Novel Catalytic Asymmetric Methodologies: Biocatalysed Synthesis of *N*-Heterocyclic Systems and Enantioselective Addition of Organozirconium Reagents to Aliphatic Aldehydes

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Novel Catalytic Asymmetric Methodologies: Biocatalysed Synthesis of *N*-Heterocyclic Systems and Enantioselective Addition of Organozirconium Reagents to Aliphatic Aldehydes

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Abstract

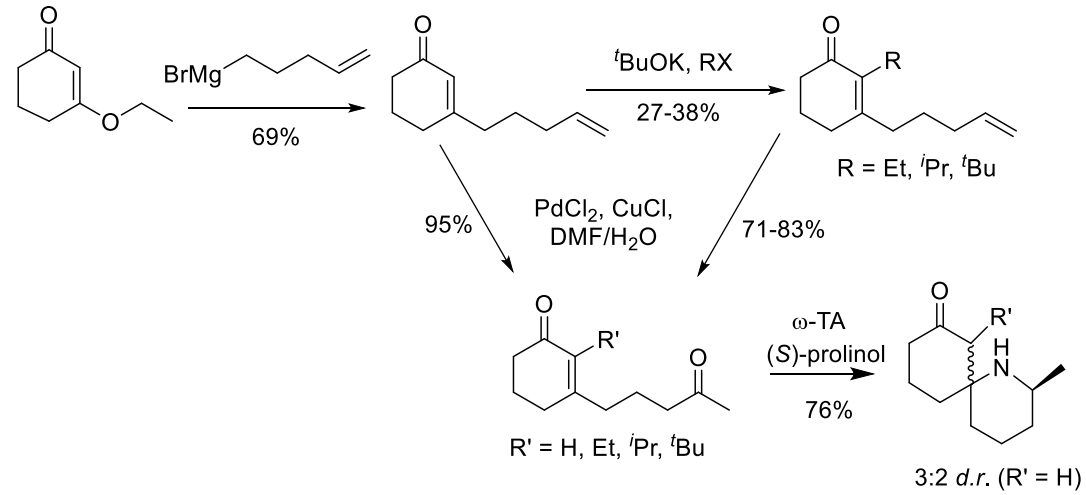
This thesis focuses on the development of new methodologies for asymmetric synthesis. Here, we will investigate two independent methodologies:

i) biocatalysed synthesis of *N*-heterocyclic systems and

ii) enantioselective C-C bond formation with organometallic reagents.

The first chapter of the thesis summarises the state of the art in the synthesis of *N*-heterocyclic systems from chiral amines. The background on asymmetric synthesis of amines *via* classical and biocatalytic methodologies, is also described here.

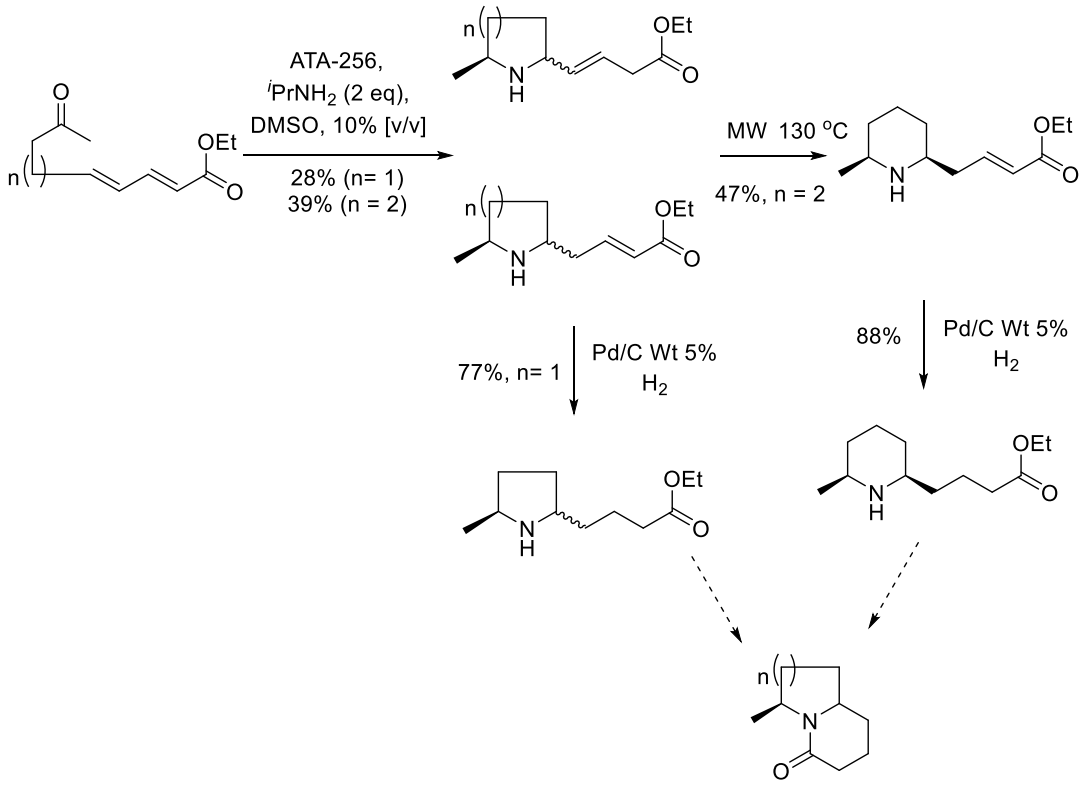
Chapter 2 - *Graphical Abstract*



The second chapter of the thesis discusses our optimisation results on the biocatalysed transaminase triggered intramolecular aza-Michael reaction (IMAMR) of a keto-cyclohexanone substrate in the presence of different organocatalysts, with the aim to improve the diastereomeric ratio and the overall efficiency of the synthesis of histrionicotoxin (HTX) derivatives. We found that the use of (*S*)-diphenyl prolinol improved the diastereoselectivity of the spontaneous IMAMR, providing the

corresponding spirocyclic HTX derivative with a modest 3:2 d.r. (*versus* the 1:1 d.r. obtained in the absence of organocatalyst). The biocatalysed IMAMR of various alkyl substituted keto-cyclohexanones in the presence of (*S*)-diphenylprolinol as organocatalysts was also attempted.

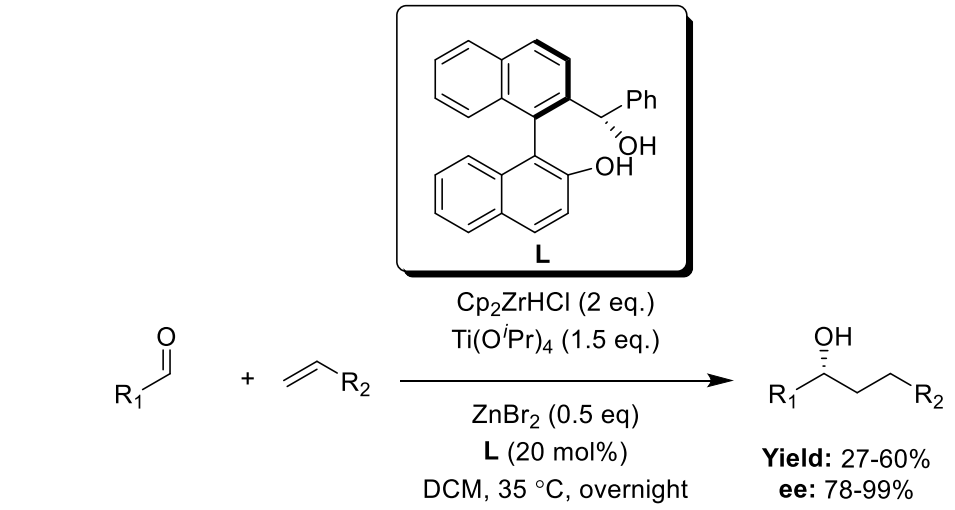
Chapter 3 - *Graphical Abstract*



The third chapter of this thesis investigates the expansion of biocatalysed IMAMR to the vinylogous aza-Michael reaction. The attempted biocatalysed transamination reaction of two different ketodienones substrates resulted in complete decomposition under the reaction conditions. However, the biocatalysed triggered vinylogous aza-Michael reaction of two different ketodieno esters proved successful, providing the corresponding 2,6-disubstituted piperidine and 2,5-disubstituted pyrrolidine as a mixture of inseparable diastereoisomers, respectively.

Subsequent epimerisation and isomerisation of the double bond, provided the *cis*-2,6-disubstituted piperidine, bearing a conjugated ester as the only diastereomer. However, in the case of the 2,5-disubstituted pyrrolidine, the tandem epimerisation-isomerisation proved unsuccessful. The hydrogenation of the double bond in the lateral ester chain, allowed for the synthesis of ethyl 4-((2*S*,6*S*)-6-methylpiperidin-2-yl)butanoate and provided a mixture of the *cis*- and *trans*- 5-methylpyrrolidin-2-yl butanoates. Subsequent cyclisation to the corresponding quinolizinone and indolizidine was attempted. In this chapter, we also describe the first attempts in the use of thioesters and nitriles as Michael acceptors for biocatalysed IMAMR.

Chapter 4 - *Graphical Abstract*



The fourth chapter of this thesis focuses on the catalytic enantioselective addition of organozirconium reagents to aliphatic aldehydes using versatile Ar-BINMOLs as ligands. The optimal catalytic procedure for the addition of 1-hexene to cyclohexanecarboxaldehyde using (R_a,*S*)-Ph-BINMOL in the presence of $Ti(O^iPr)_4$ and $ZnBr_2$ was found and the scope of the reaction was expanded to a variety of aliphatic aldehydes and functionalised nucleophiles. The reaction proceeds under mild

conditions and provides moderate yields and excellent enantioselectivities, making it an efficient procedure for the synthesis of valuable chiral aliphatic secondary alcohols.

Acknowledgements

Firstly, I would like to thank my supervisory team. A big thank you to my director of studies Dr Beatriz Maciá-Ruiz, for giving me this opportunity, for her patience and expert knowledge. Without her kindness and support, this research would not have been possible. I would also like to thank Dr Vittorio Caprio for his involvement and insightful advice with the project and thanks also to Dr Nicola Phillips.

I would like to thank the other members of the Maciá group but in particular Maria for her all of help during my first year of my PhD. A special thanks to all the people I have met during my time in the lab, but especially Mike and Nick who have been there with me every day of the project and never failed to make me smile, even on the lowest of days. I would also like to thank all the 6th and 7th floor technicians who helped me out during my time at MMU, especially Lee, John and Maira.

Finally, I would like to thank my family. My parents who have taught me the value of hard work and have always shown me endless support no matter what. I really could not have done this without them. Nico, for all the great advice, friendship and cooking. Last but not least, David. Thank you for being so understanding and for always believing in me. Here's to many more adventures together.

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$[\alpha]_D$	Optical rotation at 589 nanometers (sodium D line).
AmDHs	Amine dehydrogenase
AO	Amine oxidase
Aq.	Aqueous
Ar	Aromatic group
ARA	Asymmetric reductive amination
Cat	catalyst
CM	Cross metathesis
Conv	Conversion
DABCO	1,4-Diazabicyclo[2.2. 2]octane
DBU	1,8-Diazabicyclo[5,4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DKR	Dynamic kinetic resolution
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide

d.r.	Diasteriomeric ratio
ee	Enantiomeric excess
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
Eq.	Equivalent
EWG	Electron withdrawing group
GABA	γ-Aminobutyric acid
GC	Gas chromatography
h	Hour
Hex	Hexane
HMPA	Hexamethylphosphoramide
HMDS	Hexamethyldisilazane
HPLC	High Performance Liquid Chromatography
HTX	Histrionicotoxin
HWE	Horner-Wadsworth-Emmons
IMAMR	Intramolecular aza-Michael reaction
IPA	Isopropylamine

^{i}Pr	Isopropyl
IRED	Imine reductase
IS	Internal standard
LDA	Lithium diisopropylamide
KHDMS	Bis(trimethylsilyl) amide
MAO	Monoamine oxidase
MBA	Methylbenzylamine
Me	Methyl
mg	Milligram
MHz	Megahertz
MS	Mass spectrometry
MS	Molecular sieves
MW	Microwave
n.d.	Not determined
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PLP	Pydridoxalamine-5'-phosphate
Ph	Phenyl

$PhNTf_2$	*N*-Phenyl-bis(trifluoromethanesulfonimide)
ppm	Parts per million
psi	Pounds per square inch
RF	Retention factor
rpm	Revolutions per minute
r.t.	Room temperature
SCX	Strong cation exchange
t	Time
T	Temperature
TA	Transaminase
TBSCl	*tert*-Butyldimethylsily chloride
TFE	2,2,2,-Trifluroethanol
THF	Tetrahydrofuran
$Ti(O^iPr)$	Titanium isopropoxide
TLC	Thin layer chromatography
Tol	Toluene
t_r	Retention time
UV	Ultraviolet
IVAMR	Intramolecular Vinylogous aza-Michael reaction

NMR abbreviations:

d	doublet
dd	doublet of doublets
dt	doublet of triplets
m	multiplet
s	singlet
t	triplet

1. Introduction

1.1 Alkaloids

The alkaloid family is one of the most diverse group of compounds found in natural products, containing over 12,000 different types.[1] They often encompass nitrogen containing (hetero)cyclic systems and are secondary metabolites. Alkaloids have had a significant influence throughout organic and medicinal chemistry since they possess a wide range of pharmacological activities, including antimalarial (e.g. quinine)[2], antiasthma (e.g. ephedrine)[3], anticancer (e.g. homoharringtonine),[4] vasodilatory (e.g. vincamine)[5], analgesic (e.g. morphine)[6] and antibacterial (e.g. chelerythrine)[7] properties (Figure 1). As a result, it would be extremely beneficial to society, to attain accessible synthetic methods in the laboratory towards these naturally occurring alkaloid products.

Alkaloids often contain an aliphatic amine moiety and in most instances, the lone pair on the nitrogen enhances the solubility of the molecule, whilst the substituents increase the lipophilicity, a necessary feature to cross the blood-brain barrier.[8, 9] Amines are also really important binding groups during drug-target interactions; a plethora of aliphatic amines are widely occurring functionalities in molecules of diverse bioactivity, and their introduction is a highly important area of synthetic research.[10]

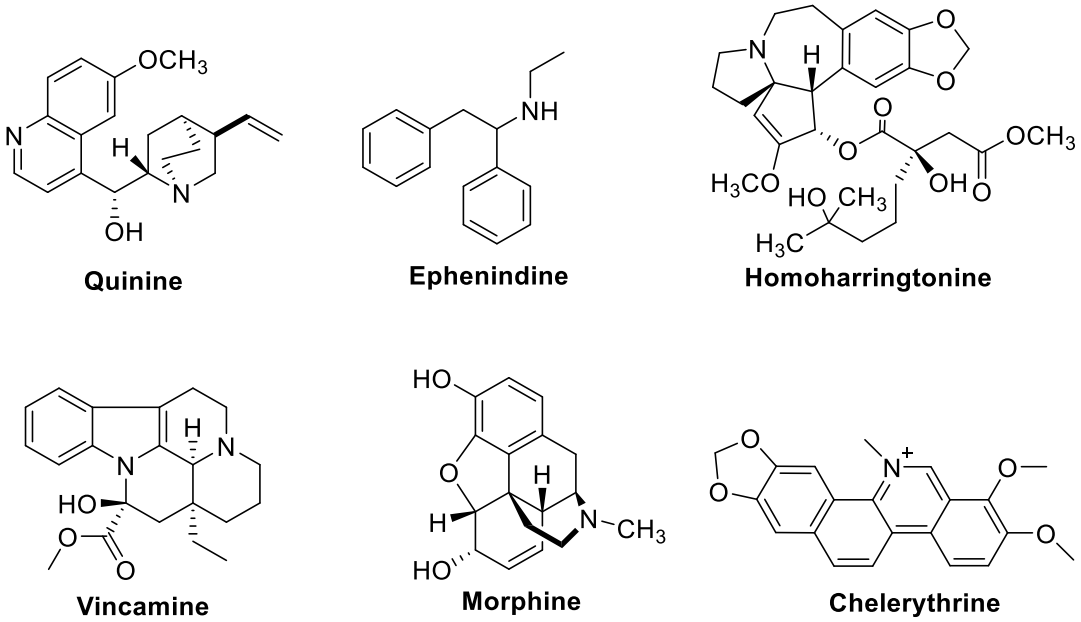


Figure 1: Structure of alkaloids with pharmacological activities.

Chiral amines are ideal precursors for these chiral *N*-heterocyclic systems. Cycloaddition, cyclisation or multicomponent condensation reactions of chiral amines are the most frequent methods used to construct *N*-heterocycles.[11] The aza-Diels Alder reaction,[12] reductive amination[13] and the intramolecular aza-versions of Michael (which will be reviewed later in section 1.4),[14] Morita-Baylis-Hillman,[15] Henry[16] and Mannich reactions[13] have been successfully employed in the synthesis of chiral *N*-heterocycles.

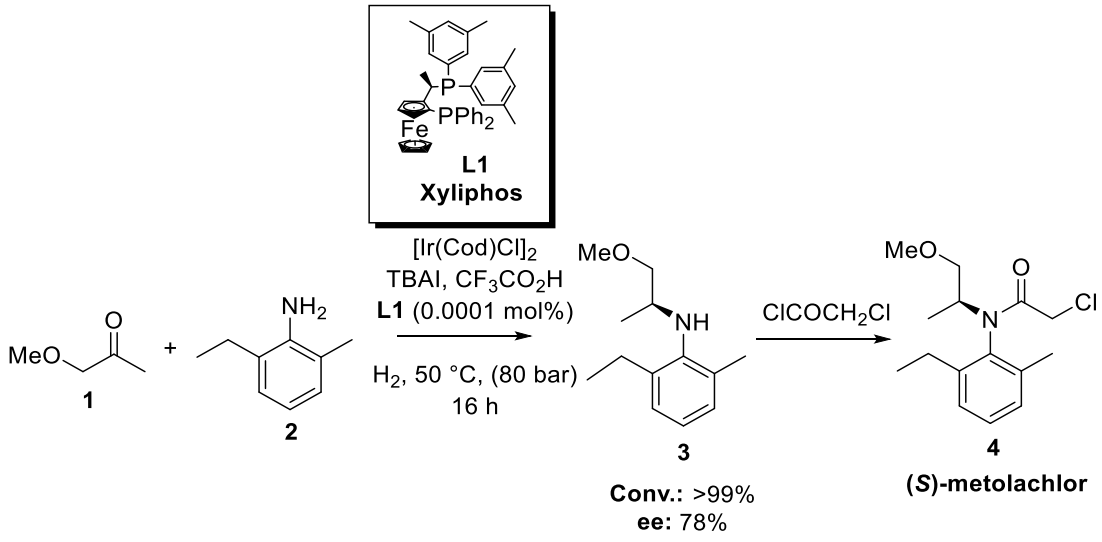
As the principal precursors of chiral *N*-heterocyclic systems, the synthesis of chiral amines has received much attention.[17] The most common methods include: nucleophilic addition to imines,[18] *N*-acetylenamide and imine reduction,[19] reductive amination,[19] nitrogen C-H insertion,[20, 21] allylic amination,[22] synthesis of propargylamines,[23] olefin hydroamination,[24, 25] organocatalytic[26] and enzymatic[27] methodologies and catalytic hydroaminoalkylation.[28]

In the next sections, we will briefly discuss the main methods to prepare chiral amines from prochiral carbonyl compounds through two methodologies: asymmetric reductive amination and biocatalysis.

1.2 Asymmetric synthesis of amines *via* reductive amination – Classical methods.

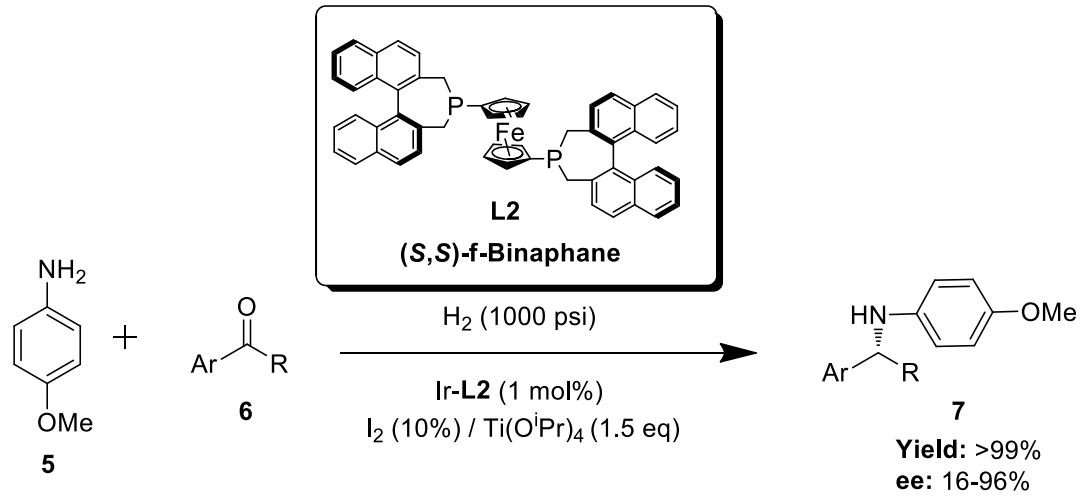
The asymmetric reductive amination (ARA) of carbonyl groups is a popular and versatile method for producing chiral amine functionality. The reaction exploits an imine formed *in-situ* from a carbonyl compound and an amine, which is then enantioselectively reduced to the desired chiral amine using a chemoselective catalyst.[29]

The first to report the enantioselective reductive amination was Blaser *et al.* during the synthesis of (*S*)-metolachlor, utilising an iridium catalyst in the presence of the chiral diphosphine ferrocene ligand **L1** (Scheme 1) in 1999.[30] The reaction proceeds with 78% ee in the presence of 0.0001 mol% of catalyst.



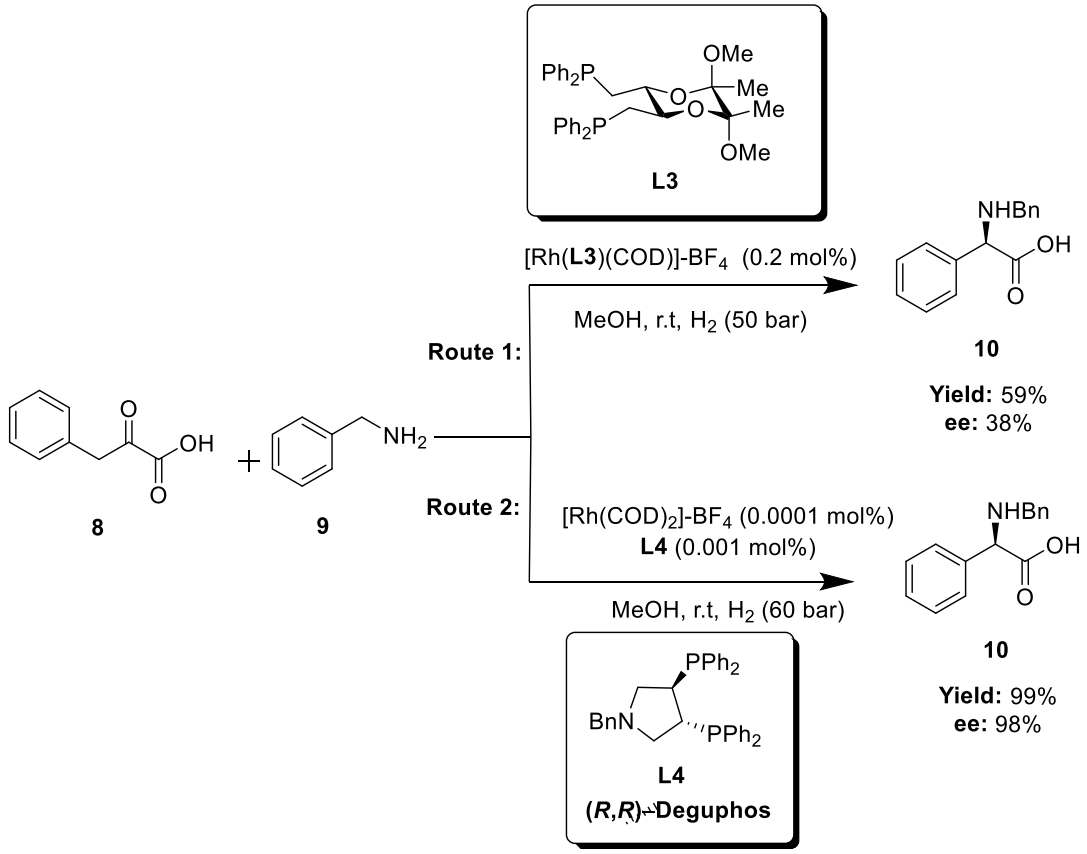
Scheme 1: Synthesis of (S)-metolachlor.

Another example of iridium-catalysed ARA was reported by Zhang and co-workers, who developed a one-pot ARA using of the (*S,S*)-f-binaphane (**L2**) as the ligand for the hydrogenation of imines formed *in situ* from aryl ketones (Scheme 2).[31] $Ti(O^iPr)_4$ and I_2 are used as additives, to accelerate the ARA by binding the Ir-f-Binaphane catalytic system. The reactions proceed with up to 96% ee.



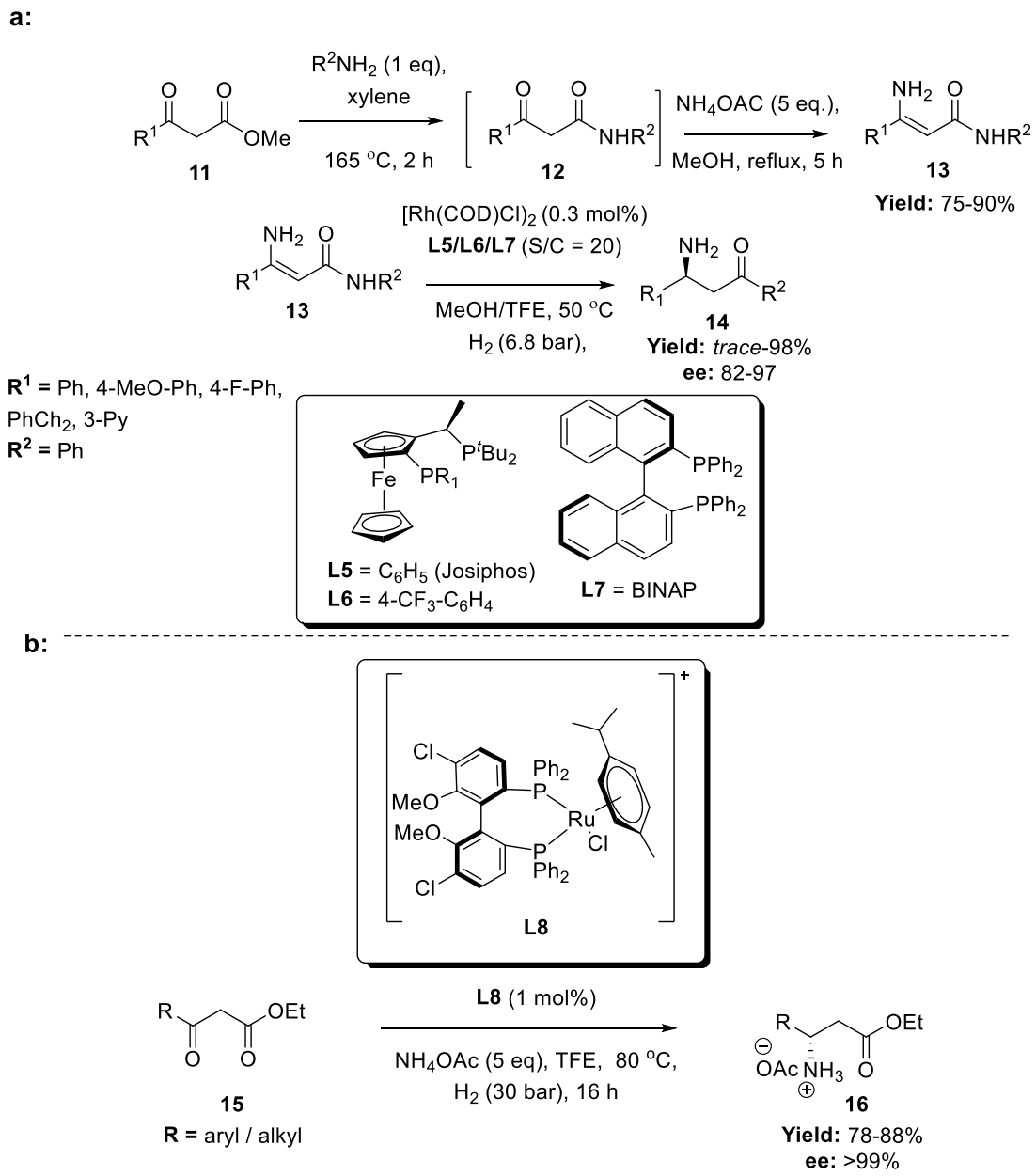
Scheme 2: Ir-Catalysed hydrogenation of imines from aryl ketones by Zhang and co-workers.

Moving on from iridium catalysis, Börner and co-workers reported the use of Rh(I) catalysts for the ARA of α-keto acids.[32] Using **L3** as ligand, (*R*)-benzylphenylalanine is obtained in 59% yield and 38% ee (Scheme 3, Route 1). Later, an extensive screening of 96 phosphorus based ligands[33] revealed that diphenylphosphino ligand Deguphos (**L4**) is a more effective catalyst and is able to produce chiral amino acids with good yield and up to 98% ee (Scheme 3, Route 2).



Scheme 3: Rh-Catalysed ARA by Börner et al.

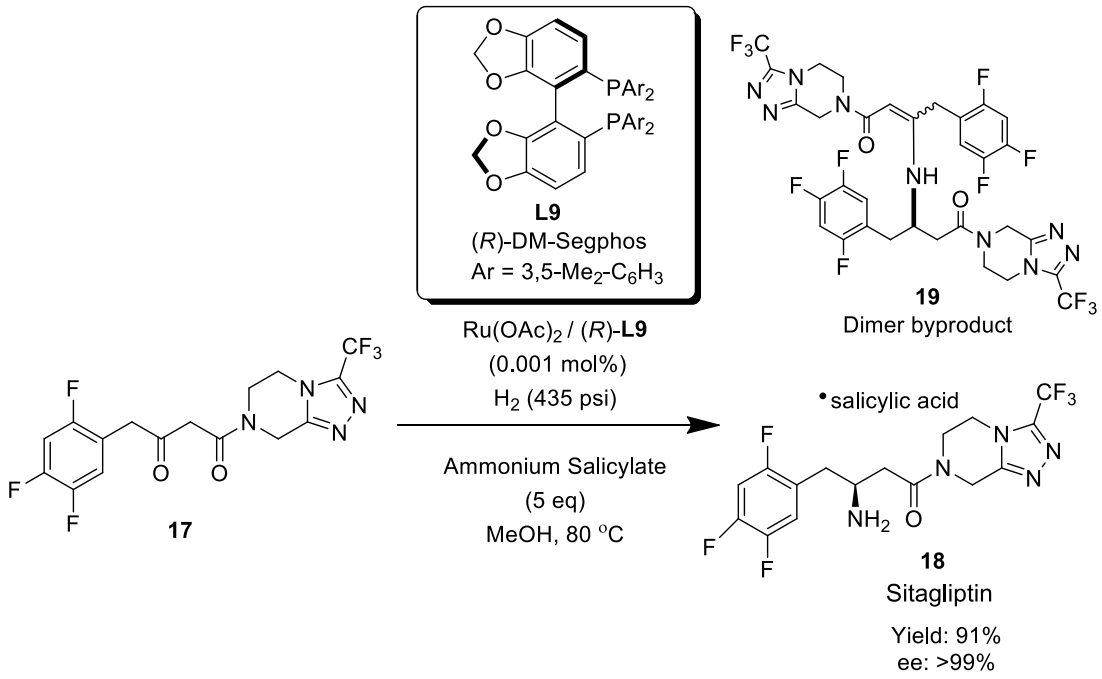
Merck[34] and Takasago,[35, 36] separately, reported the ARA of unprotected enamino esters and amides catalysed by Rh and Josiphos-type **L5** and **L6** and BINAP (**L7**) complexes, resulting in β-amino acid derivatives with high yields and enantioselectivities (Scheme 4a). This work inspired Bunlaksununusorn and co-workers to develop a one pot synthesis for chiral β–amino esters using Ru-**L8** catalyst (Scheme 4b).[37] With the use of ammonium acetate as the nitrogen donor and 2,2,2,-trifluroethanol (TFE) as a solvent, the desired amino esters are obtained in high yield and enantioselectivity.



*Scheme 4: **a:** ARA of unprotected enamino esters and amides catalysed by Rh-Josiphos-type and Ru-BINAP complexes. **b:** Bunlaksununsorn's Ru catalysed ARA synthesis of β-amino esters.*

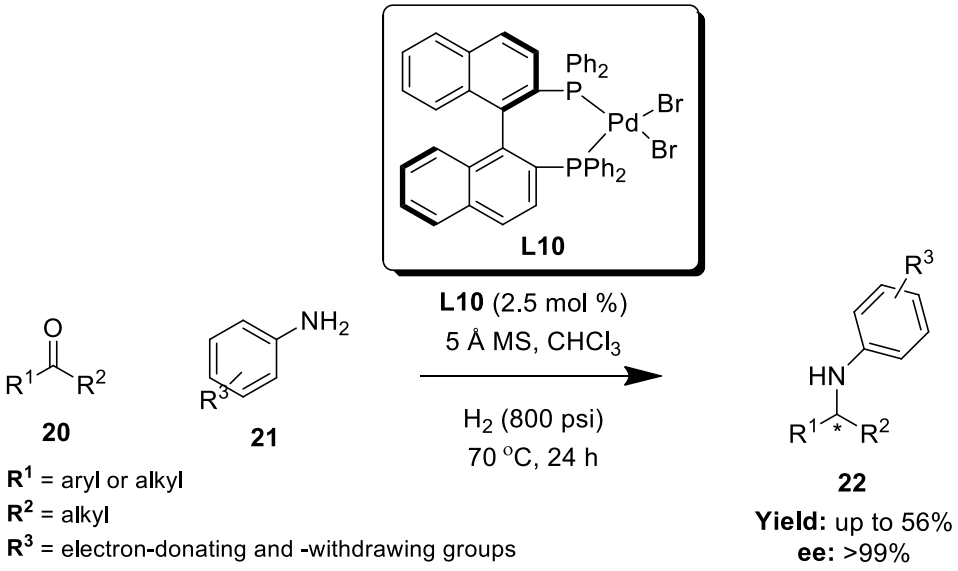
Merck later reported an ARA methodology for the synthesis of the anti-diabetic sitagliptin using the chiral Ru-**L9** catalyst and ammonium salicylate (Scheme 5).[38] The reaction provides the desired product with 91% yield and >99% *ee*. The ammonium salicylate not only pushes the equilibrium towards the desired product, but also

prevents the formation of the dimer by-product **19** (or breaks the dimer), resulting in the desired product.



Scheme 5: Merck's synthesis of Sitagliptin via Ru-Catalysed ARA.

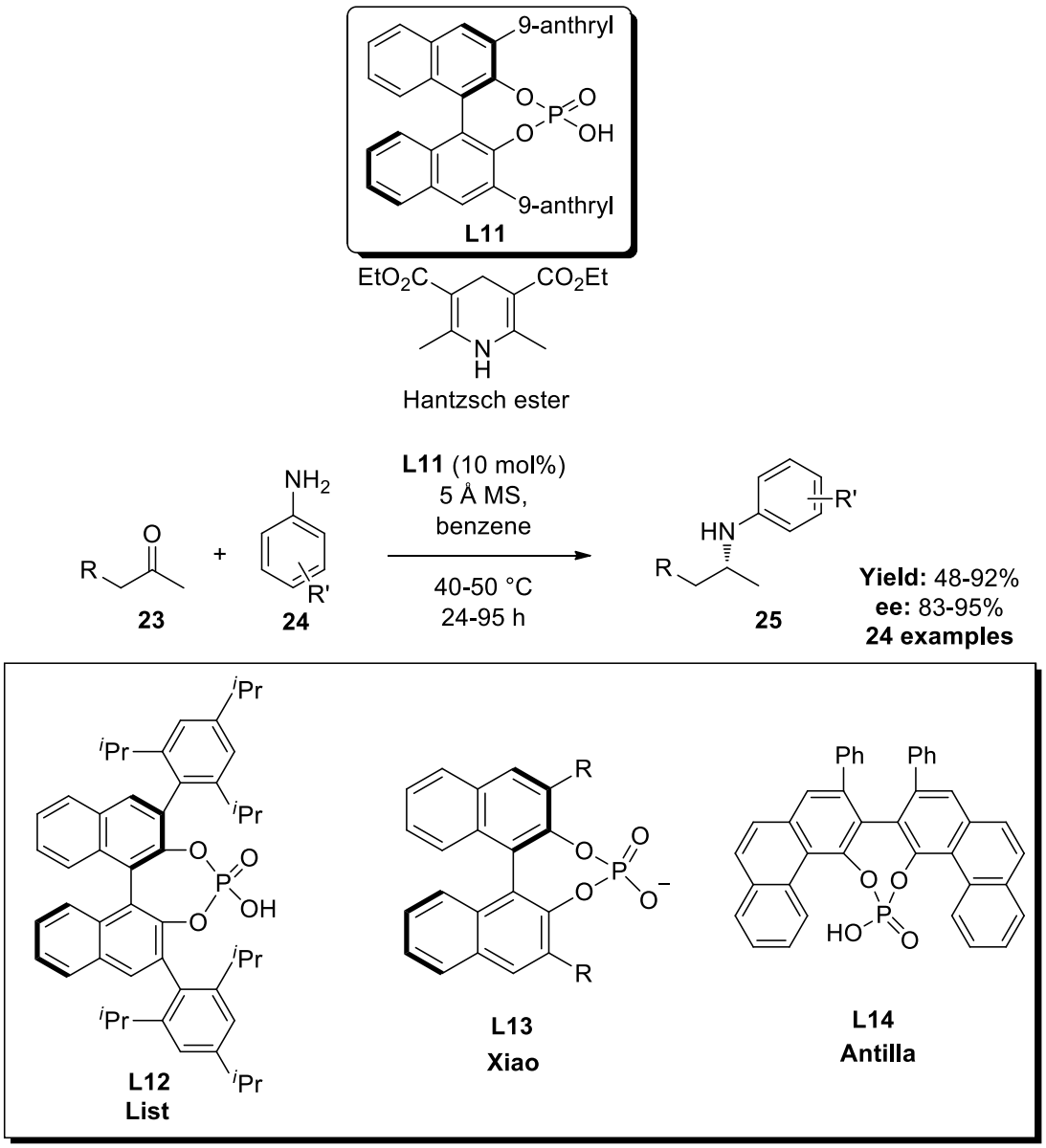
Rubio-Pérez reported in 2009 a one-pot ARA using a palladium chiral catalysts for the construction of chiral amines from various carbonyl compounds (Scheme 6).[39] The Pd-catalyst **L10** is successful with aliphatic ketones substrates, providing moderate yields and high enantioselectivities up to 99%. Unfortunately, for aromatic ketones, the palladium species fails to provide enantioselectivities higher than 43%. These results are somewhat surprising in contrast to previous ARA reports.[40-42]



Scheme 6: ARA using Pd-catalysts for the construction of chiral amines from various carbonyl compounds

So far, this chapter has focused on the use of metal catalysis for asymmetric reductive amination (ARA), however, organocatalysts are also excellent catalysts for the synthesis of chiral amines. Organocatalysts are powerful synthetic tools, easy to handle, with lower toxicity and suitable for one-pot processes. Largely, organocatalysts contain C, H, N, O and S atoms, and often provide good enantioselectivities and yields.[43, 44] The first organocatalytic ARA, reported by MacMillan *et al.* in 2005, describes the use of chiral hydrogen-bonding catalyst **L11** and Hantzsch esters for the enantioselective synthesis of primary amines from carbonyl compounds (Scheme 7).[41] The *in situ* formed imine is activated by the catalyst by either protonation by the acid or through hydrogen bonding from the OH group. The activation of the Hantzsch ester occurs *via* hydrogen bonding with the P=O group of the phosphoric acid and the NH unit on the molecule itself. Both List[45] and Xiao[46] later broadened the scope of this reaction to a metal Brønsted equivalent with the use of **L12** and **L13** (Scheme 7). Antilla *et al.*[47] expanded the battery of

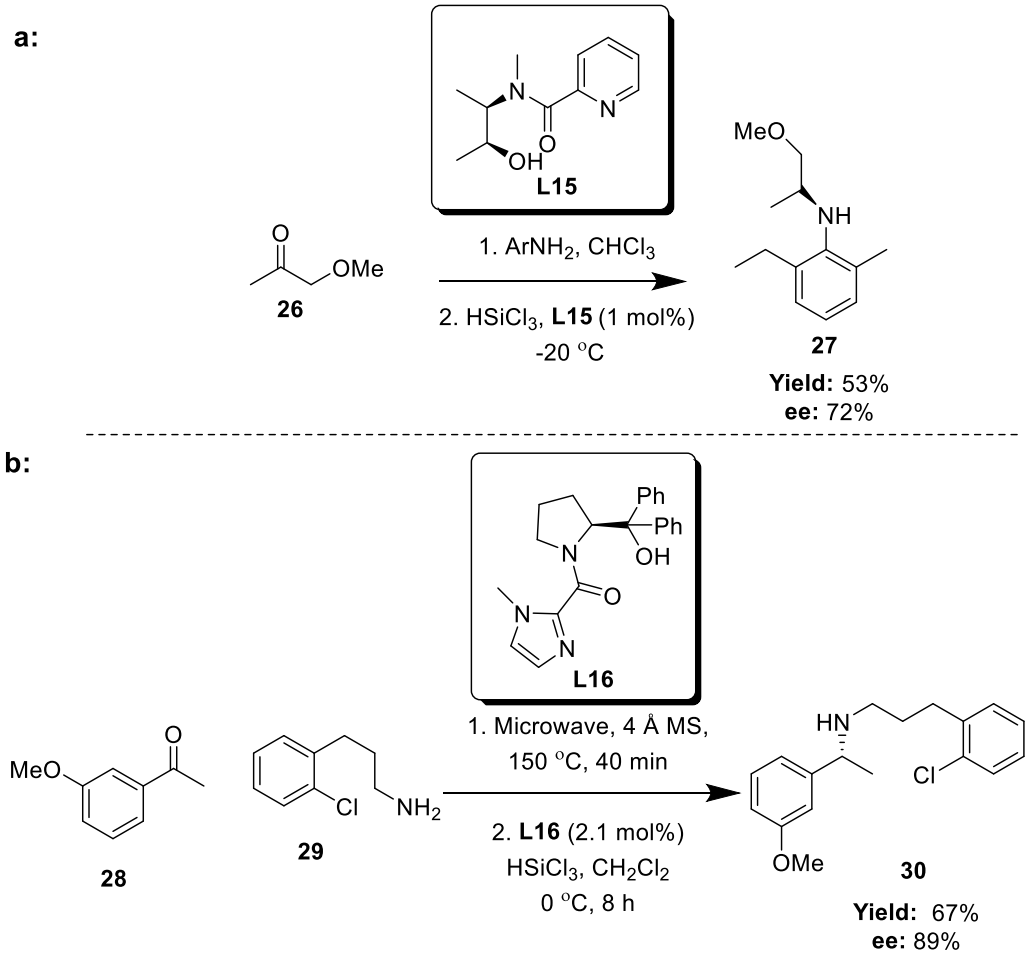
ligands by reporting the direct ARA of α-imino esters catalysed by chiral phosphoric acid **L14**.



Scheme 7: MacMillan's method for the organocatalytic ARA of ketones and other catalysts used to broaden the scope of the reaction.

Bengalia *et al.* screened various chiral Lewis bases as catalysts for the reduction of imines using tricholorosilane as reducing agent (Scheme 8a).[48] The reaction affords high yields and high enantioselectivities with **L15** as ligand for a variety of substrates. It is worth noting that the process is applied to produce a key intermediate in the

synthesis of (*S*)-metachlor in 53% yield and 72% ee, very similar to the commercial procedure by *Blaser et al*.[30] Jones and co-workers have reported the imidazole-based organocatalysed ARA of ketones, using **L16** as catalyst (Scheme 8b).[49] This microwave assisted method proceeds with good enantioselectivity, but moderate/low yields due to slow formation of the imine intermediate. However, the reaction has been successfully applied to the synthesis of the drug calciminetric (+)-NPS-R-568 with 67% yield and 89% ee.



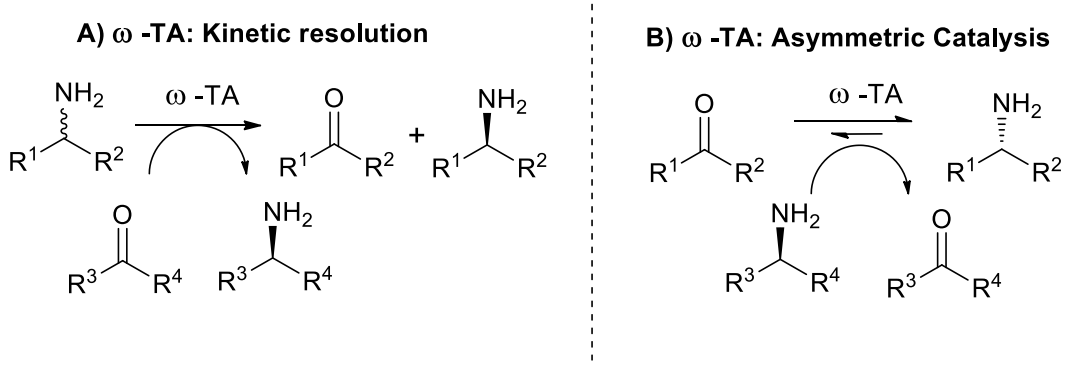
Scheme 8: Organocatalysed ARA with trichlorosilanes. a: Benaglia and co-workers methodology. b: Jones et al. methodology.

1.3 Asymmetric synthesis of amines *via* ω-transamination – Biocatalysis

Recently, the use of biocatalysis to install chiral amine functionality has been developed.[50] Compared to chemo-catalytic reactions, enzymatic syntheses are a much greener alternative to classical synthesis, as they allow milder conditions, are not usually air- or water-sensitive and usually proceed at ambient temperature and neutral pH. In addition, they avoid the need for highly flammable metal-organic or heavy metal compounds, reducing metal contamination, while providing excellent stereoselectivity in a single step.[51, 52] Lipase, transaminase (TA), imine reductase (IRED), amine dehydrogenase (AmDHs) and amine oxidase (AO) - primarily monoamine oxidase (MAO) - are the enzymes which are used in the enantioselective construction of chiral amines.[27] This chapter will focus on reviewing the use of TAs enzymes for the synthesis of chiral amines.

TA enzymes, in particular ω-TA, allow for the synthesis of optically pure chiral amines from prochiral ketones and aldehydes *via* a reversible reaction with an amino donor in the presence of a cofactor; pyridoxal-5'-phosphate (PLP).[53] By contrast, α-TA can only synthesise amino acids, as they require the presence of a carboxylic acid.[53] The ω-TA catalysed reaction can produce chiral amines from prochiral ketones *via* either a kinetic resolution (Scheme 9a) or an asymmetric synthesis, (Scheme 9b). The American biopharmaceutical company Celgene was the first to report this pioneering

work in 1990 in an industrial setting with the use of (*R*)- and (*S*)- selective ω-TAs for the production of a number of phenyl methylamines.[54]

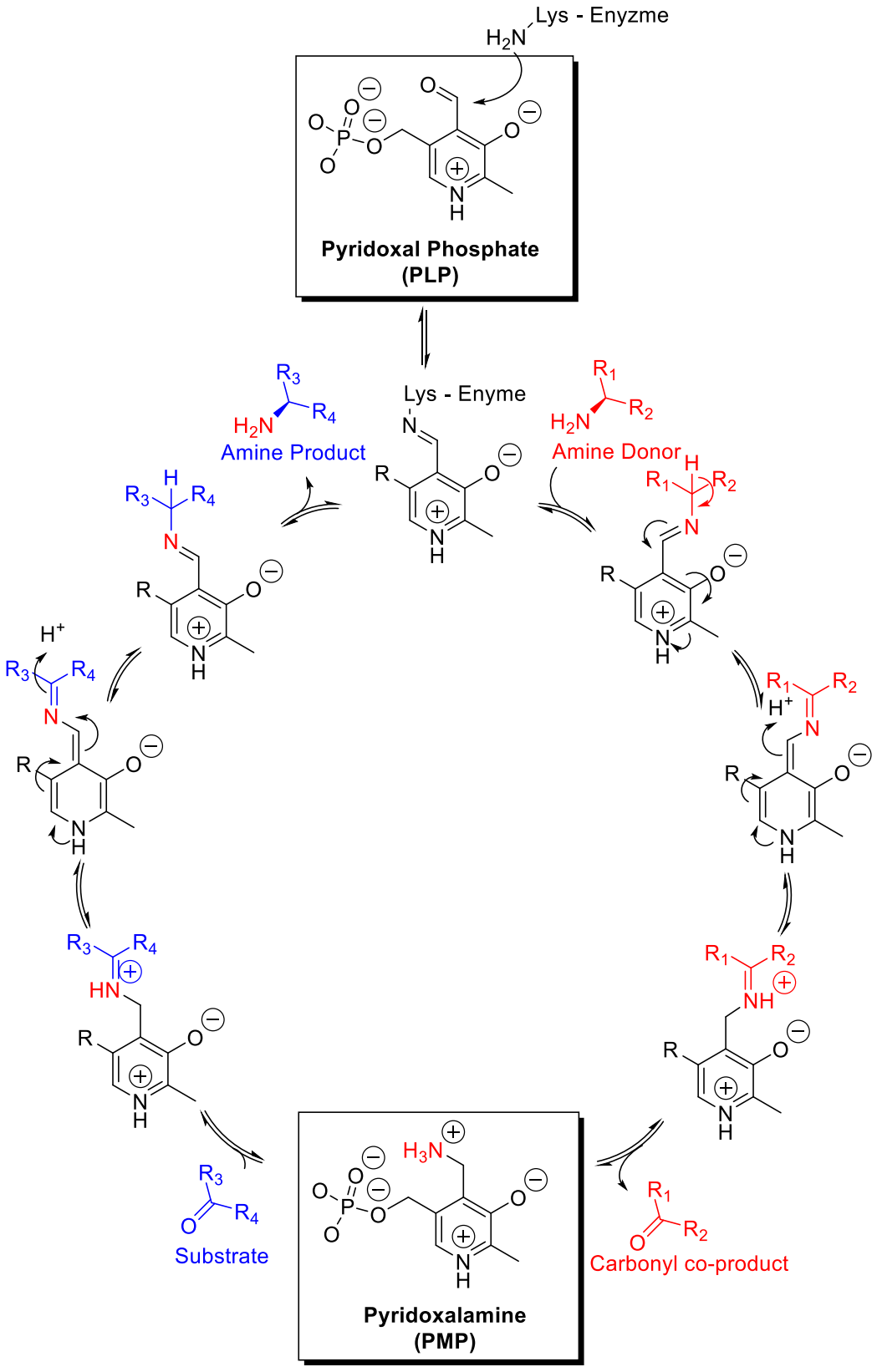


Scheme 9: Production of chiral amine via transaminase enzymes.

