Novel Phosphonium Salts and Bifunctional Organocatalysts in Asymmetric Synthesis

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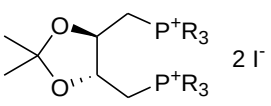
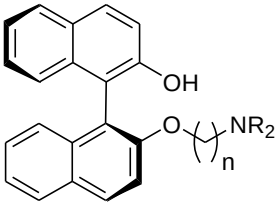
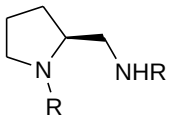
Abstract



Tartrate-derived phosphonium salt



BINOL-derived bifunctional catalyst



Proline-derived diamine

This thesis details the syntheses of catalysts and their applications in asymmetric reactions. Initially, the project focused on phase transfer catalysts; quaternary phosphonium salts derived from diethyl tartrate or from commercially available phosphorus compounds and their use primarily in the alkylation of *N*,*N*-diphenyl methylene glycine *tert*-butyl ester. Although some of the salts showed the ability to catalyse the alkylation reaction, all products obtained were racemic. The project then focused on bifunctional organocatalysis; catalysts derived from isoquinoline and BINOL were studied in Michael addition reactions between ethyl nitropropionate and MVK. Possible evidence for a bifunctional effect was observed, however, all Michael addition products obtained were racemic. Finally, an examination of proline-derived diamines as catalysts for aldol reactions is reported. Reversing the positions of the acid and base moieties of the catalyst results in the formation of the opposite enantiomer of the aldol product. In addition, these proline-derived diamines, along with two catalysts derived from a biarylazepine, were tested in a series of asymmetric reactions, with the best enantioselectivities (up to 90% ee) obtained in the conjugate addition between enones and nitro-containing compounds.

Acknowledgements

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"I have not failed. I've just found 10,000 ways that won't work."

"Just because something doesn't do what you planned doesn't mean it's useless."

"Many of life's failures are people who did not realize how close they were to success when they gave up."

– Attributed to Thomas A. Edison, US Inventor, 1847-1931

Abbreviations

2,2-DMP	2,2-Dimethoxypropane
4-NP	4-Nitrophenol
aq.	Aqueous
AMEP	Aminomethylethylpyrrolidine
AMEQ	Aminomethylethylquinuclidine
BINOL	1,1'-Bi-2-naphthol
Boc	*tert*-Butyloxycarbonyl
Cat.	Catalyst
COSY	Correlation spectroscopy
CPME	Cyclopentyl methyl ether
CSA	Camphorsulfonic Acid
Cy	Cyclohexyl
DAB	1,3-Dimethyl-5-acetylbarbituric acid
DACH	*R*,*R*-1,2-Diaminocyclohexane
DBAD	Di-*tert*-butyl azodicarboxylate
DCA	Dichloroacetic acid
DCAD	Di-4-chlorobenzyl azodicarboxylate
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization transfer
DIAD	Diisopropyl azodicarboxylate
DIPAMP	Bis[(2-methoxyphenyl)phenylphosphino]ethane
d.r.	Diastereomeric ratio
DME	1,2-Dimethoxyethane
DMED	1,2-Dimethylethyldiamine
DMPD	1,3-Dimethylpropyldiamine
EDG/EWG	Electron Donating Group/Electron Withdrawing Group
ee	Enantiomeric excess
ESI	Electrospray ionisation
Eq.	Equivalent
HATU	2-(1*H*-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HMBC	Heteronuclear multiple bond coherence
HMQC	Heteronuclear multiple quantum coherence
HPESW	Hajos-Parrish-Eder-Sauer-Wiechert reaction
HPLC	High performance liquid chromatography
imp	Impurity
IPA	Isopropyl alcohol
LDA	Lithium diisopropylamide
m.p.	Melting point
Ms	Methanesulfonyl
MBH	Morita-Baylis-Hillman reaction
MVK	Methyl vinyl ketone
NFSi	*N*-Fluorobenzenesulfonimide
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
PS	Polystyrene (supported)
PTC	Phase transfer catalysis/phase transfer catalyst
PVK	Phenyl vinyl ketone
ret.	Retention
RT	Room temperature
TADDOL	$\alpha,\alpha,\alpha,\alpha$–Tetraaryl-1,3-dioxolane-4,5-dimethanol
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography/chromatogram
TMP	2,2,6,6-Tetramethyl piperidine
TMS	Trimethylsilyl
Ts	Toluenesulfonyl
UHP	Urea hydrogen peroxide

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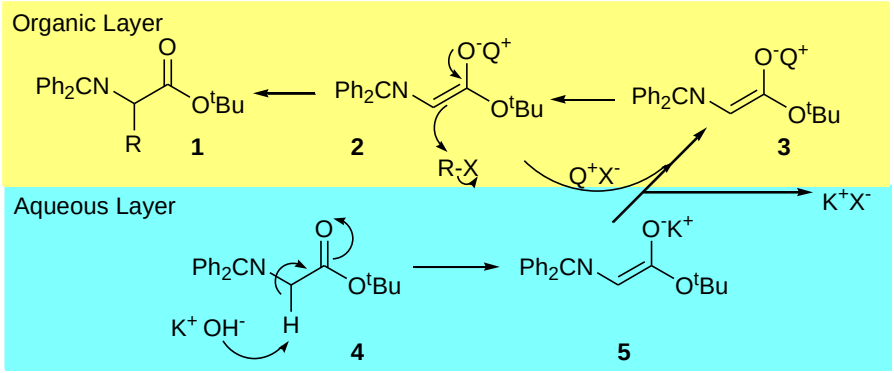
1. Introduction to Phase Transfer Catalysis

1.1. Background

In a heterogeneous system, it is often necessary to promote the reaction *via* addition of a PTC, which increases the solubility of one component in its less preferred solvent by reversibly modifying its chemical structure. An ionic compound can be more readily dissolved into an organic solvent generally by one of two methods; by addition of a crown ether, which sequesters the metal cation, or by replacing the metal cation with one that is soluble in organic solvents. In both cases, the cation is now soluble in the organic layer, and it then draws the anion into the organic layer by electrostatic attraction and the anion may proceed to react with other components dissolved in the organic layer.

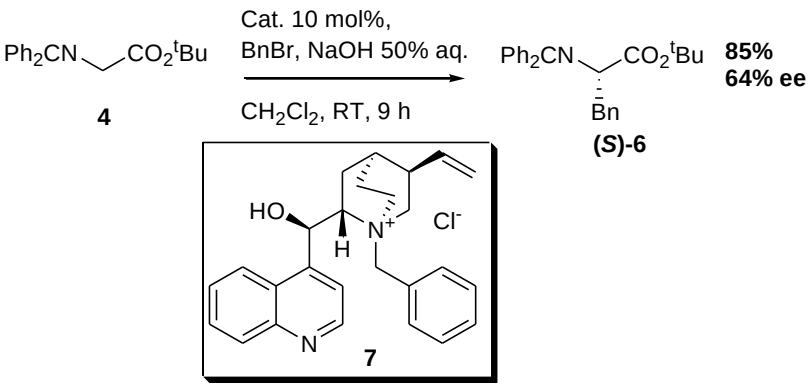
This project focuses on the use of organic-soluble cations, namely quaternary onium (ammonium and phosphonium) salts and their use in the α-carbon alkylation of amino acids. The standard amino acid used to test the effectiveness of these PTCs is glycine, as it is the only achiral naturally-occurring amino acid. However, to minimise the number of side reactions that occur, and to ensure selective deprotonation of one acidic hydrogen only, the amine group is derivatised with benzophenone and the carboxylic acid is protected with a *tert*-butyl group.[1] The reaction of the resulting *N*,*N*-diphenyl methylene glycine *tert*-butyl ester **4** with an alkyl halide and the role of the phase transfer catalyst is shown in **Scheme 1**.[2] KOH in the aqueous layer deprotonates the glycine imine **4** when it approaches the phase interface to form enolate **5**. This ionic compound sits at the interface (severely reducing its potential to react with the alkyl halide) until the metal cation exchanges with the phase transfer catalyst Q^+X^- to form **3**. It is then brought further into the organic layer where it is more likely to react with the alkyl halide (R-X).



Scheme 1: Alkylation of the glycine imine **4**. Q^+X^- represents the PTC.

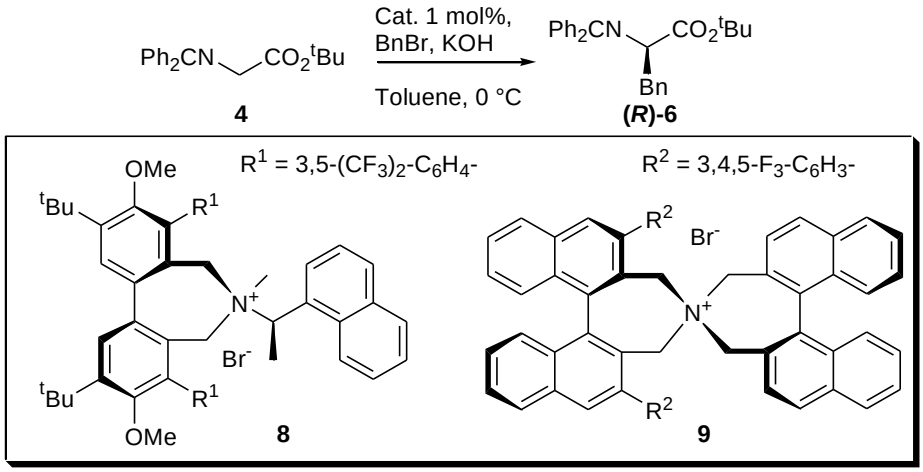
The use of quaternary ammonium salts in the asymmetric alkylation of protected amino acids was first reported by O'Donnell in 1989.[3] Using cinchona alkaloid **7**, he

obtained alkylated glycine imine **6** in good yield and moderate enantiomeric excess (85%, 64% ee, **Scheme 2**).



Scheme 2: Enantioselective alkylation reported by O' Donnell.

Since then, there have been many examples of onium-based phase transfer catalysts which have improved on these results. One prominent template is biaryl quaternary ammonium compounds, such as those used by Maruoka[4] and by Lygo,[5] shown in **Scheme 3**. Biaryl azepine catalyst **8** developed by Lygo gave good yield and high enantiomeric excess (89%, 97% ee) in 1.5 hours while binaphthyl catalyst **9** developed by Maruoka gave slightly better yield and enantiomeric excess (90%, 99% ee) in 12 hours.

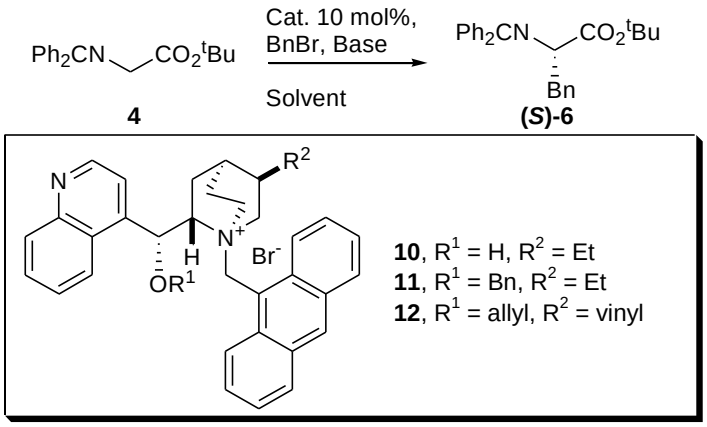


Catalyst	KOH conc. /M	Time /h	Yield /%	ee /%
8	15	1.5	89	97
9	9	12	90	99

Scheme 3: Biaryl PTCs reported by Lygo and Maruoka for enantioselective alkylation.

Following O'Donnell's pioneering work, cinchona alkaloid derivatives have become another very commonly used template (**Scheme 4**). Lygo[6] and Corey[7] both reported in 1997 that modifying O'Donnell's catalyst to replace benzyl group on the quinuclidine with a 9-methylanthracenyl group gave substantial improvement to

enantioselectivity. Lygo's catalyst **10** gave reasonable yield and high enantiomeric excess (68%, 91% ee) which was improved (85%, 94% ee) when the hydroxy group was replaced by a benzyloxy group to give catalyst **11**.[8] Corey's catalyst **12** gave fair yield and excellent enantiomeric excess (73%, 99.5% ee) when the reaction was performed at −78 °C.

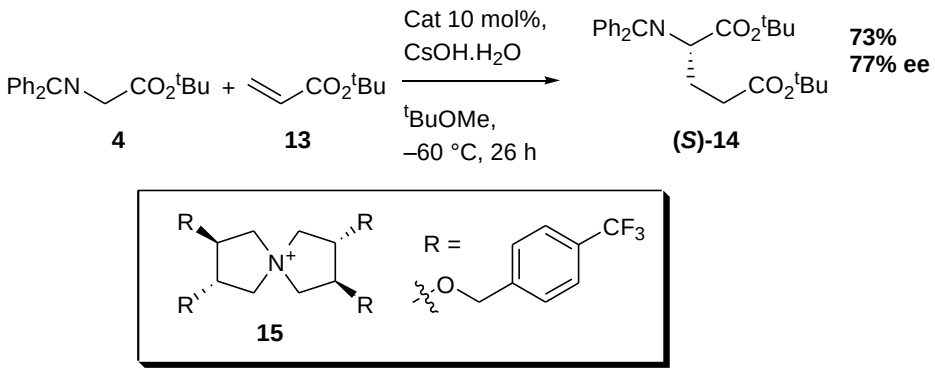


Catalyst	Base	Solvent	Temp.	Time /h	Yield /%	ee /%
10	KOH (50% aq.)	Toluene	RT	18	68	91
11	KOH (50% aq.)	Toluene	RT	18	85	94
12	$CsOH.H_2O$	CH_2Cl_2	−78 °C	23	73	99.5

Scheme 4: Cinchona alkaloid-derived PTCs used to alkylate **4**, as developed by Lygo and Corey.

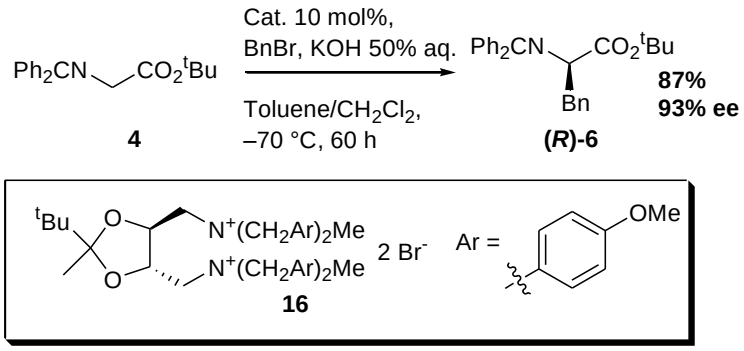
1.2. Tartrate-Derived PTCs

Due to their cheapness, availability and potential for modification, it was decided to investigate the possibility of synthesising PTCs that are derived from tartaric acid. Currently there are only a few examples of quaternary ammonium PTCs that are derived from tartrates. In 2002, Tsuji synthesised a spiro quaternary ammonium-based compound that catalysed the Michael addition of *tert*-butyl acrylate **13** to glycine imine **4** with reasonable enantioselectivity;[9] the conditions that gave the optimal result are shown in **Scheme 5**.



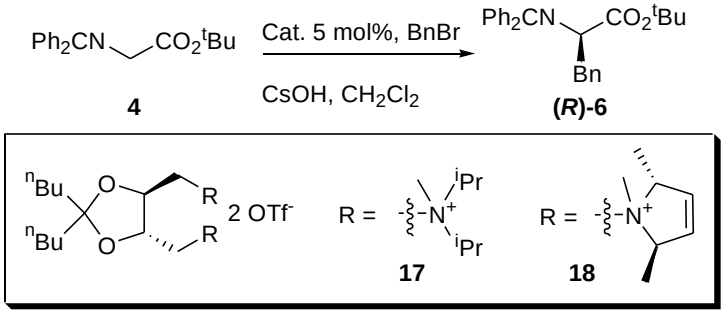
Scheme 5: Spiro quaternary ammonium tartrate derivative synthesised by Tsuji.

At the same time, Shibasaki reported a series of two-centre tartrate-derived quaternary ammonium salts for use in PTC.[10] These were tested in the alkylation of glycine imine **4** with benzyl bromide, the most effective of these catalysts was able to give the product in high enantiomeric excess (93% ee, **Scheme 6**). Since then, the effectiveness of Shibasaki's catalysts have been investigated in Michael and Mannich reactions.[11]



Scheme 6: Two centre quaternary ammonium tartrate derivative as used by Shibasaki.

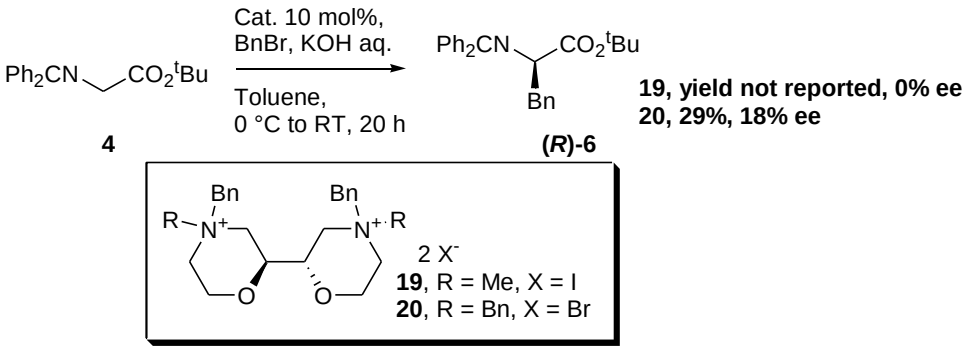
MacFarland synthesised similar catalysts, opting for long alkyl chains on the acetal groups and different substituents on the nitrogen.[12] He reported quaternary ammonium salt **17** with isopropyl substituents on the nitrogen, when this was used as a PTC, the enantioselectivities were very poor, never exceeding 9% ee (**Scheme 7**). The enantiomeric excess rose to 30% ee when the nitrogens were converted to dimethyl-pyrrolinium groups **18**.



Catalyst	Temp. /°C	Time /h	Yield /%	ee /%
17	0	1	83	9
18	–45	10	73	30

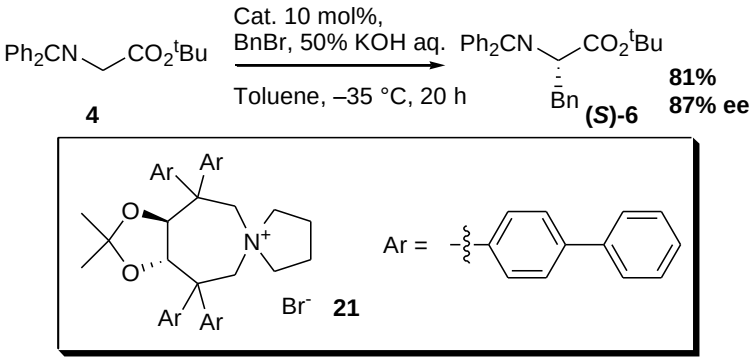
Scheme 7: MacFarland's tartrate-derived onium compounds.

Kanger synthesised 2,2'-bismorpholinium quaternary ammonium salts using tartrates as the starting material (**Scheme 8**).[13] These are poor PTCs for this reaction – **19** results in product racemic product **6**. However, the enantiomeric excess rose to 18% ee when **20** was used – the steric bulk at the nitrogen has been increased by changing the methyl groups to benzyl groups.



Scheme 8: Tartrate-derived bismorpholinium salt as synthesised by Kanger.

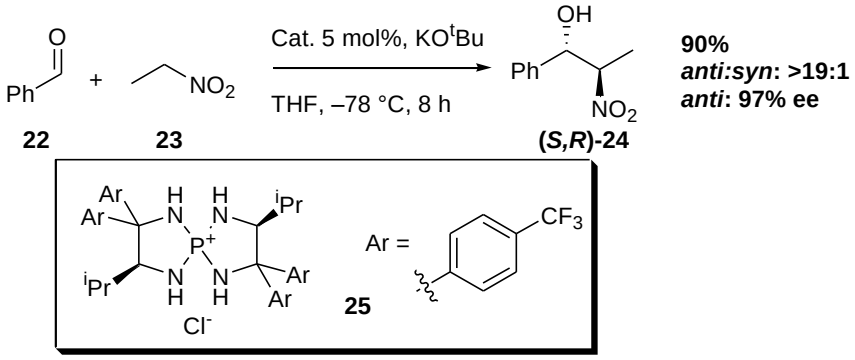
Most recently, Waser developed catalysts derived from TADDOLs, which in turn are derived from tartrates.[14] By increasing the bulk of the aryl groups to biphenyls and forming a spiro system with the quaternary ammonium in the centre, he synthesised catalyst **21**, which gave good yield and enantioselectivity in the alkylation of glycine imine **4** (81% and 87% ee, **Scheme 9**).



Scheme 9: TADDOL-derived quaternary ammonium catalyst by Waser.

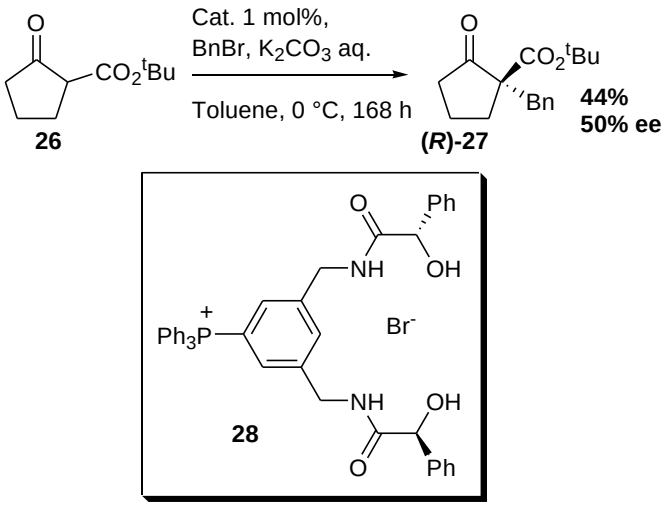
1.3. Phosphonium Catalysts in PTC

There are only a few examples of the use of quaternary phosphonium salts in asymmetric PTC. This may be due to the possibility of side reactions in phase transfer conditions, which is discussed further in Chapter 2. However, there has been some interest in utilising phosphonium based PTCs. Tetraaminophosphonium salts synthesised by Ooi were used in the Henry reaction,[15] and salt **25** was able to give product **24** in high yield, *anti/syn* selectivity and enantioselectivity (**Scheme 10**).



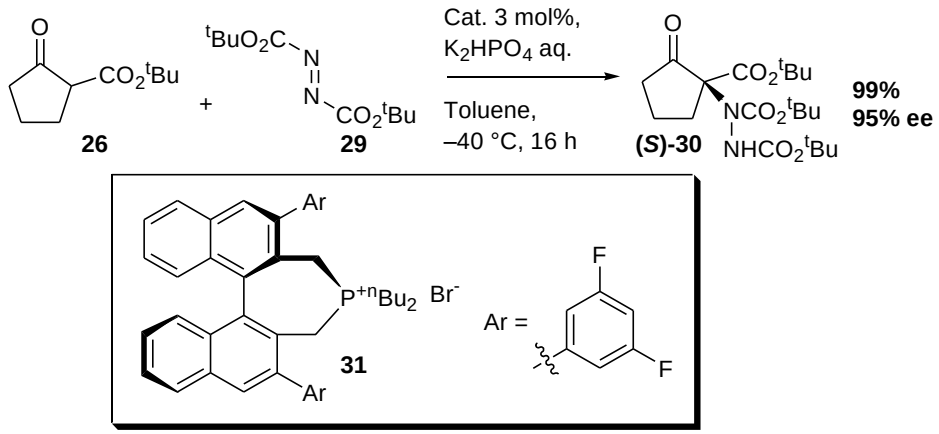
Scheme 10: Henry reaction catalysed by **25**.

No literature has been found regarding the use of quaternary phosphonium PTCs in the α-alkylation of amino acids, though there have been reports regarding alkylation of β-keto esters. The benzylation of β-keto ester **26** by quaternary phosphonium catalyst **28** was reported by Manabe (**Scheme 11**).[16] The PTC was designed to contain four hydrogen donor sites (2 OH groups and 2 NH groups) with the intention that these would hydrogen bond to the enolate, and offer greater stereoselectivity in the alkylation reaction by keeping it within close proximity of the chiral centres. However, the actual enantioselectivity was fairly modest (50% ee).



Scheme 11: PTC with four hydrogen bonding sites as reported by Manabe.

Maruoka was able to develop a binaphthyl phosphonium salt PTC that can catalyse the amination of a series of β-keto esters with high yields and enantioselectivities.[17] An example of this is shown in **Scheme 12** – catalyst **31** was able to effect the conjugate addition between β-keto ester **26** and DBAD **29** to give the product in high yield and enantioselectivity (99%, 95% ee).



Scheme 12: Binaphthyl quaternary phosphonium salt as reported by Maruoka.

At the time of writing, the chemical literature does not report any quaternary phosphonium salt PTCs derived from tartrate, though tartrate-derived phosphines are described in the literature and have been used as ligands in transition metal catalysts.[18]

In a PTC, the larger the substituents on the onium ion, the greater the charge separation is between the quaternary cation centre and the anion; this generally results in high reactivity of the anion, and hence fast reaction. Although the application of both quaternary ammonium and phosphonium salts has been investigated since PTC was first described, the latter has received far less attention, especially in the field of asymmetric PTC. Phosphorus is larger than nitrogen (**Figure 1**) and thus has a significantly different charge distribution, it is therefore possible that quaternary phosphonium salts may actually have different reactivity compared with the corresponding quaternary ammonium salts.

Synthesis of quaternary phosphonium based PTCs carries another difference; it is relatively straightforward to synthesise a compound with aryl substituents directly attached to the phosphorus, whereas it is considerably harder to make stable quaternary ammonium salts with multiple aryl substituents because of steric clashing resulting from the smaller size of the nitrogen compared to phosphorus.

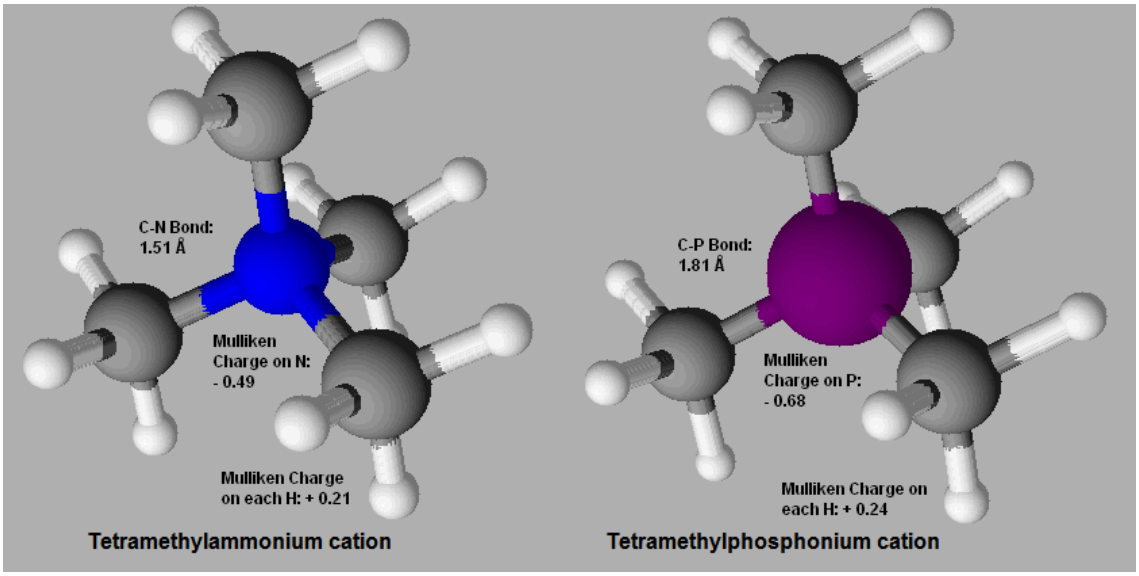


Figure 1: Comparison of bond lengths and calculated Mulliken charges in equivalent quaternary ammonium and phosphonium compounds. Values determined using DFT calculations – B3LYP/6-311++G**.[19]

This is noteworthy as in an onium compound, the positive charge does not reside on the onium ion itself but is spread across the hydrogens that surround it. It is this positive surface that forms an electrostatic interaction with the enolate. As can be seen in **Figure 1**, the effective charge on nitrogen in tetramethylammonium is −0.49 and +0.21 on each of the hydrogens. This is more pronounced in tetramethylphosphonium, with −0.68 on the phosphorus and +0.24 on the hydrogens. These hydrogens are all two bonds away from the onium centre; if one of the substituents were a phenyl group, there would be no hydrogens on the carbon attached to the onium centre, and the charge would be spread across the hydrogens in the ring. This would give a PTC with a substantially different surface charge interface for the substrate to interact with and may offer superior yield or enantioselectivity compared to previously reported PTCs.

Shibasaki suggests how a tartrate-derived quaternary ammonium salt might interact with the glycine imine enolate **3** (**Figure 2**).[11] This schematic illustrates the positioning of the benzyl groups when the PTC is coordinating to the substrate. Phenyl rings directly attached to the onium ion centre would offer a different steric environment and might result in higher stereoselectivity.

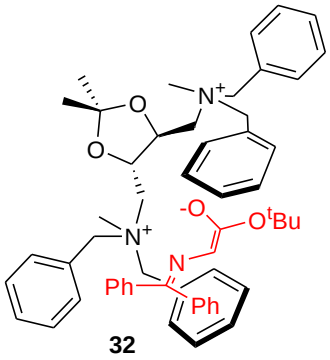


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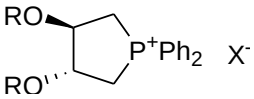
Figure 2: Proposed transition state of the interaction between the catalyst (black) and the glycine imine **3** intermediate (red), based on molecular mechanics simulations.

1.4. Project Aims

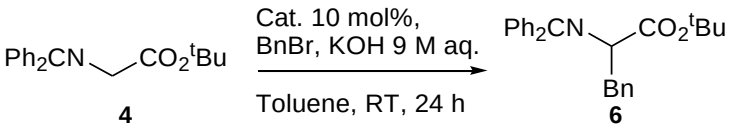
In this project, the aim was to promote phosphonium salt organocatalysis, a relatively unexplored area of organic chemistry, by synthesising a new class of quaternary phosphonium catalyst (**Figure 3**) to be used in phase transfer reactions.



33

Figure 3: Our intended phosphonium catalyst, where R is an alkyl group and X is a counterion.

Catalyst **33** is derived from tartaric acid, as this is a cheap source of chirality with the potential to be modified. Also, other PTCs based on this template have been shown to effect alkylation reactions with reasonable enantioselectivity. A ring system was opted for in the hope that the rigidity would accentuate the effect of the chiral centres on the enantiocontrol. Catalyst **33** is structurally similar to the quaternary ammonium salt reported by Tsuji,[9] but with phenyl groups in place of a second ring system. It was reasoned that it should be straightforward to synthesise from PPh_3, a very cheap source of phosphorus, and would also allow study of the effect of phenyl-substituted onium salts on the rate and enantioselectivity of the reaction. The alkylation of glycine imine with benzyl bromide (**Scheme 13**) was used to test the efficacy of **33**, as this reaction is known to proceed quickly under phase transfer conditions.



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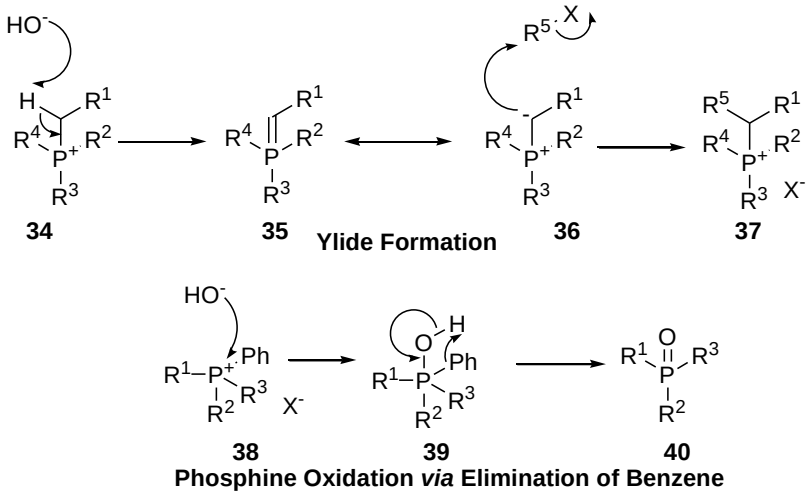
Scheme 13: Test alkylation reaction conditions for the use of catalyst **33**.

2. Synthesis and Use of Phosphonium-centred PTCs

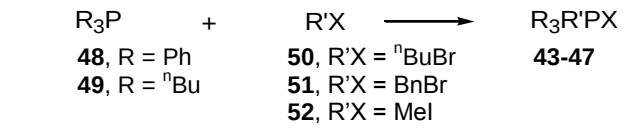
2.1. Phosphonium PTCs in Basic Conditions

PPh_4Br has often been used in PTC reactions,[20] and has proved particularly useful in high temperature processes where quaternary ammonium salts usually degrade.[21] However, quaternary phosphonium salts have not been widely used in PTC chemistry. This may be because there are two side reactions that could occur under basic PTC conditions (**Scheme 14**). One possibility is ylide formation *via* α-carbon deprotonation by the base. This could then proceed to react with the alkyl halide electrophile.[22] If the phosphine contains an aryl substituent then another possible side reaction may occur under basic conditions. The phosphonium centre could be attacked by hydroxide ion, followed by rearrangement to the corresponding phosphine oxide.[23]



Scheme 14: Potential side reactions using quaternary phosphonium salts in basic conditions.

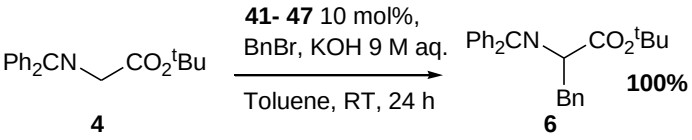
If these side reactions occur to a significant extent, then the applications of quaternary phosphonium salts as PTCs may be severely limited. To test this, a series of simple quaternary onium salts were chosen as catalysts for the alkylation of glycine imine **4**; $^{n}Bu_4NBr$ **41**, $MePh_3PBr$ **42**, $^{n}BuPh_3PBr$ **43**, $BnPh_3PBr$ **44,** $Me^{n}Bu_3PI$ **45**, $^{n}Bu_4PBr$ **46**, and $Bn^{n}Bu_3PBr$ **47**. These salts were chosen for the following reasons; **42**, **43** and **44** contain phenyl groups attached to the phosphorus centre and are therefore vulnerable to rearrangement to phosphine oxides. All of them have α-hydrogens, and can therefore potentially form ylides. **42** and **45** have methyl groups which offer reduced steric hindrance to the onium centre and salts **44** and **47** and contains benzyl groups which makes the α-methylene more acidic. **41** and **46** were used to allow a direct comparison between quaternary ammonium and phosphonium salts. **41** and **42** were acquired from commercial sources, but the rest were synthesised, as outlined in **Scheme 15**.



R_3P	R'-X	Temp. /°C	Reaction Time /h	Product	Yield /%
48	**50**	110	24	**43**	70
48	**51**	60	24	**44**	92
49	**52**	25	3	**45**	95
49	**50**	56	48	**46**	93
49	**51**	60	24	**47**	92

Scheme 15: Syntheses of quaternary phosphonium salts.

Each of the salts were then tested as PTCs in the alkylation of the glycine imine **4** (**Scheme 16**).



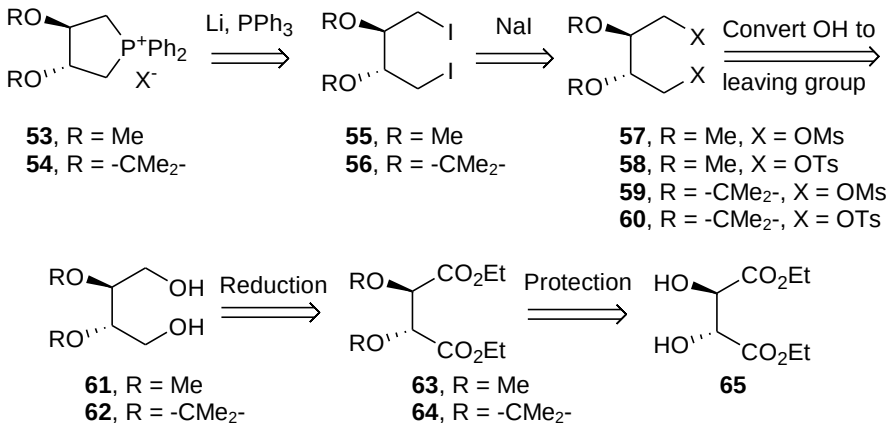
Scheme 16: Alkylation of the glycine imine **4** with benzyl bromide, catalysed by simple onium salts.

In all cases, the reactions had gone to completion within 24 hours. In this initial study, the precise rates of reaction were not measured, but all the catalysts appeared to be similarly effective. Complete conversion of the starting material implies little or no degradation of the catalysts to alkylated ylides or phosphine oxides during the reaction. This study suggests that quaternary phosphonium salts are compatible with base-mediated PTC processes.

2.2. Tartrate-Derived Phosphonium Salts

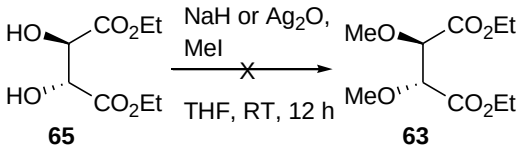
2.2.1. Synthetic Design

The retrosynthesis of catalysts **53** and/or **54** is outlined in **Scheme 17**, both the methyl- and the acetonide-protected OH versions were to be investigated if possible. The phosphonium salt would be formed by cyclisation between $LiPPh_2$ and a precursor with two leaving groups, such as the diiodides **55**/**56** or the dimesylates or ditosylates **57**-**60**. These would be formed from the diols **61**/**62**, which in turn could be formed by the reduction of diesters **63**/**64** with $LiAlH_4$. The initial step would be protection of the hydroxy groups of diethyl tartrate **65**.



Scheme 17: Retrosynthetic analysis of target compound.

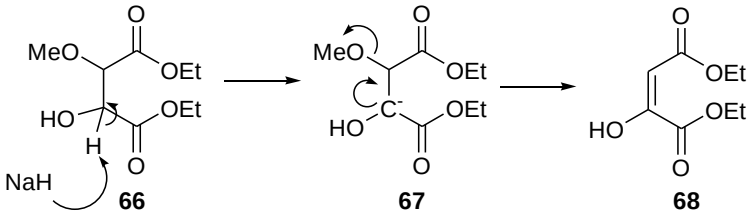
It was theorised that it might be easier to form the cyclic quaternary phosphonium salt **53** from a dimethoxy precursor (**55**, **57** or **58**) as the corresponding acetonide **54** would be more strained due to the trans-ring fusion between the two 5-membered rings and consequently, this route was investigated first. Several attempts were made to convert **65** into **63** using sodium hydride and methyl iodide (**Scheme 18**).[24] However, this method failed to produce the desired product **63** cleanly.



Scheme 18: Attempted *O*-methylation of the diol in L-diethyl tartrate using methyl groups.

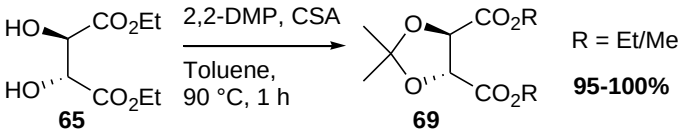
Variations of the reaction conditions were attempted; dimethyl tartrate was used instead of diethyl tartrate,[25] freshly made silver oxide was used as an alternative to sodium hydride,[26] the number of equivalents of methyl iodide used were altered, and the reaction time extended up to 84 h. Analysis of ^{1}H NMR spectra of the crude reaction mixtures showed that the mono-methylated intermediate was forming (in an otherwise complex mixture), but it was never confirmed that any di-*O*-methylated derivative was produced. Methods published since this research was performed appear to favour Me_2SO_4 over MeI.[27]

A possible explanation for the absence of product is shown in **Scheme 19**. After the mono-methylated compound **66** has formed, NaH can initiate an $E1_{cb}$ process – deprotonation at the carbon alpha to the remaining hydroxy group results in the formation of **67**, which eliminates methoxide to form **68**. This would also explain the observations that only the mono-methylated intermediate was observed in the ^{1}H NMR spectrum and that only after addition of MeI did by-products start to form.



Scheme 19: Possible side reaction preventing product formation.

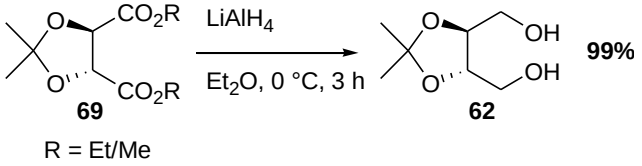
Because there was no evidence that the intended compound had been synthesised, preparation of the corresponding acetonide was investigated instead. The initial method investigated reaction of **65** with acetone, triethyl ortho-formate and CSA,[28] which gave no apparent by-products but always resulted in incomplete conversion. 2,2-DMP and TsOH in cyclohexane gave complete conversion,[29] but also a number of by-products. Switching the solvent to toluene resulted in complete reaction within one hour and gave the desired product in high yield with no observable by-products (**Scheme 20**).



Scheme 20: Protecting the diol on L-diethyl tartrate using an acetonide group.

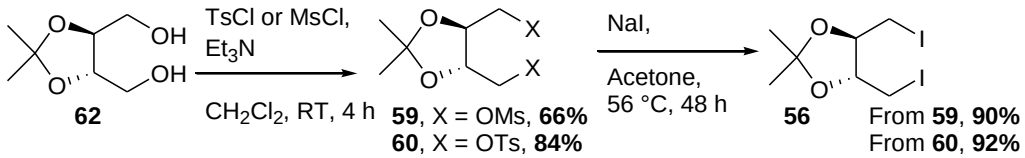
Methanol is formed as a by-product during this reaction and this results in partial transesterification, so **69** was isolated as a mixture of methyl and ethyl esters. The mixture was used without further purification, as the next step was to reduce the ester groups to the diol.

The reduction step (**Scheme 21**) proceeded smoothly, giving the diol **62** in high yield.[30] It was not necessary or beneficial to heat the reaction mixture, as this only resulted in degradation of the product. Using Et_2O rather than THF was more desirable due to it being less hygroscopic, and the isopropylidene-L-tartaric acid diester was used as a dilute solution chilled to low temperature, as the initial reaction is very rapid and vigorous.



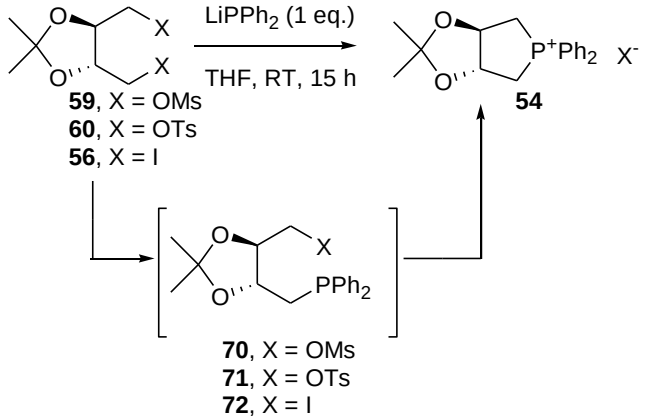
Scheme 21: Reduction of isopropylidene-L-tartaric acid diester.

The diol **62** was then converted to dimesylate **59** or ditosylate **60**,[31] then these were converted to diiodide **56** (**Scheme 22**).



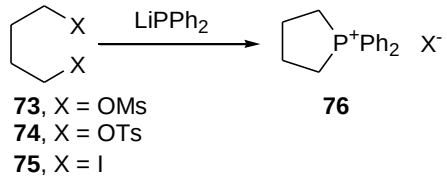
Scheme 22: Conversion of the diol in isopropylidene-L-threitol to a leaving group.

At this stage either the dimesylate **59**, ditosylate **60** or diiodide **56** could be converted to the cyclic phosphonium salt **54** (**Scheme 23**). The compounds may cyclise readily or they may proceed to form **70**-**72**. Yamagishi had shown the reaction of $LiPPh_2$ with acetonide **60** gave the mono-substituted acylic product **71** in 49% yield.[32] Subsequently, it is possible that if these are the major products of these reactions, then their intramolecular cyclisation would result in the formation of **54**.



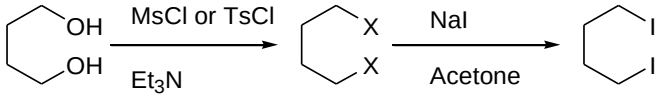
Scheme 23: Conversion of the tartrate-derived dimesylate, ditosylate or diiodide to the cyclic phosphonium salt.

As this transformation generates a relatively strained *trans*-fused ring system, an analogue for the transformation was devised using the corresponding unsubstituted precursors derived from butane-1,4-diol (**Scheme 24**).



Scheme 24: Conversion of the butanediol-derived dimesylate, ditosylate or diiodide to the cyclic phosphonium salt.

This would illustrate which moiety the best leaving group for this reaction, and whether any by-products would form as a result. The butanediol derivatives were prepared in a two step process (**Scheme 25**).



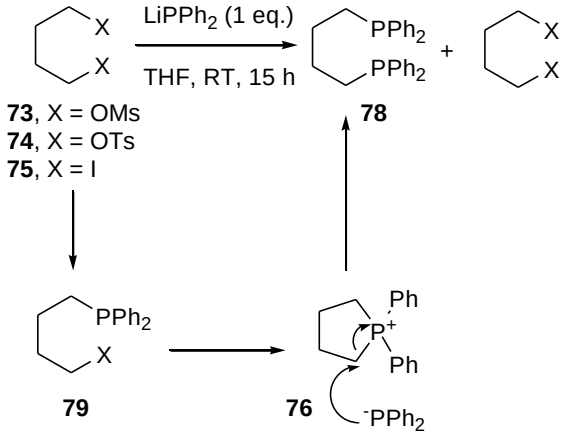
77 **73**, X = OMs; **74**, X = OTs **75**

Starting Material	Product	Yield /%
77	**73**	96
77	**74**	84
73	**75**	84
74	**75**	53

Scheme 25: Conversion of butane-1,4-diol to dimesylate **73**, ditosylate **74** or diiodide **75**.

The synthesis proceeded in good yield, affording all derivatives. Synthesising **75** directly from **77** was also possible using the Appel reaction.[33] It was noteworthy that under these conditions, the yield exceeded 100%, indicating that the solvent (THF) was, coincidentally, also reacting with the PPh_3 and I_2 to form **75**.[34]

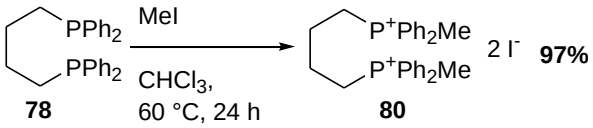
It was hoped that the cyclic phosphonium species could be formed by reacting these compounds with $LiPPh_2$. This reagent was prepared from PPh_3 by reaction with lithium metal in THF under inert atmosphere.[35] Reaction of freshly prepared $LiPPh_2$ with compounds **73-75** did not give the desired cyclic phosphonium salt **76**. Instead, a mixture of starting material and the bisphosphine **78** were produced (**Scheme 26**).



Scheme 26: Reaction between **73**-**75** and $LiPPh_2$ and proposed mechanism for the formation of **78**.

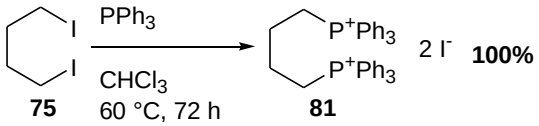
Varying the reaction conditions (time, temperature, amount of $LiPPh_2$) did not result in any formation of **76**. Addition of ^tBuCl to the $LiPPh_2$ solution was also attempted, in order to destroy any LiPh that may be present,[36] but again, this did not improve the outcome. From the result it is clear that bisphosphine **78** was by far the preferred product and even using 1 eq. of $LiPPh_2$ resulted in only formation of **78**, with no mono-substituted product **77** or cyclic phosphonium salt **76** detected. This observation may be explained if the desired phosphonium salt **76** is more reactive

than the starting material and this may account for why the disubstituted product is favoured. Given that the bisphosphines were readily formed, it was decided to investigate phosphonium salts with this type of structure instead of the cyclic phosphonium structures. Indeed, these compounds have similar structures to the quaternary ammonium salts reported by Shibasaki.[11] Following reaction of the bisphosphine **78** with methyl iodide gave the corresponding bis-phosphonium salt **80** (**Scheme 27**).



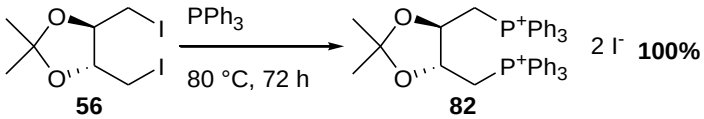
Scheme 27: Methylation of 1,4-bis(diphenylphosphino)butane.

Clearly if bisphosphonium salts such as **80** were to be prepared, a more direct method would be to react the diiodide (or dimesylate, ditosylate) with a phosphine. This was first done with diiodide **75** and triphenylphosphine and proceeded to give **81** in quantitative yield (**Scheme 28**). Chloroform was found to be superior to toluene as the solvent for this process because the monophosphonium salt precipitates from toluene and results in incomplete reaction.



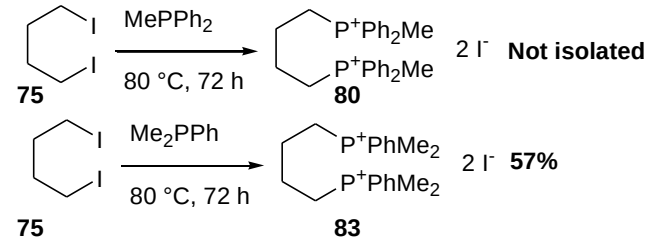
Scheme 28: Formation of 1,4-bis(triphenylphosphonium)butane.

When the same transformation was attempted using the tartrate-derived diiodide **56**, the reaction was sluggish and did not reach completion. Clearly, diiodide **56** is less reactive than 1,4-diiodobutane **75**. Heating to higher temperatures in a sealed tube did not solve the problem, but it was discovered that performing the reaction without solvent did lead to complete conversion (**Scheme 29**).[37]



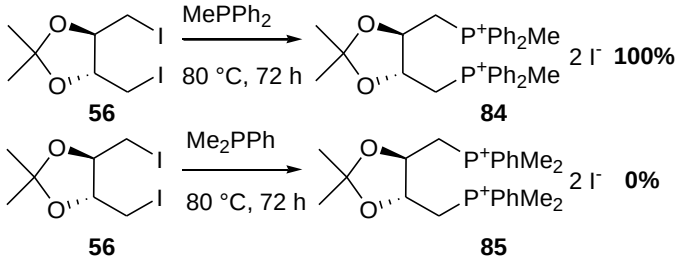
Scheme 29: Formation of 1,4-Dideoxy-1,4-di(triphenylphosphonium)-2,3-*O*-isopropylidene-L-threitol diiodide.

This reaction is best performed with an excess of PPh_3 (10 eq.), at its melting point (80 °C), so that the PPh_3 serves as reagent and solvent. This reaction could allow chiral bisphosphonium salts to be accessible in one step in good overall yield. Therefore more achiral phosphonium salts were prepared by reacting 1,4-diiodobutane **75** with $MePPh_2$ and Me_2PPh using the same method (**Scheme 30**).



Scheme 30: Formation of butanediol-derived bis-phosphonium diiodides.

The reaction with Me_2PPh gave **83** in an acceptable yield but unfortunately the reaction with $MePPh_2$ did not go to completion and the product proved difficult to separate from the monophosphonium salt. Phosphonium salt **80** had however already been prepared before by a different strategy (**Scheme 27**). The reactions of Me_2PPh and $MePPh_2$ with tartrate-derived diiodide **56** were then attempted (**Scheme 31**).

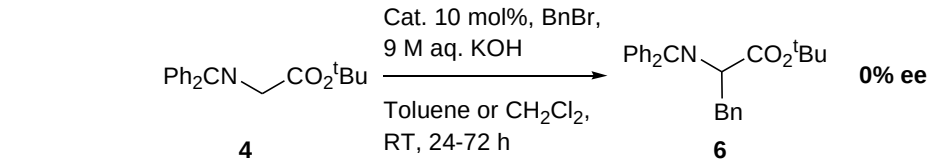


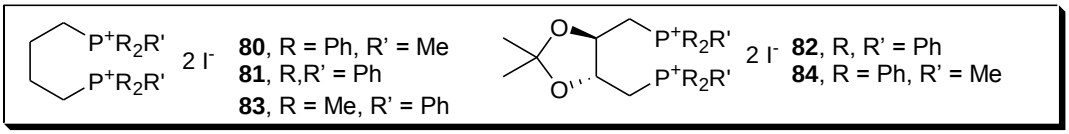
Scheme 31: Formation of tartrate-derived bis-phosphonium diiodides.

The reaction using $MePPh_2$ gave **84** in an excellent yield but the product of the reaction with Me_2PPh could not be identified. Analysis of the ^1H NMR data did not reveal the acetonide signal. Furthermore, the mass spectrum did not show the single $[M\text{-}I]^+$ peak of 493 *m/z*, with peaks at 304, 363, 413, 431, 499 and 567 *m/z* being present instead, indicating a side reaction has taken place.

2.2.2. Use of Chiral Phosphonium Salts in an Alkylation Reaction

These catalysts were tested in the alkylation of *N*,*N*-diphenyl methylene glycine *tert*-butyl ester **4** with benzyl bromide (**Scheme 32**). Toluene was the initial choice for solvent; being non-polar, it should accentuate electrostatic attraction between catalyst and reagent. Unfortunately, the catalysts only dissolve very sparingly in non-polar solvents and no significant reaction was observed. When the solvent was changed to CH_2Cl_2, a significant improvement in reactivity was observed. Yields varied from 20-30% across a 24 hour period. When the reaction time was increased to 72 hours for salts **80** and **82**, complete conversion of the starting material was then observed.





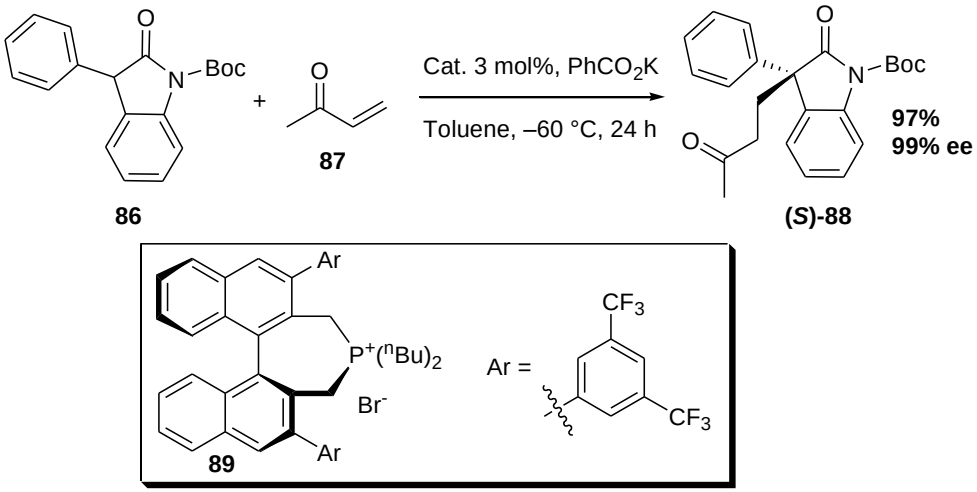
Catalyst	Solvent	Time /h	Conversion /%
80	Toluene	24	<1
81	Toluene	72	<1
82	Toluene	48	<1
83	Toluene	24	<1
84	Toluene	24	<1
80	CH_2Cl_2	24	30
81	CH_2Cl_2	24	20
82	CH_2Cl_2	24	30
84	CH_2Cl_2	24	25
80	CH_2Cl_2	72	100
82	CH_2Cl_2	72	100

Scheme 32: Efficacy of phosphonium PTCs in catalysing addition of benzyl bromide to *N*,*N*-diphenyl methylene glycine tert-butyl ester.

Regardless of catalyst or solvent, no enantioselectivity was observed, which forced the conclusion that the catalysts are unable to convey chirality onto the product in this type of reaction. Whilst it may be possible that the catalysts are degrading under the reaction conditions, this was not determined as the catalysts were not recovered. This prompted investigation to find another type of reaction that could yield better results.

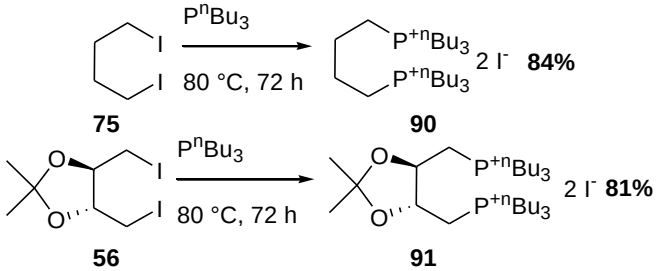
2.2.3. Use in Michael Addition Reaction

Phosphonium salts are not commonly used in phase-transfer Michael addition reactions, more commonly used catalysts include cinchona alkaloid derivatives,[38] and crown ethers.[39] However, Maruoka[40] created phosphonium catalysts that use the biaryl scaffold he previously used for his quaternary ammonium catalysts and applied them to Michael addition reactions, giving successful results (**Scheme 33**).



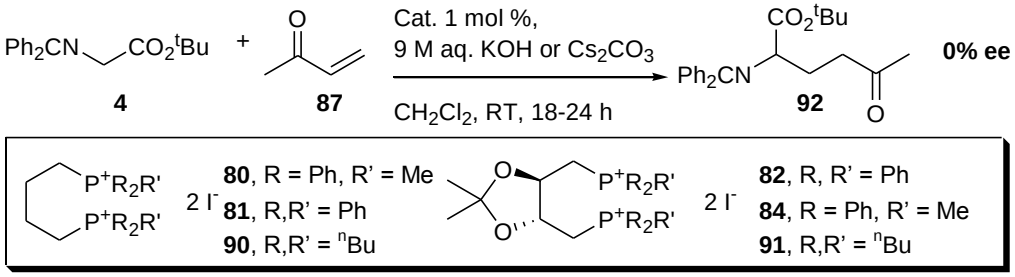
Scheme 33: Highly enantioselective Michael addition catalysed by a chiral phosphonium salt catalyst.

It was hoped that the phosphonium catalysts used for the alkylation of glycine imine **4** might be able to give better enantioselectivity in a Michael addition reaction. Additionally, two extra catalysts were synthesised that incorporate tri-*n*-butylphosphine. So far, all the catalysts tested had contained at least one phenyl group – as the positive charge on the phosphonium is spread across the beta hydrogens on its substituents, the earlier hypothesis stated that a phenyl group would offer a unique positively charged surface for the substrate to interact with, compared with a quaternary ammonium salt. This could, however, be the source of the low enantioselectivity – having catalysts without phenyl groups may eliminate this. 1,4-Bis(tributylphosphonium) butane diiodide **90** and 1,4-dideoxy-1,4-bis(tributylphosphonium)-2,3-*O*-isopropylidene-L-threitol diiodide **91** were synthesised by reacting readily available tri-*n*-butylphosphine with diiodo-compounds **75** and **56** (**Scheme 34**).



Scheme 34: Synthesis of tri-*n*-butyl phosphine derived catalysts.

These catalysts were tested then in the Michael addition of *N*,*N*-diphenyl methylene glycine *tert*-butyl ester to MVK (**Scheme 35**).



Catalyst	Base	Solvent	Time /h	Conversion /%
81	9 M aq. KOH	CH_2Cl_2	18	89
82	9 M aq. KOH	CH_2Cl_2	18	82
80	9 M aq. KOH	CH_2Cl_2	18	95
84	9 M aq. KOH	CH_2Cl_2	18	89
90	9 M aq. KOH	CH_2Cl_2	18	100
91	9 M aq. KOH	CH_2Cl_2	18	100
91	Cs_2CO_3	CH_2Cl_2	24	79
91	9 M aq. KOH	Toluene	24	100
91	9 M aq. KOH	Tol:CH_2Cl_2 3:1	24	100

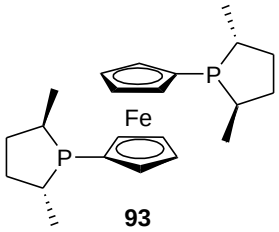
Scheme 35: Efficacy of phosphonium PTCs at catalysing Michael addition of MVK to the *N*,*N*-diphenyl methylene glycine *tert*-butyl ester.

Even at 1% catalyst loading, the catalysts were able to promote high conversion (>80%) in 18 hours at room temperature, with particularly good results from **91**. However, the catalysts were still not promoting any enantioselectivity. It was reasoned that either the source of chirality in tartrate-derived compounds is too far from the cation where the substrate associates, or that the substituents on the catalyst were not large enough to restrict the angle of approach of the two reagents.

2.3. Catalysts Derived From Commercially Available Chiral Phosphines

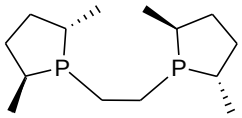
2.3.1. Synthesis of Catalysts and Their Use in a Michael Addition Reaction

It was decided to synthesise catalysts that had chiral centres closer to, or on, the phosphonium cation by deriving them directly from readily available chiral phosphines. Five were selected for investigation (**Figure 4**).



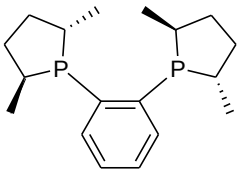
93

1,1'-Bis[(2*R*, 5*R*)-2,5-dimethyl phospholano]ferrocene



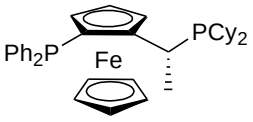
94

(-)-1,2-Bis[(2*S*, 5*S*)-2,5-dimethyl phospholano]ethane



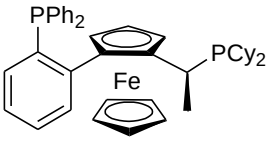
95

1,2-Bis[(2*S*, 5*S*)-2,5-dimethyl phospholano]benzene



96

(*R*)-1[(*S*)-2-(Diphenylphosphino)-ferrocenyl]ethyldicyclohexylphosphine



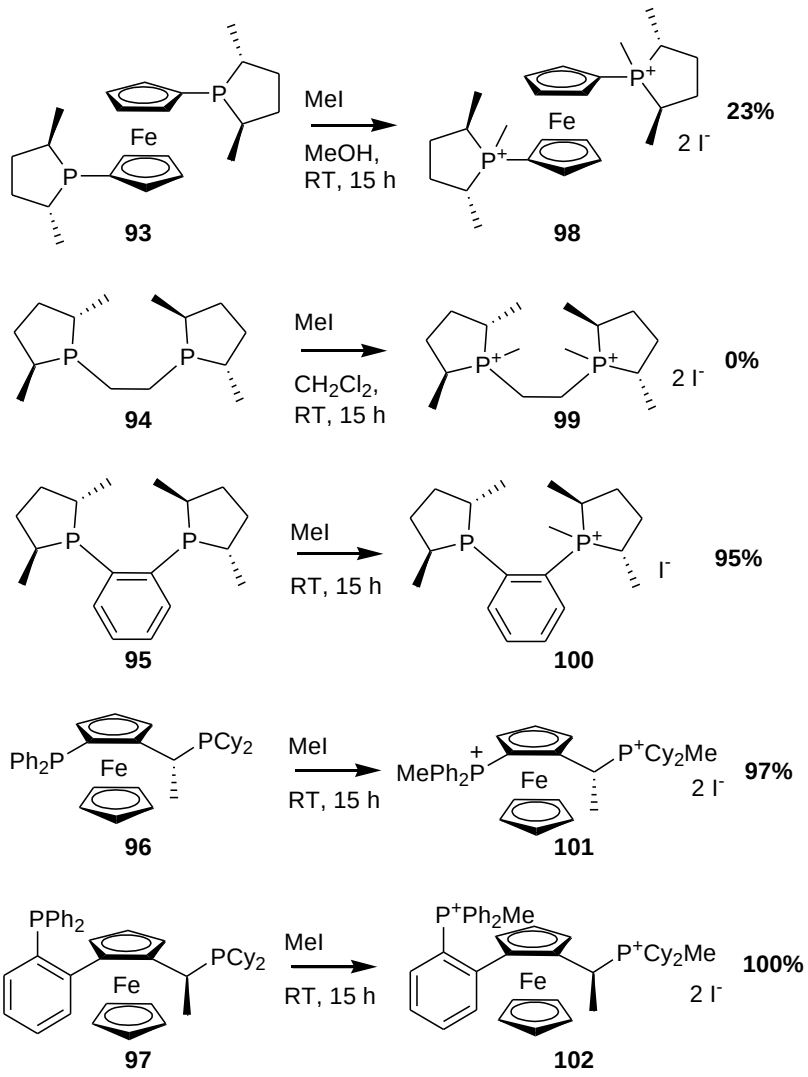
97

(*R*)-1-{(*R*)-2-[2-(Diphenylphosphino)phenyl] ferrocenyl}ethyldicyclohexylphosphine

Figure 4: Commercially available chiral phosphines used to make phosphonium PTCs.

Phosphines **93**, **96** and **97** contain a ferrocene core and could offer a new template for phosphonium-based organocatalysts. There have been reports of phenylphosphinoferrocenes used as ligands for metal-centred phase-transfer reactions,[41] though no literature focusing on ferrocene derivatives in organocatalysed phase transfer reactions could be found. Phosphines **93**-**95** all contain dimethylphospholane moieties – they are bound to the ferrocene ring in **93** linked by a simple carbon chain between the phosphorus centres in **94** and substituted onto a benzene ring in **95**. **94** also has greater flexibility in its structure compared to the other compounds.

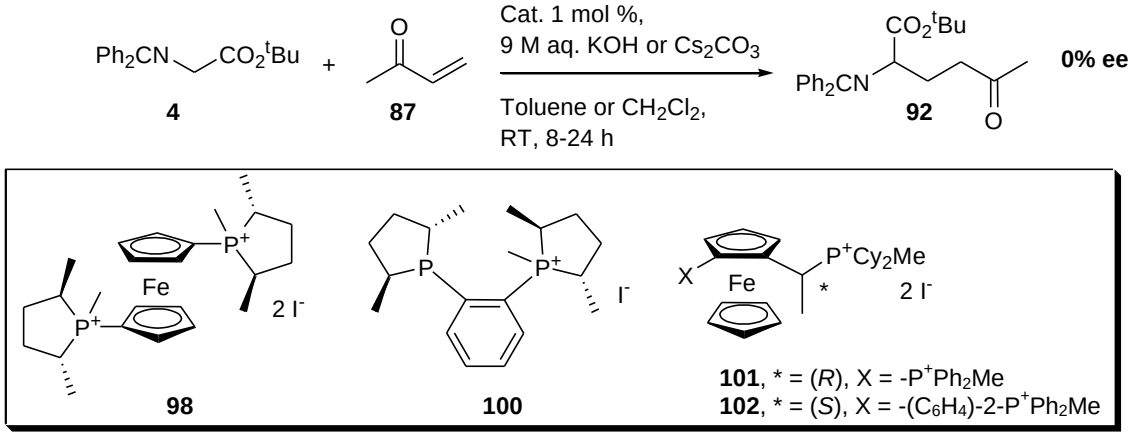
It was decided to synthesise the phosphonium salts in absence of solvent where possible, as this gave the tartrate-derived phosphonium salts in high yield and purity. However, due to the cost of the phosphines and the volatility of MeI, the reactions were performed in an excess of MeI rather than the phosphine (**Scheme 36**).



Scheme 36: Syntheses of phosphonium PTCs from commercially available chiral phosphines.

In the syntheses of **98** and **99**, it was necessary to add a minimal amount of solvent as the phosphine was not soluble in MeI. **98** was obtained in a low yield due to purification difficulties. The intended product **99** could not be detected or isolated; due to the air and moisture instability of the starting material, phosphine oxides were generated preferentially over the desired product. **101** and **102** were obtained in high yields. The methylation of **95** gave the monophosphonium salt **100** in high yield, but no bisphosphonium salt was detected; as the two phosphorus atoms are locked in close proximity, it is possible that the initial substitution blocks the second from reacting. This unintended result was still useful however, as the product could still be used as a catalyst.

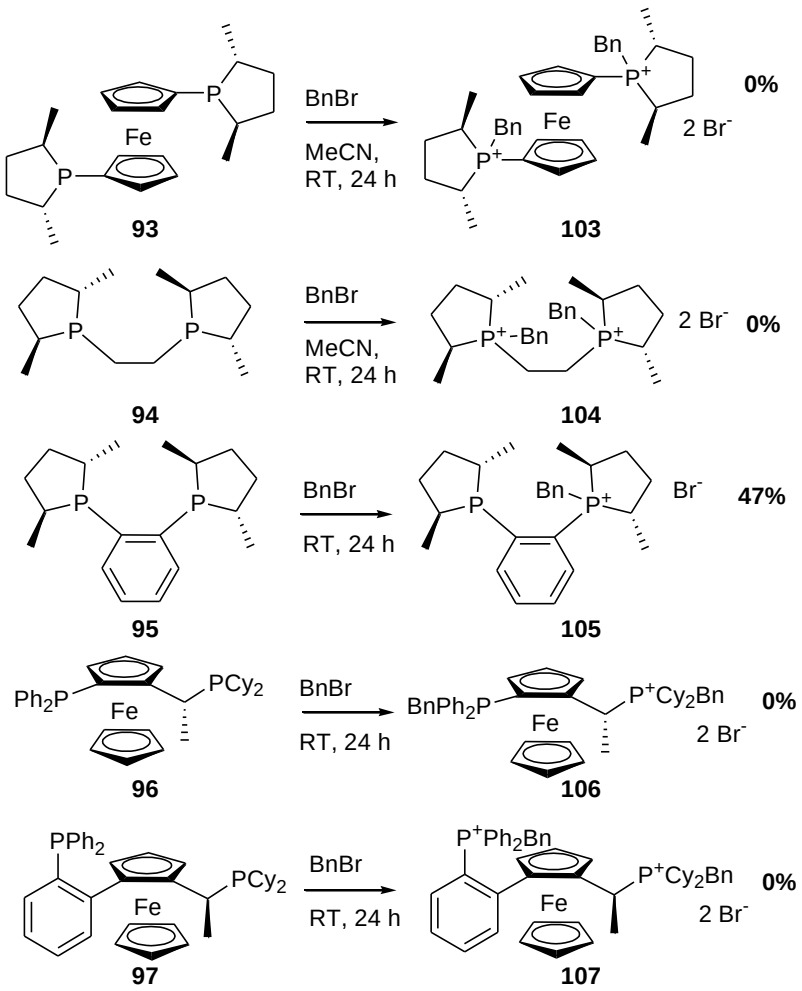
The catalysts **98**, **100**, **101** and **102** were tested in the Michael addition of *N*,*N*-diphenyl methylene glycine *tert*-butyl ester to MVK (**Scheme 37**).



Catalyst	Base	Solvent	Time /h	Conversion /%
98	9 M aq. KOH	Toluene	15	68
100	9 M aq. KOH	Toluene	24	80
101	9 M aq. KOH	Toluene	15	95
102	9 M aq. KOH	Toluene	8	99
102	Cs_2CO_3	Toluene	24	100
102	Cs_2CO_3	CH_2Cl_2	24	100

Scheme 37: Efficacy of phosphonium PTCs at catalysing Michael addition of MVK to the *N*,*N*-diphenyl methylene glycine *tert*-butyl ester.

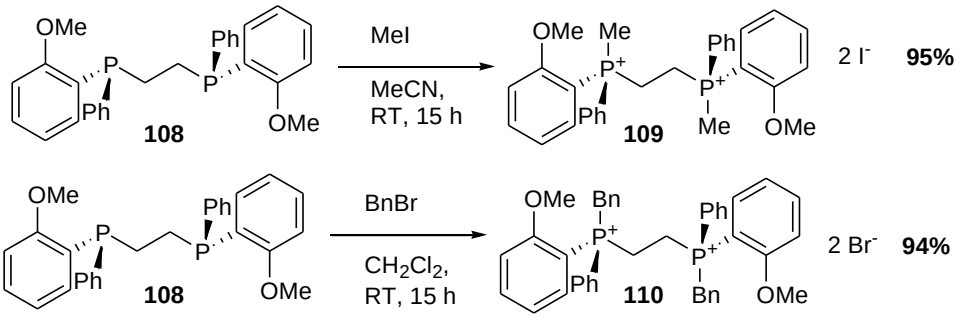
Obtained yields were high (especially from **102**) but no enantioselectivity was observed, regardless of the choice of solvent or base. It was decided to synthesise new catalysts with a larger substituents on the phosphonium centres, in the hope this would enhance the stereoselectivity of the catalyst. To this end, the chiral phosphines were each reacted with benzyl bromide (**Scheme 38**).



Scheme 38: Syntheses of phosphonium PTCs using commercially available chiral phosphines in benzyl bromide.

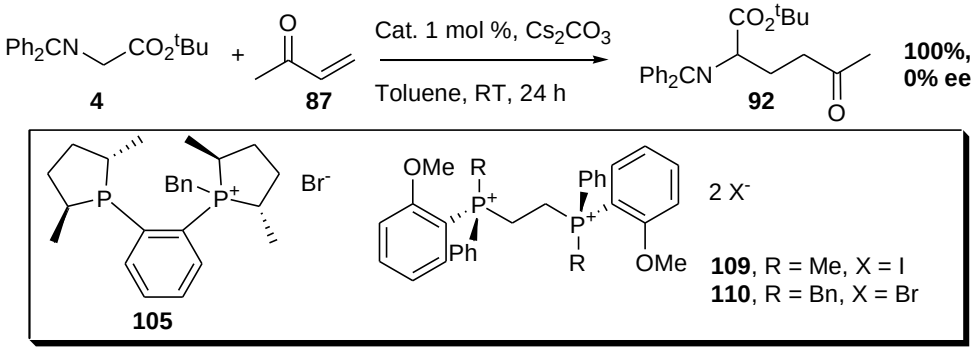
Unfortunately, the benzylation reactions did not proceed as cleanly as the methylation reactions, and in the case of the syntheses of **103**, **104**, **106** and **107**, the desired products could not be purified from the complex mixtures obtained to be characterised by ^{1}H NMR spectroscopy. The benzylation of **95** gave the monophosphonium salt **105**, which could be isolated from the rest of the mixture with ease, albeit with a yield lower to that obtained during the methylation reaction.

In addition to **105**, two extra catalysts derived from a commercially available chiral phosphine that has its chiral centre on the phosphorus, (*R*,*R*)-DIPAMP **108**, were synthesised (**Scheme 39**).



Scheme 39: Syntheses of phosphonium PTCs using *R,R*-DIPAMP.

The initial reaction between (*R*,*R*)-DIPAMP and the alkyl halide took place in the absence of solvent. This resulted in rapid formation of a white precipitate in both cases. In case this was the monophosphonium salt precipitating, solvent was then added to dissolve the precipitate and make disubstitution more likely. Catalysts **105**, **109** and **110** were then tested in the Michael addition reaction (**Scheme 40**).

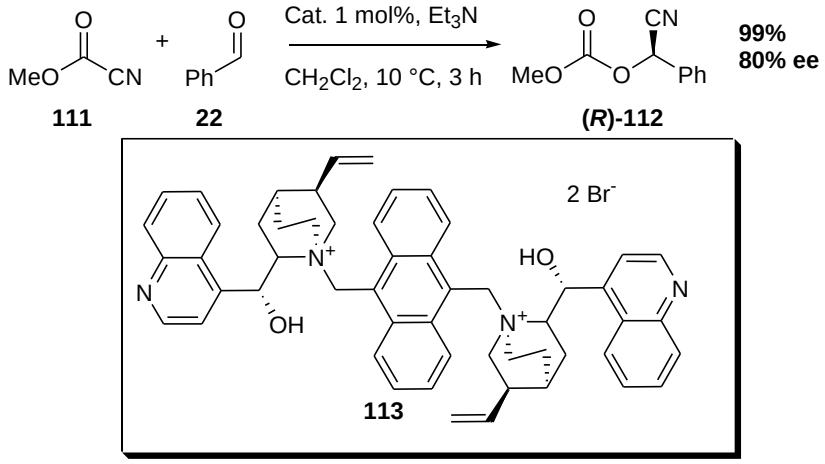


Scheme 40: PTC-catalysed Michael addition of MVK to the *N*,*N*-diphenyl methylene glycine *tert*-butyl ester using **105**, **109** and **110**.

These catalysts gave products in high yields, but no enantioselectivity was observed. From this, it was concluded that this class of catalysts is not able to catalyse Michael additions enantioselectively.

