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“Synergistic catalysis: merging amino catalysis and metal Lewis acid activation of azaarenes; Green chemistry: first organophotocatalytic approach to the synthesis of phosphoramidates”

Section 1
“Synergistic catalysis: merging amino catalysis and metal Lewis acid activation of azaarenes”

Section 2
“Green chemistry: first organophotocatalytic approach to the synthesis of phosphoramidates”

by

Marta Meazza
Thesis for the degree of Doctor of Philosophy

February 2016
ABSTRACT – Section 1

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

Organic Chemistry

Thesis for the degree of Doctor of Philosophy

DEPARTMENT OF CHEMISTRY - FACULTY OF ORGANIC CHEMISTRY: SYNTHESIS, CATALYSIS AND FLOW

Marta Meazza

The art of building complex chemical scaffolds in a totally stereoselective manner is one of the cornerstones for Organic Chemists. The quest for new catalytic methodologies that fulfil the requirements of efficiency, green chemistry and predictable stereochemical outcome have become the Holy Grail for synthetic chemists.

In the present thesis we investigated new catalytic strategies for the enantioselective synthesis of azaarene scaffolds. Alkyl-azaarenes are common motifs in natural products and pharmaceutical compounds, however few methodologies are devoted to their functionalisation in an enantioselective manner. The major part of the approaches are based on the use of stoichiometric strategies and chiral auxiliaries due to the difficulty to activate the methylene position of alkylazaarenes. Our innovative approach relies on the use of a synergistic strategy where a Lewis acid activates the azaarene moiety making it a nucleophile while a Lewis base catalyst activates the electrophile. This dual activation presents several advantages such as an easy optimisation of each catalytic cycle and a greater decrease of the activation energy required for the reaction, allowing the use of low temperatures and soft conditions.

In Chapter 4 we demonstrate the proof of concept of this approach by joining transition metal catalysis (Lewis acid) and secondary amine catalysis (Lewis base, iminium activation) achieving the enantioselective addition of alkyl-benzoxazoles and related heterocycles to enals in good yields and reasonable stereoselectivity levels. In Chapter 5 we expanded this new concept in the application of cascade reactions. We designed a cascade reaction consisting in the Michael addition of chloromethylbenzoxazoles to enals followed by a 3-exo-trig cyclisation to furnish cyclopropanes in good yields and enantioselectivities.

The value of the present work is not only the development of these methodologies for the synthesis of chiral azaarenes (aldehyde derivatives and cyclopropanes) but also to demystify some misconceptions such as that metal Lewis acid could not coexist with secondary amine catalysis.

This pioneering work is an open gate to generate new methodologies using a synergistic approach that tries to take the best of two of the pillars of catalysis: the high activity and rich chemistry of transition metal catalysis with the affordable and easy stereochemical prediction of secondary amine catalysis, avoiding the use of extreme reaction conditions or the use of chiral ligands.
Photocatalysis has become lately a common strategy for the synthesis of new atom-atom bond. Light is a renewable source that should be witnessed as the future for industrial processes.

Our research group started a quest of new green procedures and, for this reason, we turned our attention to photocatalysis. The use of light as the initiator of a chemical reaction presents several advantages in terms of renewable source of energy, cost and generation of waste.

On the other hand, atom economy should be one of the main driving forces in the design of new strategies for the synthesis of organic compounds. In this area, Cross Dehydrogenative Couplings have emerged as a useful approach. Formally, in CDC reactions two unfunctionalised molecules react together generating a new atom-atom bond and obtaining hydrogen as the only by-product. In this part of my thesis are described our last efforts in the green chemistry area joining the two concepts of photocatalysis and CDC reactions to generate new green protocols for the formation of atom-atom bonds.

Fascinated by the widely use of phosphoramidates as catalysts, flame retardants or even in biological applications, we focused the attention on their synthesis. All the methodologies previously reported in the literature are based on the use of halogens, phosphoryl chlorides, stoichiometric oxidants or transition metal catalysts. We studied the reaction between phosphites and amines to generate phosphoramidates in a CDC process using a photocatalytic oxidation with oxygen acting as a stoichiometric oxidant.

The reaction was catalysed by an organic dye (Rose Bengal), and the phosphoramidates were obtained in excellent yields in reasonable reaction times when irradiated with green LED light. Importantly, we developed a protocol to isolate the final products without the use of any chromatographic technique making all the process a clear example of green methodology. Moreover we designed a homemade photoreactor that improved reaction times.
DECLARATION OF AUTHORSHIP

I, Marta Meazza

declare that the thesis entitled

“Synergistic catalysis: merging amino catalysis and metal Lewis acid activation of azaarenes; Green chemistry: first organophotocatalytic approach to the synthesis of phosphoramidates”

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Date: ..............................................................................................................
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DECLARATION OF AUTHORSHIP

I, Marta Meazza

declare that the thesis entitled

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- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

- where I have consulted the published work of others, this is always clearly attributed;

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Acknowledgements

Undertaking this PhD would not have been possible without the support and guidance that I received from many people. Thanks to all the people with whom I shared this season of my life.

First of all, I would like to express my appreciation and sincere thanks to my supervisor, Dr Ramon Rios, for his teachings and support and for allowing me to grow as a research scientist. His passion for research is highly contagious and encouraging, I greatly benefit from his huge scientific experience. I would also like to thank my advisor Prof Bruno Linclau for motivating me to do my best.