The majority of the early research was focused towards ω-TA assisted kinetic resolution, although its use is limited as the maximum theoretical yield is 50%.[52] The ω-TA asymmetric catalysis somewhat fell behind due to ketones having low reactivity as amine acceptors and unfavourable reaction equilibria. The use of ω-TA for asymmetric synthesis was first explored by Shin and Co-workers in 1999.[55] This approach is much more beneficial for the pharmaceutical industry as it is a more economical and efficient route.[56]

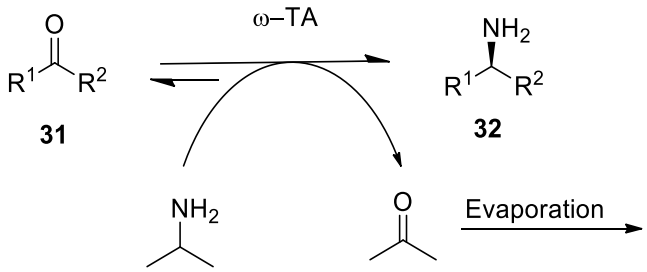
TA enzymes are PLP-dependent enzymes. PLP is a vitamin B_6 derivative and during the catalytic cycle it is covalently bonded to the active site of the enzyme.[57] The TA reaction consists of a two-step reaction (Scheme 10). First, an oxidative deamination of an amine donor occurs; the amine donor donates the amine group to the enzyme-PLP, which produces the pyridoxamine-5'-phosphate (PMP) form of the enzyme and the corresponding ketone. The second step consists of a reductive amination of the

amine acceptor. Here, the amine group of the PMP-enzyme is transferred to the amine acceptor and PLP is regenerated.



Scheme 10: General reaction mechanism of PLP with amines and carbonyls within a ω-TA active site.

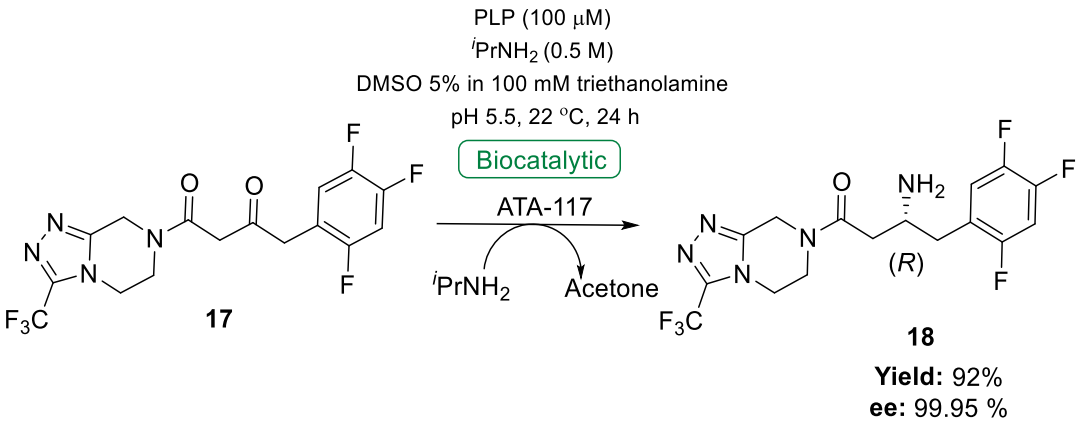
A limitation of the biocatalysed-TA reaction for the synthesis of chiral amines is that it is often difficult to obtain good yields due to the reversible character of the reaction. The low reactivity of ketones as amine acceptors, makes the thermodynamic equilibrium often unfavourable since the products are frequently less energetically stable than the substrate.[58] Several approaches, such as the use of 'smart donors'[59-61] or enzymatic cascades,[62-64] enable a shift in the equilibrium of the reaction. One of the more popular methods to shift the equilibrium, in a large-scale reactions, is the use of an excess of the amine donor and the removal of the carbonyl co-product.[63, 65, 66] In many industrial processes, isopropylamine (IPA) is the preferred amine donor as it is achiral, cheap and produces acetone as a by-product, which can be easily removed *via in-situ* evaporation, thus pushing the equilibrium towards the desired amine product, although this is technically challenging (Scheme 11).[55]



Scheme 11: Large Scale TA using IPA and the removal of acetone co-product.

Arguably, one of the most successful examples of the use of ω-TAs in industry is the synthesis of the antidiabetic drug sitagliptin (**18**). *In silico* design and directed evolution allowed for the production of the (*R*)-selective ω-TA enzyme ATA-117, capable of accepting the bulky substituted dicarbonyl derivative prositagliptin (**17**, Scheme 12).[67] This pioneering discovery highlights the potential of biocatalysis on an industrial scale and it is a great example of how beneficial protein engineering is.

Successful results were achieved by redesigning the binding pocket site on the (*R*)-selective ATA-117 enzyme. The final variant consisted of 27 mutagenesis after 11 rounds of enzyme evolution.[67] There are many examples of how protein engineering can be employed for the creation of enzymes which can be used in industrial applications like sitagliptin.[68]

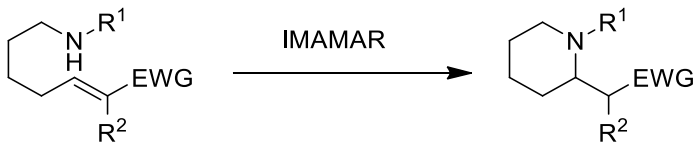


Scheme 12: Synthesis of sitagliptin via chemocatalytic and biocatalytic methods.

1.4 Synthesis of *N*-heterocyclic systems from chiral amines

1.4.1. Intramolecular Aza-Michael Reaction (IMAMR)

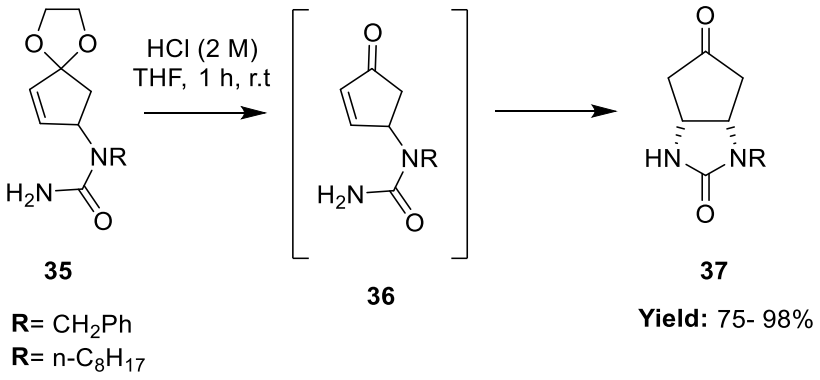
The intramolecular aza-Michael reaction (IMAMR) is a powerful tool for the production of nitrogen heterocycles – which are abundant throughout biologically active substances – from amines.[69, 70] The IMAMR consists of a conjugate addition process using nitrogen-centered nucleophiles and enables the construction of nitrogen heterocycles in a single step (Scheme 13).[69] One or more stereogenic centres are produced during the conjugate addition process, making an asymmetric variant of the IMAMR highly desirable.



33 **34**

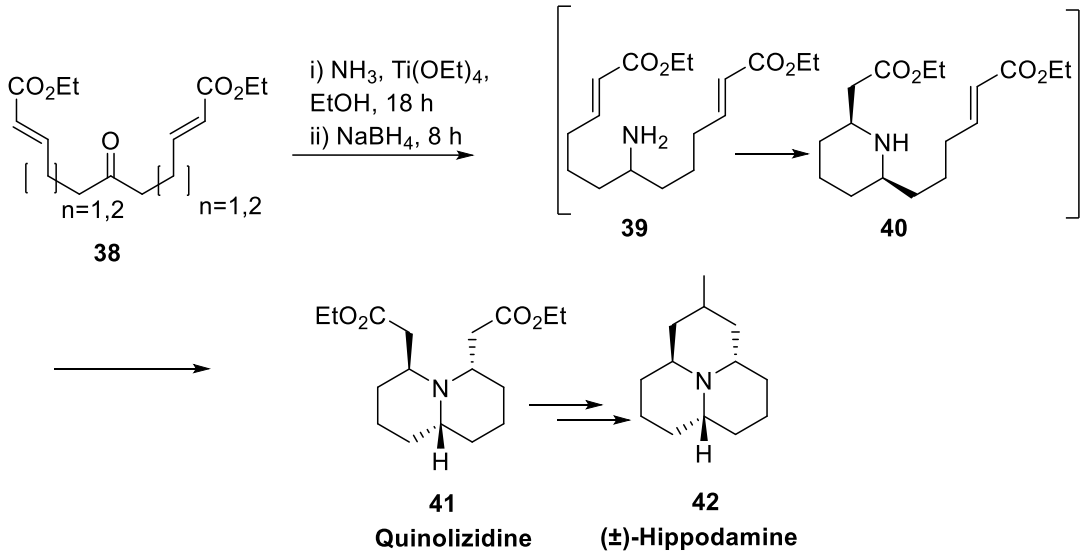
Scheme 13: General IMAMR.

One of the first examples of an IMAMR was reported by Harris and co-workers in 1980 for the synthesis of imidazolidinones **37** (Scheme 14).[71] Simple deprotection of **35** using HCl, gives intermediate **36**, which spontaneously cyclises to provide the desired product **37** in 75-98% yield.



Scheme 14: One of the first reported examples of IMAMR by Harris in 1980.

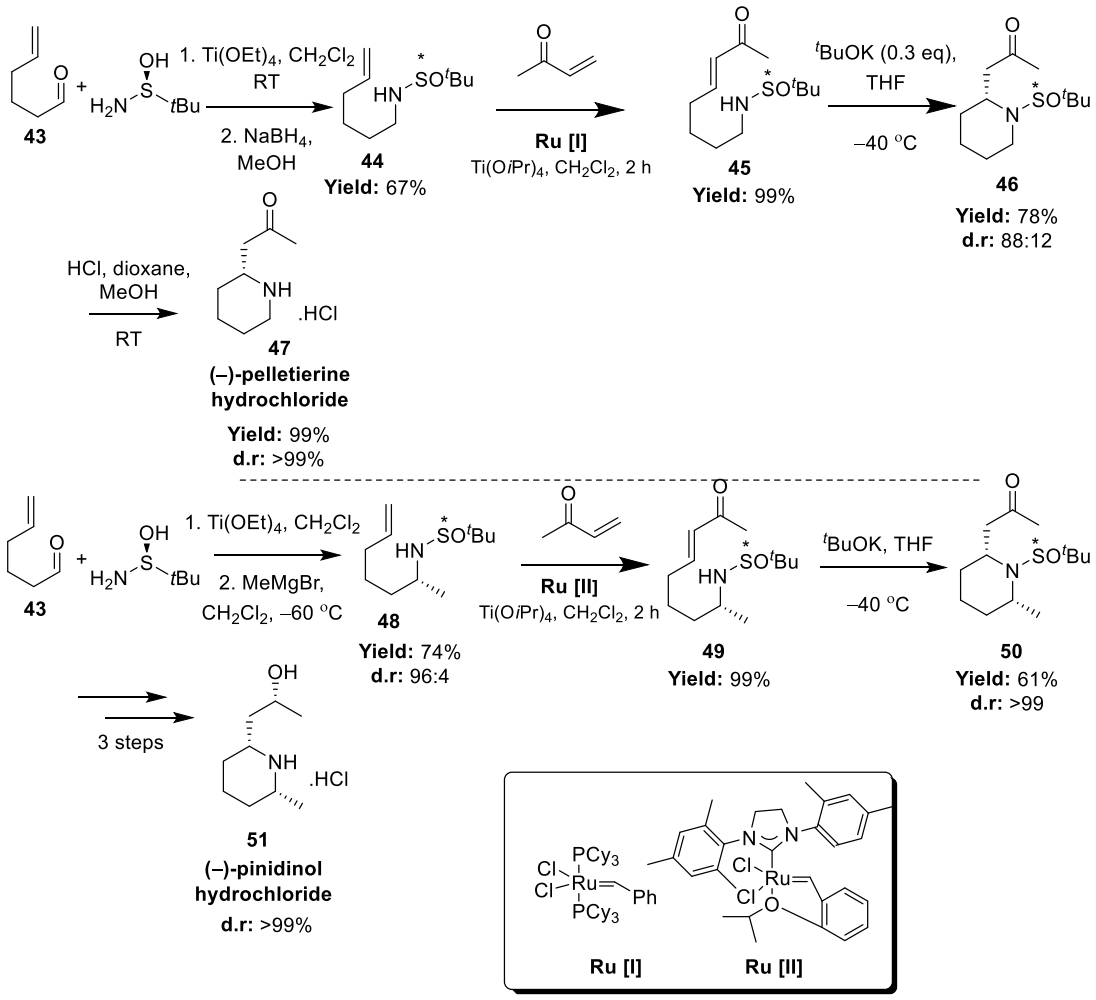
An example of a non-enantioselective (but stereoselective) IMAMR was reported by Stockman *et al.*; a double tandem IMAMR for the direct production of quinolizidine (**41**) in a single step from a symmetrical keto-diester linear precursor (**38**, Scheme 15).[72]



Scheme 15: Stereoselective IMAMR for the synthesis of (±)-Hippodamine reported by Stockman et al.

N-Sulfinyl amines have also been employed by Fustero and del Pozo for the synthesis of the alkaloid (–)-pelletierine (**47**) and (–)-pinidinol (**51**, Scheme 16).[73] The Michael acceptor is synthesised *via* a cross-metathesis (CM) of the chiral *N*-sulfinyl amines **44**

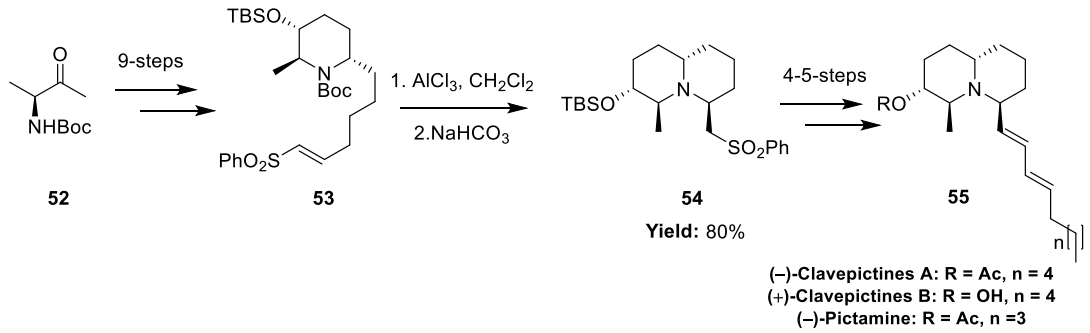
and **48** with methyl vinyl ketone. Subsequent deprotonation of intermediates **45** or **49**, using catalytic amounts of potassium *tert*-butoxide at –40 °C allows the cyclisation by IMAMR, which proceeds in high yield and diastereoselectivity. The addition of hydrochloric acid in dioxane allows the removal of the chiral *N*-sulfinyl group and affords (–)-pelletierine and (–)-pinidinol in very good yields and excellent enantioselectivities (Scheme 16).



Scheme 16: IMAMR for the synthesis of (–)-pelletierine and (–)-pinidinol.

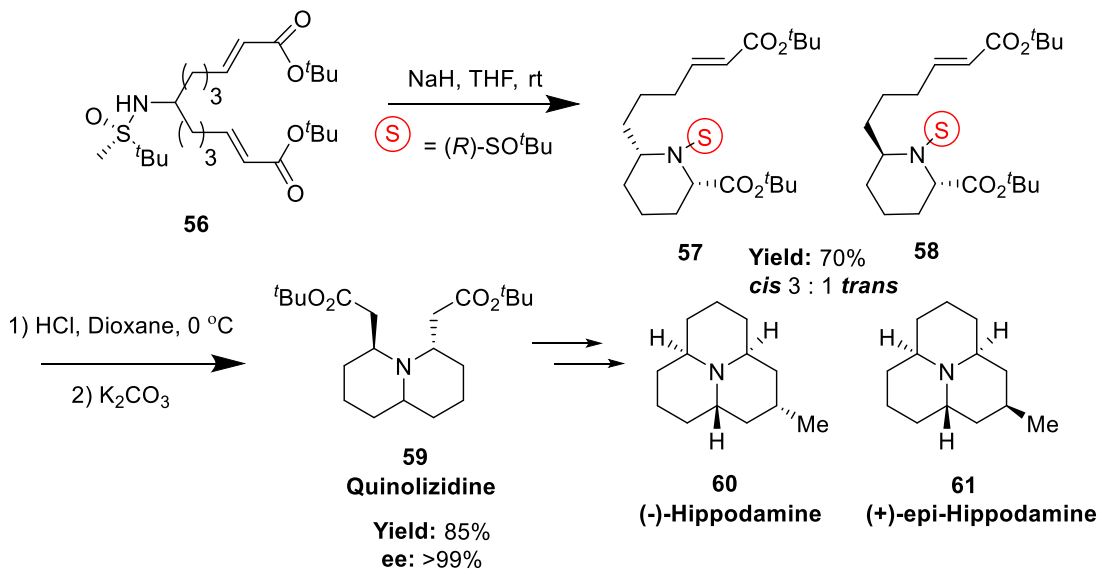
The synthesis of the natural products pictamine and clavepictines A and B utilising a diastereoselective IMAMR was achieved by Ma and co-workers in 2006 (Scheme 17).[74] Consequent to the removal of the Boc protecting group, a spontaneous aza-

Michael reaction occurs on the α,β-unsaturated sulfone **53** providing the quinolizidine **54** with high diastereoselectivity. The single isomer **54** is obtained due to steric repulsive interaction from the siloxy group and the sulfone functionality.



Scheme 17: Diastereoselective IMAMR synthesis of picatine.

Later, Fustero reported the total synthesis of hippodamine utilising a double-IMAMR approach and using chiral *N*-sulfinyl amines as both the nitrogen source and chiral auxiliary.[75] The use of a bulky *tert*-butyl moiety allows the first IMAMR to provide *cis*-**57** and *trans*-**58** in a 3:1 ratio; the selectivity is most likely due to a rigid transition state. The *tert*-butyl sulfinyl group can be removed *via* HCl in dioxane and then upon basification, the second IMAMR takes place and produces the *trans* isomer **59** in 85% yield with >99 ee (Scheme 18).

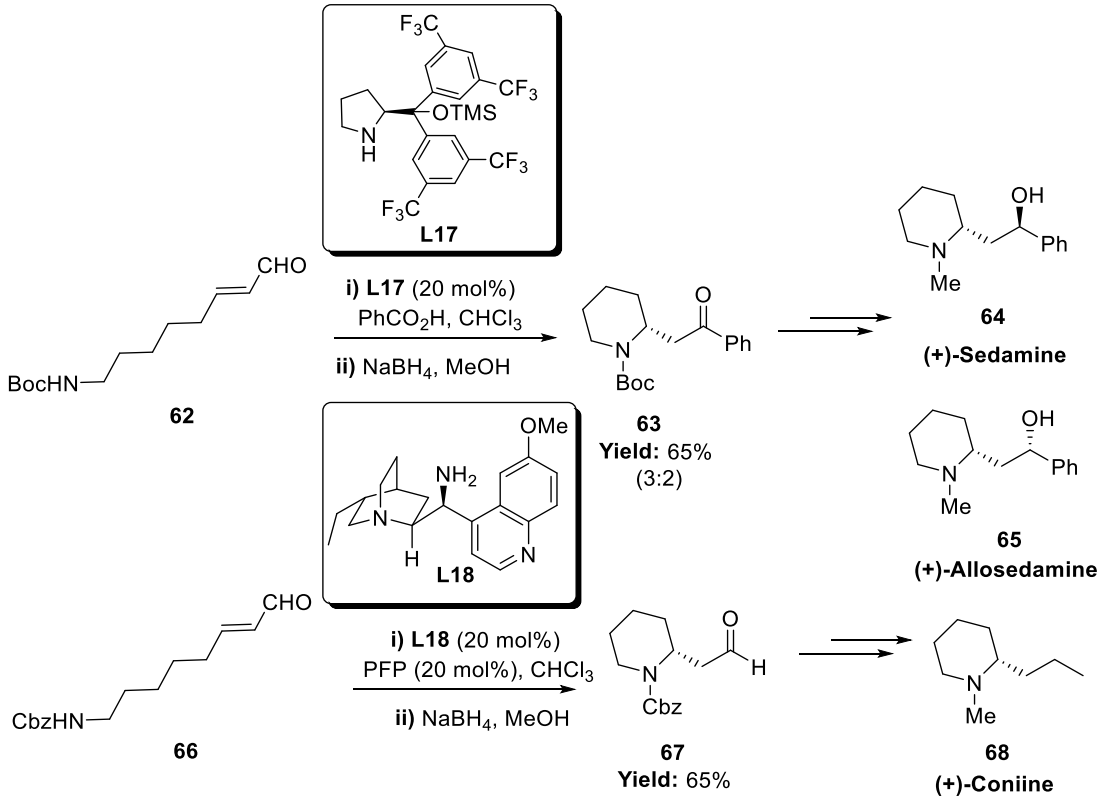


Scheme 18: Double tandem IMAMR for the synthesis of quinolizidine reported by Fustero et al.

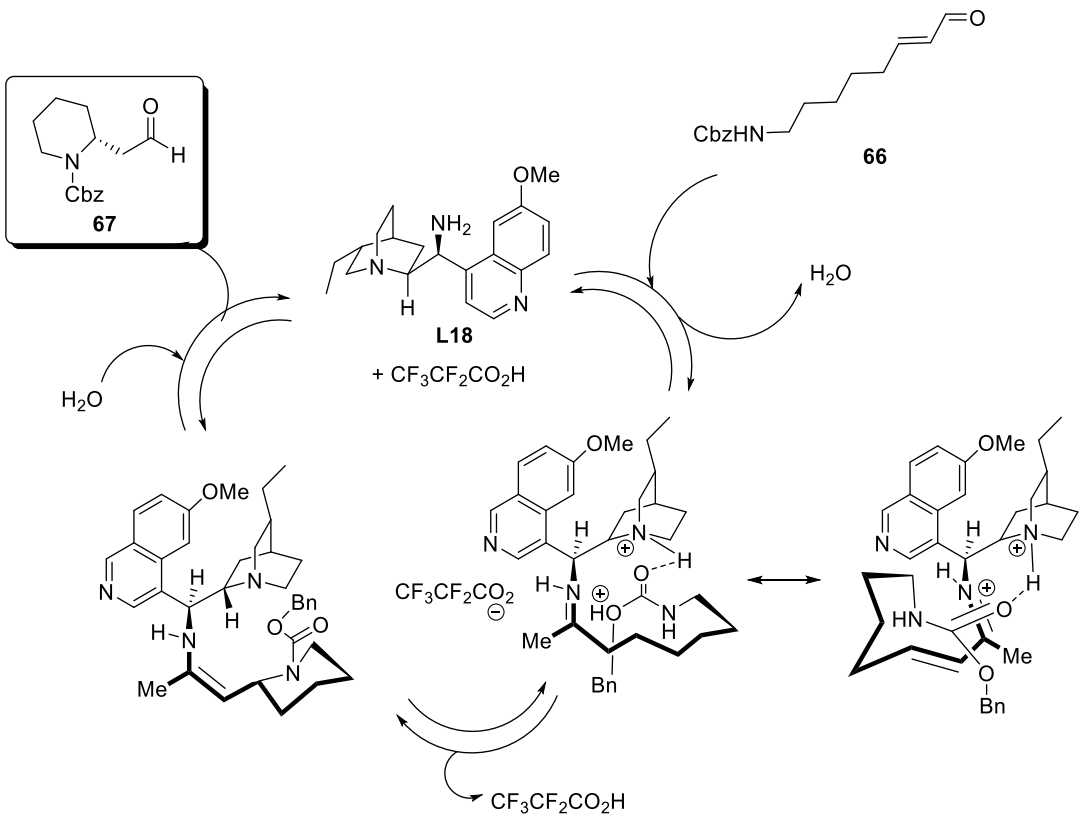
Organocatalysed aza-Michael reactions have increased in popularity for the asymmetric synthesis of *N*-containing heterocycles and have become the third pillar of asymmetric catalysis alongside metals and biocatalysis.[76]

The first examples of organocatalytic IMAMR were simultaneously discovered by Fustero[77] and Fan.[78] Fustero reported the synthesis of three piperidine alkaloids [(+)-sedamine (**64**), (+)-allosedamine (**65**) and (+)-coniine (**68**)] by an asymmetric organocatalysed IMAMR (Scheme 19). The use of Jørgensen catalyst (**L17**, 20 mol%) and *Cinchona*-based primary-tertiary diamine (**L18**, 20 mol%) allows the enantioselective IMAMR on carbamates **62** and **66**, bearing a remote α,β-unsaturated aldehyde, which provides the desired piperidines **63** and **67** in high yield and enantioselectivities.[77] The organocatalytic conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds involves the activation of the substrate by the catalyst through the corresponding iminium ion, which facilitates

the intramolecular addition of the nucleophile to the β-carbon atom. Scheme 20 demonstrates how the nitrogen nucleophile attacks the less sterically hindered iminium transition state of the organocatalysts, which produces the enantioselective IMAMR product.

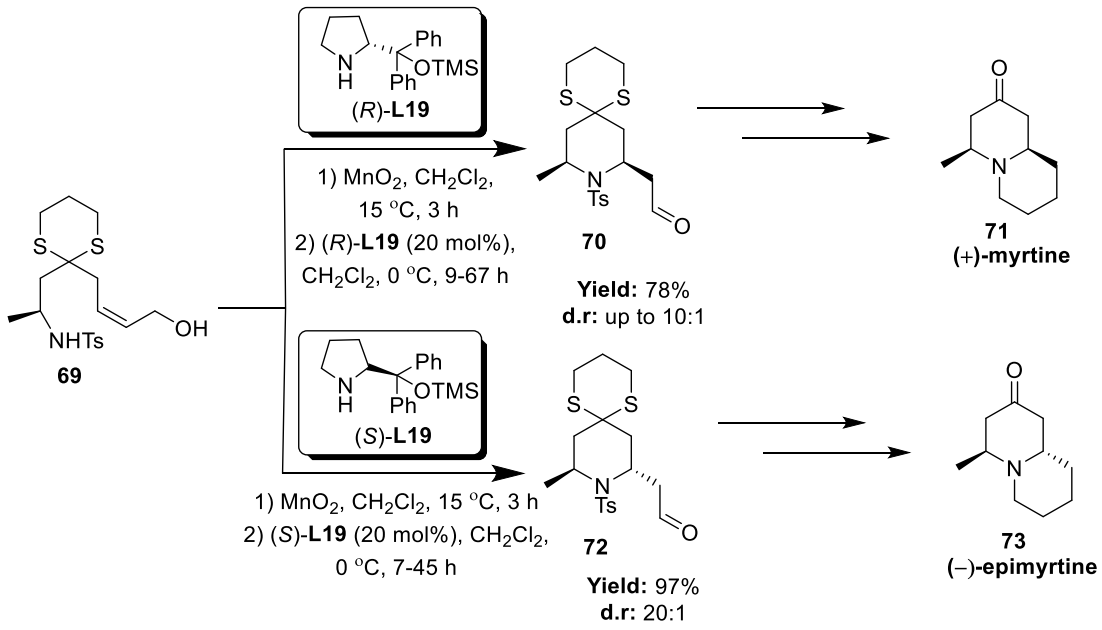


Scheme 19: Synthesis of (+)-sedamine, (+)-allosedamine and (+)-coniine via organocatalytic IMAMR.



*Scheme 20: Mechanism of the conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds using organocatalyst **L18**.*

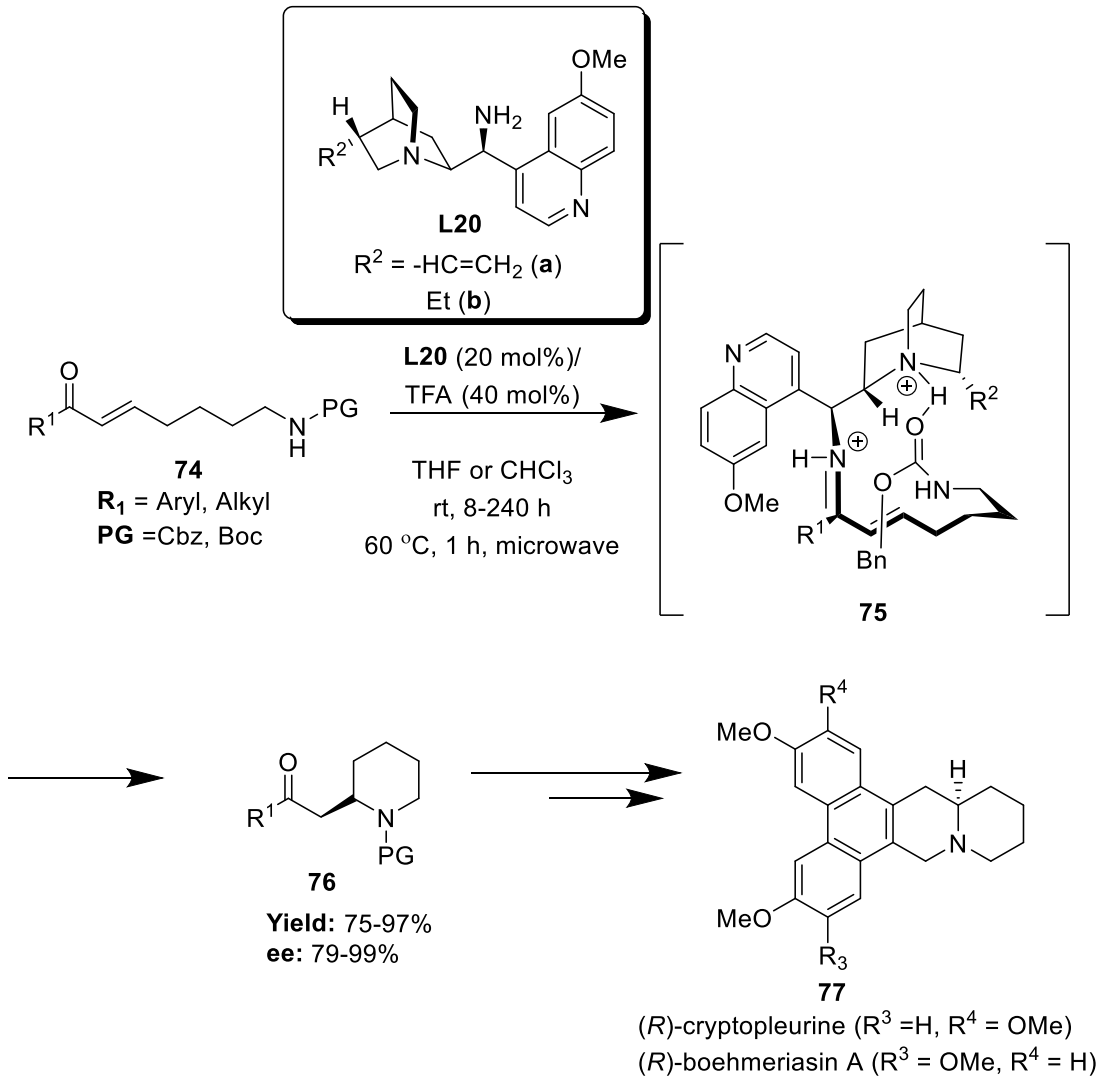
Hong *et al.* have reported the synthesis of 2,6-disubstitued piperidines **70** and **72** *via* IMAMR using the Jørgensen's pyrrolidine organocatalyst **L19** on the chiral amine **69** (Scheme 21).[79] The use of (*R*)- or (*S*)-**L19** allows the construction of both *cis*-**70** and *trans*-**72** piperidines with high yields of 97% and 78% and moderate stereoselectivity of >20:1 and 10:1, respectively. Both (+)-myrtine (**71**) and (−)-epimyrtine (**73**) were achieved after 4 steps.



Scheme 21: Synthesis of (+)-myrtine and (–)-epimyrtine by Hong and co-workers.

Unlike aldehydes, less reactive ketones or more sterically hindered substrates require primary amines rather than secondary amines as organocatalysts. The formation of the corresponding iminium ion – the active reactive intermediate – is more favoured when the organocatalysts is a primary amine.[80]

The asymmetric syntheses of piperidines *via* IMAMR of α,β-unsaturated carbamates reported separately by Sánchez[77] and Fan[81] are examples of IMAMR using a primary amine organocatalysts and ketones as substrates (Scheme 22). The formation of the corresponding iminium ion between catalyst **L20** and the enone **74** promotes the intramolecular nucleophilic addition to the β-carbon. Under acidic conditions, the quinuclidine group of the catalyst **L20** is protonated; this allows for the more favourable *Re* face attack during the transition state *via* hydrogen bonding with the carbamate oxygen atom.



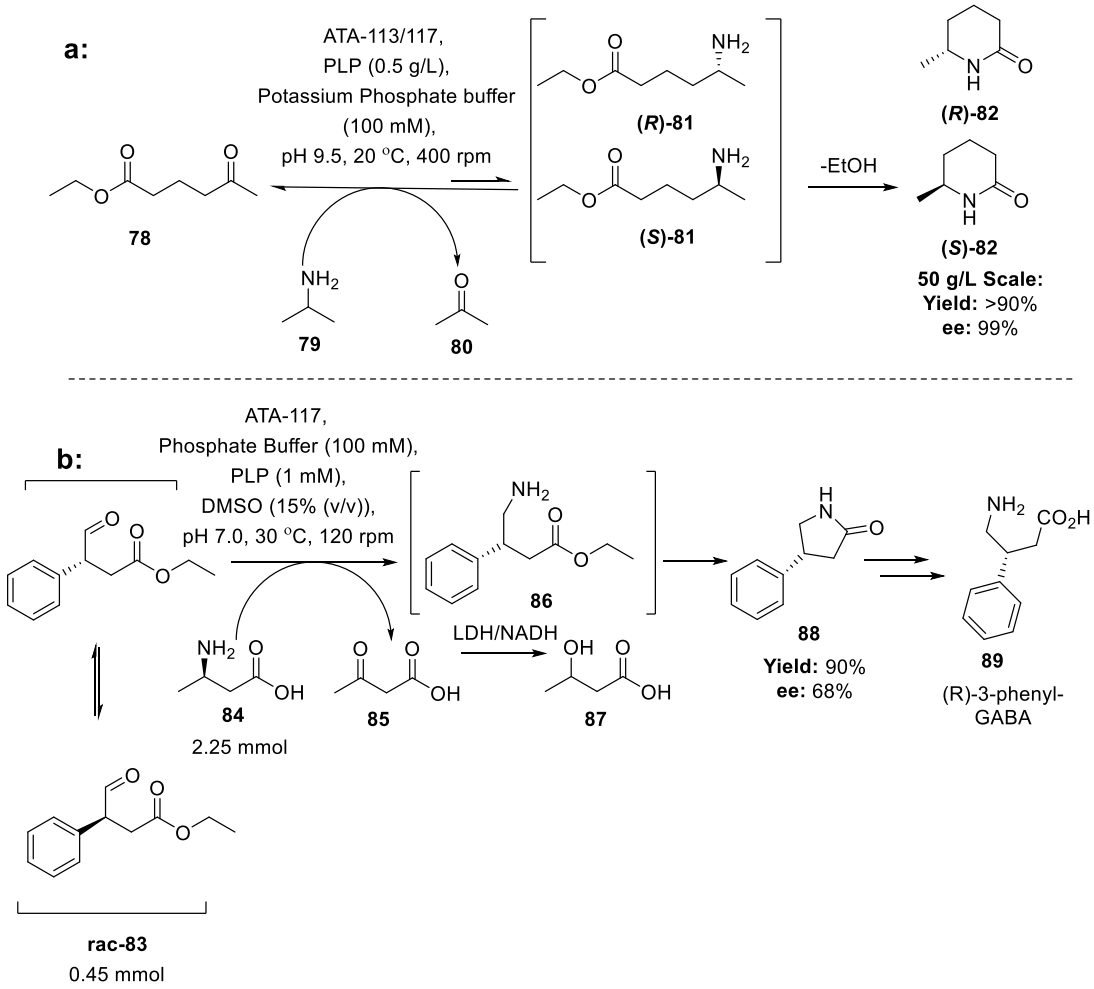
Scheme 22: Asymmetric synthesis of 2-substituted keto piperidines via an amine-catalysed IMAMR by Fan and co-workers.

1.4.2 Biocatalysed transamination reactions for the synthesis of alkaloids

More than 15% of known natural products are alkaloids.[82] The use of biocatalysis for the construction of these molecules offers attractive 'greener' alternative to classical chemical syntheses.[83-85] The first to report the use of TAs for the synthesis of alkaloids were Turner and co-workers in 2010.[86] In their work, ω-TAs are used in part of a cascade system, in which keto-ester **78** undergoes transamination using ATA-113/117 (commercially available enzymes developed by Codexis) and the product spontaneously lactamises to produce chiral piperidine **82** in excellent ee (Scheme 23a). The spontaneous lactamisation reaction drives the equilibrium towards the product, which is obtained in 90% yield. The reaction can be performed on a 50 g/L scale, illustrating the use of the methodology on an industrial scale.

Kroutil *et al.* used a dynamic kinetic resolution (DKR) strategy with ω-TAs (ATA-117) to synthesise 3-4-aryl-GABA derivatives, which are known to play an important role in the nervous system.[87] This is one of the first DKR performed involving an enzymatic enantioselective amination reaction catalysed by ω-TAs. The strategy is based on the deracemisation of 4-oxo-3-phenylbutyric acid ethyl esters **83** catalysed by a ω-transaminase. The enzyme preferentially selects the one of the enantiomers which spontaneously cyclises into the lactam precursor of GABA (Scheme 23b). The optical purity of the obtained lactam **88** results exclusively from the stereo-recognition of the ω-transaminases for the stereogenic centre in α-position of the aldehyde **83** and not from kinetic effects due to depletion of the preferred substrate enantiomer. A co-enzyme lactase dehydrogenase (LDH) removes the side product pyruvate by using

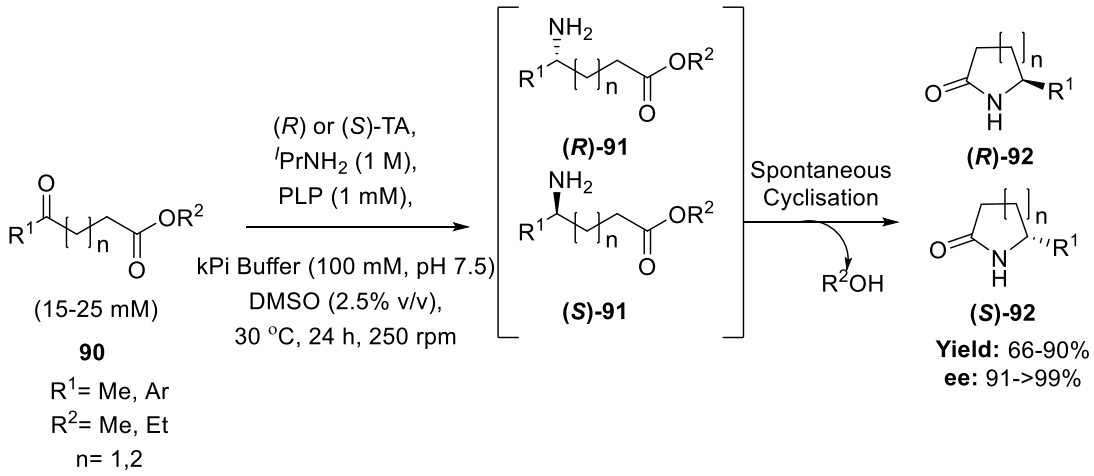
NADH to convert the product to lactate resulting in shifting the equilibrium towards the desired product.



Scheme 23: Transamination/cyclisation systems for the synthesis of chiral amines.

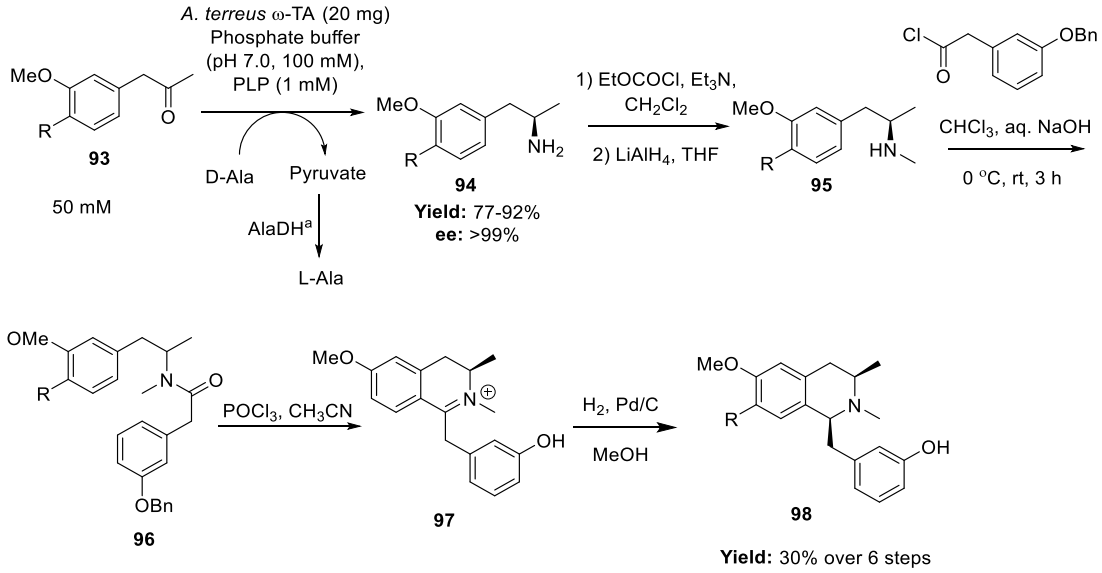
Lavandera and Gotor reported the synthesis of chiral lactams from γ- and δ-keto esters using both commercially available and *'in house'* ω-transaminases-induced cascades (Scheme 24).[88] The TA-triggered reductive amination followed by a spontaneous cyclisation proceeded under mild conditions and afforded the chiral 6-substituted piperidin-2-ones and 5-substituted pyrrolidin-2-ones (**92**) in excellent ee and predominantly good yields (94-99% and 66-90% respectively). Lower

concentrations of the substrates, as well as a careful choice of temperature were required in order to achieve the best conversion to the desired products.



Scheme 24: Transamination of γ- and δ-keto esters for the synthesis of chiral lactams by Lavandera and Gotor.

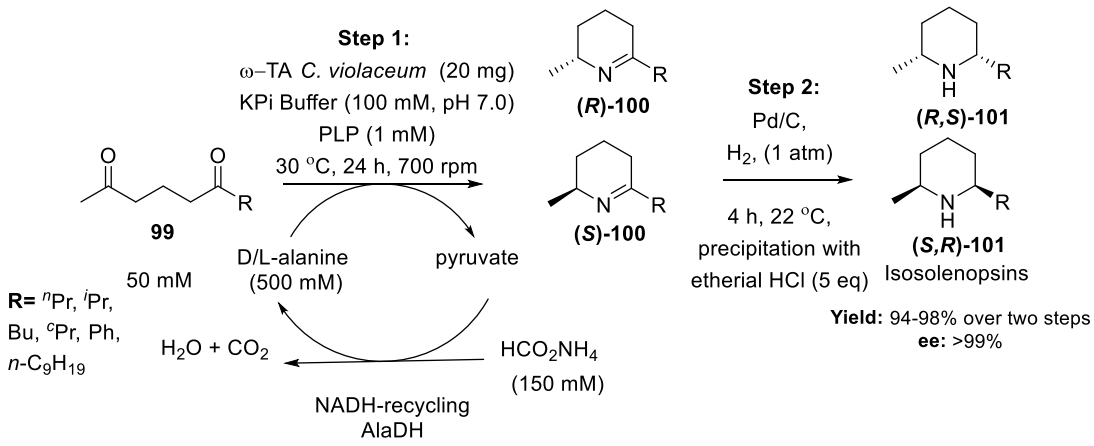
The enantiopure alkaloid 1-benzyl-2,3-dimethyl-1,2,3,4-tetrahydrosioquinoline (**98**) has been synthesised by Kroutil's methodology using a chemoenzymatic sequence (Scheme 25).[89] The enzymatic reaction of **93** using *A. terreus* ω-TA, which was adapted from *Aspergillus terreus*[90] successfully produces the corresponding 1,3-disubstituted tetrahydroisquiniline **94** with high yield of enantioselectivity. Subsequent methylation and amide formation provides **96**. Bischler-Napieralski cyclisation ring closure using palladium on charcoal succeeded by Pd-catalysed hydrogenation afforded the desired product **98** with an excellent 30% overall yield.



Scheme 25: Synthesis of 1-benzyl-2,3,4-dimethyl-1,2,3,4-tetrahydroisquinolines.

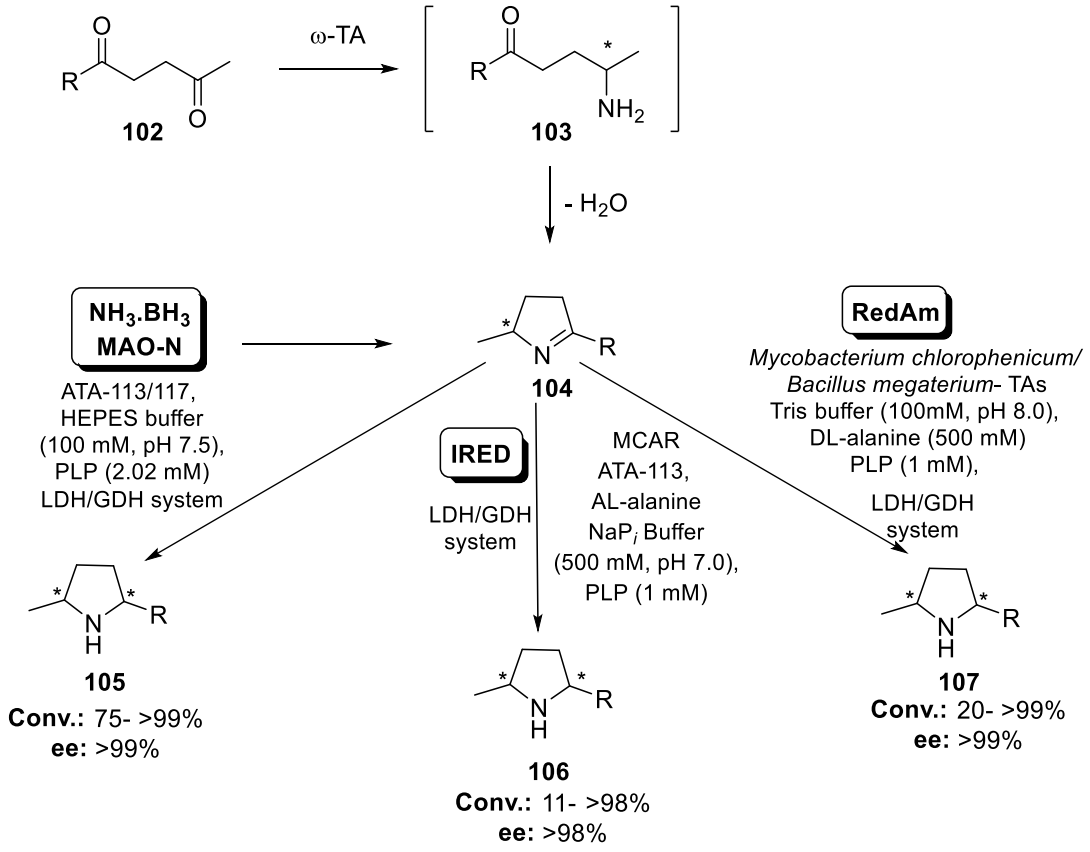
[a] Reaction conditions: AlaDH (12 U), FDH (11 U), NAD^+ (1 mM), ammonium formate (150 mM).

