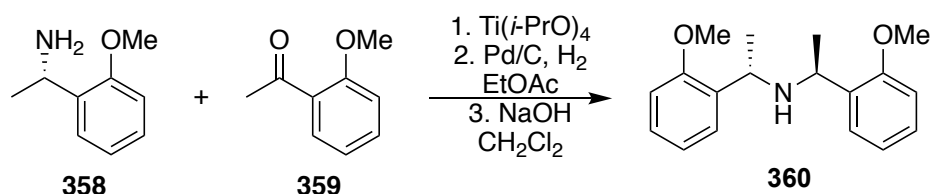
¹³C NMR (101 MHz, CDCl₃) δ 158.5 (2C), 138.0 (2C), 127.8 (4C), 113.8 (4C), 55.4 (2C), 54.4 (2C), 25.2 (2C).

$[\alpha]^{25}_{589} = -234$ (*c* = 1.0 in CHCl₃).

HRMS (CI with ammonia as reagent gas) *m/z* calcd. for C₁₈H₂₃NO₂ [M+H]⁺: 286.1802, found: 286.1806.

IR (ATR) ν (cm⁻¹, CHCl₃): 831, 1174, 1241, 1510, 1610, 2980.

(*S,S*)-Bis(1-(2-methoxyphenyl)ethyl)amine (361)



Synthesised from (*S*)-1-(2-methoxyphenyl)ethylamine (1.0 g, 6.6 mmol, 1.0 eq.) and 2'-methoxyacetophenone (910 μ L, 6.6 mmol, 1.0 eq.) according to the same procedure as for **26a**, to give the pure amine as a colourless oil (341 mg, 18% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.32 (dd, *J* = 7.5, 1.8 Hz, 2H), 7.20 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 2H), 6.94 (td, *J* = 7.4, 1.1 Hz, 2H), 6.84 (dd, *J* = 8.1, 1.1 Hz, 2H), 3.87 (q, *J* = 6.7 Hz, 2H), 3.72 (s, 6H), 1.28 (d, *J* = 6.7 Hz, 6H).

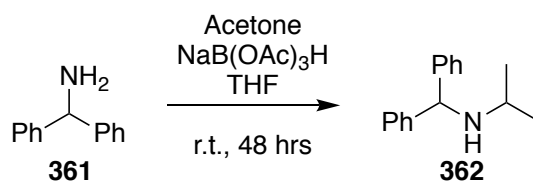
¹³C NMR (101 MHz, CDCl₃) δ 157.5 (2C), 134.1 (2C), 127.6 (2C), 127.4 (2C), 120.7 (2C), 110.6 (2C), 55.3 (2C), 50.4 (2C), 23.2 (2C).

[α]²⁵₅₈₉ = −83 (c = 1.0 in CHCl₃).

HRMS (CI with ammonia as reagent gas) *m/z* calcd. for C₁₈H₂₃NO₂ [M+H]⁺: 286.1802, found: 286.1808.

IR (ATR) ν (cm^{−1}, CHCl₃): 754, 1030, 1236, 1489, 1599, 2980.

***N*-Benzhydrylpropan-2-amine (362)**



Synthesised from diphenylmethanamine (2.2 mL, 13 mmol, 1.0 eq.) according to the same procedure as for **351**, to give the pure amine as a colourless liquid (2.84 g, 98% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.38 (m, 4H), 7.36 – 7.27 (m, 4H), 7.25 – 7.19 (m, 2H), 5.00 (d, *J* = 2.1 Hz, 1H), 2.82 – 2.73 (m, 1H), 1.11 (dd, *J* = 6.3, 1.9 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 144.7 (2C), 128.5 (4C), 127.5 (4C), 126.9 (2C), 64.4, 46.2, 23.3 (2C).

LRMS (ESI) *m/z*: 226.2 [M+H]⁺

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