I would especially like to thank my colleagues and friends: Dr Victor Ceban, for the three years spent together as PhD students, thanks for the help in the lab and for the pleasant discussions at the tea room, Maria Ashe for the friendship. Both of you are not only colleagues but also friends. Thanks also to the other past and present members of Rios’ research group, in particular: Michael Potter, Dr Piotr Putaj, Dr Tope Olomola, Dr Jiri Tauchman, India Willans, Luke Kidwell, Greg Gallagher, Aga Kowalczuk, Kane Hands, Luke Shirley and Cameron Ross. Thanks to Prof Andrea Mazzanti for the optical rotation analysis and NMR studies reported in this thesis.

I wish to thank the University of Southampton for providing the facilities and in particular Dr Neil Wells for the NMR service, Dr Mark Light, Dr Mateusz Pitak and Dr Simon Coles for the single crystal X-ray diffract, Dr John Langley and Julie Herniman for the mass spectrometry service and HRMS analysis. Thanks also to Mr Karl and Mr Keith of the store for their kindness and Ms Anne of the tea room where I could relax when I was tired but also where I had interesting discussions with my friends and colleagues.

I would like to acknowledge the AI-CHEM INTERREG IVb for the fellowships and the financial support.

Finally I thank my beloved animals Birillo, Sandokan, Maggie and Notte for their friendship while growing up and Pio and particularly Sera for her unconditional love.
and for supervising the writing of many parts of this thesis from my lap and behind the laptop.

Last I thank my family and my friends: I owe a lot to my family and in particular to my parents and grandmother Diana, who encouraged and helped me at every stage of my personal and academic life, for always being there for me and for their unconditional love.
# Definitions and Abbreviations

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<td>[α]₀</td>
<td>Specific rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AC</td>
<td>Brønsted acid</td>
</tr>
<tr>
<td>aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>β-ICPD</td>
<td>β-Isocupreidine</td>
</tr>
<tr>
<td>bd</td>
<td>Broad doublet</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1’-binaphthyl-2,2’-diol</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>n-Bu</td>
<td>Normal butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>Tertiary butyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>°C</td>
<td>degrees centigrade</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carbobenzyloxy</td>
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<tr>
<td>COSY</td>
<td>Correlated spectroscopy</td>
</tr>
<tr>
<td>Cq</td>
<td>Quaternary carbon</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
</tbody>
</table>
dd Doublet of doublets

ddd Doublet of doublets of doublets

dddd Doublet of doublets of doublets of doublets

DABCO 1,4-diazabicyclo[2.2.2]octane

DCM Dichloromethane

D-(-)-DET (-)-Diethyl D-Tartrate

DFT Density functional theory

(DHQD)$_2$PHAL 1,4-bis[(S)-[(2R,4S,5R)-5-ethylquinuclidin-2-yl]-6-methoxy-4-quinolyl)methoxy]phthalazine

DIBALH diisobutylaluminium hydride

DIPEA Diisopropylethylamine

DMF N,N Dimethylformamide

DMSO Dimethylsulfoxide

2D-NMR Two-dimensional Nuclear Magnetic Resonance

DPFGSE NOE Double Pulse Field Gradient Spin Echo Nuclear Overhauser Effect

dq Doublet of quartets

dr Diastereomeric ratio

dt Doublet of triplets

dtd Doublet of triplets of doublets

E, E$^+$ Electrophile

ECD Electronic circular dichroism
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>equiv.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>ESI+</td>
<td>Electrospray ionization (positive mode)</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl Acetate</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>Het</td>
<td>Heterocycle</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear Single Quantum Correlation</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infra Red</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>L</td>
<td>Ligand</td>
</tr>
<tr>
<td>LCMS</td>
<td>Liquid Chromatography Mass Spectrometry</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>L-(+)-DET</td>
<td>(+)-Diethyl L-Tartrate</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
</tbody>
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M Metal catalyst
m Multiplet
MacMillan II catalyst \((2S,5S)-(-)-2\text{-}\text{tert-}3\text{-methyl-}5\text{-benzyl-}4\text{-imidazolidinone}\)
MBH Morita-Baylis-Hillman
Me Methyl
mg Milligram
MHz Mega Hertz
mL Millilitre
mmol Millimoles
mp Melting point
MS Mass Spectroscopy
MTBE Methyl tertbutyl ether
\(m/z\) mass / charge ratio
NMO \(N\)-methylmorpholine-Noxide
NMR Nuclear Magnetic Resonance
NOE Nuclear Overhauser Effect
Nu Nucleophile
OR Optical rotation
PCM Polarizable continuum model
Pin 4,4,5,5-Tetramethyl-[1,3,2]dioxaborolane (pinacolborane)
PG protecting group
Ph Phenyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PPA</td>
<td>Polyphosphoric Acid</td>
</tr>
<tr>
<td>i-Pr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>qd</td>
<td>Quartet of doublets</td>
</tr>
<tr>
<td>rt</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TADDOL</td>
<td>(\alpha,\alpha,\alpha,\alpha)-tetraaryl-1,3-dioxolane-4,5- dimethanols</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TCM</td>
<td>Chloroform</td>
</tr>
<tr>
<td>td</td>
<td>Triplet of doublets</td>
</tr>
<tr>
<td>TD-DFT</td>
<td>Time-Dependent formalism</td>
</tr>
<tr>
<td>TEA</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>TOF</td>
<td>Time of Flight</td>
</tr>
<tr>
<td>$t_r$</td>
<td>Retention time</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>$p$-TSA</td>
<td>$p$-Toluensulfonic acid</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>VDC</td>
<td>Vibrational circular dichroism</td>
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1. Introduction