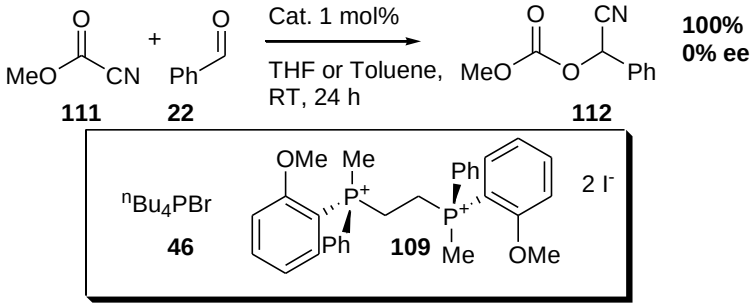
2.3.2. Use of Chiral Phosphonium Salts in Other Asymmetric Reactions

Literature precedent indicates that phosphonium salts can catalyse cyanoformylation reactions,[42] however, enantioselective procedures have not been reported. Chinchilla reported the use of quaternary ammonium cinchona alkaloid derivative **113** in the cyanoformylation of benzaldehyde (**Scheme 41**).[43]



Scheme 41: Cyanoformylation of benzaldehyde catalysed by cinchona alkaloid derivative **113**.

Two catalysts (**46** and **109**) were tested in the cyanoformylation reaction of benzaldehyde and methyl cyanoformate (**Scheme 42**). These two catalysts were chosen due to their availability at the time of experiment and because they had both shown to be capable of catalysing other phase transfer reactions in high yield.

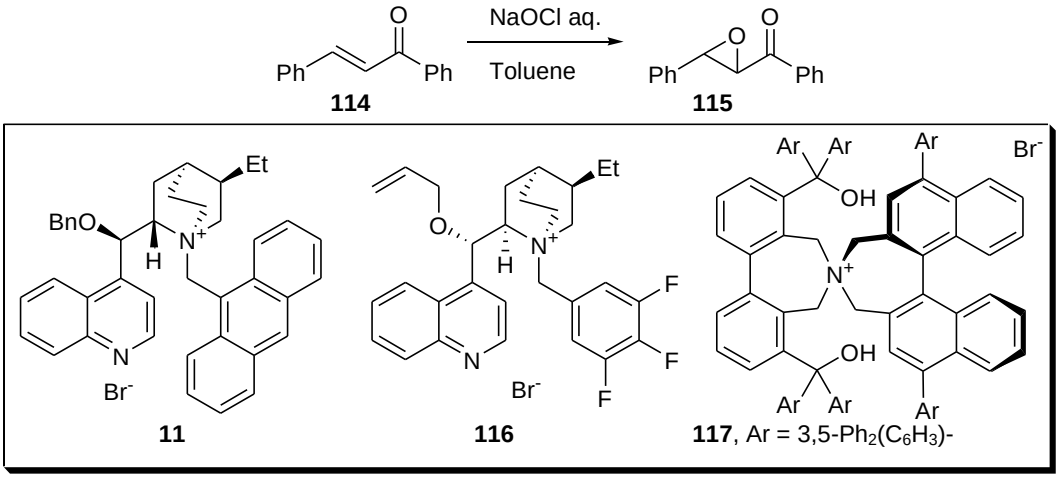


Scheme 42: PTC-catalysed asymmetric cyanoformylation between benzaldehyde and methyl cyanoformate.

It appears that the phosphonium catalysts were able to catalyse this reaction very efficiently but unfortunately, no enantioselectivity was observed.

As with cyanoformylation reactions, no reports in the chemical literature show that phosphonium salts have been used for asymmetric epoxidation reactions. However, ammonium-based phase transfer catalysts have been employed in this reaction – the epoxidation of chalcone **114** is shown in **Scheme 43**. Previously in the Lygo

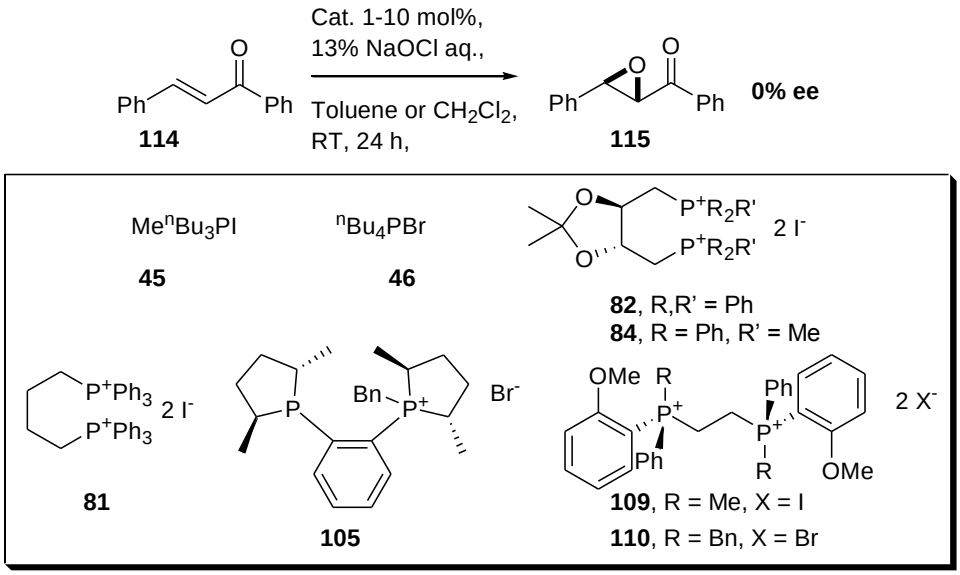
group, this reaction was attempted using catalyst **11** and chalcone epoxide **115** was obtained in high yield and enantioselectivity with only 1 mol% of catalyst (98% and 86% ee).[44] Maruoka developed catalyst **116** and improved on these results (99% and 96% ee) albeit with a higher catalyst loading.[45] Park attempted the same reaction using catalyst **117**,[46] and while the yield and enantioselectivity were not as high (82% and −91% ee), it gave the opposite enantiomer to the other two catalysts.



Catalyst	Cat. amount /mol%	NaOCl amount /mol%	Temp / °C	Time /h	Yield /%	ee /%
11	1	15	25	24	98	86 (αS,βR)
116	3	13	0	24	99	96 (αS,βR)
117	5	11	0	48	82	–91 (αR,βS)

Scheme 43: Epoxidation of chalcone catalysed by quaternary ammonium catalysts **116** and **117**.

A range of our synthesised catalysts were tested in the epoxidation of chalcone (**Scheme 44**).



Catalyst	Solvent	Catalyst %	Conversion /%
45	Toluene	10	94
46	Toluene	10	100
81	Toluene	10	0
82	Toluene	10	8
84	Toluene	10	0
105	Toluene	10	0
109	Toluene	1	0
110	Toluene	10	0
110	CH_2Cl_2	10	0

Scheme 44: Efficacy of phosphonium PTCs at catalysing asymmetric epoxidation of chalcone.

Unlike the alkylation and Michael addition reactions, the phosphonium salts were generally not successful in catalysing the epoxidation. As before, the *R,R*-DIPAMP-derived catalysts (**109**, **110**) were tested first. However, these catalysts did not successfully catalyse the formation of any product at all. Other previously synthesised chiral catalysts were tested in this epoxidation reaction (**84**, **82** and **81**) to investigate if these were capable of successfully forming product and unfortunately, the result was the same. Curiously, the only catalysts that successfully catalysed the reaction were simple and non-chiral, **45** and **46**. **82** also resulted in a small amount of product formation but it appears that two-centred catalysts do not work well in these reaction conditions.

2.4. Summary and Conclusions

In this study we were able to develop routes to new quaternary phosphonium salts, derived from 1,4-butanediol, diethyl tartrate and commercially available chiral phosphines, with reaction routes no longer than six steps and often giving products in high yield and purity. These compounds were tested as catalysts in four phase-transfer reactions.

The alkylation of glycine imine **4** with benzyl bromide was performed in toluene initially, where no observable reaction was observed over 24 h, but this improved to 20-30% when the solvent was changed to CH_2Cl_2, with catalysts **80** and **82** gave 100% conversion over 72 h. The catalysts gave high yields in the Michael addition of glycine imine **4** with MVK, ranging from 68-100% over 8-24 h, at only 1 mol% loading, with **102** giving 99% conversion in 8 h. Catalysts **46** and **109** were tested in the cyanoformylation of benzaldehyde and methyl cyanoformate and gave 100% yield in 24 h. Lastly, the epoxidation of chalcone was performed with a range of catalysts, but with only **45** and **46** giving high yield (94% and 100%) over 24 h.

The catalysts were able to effect the reactions to a generally high conversion without substantial degradation. However, no enantioselectivity was observed in any of the reactions. Although previous reports have shown high enantioselectivity from using phosphonium centred PTCs and tartrate-derived PTCs, it appears the structures investigated in this project were not suitable for this purpose.

As the applications of these compounds in asymmetric synthesis are limited, it was decided to conclude this project and work on a series of unrelated structures to be employed in a different area of asymmetric catalysis, which is discussed in the next chapter.

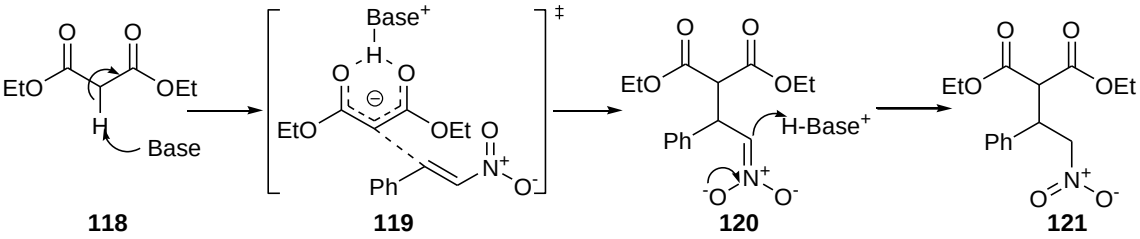
3. Introduction to Bifunctional Catalysis

3.1. Background

A bifunctional catalyst contains both a Lewis/Brønsted acid and a Lewis/Brønsted base in its structure. This has several potential advantages over other reaction systems. For example, phase transfer catalysis requires a biphasic system, as the reaction is initiated by a base that is not soluble in an organic solvent, thereby necessitating the catalyst in order to transfer components from one phase to another.

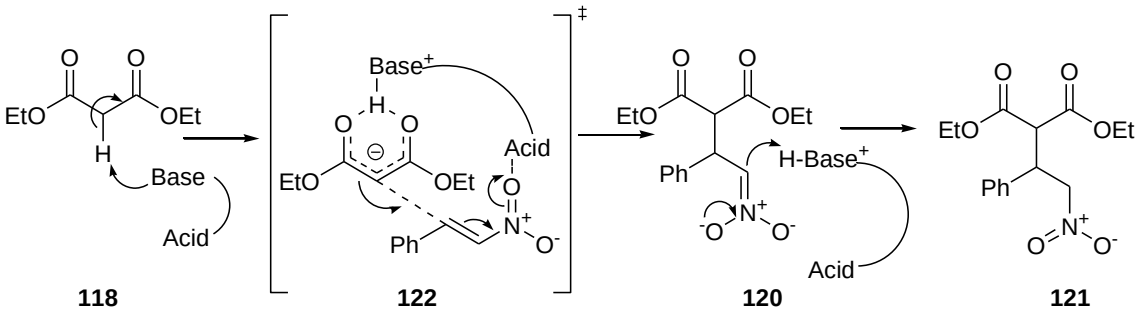
Bifunctional catalysis simplifies this by having a basic functional group as part of its structure and thus eliminating the need for both a base and the second phase. Secondly, the catalyst holds the substrate and the reagent in close proximity to one another, much like an enzyme. Most of the literature on bifunctional catalysts focuses on those with metal-centred structures.[47] There has been less focus on purely organic catalysts, *i.e.* ones that do not use a metal as the Lewis acid.

Scheme 45 shows a typical conjugate addition reaction, namely between diethyl malonate and (*E*)-nitrostyrene, using a simple base. The base deprotonates the acidic hydrogen on the malonate to produce enolate **118**, which can then react with nitrostyrene to form intermediate **119**. During the reaction, a negative charge builds up on the nitro group on the nitrostyrene, which then returns to neutral once the hydrogen is returned.



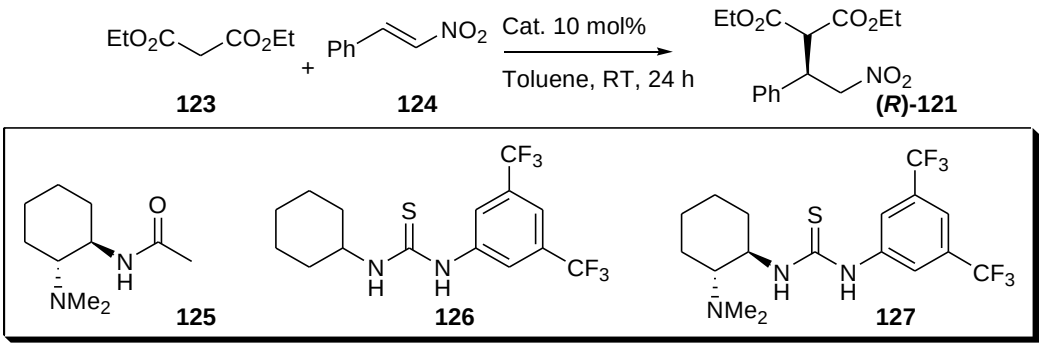
Scheme 45: Diagram giving a general overview of a conjugate addition effected by a simple base.

The advantage of using a bifunctional catalyst is shown in **Scheme 46**. The basic moiety of the bifunctional catalyst deprotonates the substrate as before, but in the transition state **122**, the acidic moiety stabilises the build up of negative charge on the nitro group, thus more readily permitting the enolate to attack the nitrostyrene. All the while the catalyst is holding the two components in close proximity to each other – the backbone of the catalyst can be modified to promote correct alignment of the two molecules, resulting in fast reaction and if chiral, high enantioselectivity.



Scheme 46: Diagram giving a general overview of a conjugate addition effected by a bifunctional catalyst.

Research reported by Takemoto shows the importance of both base and acid components and their effect on the yield in a bifunctional reaction.[48] **Scheme 47** shows a conjugate addition between diethyl malonate and (*E*)-nitrostyrene. Et_3N and **125** are both bases and capable of catalysing the reaction, but give poor yields (17% and 14% respectively). **126** contains a thiourea group which acts as an acidic moiety and can stabilise the build up of negative charge on the nitrostyrene through hydrogen bonding – when combined with Et_3N, there is a marked improvement in yield (57%). However, the best result was obtained using **127**, a bifunctional catalyst whose structure can be seen to be a combination of **125** and **126**. This gave high yield (86%), illustrating that not only is it important to have both acid and base moieties in the reaction, but that they should be part of the same molecule so that the reactants can be held in close proximity. Additionally, there was a marked improvement in enantioselectivity (93% ee over 35% ee) when **127** was use instead of **125**.

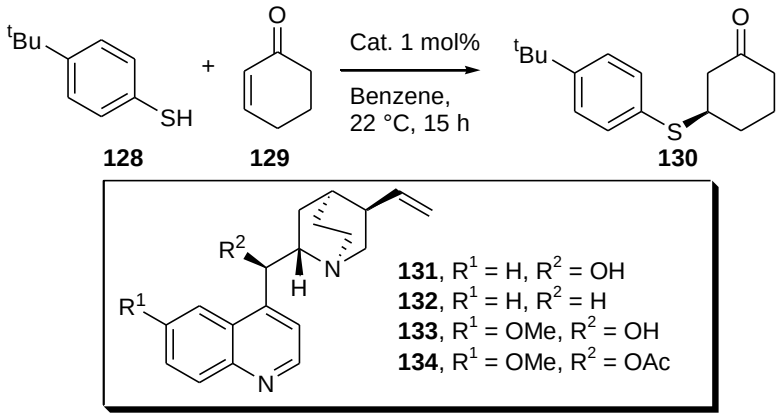


Catalyst	Yield /%	ee /%
Et_3N	17	-
125	14	35
Et_3N + **126**	57	-
127	86	93

Scheme 47: Effect of bifunctional catalysis on yield. Yield is improved when both acid and base are present, but best results are obtained when they are part of the same molecule.

One of earliest papers on bifunctional organocatalysis was published by Wynberg in 1981.[49] This study used cinchona alkaloid catalysts (**131**-**134**) to effect conjugate

addition between a thiol and an enone. The quinuclidine nitrogen of the catalyst deprotonates the thiol and initiates the reaction. In the case of catalysts **132** and **134**, the R^2 group is a non-acidic group, namely H or OAc, and the enantioselectivity was very poor (4% ee and 7% ee respectively). It was discovered that the reaction enantioselectivity was substantially higher when R^2 was OH, and thus able to hydrogen bond to the oxygen on the enone, 62% ee for **131** and 44% ee for **133**. This illustrates that bifunctional catalysis can have a beneficial effect on enantioselectivity as well as yield.



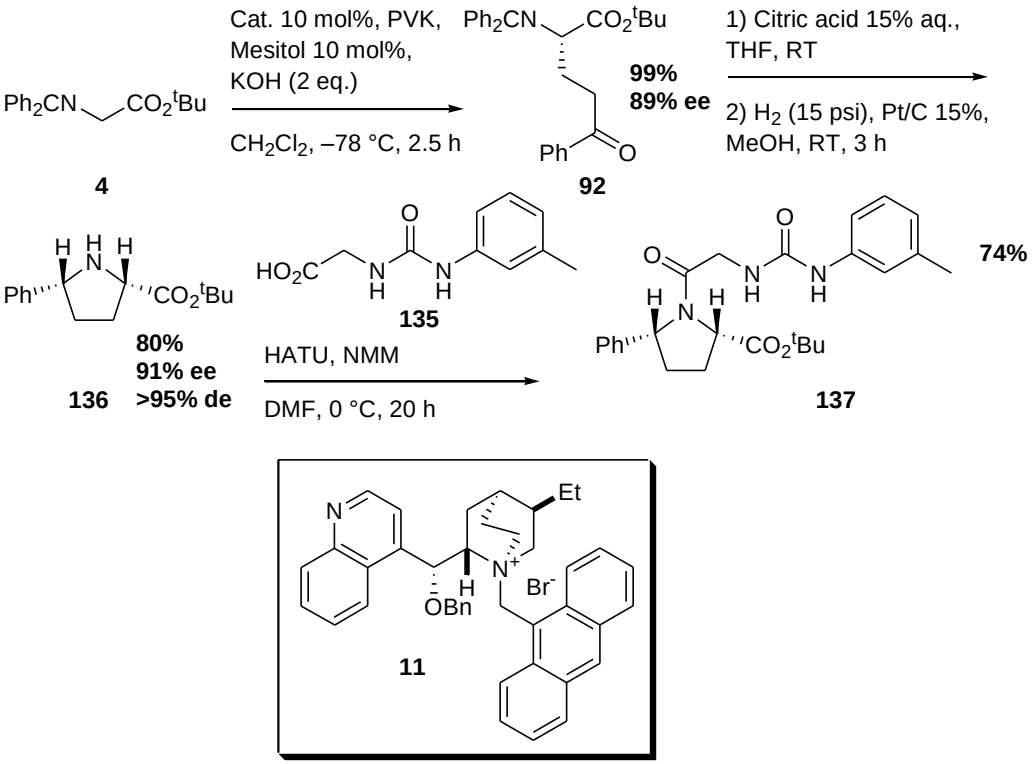
Catalyst	R^1	R^2	ee /%
131	H	OH	62
132	H	H	4
133	OMe	OH	44
134	OMe	OAc	7

Scheme 48: Effect of bifunctional catalysis on enantioselectivity; ee of the reaction is improved when there is an acidic moiety present.

3.2. Bifunctional Catalysts in the Michael Addition Reaction

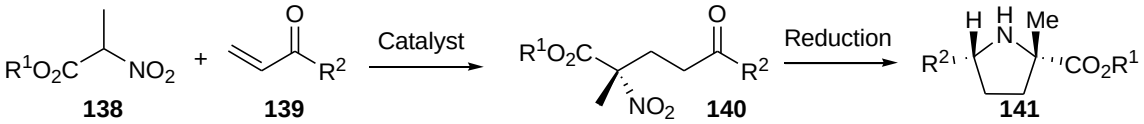
3.2.1. Previous Work in the Lygo Group

The work that precedes this project revolves around the syntheses of substituted pyrrolidine esters. Lygo[50] published a synthesis of cholecystokinin (CCK) antagonist (+)-RP 66803 **137** involving the use of phase transfer catalyst **11** (**Scheme 49**).



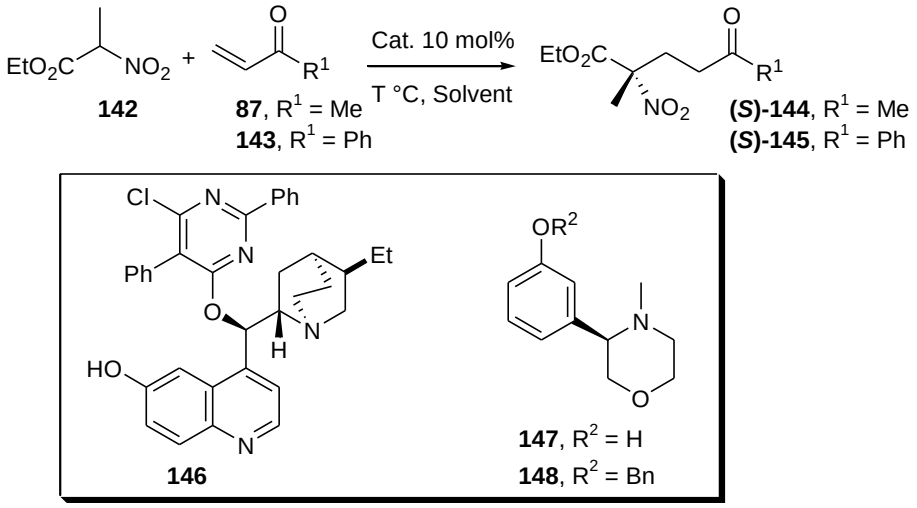
Scheme 49: Synthesis of CCK antagonist (+)-RP 66803 **137**.

Although this method is suitable for the synthesis of **137**, this chemistry cannot be universally applied to all other pyrrolidine syntheses. For example, this method does not readily allow for pyrrolidines with disubstitution at the 2-position, as the alpha carbon in the glycine imine **4** does not easily deprotonate once one substituent has already been added. A solution to this would be to use nitroesters, as these can be more easily disubstituted due to the higher acidity of the hydrogens (**Scheme 50**). This also eliminates the need for a strong base such as KOH and consequently, an aqueous phase, as the reaction can be effected by organic bases in an organic solvent and thus permitting bifunctional catalysis.



Scheme 50: Using Michael addition to synthesise pyrrolidines disubstituted at the 2-position (**141**).

This type of Michael addition was reported by Snider in 2006,[51] using Deng's catalyst **146** between ethyl nitropropionate and MVK (**Scheme 51**, entry 1) giving high yield (100%) and enantioselectivity (90%). This prompted research by the Lygo group to study Deng's catalyst in some more Michael additions and to synthesise alternative catalysts that were designed to mimic the structure of Deng's catalyst (**Scheme 51**).[52]



Catalyst	Vinyl Ketone	Solvent	Temp.	Time /h	Product	Conversion /%	ee /%
146	**87**	CH_2Cl_2	–20 °C	72	**144**	100	90
146	**87**	Toluene	RT	16	**144**	81	85
146	**143**	Toluene	RT	18	**145**	80	64
147	**87**	Toluene	RT	336	**144**	30	32
147	**143**	Toluene	RT	168	**145**	33	50
148	**143**	Toluene	RT	336	**145**	10	0
147	**143**	Neat	RT	3	**145**	90	26
148	**143**	Neat	RT	6	**145**	3	2

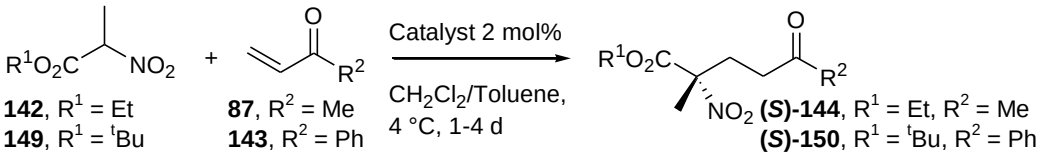
Scheme 51: Previous work from the Lygo group, plus the result from Snider for the use of chiral organocatalysts for Michael additions between ethyl nitropropionate and vinyl ketones.

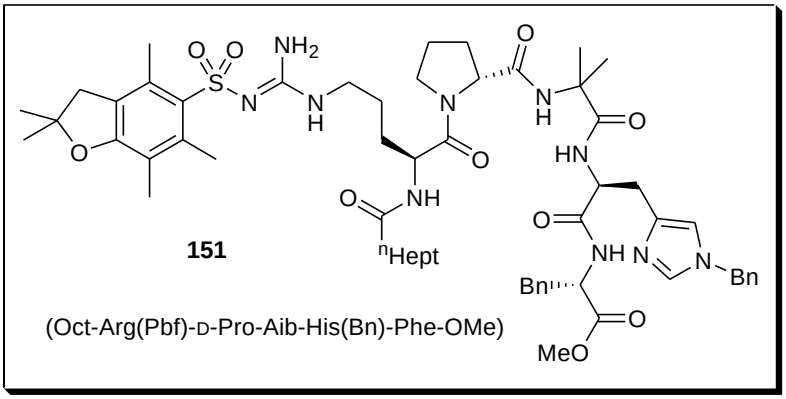
Deng's catalyst **146** gave good yields for the addition of ethyl nitropropionate to MVK **87** or PVK **143** (81% and 80% respectively) and moderate to good enantioselectivity (85% ee and 64% ee respectively). Catalyst **147** was synthesised and was able to effect these reactions, however, in lower yields and enantioselectivities. Performing the reaction in the absence of solvent gave high yield in a far shorter time period, but the enantioselectivity dropped considerably. However, it was clear that catalyst **147** was behaving bifunctionally – using **148** as an analogue with the OH group replaced with OBn saw the yield and enantioselectivity drop to virtually nothing when used under the same conditions.

Ultimately, catalyst **147** did not exceed the performance of Deng's catalyst. A problem with these types of catalysts is that the basic moiety cannot be modified easily as it is locked within the quinuclidine or morpholine ring. This established a precedent for the next project; to develop a new type of structure whose base can be easily changed in order to find one suited for effecting this type of reaction.

3.2.2. Michael Additions of α-Substituted Nitroesters

Since McLeod's research in the Lygo group, several more enantioselective Michael additions of α-substituted nitroesters have been published. In 2007, Linton attempted the same reactions using peptide catalysts (**Scheme 52**).[53] Peptide **151** was able to couple ethyl-2-nitropropionate **142** and MVK **87** to give **144** in high yield (96%) but the product was racemic. The reaction between *tert*-butyl-2-nitropropionate **149** and PVK **143** gave **150** in much greater enantioselectivity (50% ee).

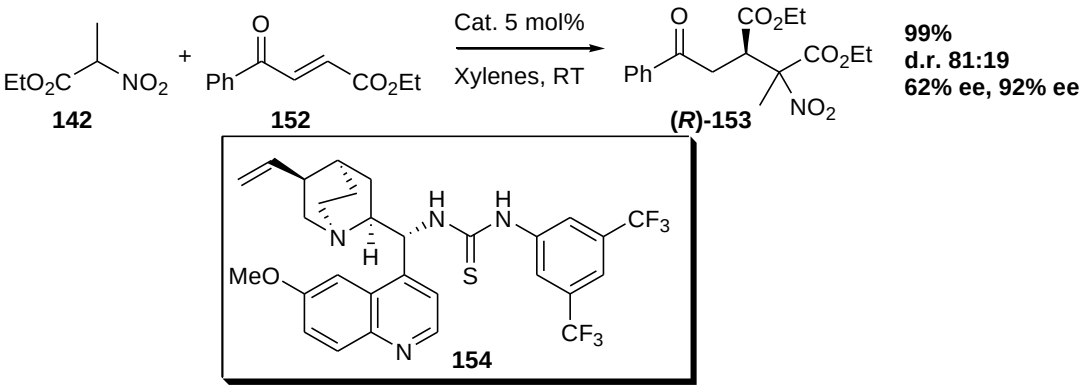




Nitroester	Vinyl Ketone	Product	Yield /%	ee /%
142	**87**	**144**	96	0
149	**143**	**150**	85	50

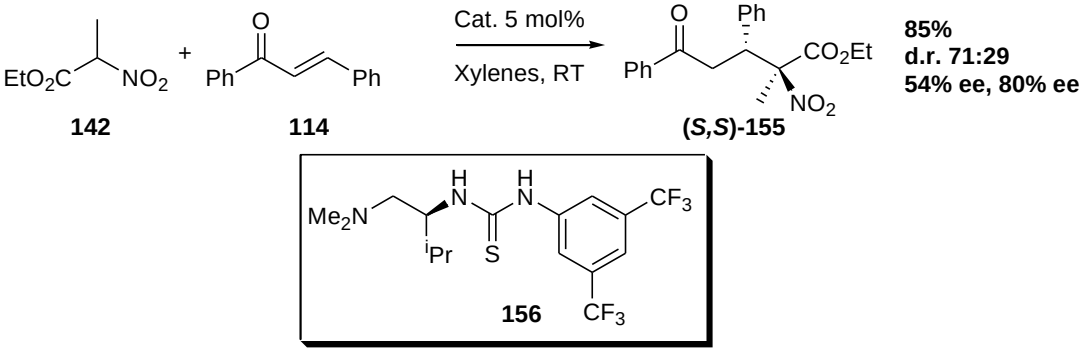
Scheme 52: Michael additions on α-substituted nitroesters using peptides by Linton.

In 2009, Xiao studied Michael additions between 4-oxoenoates and nitroalkanes (and nitroesters),[54a] the reaction between ethyl-2-nitropropionate and vinyl ketone **152** is shown in **Scheme 53**. The catalyst **154** is based on a cinchona alkaloid, but with the hydroxy group replaced by a more acidic thiourea moiety, this class of catalyst has been widely used in conjugate addition reactions.[54b] The product **153** was obtained in very high yield (99%), reasonable diastereoselectivity (d.r. 81:19) and moderate to high enantioselectivity for each diastereomer (62% ee and 92% ee).



Scheme 53: Michael addition on an α-substituted nitroester using a thiourea-substituted cinchona alkaloid by Xiao.

More recently, Pedrosa reported the Michael addition between ethyl-2-nitropropionate and chalcone using valine-derived catalyst **156** (**Scheme 54**).[55a] The same group had previously reported use of similar catalysts in the conjugate addition between ethyl nitroacetate and nitrostyrene, with successful results.[55b] Catalyst **156** gave product **155** in high yield (85%), fair diastereoselectivity (71:29) and mid to high enantioselectivity (54% ee and 80% ee).



Scheme 54: Michael addition on an α-substituted nitroester by Pedrosa.

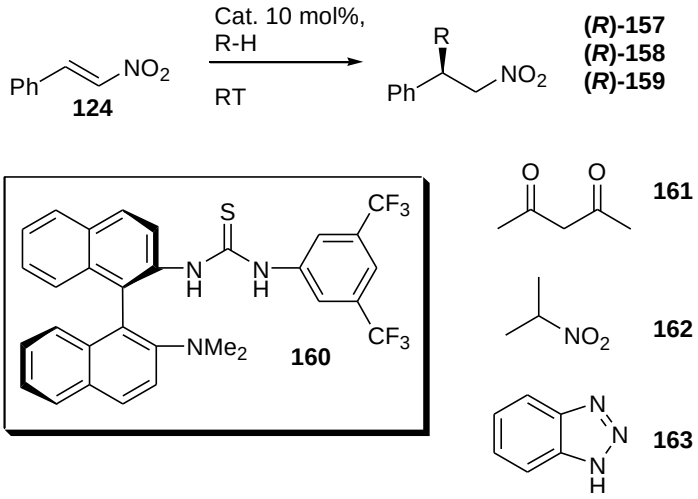
3.2.3. *Atropos* Biaryl Bifunctional Catalysts in Michael Addition Reactions

Bifunctional organocatalysts come in a range of structures, but there are common templates which are particularly prevalent, such as those derived from cinchona alkaloids, as shown in Wynberg's example and those derived from amino acids such as proline, which will be discussed in detail in Chapter 5.

Atropos biaryl templates are a popular choice for chiral bifunctional catalysts, as they are often derived from readily available starting materials (such as BINOL), their bulky size allows regulation of how reagents interact with one another, and there are multiple sites at which the template may be modified. Indeed, they have been referred to as a 'privileged' source of chirality.[56] Although the majority of these are ligands for metal-centred catalysts,[57] there are numerous examples of

biaryl templates being used in organocatalysis. A few examples of biaryl templates being used in Michael additions are shown here.

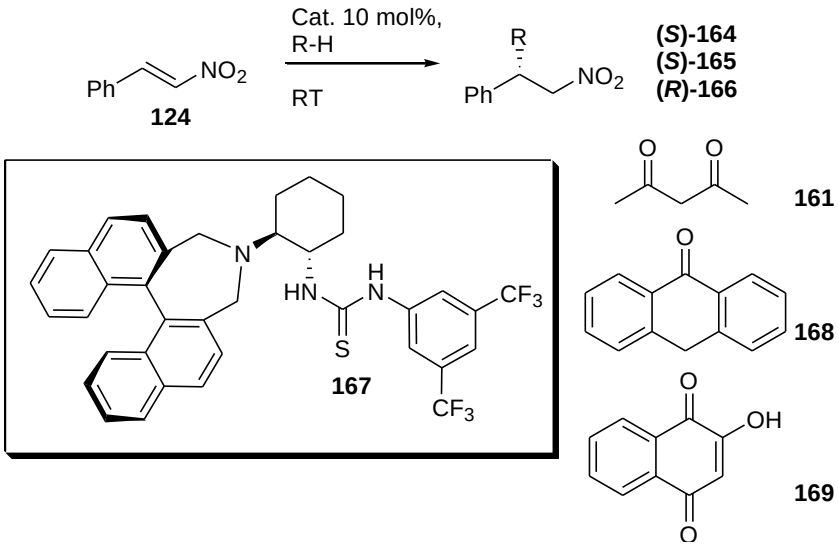
Scheme 55 shows work done by Wang using binaphthyl bifunctional organocatalyst **160**,[58] derived from 1,1'-binaphthyl-2,2'-diamine. One of the amine groups has been converted to a tertiary amine to enhance its basicity, while the other amine has been converted to a thiourea acidic moiety. This showed to be able to effect the Michael addition between acetylacetone **161** and (*E*)-nitrostyrene **124** and give very high yield and enantioselectivity (95%, 97% ee) in 5 hours. Other substrates did not perform as well however – further experiments using 2-nitropropane **162** gave poor yield and enantioselectivity (29%, 28% ee) and 1*H*-benzo[*d*][1,2,3]triazole **163** gave good yield but mediocre enantioselectivity (79%, 48% ee).



R-H	Solvent	Time /h	Product	Yield /%	ee /%
161	Et_2O	5	**157**	95	97
162	-	48	**158**	29	48
163	CH_2Cl_2	8	**159**	79	26

Scheme 55: Michael additions done by Wang using catalyst **160**.

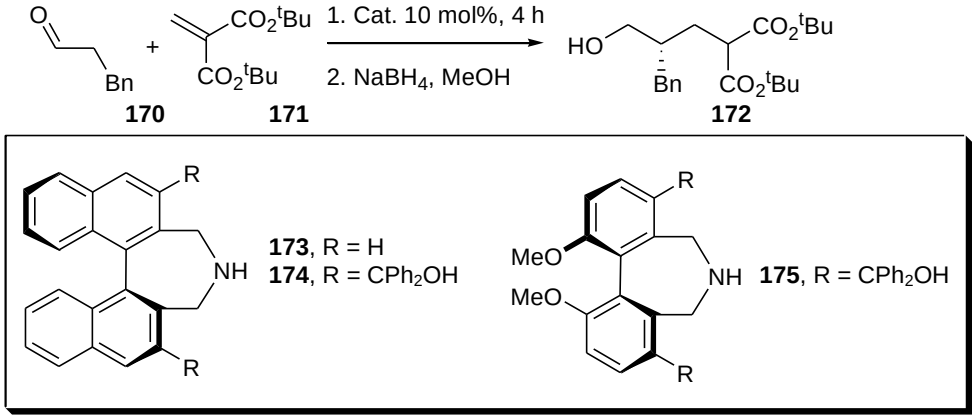
In 2008, Shao synthesised biaryl bifunctional catalyst **167** that contains two chiral carbon centres in addition to the axially chiral backbone (**Scheme 56**).[59] This was employed in the Michael addition between acetylacetone **161** and (*E*)-nitrostyrene **124**, giving product **164** in good yield and enantioselectivity (84%, 78% ee). Kim applied the same catalyst using anthrone **168** as the nucleophile – the yield and enantioselectivity were not as high (65%, 69% ee),[60] though they achieved better results when the thiourea was changed to a squaramide. When 2-hydroxy-1,4-naphthoquinone **169** was used as the nucleophile, a more impressive yield and enantioselectivity were obtained (92%, 99% ee).[61]



R-H	Solvent	Time /h	Product	Yield /%	ee /%
161	Toluene	16	**164**	84	78
168	Toluene	24	**165**	65	69
169	THF	2	**166**	92	99

Scheme 56: Michael additions that have used Shao's catalyst **167**.

Recently, Maruoka developed bifunctional biaryl catalysts that incorporate the acidic functionality onto the 3- and 3'-positions of the aryl rings.[62] Catalysts **174** and **175** both have hydroxydiphenylmethyl groups to act as acidic moieties and were used to effect the Michael addition between 3-phenypropanal **170** and di-*tert*-butylmethylenemalonate **171** (**Scheme 57**). The binaphthyl catalyst **174** gave very high yield and moderate enantioselectivity (99%, 68% ee) while the 2,2'-dimethoxydiphenyl catalyst **175** gave slightly poorer yield and slightly improved enantioselectivity (93%, 76% ee). These figures rose when the solvent was changed from THF to Et_2O and the temperature lowered to 0 °C (94%, 94% ee).



Catalyst	Solvent	Temp.	Yield /%	ee /%
173	THF	RT	0	-
174	THF	RT	99	68
175	THF	RT	93	76
175	Et_2O	0 °C	94	94

Scheme 57: Michael additions using bifunctional catalysts created by Maruoka.

3.2.4. Project Aims

This project aimed to expand the bifunctional organocatalyst library by synthesising new catalysts derived from compounds with an axially chiral biaryl backbone and two structures were envisaged (**Figure 5**). Compound **176** is formed by coupling isoquinoline and a substituted 2-methoxynaphthalene. The R group on the sulfonamide moiety should be easy to modify. Compound **177** is derived from BINOL, as this is a readily available starting material that can be substituted at numerous positions. The aim was to modify one of the OH groups into a carbon chain with a nitrogen base at the end. There are many possible variations for the length of the chain and the type of base, enabling fine tuning the structure to suit the reaction.

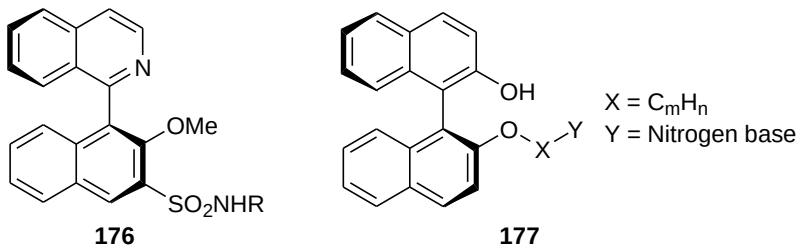


Figure 5: General structures for new catalysts. R, R' = alkyl, X = carbon chain of varying length.

Rotation about the aryl-aryl bond of binaphthol derivatives **177** is restricted due to steric hindrance, thus making these compounds chiral. It is not known whether **176** will be conformationally locked. However, the energy barrier for rotation should be sufficiently high; Chelucci reported that no racemisation was detected when similar

compounds were heated at 50 °C for 24 h,[63] and these catalysts should therefore be stable under the conditions that will be used. Computer modelling carried out in the group suggested that these compounds might fit well with the reaction transition state for the Michael addition reaction of nitroesters with MVK (**Figure 6**). The isoquinoline-derived catalyst **176** (R = Me) is interacting with ethyl-2-nitropropionate and MVK (left) and one variant of the BINOL-derived catalyst **177** (X = $-C_3H_6-$ and Y = 2-pyridinyl) interacting with dimethyl methylmalonate and MVK (right). In both cases, the catalyst can readily adopt a geometry that can hold the reactants in their preferred angle of approach, in theory promoting reaction.

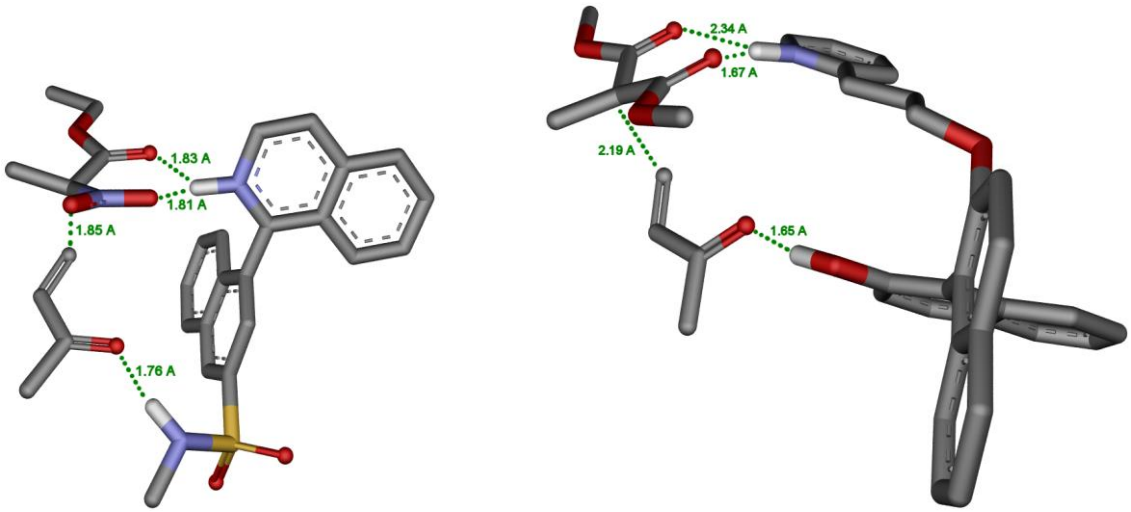
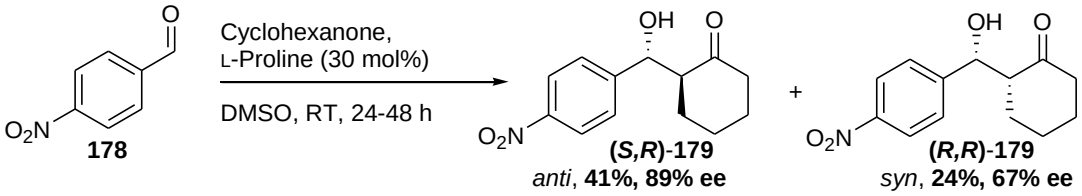


Figure 6: SPARTAN-modelled images of a) catalyst **176** promoting reaction between ethyl nitropropionate and MVK and b) catalyst **177** promoting reaction between dimethyl methylmalonate MVK.[19]

3.3. Proline-Derived Bifunctional Catalysts in an Aldol Reaction

3.3.1. Proline as a Bifunctional Catalyst

Proline and its derivatives have been used extensively in bifunctional asymmetric organocatalysis. In the 1970s, Hajos and Parrish,[64] as well as Eder, Sauer and Wiechert,[65] pioneered the use of proline in intramolecular aldol reactions and found that proline would give aldol products in high enantioselectivity. Barbas and List reported that L-proline could catalyse the intermolecular aldol reaction and give good enantioselectivity for such a simple molecule.[66] Barbas tested L-proline with further substrates, such as the reaction between 4-nitrobenzaldehyde and cyclohexanone (**Scheme 58**).[67]



Scheme 58: Aldol reaction using L-proline as the catalyst done by Barbas.

Extensive research has been undertaken by Barbas, List, Lerner, Bahmanyar and Houk to rationalise proline's ability to confer high enantioselectivity in the reactions it catalyses.[68] **Figure 7** shows the transition state that the reaction adopts proposed by Houk and List. The pyrrolidine ring forms an enamine with the ketone and the aldehyde associates with the carboxylic acid group with its R group held in an equatorial position.

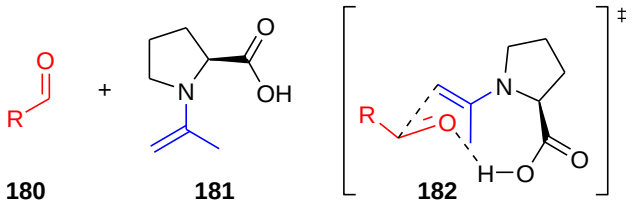
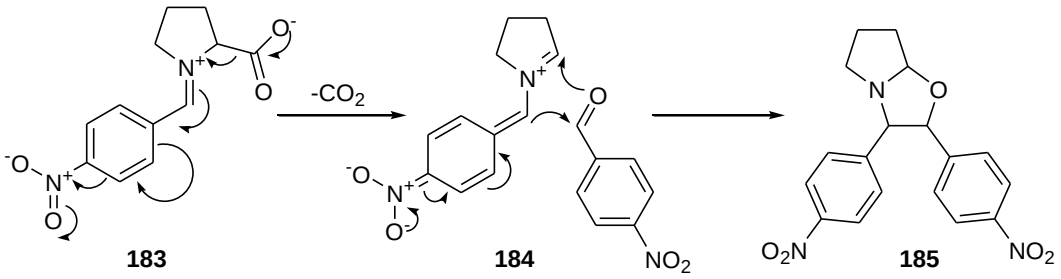


Figure 7: The Houk-List transition state of a proline-catalysed aldol reaction.

Although it is cheap, versatile and readily available, using L-proline as a catalyst for aldol reactions has numerous drawbacks. Firstly, it is insoluble in most organic solvents, and aldol reactions using proline are generally limited to using DMSO or DMF as solvents. Secondly, the yields are often stunted due to proline forming oxazolidine by-products,[69] eliminating one molecule of catalyst and two of the substrate (**Scheme 59**).

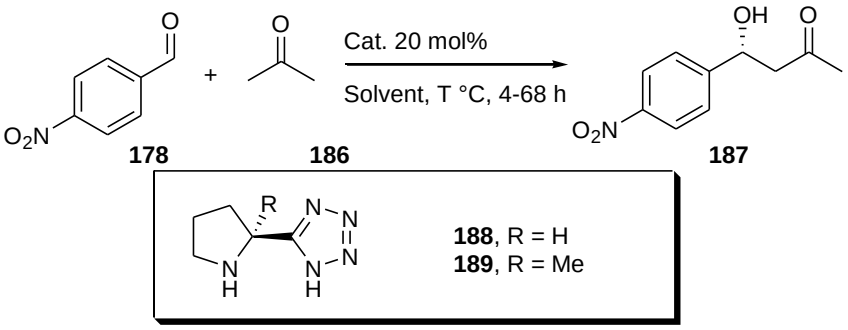


Scheme 59: Formation of oxazolidine by-products in proline-catalysed aldol reactions.

3.3.2. Proline Derivatives

A solution to the problems associated with using proline in aldol reactions is to derivatise the carboxylic acid side chain to another acidic group. In 2004, two research groups published the use of proline derivative **188**, which uses a tetrazole

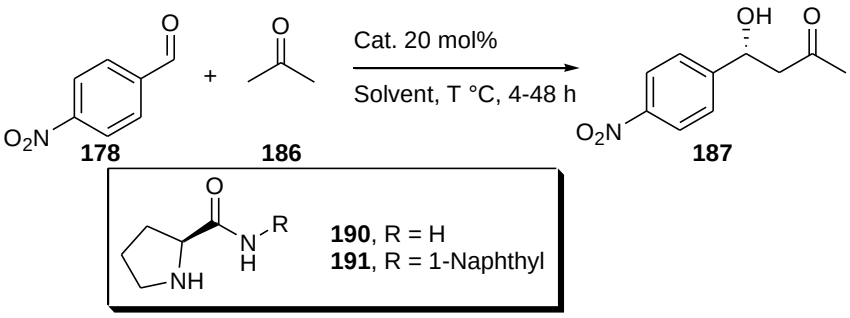
group as an acidic moiety, in aldol reactions. Yamamoto reported its use in the aldol reaction between ketones and trichloroalkanols,[70] while Hartikka reported its use with ketones and aldehydes (**Scheme 60**, entry 1).[71] He was able to obtain good yield and enantioselectivity (77%, 86% ee) in just 4 h, though it was necessary to cool the reaction to −50 °C. Brimble improved on this with related catalyst **189**,[69b] (88% ee) and performing the reaction at room temperature, though reaction time increased significantly. Importantly, no trace of oxazolidine by-products could be found in these reactions. More recent research has investigated aldol reactions with proline-tetrazole catalysts under continuous flow conditions.[72]



Catalyst	Solvent	Time /h	Temp.	Yield /%	ee /%
188	DMF	4	−50 °C	77	86
189	DMSO	68	RT	60	88

Scheme 60: Aldol reaction catalysed by tetrazole proline-derivatives.

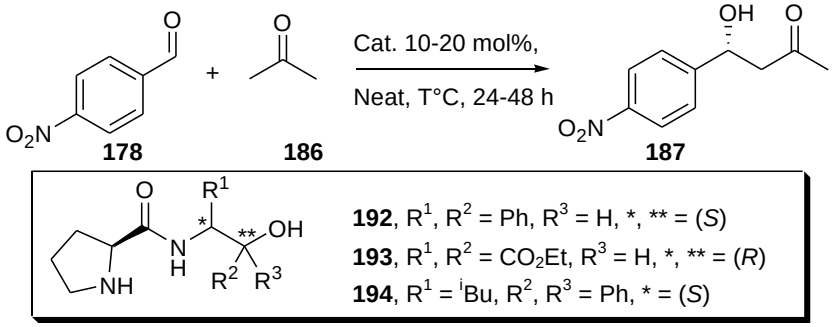
The most common functionality to replace the carboxylic acid in proline-derived catalysts are amides due to their ease of synthesis. However, prolinamides substituted with only a simple alkyl group are generally unsuitable for aldol reactions. Indeed Barbas used L-prolinamide **190** to catalyse the reaction between 4-nitrobenzaldehyde and acetone in DMSO and found it gave virtually no reaction.[67] However, much better results were obtained with the same compound by Gong and Wu when the reaction was done neat,[73a] (80% yield, 30% ee), but the limitations of this type of structure was shown as none of the alkyl-substituted prolinamides gave the aldol product with high enantioselectivity – the best results were with R = 1-naphthyl (**191**, 82% yield, 46% ee).



Catalyst	Solvent	Time /h	Temp. /°C	Yield /%	ee /%
190	DMSO	4	RT	< 10	-
190	Neat	24-48*	25	80	30
191	Neat	24-48*	25	82	46

Scheme 61: Aldol reaction catalysed by simple prolinamides. * More specific time not given.

Gong and Wu found that, however, prolinamides derived from 2-hydroxyamines give much better results.[73a,b] Catalyst **192** gave the aldol product in decent yield and high enantioselectivity (66%, 93% ee). Gong improved on this by replacing the Ph groups with CO_2Et groups to give **193** (62% yield, 99% ee).[73c] Singh's catalyst **194** was able to give slightly higher yield and the same enantioselectivity (70%, 99% ee) in a lower catalyst loading, though at −40 °C rather than −25 °C.[73d]



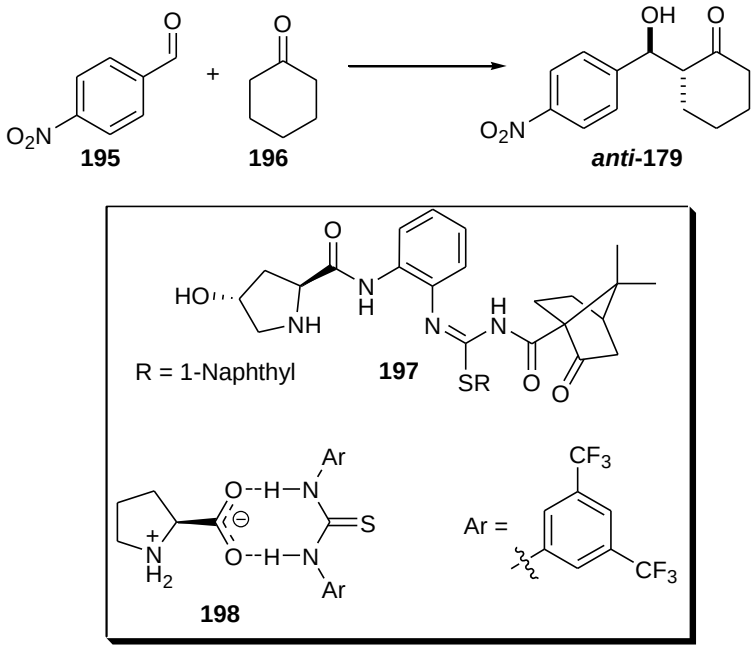
Catalyst	Amount /mol%	Temp. /°C	Yield /%	ee /%
192	20	−25	66	93
193	20	−25	62	99
194	10	−40	70	99

Scheme 62: Aldol reaction catalysed by 1,2-hydroxyamine-derived prolinamides.

The success of these catalysts appears to be as a result of the amide NH and the OH jointly coordinating to the aldehyde to give a lower energy transition state than the amide alone.[73a] Replacing NH with NMe or OH with OMe lowers the enantioselectivity, with the hydroxyl group showing the greater effect. It also appears that steric bulk and not stereochemistry at the carbon alpha to OH is what is important, as evidenced by catalyst **194**.

Interestingly, the $-C(Ar)_2OH$ structure that appears in many of these types of prolinamide catalyst is also used as the sole acidic moiety in prolinols. Prolinols (proline-derived catalysts with $-CR_2OH$ in place of the carboxylic acid) are common bifunctional catalysts, especially for Michael additions, though their application in aldol reactions is not as well studied.[74]

Recently, as with many bifunctional catalysts, there has been an interest in finding a means of using thiourea as the acid moiety in proline-derived catalysts, either by attaching it to a prolinamide or by using a thiourea as a co-catalyst to proline. Chen developed catalyst **197** which incorporates a camphor unit in addition to a thiourea moiety, which was able to catalyse the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone in very high yield, high diastereoselectivity and good enantioselectivity for the *anti*-diastereomer (99%, 89:11 *anti:syn*, 81% ee).[75] Demir reported that catalyst **198** could be generated by mixing proline and a thiourea in a 1:1 ratio.[76] Although the thiourea and the proline are not covalently bound, the combination effectively makes a bifunctional catalyst, allowing it to dissolve in non-polar solvents and catalyse the aldol reaction, giving the aldol product in high yield, diastereoselectivity and enantioselectivity for the *anti*-diastereomer (96%, 90:10 *anti:syn*, 97% ee). However, it is still possible for the oxazolidine by-product to form in these reactions.[77]



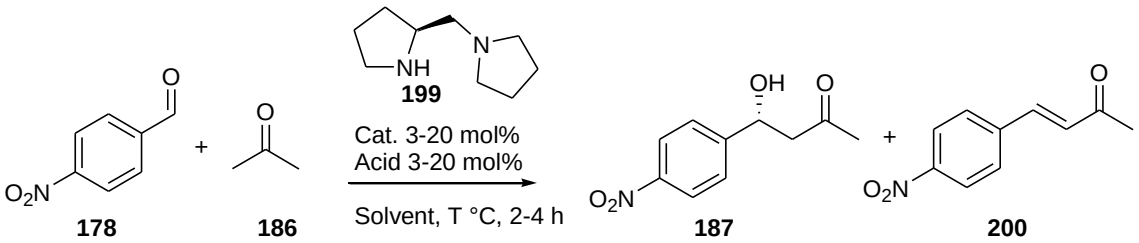
Catalyst	Amount /mol%	Solvent	Time /h	Yield /%	*anti:syn*	*anti* ee/%
197	20	H_2O	72	99	89:11	81
198	10	Hexane	16	96	90:10	97

Scheme 63: Aldol reaction catalysed by proline-derived catalysts containing thiourea groups.

3.3.3. Proline-Derived Diamines

This project will focus on prolines that have been derivatised to diamines. Although a proline-derived diamine usually has no acidic functionality, mixing the diamine with an acid (generally in a 1:1 ratio) causes one of the nitrogens to protonate, thus creating a bifunctional catalyst.

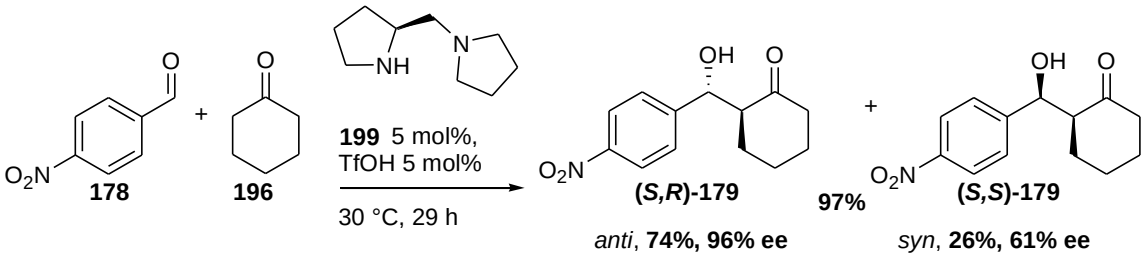
Barbas found that a stoichiometric mixture of (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine **199** with (+)-CSA,[67] could catalyse the aldol reaction between 4-nitrobenzaldehyde and acetone to give product **187** (41% yield, 81% ee) but that the condensation product **200** was the major product of this reaction (**Scheme 64**, entry 1). This work was expanded upon by Yamamoto who tested a range of diamine catalysts and a range of ketone and aldehydes.[78] He reported several observations for this aldol reaction; using catalyst **199** with TfOH as an acid in DMF gave poor yield of the aldol product (19%), with 4% of the condensation product present, but this increased to 51% when DMF was absent and the temperature was lowered by 10 °C (**Scheme 64**, entries 2 & 3).



Acid	Cat. + Acid /mol%	Solvent	Temp. /°C	Time /h	Yield of 187/%	ee /%	Yield of 200 /%
(+)-CSA	20	DMSO	RT	4	41	82	*
TfOH	3	DMF	40	2	19	83	4
TfOH	3	Neat	30	2	51	82	13

Scheme 64: Aldol reaction between 4-nitrobenzaldehyde and acetone using **199** as the catalyst. * Not given but will be in the range of 42-59%.

Yamamoto was able to produce the aldol product in very high yield (97%) for the reaction between 4-nitrobenzaldehyde and cyclohexanone, with reasonable diastereoselectivity (74:26 *anti:syn*) and acquired the *anti*-diastereomer with very high enantioselectivity (96% ee, **Scheme 65**). This showed that diamines could function well as catalysts in aldol reactions and paved the way for future research.



Scheme 65: Aldol reaction between 4-nitrobenzaldehyde and cyclohexanone using **199** as the catalyst.

3.3.4. Project Aims

Most proline-derived organocatalysts tend to be derived from L-proline, as this is about 100 times cheaper compared to D-proline.[79] As a result, if an asymmetric reaction produces one enantiomer of the product preferentially using a L-proline-derived catalyst, it would be much more costly to synthesise the opposite enantiomer of the product preferentially, as the opposite enantiomer of the catalyst would need to synthesised from D-proline.

It was noted, however, that most proline-derived diamine catalysts utilise the pyrrolidine nitrogen as the amine moiety by leaving it unsubstituted and utilise the side chain as the acidic moiety (**201**, **Figure 8**). There have been far fewer examples of catalysts that substitute the pyrrolidine nitrogen and use it as the acidic moiety while using the side chain as the free amine (**202**).

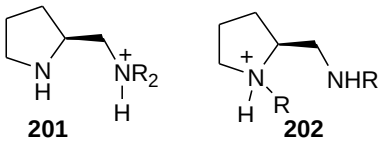
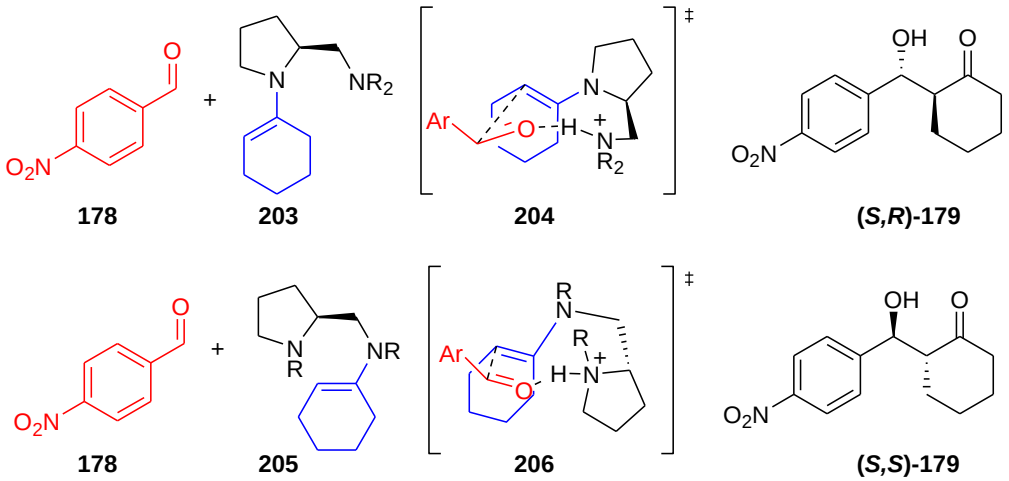


Figure 8: Changing the position of the substituents in proline-derived diamines should also change the preferential site of protonation.

Scheme 66 shows the Houk-List transition-like states resulting from using catalysts **201** and **202**. The more conventional catalyst type **201** will react with cyclohexanone to form enamine **203**, which undergo aldol reaction with 4-nitrobenzaldehyde. **204** shows the most favourable transition state and the stereochemistry of the resulting aldol product **(*S,R*)-179**. Computer modelling predicts that if the acid and base moieties of the catalyst are reversed, then the enantioselectivity should also be reversed.[19] A catalyst with structure such as **202** should form enamine **205** with cyclohexanone, and react with 4-nitrobenzaldehyde to give **206** as the transition state, which should give **(*S,S*)-179** as the product.



Scheme 66: Predicted effect of reversing the acid and base moieties in a proline-derived diamine catalyst on the enantioselectivity of an aldol reaction.

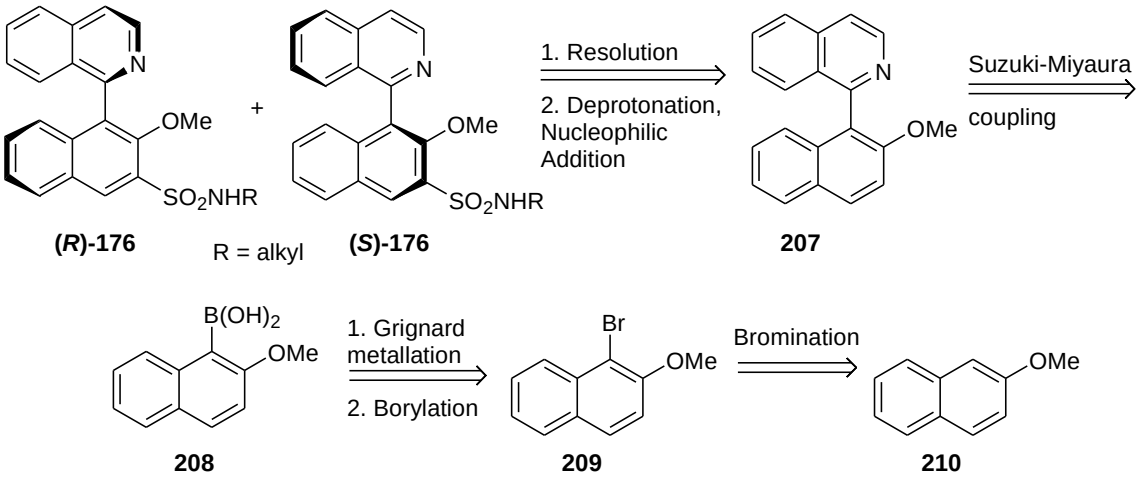
It was the aim of this project to design and synthesise catalysts that match the structure of **202** and to test them in the aldol reaction, and see whether the enantioselectivity of the product can be reversed using this method.

4. Synthesis and Use of Bifunctional Catalysts

4.1. Investigations on New Biaryl Bifunctional Catalysts

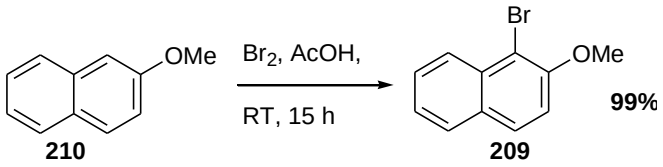
4.1.1. Catalysts Derived From Isoquinoline

A proposed route to potential catalyst **176** is shown in **Scheme 67**. It is a biaryl system made from coupling 2-methoxynaphthalene with chloroisoquinoline and then substituted with a sulfonamide group.



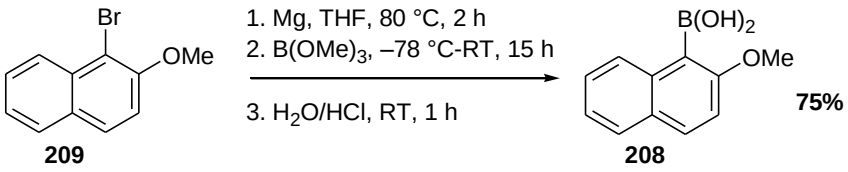
Scheme 67: Initial synthetic design for the isoquinoline-derived catalyst.

The bromination step was performed according to the methodology described by Brown,[80] which gave an excellent yield (**Scheme 68**).



Scheme 68: Bromination of 2-methoxynaphthalene.

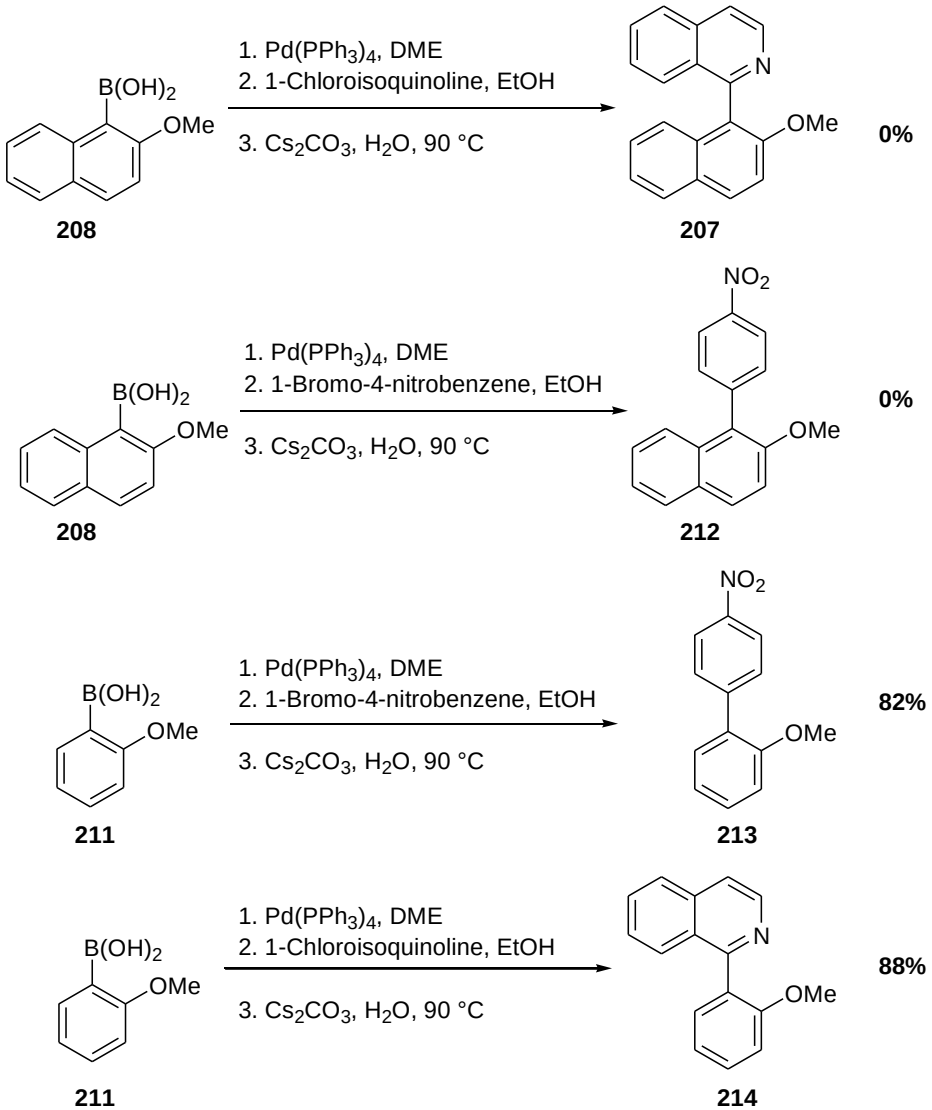
The second step was more troublesome. The Grignard reaction was difficult to initiate by the method described by Brown,[80] which required that the magnesium granules be activated mechanically by stirring under an atmosphere of argon. Periodic heating and addition of iodine did not successfully initiate the reaction either. The most successful method by far was heating the magnesium granules at reflux in THF under an argon atmosphere for one hour and gradually adding a solution of 1-bromo-2-methoxynaphthalene at reflux temperature. Following addition of trimethylborate at −78 °C, and acidic workup, boronic acid **208** was isolated in good yield (75%, **Scheme 69**).



209 **208**

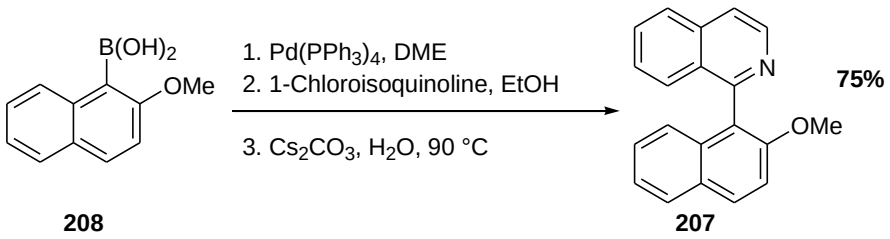
Scheme 69: Borylation of 1-bromo-2-methoxynaphthalene.

The following step, a Suzuki-Miyaura coupling following the methods described by Brown, did not yield any of the intended product on the first few attempts. The most prominent peaks on the mass spectrum were *m/z* = 257 and 279, which were likely to be self coupled isoquinoline ($C_{18}H_{12}N_2$ + H^+ and $C_{18}H_{12}N_2$ + Na^+ respectively). In order to identify the problem, three extra Suzuki-Miyaura couplings were tried; one with an alternative boronic acid, one using an alternative halide and one between both alterations (**Scheme 70**).



Scheme 70: Suzuki-Miyaura couplings used to isolate the problem with the intended reaction.

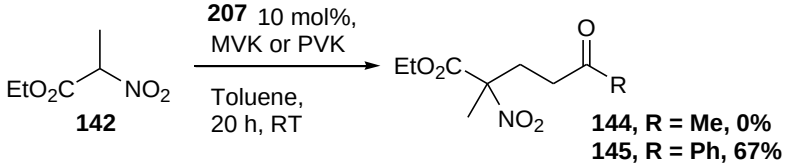
It was apparent from these results that the catalyst, the reaction conditions and the 1-chloroisoquinoline were not what was troubling the coupling and that the problem lay in the 2-methoxynaphthylboronic acid. Reports show that even a small amount of hydrochloric acid present in the boronic acid can prevent a successful coupling from occurring.[81] The purification method used previously was to dissolve the crude product **208** in CH_2Cl_2 and wash with water. In order to optimise the purification, column chromatography on silica gel (ethyl acetate: petroleum ether 4:1) was added. The subsequent Suzuki-Miyaura coupling gave the intended product in good yield (**Scheme 71**).



208 **207**

Scheme 71: Successful Suzuki-Miyaura coupling using purified 2-methoxynaphthylboronic acid.

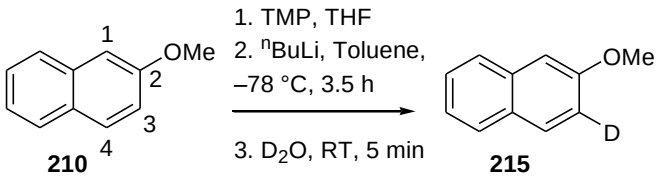
The product was then used as a benchmark for the efficacy of catalysts derived from it. It was first tested in a Michael addition reaction between ethyl-2-nitropropionate **142** and both MVK and PVK (**Scheme 72**).



Scheme 72: Use of **207** to promote Michael addition of ethyl-2-nitropropionate.

When MVK was used as the Michael acceptor, no reaction was observed. However, when PVK was used, the desired product was obtained in a 67% yield. This result is unexpected as MVK is normally more reactive than PVK, but these results do suggest that catalysts based on structure **207** may have some potential.

The next stage of this study was to investigate methods for the introduction of the sulfonamide substituent required in structure **176**. This required activation of the C-3 position of the naphthyl ring. To examine whether this was viable, we first examined deprotonation of the 2-methoxynaphthalene **210** (**Scheme 73**).



210 **215**

Scheme 73: Selective deprotonation of 2-methoxynaphthalene.

The ^{1}H NMR spectroscopic data of the product **215** shows that the intended site had indeed been deprotonated, however the reaction was incomplete after 3.5 hours (**Figure 9**).

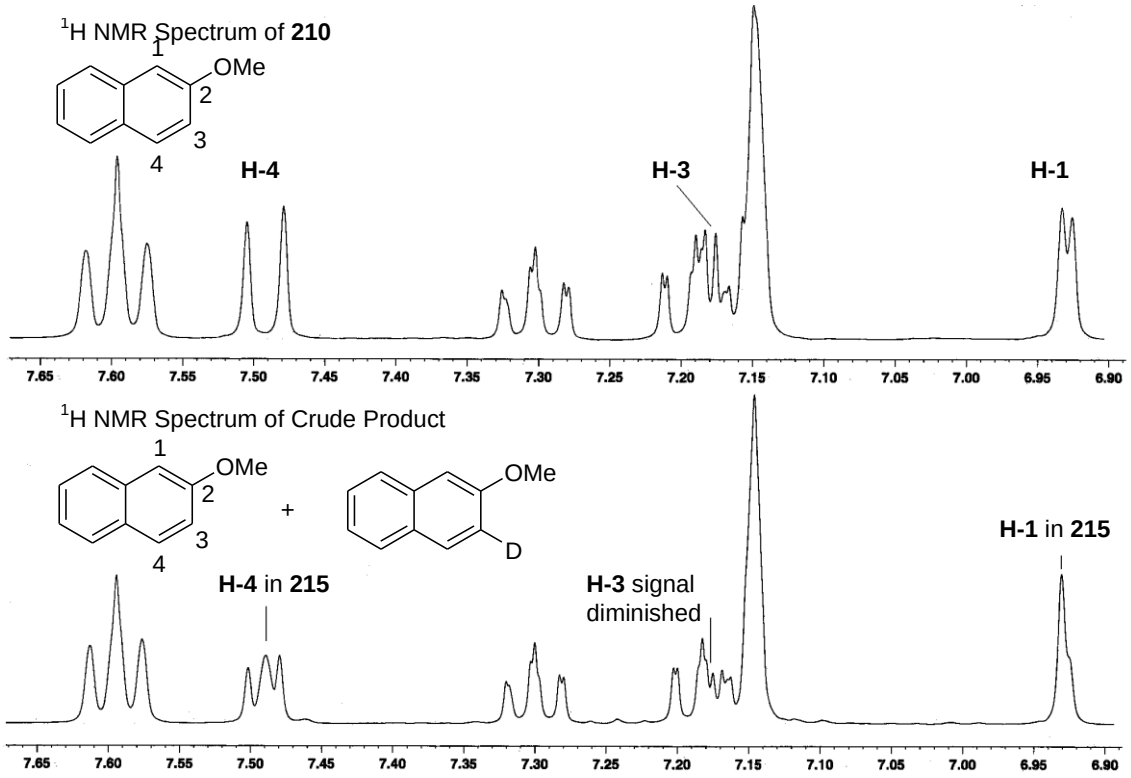
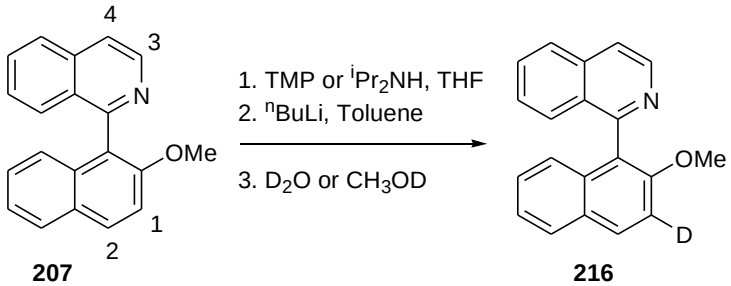


Figure 9: ^{1}H NMR data (in C_6D_6) for 2-methoxynaphthalene (top) and the partially deuterated 2-methoxynaphthalene (bottom). The doublet representing hydrogen 3 has decreased in intensity and the doublets representing the proximal hydrogens 1 and 4 are gradually being replaced by singlets.