Kroutil *et al.* described the synthesis of 2,6-disubstituted piperidines **101**, a common motif in many alkaloids, by the transamination of the least hindered ketone in 1,5-diketones **99**, followed by a spontaneous cyclisation by condensation, that provides the enantiopure chiral imine **100** in good yields and enantioselectivities (Scheme 26, Step 1).[91] Soon-after, the same group expanded this monoamination followed by subsequent hydrogenation with palladium on carbon (Scheme 26, Step 2), which affords the alkaloid isosolenopsin (**101**, R= *n*-C_9H_{19}).[92] The reaction proceeds with good regio- and stereoselectivity and the desired product is achieved over 2 steps in 64-65% yield and >99 ee (Scheme 26),[92] using DMF to pre-dissolve the substrate in order to achieve full conversion.



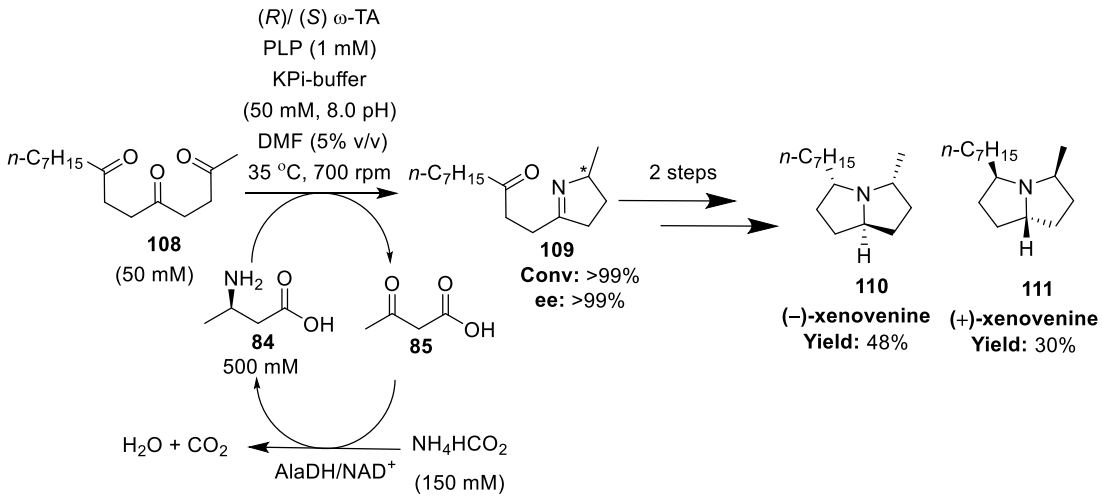
Scheme 26: Synthesis of 2,6-disubstituted piperidines via monoamination of diketones.

Other examples using enzymatic approaches for the synthesis of 2,5-disubsubstited pyrrolidines, include cascade reactions using TAs and monoamine oxidases,[93] imine reductases[94] and reductive aminases (Scheme 27).[94, 95] All of this work highlights the ability of the enzymatic cascades to provide good regio- and stereoselectivity in the synthesis of heterocyclic systems.



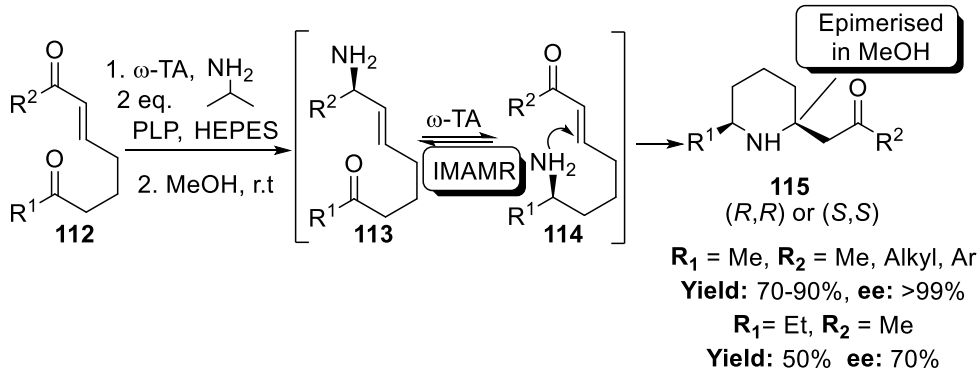
Scheme 27: TA biocatalytic cascades for the synthesis of 2,5-disubsubstited pyrrolidines.

Kroutil and co-workers have also reported the monoamination of triketones for the construction of the pyrrolizidine alkaloid xenovenine (Scheme 28);[96] a great example of how ω-TA's can be used for the synthesis of more complex, bicyclic molecules in a regio- and enantioselective manner. The bioamination (using either (*R*)- or (*S*)-ω-TA) of triketone substrate **108** is selective towards the less bulky methyl ketone and affords the enantiopure cyclic imine **109** in >99% conversion and ee. Two subsequent steps (a reduction and spontaneous condensation, followed by a second reduction) affords the target xenovenine **110** and **111** in 48% and 30% yield, respectively.



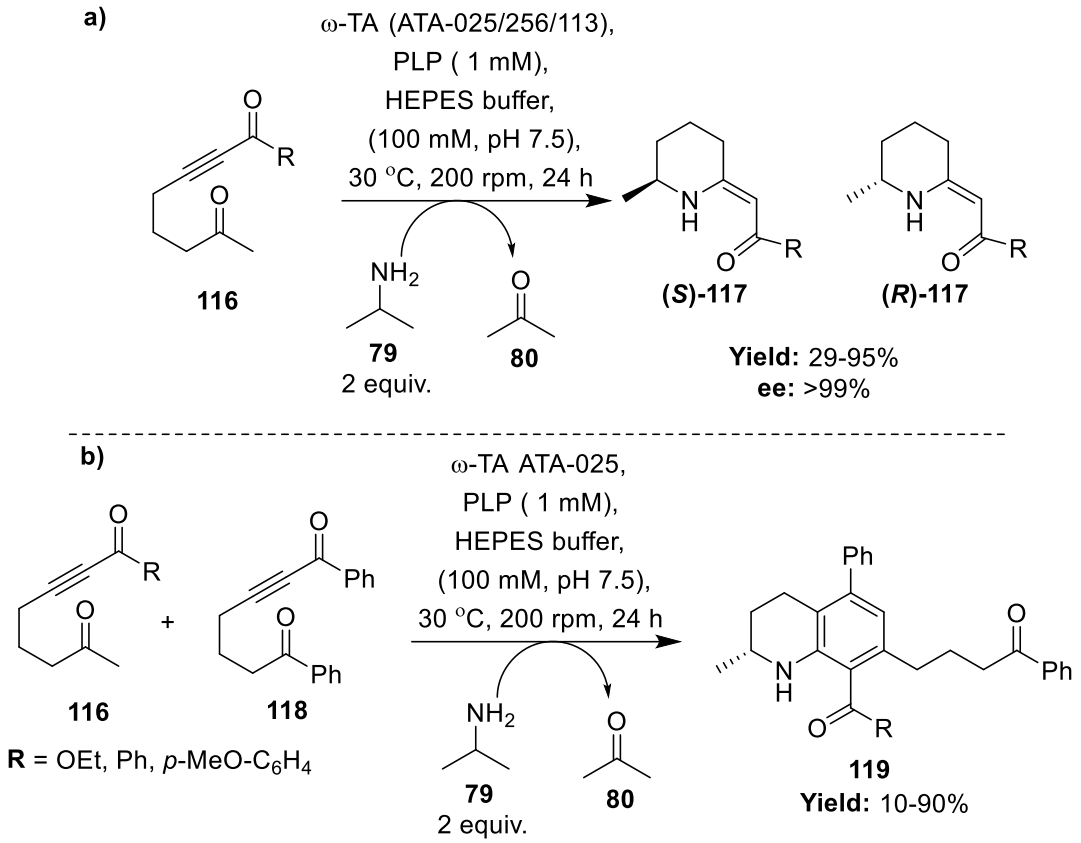
Scheme 28: Monoamination of triketones for the construction of the natural xenovenine.

Until recently, there were no examples of biocatalysis used in conjunction with a IMAMR to produce chiral heterocyclic systems. Our group, however successfully reported the TA-triggered IMAMR of several ketoenone substrates **112**, allowing the synthesis of 2,6-disubstituted piperidines **115** in a simple manner (Scheme 29).[70] The spontaneous IMAMR drives the reaction equilibrium towards the formation of the desired piperidines as a mixture of *cis*- and *trans* -isomers, making unnecessary use of an excess of amine donor (^{i}PrNH$_2$). Subsequent epimerisation *via* a retro-aza-Michael reaction occurs upon standing in MeOH, affording the desired *cis*-products **115** in >99% de. This pioneering work allows for disconnections which are not possible from using conventional chemical synthesis or catalysis. Additionally, it provides greener reaction conditions with excellent conversion and isolated yield.[70]



Scheme 29: Biocatalysed synthesis of 2,6-disubstituted piperidines from ketoenones.

This work was recently expanded to construct β-enaminones **117** from prochiral ketoynones **116** (Scheme 30a).[97] The reaction proceeds with good yields and excellent enantioselectivities (83-99%) for a variety of substrates, showing the potential of the methodology. A one-pot tandem IMAMR/ condensation cascade, to synthesise more complex, bicyclic systems **119**, has also been reported (Scheme 30b).



Scheme 30: Synthesis of β-enaminones via transamination of ketoynones.

2. Transamination of keto-cyclohexenone compounds for the synthesis of perhydrohistrionicotoxin derivatives.

2.1 Introduction

Several natural alkaloids, such as histrionicotoxins (HTXs) and pinnaic acid (Figure 2), contain very interesting spirocyclic scaffolds. In particular, HTX has shown to have potent biological activity and blocks neuromuscular transmission. It is extracted from the skin of poison arrow frogs, *Dendrobates histrionicus*, which are native to the tropical Amazon rain forest, and was first isolated by Daly, Witkop and co-workers in 1971.[98, 99] However, extraction from the original source is not feasible, as it is expensive and complicated due to the protection of the Dendrobatid source as an endangered species. Therefore, accessible synthetic routes for the stereoselective preparation of HTX and its derivatives are in need of being developed.

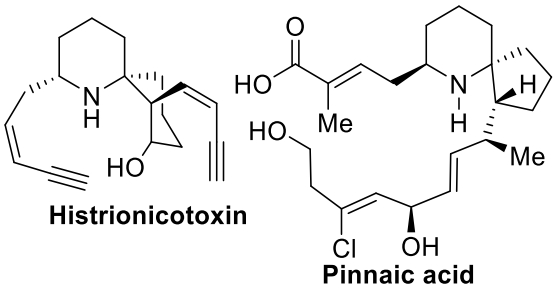


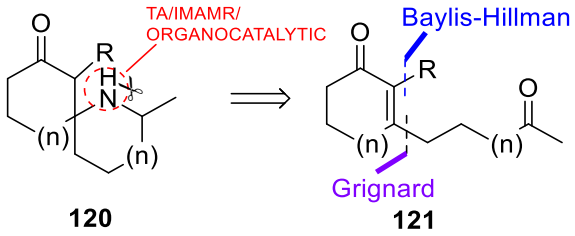
Figure 2: Structure of alkaloids -trans-Histrionicotoxin and Pinnaic acid.

2.2 Aims and Objectives

This chapter aims to explore the construction of increasingly complex chiral *N*-heterocycles *via* our recently developed TA-triggered intramolecular aza-Michael protocol.[70] The use of organocatalysis in a synergistic manner with the biocatalysed reaction will also be explored.

In particular, we intend to apply our TA-triggered IMAMR methodology for the synthesis of spirocyclic systems **120** (*i.e.* HTX derivatives, Scheme 31). Preliminary investigations by Ryan *et al.* have demonstrated that the Michael addition reactions onto α-substituted and/or β,β-disubstituted enones (e.g. **121** (n= 1, R = H, Me) are hampered by their lower reactivity.[44] We believe that activation of these substrates *via* an iminium ion formation will render the β-carbons more electrophilic for nucleophilic attack than their carbonyl precursors, facilitating the conjugate addition processes. If the formed iminium ion bears a chiral environment, we predict that a stereoselective nucleophilic addition might be possible.

Thus, this project will firstly investigate the use of organocatalysts to improve the diastereomeric ratio and the overall efficiency of the synthesis of HTX derivatives **120** (Scheme 31). A screening of different organocatalysts, such as proline, diarylprolinol ethers, peptides, MacMillan's chiral imidazolidinones and cinchonine derived organocatalysts will be carried out, in the hope that they are compatible with the reaction conditions of the bioenzymatic reaction.

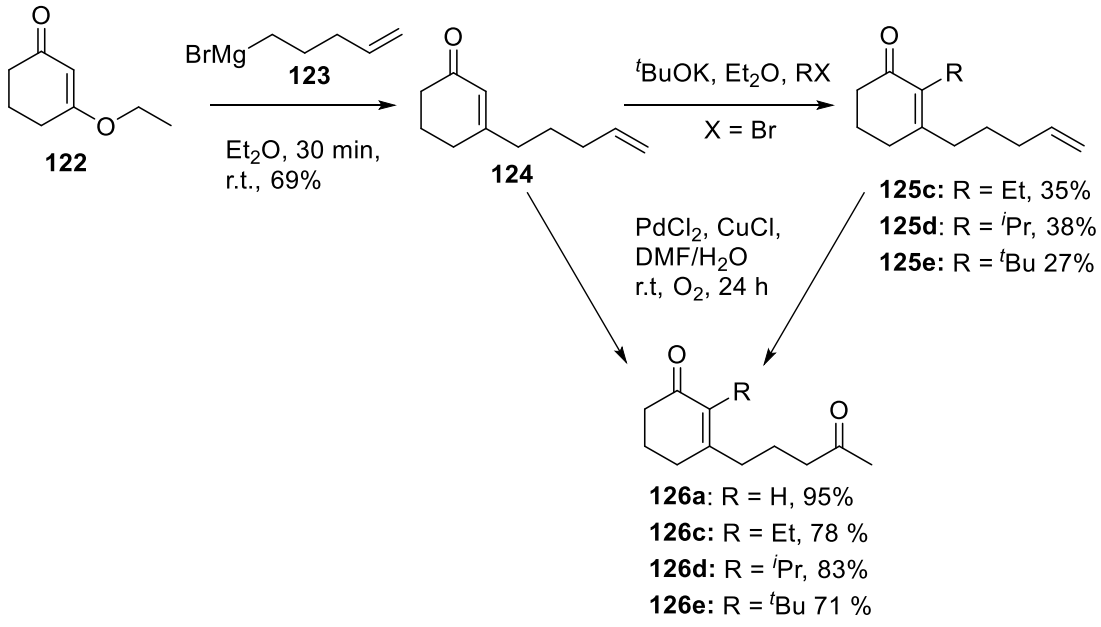


Scheme 31: Retrosynthetic analysis of the core structure of HTX.

2.3 Results and Discussion

2.3.1. Synthesis of keto-cyclohexenone substrates 126a-e.

Following known procedures proposed by Suemune *et al.*[100], the synthesis of **126a** was performed *via* a two-step process (Scheme 32). The addition of the Grignard reagent **123** onto the commercially available 3-ethoxy-2-cyclohexanone (**122**) in diethyl ether formed the desired compound **124** in 69% yield. The second step of the synthetic route consisted of a Wacker oxidation of alkene **124**. Although Suemune[100] described the use of 0.5 eq. of $PdCl_2$ and 4 eq. CuCl in 76% yield, our research group previously discovered that the use of 0.1 eq. of $PdCl_2$ and 2 eq. CuCl afforded the target compound **126a** with an improved yield of 95%.[44]

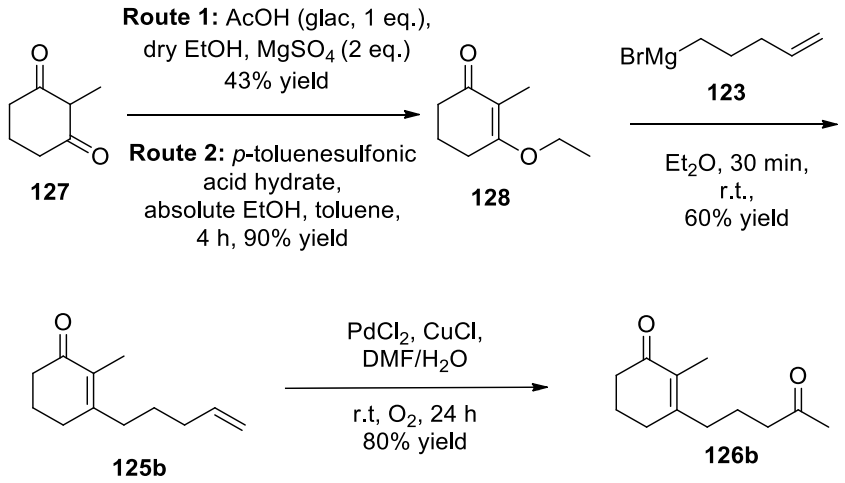


*Scheme 32: Synthetic route to desired ketocyclohexanones **126a-d**.*

The substituted cyclohexanones **125c-e** were achieved by means of a Baylis-Hillman reaction on **124**, using the corresponding bromoalkane with potassium *tert*-butoxide in Et_2O at room temperature (Scheme 32). The use of bromoethane, 1-

bromopropane and 1-bromobutane as the corresponding bromoalkanes provided **125c-e** in moderate to low yields of 35%, 38% and 27% respectively. The Wacker oxidation of substrates **125c-e** provided the subsequent substituted ketocyclohexenones **126c-e** in a good yields of 78, 83 and 71% respectively.

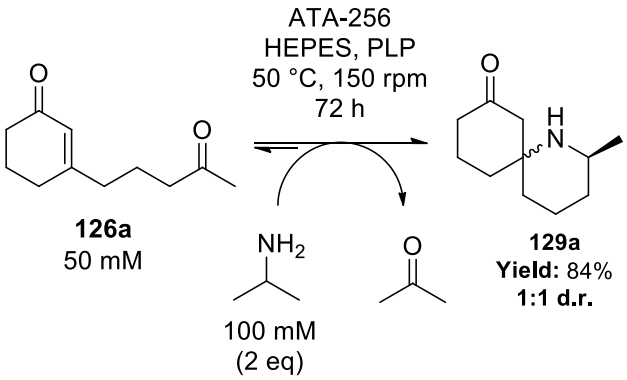
The synthesis of the α-methyl substituted keto-enone **126b** was achieved according to the synthetic route depicted in Scheme 33. The initial attempt to synthesise intermediate **128** from commercially available 2-methyl-cyclohexan-1,3-dione (**127**)**,** in the presence of glacial acetic acid only provided a moderate yield of 43% (Scheme 33, *Route 1*). Fortunately, the reaction of **127** with *p*-toluenesulfonic acid hydrate in ethanol, under reflux, with continual removal of the ethanol/toluene/water azeotrope by a Dean-Stark trap, yielded the desired **128** with an improved yield of 90% (Scheme 33, *Route 2*). Next, the reaction of **138** with 4-pentenylmagnesium bromide (**123**) provided adduct **125b** in 60% yield after column chromatography. Subsequent Wacker oxidations of **125b** provided the target methyl-substituted keto-cyclohexenone **126b** with a good yield of 80%.



*Scheme 33: Synthesis of 2-methyl-3-(4-oxopentyl)cyclohex-2-en-1-one (**126b**).*

2.3.2. Biocatalysed synthesis of spirocycles 129a-e in the presence of different organocatalysts.

Our group had previously investigated the transamination of the ketocyclohexanone substrate **126a** (Scheme 34) utilising commercially available ω-TA biocatalyst ATA-256 from the protein engineering company Codexis.[44] Ryan *et al.* reported that the use of 2 eq. of IPA as amine donor, at 50 °C afforded, after three days, the target spirocyclic system **129a** in full conversion as a 1:1 mixture of inseparable diastereomers (d.r., determined by GC-MS) in an overall isolated yield of 84%.[44] Ryan also attempted, without any success, the epimerisation of the diastereomeric mixture **129a**.[44]



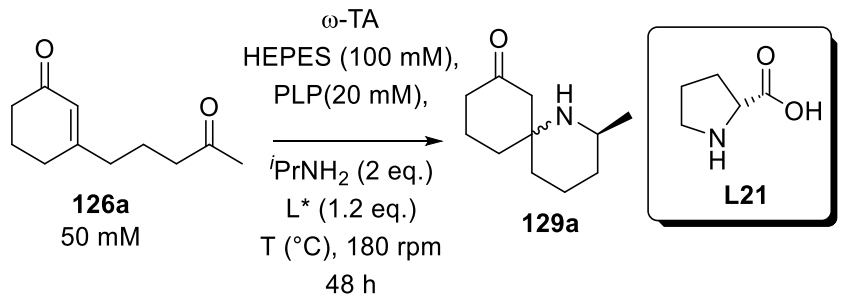
*Scheme 34: Transamination of **126a** for the synthesis of **129a** via the methodology of Ryan et al.[44]*

Due to the relevance of generating greener and more efficient reactions, we decided to explore the use of organocatalysts in a synergistic manner with the biocatalysed transformation, in the hope that it would improve the d.r. and the yield of the reaction. Our investigations started by following the same procedure as Ryan *et al.*

with the addition of stoichiometric amounts of the organocatalyst (*S*)-proline (**L21**). Under these conditions (ATA-256, DMSO 10% [v/v], HEPES (100 mM, pH 7.5), PLP (20 mM), at 50 °C), the reaction provided a conversion of 78% (determined by GC-MS by integrating both starting material and product peaks) of **129a** with a d.r. of 1:1 (Table 1, *entry 3*) after 48 h. Although the conversion in the presence of **L21** was lower than without it, we decided to lower the temperature of the reaction to check if **L21** could provide an increase in stereocontrol. Limited by the temperatures at which the enzymes can be employed, we attempted the reaction at 30 °C. As expected, at 30 °C, the reaction in the absence of organocatalyst provided lower conversion than at 50 °C (compare *entries 1 and 5*), and the addition of **L21** at this temperature, did not have any effect in either conversion or diastereoselectivity of the reaction (compare *entries 5 and 7*).

Next, we increased the amount of DMSO to 20% [v/v] (the maximum amount of DMSO allowed by the enzyme) in the hope that a higher content of organic solvent would improve the efficiency of the organocatalysts **L21**. The reaction at 30 °C without the organocatalyst provided a lower conversion when increasing the solvent to 20% (81 vs 69%, *entries 5 and 9*) and the addition of **L21** under these conditions decreased the conversion even further to 41% (85 vs 41%, *entries 7 and 10*). In all cases, the d.r. remained unchanged at 1:1. The use of MeOH as co-solvent was also investigated (10% [v/v]) at 30 °C, but the conversion of the reactions without and with the organocatalyst provided lower conversions than DMSO (37 and 12%, *entries 11 and 12*).

*Table 1: Optimisation of conditions for the synthesis of **129a** [a]*



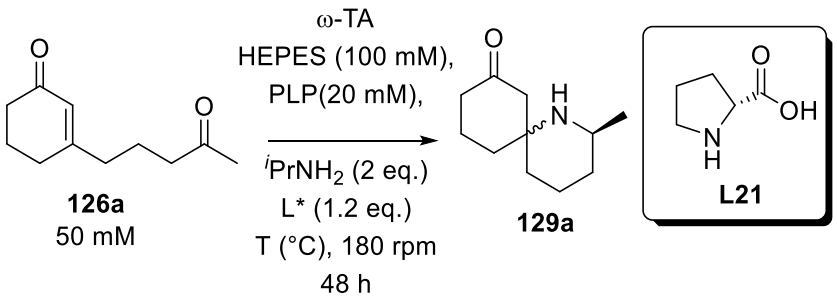
Entry	ATA (selectivity)	Solvent (%v/v)	Temp (^{o}C)	L*	Conv (%)[b] after 24 h	Conv (%)[b] after 48 h	129a d.r.[b]
1.	256 (*S*)	DMSO (10)	50	-	n.d	>99 (84)[c]	1:1
2.	-	DMSO (10)	50	-	0	0	-
3.	256 (*S*)	DMSO (10)	50	**L21**	38	78	1:1
4.	-	DMSO (10)	50	**L21**	0	0	-
5.	256 (*S*)	DMSO (10)	30	-	22	81	1:1
6.	-	DMSO (10)	30	-	0	0	-
7.	256 (*S*)	DMSO (10)	30	**L21**	38	85	1:1
8.	-	DMSO (10)	30	**L21**	0	0	-
9.	256 (*S*)	DMSO (20)	30	-	59	69	1:1
10.	256 (*S*)	DMSO (20)	30	**L21**	30	41	1:1

[a] Reaction conditions: ω-TA (5 mg/ mL), **126a** (50 mM), ^{i}PrNH$_2$ (2 eq), HEPES buffer (100 mM, pH 7.5), PLP (20 mM), 180 rpm, 48 h.

[b] Determined by GC-MS.

[c] Carried out by Dr James Ryan at Manchester Metropolitan. University during his PhD (Ref[44]). Isolated yield after column chromatography in brackets.

*Table 2 Continued: Optimisation of conditions for the synthesis of **129a** [a]*



Entry	ATA (selectivity)	Solvent (%v/v)	Temp (°C)	L*	Conv (%)[b] after 24 h	Conv (%)[b] after 48 h	129a d.r.[b]
11.	256 (*S*)	MeOH (10)	30	-	16	37	1:1
12.	256 (*S*)	MeOH (10)	30	**L21**	10	12	1:1
13.	-	MeOH (10)	30	**L21**	0	0	-
14.	256 (*S*)	DMSO (10)	25 then 28[d]	-	5	20	1:1
15.	256 (*S*)	DMSO (10)	25 then 28[d]	**L21**	3	21	1:1
16.	-	DMSO (10)	25 then 28[d]	**L21**	0	0	-
17.	256 (*S*)	DMSO (10)	30	**L21**[e]	0	0	-
18.	025 (*R*)	DMSO (10)	30	-	27	35	1:1
19.	025 (*R*)	DMSO (10)	30	**L21**	67	74	1:1

[a] Reaction conditions: ω-TA (5 mg/ mL), **126a** (50 mM), $^{i}PrNH_2$ (2 eq), HEPES buffer (100 mM, pH 7.5), PLP (20 mM), 180 rpm, 48 h.
[b] Determined by GC-MS.
[d] Temperature was set to 25 °C for 24 h and then raised to 28 °C for another 24 h.
[e] Reaction was carried out without IPA.

We also explored lowering the temperature even further (using DMSO as co-solvent), in order to slow down the aza-Michael reaction and improve the d.r. of the reaction. Thus, the reaction with ATA-256 at 25 °C for 24 h, followed by 24 h at 28 °C, resulted in a dramatic decrease of conversion (20 and 21%, entries 14 and 15) and no

improvement in the d.r in the presence of **L21** (entry 15) after 48 h. To ensure that **L21** was not acting as the amine donor, we attempted a control reaction in the absence of IPA (Table 1, *entry 17*). As expected, there was no conversion to the desired product **129a** and only starting material could be detected by GC-MS, confirming that the organocatalyst was not acting as an amine donor for the enzyme.

Finally, we substituted the (*S*)–selective ATA-256 for the (*R*)–selective ATA-025 in the reaction with (*S*)–proline (**L21**), to investigate the match/mismatch effect between the newly formed amine bearing stereocenter and the organocatalyst. The ATA-025 biocatalysed reaction at 30 °C, in the absence of **L21**, provided 35% conversion (*entry 18*). We were pleased to observe an increased 74% conversion (*entry 19*) when the same reaction was carried out in the presence of **L21**; although the d.r. remained at 1:1, there is a clear indication that the proline **L21** is accelerating the IMAMR.

It is important to mention that all the control experiments, without any enzyme were performed for all solvents and at all temperatures, and, as expected, no conversion and only starting material was observed (*entries 2, 4, 6, 8, 13 and 16*, determined by GC-MS).

Working under the reaction conditions for entry 7, Table 1 (ATA-256, 10% DMSO [v/v], 30 °C) we screened different organocatalysts, **L22-30** (Figure 3). We began the screening of organocatalysts with the proline derivatives **L22** and **L23**. Proline derivatives are popular and diverse organocatalysts; first shown to be highly effective for asymmetric intermolecular aldol reactions,[101] they have since expanded its applicability in the synthesis of heterocycles,[102] in particular *via* asymmetric Michael additions.[103] Proline derivatives are a non-toxic, stable and soluble in water,[104]

making them an ideal starting point for our investigation. The other organocatalysts which were used during the investigation were chosen as they were ready available within the lab and have been previously used for organocatalytic IMAMR.[69]

The use of **L22** and **L23** as organocatalysts did not improve conversion or d.r. (compare Table 3 *entries 1 and 2 with* Table 1, *entry 3*). However, as the reaction was only performed with 10% DMSO [v/v], not all of the organocatalyst was fully dissolved, preventing perhaps the organocatalysts from working to their full potential. Therefore, we decided to increase the amount of solvent used to 20% DMSO [v/v] and for the first time we obtained, using **L22**, an improvement in the d.r. to 3:2 with similar conversion (85%, *entry 4*) than the reaction without organocatalyst (81%, *entry 1*). When the reaction was carried out with **L23**, 74% conversion and 3:2 d.r. was obtained (Table 3, *entry 5*). We then tested a variety of other organocatalysts none of which improved either the conversion or the d.r. (Table 3, *entries 5-16*). Finally, we used **L30** within the reaction which provided an improved yield of 89% after 48 h but the d.r. obtained was 1:1 (Table 3, *entry 17*). It is also worth noting, that all the control reactions that consisted of only the organocatalyst, without any enzyme, failed to form the desired **129a**.

With **L22**, using 20% DMSO [v/v], as the most effective organocatalysts, we investigated once again the mismatch effect using the (*R*) selective ATA-025 (Table 3, *entry 20*). Unfortunately, the conversion of the reaction decreased to 64% and the d.r. reverted back to 1:1. We also attempted the reaction with a lower loading of organocatalyst (50 mol%, Table 3, *entry 21*). Although the d.r. of the reaction remained at 3:2, the conversion decreased to 69% after 48 h.

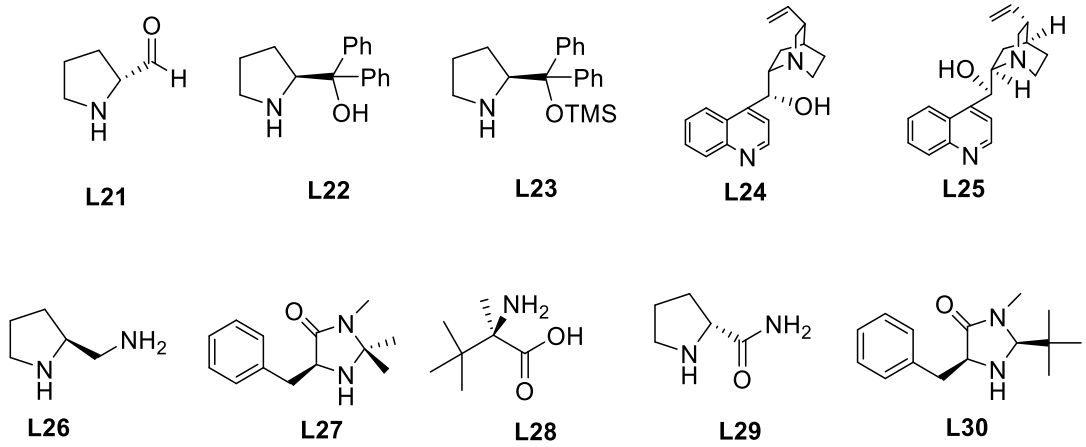
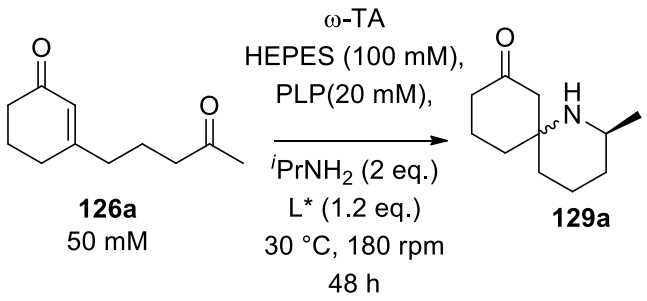


*Figure 3: Structures of organocatalysts used for the transamination of **126a**.*

*Table 3: Screening of organocatalysts for the synthesis of **129a**[a]*



Entry	ATA (selectivity)	Solvent (%v/v)	Temp (°C)	L*	Conv (%)[b] after 24 h	Conv (%)[b] after 48 h	d.r.[b]
1.	256 (*S*)	DMSO (10)	30	-	22	81	1:1
2.	256 (*S*)	DMSO (10)	30	**L22**	68	76	1:1
3.	256 (*S*)	DMSO (10)	30	**L23**	36	64	1:1
4.	256 (*S*)	DMSO (20)	30	**L22**	74	85	3:2
5.	256 (*S*)	DMSO (20)	30	**L23**	33	74	3:2
6.	256 (*S*)	DMSO (20)	30	**L24**	35	54	1:1
7.	-	DMSO (20)	30	**L24**	0	0	-
8.	256 (*S*)	DMSO (20)	30	**L25**	60	82	1:1
9.	-	DMSO (20)	30	**L25**	0	0	-
10.	256 (*S*)	DMSO (20)	30	**L26**	14	29	1:1
11.	-	DMSO (20)	30	**L26**	0	0	-
12.	256 (*S*)	DMSO (20)	30	**L27**	18	32	1:1
13.	-	DMSO (20)	30	**L27**	0	0	-
14.	256 (*S*)	DMSO (20)	30	**L28**	7	20	3:2
15.	-	DMSO (2 0)	30	**L28**	0	0	-
16.	256 (*S*)	DMSO (20)	30	**L29**	45	67	1:1
17.	-	DMSO (20)	30	**L29**	0	0	-
18.	256 (*S*)	DMSO (20)	30	**L30**	87	89	1:1
19.	-	DMSO (20)	30	**L30**	0	0	-
20.	025 (*R*)	DMSO (20)	30	**L22**	24	64	1:1
21.	256 (*S*)	DMSO (20)	30	**L22**[c]	55	69	3:2

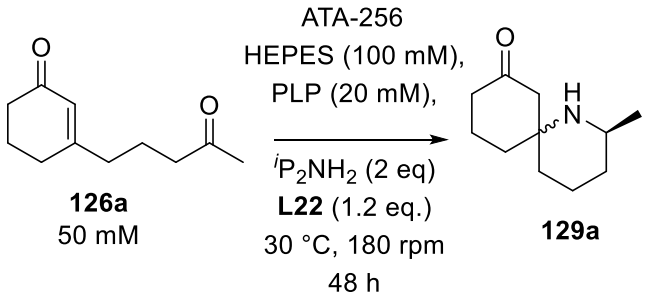
[a] Reaction conditions: ω-TA (5 mg/ mL), **126a** (50 mM), $^{i}PrNH_2$ (2 eq), HEPES buffer (100 mM, pH 7.5), PLP (20 mM), 180 rpm, 48 h.

[b] Determined by GC-MS.

[c] 50 mol% of organocatalyst **L22** was used.

As organocatalyst **L22** is not water-soluble and requires 20% DMSO [v/v] for the reaction to succeed, we decided to explore the compatibility of a range of other organic solvents with our enzyme (Table 4). We began with acetonitrile (10% [v/v]), and although the d.r. remained at 3:2, the conversion substantially decreased to 25% (Table 4, *entry 1*). THF (10% [v/v]), also showed no improvement in d.r., remaining at 3:2 ratio and dramatically decreased the conversion to 3% after 48 h. When isopropanol (10% [v/v]) was used as a co-solvent, **L22** could not be dissolved and, as a result, the d.r. of **129a** reverted back to 1:1 but with an improved conversion of 91% was achieved. It is also worth noting that no transamination occurred in any of the control reactions (Table 4, *entries 2, 4 and 6*).

*Table 4: Screening of solvents for synthesis of **129a** [a]*



Entry	ATA (selectivity)	Solvent (%v/v)	L*	Conv (%) [b] after 24 h	Conv (%) [b] after 48 h	d.r. [b]
1.	256 (*S*)	Acetonitrile (10)	**L22**	9	25	3:2
2.	-	Acetonitrile (10)	**L22**	0	0	-
3.	256 (*S*)	THF (10)	**L22**	1	3	3:2
4.	-	THF (10)		0	0	-
5.	256 (*S*)	Isopropanol (10)	**L22**	86	91	1:1
6.	-	Isopropanol (10)	**L22**	0	0	-

[a] Reaction conditions**:** ATA-256 (5 mg/ mL), **126a** (50 mM), $^{i}PrNH_2$ (2 eq), HEPES buffer (100 mM, pH 7.5), PLP (20 mM), 180 rpm, 48 h.
[b] Determined by GC-MS.
[c] Organocatalyst did not dissolve in the reaction media.

With **L22** as our optimal organocatalyst, we then assessed the amounts and different types of amine donors (Figure 4). The 'smart' amine donor **A2** and the more sterically demanding methylbenzylamine (MBA, **A4**), have shown to be extremely effective in previous work with ω-TA enzymes.[105]

Increasing the amount of isopropylamine (IPA, **A1**) to 4 eq. in the presence **L22** showed no improvement in either the conversion or the stereoselectivity of the reaction (Table 5, *entries 1 and 2*). When **A2** (2 eq.) was employed as amine donor, unfortunately, the conversion of the reaction could not be determined as the product could not be extracted from the aqueous layer as a result of the amine donor polymerising (Table 5, *entries 3 and 4*).[59] We then used 1.1 and 3.3 eq. of **A3**, neither of which provided any conversion to the desired **129a** (Table 5*, entries 5-8*). This could be due to a mismatch effect between the amine donor and the enzyme. For this reason, we tried 2 eq. of **A4** as amine donor, and, to our surprise, we obtained 100% conversion after 48 h (Table 5, *entries 9 and 10*) but a 1:1 d.r. when the organocatalyst **L22** (entry 11) was used. Revisiting the mismatch effect, we tested ATA 025 with **A4** using organocatalyst **L22** (Table 5, *entry 11*). This unfortunately, showed no improvement in d.r. and the conversion dramatically decreased to 3%.

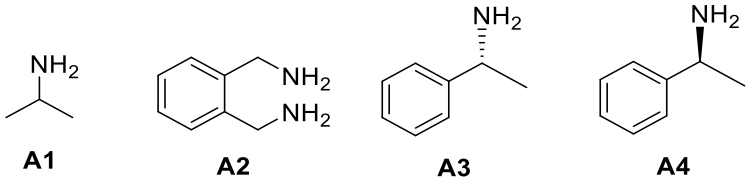
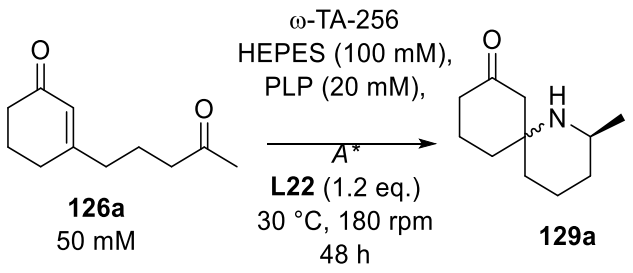


*Figure 4: Structures of different amine donors used for the synthesis of **129a**.*

*Table 5: Optimisation of amine donors for synthesis of **129a** [a]*



Entry	ATA (selectivity)	L*	A (eq.)	Conv (%)[b] after 24 h	Conv (%)[b] after 48 h	d.r.[b]
1.	256 (*S*)	**L22**	**A1** (4)	75	78	3:2
2.	256 (*S*)	-	**A1** (4)	19	67	1:1
3.	256 (*S*)	**L22**	**A2** (2)	n.d.[c]	n.d.[c]	-
4.	256 (*S*)	-	**A2** (2)	n.d.[c]	n.d.[c]	-
5.	256 (*S*)	**L22**	**A3** (1.1)	0	0	-
6.	256 (*S*)	-	**A3** (1.1)	0	0	-
7.	256 (*S*)	**L22**	**A3** (3)	0	0	-
8.	256 (*S*)	-	**A3** (3)	0	0	-
9.	256 (*S*)	**L22**	**A4** (2)	94	100	1:1
10.	256 (*S*)	-	**A4** (2)	98	100	1:1
11.	025 (*R*)	**L22**	**A4** (2)	0	3	1:1

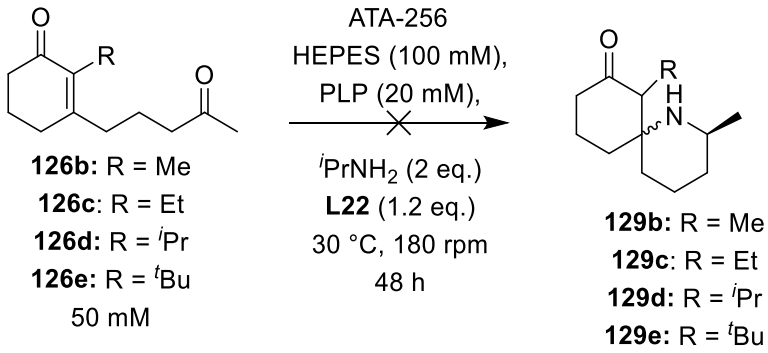
[a] Reaction conditions: ATA-256 (5 mg/ mL), **126a** (50 mM), $^{i}PrNH_2$ (2 eq), HEPES buffer (100 mM, pH 7.5), PLP (20 mM), 180 rpm, 48 h.
[b] Determined by GC-MS.
[c] Unable to extract product after amine donor polymerisation

Next, we explored the biocatalysed transamination reaction of the α,β-disubstituted keto-cyclohexenones **126b**-**126e** in the presence of **L22** as organocatalyst (Table 6). Preliminary results undertaken by Ryan *et al.* established that the transamination of α,β-disubstituted keto-cyclohexanones (using 2 eq. of IPA as amine donor, at 50 °C) provided, after three days, lower conversions as the alkyl chain length in the α position increases.[106]

Under the optimised conditions for the synthesis of **129a** (ATA-256, IPA (2 eq.), **L22** (1.2 eq.) DMSO (20% [v/v]), Table 3, *entry 7*), unfortunately, the *n*-ethyl, isopropyl

and *tert*-butyl substituted substrates **126c-e** provided no conversion to the desired **129c-e** after 48 h. For the transamination of **126b** in the presence of the organocatalyst **L22**, only traces of the corresponding cyclised product **129b** were observed *via* GC-MS (3% conversion) after 48 h. The lack of conversion for substrates **126b-e** is most likely due to tetrasubstituted enones being less reactive than **126a**, as well as steric clash from the alkyl substituent with the organocatalyst, hindering the formation of the product. Based on Ryan's previous results[106] in the absence of organocatalysts, we cannot rule out that the transamination is not taking place because the alkyl chain in the substrate is too bulky for the pocket of the enzyme.

*Table 6: Transamination of α-alkyl substituted keto-cyclohexenones **126b-e** in the presence of organocatalysts **L22**.*[a]



126b: R = Me
126c: R = Et
126d: R = ^{i}Pr
126e: R = ^{t}Bu
50 mM

129b: R = Me
129c: R = Et
129d: R = ^{i}Pr
129e: R = ^{t}Bu

Entry	Substrate	ATA (selectivity)	Conv (%)[b] after 24 h	Conv (%)[b] after 48 h
1.	**129b**	256 (*S*)	0	0
2.	**129b**	-	0	4
3.	**129c**	256 (*S*)	0	0
4.	**129c**	-	0	0
5.	**129d**	256 (*S*)	0	0
6.	**129d**	-	0	0
7.	**129e**	256 (*S*)	0	0
8.	**129e**	-	0	0

[a] Reaction conditions: ATA-256 (5 mg/ mL), **126b-e** (50 mM), ^{i}PrNH$_2$ (2 eq), **L22** (1.2 eq.) HEPES buffer (100 mM, pH 7.5), PLP (20 mM), 180 rpm, 48 h.
[b] Determined by GC-MS.

2.4 Conclusion and future work

In conclusion, we have successfully synthesised keto-cyclohexenone substrates **126a-e** in an efficient manner over 3 steps. The optimisation of the transamination triggered IMAMR of **126a** using organocatalysis was studied. (*S*)-(−)-α,α-2-pyrrolidinemethanol (**L22**) was found to be the most successful organocatalyst, alongside DMSO as a co-solvent (20% [v/v]) and IPA (2eq.) as the amine donor, affording **129a** in a 3:2 d.r. and in good isolated yield 76%. However, transamination of α,β-disubstituted keto-cyclohexenones **126b**-**e** was unsuccessful as a result of the substrates being less reactive than **126a** and possible steric interactions between substituents on the substrate and the organocatalyst. We believe that future attempts of transamination of keto-cyclohexenone substrates using organocatalysts should include TAs enzymes that have genetically engineered to withstand organic solvent such as those reported by Kroutil *et al*.[76]

2.5 Experimental

General methods and considerations.

TLC: All thin layer chromatography (TLC) was run on Sigma Aldrich silica gel 60 F_{254} aluminium plates and visualised by UV light and by either staining solutions $KMnO_4$ or phosphomolybdic acid.

FT-IR: Spectra were recorded on a Nicolet® 380 Fourier Transform Infrared Spectrometer. Only the most significant frequencies have been reported (in cm^{-1}) for characterisation.

Flash Chromatography: Purification was carried out by either column chromatography using Geduran® Silica gel 60 or by Biotage® Isolera™ Systems. The eluents used are mentioned below.

NMR: ^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR spectra were recorded on a JEOL® ECS-400 NMR spectrometer (400, 100.6 and 162 MHz, respectively) using $CDCl_3$ as solvent. The chemical shifts values are recorded in ppm with the residual $CDCl_3$ referenced to 7.26 and 77.00 for ^{1}H NMR and ^{13}C NMR respectively. Data is reported as follows: chemical shift, multiplicity (singlet = s, doublet= d, triplet= t, quartet= q, multiplet= m), coupling constants (*J*) in Hz and integration.

GC-MS: Conversion and low resolution mass spectra were recorded on either Agilent 6850 Series connected to an Agilent 5973 mass selective detector using a HP-5ms (30 m x 0.25 mm x 0.25 µm) or on an Agilent Technologies® 7890B GC connected to an Agilent Technologies® 5977b MSD using a HP-5MS (30 m x 0.25 mm x 0.25 µm).

Helium was used as the carrier gas at 10 psi, and the samples were ionised by an electronic impact (EI) source at 70 ev.

HPLC-DAD: Attempts to determine the enantioselectivity were carried out on an Agilent 1100 series HPLC equipped with a G1313B diode array detector and a G1311A Quat pump. Chiral columns used for analysis were Lux 5µ Cellulose-1 and Lux 5µ Amylose-2 (Phenomenex®, 250 mm x 4.6 mm). ATA-256 enzymes, respectively.

HRMS: High resolution mass spectra were obtained on a 6540 LC-QToF spectrometer and the samples were ionised ESI techniques and introduced through a high pressure liquid chromatography (HPLC) model Agilent Technologies® 1260 Infinity Quaternary LC system.

MW: Irradiated reactions were carried out on an Anton Paar® Monowave 300 Microwave Synthesis Reactor, using 10 or 30 mL glass vials (sealed with a PTFE-coated silicone septum and closed with a snap cap made of PEEK).

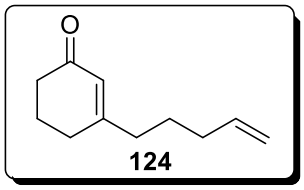
Optical rotations: All optical rotation measurements were performed on Bellingham + Stanley® ADP220 Polarimeter with a 0.5 cm cell (c given in g/100 mL) using DCM as a solvent.

Materials: All commercially available reagents were purchased from Acros, Alfa Aesar, Manchester Organics, Fisher, Fluorochem and Sigma-Aldrich and were used without further purification unless stated otherwise. Anhydrous, THF, DCMS, Et_2O and toluene were obtained from Pure Solv™ Solvent Purification Systems. All commercially available transaminase enzymes, ATA-256 and ATA-025, were purchased in the form of lyophilised cell extract from Codexis.

Glassware: All reactions which required inert conditions, the glassware was flame dried under vacuum and argon was used for the inert gas.

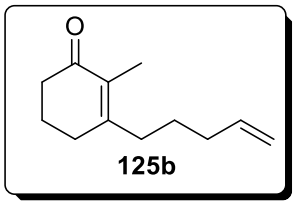
General procedure for the synthesis of 3-(4-pentenyl)-2-cyclohexen-1-one and 2-methyl-3-(pent-4-en-1-yl)cyclohex-2-en-1-one (124 and 125b):

A solution of Grignard reagent **123**, prepared from 5-bromo-1-pentene (1.3 eq, 3.08 mL, 26 mmol) and magnesium turnings (1.2 eq, 564 mg, 24 mmol) in diethyl ether (25 mL), was added to the corresponding cyclohexenones **122** or **128** (1 eq, 20 mmol) in diethyl ether (20 mL) at room temperature for 30 min. After the addition, the reaction mixture was stirred at RT for 1 h and then quenched with sat. NH_4Cl solution (50 mL). The aqueous mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with aqueous HCl (2M, 20 mL). The organic layer was then washed with brine (2 × 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography (EtOAc / cyclohexane, 1:9).



3-(4-pentenyl)-2-cyclohexen-1-one (124): Compound **124** was synthesised using the general procedure for the synthesis of **124** and **125b** from 3-ethoxy-2-cyclohexenone (**122**, 2.81 g, 20 mmol) to give the named compound as a yellow oil. **Yield:** 2.27 g, 69%. **RF:** 0.20 (EtOAc / cyclohexane, 1:9). **FTIR (neat) V_{max}:** 2931, 2867, 1666, 1624, 1251, 1191, 910, 888 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 5.86 (s, 1H), 5.82 – 5.70 (m, 1H), 5.05 – 4.90 (m, 2H), 2.34 (t, *J* = 6.6 Hz, 2H), 2.26 (t, *J* = 6.0 Hz, 2H), 2.23 – 2.15 (m, 2H), 2.06 (q, *J* = 7.0 Hz, 2H), 2.01 – 1.92 (m, 2H), 1.64 – 1.53 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 200.2, 166.5, 138.0, 125.9, 115.4, 37.5, 33.3, 29.8, 26.1, 22.8.