1.1 Asymmetric synthesis

In Nature, most of the compounds are chiral (for example hormones, enzymes, DNA ...). Two enantiomers can have different biological activities. For example the enantiomers of Limonene 1 smell differently: the enantiomer (S)-Limonene smells of lemons, while the (R)-Limonene smells of oranges (Figure 1). We are able to distinguish between the enantiomers because the nasal receptors are made of chiral molecules.

![Figure 1. Enantiomers of limonene](image)

This can also be appreciated in the context of drug receptors: as the receptors in the cells are chiral, the drug used should match the receptor. The activity of the drugs depends on which enantiomer is used. For example, while one enantiomer possesses the required activity, the other can be ineffective as in the case of Dopa. Dopa is a chiral amino acid used to treat patients with Parkinson disease, only L-Dopa (S) is effective as a psychoactive while D-dopa (R) is biologically inactive.

In other cases one of the enantiomers can be toxic (Figure 2). In the early 1960s, the drug Thalidomide 2 was manufactured as a racemic mixture of two enantiomers and was prescribed primarily as a sedative for women suffering morning sickness during pregnancy. Whilst the (R)-Thalidomide proved to be the active molecule, the (S)-Thalidomide caused birth defects such as deformities in the limbs. Recent reports show that the strongly acidic hydrogen atom at the asymmetric centre epimerises under physiological conditions, for example in the stomach.
Strategies to develop drugs that can have the beneficial effect of Thalidomide without the teratogenic effects have been developed. Shibata and co-workers synthesised 3-fluorothalidomide,\(^4\) an isosteric analogue of Thalidomide. Fluorine was chosen because of its high electronegativity and strong C-F bond and it was shown that this increased the resistance to racemisation.

This was an extreme example that highlighted the need for new strategies for the synthesis of enantiopure products.

### 1.1.1 Methods of asymmetric synthesis

#### 1.1.1.1 Chiral pool strategy

One possibility to obtain an enantiopure product is to start from an enantiomerically pure starting material. The chiral pool is a collection of cheap and available pure natural products, usually amino acids or sugars, which contain the chiral center needed in the final product.

One example is the synthesis of Aspartame 5: it is a dipeptide and is made using two constituents of the chiral pool, the natural (S) amino acids phenylalanine 3 and aspartic acid 4 (Scheme 1).\(^5\)

---

**Figure 2.** Enantiomers of Thalidomide

![Chemical structures of Thalidomide enantiomers](image-url)
Chiral pool strategy is applied to the total synthesis of pharmaceutical products for example (-)-Deoxoprosophylline 7,[6] synthesised starting from the natural amino acid L-serine 6 (Scheme 2).

Scheme 2: Total synthesis of (-)-Deoxoprosophylline

1.1.1.2 Chiral resolution

Chiral resolution is a technique to separate two enantiomers from a racemic mixture, through the precipitation of one enantiomer or converting them into diastereomers, using a resolving agent. In this way the diastereomers can be separated based on their different physical properties.

Kinetic resolution is based on the differences between the two enantiomers, as only one will react in an enantioselective way. For this reason, the enantioselectivity of the starting material will increase until only one enantiomer will remain unreacted. One example is the kinetic resolution of allylic alcohols 8 using the Sharpless epoxidation[7,8] as shown in Scheme 3.

Scheme 3. Sharpless’ kinetic resolution of allylic alcohols

The dynamic kinetic resolution (DKR) happens when the starting material is able to epimerise rendering, in this way, a theoretical yield of 100% of enantiomerically pure product. One example is the dynamic kinetic resolution of the drug Duloxetine, prescribed for depressive disorders, anxiety disorder, fibromyalgia and neurotic pain (Scheme 4).[9]
To a solution of the racemic alcohol 14 (S)-mandelic acid 15 is added. The (S)-enantiomer of the alcohol forms an insoluble salt with the mandelic acid and is then recovered by filtration. After deprotonation with NaOH the free alcohol is obtained, with 93% of enantiomeric excess (ee). The (R)-enantiomer remains in solution and is treated with HCl to epimerise and form again the racemic mixture.

In the DKR\[10\] the enantiomers of a racemic substrate are induced to equilibrate at a rate that is faster than that of the reaction of the slow-reacting enantiomer with the chiral agent (Figure 3). The theoretical yield of this process is of 100%.

When the reaction occurs with the creation of a new stereogenic centre, the DKR can be applied for the enantioselective synthesis of a diastereomer. An example reported by Buchwald\[11\] deals with the diastereoselective synthesis of 3,5-dialkylcyclopentenones 19 (Scheme 5).
As the reaction is performed under basic conditions, a rapid racemisation of the starting material occurs. The ketone product 17 is masked as silyl enol ether 18 so that the epimerisation at the α-stereocenter is obviated.