The ^{1}H NMR spectra of 2-methoxynaphthalene indicates that the base was selectively deprotonating the intended carbon, suggesting that it may be possible with to deprotonate 1-(2-methoxy-1-naphthyl)isoquinoline at the required site (**Scheme 74**). The deuteration on substrate **207** was thus tried over a range of conditions; variation of base, variation of amount of base, temperature at which the deprotonation took place, temperature at which the quenching took place and whether D_2O or CH_3OD was used (CH_3OD was always used for quenching when the reaction took place at sub-zero temperatures).



207 **216**

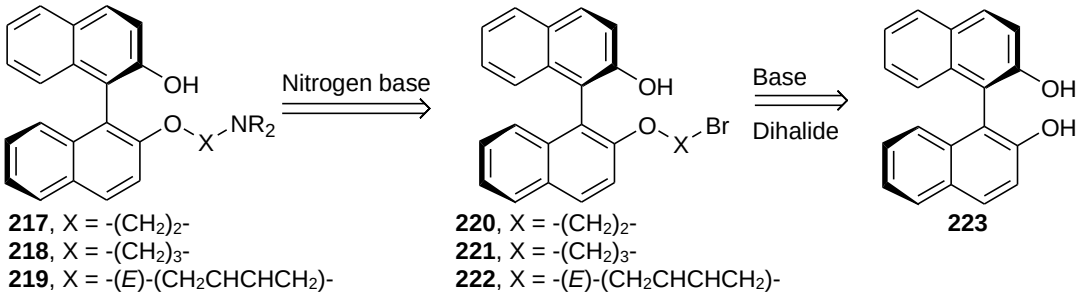
Base	Base Equivalents	Reaction Temp.	Reaction Time /h	Quench Temp.	Quench Solvent	Site of Deprotonation
LiTMP	1.5	−78 °C	3.5	RT	D_2O	-
LiTMP	5	−78 °C	3.5	RT	D_2O	3
LiTMP	10	−78 °C	3.5	RT	D_2O	3, 2, 4
LiTMP	10	−78 °C	6	−78 °C	CH_3OD	-
LiTMP	5	−30 °C	3	−30 °C	CH_3OD	-
LiTMP	5	RT	4	RT	D_2O	-
LDA	10	RT	4	RT	D_2O	3
LDA	10	RT	24	RT	D_2O	-
LDA	10	RT	24	RT	CH_3OD	-
LiTMP	10	RT	2	−78 °C	CH_3OD	3, 2, 4

Scheme 74: Attempts at selective deprotonation of 2-methoxynaphthalene.

It appears that the intended site is not the most favoured for deprotonation (perhaps unsurprisingly, the site next to the nitrogen is favoured; the pK_a of hydrogens in an isoquinoline ring are expected to be lower than the hydrogens in a methoxy-substituted ring)[82] and even the sites that do deprotonate only do so in small amounts. As this approach was not giving the desired product, the synthesis was halted at this stage and no further investigation was taken.

4.1.2. BINOL-Derived Catalysts Synthesised Using Alkyl Dihalides and Amines

In the previous chapter (section **3.2**) we outlined that binaphthol-derived structures such as **217**-**219** may have potential as catalysts for asymmetric Michael additions. As these appeared straightforward to synthesise, we next turned our attention to these systems. It should be possible to synthesise **217**-**219** in just two steps from (*R*)-BINOL **223** (**Scheme 75**). Nucleophilic substitution of halides **220**-**222** with a nitrogen base should form the amine catalysts, the halides can be formed directly from BINOL **223** with a base and the appropriate alkyl dihalide.



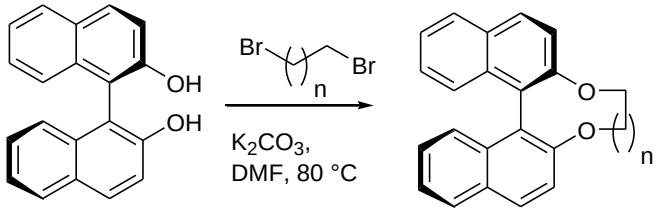
217, X = -$(CH_2)_2$-
218, X = -$(CH_2)_3$-
219, X = -(*E*)-$(CH_2CHCHCH_2)$-

220, X = -$(CH_2)_2$-
221, X = -$(CH_2)_3$-
222, X = -(*E*)-$(CH_2CHCHCH_2)$-

223

Scheme 75: Initial synthetic design of a BINOL-derived catalyst.

Reacting (*R)*-BINOL with an alkyl dihalide and strong base appeared to be the simplest and most direct route to synthesis of **217**-**219**. Although this method has been reported for synthesising cyclic products (**224** and **225**, **Scheme 76**),[83] it was hoped that with careful adjustment of the reaction conditions, the reaction could be made to favour formation of the desired compounds.

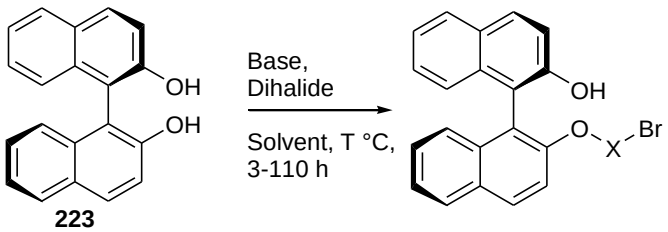


223

224, n = 1, **63%**
225, n = 2, **77%**

Scheme 76: Cyclic products that result from reacting (*R*)-BINOL directly with dibromoethane (**224**) and dibromopropane (**225**). Time of reaction not given in the report.

(*R*)-BINOL was reacted with the alkyl dihalide reagents in the hope of forming mono-alkylated derivatives (**Scheme 77**).



223

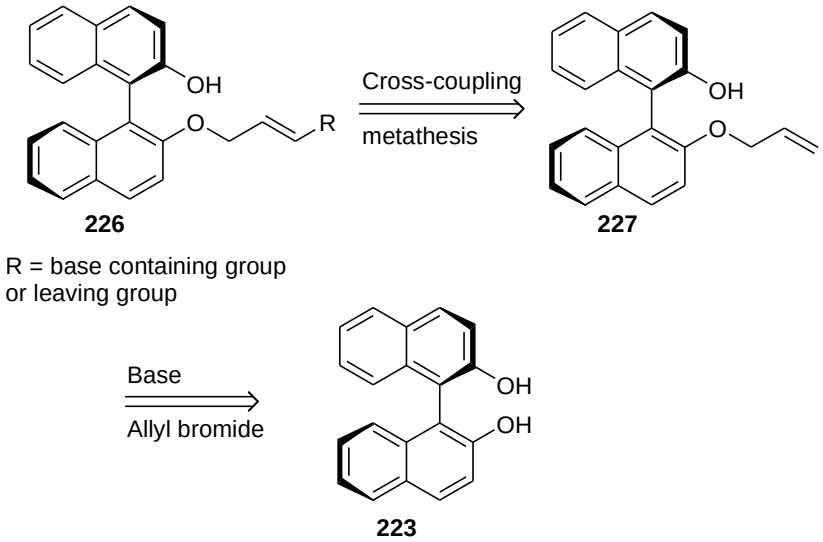
220, X = -$(CH_2)_2$-
221, X = -$(CH_2)_3$-
222, X = -(*E*)-$(CH_2CHCHCH_2)$-

Dihalide	Base	Solvent	Temp. /°C	Time /h	Product	Yield /%	By-product Yield /%
1,2-Dibromoethane	^{t}BuOK	THF	66	14	**220**	<5	20
1,3-Dibromopropane	K_2CO_3	Acetone	56	3	**221**	15	48
1,3-Dibromopropane	^{t}BuOK	THF	RT	15	**221**	0	11
1,3-Dibromopropane	NaH	THF	RT	110	**221**	<5	<5
1,3-Dibromopropane	^{t}BuOK	THF	40	15	**221**	14	55
(*E*)-1,4-Dibromobut-2-ene	^{t}BuOK	THF	66	15	**222**	9	0

Scheme 77: Attempts at monosubstituting a BINOL hydroxyl group with an alkyl dihalide.

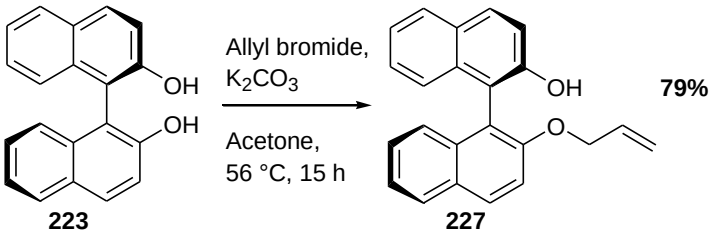
However, formation of cyclic by-products **224** and **225** was favoured and yields of the desired products did not exceed 15%. Even with (*E*)-1,4-dibromobut-2-ene, an alkyl dihalide that cannot cyclise, the yield of the intended product was only 9%.

A second strategy was devised in which allyl bromide would substitute one OH group on (*R*)-BINOL to give **227** (**Scheme 78**). There is no risk of cyclisation, but disubstitution could occur, which may be controlled with stoichiometry of reagents. An alkene-containing group (bromide or amine) could then be attached *via* cross-coupling metathesis to give **226**.



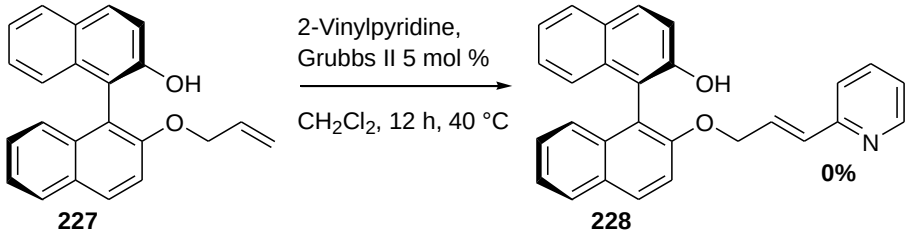
Scheme 78: Approach to BINOL-derived catalysts, using cross-coupling metathesis.

The first step, reaction between (*R*)-BINOL and allyl bromide, was far more successful than those with the alkyl dihalides, giving the mono-substituted BINOL as the major product in a 79% yield (**Scheme 79**).



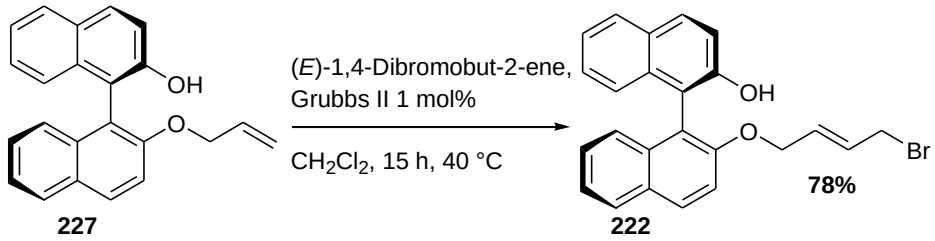
Scheme 79: Mono-*O*-alkylation of (*R*)-BINOL hydroxyl group with allyl bromide.

The cross-coupling metathesis followed the methodology described by Grubbs (**Scheme 80**).[84] It was initially hoped that a vinyl pyridine could be directly coupled to the *O*-allyl-(*R*)-BINOL **227**, as this would be a short route to a catalyst. However, when the coupling was performed with 2-vinyl pyridine, no product was detected.



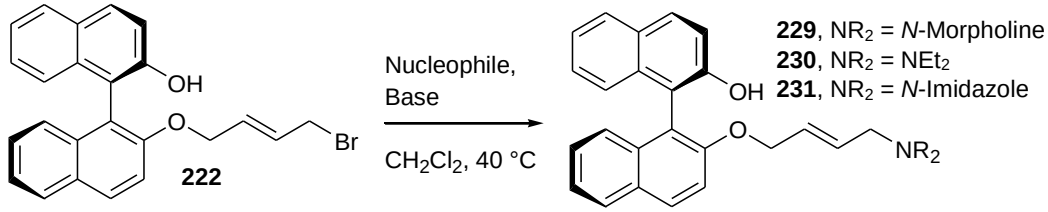
Scheme 80: Cross-coupling of **227** with 2-vinylpyridine.

On the other hand, the cross-coupling reaction between *O*-allyl-(*R*)-BINOL and (*E*)-1,4-dibromobut-2-ene gave **222** in a 78% yield (**Scheme 81**). This yield is consistent with expectations for cross-coupling between these two alkene types.[85] It was found that even with only 1 mol% Grubbs II loading, the reaction showed no drop in efficiency over the given time period.



Scheme 81: Cross-coupling of **227** with (*E*)-1,4-dibromobut-2-ene.

Finally, bromide **222** was reacted with a series of *N*-nucleophiles in order to form amines **229**-**231** (**Scheme 82**). The use of triethylamine as the base in these reactions led to a large amount of by-product where triethylamine itself has displaced the bromine. This problem was circumvented by using diisopropylethylamine as the base. Even with this modification, products **229**-**231** were formed in fairly low yields.

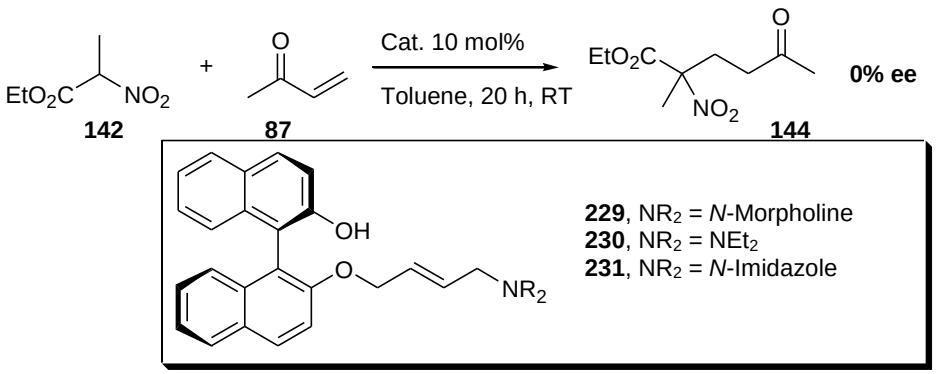


Nucleophile	Time /h	Base	Product	Yield /%
Morpholine	1	Et_3N	**229**	33
Morpholine	1	$^{i}Pr_2EtN$	**229**	59
Et_2NH	1	$^{i}Pr_2EtN$	**230**	25
Imidazole	15	$^{i}Pr_2EtN$	**231**	26

Scheme 82: Preparation of **229**-**231**.

These catalysts were then tested in the same Michael addition reaction as before. As shown in **Scheme 83**, the efficiency of the catalysts varied, (although possible

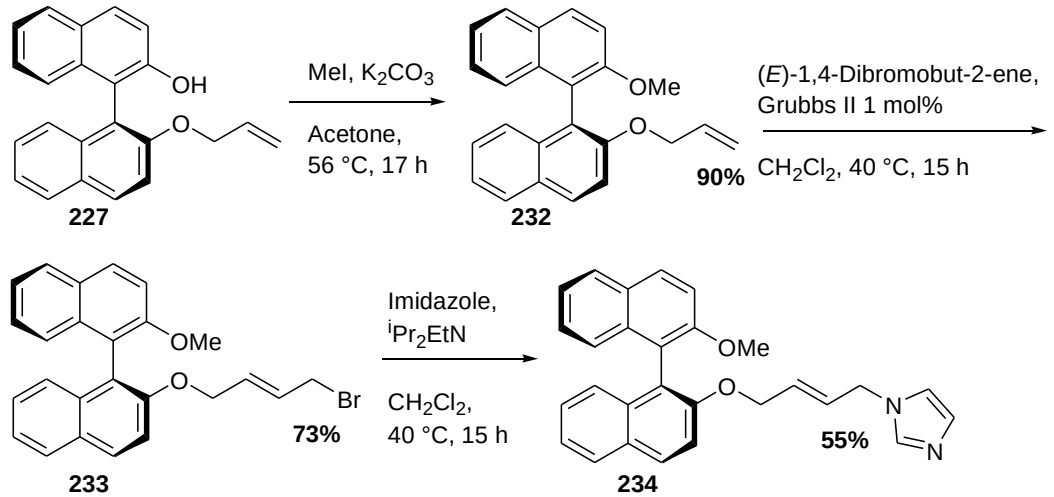
evaporation of volatile MVK might also play a role). It is apparent however that none of these catalysts perform the reaction enantioselectively.



Catalyst	Yield /%
229	37
230	2
231	99

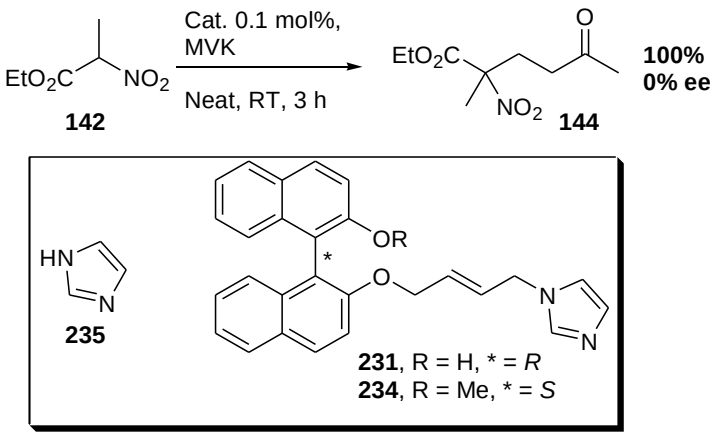
Scheme 83: Efficacy of the bifunctional catalysts in the Michael addition reaction.

In order to see if there was any evidence of this compound behaving as a bifunctional catalyst a derivative of **231** was synthesised with the free hydroxyl protected with a methyl group (**234**, **Scheme 84**). If catalyst **231** is behaving as a bifunctional catalyst, there should be a reduction in reaction rate when **234** is used, as there is no longer an acidic functionality in the molecule.



Scheme 84: Synthesis of **234**. Due to availability of starting materials, **227** was derived from (*S*)-BINOL rather than (*R*)-BINOL.

Initial studies using **231** and **234** in the Michael addition of MVK to ethyl-2-nitropropionate established that both catalysts were able to take the reaction to completion in less than one hour. Given that these catalysts are very efficient at catalysing the reaction, we reduced their loading from 10 mol% to 0.1 mol%.

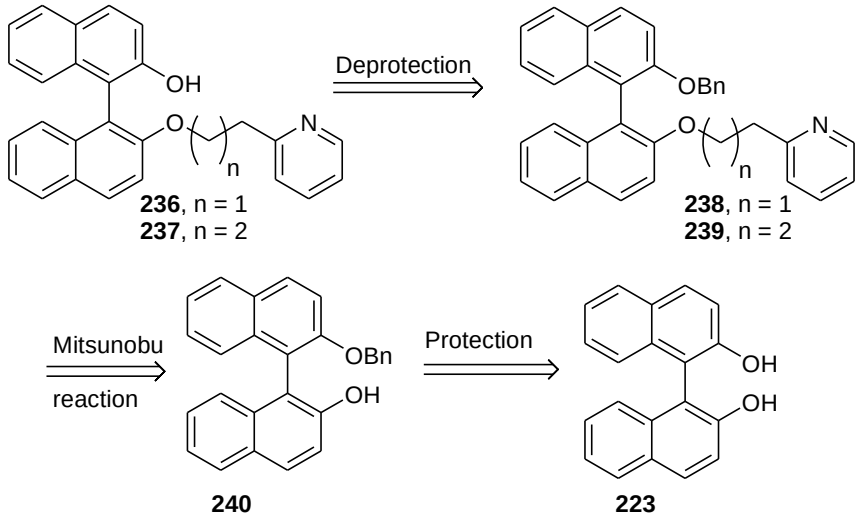


Scheme 85: Efficacy of **231** and its analogues in a Michael addition reaction.

Both **231** and **234** gave full conversion in 3 h with just 0.1 mol% loading. We also ran the reaction with 0.1 mol% imidazole and again the reaction was complete within 3 h. Given that catalyst **231** did not outperform the two non-bifunctional analogues, this suggests that the free hydroxyl does not actively participate in the reaction. This may be due to the relative rigidity and length of the but-2-ene side chain – the catalyst simply may not be able to adopt the necessary conformation in the transition state to involve the hydroxyl group. Therefore, we moved on to the examine compounds with shorter, more flexible side chains in the hope that these would perform better.

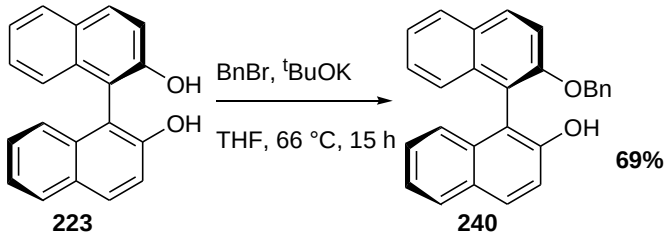
4.1.3. BINOL-Derived Catalysts Synthesised Using the Mitsunobu Reaction

Takeda Pharmaceutical Company patented a procedure to perform Mitsunobu coupling between 2-pyridine-propanol and a phenol derivative,[86] therefore a synthetic route was envisioned, based on a pyridine-alcohol coupling with BINOL (**Scheme 86**). One of the OH groups on BINOL would be protected to give **240**, leaving the other OH free to react. This could then be coupled with a pyridine alcohol using the Mitsunobu reaction to give **238**/**239**. Finally, the benzyl protecting group could be removed to give **236**/**237**.



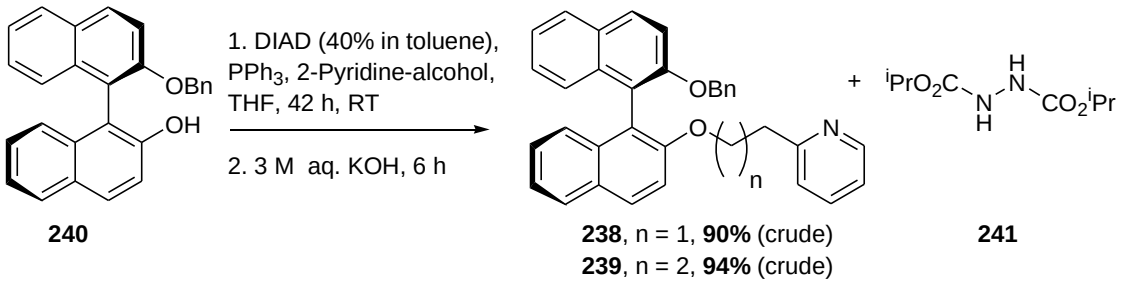
Scheme 86: Initial synthetic design of an alkyl-pyridine-substituted BINOL catalyst.

Both (*R*)- and (*S*)-BINOL were used in the syntheses of the catalysts. Protection of BINOL with benzyl bromide was straightforward and gave the benzylated derivative **240** in 69% yield (**Scheme 87**).



Scheme 87: Mono-protection of BINOL with a benzyl group.

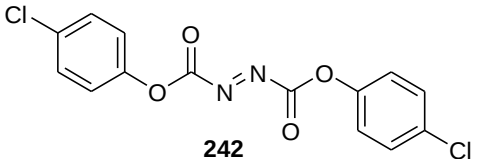
Coupling the 2'-(benzyloxy)-[1,1']-binaphthalenyl-2-ol **240** to the pyridine-alcohol was achieved using Mitsunobu chemistry outlined by Yasuma (**Scheme 88**),[86] however, DIAD was used in place of DEAD, for safety reasons.



Scheme 88: Mitsunobu coupling between benzyl-BINOL and pyridine-alcohols using DIAD.

Although the reaction consistently gives high yields, purifying the products proved to be very difficult due to multiple by-products, a common problem in Mitsunobu chemistry.[87] The concentration of the major by-product, diisopropyl hydrazinedicarboxylate **241**, can be reduced by heating the crude mixture in an aqueous solution of KOH (3 M) for six hours but this procedure does not fully

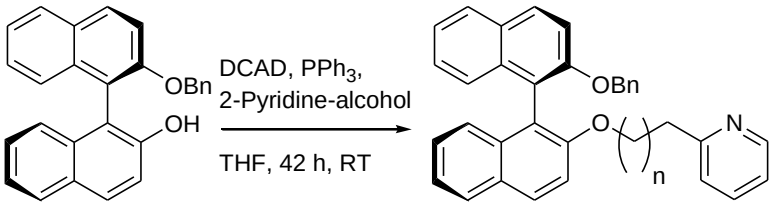
eliminate it. In an effort to solve this problem, Lipshutz reported a coupling agent DCAD, di-(4-chlorophenyl)azodicarboxylate **242**, (**Figure 10**),[88] whose hydrazine by-product can be easily removed from a Mitsunobu reaction by column chromatography on silica gel. He also demonstrated that this by-product could be readily converted back into DCAD for further use.



242

Figure 10: Di-(4-chlorophenyl)azodicarboxylate (DCAD).

The Mitsunobu couplings were repeated using DCAD and despite obtaining lower yields (61/64% compared to 90/94% using DIAD), the products were successfully purified with no trace of by-product.

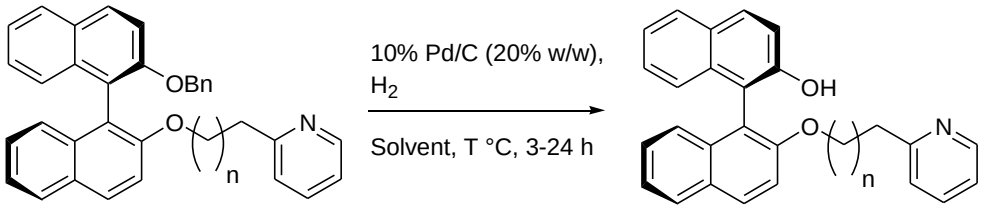


240

238, n = 1, **64%**
239, n = 2, **61%**

Scheme 89: Mitsunobu coupling between 2'-(benzyloxy)-[1,1']-binaphthalenyl-2-ol **240** and pyridine-alcohols using DCAD.

Compounds **238** and **239** can be used as catalysts themselves, though they should not demonstrate a bifunctional effect. These compounds were then subjected to hydrogenation to give compounds **236** and **237** (**Scheme 90**).



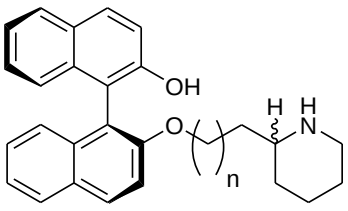
238, n = 1
239, n = 2

236, n = 1
237, n = 2

n	Time /h	Temperature /°C	Solvent	Pressure /psi	Yield of 236 or 237/%
1	3	RT	MeOH	14	0
2	3	RT	MeOH	14	0
1	18	RT	EtOH	14	0
2	18	RT	EtOH	14	0
2	18	RT	EtOH	200	9
2	18	50	EtOH	200	34
2	24	50	THF	200	19
1	15	50	THF	750	*
2	15	50	THF	800	*

Scheme 90: Yields of the hydrogenation of **238** and **239**. * Yields of **236**/**237** not determined – see discussion. Also, the (*S*)-enantiomers of **238** and **239** were used for this reaction.

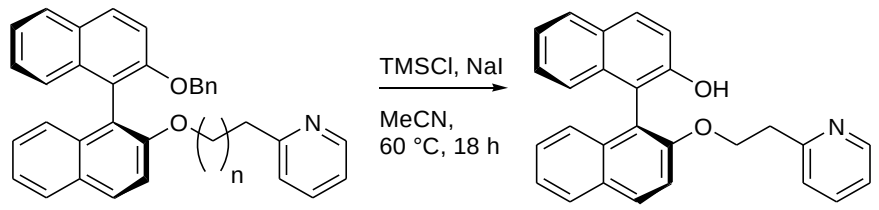
Removal of the benzyl group by hydrogenolysis proved difficult. At low hydrogen pressures no reaction was observed (entries 1-4) and at high pressures (>200 psi), hydrogenation of the pyridine ring occurred. At medium pressures, products **236**/**237** were only obtainable in low yields due to slow reaction (entries 5-7). At higher pressures, over-reaction occurred and products **236**/**237** could not be separated from the by-products *via* column chromatography due to close retention times (entries 8 & 9). Only two by-products had a significantly different retention times from the rest of the mixture and could thus be isolated. From analysis of their mass spectrograms, it was concluded that these were **243** (*m/z* = 398, $C_{27}H_{27}NO_2$ + H^+) and **244** (*m/z* = 412, $C_{28}H_{29}NO_2$ + H^+) (**Figure 11**). These were presumed to exist as a mixture of diastereomers and although their synthesis was not intended, it was reasoned they could possibly function as catalysts.



243, n = 1, **18%**
244, n = 2, **28%**

Figure 11: Piperidine-based products from the hydrogenation process.

Frigoli reported a more selective method for removing benzyl groups from aromatic alcohols that utilises TMSCl/NaI.[89] This proved to be effective in the synthesis of **236** and **237** (**Scheme 91**).

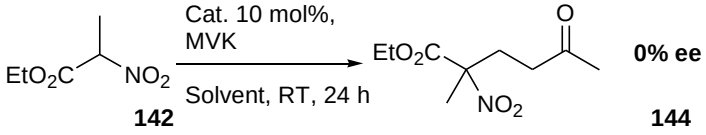


238, n = 1
239, n = 2

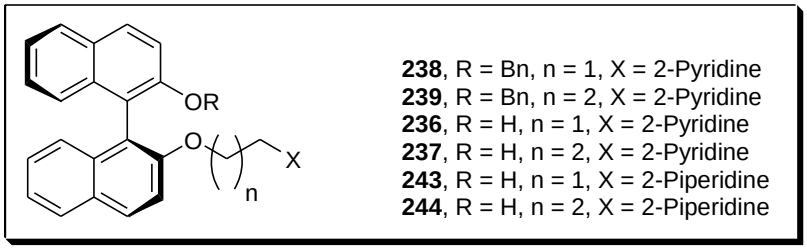
236, n = 1, **64%**
237, n = 2, **61%**

Scheme 91: TMSCl/NaI mediated method of benzyl removal.

Compounds **238-237**, **243**, and **244** were then tested as catalysts in the Michael addition of MVK to ethyl-2-nitropropionate (**Scheme 92**).



142 **144**



Catalyst	Solvent	Yield /%
238	None	88
239	None	97
236	None	99
237	None	97
243	None	29
243	Toluene	3
244	None	44
244	Toluene	3

Scheme 92: Efficiency of the bifunctional catalysts in catalysing the Michael addition of MVK to ethyl-2-nitropropionate.

Unfortunately, none of the catalysts produced any enantioselectivity. Catalysts **243** and **244** gave slow reaction and performed better under neat conditions than in toluene. Catalysts **239** and **237** gave similar rates of reaction, suggesting that there was no bifunctional effect. As before, this may be due to the side chain being too long. However, catalyst **236** did appear to outperform **238**, indicating a possible bifunctional effect.

4.2. Summary and Conclusions

In this study we were able to develop routes to new biaryl organocatalysts. Isoquinoline derivative **207** was synthesised in good yield and shown to have some capability to catalyse Michael addition reactions, giving a 67% yield for the reaction between ethyl-2-nitropropionate and PVK over 20 h. However, the intended derivative, **176**, was not synthesised as selective deprotonation of **207** was not achieved.

Three catalysts were synthesised using cross-coupling metathesis (**229**-**231**) in mediocre yield (25-59%). All three were able to catalyse the reaction between ethyl-2-nitropropionate and MVK, with **231** giving 99% yield in 20 h. Synthesis of **234**, an analogue of **231** with the free hydroxyl protected by Me, gave similar performance in the Michael addition reaction, suggesting that **231** is not behaving as a bifunctional catalyst, likely due to the length and rigidity of the carbon linker.

Six catalysts were synthesised using Mitsunobu chemistry (**236-239**, **243**, and **244**). **236-239** were synthesised in good yield, and were able to give very high yields for the reaction between ethyl-2-nitropropionate and MVK (88-99%) over 24 h. There was no difference between **239** and **237** in the Michael addition reaction, suggesting no bifunctional effect. **236** gave a slight improvement over **238**, indicating a possible bifunctional effect.

However, in all reactions, no enantioselectivity was observed for any of the catalysts. Consequently, no further investigation was made on these compounds.

4.3. Diamine Bifunctional Catalysts in an Aldol Reaction

4.3.1. Comparison of 1,2- and 1,3-Diamines

We next moved on to investigate the use of diamine bifunctional catalysts in the aldol reaction. Computer modelling suggests that the formation of the transition state in an aldol reaction catalysed by a 1,2-diamine does not require much activation energy, only 4.7 kcal/mol (**Figure 12**).[19] This is owing to the 9-membered ring being unstrained and the system being free to adopt its ideal geometry. Interestingly, the activation energy needed to form the transition state when the reaction is catalysed by a 1,3 diamine is predicted to be the same – 4.7 kcal/mol – although the entropy cost would be higher. This gives a wide range of potential structures that could be effective catalysts for this reaction.

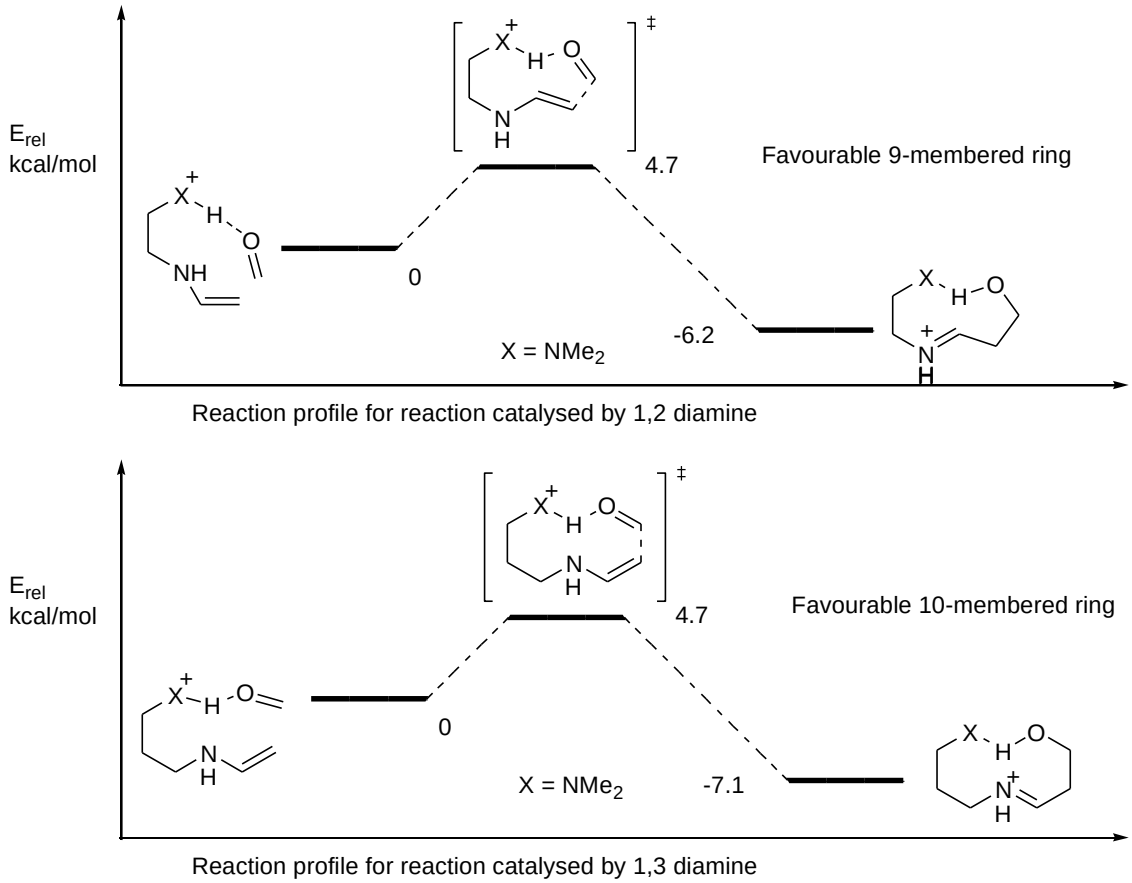


Figure 12: Energy profiles for 1,2- and 1,3-diamines in an aldol reaction. Energies were calculated using DFT - B3LYP/6-31G**.

In order to compare efficiency and selectivity of 1,2 diamines with 1,3 diamines, it was decided to investigate two simple diamines as organocatalysts. Dimethylethyldiamine (DMED) **245** and dimethylpropyldiamine (DMPD) **246** were chosen for comparison, as they are the closest structures with respect to the modelling studies and readily available (**Figure 13**).

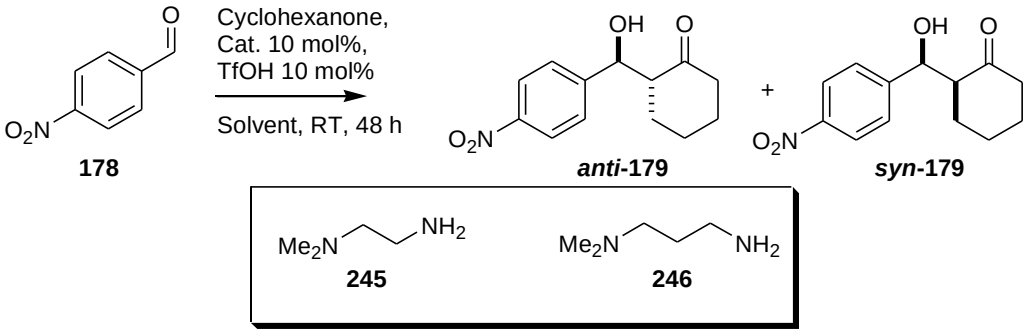
245 **246**

Figure 13: Structures of DMED and DMPD.

The aldol reaction between 4-nitrobenzaldehyde and cyclohexanone was used as the test reaction to investigate the efficacy of these catalysts. As discussed in the previous chapter, this reaction is known to be able to proceed quickly under diamine organocatalysts due to the electron-deficient aldehyde. Also, the structures of the starting materials simplify the possible outcomes – the ketone is symmetrical and the carbon alpha to the aldehyde cannot be enolised, thus favouring only one aldol product, albeit with four stereoisomers.

Although the reactants are insoluble in water, work within the Lygo group has shown this type of reaction works well on water (**Scheme 93**). A possible reason to

account for this could be the fact water is necessary for product formation. A second reason could be the fact that the components are forced together (*i.e.* cyclohexanone effectively becomes the solvent). To probe the effect of water, we investigated the aldol reaction in both dichloromethane and water. It was found that the 1,2-diamine **245** gave higher diastereoselectivity in both solvents compared to the 1,3-diamine **246**. In all cases, the *anti*-diastereomer was favoured over the *syn*-diastereomer.

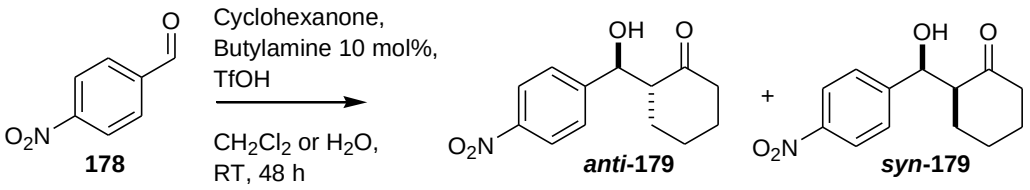


Catalyst	Solvent	Conversion /%	*anti:syn*
245	CH_2Cl_2	71	96:4
245	H_2O	81	88:12
246	CH_2Cl_2	24	72:28
246	H_2O	96	59:41

Scheme 93: Results of the aldol reaction, using DMED and DMPD as catalysts.

In order to determine whether diamines **245** and **246** were behaving as bifunctional catalysts, the aldol reaction was repeated using a mono-amine in place of the diamine. *n*-Butylamine was chosen as smaller amines were too volatile. It was theorised that if an equimolar amount of *n*-butylamine and TfOH were combined, the mixture would not be able to catalyse the reaction, as all the amine sites would be protonated and would thus be unable to participate in enamine formation. On the other hand, if the amine and TfOH were mixed in a 2:1 ratio, half of the amine molecules would be protonated to their conjugate acid while the other half would remain unprotonated, and should be able to catalyse the reaction. Work done by co-workers concluded that TfOH on its own is a poor catalyst for this reaction and so any background reaction should be minimal.

When 10 mol% of amine and 5 mol% of TfOH were used, the rate of reaction was very slow in CH_2Cl_2 and only slightly better in H_2O (**Scheme 94**). Curiously, when the amount of TfOH was increased to 10 mol%, the rate of reaction increased in CH_2Cl_2 but dropped to zero in H_2O. The lack of reaction in Entry 4 can possibly be attributed to the amine-TfOH salt being soluble only in the water phase.



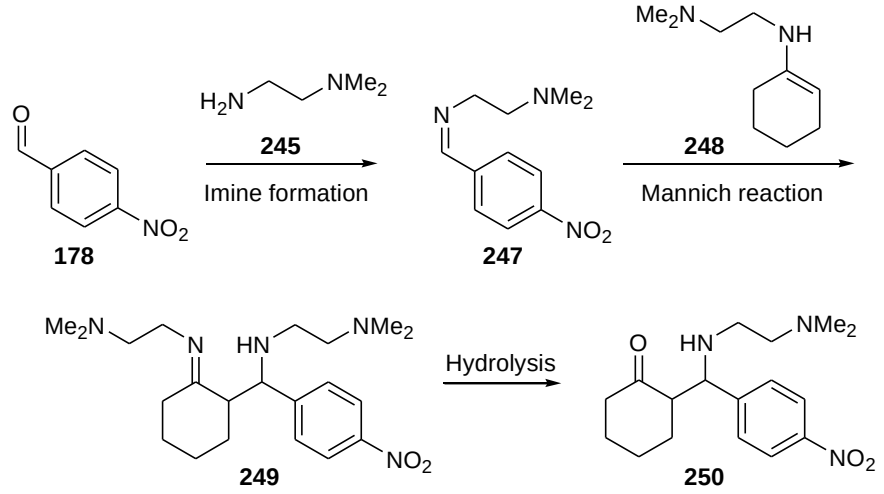
Solvent	TfOH /mol%	Conversion /%	*anti:syn*
CH_2Cl_2	5	9	29:71
H_2O	5	32	41:59
CH_2Cl_2	10	30	51:49
H_2O	10	0	-

Scheme 94: Results of the aldol reaction, using butylamine as catalyst.

Importantly, the conversions after 48 h were poor and *anti:syn* selectivity was reduced compared to the reactions that used the diamine catalysts (**Scheme 93**), this is possible evidence of a bifunctional effect for the diamine catalysts.

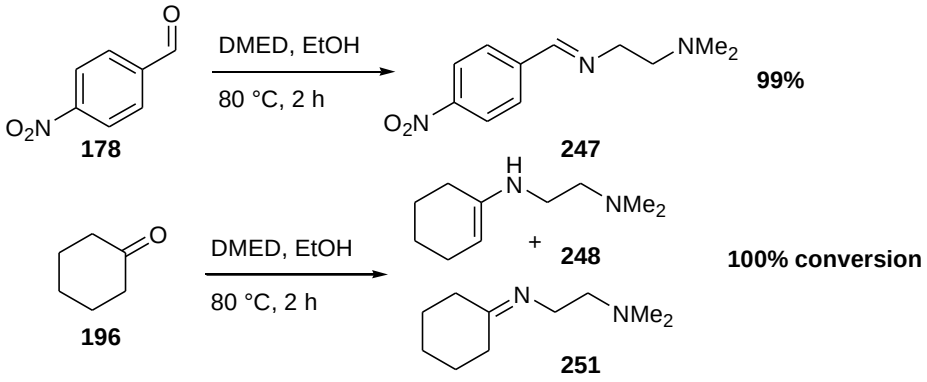
4.3.2. Investigation into Possible Side-Reactions

Because the diamines can potentially react with both the ketone and the aldehyde, it was necessary to investigate whether there were any side reactions taking place. A reversible side reaction would slow the rate of formation of the desired products while an irreversible side reaction could be detrimental to both the rate and yield, as this would remove both substrate and catalyst from the reaction mixture. For example, the formation of Mannich by-product **250** (**Scheme 95**). If 4-nitrobenzaldehyde **178** were to react with DMED **245** to form imine **247** prior to its reaction with the cyclohexanone-enamine **248**, the resulting coupling would form a Mannich product **249**.



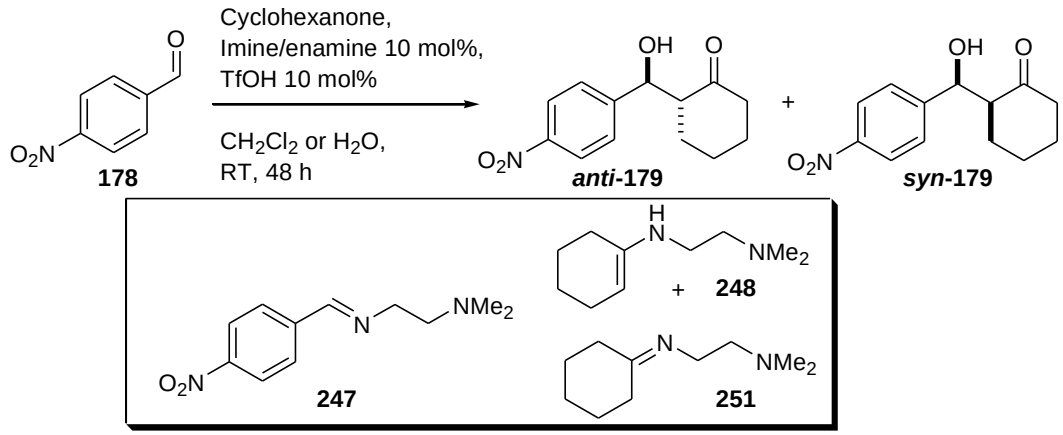
Scheme 95: Possible side-reaction resulting in formation of Mannich by-product **250**.

DMED was reacted with each of the starting materials to give their corresponding condensation products (**Scheme 96**). DMED reacted with 4-nitrobenzaldehyde following a known methodology,[90] to give imine **247**, which was stable enough to be characterised. The reaction between DMED and cyclohexanone was more problematic. The ^{1}H NMR spectrum of the crude reaction suggested that more than one compound was present, though signals for the starting materials were absent. As the dominant peak in the mass spectrogram was *m/*z = 191 ($C_{10}H_{20}N_2 + Na^+$), it was assumed that the mixture as composed of the imine and enamine products (**248** & **251**). Further characterisation was impractical as the material appeared to degrade quickly leading to complex mixtures. For subsequent studies, the adducts **247**, **248** & **251** were used without purification as prolonged exposure to moisture causes them to revert back to the starting materials.



Scheme 96: Forming condensation products of the DMED with each of the aldol reaction components; the aldehyde and the ketone.

Next, we ran a series of aldol experiments where the original diamine was replaced by the diamine aldehyde and diamine ketone adducts (**Scheme 97**).

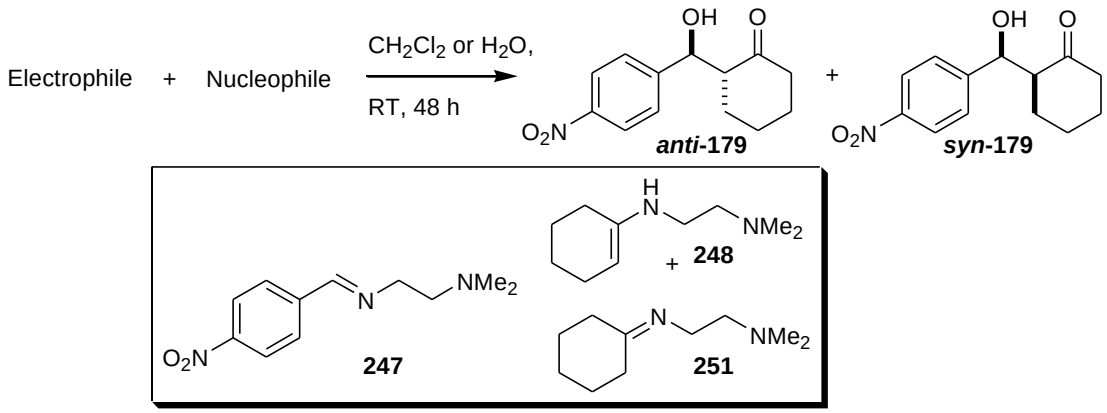


Catalyst	Solvent	Conversion (%)	*anti:syn*
247 + TfOH	CH_2Cl_2	100	88:12
247 + TfOH	H_2O	97	88:12
248 & **251** + TfOH	CH_2Cl_2	24	95:5
248 & **251** + TfOH	H_2O	98	88:12

Scheme 97: Results of the aldol reaction, using the DMED-aldehyde and DMED-ketone condensation products as catalysts.

As can be seen, the diamine ketone and diamine aldehyde adducts were found to give similar results to the diamine itself, suggesting these adducts are readily entering the catalytic cycle. Although no water was added for entries 1 & 3, it is possible that trace amounts of water present in TfOH and CH_2Cl_2 were enough to allow product formation.

We next investigated whether the adducts themselves could react with the other components of the reaction to give the aldol product. Adduct **247** was mixed with an equimolar amount of TfOH and cyclohexanone while adduct **248** was mixed with an equimolar amount of TfOH and 4-nitrobenzaldehyde (**Scheme 98**).



Electrophile	Nucleophile	Solvent	Conversion /%	*anti:syn*
247 + TfOH	Cyclohexanone	CH_2Cl_2	0	-
4-Nitrobenzaldehyde	**248** & **251** + TfOH	CH_2Cl_2	0	-
247 + TfOH	Cyclohexanone	H_2O	100	70:30
4-Nitrobenzaldehyde	**248** & **251** + TfOH	H_2O	81	75:25

Scheme 98: Results of the aldol reaction, using the DMED-aldehyde and DMED-ketone condensation products as substitutes for the reaction components.

Using CH_2Cl_2 as a solvent, both reactions (entry 1, **247** + TfOH + cyclohexanone and entry 2, **248** & **251** + TfOH + 4-nitrobenzaldehyde) did not proceed (0% yield). This is not surprising, as the salts generated were sparingly soluble in CH_2Cl_2 and water was not present in the reaction mixture. When the reactions were done in water, the reactions went to high conversion but with slightly reduced diastereoselectivity. Indeed, water would cause these to break down back into their starting components and the reaction would proceed as normal. Even under these conditions, no significant production of by-products were observed.

It is worth mentioning that in all of these aldol reactions, a by-product is produced if the reaction does not go to completion. This is due to unreacted 4-nitrobenzaldehyde forming an acetal with the aldol product (**Figure 14**). Clear signals appear in the ^{1}H NMR spectrum at δ_H ($CDCl_3$) 6.52 (1H, s, ArC*H*O_2, *anti*), 6.41 (1H, s, ArC*H*O_2, *syn*), 5.12 (1H, d, *J* 8.5, ArC*H*CH *anti*) and 5.77 (1H, d, *J* 2.5, ArC*H*CH, *syn*). These signals have been reported previously although the structures shown were not identified.[91]

Although there are theoretically sixteen possible stereoisomers (two for each chiral centre) and eight that could be visible on ^{1}H NMR spectrum, only acetal **252** is observed for the *anti*-aldol product and only acetal **253** is observed for the *syn*-aldol product – these are the only configurations that allows the dioxane ring to adopt a chair conformation with the nitrophenyl ring in an equatorial position without significant 1,3 interactions with other groups. Although the formation of these structures is reversible (the signals are lessened or absent in reactions with

high conversion due to lack of remaining 4-nitrobenzaldehyde), these do need to be considered when calculating the yield and selectivity of the reaction.

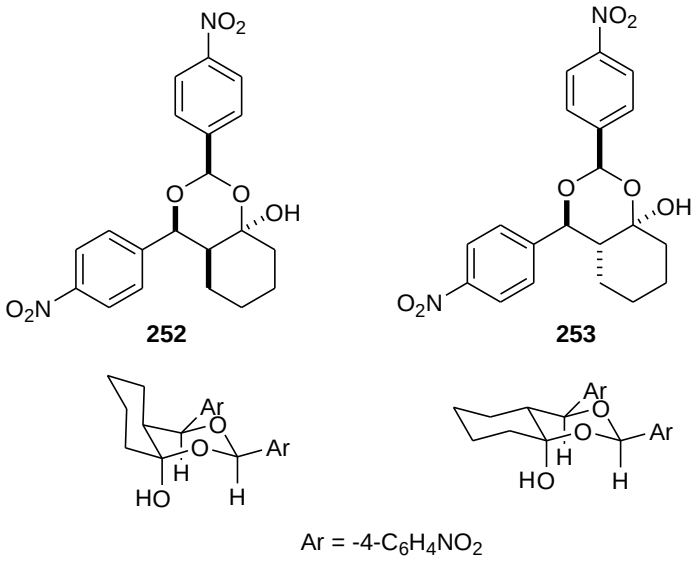


Figure 14: By-products formed by 4-nitrobenzaldehyde reacting with the aldol product. **252** is formed from the *anti*-product and **253** is formed from the *syn*-product.

4.4. Proline-Derived Bifunctional Catalysts in an Aldol Reaction

4.4.1. Primary-Tertiary Diamines Derived from Proline

The above studies show that primary-tertiary diamines are good catalysts for the aldol reaction and can generate products free of Mannich-like by-products. Thus we next moved on to investigate the synthesis and application of chiral primary-tertiary diamines derived from L-proline. As outlined in Chapter 3 (section **3.3.4.**), a key aim of this study was to establish whether this would serve as a means of accessing the opposite enantiomer of the aldol product compared with the formed using L-proline itself. We started this investigation with (*S*)-aminomethylethylpyrrolidine (AMEP, **254**) as it is commercially available (**Figure 15**). In addition, two other commercially available diamines, (*R,S,R*)- and (*S,S,R*)-aminomethylethylquinuclidine (**255** and **256** respectively), were selected for this study. These are superficially similar to AMEP in that they also possess a tertiary nitrogen, and a primary amine side chain.

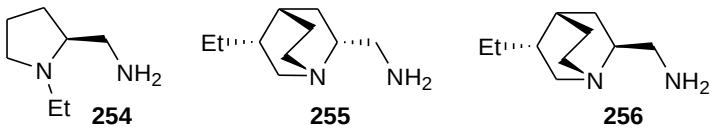
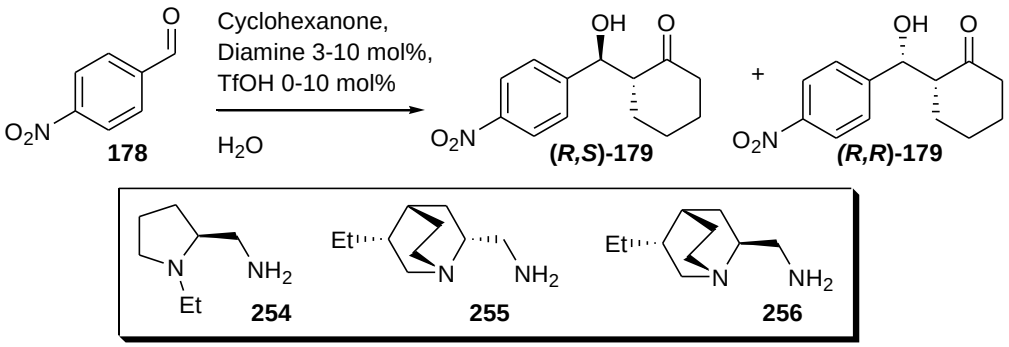


Figure 15: Structures of the commercially available 1,2-diamines used.

These diamines were tested in the aldol reaction (**Scheme 99**).

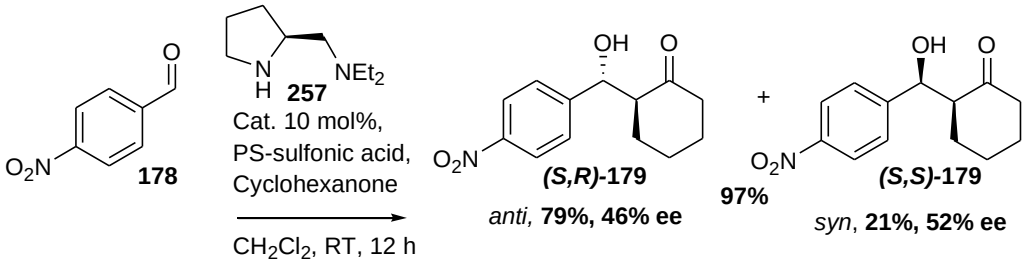


Diamine	Time /h	Temp.	Diamine /mol%	TfOH /mol%	Conversion /%	*anti:syn* Ratio	*anti* ee/%	*syn* ee/%
254	18	60 °C	3	3	99	81:19	37	14
255	18	60 °C	3	3	99	87:13	-2	5
256	5	60 °C	3	3	98	92:8	21	9
254	48	RT	10	10	95	83:17	46	12
254	48	RT	10	0	100	64:36	1	-1

Scheme 99: Results of the aldol reaction, using the commercially available 1,2-diamines as catalysts.

Initially the reactions were performed at 60 °C. All three diamines gave high conversion in a reasonable amount of time, as well as good *anti:syn* selectivity. Enantioselectivity was generally low, but **254** gave better results than the other two compounds. As such, it was decided to repeat this at room temperature. As well as a minor improvement to the *anti:syn* ratio, there was also a notable improvement in enantioselectivity for the *anti*-diastereomer. Importantly, when **254** was used in the absence of TfOH, it was able to give a similarly high conversion, but the *anti:syn* selectivity dropped and the enantioselectivity fell to almost nothing. This suggests that the TfOH is necessary for stereoselectivity and that **254** is behaving as a bifunctional catalyst.

A closely related proline derivative (**257**) has previously been utilised in the same reaction by Luo (**Scheme 100**).[92] It is interesting to note that this diamine gave similar *anti:syn* selectivity but gave the opposite enantiomer of the aldol products. This observation fit well with our original hypothesis and suggests that primary-tertiary amines derived from L-proline may have useful application in this area. This promising result led us to investigate more catalysts based on this structure.



Scheme 100: Aldol reaction done by Luo – this diamine gives similar yields and selectivities to the result using AMEP, but in opposite enantiomers.

4.4.2. Synthesis of Secondary-Tertiary Prolinamine Catalysts

After the encouraging result using **254**, it was decided to investigate potential catalysts with a similar structure with the objective of improving the enantioselectivity (**Figure 16**). In the general structure **258**, the R group on the pyrrolidine nitrogen can be substituted with other alkyl groups to increase or decrease the steric bulk and the R' group in the side chain can be altered to increase or decrease basicity of the amine or increase/decrease steric bulk or even add another chiral centre.

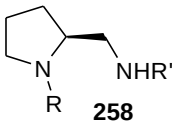
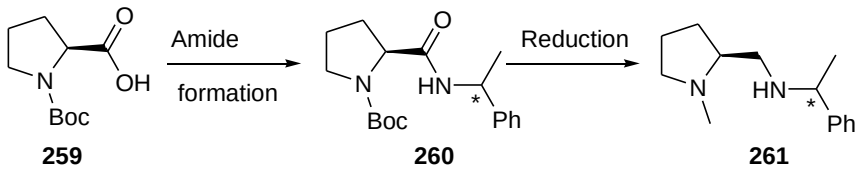


Figure 16: General structure for proline-derived diamine catalyst.

A short synthesis of a compound matching this template was envisaged (**Scheme 101**). Starting with *N*-Boc proline (**259**), α-methylbenzylamine could be attached *via* formation of a mixed anhydride to give a chiral amide (**260**). Then, both the carbamate and amide moieties could both be reduced to give a diamine with two chiral centres (**261**).

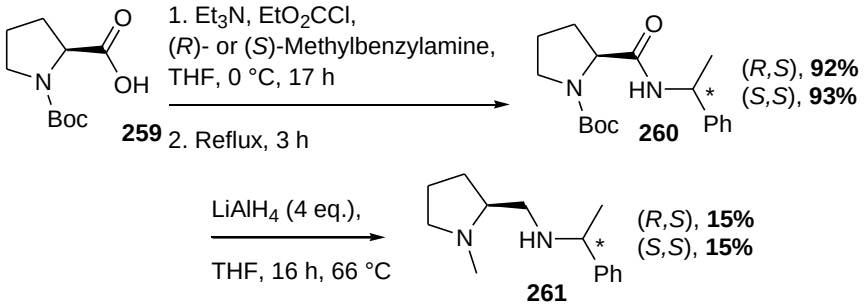


Scheme 101: Proposed synthesis of α-methylbenzylamine-based diamines.

α-Methylbenzylamine was chosen as it is a cheap chiral amine and both enantiomers are readily available. Also, the chiral centre contains a 'small' group (hydrogen), a 'medium-sized' group (methyl) and a 'large' group (phenyl). The size difference between the three substituents means that it is likely to have one particular orientation that is favoured and is most likely to confer chirality onto any

substrates it is interacting with – this and related amines have been the subject of previous PTC work within the Lygo group and have shown good results.[93]

The amide formation was performed according to literature procedure,[94] and gave high yields for both diastereomers (**Scheme 102**).

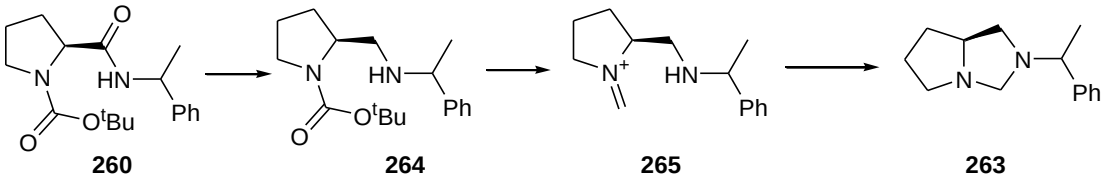


Scheme 102: Amide formation from *N*-Boc proline followed by reduction using $LiAlH_4$.

The reduction step however,[95] was more problematic – the yields for the reduction to diamines **261** were generally very poor – the resulting mixture consisted mostly of two by-products (**Figure 17**), intermediate **262** and compound **263**. The structure of **263** was initially assigned based on its *m/z* (217 = $C_{14}H_{20}N_2$ + H^+) and this was further supported by COSY HMBC and HMQC NMR data. We were able to show that **263** was not an intermediate in the reaction as further treatment with $LiAlH_4$ gave no reaction.

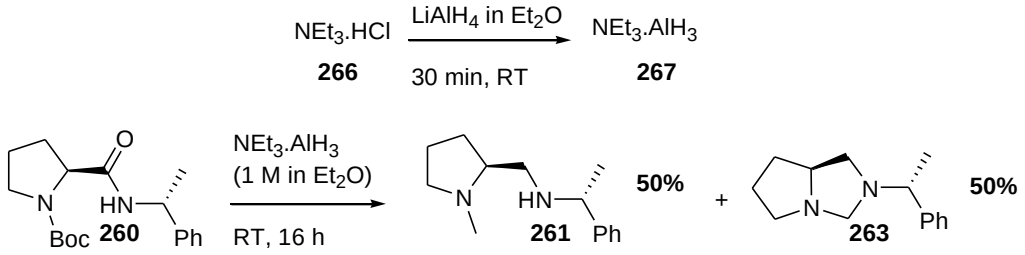
Figure 17: Structures of the two by-products.

The presence of amide **262** is simply due to incomplete reaction. The formation of bicyclic by-product **263** is harder to explain. It is suspected that it may form as outlined below (**Scheme 103**). After the amide and Boc groups have been reduced, intermediate **265** can undergo self-cyclisation as a result of the aliphatic amine attacking the iminium carbon, resulting in by-product **263**. This by-product appears to form more readily in $LiAlH_4$ reductions when THF is used as the solvent and the mixture is heated at reflux.[96]



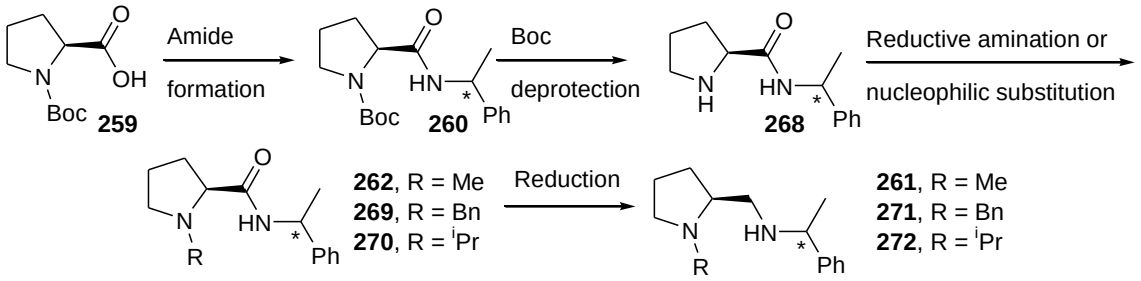
Scheme 103: Proposed formation of the bicyclic by-product.

Attempts to decrease the amount of by-product formed by increasing the amount of $LiAlH_4$ to 5 equivalents, and then 10 equivalents did not change the outcome of the reaction. We also investigated use of triethylamine-alane as a reducing agent. This is a powerful reducing agent formed by mixing NEt_3.HCl with $LiAlH_4$ in the absence of air and moisture (**Scheme 104**).[97]



Scheme 104: Synthesis of triethylamine-alane and reduction of **260** with triethylamine-alane.

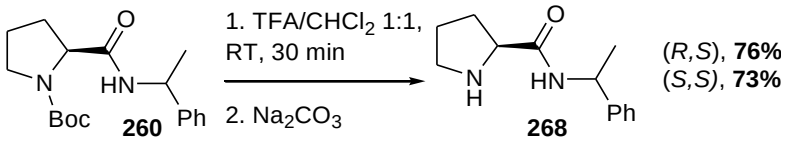
The use of triethylamine-alane as a reducing agent gave a higher yielding, cleaner reaction with no unreacted amide, however there was still a large amount of by-product **263**. A further problem with this approach was that the pyrrolidine nitrogen could not be substituted with anything other than a methyl group. Clearly, the diamine synthesis needed to be revised, so a longer but more versatile synthesis was devised (**Scheme 105**).



Scheme 105: Revised synthesis of α-methylbenzylamine-based diamines.

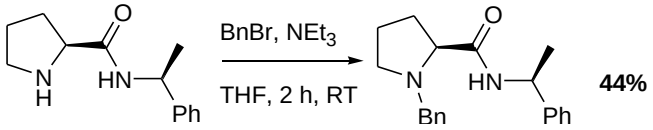
In this approach, the Boc protecting group is removed after formation of the amide to allow different groups to be added onto the pyrrolidine nitrogen. In the subsequent reduction step, there should be no formation of the bicyclic by-product as no Boc group will be present.

The initial deprotection step was straightforward and left the amide intact (**Scheme 106**).



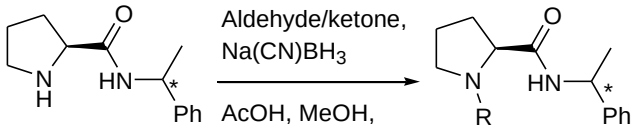
Scheme 106: Deprotection of Boc group by TFA.

Attachment of the different alkyl groups onto the pyrrolidine nitrogen could be achieved by either nucleophilic substitution or reductive amination. It was reasoned that a benzyl group could be attached using the former, as it would be slow to disubstitute and form an ammonium salt. The nucleophilic substitution was attempted according to literature procedure (**Scheme 107**).[98]



Scheme 107: Nucleophilic substitution with benzyl bromide.

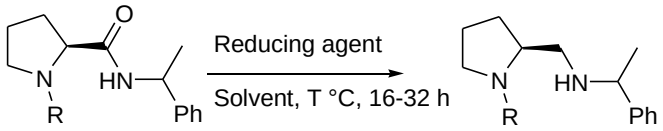
Unfortunately, this method gave **269** in moderate yield, so reductive amination was used instead (**Scheme 108**).[99] The advantage of this latter approach is that a greater range of alkyl groups can be attached to the pyrrolidine nitrogen, with no risk of disubstitution.



Aldehyde/ketone	Config.	Product	Yield /%
Formaldehyde (37% in H_2O)	*R,S*	**262**	78
Formaldehyde (37% in H_2O)	*S,S*	**262**	85
Benzaldehyde	*R,S*	**269**	93
Benzaldehyde	*S,S*	**269**	93
Acetone	*R,S*	**270**	93
Acetone	*S,S*	**270**	96

Scheme 108: Reductive amination of **268**.

The reductive amination gave good yields for all compounds. The amides were then reduced to their corresponding amines (**Scheme 109**).



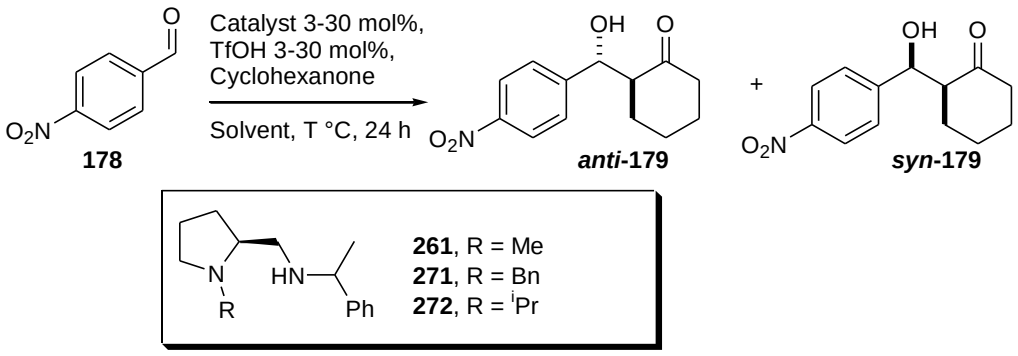
262, R = Me
269, R = Bn
270, R = ^{i}Pr

261, R = Me
271, R = Bn
272, R = ^{i}Pr

Starting Material	Config.	Reducing Agent	Equiv.	Solvent	Time /h	Temp. /°C	Product	Yield /%
262	*R,S*	$NEt_3.AlH_3$	2.5	Et_2O	16	25	**261**	76
262	*S,S*	$NEt_3.AlH_3$	2.5	Et_2O	16	25	**261**	74
269	*R,S*	$LiAlH_4$	2	THF	16	66	**271**	84
269	*S,S*	$LiAlH_4$	5.5*	THF	32*	66	**271**	93
270	*R,S*	$NEt_3.AlH_3$	2.5	Et_2O	16	25	**272**	90
270	*S,S*	$LiAlH_4$	5.5*	THF	32*	66	**272**	84

Scheme 109: Reducing the *N*-alkyl-phenylethylcarbamoylpyrrolidines with $LiAlH_4$ or $NEt_3.AlH_3$. * The reaction was done in two parts; 2.5 eq. for 16 h, then 3 eq. for another 16 h.

Both $LiAlH_4$ and $NEt_3.AlH_3$ were tested as reducing agents. It was found the $NEt_3.AlH_3$ generally gave a cleaner reaction making it easier to purify the amine products. Diamines **261**, **271** & **272** were then converted to their TfOH salts and tested in the aldol reaction (**Scheme 110**).



Catalyst	Config.	Solvent	Cat. /mol%	Temp. /°C	Conversion /%	*anti:syn*
271	*R,S*	H_2O	3	25	<1	-
271	*S,S*	H_2O	3	25	<1	-
272	*R,S*	H_2O	3	25	<1	-
272	*S,S*	H_2O	3	25	<1	-
261	*R,S*	H_2O	3	60	11	67:33
261	*S,S*	H_2O	3	60	6	64:36
271	*R,S*	CH_2Cl_2	30	25	4	73:27
271	*R,S*	H_2O	30	25	3	87:13
271	*S,S*	CH_2Cl_2	30	25	7	67:33
271	*S,S*	H_2O	30	25	9	83:17
272	*R,S*	CH_2Cl_2	30	25	<1	-
272	*R,S*	H_2O	30	25	<1	-
272	*S,S*	CH_2Cl_2	30	25	<1	-
272	*S,S*	H_2O	30	25	<1	-
261	*R,S*	CH_2Cl_2	30	25	<1	-
261	*R,S*	H_2O	30	25	<1	-
261	*S,S*	CH_2Cl_2	30	25	<1	-
261	*S,S*	H_2O	30	25	<1	-

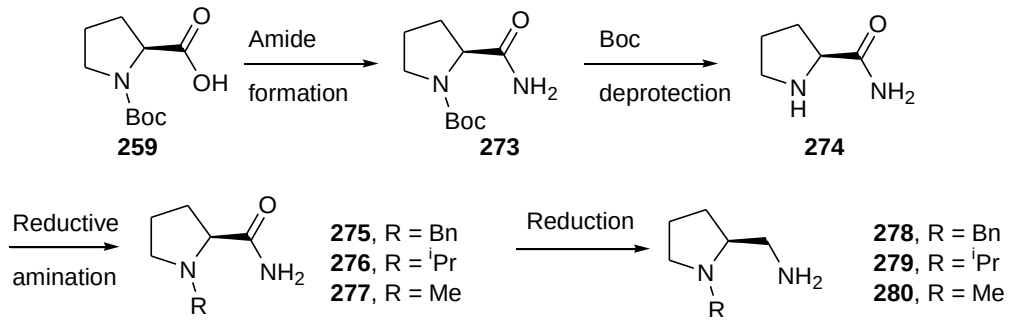
Scheme 110: Results of the aldol reaction using *N*-alkyl-(phenylethyl)aminomethylpyrrolidines as catalysts.

Initially, the amount of each diamine used was 3 mol% but little or no reaction was observed. Subsequently (entries 5 and 6), the temperature was raised to 60 °C, but again a low yield was obtained and the *anti:syn* diastereoselectivity was very low. In the next set of reactions, the catalyst loading was increased to 30 mol% and the reactions were repeated in both water and CH_2Cl_2. Although the *N*-benzyl-substituted compounds yielded a small amount of product, the *N*-isopropyl- and *N*-methyl-substituted compounds did not give any appreciable reaction. In all cases, the amount of product yielded was not enough to purify for a reliable HPLC trace to determine the enantioselectivity. A possible problem with these diamines is that they are tertiary-secondary diamines, which are possibly too sterically hindered to condense with cyclohexanone. These compounds were clearly not suited for aldol

reactions and it was decided to try some new structures.

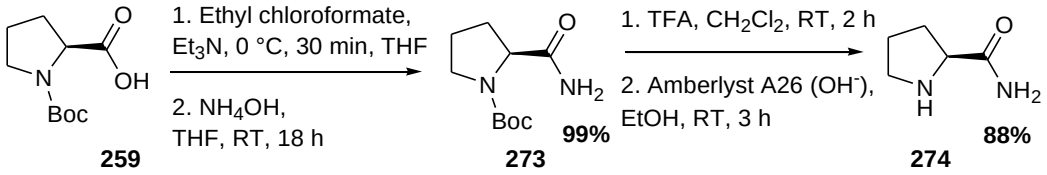
4.4.3. Synthesis of Primary-Tertiary Prolinamine Catalysts

As it appears that converting the side chain from a primary amine to a secondary amine was detrimental to the activity of these potential catalysts, we decided to go back to primary amines and vary the tertiary amine group (**Scheme 111**).



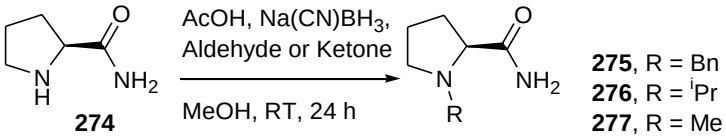
Scheme 111: Proposed synthesis for alkylated prolinamines.

Ammonia addition was straightforward and gave amide **273** in excellent yield (**Scheme 112**). The first problem arose during the Boc deprotection. The method used for the α-methylbenzylamine analogues was initially used. However, it appears that prolinamide **274** has a higher affinity for TFA and its removal proved difficult. Alteration of the work-up procedure and treatment with an ion exchange resin eventually allowed the removal of TFA and gave **274** in high yield and purity.



Scheme 112: Formation of amide by addition of ammonia followed by deprotection of *N*-Boc prolinamide with TFA.

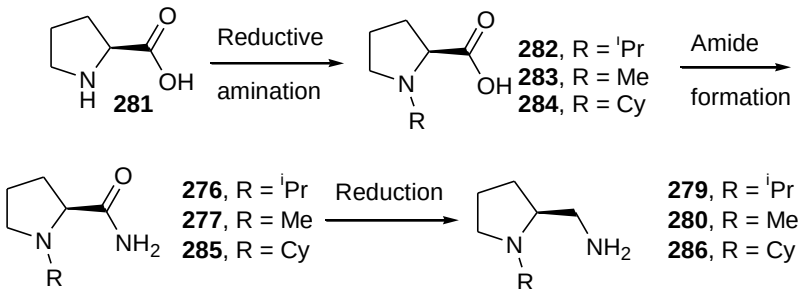
Alkyl group addition by reductive alkylation was also not as high yielding as with the previous compounds (**Scheme 108**) and the products were also harder to purify (**Scheme 113**).