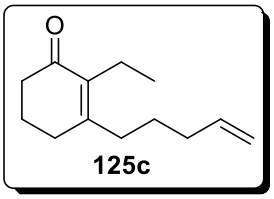
HRMS (m/z): Calculated $C_{11}H_{17}O$ $[M+H]^+$: 165.1274, found: 165.1279. Data in accordance with literature.[100]



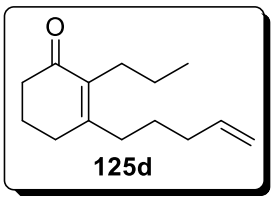
2-methyl-3-(pent-4-en-1-yl)cyclohex-2-en-1-one (125b): Compound **125b** was synthesised using the general procedure for the synthesis of **124** and **125b** from 2-methyl-3-ethoxy-2-cyclohexenone (**128**, 643 mg, 4.17 mmol) to give the named compound as a yellow oil. **Yield:** 446 mg, 60%. **RF:** 0.48 (EtOAc / cyclohexane, 3:7) **FTIR (neat) V_{max}:** 2954, 1634, 1605, 1383, 1353, 1233, 1201, 1121, 1097, 1050, 934, 919 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 5.86 – 5.74 (m, 1H), 5.08 – 4.95 (m, 2H), 2.38 (t, *J* = 4 Hz, 2H), 2.35 – 2.29 (m, 2H), 2.28 – 2.19 (m, 2H), 2.13 – 2.05 (m, 2H), 1.95 – 1.88 (m, 2H), 1.76 (s, 3H), 1.59 – 1.49 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 199.8, 159.0, 138.1, 131.1, 115.3, 37.9, 34.9, 33.9, 31.0, 26.8, 22.8, 10.8. **HRMS (m/z):** Calculated $C_{12}H_{19}O$ $[M+H]^+$: 179.1236, found: 179.1325. Data in accordance with literature.[107]

General procedure for the alkylation of 3-(4-pentenyl)-2-cyclohexen-1-one (125c-e):

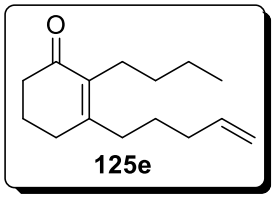
t-BuOK (1.5 eq, 1.44 g, 12.8 mmol) was added to 3-(4-pentenyl)-2-cyclohexen-1-one (**124**, 1 eq, 1.39 g, 8.4 mmol) in dry Et_2O (34 mL) and the mixture was left to stir at RT for 15 min. The appropriate alkyl halide (1.2 eq, 10.2 mmol) was then added dropwise to the reaction and left to stir for 1 h at RT. The reaction mixture was quenched with sat. NH_4Cl solution (50 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The organic layer was then washed with brine (2 × 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography (EtOAc 1:9 cyclohexane) to provide **125c-e.**



2-ethyl-3-(4-pentenyl)-2-cyclohexen-1-one (125c): Compound **125c** was synthesised using the general procedure for the alkylation of 3-(4-pentenyl)-2-cyclohexen-1-one, using bromoethane (1.2 eq, 0.39 mL, 5.16 mmol) as the corresponding alkyl halide to give the named compound as a yellow oil. **Yield:** 287 mg, 35%. **RF:** 0.64 (EtOAc / cyclohexane, 3:7). **FTIR (neat) V_{max}:** 2954, 2930, 2868, 1706, 1641, 1620, 1456, 1431, 1363, 1350, 1188, 991, 909 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 5.87 – 5.74 (m, 1H), 5.07 – 4.96 (m, 2H), 2.37 – 2.21 (m, 8H), 2.10 (q, *J* = 6.8 Hz, 2H), 1.95 – 1.85 (m, 2H), 1.61 – 1.51 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 198.9, 158.4, 137.9, 136.9, 115.1, 38.0, 34.2, 33.8, 30.5, 27.2, 22.5, 18.2, 14.1. Data in accordance with literature.[106]



2-propyl-3-(4-pentenyl)-2-cyclohexen-1-one (125d): Compound **125d** was synthesised using the general procedure for the alkylation of 3-(4-pentenyl)-2-cyclohexen-1-one using 1-bromopropane (1.2 eq, 0.33 mL, 3.7 mmol) as the corresponding alkyl halide to give the named compound as a yellow oil. **Yield:** 239 mg, 38%. **RF:** 0.68 (EtOAc / cyclohexane, 3:7). **FTIR (neat) V_{max}:** 2956, 2929, 2868, 1704, 1662, 1641, 1619, 1456, 1431, 1417, 1327, 1108, 991, 909 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 5.88 – 5.73 (m, 1H), 5.09 – 4.96 (m, 2H), 2.37 (t, *J* = 4.0 Hz, 2H), 2.32 (t, *J* = 6.0 Hz, 2H), 2.28 – 2.20 (m, 4H), 2.14 – 2.07 (m, 2H), 1.95 – 1.87 (m, 2H), 1.61 – 1.51 (m, 2H), 1.37 – 1.26 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 199.5, 159.0, 138.2, 135.8, 115.4, 38.3, 34.5, 34.0, 30.8, 27.4, 27.3, 23.1, 22.8, 14.5. **HRMS (m/z):** Calculated $C_{14}H_{23}O$ $[M+H]^+$: 207.1749, found: 207.1723. Data in accordance with literature.[106]

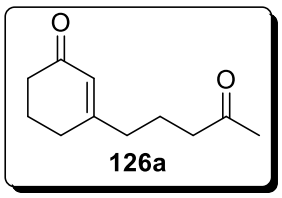


125e

2-butyl-3-(4-pentenyl)-2-cyclohexen-1-one (125e): Compound **125e** was synthesised using the general procedure for the alkylation of 3-(4-pentenyl)-2-cyclohexen-1-one, using 1-bromobutane (1.2 eq, 0.39 mL, 13.6 mmol) as the alkyl halide, to give the named compound as a yellow oil. **Yield:** 183 mg, 27%. **RF:** 0.7 (EtOAc / cyclohexane, 3:7). **FTIR (neat) V_{max}:** 2953, 2929, 2861, 1705, 1662, 1620, 1456, 1431, 1530, 1326, 1187, 1112, 991, 909 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** δ 5.92 – 5.64 (m, 1H), 5.02 (m, 2H), 2.37 –2.34 (m, 2H), 2.32 -2.29 (m, 2H), 2.26 – 2.22 (m, 2H), 2.13 – 2.08 (m, 2H), 1.94 – 1.88 (m, 2H), 1.60 – 1.52 (m, 4H), 1.33-1.25 (m, 4H), 0.87 (t, *J* = 9.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 199.4, 158.7, 138.1, 135.9, 115.3, 38.2, 34.4, 33.9, 32.0, 30.7, 27.3, 25.0, 23.1, 22.7, 14.1. **HRMS (m/z):** Calculated $C_{15}H_{25}O$ $[M+H]^+$: 221.1905, found: 221.1906. Data in accordance with literature.[106]

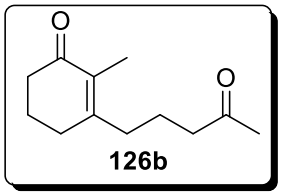
General procedure for Wacker oxidation of intermediates 124 and 125b-e:

To a solution of $PdCl_2$ (10%, 50 mg, 0.60 mmol) and CuCl (2 eq, 12.0 mmol) in DMF (20 mL) and water (5 mL), that had been stirred under an O_2 atmosphere for 1 h, a solution of **124** or **125c-e** (1 eq, 6.00 mmol) in DMF (5 mL) was added drop wise and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with NH_4Cl (20 mL) and ammonia hydroxide solution (1M, 10 mL) and extracted with diethyl ether (3 x 40 mL). The combined organic extracts were then washed with brine (2 x 60 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography (EtOAc / cyclohexane 3:7) to provide compounds **126a-e**.



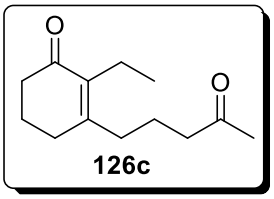
126a

3-(4-oxopentenyl)-2-cyclohexen-1-one (126a): Compound **126a** was synthesised from **124** (988 mg, 6.02 mmol) using the general procedure for Wacker oxidation of intermediates **124** and **125b-e** to give the named compound as a yellow oil. **Yield:** 1.03 g, 95%. **RF:** (EtOAc / cyclohexane, 1:1). **FTIR (neat) V_{max}:** 2940, 2889, 1712, 1668, 1623, 1455, 1428, 1348, 1252, 1181, 1159, 966, 887, 757, 499, 487 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 5.75 (s, 1H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.25 (t, *J* = 8.0 Hz, 2H), 2.20 (t, *J* = 5.9 Hz, 2H), 2.12 (t, *J* = 7.6 Hz, 2H), 2.04 (s, 3H), 1.93 – 1.84 (m, 2H), 1.74 – 1.62 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ**: 208.1, 199.9, 165.6, 126.1, 42.7, 37.4, 37.3, 30.2, 29.6, 22.7, 20.7. **HRMS (m/z):** Calculated $C_{11}H_{17}O_2$ $[M+H]^+$: 181.1223, found: 181.1223. Data in accordance with literature.[100]



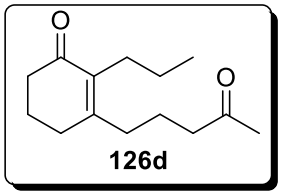
126b

2-methyl-3-(4-oxopentenyl)-2-cyclohexen-1-one (126b): Compound **126b** was synthesised from **125b** (227 mg, 1.28 mmol) using the general procedure for the general procedure for Wacker oxidation of intermediates **124** and **125b-e** to give the named compound as a yellow oil. **Yield:** 198 mg, 80%. **RF:** (EtOAc / cyclohexane, 1:1). **FTIR (neat) V_{max}:** 2935, 2869, 1713, 1658, 1430, 1355, 1170, 1085. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 2.46 (t, *J* = 7.2 Hz, 2H), 2.37 (t, *J* = 8.0 Hz, 2H), 2.35 – 2.29 (m, 2H), 2.26 – 2.19 (m, 2H), 2.14 (s, 3H), 1.96 – 1.86 (m, 2H), 1.77 – 1.67 (m with a s at 1.75, 5H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 208.2, 199.6, 158.1, 131.3, 43.0, 37.8, 34.5, 30.7, 30.1, 22.6, 21.3, 10.8. **HRMS (m/z):** Calculated $C_{12}H_{19}O_2$ $[M+H]^+$: 195.1385, found: 195.1371. . Data in accordance with literature.[106]



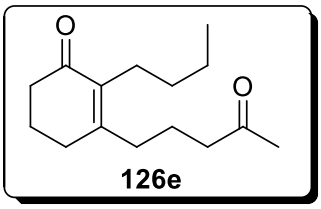
126c

2-ethyl-3-(4-oxopentenyl)-2-cyclohexen-1-one (126c): Compound **126c** was synthesised from **125c** (240 mg, 1.25 mmol) using the general procedure for the general procedure for Wacker oxidation of intermediates **124** and **125b-e** to give the named compound as a yellow oil. **Yield:** 203 mg, 78%. **RF:** 0.57 (EtOAc 1:1 cyclohexane). **FTIR (neat) V_{max}:** 2934, 2872, 1713, 1658, 1620, 1362, 1169, 1102 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 2.53 – 2.45 (m, 2H), 2.39 – 2.20 (m, 8H), 2.15 (s, 3H), 1.95 – 1.87 (m, 2H), 1.81 – 1.69 (m, 2H), 0.97 – 0.88 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 208.3, 199.3, 157.6, 138.0, 43.2, 38.2, 34.0, 30.5, 30.2, 22.7, 21.9, 18.5, 14.3. **HRMS (m/z):** Calculated $C_{13}H_{21}O_2$ $[M+H]^+$: 209.1536, found: 209.1534. Data in accordance with literature.[106]

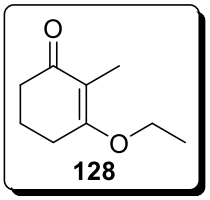


126d

2-propyl-3-(4-oxopentenyl)-2-cyclohexen-1-one (126d): Compound **126d** was synthesised from **125d** (96 mg, 0.47 mmol) using the general procedure for the general procedure for Wacker Oxidation of intermediates **124** and **125b-e** to give the named compound as a yellow oil**. Yield:** 86 mg, 83%. **RF:** 0.35 (EtOAc / cyclohexane, 3:7). **FTIR (neat) V_{max}:** 2957, 2932, 2870, 1714, 1659, 1456, 1430, 1365, 731 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 2.46 (t, *J* = 7.1 Hz, 2H), 2.39 – 2.26 (m, 4H), 2.26 – 2.17 (m, 4H), 2.13 (s, 3H), 1.94 – 1.84 (m, 2H), 1.79 – 1.66 (m, 2H), 1.34 – 1.20 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz) δ:** 208.2, 199.3, 158.0, 136.0, 43.2, 38.2, 34.1, 30.5, 30.1, 27.2, 23.0, 22.6, 21.8, 14.4. **HRMS (m/z):** Calculated $C_{14}H_{23}O_2$ $[M+H]^+$: 223.1693, found: 223.1699. Data in accordance with literature.[106]



2-butyl-3-(4-oxopentenyl)-2-cyclohexen-1-one (126e): Compound **126e** was synthesised from **125e** (105 mg, 0.48 mmol) using the general procedure for the general procedure for Wacker Oxidation of intermediates **124** and **125b-e** to give the named compound as a yellow oil. **Yield:** 75 mg, 71%. **RF:** 0.38 (EtOAc / cyclohexane, 3:7). **FTIR (neat) V_{max}:** 2954, 2931, 2870, 1714, 1659, 1620, 1456, 1430, 1364, 1170 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 2.47 (t, *J* = 7.2 Hz, 2H), 2.38 – 2.28 (m, 4H), 2.26 – 2.19 (m, 4H), 2.14 (s, 3H), 1.93 – 1.85 (m, 2H), 1.78 – 1.68 (m, 2H), 1.35 – 1.18 (m, 4H), 0.87 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 208.2, 199.3, 157.7, 136.3, 43.2, 38.2, 34.1, 32.1, 30.5, 30.2, 25.0, 23.1, 22.7, 21.8, 14.1. **HRMS (m/z):** Calculated $C_{15}H_{25}O_2$ $[M+H]^+$: 237.1849, found: 237.1844. Data in accordance with literature.[106]



2-methyl-3-ethoxy-2-cyclohexenone (128): To a solution of 2-methyl-1,3-cyclohexanedione (**127**, 2.60 g, 10.00 mmol) in toluene (20 mL) was added *p*-toluenesulfonic acid hydrate (49 mg, 0.25 mmol) and ethanol (6 mL). The mixture was stirred under Dean Stark conditions with continuous removal of water formed. An extra portion (5-10 mL) of a mixture of ethanol/toluene (1:3) was added to the reaction mixture every hour. After 12 h, TLC analysis showed that the reaction was complete. The reaction was concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc / cyclohexane, 1:1), to give the named compound as a colourless oil. **Yield:** 2.33 g, 73%. **RF:** 0.37 (EtOAc / cyclohexane 1:1). **FTIR (neat) V_{max}:** 2955, 1634, 1605, 1383, 1354, 1233, 1200, 1121, 1096 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 4.05 (q, *J* = 8.0 Hz, 2H), 2.59 – 2.47 (m, 2H), 2.33 (t, *J* = 8.0 Hz, 2H), 2.03 – 1.90 (m, 2H), 1.69 (s, 3H),

1.34 (t, *J* = 7.0 Hz, 3H).**^{13}C NMR (101 MHz, $CDCl_3$) δ:** 199.1, 171.6, 115.2, 63.6, 36.4, 25.5, 21.1, 15.5, 7.6. **HRMS (m/z):** Calculated $C_9H_{15}O_2$ $[M+H]^+$: 155.1072, found: 155.1066. Data in accordance with literature.[108]

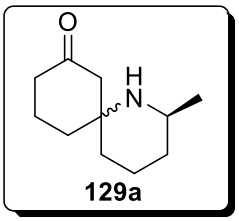
General procedure A, for the transamination of ketoenones 126a-e in the presence of organocatalyst:

Commercially available (*S*)-selective ATA-256 or (*R*)-selective ATA-025 (25 mg) was rehydrated in HEPES buffer (4.0 mL, 100 mM, pH 7.5) containing PLP (2.00 mM), isopropylamine (2 eq, 43 µL, 0.5 mmol) and the corresponding **L21-30** organocatalyst (1.2 eq, 0.298 mmol). The pH of the mixture was adjusted to 7.5, using aq. HCl solution (1 M), and the total volume of the reaction was adjusted to 4.5 mL by addition of HEPES buffer. The ketoenone substrate **126a-e** was added (50 mM, 0.5 mL in DMSO) and the reaction mixture incubated at 30 ^oC, 180 rpm for 48-72 h. The reaction was monitored by GC-MS. After completion, the pH of the supernatant was adjusted to 12 using aq. NaOH solution (4 M) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with NaOH solution (1 M, 10 mL). The organic layer was then dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash chromatography.

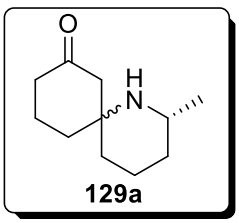
General procedure B, for the transamination of ketoenones 126a-e in the absence of organocatalysts: The general procedure A above was followed, omitting the addition of the organocatalyst.

General procedure C1, for the control experiments for the transamination of ketoenones 126a-e in the presence of organocatalysts: The general procedure A above was followed, omitting the addition of the enzyme.

General procedure C2, for the control experiments for the transamination of ketoenones 126a-e in the absence of organocatalysts: The general procedure A above was followed, omitting the addition of both the enzyme and the organocatalyst.



(–)-(2*S*)-2-methyl-1-azaspiro[5.5]undecan-8-one [(–)-129a)]: Compound **129a** was synthesised from **126a** (45 mg, 0.25 mmol) using general procedure A, with ATA-256 as the enzyme and **L21** as organocatalyst, to give the named compound as pale yellow oil. Unseparable mixture of diastereomers, **d.r.** 3:2 (determined GC-MS). **Yield:** 34 mg, 76% **RF:** 0.13 (MeOH CH_2Cl_2, 1:1). **$[\alpha]_D^{23}$** = – 103.5 (*c* 0.85, $CHCl_3$). **^{1}H NMR: (400 MHz, $CDCl_3$) δ:** 2.90 – 2.78 (m, 1H, diastereomer 1), 2.78 – 2.65 (m, 1H, diastereomer 2), 2.53 (br s, 2H), 2.30 – 1.98 (m, 8H), 1.95 – 1.48 (m, 16H), 1.19 – 1.05 (m, 2H), 0.96 (d, *J* = 7.3 Hz, 3H, diastereomer 1), 0.94 (d, *J* = 7.3 Hz, 3H, diastereomer 2), 0.91 – 0.78 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 211.1, 57.2, 56.9, 56.9, 48.4, 45.8, 45.6, 41.3, 41.1, 40.1, 35.9, 35.4, 34.6, 34.5, 30.1, 23.2, 21.0, 20.8, 20.7, 20.2 **HRMS (m/z):** Calculated $C_{11}H_{20}NO$ $[M+H]^+$: 182.1525, found: 182.1538. Data in accordance with literature.[106]



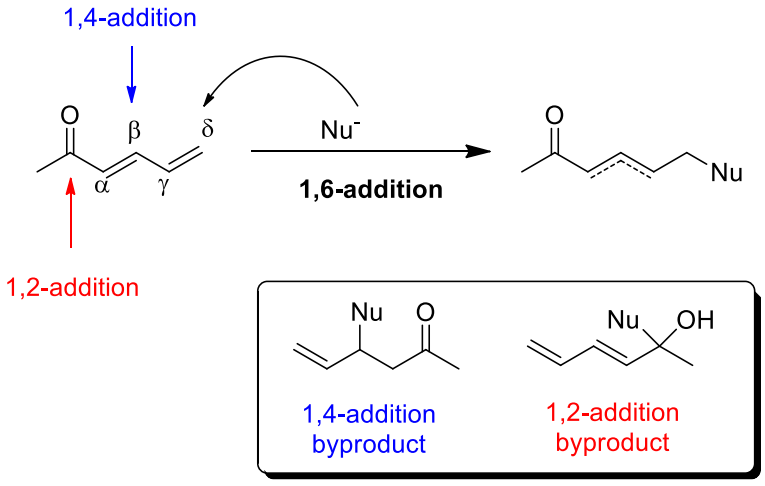
(+)-(2*R*)-2-methyl-1-azaspiro[5.5]undecan-8-one [(+)-129a)]:Compound **129a** was synthesised from **126a** (45 mg, 0.25 mmol) using general procedure A, using ATA-025 as enzyme and **L21** as organocatalyst, to give the named compound as pale yellow oil. **d.r.** 1:1.

(determined GC-MS). **Yield:** 32 mg, 32% **RF:** 0.13 (MeOH 1:1 CH_2Cl_2). **$[\alpha]_D^{26}$** = + 23.3 (*c* 1.2, $CHCl_3$) Data in accordance with literature.[106]

3. Tandem biocatalysed transamination- vinylogous aza-Michael reaction of ketodienones and ketodieno esters

3.1 Introduction

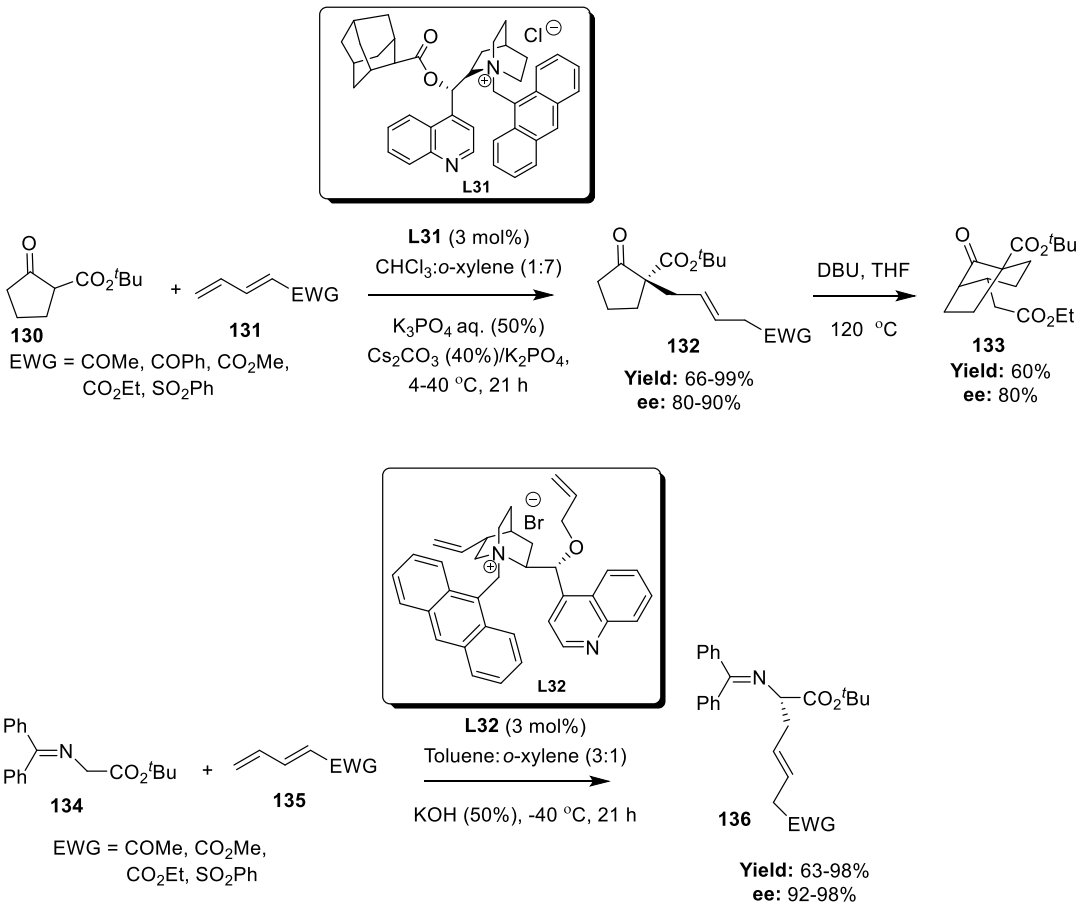
The vinylogous Michael reaction is a 1,6-conjugate addition where the nucleophilic attack occurs at the δ position in the α,β,γ,δ-bisunsaturated system (Scheme 35).[109] Whilst asymmetric nucleophilic 1,2- and 1,4-additions have been extensively studied,[110] research on the asymmetric 1,6-addition is somewhat limited, as the regio- and stereocontrolled addition is more challenging. This is a consequence of the lower reactivity of α,β,γ,δ-bisunsaturated system. The longer distance between the electron with drawing group (EWG) and the reactive site (δ position) results is less stereo- and regio- control.[111] Regioselectivity issues also arise from competition with the other reactivity sites (the β-position and the carbon of the carbonyl), leading to a number of regioisomeric by-products (Scheme 35). In fact, Hayashi reported that for organocatalytic additions to α,β,γ,δ-bisunsaturated carbonyls, 1,2- and 1,4-additions are actually favoured over the 1,6-addition.[112]



Scheme 35: Vinylogous Michael reaction with 1,2- and 1,4-addition by-products.

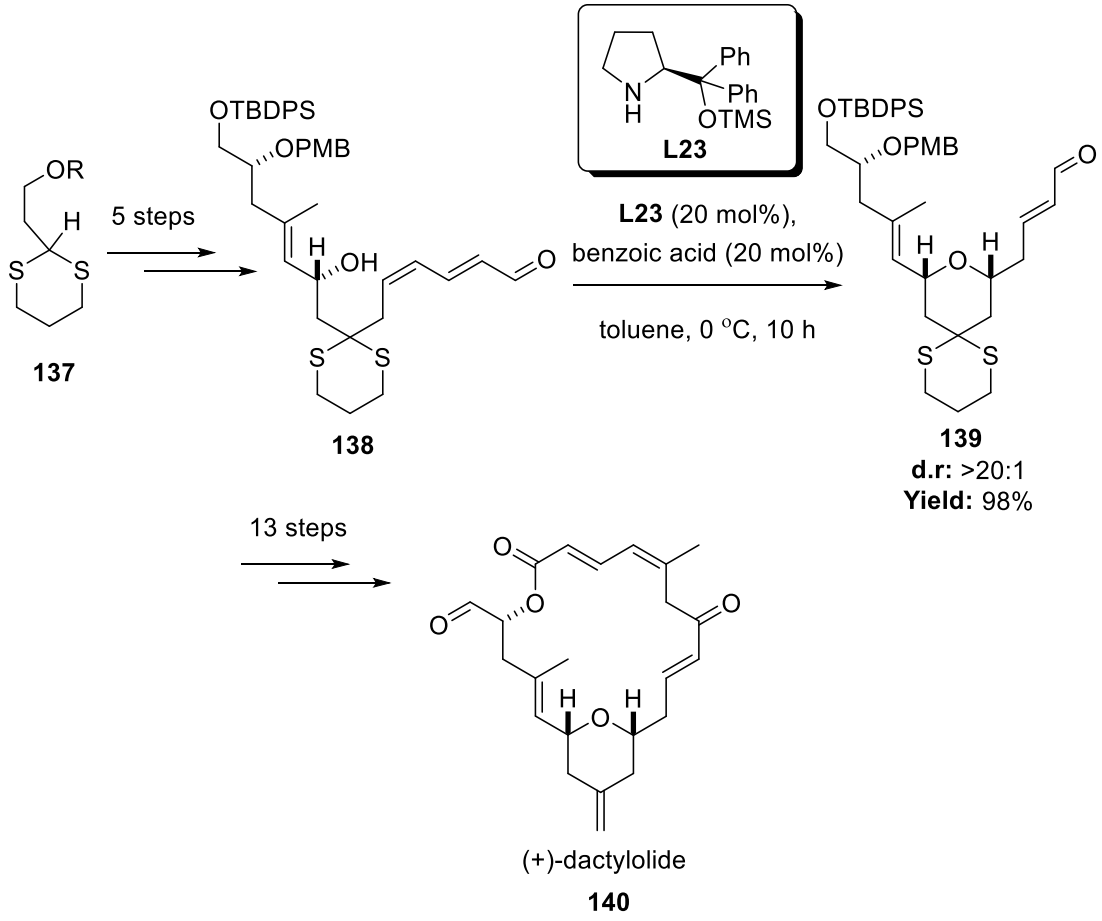
Over the past decade, there has been an increase in research into the asymmetric vinylogous Michael reaction. However, most examples in this area use carbon and oxygen as nucleophiles, with very few examples of the use of nitrogen nucleophiles, and most of them of non-asymmetric.

The first organocatalytic enantioselective 1,6-addition of β-ketoesters and glycine imine derivatives using carbon nucleophiles, was reported by Jørgensen (Scheme 36).[109] Under phase-transfer conditions, using the Cinchona derived catalyst **L31**, the 1,6-addition reaction of the β-ketoesters **130** to the different ketones, esters and sulfones acceptors **131** proceeds with high yield and ee's of 80-90%. The group also reported that treatment of **132** (EWG =CO_2Et) with 1,8-diazabicyclo[5,4.0]undec-7-ene (DBU) in THF promoted isomerisation of the double bond, resulting in a spontaneous IMAMR to afford **133** as a single isomer and no change in the enantioselectivity. The conjugate addition with benzophenone imine derivatives **134** to the unsubstituted dienes **135** also affords the desired products **136** with high enantioselectivity and moderate-high yields using **L32** (Scheme 36).



Scheme 36: Organocatalytic 1,6-addition of β-ketoeters and benzophenone imines to unsubstituted dienes by Jørgensen.

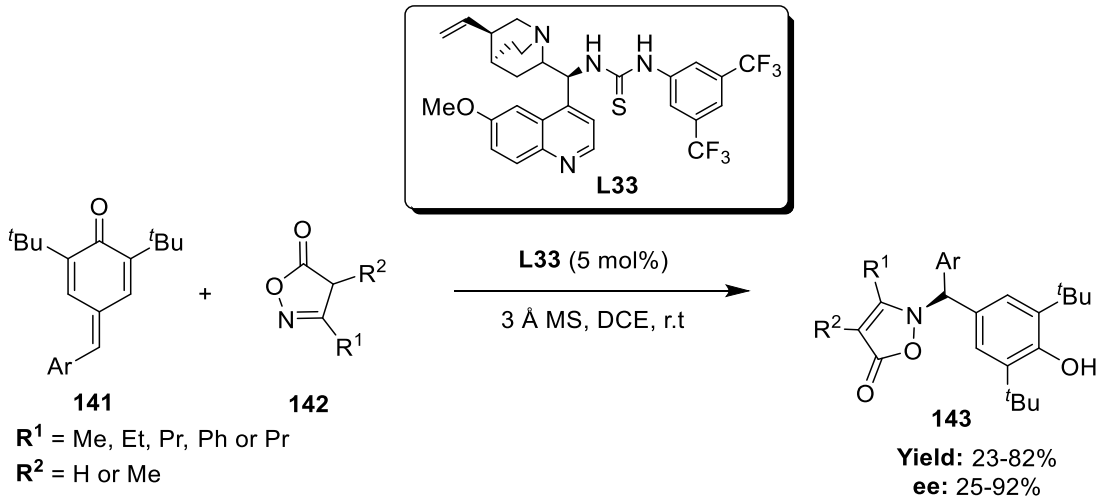
There are a number of asymmetric 1,6-additions reactions using carbon nucleophiles that have been reported, including the work of Jørgensen,[113] Melchiorre,[114] and Ye,[115, 116] using a variety of substrates such as dienals and dienones. The use of oxygen nucleophiles in asymmetric 1,6-addition reactions has also been reported in the literature by Jørgensen,[117] Enders[118] and Hong.[119] For example, Hong *et al.* reported a organocatalytic intramolecular oxa-1,6-addition of a 2,4-dienal as part of the total synthesis of (+)-dactylolide (Scheme 37). Melchiorre and co-workers have also reported the use of thiols as nucleophiles for the asymmetric 1,6-addition of alkyl thiols to cyclic dienones.[120]



Scheme 37: Organocatalytic intramolecular oxa-1,6- addition of a 2,4-dienal reported by Hong et al.

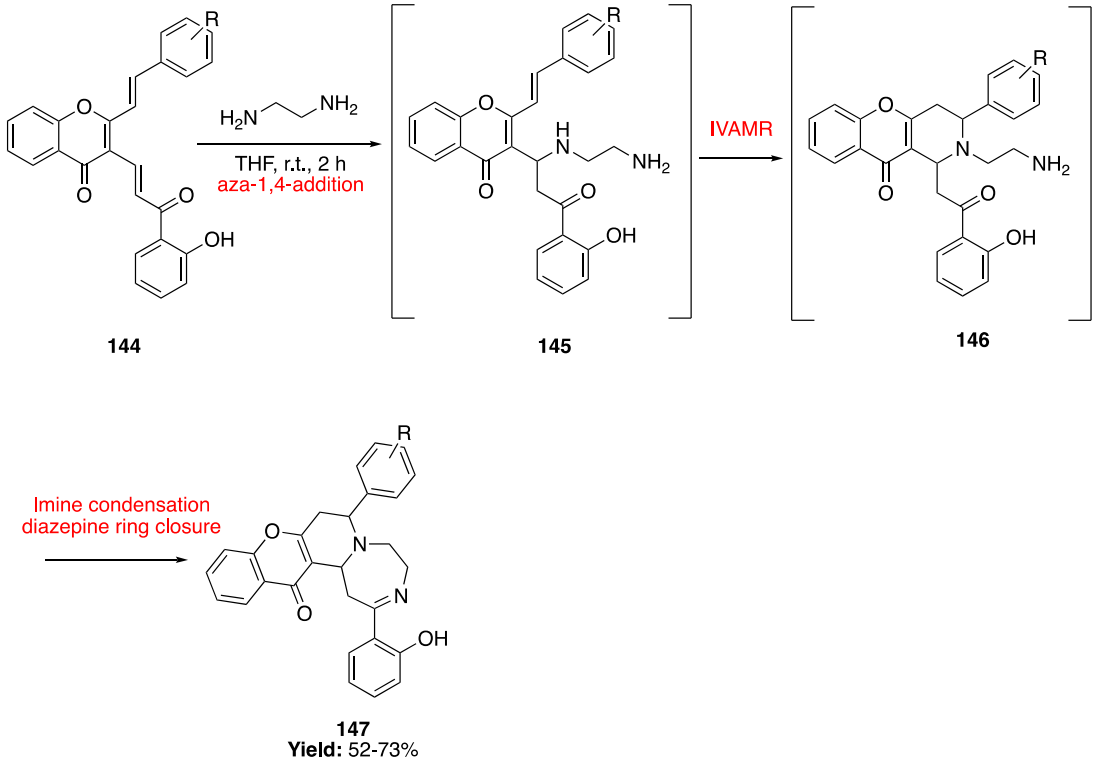
Nitrogen-centered nucleophiles have not been a popular choice for 1,6-addition reactions, with few examples known, even for non-asymmetric variants of the reaction. Blay *et al.* described an intermolecular enantioselective aza-1,6-addition using a bifunctional thiourea-Brønsted base **L33** as catalyst for the synthesis of isoxazolin-5-ones **139** (Scheme 38).[111] They were the first to report the use of isoxazolinones *N*-nucleophiles **138** for the addition to *p*-quinone methides **137**. *p*-*Q*uinone methides have a cyclic bis-vinylogous framework, and the aromatisation in

the final product (**139**) facilitates the 1,6-addition. The desired product **139** is achieved with moderate to good yields and with high ee.



*Scheme 38: Organocatalytic enantioselective aza-1,6-addition of isoxazolin-5-ones **138** to p-quinone methides **137** by Blay et al.*

There are very few examples intramolecular vinylogous aza-Michael reactions (IVAMR) in the literature. Silva and co-workers reported the use of a IVAMR in the synthesis of the chromenopyridodiazepinone polyheterocycle **147** (Scheme 39).[121] The one-pot reaction proceeds initially with a intramolecular aza-1,4-addition to provide intermediate **145**, which undergoes an spontaneous aza-1,6-addition reaction to generate intermediate **146**. A subsequent imine condensation generates the diazepines **147**. The reaction, performed at room temperature in THF, provides the desired polyheterocyclic products **147** in moderate-good yields 52-73%.



Scheme 39: Tandem reaction for the synthesis of chromenopyridodiazepinone polyheterocycles by Silva and co-workers.

3.2 Aims and Objectives

As discussed in section 1.1 of this thesis, alkaloids are vitally important molecules in medicinal chemistry and more efficient and stereoselective routes towards these diverse compounds is a constant need. In particular, a large number of these alkaloids contain a 2,6-disubstitued piperidine motif and have become a specific target as a result of their strong pharmacological properties (Figure 5).[122]

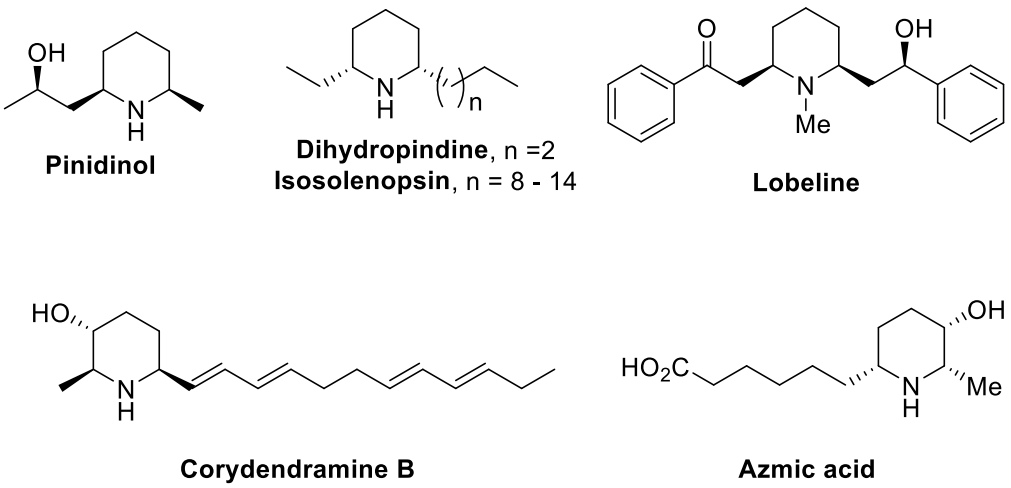


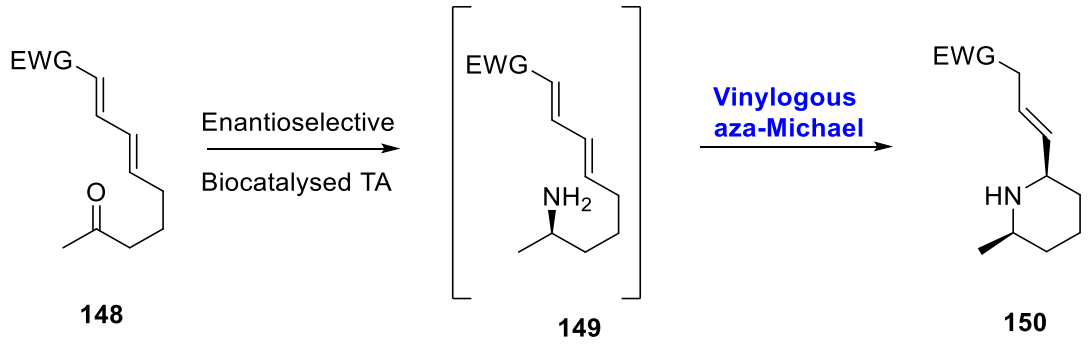
Figure 5: Examples of alkaloids that contain a 2,6-disubstituted piperidine motif.

Being aware of the potential of the biocatalytic IMAMR methodology that has been previously developed by our group,[70] herein, we propose to expand our work to develop a biocatalysed intramolecular vinylogous aza-Michael reaction (IVAMR, Scheme 40). This reaction would be synthetically relevant since, as to the best of our knowledge, the enantioselective vinylogous aza-Michael reaction is not even known under classical conditions (metal catalysis or organocatalysis). Moreover, this strategy would provide access to piperidines/pyrrolidines with side chains that would be readily suitable for further functionalisation (e.g.hydrogenation and imine/lactam

formation to provide bicyclic quinolizidines and indolizidines). Both these scaffolds are seen in a plethora of bioactive (often neuroactive) compounds.[123-125] To achieve this, the aims of this chapter will be as follows:

(i) synthesise keto-α,β,γ,δ-unsaturated substrates with a range of electron withdrawing functionalities.

(ii) Transamination of the vinylogous precursors using ready available ω-TA enzymes with full characterisation.

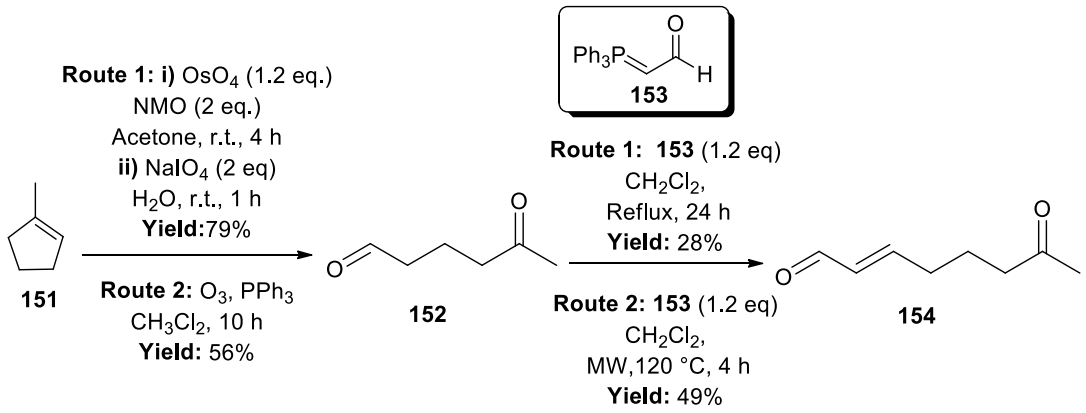


Scheme 40: Proposed intramolecular vinylogous aza-Michael reaction promoted by a biocatalysed transamination reaction

3.3 Results and Discussion

3.3.1 Synthesis of ketodienones 156a-b and ketodieno esters 162a-b.

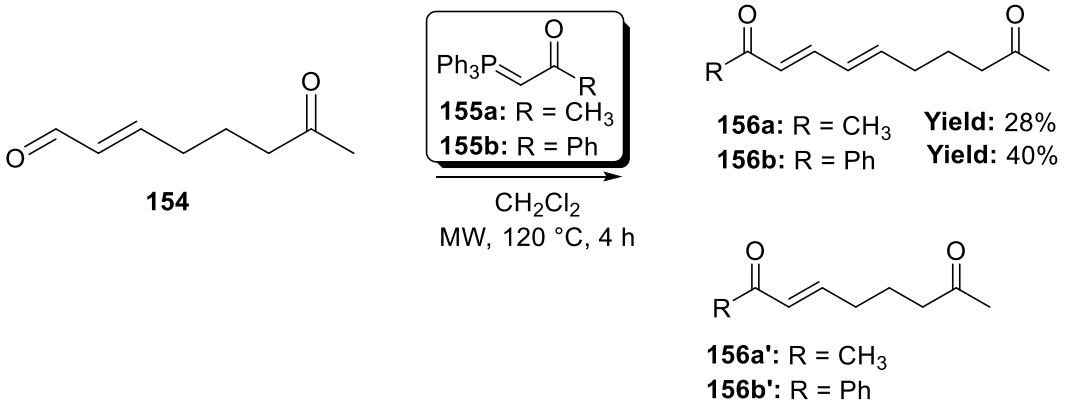
The synthesis of the desired substrates **156a-b** to study the intramolecular vinylogous aza-Michael reaction (IVAMR) started with a Lemieux-Johnson oxidation of 1-methyl-cyclopetene (**151**) using osmium tetroxide in catalytic amounts and *N*-methylmorpholine *N*-oxide (NMO) as the re-oxidant. This reaction afforded the desired aldehyde **152** with a good yield of 79% with no purification needed (Scheme 41, *Route 1*). However, with the desire to utilise a more sustainable oxidation, and avoid the expensive and toxic OsO_4, we also performed the oxidative ring opening of **151** using ozone. Thus, the ozonolysis reaction of **151**, using the conditions reported by Lee and co-workers,[126] provided 5-oxohexanal (**152**) in a moderate yield of 56% (Scheme 41, *Route 2*). Although the yield of the ozonolysis reaction was lower than that of the Lemieux-Johnson oxidation, the reaction is easier, cheaper, safer (if kept inside a fume cupboard) and can be readily scaled up, making it the preferred methodology for the synthesis of **152**. Next, the Wittig olefination of **152** using ylid **153** was explored. Under classical reflux conditions in dichloromethane, **154** was obtained in 28% isolated yield 48 h. However, we found that under microwave irradiation, the reaction proceeded at a higher rate, reaching completion after 4 h and providing **154** in 49% isolated yield.



*Scheme 41: STEP 1: Synthesis of 5-oxohexanal (**152**) via Lemieux-Johnson oxidation (route 1) and ozonolysis reaction (route 2). STEP 2: Synthesis of **154** via Wittig reaction under reflux (route 1) and MW irradiation (route 2).*

The synthesis of the methyl ketodienone **156a** was then achieved by a second Wittig reaction on the intermediate **154**, under microwave irradiation, using the ylide **155a**. The isolated yield for **156a** was low (28%), due to the complexity of the purification step (Table 7, *entry 1*). The enone **156a'** was identified as a side product (19%) in the microwave assisted reaction(Table 7, *entry 1*). We believe that **156a'** is formed *via* a retro-aldol reaction from **154**. Separation of **156a** and **156a'** by column chromatography proved challenging, as both compounds have very similar RF values. Fortunately, when the reaction was performed in a pressure tube, with dichloromethane at 90 °C (Table 7, *entry 2*), full conversion to the desired **156a** was achieved after 48 h, and the formation of the retro aldol product **156a'** was not observed under these conditions (Table 7, *entry 2*).

*Table 7 Synthesis of ketodienone substrates **156a** and **156b**.[a,b]*



Entry	Product	Method	Conv. to desired product 156a-b (%)[c]	Conv. to retro aldol product 156a'-b' (%)[c]	Yield 156a-b (%)[d]
1	**156a**	Microwave[a]	81	19	28
2	**156a**	Pressure tube[b]	>99[e]	0	37
3	**156b**	Microwave[a]	75	25	23
4	**156b**	Pressure tube[b]	>99[e]	0	40

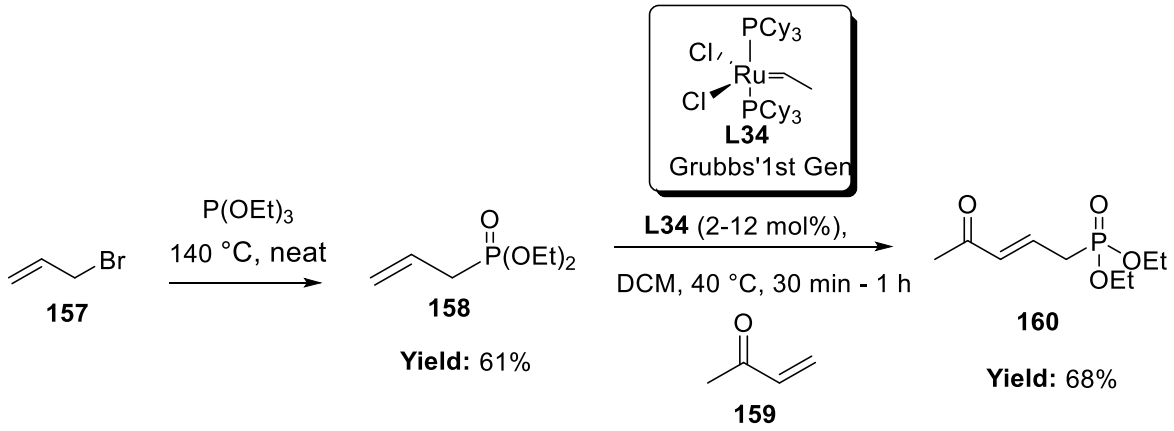
[a] Reaction conditions**:** **154** (0.2 mmol), **155a** or **155b** (0.4 mmol), DCM (1 mL), MW 120 °C, 4 h.
[b] Reaction conditions**:** **154** (0.2 mmol), **155a** or **155b** (0.4 mmol), DCM (1 mL), pressure tube, 90 °C, 48 h.
[c] Determined by GC-MS.
[d] Isolated yield after flash chromatography.
[e] Determined by ^{1}H NMR.

The synthesis of the phenyl ketone **156b** was also achieved using the same strategy, by Wittig reaction of **154** and ylide **155b**. When the reaction was performed under microwave irradiation, both the desired product **156b** and the side product **156b'** could be seen in the crude product in a ratio of 75:25, respectively (Table 7, *entry 4*). All the attempts to separate **156b** and **156b'** by column chromatography were unsuccessful. After 3 chromatography columns and a crude yield of 23%, the product was still not pure. Conversely, when the Wittig reaction of **154** with the ylide **155b** was performed in a pressure tube with DCM at 90 °C for 48 h, full conversion to the desired product **156b** was obtained with a moderate yield of 40% (after purification

by column chromatography), without any formation of the undesired **156b'**. In summary, the Wittig olefination by means of heating the reaction in a pressure tube was a much more effective methodology, as no retro-aldol side products **156a'-b'** were observed making purification much easier and thus providing a higher yield.