1.1.1.3 Chiral auxiliaries

A chiral auxiliary is a molecule that is temporarily covalently bonded to a substrate of interest to control the stereochemical outcome of the reaction. As shown in Scheme 6, the chiral auxiliary is incorporated in the initial substrate 20 and can influence the stereochemistry of one or more following reactions. Then it can be removed, recycled and reused.

An efficient chiral auxiliary should possess the following characteristics: (a) cheap and readily available, (b) easy to attach to the substrate, (c) able to induce the correct
stereochemistry, (d) chemically inert under the reaction conditions and (e) easy to remove.

The most common chiral auxiliaries are: Evan’s oxazolidinones, Ellman’s, Enders’ and Oppolzer’s auxiliaries.

Evans’ auxiliaries 25 are oxazolidinones applied to different stereoselective reactions, including aldol reactions,[12] alkylation reactions (Scheme 7)[13] and Diels-Alder reactions.[14]

![Scheme 7. Example of alkylation with Evans oxazolidinone](image)

The intermediate 29 is the (Z)-enolate formed under kinetic conditions. A nucleophilic addition to the aldehyde 30 gives the syn product 31 as the aldehyde reacts preferentially with one face of the enolate due to steric hindrance of the substituent on the oxazolidinone. An additional advantage of the oxazolidinones is the fact that the products are easy to crystallise, making it easier to obtain enantioenriched compounds.

Ellman’s auxiliaries are N-tert-butanesulfinyl aldimines 33 and ketimines 36 and are useful intermediates for the asymmetric synthesis of amines 38.[15] The tert-butanesulfinyl group activates the imine for the addition of different nucleophiles and acts as a chiral directing group. After the addition it is cleaved by treatment with acid (Scheme 8).
Ender’s auxiliaries 39 is a chiral hydrazine that reacts with an aldehyde or ketone forming an hydrazone 41.\textsuperscript{[16]} Then it is deprotonated with lithium diisopropylamide (LDA) forming an azaenolate that reacts with an electrophile and after ozonolysis or hydrolysis the final alkylated product 43 is obtained (Scheme 9).

Oppolzer’s auxiliary 44 is a camphorsultam that has become a common auxiliary demonstrating its utility in enantioselective Diels-Alder\textsuperscript{[17]} or allylic addition reactions (Scheme 10).\textsuperscript{[18]}
1.1.1.4 Enantioselective catalysis

The enantioselective catalysis consists in the use of substoichiometric amounts of a catalyst to control the stereochemistry of the reaction while decreasing the activation energy of the reaction and making, in this way, the reaction occur.

Enantioselective synthesis can be divided into three classes.

The first one is based on the use of metal catalysts.

One of the major breakthroughs in this area was in 1968 when Knowles at Monsanto showed that rhodium complexes containing chiral phosphine ligands 49 were able to catalyse the enantioselective hydrogenation of prochiral olefins 48, obtaining the products 50 with high enantioselectivities. This process was applied in the industrial synthesis of the anti-Parkinson drug L-Dopa 51 as shown in Scheme 11.\textsuperscript{19,20}

\begin{align*}
\text{MeO} & \text{COOH} + H_2 \xrightarrow{[\text{Rh}((R,R)-\text{DiPAMP})\text{COD}][\text{BF}_4^-]} \text{MeO} & \text{COOH} \\
\text{AcO} & \text{NHAc} & \text{AcO} & \text{NHAc} \\
48 & \xrightarrow{(R,R)-\text{DiPAMP}} & 49 & \text{MeO} & \text{COOH} \quad \text{H}_2 \text{O}^+ \\
\text{MeO} & \text{COOH} & \text{NHAc} & \text{MeO} & \text{NH}_2 \\
\text{AcO} & \text{AcO} & \text{AcO} & \text{AcO} & \text{H}_2 \text{O}^+
\end{align*}
Noyori developed the field of asymmetric hydrogenations reporting the discovery of an atropoisomeric chiral diphosphine 52 (BINAP) \textbf{(Figure 4)}. Rhodium(I) complexes with BINAP were effective to perform enantioselective reactions, including an enantioselective hydrogenation of α-(acylamino)acrylic acids or esters, rendering amino acid derivatives.\textsuperscript{[21]}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{binap.png}
\caption{Structure of BINAP}
\end{figure}

Subsequently Noyori discovered the BINAP-Ru(II) complex catalyst 54, active in the enantioselective hydrogenation of unsaturated carboxylic acids\textsuperscript{[22]} and differently functionalized ketones 53 (Scheme 12).\textsuperscript{[23]}

\begin{equation}
\text{HO-}^\text{Me} + \text{H}_2 \xrightarrow{(R)\text{-BINAP-Ru(II)X}_2\text{L}_2} \text{HO-}^\text{Me}
\end{equation}

\textbf{Scheme 12. Asymmetric hydrogenation of ketones}

In parallel with the development of asymmetric hydrogenations, Sharpless developed a chiral catalyst for oxidation reactions. In 1980 Sharpless and Katsuki reported an asymmetric epoxidation of allylic alcohols 56, using titanium(IV) tetraisopropoxide 10, tert-butyl hydroperoxide 11 and enantiomerically pure dialkyl tartrate 9 (Scheme 13).\textsuperscript{[24]}
Sharpless also developed a catalytic asymmetric dihydroxylation using N-methylmorpholine N-oxide (NMO) 61 as stoichiometric oxidant, osmium tetroxide 60 (OsO₄) as catalytic oxidant and a cinchona alkaloid 59 as ligand (Scheme 14).[25]

For their discoveries in the field of asymmetric catalysis, Knowles,[26] Noyori[27] and Sharpless[28] were rewarded with the Nobel Prize in 2001.