R	Aldehyde/ketone	Product	Yield /%
Bn	Benzaldehyde	**275**	48
^{i}Pr	Acetone	**276**	32
Me	Formaldehyde (37% in H_2O)	**277**	23

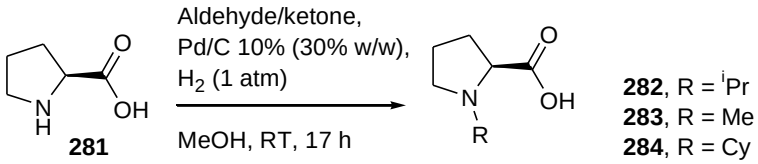
Scheme 113: Reductive amination to prolinamide using sodium cyanoborohydride.

Using $Na(CN)BH_3$ for reductive amination on these compounds was not as successful as it was with the α-methylbenzylamine substituted prolinamides. During the work-up, unreacted $Na(CN)BH_3$ was quenched using water. It was considered that these compounds might be more soluble in water than their α-methylbenzylamine counterparts owing to their lower carbon count. This is in part evidenced by the observation that yields decreased as the size of the *N*-substituent decreased (*i.e.* benzyl>isopropyl>methyl). It was reasoned that using Pd/C and H_2 for reductive amination might circumvent this issue, but performing this reaction at this stage of the synthesis might result in partial reduction of the amide and lead to unwanted side reactions. Thus, the synthesis was revised and the steps order was altered to add the alkyl substituent first (**Scheme 114**).



Scheme 114: Revised synthesis for alkylated prolinamines.

The reductive amination of proline was based on methodology previously reported in the literature.[100] It was not attempted with benzaldehyde as *N*-debenzylation would be promoted by the same reagents.[101] Therefore in addition to formaldehyde and acetone, cyclohexanone was investigated (**Scheme 115**).

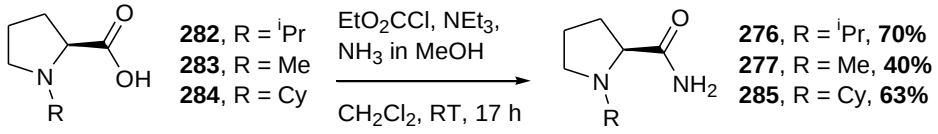


R	Aldehyde/Ketone	Product	Yield /%
^{i}Pr	Acetone	**282**	98
Me	Formaldehyde	**283**	99
Cy	Cyclohexanone	**284**	100

Scheme 115: Reductive amination to prolinamide using sodium cyanoborohydride.

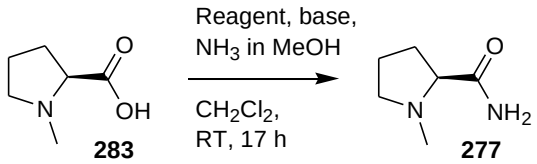
The reductive amination using Pd/C and H_2 gave excellent yields for all substrates, and featured ease of purification; only filtration and removal of the solvent under vacuum were required and thus the need for aqueous extraction was avoided.

This issue concerning extractions also needed to be considered for the formation of the amide in the following step. Instead of using NH_4OH, as with *N*-Boc proline, methanolic NH_3 was used instead (**Scheme 116**).



Scheme 116: Amide formation from *N*-alkyl prolines.

The yields obtained for the amide formation were good for *N*-isopropyl- and *N*-cyclohexyl prolinamide, but dropped (40%) for *N*-methyl prolinamide. Alternative reaction conditions were attempted in order to improve yield (**Scheme 117**).

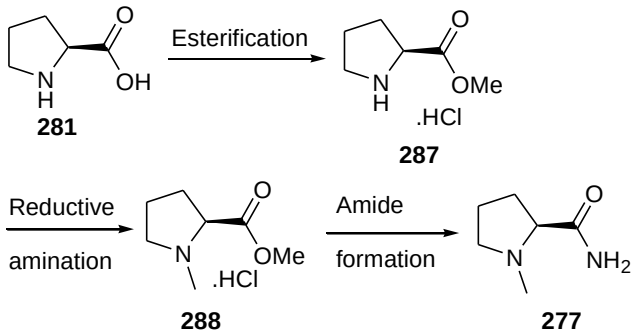


Base	Reagent	Yield /%
-	EtO_2CCl	0
NEt_3	$SOCl_2$	0
NEt_3	$^i BuO_2CCl$	15

Scheme 117: Amide formation from *N*-methyl proline using alternative reagents.

Unfortunately, none of these reactions gave better yields than that obtained previously (**Scheme 116**). One other route was envisaged (**Scheme 118**), here

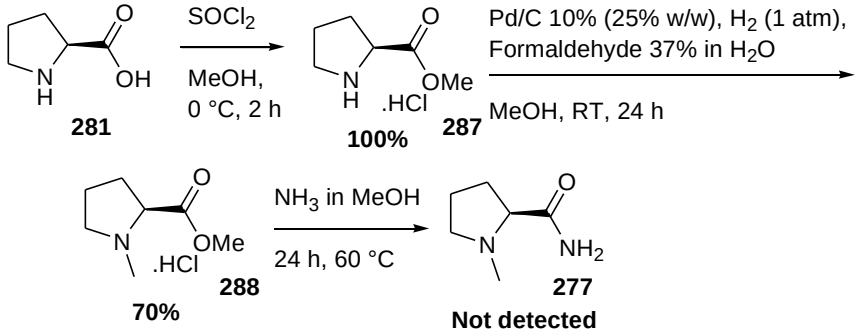
amide formation occurs *via* reaction between ammonia and ester hydrochloride **288**.



281 **287** **288** **277**

Scheme 118: Formation of *N*-methyl prolinamide *via* esterification route.

The esterification of proline **281** to was straightforward (**Scheme 119**).[102] Reductive amination then gave *N*-alkylated compound **288** in good yield. The lower yield compared to proline can be attributed to the water causing ester hydrolysis of both starting material and product. Unfortunately all attempts to convert ester **288** into amide **277** failed, so this approach was abandoned.

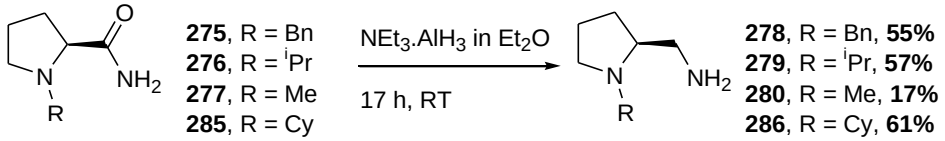


281 **100%** **287** **288** **70%** **277** **Not detected**

Scheme 119: Formation of N-methyl proline ester hydrochloride.

Ultimately, the 40% yield of *N*-methyl prolinamide by reaction of *N*-methyl proline with NH_3 was the best that could be achieved.

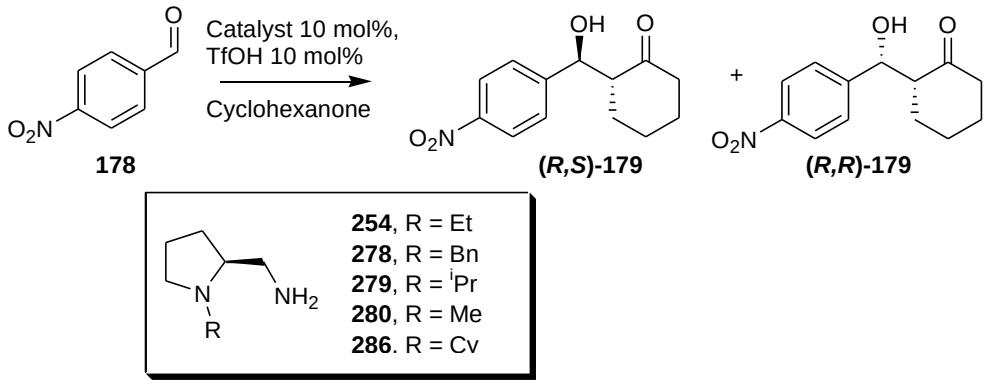
Given that triethylamine-alane appeared to be a cleaner and more efficient reducing agent than $LiAlH_4$, this was used to reduce the prolinamides to their corresponding prolinamines (**Scheme 120**).



Scheme 120: Reduction of *N*-alkyl prolinamides to prolinamines.

The yields for *N*-benzyl, *N*-isopropyl and *N*-cyclohexyl prolinamines were similar but *N*-methyl prolinamine was harder to isolate and purify due to its higher volatility.

Although the yields were not high, enough of each diamine was isolated to test in the aldol reaction (**Scheme 121**).



Catalyst	Time /h	Solvent	Conversion /%	*anti:syn*	*anti* ee /%	*syn* ee /%
254	48	H_2O	95	83:17	46	12
254	21	None	100	85:15	48	3
278	21	H_2O	100	83:17	56	-32
279	96	H_2O	42	86:14	67	28
280	168	None	24	82:18	51	-6
280	21	H_2O	100	88:12	48	21
286	33	H_2O	100	83:17	63	30

Scheme 121: Aldol reaction using alkylated prolinamines as catalysts.

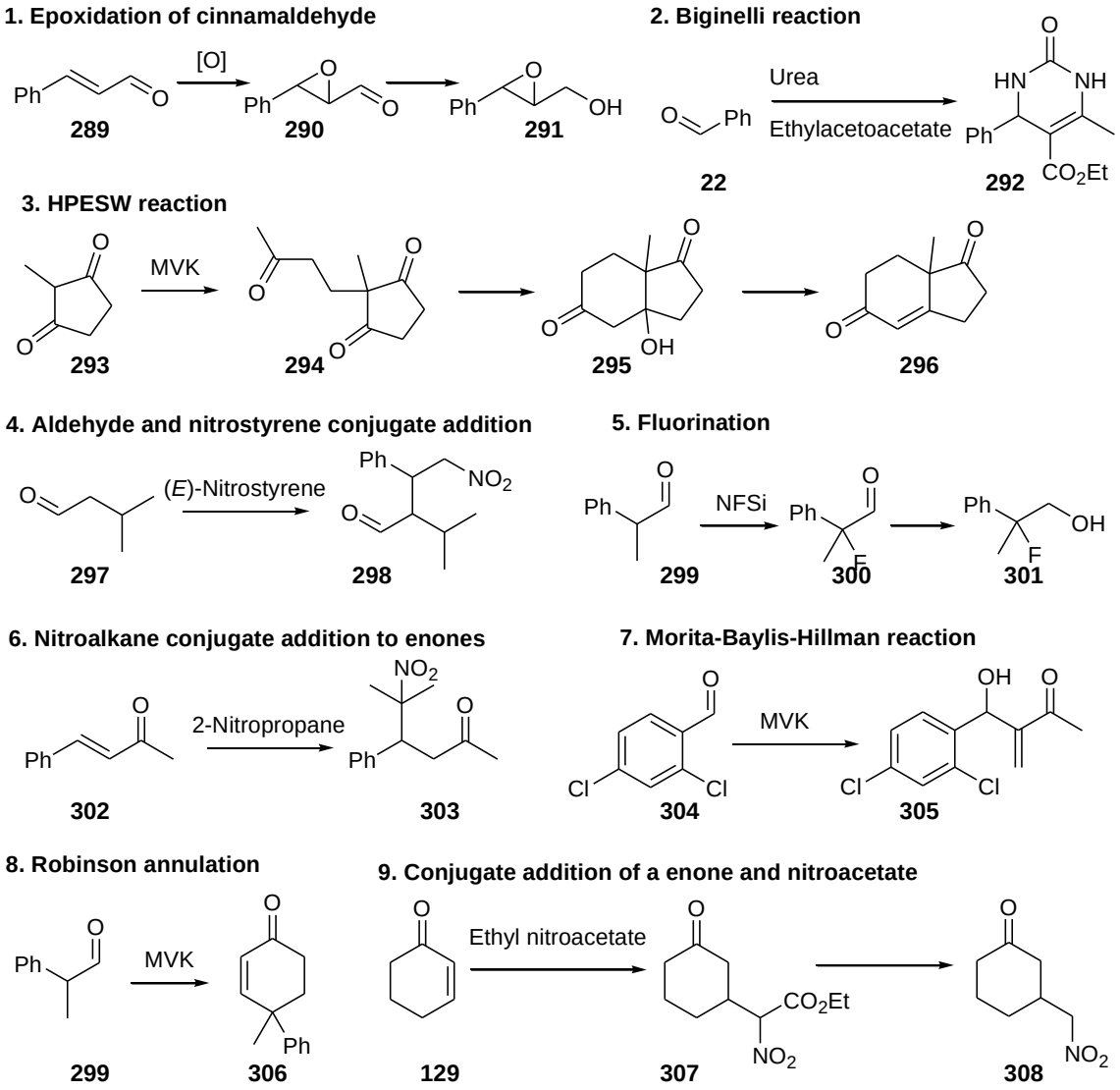
For all the reactions, the *anti:syn* selectivity was fairly consistent. The catalysts also appeared to show moderate consistency in the enantioselectivity of the *anti*-diastereomer (46-67% ee). The enantioselectivity for the *syn*-diastereomer, however, was highly variable. This observation is consistent with other studies done in the Lygo group, and rationalised by the fact that as the *syn*-diastereomer is less abundant, its enantiopurity is more affected by any background reactions. There appears to be no benefit to performing these reactions in water as the two examples where the reactions were run neat give essentially the same result. Although the enantioselectivities observed here were not high, they were sufficient to encourage us to investigate application of these diamines in a wider range of reactions.

4.4.4. Substituted Prolinamine Catalysts in Other Asymmetric Reactions

It is known that diamines are capable of promoting a wide range of different reactions including Diels-Alder cycloadditions,[103] conjugate additions,[104,105] Strecker synthesis,[106] Friedel-Crafts reactions,[107] Mannich reactions,[108] and even Wittig rearrangements.[109]

We undertook a comprehensive survey of all these processes and selected nine reaction types (**Scheme 122**) as suitable for testing the prolinamine-derived diamine catalysts. These reactions were chosen as a) they had been shown to give high yields and enantioselectivities with diamine catalysts, b) the starting materials were cheap and readily available and c) we possessed the necessary HPLC columns with which to determine the enantioselectivity. The reactions selected were:-

1. Epoxidation of cinnamaldehyde.
2. Bignelli reaction between benzaldehyde, urea and ethyl acetoacetate.
3. Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) reaction with 2-methyl-2-(3-oxobutyl)cyclopentane-1,3-dione.
4. Conjugate addition between an aldehyde and nitrostyrene.
5. Fluorination of DL-2-phenylpropionaldehyde.
6. Conjugate addition between 2-nitropropane and an enone.
7. Morita-Baylis-Hillman reaction between 2,4-dichlorobenzaldehyde and MVK.
8. Robinson annulation between DL-2-phenylpropionaldehyde and MVK.
9. Conjugate addition between ethyl nitroacetate and cyclohexenone.

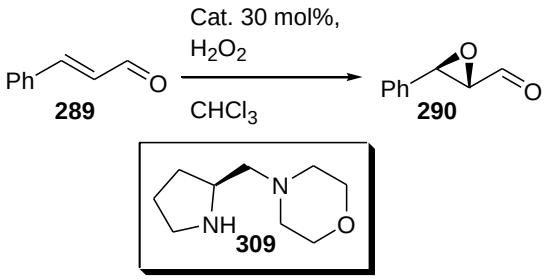


Scheme 122: Nine diamine catalysed reactions for testing prolinamines.

For each of these processes, it was first necessary to confirm that we could assay the enantiomers of the products. Consequently, racemic products had to be synthesised.

1. Epoxidation

Work published by Cordova in 2006 showed that various proline derivatives, including diamines, could be used to effect epoxidation of enals.[110] Diamine **309** was shown to give good conversion, reasonable *cis:trans* selectivity and moderate enantioselectivity when used in the epoxidation of cinnamaldehyde (**Scheme 123**).

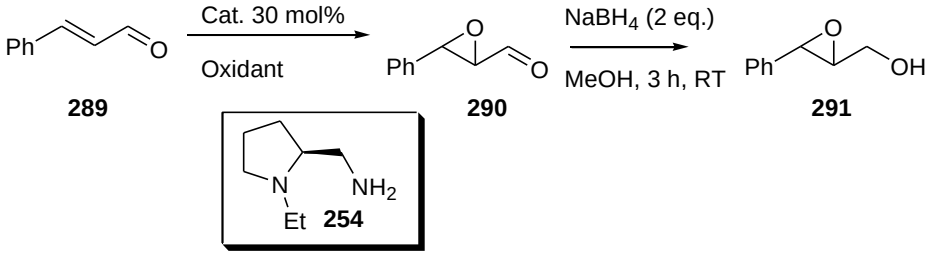


Solvent	Time /h	Temp /°C	Conversion /%	*cis:trans*	ee /%
$CHCl_3$	22	4	60	53:47	66
$CHCl_3$	19	–20	94	81:19	60
CH_2Cl_2	19	–20	97	82:18	50

Scheme 123: Cordova's epoxidation of cinnamaldehyde using **309**.

Cordova determined the enantiopurity of **290** by HPLC using a Chromasil® CP-Chirasil-Dex CB column, which we did not possess. However, by reducing aldehyde **290** to alcohol **291**, the enantiopurity can be determined with a Chiralcel® OD-H HPLC column.[111]

Racemic **290** was synthesised by using UHP as the oxidant, based on previous work in the Lygo group. The aldehyde was then reduced to alcohol **291**. The use of diamine **254** and H_2O_2 under the same conditions as reported by Cordova failed to produce any product (**Scheme 123**). The reaction mixture was allowed to reach room temperature, but still no conversion was observed. Switching the oxidant to UHP gave a low yield (14%) as well as a poor *cis:trans* selectivity and a racemic mixture. As no enantioselectivity was observed, no further investigation was done on this reaction.

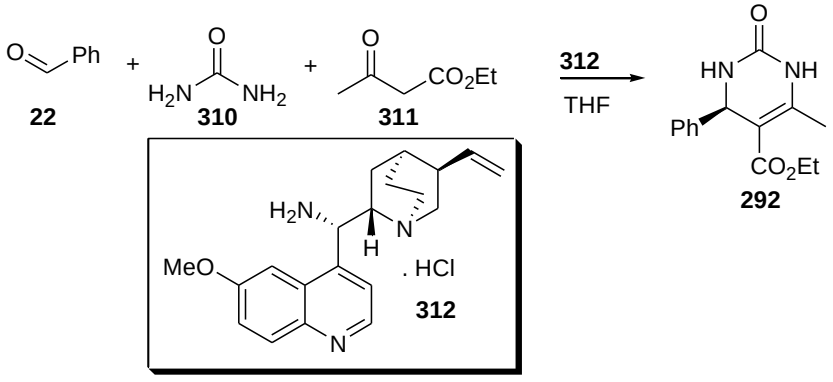


Oxidant	Catalyst	Temp. / °C	Solvent	Time /h	Yield /%[a]	*cis: trans*[a]	Yield /%[b]	ee /%[b]
UHP	NaOH	0	MeOH	3	67	1:4	90	-
H_2O_2*	**254**	–20	$CHCl_3$	24	0	-	-	-
H_2O_2*	**254**	RT	$CHCl_3$	24	0	-	-	-
UHP	**254**	RT	$CHCl_3$	24	14	3:2	76	0

Scheme 124: Results of the epoxidation reactions. a = for epoxidation step, b = for reduction step. * 50% in water.

2. Biginelli Reaction

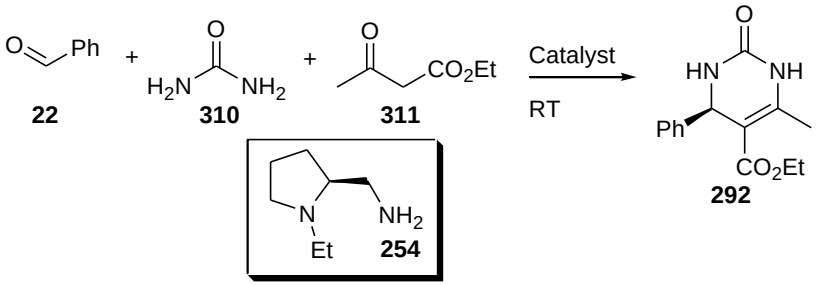
Zhao and Ding used diamines derived from cinchona alkaloids and diaminocyclohexane to catalyse a Biginelli reaction between benzaldehyde **22**, urea **310** and ethylacetoacetate **311**.[112] The most successful catalyst, **312**, gave **292** in moderate yield and enantioselectivity (64%, 66% ee). By doubling the catalyst loading, lowering the temperature to 0 °C, and increasing the reaction time to 6 days, both the yield and enantioselectivity were improved (81%, 73% ee). Lowering the temperature any further resulted in the reaction becoming impractically slow (**Scheme 125**).



Temp.	Time /d	312 /mol%	Yield /%	ee /%
RT	5	10	64	66
0 °C	6	20	81	73

Scheme 125: Bignelli reaction using **312** as the catalyst reported by Zhao.

Following literature procedure,[113] racemic **292** was synthesised in high yield (80%) using TMSCl and NaI. When AMEP **254** and HCl was used as a catalyst, no reaction was observed after 6 days at 0 °C. The reaction was repeated at room temperature. This gave the desired product but in low yield and with low enantiopurity (44%, 7% ee, **Scheme 126**). As the enantioselectivity was so poor, there was no further investigation of this reaction with prolinamine catalysts.

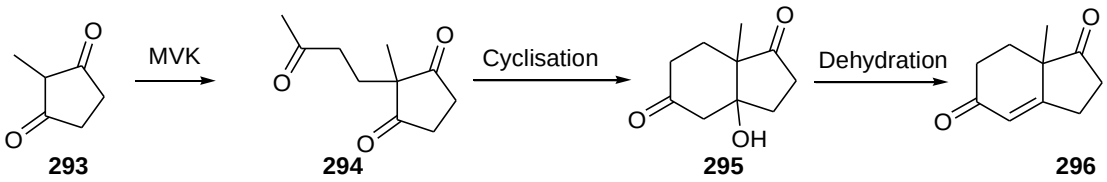


Catalyst	Cat. Amount /mol%	Solvent	Temp.	Time /h	Yield /%	ee /%
TMSCl + NaI	80	MeCN	RT	0.5	80	-
254.HCl	10	THF	0 °C	144	0	-
254.HCl	10	THF	RT	144	44	7

Scheme 126: Results of the Biginelli reactions.

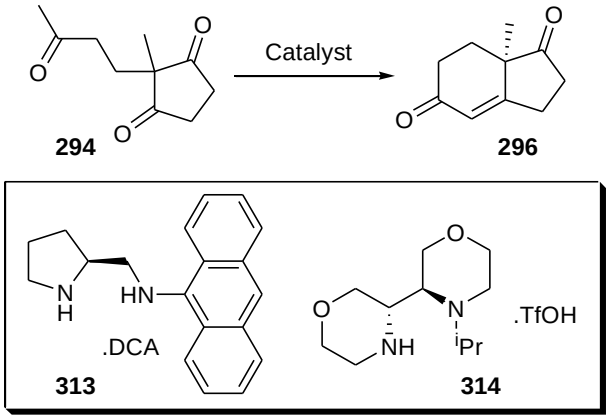
3. HPESW Reaction

The HPESW reaction (**Scheme 127**) is the intramolecular aldol reaction of **294**. Depending on the reaction conditions, the intramolecular aldol reaction can give either the alcohol **295** or the enone **296**.[114] If **295** is obtained, it can be readily dehydrated to **296** using acid or base.



Scheme 127: The four stages of the HPESW reaction.

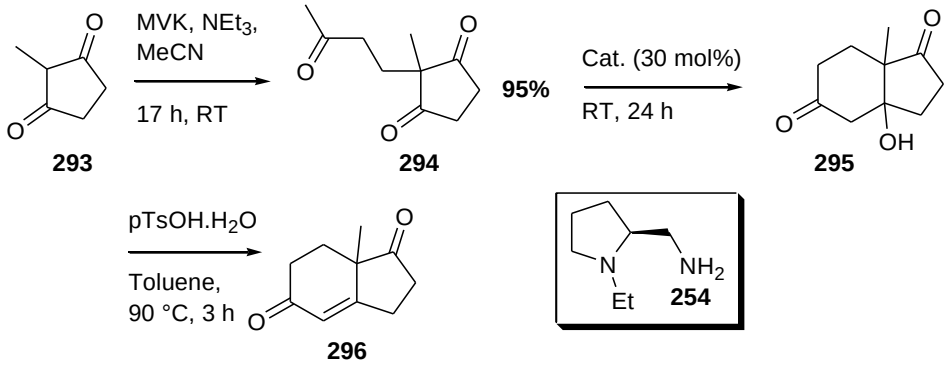
A range of diamine catalysts have been used in this reaction, the most relevant with respect to our studies are the proline-derived diamine **313**,[115] and the bis-morpholine-derivative **314**.[116] Typical conditions and results using these catalysts are shown in **Scheme 128**.



Catalyst	Amount /mol%	Solvent	Diamine: Acid ratio	Temp. /°C	Time /h	Yield /%	ee /%
313	30	DMSO	1:1.5	RT	20	68	84
314	5	MeCN	1:1	82	216	68	87

Scheme 128: HPESW reactions effected by two diamine catalysts.

In order to study this reaction using our diamine derivatives, we first need to prepare the triketone intermediate **294**. This was achieved by reacting diketone **293** with MVK following literature protocol.[117] We next prepared the racemic enone **296**, using DL-proline, again following a literature protocol.[114] Unfortunately, when we performed the reaction using AMEP.TfOH, the enone product was only formed in low yield and no enantioselectivity (**Scheme 129**).

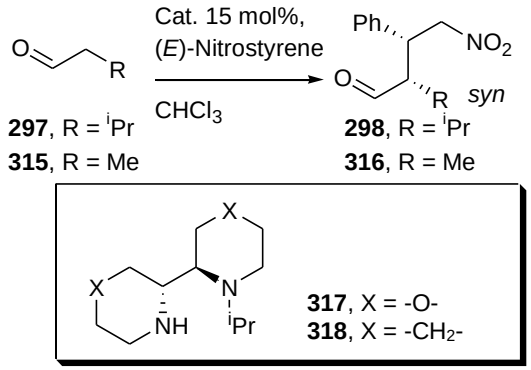


Catalyst[a]	Solvent[a]	Yield /%[a]	Yield/ %[b]	ee /%[b]
DL-Proline	DMF	60	89	-
254.TfOH	DMF	26	85	0

Scheme 129: Results of the HPESW reactions. a = for cyclisation step, b = for dehydration step.

4. Aldehyde and nitrostyrene conjugate addition

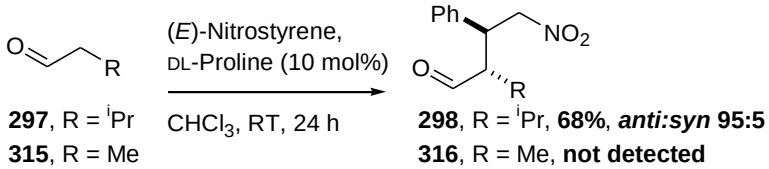
Kanger and Alexakis reported that bis-piperidines and bis-morpholines were effective catalysts in the conjugate addition between aldehydes and nitrostyrene (**Scheme 130**).[118] It appears that the diamines are not behaving as bifunctional catalysts, as adding HCl did not have a significant impact on selectivity but was detrimental to the yield (entries 1 & 2). **317** catalysed the addition of propionaldehyde **315** and 3-methyl butyraldehyde **297** to nitrostyrene and gave good yields (~85%), good *syn:anti* selectivity (>9:1) and good enantioselectivity for the *syn*-diastereomer (80% ee and 88% ee respectively). The bis-piperidine catalyst **318** improved these results slightly and effected the reaction in a shorter time.



Catalyst	Aldehyde	Temp. / °C	Time /h	Yield /%	*syn:anti*	*syn* ee /%
317.HCl	**297**	RT	72	68	95:5	91
317	**297**	RT	72	85	94:6	88
317	**315**	−3 °C	72	86	90:10	80
318	**297**	RT	8	85	96:4	89
318	**315**	−25 °C	23	82	94:6	96

Scheme 130: Conjugate addition of aldehydes to nitrostyrene, reported by Kanger and Alexakis.

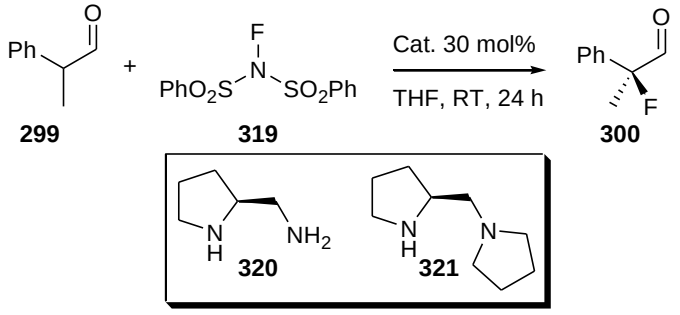
We prepared the racemate of **298** *via* conjugate addition of aldehyde **297** to nitrostyrene using DL-proline as the catalyst (**Scheme 131**). This gave good selectivity for the *anti*-diastereomer, unfortunately we were unable to reproduce the HPLC assay reported for this product. We were also unable to produce the alternative adduct **316** using this chemistry. Due to time constraints, this reaction was not pursued further.



Scheme 131: Conjugate addition of nitrostyrene and an aldehyde using DL-proline.

5. Fluorination

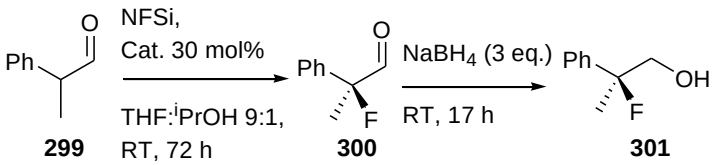
Barbas reported use of proline-derived catalysts in the fluorination of DL-2-phenylpropionaldehyde with fluorinating agent NSFi **319**.[119] Two of the catalysts reported were diamines; prolinamine **320** and pyrrolidinylmethylpyrrolidine **321**, (**Scheme 132**). Prolinamine **320** is closely related to the diamines in this project, as the amine side chain is a primary amine. It was reported to give an excellent yield in the fluorination reaction, but poor enantioselectivity (99%, 12% ee). **321** also gave high yield and poor enantioselectivity (84%, 12% ee) – addition of TFA gave a minor improvement in yield and enantioselectivity, but not enough to suggest a bifunctional effect.

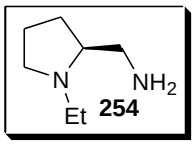


Catalyst	Yield /%	ee /%
320	99	12
321	84	12
321.TFA	85	16

Scheme 132: Barbas' use of diamine catalysts in the fluorination of DL-2-phenylpropionaldehyde. Absolute stereochemistry of the product was not determined.

Barbas analysed the formation of **300** by chiral GLC analysis, which was not available to us. Because the fluorinated aldehyde **300** is relatively volatile and cannot be isolated easily, the progress of the reaction was observed by ^{1}H NMR spectroscopy and mass spectrometry. Once no further reaction was observed, $NaBH_4$ was then added to reduce aldehyde **300** to alcohol **301**. This could be isolated, purified and subjected to HPLC to determine the enantioselectivity. We first prepared the racemate of **301** using DL-proline, and confirmed that the resulting alcohol could be assayed by chiral HPLC. We also found that AMEP was an effective catalyst for this reaction, but again the enantioselectivity was low (**Scheme 133**).



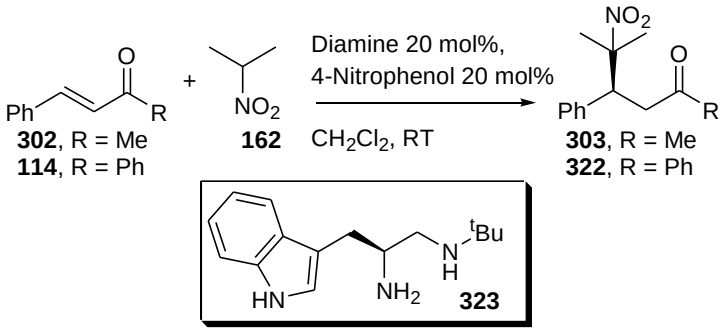


Catalyst	Yield /%	ee /%
DL-Proline	95	-
254.TFA	53	10

Scheme 133: Results of the fluorination reactions.

6. Nitroalkane conjugate addition to enones

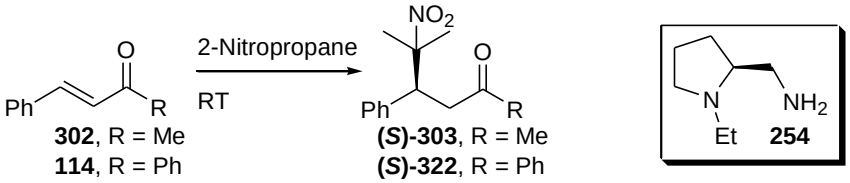
Zhao reported that the diamine catalyst **323** would promote conjugate addition between enones **302** and **114** with 2-nitropropane **162** (**Scheme 134**).[120] 4-Nitrophenol (4NP) was used as the acid. High yield and enantioselectivity (90%, 88% ee) were obtained for **303**, while reasonable yield and high enantioselectivity (62%, 92% ee) were obtained for **322**.



R	Time /h	Yield /%	ee /%
Me	24	90	88
Ph	96	62	92

Scheme 134: Zhao's use of diamine catalyst **323** in the conjugate addition of enones and 2-nitropropane.

We found that DL-proline did not successfully catalyse the reaction, but a reasonable yield of racemic **303** was achieved using KF/Al_2O_3 (**Scheme 135**).[121] However, despite following literature procedure, the enantiomers could not be resolved on HPLC. A racemic sample of **322** was also synthesised and this time the enantiomers were separable by HPLC. **254**.4NP was then tested as a catalyst. It gave high yield (90%) in 24 h, although the enantioselectivity was low (20% ee).

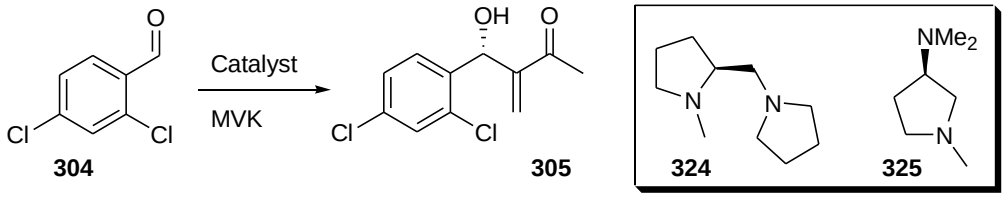


R	Catalyst	Amount	Solvent	Time /h	Yield /%	ee /%
Me	DL-Proline	10 mol%	CH_2Cl_2	24	0	-
Me	KF/Al_2O_3	35% w/w	-	7	63	-
Ph	KF/Al_2O_3	35% w/w	-	10	90	-
Ph	**254**.4NP	20 mol%	-	24	90	20

Scheme 135: Results of the enone and nitroalkane conjugate addition reactions.

7. Morita-Baylis-Hillman reaction

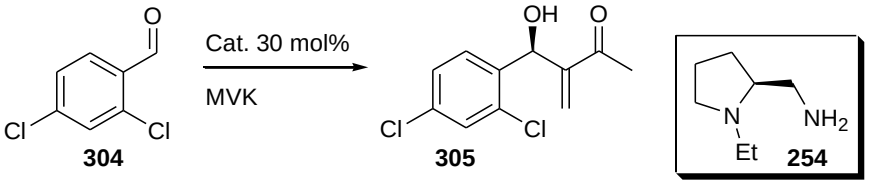
Hayashi[122] and Rouden[123] reported use of diamines as catalysts for the Morita-Baylis-Hillman reaction, between 2,4-dichlorobenzaldehyde and MVK (**Scheme 136**). Hayashi's catalyst **324** gave good yield and enantioselectivity (72%, 75% ee) while Rouden's catalyst **325** gave very high yield while only moderate enantioselectivity (99%, 56% ee).



Catalyst	Cat. /mol%	Solvent	Temp.	Time /h	Yield /%	ee /%
324	30	EtOH	0 °C	72	72	75
325	16	^{i}PrOH	RT	96	99	56

Scheme 136: Results reported by Hayashi and Rouden using diamine catalysts **324** and **325** to catalyse the MBH reaction between 2,4-dichlorobenzaldehyde and MVK.

In our study, racemic compound was prepared using PPh_3 and 4-nitrophenol.[124] Catalyst **254** was then tested using Hayashi's conditions, both the yield and enantioselectivity were very poor (5%, 11% ee) (**Scheme 137**). However, it did give the opposite enantiomer to that obtained by Hayashi.

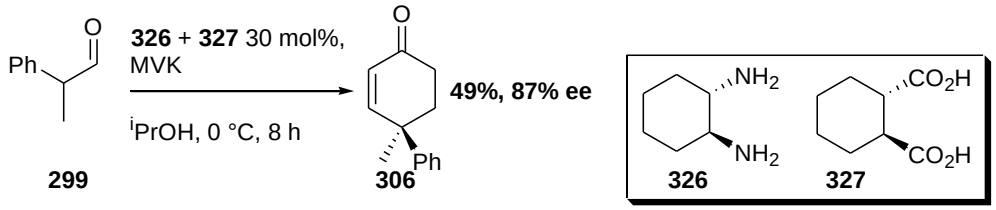


Catalyst	Time /h	Solvent	Temp. /°C	Yield /%	ee /%
PPh_3 + 4NP	18	THF	RT	46	-
254	72	EtOH	0	5	11

Scheme 137: Results of the Morita-Baylis-Hillman reaction.

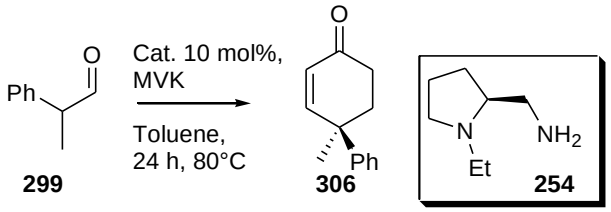
8. Robinson Annulation

Kotsuki[125] reported the cyclisation between DL-2-phenylpropionaldehyde and MVK catalysed by a salt comprising of (*S,S*)-1,2-diaminocyclohexane **326** and (*S,S*)-cyclohexane-1,2-dicarboxylic acid **327**. This gave enone **306** a moderate yield and high enantioselectivity (49%, 87% ee, **Scheme 138**).



Scheme 138: Robinson annulation catalysed by **326** and **327** as reported by Kotsuki.

We prepared racemic enone **306** *via* a reported procedure.[126] Unfortunately, AMEP.TfOH gave very poor yield and enantioselectivity (5% and 5%, **Scheme 139**).

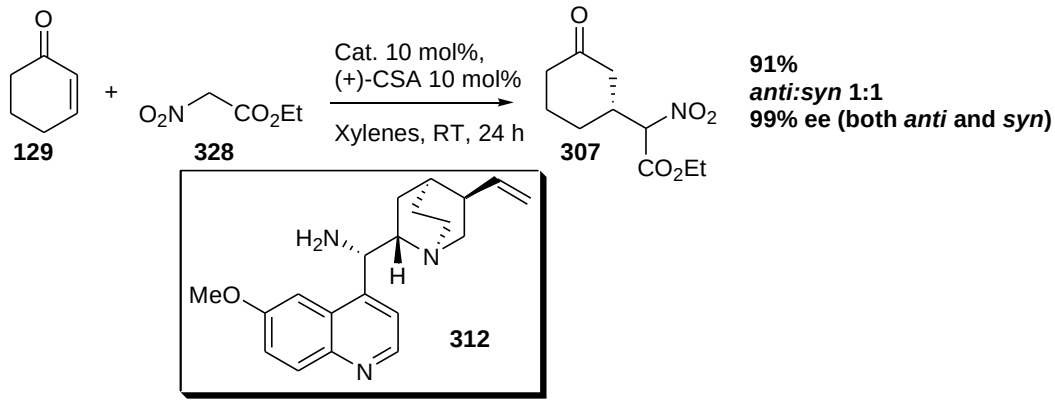


Catalyst	Yield /%	ee /%
pTsOH.H_2O	74	-
254.TfOH	5	5

Scheme 139: Results of the Robinson annulation reactions.

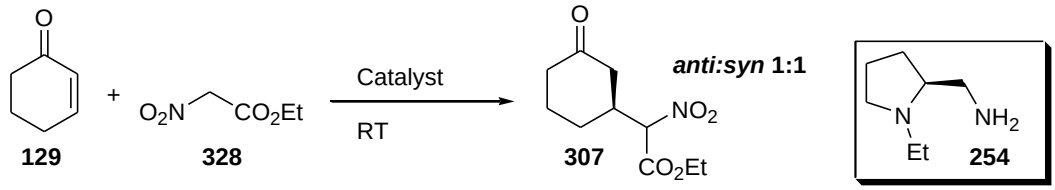
9. Enone and nitroacetate conjugation addition

Lu reported that quinine-derived diamine **312** was an effective catalyst for the conjugate addition of nitroesters to cyclohexanone (**Scheme 140**).[127a] The reaction between cyclohexenone **129** and ethyl nitroacetate **328** gave adduct **307** in excellent yield and enantioselectivity (91%, 99% ee for both diastereomers). The two diastereomers were isolated in a 1:1 ratio due to the acidity of the hydrogen alpha to the nitro and ester group.



Scheme 140: Conjugate addition of **129** and **328** reported by Lu.

AMEP **254** was tested in this reaction (**Scheme 141**) and gave better results than the other reactions listed above. Using **254**.(+)-CSA, the product **307** was obtained in a high yield and low enantioselectivity (90%, 30% ee). When **254**.(-)-CSA was used the yield and enantioselectivity improved (97%, 40% ee). In order to confirm that the enantioselectivity was not simply due to CSA, the reactions were repeated in absence of diamine **254**. No product was obtained, confirming the need for the diamine. The reactions were also repeated in the absence of solvent, however, the yields and enantioselectivities were lower.



Catalyst	Cat. Amount	Solvent	Time /h	Yield /%	ee /%
KF/Al_2O_3	35% w/w	None	24	99	-
254.(+)-CSA	10 mol%	Xylenes	48	90	30
254.(-)-CSA	10 mol%	Xylenes	48	97	40
(+)-CSA	10 mol%	Xylenes	48	0	-
(-)-CSA	10 mol%	Xylenes	48	0	-
254.(+)-CSA	10 mol%	None	48	66	3
254.(-)-CSA	10 mol%	None	48	90	19
(+)-CSA	10 mol%	None	48	0	-
(-)-CSA	10 mol%	None	48	0	-

Scheme 141: Results of the conjugate addition of cyclohexenone and ethyl nitroacetate using AMEP.

The enantiopurity of **307** was calculated from the HPLC chromatogram (**Figure 18**). A & B and C & D are interconverting diastereomeric pairs. The enantioselectivities reported refer to the enantiomeric excess of the non-equilibrating centre. So from the HPLC shown, ee was calculated from the areas of (A+B) and (C+D).

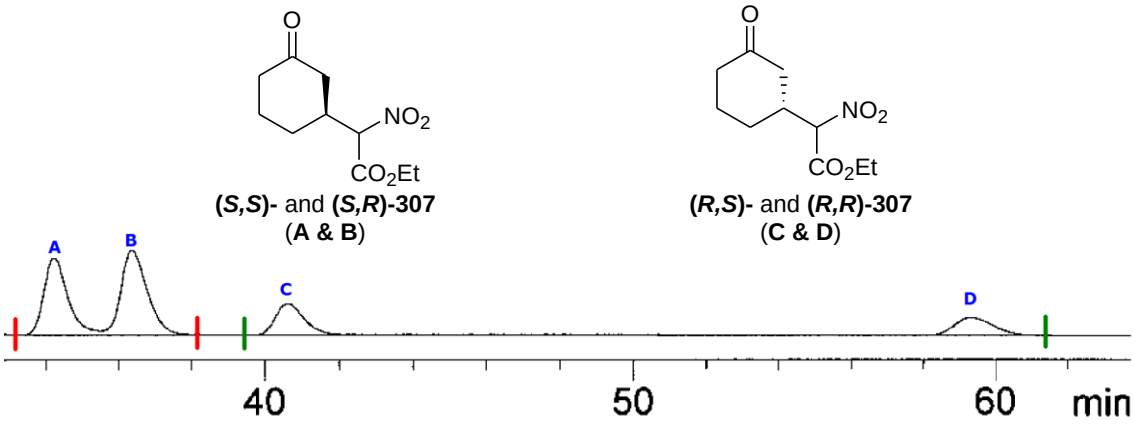
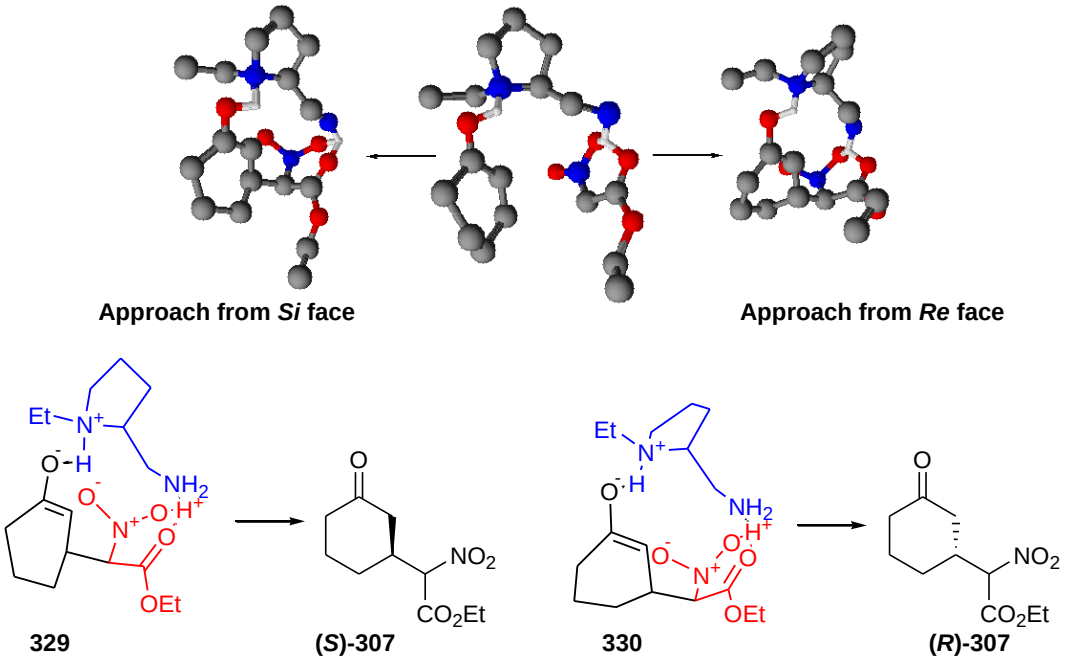


Figure 18: HPLC chromatogram of **307**. A and C are *syn*, B and D are *anti*. Conditions used were Chiralpak AD-H column (25 x 0.46 cm), hexane:^{i}PrOH 95:5, 20 °C, 1 mL/min, 38 bar.

A possible explanation for the enantioselectivity has been is that the reaction proceeds through the transition state shown below (**Scheme 142**). AMEP coordinates to ethyl nitroacetate and cyclohexenone. The ethyl nitroacetate has been shown with the ester group in the foreground and the nitro group in the background, although they could be reversed. If the nitroacetate approaches the cyclohexenone from the *Si* face (**329**), then (***S***)-**307** will be formed. To form the

opposite enantiomer (***R***)-**307**, the ethyl nitroacetate must approach the cyclohexenone from the *Re* face (**330**). It would appear in the latter case, one of the electron withdrawing groups (EWG) of ethyl nitroacetate must be in close proximity to the cyclohexenone ring, likely causing steric clashing. In the former case, a larger distance between the EWGs and the cyclohexenone is maintained, thus allowing easier attack.



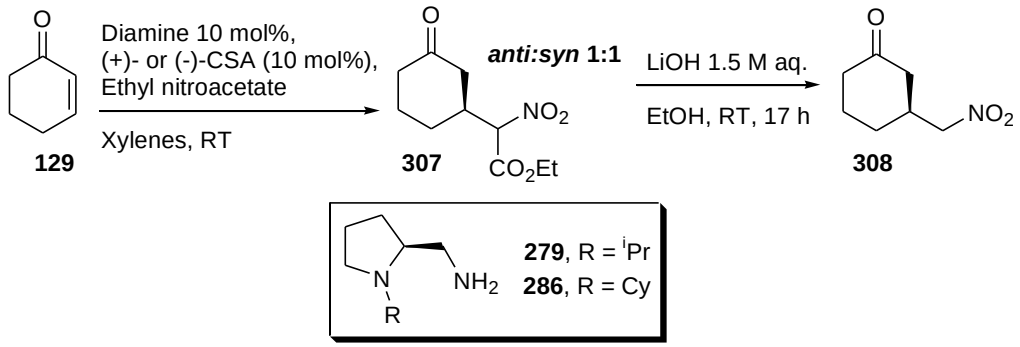
Scheme 142: Possible explanation for enantioselectivity in the prolinamine-catalysed formation of **307**. The 3D models show the transition states with all hydrogens removed apart from those involved in hydrogen bonding.[128]

The success of AMEP in this reaction prompted us to investigate other diamines in the same reaction. However, a fault with the AD-H HPLC column (and inability to separate the enantiomers on any other column) resulted in the need to find an alternative means of determining enantioselectivity. As the stereochemistry at the carbon between the nitro- and ester groups is unimportant, we decided to convert **307** into nitromethylcyclohexanone **308** by decarboxylation.[127a]

To test this, two samples of ethyl nitro(oxocyclohexyl)acetate **307** were decarboxylated; the racemic sample prepared using KF/Al_2O_3 and the one prepared using **254**.(+)-CSA (**Scheme 141**, entries 1 & 2 respectively). Nitromethylcyclohexanone **308** was obtained in good yields (75%, 71% respectively) and latter retained its enantiopurity (30% ee), indicating decarboxylation does not racemise the chiral centre.

Subsequently, two more diamines were tested in this reaction (**Scheme 143**). As with AMEP, the catalysts showed an improvement in enantioselectivity when (-)-

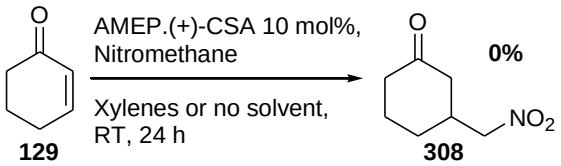
CSA was used over (+)-CSA. Both gave poorer yields, but slightly better enantioselectivity than AMEP (**279**; 82%, 46% ee, **286**; 25%, 44% ee).



Conjugate addition			Decarboxylation	
Catalyst	**Time /h**	**Yield /%**	**Yield /%**	**ee /%**
KF/Al_2O_3	*	*	75	-
254.(+)-CSA	*	*	71	30
279.(+)-CSA	48	67	78	44
279.(-)-CSA	48	67	82	46
286.(+)-CSA	24	25	60	41
286.(-)-CSA	24	25	68	44

Scheme 143: Results of the conjugate addition of a ketone and nitroester. * Sample from **Scheme 141**.

The possibility of directly forming nitromethylcyclohexanone **308** from cyclohexenone **129** by conjugate addition with nitromethane was also considered. This has been demonstrated by other organocatalysts,[129] though no reports using diamines could be found. This reaction was attempted using AMEP.(+)-CSA as the diamine catalyst (**Scheme 144**), unfortunately no product was formed.

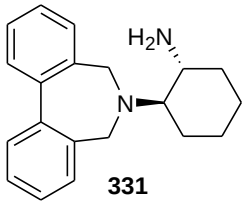


Scheme 144: Conjugate addition of nitromethane and cyclohexenone.

4.5. Biaryl Azepine Catalysts in Asymmetric Reactions

4.5.1. Use of an Azepinylamine in Asymmetric Reactions

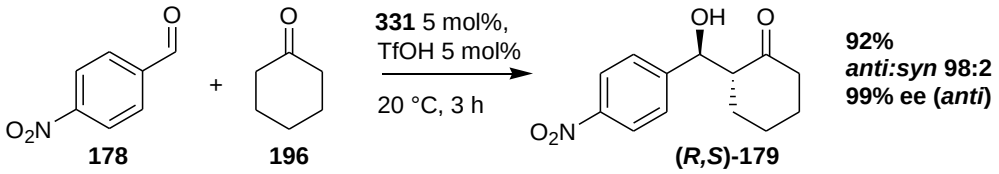
As part of ongoing work within the Lygo group, we also examined use of (1′*R*,2′*R*)-6-(2′-aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine **331** (**Figure 19**) in some of the reactions mentioned in the previous section.



331

Figure 19: (1′*R*,2′*R*)-6-(2′-Aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine.

331 has been shown to give very high yield, diastereoselectivity and enantioselectivity for a range of substrates in the aldol reaction (**Scheme 145**).[130]

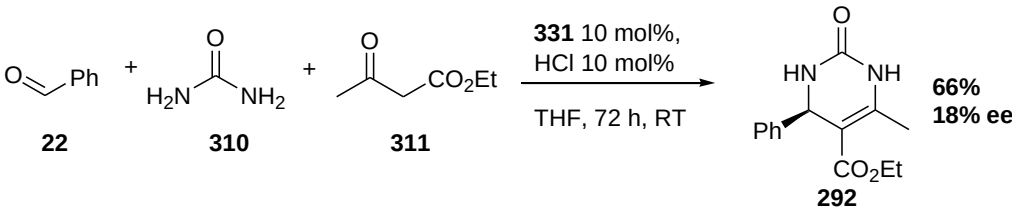


178 **196** **(*R*,*S*)-179**

Scheme 145: Aldol reaction catalysed by biaryl azepine **331**.

1. Biginelli reaction

Biaryl azepine **331** was first examined in the Biginelli reaction (**Scheme 146**). There was a minor improvement to both yield and enantioselectivity over AMEP, but not enough to justify further investigation.

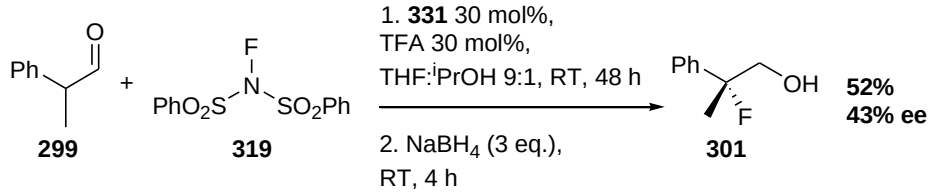


22 **310** **311** **292**

Scheme 146: Biginelli reaction, using biaryl azepine **331**.

2. Fluorination reaction

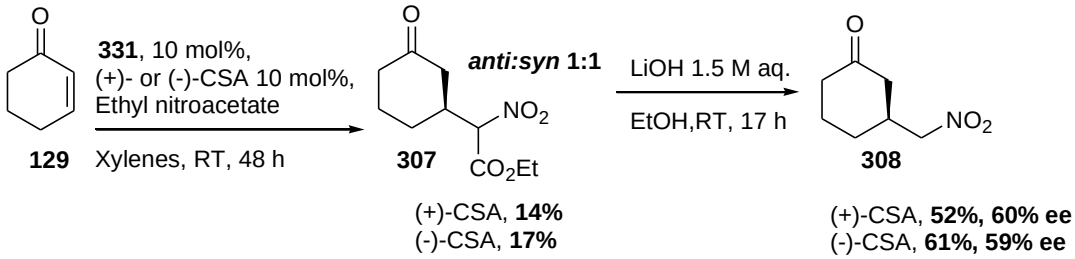
Biaryl azepine **331** was next tested as a catalyst for the fluorination of DL-2-phenylpropionaldehyde (**Scheme 147**). When compared to the AMEP-catalysed reaction, there was no improvement to the yield and although there a substantial improvement to enantioselectivity, it was still mediocre (43% ee).



Scheme 147: Fluorination reaction, using biaryl azepine **331**.

3. Nitroester conjugate addition to cyclohexenone

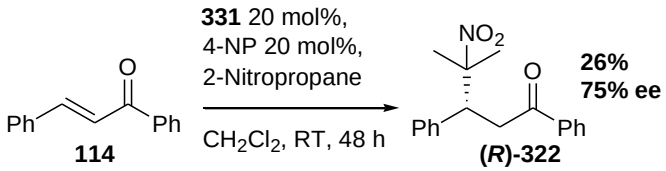
Biaryl azepine **331** was used as the catalyst in the conjugate addition between cyclohexenone and ethyl nitroacetate (**Scheme 148**). The reaction resulted in low yields but enantioselectivity showed a slight improvement over AMEP.



Scheme 148: Enone and nitroester conjugate addition, using biaryl azepine **331**.

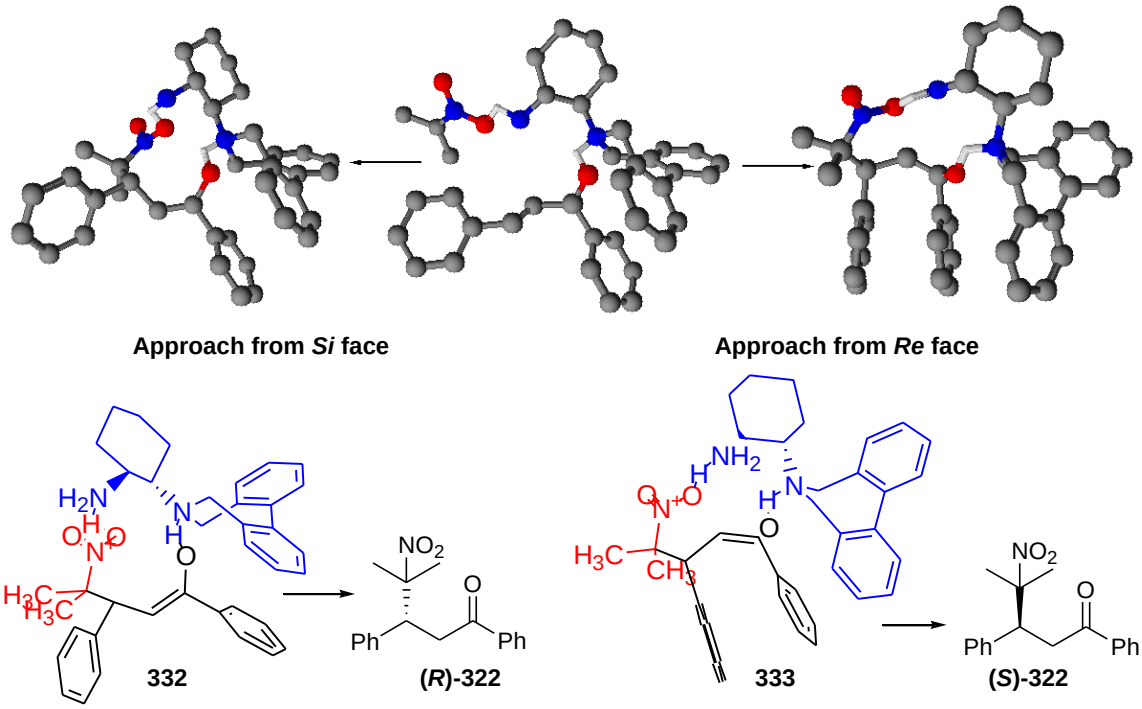
4. Nitroalkane conjugate addition to chalcone

Biaryl azepine **331** was used as the catalyst in the conjugate addition between chalcone and 2-nitropropane (**Scheme 149**). The reaction resulted in low yield of **322**, but a substantial increase in enantioselectivity was observed (75% ee).



Scheme 149: Enone and nitroalkane conjugate addition, using **331**.

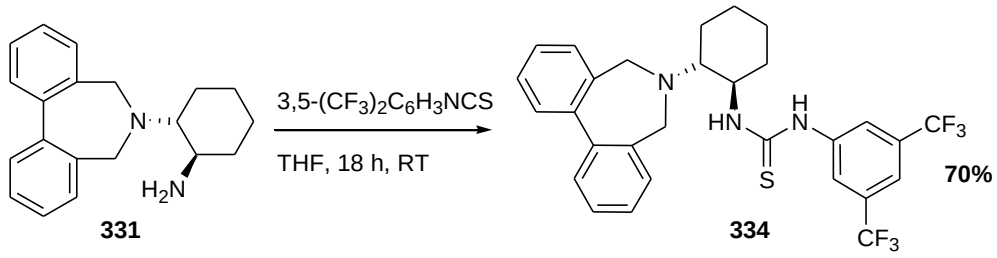
A possible explanation for the enantioselectivity is shown below (**Scheme 150**). In order to form **(*S*)-322**, the nitropropane must approach from the *Re* face (**333**), which will require rotation in chalcone's CO-CH bond, ultimately causing unfavourable steric clashing between its own phenyl groups.



Scheme 150: Possible explanation for enantioselectivity in the biaryl **331**-catalysed formation of **322**. The 3D models show the transition states with all hydrogens removed apart from those involved in hydrogen bonding.[128]

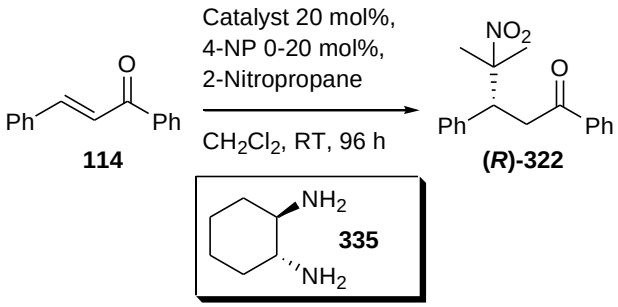
4.5.2. Use of an Azepinylthiourea in Asymmetric Reactions

Following these promising results, it was decided to select the two conjugate addition reactions for further investigation and to also synthesise a thiourea-substituted derivative, **334** (**Scheme 151**).



Scheme 151: Synthesis of (1'*R*,2'*R*)-6-(2'-(3'',5''-bis(trifluoromethyl)phenylthiourea) cyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine **334**.

Biaryl azepines **331** and **334** and (1*R*,2*R*)-1,2-diaminocyclohexane **335** were tested in the conjugate addition between chalcone and 2-nitropropane (**Scheme 152**). Because catalyst **334** contains an acidic thiourea moiety, it was always used without any other acid additive. The results obtained were generally poor, with the exception of **331**.4-NP, which gave a moderate enantioselectivity (54% ee).

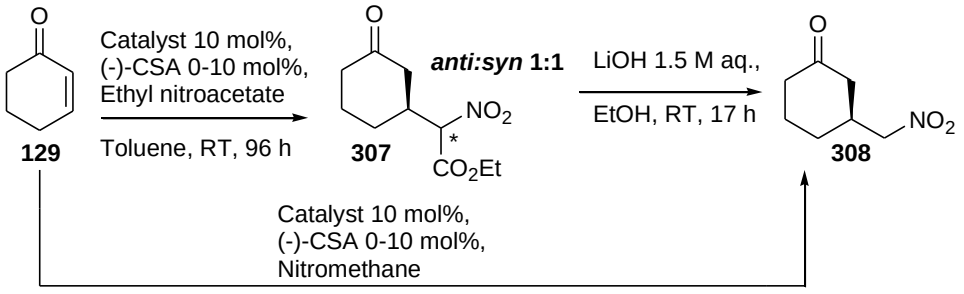


Catalyst	4-NP /mol%	Yield /%	ee /%
331	0	5	29
331	20	29	54
334	0	0*	-
335	20	15	15
335	0	0	-

Scheme 152: Results of enone conjugate addition with 2-nitropropane as catalysed by **331**, **334** or **335**. *All starting materials were visible by either ^{1}H NMR spectroscopy or mass spectroscopy. No product was apparent.

Catalysts **331**, **334** and **335** were also tested in the conjugate addition of cyclohexenone with both ethyl nitroacetate and nitromethane. The reactions using nitromethane generally gave low yields and enantioselectivities, the exception being with diamine **335** and (-)-CSA (51%, 63% ee).

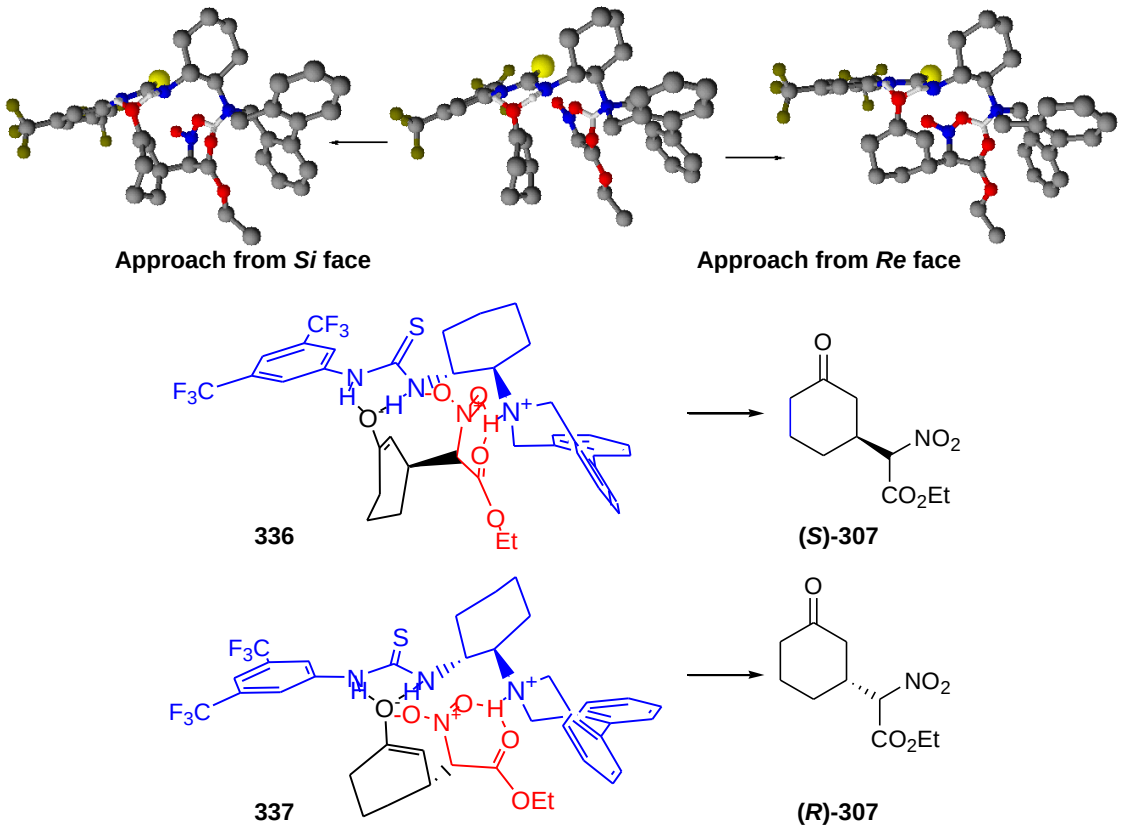
The reactions using ethyl nitroacetate gave better yields all around. When **331** was used as the catalyst, the yield and ee were 92% and 32% respectively – the yield dropped to 21% when (-)-CSA was added but the ee rose to 58%. An excellent yield and ee was obtained using **334** as the catalyst (91%, 90% ee).



Catalyst	(-)-CSA /mol %	Reagent	Conjugate Addition Yield /%	Decarboxylation Yield /%	ee /%
331	0	$EtO_2CCH_2NO_2$	92	77	32
331	10	$EtO_2CCH_2NO_2$	21	64	58
331	0	$MeNO_2$	16	-	24
331	10	$MeNO_2$	< 2	-	-
334	0	$EtO_2CCH_2NO_2$	92	91	90
334	0	$MeNO_2$	< 1	-	-
335	0	$EtO_2CCH_2NO_2$	89	73	27
335	10	$EtO_2CCH_2NO_2$	86	88	41
335	0	$MeNO_2$	28	-	40
335	10	$MeNO_2$	51	-	63

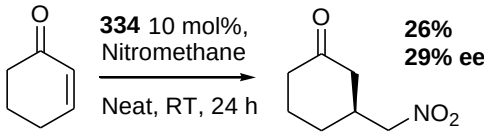
Scheme 153: Results of cyclohexanone conjugate addition with nitroester or nitroalkane as catalysed by **331**, **334** or **335**.

A possible explanation for the enantioselectivity when catalyst **334** was used is outlined below (**Scheme 154**). In both approaches, one of the EWGs in the nitroester will come into close proximity to the cyclohexenone, so this is unlikely to be the source of enantioselectivity here. However, when the ethyl nitroacetate approaches from the *Si* face (**336**), the cyclohexenone ring can remain almost parallel to the nearby trifluoromethyl-substituted phenyl ring of the catalyst while the ethyl nitroacetate ring system can remain almost parallel to the nearby phenyl ring of the catalyst, thus minimising steric clashing. When the ethyl nitroacetate approaches from the *Re* face (**337**), both reagents must rotate so that they are almost perpendicular to the nearby aryl rings of the catalyst, which will cause a substantial increase in steric clashing and hinder this direction of approach.



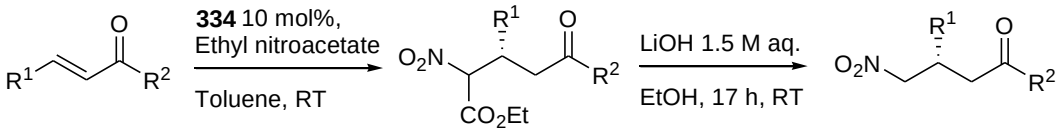
Scheme 154: Possible explanation for enantioselectivity in the biaryl **334**-catalysed formation of **307**. The 3D models show the transition states with all hydrogens removed apart from those involved in hydrogen bonding.[128]

As azepine **334** had given high yield and enantioselectivity in the reaction between ethyl nitroacetate **328** and cyclohexenone **129**, it was decided to test it across a range of substrates. Firstly, we tested the direct addition of nitromethane to cyclohexenone **129** (**Scheme 155**). However, only poor yield and enantioselectivity were obtained (26%, 29% ee).



Scheme 155: Addition of nitromethane to cyclohexenone catalysed by azepine **334**.

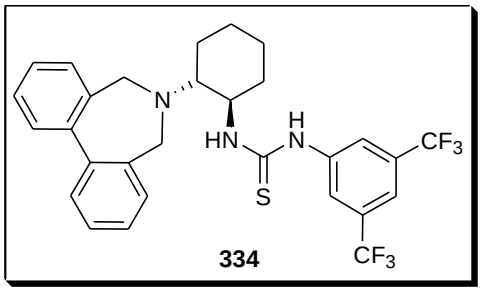
Next we tested azepine **334** as a catalyst for the addition of ethyl nitroacetate to three enones; chalcone **114**, 4-phenyl-3-buten-2-one **302** and 1-phenyl-3-buten-2-one **338** (**Scheme 156**). These gave adducts **339**, **340** and **341** respectively, which were then decarboxylated to give compounds **342**, **343** and **344** respectively. The formations of adducts **339** and **340** have been previously reported;[55, 127, 131] no previous reports on the formation of **341** are known to us, but the decarboxylated nitro-product **343** has been reported.[55]



114, R^1, R^2 = Ph
302, R^1 = Ph, R^2 = Me
338, R^1 = Me, R^2 = Ph

339, R^1, R^2 = Ph
340, R^1 = Ph, R^2 = Me
341, R^1 = Me, R^2 = Ph

342, R^1, R^2 = Ph
343, R^1 = Ph, R^2 = Me
344, R^1 = Me, R^2 = Ph



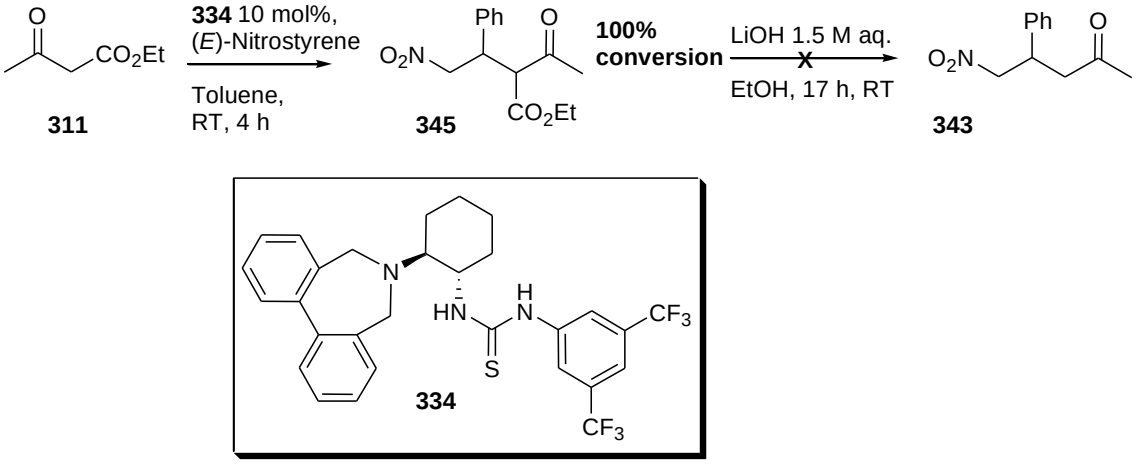
334

Conjugate Addition				Decarboxylation		
Substrate	**Product**	**Time /h**	**Conversion /%**	**Product**	**Yield /%**	**ee /%**
114	**339**	48	100	**342**	14	84
302	**340**	120	39	**343**	55	70
338	**341**	12	100	**344**	0	-

Scheme 156: Conjugate addition reactions of ethyl nitroacetate to a range of enones using azepine **334**.

Chalcone **114** was fully converted to adduct **339** (**Scheme 156**, entry 1) in 48 h. However, product **339** could not be separated from ethyl nitroacetate by column chromatography and subsequently, the crude mixture subjected to decarboxylation. The ethyl nitroacetate was converted to nitromethane, which was removed during work-up. The resulting nitro-compound **342** was isolated in low yield but high enantiopurity (14%, 84% ee). 4-Phenyl-3-buten-2-one **302** reacted slower and produced adduct **340** in a mediocre yield (39%) in 120 h. This could however, be purified and was decarboxylated to **343**, which was isolated in moderate yield and good enantiopurity (55%, 70% ee). Although 1-phenyl-3-buten-2-one **338** gave full conversion to adduct **341** in only 12 h, the resulting mixture did not give the desired compound **344** when subjected to decarboxylation. The resulting by-product was not identified and unexpectedly, its ^{1}H NMR spectrogram contained a signal characteristic of an aldehyde.

Finally, we tested azepine **334** as a catalyst in the conjugate addition reaction between (*E*)-nitrostyrene and ethyl acetoacetate **311** (**Scheme 157**) to form adduct **345**, whose preparation has been previously reported.[132] The reaction proceeded quickly, giving 100% conversion in 4 h, but decarboxylation of adduct **345** did not give the desired compound **343**. As before, an unidentified by-product with a 1H NMR signal characteristic of an aldehyde seemed to form preferentially.



Scheme 157: Conjugate addition reaction of ethyl acetoacetate and (*E*)-nitrostyrene using azepine **334**.

4.6. Summary and Conclusions

In this part of the project, we developed the synthesis of a range of proline-derived diamine catalysts **202** with the positions of the acid and amine moieties reversed compared to those more commonly reported in the literature (**201**).

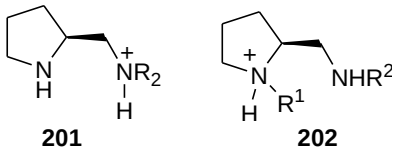


Figure 20: Prolinamine catalysts with positions of the acid and amine moieties reversed.

Diamines **202** that had the side chain substituted with α-methylbenzylamine could be synthesised in reasonable yields. However, they showed little or no activity in the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone. The diamines with R^2 = H could be synthesised in good yields. These diamines were found to catalyse the aldol reaction in good yield (several reached 100% conversion in 21-33 h), reasonable diastereoselectivity (typical *anti*:*syn* ratio ~85:15) and reasonable enantioselectivity (46-67% ee). Importantly, it appears that reversing the functionalities on the diamine also reverses the enantioselectivity.

The same catalysts were tested across a range of other asymmetric reactions and four of them showed promising results in terms of yield and/or enantioselectivity; the fluorination of DL-2-phenylpropionaldehyde (53%, 10% ee), the Biginelli reaction (44%, 7% ee), the conjugate addition between chalcone and 2-nitropropane (90%, 20% ee) and the conjugate addition of cyclohexenone and ethyl nitroacetate (97%, 40% ee).

These four reactions were then attempted using biarylazepine catalyst **331**, these all showed general improvement (Biginelli reaction: 66%, 18% ee, fluorination

reaction: 52%, 43% ee) with high enantioselectivities obtained for the two conjugate addition reactions (ethyl nitroacetate and cyclohexanone: ~60% ee, 2-nitropropane and chalcone: 75% ee).

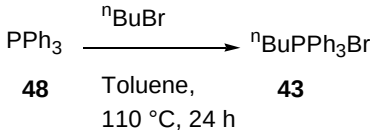
Finally, the two conjugate addition reactions mentioned above were also attempted using azepinylthiourea **334** and diamine **335**, with a particularly good result obtained using **334** (91% yield, 90% ee) for cyclohexenone and nitroacetate. Azepinylthiourea **334** gave high enantioselectivities in two other conjugate addition reactions (chalcone and ethyl nitroacetate: 100%, 84%, 4-phenyl-3-buten-2-one and ethyl nitroacetate: 39%, 70% ee) and showed to be able to give 100% conversion in short time for two others (ethyl nitroacetate and 1-phenyl-3-buten-2-one: 12 h, (*E*)-nitrostyrene and ethyl acetoacetate: 4 h) though the enantioselectivity was not determined.