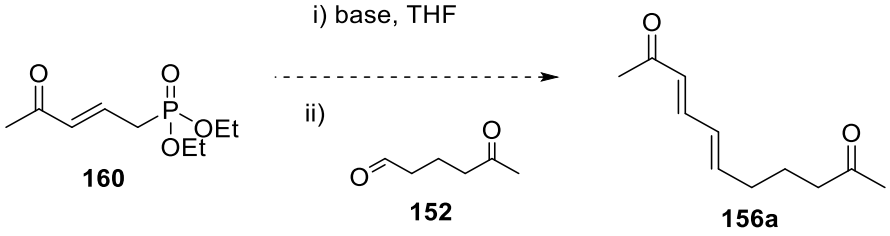
As the Wittig olefination reactions of intermediate **154** proceeded with a somewhat low yield, we decided to explore an alternative synthetic route to our target substrates **156a-b**, performing a Horner-Wadsworth-Emmons reaction (HWE) between the aldehyde **152** and the phosphonate **160** (Scheme in Table 8). The preparation of phosphonate **160** was achieved by means of an Arbuzov reaction with allyl bromide (**157**) and triethylphosphite at 140 °C, which provided the desired diethyl allylphosphonate (**158**) in 61% yield.[127] A subsequent cross metathesis (CM) reaction with **159** using Grubbs 1st generation catalyst (**L34**) afforded **160** in a moderate yield of 68% (Scheme 42).

Unfortunately, the HWE reaction of **160** and **152**, using sodium hydride as the base for the deprotonation of the phosphonate proved unsuccessful (Table 8, *entry 1*) and only starting material was observed in the crude reaction mixture. We then tried lithium diispropylamide (LDA) as the base, which also did not provide the desired product, and only the starting materials **152** and **160** could be seen in the crude ^{1}H NMR (Table 8, *entry 2*). We then attempted the deprotonation of **160** with ^{n}BuLi, using HMPA and HDMS as additives, neither of which was successful (Table 8, *entries 3 and 4*). As a result of the unsuccessful HWE reaction, this synthetic route was not viable and we decided to pursue the original route using the original Wittig olefination (Scheme in Table 7) even despite the low yields.



*Scheme 42: Synthesis of phosphonate **160.***

*Table 8: Study of HWE reaction as an alternative synthesis for ketodienone **156a**[a]*

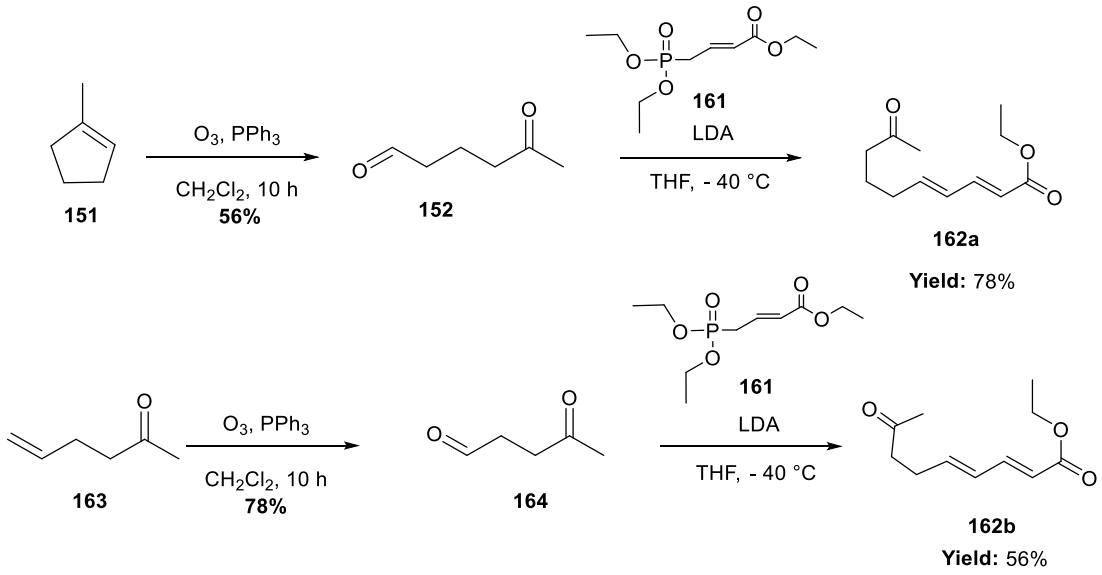


Entry	Base (eq)	Additive (eq)	Temp (^{o}C)	Conv. (%)[b]
1	NaH (1)	-	0	0
2	LDA (1)	-	—40	0
3	^{n}BuLi (1)	HMPA (1)	—78	0
4	^{n}BuLi (1)	HMDS (1)	—78	0

[a] Reaction conditions: (i) **160** (0.45 mmol), base (1 eq, 0.45 mmol), THF (5 mL), 0.5 h. (ii) **152** (0.45 mmol), THF (4 mL)
[b] Determined by GC-MS

Next, we applied a HWE reaction to synthesise the ketodieno esters **162a** and **162b**. Substrate **162a** was prepared using a methodology reported by Hong and co-workers[126] *via* HWE reaction of **152** with commercially available phosphonate **161**, using LDA in THF at – 40 °C for the deprotonation step. Gratifyingly, the reaction was successful affording **162a** in 78% yield. The synthesis of substrate **162b** was

performed by the oxidative cleavage of commercially available 5-hexen-2-one (**163**) to afford 4-oxopentanal (**164**) in good yield, followed by a HWE reaction using phosphonate **161** (56% yield).



*Scheme 43: Synthesis of ketodieno esters **162a**-**b**.*

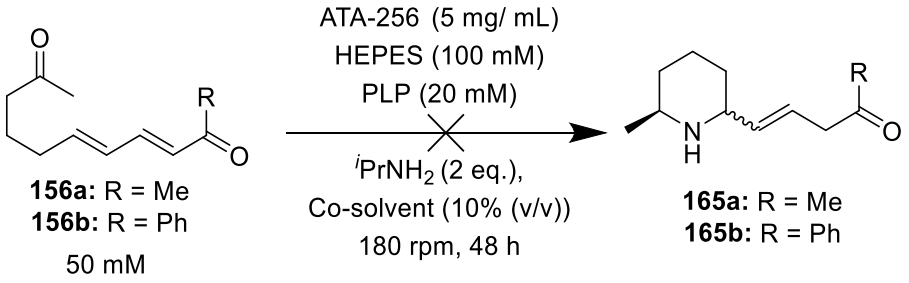
3.3.2 Transamination of substrates 156a-b, and 162a-b.

We began our investigation on the biocatalyst-promoted aza-1,6-addition reaction using commercially available ATA-256, with 2 equivalents of IPA as the amine donor and DMSO (10% [v/v]) as the organic solvent, as those were the optimal conditions found for the synthesis of 2,6-disubstituted piperidines from ketoenone substrate **112** (Scheme 29).[70] Firstly, we attempted the transamination of the methyl ketodienone substrate **156a** at 30 °C in DMSO (10% [v/v], Table 9, *entry 1*). Unfortunately, we saw no conversion to the desired **165a**. Instead, we observed decomposition of the starting material **156a**, which could no longer be detected *via* GC-MS or in the crude ^{1}H-NMR spectrum. The decomposition of **156a** was also observed in the control experiment (in the absence of the enzyme) carried out under the same conditions (Table 9, *entry 2*). We believe that the decomposition could be taking place *via* retro-aldol reactions, although possible products of the retro-aldol reactions, such as the aldehyde **152**, were not observed by GC-MS or by ^{1}H-NMR analysis of the reaction crude. With the aim to increase the reaction rate of the TA step and thus avoid the decomposition of **156a**, we increased the temperature of the ATA-256 biocatalysed reaction to 50 °C (Table 9, *entry 3*), but the outcome of the experiment did not change and decomposition of the starting material **156a** still took place. Similarly, when MeOH (10% [v/v]) was used as a co-solvent instead of DMSO decomposition also occurred (Scheme 8, *entry 5*).

Next, we attempted the reaction with the phenyl ketodienone substrate **156b** in the hope that the substrate would be more stable with a bigger functional group and would not decompose. However, using ATA-256 and 2 eq of ^{i}PrNH$_2$, with 10% [v/v]

DMSO, no transamination took place and again decomposition occurred at 30 and 50 °C, and when MeOH (10% [v/v]) was used as a co-solvent in place of DMSO (Table 9, *entries 7, 9 and 11*). The control reactions (with no enzyme present) for the phenyl substrate **156b** also yielded no conversion to the desired amine at either 30 or 50 °C, and, as expected, all also resulted in decomposition of the starting material (Table 9, *entries 8, 10 and 12*).

*Table 9: Attempted transamination of ketodienone substrates **156a-b**[a]*



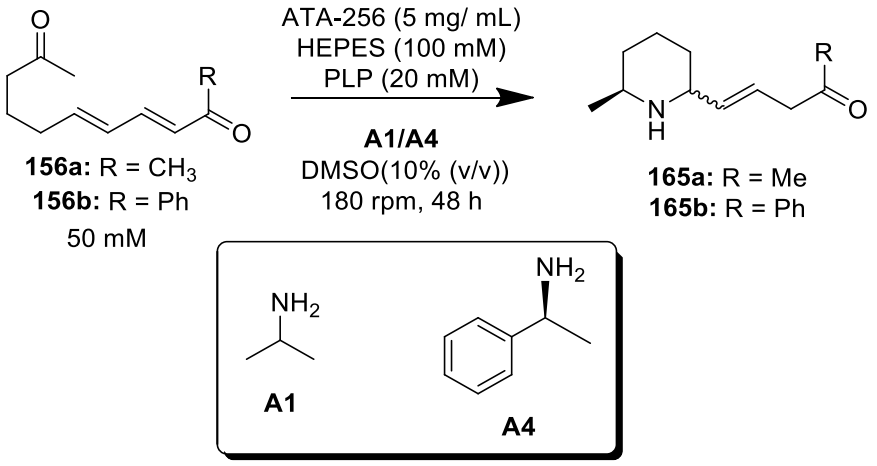
Entry	ATA (selectivity)	Substrate	Solvent	Temp (°C)	Conv to 165 (%)[b] after 24 h	Conv to 165 (%)[b] after 48 h
1.	256 (*S*)	**156a**	DMSO	30	0[c]	0[c]
2.		**156a**	DMSO	30	0[c]	0[c]
3.	256 (*S*)	**156a**	DMSO	50	0[c]	0[c]
4.		**156a**	DMSO	50	0[c]	0[c]
5.	256 (*S*)	**156a**	MeOH	30	0[c]	0[c]
6.		**156a**	MeOH	30	0[c]	0[c]
7.	256 (*S*)	**156b**	DMSO	30	0[c]	0[c]
8.		**156b**	DMSO	30	0[c]	0[c]
9.	256 (*S*)	**156b**	DMSO	50	0[c]	0[c]
10.		**156b**	DMSO	50	0[c]	0[c]
11.	256 (*S*)	**156b**	MeOH	30	0[c]	0[c]
12.		**156b**	MeOH	30	0[c]	0[c]

[a] Reaction conditions: ω-TA ATA-256 (5 mg/ mL), **156a** or **156b** (50 mM), amine donor (2 eq), HEPES buffer (100 mM, pH 7.5), PLP (20 mM), Solvent (10% [v/v]), 180 rpm, 48 h.
[b] Determined by GC-MS.
[c] Complete decomposition of the starting material **156** was observed.

Following this, we began a small optimisation of the amine donor with the hope that it would drive the equilibrium towards the desired **165a-b** at an increased reaction

rate preventing decomposition of **156a-b** (Table 10). We began by increasing the amount of IPA (**A1**) to 4 eq. (instead of 2 eq.), unfortunately no conversion to either of the desired products **165a-b** was observed (Table 10, *entries 1 and 3*). During the investigation for the transamination of keto-cyclohexenone substrates, discussed in section 2.3.2, we found that the use of MBA (**A4**) as an amine donor had a faster reaction rate than IPA (**A1**, Table 5, *entry 10*). However, when these conditions were applied to the biocatalysed transamination of substrates **156a-b**, no conversion was observed to **165a-b** and decomposition of the starting material took place. It is also worth noting that in all the control reactions, in the absence of enzyme, the decomposition of substrates **156a-b** was also observed (Table 10, *entries 2, 4, 6 and 8*).

*Table 10: Optimisation of amine donors for the synthesis of **165a-b**[a]*



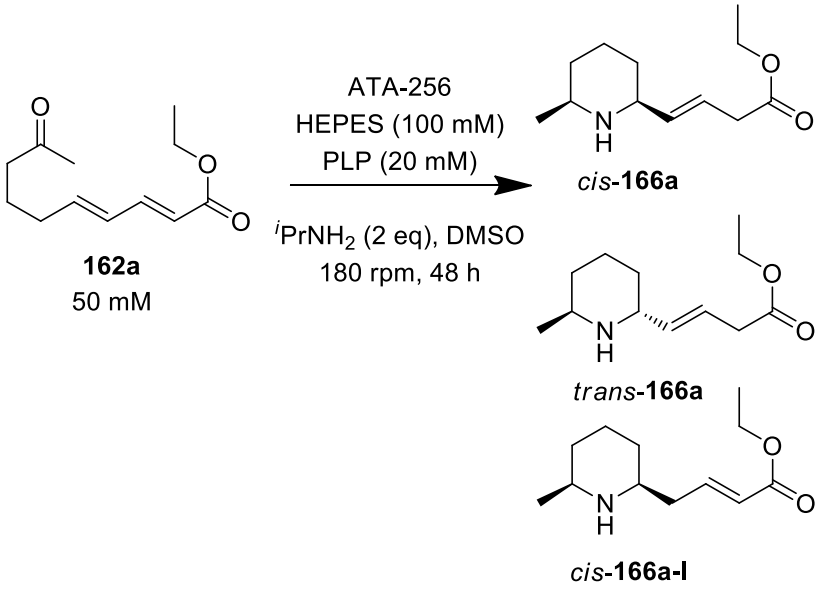
Entry	ATA (selectivity)	Substrate	Amine donor (eq.)	Conv to 165 (%)[b] after 24 h	Conv to 165 (%)[b] after 48 h
1.	256 (*S*)	**156a**	**A1** (4)	0[c]	0[c]
2.	-	**156a**	**A1** (4)	0[c]	0[c]
3.	256 (*S*)	**156b**	**A1** (4)	0[c]	0[c]
4.	-	**156b**	**A1** (4)	0[c]	0[c]
5.	256 (*S*)	**156a**	**A4** (2)	0[c]	0[c]
6.	-	**156a**	**A4** (2)	0[c]	0[c]
7.	256 (*S*)	**156b**	**A4** (2)	0[c]	0[c]
8.	-	**156b**	**A4** (2)	0[c]	0[c]

[a] Reaction conditions: ATA-256 (5 mg/ mL), **156a** or **156b** (50 mM), amine donor (x eq), HEPES buffer (100 mM, pH 7.5), PLP (20 mM), DMSO (10% (v/v)), 180 rpm, 48 h.
[b] Determined by GC-MS.
[c] Complete decomposition of the starting material was observed.

As neither of the ketodienone substrates **156a-b** yielded the desired products **165a-b**, we moved onto the transamination of the ketodieno ester substrate **162a**. The transamination of **162a** with ATA-256 at 30 °C provided **166a** in 48% conversion (determined by GC-MS) after 48 h (Table 11, *entry 1*). The crude ^{1}H-NMR spectrum revealed that the product was obtained as a mixture of isomers**:** *cis*-**166a,** *trans*-**166a** and *cis*-**166a-I** in a ratio of 1:0.3:0.1. At 38 °C, the reaction proceeded with 61% conversion after 48 h and only *cis*-**166a** was observed.(Table 11, *entry 4*). Increasing

the temperature to 50 °C, which is the maximum temperature the enzyme could withstand, the reaction proceeded with full conversion to the desired product **166a** after 48 h (Table 11, *entry 5*) in a 3:2.5:1 (*cis*-**166a,** *trans*-**166a** and *cis*-**166a-I**)). When EtOH was used as the co-solvent in the reaction (10% [v/v]), the conversion, at 50 ^{o}C, after 48 h dropped to 67% (Table 9, *entry 7*). All the control reactions in the absence of enzyme were performed, and no transamination reaction was observed in any case. (Table 11, *entries 2, 4, 6 and 8*).

*Table 11: Optimisation for the biocatalysed synthesis of **166a**[a]*



Entry	ATA (selectivity)	Solvent (%v/v)	Temp (°C)	Conv to 166a (%)[b] after 48 h	Ratio[c] (*cis*-**166a**:*trans*-**166a**:*cis*-**166a-I**)
1	256 (*S*)	DMSO	30	40	1 : 0.3 : 0.1
2	-	DMSO	30	-	-
3	256 (*S*)	DMSO	37	61	1 : 0 : 0
4	-	DMSO	37	-	-
5	256 (*S*)	DMSO	50	>99	3 : 2.5 : 1
6	-	DMSO	50	-	-
7	256 (*S*)	EtOH	50	67	2 : 1.5 : 1
8	-	EtOH	50	-	-

[a] **Reaction conditions:** ATA-256 (5 mg/ mL), **162a** (50 mM), $^{i}PrNH_2$ (2 eq.), HEPES buffer (100 mM, pH 7.5), PLP (20 mM), solvent (10% [v/v]), 180 rpm, 48 h.
[b]Determined by GC-MS.
[c]Determined by ^{1}H NMR on the reaction crude.

The standard work up after a biocatalysed transamination reaction usually consists of 3 steps: (1) adjusting the pH of the reaction to 12 using NaOH (5M); (2) carrying out an extraction using ethyl acetate (3 x EtOAc); and (3) washing the combined organic layers with 2 M NaOH (Figure 6, *work-up 1* and experimental section for further details).[70] Although the conversion of the reaction at 50 °C (Table 11, *entry*

5), determined by GC-MS and ^{1}H-NMR, was <99%, the isolation of **166a** was unsuccessful after a standard work-up (Figure 6, *work-up 1*).

Therefore, we began optimisation of the work-up of the transamination reaction. Performing the first 2 steps of the standard work-up process and replacing the final step (washing the organic layer with 2 M NaOH) with passing the crude sample through a quick silica plug (using acetone as eluent), provided 23 mg of crude material (note that 52 mg of **166a** corresponds to 100% theoretical yield), with a large amount of DMSO present, indicating 1% yield for **166a** (determined by ^{1}H NMR spectroscopy) (Figure 6, *work-up 2*).

An alternative work-up for biocatalysed reactions, reported by Kroutil and co-workers,[128] involves preliminary removal of the enzyme *via* filtration using a HPLC filter. Our first attempt using this methodology consisted of filtration of the reaction mixture using a 0.2 µL HPLC filter, having previously adjusted the pH of the reaction mixture to 12 using 6 M NaOH. A subsequent extraction of the filtrate with EtOAc did not provide any crude product **166a** (Figure 6, *work-up 3*).

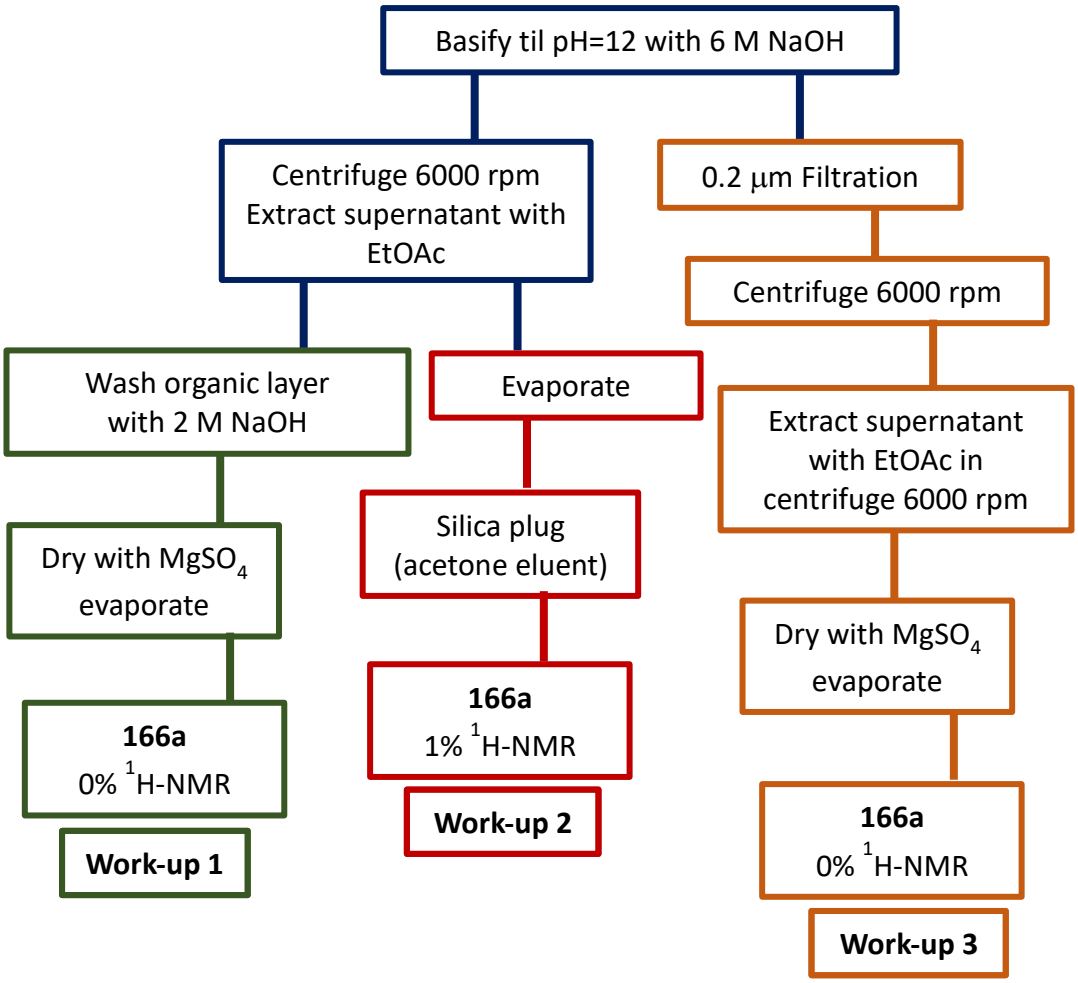


*Figure 6: Optimisation of work up for the transamination of **162a** based on traditional biocatalysis work-ups.*

Increasing the rotational speed to 14,000 rpm (opposed to 6000 rpm) when extracting the supernatant, whilst using the traditional biocatalysis work-up showed a negligible improvement in yield (4%, determined by ^{1}H NMR on the crude reaction) of the desired **166a** (Figure 7, *work-up 4*). Passing the reaction solution through a 0.2 µL HPLC filter, followed by extraction of the supernatant with EtOAc in a centrifuge apparatus at 14,000 rpm, without performing a basic wash, increased the yield to 6% (Figure 7, *work-up 5*).

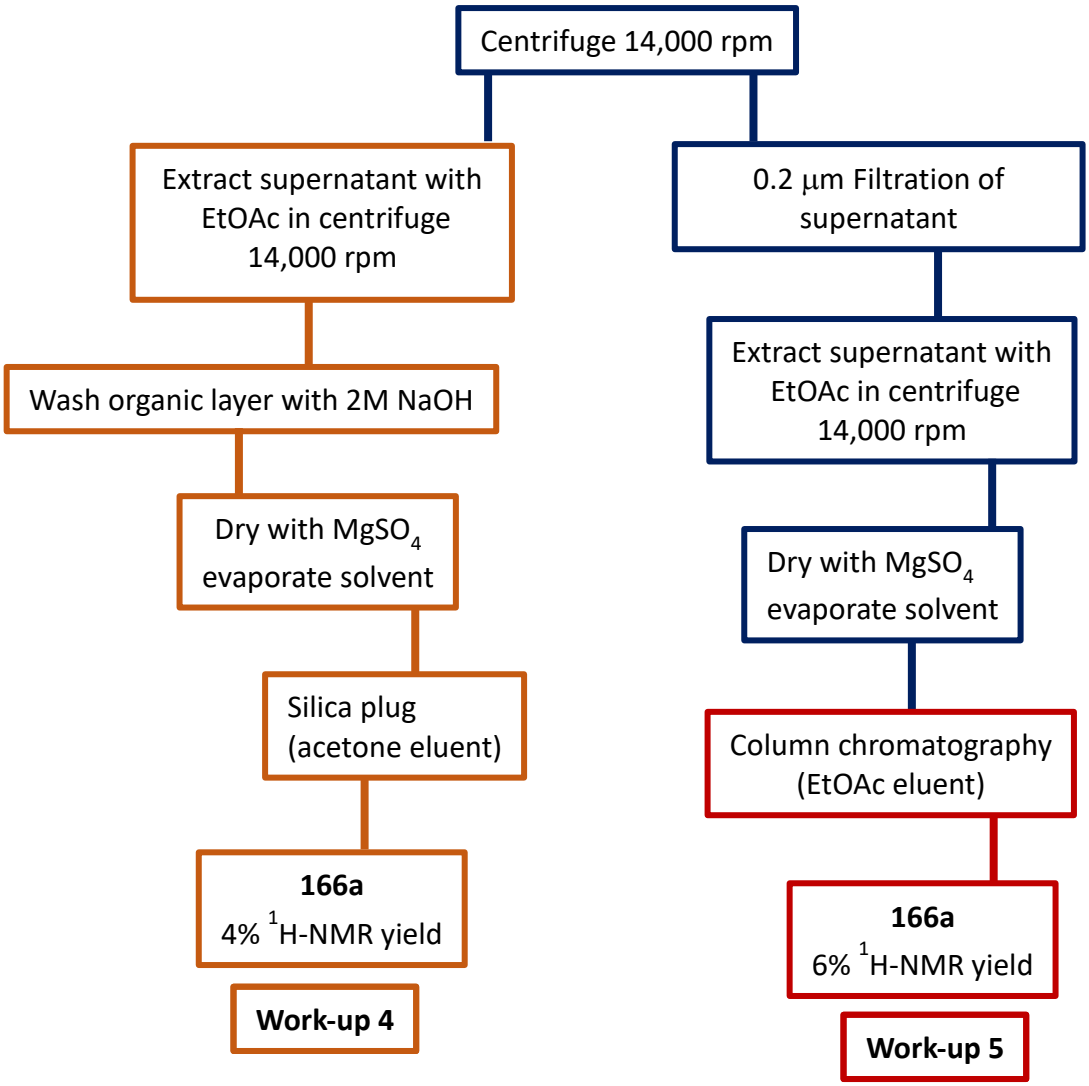


*Figure 7: Optimisation of work up for the transamination of **162a** using a centrifuge apparatus at 14,000 rpm.*

We believe that a likely cause for the low yields for the isolation of **166a** are a result of our product being water-soluble. In an attempt to overcome this problem, we investigated basifying the reaction mixture using solid sodium bicarbonate instead of aqueous NaOH (2 M) (Figure 8). *Work-up 6* (basify with solid $NaCO_3$ till pH = 8, followed by extraction with EtOAc and two chromatography purification steps) showed an improved yield of 26% (determined by ^{1}H NMR). Following a similar

approach, only basifying the reaction solution until the highest pH was reached (pH= 8.6) and passing the reaction solution through a 0.2 µL HPLC filter slightly decreased the yield of **166a** to 23% (Figure 8, *work-up 7*).

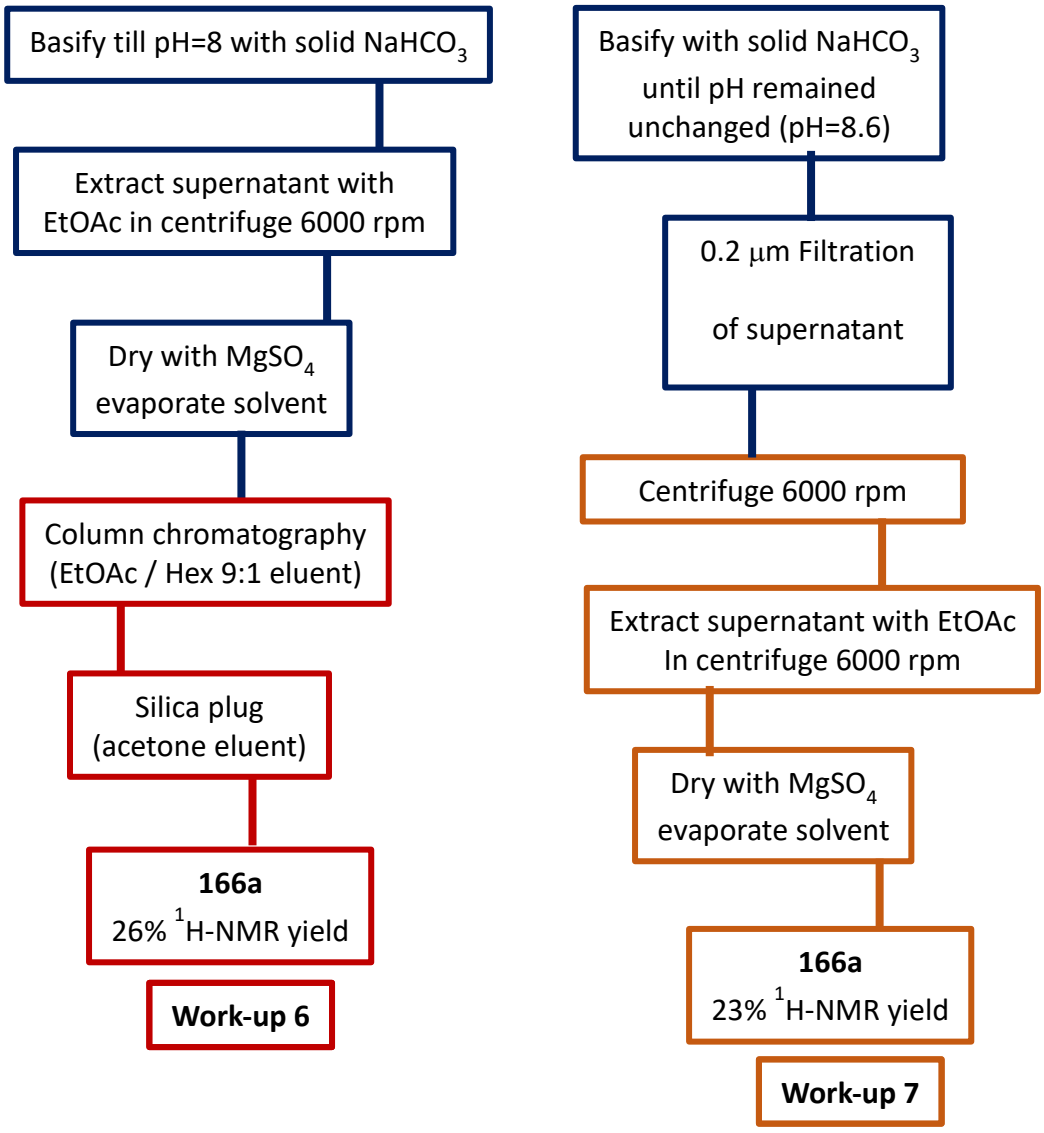


*Figure 8: Optimisation of work up for the transamination of **162a** using solid $NaHCO_3$ as a base.*

Savile and co-workers reported that, for larger scale reactions, acidification to destroy the enzyme can be used prior to extraction.[66] However, when we attempted this method, we were unable to retrieve any of the desired product, most likely due to the acid decomposing of **166a** (Figure 9, *work-up 8*). We also explored the use of a MiVac vacuum concentrator to remove all the aqueous and organic solvent from the crude mixture (Figure 9, *work-up 9*), unfortunately this provided an insoluble pellet from which the product could not be extracted.

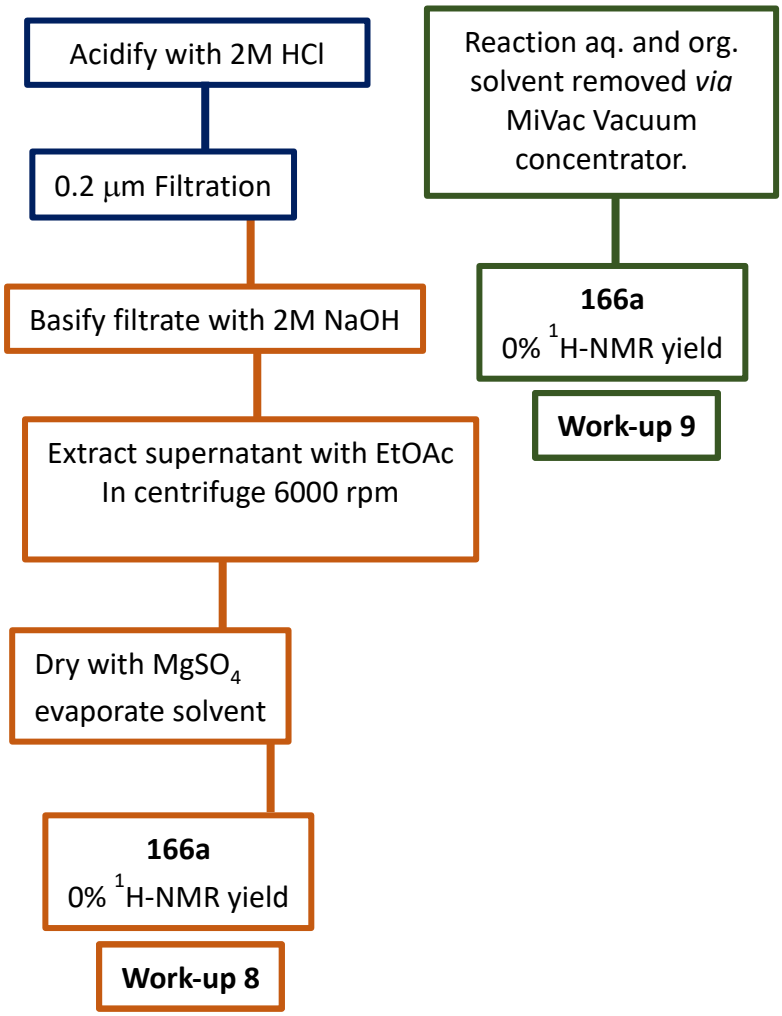


*Figure 9: Optimisation of work up for the transamination of **162a**. Work-up 8: Acidification. Work-up 9: Removal of solvent using a MiVac vacuum concentrator.*

Strong cation exchange (SCX) chromatography columns are composed of resins, which have acidic functionalised groups, and are able to capture amines and other basic compounds in order to extract them from aqueous solutions.[129, 130] The SCX-2 isolute column consists of a propylsulfonic acid bonded functionalised silica. The columns are specially designed to trap amines, which can be easily liberated from the column using a methanolic ammonia solution.[131] Passing the reaction mixture (previously filtered with a 0.2 μm HPLC filter) through a SCX-2 isolute column, using EtOAc as eluent, followed by release of the amine with methanolic solution (see experimental section for further details), we were able to isolate **166a** in 39% yield (Figure 10, *work-up 10*). Initial sonication of the reaction solution, in an attempt to destroy the enzyme as a preliminary step, followed by passing either the crude reaction through an HPLC filter and an isolute column (Figure 10, *work-ups 11 and 12*) showed no improvement in the yield of **166a**.

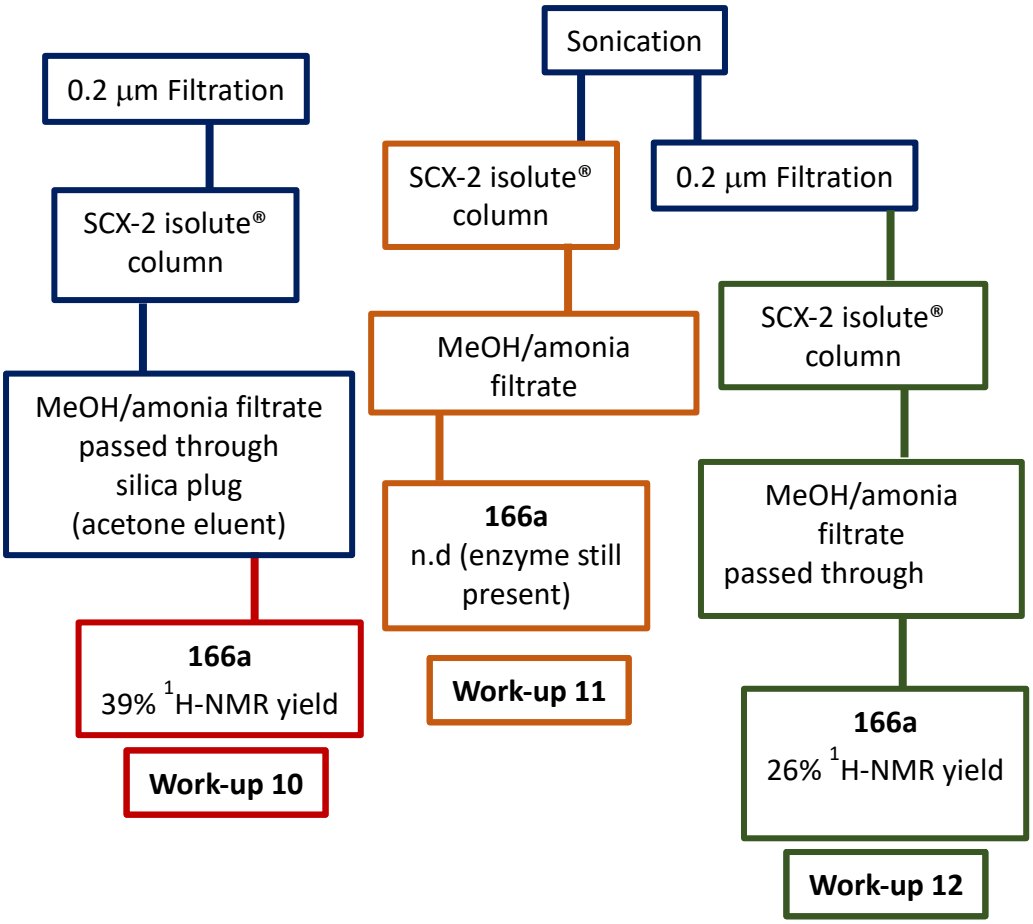
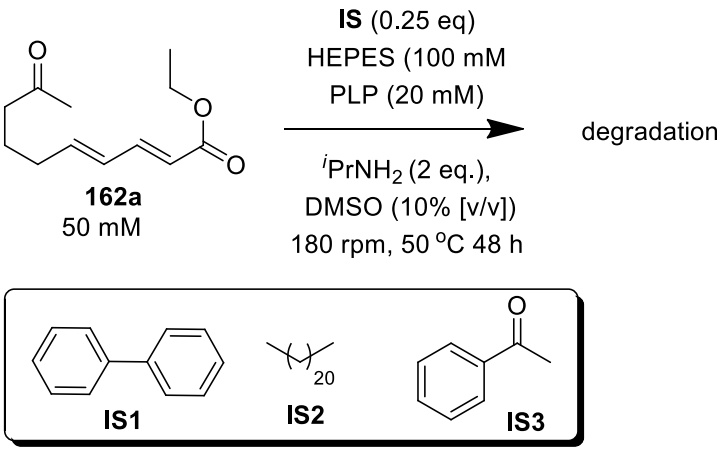


*Figure 10: Optimisation of work up for the transamination of **162a** using sonication.*

In a last attempt, we performed the reaction with the ATA-256 enzyme absorbed onto a resin (ECR1030M), in the hope that the immobilised enzyme would simplify the work up. Unfortunately, transamination to the desired product **166a** did not occur and only starting material **162a** could be seen by both GC-MS and ^{1}H NMR spectroscopy.

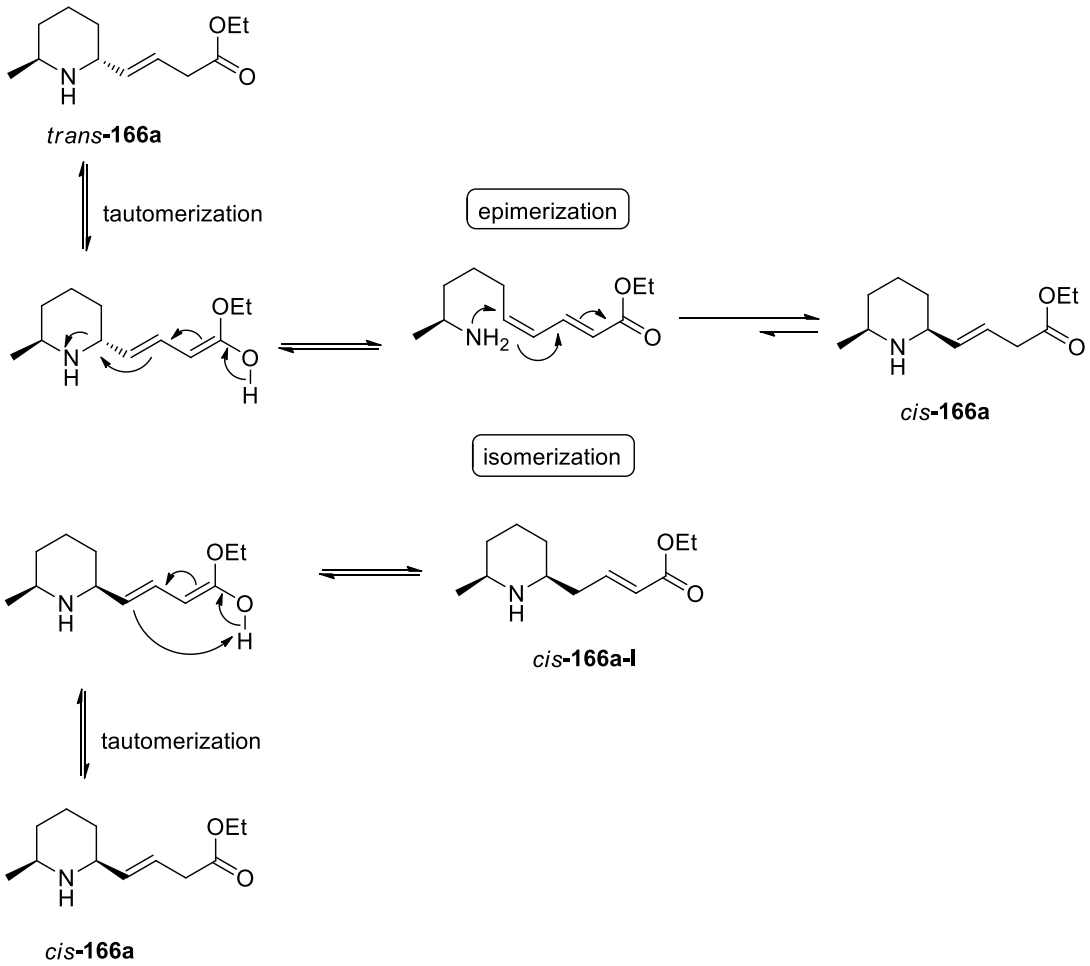
To conclude, we chose to adopt *Work-up 10* (Figure 10) as the optimal work-up methodology for the transamination of **162a**, which provided the highest isolated yield (39%).

Since the crude yields of the reaction did not match the full conversion observed in the GC-MS, we investigated the stability of the starting material **162a** under the reaction conditions. The control reaction (in the absence of enzyme) at 50 °C ($^{i}PrNH_2$ (2 eq), HEPES buffer (100 mM, pH 7.5), PLP (20 mM), DMSO (10% [v/v]), 180 rpm, 48 h) provided less than 1% recovery of the starting material, indicating that the starting material **162a** is degrading. In an attempt to monitor the decomposition in real time three different internal standards; biphenyl (**IS1**), docosane (**IS2**) and acetophenone (**IS2**) were investigated in the control reactions (Scheme 44). These were chosen as they were readily available in the lab and appear in the GC-MS at a different retention time to our substrate **162a**. Unfortunately, due to the low solubility of the internal standards in the reaction media, all attempts to monitor the decomposition of **162a** by GC-MS analysis failed.



*Scheme 44: Investigations into the stability of **162a**.*

Next, we investigated the isomerisation of the isolated products **166a**. The crude product of the IVAMR provided a mixture of the isomers *cis*-**166a**, *trans*-**166a** and *cis*-**166a**-**I** in a 3:2.5:1 ratio, respectively (Table 11, *entry 5*). The epimerisation reaction in 2,6-disubstituted piperidines towards the most stable *cis*-isomer is a well known reaction.[132-136] We believe that a tandem epimerisation of carbon 2 - *via* retro vinylogous aza-Michael reaction - followed by a subsequent olefin isomerisation could provide *cis*-**166a**-**I** as the only isomer in our reaction (Scheme 45).



*Scheme 45: Proposed mechanism of tandem epimerisation-isomerisation for the synthesis of cis-**166a**--**I**.*

Stirring the isolated mixture of *cis*-**166a**, *trans*-**166a** *and cis*-**166a**-**I** (3:2.5:1) in EtOH at 60 °C for 24 h, unfortunately, did not induce any isomerisation to the desired product *cis*-**166a**-**I** (Table 12, *entry 1*). Increasing the temperature to 80 °C for 24 h increased the ratio 0.3:0:1 (*cis*-**166a**, *trans*-**166a** *and cis*-**166a**-**I**) but after 48 h no more isomerisation occurred (Table 12, *entries 2 and 3*). Stirring the mixture in ethanol at RT, in the presence of silica gel, only slightly promoted the isomerisation process (Table 12, *entry 4*), with the ratio of *cis*-**166a**, *trans*-**166a** *and cis*-**166a**-**I** to 4.5: 0:1. Heating the mixture, with silica gel, to 60 °C increased the ratio of *cis*-**166a**, *trans*-**166a** *and cis*-**166a**-**I** to 3:0 :1. Whilst raising the temperature to 80 °C in a pressure tube combined with silica gel resulted in an improved ratio of 0.5:0:1 (*cis*-**166a**, *trans*-**166a** *and cis*-**166a**-**I**,Table 12, *entries 7 and 8***)**.

The isomerisation was also attempted at RT in the presence of solid NaOH but unfortunately, the sample decomposed under these conditions (Table 12, *entry 8*). A similar result was observed when the isomerisation was performed at RT, in the presence of neutral alumina (Table 12, *entry 9*). When the mixture was heated at 120 °C for 8 h using MW, full conversion to the desired *cis*-**166a**-**I** was observed (Table 12, *entry 10*). Analysis of the 2D-NOESY spectrum (Figure 11), showed that there is coupling between H_A and H_B indicating that there is interaction across space and confirms that the *cis*-isomer *cis*-**166a**-**I** was formed during the epimerisation/isomerisation process.

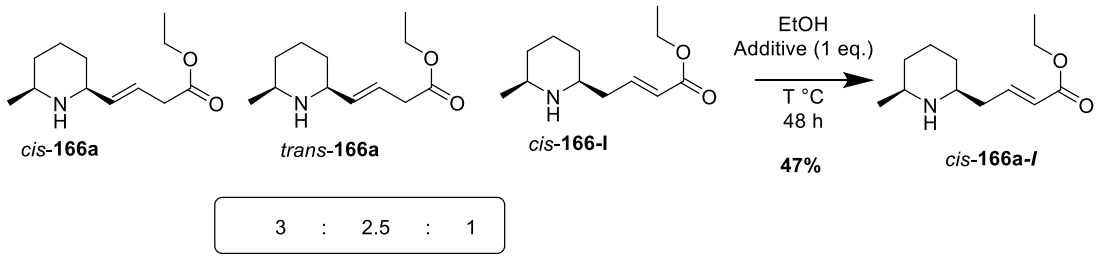


*Table 12: Optimisation for the isomerisation of **166a.**[a]*

Entry	Additive	Temp (°C)	Time (h)	*cis*-**166a** : *trans*-**166a** : *cis*-**166a-I Ratio**[b]
1.	-	60	24	3:2.5 :1
2.	-	80[c]	24	0.3: 0:1
3.	-	80[c]	48	0.3:0:1
4.	Silica	RT	48	4.5:0:1
5.	Silica	60	24	3:0:1
6.	Silica	80[c]	24	0.5:0:1
7.	Silica	80[c]	48	0.5:0:1
8.	NaOH	RT	24	Degraded
9.	Neutral Alumina	RT	24	Degraded
10.	-	120[d]	8	0 : 0 : 1

[a] Reaction conditions: **166a** (21 mg, 0.01 mmol), additive (1 eq), EtOH (7 mL)

[b] Determined by ^{1}H NMR

[c] Reaction carried out in a pressure tube.

[d] Irradiated in a microwave at 120 °C.