Another method of enantioselective catalysis is biocatalysis[29] that is based on the use of enzymes as catalysts. The advantages of biocatalysis are (a) high stereo-selectivity, chemo-selectivity and regioselectivity, (b) reduced use of protecting groups, (c) minimised side reactions and (d) fewer environmental problems compared to organometallic catalysis. The drawbacks are (a) limited substrate scope for each
enzyme and (b) the fact that most of the reactions are carried out in water as solvent and most organic substrates have limited solubility in water.

An example of such methodology is the work reported by Rosenthaler regarding the preparation of \((R)\)-mandelonitrile by treating benzaldehyde with HCN in the presence of the enzyme emulsin, extracted from bitter almonds.\(^{30}\)

The third pillar is organocatalysis, the use of small, chiral, organic molecules to catalyse asymmetric organic reactions. This topic is developed in depth in Chapter 1.2.
1.2 Organocatalysis

The name ‘organocatalysis’ was coined by MacMillan in 2000, even if some reactions catalysed by small, organic molecules were known since the beginning of the XX century. From the beginning of this century organocatalysis has become a powerful tool, added to other well established techniques such as biocatalysis and metal catalysis. Organocatalysis relies on the capability of small organic molecules to catalyse organic transformations, the most useful of which belong to the area of asymmetric synthesis. Today most of the reactions in asymmetric catalysis still rely on organometallic complexes, but organocatalysis is becoming more and more important because it presents a series of advantages: (a) reactions can be performed in an aerobic atmosphere (the presence of water is often beneficial), (b) the catalysts used are more stable and less expensive as often they are obtained from natural compounds, (c) organocatalysis is best suited for the synthesis of more complex structures through domino reactions thanks to the easy prediction of stereoselectivity and (d) it presents fewer toxicity issues being safer, cheaper and not requiring expensive waste treatment.

Despite the advantages offered by organocatalysis, there are also some drawbacks as, for example, the high catalyst loading needed in most of the reactions and the limited substrate scope for a particular organocatalyst in a particular transformation.

1.2.1 Historical development of organocatalysis

The initial experiments in this field dated back to the end of the XIX century. It takes a long time for asymmetric organocatalysis to become a practical synthetic paradigm. For a long time it was considered to be limited both in efficiency and scope if compared to organometallic catalysis.

Organocatalysis seems to have operated in the formation of prebiotic fundamental chiral organic molecules such as sugars (for example L-isovaline, found in meteorites, was able to catalyse reactions that lead to the formation of sugars). Then, the discovery of the catalytic properties of enzymes played an important role in the
development of asymmetric catalytic reactions (biocatalysis).\textsuperscript{[34]} It has to be noted that more than half of the enzymes work without the presence of a metal. Combining these two concepts, the potential role of small optically active organic molecules as asymmetric catalysts becomes evident. To name just a few examples: the first asymmetric carbon-carbon bond formation was described by Bredig, that obtained mandelonitrile \textsuperscript{66}, with an enantiomeric excess of less than 10\%, by the addition of HCN to benzaldehyde \textsuperscript{63} using the alkaloids quinine \textsuperscript{64} and quinidine \textsuperscript{65} as catalysts (Scheme 15).\textsuperscript{[35]} This work was inspired by the previous achievement of Rosenthaler, who prepared mandelonitrile, by the same reaction catalysed by the isolated enzyme emulsin.\textsuperscript{[30]}

\[ \text{Bredig's work} \]

\begin{center}
\begin{tikzpicture}
    \node (A) at (0,0) {\textbf{63}};\node (B) at (2,0) {\textbf{64}};\node (C) at (4,0) {\textbf{65}};\node (D) at (2,-1) {\textbf{66}};
    \path[->] (A) edge node {HCN} (B);
    \path[->] (A) edge node {\text{(-)-quinine}} (D);
    \path[->] (B) edge node {\text{(+)-quinidine}} (C);
    \path[->] (B) edge node {< 10\% ee} (D);
\end{tikzpicture}
\end{center}

\textit{Scheme 15.} Bredig’s work

In the late 1950s Pracejus converted methyl phenyl ketene \textsuperscript{67} to (-)-α-phenyl methylpropionate \textsuperscript{69} in 99\% yield, with 74\% ee, employing O-acetylquinine \textsuperscript{68} as catalyst (Scheme 16).\textsuperscript{[36]}

\[ \text{Pracejus’ work} \]

\begin{center}
\begin{tikzpicture}
    \node (A) at (0,0) {\textbf{67}};\node (B) at (2,0) {\textbf{68}};\node (C) at (4,0) {\textbf{69}};
    \path[->] (A) edge node {MeOH} (B);
    \path[->] (A) edge node {toluene, -111 °C} (C);
    \path[->] (B) edge node {99\% yield 74\% ee} (C);
\end{tikzpicture}
\end{center}