Of all the catalysts developed over the course of this research project, the diamine/diamine-derived catalysts in this chapter were the most successful in terms of enantioselectivity, and further investigation into their application in asymmetric synthesis is recommended. Reversing the positions of the acid and base moieties in proline-derived diamines reverses enantioselectivity; applying this to similar compounds may be a substantially cheaper means of synthesising enantiomers normally only obtainable from D-proline-derived catalysts. Likewise, the biaryl azepine catalysts showed ability to catalyse a variety of conjugate addition reactions in good yield and enantioselectivity and may be applicable to similar reaction types – ultimately time restraints limited the amount of research that could be done.

5. Experimental

All chemicals were bought from commercial sources and used as received, with the exception of (1'*R*,2'*R*)-6-(2'-aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine, phenyl vinyl ketone and *N*,*N*-diphenyl methylene glycine *tert*-butyl ester, which were prepared by co-workers. All NMR spectra were obtained at room temperature from either a Jeol EX270 spectrometer, Bruker AV400, AV(III)400 or DPX400 spectrometer. All chemical shifts (δ) are reported in parts per million (ppm). The multiplicities of the signals are designated by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, sept = septet, m = multiplet, br = broad, app = apparent, imp = impurity, dia = diastereomer. All coupling constants *J* are reported in Hertz. Assignment of peaks was assisted by DEPT45, DEPT90, DEPT135, COSY, HMQC and HMBC when necessary. ^{13}C and ^{31}P NMR spectra are proton decoupled. Mass spectra were obtained from a Bruker microTOF mass spectrometer, using electrospray ionisation. Melting points were determined using a Stuart SMP3 electrothermal apparatus. Infrared spectra were recorded using a Bruker Tensor 27 spectrometer. Optical rotations were determined on a Bellingham and Stanley ADP440 polarimeter at wavelength 589 nm and are given in units of 0.1 deg cm^2/g, concentration (c) is in g/100 mL of solvent. High Performance Liquid Chromatography (HPLC) was performed on a Hewlett-Packard LC-100 chromatograph and the absolute stereochemistry of all products was determined by comparison of HPLC retention times to previously reported data. Column chromatography used C60 (35-70) silica gel and TLC used Kieselgel 60 pre-coated glass sheets with a 0.25 mm layer of silica. The petroleum ether used was in the 40-60 °C boiling range.

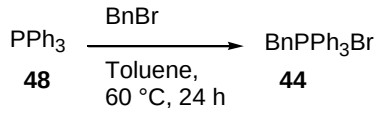
n-Butyltriphenylphosphonium bromide 43 [133,134]



^{n}BuBr (2.36 g, 17.2 mmol, 3 eq.) was added a solution of PPh_3 (1.50 g, 5.72 mmol, 1 eq.) in toluene (15 mL) and the reaction mixture was heated under reflux for 24 h. The reaction mixture was concentrated under reduced pressure to give the product as a colourless crystalline solid (1.59 g, 70%). m.p. 238-242 °C [lit. 239-241 °C][133]; R_f ($CHCl_3$:MeOH 19:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 2936, 2875, 1439, 1242, 1114, 998, 908; δ_H ($CDCl_3$, 400 MHz) 7.87-7.79 (9H, m, Ar*H*), 7.74-7.69 (6H, m, Ar*H*), 3.81-3.74 (2H, m, PCH_2), 1.72-1.57 (4H, m, $CH_2CH_2CH_3$), 0.91 (3H, t, *J* 7.0, CH_3); δ_C ($CDCl_3$, 100 MHz) 135.0 (d, *J* 3.0, CH), 133.7 (d, *J* 10.0, CH), 130.5 (d, *J* 13.0, CH), 118.4 (d, *J* 86.0, C_q), 24.7 (d, *J* 4.0, CH_2), 23.8 (d, *J* 16.0, CH_2), 22.7 (d, *J* 50.0, CH_2), 13.8 (CH_3); δ_P ($CDCl_3$, 167 MHz) 23.1; *m/z* (ES) 319 ($M\text{-}Br^+$,

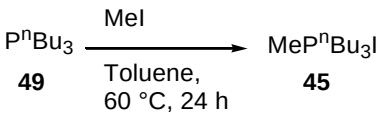
100%); *m/z* (ES) found $[M\text{-}Br]^+$ 319.1599. $C_{22}H_{24}P^+$ requires 319.1610. The ^1H and ^{13}C NMR data are in agreement with those previously reported.[134]

Benzyltriphenylphosphonium bromide 44 [135,136]



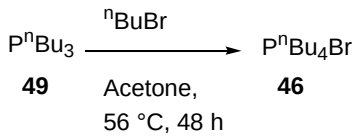
BnBr (1.63 g, 9.53 mmol, 5 eq.) was added to a solution of PPh_3 (0.50 g, 1.91 mmol, 1 eq.) in toluene (5 mL) and the reaction mixture was heated at 60 °C for 24 h. The solvent was removed under reduced pressure to give the product as a colourless solid (0.76 g, 92%). m.p. 293-295 °C (dec.) [lit. 294-295 °C][135]; R_f ($CHCl_3$:MeOH 19:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 3064, 3011, 2936, 2782, 2450, 1601, 1589, 1496, 1486, 1456, 1439, 1400, 1339, 1316, 1242, 1164, 1141, 1112, 1072, 1030, 998, 909, 834; δ_H ($CDCl_3$, 400 MHz) 7.79-7.68 (9H, m, ArH), 7.65-7.59 (6H, m, Ar*H*), 7.24-7.18 (1H, m, Ar*H*), 7.13-7.06 (4H, m, Ar*H*), 5.34 (2H, d, *J* 14.0, C*H*$_2$Ph); δ_C ($CDCl_3$, 100 MHz) 135.0 (d, *J* 2.0, CH), 134.4 (d, *J* 10.0, CH), 131.5 (d, *J* 5.0, CH), 130.2 (d, *J* 13.0, CH), 128.8 (d, *J* 3.0, CH), 128.4 (d, *J* 4.0, CH), 127.1 (d, *J* 8.0, CH), 117.7 (d, *J* 9.0, C_q), 30.9 (d, *J* 47.0, CH_2); δ_P ($CDCl_3$, 167 MHz) 23.13; *m/z* (ES) 353 ($M\text{-}Br^+$, 100%); *m/z* (ES) found $[M\text{-}Br]^+$ 353.1444. $C_{25}H_{22}P$ requires 353.1459. ^1H and ^{13}C NMR data are consistent with literature.[136]

Methyltri(*n*-butyl)phosphonium iodide 45 [137]



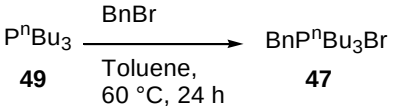
MeI (1.75 g, 12.4 mmol, 5 eq.) was added to a solution $^nBu_3P$ (0.50 g, 2.47 mmol, 1 eq.) in toluene (5 mL) under an inert atmosphere of argon and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to give the product as a colourless solid (0.81 g, 95%). m.p. 131-133 °C [lit. 131-132 °C][137]; R_f ($CHCl_3$:MeOH 19:1) 0.4; ν_{max} ($CHCl_3$)/cm^{-1} 3405, 2967, 2877, 2436, 1465, 1415, 1384, 1308, 1240, 1098, 933; δ_H ($CDCl_3$, 400 MHz) 2.51-2.43 (6H, m, PC*H*$_2$), 2.11 (3H, d, *J* 13.0, C*H*$_3$), 1.61-1.52 (12H, m, C*H*$_2$C*H*$_2$CH$_3$), 1.01-0.97 (9H, t, *J* 7.0, C*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 23.8 (d, *J* 16.0, CH_2), 23.7 (d, *J* 5.0, CH_2), 20.6 (d, *J* 48.0, CH_2), 13.5 (CH_3), 5.6 (d, *J* 52.0, CH_3); δ_P ($CDCl_3$, 167 MHz) 31.51; *m/z* (ES) 217 ($M\text{-}I^+$, 100%), 319 (19), 561 (13); *m/z* (ES) found $[M\text{-}I]^+$ 217.2078. $C_{13}H_{30}P^+$ requires 217.2080.

Tetra(*n*-butyl)phosphonium bromide 46 [138]



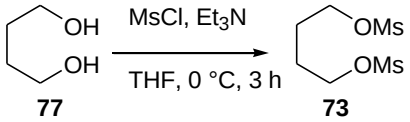
^{n}BuBr (1.52 g, 11.1 mmol, 1.5 eq.) was added to a solution of $^{n}Bu_3P$ (1.50 g, 7.41 mmol, 1 eq.) in acetone (60 mL) under an inert atmosphere of argon and the reaction mixture was heated under reflux for 48 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and precipitation was induced by addition of Et_2O (40 mL). The resulting precipitate was collected by filtration, giving the product as a colourless crystalline solid (1.39 g, 93%). m.p. 101-103 °C [lit. 101-103 °C][138]; R_f ($CHCl_3$:MeOH 19:1) 0.5; ν_{max} ($CHCl_3$)/cm^{-1} 2935, 2876, 1465, 1384, 1242, 1098; δ_H ($CDCl_3$, 400 MHz) 2.49-2.43 (8H, m, PC*H*$_2$), 1.55-1.51 (16H, m, C*H*$_2$C*H*$_2$CH$_3$), 0.97 (12H, t, *J* 7.0, C*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 24.0 (d, *J* 22.0, C*H*$_2$), 23.9 (s, C*H*$_2$), 19.2 (d, *J* 47.0, C*H*$_2$), 13.5 (CH_3); δ_P ($CDCl_3$, 167 MHz) 32.8; *m/z* (ES) 259 (M-Br$^+$, 100%); *m/z* (ES) found [M-Br$^+$] 259.2536. $C_{16}H_{36}P^+$ requires 259.2549.

Benzyltri(*n*-butyl)phosphonium bromide 47 [139]



BnBr (2.11 g, 12.4 mmol, 5 eq.) was added to a solution of $^{n}Bu_3P$ (0.50 g, 2.47 mmol, 1 eq.) in toluene (5 mL) under an inert atmosphere of argon and the reaction mixture was heated at 60 °C for 24 h. The solvent was removed under reduced pressure to give the product as a colourless solid (0.85 g, 92%). m.p. 148-150 °C [lit. 149 °C][139]; R_f ($CHCl_3$:MeOH 19:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 2936, 2876, 1497, 1465, 1407, 1383, 1242, 1097, 1076, 909; δ_H ($CDCl_3$, 400 MHz) 7.49-7.31 (5H, m, Ar*H*), 4.28 (2H, d, *J* 7.5, C*H*$_2$Ph), 2.46-2.39 (6H, m, PC*H*$_2$), 1.49-1.43 (12H, m, C*H*$_2$C*H*$_2$CH$_3$), 0.92 (9H, t, *J* 7.0, C*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 130.2 (d, *J* 5.0, CH), 129.4 (d, *J* 3.0, CH), 128.4 (d, *J* 4.0, CH), 128.5 (C_q), 27.0 (d, *J* 45.0, CH_2), 24.0 (d, *J* 15.0, CH_2), 23.7 (d, *J* 5.0, CH_2), 18.8 (d, *J* 46.0, CH_2), 13.4 (CH_3); δ_P ($CDCl_3$, 167 MHz) 31.54; *m/z* (ES) 293 (M-Br$^+$, 100%); *m/z* (ES) found [M-Br]$^+$ 293.2376. $C_{19}H_{34}P^+$ requires 293.2393. The ^{1}H NMR data was in agreement with that previously reported.[139]

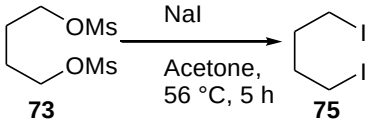
1,4-Di-(methanesulfonyloxy)butane 73 [140,141]



77 **73**

Et_3N (7.72 mL, 55.5 mmol, 2.5 eq.) was added dropwise to solution of 1,4-butanediol (2.00 g, 22.2 mmol, 1 eq.) in THF (30 mL) at 0 °C, followed by MsCl (3.77 mL, 48.8 mmol, 2.2 eq.) and the reaction mixture stirred for 2 h, allowing warming to room temperature. The reaction mixture was concentrated under reduced pressure and the residue dissolved in CH_2Cl_2 (40 mL). The solution was washed successively with H_2O (30 mL), 5% aqueous HCl solution (10 mL), and brine (30 mL). The organic layer was then dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by recrystallization from cyclohexane to yield the product as a crystalline colourless solid (5.25 g, 96%). m.p. 116-118 °C [lit. 116 °C][140]; R_f (petroleum ether:EtOAc 4:1) 0.2; ν_{max} ($CHCl_3$)/cm^{-1} 3045, 2966, 1471, 1414, 1361, 1341, 1175, 1024, 972, 937, 826; δ_H ($CDCl_3$, 400 MHz) 4.32-4.29 (4H, m, OCH_2), 3.04 (6H, s, CH_3), 1.95-1.92 (4H, m, OCH_2CH_2); δ_C ($CDCl_3$, 100 MHz) 68.8 (CH_2), 37.5 (CH_3), 25.5 (CH_2); *m/z* (ES) 269 ($M+Na^+$, 100%); *m/z* (ES) found $[M+Na]^+$ 269.0122. $C_6H_{14}S_2O_6Na^+$ requires 269.0130. The ^1H NMR data was in agreement with that previously reported.[141]

1,4-Diiodobutane 75 [142]



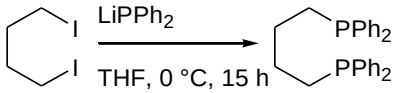
73 **75**

NaI (4.68 g, 31.2 mmol, 2.2 eq.) was added to a solution of 1,4-dimethanesulfonylbutane (3.50 g, 14.2 mmol, 1 eq.) in acetone (30 mL) and the reaction mixture was heated under reflux for 4 h. The resulting suspension was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in Et_2O (30 mL) and was washed with water (30 mL), brine (30 mL). Saturated aq. $Na_2S_2O_3$ solution was added dropwise while stirring until the brown colour had vanished. The organic layer was separated and dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether:EtOAc 9:1) to give the product as a light yellow oil (3.70 g, 84%). R_f (petroleum ether:EtOAc 9:1) 0.9; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2963, 2939, 2840, 1732, 1442, 1429, 1360, 1287, 1241, 1187, 1159, 1141, 1121, 1046, 951, 887; δ_H ($CDCl_3$, 400 MHz) 3.24-3.20 (4H, m, ICH_2), 2.19-1.95 (4H, m, ICH_2CH_2); δ_C ($CDCl_3$, 100 MHz) 33.9 (CH_2), 5.1 (CH_2). The ^1H NMR data was in agreement with that previously reported.[142]

Preparation of lithium diphenylphosphide in THF [32]

A solution of PPh_3 (2.10 g, 8.01 mmol) in dry THF (20 mL) was added dropwise to lithium (0.30 g, 43.2 mmol, 5.4 eq.) under an inert atmosphere of argon and the mixture was stirred at 0 °C for 4 h, during which time the solution turns a dark red colour. This resulting solution was assumed to contain 0.4 M $LiPPh_2$ and was used directly in subsequent reactions.

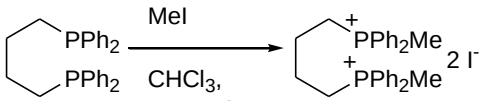
1,4-Bis(diphenylphosphino)butane 78 [143,144]



75 **78**

$LiPPh_2$ (7.66 mL of 0.4 M solution in THF, 3.07 mmol, 1.9 eq.) was added dropwise to a solution of 1,4-diiodobutane (0.50 g, 1.61 mmol, 1 eq.) in dry THF (5 mL) under an inert atmosphere of argon at 0 °C and the reaction mixture was allowed to warm to room temperature over 15 h. Unreacted $LiPPh_2$ was quenched by addition of water (100 mL), which results in product precipitation. Filtration gave the crude product as an off-white solid (0.57 g, 83%). m.p. 130-133 °C. [lit. 132 °C] [143]; ν_{max} ($CHCl_3$)/cm^{-1} 3073, 3058, 3011, 2937, 2859, 1586, 1481, 1434, 1171, 1121, 1097, 1069, 1027, 1000, 909; δ_H ($CDCl_3$, 400 MHz) 7.42-7.34 (20H, m, Ar*H*), 2.07-2.03 (4H, m, PCH_2), 1.70-1.50 (4H, m, PCH_2CH_2); δ_C ($CDCl_3$, 100 MHz) 138.9 (d, *J* 12.5, C_q), 132.7 (d, *J* 19.0, CH), 128.5 (CH), 128.4 (d, *J* 6.0, CH), 27.8 (dd, *J* 12.5, 8.5, CH_2), 27.7 (d, *J* 14.0, CH_2); δ_P ($CDCl_3$, 162 MHz) –16.11. The above ^{1}H NMR data was in agreement with those previously reported.[144]

1,4-Bis(methyldiphenylphosphonium)butane diiodide 80

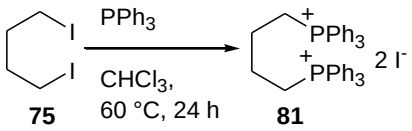


78 **80**

MeI (0.17 g, 1.17 mmol, 5 eq.) was added to a solution of 1,4-bis(diphenylphosphino)butane (0.10 g, 0.23 mmol, 1 eq.) in CH_2Cl_2 (3 mL) and MeOH (5 mL) and the reaction mixture was stirred for 14 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was dissolved in water (25 mL) and cooled to 10 °C. The aqueous solution was extracted with CH_2Cl_2 (5 mL x 2). Addition of Et_2O (40 mL) to the organic layer resulted in precipitation of the product. Filtration of the suspension gave a colourless crystalline solid (96 mg, 60%). m.p. 133-135 °C; R_f ($CHCl_3$:MeOH 19:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 3403, 2949,

1439, 1240, 1117, 913, 898; δ_H ($CDCl_3$, 400 MHz) 7.95-7.90 (8H, m, Ar*H*), 7.77-7.73 (4H, m, Ar*H*) 7.70-7.66 (8H, m, Ar*H*), 3.61-3.47 (4H, m, PCH_2), 2.73 (6H, *J*, 13.0, CH_3) 2.19-2.13 (4H, m, PCH_2CH_2); δ_C ($CDCl_3$, 100 MHz) 134.9 (d, *J* 3.0, CH), 132.6 (d, *J* 10.0, CH), 130.5 (d, *J* 12.0, CH), 119.1 (d, *J* 85.0, C_q), 22.2 (dd, *J* 15.0, 5.0, CH_2), 21.8 (d, *J* 52.0, CH_2), 8.6 (d, *J* 55.0, CH_3); δ_P ($CDCl_3$, 162 MHz) 24.4; *m/z* (ES) 457 (100%) 583 (M-I^+, 48); (ES) found $[M-I]^+$ 583.1158. $C_{30}H_{34}IP_2^+$ requires 583.1175.

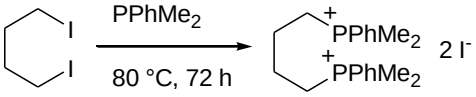
1,4-Bis(triphenylphosphonium)butane diiodide 81



75 **81**

Diiodobutane (0.50 g, 1.61 mmol, 1 eq.) was added to a solution of PPh_3 (0.93 g, 3.55 mmol, 2.2 eq.) in chloroform (20 mL) and the reaction mixture was heated at 60 °C for 24 h. Precipitation of the product was induced by addition of Et_2O (40 mL) and the reaction mixture was filtered to give the product as a colourless crystalline solid, which was then dried under high vacuum (1.30 g, 97%). m.p. 230-235 °C; R_f ($CHCl_3$:MeOH 19:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 3407, 2941, 2872, 2436, 1711, 1589, 1486, 1439, 1363, 1240, 1114, 998; δ_H ($CDCl_3$, 400 MHz) 7.93-7.72 (30H, m, Ar*H*), 4.00-3.85 (4H, m, PCH_2), 2.35-2.20 (4H, m, PCH_2CH_2); δ_C ($CDCl_3$, 100 MHz) 134.9 (d, *J* 3.0, CH), 134.2 (d, *J* 10.0, CH), 130.6 (d, *J* 6.0, CH), 117.9 (d, *J* 85.0, C_q) 23.4 (dd, *J* 19.0, 4.0, CH_2) 22.7 (d, *J* 51.0, CH_2); δ_P ($CDCl_3$, 162 MHz) 24.4; *m/z* (ES) 290 (100), 353 (16), 445 (84), 579 (19), 707 (M-I^+, 39%); (ES) found $[M-I]^+$ 707.1467. $C_{40}H_{38}IP_2^+$ requires 707.1488.

1,4-Bis(dimethylphenylphosphonium)butane diiodide 83 [145]

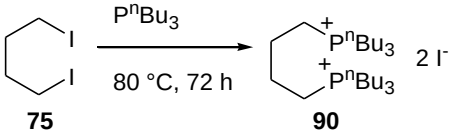


75 **83**

Me_2PPh (0.23 mL, 1.60 mmol, 5 eq.) was added to 1,4-diiodobutane (0.10 g, 0.32 mmol, 1 eq.) under an inert atmosphere of argon and the reaction mixture was heated at 80 °C for 72 h. The resulting mixture was dissolved in MeOH (2 mL). Precipitation of the product was induced by addition of Et_2O (40 mL). The solution was filtered to obtain the product as a colourless solid (0.12 g, 57%). m.p. 213-215 °C (dec.) [lit. 217 °C][145]; R_f ($CHCl_3$:MeOH 4:1) 0.3; δ_H (400 MHz, CD_3OD) 8.00-7.94 (4H, m, Ar*H*), 7.83-7.78 (2H, m, Ar*H*), 7.73-7.67 (4H, m, Ar*H*), 2.73-2.65 (4H, m, PCH_2), 2.27 (12H, d, *J* 14.0, CH_3), 1.72-1.69 (4H, m, PCH_2CH_2); δ_C (100 MHz, CD_3OD) 135.6 (d, *J* 4.0, CH), 132.6 (d, *J* 12.0, CH), 131.1 (d, *J* 11.0, CH), 121.5 (d, *J* 80.0, C_q), 24.3 (d, *J* 52.0, CH_2), 23.49 (dd, *J* 19.0, 4.0, CH_2), 7.60

(d, *J* 60.0, CH_3); δ_P (162 MHz, CD_3OD) 25.24; *m/z* (ES) 331 (43%), 459 ($M\text{-}I^+$, 100); *m/z* found $[M\text{-}I]^+$ 459.0849. $C_{20}H_{30}P_2I^+$ requires 459.0862.

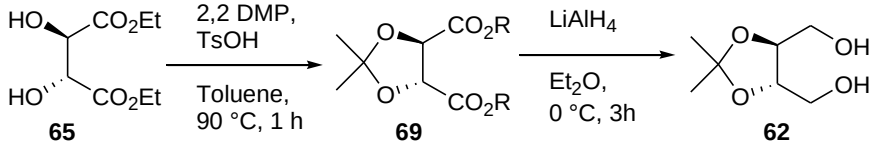
1,4-Bis(tributylphosphonium)butane diiodide 90



75 **90**

Tri-*n*-butylphosphine (0.40 mL, 1.60 mmol, 5 eq.) was added to 1,4-diiodobutane (0.10 g, 0.32 mmol, 1 eq.) under an inert atmosphere of argon and the reaction mixture was heated at 80 °C for 72 h. The resulting mixture was dissolved in CH_2Cl_2 (5 mL). Precipitation of the product was induced by addition of Et_2O (100 mL). The solution was filtered to obtain the product as a colourless solid (0.19 g, 84%), which was dried under high vacuum. m.p. 190-195 °C; R_f ($CHCl_3$:MeOH 19:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 2936, 2876, 1465, 1384, 1240, 1098, 915; δ_H (400 MHz, $CDCl_3$) 2.82-2.75 (4H, m, C*H*$_2$CH$_2$CH$_2$C*H*$_2$), 2.34-2.26 (12H, m, C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.14-2.05 (4H, m, CH$_2$C*H*$_2$C*H*$_2$CH$_2$), 1.62-1.50 (24H, m, C*H*$_2$C*H*$_2$CH$_3$), 1.00 (18H, t, *J* 7.0, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 24.0 (d, *J* 15.0, CH_2), 23.8 (d, *J* 4.0, CH_2), 22.5 (dd, *J* 17.0, 4.0, CH_2), 19.2 (d, J 48.0, CH_2), 13.5 (CH_3); δ_P (162 MHz, $CDCl_3$) 33.6; *m/z* (ES) 459 (22), 587 ($M\text{-}I^+$, 100%); *m/z* found $[M\text{-}I]^+$ 587.3344. $C_{28}H_{62}P_2I^+$ requires 587.3373.

(-)-(4*R*,5*R*)-2,3-*O*-Isopropylidene-L-threitol 62 [146,147]



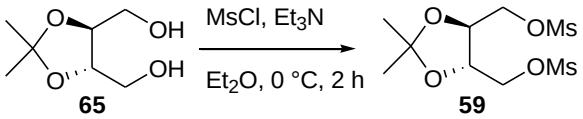
65 **69** **62**

R = Me/Et

TsOH (0.18 g, 0.97 mmol, 0.1 eq.) and 2,2 DMP (2.53 g, 24.3 mmol, 2.5 eq.) are added to a solution of L-(+)-diethyl tartrate (2.00 g, 9.70 mmol, 1 eq.) in toluene (50 mL) and the reaction mixture heated to 90 °C for 1 h. The mixture was concentrated under reduced pressure, dissolved in Et_2O (30 mL), and was washed successively with H_2O (30 mL), brine (30 mL) and then saturated aq. $NaHCO_3$ solution (5 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to give (*R*,*R*)-*O*,*O*-isopropylidene-L-tartaric acid diester (*ca.* 99%) as a mixture of methyl and ethyl esters (*ca.* 1:2 mixture). This material was then dissolved in Et_2O (15 mL) and cooled to –5 °C. $LiAlH_4$ (0.81 g, 21.2 mmol, 2.2 eq.) was stirred in dry Et_2O (15 mL) and cooled to –5 °C. The ester solution was added slowly to the $LiAlH_4$ suspension. The mixture was allowed to warm up to room temperature and was stirred for 3 h. The reaction was quenched by slow addition of EtOAc (1 mL), H_2O (1 mL) and 10% NaOH (1 mL). The reaction mixture was

extracted with EtOAc (3 x 25 mL) and filtered. The mixture was concentrated under reduced pressure to give the product as a thick yellow oil (1.57 g, 99%). R_f ($CHCl_3$:MeOH 19:1) 0.4; $[\alpha]_D^{22}$ −3.7 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3602, 3470, 2991, 2935, 2882, 1456, 1243, 1164, 1108, 1074, 1052, 982, 913, 870, 844; δ_H ($CDCl_3$, 400 MHz) 4.05-3.99 (2H, m, C*H*), 3.84-3.78 (2H, m, CH_2CHCHCH_2), 3.74-3.68 (2H, m, CH_2CHCHCH_2), 2.25 (2H, dd, *J* 7.0, 5.0, O*H*), 1.44 (6H, s, CH_3); δ_C ($CDCl_3$, 100 MHz) 109.1 (C_q), 77.9 (CH_2), 62.0 (CH_2), 27.1 (CH_3). The ^1H and ^{13}C NMR data was in agreement with those previously reported.[146, 147]

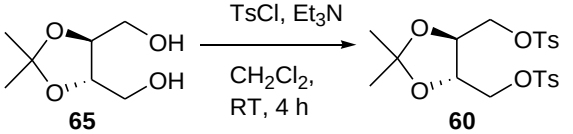
1,4-Di-*O*-methanesulfonyl-2,3-*O*-isopropylidene-L-threitol 59 [148]



65 **59**

Et_3N (1.30 mL, 9.32 mmol, 2.5 eq.) and MsCl (0.60 mL, 7.92 mmol, 2.2 eq.) were added sequentially to a solution of (-)-(4*R*,5*R*)-2,3-*O*-isopropylidene-L-threitol (0.70 g, 3.60 mmol, 1 eq.) in Et_2O (30 mL) and the reaction mixture was stirred for 2 h at 0 °C. The mixture was concentrated under reduced pressure and dissolved in CH_2Cl_2 (10 mL), washed with water (30 mL) and brine (30 mL) and dried with $MgSO_4$. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (toluene:MeOH 9:1), visualising TLC plates with concentrated sulfuric acid and heating, to give the product as a colourless solid (0.76 g, 66%). m.p. 82-86 °C [lit. 83-84 °C][148]; R_f (toluene:MeOH 9:1) 0.4; $[\alpha]_D^{22}$ −4.4 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3045, 2993, 2941, 1456, 1414, 1364, 1242, 1178, 1105, 995, 963, 850, 821; δ_H ($CDCl_3$, 400 MHz) 4.43-4.34 (4H, m, CH_2), 4.23-4.18 (2H, m, C*H*), 3.10 (6H, s, SCH_3), 1.46 (6H, s, CCH_3); δ_C ($CDCl_3$, 100 MHz) 111.0 (C_q), 75.2 (CH), 67.9 (CH_2), 37.7 (CH_3), 26.9 (CH_3); *m/z* (ES) 341 ($M+Na^+$, 100%), 659 ($2M+Na^+$, 21); *m/z* found $[M+Na]^+$ 341.0334. $C_9H_{18}S_2O_8Na^+$ requires 341.0335. The ^1H and ^{13}C NMR data was in agreement with those previously reported.[148]

1,4-Di-*O*-toluenesulfonyl-2,3-*O*-isopropylidene-L-threitol 60 [149,150,151]

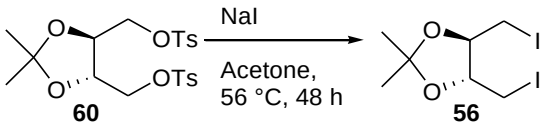


65 **60**

Et_3N (0.52 mL, 3.75 mmol, 2.5 eq) and TsCl (0.65 g, 3.30 mmol, 2.2 eq.) were added sequentially to a solution of (-)-(4*R*,5*R*)-2,3-*O*-isopropylidene-L-threitol (0.25 g, 1.50 mmol, 1 eq.) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred for 4 h. The mixture was washed with water (30 mL) and dried with $MgSO_4$. The

reaction mixture was concentrated under reduced pressure and then recrystallised from ethanol to give the product as a colourless crystalline solid (0.57 g, 79%). m.p. 90-91 °C [lit. 88-90 °C][149]; R_f (petroleum ether:EtOAc 4:1) 0.2; $[\alpha]_D^{22}$ −12.0 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3046, 2992, 2938, 1599, 1495, 1454, 1372, 1308, 1292, 1190, 1178, 1096, 1020, 991, 963, 919, 927; δ_H ($CDCl_3$, 400 MHz) 7.79 (4H, d, *J* 8.5, ArH), 7.37 (4H, d, *J* 8.0, ArH), 4.14-4.06 (4H, m, C*H*$_2$), 4.05-3.99 (2H, m, C*H*), 2.47 (6H, s, ArC*H*$_3$), 1.31 (6H, s, CC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 145.3 (C_q), 132.5 (C_q), 130.0 (CH), 128.0 (CH), 110.9 (C_q), 75.1 (CH), 68.4 (CH_2), 26.8 (CH_3), 21.7 (CH_3); *m/z* (ES) 471 ($M+H^+$, 77%), 493 ($M+Na^+$, 100); *m/z* found $[M+Na]^+$ 493.0961. $C_{21}H_{26}S_2O_8Na^+$ requires 493.0967. The ^1H and ^{13}C NMR data was in agreement with those previously reported.[150,151]

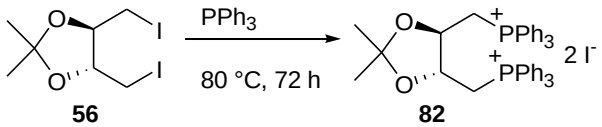
1,4-Dideoxy-1,4-diiodo-2,3-*O*-isopropylidene-L-threitol 56 [152]



60 **56**

NaI (0.21 g, 1.41 mmol, 2.2 eq.) was added to solution of 1,4-di-*O*-toluenesulfonyl-2,3-*O*-isopropylidene-L-threitol (0.30 g, 0.64 mmol, 1 eq.) in acetone (10 mL) and the reaction mixture was heated under reflux for 48 h. The mixture was filtered to remove any NaOTs and the filtrand was washed with Et_2O (30 mL). The filtrates were combined and washed successively with water (30 mL), brine (30 mL) and saturated aq. $Na_2S_2O_3$ solution was added dropwise until all brown coloration had been removed. The organic layer was separated, dried with $MgSO_4$ and concentrated under reduced pressure to give the product as a yellow-orange oil (0.22 g, 90%). R_f (petroleum ether:EtOAc 4:1) 0.6; $[\alpha]_D^{22}$ +0.9 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2993, 2937, 1740, 1602, 1455, 1429, 1415, 1383, 1374, 1333, 1242, 1184, 1154, 1109, 1043, 885; δ_H ($CDCl_3$, 400 MHz) 3.88-3.86 (2H, m, C*H*), 3.40-3.38 (4H, m, C*H*$_2$) 1.49 (6H, s, C*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 110.2 (C_q), 80.3 (CH), 27.7 (CH_2), 6.4 (CH_3); The ^1H and ^{13}C NMR data were in agreement with those previously reported.[152]

1,4-Dideoxy-1,4-di(triphenylphosphonium)-2,3-*O*-isopropylidene-L-threitol diiodide 82

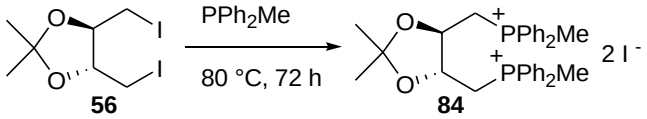


56 **82**

1,4-Dideoxy-1,4-diiodo-2,3-*O*-isopropylidene-L-threitol (0.10 g, 0.26 mmol, 1 eq.) was added to molten PPh_3 (m.p. 80 °C) (0.68 g, 2.62 mmol, 10 eq.) and the reaction mixture was heated at 80 °C for 72 h, over which time a solid precipitated. Et_2O (40 mL) was added and the mixture was filtered to give the product as a

colourless crystalline solid (0.22 g, 100%). R_f ($CHCl_3$:MeOH 19:1) 0.3; m.p. 260-264 °C (dec.); $[\alpha]_D^{22}$ −20.0 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3400, 3011, 2942, 2436, 1589, 1486, 1439, 1384, 1240, 1183, 1111, 1028, 1011, 889; δ_H ($CDCl_3$, 400 MHz) 7.97-7.92 (12H, m, Ar*H*), 7.78-7.74 (6H, m, Ar*H*) 7.71-7.66 (12H, m, Ar*H*) 4.88-4.79 (2H, m, C*H*), 4.63-4.55 (2H, t, *J* 15.0, CH_2), 4.45-4.41 (2H, m, CH_2), 1.06 (6H, s, CH_3); δ_C ($CDCl_3$, 100 MHz) 134.7 (d, *J* 3.0, CH), 134.5 (d, *J* 11.0, CH) 130.1 (d, *J* 13.0, CH) 118.4 (d, *J* 87.0, C_q), 110.6 (C_q), 74.80 (dd, *J* 7.0, 6.0, CH), 26.5 (CH_3), 26.2 (d, *J* 53.0, CH_2); δ_P ($CDCl_3$, 162 MHz) 23.9; *m/z* (ES) 779 (M-I^+, 29%), 517 (42), 326 (100), *m/z* (ES) found $[M-I]^+$ 779.1695. $C_{43}H_{42}IO_2P_2^+$ requires 779.1699.

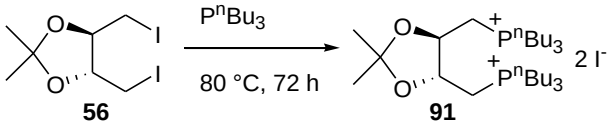
1,4-Dideoxy-1,4-di(methyldiphenylphosphonium)-2,3-*O*-isopropylidene-L-threitol diiodide 84 [153]



56 **84**

1,4-Dideoxy-1,4-diiodo-2,3-*O*-isopropylidene-L-threitol (0.10 g, 0.26 mmol, 1 eq.) was added to $MePPh_2$ (0.24 mL, 1.31 mmol, 5 eq.) under an inert atmosphere of argon the reaction mixture was heated at 80 °C for 72 h. The reaction mixture was dissolved in CH_2Cl_2 (2 mL) and addition of Et_2O (40 mL) resulted in precipitation of a yellow solid. The mixture was filtered and filtrand was dried to give the product as a yellow solid (0.20 g, 100%). R_f ($CHCl_3$:MeOH 19:1) 0.3; m.p. 160-162 °C (dec.); $[\alpha]_D^{22}$ −4.3 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3411, 3063, 3011, 2950, 2602, 1439, 1385, 1240, 1114, 1076, 904, 879; δ_H ($CDCl_3$, 400 MHz) 8.02-7.95 (8H, dt, *J* 13.0, 8.0, Ar*H*) 7.76-7.72 (4H, t, *J* 8.0, Ar*H*), 7.69-7.65 (8H, m, Ar*H*), 5.00-4.92 (2H, m, C*H*), 4.46-4.39 (2H, t, *J* 15.0, CH_2) 3.98-3.88 (2H, dt, *J* 16.0, 6.0, CH_2), 2.78 (6H, d, *J* 14.0, PCH_3), 1.16 (6H, s, CCH_3); δ_C ($CDCl_3$, 100 MHz) 134.7 (dd, *J* 20.0, 6.0, CH), 132.6 (dd, *J* 10.0, 5.0, CH), 130.1 (dd, *J* 35.0, 13.0, CH), 119.6 (dd, *J* 85.0, 11.0, C_q), 111.0 (C_q), 74.7 (dd, *J* 15.0, 6.0, CH), 26.8 (CH_3), 25.5 (d, *J* 54.0 CH_2), 9.7 (d, *J* 55.0, CH_3); δ_P ($CDCl_3$, 167 MHz) 23.15; *m/z* (ES) 243 (12%), 253 (11), 264 (27), 455 (13), 655 (M-I^+, 100); *m/z* (ES) found $[M-I]^+$ 655.1369. $C_{33}H_{38}IO_2P_2^+$ requires 655.1386.

1,4-Dideoxy-1,4-bis(tributylphosphonium)-2,3-*O*-isopropylidene-L-threitol diiodide 91

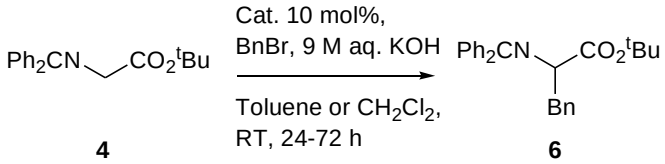


56 **91**

Tri-*n*-butylphosphine (0.33 mL, 1.31 mmol, 5 eq.) was added using a syringe to 1,4-dideoxy-1,4-diiodo-2,3-*O*-isopropylidene-L-threitol (0.10 g, 0.26 mmol, 1 eq.)

under an inert atmosphere argon and the reaction mixture was heated at 80 °C for 72 h. The resulting mixture was dissolved in CH_2Cl_2 (5 mL) and precipitation of the product was induced by addition of Et_2O (100 mL). The solution was filtered to remove the solid product, which was then dried under high vacuum to give the product as a crystalline solid (0.17 g, 81%). m.p. 144-146 °C; R_f ($CHCl_3$:MeOH 19:1) 0.4; $[\alpha]_D^{22}$ −3.4 (*c* 0.6 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2962, 2876, 1465, 1385, 1240, 1095, 1012; δ_H (400 MHz, $CDCl_3$) 4.92-4.89 (2H, m, C*H*) 3.73 (2H, app dd, *J* 15.0, 15.0, PC*H*$_2$CH), 3.19-3.10 (2H, m, PC*H*$_2$CH), 2.40-2.28 (12H, m, PC*H*$_2$CH$_2$), 1.72-1.53 (24H, m, PCH$_2$C*H*$_2$), 1.51 (6H, s, CC*H*$_3$), 1.00 (18H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 111.2 (C_q), 75.0-74.8 (m, CH), 27.5 (CH_3), 24.0 (d, *J* 15.0, CH_2), 23.7 (d, *J* 5.0, CH_2), 23.4 (d, *J* 50.0, CH_2), 19.8 (d, *J* 46.0, CH_2), 13.5 (CH_3); δ_P (162 MHz, $CDCl_3$) 33.84; *m/z* (ES) 266 (38%), 363 (27), 431 (40), 473 (66), 485 (32), 499 (25), 559 (27), 610 (27), 659 (M-I$^+$, 100); *m/z* found $[M\text{-}I]^+$ 659.3563. $C_{31}H_{66}P_2O_2I^+$ requires 659.3584.

General procedure for the synthesis of *tert*-butyl-2-(diphenylmethylene amino)-3-phenylpropanoate 6 [154,155]



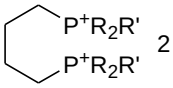
4 **6**

BnBr (33 mg, 0.19 mmol, 1.1 eq.), 9 M aq. KOH (0.37 mL, 3.34 mmol, 20 eq.) and catalyst (17.0 μmol, 0.1 eq.) were added to a solution of *N*,*N*-diphenyl methylene glycine *tert*-butyl ester (50 mg, 0.17 mmol, 1 eq.) in toluene or CH_2Cl_2 (1.5 mL) and the reaction mixture was stirred for 24-72 h, monitored by TLC. The aqueous layer was removed and the organic layer was filtered through a short plug of $MgSO_4$. The solution was then concentrated under reduced pressure to give the product as a colourless oil. R_f (petroleum ether:EtOAc 9:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3607, 3063, 3009, 2981, 2981, 2932, 1726, 1601, 1577, 1495, 1455, 1446, 1394, 1369, 1315, 1285, 1245, 1152, 1083, 1029, 977, 939, 910, 847; δ_H ($CDCl_3$, 400 MHz) 7.61-7.58 (2H, m, Ar*H*), 7.41-7.27 (6H, m, Ar*H*), 7.23-7.15 (3H, m, Ar*H*), 7.09-7.06 (2H, m, Ar*H*), 6.63 (2H, br d, *J* 6.5, Ar*H*), 4.13 (1H, dd, *J* 9.0, 4.5, C*H*), 3.26 (1H, dd, *J* 13.5, 4.5, CHC*H*$_2$), 3.18 (1H, dd, *J* 13.5, 9.0, CHC*H*$_2$), 1.46 (9H, s, C*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 170.9 (C_q), 170.3 (C_q), 139.6 (C_q), 138.9 (C_q), 136.4 (C_q), 130.1 (CH), 129.9 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 128.1 (CH), 129.0 (CH), 127.7 (CH), 126.2 (CH), 81.1 (C_q), 68.0 (CH), 39.6 (CH_2), 28.1 (CH_3); enantioselectivity determined by chiral HPLC, R_t (Chiralcel OD-H, 500:2.5 hexane:^{i}PrOH, 254 nm, 1 mL/min, 20 °C) 9.8, 16.8 min. The ^{1}H and ^{13}C NMR data was in agreement with those previously reported.[154,155]

$^{n}Bu_4NBr$, **41** $BnPh_3PBr$, **44** $^{n}Bu_4PBr$, **46**

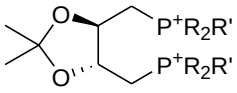
$MePh_3PBr$, **42** $Me^{n}Bu_3PI$, **45** $Bn^{n}Bu_3PBr$, **47**

$^{n}BuPh_3PBr$, **43**



2 I^-

80, R = Ph, R' = Me
81, R,R' = Ph
83, R = Me, R' = Ph

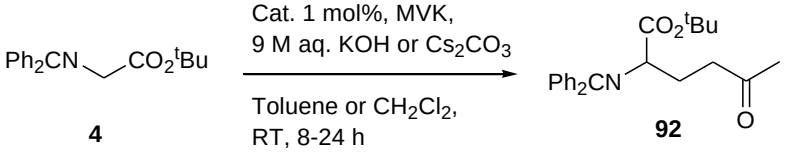


2 I^-

82, R, R' = Ph
84, R = Ph, R' = Me

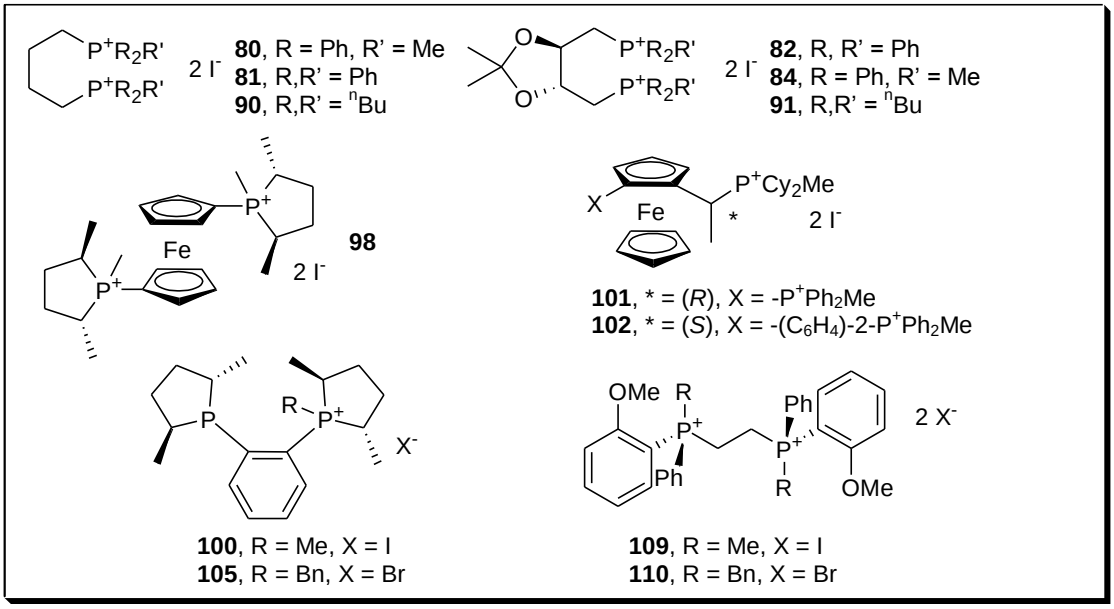
Catalyst	Solvent	Time /h	Yield /%	ee /%
41	Toluene	24	100	-
42	Toluene	24	100	-
43	Toluene	24	100	-
44	Toluene	24	100	-
45	Toluene	24	100	-
46	Toluene	24	100	-
47	Toluene	24	100	-
80	Toluene	24	<1	0
81	Toluene	72	<1	0
82	Toluene	48	<1	0
83	Toluene	24	<1	0
84	Toluene	24	<1	0
80	CH_2Cl_2	24	30	0
81	CH_2Cl_2	24	20	0
82	CH_2Cl_2	24	30	0
84	CH_2Cl_2	24	25	0
80	CH_2Cl_2	72	100	0
82	CH_2Cl_2	72	100	0

General procedure for the synthesis of *tert*-butyl-2-(diphenylmethylene amino)-5-oxohexanoate 92 [156]



MVK (24 mg, 0.34 mmol, 2 eq.), catalyst (1.70 µmol, 0.01 eq.) and either 9 M aq. KOH (0.19 mL, 1.70 mmol, 10 eq.) or Cs_2CO_3 (28 mg, 85.0 µmol, 0.5 eq.) were added to a solution *N*,*N*-diphenyl methylene glycine *tert*-butyl ester (50 mg, 0.17 mmol, 1 eq.) in toluene or CH_2Cl_2 (1.5 mL) and the reaction mixture was stirred at room temperature and the formation of product was monitored by TLC. At the end of reaction, the reaction mixture was filtered through a short column of $MgSO_4$ and was purified by column chromatography (94:5:1 petroleum

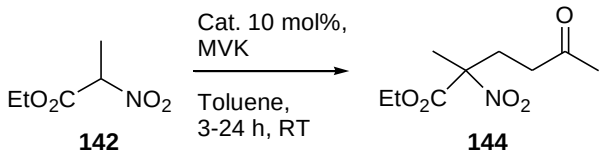
ether:EtOAc:Et_3N) to give the product as a colourless oil. R_f (petroleum ether:EtOAc 4:1) 0.5; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2981, 2934, 1718, 1624, 1599, 1577, 1491, 1446, 1394, 1369, 1316, 1290, 1252, 1153, 1094, 1074, 1029, 989, 846; δ_H ($CDCl_3$, 400 MHz) 7.66-7.63 (2H, m, Ar*H*), 7.48-7.31 (6H, m, Ar*H*) 7.20-7.16 (2H, m, Ar*H*), 3.96 (1H, dd, *J* 6.0, 6.0, C*H*) 2.60-2.45 (2H, m, COCH_2), 2.18-2.12 (2H, m, CHCH_2), 2.13 (3H, s, COCH_3), 1.44 (9H, s, CCH_3); δ_C ($CDCl_3$, 100 MHz) 208.3 (C_q), 171.0 (C_q), 170.5 (C_q), 139.5 (C_q), 136.5 (C_q), 130.3 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.7 (CH), 81.2 (C_q), 64.7 (CH), 39.9 (CH_2), 29.9 (CH_3), 28.1 (CH_3), 27.8 (CH_2). Enantiomeric excess was determined by HPLC; Chiralcel OD-H, hexane: ^{i}PrOH 97.5:2.5, 254 nm, 0.5 mL/min, 20 °C, R_t 18.5 min, 21.2 min. The above ^{1}H and ^{13}C NMR data were in agreement with those previously reported.[156]



Catalyst	Base	Solvent	Time /h	Yield /%	ee /%
81	9 M aq. KOH	CH_2Cl_2	18	89	0
82	9 M aq. KOH	CH_2Cl_2	18	82	0
80	9 M aq. KOH	CH_2Cl_2	18	95	0
84	9 M aq. KOH	CH_2Cl_2	18	89	0
90	9 M aq. KOH	CH_2Cl_2	18	100	0
91	9 M aq. KOH	CH_2Cl_2	18	100	0
91	Cs_2CO_3	CH_2Cl_2	24	79	0
91	9 M aq. KOH	Toluene	24	100	0
91	9 M aq. KOH	Tol:CH_2Cl_2 3:1	24	100	0
98	9 M aq. KOH	Toluene	15	68	0
100	9 M aq. KOH	Toluene	24	80	0
101	9 M aq. KOH	Toluene	15	95	0
102	9 M aq. KOH	Toluene	8	99	0

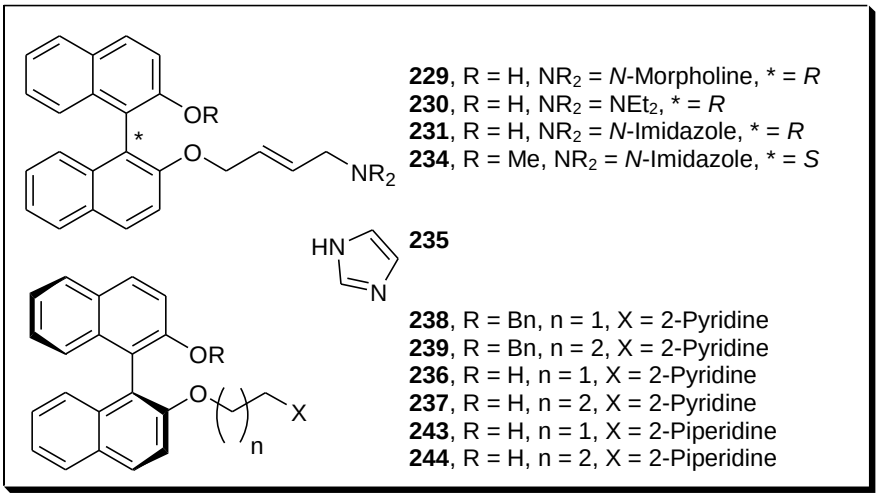
102	Cs_2CO_3	Toluene	24	100	0
102	Cs_2CO_3	CH_2Cl_2	24	100	0
105	Cs_2CO_3	Toluene	24	100	0
109	Cs_2CO_3	Toluene	24	100	0
110	Cs_2CO_3	Toluene	24	100	0

General procedure for the synthesis of ethyl 2-methyl-2-nitro-5-oxo-hexanoate 144 [157]



142 **144**

A catalyst (34.0 µmol, 0.1 eq.) and MVK (0.14 mL, 1.70 mmol, 5 eq.) are added to a solution of ethyl 2-nitropropionate (50 mg, 0.34 mmol, 1 eq.) in toluene (0.5 mL) and the reaction mixture was stirred at room temperature, monitored periodically by TLC. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (petroleum ether: EtOAc 4:1) to give the product as a colourless oil. R_f (petroleum ether: EtOAc 4:1) 0.4; ν_{max} ($CHCl_3$)/cm^{-1} 2987, 2942, 2908, 1748, 1555, 1447, 1387, 1370, 1353, 1300, 1256, 1170, 1133, 1110, 1017, 858; δ_H ($CDCl_3$, 400 MHz) 4.27 (2H, q, *J* 7.0, C*H*$_2$CH$_3$), 2.59-2.54 (2H, m, CC*H*$_2$), 2.50-2.42 (2H, m, COC*H*$_2$), 2.17 (3H, s, COC*H*$_3$), 1.78 (3H, s, CC*H*$_3$), 1.30 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 205.8 (C_q), 167.1 (C_q), 91.9 (C_q), 63.0 (CH_2), 37.9 (CH_2), 30.2 (CH_2), 29.9 (CH_3), 22.0 (CH_3), 13.8 (CH_3); *m/z* (ES) 240 ($M+Na^+$, 100%); *m/z* (ESI) found $[M+Na]^+$ 240.0852. $C_9H_{15}NO_5Na^+$ requires 240.0842. Enantiomeric excess was determined by HPLC; Chiralpak AD-H, hexane: ^{i}PrOH 99:1 at 0.8 mL/min, 20 °C, R_t 23.2 min, 24.2 min. ^{1}H and ^{13}C NMR data are consistent with literature.[157]



229, R = H, NR_2 = *N*-Morpholine, * = *R*
230, R = H, NR_2 = NEt_2, * = *R*
231, R = H, NR_2 = *N*-Imidazole, * = *R*
234, R = Me, NR_2 = *N*-Imidazole, * = *S*

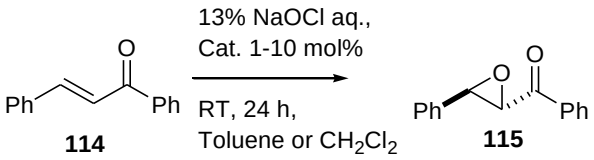
235

238, R = Bn, n = 1, X = 2-Pyridine
239, R = Bn, n = 2, X = 2-Pyridine
236, R = H, n = 1, X = 2-Pyridine
237, R = H, n = 2, X = 2-Pyridine
243, R = H, n = 1, X = 2-Piperidine
244, R = H, n = 2, X = 2-Piperidine

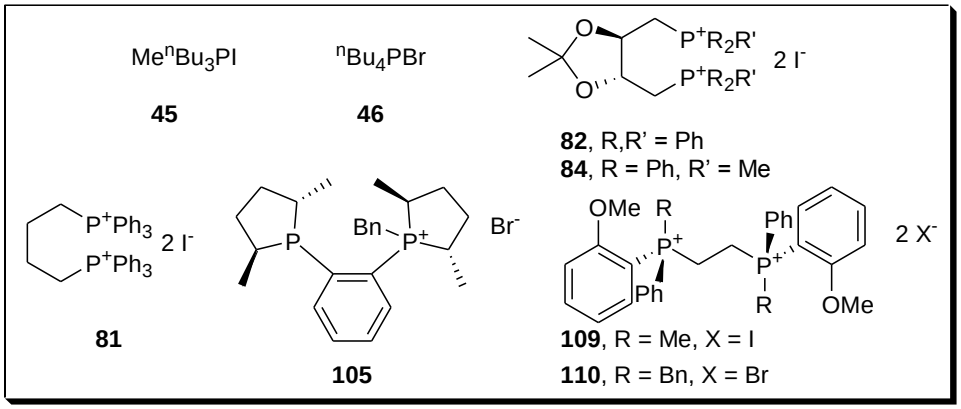
Catalyst	Time /h	Solvent	Yield /%	ee /%
229	20	Toluene	37	0
230	20	Toluene	2	0
231	20	Toluene	99	0
238	24	None	88	0
239	24	None	97	0
236	24	None	99	0
237	24	None	97	0
243	24	None	29	0
243	24	Toluene	3	0
244	24	None	44	0
244	24	Toluene	3	0
234*	3	None	100	0
235*	3	None	100	0

* = 0.1 mol% catalyst loading

General procedure for the synthesis of chalcone epoxide 115 [158,159]

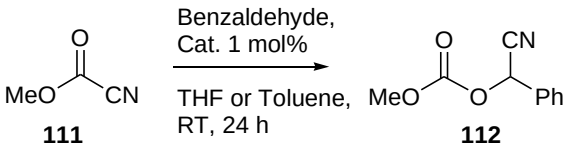


13% NaOCl aq. (0.25 mL, 0.48 mmol, 2 eq.) and a catalyst (0.01 or 0.1 eq.) was added to a solution of chalcone (50 mg, 0.24 mmol, 1 eq.) in toluene or CH_2Cl_2 (1 mL) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was dissolved in Et_2O (5 mL) and washed with water (3 x 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the product as a colourless solid. m.p. 86-88 °C [lit. 87-89 °C][158]; R_f (petroleum ether: EtOAc 4:1) 0.4; ν_{max} ($CHCl_3$)/cm^{-1} 3068, 3011, 1691, 1599, 1581, 1496, 1450, 1407, 1346, 1292, 1242, 1179, 1079, 1030, 1009, 888, 833; δ_H ($CDCl_3$, 400 MHz) 8.04-8.02 (2H, m, Ar*H*), 7.64 (1H, tt, *J* 7.5, *J* 1.0, Ar*H*), 7.50 (2H, app t, *J* 8.0, Ar*H*), 7.45-7.37 (5H, m, Ar*H*), 4.31 (1H, d, *J* 2.0, COC*H*), 4.09 (1H, d, *J* 2.0, PhC*H*); δ_C ($CDCl_3$, 100 MHz) 193.1 (C_q), 135.5 (C_q), 134.0 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 125.8 (CH), 61.1 (CH), 59.4 (CH). *m/z* (ES) 247 ($M+Na^+$, 100%); *m/z* found $[M+Na]^+$ 247.0731. $C_{15}H_{12}O_2Na^+$ requires 247.0735; Enantiomeric excess was determined by HPLC; Chiralpak AD, hexane:EtOH 90:10, 1 mL/min, 20 °C, R_t 22.46 min, 32.43 min. ^1H and ^{13}C NMR data is consistent with literature.[159]

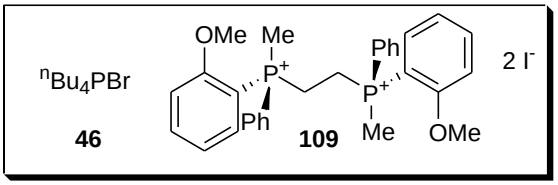


Catalyst	Solvent	Catalyst %	Yield /%
45	Toluene	10	94
46	Toluene	10	100
81	Toluene	10	0
82	Toluene	10	8
84	Toluene	10	0
105	Toluene	10	0
109	Toluene	1	0
110	Toluene	10	0
110	CH_2Cl_2	10	0

General procedure for synthesis of 2-(methoxycarbonyloxy)-2-phenylacetonitrile 112 [160]

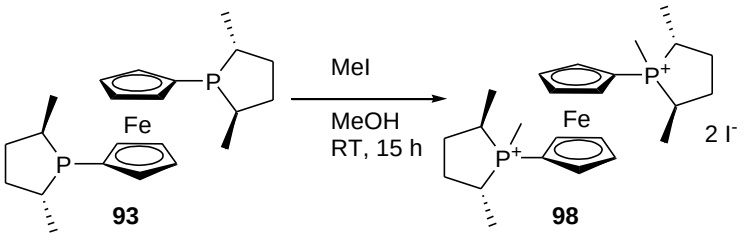


Benzaldehyde (48 µL, 0.47 mmol, 1 eq.) was stirred in THF or toluene (1.5 mL). To this, methyl cyanoformate (75 µL, 0.94 mmol, 2 eq.) and the catalyst (4.70 µmol, 0.01 eq.) were added and the reaction mixture was stirred at room temperature for 24 h. The volatiles were removed and the resulting residue was dissolved in EtOAc (5 mL) and washed with water (3 x 5 mL). The organic layer was dried over of $MgSO_4$ and concentrated under reduced pressure to give the product as a colourless oil. R_f (petroleum ether: EtOAc 4:1) 0.4; ν_{max} ($CHCl_3$)/cm^{-1} 3043, 2960, 1760, 1496, 1443, 1319, 1262, 1104, 994, 950, 911; δ_H ($CDCl_3$, 400 MHz) 7.58-7.56 (2H, m, Ar*H*), 7.51-7.48 (3H, m, Ar*H*), 6.30 (1H, s, C*H*), 3.90 (3H, s, CH_3); δ_C ($CDCl_3$, 100 MHz) 154.1 (C_q), 131.2 (C_q), 130.7 (CH), 129.8 (CH), 129.3 (CH), 127.9 (CH), 115.7 (C_q), 66.6 (CH), 55.9 (CH_3). Enantiomeric excess was determined by HPLC; Chiralcel OD-H, hexane:EtOH 95:5, 0.75 mL/min, 20 °C, R_t 11.8 min, 13.9 min. ^{1}H NMR data is consistent with literature.[160]



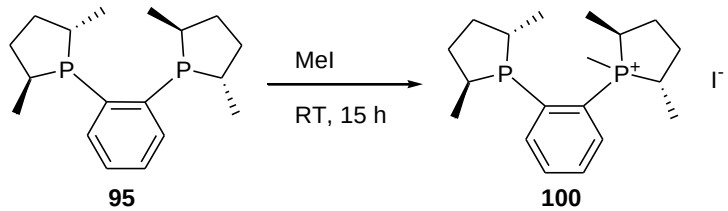
Catalyst	Yield /%	ee /%
46	100	0
109	100	0

1,1'-Bis[(2*R*,5*R*)-2,5-dimethyl(methylphospholanium)ferrocene diiodide 98



MeI (0.50 mL, 8.03 mmol) was added to a solution of 1,1'-bis[(2*R*,5*R*)-2,5-dimethylphospholano]ferrocene (15 mg, 35.0 μmol) in MeOH (0.5 mL) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in MeCN (1 mL). Precipitation of the product was induced by addition of Et_2O (100 mL) with stirring. The resulting solid was collected by filtration and was dried to give the product as a black solid (5.5 mg, 23%). m.p. 155-160 °C; δ_H (400 MHz, $CDCl_3$) 5.08 (4H, m, Ar*H*), 4.98 (4H, m, Ar*H*), 3.25-3.10 (2H, m, CHCH_2), 2.73-2.59 (2H, m, CHCH_2), 2.22 (6H, d, *J* 14.0, PCH_3), 2.57-1.16 (8H, m, C*H*CH_2), 1.53 (6H, dd, *J* 18.5, 7.0, CHCH_3), 0.86 (6H, dd, *J* 18.0, 7.0, CHCH_3); δ_P (162 MHz, CD_3CN) 51.7; *m/z* (ES) 195 (15%), 222 (100), 227 (19), 289 (26), 571 (M-I^+, 20); *m/z* found $[M\text{-}I]^+$ 571.0821. $C_{24}H_{38}FeP_2I^+$ requires 571.0837.

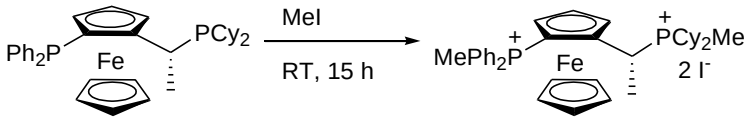
(+)-1-[(2*S*,5*S*)-2,5-Dimethyl(methylphospholanium)]-2-[(2*S*,5*S*)-2,5-dimethylphospholano]-benzene iodide 100



MeI (0.50 mL, 8.03 mmol, 250 eq.) was added to (+)-1,2-bis[(2*S*,5*S*)-2,5-dimethylphospholano]benzene (10 mg, 32.6 μmol, 1 eq.) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (1 mL).

Precipitation of the product was induced by addition of Et_2O (100 mL) with stirring. The resulting solid was collected by filtration and was dried to give the product as a colourless solid (15 mg, 95%). m.p. 145-150 °C; $[\alpha]_D^{22}$ +56.7 (*c* 0.2 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3414, 2939, 2869, 1602, 1459, 898; δ_H (400 MHz, $CDCl_3$) 8.01-7.94 (1H, m, Ar*H*), 7.84-7.72 (3H, m, Ar*H*), 3.72-3.58 (1H, m, PMeC*H*), 3.39-3.25 (1H, m, PMeC*H*), 2.78-2.63 (2H, m, PMeCHCH_2), 2.63-2.40 (2H, m, PMeCHCH_2), 2.45 (3H, dd, *J* 13.0, 2.5, PCH_3), 2.39-2.25 (1H, m, PCHCH_2), 2.24-2.07 (2H, m, PCHCH_2), 1.98-1.76 (1H, m, PCHCH_2), 1.76-1.63 (1H, m, PC*H*), 1.56 (3H, dd, *J* 16.0, 7.0, PMeCHCH_3), 1.51-1.38 (1H, m, PC*H*), 1.31 (3H, dd, *J* 19.0, 7.0, PMeCHCH_3), 1.18 (3H, dd, *J* 20.0, 7.5, PCHCH_3), 0.78 (3H, dd, *J* 10.5, 7.0, PCHCH_3); δ_P (162 MHz, $CDCl_3$) 49.2, 3.4; *m/z* (ES) 321 ([M-I]$^+$, 100%); *m/z* found [M-I]$^+$ 321.1896. $C_{19}H_{31}P_2^+$ requires 321.1901.

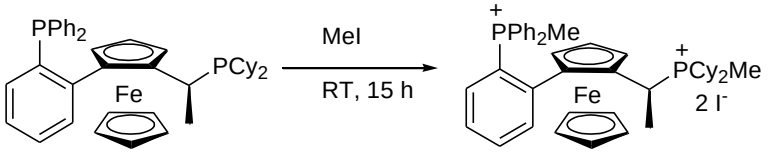
(*R*)-1-[(*S*$_P$)-2-(Methyldiphenylphosphonium)ferrocenyl]ethyldicyclohexyl methylphosphonium diiodide 101



96 **101**

MeI (0.50 mL, 8.03 mmol, 480 eq.) was added to (*R*)-1-[(*S*$_P$)-2-(diphenylphosphino) ferrocenyl]ethyldicyclohexylphosphine (10 mg, 16.8 µmol, 1 eq.) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced under reduced pressure and the residue was dissolved in CH_2Cl_2 (1 mL). Precipitation of the product was induced by addition of Et_2O (100 mL) while stirring. The resulting suspension was filtered and the filtrand was dried under high vacuum to give the product as an orange solid (14 mg, 97%). m.p. 90-95 °C; $[\alpha]_D^{22}$ +9.9 (*c* 0.1 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3689, 3406, 2941, 2859, 1602, 1439, 1239, 1113; δ_H (400 MHz, $CDCl_3$) 8.07-7.91 (4H, m, Ar*H*), 7.87-7.75 (6H, m, Ar*H*), 5.38 (1H, s, Ar*H*), 5.20 (1H, d, *J* 1.5, Ar*H*), 4.56 (5H, s, Ar*H*), 4.51 (1H, s, Ar*H*), 3.53 (3H, d, *J* 12.5, PPh_2CH_3), 3.26 (1H, dq, *J* 12.0, 6.0, CH_3CH), 2.62-2.40 (2H, m, C*H*CH_2), 2.12 (3H, dd, *J* 16.0, 7.0, PCy_2CH_3), 1.97-0.81 (20H, m, $CH_2CH_2CH_2CH_2CH_2$), 1.47 (3H, d, *J* 12.0, CHCH_3); δ_P (162 MHz, $CDCl_3$) 39.9, 20.3; *m/z* (ES) 291 (48%), 312 ([M-2I]$^{2+}$, 100), 503 (32), 751 ([M-I]$^+$, 16); *m/z* found [M-I]$^+$ 751.1749. $C_{38}H_{50}FeP_2I^+$ requires 751.1782.

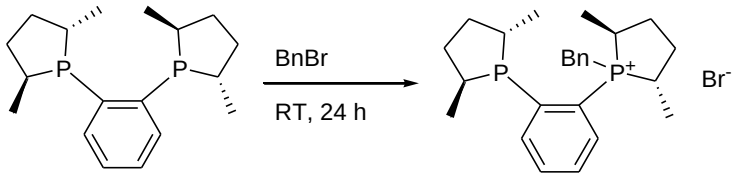
(*S*)-1-{(*S*$_P$)-2-[2-(Methyldiphenylphosphonium)phenyl]ferrocenyl}ethyl dicyclohexylmethylphosphonium diiodide 102



97 **102**

MeI (0.50 mL, 8.03 mmol, 540 eq.) was added to (*S*)-1-{(*S*$_P$)-2-[2-(diphenylphospholano)phenyl]ferrocenyl}ethyldicyclohexylphosphine (10 mg, 14.9 µmol, 1 eq.) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (1 mL). Precipitation of the product was induced by addition of Et_2O (100 mL) with stirring. The resulting solid was collected by filtration and was dried to give the product as a orange solid (14 mg, 100%). m.p. 185-190 °C; $[\alpha]_D^{22}$ +72.3 (*c* 0.1 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 2942, 2860, 1602, 1439, 1240, 908; δ_H (400 MHz, $CDCl_3$) 9.15 (1H, t, *J* 7.0, Ar*H*), 8.34 (1H, t, *J* 7.5, Ar*H*), 7.98 (1H, dt, *J* 7.5, 2.0, Ar*H*), 7.87 (2H, dt, *J* 7.5, 3.0, Ar*H*), 7.79-7.59 (7H, m, Ar*H*), 7.44 (1H, br t, *J* 7.5, Ar*H*), 7.03 (1H, ddd, *J* 16.5, 8.0, 1.0, Ar*H*), 4.57 (1H, dq, *J* 13.0, 6.0, C*H*CH$_3$), 4.51 (1H, br s, Ar*H*), 4.37 (1H, br t, *J* 3.0, Ar*H*), 4.33 (5H, s, Ar*H*), 3.79 (1H, d, *J* 1.0, Ar*H*), 2.87 (3H, d, *J* 13.0, PPh$_2$C*H*$_3$), 2.40-2.10 (2H, m, PC*H*), 2.18 (3H, dd, *J* 16.0, 7.0, PCy$_2$C*H*$_3$), 1.97-1.63 (10H, m, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$), 1.53-1.06 (10H, m, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$); δ_P (162 MHz, $CDCl_3$) 37.7, 24.9; *m/z* (ES) 350 (M-2I^{2+}, 100%), 827 (M-I$^+$, 17); *m/z* found [M-I]$^+$ 827.2063. $C_{44}H_{54}FeP_2I^+$ requires 827.2095.

(+)-1-[(2*S*,5*S*)-2,5-Dimethylphospholano]-2-[(2*S*,5*S*)-2,5-dimethyl(benzyl phospholanium)]benzene bromide 105

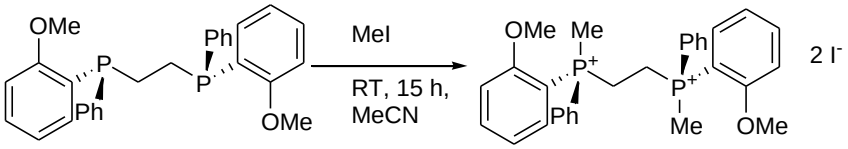


95 **105**

BnBr (0.10 mL, 0.84 mmol, 25 eq.) was added to 1,2-bis((2*S*,5*S*)-2,5-dimethylphospholano)benzene (9.9 mg, 32.3 µmol, 1 eq.) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was dissolved in CH_2Cl_2 (1 mL) and precipitation of the product was induced by addition of Et_2O (50 mL) while stirring. The resulting solution was filtered and the filtrand was washed and dried to give the product as a colourless solid (7.2 mg, 47%). m.p. 246-248 °C; $[\alpha]_D^{22}$ +74.7 (*c* 0.1 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3693, 3010, 2938, 2869, 1602, 1454; δ_H (400 MHz, $CDCl_3$) 8.03-7.97 (1H, m, Ar*H*), 7.88-7.82 (1H, m, Ar*H*), 7.78 (1H, tt, *J* 7.5, 2.0, Ar*H*), 7.72 (1H, tq, *J* 7.5, 1.5, Ar*H*), 7.36-7.28 (5H,

m, Ar*H*), 4.61 (2H, d, *J* 14.5, PCH_2), 3.79-3.64 (2H, m, PCHCH_2), 2.75 (1H, dddddd, *J* 11.0, 7.0, 7.0, 7.0, 7.0, 7.0, PBnC*H*), 2.62-2.18 (6H, m, PBnCH_3), 2.00-1.89 (1H, m, PBnC*H*), 1.86-1.59 (1H, m, C*H*) 1.71 (3H, dd, *J* 16.5, 7.0, PBnCHCH_2CH_2), 1.58-1.46 (1H, m, PCHCH_2), 1.37 (3H, dd, *J* 19.0, 7.0, PCHCH_2), 1.19 (3H, dd, *J* 18.0, 7.5, PCHCH_3), 0.83 (3H, dd, *J* 10.5, 7.0, PCHCH_3); δ_P (162 MHz, $CDCl_3$) 49.4, 0.5; *m/z* (ES) 397 (M-Br^+, 100%); *m/z* found $[M\text{-}Br]^+$ 397.2221. $C_{25}H_{35}P_2^+$ requires 397.2214.

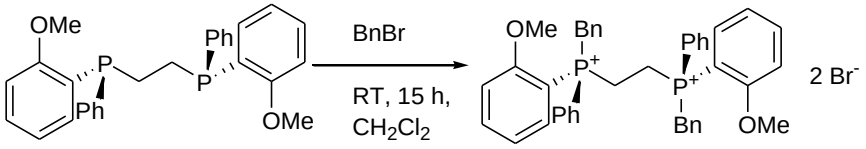
{(1*R*,2*R*)-(-)-Bis[(2-methoxyphenyl)phenylmethylphosphonium)]}ethane diiodide 109



108 **109**

MeI (0.50 mL, 8.03 mmol, 365 eq.) was added to a solution of (*R*,*R*)-DIPAMP (10 mg, 22.0 µmol, 1 eq.) in MeCN (1 mL) and the reaction mixture was stirred at room temperature for 24 h. Excess MeI was removed under reduced pressure and the resulting residue was dissolved in MeCN (1 mL). Precipitation of the product was induced by addition of Et_2O (50 mL) and stirring. The resulting solution was filtered and the filtrand washed and was dried to give the product as a colourless solid (15 mg, 95%). m.p. 227-230 °C; $[\alpha]_D^{22}$ +14.3 (*c* 0.2 in MeCN); δ_H (400 MHz, CD_3CN) 7.86 (2H, td, *J* 8.0, 1.5, Ar*H*), 7.81-7.72 (6H, m, Ar*H*), 7.67-7.59 (6H, m, Ar*H*), 7.29 (2H, br t, *J* 7.5, Ar*H*), 7.22-7.19 (2H, m, Ar*H*), 3.58 (6H, s, OCH_3), 3.27-3.18 (2H, m, PCH_2CH_2), 3.07-3.00 (2H, m, PCH_2CH_2), 2.60 (6H, dd, *J* 7.0, 7.0, PCH_3); δ_P (162 MHz, CD_3CN) 25.2; *m/z* (ES) 244 (M-$2I^{2+}$, 100%), 257 (26), 615 (M-I^+, 19); *m/z* found $[M\text{-}I]^+$ 615.1066. $C_{30}H_{34}P_2O_2I^+$ requires 615.1079.

[(1*R*,2*R*)-(-)-Bis[2-methoxyphenyl)phenylbenzylphosphonium)ethane dibromide 110

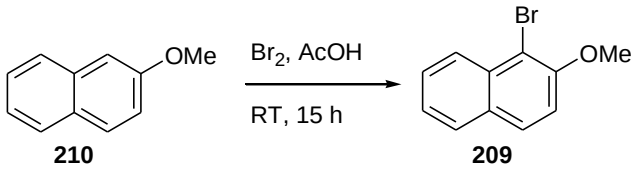


108 **110**

BnBr (0.10 mL, 0.84 mmol, 38 eq.) was added to a solution of (*R*,*R*)-DIPAMP (10 mg, 22.0 µmol, 1 eq.) in CH_2Cl_2 (1 mL) and the reaction mixture was stirred at room temperature for 15 h. Precipitation of the product was induced by addition of Et_2O (50 mL) while stirring. The resulting solution was filtered and the filtrand was to give the product as a colourless solid (16 mg, 94%). m.p. 238-240 °C; $[\alpha]_D^{22}$ +2.1 (*c* 0.2 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2944, 2877, 1592, 1480, 1464, 1438, 1286, 1257, 1239, 1016; δ_H (400 MHz, $CDCl_3$) 8.32 (2H, ddd, *J* 7.5, 6.0, 1.0, ArH),

8.12 (4H, br dd, *J* 7.0, 6.0, Ar*H*), 7.77-7.70 (4H, m, Ar*H*), 7.65-7.62 (4H, m, Ar*H*), 7.36 (2H, br t, *J* 7.0, Ar*H*), 7.08 (2H, br t, *J* 7.0, ArH), 7.00 (2H, dt, *J* 8.5, 2.5, Ar*H*), 6.92-6.85 (8H, m, Ar*H*), 5.20 (4H, br d, *J* 92.0, PCH_2Bn), 3.64 (6H, s, OCH_3) 3.40 (4H, br d, *J* 96.0, PCH_2CH_2); δ_P (162 MHz, $CDCl_3$) 26.7; *m/z* (ES) 320 (M-$2Br^{2+}$, 100%), 333 (21), 719 (M-$^{81}Br^+$, 18), 721 (M-$^{79}Br^+$, 20). *m/z* found [M-^{81}Br]$^+$ 719.1823, $C_{42}H_{42}P_2O_2{}^{79}Br^+$ requires 719.1843.