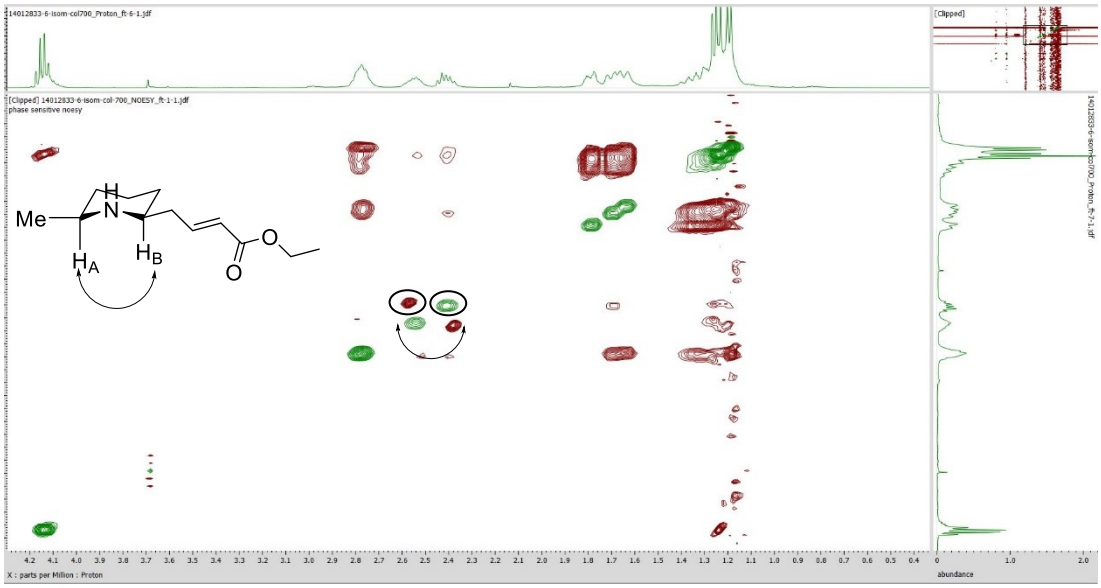
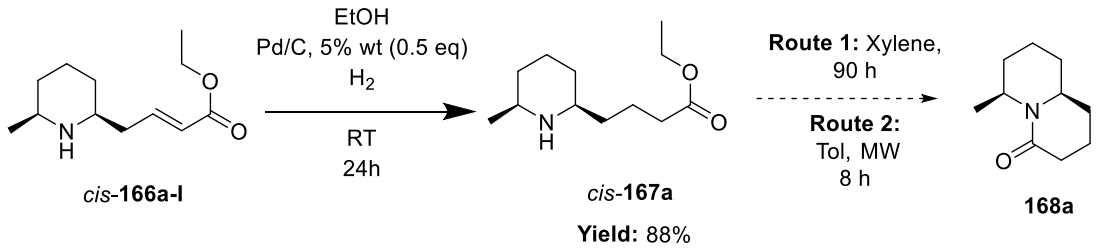


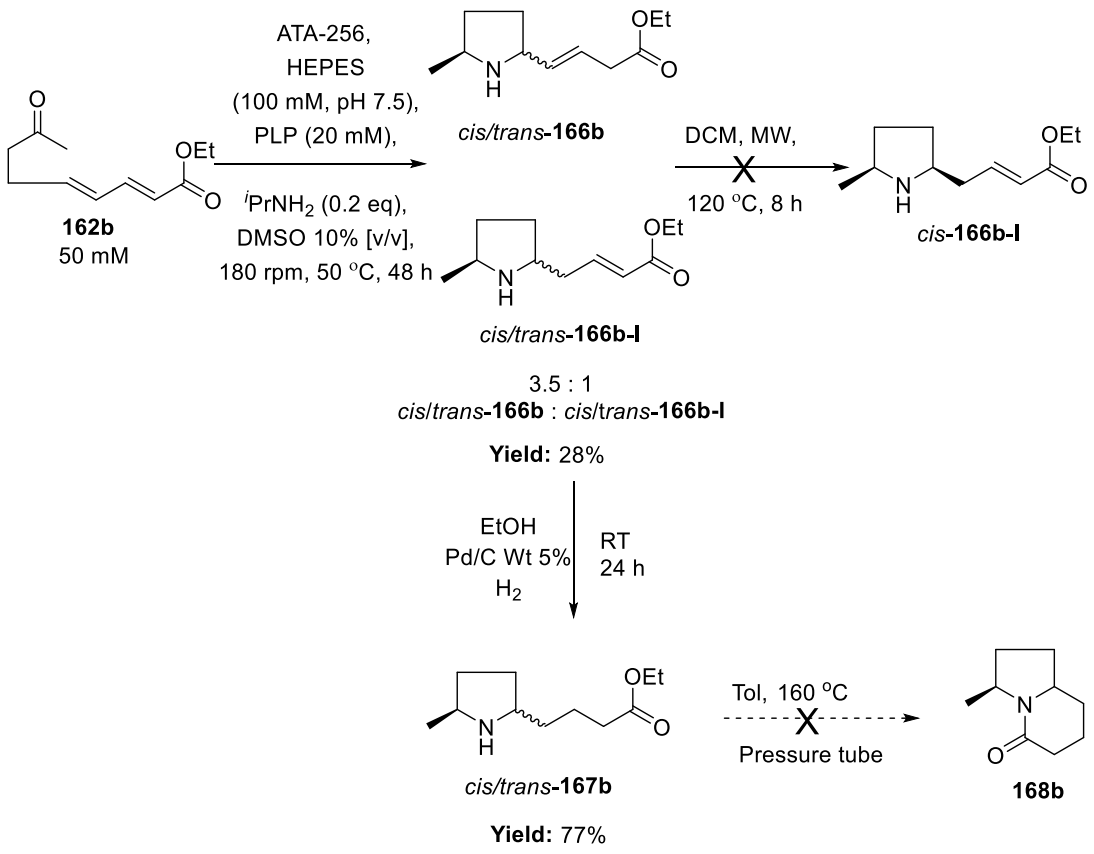
*Figure 11: NOESY spectrum of cis-**166a-I** (400 MHz, 20 °C, $CDCl_3$).*

With the optimised conditions for the isomerisation in hand (heated at 130°C in MW for 8 h, Table 12, *entry 10*) we moved onto the synthesis of *cis*-**167a**. Hydrogenation of the corresponding alkene was achieved by stirring *cis*-**166a**-**I** at RT in the presence of palladium under a hydrogen atmosphere for 24 h, yielding *cis*-**167a** in 88%. Crowley had previously reported that boiling **167** derivatives in xylene for 90 h, allows the cyclisation to perhydroquinolizinones **168**.[137] However, in our hands, no conversion of *cis*-**167a** to the desired **168a** occurred under these conditions (Scheme 46, *route 1*). Similar results occurred when heating *cis*-**167a** in toluene in the MW for 8 h. Further optimisation for the synthesis of quinolizinones **168a** will be required. In both cases 53% of the starting material *cis*-**167a** was recovered, indicating that some decomposition took place.



*Scheme 46: Synthetic route to quinolizinone **168a.***

Utilising the optimised conditions for the transamination of **162a** [ATA 256, IPA (2 eq.), DMSO (10% [v/v], 50 °C, Table 11, *enty 5*], the same reaction was performed for the transamination of **162b** (Scheme 47). A mixture of *cis/trans*-**166b** and *cis/trans*-**166b-l** was obtained in a 3.5:1 ratio, in 28% overall yield. The epimerisation/isomerisation of the **166b** mixture was attempted under the same optimised conditions for **166a** (heated in a microve at 120 °C for 8 h, Table 12, *entry 10*), without any success. This was not surprising, as the epimerisation of 2,5-disubstituted pyrrolidines is known to be problematic, since the *cis*-isomer is no longer thermodynamically more stable.[132-134, 138] Next, we performed an olefin hydrogenation by stirring the mixture of isomers *cis*/*trans*-**163b** and *cis*/*trans*-**163a-l** at RT in the presence of palladium under a hydrogen atmosphere for 24 h, yielding *cis/trans*-**167b** in 77% yield. Cyclisation to the indolizidine **168b** was also attempted by heating in toluene in a pressure tube at 160 °C, but unfortunately, cyclisation did not occur and further optimisation will be required.



*Scheme 47: Synthetic route to perhydroindolizinone **168b**.*

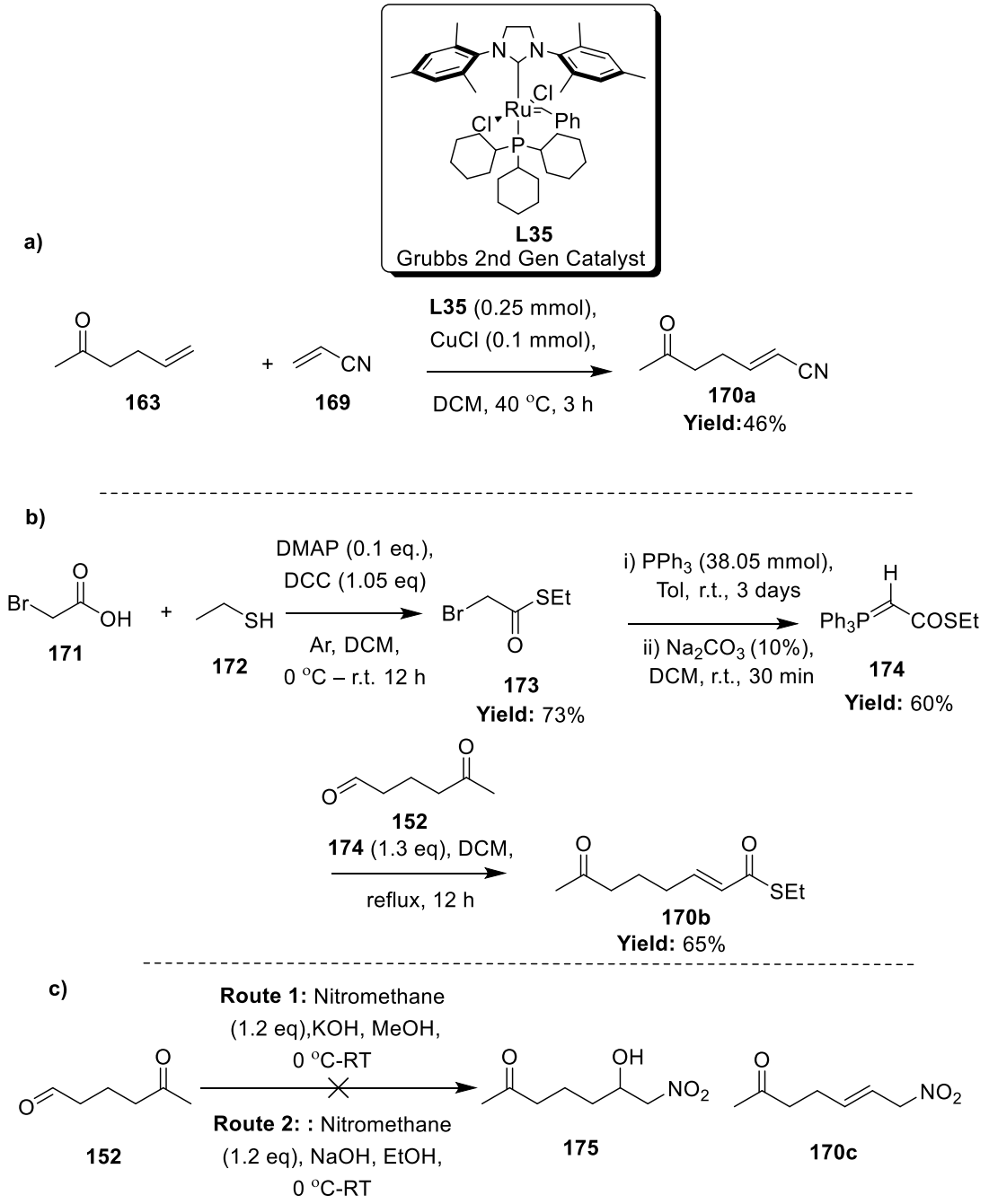
3.3.3 Synthesis of keto-unsaturated substrates 170a-c and subsequent transamination.

Although the transaminase triggered IVAMR of the ketodieno esters **162a-b** was successful, the reaction proceeded in moderate yields. This could be due to the low reactivity of unsaturated esters as Michael acceptors. We envisioned that bis-unsaturated systems bearing other electron withdrawing groups, such as thioesters, nitrile and nitro groups, could provide substrates that are more reactive for the IVAMR. The biocatalysed transaminase triggered IMAMR of keto-α,β-unsaturated -thioesters, -nitriles and -nitro compounds, however, has never been reported, so we

decided to focus our initial investigations on these type of substrates before moving to the vinylogous counterparts.

The synthesis of the keto-α,β-unsaturated nitrile substrate **170a** was achieved through a method reported by Blechert *et al,*[139] consisting on a cross metathesis reaction between commercially available 5-hexen-2-one (**163**) and acrylonitrile (**169**), employing Grubbs 2nd generation catalyst **L35** (Scheme 48*a*). The reaction afforded the desired **170a** in a moderate 46% yield. The keto-α,β-unsaturated thioester **170b** was synthesised in 3 steps, following methods reported by Mabury (Scheme 48*b*).[140] The first step was the preparation of ylide **174**. Thioester **173** was produced in good yield (73%) from bromoacetic acid (**171**) and ethanethiol (**172**), in the presence of DMAP and DCC. Stirring the crude product in dichloromethane with triphenylphosphine, followed by treatment of Na_2CO_3 provided ylide **174** in a moderate yield of 60%. Subsequent Wittig reaction with 5-hexen-2-one (**163**) yielded the desired keto-α,β-unsaturated thioester **170b** in 65% yield .

The synthesis of **170c** *via* a Henry reaction between aldehyde **152** and nitromethane (Scheme 48*c*) was also attempted. However, the reaction using potassium hydroxide as a base, did not provide the desired **175** or **170c** products, and only starting material **152** was observed by ^{1}H NMR analysis,. Similar results were obtained when using a method reported by Peters and co-workers[141] using NaOH as base. Further optimisation of this reaction will be required in future investigations.

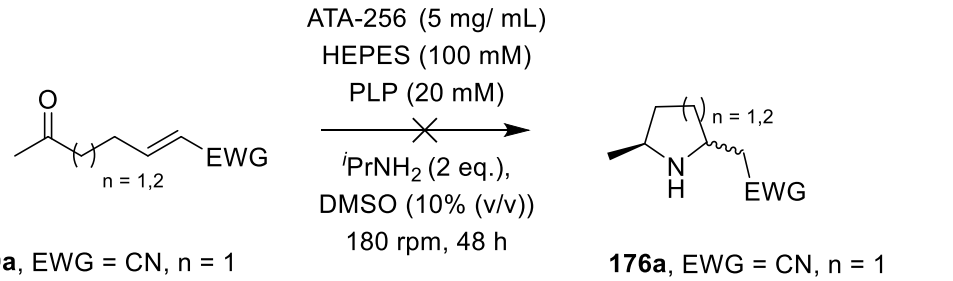


*Scheme 48: Synthetic route to keto-α,β-unsaturated substrates **170a-b** and attempted synthesis of **170c**.*

Next, we investigated the biocatalysed IMAMR of keto- α,β--unsaturated substrates **170a-b** using the optimal conditions found for the ketodieno esters **162a-b** (ATA-256, IPA (2 eq.), DMSO (10% [v/v], 50 °C, Table 11, *entry 5*). Unfortunately, the

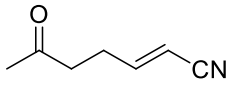
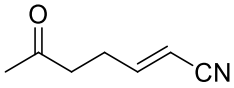
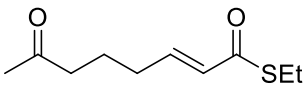
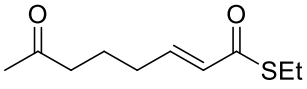
transamination of both substrates **170a-b** was unsuccessful and only starting material was observed in both cases (determined by GC-MS) (Table 13, *entries 1 and 3* and corresponding control reactions, *entries 2 and 4*). Further optimisation of the reaction will need to be performed. Other amine donors, solvents and enzymes could be screened in an attempt to optimise the reaction.

*Table 13: Attempted transamination of keto-α,β-unsaturated substrates **170a-b*** [a]



170a, EWG = CN, n = 1
170b, EWG = C(O)SEt, n = 2

176a, EWG = CN, n = 1
176b, EWG = C(O)SEt, n = 2

Entry	Substrate	ATA (selectivity)	Conv (%)[b] after 48 h
1.	 **170a**	ATA-256 (*S*)	0[c]
2.	 **170a**	-	0[c]
3.	 **170b**	ATA-256 (*S*)	0[c]
4.	 **170b**	-	0[c]

[a] **Reaction conditions:** ATA-256 (5 mg/ mL), **170a-b** (50 mM), $^{i}PrNH_2$ (2 eq), HEPES buffer (100 mM, pH 7.5), PLP (20 mM), DMSO (10% [v/v]), 50 °C, 180 rpm, 48 h

[b] Determined by GC-MS.

[c] Only starting material observed in the GC-MS.

3 Conclusion and future work

In conclusion, ketodienones **156a-b** and ketodieno esters **162a-b** were successfully synthesised utilising an ozonolysis reaction followed by subsequent Wittig or HWE reaction. Unfortunately, the attempted transamination reaction of ketodienones **156a-b** resulted in complete decomposition of the starting material. However, the biocatalysed transaminase triggered IVAMR of ketodieno esters **162a-b** proved successful, yielding the desired piperidine and pyrrolidine products **162a-b** in a 39 and 28% yield, respectively. Both crude samples were obtained as a mixture of isomers: *cis*-**166a**, *trans*-**166a** *and cis*-**166a-I** in a ratio of 3:2.5:1 and *cis*/*trans*-**166b** and *cis*/*trans*-**166b**-**I** in a ratio 3.5:1.

A tandem epimerisation-isomerisation of the 2,6-disubstituted piperidines **166a** provided *cis*-**166a-I** as the only diastereomer in a 47% yield. Hydrogenation of the double bond in the lateral ester chain of *cis*-**166a-I** was performed, and *cis*-**167a** was obtained in good yield (88%). In the case of the 2,5-disubstituted pyrolidines **166b**, the epimerisation-isomerisation proved unsuccessful. The hydrogenation of the double bonds in the lateral ester chains of the **166b** isomers provided a mixture of *cis/trans*-**167b** in 77% yield. Cyclisation of **167a-b** to the corresponding quinolizinone **168a** and indolizidine **168b** was attempted, but further optimisation is required.

Finally, the keto-α,β-unsaturated thioester **170a** and the keto-α,β-unsaturated nitrile **170b** were synthesised, in order to explore new Michael acceptors in the biocatalysed transaminase triggered IMAMR. Our first attempts with these novel substrates, using our standard biotransamination conditions (ATA-256, IPA (2 eq.),

DMSO (10% [v/v], 50 °C), were, however, not successful. Optimisation of the TA reaction could be investigated using different enzymes, amine donors and solvents as well as expanding the scope towards the study of the corresponding vinylogous aza-Michael reaction if optimal conditions are found.

3.5 Experimental

General methods and considerations:

For materials, glassware, TLC, flash chromatography, FT-IR, NMR, GC-MS, MW and optical rotations: see Section 2.5

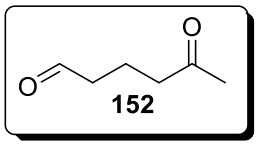
Ozone Generator: All ozonolysis reactions were carried out using a Triogen® model LAB 2B generating ozone at 10 g/h.

Melting Points: Melting points were measured using a Stuart® SMP10 melting point apparatus and are not corrected.

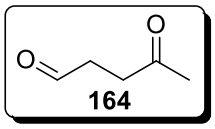
HPLC-DAD: Attempts to determine the enantioselectivity were carried out on an Agilent 1100 series HPLC equipped with a G1313B diode array detector and a G1311A Quat pump. Chiral columns tried for analysis were: Lux 5µ Cellulose-1, Lux 5µ Cellulose-3 Lux 5µ Cellulose-5 Lux 5µ Amylose-1, Lux 5µ Amylose-2 (Phenomenex®, 250 mm x 4.6 mm). Racemic standards were prepared by reductive amination using sodium cyanoborohydride and ammonium acetate (see experimental procedure for further details).[142]

General procedure for ozonolysis reaction: A stream of ozone was bubbled through a solution of the corresponding alkenes 1-methylcyclopentene (**151**, 9.50 mmol) and

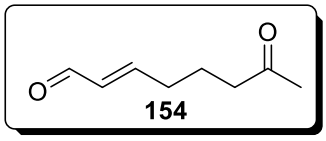
5-hexen-2-one (**163**, 9.50 mmol) in CH_2Cl_2 (100 mL) at −78 °C until the solution had turned into a pale blue colour that persisted. Triphenylphosphine (2.60 g, 9.94 mmol) was added slowly and warmed up to room temperature over a 10 h period. The solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography.



5-oxohexanal (152): Compound **152** was synthesised from 1-methylcyclopentene (**151,** 743 mg, 9.1 mmol) using the general procedure for ozonolysis to give the named compound as a colourless oil. **Yield:** 806 mg, 78%. **RF:** 0.40 (EtOAc / cyclohexane 7:3). **FTIR (neat) V_{max}:** 2985, 2941, 2831, 2729, 1710, 1411, 1369, 1162, 587, 519 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 9.74 (s, 1H), 2.52 – 2.45 (m, 4H), 2.12 (s, 3H), 1.91 – 1.82 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 208.2, 202.1, 43.0, 42.4, 30.1, 16.1. **HRMS (m/z):** Calculated $C_6H_{11}O_2$ $[M+H]^+$: 115.0759, found: 115.0756. Data in accordance with literature.[143]



4-oxopentanal (164): Compound **164** was synthesised from 5-hex-en-2-one (**163**, 1.06 g, 10.8 mmol) using the general procedure for ozonolysis to give the named compound as a yellow oil. **Yield:** 604 mg, 56%. **RF:** 0.45 (EtOAc / cyclohexane 7:3). **FTIR (neat) V_{max}:** 2910, 2834, 2731, 1709, 1367, 1169 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** δ 9.78 (s, 1H), 2.74 (s, 4H), 2.19 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$) δ:** 206.6, 200.6, 37.5, 35.6, 29.9. **HRMS (m/z):** Calculated $C_5H_9O_2$ $[M+H]^+$: 101.0602, found: 101.0599. Data in accordance with literature.[144]

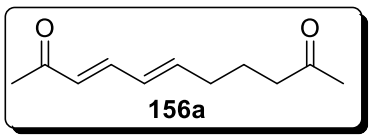


(2*E*)-7-oxooct-2-enal (154): (Triphenylphosphoranylidene) acetaldehyde (**153**, 1.2 eq, 2.37 g, 7.8 mmol) was added to 5-oxohexanal (**152**, 905 mg, 6.5 mmol) in dry CH_2Cl_2,

the reaction was irradiated in a microwave at 120 °C for 4 h to give the titled compound as a yellow oil. **Yield:** 545 mg, 49%. **RF:** 0.78 (EtOAc / cyclohexane 8:2) **FTIR (neat) V_{max}:** 2941, 2819, 1712, 1684, 1637, 1128, 967, 917, 730 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 9.48 (d, *J* = 7.8 Hz, 1H), 6.80 (dt, *J* = 15.6, 6.7 Hz, 1H), 6.10 (ddd, *J* = 15.6, 7.9, 1.1 Hz, 1H), 2.48 (t, *J* = 7.2 Hz, 2H), 2.37 – 2.28 (m, 2H), 2.13 (s, 3H), 1.83 – 1.73 (m, 2H).**^{13}C NMR (101 MHz, $CDCl_3$) δ:** 208.0, 194.0, 157.7, 133.4, 42.5, 32.0, 30.1, 21.6. **HRMS (m/z):** Calculated $C_8H_{13}O_2$ $[M+H]^+$: 141.0915, found: 141.0908. Data in accordance with literature.[145]

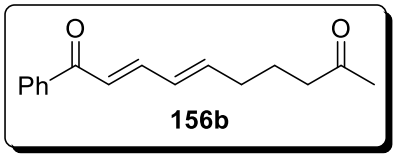
General Procedure for Wittig reaction for the synthesis of 156a-b:

Ylide **155a** or **155b** (1.06 mmol, 2 eq.) was added to the corresponding aldehyde **1156a-b** (0.53 mmol) in dry CH_2Cl_2 and the reaction mixture was heated in a pressure tube at 40 °C for 48 h.



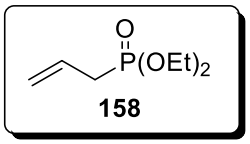
156a

(3E,5*E*)-deca-3,5-diene-2,9-dione (156a): Compound **156a** was synthesised from **154** (73 mg, 0.53 mmol) and 1-(triphenylphosphoranylidene)-2-propanone (**155a**, 337 mg, 1.06 mmol), using the general procedure for Wittig reaction for the synthesis of **156a-b** to give the named compound as a yellow oil. **Yield:** 35 mg, 37%. **RF:** 0.42 (EtOAc / cyclohexane 7:3) **FTIR (neat) V_{max}:** 2939, 1710, 1675, 1359, 1254, 1164, 979, 535 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.07 (dd, *J* = 16.0, 10.0 Hz, 1H), 6.24 – 6.09 (m, 2H), 6.05 (d, *J* = 15.7 Hz, 1H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 2.18 (q, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 1.76 – 1.67 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 208.3, 199.3, 157.7, 157.6, 137.5, 136.3, 43.2, 38.2, 34.0, 30.5, 22.7. **HRMS (m/z):** Calculated $C_{11}H_{17}O_2$ $[M+H]^+$: 181.1222, found: 181.1223.



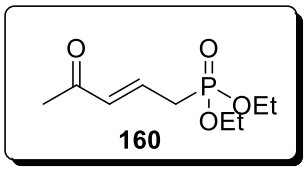
156b

(2*E*,4*E*)-1-phenylnona-2,4-diene-1,8-dione (156b): Compound **156b** was synthesised from **154** (73 mg, 0.53 mmol) and (benzoylmethylene)triphenylphosphorane (**155b**, 403 mg, 1.06 mmol) using the general procedure for Wittig reaction for the synthesis of **156a-b** to give the named compound as a brown oil. **Yield:** 149 mg, 40%. **RF:** 0.35 (EtOAc / cyclohexane 7:3). **FTIR (neat) V_{max}:** 2934, 2934, 1707, 1658, 1597, 1584, 1574, 1007, 694, 666 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 7.96 – 7.90 (m, 2H), 7.58 – 7.53 (m, 1H), 7.48 (t, *J* = 8 Hz, 2H), 7.45 – 7.35 (m, 1H), 6.90 (d, *J* = 15.0 Hz, 1H), 6.39 – 6.16 (m, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 2.23 (q, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 1.75 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 208.6, 191.0, 145.1, 138.3, 132.7, 130.0, 128.7, 128.5, 128.4, 124.1, 42.8, 32.5, 30.2, 22.7. **HRMS (m/z):** Calculated $C_{16}H_{19}O_2$ $[M+H]^+$: 243.1385, found: 243.1382.



158

Diethyl allylphosphonate (158): Triethylphosphite (2 mL, 11.7 mmol) and allyl bromide (**157**, 1.1 mL, 12.7 mmol) were heated at 140 °C for 4 h. Some of the excess of allyl bromide was removed under reduced pressure and the crude product was purified by column chromatography to give the titled compound as a yellow oil. **Yield:** 1.27 g, 61%. **RF:** 0.37 (EtOAc / cyclohexane 2:8). **M_p** = 190-194 °C. **FTIR (neat) V_{max}:** 3474, 2983, 1640, 1250, 1020, 957, 825, 621, 486 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 5.84 – 5.68 (m, 1H), 5.23 – 5.12 (m, 2H), 4.15 – 3.99 (m, 4H), 2.58 (ddd, *J* = 9.7, 8.0, 1.2 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 6H). **^{31}P NMR (162 MHz, $CDCl_3$) δ**: 27.7. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 127.6 (d, *J* = 11.3 Hz), 120.0 (d, *J* = 14.4 Hz), 62.0 (d, *J* = 6.6 Hz), 31.9 (d, *J* = 139.2 Hz), 16.5 (d, *J* = 6.2 Hz). **HRMS (m/z):** Calculated $C_7H_{16}O_3P$ $[M+H]^+$: 179.0831, found: 179.0834. Data in accordance with literature.[127]



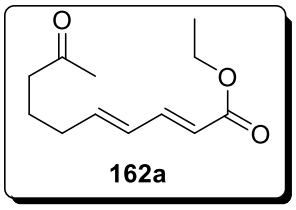
160

(4*E*)-6-(diethylphosphoryl)hex-4-en-2-one (160): To a solution of diethyl allylphosphonate (**158**, 500 mg, 2.80 mmol) and methyl vinyl ketone (**159**, 0.24 mL, 2.79 mmol) in dry CH_2Cl_2 (500 mL), Grubbs 2nd generation catalyst (**L35**, 48 mg, 0.002 mmol) was added. The mixture was stirred under reflux for 1.5 h. The reaction was monitored by ^{31}P NMR. If no gas evolution occurred, 1% mol of additional catalyst (**L34)** was added. Once the reaction had reached completion, solvent was removed under reduced pressure and the residue was purified by column chromatography, to give the titled compound as a dark brown oil. **Yield:** 432 mg, 66%. **RF:** 0.4 (MeOH / CH_2Cl_2 1:9). **FTIR (neat) V_{max}:** 3375, 2983, 2932, 1701, 1656, 1629, 1237, 1163, 1020, 969, 792, 730, 542, 509 cm^{-1}. **^{31}P NMR (162 MHz, $CDCl_3$) δ**: 24.8. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 6.72 – 6.59 (m, 1H), 6.17 – 6.08 (m, 1H), 4.12 – 3.98 (m, 4H), 2.70 (ddd, *J* = 23.0, 7.8, 1.2 Hz, 2H), 2.20 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 136.6 (d, *J* = 11.3 Hz), 135.1 (d, *J* = 13.3 Hz), 62.3 (d, *J* = 6.6 Hz), 30.9 (d, *J* = 138.3 Hz), 16.4 (d, *J* = 6.0 Hz). **HRMS (m/z):** Calculated $C_9H_{18}O_4P$ $[M+H]^+$: 221.0942, found: 221.0935. Data in accordance with literature.[146]

General Procedure for the Horner- Wadsworth -Emmons reaction for the synthesis of 162a-b:

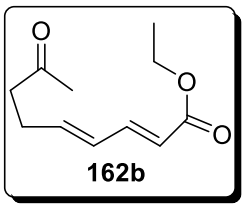
To a solution of the commercially available triethyl-4-phosphocrotonate (**161**, 0.8 mL, 3.6 mmol) in THF (40 mL), LDA (1 M in THF, 1.84 mL, 1.84 mmol) was added at −40 °C and the solution was left to stir for 30 min at −40 °C. The corresponding ketoaldehyde **152** or **164** was added (3.5 mmol) in THF (12 mL), the resulting mixture was stirred for 20 min at −40 °C, then warmed up to room temperature and stirred

for an additional 10 min. The reaction was quenched with saturate aq. NH_4Cl (10 mL) and the solution was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $NaSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography.



162a

Ethyl-(2*E*,4*E*)-9-oxodeca-2,4-dienoate (162a): Compound **162a** was synthesised from **152** (400 mg, 3.5 mmol) using the general procedure for Horner-Wadsworth-Emmons reaction to give the named compound as a yellow oil. **Yield:** 354 mg, 48%. **RF:** 0.37 (EtOAc / cyclohexane 2:8). **FTIR (neat) V_{max}:** 2940, 2889, 1712, 1662, 1623, 1427, 1454, 1348, 1252, 1191, 1159, 966, 887 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 7.23 (dd, *J* = 16, 8 Hz, 1H), 6.21 – 6.01 (m, 2H), 5.78 (d, *J* = 15.3 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 2.44 (dd, *J* = 9.3, 5.3 Hz, 2H), 2.17 (q, *J* = 7.2 Hz, 2H), 2.13 (s, 3H), 1.71 (dt, *J* = 13.6, 6.8 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H).**^{13}C NMR (101 MHz, $CDCl_3$) δ:** 208.6, 167.3, 144.8, 143.2, 129.2, 119.9, 60.4, 42.8, 32.3, 30.2, 22.7, 14.4. **HRMS (m/z):** Calculated $C_{12}H_{19}O_3$ $[M+H]^+$: 211.1329, found: 211.1328.



162b

Ethyl-(2*E*,4*E*)-8-oxonona-2,4-dienoate (162b): Compound **162b** was synthesised from **164** (440 mg, 4.4 mmol) using the general procedure for Horner-Wadsworth-Emmons reaction to give the named compound as a yellow oil. **Yield:** 338 mg, 39%. **RF:** 0.54 (EtOAc / cyclohexane 1:1). **FTIR (neat) V_{max}:** 3436, 2983, 2913, 1705, 1641, 1616, 1367, 1243, 1196, 1156, 1133, 1031, 1002 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.22 (dd, *J* = 12, 8 Hz, 1H), 6.24 – 6.00 (m, 2H), 5.79 (d, *J* = 15.5 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 2.61 – 2.54 (m, 2H), 2.43 (q, *J* = 6.9 Hz, 2H), 2.15 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR**

(101 MHz, $CDCl_3$) δ: 207.5, 167.3, 144.6, 142.1, 129.3, 120.2, 60.4, 42.4, 30.2, 27.0, 14.0. **HRMS (m/z):** Calculated $C_{11}H_{17}O_3$ $[M+H]^+$: 197.1172, found: 197.1172.

General procedure D, for the transamination of ketodieno esters 162a-b: Commercially available (*S*)-selective ATA-256 (25 mg) or (*R*)-selective ATA-025 (25 mg) was rehydrated in HEPES buffer (4.0 mL, 100 mM, pH 7.5) containing PLP (2.00 mM) and isopropylamine (2 eq, 43 µL, 0.5 mmol). The pH of the mixture was adjusted to 7.5, using aq HCl solution (1 M) and the total volume of the reaction was adjusted to 4.5 mL by addition of HEPES buffer (100 mM, pH 7.5). The corresponding substrate**162a-b** was added (50 mM, 0.5 mL in DMSO) and the reaction mixture was incubated at 50 °C, 180 rpm for 48 h. The reaction was monitored by GC-MS. After completion, the reaction mixture was filtered through a 0.2 µL HPLC filter and the corresponding filtrate was passed through an Isolute® column SX-C2 using MeOH as eluent (75 mL). This first filtrate was discarded and the Isolute column was then flushed with methanolic ammonia solution (75 mL) to release the corresponding amines **166a-b.** This second filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography to provide the corresponding amines **166a-b** as an isomeric mixture.

General procedure E, for the control experiments for the transamination of 162a-b: The general procedure A above was followed, omitting the addition of the enzyme.

General Procedure F, for enzyme immobilisation onto resin:

Enzyme ATA-256 (31.2 mg) was dissolved in HEPES buffer (100 mM, 2 mL). The resin (ECR1030M, 516 mg) was washed with a small volume of HEPES buffer (0.1 M), filtered, and added to the enzyme-buffer solution. The mixture was incubated (25 °C,

80 rpm, 24 h) and then centrifuged (5000 rpm, 3 min). The enzyme carrier resin was filtrated and dried under vacuum. The enzyme absorption onto the resin was measured, from the solution, using a Nanodropä One spectrophotometer, to be 7.54 mg/mL (250 mg resin). The resin beads were then filtered and stored below 5 °C.

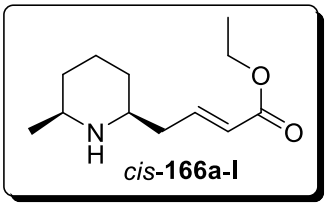
General procedure G, for the biotransformations of 162a using resin-supported transaminase (ECR1030M):

HEPES buffer solution (100 mM, 1.5 mL, pH 7.5), IPA (17.2 mL) and PLP (2.00 mM, 0.2 mL in HEPES) were added to an Eppendorf vial (10 mL), and the pH was adjusted to 7.5 using HCl and NaOH solutions (2 M). The resin-supported ω-TA enzyme [(*S*)-selective ATA-256 supported onto ECR1030M)] was then added (10 mg), followed by substrate **162a** (21 mg) in DMSO (0.25 mL). The mixture was then incubated (50 ^{o}C, 180 rpm) for 48 h, and the progress of the reaction was monitored by GC-MS. After 48 h, the solution was centrifuged for 5 min (5000 rpm) and decanted. The solution was made basic using NaOH solution (2 M), extracted with ethyl acetate (4 x 10 mL), and further centrifuged. The combined organic layers were then passed through an Isolute SCX-2 column, using MeOH as eluent (75 mL). This first filtrate was discarded and the Isolute column was then flushed with methanolic ammonia solution (75 mL) in an attempt to release the corresponding amines. This second filtrate was concentrated under reduced pressure. No product **166a** was observed.

General procedure H, for the epimerisation/isomerisation of 166a-b: The corresponding mixture of isomers (0.255 mmol) was dissolved in EtOH (7 mL) and irradiated in MW at 120 °C for 8 h. The solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography to give *cis*-**166a-l** as a dark brown oil.

General procedure I, for reductive amination of 162a-b for the synthesis of racemic 166a-b:[142]

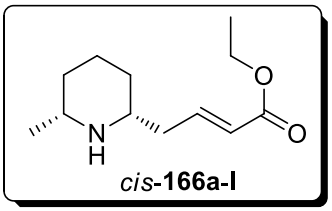
Ammonium acetate (13 eq, 2.15 mg, 2.8 mmol) was added to the corresponding ketodieno esters **162a-b** (1 eq, 0.22 mmol) in ethanol (3 mL) at RT and stirred for 25 min. Sodium cyanoborohydride (0.7 equiv, 10 mg, 0.16 mmol) was added at RT and then the reaction mixture was stirred for 4-8 days at room temperature. The reaction was then quenched with HCl (6 M), washed with diethyl ether (2 x 10 mL) and the aqueous extract was basified to pH 8 with NaOH (2 M). The liberated amine was extracted with CH_2CL_2(3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography.



cis-**166a-l**

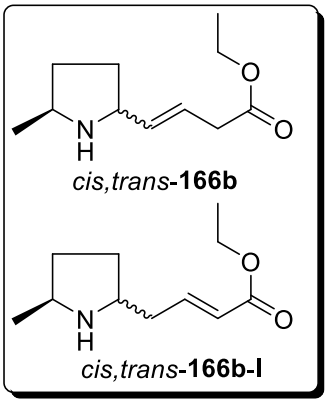
Ethyl (2*E*)-4-[(2*S*,6*S*)-6-methylpiperidin-2-yl]but-2-enoate [*cis*-(–)-166-l]: Compound *cis*-**166a-l** was synthesised from **162a** (53 mg, 0.25 mmol) using general procedure D with ATA-256, followed by epimerisation/isomerisation (general procedure G) to give the named compound as a dark brown oil. **Yield:** 21 mg, 39%. **RF:** 0.28 (MeOH / DCM 5:95). **$[\alpha]_D^{26}$** = – 8.8 (*c* 0.9, EtOH). **FTIR (neat) V_{max}:** 3315, 2928, 2857, 1717, 1654, 1441, 1309, 1265, 1177, 1034, 982 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**

δ: 6.90 – 6.78 (m, 1H), 5.88 (d, *J* = 15.6 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 2.88 – 2.70 (m, 2H), 2.69 – 2.49 (m, 1H), 2.48 – 2.36 (m, 1H), 1.85 – 1.76 (m, 1H), 1.75 – 1.59 (m, 1H), 1.44 – 1.08 (m, with a t at 1.26, *J* = 8 Hz, and a d at 1.20, *J* = 4 Hz, 8H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 166.3, 144.5, 124.3, 60.5, 56.3, 53.3, 38.6, 32.7, 30.5, 24.0, 21.7, 14.3. **HRMS (m/z):** Calculated $C_{12}H_{22}NO_2$ $[M+H]^+$: 212.1645, found: 212.1662.



cis-**166a-I**

(*E*)-ethyl 4-((2*R*,6*R*)-6-methylpiperidin-2-yl)but-2-enoate [*cis*-(+)-166a-I]: Compound *cis*-**166a-I** was synthesised from **162a** (53 mg, 0.25 mmol) using general procedure D with ATA-025, followed by epimerisation/isomerisation (general procedure G) to give the named compound as a dark brown oil. **Yield:** 19 mg, 37%. **RF:** 0.28 (MeOH / DCM 5:95). **$[\alpha]_D^{26}$** = + 5.7 (*c* 0.7, EtOH). **HRMS (m/z):** Calculated $C_{12}H_{21}NO_2$ $[M+H]^+$: 212.1645, found: 212.1662.

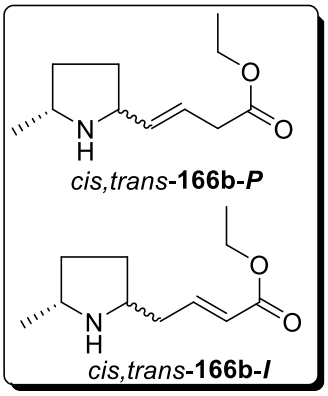


cis,trans-**166b**

cis,trans-**166b-I**

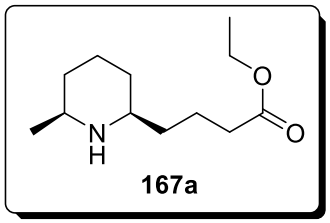
Mixture of *cis*/*trans*-ethyl-(2*E*)-4-[(5*S*)-5-methylpyrrolidin-2-yl]but-2-enoate and *cis*/*trans*-ethyl-(3*E*)-4-[(5*S*)-5-methylpyrrolidin-2-yl]but-3-enoate (166b): The mixture *cis/trans*-**166b** and *cis/trans*-**166b-I** were synthesised from **162a** (49 mg, 0.25 mmol) following general procedure D with ATA-256, to give the named compound as a yellow oil as an isomeric mixture (*cis/trans*-**166b** and *cis/trans*-**166b-I,** 3.5:1). **Yield:** 14 mg, 28%. **RF:** 0.45 (MeOH / DCM 5:95). **$[\alpha]_D^{26}$** = – 11.42 (*c* 0.7, $CHCl_3$). **FTIR (neat) V_{max}:** 2966, 2929, 1872, 1640, 1441, 1410, 1145, 976 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 6.53 – 6.48 (m, 1H, **166b-I**, *diastereomer 1*), 6.44 – 6.39 (m, 1H, **166b-I**, *diastereomer 2*), 5.94 – 5.71 (m, 6H, *cis/trans*-**166b** *and*

cis/trans-**166b**-**I**), 4.28 – 4.07 (m, 8H, *cis/trans*-**166*b*** *and cis/trans*-**166b**-**I**), 3.55 – 3.44 (m, 2H, *cis/trans*-**166b**), 3.01 – 2.81 (m, 10H, *cis/trans*-**166b** *and cis/trans*-**166b**-**I**), 2.22 – 2.02 (m, 4H, *cis/trans*-**166b**-**I**), 1.79 – 1.48 (m, 8H, *cis/trans*-**166b** *and cis/trans*-**166b**-**I**), 1.47 – 1.37 (m, 8H, *cis/trans*-**166*b*** *and cis/trans*-**166b**-**I**), 1.33 – 1.15 (m, 24H, *cis/trans*-**166*b*** *and cis/trans*-**166b**-**I**). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 167.9, 167.2, 166.0, 164.0, 162.9, 140.1, 138.9, 137.2, 127.3, 126.7, 124.8, 124.9, 122.5, 63.9, 59.3, 58.3, 58.1, 55.5, 52.9, 52.7, 52.3, 52.2, 51.6, 34.5, 33.2, 32.5, 32.2, 31.6, 31.5, 31.2, 29.1, 21.1, 20.8, 20.0, 19.8, 18.4, 15.6. **HRMS (m/z):** Calculated $C_{11}H_{19}NO_2$ $[M+H]^+$: 198.1494, found: 198.149.



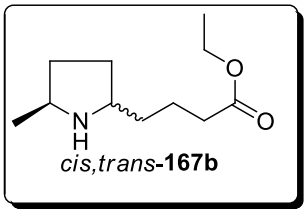
Mixture of *cis*/*trans*-ethyl-(2*E*)-4-[(5*R*)-5-methylpyrrolidin-2-yl]but-2-enoate and *cis*/*trans*-ethyl-(3*E*)-4-[(5*R*)-5-methylpyrrolidin-2-yl]but-3-enoate (166b): Compound *cis/trans*-**166b**-***P*** and *cis/trans*-**166b**-were synthesised from **162b** using general procedure A with ATA-025 to give the named compound as a yellow oil. **Yield:** 12 mg, 24%. **RF:** 0.45 (MeOH / DCM 5:95). **$[\alpha]_D^{26}$** = –80 (*c* 0.6, $CHCl_3$)

General procedure for the hydrogenation reaction for the synthesis of 167a-b: Compound *cis*-**166a-I** or the isomeric mixture *cis/trans*-**166b** and *cis/trans*-**166b**-**I** (0.128 mmol) was dissolved in ethanol (3 mL) in the presence of Pd/C (10% wt, 0.046 mmol) and stirred at RT for 24 h. The crude mixture was filtered over Celite, concentrated under reduced pressure and purified by flash column chromatography.



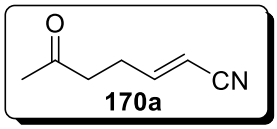
167a

1-hydroxy-6-[(2*S*,6*S*)-6-methylpiperidin-2-yl]hexan-3-one (167a): Compound **167a** was synthesised from *cis*-**166a-I** (27 mg, 0.123 mmol) following the general procedure for the hydrogenation reaction to give the named compound as a yellow oil. **Yield:** 24 mg, 88%. **RF:** 0.32 (MeOH / DCM 5:95). **$[\alpha]_D^{26}$** = –27.7 (*c* 0.52, $CHCl_3$) . **FTIR (neat) V_{max}:** 2936, 2853, 2746, 1733, 1279, 1032, 1960 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 4.11 (q, *J* = 7.2 Hz, 2H), 3.12 – 3.00 (m, 1H), 2.98 – 2.86 (m, 1H), 2.40 – 2.19 (m, 2H), 2.15 – 2.02 (m, 1H), 1.93 (m, 2H), 1.86 – 1.52 (m, 7H), 1.49 (d, *J* = 6.5 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 173.3, 60.7, 58.1, 54.6, 33.8, 32.9, 30.8, 27.9, 23.0, 20.9, 19.6, 14.4. **HRMS (m/z):** Calculated $C_{12}H_{23}NO_2$ $[M+H]^+$: 214.1807, found: 214.1803.[147]



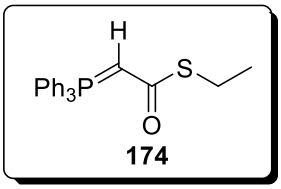
cis,trans-**167b**

Ethyl 4-[(2*S*,5*S*)-5-methylpyrrolidin-2-yl]butanoate and ethyl 4-[(2*R*,5*S*)-5-methylpyrrolidin-2-yl]butanoate (167b): Compound *cis*/*trans*-**167b** was synthesised from the isomeric mixture *cis/trans*-**166b** and *cis/trans*-**166b-I** (18 mg, 0.091 mmol) following the general procedure for the hydrogenation reaction to give the named compound as a yellow oil. d.r. n.d. **Yield:** 14 mg, 77%. **RF:** 0.32 (MeOH / DCM 5:95) **$[\alpha]_D^{26}$** = – 5.71 (*c* 0.7, $CHCl_3$) . **FTIR (neat) V_{max}:** 2920, 1700, 1656, 1550, 756 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 4.18 – 4.06 (m, 4H), 3.53 – 3.39 (m, 4H), 3.00 – 2.78 (m, 4H), 2.50 – 1.49 (m, 18H), 1.43 – 1.13 (m, 12H).**^{13}C NMR (101 MHz, $CDCl_3$) δ:** 198.2, 63.9, 60.6, 58.5, 57.2, 53.6, 53.0, 36.7, 33.2, 31.8, 31.3, 29.8, 29.4, 29.0, 21.07, 20.95, 20.06, 18.41, 1.16**.** **HRMS (m/z):** Calculated $C_{11}H_{21}NO_2$ $[M+H]^+$: 200.1650, found: 200.1645.



170a

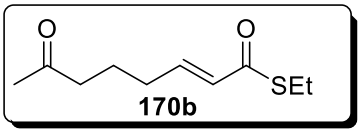
(2*E*)-6-oxohept-2-enenitrile (170a): To an equimolar solution of 5-hexen-2-one (**163**, 117 µL, 1.01 mmol) and acrylonitrile (67 µL, 1.02 mmol) in dry DCM (22 mL), copper chloride (10 mg, 0.074 mmol) was added. Grubbs 2nd Generation (**L34**, 21.5 mg, 0.025 mmol) was added and the reaction was stirred for 3 h at 40 °C. The solvent was removed under reduced pressure and the product was purified by flash silica gel chromatography to give the named compound as a colourless oil. **Yield:** 57 mg, 46%. **RF:** 0.55 (EtOAc / cyclohexane 3:2). **FTIR (neat) V_{max}:** 2221, 1713, 1412, 1363, 1163, 971, 741 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 6.57 – 6.47 (m, 1H), 5.32 (d, *J* = 16 Hz, 1H), 2.60 (t, *J* = 8 Hz, 2H), 2.51 – 2.43 (m, 2H), 2.16 (s, 3H).**^{13}C NMR (101 MHz) δ:** 206.2, 154.1, 115.8, 100.9, 53.6, 30.1, 27.1. **HRMS (m/z):** Calculated $C_7H_{10}NO$ $[M+H]^+$: 124.07623, found: 124.0757.[148]



174

Ethyl 2-(triphenylphosphoranylidene)ethanethioate (174): A solution of bromoacetic acid (**173**, 6.97 g, 50.16 mmol), 4-(dimethylamino)pyridine (610 mg, 4.99 mmol) and ethanethiol (4.83 mL, 65.22 mmol) in dry DCM (225 mL) was cooled to 0 °C. Dicyclohexylcarbodiimide (10.86 g, 52.63 mmol) was added slowly and the solution was warmed to room temperature overnight. The solution was filtered over Celite and the Celite cake was washed multiple times with Et_2O. The filtrate was washed with sat aq. $NaHCO_3$, followed by water and then brine. The organic layer was dried over Na_2SO_4 and concentrated under vacuum to yield a yellow oil (6.64 g, 73%). Triphenyl phosphine (9.98 g, 8.64 mmol) was added to the crude product in toluene (57 mL) and the resulting mixture was stirred at room temperature for 3 days. The toluene was removed under vacuum to give a white solid which was then dissolved

in CH_2Cl_2 (75 mL) and vigorously stirred with 50 mL of 10% aq Na_2CO_3 solution for 30 min. The layers were separated and the aqueous layer was extracted CH_2Cl_2 (2 x 30 mL). The combined organic phases were partially concentrated in vacuo to give the named compound in salt like white crystals. **Yield:** 10.98 g, 60%. **RF:** 0.35 (EtOAc / cyclohexane 1:1). **Mp** = 186–191 °C. **FTIR (neat) V_{max}:** 1579, 1337, 1085, 871, 692, 512, 302 cm^{-1}. **^{1}H NMR (400 MHz) δ:** 7.65 – 7.58 (m, 6H), 7.57 – 7.51 (m, 3H), 7.49 – 7.41 (m, 6H), 3.65 (d, *J* = 21.8 Hz, 1H), 2.83 (q, *J* = 7.3 Hz, 2H), 1.24 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 180.6, 180.5, 133.2, 133.1, 132.3, 132.3, 129.1, 128.9, 127.3, 126.4, 47.6, 46.5, 23.2, 16.5. **^{31}P NMR (162 MHz, $CDCl_3$) δ**: 14.2. **HRMS (m/z):** Calculated $C_{22}H_{21}OPS$ $[M+H]^+$: 365.1129, found: 365.1133. Data in accordance with literature.[149]



170b

***(E)-S*-ethyl 7-oxooct-2-enethioate (170b):** A solution of 5-oxohexanal (**152**, 64 mg, 0.56 mmol) and ylide **174** (277 mg, 0.73 mmol) in DCM (5 mL) was heated in a pressure vial at 40 °C overnight. The solution was concentrated under vacuum and purified by column chromatography to give the named compound as a dark brown oil. **Yield:** 68 mg, 65%. **RF:** 0.65 (EtOAc / cyclohexane 1:1), **FTIR (neat) V_{max}:** 2931, 1713, 1664, 1630, 1450, 1413, 1358, 1264, 1159, 1137, 1060, 973, 802, 732 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 6.83 (dt, *J* = 12, 4 Hz, 1H), 6.10 (dt, *J* = 16, 4 Hz, 1H), 2.93 (q, *J* = 7.4 Hz, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.27 – 2.16 (m, 2H), 2.13 (s, 3H), 1.80 – 1.69 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR (101 MHz, $CDCl_3$) δ:** 208.2, 144.1, 129.4, 42.7, 31.4, 30.2, 23.2, 21.9, 14.9. **HRMS (m/z):** Calculated $C_{10}H_{27}O_2S$ $[M+H]^+$: 201.0949, found: 201.0944.