\textit{Scheme 16.} Pracejus’ work

In the early 1970s, the Hajos-Parrish-Eder-Sauer-Wiechert reaction, a (S)-proline \textsuperscript{71} catalysed asymmetric desymmetrisation by aldol reaction, led to the preparation of
the Wieland-Miescher ketone 73, a useful intermediate in the synthesis of natural compounds. The bicyclic ketol 72 was obtained in 93% ee, using only 3% of (S)-proline catalyst (Scheme 17).\textsuperscript{[37,38]}

![Scheme 17. Hajas-Parrish-Eder-Sauer-Wiechert reaction](image)

In the 1980s, the Julia-Colonna epoxidation of enones 74 with H\textsubscript{2}O\textsubscript{2} catalysed by poly-L-leucine 75, represented the first example of hydrogen-bonding catalysis, another important tool in asymmetric synthesis (Scheme 18).\textsuperscript{[39,40]}

![Scheme 18. Julia-Colonna epoxidation](image)

The year 2000 can be considered the start of the “Renaissance” of organocatalysis thanks to the pioneering works of List\textsuperscript{[41]} and MacMillan.\textsuperscript{[42]} List published an intermolecular asymmetric aldol reaction catalysed by proline 71, while MacMillan studied the first enantioselective organocatalytic Diels-Alder reaction (Scheme 19).
Since then a plethora of asymmetric reactions have been developed.\textsuperscript{[43–47]}

1.2.2 Classification of the organic catalysts

According to List\textsuperscript{[43]} it is possible to classify most of the organic catalysts in four classes: Lewis bases, Lewis acids, Brønsted bases, Brønsted acids (Figure 5).

In the case of Lewis base catalyst (B:) the cycle starts with the nucleophilic addition of the catalyst to the substrate (S). The complex undergoes a reaction and then releases
the product (P) and the catalyst, ready to participate in another catalytic cycle. An example of Lewis base catalysis is the enamine catalysis that involves an enamine intermediate generated via deprotonation of an iminium ion that can react with an electrophile. An example of this type of catalysis is presented in the work of List,[48] shown in Scheme 20.

![Scheme 20. Lewis base catalysis](image)

In the case of the Lewis acid (A) there are the addition of the nucleophilic substrate (S-) to the catalyst, the formation of the product and the release of the product (P-) and the catalyst as in the previous case. It is characterised by the electrophilic activation of functional groups towards a nucleophilic attack. An example is given by the work of Denmark that used a chiral bidentate Lewis base and SiCl₄ to create a Lewis acid in situ (Scheme 21).[49]

![Scheme 21. Lewis acid catalysis](image)

Brønsted acid and base catalytic cycles start with a partial deprotonation or protonation of the substrate, respectively. Typical examples of Brønsted base catalysed reactions are the hydrocyanation reactions as shown in Inoue work in Scheme 22.[50] This catalyst 91 can act as a bifunctional catalyst as not only the imidazolyl moiety deprotonates HCN forming the cyanide anion (that then interacts...

16
with the same moiety) but also the oxygen of the benzaldehyde forms a hydrogen bond with the hydrogen of the istidine residue.

Scheme 22. Brønsted base and acid bifunctional catalyst

The Takemoto catalyst 96 is a bifunctional organic catalyst that can act as a Brønsted acid and as a Brønsted base catalyst: the thiourea interacts with the nitro group via hydrogen-bonding activation, while the tertiary amine activates the nucleophile acting as a Brønsted base (Scheme 23).[51]

Scheme 23. Takemoto bifunctional catalyst
One of the limitations of this classification is the lack of information on the mechanisms of most of the organocatalytic reactions due to the lack of kinetic data.

1.2.3 Modes of activation: aminocatalysis

For the purpose of this thesis, only the Lewis base catalysis will be discussed in depth, in particular the aminocatalysis. This term was first used by List in 2001[44] to designate reactions catalysed by secondary and primary amines, taking place via enamine and iminium ion intermediates (Scheme 24). Enamine activation 99 produces an increased electron density at the α-carbon atom, while the iminium activation 101 results in a decreased electron density at the carbonyl carbon atom, thus activating the β-position of the aldehyde 80. In both cases there is an amplified reactivity of the reaction center.

![Scheme 24. Enamine and iminium intermediates](image)

1.2.3.1 Iminium catalysis

Iminium catalysis is now an established strategy for the asymmetric addition of nucleophiles at the β position of enals. An example of a catalytic cycle is shown in Scheme 25.
The cycle starts with the acid-promoted condensation of the carbonyl 80 with the amine 103 to form the iminium ion 104, more electrophilic than the starting enal. The equilibrium between the $E$-iminium ion and the $Z$-iminium ion is shifted heavily towards the $E$ form as it is the more stable one. The nucleophile then attacks the $\beta$-position with the formation of the anti-enamine 105 in equilibrium with the iminium ion 106. The hydrolysis of the iminium releases the product 107 and the catalyst which can re-enter the catalytic cycle.

The facial selectivity of the attack is determined by the chirality of the secondary amine. The bigger the substituents on the pyrrolidine the better the selectivity will be, but conversely the rate of the reaction will decrease. The stereochemistry can be predicted from the transition state depicted in Scheme 26: the attack of the nucleophile will be from the face opposite to the bulky amine substituent in the energetically favoured $trans$ conformer of the ($E$)-iminium ion.
Scheme 26. Stereochemical outcome of amine-catalysed addition to enals

Some examples of C-C bond formation based on the iminium activation are: the addition of malonates 95 to α,β-unsaturated aldehydes 80 developed by Jørgensen,[52] the addition of fluorobis(phenylsulfonyl)methane to enals[53–55] or the synthesis of spirocyclic compounds developed by Melchiorre[56] and Rios[57] (Scheme 27).