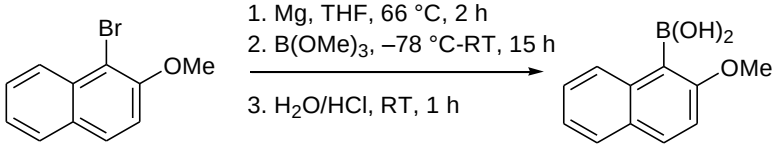
1-Bromo-2-methoxynaphthalene 209 [161]



210 **209**

Bromine (3.20 mL, 64.0 mmol, 1 eq.) was added to a solution of 2-methoxynaphthalene (10.0 g, 64.0 mmol, 1 eq.) in AcOH (150 mL) and the reaction mixture was stirred at room temperature for 15 h. Water (300 mL) was added to precipitate the product, which was subsequently filtered and washed with water (100 mL). The filtrand was dissolved in Et_2O (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the product as an off-white solid (15.1 g, 99%). m.p. 81-83 °C [lit. 85-86 °C][161]; R_f (petroleum ether:EtOAc 4:1) 0.5; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2944, 2844, 1625, 1597, 1561, 1504, 1469, 1442, 1430, 1354, 1335, 1271, 1247, 1182, 1150, 1135, 1071, 1023, 972, 895; δ_H (400 MHz, $CDCl_3$) 8.25 (1H, d, *J* 8.0, Ar*H*), 7.85 (1H, d, *J* 9.0, Ar*H*), 7.81 (1H, d, *J* 8.0, Ar*H*), 7.59 (1H, dd, *J* 8.5, 8.5, Ar*H*), 7.44 (1H, dd, *J* 8.0, 8.0, Ar*H*), 7.31 (1H, d, *J* 8.5, Ar*H*), 4.06 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 153.8 (C_q), 133.1 (C_q), 129.8 (C_q), 129.0 (CH), 128.1 (CH), 127.8 (CH), 126.1 (CH), 113.6 (CH), 108.6 (C_q), 57.1 (CH_3). ^{1}H NMR and ^{13}C NMR data are consistent with literature.[161]

2-Methoxy-1-naphthylboronic acid 208 [162]

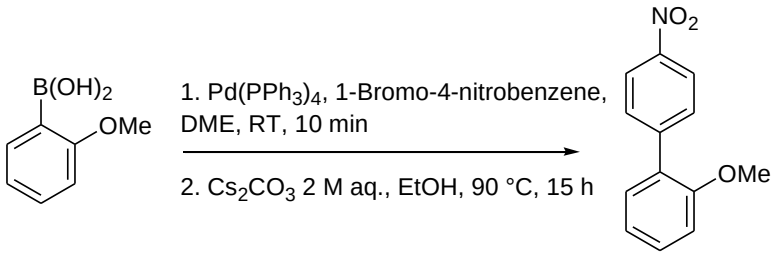


209 **208**

Magnesium turnings (2.25 g, 93.0 mmol, 1.5 eq.) were activated by heating under reflux in THF (45 mL) under an inert atmosphere for 1 h. 1-Bromo-2-methoxynaphthalene (15.0 g, 62.0 mmol, 1 eq.) in THF (90 mL) was added over a period of 10 min and the reaction mixture was heated under reflux for 2 h. The reaction mixture was then cooled to −78°C and extra THF (160 mL) was added. $B(OMe)_3$ (14.3 mL, 0.12 mol, 2 eq.) was added and the reaction mixture was allowed to warm to room temperature over 15 h. The reaction mixture was quenched by addition of 1 M aq. HCl (300 mL) while stirring for 1 h. The mixture

was filtered to remove excess magnesium and solid by-product, washing through with CH_2Cl_2 (100 mL) and concentrated under reduced pressure. The resulting crude product was washed with petroleum ether (50 mL x 3) and purified by column chromatography (EtOAc:petroleum ether 4:1) to give the product as a colourless solid (9.40 g, 75%). R_f (EtOAc:petroleum ether 4:1) 0.8; m.p. 151-152 °C [lit. 150 °C][162]; ν_{max} ($CHCl_3$)/cm^{-1} 3611, 3484, 3011, 2946, 2845, 1621, 1593, 1568, 1510, 1466, 1433, 1385, 1334, 1296, 1255, 1242, 1180, 1148, 1072, 1026, 977, 896, 821; δ_H (400 MHz, $CDCl_3$) 8.87 (1H, d, *J* 9.0, Ar*H*), 7.98 (1H, d, *J* 8.0, Ar*H*), 7.82 (1H, d, *J* 8.0, Ar*H*), 7.53 (1H, dd, *J* 9.0, 9.0, Ar*H*), 7.41 (1H, dd, *J* 7.5, 7.5, Ar*H*), 7.32 (1H, d, *J* 9.0, Ar*H*), 6.23 (2H, s, O*H*), 4.07 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 163.4 (C_q), 137.9 (C_q), 133.4 (CH), 129.5 (C_q), 128.3 (CH), 128.1 (CH), 127.2 (CH), 123.9 (CH), 112.4 (CH), 56.7 (CH_3). ^{1}H and ^{13}C NMR data are consistent with literature.[162]

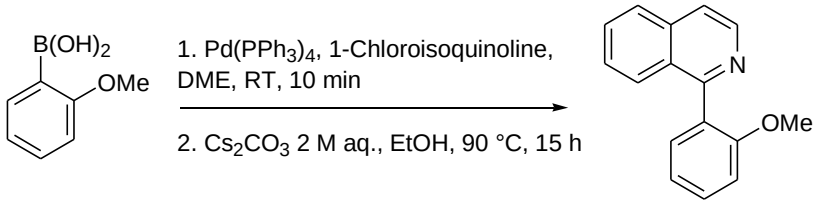
2-Methoxy-4'-nitro-1,1'-biphenyl 213 [163]



211 **213**

1-Bromo-4-nitrobenzene (0.13 g, 0.66 mmol, 1 eq.) was added to a solution $Pd(PPh_3)_4$ (23 mg, 20.0 µmol, 0.03 eq.) in DME (15 mL) and the reaction mixture was stirred for 10 min under an inert atmosphere of argon. 2-Methoxyboronic acid (0.10 g, 0.66 mmol, 1 eq.) in EtOH (2 mL) and 2 M aq. Cs_2CO_3 (6 mL) were added sequentially and the reaction mixture was heated at 90 °C for 15 h. The reaction mixture was concentrated under reduced pressure and dissolved in CH_2Cl_2 (50 mL), washed with water (10 mL x 3), dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc 4:1) to give the product as a yellow oil (0.12 g, 82 %). R_f (petroleum ether: EtOAc 4:1) 0.6; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2943, 2840, 1602, 1518, 1482, 1465, 1437, 1404, 1349, 1315, 1264, 1242, 1182, 1164, 1125, 1113, 1056, 1028, 1008, 909, 855; δ_H (400 MHz, $CDCl_3$) 8.31-8.27 (2H, m, Ar*H*), 7.75-7.71 (2H, m, Ar*H*), 7.45 (1H, ddd, *J* 8.0, 7.5, 2.0, Ar*H*), 7.37 (1H, dd, *J* 7.5, 2.0, Ar*H*), 7.11 (1H, td, *J* 7.5, 7.5, 1.0, Ar*H*), 7.07 (1H, br d, *J* 8.5, Ar*H*), 3.88 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 156.5 (C_q), 146.7 (C_q), 145.5 (C_q), 130.7 (CH), 130.4 (CH), 130.2 (CH), 128.3 (C_q), 123.2 (CH), 121.1 (CH), 111.5 (CH), 55.6 (CH_3); *m/z* (ES) 230 ($M+H^+$, 17), 252 ($M+Na^+$, 100%); *m/z* found $[M+Na]^+$ 252.0627. $C_{13}H_{11}NO_3Na$ requires 252.0631. ^{1}H and ^{13}C NMR data are consistent with literature.[163]

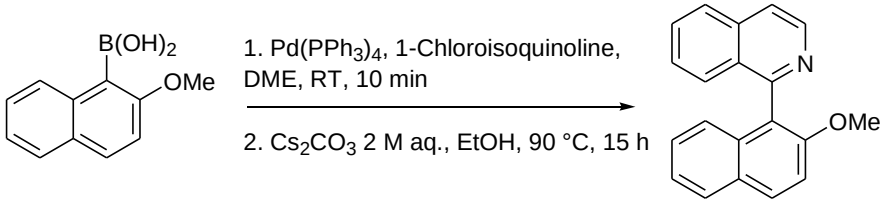
1-(2-Methoxyphenyl)isoquinoline 214 [164]



211 **214**

1-Chloroquinoline (0.11 g, 0.66 mmol, 1 eq.) was added to a solution of $Pd(PPh_3)_4$ (23 mg, 19.8 µmol, 0.03 eq.) in DME (15 mL) and the reaction mixture was stirred for 10 min under an inert atmosphere of argon. 2-Methoxyboronic acid (0.10 g, 0.66 mmol, 1 eq.) in EtOH (2 mL) and Cs_2CO_3 2 M aq. (6 mL) were added sequentially and the reaction mixture was heated at 90 °C for 15 h. The reaction mixture was concentrated under reduced pressure and dissolved in CH_2Cl_2 (50 mL), washed with water (10 mL x 3), dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc 1:1) to give the product as a yellow oil (0.14 g, 88%). R_f (petroleum ether: EtOAc 1:1) 0.6; ν_{max} ($CHCl_3$)/cm^{-1} 3057, 3011, 2838, 1623, 1602, 1585, 1560, 1494, 1463, 1435, 1390, 1358, 1321, 1296, 1273, 1248, 1183, 1131, 1109, 1049, 1027, 976, 909, 872, 827; δ_H (400 MHz, $CDCl_3$) 8.66 (1H, d, *J* 5.5, Ar*H*), 7.88 (1H, d, *J* 8.5, Ar*H*), 7.75 (1H, d *J* 8.5, Ar*H*), 7.71-7.66 (2H, m, Ar*H*), 7.50 (2H, td, *J* 8.0, 8.0, 1.5, Ar*H*), 7.43 (1H, dd, *J* 7.5, 2.0, Ar*H*), 7.15 (1H, td, *J* 7.0, 7.0, 0.5, Ar*H*), 7.09 (1H, d, *J* 8.5, Ar*H*), 3.72 (3H, s, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 159.1 (C_q), 157.2 (C_q), 142.3 (CH), 136.2 (C_q), 131.3 (CH), 130.1 (CH), 129.9 (CH), 128.7 (C_q), 127.9 (CH), 127.8 (C_q), 126.9 (CH), 126.7 (CH), 120.8 (CH), 111.2 (CH), 55.6 (CH_3); *m/z* (ES) 236 ($M+Na^+$, 100%); *m/z* found $[M+Na]^+$ 258.0891. $C_{16}H_{13}NONa$ requires 258.0889. ^1H and ^{13}C NMR data are consistent with literature.[164]

1-(2-Methoxy-1-naphthyl)isoquinoline 208 [165,166]

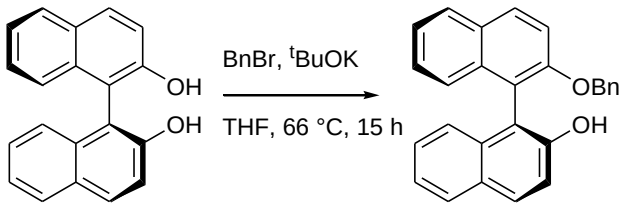


209 **208**

1-Chloroisoquinoline (6.75 g, 41.0 mmol, 1 eq.) in DME (300 mL) was added to $Pd(PPh_3)_4$ (1.43 g, 0.12 mmol, 0.03 eq.) and the reaction mixture was stirred for 10 min under an inert atmosphere of argon. 2-Methoxy-1-naphthylboronic acid (10.0 g, 49.2 mmol, 1.2 eq.) in EtOH (2 mL) and 2 M aq. Cs_2CO_3 (54 mL) were added sequentially to the reaction mixture and heated to reflux for 15 h. The reaction mixture was concentrated under reduced pressure, dissolved in $CHCl_3$ (50 mL), washed with water (50 mL x 3), dried with $MgSO_4$, concentrated under reduced

pressure, triturated in petroleum ether (50 mL x 3), filtered and purified by column chromatography (petroleum ether: EtOAc 1:1) to give the product as an off-white solid (8.80 g, 75%). Elemental analysis found: C, 84.21; H, 5.38; N, 4.91. $C_{13}H_{15}NO_4$ requires C, 84.19; H, 5.30, N, 4.91; m.p. 125-127 °C [lit. 130-133 °C][165]; R_f (petroleum ether: EtOAc 1:1) 0.6; v_{max} ($CHCl_3$)/cm^{-1} 3058, 3009, 2964, 2842, 1624, 1596, 1559, 1512, 1474, 1463, 1434, 1407, 1374, 1344, 1318, 1265, 1252, 1180, 1149, 1087, 1064, 1046, 1020, 960, 911, 871, 827; δ_H (400 MHz, CDCl3) 8.76 (1H, d, *J* 5.5, Ar*H*), 8.04 (1H, d, *J* 9.0, Ar*H*), 7.94 (1H, d, *J* 8.0, Ar*H*), 7.89 (1H, d, *J* 8.0, Ar*H*), 7.77 (1H, d, *J* 6.0, Ar*H*), 7.69 (1H, t, *J* 7.5, Ar*H*), 7.53 (1H, d, *J* 8.5, Ar*H*), 7.46 (1H, d, *J* 9.0, Ar*H*), 7.41 (1H, t, *J* 7.5, Ar*H*), 7.34 (1H, t, *J* 7.0, Ar*H*), 7.26 (1H, t, *J* 7.5, Ar*H*), 7.05 (1H, d, *J* 8.5, Ar*H*), 3.78 (3H, s, C*H*$_3$); δ_C (100 MHz, CDCl3) 158.2 (C_q), 154.8 (C_q), 142.8 (CH), 136.3 (C_q), 133.9 (C_q), 130.4 (CH), 130.1 (CH), 129.1 (C_q), 128.8 (C_q), 127.9 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.8 (CH), 124.8 (CH) 123.7 (CH), 122.0 (C_q), 120.1 (CH), 113.5 (CH), 56.7 (CH_3); *m/z* (ES) 286 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 286.1238. $C_{20}H_{15}NO$ requires 286.1232. Melting point, ^1H and ^{13}C NMR data are consistent with literature.[166]

(*S*)-2'-(Benzyloxy)-[1,1']-binaphthalenyl-2-ol 240 [167]

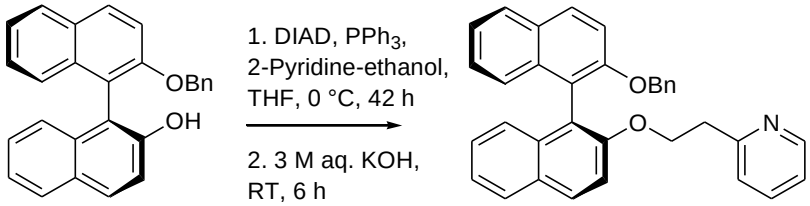


223 **240**

(*S*)-BINOL (2.00 g, 6.96 mmol, 1 eq.) and ^{t}BuOK (0.80 g, 6.96 mmol, 1 eq.) in THF (80 mL) was heated under reflux for 1 h under an inert atmosphere of argon. BnBr (0.80 mL, 6.96 mmol, 1 eq.) was added and the reaction was heated under reflux for a further 18 h. The reaction mixture was neutralised with 1 M aq. HCl (10 mL), concentrated under reduced pressure, dissolved in $CHCl_3$ (50 mL), washed with water (3 x 50 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (toluene) to give the product as an off-white solid (1.80 g, 69%). Disubstituted by-product was also isolated as an off-white solid (0.49 g, 15%). R_f (toluene) 0.4; Elemental analysis found: C, 86.07; H, 5.39; N, 0. $C_{27}H_{20}O_2$ requires C, 86.14; H, 5.36, N, 0; m.p. 116-118 °C [lit. 120.5-121.5 °C][167]; $[\alpha]_D^{22}$ –5.1 (*c* 0.7 in $CHCl_3$); v_{max} ($CHCl_3$)/cm^{-1} 3538, 3064, 3011, 2942, 1952, 1622, 1593, 1508, 1455, 1432, 1382, 1362, 1330, 1263, 1242, 1173, 1129, 1085, 1075, 1050, 1019, 973, 941, 914, 863; δ_H (400 MHz, CDCl3) 8.01 (1H, d, *J* 9.0, Ar*H*), 7.95 (1H, d, *J* 9.0, Ar*H*), 7.91 (2H, d, *J* 8.5, Ar*H*), 7.49 (1H, d, *J* 9.0, Ar*H*), 7.43-7.2 (9H, m, Ar*H*), 7.11 (1H, d, *J* 8.5, Ar*H*), 7.08-7.06 (2H, m, Ar*H*), 5.15 (1H, d, *J* 13.0, C*H*$_2$), 5.1 (1H, d, *J* 13.0, C*H*$_2$), 4.95 (1H, s, O*H*); δ_C (100 MHz,

CDCl3) 155.0 (C_q), 151.4 (C_q), 137.0 (C_q), 134.1 (C_q), 133.9 (C_q), 130.9 (CH), 129.9 (CH), 129.7 (C_q), 129.2 (C_q), 128.4 (CH), 128.2 (CH), 128.2 (CH), 127.7 (CH), 127.3 (CH), 126.9 (CH), 126.5 (CH), 125.1 (CH), 125.0 (CH), 124.5 (CH), 123.3 (CH), 117.6 (CH), 116.9 (C_q), 116.0 (CH), 115.1 (C_q), 71.2 (CH_2); *m/z* (ES) 377 ($M+H^+$, 33%), 399 ($M+Na^+$, 100); *m/z* found $[M+Na]^+$ 399.1370. $C_{27}H_{20}O_2Na$ requires 399.1356. The *R* enantiomer was synthesised under same conditions and referenced to the same data; $[\alpha]_D^{22}$ +7.4 (*c* 0.7 in $CHCl_3$). ^1H and ^{13}C NMR data are consistent with literature.[167]

(*S*)-1'-(Benzyloxy)-2'-(1-(2-pyridine)-ethyloxy)-[1,1']-binaphthalene 238

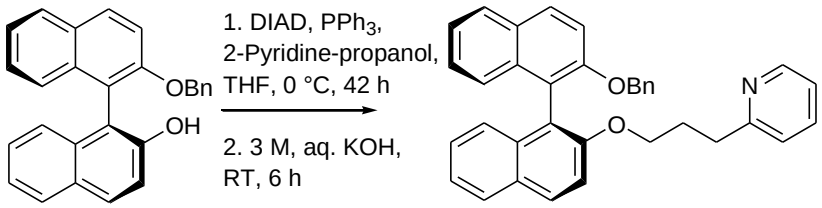


240 **238**

2-Pyridine-ethanol (0.58 mL, 4.98 mmol, 3.75 eq.) was added to a stirred solution of (*S*)-2'-(benzyloxy)-[1,1']binaphthalenyl-2-ol (0.50 g, 1.33 mmol, 1 eq.) and PPh_3 (1.30 g, 4.98 mmol, 3.75 eq.) in THF (10 mL) and the reaction mixture was cooled with ice under an inert atmosphere of argon. DIAD 40% in toluene (2.50 mL, 4.98 mmol, 3.75 eq.) was added slowly and the reaction mixture was allowed to warm to room temperature for 42 h. 3 M aq. KOH (30 mL) was added and the reaction mixture was heated under reflux for 6 h. The reaction mixture was concentrated under reduced pressure, the crude product was extracted from the aqueous layer with CH_2Cl_2 (3 x 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The reaction mixture was purified by column chromatography (petroleum ether:EtOAc 1:1) to give the product as a clear viscous liquid (0.60 g, 94%). R_f (petroleum ether:EtOAc 1:1) 0.5; $[\alpha]_D^{26}$ –39.9 (*c* 0.7 in THF); ν_{max} ($CHCl_3$)/cm^{-1} 3063, 3011, 2940, 2878, 1623, 1593, 1571, 1509, 1476, 1458, 1434, 1354, 1272, 1242, 1148, 1133, 1088, 1053, 1020; δ_H (400 MHz, $CDCl_3$) 8.33 (1H, br ddd, *J* 5.0, 2.0, 1.0, Ar*H*), 7.95 (1H, d, *J* 14.0, Ar*H*), 7.93 (1H, d *J* 14.0, Ar*H*), 7.87 (2H, d, *J* 8.0, Ar*H*), 7.42 (1H, d, *J* 12.0, Ar*H*), 7.4 (1H, d, *J* 12.0, Ar*H*), 7.33 (2H, dddd, *J* 8.0, 6.5, 5.5, 1.5, Ar*H*), 7.25-7.10 (7H, m, Ar*H*), 7.01 (1H, td, *J* 7.5, 2.0, Ar*H*), 6.97-6.93 (2H, m, Ar*H*), 6.96-6.87 (1H, m, Ar*H*), 6.27 (1H, d, *J* 8.0, Ar*H*), 4.96 (2H, s, PhCH_2), 4.38-4.26 (2H, m, PyCH_2), 2.92-2.81 (2H, m, OCH_2); δ_C (100 MHz, $CDCl_3$) 158.5 (C_q), 154.1 (C_q), 154.1 (C_q), 148.8 (CH), 137.6 (C_q), 135.7 (CH), 134.2 (C_q), 134.1 (C_q), 129.5 (C_q), 129.4 (CH), 129.3 (C_q), 129.0 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.3 (CH), 126.7 (CH), 126.3 (CH), 126.2 (CH), 125.6 (CH), 125.4 (CH), 123.8 (CH), 123.7 (CH), 123.5 (CH), 121.1 (C_q), 121.0 (CH), 119.9 (C_q), 116.3 (CH), 114.9 (CH), 71.3 (CH_2), 68.4 (CH_2), 38.4

(CH_2); *m/z* (ES) 482 ($M+H^+$, 100%), 504 ($M+Na^+$, 21); *m/z* found $[M+H]^+$ 482.2116. $C_{34}H_{28}NO_2$ requires 482.2115. The *R* enantiomer was synthesised under same conditions, but with DCAD (0.90 g, 2.66 mmol, 2 eq.) in place of DIAD, and referenced to the same data; $[\alpha]_D^{22}$ +5.8 (*c* 0.7 in $CHCl_3$).

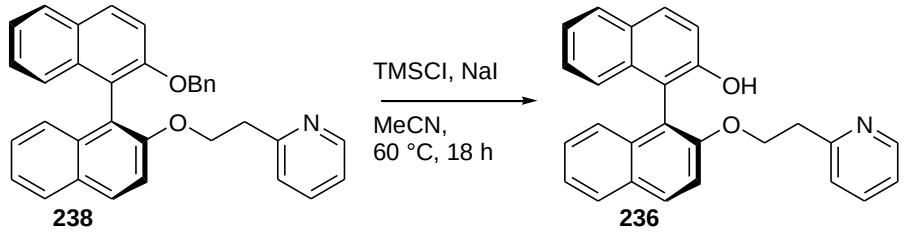
(*S*)-1'-(Benzyloxy)-2'-(1-(2-pyridine)-propyloxy)-[1,1']-binaphthalene 239



240 **239**

2-Pyridinepropanol (0.65 mL, 4.98 mmol, 3.75 eq.) was added to a solution of (*S*)-2'-(benzyloxy)-[1,1']binaphthalenyl-2-ol (0.50 g, 1.33 mmol, 1 eq.) and PPh_3 (1.30 g, 4.98 mmol, 3.75 eq.) in THF (10 mL) and the reaction mixture was cooled with ice under an inert atmosphere of argon. DIAD 40% in toluene (2.50 mL, 4.98 mmol, 3.75 eq.) was added slowly and the reaction mixture was allowed to warm to room temperature for 42 h. 3 M aq. KOH (30 mL) was added and the reaction mixture was heated under reflux for 6 h. The reaction mixture was concentrated under reduced pressure, the crude product was extracted from the aqueous layer with CH_2Cl_2 (3 x 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The reaction mixture was purified by column chromatography (petroleum ether:EtOAc 1:1) to give the product as a clear viscous liquid (0.59 g, 90%). R_f (petroleum ether:EtOAc 1:1) 0.5; $[\alpha]_D^{22}$ –45.6 (*c* 0.7 in THF); ν_{max} ($CHCl_3$)/cm^{-1} 3064, 3011, 2954, 2876, 1622, 1593, 1570, 1508, 1476, 1455, 1433, 1355, 1330, 1263, 1245, 1148, 1090, 1052, 1020, 999; δ_H (400 MHz, $CDCl_3$) 8.45 (1H, br d, *J* 4.0, Ar*H*), 7.99 (1H, d, *J* 9.0, Ar*H*), 7.95 (1H, d, *J* 9.0, Ar*H*), 7.93 (1H, d, *J* 9.0, Ar*H*) 7.89 (1H, d, *J* 9.0, Ar*H*), 7.47 (1H, d, *J* 4.0, Ar*H*), 7.44 (1H, d, *J* 4.0, Ar*H*), 7.39-7.22 (3H, m, Ar*H*), 7.29-7.25 (4H, m, Ar*H*), 7.18-7.14 (3H, m, Ar*H*), 7.03-6.99 (3H, m, Ar*H*), 6.53 (1H, d, *J* 8.0, Ar*H*), 5.10 (1H, d, *J* 13.0, PhCH_2), 5.06 (1H, d, *J* 13.0, PhCH_2), 4.09-4.02 (1H, m, PyCH_2), 3.99-3.93 (1H, m, PyCH_2), 2.47-2.34 (2H, m, OCH_2), 1.94-1.87 (2H, m, OCH_2CH_2); δ_C (100 MHz, $CDCl_3$) 161.3 (C_q), 154.4 (C_q), 154.2 (C_q), 149.0 (CH), 137.6 (C_q), 136.1 (CH), 134.3 (C_q), 134.2 (C_q), 129.5 (C_q), 129.4 (CH), 129.3 (C_q), 129.2 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.4 (CH), 126.8 (CH), 126.3 (CH), 126.3 (CH), 125.7 (CH), 125.5 (CH), 123.8 (CH), 123.6 (CH), 123.1 (CH), 121.1 (C_q), 120.9 (CH), 120.3 (C_q), 116.2 (CH), 115.5 (CH), 71.3 (CH_2), 68.4 (CH_2), 33.9 (CH_2), 29.3 (CH_2); *m/z* (ES) 496 ($M+H^+$, 100%), *m/z* found $[M+H]^+$ 496.2275, $C_{35}H_{30}NO_2$ requires 496.2276. The *R* enantiomer was synthesised under same conditions, but with DCAD (0.90 g, 2.66 mmol, 2 eq.) in place of DIAD, and referenced to the same data; $[\alpha]_D^{22}$ +3.5 (*c* 0.7 in $CHCl_3$).

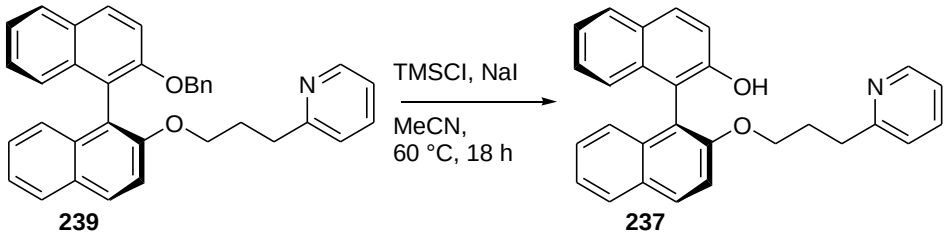
(*S*)-2'-(1-(2-Pyridine)-ethyloxy)-[1,1']-binaphthenyl-2-ol 236



238 **236**

TMSCl (0.10 mL, 0.80 mmol, 8 eq.) was added to a solution of NaI (0.12 g, 0.80 mmol, 8 eq.) in dry MeCN (1 mL) and the reaction mixture was stirred for 20 min under an inert atmosphere of argon. To this, (*S*)-1'-(benzyloxy)-2'-(1-(2-pyridine)ethyloxy)-[1,1']-binaphthalene (50 mg, 0.10 mmol, 1 eq.) in dry MeCN (5 mL) was added and the reaction mixture was heated under reflux at 60 °C for 18 h. The reaction mixture was quenched with water (10 mL), MeCN was removed under low pressure, saturated aq. Na_2SO_3 (1 mL) was added and the product was extracted in Et_2O (3 x 10 mL) and concentrated under reduced pressure. The crude material was purified by column chromatography (petroleum ether:EtOAc 4:1 to remove impurities, then toluene:MeOH 19:1) to give the product as a colourless solid (25 mg, 64%). R_f (toluene:MeOH 19:1) 0.3; m.p. 110-115 °C; $[\alpha]_D^{22}$ −58.9 (*c* 0.68 in THF); ν_{max} ($CHCl_3$)/cm^{-1} 3538, 3062, 3011, 2962, 1629, 1595, 1572, 1472, 1433, 1381, 1360, 1331, 1265, 1242, 1174, 1148, 1129, 1081, 1054, 1020, 976, 864, 821; δ_H (400 MHz, $CDCl_3$), 8.08 (1H, br d, *J* 5.0, Ar*H*), 7.91 (1H, d, *J* 8.0, Ar*H*), 7.87 (1H, d, *J* 8.0, Ar*H*), 7.83 (1H, d, *J* 8.0, Ar*H*), 7.38-7.13 (7H, m, Ar*H*), 6.97 (1H, br d, *J* 7.0, Ar*H*), 6.90 (1H, ddd, *J* 7.0, 5.0, 1.0, Ar*H*), 6.57 (1H, d, *J* 8.0, Ar*H*), 6.40 (1H, br s, O*H*), 4.52-4.45 (1H, m, PyCH_2), 4.37-4.31 (1H, m, PyCH_2), 3.04-2.90 (2H, m, OCH_2); δ_C (100 MHz, $CDCl_3$), 158.4 (C_q), 155.0 (C_q), 151.9 (C_q), 148.3 (CH), 136.2 (CH), 134.1 (C_q), 134.0 (C_q), 130.5 (CH), 129.5 (CH), 129.4 (C_q), 129.0 (C_q), 128.0 (CH), 127.9 (CH), 127.1 (CH), 126.3 (CH), 125.1 (CH), 124.9 (CH), 124.1 (CH), 123.9 (CH), 123.1 (CH), 121.2 (CH), 118.2 (CH), 117.1 (C_q), 115.4 (C_q), 114.9 (CH), 68.4 (CH_2), 38.5 (CH_2); *m/z* (ES) 392 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 392.1641. $C_{27}H_{22}NO_2$ requires 392.1645.

(*S*)-2'-(1-(2-Pyridine)-propyloxy)-[1,1']-binaphthenyl-2-ol 237

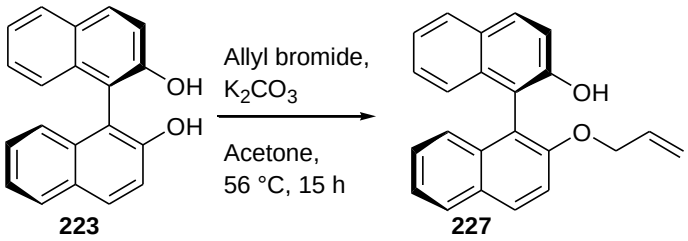


239 **237**

TMSCl (0.10 mL, 0.80 mmol, 8 eq.) was added to a solution of NaI (0.12 g, 0.80 mmol, 8 eq.) in dry MeCN (1 mL) and the reaction mixture was stirred for 20 min under an inert atmosphere of argon. To this, (*S*)-1'-(benzyloxy)-2'-(1-

(2-pyridine)-propyloxy)-[1,1']-binaphthalene (50 mg, 0.10 mmol, 1 eq.) in dry MeCN (5 mL) was added and the reaction mixture was heated at 60 °C for 18 h. The reaction mixture was quenched with water (10 mL), MeCN was removed under low pressure, saturated aq. Na_2SO_3 (1 mL) was added and the product was extracted in Et_2O (3 x 10 mL) and concentrated under reduced pressure. The crude material was purified by column chromatography (petroleum ether:EtOAc 4:1 to remove impurities, then toluene:MeOH 19:1) to give the product as a colourless solid (25 mg, 61%). R_f (toluene:MeOH 19:1) 0.4; $[\alpha]_D^{22}$ −69.1 (*c* 0.44 in THF); ν_{max} ($CHCl_3$)/cm^{-1} 3643, 3538, 3061, 2959, 2876, 1620, 1594, 1571, 1508, 1469, 1433, 1381, 1331, 1264, 1245, 1173, 1148, 1129, 1080, 1022, 909; δ_H (400 MHz, $CDCl_3$), 8.37 (1H, br d, *J* 4.0, Ar*H*), 7.98 (1H, d, *J* 9.0, Ar*H*), 7.88 (3H, m, Ar*H*), 7.51 (1H, td, *J* 8.0, 2.0, Ar*H*), 7.41 (1H, d, *J* 9.0, Ar*H*), 7.39-7.17 (6H, m, Ar*H*), 7.10 (1H, d, *J* 8.0, Ar*H*), 7.07 (1H, ddd, *J* 8.0, 5.0, 1.0, Ar*H*), 6.82 (1H, d, *J* 8.0, Ar*H*), 4.10-4.00 (2H, m, OCH_2), 2.64-2.56 (1H, m, PyCH_2), 2.53-2.46 (1H, m, PyCH_2), 1.97-1.89 (2H, m, OCH_2CH_2); δ_C (100 MHz, $CDCl_3$), 158.9 (C_q), 154.8 (C_q), 151.8 (C_q), 148.6 (CH), 136.8 (CH), 134.2 (C_q), 134.2 (C_q), 130.3 (CH), 129.5 (CH), 129.4 (C_q), 129.2 (C_q), 128.1 (CH), 128.0 (CH), 127.0 (CH), 126.3 (CH), 125.3 (CH), 125.1 (CH), 124.1 (CH), 123.4 (CH), 123.1 (CH), 121.2 (CH), 118.9 (CH), 118.1 (C_q), 117.0 (C_q), 115.4 (CH), 68.0 (CH_2), 33.8 (CH_2), 29.7 (CH_2); *m/z* (ES) 406 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 406.1800. $C_{28}H_{24}NO_2$ requires 406.1807.

(*R*)-2'-(Allyloxy)-[1,1']-binaphthalenyl-2-ol 227 [168]

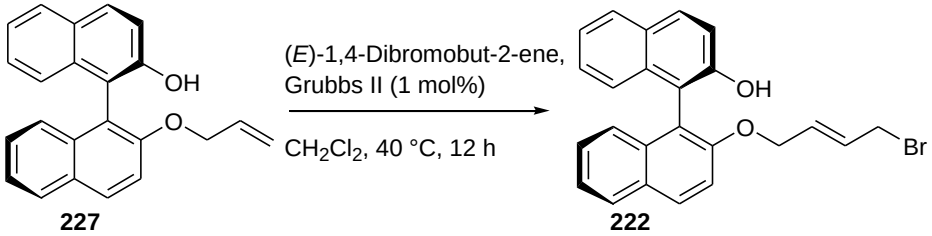


223 **227**

K_2CO_3 (0.48 g, 3.48 mmol, 1 eq.) was added to a solution of (*R*)-BINOL (1.00 g, 3.48 mmol, 1 eq.) in acetone (5 mL) and the reaction mixture was stirred for 1 h under an inert atmosphere of argon. Allyl bromide (0.30 mL, 3.48 mmol, 1 eq.) was added and the reaction mixture was stirred at room temperature for 2 h and then heated under reflux for 15 h. The reaction mixture was neutralised with 1 M aq. HCl (5 mL), concentrated under reduced pressure, dissolved in $CHCl_3$ (20 mL), washed with water (20 mL x 3), dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (toluene) to give the product as an off-white solid (0.90 g, 79%). R_f (toluene) 0.3; m.p. 97-100 °C; $[\alpha]_D^{22}$ −28.8 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3539, 3012, 3011, 2887, 1621, 1593, 1508, 1463, 1431, 1381, 1361, 1330, 1265, 1243, 1173, 1147, 1129, 1111, 1076, 1047, 1017, 998,

973, 931, 863, 821; δ_H (400 MHz, $CDCl_3$) 8.02 (1H, d, *J* 9.0, Ar*H*), 7.93 (2H, d, *J* 9.0, Ar*H*), 7.80 (1H, dd, *J* 12.0, 8.0, Ar*H*), 7.45 (1H, d, *J* 9.0, Ar*H*), 7.40 (1H, ddd, *J* 8.0, 6.5, 1.0, Ar*H*), 7.37 (2H, d, *J* 9.0, Ar*H*), 7.36-7.22 (3H, m, Ar*H*), 7.09 (1H, br d, *J* 8.0, Ar*H*), 5.78 (1H, dddd, *J* 17.0, 11.0, 5.0, 5.0, C*H*), 5.08 (1H, dddd, *J* 11.0, 2.0, 2.0, 1.5, $OCH_2CHCHCH_2$), 5.06 (1H, dddd, *J* 17.0, 2.0, 2.0, 1.5, $OCH_2CHCHCH_2$), 4.97 (1H, s, O*H*), 4.59 (1H, dddd, *J* 12.0, 5.0, 2.0, 1.5, OCH_2), 4.57 (1H, dddd, *J* 12.0, 5.0, 2.0, 1.5, OCH_2); δ_C (100 MHz, $CDCl_3$) 155.0 (C_q), 151.3 (C_q), 134.1 (C_q), 133.8 (C_q), 133.2 (CH), 130.9 (CH), 129.8 (CH), 129.7 (C_q), 129.1 (C_q), 128.2 (CH), 128.1 (CH), 127.3 (CH), 126.4 (CH), 125.1 (CH), 125.0 (CH), 123.2 (CH), 117.5 (CH), 117.3 (CH_2), 116.5 (C_q), 115.8 (CH), 70.0 (CH_2). Melting point, ^{1}H and ^{13}C NMR data are consistent with literature.[168]

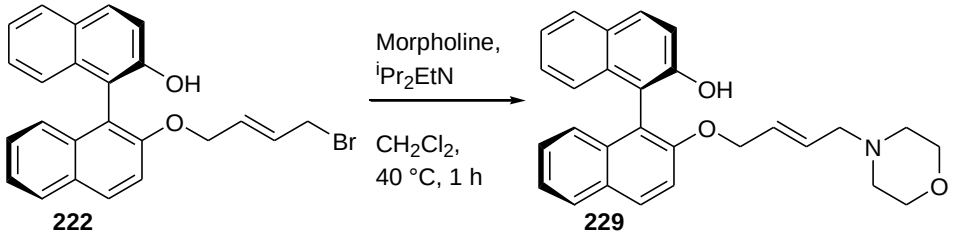
(*R*)-2'-((*E*)-1-Bromo-but-2-enyloxy)-[1,1']binaphthalenyl-2-ol 222



227 **222**

(*E*)-1,4-Dibromo-but-2-ene (1.04 g, 4.84 mmol, 2 eq.) was added to a solution of (*R*)-2'-(allyloxy)-[1,1']-binaphthalenyl-2-ol (0.80 g, 2.45 mmol, 1 eq.) and Grubbs 2nd Generation catalyst (20 mg, 20.0 µmol, 0.01 eq.) in CH_2Cl_2 (10 mL) and the reaction mixture was heated under reflux for 12 h under an inert atmosphere of argon. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (toluene) and to give the product as a viscous yellow liquid (0.80 g, 58%). R_f (toluene) 0.4; $[\alpha]_D^{22}$ −1.4 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3539, 3062, 3011, 1621, 1593, 1508, 1462, 1432, 1381, 1330, 1263, 1242, 1173, 1147, 1129, 1077, 1043, 1017, 970, 909; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, *J* 9.0, Ar*H*), 7.93 (1H, d, *J* 4.0, Ar*H*), 7.91 (1H, d, *J* 4.0, Ar*H*), 7.88 (1H, d, *J* 8.0, Ar*H*), 7.44-7.22 (7H, m, Ar*H*) 7.06 (1H, d, *J* 8.0, Ar*H*), 5.65-5.53 (2H, m, C*H*), 4.92 (1H, s, O*H*), 4.57-4.56 (2H, m, OCH_2), 3.77-3.75 (2H, m, $BrCH_2$); δ_C (100 MHz, $CDCl_3$) 154.8 (C_q), 151.3 (C_q), 134.0 (C_q), 133.8 (C_q), 131.0 (CH), 130.0 (CH), 129.8 (C_q), 129.1 (C_q), 128.9 (CH), 128.2 (CH), 128.2 (CH), 127.4 (CH), 126.5 (CH), 125.1 (CH), 124.9 (CH), 124.4 (CH), 123.3 (CH), 117.5 (CH), 117.0 (CH), 116.0 (CH), 115.0 (CH), 68.9 (CH_2), 31.6 (CH_2); *m/z* (ES) 339 (M-Br$^+$, 61%), 354 (29), 361 (33), 441 (M+Na$^+$, ^{79}Br, 100), 443 (M+Na$^+$, ^{81}Br, 100); *m/z* found [M+Na]$^+$ 441.0461. $C_{24}H_{19}O_2BrNa$ requires 441.0466.

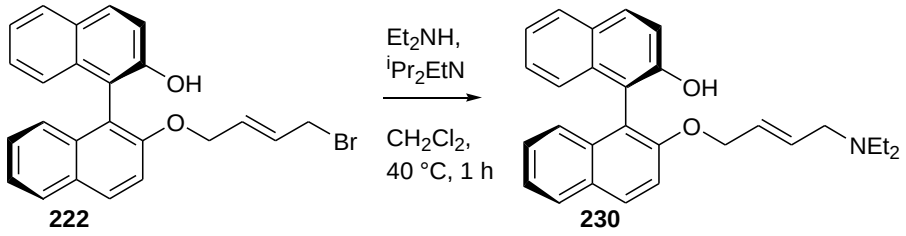
(*R*)-2'-((*E*)-*N*-Morpholin-but-2-enyloxy)-[1,1']binaphthalenyl-2-ol 229



222 **229**

Morpholine (21 µL, 0.24 mmol, 1 eq.) was added to a solution of (*R)*-2'-(1-bromo-but-2-enyloxy)-[1,1']binaphthalenyl-2-ol (0.20 g, 0.24 mmol, 1 eq.) and $^{i}Pr_2EtN$ (84 µL, 0.48 mmol, 2 eq.) in CH_2Cl_2 (1 mL) and the reaction mixture was heated under reflux for 1 h. The reaction mixture was diluted in CH_2Cl_2 (10 mL), washed with water (3 x 10 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH, 19:1) to give the product as an off-white solid (50 mg, 59%). m.p. 65-70 °C; R_f ($CHCl_3$:MeOH, 19:1) 0.6; $[\alpha]_D^{22}$ +1.7 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3538. 3061, 3009, 2966, 2956, 2863, 2817, 1621, 1593, 1507, 1457, 1432, 1381, 1350, 1331, 1264, 1244, 1173, 1147, 1116, 1076, 1041, 1002, 973, 865; δ_H (400 MHz, $CDCl_3$) 8.01 (1H, d, *J* 9.0, Ar*H*), 7.90 (2H, d, *J* 9.0, Ar*H*), 7.86 (1H, d, *J* 8.0, Ar*H*), 7.45 (1H, d, *J* 9.0, Ar*H*), 7.41-7.20 (6H, m, Ar*H*), 7.06 (1H, br d, *J* 8.0, Ar*H*), 5.56-5.53 (2H, m, C*H*), 4.58-4.50 (2H, m, OCH_2CH), 3.62-3.50 (4H, m, OCH_2CH_2), 2.87-2.78 (2H, m, NCH_2CH), 2.28-2.17 (4H, m, NCH_2CH_2); δ_C (100 MHz, $CDCl_3$) 154.8 (C_q), 151.3 (C_q), 134.0 (C_q), 133.8 (C_q), 130.7 (CH), 130.1 (CH), 129.8 (CH), 129.7 (CH), 129.1 (CH), 128.9 (CH), 128.1 (CH), 128.1 (CH), 127.3 (CH), 126.3 (CH), 125.3 (CH), 124.9 (CH), 124.5 (CH), 123.2 (CH), 117.7 (CH), 117.6 (C_q), 116.4 (CH), 115.2 (C_q), 69.6 (CH_2), 66.8 (CH_2), 60.2 (CH_2), 53.3 (CH_2); *m/z* (ES) 426 ($M+H^+$, 100), 448 ($M+Na^+$, 10); *m/z* (ES) 424 ($M-H^-$, 48%), 470 (53), 849 ($2M-H^-$, 100); *m/z* found $[M-H]^-$ 424.1897. $C_{28}H_{26}NO_3$ requires 424.1918.

(*R*)-2'-((*E*)-*N*-Diethylamino-but-2-enyloxy)-[1,1']binaphthalenyl-2-ol 230

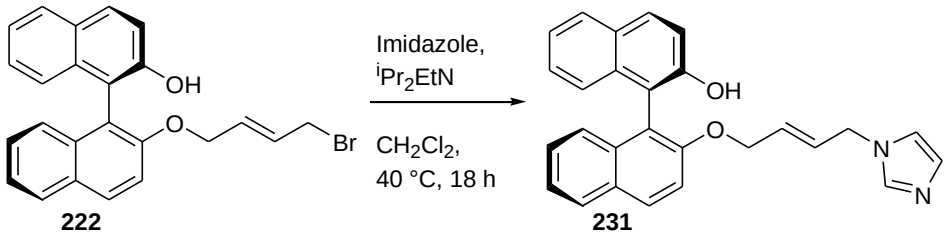


222 **230**

Diethylamine (48 µL, 0.48 mmol, 1 eq.) was added to a solution of (*R*)-2'-(1-bromo-but-2-enyloxy)-[1,1']binaphthalenyl-2-ol (0.20 g, 0.48 mmol, 1 eq.) and $^{i}Pr_2EtN$ (168 µL, 0.96 mmol, 2 eq.) in CH_2Cl_2 (1 mL) and the reaction mixture was heated under reflux for 1 h. The reaction mixture was diluted in CH_2Cl_2 (10 mL), washed with water (3 x 10 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH, 9:1) to give the

product as an off-white solid (50 mg, 25%). m.p. 50-53 °C; R_f ($CHCl_3$:MeOH, 9:1) 0.5; $[\alpha]_D^{22}$ +4.2 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3538, 3061, 3011, 2973, 2936, 2820, 1621, 1593, 1508, 1463, 1382, 1346, 1330, 1264, 1241, 1172, 1147, 1129, 1076, 1041, 1016, 973; δ_H (400 MHz, $CDCl_3$) 8.01 (1H, d, *J* 9.0, Ar*H*), 7.89 (2H, d, *J* 9.0, Ar*H*), 7.86 (1H, d, *J* 8.0, Ar*H*), 7.45 (1H, d, *J* 9.0, Ar*H*), 7.40-7.20 (8H, m, Ar*H*) 7.07 (1H, d, *J* 8.0, Ar*H*), 5.65-5.50 (2H, m, C*H*), 4.65-4.50 (2H, m, OCH_2), 2.99 (2H, br d, *J* 4.0, NCH_2CH), 2.38 (4H, q, *J* 7.0, CH_2CH_3), 0.95 (6H, t, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 154.8 (C_q), 151.4 (C_q), 134.1 (C_q), 133.9 (C_q), 130.6 (CH), 129.7 (C_q), 129.6 (CH), 129.1 (C_q), 128.6 (CH), 128.1 (CH), 128.1 (CH), 127.2 (CH), 126.3 (CH), 125.2 (CH), 125.0 (CH), 124.4 (CH), 123.1 (CH), 117.8 (CH), 117.4 (C_q), 116.2 (CH), 115.4 (C_q), 69.5 (CH_2), 54.2 (CH_2), 46.4 (CH_2), 11.3 (CH_3); *m/z* (ES) 412 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 412.2287. $C_{28}H_{30}NO_2$ requires 412.2271.

(*R*)-2'-((*E*)-*N*-imidazol-but-2-enyloxy)-[1,1']binaphthalenyl-2-ol 231

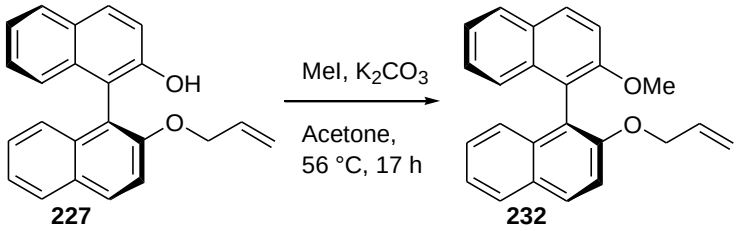


222 **231**

Imidazole (70 mg, 0.96 mmol, 2 eq.) was added to a solution of (*R*)-2'-(1-bromo-but-2-enyloxy)-[1,1']binaphthalenyl-2-ol (0.20 g, 0.48 mmol, 1 eq.) and EtN^iPr_2 (168 µL, 0.96 mmol, 2 eq.) in CH_2Cl_2 (1 mL) and the reaction mixture was heated under reflux for 1 h. The reaction mixture was diluted in CH_2Cl_2 (10 mL), washed with water (3 x 10 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH, 9:1) to give the product as an off-white solid (50 mg, 25%). An unknown contaminant could not be removed by column chromatography and the compound was used without further purification. R_f ($CHCl_3$:MeOH, 19:1) 0.4; δ_H (400 MHz, $CDCl_3$) 8.04 (s, imp), 8.00 (1H, d, *J* 12.0, Ar*H*), 7.87 (3H, app q, *J* 9.0, Ar*H*), 7.82-7.78 (imp, m), 7.41 (imp, d), 7.39 (imp, d), 7.38 (1H, d, *J* 10.0, Ar*H*), 7.34 (1H, d, *J* 11.0, Ar*H*), 7.32-7.25 (5H, m, Ar*H*), 7.22-7.17 (2H, m, Ar*H*), 7.05 (1H, d, *J* 8.0, Ar*H*), 6.96 (1H, s, Ar*H*), 6.89 (imp, s), 6.66 (1H, s, O*H*), 6.51 (imp, s), 5.67-5.61 (imp, m), 5.45 (2H, qtt, *J* 16.0, 6.0, 2.0, C*H*), 4.63-4.60 (imp, m), 4.58-4.47 (2H, m, OCH_2), 4.26 (2H, d, *J* 8.0, NCH_2), 4.14 (imp, q), 4.01 (imp, dd), 3.87 (imp, dd), 2.06 (imp, d) 1.27 (imp, m); δ_C (100 MHz, $CDCl_3$) 154.6 (C_q), 151.8 (C_q), 134.1 (C_q), 133.9 (C_q), 130.7 (CH), 129.9 (C_q), 129.7 (CH), 129.2 (CH), 129.1 (CH), 129.0 (C_q), 128.2 (CH), 128.1 (CH), 127.3 (CH), 126.7 (CH), 126.4 (CH), 125.3 (CH), 124.8 (CH), 124.5 (CH), 123.1 (CH), 118.8 (CH), 118.0 (C_q), 117.8 (CH), 116.0 (CH), 115.1 (C_q),

68.7 (CH_2), 48.1 (CH_2); *m/z* (ES) 361 (11%), 407 ($M+H^+$, 100), 468 (19), 745 (12); *m/z* found $[M+H]^+$ 407.1771. $C_{27}H_{22}N_2O_2$ requires 407.1754.

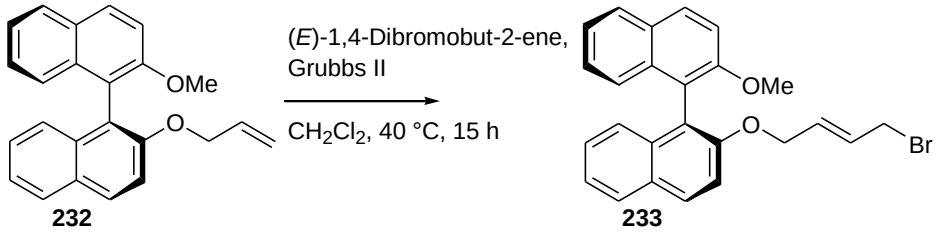
(*S*)-2-Allyloxy-2'-methoxy-1,1'-binaphthyl 232



227 **232**

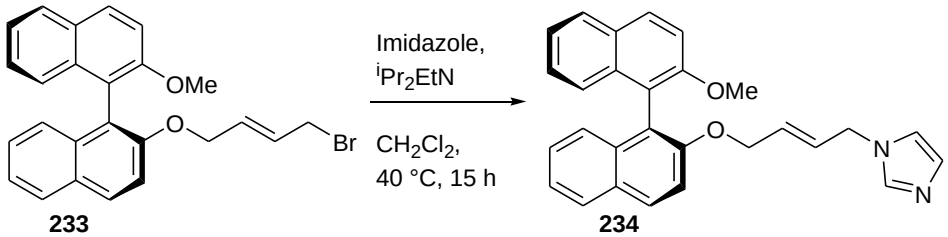
K_2CO_3 (0.21 g, 1.50 mmol, 1 eq.) was added to a solution of (*S*)-2-allyloxy-2'-hydroxy-1,1'-binaphthyl (0.50 g, 1.50 mmol, 1 eq.) in acetone (5 mL) and the reaction mixture were stirred for 1 h under an inert atmosphere of argon. Methyl iodide (0.47 mL, 7.50 mmol, 5 eq.) was added and the reaction mixture was stirred at room temperature for 2 h before being heated under reflux for 15 h. The reaction mixture was neutralised with 1 M HCl (5 mL), then the product was extracted into $CHCl_3$ (5 mL x 3) and the organic layer was dried over $MgSO_4$. The organic layer was concentrated under reduced pressure, purified by column chromatography (toluene) to give the product as a colourless solid (0.46 g, 90%). m.p. 100-105 °C; R_f (toluene) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 3061, 3011, 2938, 2840, 1622, 1592, 1509, 1464, 1431, 1355, 1331, 1264, 1249, 1179, 1148, 1134, 1088, 1060, 1019, 929; $[\alpha]_D^{22}$ −35.0 (*c* 0.7 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.02 (1H, d, *J* 14.5, Ar*H*), 8.00 (1H, d, *J* 14.5, Ar*H*), 7.90 (2H, d, *J* 8.0, Ar*H*), 7.48 (2H, dd, *J* 16.0, 9.0, Ar*H*), 7.38-7.32 (2H, m, Ar*H*), 7.27-7.22 (2H, m, Ar*H*), 7.18 (2H, app t, *J* 8.0, Ar*H*), 5.78 (1H, dddd, *J* 17.0, 10.5, 5.0, 5.0, C*H*), 5.05 (1H, dddd, *J* 17.0, 2.0, 2.0, 1.5 OCH_2CHCH_2), 5.03 (1H, ddd, *J* 10.5, 2.0, 2.0, 1.5, OCH_2CHCH_2), 4.58 (1H, dddd, *J* 12.0, 5.0, 2.0, 1.5, OCH_2), 4.53 (1H, dddd, *J* 12.0, 5.0, 2.0, 1.5, OCH_2), 3.82 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 155.0 (C_q), 154.1 (C_q), 134.2 (C_q), 134.1 (C_q), 133.8 (CH), 129.4 (C_q), 129.4 (C_q), 129.3 (CH), 129.2 (C_q), 128.0 (CH), 127.9 (CH), 126.4 (CH), 126.3 (CH), 125.5 (CH), 125.4 (CH), 123.7 (CH), 123.5 (CH), 120.5 (C_q), 119.6 (C_q), 116.5 (CH_2), 116.0 (CH), 114.0 (CH), 70.1 (CH_2), 56.8 (CH_3); *m/z* (ES) 341 ($M+H^+$, 27%), 358 ($M+NH_4^+$, 14), 363 ($M+Na^+$, 100), 703 ($2M+Na^+$, 23); *m/z* found $[M+Na^+]$ 363.1365. $C_{24}H_{20}NaO_2$ requires 363.1361.

(*S*)-2-((*E*)-1-Bromo-but-2-enyloxy)-2'-methoxy-1,1'-binaphthyl 233



(*E*)-1,4-Dibromobut-2-ene (0.50 g, 2.36 mmol, 2 eq.) was added to a solution of (*S*)-2-allyloxy-2'-methoxy-1,1'-binaphthyl (0.40 g, 1.18 mmol, 1 eq.) and Grubbs II catalyst (10 mg, 11.8 μmol, 0.01 eq.) in CH_2Cl_2 (5 mL) and the reaction mixture was heated under reflux for 15 h under an inert atmosphere of argon. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (100% toluene) to give the product as an off-white hygroscopic solid (0.36 g, 73%). m.p. 39-43 °C; R_f (toluene) 0.7; ν_{max} ($CHCl_3$)/cm^{-1} 3060, 3011, 2937, 2841, 1622, 1593, 1509, 1464, 1431, 1356, 1250, 1180, 1148, 1133, 1087, 1058, 1019, 967; $[\alpha]_D^{22}$ −20.4 (*c* 0.7 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.04 (1H, d, *J* 9.0, Ar*H*), 7.99 (1H, d, *J* 9.0, Ar*H*), 7.92 (2H, dd, *J* 8.0, 3.0, Ar*H*), 7.51 (1H, d, *J* 9.0, Ar*H*), 7.42 (1H, d, *J* 9.0, Ar*H*), 7.41-7.34 (1H, m, Ar*H*), 7.32-7.24 (2H, m, Ar*H*), 7.23-7.13 (2H, m, Ar*H*), 5.67-5.63 (2H, m, C*H*), 4.59-4.55 (2H, m, OCH_2), 3.83 (3H, s, OCH_3), 3.85-3.75 (2H, m, BrCH_2); δ_C (100 MHz, $CDCl_3$) 155.0 (C_q), 153.9 (C_q), 134.1 (C_q), 134.1 (C_q), 130.7 (CH), 129.6 (C_q), 129.5 (CH), 129.4 (CH), 129.2 (C_q), 128.0 (CH), 128.0 (CH x 2), 126.4 (CH), 126.4 (CH), 125.5 (CH), 125.3 (CH), 123.9 (CH), 123.5 (CH), 120.9 (C_q), 119.3 (C_q), 116.1 (CH), 113.9 (CH), 68.8 (CH_2), 56.7 (CH_3), 32.0 (CH); *m/z* (ES) 353 (M-Br^+, 27%), 407 (M-Br+MeOH+Na^+, 79), 433 (M+H^+, ^{79}Br, 23), 435 (M+H^+, ^{81}Br, 23), 450 (M+NH_4^+, ^{79}Br, 11), 452 (M+NH_4^+, ^{81}Br, 11), 455 (M+Na^+, ^{79}Br, 98), 457 (M+Na^+, ^{81}Br, 100); *m/z* found [M+Na^+, ^{79}Br] 455.0622. $C_{25}H_{21}O_2{}^{79}BrNa$ requires 455.0623.

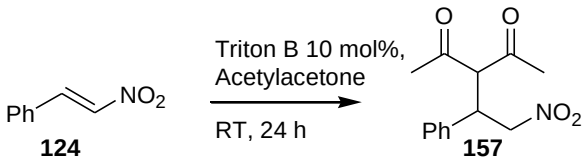
(*S*)-1'-Methoxy-2'-((*E*)-*N*-imidazol-but-2-enyloxy)-[1,1']binaphthalene 234



Imidazole (70 mg, 0.96 mmol, 2 eq.) was added to a solution of (*S*)-2-((*E*)-1-bromo-but-2-enyloxy)-2'-methoxy-1,1'-binaphthyl (0.20 g, 0.48 mmol, 1 eq.) and $^{i}Pr_2EtN$ (168 μL, 0.96 mmol, 2 eq.) in CH_2Cl_2 (1 mL) and the reaction mixture was heated under reflux for 1 h. The reaction mixture was diluted in CH_2Cl_2 (10 mL), washed with water (3 x 10 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH, 19:1) to give the

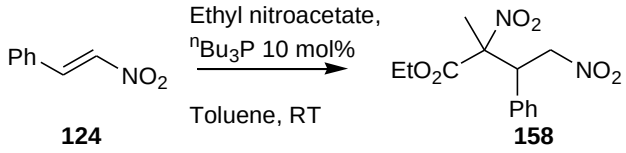
product as an off-white solid (0.11 g, 55%). An unknown contaminant could not be removed by column chromatography and the compound was used without further purification. δ_H (400 MHz, $CDCl_3$) 7.96 (2H, dd, *J* 9.0, 9.0, Ar*H*), 7.88 (2H, app d, 8.5, Ar*H*), 7.42 (1H, d, *J* 9.0, Ar*H*), 7.40-7.15 (8H, m, Ar*H*), 7.11 (1H, d, *J* 8.5, Ar*H*), 7.03 (1H, s, Ar*H*), 6.66 (1H, s, O*H*), 5.49 (1H, dt, *J* 15.5, 4.5, OCH_2CH), 5.37 (1H, dt, 15.5, 6.0, NCH_2CH), 4.57-4.45 (2H, m, OCH_2), 4.27 (2H, app d., *J* 6.0, NCH_2), 3.71 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 154.9 (C_q), 153.8 (C_q), 136.9 (CH), 134.1 (C_q), 134.0 (C_q), 129.7 (CH), 129.6 (C_q), 129.5 (CH), 129.4 (CH x 2), 129.1 (C_q), 128.0 (CH x 2), 126.5 (CH x 2), 125.5 (CH), 125.3 (CH), 120.9 (C_q), 119.3 (C_q), 118.9 (CH), 116.0 (CH), 113.9 (CH), 68.7 (CH_2), 56.6 (CH_3), 48.2 (CH_2); *m/z* (ES) 421 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 421.1905. $C_{28}H_{25}N_2O_2$ requires 421.1911.

3-(2-Nitro-1-phenylethyl)pentane-2,4-dione 157 [169]



(*E*)-Nitrostyrene (50 mg, 0.34 mmol, 1 eq.) was added to a solution of Triton B (5.7 mg, 34.0 µmol, 0.1 eq.) in acetylacetone (0.5 mL, 4.87 mmol, 14 eq.) and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated under low pressure and purified by column chromatography (petroleum ether:EtOAc 4:1) to give the product as an off-white solid (53 mg, 63%). m.p. 108-110 °C; R_f (petroleum ether:EtOAc 4:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 3045, 2922, 1734, 1703, 1557, 1496, 1455, 1433, 1328, 1360, 1181, 1154, 953, 916; δ_H (400 MHz, $CDCl_3$) 7.36-7.27 (3H, m, Ar*H*), 7.21-7.17 (2H, m, Ar*H*), 4.66 (1H, dd, *J* 12.5, 7.7, CH_2), 4.62 (1H, dd, *J* 12.5, 5.0, CH_2), 4.38 (1H, d, *J* 11.0, COC*H*), 4.25 (1H, ddd, *J* 11.0, 7.5, 5.0, PhC*H*), 2.30 (3H, s, CH_3), 1.95 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 201.8 (C_q), 201.0 (C_q), 136.0 (C_q), 129.4 (CH), 128.6 (CH), 128.0 (CH), 78.2 (CH_2), 70.7 (CH), 42.8 (CH), 30.5 (CH_3), 29.6 (CH_3); *m/z* (ES) 272 ($M+Na^+$, 100%); *m/z* found $[M+Na^+]$ 272.0891. $C_{13}H_{15}NO_4$ requires 272.0893. Enantiomeric excess was determined by HPLC; Chiralpak AD-H, Hexane:^{i}PrOH 85:15, 1 mL/min, 20 °C, 13.4, 15.8 min. ^1H and ^{13}C NMR data consistent with literature.[169]

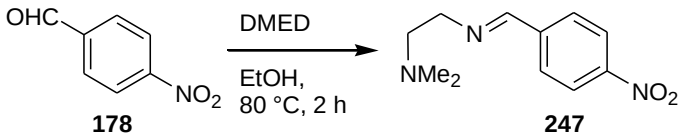
Ethyl 2-methyl-2,4-dinitro-3-phenylbutanoate 158 [170]



124 **158**

(*E*)-Nitrostyrene (0.10 g, 0.68 mmol, 2 eq.) was added to a solution of ethyl nitropropionate (50 mg, 0.34 mmol, 1 eq.) and $^{n}Bu_3P$ (6.9 mg, 34.0 µmol, 0.1 eq.) in toluene (2 mL) and the reaction mixture was stirred at room temperature with the extent of reaction being monitored by TLC. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (petroleum ether: EtOAc 9:1) to give the product as a yellow oil as a mixture of diastereomers (50 mg, 50%). *Minor diastereomer:* R_f 0.6 (petroleum ether:EtOAc 9:1); ν_{max} ($CHCl_3$)/cm^{-1} 2987, 1750, 1561, 1497, 1456, 1378, 1342, 1311, 1250, 1175, 1130, 1013, 857; δ_H (400 MHz, $CDCl_3$) 7.38-7.33 (3H, m, Ar*H*), 7.17-7.12 (2H, m, Ar*H*), 5.15 (1H, dd, *J* 14.0, 3.5, NO_2CH_2), 5.07 (1H, dd, *J* 14.0, 10.0, NO_2CH_2), 4.42 (1H, dd, *J* 10.0, 3.5, C*H*), 4.35 (1H, dd, *J* 7.0, 0.5, CH_2CH_3), 4.31 (1H, dd, *J* 7.0, 0.5, CH_2CH_3), 1.66 (3H, s, CCH_3), 1.32 (3H, t, *J* 7.0, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 166.6 (C_q), 132.4 (C_q), 129.4 (CH), 128.9 (CH), 93.8 (C_q), 77.1 (CH_2), 63.9 (C_q), 48.7 (CH), 22.0 (CH_3), 13.8 (CH_3); *m/z* (ES) 319 ($M+Na^+$, 100%); *m/z* found [$M+Na^+$] 319.0898. $C_{13}H_{16}N_2O_6Na$ requires 319.0906. *Major diastereomer:* R_f 0.5 (petroleum ether:EtOAc 9:1); ν_{max} ($CHCl_3$)/cm^{-1} 2987, 1750, 1561, 1456, 1378, 1342, 1311, 1250, 1130, 1013, 857; δ_H (400 MHz, $CDCl_3$) 7.38-7.34 (3H, m, ArH), 7.26-7.22 (2H, m, ArH), 5.13 (1H, dd, *J* 14.0, 11.0, NO_2CH_2), 4.97 (1H, dd, *J* 14.0, 3.0, NO_2CH_2), 4.55 (1H, dd, *J* 11.0, 3.0, C*H*), 4.40-4.32 (2H, m, CH_2CH_3), 1.70 (3H, s, CCH_3), 1.34 (3H, t, *J* 7.0, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 165.6 (C_q), 132.7 (C_q), 129.3 (CH), 129.2 (CH), 129.1 (CH), 94.1 (C_q), 76.2 (CH_2), 49.3 (CH), 22.1 (CH_3), 13.7 (CH_3); *m/z* (ES) 319 ($M+Na^+$, 100%); *m/z* found [$M+Na^+$] 319.0899. $C_{13}H_{16}N_2O_6Na$ requires 319.0906. Enantioselectivity determined by chiral HPLC, R_t (Chiralcel OD, 4:1 hexane:^{i}PrOH, 210 nm, 1 mL/min) 7.9 min, 15.6 min. ^1H and ^{13}C NMR data are consistent with literature.[170]

***N*-[2-(Dimethylamino)-ethyl]-4-nitrobenzylidenimine 247** [171]

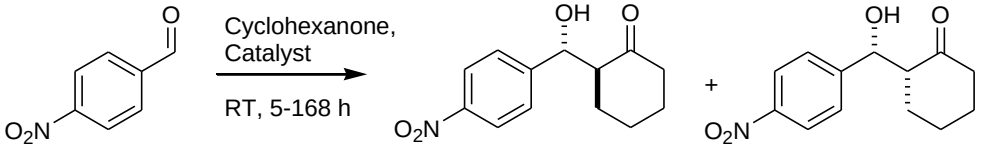


178 **247**

N,*N*-Dimethylethyldiamine (0.29 g, 3.30 mmol, 1 eq.) was added to a solution of 4-nitrobenzaldehyde (0.50 g, 3.30 mmol, 1 eq.) in EtOH (20 mL) and the reaction mixture was heated under reflux for 2 h at 80 °C. The reaction mixture was concentrated to give the product as an orange solid (0.72 g, 99%). m.p. 30-35 °C;

v_{max} ($CHCl_3$)/cm^{-1} 2978, 2948, 2858, 2826, 2780, 1647, 1603, 1525, 1465, 1347, 1294, 1108, 1015, 852, 835; δ_H (400 MHz, $CDCl_3$) 8.39 (1H, s, C*H*), 8.24 (2H, dd, *J* 8.5, 1.5, Ar*H*), 7.89 (2H, dd, *J* 8.5, 1.5, Ar*H*), 3.79 (2H, t, *J* 6.5, CHNCH_2), 2.67 (2H, t, *J* 6.5, CH_3NCH_2), 2.31 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 159.5 (CH), 149.0 (C_q), 141.7 (CH), 128.8 (CH), 123.8 (CH), 60.0 (CH_2), 59.8 (CH_2), 45.8 (CH_3); *m/z* (EI) 59 (100%), 71 (40), 77 (25), 90 (70), 103 (25), 117 (30), 130 (20), 149 (20), 177 (30), 221 (M^+, 10); *m/z* found $[M]^+$ 221.1166. $C_{11}H_{15}N_3O_2$ requires 221.1164.