General procedure for the attempted synthesis of 170c:

To a solution of **152** (394 mg, 3.24 mmol) and nitromethane (178 µL, 3.29 mmol) in EtOH or MeOH (1 mL), NaOH or KOH (10 M, 0.32 mL) was added dropwise at 0 °C and left stir for 30 min and the reaction mixture went yellow. The reaction was acidified with acetic acid (185 µL, 3.18 mmol) and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. No product **170c** was observed.

4. Enantioselective Addition of Organozirconium Reagents to Aliphatic Aldehydes

This chapter has been published:

Vaccari, J.; González-Soria, M.J.; Carter, N.; Maciá, B. Catalytic Enantioselective Addition of Alkylzirconium Reagents to Aliphatic Aldehydes. *Molecules* **2021**, *26*, 4471.

4.1 Introduction

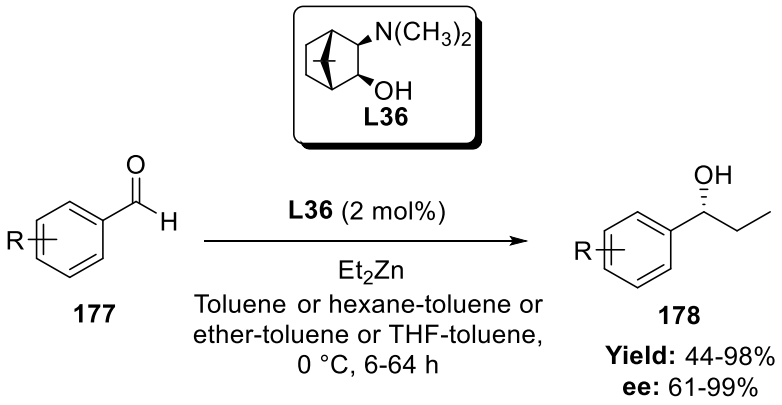
Chiral molecules are ubiquitous throughout nature. They play a crucial role in many areas of academia and industry and the use of asymmetric catalysis for their construction has become an important area of research.[150] The enantioselective hydrogenation of ketones and the enantioselective addition of organometallic reagents to prochiral carbonyl compounds are amongst the most popular methods to produce chiral alcohols, which are very relevant building blocks. In particular, this chapter will exclusively focus on the enantioselective addition of organometallic reagents to aldehydes.

4.1.1 Enantioselective addition of organometallic reagents to aldehydes.

Chiral alcohols are highly valuable building blocks and the use of organometallic reagents for their construction is one of the most efficient approaches.[151-154] Catalytic enantioselective versions of this reaction have been broadly studied for species of low to medium reactivity, such as organozinc,[155-163] organoaluminium[164-167] and organotitanium reagents.[168-171] In the last five years, a few examples with the more reactive organomagnesium and organolithium reagents have also been described.[172-178]

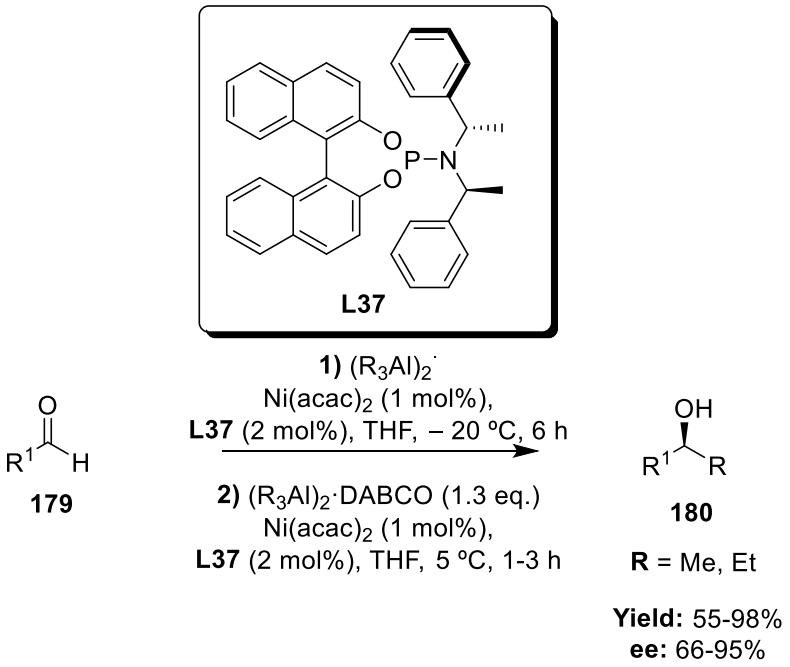
The first catalytic enantioselective addition of organozinc reagents to carbonyl compounds dates back to 1886 (Scheme 49). Noyori *et al.* reported the alkylation of aromatic aldehydes with diethylzinc in the presence of chiral ligand **L36**.[172] Since then, a substantial amount of research has been achieved in this area with an

extensive library of chiral ligands which are able to perform this transformation.[151, 152, 154, 155, 179, 180]



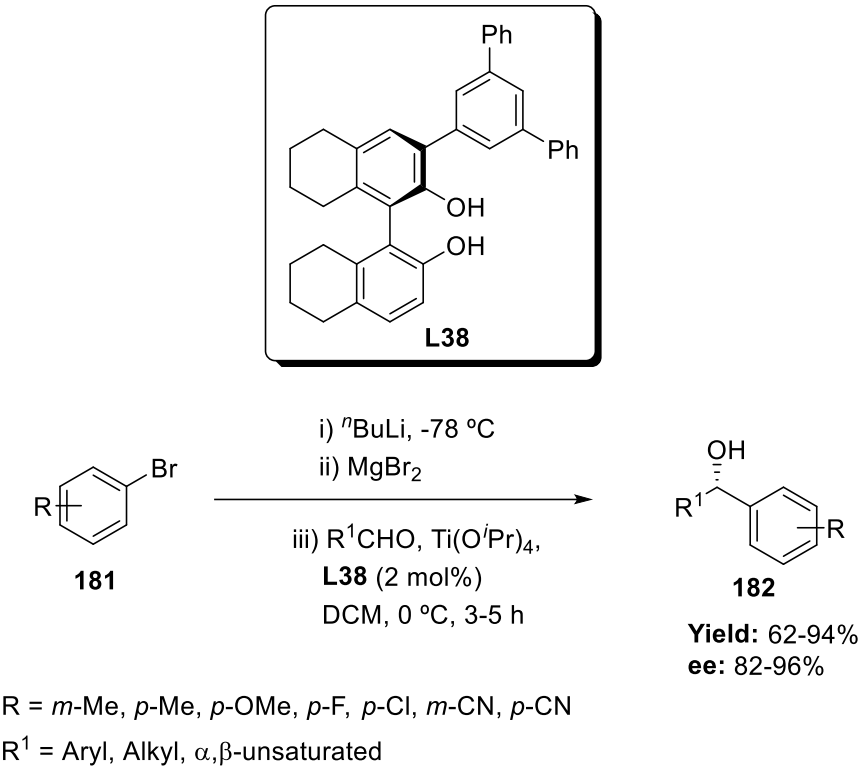
Scheme 49: Catalytic enantioselective addition of diethylzinc to aldehydes

Woodward and co-workers reported the addition of organoaluminium reagents to aliphatic and aromatic aldehydes using chiral phosphoramidite **L37** and $Ni(acac)_2$ as catalyst for the synthesis of secondary alcohols (Scheme 50, method 1).[181] Milder reaction conditions are achieved when a DABCO-$(R_3Al)_2$ complex is used (Scheme 50, method 2). Unfortunately, yields and ee are lower for aliphatic aldehydes, compared to aromatic aldehydes, for both of the reaction conditions.



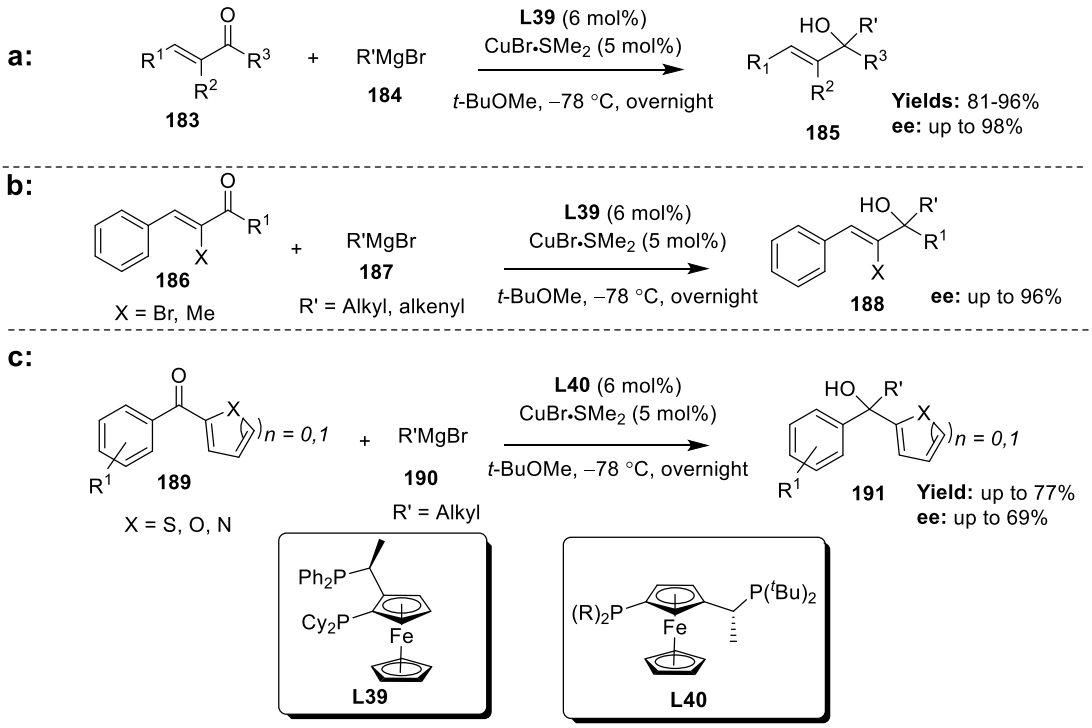
Scheme 50: Synthesis of secondary alcohols from the addition of organoaluminium reagents to aldehydes reported by Woodward et al.

The enantioselective addition to carbonyl compounds with the more readily available lower-cost organolithium and organomagnesium reagents (compared to organozinc and organoaluminium compounds) has been explored for several decades. However, the high reactivity profile of these reagents limits their use in catalytic enantioselective methodologies, and most of the few examples known involve the use of stoichiometric amounts of chiral ligands and low temperatures.[175] The first successful catalytic enantioselective addition of Grignard reagents to aldehydes was described by Harada and co-workers for the alkylation reaction of aldehydes, using the chiral ligand **L38** (Scheme 51) and titanium tetraisopropoxide ($Ti(O^iPr)_4$).[176] Other examples on the catalytic enantioselective addition of Grignard reagents to aldehydes were reported later by Maciá,[182] Harada,[183, 184] Da[185, 186] and Harutyunyan.[187]



Scheme 51: Catalytic enantioselective Harada's addition of Grignard reagent to aldehydes.

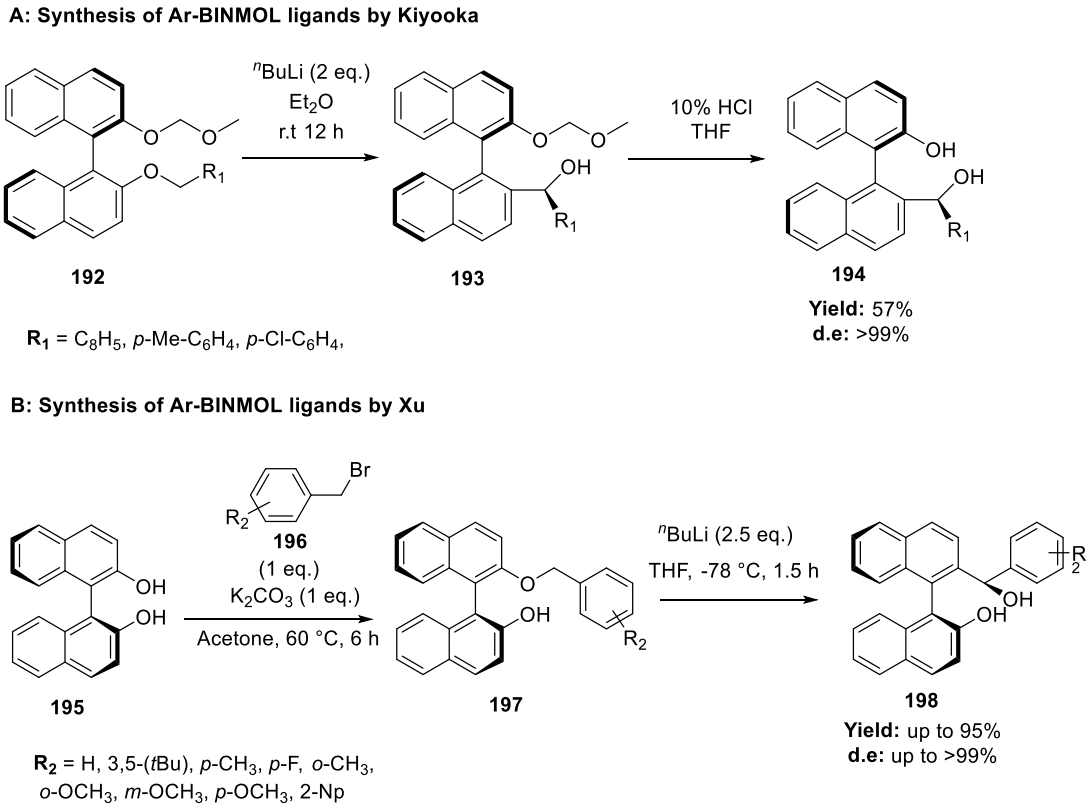
Harutyunyan *et al.* reported the catalytic enantioselective 1,2-addition of β-branched Grignard reagents to a variety of α,β-unsaturated ketones (Scheme 52a,[188-191] b)[192] and heteroaryl ketones (Scheme 52c).[193] The 1,2-addition reactions with Grignard reagents uses a copper- Josiphos-type (5 mol%) catalysts to enantioselective construct chiral tertiary alcohols with high yields and ee. They report that bulkier Grignard reagents are required to provide higher enantioselectivities and without the use of copper as part of the catalytic system no tertiary alcohols are observed.



Scheme 52: Catalytic enantioselective 1,2-addition of Grignard reagents to α,β-unsaturated ketones and heteroaryl ketones by Harutyunyan.

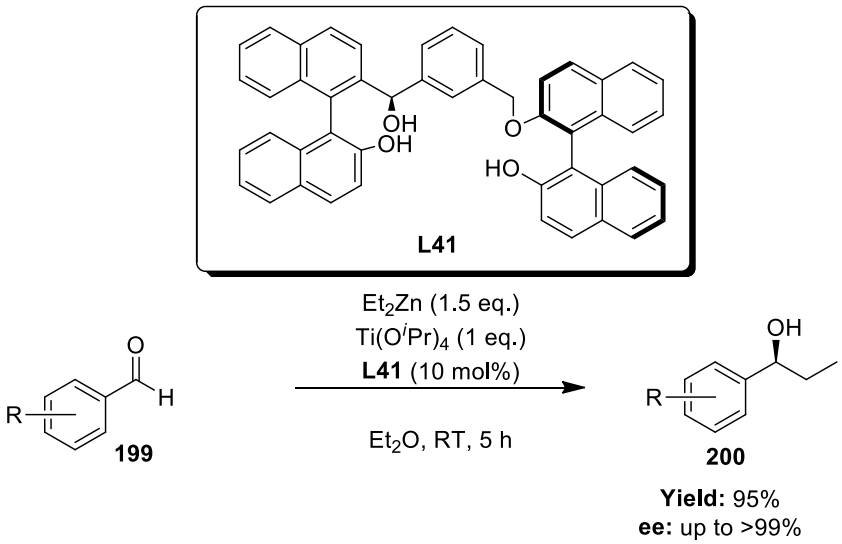
4.1.2 Ar-BINMOLs in the enantioselective addition to carbonyl compounds.

Enantiopure 1,1-binaphthalene-2-α-arylmethan-2-ols (Ar-BINMOL) were first synthesised by Kiyooka and co-workers in 1996 *via* a [1,2]-Wittig rearrangement (Scheme 53a) and later an improved synthesis was reported by Xu *et al.* (Scheme 53b), consisting of the benzylation of enantiopure (*S*)-BINOL with an aryl bromide, followed by a lithium-assisted [1,2]-Wittig arrangement.



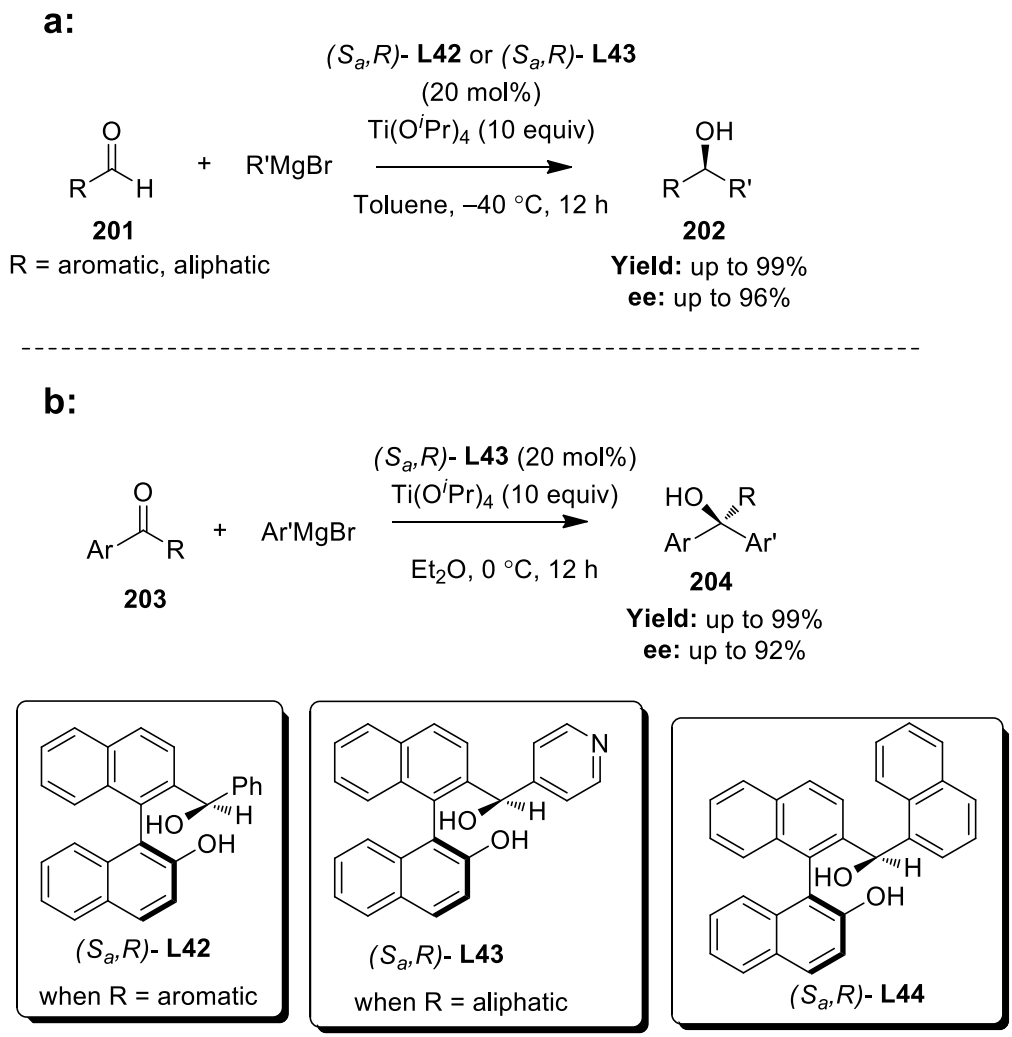
*Scheme 53: Synthesis of Ar-BINMOL ligands via Kyooka (**A**) and Xu (**B**) methods.*

Enantiopure Ar-BINMOL ligands have proven efficient in the addition of organozinc reagents to carbonyl compounds.[185, 194] Xu *et al.* reported excellent yields and enantioselectivities for the addition of Et_2Zn to aromatic aldehydes using Ar-BINMOL **L41** in the presence of $Ti(O^iPr)_4$ (Scheme 54).



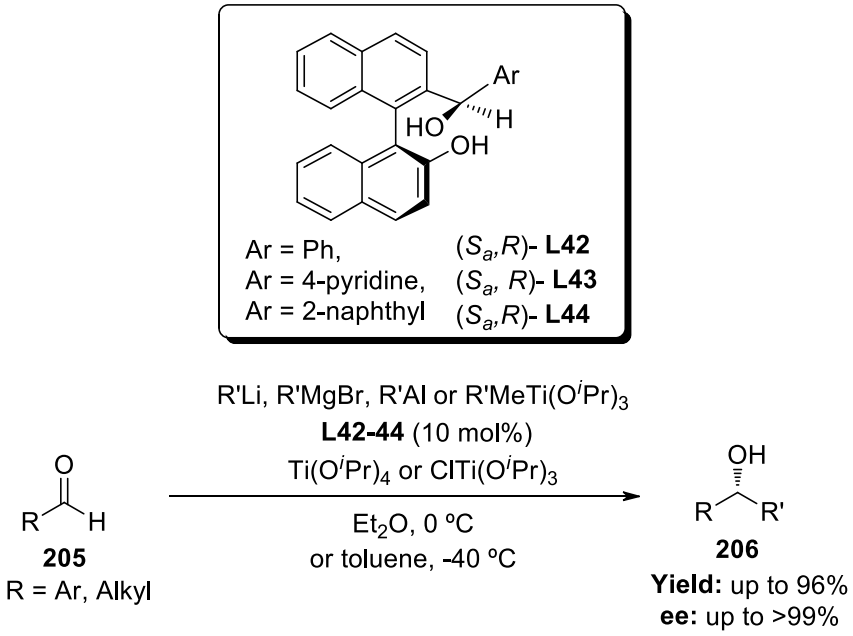
Scheme 54: Enantioselective synthesis of secondary alcohols by asymmetric addition of Et_2Zn to aromatic aldehydes reported by Xu and co-workers.

Maciá *et al.* reported the addition of alkyl Grignard reagents (including the more challenging MeMgBr) to both aliphatic[182] and aromatic aldehydes[195] and aryl Grignard reagents[196] to the more challenging ketone substrates,[177] with the use of Ar-BINMOL derived ligands **L42, L43** and **L44** as well as super-stoichiometric amounts of titanium tetraisopropoxide ($Ti(O^iPr)_4$) (Scheme 55).



Scheme 55: Catalytic enantioselective addition of Grignard reagents to aldehydes and ketones by Maciá et al.

Maciá *et al.* have also reported the use of Ar-BINMOL chiral ligands with other readily accessible nucleophiles such as organolithium,[197, 198] organoaluminum,[199] and organotitanium[200] for the catalytic enantioselective alkylation of aldehydes(Scheme 56).



Scheme 56: Use of Ar-BINMOL ligands for the catalytic enantioselective addition of nucleophiles to aldehydes.

4.1.3 Hydrozirconation reaction for the use of alkenes as nucleophiles.

The catalytic enantioselective 1,2-addition of organometallic reagents to carbonyl compounds has its limitations. The use of these very reactive (and sometimes pyrophoric) non-stabilised carbanions as nucleophiles is restricted in a variety of situations. In order to produce high levels of enantioselectivity, many organometallic reagents require the use of cryogenic temperatures, which is extremely expensive in large scale reactions.[201] Furthermore, there are other complicating factors when using various organometallic reagents, such as difficulties in the use of functionalised reagents as well as safety implications which prevent their use in large scale reactions and thus in industrial processes.[202] Taking in to consideration the importance of establishing sustainable enantioselective catalytic systems, it is of paramount

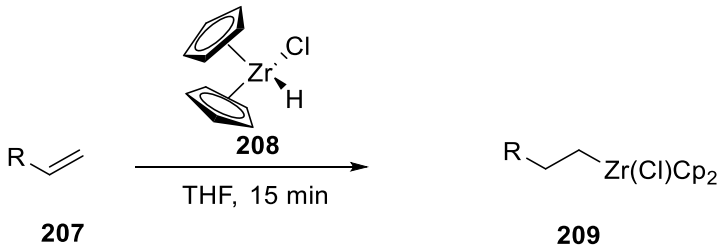
importance that methods are develop for the nucleophilic 1,2-addition to carbonyl compounds at room temperature.

Organozirconium reagents are becoming increasingly popular and play an important role in organic synthesis.[203] These reagents are less reactive compared to other organometallic reagents, do not have severe toxicity and zirconium is one of the cheapest transition metals. Zirconium has an abundance of 0.022% within the lithosphere,[204] making it almost as abundant as C. Additionally, the hydrozirconation of alkenes is performed at room temperature, as well as being highly tolerant towards functional groups.[205]

The widely used hydrozirconation reagent **208**, was prepared from Cp_2ZrCl with $LiAlH_4$ by *Walies et al*.[206] However, as a result of the pioneering work performed by Schwartz *et al.*, the reagent is often referred to as 'Schwartz reagent'(**208**, Scheme 57).[207, 208]

The hydrozirconation reaction of an alkene with the commercially available (or *in-situ* prepared) Schwartz reagent (**208**) allows the preparation of alkylzirconium reagents.[209, 210] The bulky zirconocene moiety leads to high regioselectivity during the hydrozirconation reaction on terminal alkenes, with the metal being attached at the less-hindered terminal position of the alkyl group. The hydrozirconation reaction of internal olefins is also possible, but the hydrozirconation products will rearrange *via* Zr–H elimination and re-addition, to lead to alkylzirconocenes with the metal at the less-hindered terminal position of the alkyl group (Scheme 57). The carbon-zirconium bond resembles that of a Grignard reagent, however only small electrophiles are able to directly attack the complex due to steric crowding around

the zirconium atom; the bulky zirconocene moiety contributes to good functional group tolerance by sheltering the reactive point.[210] Despite of this, organozirconium reagents are able to undergo C-C bond-formation. An essential example of applicability of these reagents are the nickel- or palladium catalysed cross coupling reactions of organozirconium derivatives.[203]

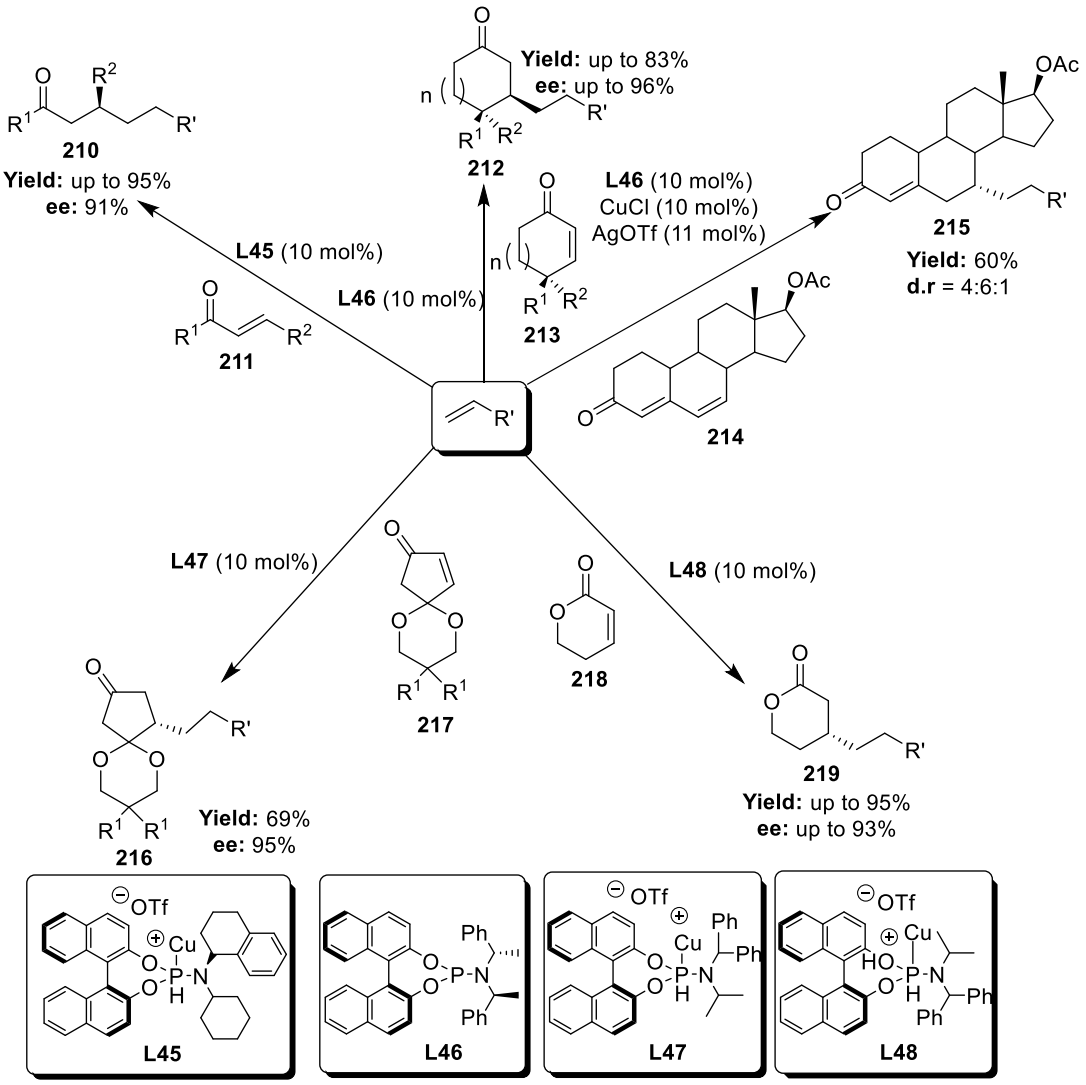


Scheme 57:Hydrozirconation reaction of an alkene using Schwartz reagent.

Organozirconocene chloride compounds are restricted synthetic reagents as they have naturally low reactivity towards electrophilic reagents. This is most likely a result of large steric hindrance or from specific interactions of C-C and C-H bonds of alkyl groups with low-lying empty d-orbitals. Organozirconium reagents are generally inert towards carbonyl compounds, but with the combination of an additive such as dialkylzinc reagents will result in a rapid 1,2-addition. The use of additives such as $ZnBr_2$, Ag (I) or Me_2Zn allows organozirconium reagents to be readily added to aldehydes.[175, 211-213] Srebnik *et al.* described the use of $ZnBr_2$ as effective catalysts for the additon of organozirconocene chloride compounds to aromatic and aliphatic aldehydes.[213] In similar fashion, Wipf *et al.* reported the use of Me_2Zn as additive for the addition of organozirconium compounds to aldehydes. However, none of these methodologies are enantioselective.

The use of organozirconium reagents in catalytic enantioselective additions is exceedingly beneficial as it enables the use of alkenes which are readily available, easy to handle and inexpensive. Furthermore, compared to other organometallic reagents, organozirconium reagents provide an increased scope of compatible functional groups.[214]

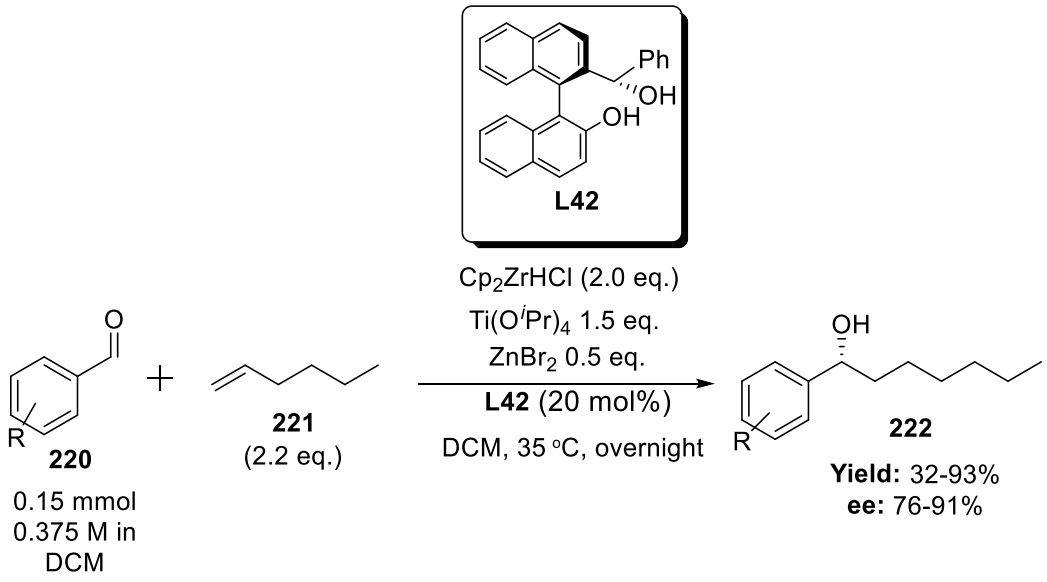
In particular, Fletcher *et al.* have developed an enantioselective copper-catalysed 1,4-addition of organozirconium reagents to enones[215-219], acyclic enones[220] cyclopent-4-ene-1,3-dione monoacetals[221] α,β-unsaturated ketones[222] and lactones (Scheme 58).[223] Enantioselective 1,6-additions or organozirconium reagents to produce functionalised steroid derivatives (**200**)[224] and the breast cancer drug fulvestrant (Faslodex®, Scheme 58) have also been reported.[225] In all cases, the organozirconium nucleophile was prepared *via* an *in situ* hydrozirconation reaction of the corresponding alkene.



Scheme 58: Enantioselective copper-catalysed 1,4- and 1,6-additon of organozirconium reagents by Fletcher et al.

Our group recently developed a methodology for the catalytic enantioselective 1,2-addition of organozirconium reagents to aldehydes (Scheme 60).[214] This methodology consists on the use of the Schwartz reagent to generate alkylzirconium nucleophiles *via in situ* hydrozirconation of alkenes, followed by the Ar-BINMOL catalysed enantioselective addition to aromatic aldehydes, which is facilitated by the use of $ZnBr_2$ and $Ti(O^iPr)_4$ as additives. The reaction proceeds under mild conditions and provides good yield and enantioselectivity. However, the substrate scope did not

include aliphatic aldehydes, which are of particularly relevance as they give access to chiral alkyl alcohols, which play a crucial role in many biological systems and are ubiquitous throughout pharmaceuticals, food additives, agrochemicals and cosmetics.[187] The synthesis of chiral secondary alkyl alcohols by nucleophilic addition to alkyl carbonyl compounds is hampered by the highly enolisable character of the alkyl aldehyde, together with its multiple conformations and the lack of π-stacking interactions with the catalyst.



Scheme 60: Catalytic enantioselective addition of in situ generated organozirconium reagents to aromatic aldehydes.

4.2 Aims and Objectives

Chiral aliphatic alcohols are ubiquitous throughout daily life. They are a fundamental figure throughout biological activity. Sexual, trail, alarm and aggregation pheromones, fragrance emitted by flowers, chemical communication and attraction or repulsion between living organisms are just some examples of how they are used within biological systems.[226] Enantiopure alkyl alcohols are very valuable in a number of industries, such as cosmetic and fragrance, pharmaceutical and agriculture.[226]

A variety of catalytic asymmetric methodologies[227] have been developed for preparing these valuable chiral aliphatic secondary alcohols in high enantiomeric excess, including reduction or hydrogenation of prochiral aliphatic ketones[228-230] and addition of organometallic reagents (alkylzinc,[152, 155, 157, 231] alkyl aluminium[165-167, 232] and alkyltitanium[169-171] to aliphatic aldehydes[150, 233-235]). The addition of organozirconium compounds to aliphatic aldehydes, however, has not been studied. Organozirconium reagents offer advantages such as being one of the cheapest transition metals, have low toxicity and are mild and versatile organometallic reagents.

Under the current global climate, the growing need for 'greener' methodologies is ever more important. Therefore, we envisaged the use of the organozirconium reagents to create a more sustainable catalytic methodology for the 1,2-addition to aliphatic aldehydes.

Based on preliminary results by Maciá *et al.*,[214] and the recognising the potential of this methodology the aims of this chapter will be as follows:

(i) Optimisation of the catalytic enantioselective addition of organozirconium reagents to aliphatic aldehydes using Ar-BINMOLs as ligands.

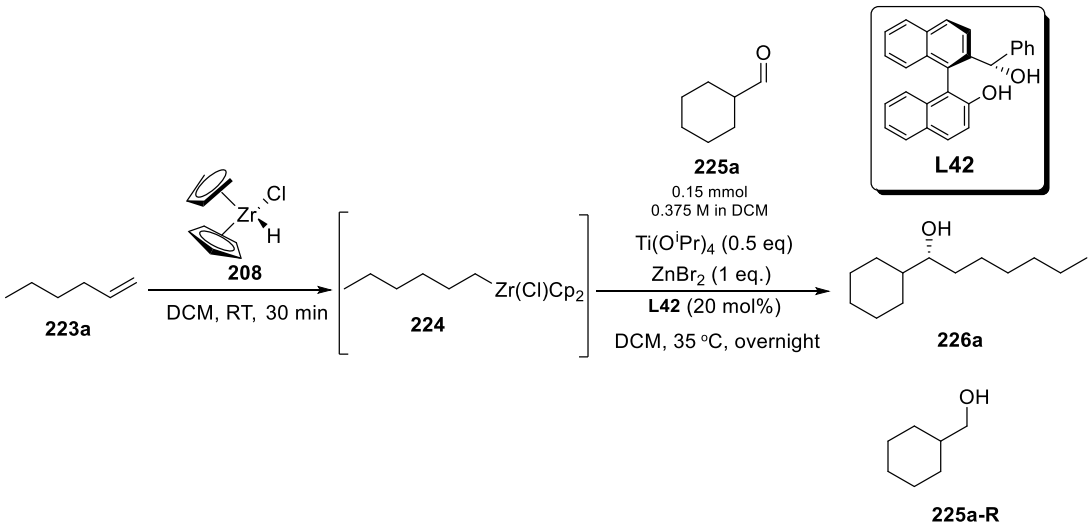
(ii) Expand the scope of the reaction to a range of aliphatic aldehydes and alkenes.

4.3 Results and Discussion- Catalytic enantioselective 1,2-addition of organozirconium reagents to aliphatic aldehydes using Ar-BINMOL ligands.

The catalytic enantioselective 1,2-addition of organozirconium reagents to aromatic aldehydes with Ar-BINMOLs and organozirconium reagents has been recently reported by our group.[214] This is a significant achievement as it is the first of its kind to use readily available and easy-to-handle alkenes as nucleophiles. Herein, we aim to explore the catalytic enantioselective 1,2-addition of organozirconium reagents – prepared *in situ* from the corresponding alkenes – to more challenging, enolisable aliphatic aldehydes.

The addition of 1-hexene (**223a**) to cyclohexanecarboxaldehyde (**225a**) using the very versatile (R_a,*S)*-Ph-BINMOL (**L42**)[173, 174, 195, 236, 237] as the ligand for the reaction was chosen a model reaction for these studies. Our investigation commenced by testing the optimised conditions for the addition of organozirconium reagents to aromatic aldehydes.[214] The first step of the reaction consisted of the treatment of 1-hexene (**223a**, 2.2 eq.) with Schwartz reagent (**208**, 2 eq.), resulting in a change from a white suspension to a clear yellow solution, which suggested that the corresponding organozirconium compound (**224**) had been successfully formed. The use of Schwartz

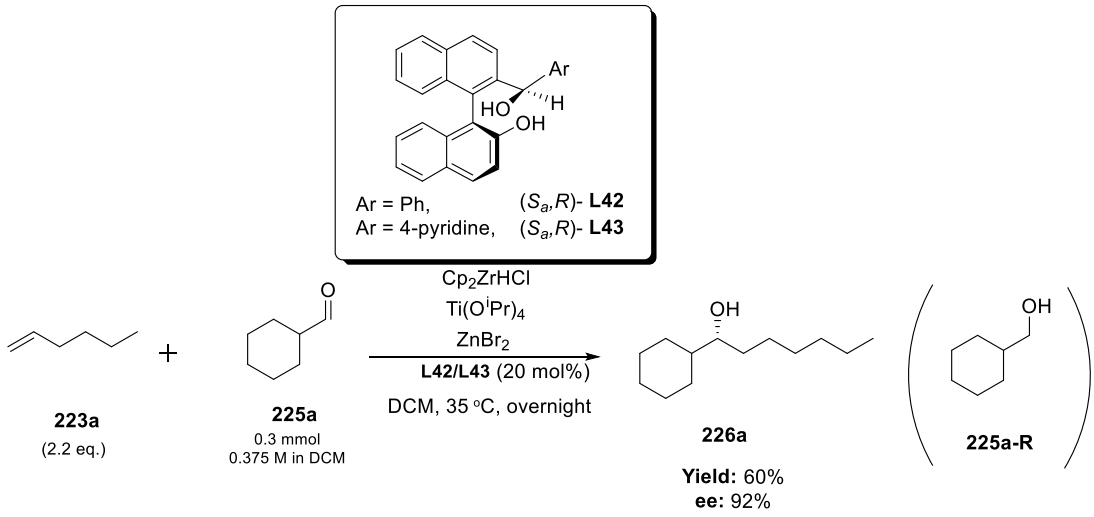
reagent allows the hydrozirconation of 1-hexene (**223a**), providing the corresponding organometallic reagent **224**, which acts as the nucleophile for the addition to the carbonyl. Next, $ZnBr_2$ (1 eq.) was added to the *in situ* prepared **224**, followed by the addition of a solution of $Ti(O^iPr)_4$ (0.5 eq.) and (R_a,*S*)-Ph-BINMOL (**L42**, 20 mol%) in dichloromethane. Last, cyclohexanecarboxaldehyde (**225a**, 1.0 eq, 0.125 M) was added dropwise and the reaction was left stirring at 35 °C overnight. To our delight, 99% conversion to the desired **226a** was obtained, in 86% ee and a moderate yield of 60% (Table 14*, entry 1*). In addition, only 1% of the reduced product **225a-R** was observed. We believe this by-product is formed by reduction of aldehyde **225a**, *via* β-hydride elimination in the organozirconium reagent, to provide a metal-bonded hydride (and the corresponding alkene), which adds to the carbonyl substrate, generating the corresponding alcohol.



Scheme 59: Model reaction for the study of the catalytic enantioselective 1,2-addition of organozirconium reagents to aliphatic aldehydes.

In order to improve both yield and ee, we began the optimisation with an extensive screening of the zinc and titanium additives loading, in order to find the best ratio between the two that provides desired alcohol **226a**. Firstly, we focused on changing the loading of $ZnBr_2$; both lowering the amount to 0.025 eq. and increasing it to 1 eq. resulted in no conversion to **226a**, with >99% conversion to the reduced product **226a-R** (Table 14*, entries 2 and 3*). The use of 1.5 eq. of $ZnBr_2$ provided 95% conversion to **226a** (along with 1% of **225a-R**) but a lower enantioselectivity of 18% (Table 14*, entry 4*). Keeping $ZnBr_2$ at 0.5 eq., we adjusted the amount of titanium tetraisopropoxide that was present in the reaction. Increasing the $Ti(O^iPr)_4$ loading to 2 eq., resulted in a large decrease in conversion to the desired product **226a** (24%) and 75% conversion to the reduced product **225a-R**, as well as lower ee (Table 14*, entry 5*). Lowering the equivalents of $Ti(O^iPr)_4$ to 1 eq. resulted in >99% conversion to the reduced product **225a-R** (Table 14*, entry 6*). Varying the ratios between $Ti(O^iPr)_4$ and $ZnBr_2$ to 2:1 and 2:2 (Table 14*, entries 7 and 8)* showed no improvement in enantioselectivity or conversion when compared with the original ratio of 3:1 (Table 14*, entry 1*).

*Table 14: Optimisation for the synthesis of **226a**[a]*



Entry	223a (eq.)	L	Cp_2ZrHCl (eq)	T (°C)	$Ti(O^iPr)_4$ (eq)	$ZnBr_2$ (eq)	Conv. 226a (%)[b]	Conv. 225a-R (%)[b]	ee (%)[c]
1.	2.2	42	2	35	1.5	0.5	99	1	86
2.	2.2	42	2	35	1.5	0.025	0	>99	-
3.	2.2	42	2	35	1.5	1	0	>99	-
4.	2.2	42	2	35	1.5	1.5	95	1	18
5.	2.2	42	2	35	2	0.5	24	75	48
6.	2.2	42	2	35	1	0.5	0	>99	-
7.	2.2	42	2	35	2	1	97	1	58
8.	2.2	42	2	35	2	2	94	2	52
9.	3	42	2	35	1.5	0.5	96	3	44
10.	2.2	42	1.5	35	1.5	0.5	98	1	72
11. [d]	2.2	42	2	35	1.5	0.5	99	1	64
12.	2.2	42	2	r.t	1.5	0.5	36	64	70
13. [d]	2.2	42	2	r.t	1.5	0.5	85	15	40
14.	2.2	43	2	35	1.5	0.5	32	62	8
15.	2.2	42	2	35	1.5	0	0	>99	-
16.	2.2	-	2	35	1.5	0.5	0	>99	-
17.	2.2	42	2	35	-	0.5	0	11	-

[a] Reaction conditions: **225a**, (0.3 mmol), **223a** (x eq.), **L42** or **L43** (20 mol%), Cp_2ZrHCl (x eq), $Ti(O^iPr)_4$ (x eq), $ZnBr_2$ (x eq), DCM (0.3 + 0.1 mL), T, 12 h

[b] Determined by GC-MS

[c] Determined by Chiral GC (see experimental for further details)

[d] Reaction carried out with CuCl (1.5 eq) instead of $ZnBr_2$

With the optimal ratio between the zinc additive and the titanium source, we increased the amount of 1-hexene used within the reaction to 3 eq., which unfortunately showed a decrease in both conversion to **226a** (72%) and ee (44%) (Table 14, *entry 9*). Lowering the amount of Schwartz reagent to 1.5 eq., slightly decreased the ee to 72% (Table 14, *entry 10*). We then decided to try CuCl as an alternative additive instead of $ZnBr_2$, which afforded 98% conversion and lower enantioselectivity (64% ee) (Table 14, *entry 11*). We decreased the temperature to room temperature, in the hope that the enantioselectivity would be higher (Table 14, *entries 12 and 13*) and would make the reaction more sustainable. Unfortunately, the conversion to **225a-R** substantially increased, especially when using the zinc based additive (Table 14, *entry 12*).

It has been previously reported that 4-Py-BINMOL (**L43**) is the most effective ligand for the catalytic enantioselective 1,2-addition of Grignard reagents to aliphatic aldehydes .[187] However, when **L43** was employed as the ligand for the addition of 1-hexene (**223a**) to cyclohexanecarboxaldehyde (**225a**), only 32% conversion was observed for the desired **226a** with lower ee (8%), whilst the amount of reduced by-product **225a-R** detected substantially increased (Table 14, *entry 14*).

Previous mechanistic studies on the Ar-BINMOL catalysed enantioselective 1,2-additon of organolithium reagents to carbonyl compounds,[238] indicate that the catalytic active species are monomeric and the autoinduction effect (the chiral product participating in the catalytic system) is neglectable in the presence of the ligand. Based on previous studies by Seebach and Walsh onthe $Ti(O^iPr)_4$ assisted

addition of organozinc reagents to aldehydes ,[169, 170] we propose intermediates **227** and **228** (Figure 12) as possible catalytic species in our system.