Scheme 27. Examples of organocatalytic nucleophilic addition

There are still big challenges in this area of organocatalysis such as the fact that the addition of enals requires the use of good nucleophiles like malonates or, in general, dicarbonyl compounds containing acidic hydrogens. There are only two examples in the literature on the addition of benzylic nucleophiles to enals: Melchiorre reported the addition of diarylmethylenes to the β position of the enals but this reaction has some limits such as the very low diastereoselectivity and the need to use two activated aryl groups bearing electro-withdrawing groups.[58] In 2010 Ruano reported the addition of nitrophenylacetonitriles to enals catalysed by secondary amines with good enantioselectivity.[59]
1.2.3.2 Enamine catalysis

Enamine catalysis has become one of the most employed organocatalytic mode of activation, allowing the enantioselective α-functionalisation of enolisable aldehydes and ketones with a variety of electrophiles.\cite{60}

In Scheme 28 is presented the general mechanism. A chiral 2-substituted pyrrolidine 116 is the most representative catalyst, acting with a Brønsted acid co-catalyst AH. The acid can be a protic solvent (water, alcohols), an added external acid or a functional group present in the amine catalyst. The first step of the catalytic cycle is the acid promoted condensation of the carbonyl 111 with the amine forming an iminium ion 112. One of the α-acidic protons of the iminium ion is removed by the conjugate base of the Brønsted acid, forming the nucleophilic enamine intermediate 113. The reaction with an electrophile generates an iminium ion 114 that, after hydrolysis, liberates the final product 115, the acid and the amine catalyst. The efficiency of this catalytic cycle is based on the fast and quantitative generation of the iminium ion, its interconversion in the (\(E\))-enamine intermediate and a high stereochemical control over the electrophilic attack. Finally it is important that the possible reaction between the amine and the electrophile is slow or reversible.
The stereochemical outcome of the reaction can be predicted based on the substituent present in position 2 of the pyrrolidine. If the chiral amine bears a hydrogen-bond directing group (carboxylic acid, amide) the attack of the electrophile takes place via a cyclic transition state (List-Houk model, Figure 6 A). Seebach and Eschenmoser\cite{61} proposed an alternative transition state based on the protonation of the electrophile followed by an electrophilic attack directed by an intramolecular reaction of the conjugate base of the substituent on the amine (Figure 6 B). If the amine substituent is bulky and without acidic protons, the attack of the electrophile is directed by steric effect, leading to the opposite facial stereoselectivity (Figure 6 C).
1.2.3.3 Sequential iminium-enamine catalysis

Iminium catalysis proceeds, after the addition of the nucleophile, via an (E)-enamine 105. In the presence of a suitable electrophile, an electrophilic addition occurs, forming an iminium ion 117 that, after hydrolysis, releases the catalyst and an α,β-difunctionalised carbonyl product 118 (Scheme 29).
Some examples are reported in 2005 by List, MacMillan and Jørgensen. The absolute stereochemistry can be predicted by the application of the steric model for the Michael addition to iminium ions and of the steric model for the electrophilic attack to enamines.

A limitation is that the electrophile and the nucleophile must be simultaneously present in the reaction mixture without reacting with each other. A way to overcome this limitation is the use of a reagent that exhibits sequentially nucleophilic and electrophilic character. As it is shown in Scheme 30, a good reagent could be one with a nucleophilic center attached to a leaving group; after the initial addition of the nucleophile to the iminium ion, an intramolecular attack of the enamine will form a cyclic product 121.

Scheme 30. Intramolecular sequential iminium-enamine catalysis

An example of an intramolecular sequential iminium-enamine catalysis is the work of MacMillan on the amine-catalysed cyclopropanation of α,β-unsaturated aldehydes 80 by β-oxosulfonium ylides 122 (Scheme 31).
1.3 Multicatalysis

The development of organocatalysis has recently regarded its use in combination with transition metal complexes to take advantage of both catalysts. The driving force is to discover more efficient approaches to synthesise complex molecules with good chemo and stereoselectivity, inaccessible with the use of a single catalytic system.[66]

The advantages of combining organo- and transition metal catalysts are: (a) enabling the development of new transformations and new reactivity, (b) creating or improving enantioselectivity by using an appropriate combination of an organocatalyst and a chiral or achiral transition metal catalyst, (c) improving the efficiency and expanding the substrate scope.

The main challenges are to ensure the compatibility of the catalysts, substrates, intermediates and solvents.[67]

As presented in a review of MacMillan[68] there are four type of multicatalysis mechanisms (Figure 7):

1. Bifunctional catalysis when both the nucleophile and electrophile are activated separately by functional groups present on the same catalyst.
2. Double activation catalysis when both catalysts work in concert to activate one of the substrates.
3. Cascade catalysis when both catalysts activate the same substrate in a sequential way.
4. Synergistic catalysis when the nucleophile and the electrophile are simultaneously activated by two separate and distinct catalysts.
1.3.1 Synergistic catalysis

Synergistic catalysis is prevalent in nature as most enzymes work through the cooperation of two or more catalytic moieties to afford one transformation. In organic chemistry is now beginning to emerge as a powerful tool for the formation of new bonds, especially carbon-carbon bonds.