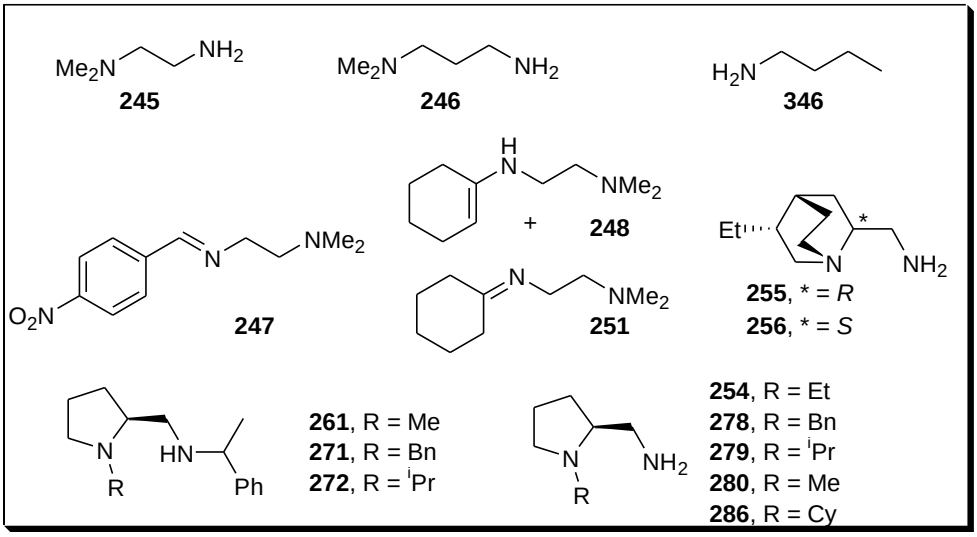
General procedure for synthesis of 2-[hydroxy(4-nitrophenyl)methyl]cyclo hexan-1-one 179 [172,173]



178 ***anti*-179** ***syn*-179**

4-Nitrobenzaldehyde (50 mg, 0.33 mmol, 1 eq.) was added to a solution of cyclohexanone (0.10 mL, 0.99 mmol, 3 eq.) and a catalyst in a solvent (0.50 mL) and the reaction mixture stirred at room temperature for 5-168 h. The organic reaction mixture was extracted from the aqueous layer with $CHCl_3$ (3 x 1 mL) and filtered through a short column of $MgSO_4$ to give the crude product, from which conversion and syn/anti selectivity could be determined. Further purification by column chromatography (petroleum ether: EtOAc 4:1) gave the product as a colourless solid. Elemental analysis found: C, 62.78; H, 6.09; N, 5.52. $C_{13}H_{15}NO_4$ requires C, 62.64; H, 6.07, N, 5.62; s*yn diastereomer*: m.p. 130-132 °C; R_f (petroleum ether:EtOAc 4:1) 0.2; v_{max} ($CHCl_3$)/cm^{-1} 3578, 3011, 2946, 2871, 1700, 1605, 1522, 1451, 1401, 1349, 1311, 1186, 1130, 1110, 1092, 1065, 1015, 982, 866, 854; δ_H (400 MHz, $CDCl_3$) 8.22 (2H, app d., *J* 9.0, Ar*H*), 7.50 (2H, app d., *J* 9.0, Ar*H*), 5.50 (1H, dd, *J* 2.5, 2.5, PhC*H*), 3.17 (1H, d, *J* 3.5, O*H*), 2.67-2.64 (1H, m, COC*H*), 2.64-2.47 (1H, m, COCH_2), 2.41 (1H, dddd, *J* 13.5, 13.5, 6.0, 1.0, COCH_2), 2.16-2.09 (1H, m, CHCH_2), 1.91-1.84 (1H, m, CHCH_2), 1.80-1.48 (4H, m, CHCH$_2$CH_2CH_2); δ_C (100 MHz, $CDCl_3$) 214.1 (C_q), 149.1 (C_q), 147.1 (C_q), 126.6 (CH), 123.5 (CH), 70.2 (CH), 56.8 (CH), 42.6 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 24.8 (CH_2); *m/z* (ES) 272 ($M+Na^+$, 100%), 521 ($2M+Na^+$, 57); *m/z* found $[M+Na^+]$ 272.0886. $C_{13}H_{15}NO_4$ requires 272.0893. a*nti diastereomer*: m.p. 156-159 °C; R_f (petroleum ether:EtOAc 4:1) 0.1; v_{max} ($CHCl_3$)/cm^{-1} 3536, 3011, 2947, 2868, 1607, 1526, 1450, 1398, 1349, 1313, 1296, 1190, 1131, 1097, 1066, 1044, 1016, 856, 842; δ_H (400 MHz, $CDCl_3$) 8.22 (2H, app d., *J* 9.0, Ar*H*), 7.52 (2H, app d., *J* 8.5, Ar*H*), 4.91 (1H, dd, *J* 8.5, 3.0, PhC*H*), 4.07 (1H, d, *J* 3.0, O*H*), 2.64-2.56 (1H, m, COC*H*), 2.54-2.48 (1H, m, COCH_2), 2.37 (1H, dddd, *J* 13.5, 13.5, 6.0, 1.0, COCH_2), 2.17-2.09 (1H, m, CHCH_2), 1.88-1.81 (1H, m, CHCH_2), 1.75-1.50 (3H, m, CHCH$_2$CH_2CH_2), 1.45-1.34 (1H, m, CHCH$_2$CH_2); δ_C (100 MHz, $CDCl_3$) 214.8 (C_q),

148.4 (C_q), 147.6 (C_q), 127.9 (CH), 123.6 (CH), 74.1 (CH), 57.2 (CH), 42.7 (CH_2), 30.8 (CH_2), 27.7 (CH_2), 24.7 (CH_2); *m/z* (ESI +ve) 272 ($M+Na^+$, 100%), 521 ($2M+Na^+$, 9%), *m/z* found $[M+Na^+]$ 272.0891, $C_{13}H_{15}NO_4$ requires 272.0893. Enantioselectivity determined by chiral HPLC, R_t (Chiralpak AD-H, 85:15 hexane:^{i}PrOH, 210 nm, 0.8 mL/min, 20 °C) 18.8 (syn), 20.6 (syn), 22.6 (anti), 29.5 (anti) min. ^1H and ^{13}C NMR data are consistent with literature.[172,173]

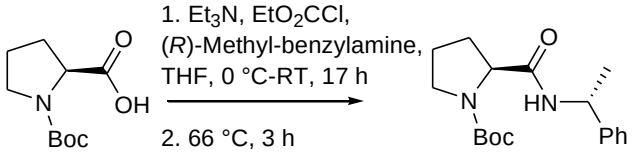


Diamine	Time /h	Solvent	Diamine /mol%	TfOH /mol%	Yield /%	*anti:syn* Ratio	*anti* ee/%	*syn* ee/%
245	48	CH_2Cl_2	10	10	71	96:4	-	-
245	48	H_2O	10	10	81	88:12	-	-
246	48	CH_2Cl_2	10	10	24	72:28	-	-
246	48	H_2O	10	10	96	59:41	-	-
346	48	CH_2Cl_2	10	5	9	29:71	-	-
346	48	H_2O	10	5	32	41:59	-	-
346	48	CH_2Cl_2	10	10	30	51:49	-	-
346	48	H_2O	10	10	0	-	-	-
247	48	CH_2Cl_2	10	10	100	88:12	-	-
247	48	H_2O	10	10	97	88:12	-	-
248 & **251**	48	CH_2Cl_2	10	10	24	95:5	-	-
248 & **251**	48	H_2O	10	10	98	88:12	-	-
254*	18	H_2O	3	3	99	81:19	37	14
255*	18	H_2O	3	3	99	87:13	-2	5
256*	5	H_2O	3	3	98	92:8	21	9
254	48	H_2O	10	10	95	83:17	46	12
254	48	H_2O	10	0	100	64:36	1	-1
R,S-**271**	24	H_2O	3	3	<1	-	-	-
S,S-**271**	24	H_2O	3	3	<1	-	-	-
R,S-**272**	24	H_2O	3	3	<1	-	-	-
S,S-**272**	24	H_2O	3	3	<1	-	-	-

R,S-**261***	24	H_2O	3	3	11	67:33	-	-
S,S-**261***	24	H_2O	3	3	6	64:36	-	-
R,S-**271**	24	CH_2Cl_2	30	30	4	73:27	-	-
R,S-**271**	24	H_2O	30	30	3	87:13	-	-
S,S-**271**	24	CH_2Cl_2	30	30	7	67:33	-	-
S,S-**271**	24	H_2O	30	30	9	83:17	-	-
R,S-**272**	24	CH_2Cl_2	30	30	<1	-	-	-
R,S-**272**	24	H_2O	30	30	<1	-	-	-
S,S-**272**	24	CH_2Cl_2	30	30	<1	-	-	-
S,S-**272**	24	H_2O	30	30	<1	-	-	-
R,S-**261**	24	CH_2Cl_2	30	30	<1	-	-	-
R,S-**261**	24	H_2O	30	30	<1	-	-	-
S,S-**261**	24	CH_2Cl_2	30	30	<1	-	-	-
S,S-**261**	24	H_2O	30	30	<1	-	-	-
254	21	None	10	10	100	85:15	48	3
278	21	H_2O	10	10	100	83:17	56	-32
279	96	H_2O	10	10	42	86:14	67	28
280	168	None	10	10	24	82:18	51	-6
280	21	H_2O	10	10	100	88:12	48	21
286	33	H_2O	10	10	100	83:17	63	30

* = done at 60 °C

tert-Butyl-(2*S*)-2-{[(1*R*)-1-phenylethyl]carbamoyl}pyrrolidine-1-carboxylate (*R,S*)-260 [174]

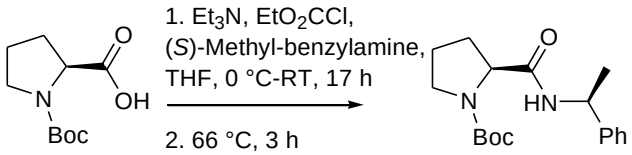


259 **(*R,S*)-260**

NEt_3 (1.28 mL, 9.30 mmol, 1 eq.) was added to a solution of *N*-Boc-L-proline (2.00 g, 9.30 mmol, 1 eq.) in THF (20 mL) and the reaction mixture was stirred at 0 °C for 10 min. Ethyl chloroformate (0.88 mL, 9.30 mmol, 1 eq.) was added dropwise over 15 min and then stirred for 30 min, during which time a colourless precipitate formed. (*R*)-Methylbenzylamine (1.20 mL, 9.30 mmol, 1 eq.) was added over 15 min and the reaction mixture was allowed to warm to room temperature over 17 h before being heated under reflux for 3 h. The precipitate was removed by filtration through kieselguhr and the filtrate was concentrated under reduced pressure before purification by column chromatography (petroleum ether: EtOAc 4:1 to remove main impurity, then petroleum ether:EtOAc 1:1). The collected residue was redissolved in Et_2O, concentrated under reduced pressure and dried under high vacuum for several days to give the product as a colourless solid in a mixture of rotamers (2.74 g, 92%). Elemental analysis found: C, 67.95; H, 8.30; N,

8.79. $C_{18}H_{26}N_2O_3$ requires C, 67.90; H, 8.23, N, 8.8; m.p. 77-79 °C; R_f (petroleum ether:EtOAc 1:1) 0.5; $[\alpha]_D^{22}$ −86.6 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3420, 3319, 3010, 2982, 2933, 2884, 1677, 1512, 1478, 1454, 1394, 1368, 1242, 1364, 1125, 1088, 1023, 983, 923, 883, 851; δ_H (400 MHz, d^6-DMSO) 8.27-8.18 (1H, m, N*H*), 7.39-7.27 (4H, m, Ar*H*), 7.25-7.19 (1H, m, Ar*H*), 5.00-4.85 (1H, m, PhC*H*), 4.20-4.13 (0.3H, m, COC*H*), 4.08 (0.7H, dd, *J* 8.5, 3.0, COC*H*), 3.45-3.35 (1H, m, NCH_2), 3.32-3.24 (1H, m, NCH_2), 2.21-1.99 (1H, m, CHCH_2), 1.94-1.69 (3H, m, CH_2CH_2), 1.45-1.32 (6H, m, CCH_3), 1.23 (6H, br s, CCH_3); δ_C (100 MHz, d^6-DMSO) 171.9 (C_q), 153.8 (C_q), 145.0 (C_q), 128.5 (CH), 127.1 (CH), 126.9 (CH), 126.6 (CH), 126.5 (CH), 78.7 (C_q), 60.1 (CH), 48.1 (CH), 47.0 (CH_2), 31.7 (CH_2), 28.6 (CH_3), 28.4 (2 x CH_3), 23.6 (CH_2), 22.5 (CH_3); *m/z* (ES) 341 (M+Na^+, 100%), 659 (2M+Na^+, 13); *m/z* found $[M+Na]^+$ 341.1831, $C_{18}H_{26}N_2O_3Na$ requires 341.1836. ^1H and ^{13}C NMR data are consistent with literature.[174]

tert-Butyl-(2*S*)-2-{[(1*S*)-1-phenylethyl]carbamoyl}pyrrolidine-1-carboxylate (*S,S*)-260 [174]

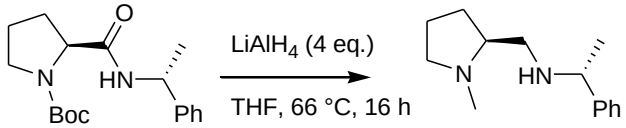


259 **(*S,S*)-260**

NEt_3 (1.28 mL, 9.30 mmol, 1 eq.) was added to a solution of *N*-Boc-L-proline (2.00 g, 9.30 mmol, 1 eq.) in THF (20 mL) and the reaction mixture was stirred at 0 °C for 10 min. Ethyl chloroformate (0.88 mL, 9.30 mmol, 1 eq.) was added dropwise over 15 min and then stirred for 30 min, during which time a colourless precipitate formed. (*S*)-Methylbenzylamine (1.20 mL, 9.30 mmol, 1 eq.) was added over 15 min and the reaction mixture was allowed to warm to room temperature over 17 h before being heated under reflux for 3 h. The precipitate was removed by filtration through kieselguhr and the filtrate was concentrated under reduced pressure before purification by column chromatography (petroleum ether: EtOAc 4:1 to remove main impurity, then petroleum ether:EtOAc 1:1). The collected residue was redissolved in Et_2O, concentrated under reduced pressure and dried under high vacuum for several days to give the product as a colourless solid in a mixture of rotamers (2.75 g, 93%). Elemental analysis found: C, 68.05; H, 8.29; N, 8.70. $C_{18}H_{26}N_2O_3$ requires C, 67.90; H, 8.23, N, 8.8; m.p. 98-100 °C; R_f 0.4 (petroleum ether:EtOAc 1:1); $[\alpha]_D^{22}$ −121.1 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3419, 3316, 3010, 2982, 2884, 1677, 1512, 1454, 1393, 1369, 1242, 1163, 1124, 1088, 1021, 981, 923, 881, 851; δ_H (400 MHz, d^6-DMSO) 8.27 (0.7H, d, *J* 8.0, N*H*), 8.22 (0.3H, d, *J* 8.0, N*H*), 7.37-7.27 (4H, m, Ar*H*), 7.27-7.18 (1H, m, Ar*H*), 5.02-4.86 (1H, m, PhC*H*), 4.18-4.07 (1H, m, COC*H*), 3.42-3.33 (1H, m, NCH_2), 3.32-

3.24 (1H, m, NCH_2), 2.19-2.00 (1H, m, CHCH_2), 1.84-1.67 (3H, m, CH_2CH_2), 1.42 (3H, br s, CHCH_3), 1.40-1.35 (3H, m, CCH_3), 1.35 (6H, br s, CCH_3); δ_C (100 MHz, d^6-DMSO) 171.0 (C_q), 153.9 (C_q), 145.1 (C_q), 128.7 (CH), 127.1 (CH), 126.9 (CH), 126.4 (CH), 126.2 (CH), 78.8 (C_q), 60.1 (CH), 47.9 (CH), 47.0 (CH), 31.5 (CH_2), 28.6 (CH_3), 28.5 (2 x CH_3), 23.6 (CH_2), 22.7 (CH_3); *m/z* (ES) 319 ($M+H^+$, 14%), 341 ($M+Na^+$, 100), 659 ($2M+Na^+$, 13); *m/z* found $[M+Na]^+$ 341.1825, $C_{18}H_{26}N_2O_3Na$ requires 341.1836. ^1H and ^{13}C NMR data are consistent with literature.[174]

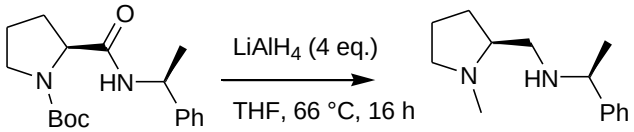
(2*S*)-2-{[(1*R*)-1-Phenylethyl]aminomethyl}-*N*-methylpyrrolidine (*R,S*)-261



(*R,S*)-260 **(*R,S*)-261**

tert-Butyl-(2*S*)-2-{[(1*R*)-1-phenylethyl]carbamoyl}pyrrolidine-1-carboxylate (0.20 g, 0.63 mmol, 1 eq.) in THF (10 mL) was added to a suspension of $LiAlH_4$ (95 mg, 2.52 mmol, 4 eq.) in dry THF (5 mL) and the reaction mixture was heated under reflux for 16 h under an inert atmosphere of argon. The reaction mixture was quenched by slow addition of saturated aq. Na_2SO_4 (5 mL) and the resulting solids were removed by filtration and washed with EtOAc (5 mL). The combined organic solution was concentrated under reduced pressure to give a brown oil. This was purified by column chromatography (PhMe:MeOH:Et_3N 98:1:1) to give the product as a yellow oil (21 mg, 15%). R_f 0.2 (PhMe:MeOH:Et_3N 98:1:1); $[\alpha]_D^{22}$ +10.8 (*c* 0.72 in THF); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2967, 2843, 2791, 1492, 1452, 1371, 1353, 1132; δ_H (400 MHz, $CDCl_3$) 7.36-7.29 (4H, m, Ar*H*), 7.25-7.20 (1H, m, Ar*H*), 3.76 (1H, q, *J* 6.5, PhC*H*), 3.07-3.01 (1H, m, NC*H*CH_2), 2.53 (1H, dd, *J* 11.5, 4.0, NCH_2CH), 2.50 (1H, dd, *J* 11.5, 5.5, NCH_2CH), 2.28 (3H, s, NCH_3), 2.24-2.11 (2H, m, NCH_2), 1.93-1.53 (5H, m, N*H* + CHCH_2CH_2), 1.35 (3H, d, *J* 6.5, CHCH_3); δ_C (100 MHz, $CDCl_3$) 146.1 (C_q), 128.1 (CH), 126.7 (CH), 126.7 (CH), 65.8 (CH), 58.8 (CH), 57.6 (CH_2), 50.3 (CH_2), 41.1 (CH_3), 29.0 (CH_2), 24.7 (CH_3), 22.6 (CH_2); *m/z* (ES +ve) 219 ($M+H^+$, 100), *m/z* found $[M+H]^+$ 219.1850, $C_{14}H_{23}N_2$ requires 219.1856.

(2*S*)-2-{[(1*S*)-1-Phenylethyl]aminomethyl}-*N*-methylpyrrolidine (*S,S*)-261

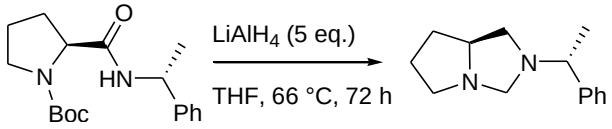


(*S,S*)-260 **(*S,S*)-261**

tert-Butyl-(2*S*)-2-{[(1*S*)-1-phenylethyl]carbamoyl}pyrrolidine-1-carboxylate (0.20 g, 0.63 mmol, 1 eq.) in THF (10 mL) was added to a suspension of $LiAlH_4$ (95 mg, 2.52 mmol, 4 eq.) in dry THF (5 mL) and the reaction mixture was heated

under reflux for 16 h under an inert atmosphere of argon. The reaction mixture was quenched by slow addition of saturated aq. Na_2SO_4 (5 mL) and the resulting solids were removed by filtration and washed with EtOAc (5 mL). The combined organic solution was concentrated under reduced pressure to give a brown oil. This was purified by column chromatography (PhMe:MeOH:Et_3N 98:1:1) to give a yellow oil (21 mg, 15%). R_f 0.2 (PhMe:MeOH:Et_3N 98:1:1); $[\alpha]_D^{22}$ −54.5 (*c* 0.64 in THF); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2967, 2847, 2790, 1493, 1452, 1372, 1351, 1246, 1128, 1045; δ_H (400 MHz, $CDCl_3$) 7.34-7.29 (4H, m, Ar*H*), 7.25-7.20 (1H, m, Ar*H*), 3.73 (1H, q, *J* 6.5, PhC*H*), 3.03 (1H, ddd, *J* 9.0, 7.0, 2.5, NC*H*), 2.64 (1H, dd, *J* 11.5, 4.0, NCH_2CH), 2.37 (1H, dd, *J* 11.0, 7.0, NCH_2CH), 2.26 (3H, s, NCH_3), 2.30-2.12 (2H, m, NCH_2CH_2), 1.96-1.86 (2H, m, CHCH_2), 1.80-1.55 (3H, m, N*H* + $CHCH_2CH_2$), 1.37 (3H, d, *J* 6.5, CHCH_3); δ_C (100 MHz, $CDCl_3$) 146.1 (C_q), 128.4 (CH), 126.8 (CH), 126.6 (CH), 65.6 (CH), 58.8 (CH), 57.6 (CH_2), 50.7 (CH_2), 41.1 (CH_3), 29.3 (CH_2), 24.4 (CH_3), 22.6 (CH_2); *m/z* (ES +ve) 227 (21%), 219 ($M+H^+$, 100), *m/z* found $[M+H]^+$ 219.1854, $C_{14}H_{23}N_2$ requires 219.1856.

(5*S*)-3-[(*R*)-1-Phenylethyl]-1,3-diazabicyclo[3.3.0]octane 263

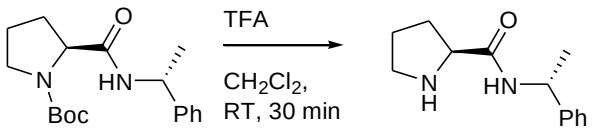


(*R*,*S*)-260 **263**

tert-Butyl-(2*S*)-2-{[(1*R*)-1-phenylethyl]carbamoyl}pyrrolidine-1-carboxylate (0.20 g, 0.63 mmol, 1 eq.) in THF (10 mL) was added to a suspension of $LiAlH_4$ (0.12 g, 3.13 mmol, 5 eq.) in dry THF (5 mL) and the reaction mixture was heated under reflux for 16 h under an inert atmosphere of argon. The reaction mixture was quenched by slow addition of EtOAc (1 mL), followed by saturated aq. Na_2SO_4 (5 mL) and the resulting solids were removed by filtration and washed with EtOAc (5 mL). The combined organic solution was concentrated under reduced pressure to give a brown oil. This was purified by column chromatography (PhMe:MeOH:Et_3N 98:1:1) to give the product as a yellow oil (56 mg, 40%). R_f 0.1 (PhMe:MeOH:Et_3N 98:1:1); ν_{max} ($CHCl_3$)/cm^{-1} 3085, 3064, 2970, 2510, 1657, 1601, 1492, 1453, 1373, 1349, 1311, 1152, 1113, 1027, 967, 909, 881, 859; δ_H (400 MHz, $CDCl_3$) 7.36-7.21 (5H, m, Ar*H*), 3.67 (1H, d, *J* 7.0, NCH_2N), 3.54 (1H, ddd, *J* 14.0, 7.0, 3.0, PhC*H*), 3.31 (1H, d, *J* 7.0, NCH_2N), 3.21-3.11 (2H, m, NCH_2C*H*), 2.76 (1H, dd, *J* 9.0, 6.0, NCH_2CH), 2.37 (1H, dd, *J* 9.0, 3.0, NCH_2CH_2), 2.33 (1H, dd, *J* 9.0, 7.0, NCH_2CH_2), 1.96-1.83 (2H, m, CHCH_2CH_2), 1.74-1.83 (1H, m, NCH_2CH_2), 1.74-1.63 (1H, m, NCH_2CH_2), 1.54-1.45 (1H, m, CHCH_2CH_2), 1.32 (3H, d, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 145.8 (C_q), 128.3 (CH), 127.0 (CH), 126.8 (CH), 76.6 (CH_2), 63.2 (CH), 63.1 (CH), 58.5 (CH_2), 56.2 (CH_2), 32.9 (CH_2), 26.4 (CH_2), 23.6 (CH_3);

m/z (ES) 217 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 217.1693. $C_{14}H_{21}N_2$ requires 217.1699.

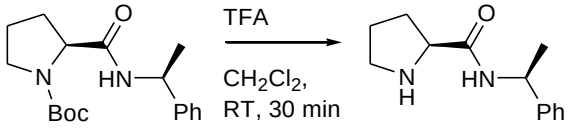
_N_-(1-(_R_)-Phenylethyl)-(_S_)-prolinamide (_R,S_)-268 [175]



(_R,S_)-260 **(_R,S_)-268**

tert-Butyl-(2*S*)-2-{[(1*R*)-1-phenylethyl]carbamoyl}pyrrolidine-1-carboxylate (1.00 g, 3.10 mmol, 1 eq.) was stirred in a 1:1 mixture of CH_2Cl_2/TFA (24 mL) at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure to remove TFA, then redissolved in CH_2Cl_2 (10 mL) and washed with saturated aq. Na_2CO_3 (20 mL). The organic layer was dried over $MgSO_4$ before being concentrated and purified by column chromatography (CH_2Cl_2:MeOH:NEt_3 95:5:0.5) to give the product as an off-white solid (0.52 g, 76%). m.p. 104-105 °C; R_f (CH_2Cl_2:MeOH 95:5) 0.2; $[\alpha]_D^{22}$ −24.5 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3343, 3066, 3007, 2875, 2813, 1659, 1604, 1513, 1453, 1376, 1354, 1307, 1245, 1120, 1076, 1028, 914; δ_H (400 MHz, $CDCl_3$) 7.96 (1H, br d, *J* 6.5, CON*H*), 7.35-7.22 (5H, m, Ar*H*), 5.09 (1H, dq, *J* 8.5, 7.0, 7.0, 7.0, PhC*H*), 3.79 (1H, dd, *J* 9.0, 5.5, COC*H*), 3.04-2.98 (1H, m, NCH_2), 2.92-2.86 (1H, m, NCH_2), 2.81 (1H, br s, CH_2N*H*), 2.17-2.08 (1H, m, CHCH_2), 1.94-1.86 (1H, m, CHCH_2), 1.69 (2H, app quin., *J* 7.0, $CHCH_2CH_2$), 1.48 (3H, d, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 173.9 (C_q), 143.8 (C_q), 128.6 (CH), 127.1 (CH), 125.9 (CH), 60.6 (CH), 48.0 (CH), 47.3 (CH_2), 30.7 (CH_2), 26.2 (CH_2), 22.3 (CH_3); *m/z* (ES) 219 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 219.1494. $C_{13}H_{19}N_2O$ requires 219.1492. ^1H and ^{13}C NMR data are consistent with literature.[175]

_N_-(1-(_S_)-Phenylethyl)-(_S_)-prolinamide (_S,S_)-268 [175]

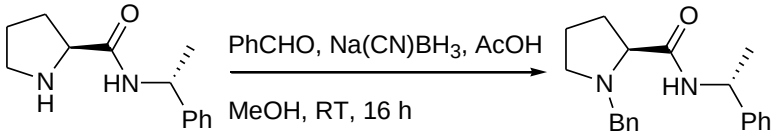


(_S,S_)-260 **(_S,S_)-268**

tert-Butyl-(2*S*)-2-{[(1*S*)-1-phenylethyl]carbamoyl}pyrrolidine-1-carboxylate (1.00 g, 3.10 mmol, 1 eq.) was stirred in a 1:1 mixture of CH_2Cl_2/TFA (24 mL) at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure to remove TFA, then redissolved in CH_2Cl_2 (10 mL) and washed with saturated aq. Na_2CO_3 (20 mL). The organic layer was dried over $MgSO_4$ before being concentrated and purified by column chromatography (CH_2Cl_2:MeOH:NEt_3 95:5:0.5) to give the product as an off-white solid (0.50 g, 73%). m.p. 71-74 °C; R_f (CH_2Cl_2:MeOH 95:5) 0.2; $[\alpha]_D^{22}$ −102.3 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3328, 3066, 3010, 2980, 2874, 1654, 1514, 1451, 1403, 1377, 1298, 1242, 1158, 1103,

1021, 856; δ_H (400 MHz, $CDCl_3$) 7.98 (1H, br d, *J* 7.5, CON*H*), 7.36-7.31 (4H, m, Ar*H*), 7.29-7.23 (1H, m, Ar*H*), 5.09 (1H, dq, *J* 8.5, 7.0, 7.0, 7.0, PhC*H*), 3.81 (1H, dd, *J* 9.0, 5.5, NC*H*), 3.15 (1H, br s, CH_2NH), 3.09-3.02 (1H, m, NCH_2), 2.98-2.92 (1H, m, NCH_2), 2.22-2.13 (1H, m, $CHCH_2$), 1.99-1.90 (1H, m, $CHCH_2$), 1.80-1.70 (2H, m, $CHCH_2CH_2$), 1.48 (3H, d, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 173.5 (C_q), 143.5 (C_q), 128.6 (CH), 127.2 (CH), 126.1 (CH), 60.5 (CH), 48.2 (CH), 47.2 (CH_2), 30.7 (CH_2), 26.1 (CH_2), 22.2 (CH_3); *m/z* (ES) 219 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 219.1502. $C_{13}H_{19}N_2O$ requires 219.1492. ^1H and ^{13}C NMR data are consistent with literature.[175]

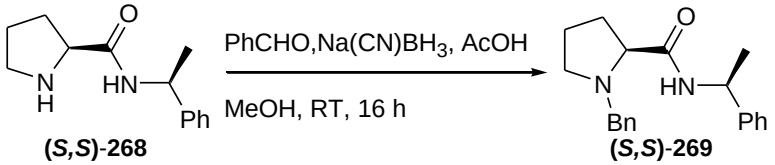
(*S*)-*N*-Benzyl-2-((*R*)-phenylethylcarbamoyl)pyrrolidine (*R,S*)-269 [176]



(*R,S*)-268 **(*R,S*)-269**

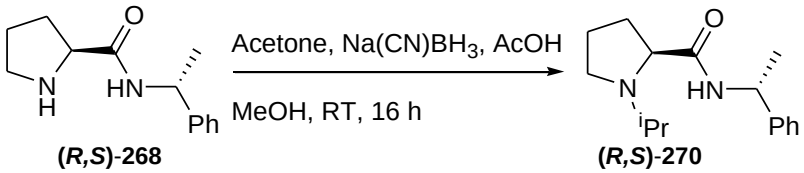
Benzaldehyde (0.19 mL, 1.84 mmol, 4 eq.) was added to a solution of *N*-(1-(*R*)-phenylethyl)-(*S*)-prolinamide (0.10 g, 0.46 mmol, 1 eq.), $Na(CN)BH_3$ (57 mg, 0.92 mmol, 2 eq.) and AcOH (5.25 µL, 92.0 µmol, 0.2 eq.) in MeOH (5 mL) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (20 mL) and washed with water (10 mL) and saturated aq. Na_2CO_3 solution (10 mL). The organic layer was then dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc:NEt_3 4:1:0.05) to give the product as a colourless solid (0.13 g, 93%). m.p. 100-104 °C; R_f (petroleum ether:EtOAc 1:1) 0.2; ν_{max} ($CHCl_3$)/cm^{-1} 3344, 3087, 3066, 3011, 2875, 2813, 1659, 1513, 1453, 1376, 1354, 1309, 1241, 1120, 1075; $[\alpha]_D^{22}$ −42.0 (*c* 0.7 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.70 (1H, br d, *J* 6.5, N*H*), 7.38-7.25 (10H, m, Ar*H*) 5.06 (1H, dq, *J* 8.5, 7.0, 7.0, 7.0, PhC*H*), 3.90 (1H, d, *J* 13.0, $PhCH_2$) 3.56 (1H, d, *J* 13.0, $PhCH_2$), 3.26 (1H, dd, *J* 14.5, 4.5, COC*H*), 3.06 (1H, app t, *J* 7.5, NCH_2), 2.41 (1H, app dd, *J* 16.0, 9.5, NCH_2), 2.28-2.18 (1H, m, $CHCH_2$) 1.92-1.82 (1H, m, $CHCH_2$), 1.82-1.72 (1H, m, $CHCH_2CH_2$), 1.72-1.62 (1H, m, $CHCH_2CH_2$), 1.40 (3H, d, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 173.6 (C_q), 143.7 (C_q), 138.8 (C_q), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.4 (CH), 127.2 (CH), 125.9 (CH), 67.5 (CH), 60.1 (CH_2), 54.3 (CH_2), 47.9 (CH), 30.7 (CH_2), 24.2 (CH_2), 22.2 (CH_3); *m/z* (ES +ve) 309 ($M+H^+$, 100), *m/z* found $[M+H]^+$ 309.1953, $C_{20}H_{25}N_2O$ requires 309.1961.

(*S*)-*N*-Benzyl-2-((*S*)-phenylethylcarbamoyl)pyrrolidine (*S,S*)-269 [176]



Benzaldehyde (0.19 mL, 1.84 mmol, 4 eq.) was added to a solution of *N*-(1-(*S*)-phenylethyl)-(*S*)-prolinamide (0.10 g, 0.46 mmol, 1 eq.), $Na(CN)BH_3$ (57 mg, 0.92 mmol, 2 eq.) and AcOH (5.25 µL, 92.0 µmol, 0.2 eq.) in MeOH (5 mL) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (20 mL) and washed with water (10 mL) and saturated aq. Na_2CO_3 solution (10 mL). The organic layer was then dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc:NEt_3 4:1:0.05) to give the product as a colourless solid (0.13 g, 93%). m.p. 60-63 °C; R_f (petroleum ether:EtOAc 1:1) 0.2; $[\alpha]_D^{22}$ −51.7 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3340, 3066, 3008, 2875, 2812, 1657, 1512, 1453, 1376, 1354, 1306, 1242, 1120, 1076; δ_H (400 MHz, $CDCl_3$) 7.76 (1H, br d, *J* 8.0, N*H*), 7.36-7.25 (5H, m, Ar*H*), 7.24-7.20 (3H, m, Ar*H*), 7.07-7.03 (2H, m, Ar*H*), 5.12 (1H, dq, *J* 8.5, 7.0, 7.0, 7.0, PhC*H*), 3.81 (1H, d, *J* 13.0, PhCH_2), 3.78 (1H, d, *J* 13.0, PhCH_2), 3.22 (1H, dd, *J* 10.0, 5.0, NC*H*), 3.00 (1H, ddd, *J* 9.0, 7.0, 2.0, NCH_2), 2.35 (1H, ddd, *J* 16.5, 10.0, 6.5, NCH_2), 2.30-2.20 (1H, m, CHCH_2), 1.97-1.89 (1H, m, CHCH_2), 1.85-1.65 (2H, m, $CHCH_2CH_2$), 1.51 (3H, d, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 173.6 (C_q), 143.3 (C_q), 138.6 (C_q), 128.7 (2 x CH), 128.4 (CH), 127.2 (CH), 126.3 (CH), 67.5 (CH), 59.9 (CH_2), 53.8 (CH_2), 48.2 (CH), 30.6 (CH_2), 24.2 (CH_2), 21.9 (CH_3); *m/z* (ES) 309 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 309.1958. $C_{20}H_{25}N_2O$ requires 309.1961.

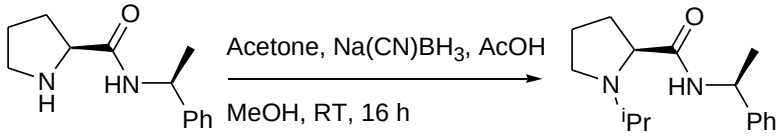
(*S*)-*N*-Isopropyl-2-((*R*)-phenylethylcarbamoyl)pyrrolidine (*R,S*)-270 [177]



Acetone (0.13 mL, 1.84 mmol, 4 eq.) was added to a solution of *N*-(1-(*R*)-phenylethyl)-(*S*)-prolinamide (0.10 g, 0.46 mmol, 1 eq.), $Na(CN)BH_3$ (57 mg, 0.92 mmol, 2 eq.) and AcOH (5.25 µL, 92.0 µmol, 0.2 eq.) in MeOH (5 mL) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (20 mL) and washed with water (10 mL) and saturated aq. Na_2CO_3 solution (10 mL). The organic layer was then dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc:NEt_3 1:1:0.05) to give the product as a colourless solid (0.11 g, 93%). m.p. 48-50 °C; R_f (petroleum

ether:EtOAc 1:1) 0.1; $[\alpha]_D^{22}$ −37.5 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3317, 2974, 2874, 2810, 1655, 1514, 1450, 1387, 1374, 1324, 1302, 1159, 1009; δ_H (400 MHz, $CDCl_3$) 7.90 (1H, br d, *J* 7.0, N*H*), 7.37-7.23 (5H, m, Ar*H*), 5.13 (1H, dq, *J* 8.5, 7.0, PhC*H*), 3.29 (1H, dd, *J* 10.5, 3.0, COC*H*), 3.08 (1H, app t, *J* 7.5, NCH_2), 2.79 (1H, sept, *J* 6.5, CH_3CHCH_3), 2.51 (1H, ddd, *J* 15.0, 9.0, 6.0, NCH_2), 2.12-2.00 (1H, m, CHCH_2), 1.94-1.87 (1H, m, CHCH_2), 1.78-1.71 (1H, m, $CHCH_2CH_2$), 1.68-1.51 (1H, m, $CHCH_2CH_2$) 1.49 (3H, d, *J* 7.0, PhCHCH_3), 1.08 (3H, d, *J* 6.5, CH_3CHCH_3), 1.07 (3H, d, *J* 6.5, CH_3CHCH_3); δ_C (100 MHz, $CDCl_3$) 175.2 (C_q), 143.8 (C_q), 128.6 (CH), 127.1 (CH), 125.9 (CH), 64.2 (CH), 53.1 (CH), 50.7 (CH_2). 47.7 (CH), 31.3 (CH_2), 24.8 (CH_2), 22.1 (CH_3), 21.6 (CH_3), 20.2 (CH_3); *m/z* (ES) 261 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 261.1961. $C_{16}H_{25}N_2O$ requires 261.1961.

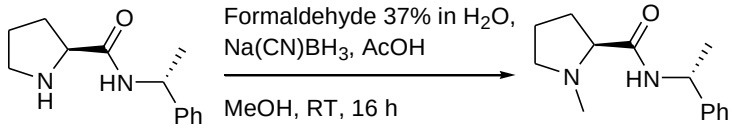
(*S*)-*N*-Isopropyl-2-((*S*)-phenylethylcarbamoyl)pyrrolidine (*S,S*)-270 [177]



(*S,S*)-268 **(*S,S*)-270**

Acetone (0.13 mL, 1.84 mmol, 4 eq.) was added to a solution of *N*-(1-(*R*)-phenylethyl)-(*S*)-prolinamide (0.10 g, 0.46 mmol, 1 eq.), $Na(CN)BH_3$ (57 mg, 0.92 mmol, 2 eq.) and AcOH (5.25 µL, 92.0 µmol, 0.2 eq.) in MeOH (5 mL) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (20 mL) and washed with water (10 mL) and saturated aq. Na_2CO_3 solution (10 mL). The organic layer was then dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc:NEt_3 1:1:0.05) to give the product as a colourless solid (0.12 g, 96%). R_f (petroleum ether:EtOAc 1:1) 0.1; m.p. 73-75 °C; $[\alpha]_D^{22}$ −118.3 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3318, 2974, 2874, 2811, 1655, 1512, 1450, 1387, 1373, 1324, 1301, 1159, 1119, 1022; δ_H (400 MHz, $CDCl_3$) 7.87 (1H, br d, *J* 7.0, N*H*), 7.36-7.29 (4H, m, Ar*H*), 7.28-7.23 (1H, m, Ar*H*), 5.12 (1H, dq, *J* 8.5, 7.0, 7.0, 7.0, PhC*H*), 3.27 (1H, dd, *J* 10.5, 3.0, COC*H*), 3.06 (1H, app t, *J* 15.0, 7.5, NCH_2), 2.71 (1H, sept, *J* 6.5, CH_3CHCH_3), 2.51 (1H, ddd, *J* 15.0, 9.0, 6.0, NCH_2), 2.13-2.02 (1H, m, CHCH_2), 1.99-1.92 (1H, m, CHCH_2), 1.81-1.73 (1H, m, $CHCH_2CH_2$), 1.72-1.61 (1H, m, $CHCH_2CH_2$) 1.48 (3H, d, *J* 7.0, PhCHCH_3), 0.97 (3H, d, *J* 6.5, CH_3CHCH_3), 0.93 (3H, d, *J* 6.5, CH_3CHCH_3); δ_C (100 MHz, $CDCl_3$) 175.0 (C_q), 143.4 (C_q), 128.6 (CH), 127.2 (CH), 126.1 (CH), 64.1 (CH), 52.7 (CH), 50.1 (CH_2). 47.9 (CH), 31.4 (CH_2), 24.8 (CH_2), 22.1 (CH_3), 21.6 (CH_3), 19.4 (CH_3); *m/z* (ES) 261 ($M+H^+$, 100%), *m/z* found $[M+H]^+$ 261.1963. $C_{16}H_{25}N_2O$ requires 261.1961.

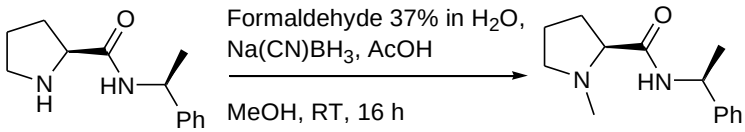
(*S*)-*N*-Methyl-2-((*R*)-phenylethylcarbamoyl)pyrrolidine (*R,S*)-262 [178]



(*R,S*)-268 **(*R,S*)-262**

Formaldehyde 37% in H_2O (0.44 mL, 5.52 mmol, 4 eq.) was added to a solution of *N*-(1-(*R*)-phenylethyl)-(*S*)-prolinamide (0.30 g, 1.38 mmol, 1 eq.), $Na(CN)BH_3$ (0.17 g, 2.76 mmol, 2 eq.) and AcOH (15.8 µL, 0.27 mmol, 0.2 eq.) in MeOH (5 mL) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (20 mL) and washed with water (10 mL) and saturated aq. Na_2CO_3 solution (10 mL). The organic layer was then dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc:NEt_3 1:1:0.05) to give the product as a colourless solid (0.25 g, 78%). m.p. 82-84 °C [lit 85.5-87 °C][178]; R_f (petroleum ether:EtOAc 1:1) 0.3; $[\alpha]_D^{22}$ −32.6 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3340, 3011, 2977, 2875, 2853, 2795, 1659, 1514, 1451, 1377, 1352, 1313, 1242, 1173, 1134, 1046, 1021, 912, 871; δ_H (400 MHz, $CDCl_3$) 7.63 (1H, br s, Ar*H*), 7.40-7.24 (5H, m, Ar*H*), 5.16 (1H, dq, *J* 8.5, 7.0, PhC*H*), 3.12-3.08 (1H, m, NCH_2), 2.94 (1H, dd, *J* 9.5, 5.0, COC*H*), 2.42 (3H, s, NCH_3), 2.42-2.33 (1H, m, NCH_2), 2.29-2.17 (1H, m, CHCH_2), 1.87-1.67 (3H, m, CHCH_2CH_2), 1.52 (3H, d, *J* 7.0, CHCH_3); δ_C (100 MHz, $CDCl_3$) 173.5 (C_q), 143.6 (C_q), 128.6 (CH), 127.1 (CH), 125.9 (CH), 69.0 (CH), 56.6 (CH_2), 47.6 (CH), 41.7 (CH_3), 30.9 (CH_2), 24.3 (CH_2), 22.2 (CH_3); *m/z* (ES) 233 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 233.1651. $C_{14}H_{21}N_2O$ requires 233.1648.

(S)-*N*-Methyl-2-((*S*)-phenylethylcarbamoyl)pyrrolidine (*S,S*)-262 [178]

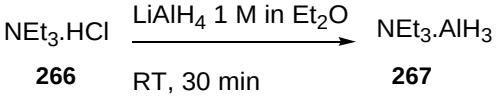


(*S,S*)-268 **(*S,S*)-262**

Formaldehyde 37% in H_2O (0.44 mL, 5.52 mmol, 4 eq.) was added to a solution of *N*-(1-(*S*)-phenylethyl)-(*S*)-prolinamide (0.30 g, 1.38 mmol, 1 eq.), $Na(CN)BH_3$ (0.17 g, 2.76 mmol, 2 eq.) and AcOH (15.8 µL, 0.27 mmol, 0.2 eq.) in MeOH (5 mL) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (20 mL) and washed with water (10 mL) and saturated aq. Na_2CO_3 solution (10 mL). The organic layer was then dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc:NEt_3 1:1:0.05) to give the product as a colourless solid (0.27 g, 85%). m.p. 59-61 °C [lit 58-60 °C][178]; R_f (petroleum ether:EtOAc 1:1) 0.3; $[\alpha]_D^{22}$ −129.8

(*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3341, 3011, 2977, 2853, 2795, 1658, 1513, 1452, 1377, 1351, 1311, 1242, 1174, 1132, 1046, 1021, 871; δ_H (400 MHz, $CDCl_3$) 7.38 (1H, br d, *J* 7.5, Ar*H*), 7.35-7.28 (5H, m, Ar*H*), 5.16 (1H, dq, *J* 8.5, 7.0, PhC*H*), 3.12-3.09 (1H, m, NCH_2), 2.90 (1H, dd, *J* 10.0, 5.5, COC*H*), 2.40-2.25 (2H, m, NCH_2CH_2CH_2), 2.34 (3H, s, NCH_3), 1.90-1.76 (3H, m, CHCH_2CH_2), 1.51 (3H, d, *J* 7.0, CHCH_3); δ_C (100 MHz, $CDCl_3$) 173.7 (C_q), 143.5 (C_q), 128.6 (CH), 127.2 (CH), 126.1 (CH), 69.0 (CH), 56.7 (CH_2), 47.7 (CH), 41.8 (CH_3), 31.1 (CH_2), 24.2 (CH_2), 22.0 (CH_3); *m/z* (ES) 233 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 233.1651. $C_{14}H_{21}N_2O$ requires 233.1648.

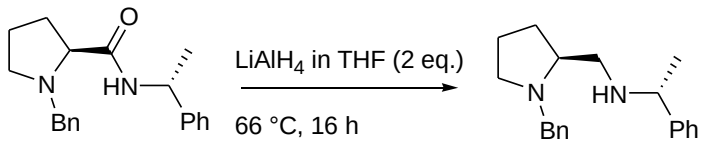
General procedure for the preparation of triethylamine-alane 267 [97]



266 **267**

NEt_3·HCl (0.25 g, 1.81 mmol, 1 eq.) was dried by heating to 100 °C under vacuum for 1 h. The vessel was fitted with an argon balloon and $LiAlH_4$ 1 M in Et_2O (2.00 mL, 2.00 mmol, 1.1 eq.) was added dropwise to the vessel and stirred at room temperature for 30 min. The resulting solution was assumed to contain 1 M NEt_3·AlH_3 and was used for subsequent reduction reactions.

(*S*)-*N*-Benzyl-5-((*R*)-phenylethyl)aminomethylpyrrolidine (*R,S*)-271

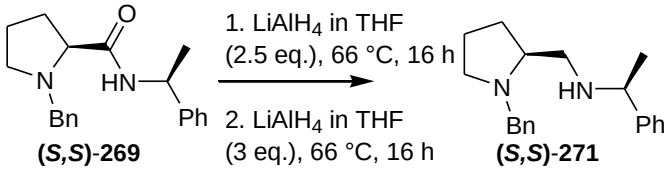


(*R,S*)-269 **(*R,S*)-271**

$LiAlH_4$ 1 M in THF (0.40 mL, 0.40 mmol, 2.5 eq.) was added to a solution of (*S*)-*N*-benzyl-2-((*R*)-phenylethylcarbamoyl)pyrrolidine (50 mg, 0.16 mmol, 1 eq.) in THF (1 mL) and the reaction mixture was heated under reflux for 16 h under an inert atmosphere of argon. The reaction mixture was quenched by slow addition of saturated aq. Na_2SO_4 solution (1 mL), which were then filtered through kieselguhr, and washed through with EtOAc (10 mL). The filtrate was concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH 95:5) to give the product as a yellow oil (40 mg, 84%). R_f ($CHCl_3$:MeOH 9:1) 0.4; $[\alpha]_D^{22}$ −15.3 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3085, 3065, 3011, 2965, 2877, 2802, 1603, 1494, 1452, 1372, 1354, 1306, 1248, 1119, 1074, 1028, 911; δ_H (400 MHz, $CDCl_3$) 7.36-7.28 (8H, m, Ar*H*), 7.27-7.20 (2H, m, Ar*H*), 3.91 (1H, d, *J* 13.0, CH_2Ph), 3.66 (1H, q, *J* 6.5, PhC*H*), 3.33 (1H, d, 13.0, CH_2Ph), 2.96 (1H, ddd, *J* 9.5, 7.0, 3.0, NHC*H*N), 2.65-2.58 (1H, m, NCH_2CH_2), 2.53 (1H, dd, *J* 11.5, 4.5, NCH_2CH), 2.50 (1H, dd, *J* 11.5, 4.5, NCH_2CH), 2.30-1.95 (1H, v br s, N*H*), 2.22 (1H, dd, *J* 9.0, 7.5, NCH_2CH_2), 1.93-1.64 (4H, m, CHCH_2CH_2), 1.34 (3H, d, *J* 6.5,

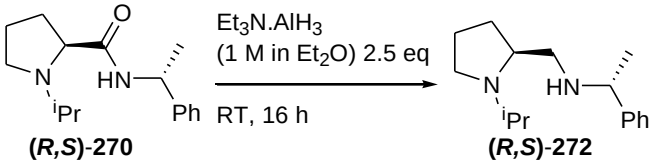
C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 145.9 (C_q), 139.8 (C_q), 128.8 (CH), 128.4 (CH), 128.3 (CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 63.8 (CH), 59.2 (CH_2), 54.7 (CH_2), 50.2 (CH_2), 28.8 (CH_3), 24.8 (CH_3), 22.9 (CH_2); *m/z* (ES) 295 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 295.2169. $C_{20}H_{27}N_2$ requires 295.2175.

(*S*)-*N*-Benzyl-5-((*S*)-phenylethyl)aminomethylpyrrolidines (S,S)-271



$LiAlH_4$ 1 M in THF (0.40 mL, 0.40 mmol, 2.5 eq.) was added to a solution of (*S*)-*N*-benzyl-2-((*S*)-phenylethylcarbamoyl)pyrrolidine (50 mg, 0.16 mmol, 1 eq.) in THF (1 mL) and the reaction mixture was heated under reflux for 16 h under an inert atmosphere of argon. The reaction mixture was quenched by slow addition of saturated aq. Na_2SO_4 solution (1 mL), which were then filtered through kieselguhr, and washed through with EtOAc (10 mL). The filtrate was concentrated under reduced pressure and analysed by mass spectrometry. It was apparent that the reaction was incomplete, so the residue was subjected to the same reaction conditions and work-up as mentioned above (except that the amount of $LiAlH_4$ used was increased to 0.96 mL (3 eq.)) before being purified by column chromatography ($CHCl_3$:MeOH 95:5) to give the product as a yellow oil (44 mg, 93%). R_f ($CHCl_3$:MeOH 9:1) 0.4; $[\alpha]_D^{22}$ −72.4 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3085, 3065, 3011, 2967, 2877, 2800, 1603, 1494, 1453, 1372, 1353, 1324, 1242, 1116, 1075, 1028, 910; δ_H (400 MHz, $CDCl_3$) 7.35-7.20 (10H, m, Ar*H*), 3.92 (1H, d, *J* 13.0, PhCH_2), 3.72 (1H, q, *J* 6.5, PhC*H*), 3.23 (1H, d, 13.0, PhCH_2), 2.94-2.89 (1H, m, NC*H*CH_2), 2.68 (1H, dd, *J* 11.0, 4.0, NCH_2CH), 2.65-2.59 (1H, m, NCH_2CH_2), 2.47 (1H, dd, *J* 11.0, 6.0, NCH_2CH), 2.17 (1H, app q, *J* 8.5, NCH_2CH_2), 2.00-1.85 (2H, m, NC$H_2CH_2CH_2$), 1.78-1.64 (3H, m, CHCH_2CH_2), 1.37 (3H, d, *J* 6.5, CH_3); δ_C (100 MHz, $CDCl_3$) 146.1 (C_q), 139.9 (C_q), 128.8 (CH), 128.4 (CH), 128.2 (CH), 126.81 (CH), 126.77 (CH), 126.6 (CH), 63.9 (CH), 59.2 (CH_2), 58.7 (CH), 54.5 (CH_2), 50.7 (CH_2), 29.0 (CH_3), 24.3 (CH_3) 22.8 (CH_2); *m/z* (ES) 295 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 295.2163. $C_{20}H_{27}N_2$ requires 295.2175.

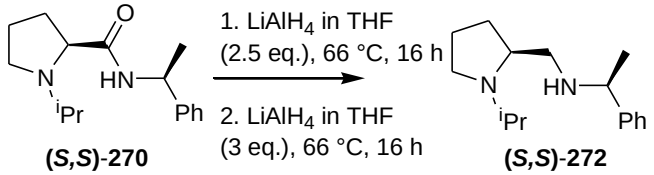
(*S*)-*N*-Isopropyl-5-((*R*)-phenylethyl)aminomethylpyrrolidine (*R,S*)-272



$NEt_3{\cdot}AlH_3$ 1 M in Et_2O (0.96 mL, 0.96 mmol, 2.5 eq.) was added to a solution of (*S*)-*N*-isopropyl-2-((*R*)-phenylethylcarbamoyl)pyrrolidine (0.10 g, 0.38 mmol,

1 eq.) in THF (1 mL) and the reaction mixture was heated under reflux for 16 h under an inert atmosphere of argon. The reaction mixture was quenched by slow addition of saturated aq. Na_2SO_4 solution (1 mL), which were then filtered through kieselguhr, and washed through with EtOAc (10 mL). The filtrate was concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH 95:5) to give the product as a yellow oil (85 mg, 90%). R_f ($CHCl_3$:MeOH 9:1) 0.1; $[\alpha]_D^{22}$ −73.2 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3064, 3011, 2968, 2874, 2829, 1602, 1493, 1451, 1371, 1322, 1173, 1116, 1026, 910; δ_H (400 MHz, $CDCl_3$) 7.35-7.29 (4H, m, Ar*H*), 7.24-7.19 (1H, m, Ar*H*), 3.73 (1H, q, *J* 6.5, PhC*H*), 2.95-2.76 (2H, m, NCH_2CH), 2.86 (1H, sept, *J* 6.5, CH_3CHCH_3), 2.52-2.44 (1H, m, NC*H*CH_2), 2.45 (3H, app d, *J* 5.5, NC$H_2CH_2CH_2$), 1.85-1.63 (4H, m, N*H* + $CHCH_2CH_2$), 1.35 (3H, d, *J* 6.5, PhCHCH_3), 1.05 (3H, d, *J* 6.5, CH_3CHCH_3), 0.94 (3H, d, *J* 6.5, CH_3CHCH_3); δ_C (100 MHz, $CDCl_3$) 146.2 (C_q), 128.4 (CH), 128.3 (CH), 126.7 (CH), 126.6 (CH), 126.5 (CH), 60.0 (CH), 58.8 (CH), 52.0 (CH_2), 50.6 (CH), 47.9 (CH_2), 29.6 (CH_2), 24.6 (CH_3), 23.6 (CH_2), 22.1 (CH_3), 16.8 (CH_3); *m/z* (ES) 247 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 247.2164. $C_{16}H_{27}N_2$ requires 247.2169.

(*S*)-*N*-Isopropyl-5-((*S*)-phenylethyl)aminomethylpyrrolidine (*S,S*)-272

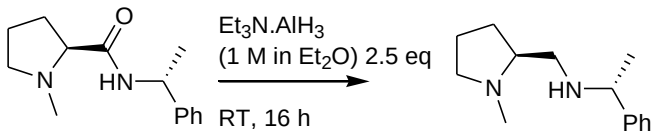


(*S,S*)-270 **(*S,S*)-272**

$NEt_3 \cdot AlH_3$ 1 M in Et_2O (0.96 mL, 0.96 mmol, 2.5 eq.) was added to a solution of (*S*)-*N*-isopropyl-2-((*S*)-phenylethylcarbamoyl)pyrrolidine (0.10 g, 0.38 mmol, 1 eq.) in THF (1 mL) and the reaction mixture was heated under reflux for 16 h under an inert atmosphere of argon. The reaction mixture was quenched by slow addition of saturated aq. Na_2SO_4 solution (1 mL), which were then filtered through kieselguhr, and washed through with EtOAc (10 mL). The filtrate was concentrated under reduced pressure and analysed by mass spectrometry. It was apparent that the reaction was incomplete, so the residue was subjected to the same reaction conditions and work-up as mentioned above (except that the amount of $LiAlH_4$ used was increased to 1.15 mL (3 eq.)) before being purified by column chromatography ($CHCl_3$:MeOH 95:5) to give the product as a yellow oil (79 mg, 84%). R_f ($CHCl_3$:MeOH 9:1) 0.1; $[\alpha]_D^{22}$ −70.0 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3064, 2968, 2874, 2494, 1602, 1493, 1452, 1385, 1371, 1322, 1172, 1117, 1026, 910; δ_H (400 MHz, $CDCl_3$) 7.33-7.26 (4H, m, Ar*H*), 7.24-7.20 (1H, m, Ar*H*), 3.74 (1H, q, *J* 6.5, PhC*H*), 2.95-2.80 (3H, m, CH_2CHNCH), 2.60 (1H, dd, 11.0, 3.5, NCH_2CH_2), 2.48 (1H, app dd, *J* 8.5, 7.5, NCH_2CH_2), 2.34-2.28 (2H, m, NCHCH_2), 3.00-2.00 (1H, v br s, N*H*), 1.85-1.60 (3H, m, CHCH_2CH_2), 1.36 (3H, d, *J* 6.5, PhCHCH_3), 1.10

(3H, d, *J* 6.5, CH_3CHCH_3), 0.96 (3H, d, *J* 6.5, CH_3CHCH_3); δ_C (100 MHz, $CDCl_3$) 146.0 (C_q), 128.4 (2 x CH), 126.8 (CH), 126.6 (2 x CH), 60.1 (CH), 58.7 (CH), 52.0 (CH_2), 50.6 (CH), 47.7 (CH_2), 29.6 (CH_2), 24.4 (CH_3), 23.6 (CH_2), 22.2 (CH_3), 16.5 (CH_3); *m/z* (ES) 247 ($M+H^+$, 100%); *m/z* found $[M+H]^+$ 247.2170. $C_{16}H_{27}N_2$ requires 247.2169.

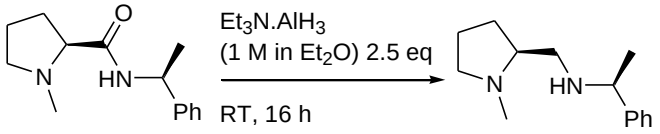
(*S*)-*N*-Methyl-5-((*R*)-phenylethyl)aminomethylpyrrolidine (*R,S*)-261



(*R,S*)-262 **(*R,S*)-261**

$NEt_3{\cdot}AlH_3$ 1 M in Et_2O (0.96 mL, 0.96 mmol, 2.5 eq.) was added to a solution of (*S*)-*N*-methyl-2-((*R*)-phenylethylcarbamoyl)pyrrolidine (0.10 g, 0.38 mmol, 1 eq.) in THF (1 mL) and the reaction mixture was heated under reflux for 16 h under an inert atmosphere of argon. The reaction mixture was quenched by slow addition of EtOAc (1 mL) and saturated aq. Na_2SO_4 solution (1 mL), which were then filtered through kieselguhr, and washed through with EtOAc (10 mL). The filtrate was concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH 95:5) to give the product as a yellow oil (71 mg, 76%). This compound was referenced to the same data as before.

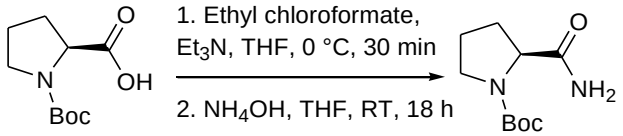
(*S*)-*N*-Methyl-5-((*S*)-phenylethyl)aminomethylpyrrolidine (*S,S*)-261



(*S,S*)-262 **(*S,S*)-261**

$NEt_3{\cdot}AlH_3$ 1 M in Et_2O (0.96 mL, 0.96 mmol, 2.5 eq.) was added to a solution of (*S*)-*N*-methyl-2-((*S*)-phenylethylcarbamoyl)pyrrolidine (0.10 g, 0.38 mmol) in THF (1 mL) and the reaction mixture was heated under reflux for 16 h under an inert atmosphere of argon. The reaction mixture was quenched by slow addition of EtOAc (1 mL) and saturated aq. Na_2SO_4 solution (1 mL), which were then filtered through kieselguhr, and washed through with EtOAc (10 mL). The filtrate was concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH 95:5) to give the product as a yellow oil (69 mg, 73%). This compound was referenced to the same data as before.

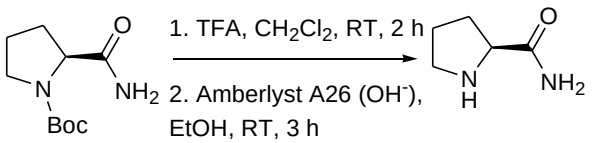
(*S*)-*N*-Boc-prolinamide 273 [179]



259 **273**

Ethyl chloroformate (2.40 mL, 25.3 mmol, 1.1 eq.) was added slowly to a solution of (*S*)-*N*-Boc proline (5.00 g, 23.0 mmol, 1 eq.) and (3.50 mL, 25.3 mmol, 1.1 eq.) in THF (120 mL) cooled with ice and the reaction mixture was stirred for 30 min. NH_4OH 35% in H_2O (1.90 mL, 25.3 mmol, 1.1 eq.) was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was filtered through kieselguhr to remove a solid by-product, then the filtrate was concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc 1:1 to remove by-products, then $CHCl_3$:MeOH 9:1). The resulting residue was triturated in hexane (25 mL) and concentrated under reduced pressure to give the product as a colourless solid (4.93 g, 99%). Elemental analysis found: C, 55.91; H, 8.47; N, 13.15. $C_{13}H_{15}NO_4$ requires C, 56.06; H, 8.47, N, 13.07; m.p. 103-106 °C [lit. 104-106 °C][179]; R_f (Toluene:MeOH 9:1) 0.2; $[\alpha]_D^{22}$ −126.5 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3523, 3484, 3409, 3337, 3011, 2982, 2886, 1686, 1588, 1572, 1477, 1394, 1369, 1242, 1164, 1124, 976, 914, 885, 851; δ_H (400 MHz, d^6-DMSO) 7.29 (0.7H, s, N*H*$_2$), 7.26 (0.3H, s, N*H*$_2$), 6.90 (0.7H, s, N*H*$_2$), 6.86 (0.3H, s, N*H*$_2$), 4.05-3.95 (1H, m, C*H*) 3.42-3.31 (1H, m, NC*H*$_2$), 3.31-3.22 (1H, m, NC*H*$_2$), 2.17-1.97 (1H, m, CHC*H*$_2$), 1.90-1.67 (3H, m, CHC*H*$_2$C*H*$_2$), 1.40 (3H, s, C*H*$_3$), 1.35 (6H, s, C*H*$_3$); δ_C (100 MHz, d^6-DMSO) 175.1 & 174.7 (C_q, rotamers), 153.8 (C_q), 78.9 & 78.8 (C_q, rotamers), 60.0 & 59.8 (CH, rotamers), 47.0 & 46.8 (CH_2, rotamers), 31.5 & 30.5 (CH_2, rotamers), 28.6 & 28.5 (CH_3, rotamers), 24.4 & 23.7 (rotamers, CH_2); *m/z* (ES) 115 (M-Boc+H^+, 22%), 137 (M-Boc+Na^+, 10), 237 (M+Na^+, 100), 451 (2M+Na^+, 43); *m/z* found [M+Na^+] 237.1216. $C_{10}H_{18}N_2O_3$ requires 237.1210.

(*S*)-Prolinamide 274 [180]

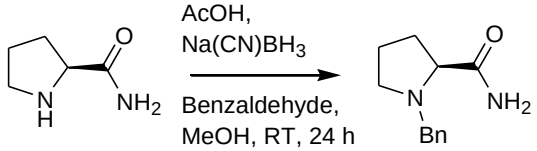


273 **274**

(*S*)-*N*-Boc-prolinamide (1.00 g, 4.67 mmol, 1 eq.) was stirred in a mixture of CH_2Cl_2 (25 mL) and TFA (3.50 mL) at room temperature for 2 h. The solvent and excess TFA were removed under low pressure and the resulting residue was stirred in Et_2O (25 mL) to precipitate a salt, which was isolated from the solution *via* filtration. Amberlyst A26 (OH^-) ion exchange resin (3.25 g) was activated by stirring in 1 M aq. NaOH (100 mL) for 40 min, before filtration and washing with EtOH

(10 mL). The prepared Amberlyst resin and TFA salt of the product were stirred in EtOH (50 mL) for 3 h at room temperature. The Amberlyst resin was removed *via* filtration and the filtrate was concentrated under low pressure to give the product as a colourless solid (0.47 g, 88%). m.p. 98-101 °C [lit. 98-101 °C][180]; R_f ($CHCl_3$:MeOH 9:1) 0.1; $[\alpha]_D^{22}$ −144.5 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3670, 3502, 3360, 3010, 2467, 1679,, 1546, 1460, 1366, 1300, 1242, 1178, 1104, 909, 611; δ_H (400 MHz, $CDCl_3$) 7.42 (1H, br s, CON*H*$_2$), 6.01 (1H, br s, CON*H*$_2$), 3.73 (1H, dd, *J* 9.0, 5.5, C*H*), 3.06-2.98 (1H, m, NC*H*$_2$), 2.96-2.89 (1H, m, NC*H*$_2$), 2.20-2.09 (1H, m, CHC*H*$_2$), 2.11 (1H, br s, CH_2N*H*), 1.98-1.89 (1H, m, CHC*H*$_2$), 1.83-1.64 (2H, m, $CHCH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 178.9 (C_q), 60.5 (CH), 47.4 (CH_2), 30.7 (CH_2), 26.3 (CH_2); *m/z* (ES) 115 ($M+H^+$, 100%), 137 ($M+Na^+$, 32); *m/z* found [$M+H^+$] 115.0865. $C_5H_{11}N_2O$ requires 115.0866.

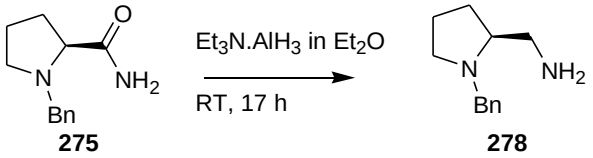
(*S*)-*N*-Benzyl prolinamide 275 [181]



274 **275**

Benzaldehyde (0.53 mL, 4.92 mmol, 4 eq.) was added to a solution of (*S*)-prolinamide (0.14 g, 1.23 mmol, 1 eq.), AcOH (15 µL, 0.25 mmol, 0.2 eq.) and $Na(CN)BH_3$ (0.16 g, 2.46 mmol, 2 eq.) in MeOH (25 mL) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted in EtOAc (20 mL), washed with water (20 mL) and saturated aq. Na_2CO_3 solution (20 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by ($CHCl_3$:MeOH 95:5) to give the product as a colourless solid (0.12 g, 48%). m.p. 63-65 °C [lit. 61.1-62.7 °C][181]; R_f ($CHCl_3$:MeOH 9:1) 0.8; $[\alpha]_D^{22}$ −72.8 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3504, 3372, 3010, 2812, 2360, 1681, 1550, 1495, 1454, 1355, 1310, 1242, 1121, 1076, 1028, 914; δ_H (400 MHz, $CDCl_3$) 7.40-7.25 (5H, m, Ar*H*), 7.25 (1H, s, N*H*$_2$), 5.80 (1H, s, N*H*$_2$), 3.98 (1H, d, *J* 13.0, PhC*H*$_2$), 3.51 (1H, d, *J* 13.0, PhC*H*$_2$), 3.21 (1H, dd, *J* 10.0, 5.5, NC*H*), 3.09-3.03 (1H, m, NC*H*$_2$), 2.43-2.33 (1H, m, NC*H*$_2$), 2.33-2.21 (1H, m, CHC*H*$_2$), 2.01-1.91 (1H, m, CHC*H*$_2$), 1.88-1.73 (2H, m, $CHCH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 178.2 (C_q), 138.6 (C_q), 128.7 (CH), 128.5 (CH), 127.3 (CH), 67.4 (CH), 59.8 (CH_2), 53.8 (CH_2), 30.6 (CH_2), 24.1 (CH_2).

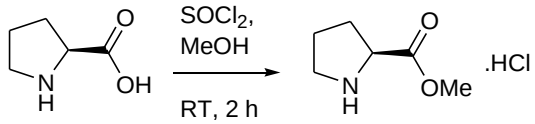
(*S*)-*N*-Benzyl prolinamine 278 [181]



275 **278**

$NEt_3.AlH_3$ (2.00 mL, 2.00 mmol, 4 eq.) was added to (*S*)-*N*-benzyl prolinamide (0.10 g, 0.49 mmol, 1 eq.) and the reaction mixture was stirred at room temperature for 17 h under an inert atmosphere of argon. The reaction was quenched with slow addition of saturated aq. Na_2SO_4 solution until no further effervescence was observed. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure before purification by column chromatography ($CHCl_3$:MeOH:NEt_3 40:40:1) to give the product as an oil (52 mg, 55%). $[\alpha]_D^{22}$ −80.7 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2948, 2873, 2798, 1585, 1495, 1453, 1372, 1261, 1121, 1072, 1028, 888; δ_H (400 MHz, $CDCl_3$) 7.38-7.23 (5H, m, Ar*H*), 4.00 (1H, d, *J* 13.0, PhCH_2), 3.34 (1H, d, *J* 13.0, PhCH_2), 3.02-2.95 (1H, m, NC*H*), 2.81 (1H, dd, *J* 13.0, 5.5, NCH_2CH), 2.75 (1H, dd, *J* 13.0, 3.5, NCH_2CH), 2.64-2.56 (1H, m, NCH_2), 2.28-2.20 (1H, m, NCH_2), 2.00-1.87 (1H, m, CHCH_2), 1.77-1.65 (3H, m, CHCH_2CH_2), 1.58 (2H, s, NH_2); δ_C (100 MHz, $CDCl_3$) 139.9 (C_q), 128.7 (CH), 128.2 (CH), 126.8 (CH), 65.5 (CH), 59.1 (CH_2), 54.6 (CH_2), 44.2 (CH_2), 28.0 (CH_2), 23.9 (CH_2); *m/z* (ES) 174 (32%), 191 ($M+H^+$, 100). *m/z* found $[M+H^+]$ 191.1549. $C_{12}H_{19}N_2$ requires 191.1543.

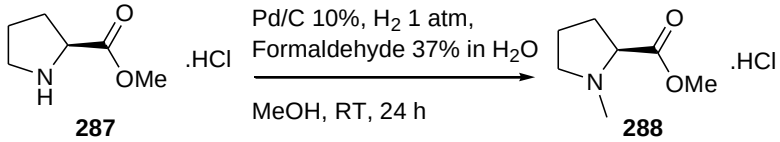
(*S*)-Proline methyl ester hydrochloride 287 [102]



281 **287**

$SOCl_2$ (0.70 mL, 9.57 mmol, 1.1 eq.) was dropwise to a solution of L-proline (1.00 g, 8.70 mmol, 1 eq.) in MeOH (10 mL) and the reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was concentrated under reduced pressure to give the product as a very viscous liquid (1.44 g, 100%). The product is very hygroscopic and can hydrolyse back to proline. Traces of *S*-proline hydrochloride are present in NMR samples due the product reacting with trace amounts of water. $[\alpha]_D^{22}$ −45.5 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2975, 2711, 1750, 1566, 1422, 1391, 1355, 1319, 1242, 1185, 1093, 1043, 1014, 927, 862; δ_H (400 MHz, d^6-DMSO) 10.5-7.5 (1H, v br s, H^+), 6.00-4.00 (1H, v. br s, N*H*), 4.35 (1H, t, *J* 8.0, C*H*), 4.10 (1H, t, imp), 3.75 (3H, s, CH_3), 3.25-3.16 (2H, m, NCH_2), 2.31-2.16 (1H, m, CHCH_2), 2.09-1.87 (3H, m, CHCH_2CH_2); δ_C (100 MHz, d^6-DMSO) 171.1 (C_q, imp), 169.6 (C_q), 59.6 (CH, imp), 58.8 (CH), 53.4 (CH_3), 45.5 (CH_3), 28.8 (CH_2, imp), 28.2 (CH_2), 23.8 (CH_2, imp), 23.5 (CH_2).

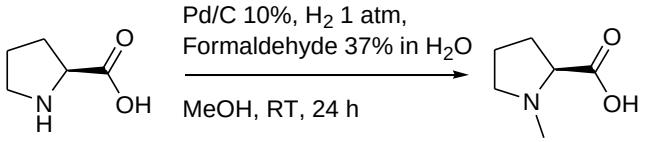
(*S*)-*N*-Methyl-proline methyl ester hydrochloride 288 [182]



287 **288**

Formaldehyde 37% in H_2O (1.44 mL, 20.9 mmol, 2.4 eq.) was added to a solution of (*S*)-proline methyl ester hydrochloride (1.44 g, 8.70 mmol, 1 eq.) and Pd/C 10% (0.36 g, 25% w/w) in MeOH (20 mL) and the reaction mixture was stirred under an atmosphere of H_2 (1 atm.) at room temperature for 24 h. The solution was filtered through kieselguhr to remove the catalyst and concentrated under reduced pressure. The residue was re-dissolved in $CHCl_3$ (10 mL) and filtered to remove the hydrolysed by-product. The solution was concentrated under reduced pressure to give the product as an off-white solid (1.10 g, 70%). m.p. 92-96 °C; $[\alpha]_D^{22}$ −72.4 (*c* 0.7 in MeOH); ν_{max} ($CHCl_3$)/cm^{-1} 3664, 2969, 2258, 1749, 1456, 1439, 1365, 1348, 1242, 1180, 1125, 1070, 1039, 1019, 939, 922; δ_H (400 MHz, d^6-DMSO) 14.0-10.0 (1H, v br s, H^+), 4.42 (1H, t, 8.5, 8.5, C*H*), 3.61-3.51 (1H, m, NCH_2), 3.75 (3H, s, OCH_3), 3.19-3.09 (1H, m, NCH_2), 2.88 (3H, br s, NCH_3), 2.45-2.31 (1H, m, CHCH_2), 2.12-1.97 (2H, m, CHCH_2CH_2), 1.97-1.82 (1H, m, CHCH_2CH_2); δ_C (100 MHz, d^6-DMSO) 168.7 (C_q), 66.4 (CH_2), 56.2 (CH_2), 53.3 (CH_3), 40.1 (CH_3), 27.7 (CH_2), 22.0 (CH_2).

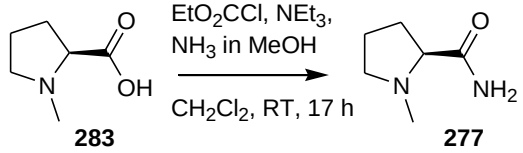
(*S*)-*N*-Methyl proline 283 [183]



281 **283**

L-Proline (5.00 g, 43.4 mmol, 1 eq.), Pd/C 10% (1.25 g, 25% w/w) and formaldehyde 37% in H_2O (5.00 mL, 73.1 mmol, 1.7 eq.) were stirred in MeOH (100 mL) under an atmosphere of H_2 (1 atm.) at room temperature for 24 h. The reaction mixture was filtered through kieselguhr to remove the catalyst and concentrated under reduced pressure to give the product as a colourless solid (5.50 g, 99%). m.p. 114-118 °C (dec.); $[\alpha]_D^{22}$ −121.5 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3427, 3357, 1664, 1604, 1469, 1400, 1365, 1347, 1322, 1184, 1117, 1056, 1025, 925, 772; δ_H (400 MHz, d^6-DMSO) 7.50-3.90 (1H, v br s, O*H*), 3.40-3.39 (2H, m, C*H*NCH_2), 2.85 (1H, ddd, *J* 10.5, 9.5, 7.5, NCH_2), 2.69 (3H, s, CH_3), 2.26-2.13 (1H, m, CHCH_2), 1.95-1.84 (2H, m, CHCH_2CH_2), 1.79-1.67 (1H, m, CHCH_2CH_2); δ_C (100 MHz, d^6-DMSO) 169.7 (C_q), 70.4 (CH), 55.8 (CH_2), 40.9 (CH_3), 29.1 (CH_2), 23.5 (CH_2). ^{1}H NMR data is consistent with literature.[183]

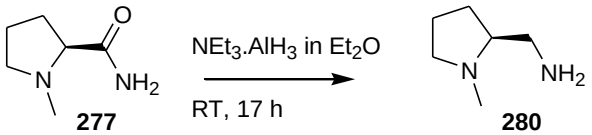
(*S*)-*N*-Methyl prolinamide 277 [184]



283 **277**

EtO_2CCl (0.38 mL, 3.87 mmol, 1 eq.) was added to a solution of (*S*)-*N*-methyl proline (0.50 g, 3.87 mmol, 1 eq.) and NEt_3 (0.55 mL, 3.87 mmol, 1 eq.) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred at room temperature for 1 h. A saturated solution of NH_3 in MeOH (20 mL) was added and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and dissolved in saturated K_2CO_3 in MeOH (20 mL) and formed solid KCl as a by-product. The solution was concentrated under reduced pressure and crude product was extracted by washing with CH_2Cl_2 (3 x 10 mL) and filtration to remove the inorganic material. The organic layer was concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH:NEt_3 19:1:0.05) to give the product as a colourless solid (0.20 g, 40%). m.p. 137-140 °C [lit. 139-141 °C][184]; R_f ($CHCl_3$:MeOH 19:1) 0.2; $[\alpha]_D^{22}$ −116.6 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3504, 3368, 3011, 2977, 2854, 2795, 1681, 1550, 1370, 1314, 1242, 1144, 1089, 1045; δ_H (400 MHz, $CDCl_3$) 7.14 (1H, br s, N*H*$_2$), 5.70 (1H, br s, N*H*$_2$), 3.13-3.07 (1H, m, C*H*), 2.84 (1H, dd, *J* 10.0, 5.5, NC*H*$_2$), 2.39 (3H, s, C*H*$_3$), 2.38-2.18 (2H, m, C*H*$_2$NCHC*H*$_2$), 1.92-1.84 (1H, m, CHC*H*$_2$), 1.84-1.74 (2H, m, CHCH$_2$C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 178.0 (C_q), 69.0 (CH), 56.8 (CH_2), 41.7 (CH_3), 31.1 (CH_2), 24.2 (CH_2).

(*S*)-*N*-Methyl prolinamine 280 [185]

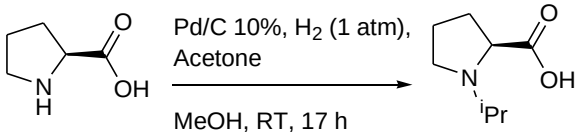


277 **280**

$NEt_3.AlH_3$ 1 M in Et_2O (8.00 mL, 8.00 mmol, 5 eq.) was added to (*S*)-*N*-methyl prolinamide (0.20 g, 1.60 mmol, 1 eq.) and the reaction mixture was stirred at room temperature for 17 h under an inert atmosphere of argon. The reaction was quenched with slow addition of saturated aq. Na_2SO_4 solution. The inorganic precipitate was removed by filtration through kieselguhr and the filtrate was concentrated under reduced pressure before purification by column chromatography ($CHCl_3$:MeOH:NEt_3 1:1:0.025) to give the product as an oil (30 mg, 17%). $[\alpha]_D^{22}$ −38.9 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3384, 2948, 2789, 2500, 1671, 1601, 1457, 1365, 1241, 1141, 1117, 1040, 888; δ_H (400 MHz, $CDCl_3$) 3.07 (1H, ddd, *J* 9.0, 6.5, 2.5, C*H*), 2.78 (1H, dd, *J* 13.0, 3.5, NC*H*$_2$CH), 2.69 (1H, dd, *J* 13.0, 6.0, NC*H*$_2$CH), 2.34 (3H, s, C*H*$_3$), 2.25-2.16 (2H, m, NC*H*$_2$), 2.00-1.86

(1H, m, NCHCH_2), 1.81-1.67 (2H, m, CHCH_2CH_2), 1.67-1.58 (1H, m, CHCH_2CH_2), 1.51 (2H, br s, NH_2); δ_C (100 MHz, $CDCl_3$) 67.6 (CH), 57.6 (CH_2), 44.1 (CH_2), 40.9 (CH_3), 28.3 (CH_2), 22.6 (CH_2). ^{1}H and ^{13}C NMR data are consistent with literature.[185]

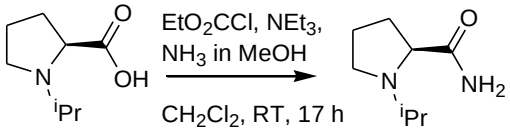
(*S*)-*N*-Isopropyl proline 282 [186]



281 **282**

Acetone (1.00 mL, 13.6 mmol, 3 eq.) was added to a solution of L-proline (0.50 g, 4.34 mmol, 1 eq.) and Pd/C 10% (0.25 g, 50% w/w) in MeOH (20 mL) and stirred under an atmosphere of H_2 (1 atm.) at room temperature for 24 h. The reaction mixture was filtered through kieselguhr to remove the catalyst and concentrated under reduced pressure to give the product as a colourless solid (0.68 g, 98%). Elemental analysis found: C, 60.89; H, 9.72; N, 8.86. $C_{13}H_{15}NO_4$ requires C, 61.12; H, 9.62, N, 8.91; m.p. 195-197 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2988, 1638, 1453, 1389, 1328, 1242; $[\alpha]_D^{22}$ −7.7 (*c* 0.7 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 9.35 (1H, br s, O*H*), 3.83 (1H, ddd, *J* 11.0, 6.5, 4.0, NCH_2), 3.78 (1H, dd, *J* 9.5, 5.0, C*H*), 3.55 (1H, sept, *J* 6.5, CH_3CHCH_3), 2.89-2.81 (1H, ddd, *J* 10.5, 10.0, 7.5, NCH_2), 2.29-2.11 (2H, m, CHCH_2), 1.90-1.79 (2H, m, CHCH_2CH_2), 1.29 (3H, d, *J* 6.5, CH_3CHCH_3), 1.28 (3H, d, *J* 6.5, CH_3CHCH_3); δ_C (100 MHz, $CDCl_3$) 170.6 (C_q), 65.8 (CH), 55.4 (CH), 51.2 (CH_2), 30.3 (CH_2), 24.1 (CH_2), 18.2 (CH_3), 17.9 (CH_3).