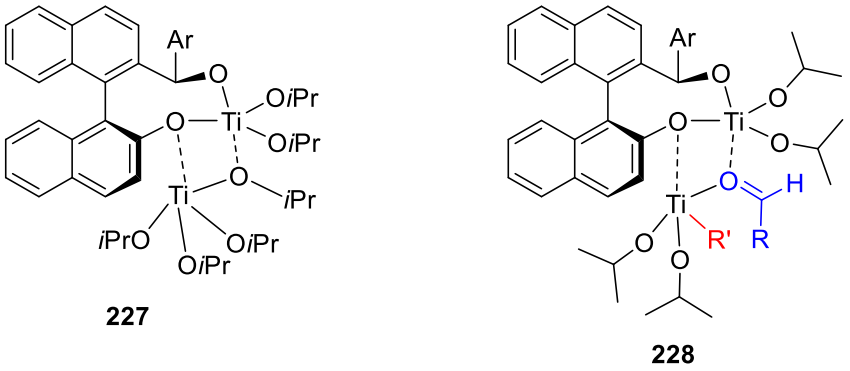


*Figure 12: Proposed Intermediates **227** and **228** from mechanistic studies reported by Fernández, Seebach and Walsh.*

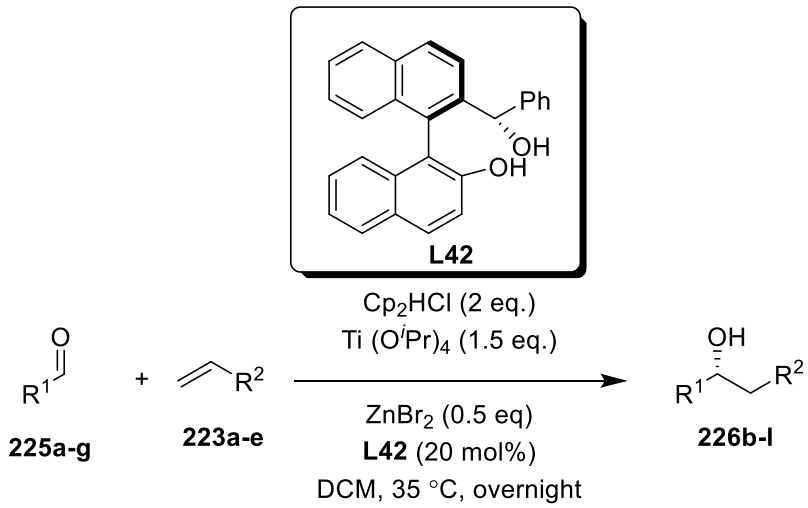
There are multiple mechanistic pathways by these catalytic enantioselective 1,2-addition reaction of organozirconium reagents could proceed. We believe the *in situ* generated organozirconium reagents undergo transmetallation with the zinc bromide, followed by a second transmetallation with the excess of titanium isopropoxide to provide catalytic intermediate/species **227** (Figure 12).[209, 210, 239] A control reaction, performed in the absence of $ZnBr_2$, showed no conversion to the desired **226a** and only the reduced product **225a-R** was obtained (Table 14, *entry 15*), which supports our hypothesis. It cannot be ignored, however, that the activation of aldehydes *via* a zinc-halide complexation is a well known effect.[240] Additional control reactions, performed in the absence of $Ti(O^iPr)_4$ and (R_a,*S*)-Ph-BINMOL (**L42**), also resulted in no conversion to our desired product but 11% and >99% conversion to the reduced product **225a-R** respectively, was observed (Table 14, *entries 16 and 17*).

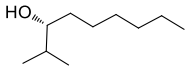
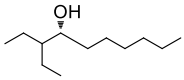
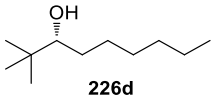
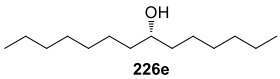
With the now optimised conditions (**L42**, 20 mol%), 2.2 eq. of alkene, 2 eq. Cp_2ZrCl, 1.5 eq. $Ti(O^iPr)_4$, 0.5 eq. $ZnBr_2$, 35 °C Table 14, *entry 1*), the scope of the reaction with different aliphatic aldehydes was investigated (Table 15). The addition of 1-hexene (**223a**) to isobutyraldehyde (**225b**) and 2-ethylbutanal (**225c**) afforded the corresponding products **226b** and **226c** with excellent conversions (>99%) and high enantioselectivities of 76 and 70%, respectively (Table 15, *entries 1 and 2*). The isolated yields (42% and 54%, respectively) were moderate, due to the high volatility of the products, but the reduced by-products **225b**-**R** and **225c**-**R** were not observed in any case. Similar results were obtained for the reaction with pivaldehyde (**225d**) and 1-hexene (**223a**) which afforded **226d** with 93% conversion (7% reduced product), moderate yield (50%, due to volatility of the product) and high enantioselectivity of 84% (Table 15, *entry 3*). The use of octanal (**225e**) as the substrate resulted in excellent conversion to the desired product **226e** (91%) – along with 4% conversion to the reduced product **225e-R** – and moderate isolated yield of 50%. The enantiomeric excess of **226e** was determined by HPLC analysis on the corresponding acetal (see Exp section for further details, Table 15, *entry 4*). The addition of 1-hexene (**223a**) to both 3-phenylpropionaldehyde (**225f**) and cinnamaldehyde (**225g**) led to the desired products **226f** and **226g** with relatively low yields (39% and 25% respectively) and high ee of 74% and 78% (Table 15, *entries 5 and 6*). The addition of 1-hexene (**223a**) to phenylpropargyl aldehyde (**225h**) proceeded with a moderate yield and high ee 56% (Table 15, *entry 7).*

Next, we tested the use of a variety of alkenes as nucleophiles for the addition to aliphatic aldehydes. The reaction with cyclohexanecarboxaldehyde (**225a**) and 4-phenyl-1-butene (**223b**) provided moderate yield (33%) but high enantioselectivity

(68%) (Table 15, *entry 8*). Entries 9-10 (Table 15) show that this methodology is also compatible with functionalised alkenes. The use of 4–[(*tert*-butyldimethylsilyl)oxy]-1-butene (**223c**) as a nucleophile afforded **226j** with a low yield of 27% and a moderate ee 58% (Table 15, *entry 9*). The reactions with 4-halo-1-butenes as nucleophiles provided the desired alcohols **226k** and **226l** in 51 and 36% yield, respectively, and high enantioselectivity (84 and 60% ee, respectively, determined on the corresponding acetates). It is worth noting that the majority of the yields are low to moderate as a result of the secondary alkyl alcohols being volatile.

Table 15: Catalytic enantioselective addition of alkenes to aliphatic aldehydes.[a]



Entry	Product	Conv. (%)[b]	Conv. to Reduced by-product (%)[b]	Yield (%)[c]	ee (%)[d]
1.	 226b	>99	0	42	76(*R*)[e]
2.	 226c	>99	0	54	70(*R*)[e]
3.	 226d	93	7	50	84(*R*)[e]
4.	 226e	91	4	48	74(*R*)[f,g]

[a] Reaction conditions: **225a-g**, (0.3 mmol), **223a-c** (2.2 eq), **L42** (20 mol%), Cp_2ZrHCl (2 eq), $Ti(O^iPr)_4$ (1.5 eq), $ZnBr_2$ (0.5 eq), DCM (0.3 + 0.1 mL) 35 °C, 12 h.

[b] Determined by GC-MS.

[c] Isolated yield after flash chromatography

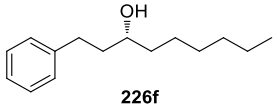
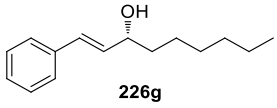
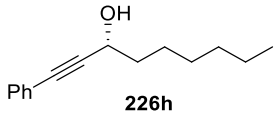
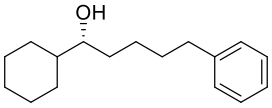
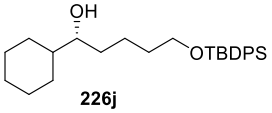
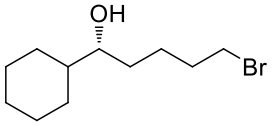
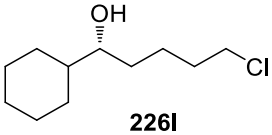
[d] Configuration in brackets assigned by comparison of the optical rotation with the literature (see experimental for further details).

[e] Determined by Chiral GC (see experimental for further details).

[f] Determined by Chiral HPLC (see experimental for further details).

[g] Determined on the corresponding acetate derivative (see experimental for further details).

Table 16 Continued: Catalytic enantioselective addition of alkenes to aliphatic aldehydes.[a]

Entry	Product	Conv. (%)[b]	Conv. to Reduced product (%)[b]	Yield (%)[c]	ee (%)[d]
5.	 **226f**	>99	0	39	74(*R*)[f]
6.	 **226g**	87	13	35	78(*R*)[f]
7.	 **226h**	53	49		56(*R*)[f]
8.	 **226i**	60	39	33	68(*R*)[f]
9.	 **226j**	n.d	n.d.	27	58(*R*)[f]
10.	 **226k**	73	20	51	84(*R*)[e,f]
11.	 **226l**	66	34	36	60(*R*)[e,f]

[a] Reaction conditions: **225a-g**, (0.3 mmol), **223a-c** (2.2 eq), **L42** (20 mol%), Cp_2ZrHCl (2 eq), $Ti(O^iPr)_4$ (1.5 eq), $ZnBr_2$ (0.5 eq), DCM (0.3 + 0.1 mL) 35 °C, 12 h.

[b] Determined by GC-MS.

[c] Isolated yield after flash chromatography.

[d] Configuration in brackets assigned by comparison of the optical rotation with the literature (see experimental for further details).

[e] Determined by Chiral GC (see experimental for further details).

[f] Determined by Chiral HPLC (see experimental for further details).

[g] Determined on the corresponding acetate derivative (see experimental for further details).

4.4 Conclusion

In conclusion, we have successfully developed and optimised an enantioselective 1,2-addition of alkenes to aliphatic aldehydes using the very versatile (R_a,*S*)-Ph-BINMOL ligand **L42**. This is of significant value as, to the best of our knowledge, it is the first example of the addition of organozirconium reagents to aliphatic aldehydes. Addition to aliphatic substrates is more challenging as they are enolisable and have multiple conformations. However, this methodology overcomes these problems and the scope of the reaction includes not only a variety of aliphatic aldehydes but also allows for a range of functionalised nucleophiles. This is a substantial improvement as usually not many functionalised nucleophiles are suitable for addition to aliphatic aldehydes. The reaction proceeds with enantioselectivities, ranging from 56-86%, good to high conversions (53–99%) and moderate yields (27-60%), are obtained under the optimised conditions (**L42** 2.2 eq. of alkene, 2 eq. Cp_2ZrCl, 1.5 eq. $Ti(O^iPr)_4$, 0.5 eq. $ZnBr_2$, 35 °C). The one-pot reaction is more sustainable as it is performed under mild conditions, making it an efficient procedure for the synthesis of valuable chiral aliphatic secondary alcohols.

4.5 Experimental

General Considerations.

For Materials, Glassware, TLC, Flash Chromatography, FT-IR, NMR, GC-MS, MW and Optical rotations: see Section 2.5

The assignment of the configuration in products 226 was performed by comparison of the sign of the optical rotation with the literature for known samples. In the case of unknown samples, the same configuration was assigned by analogy.

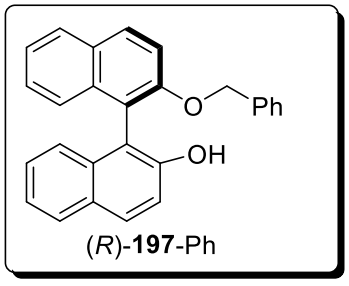
Enantioselectivity determination was carried out by gas chromatography or HPLC analysis:

GC-FID: Gas chromatography analysis was performed on an Agilent Technologies® 7890A GC System and a Hewlett Packard® 5890 Series II GC System, with a CycloSil-β (Agilent Technologies, 30 m x 0.25 mm) and a CP-Chirasil-DEX CB (Varian, 25 m x 0.25 mm) column, respectively; injector and detector temperatures: 250 °C.

HPLC-DAD: HPLC analysis was carried out on an Agilent 1100 series HPLC equipped with a G1313B diode array detector and a G1311A Quat pump. Chiral columns used for analysis were Lux 5µ Cellulose-1.

Melting Point: Melting point analysis were measured in a Stuart® SMP10 melting point apparatus.

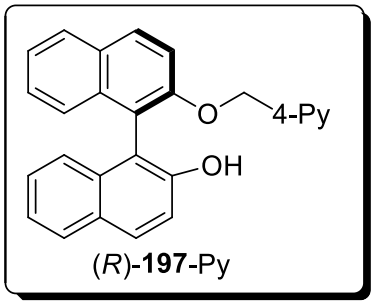
Ligands (*Ra,S*)-Ph-BINMOL (L42) and (*Ra,S*)-4-py-BINMOL (L43)- were prepared according to literature procedures.[182]



(*R*)-**197**-Ph

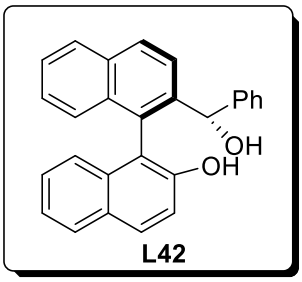
Synthesis of (*R*)-2'-(benzyloxy)-[1,1'-binaphthalen]-2-ol (197, R = Ph, precursor to L42): (*R*)-BINOL (**195**, 2.0 g, 7.0 mmol) was dissolved in acetone (50 mL), then K_2CO_3 (1.5 eq, 1.5 g, 10.5 mmol) and benzyl bromide (1.0 eq, 0.83 mL, 7.0 mmol) were added and the mixture was heated at 60 °C for 6 h. The

reaction crude was concentrated under reduced pressure and extracted with EtOAc (3 × 15 mL). The combined organic layers were then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was then used in the next step without further purification.



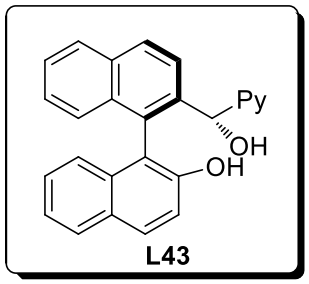
(*R*)-**197**-Py

Synthesis of *(R)*-2'-(pyridin-4-ylmethoxy)-(1,1'-binaphthalen)-2-ol (197, R = 4-Py, precursor of L43): (*R*)-BINOL (**195**, 2.0 g, 7.0 mmol) was dissolved in acetone (40 mL) and a solution of K_2CO_3 (3.0 eq, 2.9 g, 21.0 mmol) in 4 mL of water was added. Next, 4-(bromomethyl)pyridine (1.0 eq, 1.77 g, 7.0 mmol) was added and the mixture was heated at 65 °C for 12 h. The reaction crude was filtered under vacuum over Celite®, washing the cake with EtOAc (3 × 50 mL) and solvent was evaporated under vacuum. The crude material was purified by flash chromatography to give the named compound as a white powder. **Yield:** 66%. **RF:** 0.15 (EtOAc/ hexane 1:1) **M_p** = 182–184 °C. **FTIR (neat):** 3064, 1610, 1504, 1325, 1264, 1044, 798 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 8.26 (d, *J* = 4.5 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.91 (d, *J* = 8.9 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.42–7.34 (m, 3H), 7.34–7.26 (m, 3H), 7.21 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 5.2 Hz, 2H), 5.08 (d, *J* = 13.9 Hz, 1H), 5.03 (d, *J* = 13.8 Hz, 1H), 3.18 (br s, 1H). **^{13}C NMR (100.6 MHz, $CDCl_3$) δ:** 154.3, 151.6, 148.9, 146.9, 134.0, 133.8, 130.9, 129.9, 129.1, 128.2, 127.5, 126.5, 125.2, 124.7, 123.3, 121.2, 117.7, 115.4, 114.8, 69.4. Data in accordance with literature.[182]



L42

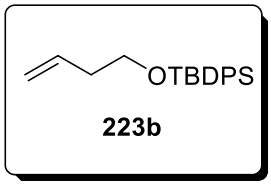
(*Ra*)-2'-[(*S*)-Hydroxy(phenyl)methyl]-5,5',6,6',7,7',8,8'-octahydro-(1,1'-binaphthalen)-2-ol (L42):. *n*-BuLi (2.5 M in hexane, 2.5 eq.) was slowly added to a solution of the corresponding precursor **197-Ph** (1.5 g, 4.0 mmol) in dry THF (30 mL) at –78 °C. The mixture was stirred for 2 h at –78 °C and then quenched with water at 0 °C. The resulting mixture was extracted with EtOAc (3 × 10 mL), filtered and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified by flash chromatography to give the desired product as a white powder. **Yield:** 85% **RF:** 0.21 (EtOAc/ hexane 1:1). **M_p** = 72–75 °C. **FTIR (neat) V_{max}:** 3297, 3337, 2927, 1591, 1448, 1018, 808, 698 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.30 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.17 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.11 – 7.06 (m, 2H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 5.43 (s, 1H), 4.96 (br s, 1H), 2.80 (t, *J* = 6.0 Hz, 3H), 2.69 (dd, *J* = 13.3, 6.7 Hz, 2H), 2.19 (dd, *J* = 14.2, 6.1 Hz, 2H), 1.99 – 1.89 (m, 1H), 1.80 – 1.50 (m, 9H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 149.8, 142.7, 139.9, 137.8, 136.5, 136.1, 133.6, 129.8, 129.7, 129.6, 128.1, 127.3, 126.8, 124.7, 124.3, 113.1, 73.5, 29.9, 29.2, 27.4, 27.2, 23.2, 22.9, 22.8, 22.7. Data in accordance with literature.[182]



L43

(*Ra*)-2'-[(*S*)-Hydroxy(pyridin-4-yl)methyl]-(1,1'-binaphthalen)-2-ol (L43): *n*-BuLi (5.0 eq, 2.5 M in hexane) was slowly added to a solution of **197-Py** (1.51 g, 4.0 mmol) in dry THF (40 mL) at room temperature. The mixture was stirred for 12 h at 70 °C and then the reaction was quenched with water at 0 °C. The resulting mixture was extracted with EtOAc (3 × 15 mL), filtered and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The

crude product was purified by chromatography on flash silica gel to give the desired product as a white solid. **Yield:** 164 mg, 21%. **RF:** 0.17 (EtOAc /hexane 1:1). **M_p:** 100–103 °C. **FTIR (neat) V_{max}:** 3297, 3055, 1606, 1506, 1342, 813, 747 cm^{-1}.**^{1}H NMR (300 MHz, $CDCl_3$) δ:** 8.15 (d, *J* = 6.2 Hz, 2H), 7.95 – 7.73 (m, 4H), 7.42 (ddd, *J* = 8.1, 6.5, 1.6 Hz, 1H), 7.36 – 7.26 (m, 3H), 7.25 – 7.13 (m, 3H), 6.97 (d, *J* = 5.8 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 1H), 5.64 (s, 1H), 3.56 (br s, 2H). **^{13}C NMR (75 MHz, $CDCl_3$) δ:** 152.8, 152.0, 148.3, 139.8, 134.2, 133.4, 132.9, 131.8, 130.2, 129.4, 128.9, 128.2, 128.1, 126.8, 126.8, 126.5, 125.0, 124.8, 123.6, 121.5, 118.3, 117.3, 72.1. Data in accordance with literature.[182]



223b

Synthesis of *tert*-butyl(diphenyl)silyl-3-butenyl ether (223b): was carried out according to literature procedure To a solution of 3-buten-1-ol (1 eq, 0.43 mL, 5 mmol) and imidazole (2 eq, 681 mg, 10 mmol) in DMF (10 mL) at 0 °C was added dropwise *tert*-butyldiphenylsilyl chloride (1.2 eq, 1.29 mL, 6 mmol). The reaction mixture was warmed up to RT and then stirred for 3 h. The reaction was quenched with water (10 mL) and the organic layer was separated. The aqueous phase was then extracted with Et_2O (3 × 10 mL) and the combined organic extracted were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The isolated product was purified by flash chromatography to afford the named compound as a colourless oil **Yield:** 1.14 g, 74% **RF:** 0.24 (Et_2O /hexane 1:1). **FTIR (neat) V_{max}:** 2958, 2858, 1473, 1428, 1195, 1088, 736, 699, 611, 504, 489 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 8.20 – 7.96 (m, 4H), 7.68 (m, 6H), 6.17 (tdd, *J* = 17.1, 8.9, 5.4 Hz, 1H), 5.46 – 5.23 (m, 2H), 4.07 (dq, *J* = 14.1, 7.0 Hz, 2H), 2.80

– 2.57 (m, 2H), 1.51 – 1.32 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 135.7, 135.4, 134.0, 129.7, 127.8, 116.6, 63.6, 37.4, 27.0, 19.4. Data in accordance with literature.[241]

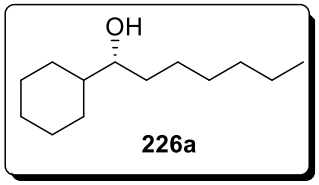
General procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes: To a stirred suspensions of Cp_2ZrHCl (1 eq, 154 mg, 0.6 mmol) in dry CH_2Cl_2 (0.3 mL) under argon at RT, the corresponding alkene (2.2 eq, 0.66 mmol) was added dropwise and the solution was stirred for 30 min. The mixture turned to a clear yellow solution, which indicated the successful formation of the organozirconium reagent. Next, flame-dried $ZnBr_2$ (0.5 eq, 34 mg, 0.15 mmol) was added to the solution at RT and stirred for 2 min. Next, a solution of $Ti(O^iPr)_4$ (1.5 eq, 134 μL, 0.45 mmol) and (*R*$_a$,*S*)-Ph-BINMOL (23 mg, 20 mol%) in dry CH_2Cl_2 (0.1 mL) was added and stirred for an additional 2 min at RT. Finally, the freshly distilled aldehyde (0.3 mmol) was added and the solution was stirred at 35 °C overnight. The reaction was quenched with water (2 mL) and the layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash silica gel chromatography.

General procedure for the preparation of racemic alcohols 226a-h:

A solution of Grignard reagent (hexylmagnesium bromide), prepared from 1-bromohexane (1.3 eq, 0.85 mL, 6.03 mmol) and magnesium turnings (1.2 eq, 133 mg, 5.49 mmol) in diethyl ether (6 mL), was added dropwise to the corresponding aldehyde **225a-h** (1 eq, 4.56 mmol) in diethyl ether (3 mL) . After the addition, the reaction mixture was stirred at RT for 2 h and then quenched with water (3 mL). The

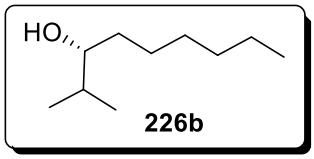
aqueous mixture was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with aqueous HCl (1M, 10 mL). The organic layer was then washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography (Et_2O/ cyclohexane, 3:7).

General procedure for the preparation of racemic alcohols 226i-l: Racemic alcohols **226i-l** were prepared using the general procedure for the catalytic enantioselective 1,2-addition of alkenes above using *rac*-**L42**.

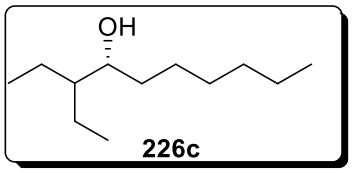


226a

(*R*)-1-Cyclohexylheptan-1-ol (226a): Compound **226a** was synthesised using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes, from cyclohexanecarboxaldehyde (**225a**, 36 µL, 0.3 mmol) and 1-hexene (**223a**, 82 µL, 0.66 mmol) to give the named compound as a yellow oil. **Yield:** 36 mg, 60%. **RF:** 0.36 (Et_2O / hexane 3:7). **ee*:*** 86%. **$[\alpha]_D^{23}$** = +17.4 (*c* 1.5, CH_2Cl_2). {Lit $[\alpha]_D^{25}$ = −10.5 (*c* 0.2, $CHCl_3$) for 84% ee of *S* enantiomer}. **FTIR (neat) V_{max}:** 3380, 2919, 2852, 1449, 1377, 1084, 1064 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 3.39 – 3.29 (m, 1H), 1.81 – 1.70 (m, 3H), 1.70 – 1.60 (m, 2H), 1.51 – 1.42 (m, 2H), 1.36 – 0.93 (m, 15H), 0.87 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 76.1, 43.8, 34.0, 33.3, 33.0, 29.4, 27.8, 26.6, 26.5, 26.3, 24.8. ***m/z*:** 180 (M^+-H_2O, 11%), 115 (26), 114 (14), 113 (47), 97 (76), 96 (21), 95 (100), 83 (10), 82 (14), 81 (10), 69 (14), 67 (16), 57 (12), 55 (59). **HRMS (m/z):** Calculated $C_{13}H_{25}O$ $[M-H]^+$: 197.1905, found: 197.1904. ee determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 86°C retention times: t_r = 42.1 min, t_r = 42.8 min (major enantiomer). Data in accordance with literature.[242]

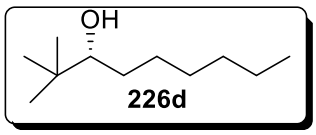


(*R*)-2-Methylnonan-3-ol (226b): Compound **226b** was synthesised from isobutyraldehyde (**225b**, 27 µL, 0.3 mmol) and 1-hexene (**223a**, 82 µL, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a yellow oil. **Yield:** 20 mg, 42%. **RF:** 0.42 (Et_2O / hexane 4:8) **ee:** 76%. **$[\alpha]_D^{23}$** = +13.3 (*c* 0.6, CH_2Cl_2). (*c* 0.6, CH_2Cl_2). {Lit $[\alpha]_D^{25}$ = −14.1 (c 0.7, $CHCl_3$) for 96% ee of *S* enantiomer}. **FTIR (neat) V_{max}:** 3352, 2950, 2923, 2872, 2854, 1446, 1378, 1059 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 3.41 – 3.30 (m, 1H), 1.64 (m, 1H), 1.50 – 1.41 (m, 2H), 1.41 – 1.22 (m, 9H), 0.93 – 0.82 (m, 9H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 76.9, 34.3, 33.6, 32.0, 29.6, 26.2, 22.8, 19.0, 17.2, 14.3. ***m/z*:** 140 (M^+-H_2O, 11%), 115 (26), 97 (82), 73 (47), 69 (20), 57 (14), 55 (100). **HRMS (m/z):** Calculated $C_{10}H_{21}O$ $[M-H]^+$: 157.1592, found: 157.1587. ee determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 89°C, retention times: t_r = 43.3 min, t_r = 42.5 min (major enantiomer). Data in accordance with literature.[243]



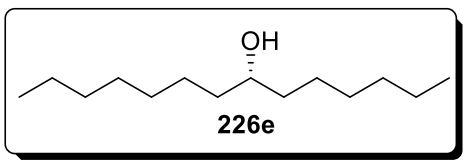
(*R*)-3-Ethylnonan-4-ol (226c): Compound **226c** was synthesised from 2-ethylbutyraldehyde (**225c**, 37 µL, 0.3 mmol) and 1-hexene (**223a**, 82 µL, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a yellow oil. **Yield:** 30 mg, 54%. **RF:** 0.33 (Et_2O / cyclohexane 2:8) **ee:** 70% **$[\alpha]_D^{23}$** = +6.7 (*c* 0.4, CH_2Cl_2). **FTIR (neat) V_{max}:** 3373, 2958, 2925, 2873, 2858, 1461, 1379, 1143 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 3.69 – 3.52 (m, 1H), 1.45 – 1.16 (m, 16H), 1.06 – 0.81 (m, 9H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 73.3, 46.9, 34.2, 32.0, 29.6, 26.4, 22.8, 22.2, 21.3, 14.3, 12.1, 12.0. ***m/z*:** 168 (M^+-H_2O, 1%), 115 (28), 101 (23), 97 (98), 83 (15), 70 (15), 69 (21), 59 (24), 57 (19), 55 (100)

HRMS (m/z): Calculated $C_{12}H_{25}O$ $[M\text{-}H]^+$: 185.1905, found: 185.1909. ee determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 102°C, retention times: t_r = 75.1 min, t_r = 75.2 min (major enantiomer).



226d

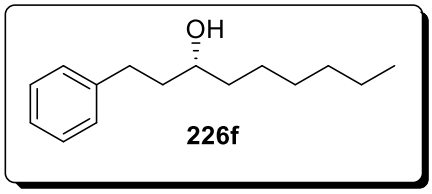
(*R*)-2,2-Dimethylnonan-3-ol (226d): Compound **226d** was synthesised from trimethylacetaldehyde (**225d**, 33 µL, 0.3 mmol) and 1-hexene (**223a**, 82 µL, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a yellow oil. **Yield:** 26 mg, 50%. **RF:** 0.29 (Et_2O / cyclohexane 3:7). **ee*:*** 84%. **$[\alpha]_D^{23}$** = +8.9 (*c* 0.9, CH_2Cl_2). {^{Lit} $[\alpha]_D^{25}$ = +15.0 (*c* 5.1, benzene) for 84% *ee*}. **FTIR (neat) V_{max}:** 3392, 2954, 2925, 2859, 1479, 1466, 1393, 1364, 1075, 1009, 957, 734, 703, 566, 543 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 3.17 (d, *J* = 7.4 Hz, 1H), 1.64 – 1.40 (m, 3H), 1.36 – 1.18 (m, 8H), 0.87 (br s, 12H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 80.1, 35.1, 32.1, 31.6, 29.6, 27.2, 25.8, 22.8, 14.3. ***m/z*:** 154 (M^+-H_2O, 0.18%), 115 (31), 114 (13), 97 (100), 87 (28), 69 (31), 57 (40), 56 (12), 55 (80). **HRMS (m/z):** Calculated $C_{11}H_{23}O$ $[M\text{-}H]^+$: 171.1749, found: 171.1743. ee determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 102°C, retention times: t_r = 38.6 min, t_r = 40.2 min (major enantiomer). Data in accordance with literature.[244]



226e

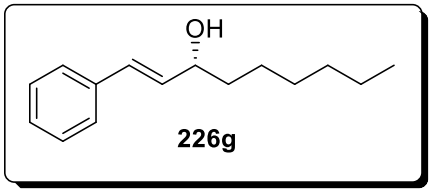
(*R*)-Tetradecan-7-ol (226e): Compound **226e** was synthesised from octanal (**225e**, 47 µL, 0.3 mmol) and 1-hexene (**223a**, 82 µL, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a white solid. **Yield:** 31 mg, 48% **RF:** 0.37 (Et_2O / cyclohexane 3:7). **M_p** = 36–39 °C. **ee:** 74% (determined on the

corresponding acetate). **$[\alpha]_D^{22}$** = +13.3 (*c* 0.7, CH_2Cl_2). **FTIR (neat) V_{max}:** 3343, 2956, 2929, 2872, 1470, 1381, 1045, 952, 817 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 3.55 (s, 1H), 1.40 (br s, 7H), 1.26 (br s, 16H), 0.86 (t, *J* = 6.1 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 72.2, 37.6, 32.0, 30.0, 30.0, 29.5, 27.0, 25.8, 25.8, 22.9, 22.8, 14.3**.** ***m/z*:** 196 (M^+-H_2O, 8%), 129 (36), 115 (38), 111 (41), 97 (100), 83 (11), 69 (94), 57 (20), 55 (74). **HRMS (m/z):** Calculated $C_{14}H_{29}O$ $[M-H]^+$: 213.2219, found: 213.2213.

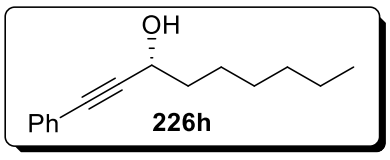


226f

(*R*)-1-Phenylnonan-3-ol (226f): Compound **226f** was synthesised from 3-phenylpropionaldehyde (**225f**, 37 µL, 0.3 mmol) and 1-hexene (**223a**, 82 µL, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a yellow oil. **Yield:** 26mg, 40%. **RF:** 0.34 (Et_2O / cyclohexane 3:7). **ee:** 74%. **$[\alpha]_D^{23}$** = +40 (*c* 0.3, CH_2Cl_2). {Lit $[\alpha]_D^{21}$ = −8.2 (*c* 0.3, $CHCl_3$) for 72% ee}. **FTIR (neat) V_{max}:** 3372, 2951, 2857 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.26 – 7.07 (m, 5H), 3.65 – 3.49 (m, 1H), 2.78 – 2.56 (m, 2H), 1.78 – 1.61 (m, 2H), 1.51 (s, 1H), 1.45 – 1.12 (m, 10H), 0.81 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 142.4, 128.6, 128.5, 125.9, 71.6, 39.2, 37.7, 32.2, 32.0, 29.5, 25.7, 22.8, 14.2. ***m/z*:** 202 (M^+-H_2O, 32%), 131 (50), 117 (47), 115 (18), 105 (22), 104 (92), 92 (23), 91 (100), 69 (17), 55 (13). **HRMS (m/z):** Calculated $C_{15}H_{23}O$ $[M-H]^+$: 219.1754, found: 219.1755. ee determination by chiral **HPLC** analysis, Phenomenex® LUX Cellulose-1, Hex/*i*-PrOH 98:2, flow = 1 mL/min, T = RT, retention times: t_r = 16.1 min (major enantiomer), t_r = 27.6 min. Data in accordance with literature.[245]

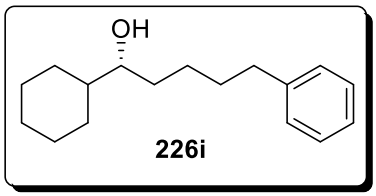


(*E*,*R*)-1-Phenylnon-1-en-3-ol (226g): Compound **226g** was synthesised from *trans*-cinnamaldehyde (**225g**, 38 µL, 0.3 mmol) and 1-hexene (**223a**, 82 µL, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a yellow oil. **Yield:** 22 mg, 34%. **RF:** 0.18 (Et_2O / cyclohexane 2:8). **ee:** 78%. **$[\alpha]_D^{26}$** = −66.7 (*c* 1.2, CH_2Cl_2). {$^{Lit}[\alpha]_D^{21}$ = −5.6 (*c* 1.07, $CHCl_3$) for 91% ee}. **FTIR (neat) V_{max}:** 3357, 2954, 2927, 2856, 1600, 1465, 1450, 1204 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.40 – 7.36 (m, 2H), 7.33 – 7.28 (m, 2H), 7.24 – 7.20 (m, 1H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.21 (dd, *J* = 15.9, 6.8 Hz, 1H), 4.35 – 4.18 (m, 1H), 1.76 – 1.51 (m, 3H), 1.42 – 1.17 (m, 7H), 0.87 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 136.9, 132.7, 130.4, 128.7, 127.8, 126.6, 73.3, 37.5, 31.9, 29.4, 25.6, 22.8, 14.2. ***m/z***: 218 (M^+ 3%), 148 (14), 134 (11), 133 (100), 131 (17), 130 (29), 129 (16), 128 (16), 115 (64), 113 (14), 105 (47), 104 (21), 103 (31), 91 (45) 79 (17), 78 (18), 77 (46), 55 (55), 51 (14). **HRMS (m/z):** Calculated $C_{15}H_{23}O$ $[M+H]^+$: 219.1749, found: 219.1749. ee determination by chiral **HPLC** analysis, Phenomenex® LUX Cellulose-1, Hex/*i*-PrOH 97:3, flow = 1 mL/min, T = RT, retention times: t_r = 20.4 min, (major enantiomer), t_r = 37.8 min.[246]



(*R*)-1-Phenylnon-1-yn-3-ol (226h): Compound **226h** was synthesised from phenylpropargyl aldehyde **225h** (40 µL, 0.3 mmol) and 1-hexene **223a** (82 µL, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a yellow oil. **Yield:** 26 mg, 40% **RF:** 0.24 (Et_2O / cyclohexane 2:8) **ee:** 56% **$[\alpha]_D^{23}$** = −22.2 (*c* 3.6, CH_2Cl_2). {$^{Lit}[\alpha]_D^{23}$ = −1.5 (*c* 0.69, $CHCl_3$) for 92% ee). **FTIR (neat) V_{max}:** 3338, 2927, 2857, 1667, 1598,

1489, 1443 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.46 – 7.40 (m, 2H), 7.35 – 7.28 (m, 3H), 4.60 (t, *J* = 6.6 Hz, 1H), 2.18 (br s, 1H), 1.85 – 1.73 (m, 2H), 1.56 – 1.43 (m, 2H), 1.40 – 1.25 (m, 6H), 0.90 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 131.8, 128.4, 122.8, 90.4, 84.9, 63.1, 38.0, 31.9, 29.1, 25.3, 22.7, 14.2. ***m/z***: 216 (M^+ 4%), 198 (58), 155 (40), 154 (14), 152 (10), 142 (15), 141 (67), 139 (12), 129 (69), 128 (100), 127 (11), 115 (65), 105 (15), 103 (21), 102 (86), 91 (16), 77 (20), 76 (18), 75 (10), 74 (10), 70 (14), 55 (12). **HRMS (m/z):** Calculated $C_{15}H_{19}O$ $[M-H]^+$: 215.1436, found: 215.1445. ee determination by chiral **HPLC** analysis, Phenomenex® LUX Cellulose-1, Hex/*i*-PrOH 97:3 flow = 1 mL/min, retention times: t_r = 15.0 min, (major enantiomer). t_r = 44.5 min. Data in accordance with literature.[247]

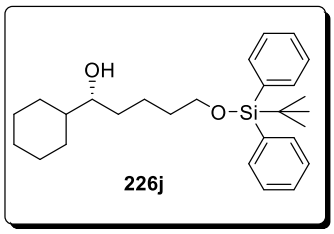


226i

(*R*)-1-Cyclohexyl-6-phenylhexan-1-ol (226i):

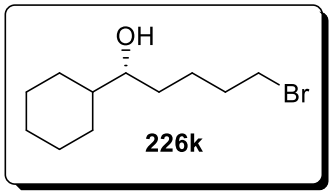
Compound **226i** was synthesised from aldehyde cyclohexcarboxaldehyde **225a** (36 µL, 0.3 mmol) and 4-phenyl-1-butene **223b** (99 µL, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a yellow oil. **Yield:** 24 mg, 33% **RF:** 0.19 (Et_2O / cyclohexane 3:7) ***ee*:** 68% **$[\alpha]_D^{23}$** = +40 (*c* 0.4, CH_2Cl_2). **FTIR (neat) V_{max}:** 3368, 3026, 2922, 2852, 1603, 1496, 1450, 1077, 977, 745, 697 cm^{-1} **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.23 – 7.17 (m, 2H), 7.15 – 7.08 (m, 3H), 3.36 – 3.19 (m, 1H), 2.61 – 2.49 (m, 2H), 1.77 – 1.63 (m, 3H), 1.64 – 1.51 (m, 4H), 1.49 – 0.86 (m, 11H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 142.8, 128.5, 128.4, 125.7, 76.2, 43.7, 36.1, 34.0, 31.7, 29.3, 27.8, 26.6, 26.4, 26.3, 25.8. ***m/z***: 228 (M^+ 21%) 145 (27), 128 (16), 132 (23), 117 (29), 105 (16), 104 (100), 95 (29), 92 (19), 91 (89) 83 (10), 81 (14), 67 (17), 55 (23). **HRMS (m/z):** sample could not be ionised. ee

determination by chiral **HPLC** analysis, Phenomenex® LUX Cellulose-1, Hex/*i*-PrOH 97:3 flow = 1 mL/min, T= RT, t_r = 9.67 min, t_r = 10.12 min (major enantiomer).



226j

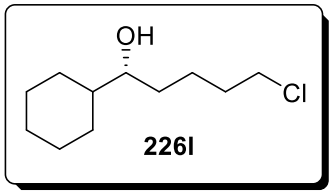
(*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-1-cyclohexylheptan-1-ol (226j): Compound **226j** was synthesised from cyclohexcarboxaldehyde (**225a**, 36 µL, 0.3 mmol) and *tert*-butyl(diphenyl)silyl-3-butenyl ether (**223b**, 205 mg, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a brown oil. **Yield:** 34 mg, 27%. **RF:** 0.25 (Et_2O / hexane 3:7)**. ee:** 58%. **$[\alpha]_D^{23}$** = +10.81 (*c* 3.7, CH_2Cl_2). **FTIR (neat) V_{max}:** 3369, 2927, 2854, 1428, 1106, 823, 699, 613, 503, 187 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.67 (dd, *J* = 4.2, 3.4 Hz, 4H), 7.44 – 7.34 (m, 6H), 3.67 (t, *J* = 6.1 Hz, 2H), 3.36 – 3.29 (m, 1H), 1.83 – 1.70 (m, 3H), 1.70 – 0.88 (m with s at 1.05 25H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 135.5, 134.0, 129.5, 127.6, 76.0, 63.8, 43.5, 33.7, 32.5, 29.2, 27.6, 26.8, 26.5, 26.3, 26.2, 22.1, 19.2. **HRMS (m/z):** Calculated $C_{27}H_{41}O_2Si$ $[M+H]^+$: 425.2876, found: 425.2867. ee determination by chiral **HPLC** analysis, Phenomenex® LUX Cellulose-1, Hex/*i*-PrOH 97:3, flow = 1 mL/min, T= RT retention times: t_r = 5.92 min (major enantiomer), t_r = 7.41 min.



226k

(*R*)-5-Bromo-1-cyclohexylpentan-1-ol (226k): Compound **226k** was synthesised from cyclohexcarboxaldehyde (**225a**, 36 µL, 0.3 mmol) and 4-bromo-1-butene (**223c**, 67 µL, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a yellow oil. **Yield:** 38mg**,** 51%. **RF:** 0.60 (Et_2O / cyclohexane 1:1). **ee:**

84% (determined on the corresponding acetate). **$[\alpha]_D^{25}$** = +12 (*c* 1, CH_2Cl_2). **FTIR (neat) V_{max}:** 3368, 2928, 2851, 1450, 1237, 1087, 1064, 1047, 975, 893, 562 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 3.41 (t, *J* = 6.9 Hz, 2H), 3.37 – 3.32 (m, 1H), 1.94 – 1.83 (m, 2H), 1.83 – 1.69 (m, 4H), 1.69 – 1.57 (m, 4H), 1.57 – 0.89 (m, 8H). **^{13}C NMR (101 MHz, $CDCl_3$) δ**: 76.1, 43.8, 34.0, 33.3, 33.0, 29.4, 27.8, 26.6, 26.5, 26.3, 24.8. ***m/z***: 230 (M^+ -H_2O 1%) 167 (41), 165 (40), 113 (62), 96 (12), 95 (100), 85 (85), 84 (20), 83 (19), 82 (13), 68 (10), 67 (48), 57 (25), 55 (51). **HRMS (m/z):** Calculated $C_{11}H_{21}OBr$ $[M+Na]^+$: 271.0673, found: 271.0668.

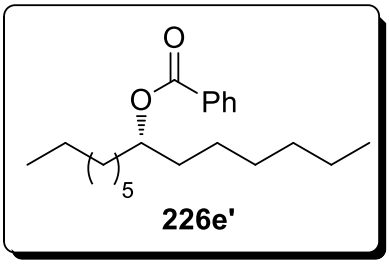


226l

(*R*)-5-Chloro-1-cyclohexylpentan-1-ol (226l): Compound **226l** was synthesised from cyclohexcarboxaldehyde (**225a**, 36 µL, 0.3 mmol) and 4-chloro-1-butene (**223c**, 65 µL, 0.66 mmol) using the general procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes to give the named compound as a yellow oil. **Yield:** 22 mg, 36%. **RF:** 0.58 (Et_2O / cyclohexane 1:1). **ee:** 60% (determined on the corresponding acetate). **$[\alpha]_D^{25}$** = +20 (*c* 0.8, CH_2Cl_2). **FTIR (neat) V_{max}:** 3369, 2923, 2851, 1449, 1309, 1088, 1065, 977, 892, 734, 651 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:**3.57 – 3.48 (m, 2H), 3.39 – 3.27 (m, 1H), 1.84 – 1.70 (m, 5H), 1.70 – 1.55 (m, 4H), 1.53 – 0.90 (m, 9H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 76.0, 45.1, 43.7, 33.3, 32.7, 29.3, 27.7, 26.6, 26.4, 26.2, 23.4. ***m/z***: 186 (M^+-H_2O 2%), 123 (21), 121 (62), 120 (13), 113 (44), 101 (13), 96 (13), 95 (100), 85 (62), 84 (17), 82 (14), 81 (15), 67 (47), 57 (22), 55 (49). **HRMS (m/z):** Calculated $C_{11}H_2OCl$ $[M-H]^+$: 203.1197, found: 203.1206.

General procedure for the synthesis benzoate derivatives (226e', 226k' and 226l'):[214] The corresponding chiral aliphatic alcohol (0.10 mmol) was dissolved in

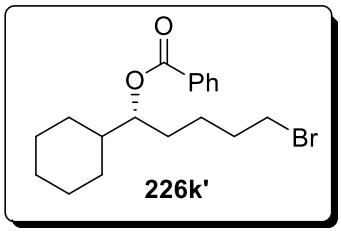
anhydrous DCM (1 mL, 0.1 M). Sequentially, at 0 °C, Et_3N (28 µL, 0.2 mmol, 2.0 eq), DMAP (1.3 mg, 0.20 mmol, 2.0 eq) and benzyl chloride (12 µL, 0.1 mmol, 1.0 eq.) were added. The reaction mixture was stirred overnight at RT. The reaction was quenched with water (1 mL), extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified by flash silica gel chromatography.



226e'

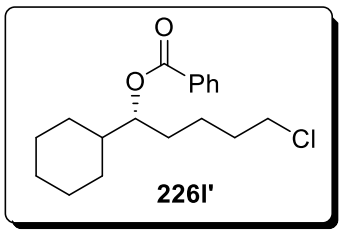
(*R*)-Tetradecan-7-yl benzoate (226e'): The corresponding compound was synthesised from (*R*)-**226e** (10 mg, 0.047 mmol) using the general procedure for the synthesis of benzoate derivatives to give the named compound as a white solid. **Yield:** 7 mg, 55%. **RF:** 0.73 (Et_2O/ hexane 2:8) **M_p** = 42–45 °C. **ee:** 74% **$[\alpha]_D^{23}$** = +20 (*c* 1.2, CH_2Cl_2). **FTIR (neat) V_{max}:** 3349, 2926, 2855, 190, 1723, 1211, 1936, 1014, 703 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 8.17 (d, *J* = 8.1 Hz, 2H), 7.76 – 7.57 (m, 1H), 7.53 (t, *J* = 7.7 Hz, 2H), 3.63 – 3.53 (m, 1H), 1.50 – 1.36 (m, 6H), 1.28 (br s, 16H), 0.88 (t, *J* = 6.3 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 162.5, 134.7, 130.7, 129.0, 72.2, 37.6, 32.0, 29.8, 29.5, 29.5, 25.8, 25.8, 22.8, 22.8, 14.3. ***m/z***: 281 (14), 208 (15), 207 (100), 105 (68), 77 (11). **HRMS (m/z):** Calculated $C_{21}H_{35}O_2$ $[M+H]^+$: 319.2637, found: 319.2630. ee determination by chiral **HPLC** analysis, Phenomenex® LUX Cellulose-1, Hexane 100, flow = 1 mL/min, T = RT. retention times: t_r = 9.97 min, t_r = 10.27 min (major enantiomer).

(*R*)-5-Bromo-1-cyclohexylpentyl benzoate (226k'): The corresponding compound was synthesised from (*R*)- **226k** (40 mg, 0.16 mmol) using the general procedure for



226k'

the synthesis of benzoate derivatives to give the named compound as a brown oil. **Yield:** 11 mg, 19%. **RF:** 0.79 (Et_2O/ cyclohexane 3:7) **ee:** 84%**. FTIR (neat) V_{max}:** 2927, 2854, 1716, 1450, 1273, 1113, 712 cm^{-1}. **$[\alpha]_D^{23}$** = +24 (*c* 0.5, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 8.09 – 8.01 (m, 2H), 7.58 – 7.53 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 5.08 – 4.97 (m, 1H), 3.38 (t, *J* = 6.8 Hz, 1H), 1.95 – 1.00 (m, 5H). **^{13}C NMR (101 MHz, $CDCl_3$) δ**: 166.5, 132.9, 130.6, 129.7, 128.5, 78.3, 41.5, 33.7, 32.7, 30.6, 29.9, 29.3, 28.2, 26.5, 26.2, 24.2. ***m/z***: 313 (1), 232 (12), 230 (13), 122 (17), 109 (18), 105 (100), 96 (19), 95 (24), 82 (11), 81 (29), 79 (13), 77 (37) 67 (26), 55 (14). **HRMS (m/z):** Calculated $C_{18}H_{25}O_2Br$ $[M+Na]^+$: 375.0936, found: 375.0952. ee determination by chiral **HPLC** analysis, Phenomenex® LUX Cellulose-1, Hex/*i*-PrOH 99:1, flow = 1 mL/min, T = RT, retention times: t_r = 16.34 min, t_r = 17.40 min (major enantiomer).



226l'

(*R*)-5-Chloro-1-cyclohexylpentyl benzoate (226l'): The corresponding compound was synthesised from (*R*)-**226l** (15 mg, 0.073 mmol) using the general procedure for the synthesis of benzoate derivatives to give the named compound as a brown oil. **Yield:** 6mg, 27%. **RF:** 0.82 (Et_2O / cyclohexane 3:7) **ee:** 60% **$[\alpha]_D^{23}$** = +10 (*c* 0.4, CH_2Cl_2). **FTIR (neat) V_{max}:** 3369, 2927, 1423, 1106, 823, 700, 613, 503, 487 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 8.09 – 8.00 (m, 2H), 7.59 – 7.52 (m, 1H), 7.47 – 7.41 (m, 2H), 5.07 – 4.93 (m, 1H), 3.50 (t, *J* = 6.7 Hz, 2H), 1.88 – 1.57 (m, 10H), 1.54 – 1.42 (m, 2H), 1.36 – 0.98 (m, 5H). **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 166.5, 133.0, 130.8, 129.7, 128.5, 78.3, 45.0, 41.5, 32.6, 30.7, 29.9, 29.3, 28.2, 26.5, 26.3, 23.0. ***m/z***: 281 (M0.4%), 186 (17), 109 (10), 105 (100), 96 (16), 81 (15), 77 (24) 67 (15), 55 (10). **HRMS (m/z):** Calculated $C_{18}H_{25}O_2Cl$ $[M+Na]^+$: 331.1441, found:

331.1425. ee determination by chiral **HPLC** analysis, Phenomenex® LUX Cellulose-1, Hex/*i*-PrOH 97:3, flow = 1 mL/min, T = °C, retention times: t_r = 15.64 min, t_r = 16.12 min (major enantiomer).

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