(*S*)-*N*-Isopropyl prolinamide 276 [187]

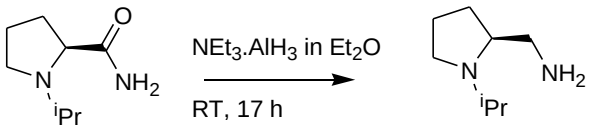


282 **276**

EtO_2CCl (0.38 mL, 3.94 mmol, 1.2 eq.) was added to a solution of (*S*)-*N*-isopropyl proline (0.50 g, 3.18 mmol, 1 eq.) and NEt_3 (0.55 mL, 3.94 mmol, 1.2 eq.) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred at room temperature for 1 h. A saturated solution of NH_3 in MeOH (20 mL) was added and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and dissolved in saturated K_2CO_3 in MeOH (20 mL) and formed solid KCl as a by-product. The solution was concentrated under reduced pressure and crude product was extracted by washing with CH_2Cl_2 (3 x 10 mL) and filtration to remove the inorganic material. The organic layer was concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc:NEt_3 200:200:1) to give the product as a colourless solid (0.35 g,

70%). m.p. 102-104 °C; R_f 0.1 (petroleum ether:EtOAc 1:1); $[\alpha]_D^{22}$ −101.7 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3500, 3357, 2974, 2875, 2810, 1677, 1543, 1387, 1367, 1324, 1304, 1241, 1165, 1098, 1056, 1008, 890; δ_H (400 MHz, $CDCl_3$) 7.38 (1H, br s, N*H*$_2$), 5.82 (1H, br s, N*H*$_2$), 3.22 (1H, dd, *J* 10.5, 3.5, C*H*), 3.10-3.04 (1H, m, NC*H*$_2$), 2.77 (1H, sept, *J* 6.5, CH_3CHCH_3), 2.50 (1H, ddd, *J* 10.5, 9.0, 6.0, NC*H*$_2$), 2.12-2.01 (1H, m, CHC*H*$_2$), 1.97-1.90 (1H, m, CHC*H*$_2$), 1.80-1.60 (2H, m, $CHCH_2CH_2$), 1.06 (3H, d, *J* 6.5, CH_3CHCH_3), 1.04 (3H, d, *J* 6.5, CH_3CHCH_3); δ_C (100 MHz, $CDCl_3$) 179.8 (C_q), 64.2 (CH), 52.9 (CH), 50.4 (CH_2), 31.4 (CH_2), 24.7 (CH_2), 21.7 (CH_3), 19.6 (CH_3). ^{1}H and ^{13}C NMR data is consistent with literature.[187]

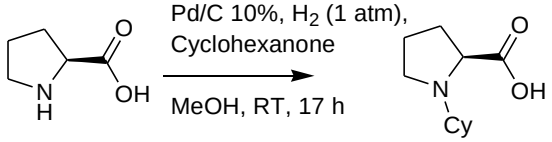
(*S*)-*N*-Isopropyl prolinamine 279 [187]



276 **279**

$NEt_3.AlH_3$ 1 M in Et_2O (10.0 mL, 10.0 mmol, 4 eq.) was added to (*S*)-*N*-isopropyl prolinamide (0.40 g, 2.50 mmol, 1 eq.) and the reaction mixture was stirred at room temperature for 17 h under an inert atmosphere of argon. The reaction was quenched with slow addition of saturated aq. Na_2SO_4 solution. The inorganic precipitate was removed by filtration through kieselguhr and the filtrate was concentrated under reduced pressure before purification by column chromatography ($CHCl_3$:MeOH:NEt_3 40:40:1) to give the product as an oil (0.21 g, 57%). $[\alpha]_D^{22}$ −13.1 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2968, 2874, 2497, 1602, 1462, 1385, 1369, 1322, 1242, 1172, 1116, 1082, 993, 898, 858; δ_H (400 MHz, $CDCl_3$) 2.95-2.87 (2H, m, C*H*NC*H*), 2.76-2.49 (3H, m, CH_2, NC*H*$_2$C*H*$_2$C*H*$_2$), 1.85-1.57 (3H, m, NCH$_2$C*H*$_2$C*H*$_2$), 1.32 (2H, br s, N*H*$_2$), 1.12 (3H, d, *J* 6.5, CH_3CHCH_3), 0.99 (3H, d, *J* 6.5, CH_3CHCH_3); δ_C (100 MHz, $CDCl_3$) 61.9 (CH), 50.7 (CH), 47.9 (CH_2), 46.0 (CH_2), 28.8 (CH_2), 23.7 (CH_2), 22.3 (CH_3), 16.7 (CH_3).

(*S*)-*N*-Cyclohexyl proline 284 [182]

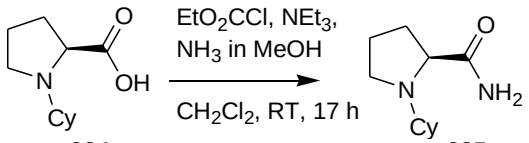


281 **284**

Cyclohexanone (2.69 mL, 26.1 mmol, 3 eq.) was added to a solution of L-proline (1.00 g, 8.69 mmol, 1 eq.) and Pd/C 10% (0.30 g, 30% w/w) in MeOH (20 mL) and stirred under an atmosphere of H_2 (1 atm.) at room temperature for 24 h. The reaction mixture was filtered through kieselguhr to remove the catalyst and concentrated under reduced pressure to give the product as a colourless solid (1.68 g, 100%) m.p. 169-174 °C (dec.); $[\alpha]_D^{22}$ −18.6 (*c* 0.7 in $CHCl_3$); ν_{max}

($CHCl_3$)/cm^{-1} 2987, 2947, 2863, 1635, 1453, 1374, 1329, 1242, 1062, 972, 928, 898, 841; δ_H (400 MHz, $CDCl_3$) 7.50-4.50 (1H, v br s, O*H*), 3.90 (1H, dd, *J* 9.5, 4.5, COC*H*), 3.90-3.82 (1H, m, NCH_2), 3.16 (1H, tt, *J* 12.0, 3.5, CH_2CHCH_2), 2.96 (1H, td, *J* 10.5, 7.5, NCH_2), 2.42-2.34 (1H, m, $COCHCH_2$), 2.29-2.19 (1H, m, $COCHCH_2$), 2.18-2.08 (2H, m, NCH_2CH_2), 2.02-1.87 (4H, m, CH_2CHCH_2), 1.73 (1H, app d, *J* 13.0, $CHCH_2CH_2CH_2$), 1.59-1.43 (2H, m, $CHCH_2CH_2CH_2CH_2$), 1.40-1.10 (3H, m, $CHCH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 170.6 (C_q), 66.3 (CH), 63.3 (CH), 51.6 (CH_2), 30.1 (CH_2), 28.8 (CH_2), 28.2 (CH_2), 25.1 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 24.1 (CH_2); *m/z* (ES) 198 ($M+H^+$, 100%), 220 ($M+Na^+$, 29); *m/z* found [$M+H^+$] 198.1489. $C_{11}H_{20}NO_2$ requires 198.1480.

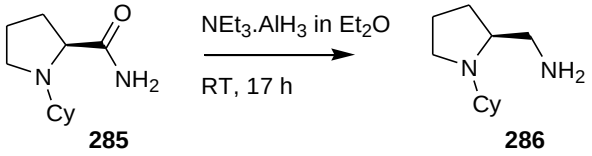
(*S*)-*N*-Cyclohexyl prolinamide 285 [187]



284 **285**

EtO_2CCl (0.53 mL, 5.61 mmol, 1.1 eq.) was added to a solution of (*S*)-*N*-cyclohexyl proline (1.00 g, 5.10 mmol, 1 eq.) and NEt_3 (0.78 mL, 5.61 mmol, 1.1 eq.) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred at room temperature for 1 h. A saturated solution of NH_3 in MeOH (40 mL) was added and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and dissolved in saturated K_2CO_3 in MeOH (20 mL) and formed solid KCl as a by-product. The solution was concentrated under reduced pressure and crude product was extracted by washing with CH_2Cl_2 (3 x 10 mL) and filtration to remove the inorganic material. The organic layer was concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc 1:1) to give the product as a colourless solid (0.63 g, 63%). Elemental analysis found: C, 67.15; H, 10.33; N, 14.25. $C_{13}H_{15}NO_4$ requires C, 67.31; H, 10.27, N, 14.27; m.p. 155-158 °C; R_f (petroleum ether:EtOAc 1:1) 0.3; $[\alpha]_D^{22}$ −74.0 (*c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3500, 3356, 3005, 2933, 2858, 1676, 1543, 1450, 1377, 1300, 1242, 1163, 1133, 991, 895; δ_H (400 MHz, $CDCl_3$) 7.40 (1H, br s, NH_2), 5.35 (1H, br s, NH_2), 3.30 (1H, dd, *J* 10.5, 3.0, COC*H*), 3.14-3.08 (1H, m, CH_2CHCH_2), 2.54 (1H, ddd, *J* 10.5, 9.0, 6.0, NCH_2), 2.39-2.31 (1H, m, NCH_2), 2.15-2.03 (1H, m, $COCHCH_2$), 1.99-1.88 (2H, m, NCH_2CH_2), 1.85-1.59 (5H, m, $CH_2CH_2CHCH_2$), 1.32-1.05 (5H, m, $CHCH_2CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 180.0 (C_q), 64.1 (CH), 50.7 (CH_2), 32.3 (CH_2), 31.2 (CH_2), 30.4 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 25.4 (CH_2), 24.7 (CH_2); *m/z* (ES) 197 ($M+H^+$, 100%); *m/z* found [$M+H^+$] 197.1649. $C_{11}H_{20}N_2O$ requires 197.1648. ^1H and ^{13}C NMR data is consistent with literature.[187]

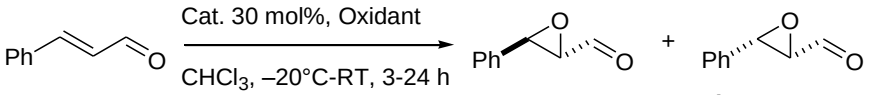
(*S*)-*N*-Cyclohexyl prolinamine 286 [187]



285 **286**

$NEt_3.AlH_3$ 1 M in Et_2O (4.00 mL, 4.00 mmol, 4 eq.) was added to (*S*)-*N*-cyclohexyl prolinamide (0.20 g, 1.00 mmol, 1 eq.) and the reaction mixture was stirred at room temperature for 17 h under an inert atmosphere of argon. The reaction was quenched with slow addition of saturated aq. Na_2SO_4 solution. The inorganic precipitate was removed by filtration through kieselguhr and the filtrate was concentrated under reduced pressure before purification by column chromatography ($CHCl_3$:MeOH:NEt_3 40:40:1) to give the product as an oil (0.11 g, 61%). R_f ($CHCl_3$:MeOH 1:1) 0.1; $[\alpha]_D^{22}$ −34.8 (*c* 0.7 in $CHCl_3$); v_{max} ($CHCl_3$)/cm^{-1} 3664, 3380, 2932, 2857, 2496, 1670, 1575, 1450, 1379, 1347, 1262, 1114, 991, 893, 860; δ_H (400 MHz, $CDCl_3$) 2.98-2.91 (1H, m, NCH_2CH), 2.86-2.79 (1H, m, NCH_2CHNCH), 2.70-2.54 (3H, m, NCH_2CHNCH_2), 2.50-2.40 (1H, m, NCH_2CH_2), 1.90-1.57 (9H, m, $NCH_2CH_2CH_2$ + $CH_2CH_2CHCH_2CH_2$), 1.43 (2H, br s, NH_2), 1.33-1.05 (5H, m, $CHCH_2CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 61.7 (CH), 60.1 (CH), 49.1 (CH_2), 46.3 (CH_2), 33.0 (CH_2), 28.8 (CH_2), 27.9 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 23.9 (CH_2); *m/z* (ES) 166 (20%), 183 ($M+H^+$, 100); *m/z* found [$M+H^+$] 183.1856. $C_{11}H_{23}N_2$ requires 183.1855. ^1H and ^{13}C NMR data is consistent with literature.[187]

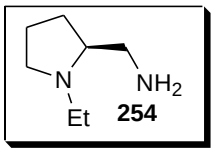
General procedure for synthesis of 2,3-epoxy-3-phenyl-1-propionaldehyde 290 [110]



289 ***trans*-290** ***cis*-290**

An oxidant (4.77 mmol, 3 eq.) was added to a solution of (*E*)-cinnamaldehyde (0.20 g, 1.59 mmol, 1 eq.) and a catalyst (0.48 mmol, 0.3 eq.) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (petroleum ether: EtOAc 4:1) to give the product as a clear oil. R_f (petroleum ether:EtOAc 4:1) 0.5; v_{max} ($CHCl_3$)/cm^{-1} 3438, 3069, 3011, 2961, 2929, 2822, 2728, 1729, 1604, 1498, 1459, 1418, 1377, 1331, 1314, 1279, 1242, 1184, 1066, 1028, 1011, 990, 909, 869, 839; *Trans diastereomer* δ_H (400 MHz, $CDCl_3$) 9.22 (1H, d, *J* 6.0, CO*H*), 7.50-7.30 (5H, m, Ar*H*), 4.20 (1H, d, *J* 2.0, PhC*H*), 3.47 (1H, dd, *J* 6.0, 2.0, COC*H*); δ_C (100 MHz, $CDCl_3$) 196.9 (CH), 134.2 (C_q), 129.2 (CH), 128.8 (CH), 125.7 (CH), 62.9 (CH), 56.6 (CH); *Cis diastereomer* δ_H (400 MHz, $CDCl_3$) 9.11 (1H, d, *J* 6.0, CO*H*), 7.50-7.30 (5H, m, Ar*H*), 4.42 (1H, d, *J* 4.0,

PhC*H*), 3.56 (1H, dd, *J* 6.0, 4.5, COC*H*); δ_C (100 MHz, $CDCl_3$) 199.1 (CH), 131.6 (C_q), 128.7 (CH), 128.6 (CH), 126.2 (CH), 59.2 (CH), 58.3 (CH); *m/z* (ES) 203 (M+MeOH+Na^+, 100); *m/z* found [M+MeOH+Na^+] 203.0686. $C_{10}H_{12}O_3Na$ requires 203.0684.

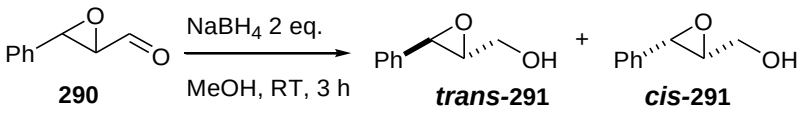


254

Oxidant	Catalyst	Temp. / °C	Time /h	Yield /%[a]	*cis:* *trans*[a]	Yield /%[b]	ee /%[b]
UHP	NaOH	0	3	67	1:4	90	-
H_2O_2 50% in H_2O	**254**	−20	24	0	-	-	-
H_2O_2 50% in H_2O	**254**	RT	24	0	-	-	-
UHP	**254**	RT	24	14	3:2	76	0

* = Solvent was MeOH

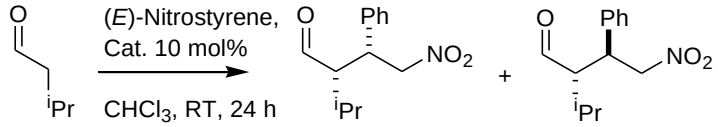
2,3-Epoxy-3-phenyl-1-propanol 291 [188,189]



290 ***trans*-291** ***cis*-291**

2,3-Epoxy-3-phenyl-1-propionaldehyde (0.15 g, 1.00 mmol, 1 eq.) and $NaBH_4$ (82 mg, 2.20 mmol, 2.2 eq.) in MeOH (5 mL) were stirred at room temperature for 3 h. The reaction mixture was quenched with saturated aq. NH_4Cl (5 mL), concentrated under reduced pressure and purified by column chromatography (petroleum ether: EtOAc 3:1) to give the product as a clear oil (0.13 g, 90%). R_f (petroleum ether:EtOAc 4:1) 0.2; ν_{max} ($CHCl_3$)/cm^{-1} 3689, 3606, 3009, 2958, 2928, 2874, 1724, 1604, 1497, 1456, 1388, 1309, 1240, 1068, 1030, 984, 930, 909, 862, 839; *Cis isomer* δ_H (400 MHz, $CDCl_3$) 7.42-7.29 (5H, m, Ar*H*), 4.22 (1H, d, *J* 4.0, PhC*H*), 3.63-3.53 (1H, m, CH_2), 3.52-3.44 (2H, m, C*H*CH_2), 2.04 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 134.7 (C_q), 128.4 (CH), 127.9 (CH), 126.2 (CH), 60.5 (CH), 58.7 (CH_2), 57.1 (CH); *Trans isomer* δ_H (400 MHz, $CDCl_3$) 7.42-7.29 (5H, m, Ar*H*), 4.09 (1H, ddd, *J* 12.5, 5.0, 2.5, CH_2), 3.97 (1H, d, *J* 2.5, PhC*H*), 3.85 (1H, ddd, 12.5, 7.5, 3.5, CH_2), 3.25 (1H, dt, 4.0, 2.5, CH_2C*H*), 1.79 (1H, dd, *J* 8.0, 5.0, O*H*); δ_C (100 MHz, $CDCl_3$) 136.7 (C_q), 128.6 (CH), 128.3 (CH), 125.8 (CH), 62.5 (CH), 61.3 (CH_2), 55.6 (CH); *m/z* (ES) 173 (M+Na^+, 100); *m/z* found [M+Na^+] 173.0582. $C_9H_{10}O_2Na$ requires 173.0573. ^1H and ^{13}C NMR data are consistent with literature.[188,189]

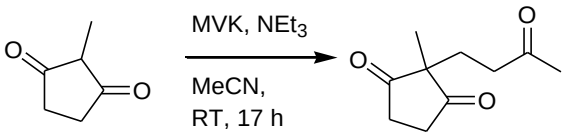
2-(1-Methylethyl)-4-nitro-3-phenylbutyraldehyde 298 [190]



297 **syn-298** **anti-298**

3-Methylbutyraldehyde (0.29 g, 0.36 mL, 3.40 mmol, 10 eq.) was added to a solution of (*E*)-nitrostyrene (50 mg, 0.34 mmol, 1 eq.) and DL-proline (3.9 mg, 34.0 μmol, 0.1 eq.) in $CHCl_3$ (3 mL) and was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc 9:1) to give the product as a mixture of diastereomers as a colourless oil (51 mg, 68%, *anti:syn* 95:5). R_f (petroleum ether:EtOAc 9:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 3045, 2966, 2935, 2875, 2742, 1719, 1557, 1496, 1467, 1456, 1432, 1378, 1241, 1145, 1044, 993, 913; a*nti isomer* δ_H (400 MHz, $CDCl_3$) 9.96 (1H, d, *J* 2.5, CO*H*), 7.41-7.30 (3H, m, Ar*H*), 7.24-7.17 (2H, m, Ar*H*), 4.70 (1H, dd, *J* 12.5, 4.5, CH_2), 4.60 (1H, dd, *J* 12.5, 10.0, CH_2), 3.93 (1H, ddd, *J* 10.5, 10.5, 4.5, PhC*H*), 2.80 (1H, ddd, *J* 10.5, 4.0, 2.5, COC*H*), 1.75 (1H, dsept, *J* 7.0, 4.5, CH_3CHCH_3), 1.13 (3H, d, *J* 7.0, CH_3CHCH_3), 0.91 (3H, d, *J* 7.0, CH_3CHCH_3); δ_C (100 MHz, $CDCl_3$) 204.4 (CH), 137.1 (C_q), 129.1 (CH), 128.1 (CH), 128.0 (CH), 79.0 (CH_2), 58.8 (CH), 42.0 (CH), 27.9 (CH), 21.7 (CH_3), 17.0 (CH_3); s*yn isomer* δ_H (400 MHz, $CDCl_3$) 9.51 (1H, d, *J* 4.0, CO*H*), 7.41-7.30 (3H, m, Ar*H*), 7.24-7.17 (2H, m, Ar*H*), 4.80 (1H, dd, *J* 13.0, 6.5, CH_2), 4.70 (1H, dd, *J* 13.0, 6.5, CH_2), 4.00 (1H, ddd, *J* 9.0, 6.5, 6.5, PhC*H*), 2.40 (1H, ddd, *J* 7.5, 7.5, 4.0, COC*H*), 2.05 (1H, dsept, *J* 7.0, 4.5, CH_3CHCH_3), 1.18 (3H, d, *J* 7.0, CH_3CHCH_3), 1.00 (3H, d, *J* 7.0, CH_3CHCH_3); δ_C (100 MHz, $CDCl_3$) 207.4 (CH), 135.9 (C_q), 129.2 (CH), 128.4 (CH), 128.3 (CH), 79.0 (CH_2), 68.4 (CH), 63.3 (CH), 26.6 (CH), 21.0 (CH_3), 20.0 (CH_3); *m/z* (ES) 258 ($M+Na^+$, 100), 290 (67, $M+MeOH+Na^+$); *m/z* found [$M+Na^+$] 258.1104. $C_{13}H_{17}NO_3Na$ requires 258.1101. ^{13}C NMR data is consistent with literature.[190]

2-Methyl-2-(3-oxobutyl)cyclopentane-1,3-dione 294 [117]

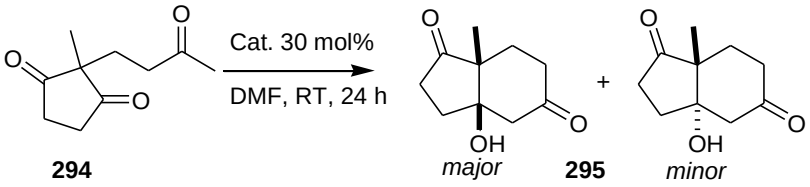


293 **294**

MVK (1.90 mL, 22.5 mmol, 5 eq.) was added to a solution of 2-methyl-1,3-cyclopentadione (0.50 g, 4.50 mmol, 1 eq.) and NEt_3 (3 mL) in MeCN (10 mL) and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc 1:1) to give the product as a yellow oil (0.78 g, 95%). R_f (petroleum ether:EtOAc 1:1) 0.5; ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2972,

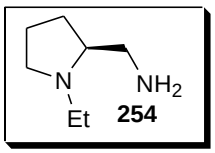
2930, 1764, 1722, 1453, 1420, 1369, 1301, 1240, 1172, 1078, 992; δ_H (400 MHz, $CDCl_3$) 2.95-2.70 (4H, m, $COCH_2CH_2CO$), 2.48 (2H, d, *J* 7.0, $COCH_2$), 2.13 (3H, s, $COCH_3$), 1.92 (2H, d, *J* 7.0, CCH_2), 1.13 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 215.8 (C_q), 207.9 (C_q), 55.1 (C_q), 37.4 (CH_2), 30.0 (CH_3), 27.8 (CH_2), 19.0 (CH_3); *m/z* (ES) 205 ($M+Na^+$, 100%); *m/z* found [$M+Na^+$] 205.0844. $C_{10}H_{14}O_3Na$ requires 205.0835. ^1H and ^{13}C NMR data are consistent with literature.[117]

General procedure for synthesis of 3-hydroxy-7-methyloctahydroindene-1,5-dione 295 [118]



294 **295**

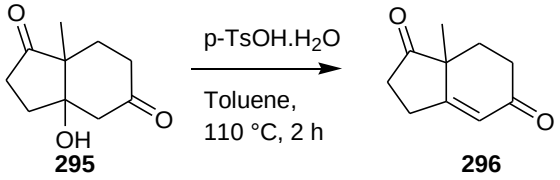
2-Methyl-2-(3-oxobutyl)cyclopentane-1,3-dione (0.10 g, 0.55 mmol, 1 eq.) and a catalyst (0.17 mmol, 0.3 eq.) were stirred in DMF (2 mL) at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure to remove most of the DMF, then purified by column chromatography (Et_2O) to give the product as a colourless solid. R_f (Et_2O) 0.4; m.p. 114-116 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3600, 3467, 3011, 2973, 2950, 2877, 2453, 1744, 1739, 1470, 1446, 1410, 1379, 1342, 1289, 1241, 1154, 1072, 1057, 1031, 1016, 990, 955; *syn diastereomer* δ_H (400 MHz, $CDCl_3$) 2.63 (2H, s, CCH_2CO), 2.55 (1H, dd, *J* 9.0, 9.0, $CCOCH_2$), 2.50-2.39 (2H, m, $CCOCH_2CH_2$), 2.35 (1H, dd, *J* 5.0, 5.0, $CH_2COCH_2CH_2$), 2.02 (2H, dd, *J* 9.0, 6.5, $CCOCH_2CH_2$), 1.86 (1H, s, O*H*), 1.79 (1H, dd, 11.5, 5.0, $CH_3CCH_2CH_2$), 1.73 (1H, dd, 6.0, 5.0, $CH_3CCH_2CH_2$), 1.27 (3H, s, CH_3); a*nti diastereomer* 2.63 (2H, s, CCH_2CO), 2.60 (1H, dd, *J* 9.0, 9.0, $CCOCH_2$), 2.50-2.39 (2H, m, $CCOCH_2CH_2$), 2.31 (1H, dd, *J* 5.0, 5.0, $CH_2COCH_2CH_2$), 2.02 (2H, dd, *J* 9.0, 6.5, $CCOCH_2CH_2$), 1.86 (1H, s, O*H*), 1.82 (1H, dd, *J* 11.5, 5.0, $CH_3CCH_2CH_2$), 1.69 (1H, dd, 6.0, 5.0, $CH_3CCH_2CH_2$), 1.27 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 218.1 (C_q), 208.2 (C_q), 81.4 (C_q), 52.6 (C_q), 50.5 (CH_2), 36.6 (CH_2), 33.5 (CH_2), 32.8 (CH_2), 29.7 (CH_2), 14.0 (CH_3); *m/z* (ES) 205 ($M+Na^+$, 100%), 237 ($M+MeOH+Na^+$, 37); *m/z* found [$M+Na^+$] 205.0844. $C_{10}H_{14}O_3Na$ requires 205.0835.



254

Catalyst	Yield /%	ee /%
DL-Proline	60	-
254.TfOH	26	0

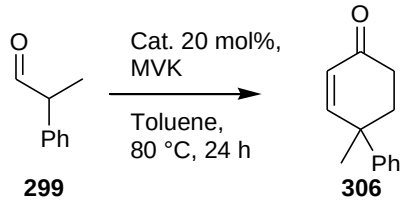
Parrish Ketone 296 [192]



295 **296**

3-Hydroxy-7-methyloctahydroindene-1,5-dione (50 mg, 0.27 mmol, 1 eq.) and p-TsOH.H_2O (5 mg, 27.0 μmol, 0.1 eq.) were heated under reflux in toluene (10 mL) in a Dean-Stark apparatus for 2 h. The reaction mixture was concentrated and purified by column chromatography (Et_2O) to give the product as an off-white solid (39 mg, 89%). m.p. 71-74 °C [lit. 72-73 °C][191]; R_f (Et_2O) 0.6; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2971, 2872, 1747, 1667, 1448, 1408, 1374, 1349, 1319, 1247, 1149, 1059, 1007, 958, 868; δ_H (400 MHz, $CDCl_3$) 5.98 (1H, d, *J* 2.0, C*H*), 3.03-2.91 (1H, m, CHCCH_2), 2.85-2.71 (2H, m, CHCCH_2CH_2), 2.59-2.39 (3H, m, CH_2COCHCCH_2CH_2), 2.12 (1H, ddd, *J* 13.5, 5.0, 2.5, CH_3CCH_2), 1.86 (1H, ddd, *J* 14.0, 13.5, 5.5, CH_3CH_2), 1.33 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 216.5 (C_q), 198.2 (C_q), 169.7 (C_q), 123.9 CH), 48.7 (C_q), 35.9 (CH_2), 32.9 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 20.6 (CH_3); *m/z* (ES) 165 ($M+H^+$, 12%), 187 ($M+Na^+$, 100) 351 ($2M+Na^+$, 10); *m/z* found [$M+Na^+$] 187.0734. $C_{10}H_{12}O_2Na$ requires 187.0730; enantioselectivity determined by chiral HPLC, R_t HPLC (Chiralpak AS, 95:5 hexane:^{i}PrOH, 230 nm, 0.8 mL/min, 20 °C) 21.5 min, 22.7 min. ^1H and ^{13}C NMR data consistent with literature.[192]

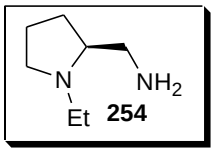
General procedure for synthesis of 4-methyl-4-phenyl-2-cyclohexenone 306 [193]



299 **306**

2-Phenylpropionaldehyde (0.20 g, 1.50 mmol, 1 eq.), MVK (0.63 mL, 7.50 mmol, 5 eq.) and a catalyst (0.15 mmol, 0.2 eq.) were heated at 80 °C in toluene (10 mL) in a Dean-Stark apparatus for 24 h. The reaction mixture was concentrated and purified by column chromatography (toluene:Et_2O 9:1) to give the product as a yellow oil. R_f (toluene:Et_2O 9:1) 0.6; ν_{max} ($CHCl_3$)/cm^{-1} 3087, 3063, 3009, 2970, 2870, 1676, 1601, 1494, 1458, 1445, 1417, 1389, 1373, 1328, 1266, 1240, 1174, 1112, 1072, 1030, 992, 962, 936, 909, 865; δ_H (400 MHz, $CDCl_3$) 7.42-7.35 (4H, m, Ar*H*), 7.32-7.26 (1H, m, Ar*H*), 6.97 (1H, dd, *J* 10.0, 1.0, PhCC*H*), 6.16 (1H, d, *J* 10.0, COC*H*), 2.48-2.39 (1H, m, COCH_2), 2.36-2.26 (2H, m, COCH_2CH_2), 2.22-2.13 (1H, m, COCH_2CH_2), 1.58 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 199.5 (C_q), 157.1 (CH), 145.3 (C_q), 128.7 (CH), 128.6 (CH), 126.8 (CH), 126.2 (CH), 40.6 (C_q), 38.1

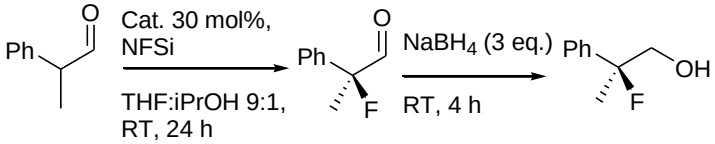
(CH_2), 34.7 (CH_2), 27.6 (CH_3); *m/z* (ES) 187 ($M+H^+$, 54%), 209 ($M+Na^+$, 100); *m/z* found [$M+Na^+$] 209.0939. $C_{13}H_{14}ONa$ requires 209.0937; enantioselectivity determined by chiral HPLC, R_t (Chiralpak AD-H, 95:5 hexane:^{i}PrOH, 210 nm, 0.3 mL/min, 20 °C) 25.3 min (*R*)-enantiomer, 28.8 min (*S*)-enantiomer. ^{1}H and ^{13}C NMR data are consistent with literature.[193]



254

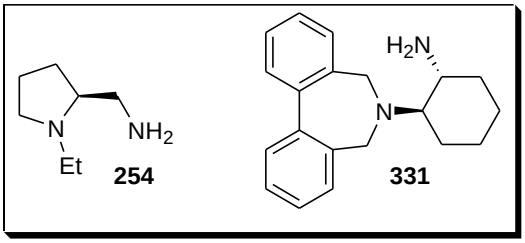
Catalyst	Yield /%	ee /%
pTsOH.H_2O	74	-
254.TfOH	5	5

General procedure for synthesis of 2-fluoro-2-phenylpropanol 301 [194]



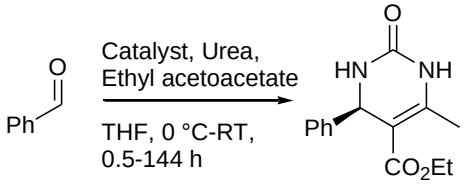
299 **300** **301**

NFSi (0.28 g, 0.90 mmol, 1.2 eq.) was added to a solution of 2-phenylpropionaldehyde (0.10 g, 0.75 mmol, 1 eq.) and a catalyst (0.23 mmol, 0.3 eq.) in a 9:1 mixture of THF:^{i}PrOH (2.5 mL), the vessel was sealed and the reaction mixture was stirred at room temperature over 24 h. The fluorinated aldehyde was not isolated due to its volatility, but its formation was observed by ^{1}H NMR; the aldehyde singlet is replaced by a doublet. $NaBH_4$ (86 mg, 2.25 mmol, 3 eq.) and THF (1 mL) were added and the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with addition of water (5 mL) and the product was extracted by addition of Et_2O (3 x 5 mL). The organic layers were combined and dried over $MgSO_4$, then concentrated under reduced pressure, then purified by column chromatography (petroleum ether:Et_2O 4:1) to give the product as a clear oil. R_f (petroleum ether:Et_2O 4:1) 0.4; ν_{max} ($CHCl_3$)/cm^{-1} 3590, 3088, 3063, 3011, 2981, 2931, 2878, 1727, 1603, 1495, 1448, 1376, 1279, 1241, 1146, 1080, 1061, 1028, 970; δ_H (400 MHz, $CDCl_3$) 7.45-7.32 (5H, m, Ar*H*), 3.95-3.72 (2H, m, C*H*$_2$), 1.83 (1H, br t, *J* 6.5, O*H*), 1.73 (3H, d, *J* 23.0, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 141.6 (C_q, d, *J* 22.0), 128.5 (CH, d, *J* 1.5), 127.9 (CH), 124.5 (CH, d, *J* 10.0), 97.8 (C_q, d, *J* 171.0), 69.6 (CH_2, d, *J* 25.0), 23.2 (CH_3, d, 24.0); δ_F (376 MHz, $CDCl_3$) −157.2 (1F, m); enantioselectivity determined by chiral HPLC, R_t (Chiralpak AD-H, 95:5 hexane:^{i}PrOH, 210 nm, 0.3 mL/min, 20 °C) 11.7, 13.1 min. ^{1}H, ^{13}C and ^{19}F NMR data consistent with literature.[194]



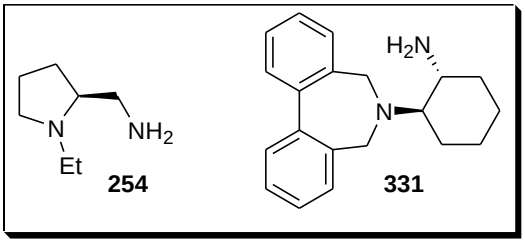
Catalyst	Yield /%	ee /%
DL-Proline	95	-
254.TFA	53	10
331.TFA	52	–43

General procedure for synthesis of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 292 [195,196]



22 **292**

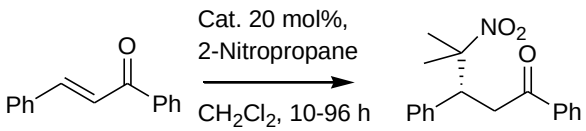
Benzaldehyde (0.15 mL, 1.40 mmol) was added to a solution of ethyl acetoacetate (0.18 g, 1.40 mmol, 1 eq.), urea (0.10 g, 1.68 mmol, 1.2 eq.) and a catalyst (0.14 mmol, 0.1 eq.) in THF (10 mL) and the reaction mixture was stirred at room temperature or 0 °C for 0.5-144 h. The reaction mixture was concentrated and purified by column chromatography (toluene:MeOH 9:1) to give the product as a colourless solid. Elemental analysis found: C, 64.36; H, 6.18; N, 10.80. $C_{13}H_{15}NO_4$ requires C, 64.60; H, 6.20, N, 10.76; m.p. 210-211 °C [lit. 210-211 °C][195]; R_f (toluene:MeOH 9:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 3432, 3227, 3108, 3009, 1701, 1646, 1494, 1456, 1404, 1370, 1310, 1269, 1172, 1093, 1028; δ_H (400 MHz, $CDCl_3$) 7.62 (1H, br s, CN*H*), 7.37-7.25 (5H, m, Ar*H*), 5.57 (1H, app br s, PhCHN*H*), 5.43 (1H, dd, *J* 3.0, 0.5, C*H*), 4.16-4.03 (2H, m, CH_2), 2.38 (3H, d, *J* 0.5, CCH_3), 1.19 (3H, t, *J* 7.0, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 165.63 (C_q), 153.31 (C_q), 146.29 (C_q), 143.71 (C_q), 128.72 (CH), 127.96 (CH), 126.61 (CH), 101.37 (CH), 60.03 (C_q), 55.76 (CH), 18.68 (CH_3), 14.14 (CH_3); *m/z* (ES) 261 ($M+H^+$, 24%), 283 ($M+Na^+$, 100); *m/z* found [$M+H^+$] 261.1230. $C_{14}H_{17}N_2O_3$ requires 261.1234; enantioselectivity determined by chiral HPLC, R_t (Chiralcel OD-H, 85:15 hexane:^{i}PrOH, 210 nm, 0.7 mL/min, 20 °C) 11.9 min (*S*)-enantiomer, 15.6 min (*R*)-enantiomer. ^{1}H NMR data is consistent with literature.[196]



Catalyst	Cat. Amount /mol%	Temp.	Time /h	Yield /%	ee /%
TMSCl + NaI*	80	RT	0.5	80	-
254.HCl	10	0 °C	144	0	-
254.HCl	10	RT	144	44	7
331.HCl	10	RT	72	66	18

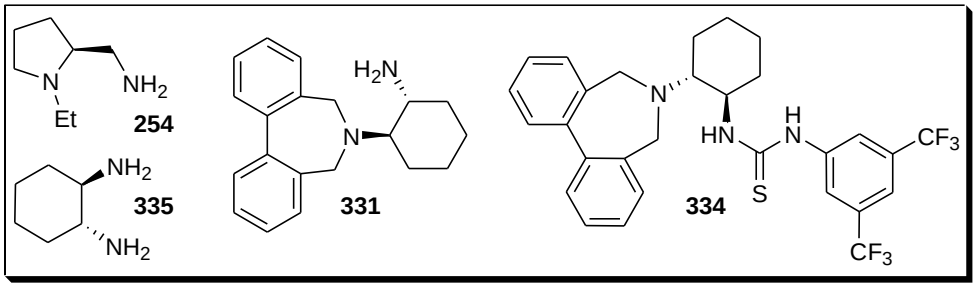
* = Solvent was MeCN

General procedure for synthesis of 4-methyl-4-nitro-1,3-diphenylpentan-1-one 322 [198]



114 **322**

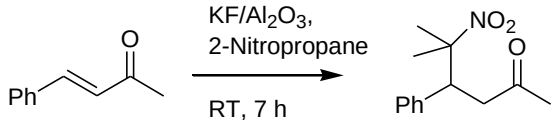
2-Nitropropane (0.20 mL, 2.22 mmol, 3.3 eq.) was added to a solution of (*E*)-chalcone (0.14 g, 0.67 mmol, 1 eq.) and a catalyst (0.13 mmol, 0.2 eq.) in CH_2Cl_2 (1 mL) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated and purified by column chromatography (petroleum ether:EtOAc 4:1) to give the product as a colourless solid. R_f (petroleum ether:EtOAc 4:1) 0.7; m.p. 150-151 °C [lit. 150 °C][197]; ν_{max} ($CHCl_3$)/cm^{-1} 3065, 3009, 2928, 1689, 1598, 1538, 1496, 1449, 1398, 1374, 1344, 1302, 1240, 1182, 1134, 1087, 1003, 963, 923, 847; δ_H (400 MHz, $CDCl_3$) 7.89 (2H, app d, *J* 7.5, Ar*H*), 7.59-7.55 (1H, m, Ar*H*), 7.48-7.44 (2H, m, Ar*H*), 7.34-7.22 (5H, m, Ar*H*), 4.18 (1H, dd, *J* 10.5, 3.5, C*H*), 3.70 (1H, dd, *J* 17.5, 10.5, CH_2), 3.31 (1H, dd, *J* 17.0, 3.5, CH_2), 1.66 (3H, s, CH_3), 1.58 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 196.8 (C_q), 137.9 (C_q), 136.7 (CH), 133.3 (CH), 129.3 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.8 (CH), 91.3 (CH), 49.0 (CH), 39.2 (CH_2), 26.2 (CH_3), 22.7 (CH_3); enantioselectivity determined by chiral HPLC, R_t (Chiralpak AD-H, 95:5 hexane:^{i}PrOH, 210 nm, 1 mL/min, 20 °C) 15.6, 19.1 min. ^{1}H NMR data consistent with literature.[198]



Catalyst	Time /h	Yield /%	ee /%
KF/Al_2O_3*	10	90	-
254.4NP	24	90	−20
331.4NP	48	26	75
331	96	5	29
331.4NP	96	29	54
334	96	0	-
335.4NP	96	15	15
335	96	0	-

* = 35% w/w

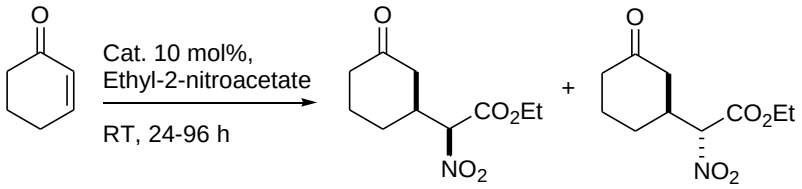
5-Methyl-5-nitro-4-phenylhexan-2-one 303 [199]



302 **303**

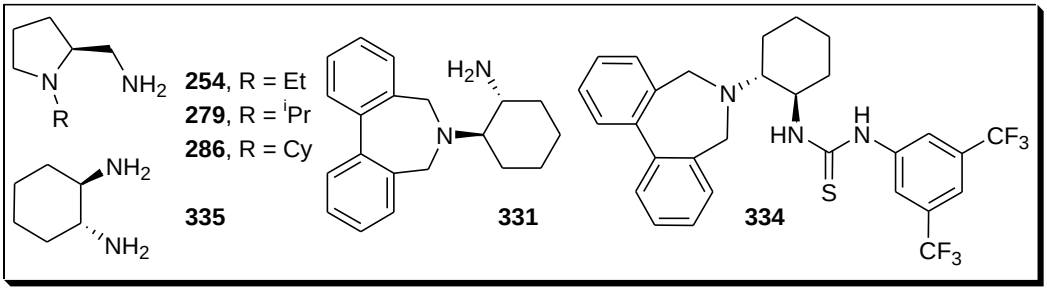
KF/Al_2O_3 (68 mg, 35% w/w) was added to a solution of 4-phenyl-3-buten-2-one (0.20 g, 0.68 mmol, 1 eq.) in 2-nitropropane (0.12 mL, 1.36 mmol, 2 eq.) and the reaction mixture was stirred at room temperature for 7 h. The reaction mixture was filtered to remove the catalyst, concentrated under reduced pressure and purified by column chromatography (petroleum ether:Et_2O 4:1) to give the product as a colourless solid (0.10 g, 63%). m.p. 50-52 °C [lit. 51-52 °C][199]; R_f (petroleum ether:Et_2O 4:1) 0.2; ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2948, 1721, 1603, 1538, 1496, 1469, 1456, 1418, 1398, 1374, 1345, 1300, 1241, 1162, 1133, 1088, 1024, 851; δ_H (400 MHz, $CDCl_3$) 7.35-7.28 (3H, m, Ar*H*), 7.23-7.20 (2H, m, Ar*H*), 3.95 (1H, dd, *J* 11.0, 3.5, C*H*), 3.11 (1H, dd, *J* 17.0, 11.0, CH_2), 2.74 (1H, dd, 17.0, 3.0, CH_2), 2.05 (3H, s, COCH_3), 1.58 (3H, s, CH_3CCH_3), 1.51 (3H, s, CH_3CCH_3); δ_C (100 MHz, $CDCl_3$) 205.1 (C_q), 137.6 (C_q), 129.2 (CH), 128.6 (CH), 127.9 (CH), 91.1 (C_q), 48.8 (CH), 44.1 (CH_2), 30.3 (CH_3), 25.9 (CH_3), 22.4 (CH_3); *m/z* (ES) 189 (M-NO_2+H^+, 31%), 211 (M-NO_2+Na^+, 26), 258 (M+Na^+, 100); *m/z* found [M+Na^+] 258.1095. $C_{13}H_{17}NO_3Na$ requires 258.1101.

General procedure for synthesis of ethyl 2-nitro-2-(3-oxocyclohexyl)acetate 307 [127a]



129 **307**

Ethyl-2-nitroacetate (0.12 mL, 1.04 mmol, 2 eq.) was added to a solution of cyclohexenone (50 mg, 0.52 mmol, 1 eq.) and a catalyst (52.0 μmol, 0.1 eq.) in a solvent (1 mL) and the reaction mixture was stirred at for 24-96 h at room temperature. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (toluene:Et_2O 9:1) to give the product a colourless oil. The product was isolated as a 1:1 mixture of interchanging diastereomers. R_f (toluene:Et_2O 9:1) 0.4; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2953, 2875, 1753, 1564, 1449, 1422, 1373, 1360, 1316, 1252, 1180, 1096, 1019, 858; δ_H (400 MHz, $CDCl_3$) 5.09 (0.5 H, d, *J* 7.0, NO_2CH), 5.04 (0.5 H, d, *J* 8.0, NO_2CH), 4.40-4.30 (2H, m, CH_2CH_3), 2.90-2.75 (1H, m, CH_2CH), 2.57-2.23 (4H, m, CH_2COCH_2), 2.22-2.12 (1H, m, $CHCH_2CH_2$), 2.11-1.96 (1H, m, $CHCH_2CH_2$), 1.82-1.53 (2H, m, $CHCH_2CH_2$), 1.35 (1.5H, t, *J* 7.0, CH_3), 1.34 (1.5H, t, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 207.7 & 207.6 (C_q, dia.), 163.0 & 162.8 (C_q, dia.), 91.2 & 91.1 (CH, dia.), 63.3 & 63.2 (CH_2, dia.), 43.2 & 43.1 (CH_2, dia.), 40.8 & 40.8 (CH_2, dia.), 39.00 & 38.9 (CH, dia.), 27.3 & 27.2 (CH_2, dia.), 24.2 & 24.0 (CH_2, dia.), 13.9 & 13.9 (CH_3, dia); *m/z* (ES) 252 ($M+Na^+$, 100%), 284 ($M+MeOH+Na^+$, 34%); *m/z* found [$M+Na^+$] 252.0840. $C_{10}H_{15}NO_5Na$ requires 252.0842; enantioselectivity determined by chiral HPLC, R_t (Chiralpak AD-H, 95:5 hexane:^{i}PrOH, 210 nm, 1 mL/min) *syn* diastereomer 34.1, 40.6 min, *anti* diastereomer 36.4, 59.7 min.

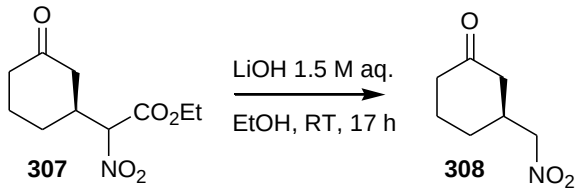


Catalyst	Solvent	Time /h	Yield /%	ee /%
KF/Al_2O_3*	None	24	99	-
254.(+)-CSA	Xylenes	48	90	30
254.(-)-CSA	Xylenes	48	97	40
(+)-CSA	Xylenes	48	0	-
(-)-CSA	Xylenes	48	0	-

254.(+)-CSA	None	48	66	3
254.(-)-CSA	None	48	90	19
(+)-CSA	None	48	0	-
(-)-CSA	None	48	0	-
279.(+)-CSA	Xylenes	48	67	44
279.(-)-CSA	Xylenes	48	67	46
286.(+)-CSA	Xylenes	24	25	41
286.(-)-CSA	Xylenes	24	25	44
331.(+)-CSA	Xylenes	48	14	60
331.(-)-CSA	Xylenes	48	17	59
331	Toluene	96	92	32
331.(-)-CSA	Toluene	96	21	58
334	Toluene	96	92	90
335.(-)-CSA	Toluene	96	89	27
335	Toluene	96	86	40

* = 35% w/w

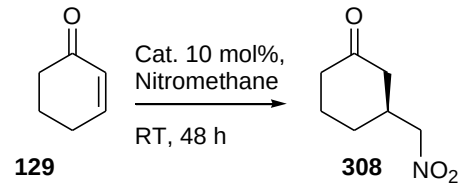
3-Nitromethyl-cyclohexanone 308 [127a]



Ethyl 2-nitro-2-(3-oxocyclohexyl)acetate (70 mg, 0.30 mmol, 1 eq.) and LiOH 1.5 M aq. (0.60 mL, 0.90 mmol, 3 eq.) in EtOH (0.6 mL) was stirred at room temperature for 17 h. The reaction mixture was neutralised by addition of HCl 1 M aq. (1 mL) to achieve a pH of 7. This was followed by addition of solid $NaHCO_3$ until no further effervescence was observed. The product was extracted by addition of $CHCl_3$ (3 x 5 mL), partitioning with brine (3 mL) if necessary. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure before purification by column chromatography (toluene:Et_2O 9:1) to give the product as a colourless oil (39 mg, 83%). R_f (toluene:Et_2O 9:1) 0.4; ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2948, 2876, 1716, 1556, 1450, 1433, 1383, 1347, 1316, 1241, 1110, 1062, 959, 868; δ_H (400 MHz, $CDCl_3$) 4.40 (1H, dd, *J* 12.0, 7.0, NO_2CH_2), 4.35 (1H, dd, *J* 12.0, 7.0, NO_2CH_2), 2.72-2.60 (1H, m, C*H*), 2.54-2.42 (2H, m, $COCH_2CH$), 2.38-2.26 (1H, m, $COCH_2CH_2$) 2.23-2.09 (2H, m, $COCH_2CH_2$), 2.04-1.96 (1H, m, $COCH_2CH_2$), 1.82-1.68 (1H, m, $CHCH_2CH_2$), 1.59-1.47 (1H, m, $CHCH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 208.3 (C_q), 80.1 (CH_2), 44.5 (CH_2), 40.9 (CH_2), 37.2 (CH), 28.2 (CH_2), 24.2 (CH_2); *m/z* (ES) 158 ($M+H^+$, 33%), 180 ($M+Na^+$, 100); *m/z* found [$M+H^+$] 158.0811. $C_7H_{12}NO_3$ requires 158.0812; enantioselectivity

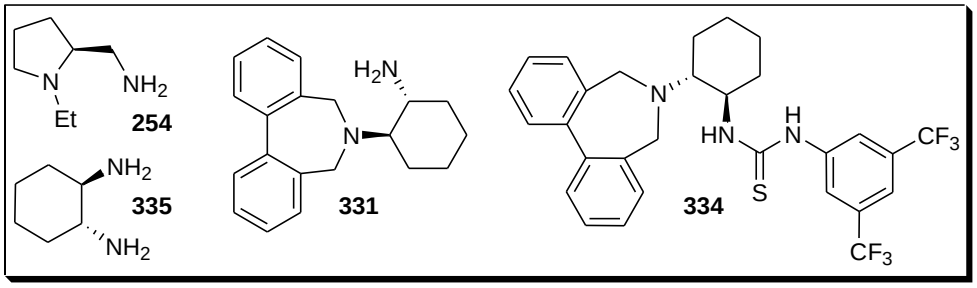
determined by chiral HPLC, R_t (Chiralpak AS, 50:50 hexane:^{i}PrOH, 210 nm, 0.7 mL/min, 20 °C) 25.3, 41.8 min.

General procedure for synthesis of 3-nitromethyl-cyclohexanone 308 [127a]



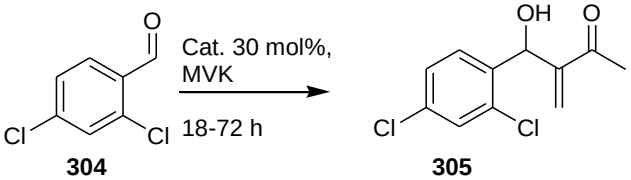
129 **308**

Nitromethane (56 µL, 1.04 mmol, 2 eq.) was added to a solution of cyclohexenone (50 mg, 0.52 mmol, 1 eq.) and a catalyst (52.0 µmol, 0.1 eq.) in a solvent (1 mL) and the reaction mixture was stirred at for 48 h at room temperature. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (toluene:Et_2O 9:1) to give the product a colourless oil. This compound was referenced to the same data as before.



Catalyst	Solvent	Yield /%	ee /%
254.(+)-CSA	Xylenes	0	-
331	Toluene	16	24
331.(-)-CSA	Toluene	< 2	-
334	Toluene	< 1	-
335	Toluene	28	40
335(-)-CSA	Toluene	51	63
334*	Neat	26	29

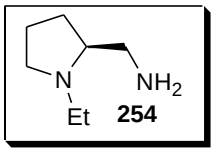
General procedure for synthesis of 4-hydroxy-4-(2,4-dichlorophenyl)-3-methylenebutan-2-one 305 [200]



304 **305**

MVK (0.48 mL, 5.50 mmol, 5 eq.) was added to a solution of 2,4-dichlorobenzaldehyde (0.20 g, 1.10 mmol, 1 eq.), a catalyst (0.33 mmol, 0.3 eq.)

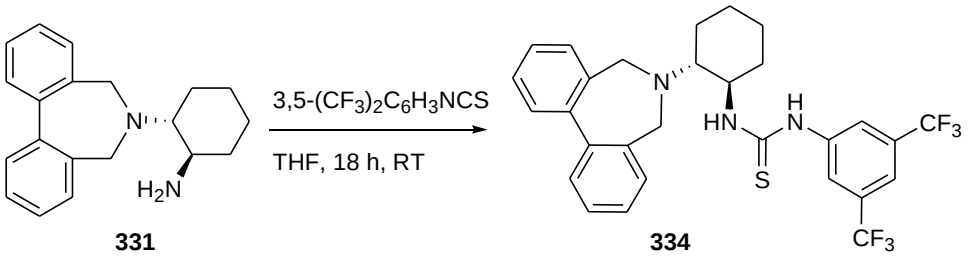
in a solvent (1 mL) and the reaction mixture was stirred for 18-72 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (petroleum ether:Et_2O 4:1) to give the product as a colourless oil. R_f (petroleum ether:Et_2O 2:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 3599, 3009, 1672, 1630, 1591, 1591, 1563, 1473, 1366, 1282, 1192, 1118, 1103, 1059, 1032, 974, 960, 869, 854, 824; δ_H (400 MHz, $CDCl_3$) 7.55 (1H, d, *J* 8.5, Ar*H*), 7.39 (1H, d, *J* 2.0, Ar*H*), 7.32 (1H, ddd, *J* 8.5, 2.0, 0.5, Ar*H*), 6.20 (1H, s, CH_2), 5.94 (1H, d, *J* 4.0, C*H*), 5.69 (1H, d, *J* 1.0, CH_2), 3.50 (1H, d, *J* 4.5, O*H*), 2.42 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 200.7 (C_q), 148.1 (C_q), 137.2 (C_q), 134.0 (C_q), 133.2 (C_q), 129.2 (CH), 129.2 (CH), 127.7 (CH_2), 127.4 (CH), 68.8 (CH), 26.3 (CH_3); *m/z* (ES) 267 ($M+H^+$, 100%), 269 ($M+Na^+$, 65); *m/z* found [$M+Na^+$] 266.9948. $C_{11}H_{10}O_2Cl_2Na$ requires 266.9950; enantioselectivity determined by chiral HPLC, R_t (Chiralpak AD-H, 95:5 hexane:^{i}PrOH, 210 nm, 0.8 mL/min) 15.2, 16.5 min. ^1H and ^{13}C NMR data are consistent with literature.[200]



254

Catalyst	Time /h	Solvent	Temp. /°C	Yield /%	ee /%
PPh_3 + 4NP	18	THF	RT	46	-
254	72	EtOH	0	5	11

(1'*R*,2'*R*)-6-(2'-(3'',5''-Bis(trifluoromethyl)phenylthiourea)cyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine 334

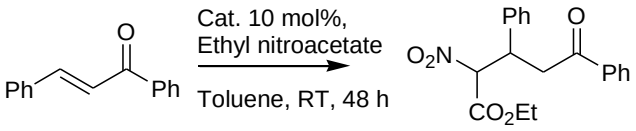


331 **334**

3,5-Bis(trifluoromethyl)phenyl isothiocyanate (0.12 g, 0.44 mmol, 1 eq.) was added to a solution of (1'*R*,2'*R*)-6-(2'-aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (0.13 g, 0.44 mmol, 1 eq.) in dry THF (5 mL) and the reaction mixture was stirred at room temperature for 18 h under an inert atmosphere of argon. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc 4:1 to remove impurities, followed by petroleum ether: EtOAc 1:1) to give the product as an off-white solid (0.18 g, 72%). m.p. 109-112 °C; $[\alpha]_D^{22}$ 52.7 (*c* 0.7 in $CHCl_3$); R_f (petroleum

ether:EtOAc 1:1) 0.4; ν_{max} ($CHCl_3$)/cm^{-1} 3402, 3011, 2944, 2864, 1495, 1450, 1384, 1278, 1181, 1141, 1108, 989, 888; δ_H (400 MHz, d^6-DMSO) 10.06 (1H, s, ArN*H*), 8.35-8.30 (1H, m, CHN*H*), 8.16 (2H, s, Ar*H*), 7.68 (1H, s, Ar*H*), 7.47 (4H, app t, *J* 8.0, Ar*H*), 7.42 (2H, td, *J* 7.5, 1.5, Ar*H*), 7.34 (2H, td, *J* 7.5, 1.5, Ar*H*), 4.48 (1H, br s, NHC*H*), 3.65 (2H, d, *J* 12.0, NCH_2), 3.48 (2H, d, *J* 12.0, NCH_2), 2.97 (1H, dd, 10.0, 10.0, NC*H*), 2.20-2.10 (1H, m, NHCHCH_2), 1.90 (1H, m, NHCHCH_2), 1.75-1.60 (2H, m, NCHCH_2), 1.42 (1H, m, NHCHCH$_2$CH_2), 1.27 (3H, m, NHCHCH$_2$CH_2CH_2); δ_c (100 MHz, d^6-DMSO) 179.5 (C_q), 142.3 (C_q), 140.8 (C_q), 136.8 (C_q), 130.8 (q, *J* 33.0, *C*CF_3), 130.1 (CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 123.7 (q, *J* 273.0, CF_3), 122.3 (CH), 116.4-116.1 (m, CH), 79.7 (C_q), 68.3 (CH), 55.9 (CH), 51.7-51.6 (m, CH_2), 32.3 (CH_2), 27.1 (CH_2), 25.5 (CH_2), 25.0 (CH_2); δ_F (376 MHz, d^6-DMSO) −61.6 (s); *m/z* (ES) 546 ($M+H^+$, 33%); *m/z* found [$M+H^+$] 564.1897. $C_{29}H_{28}F_6N_3S$ requires 564.1903.

Ethyl 4-nitro-2-oxo-1,3-diphenyl-pentanoate 339 [55a]

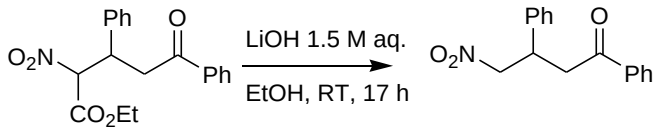


114 **339**

Ethyl nitroacetate (0.17 mL, 1.56 mmol, 3 eq.) was added to a solution of (*E*)-chalcone (0.14 g, 0.52 mmol, 1 eq.) and (1'*R*,2'*R*)-6-(2'-(3'',5''-bis(trifluoromethyl)phenylthiourea)cyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (29 mg, 52.0 μmol, 0.1 eq.) in toluene (1 mL) and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated under reduced pressure to give a crude residue. Impurities, starting material and the catalyst were removed by column chromatography (petroleum ether:EtOAc 4:1), though ethyl nitroacetate could not be removed. The product-ethyl nitroacetate mixture was isolated as a yellow oil (0.20 g, 100%). R_f (petroleum ether:EtOAc 4:1) 0.4; δ_H (400 MHz, $CDCl_3$) 7.93-7.89 (2H, m, Ar*H*), 7.61-7.54 (1H, m, Ar*H*), 7.49-7.43 (2H, m, Ar*H*), 7.37-7.22 (5H, m, Ar*H*), 5.63 (0.5H, d, *J* 10.0, NO_2C*H*), 5.56 (0.5H, d, *J* 8.5, NO_2C*H*), 5.18 (s, imp. $CH_3CH_2O_2CCH_2NO_2$), 4.57-4.46 (1H, m, PhC*H*), 4.34 (q, imp. $CH_3CH_2O_2CCH_2NO_2$), 4.38-4.15 (1H, m, C$H_2$$CH_3$), 4.13-4.03 (1H, m, C$H_2$$CH_3$), 3.74 (0.5H, dd, *J* 17.5, 9.0, COCH_2), 3.65 (0.5H, dd, *J* 18.0, 6.0, COCH_2), 3.53 (0.5H, dd, *J* 17.5, 7.5, COCH_2), 3.51 (0.5H, dd, *J* 17.5, 4.0, COCH_2), 1.34 (t, imp. C$H_3$$CH_2O_2CCH_2NO_2$), 1.25 (1.5H, t, 7.0, C$H_3$), 1.08 (1.5H, t, 7.0, C$H_3$); δ_C (100 MHz, $CDCl_3$) 196.4 & 196.3 (C_q, dia), 163.7 & 163.3 (C_q, dia), 161.9 (C_q, imp), 138.1 & 137.0 (C_q, dia), 136.4 (C_q, dia), 133.5 (CH, dia), 128.9 (CH, dia), 128.7 (CH, dia), 128.5 & 128.2 (CH, dia), 128.0 (CH, dia), 91.6 & 91.5 (CH, dia), 76.4 (CH_2, imp.), 63.3 (CH_2, imp), 63.3 & 63.0 (CH_2, dia), 41.9 & 41.5 (CH, dia),

40.8 & 40.4 (CH_2, dia), 13.9 (CH_3, imp), 13.7 & 13.6 (CH_3, dia); *m/z* (ES) 364 ($M+Na^+$, 100); *m/z* found [$M+Na^+$] 364.1159. $C_{19}H_{19}NO_5Na$ requires 364.1155.

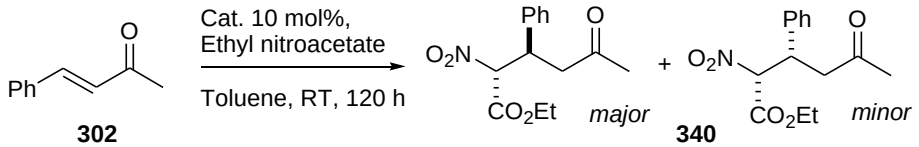
4-Nitro-1,3-diphenylbutan-1-one 342 [201]



339 **342**

Ethyl 4-nitro-2-oxo-1,3-diphenyl-pentanoate (contaminated with ethyl nitroacetate) (0.20 g, 1.00 mmol, 1 eq.) and LiOH 1.5 M aq. (2.00 mL, 3.00 mmol, 3 eq.) in EtOH (2 mL) was stirred at room temperature for 17 h. The reaction mixture was neutralised by addition of HCl 1 M aq. (1 mL) to achieve a pH of 7. This was followed by addition of solid $NaHCO_3$ until no further effervescence was observed. The product was extracted by addition of $CHCl_3$ (3 x 5 mL), partitioning with brine (3 mL) if necessary. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure before purification by column chromatography (petroleum ether:EtOAc 4:1) to give the product as a colourless solid (38 mg, 14%, 84% ee). m.p. 92-94 °C [lit. 95-97 °C]; R_f (petroleum ether:EtOAc 4:1) 0.5; ν_{max} ($CHCl_3$)/cm^{-1} 3067, 3011, 2920, 1966, 1813, 1687, 1598, 1581, 1557, 1491, 1450, 1433, 1412, 1378, 1272, 1242, 1187, 1079, 1029, 1002, 910, 877; δ_H (400 MHz, $CDCl_3$) 7.95 (2H, app d, *J* 8.0, Ar*H*), 7.64-7.58 (1H, m, Ar*H*), 7.52-7.46 (2H, m, Ar*H*), 7.40-7.27 (5H, m, Ar*H*), 4.87 (1H, dd, *J* 12.5, 7.0, NO_2CH_2), 4.72 (1H, dd, *J* 12.5, 7.0, NO_2CH_2), 4.27 (1H, dddd, *J* 7.0, 7.0, 7.0, 7.0, PhC*H*), 3.52 (1H, dd, *J* 17.5, 7.0, $COCH_2$), 3.46 (1H, dd, *J* 17.5, 7.5, $COCH_2$); δ_C (100 MHz, $CDCl_3$) 196.9 (C_q), 139.2 (C_q), 136.4 (C_q), 133.6 (CH), 129.1 (CH), 128.8 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 79.6 (CH_2), 41.6 (CH_2), 39.3 (CH); *m/z* (ES) 223 ($M-NO_2^+$, 13%), 292 ($M+Na^+$, 100); *m/z* found [$M+Na^+$] 292.0939. $C_{16}H_{15}NO_3Na$ requires 292.0950. ^{13}C NMR data is consistent with literature.[201]

Ethyl 2-nitro-5-oxo-3-phenylhexanoate 340 [131]

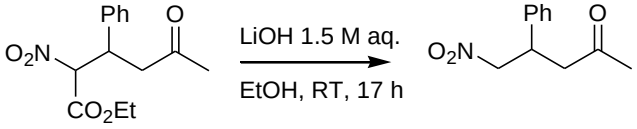


302 **340**

Ethyl nitroacetate (0.17 mL, 1.56 mmol, 3 eq.) was added to a solution of 4-phenyl-3-buten-2-one (76 mg, 0.52 mmol, 1 eq.) and (1'*R*,2'*R*)-6-(2'-(3'',5''-bis(trifluoromethyl)phenylthiourea)cyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (29 mg, 52.0 µmol, 0.1 eq.) in toluene (1 mL) and the reaction mixture was stirred at room temperature for 120 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc

4:1) to give the product as a yellow oil (56 mg, 39%). R_f (petroleum ether:EtOAc 4:1) 0.4; ν_{max} ($CHCl_3$)/cm^{-1} 2987, 2941, 2909, 1750, 1722, 1603, 1564, 1496, 1455, 1361, 1301, 1278, 1242, 1185, 1163, 1097, 1024, 910, 858; *Major diastereomer* δ_H (400 MHz, $CDCl_3$) 7.37-7.25 (5H, m, Ar*H*), 5.50 (1H, d, *J* 9.5, NO_2CH), 4.34-4.24 (2H, m, CH_2CH_3), 4.15-4.03 (1H, m, PhC*H*), 3.09 (1H, dd, *J* 17.5, 6.5, $COCH_2$), 3.00 (1H, d, *J* 17.5, $COCH_2$), 2.10 (3H, s, $COCH_3$), 1.32 (3H, t, *J* 7.0, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 204.9 (C_q), 163.6 (C_q), 137.9 (C_q), 129.0 (CH), 128.4 (CH), 128.1 (CH), 91.2 (CH), 63.3 (CH_2), 45.5 (CH_2), 41.3 (CH), 30.3 (CH_3), 13.8 (CH_3); *Minor diastereomer* δ_H (400 MHz, $CDCl_3$) 7.37-7.25 (5H, m, Ar*H*), 5.44 (1H, d, *J* 9.0, NO_2CH), 4.34-4.24 (2H, m, CH_2CH_3), 4.15-4.03 (1H, m, PhC*H*), 3.14 (1H, dd, *J* 17.5, 9.0, $COCH_2$), 2.98 (1H, dd, *J* 17.5, 2.5, $COCH_2$), 2.10 (3H, s, $COCH_3$), 1.10 (3H, t, *J* 7.0, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 204.8 (C_q), 163.1 (C_q), 136.9 (C_q), 129.0 (CH), 128.2 (CH), 128.1 (CH), 91.3 (CH), 63.0 (CH_2), 45.2 (CH_2), 41.6 (CH), 30.4 (CH_3), 13.6 (CH_3); *m/z* (ES) 302 ($M+Na^+$, 100); *m/z* found [$M+Na^+$] 302.0997. $C_{14}H_{17}NO_5Na$ requires 302.0999.

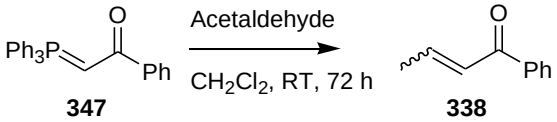
5-Nitro-4-phenylpentan-2-one 343 [201]



340 **343**

Ethyl 2-nitro-5-oxo-3-phenylhexanoate (56 mg, 0.20 mmol, 1 eq.) and LiOH 1.5 M aq. (1.00 mL, 1.50 mmol, 7.5 eq.) in EtOH (1 mL) were stirred at room temperature for 17 h. The reaction mixture was neutralised by addition of HCl 1 M aq. (1 mL) to achieve a pH of 7. This was followed by addition of solid $NaHCO_3$ until no further effervescence was observed. The product was extracted by addition of $CHCl_3$ (3 x 5 mL), partitioning with brine (3 mL) if necessary. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and purified by column chromatography (petroleum ether:EtOAc 4:1) to give the product as a colourless solid (23 mg, 55%, 70% ee). m.p. 119-120 °C; R_f (petroleum ether:EtOAc 4:1) 0.3; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2922, 2360, 1719, 1555, 1496, 1455, 1433, 1378, 1163, 1081, 1023, 912; δ_H (400 MHz, $CDCl_3$) 7.39-7.33 (2H, m, Ar*H*), 7.33-7.27 (1H, m, Ar*H*), 7.27-7.22 (2H, m, Ar*H*), 4.73 (1H, dd, *J* 12.5, 7.0, NO_2CH_2), 4.63 (1H, dd, 12.5, 7.0, NO_2CH_2), 4.04 (1H, dddd, *J* 7.0, 7.0, 7.0, 7.0, PhC*H*), 2.95 (2H, d, *J* 7.0, $COCH_2$), 2.15 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 205.4 (C_q), 138.8 (C_q), 129.1 (CH), 127.9 (CH), 127.4 (CH), 79.5 (CH_2), 46.2 (CH_2), 39.1 (CH), 30.4 (CH_2); *m/z* (ES) 161 ($M-NO_2^+$, 11%), 230 ($M+Na^+$, 100); *m/z* found [$M+Na^+$] 230.0791. $C_{11}H_{13}NO_3Na$ requires 230.0793.

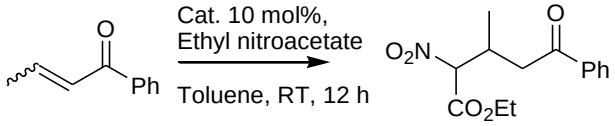
(*E* and *Z*)-1-Phenyl-3-buten-2-one 338 [202]



347 **338**

Acetaldehyde (0.59 mL, 10.6 mmol, 2 eq.) was added to a solution of benzoylmethylenetriphenylphosphorane (2.00 g, 5.30 mmol, 1 eq.) in CH_2Cl_2 (20 mL) and the reaction mixture was stirred for 72 h at room temperature under an inert atmosphere of argon. The reaction mixture was concentrated under reduced pressure to give a crude solid which was then triturated in petroleum ether (25 mL) and filtered to remove triphenylphosphine oxide (~1.4 g). The solution was concentrated and purified by column chromatography (petroleum ether:EtOAc 9:1) to give the product as a mixture of isomers (*trans:cis* 95:5) as a colourless oil (0.52 g, 67%). R_f (petroleum ether 9:1) 0.6; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2943, 2916, 2851, 1668, 1650, 1625, 1599, 1579, 1448, 1376, 1331, 1298, 1242, 1179, 1039, 1024, 1001, 965, 910, 833; *Trans isomer*: δ_H (400 MHz, $CDCl_3$) 8.01-7.92 (2H, m, Ar*H*), 7.60-7.53 (1H, m, Ar*H*), 7.51-7.45 (2H, m, Ar*H*), 7.10 (1H, dq, *J* 15.5, 7.0, CH_3CH), 6.93 (1H, dq, *J* 15.5, 1.5, COC*H*), 2.02 (3H, dd, *J* 7.0, 1.5, CH_3); δ_C (100 MHz, $CDCl_3$) 190.8 (C_q), 145.0 (CH), 138.0 (C_q), 132.6 (CH), 128.5 (CH), 127.5 (CH), 18.6 (CH); *Cis isomer*: δ_H (400 MHz, $CDCl_3$) 8.01-7.92 (2H, m, Ar*H*), 7.60-7.53 (1H, m, Ar*H*), 7.51-7.45 (2H, m, Ar*H*), 6.86 (1H, dq, *J* 11.5, 1.5, COC*H*), 6.46 (1H, dq, *J* 11.5, 7.0, CH_3CH), 2.17 (3H, dd, *J* 7.5, 2.0, CH_3); δ_C (100 MHz, $CDCl_3$) 192.2 (C_q), 143.9 (CH), 138.6 (C_q), 132.7 (CH), 128.6 (CH), 128.3 (CH), 125.3 (CH), 16.2 (CH). ^1H and ^{13}C NMR data are consistent with literature.[202]

Ethyl 2-nitro-5-oxo-1-phenylhexanoate 341

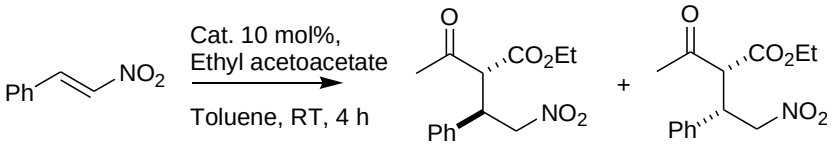


338 **341**

Ethyl nitroacetate (0.17 mL, 1.56 mmol, 3 eq.) was added to a solution of (*E* and *Z*)-1-phenyl-3-buten-2-one (*trans:cis* 95:5) (76 mg, 0.52 mmol, 1 eq.) and (1'*R*,2'*R*)-6-(2'-(3'',5''-bis(trifluoromethyl)phenylthiourea)cyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (29 mg, 52.0 µmol, 0.1 eq.) in toluene (1 mL) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. Impurities, starting material and the catalyst were removed by column chromatography (petroleum ether:EtOAc 4:1), though ethyl nitroacetate could not be removed. The product-ethyl nitroacetate mixture was isolated as 1:1 mixture of diastereomers as a colourless oil (0.15 g, 100%). R_f (petroleum ether:EtOAc 4:1) 0.4; δ_H (400 MHz, $CDCl_3$) 7.99-7.21 (2H, m, Ar*H*), 7.59 (1H, app t., 7.5, Ar*H*), 7.48 (2H, app t., *J* 7.5,

Ar*H*), 5.40 (0.5H, d, *J* 6.0, NO_2CH), 5.30 (0.5H, d, *J* 5.5, NO_2CH), 5.18 (s, imp), 4.36-4.25 (2H, m, CH_2CH_3), 4.32 (q, *J* 7.0, imp) 3.32-3.19 (2H, m, $COCH_2$), 3.15-3.01 (1H, m, CH_3CH), 1.32 (t, *J* 7.0, imp), 1.29 (3H, app t, *J* 7.0, CH_2CH_3), 1.19 (3H, app t, *J* 6.5, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 197.5 (C_q, dia.), 163.9 (C_q, dia.), 161.9 (C_q, imp.), 136.6 & 136.5 (C_q, dia), 133.5 (CH, dia.), 128.7 (CH, dia.), 128.0 (CH, dia.), 91.2 & 91.0 (CH, dia.), 76.3 (CH_2, imp.), 63.2 (CH_2, imp.), 63.2 & 62.9 (CH_2, dia.), 40.9 & 40.8 (CH_2, dia.), 30.6 (CH, dia.), 16.3 & 16.2 (CH_3, dia.), 13.9 (CH_3, imp.), 13.9 & 13.8 (CH_3, dia); *m/z* (ES) 302 ($M+Na^+$, 100); *m/z* found [$M+Na^+$] 302.0999. $C_{14}H_{17}NO_5Na$ requires 302.0990.

Ethyl-2-acetyl-4-nitro-3-phenylbutanoate 331 [203]



124 *major* **331** *minor*

Ethyl acetoacetate (0.19 mL, 1.56 mmol, 3 eq.) was added to a solution of (*E*)-nitrostyrene (78 mg, 0.52 mmol, 1 eq.) and (1'*R*,2'*R*)-6-(2'-(3'',5''-bis(trifluoromethyl)phenylthiourea)cyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (29 mg, 52.0 µmol, 0.1 eq.) in toluene (1 mL) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated and purified by column chromatography (petroleum ether:EtOAc 9:1) to give the product as a colourless oil (0.15 g, 100%). R_f (petroleum ether:EtOAc 9:1) 0.2; ν_{max} ($CHCl_3$)/cm^{-1} 2986, 1742, 1718, 1603, 1557, 1497, 1456, 1433, 1378, 1247, 1180, 1147, 1096, 1019, 910, 858; *major diastereomer* δ_H (400 MHz, $CDCl_3$) 7.37-7.27 (3H, m, Ar*H*), 7.23 (2H, v br d, *J* 7.5, Ar*H*), 4.78 (2H, app d, *J* 6.0, NO_2CH_2), 4.26-4.18 (1H, m, PhC*H*), 4.14 (1H, d, *J* 10.0, COC*H*), 3.99 (2H, q, *J* 7.0, CH_2CH_3), 2.33 (3H, s, $COCH_3$), 1.30 (3H, t, *J* 7.0, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 201.2 (C_q), 166.9 (C_q), 136.5 (C_q), 129.0 (CH), 128.3 (CH), 128.0 (CH), 77.9 (CH_2), 62.3 (CH_2), 62.0 (CH), 42.3 (CH), 30.1 (CH_3), 13.7 (CH_3); *minor diastereomer* δ_H (400 MHz, $CDCl_3$) 7.37-7.27 (3H, m, Ar*H*), 7.23 (2H, v br d, *J* 7.5, Ar*H*), 4.88 (1H, dd, *J* 13.0, 5.0, NO_2CH_2), 4.84 (1H, dd, *J* 13.0, 8.5, NO_2CH_2), 4.26 (2H, q, *J* 7.0, CH_2CH_3), 4.30-4.21 (1H, m, PhCH), 4.05 (1H, d *J* 10.0, COC*H*), 2.08 (3H, s, $COCH_3$), 1.03 (3H, t, *J* 7.0, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 200.4 (C_q), 167.6 (C_q), 136.4 (C_q), 129.2 (CH), 128.4 (CH), 127.9 (CH), 77.8 (CH_2), 62.0 (CH_2), 61.7 (CH), 42.6 (CH), 30.3 (CH_3), 14.0 (CH_3); *m/z* (ES) 302 ($M+Na^+$, 100); *m/z* found [$M+Na^+$] 302.0994. $C_{14}H_{17}NO_5Na$ requires 302.0999. ^1H and ^{13}C NMR consistent with literature.[203]

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