Traditional catalysis is based on the interaction of a single catalyst with a single substrate lowering the energetic barrier to favour the reaction with a second, not activated, substrate. Synergistic catalysis is based on the activation of both the nucleophile and the electrophile creating two reactive species, respectively one with a higher HOMO (highest occupied molecular orbital) and one with a lower LUMO (lowest unoccupied molecular orbital) (Figure 8).
One of the most common approaches in organocatalysis has been the bifunctional catalysis for example the use of tertiary amine/thiourea catalysts as in the Takemoto catalyst. This catalyst activates the nucleophile via the amine while the two hydrogen atoms of the thiourea activate the electrophile via hydrogen bond-activation as presented before in Scheme 23. The main drawback of this type of catalysis is the need to synthesise a new catalyst each time one of the subunits is modified; this will cost money and time and the results could be difficult to predict.

Synergistic catalysis, on the other hand, allows the optimisation of each catalyst independently from the other co-catalyst and allows the use of more varied sources of chirality in each of the catalysts. This increased flexibility leads to an enhancement of the chemical reactivity, allowing the synthesis of more complex products.

A drawback of this type of catalysis is the possible auto-quenching of the two catalysts, rendering them inactive. The solution is to carefully choose an appropriate combination of catalysts, for example a hard Lewis acid and a soft Lewis base that will avoid the formation of strongly coordinated complexes.

Another apparent drawback is related to the kinetic of the reaction. As the two catalysts are present in substoichiometric concentrations, the concentrations of the two active intermediates will be low and the reaction rate should be low. But this does not take into consideration the rate constant \( k \) of the kinetic equation. Compared to traditional catalysis, there is a narrower gap between HOMO and LUMO (Figure 8). This causes a decrease in the activation energy, increasing the rate constant \( k \) of the reaction and overcoming the kinetic effect.

An example of this type of catalysis is the enantioselective silyl addition to enals 80 catalysed by copper and a chiral amine 103, reported by Córdova in 2011.\(^\text{[69]}\) As shown in Scheme 32, Me₂PhSi-B(pin) (pin = pinacolborane) 125 acts as a nucleophile after treatment with CuCl. CuCl induces transmetallation to form the nucleophilic Cu(I)-SiMe₂Ph. This complex attacks the \( \beta \) position of the iminium ion 104. After the subsequent protonation and hydrolysis of the amine catalyst the desired \( \beta \)-silyl aldehyde 126 is obtained with good yields and selectivities although selectivities are higher with aromatic enals.
Scheme 32. Córdova’s enantioselective silyl addition to enals catalysed by copper and a chiral amine

Recently our research group developed a diastereoselective addition of benzoxazoles 132 to Morita-Baylis-Hillman carbonates (MBH) 139 using the concurrent activation with a Lewis acid and a tertiary amine respectively. This is the first synergistic catalysis example of alkyl-azaarenes addition to MBH carbonates. As presented in the proposed mechanism in Scheme 33, the metal Lewis acid (AgOAc) interacts with the alkyl-azaarene via nitrogen coordination, thus increasing the acidity of the α carbon that can be deprotonated by a base. A simultaneous reaction happens between an organic Lewis base (DABCO) 138 and an MBH carbonate 139 via $S_N2$ addition with the formation of the intermediate 135 and the release of carbonic acid. This intermediate reacts with the previously activate nucleophilic intermediate 134 to obtain the intermediate 136. After the release of the catalyst the final product 137 is obtained with very good diastereoselectivities.
Córdova and co-workers also successfully combined transition metal catalysis with the iminium and enamine catalysis.\textsuperscript{[71]} They developed a highly enantioselective dynamic kinetic asymmetric transformation (DYKAT) between $\alpha,\beta$-unsaturated aldehydes 80 and propargylated carbon acids 141 to form enantiomerically pure cyclopentenes 144 with good diastereoselectivities and high enantioselectivities (Scheme 34).

\textbf{Scheme 33.} Proposed mechanism of benzoxazole addition to MBH carbonates
Scheme 34. Mechanism of Córdova’s DYKAT between α,β-unsaturated aldehydes and propargylated carbon acids to form enantiomerically pure cyclopentenes

This reaction proceeds through a Michael addition catalysed by the secondary amine organocatalyst 103, followed by a cycloisomerisation catalysed by Pd(0)/enamine, rendering cyclopentenes 144’. The intermediates 143 and 143’ are formed in equal amounts, but the cyclisation step is irreversible and proceeds with different rates for the two diastereomers.
2. Objectives

The synthesis of new scaffolds based on alkyl-\(N\)-heteroaromatics is of paramount importance in medicinal chemistry and agrochemistry. There are very few methodologies for the enantioselective synthesis of \(N\)-heterocyclic compounds because of the lack of synthetic options currently available.

The objectives of this thesis involve the development of new enantioselective methodologies for the synthesis of alkyl-azaarenes. In particular we want to study the activation of the pseudo benzylic position of alkyl-azaarenes in nucleophilic additions to enals.

- The aim of the first project (Chapter 4) is to study the activation of alkyl-azaarenes through the application of synergistic catalysis. In particular a metal Lewis acid activates the alkyl-azaarenes and an organocatalyst activates the enals.

- The aim of the second project (Chapter 5) is to expand the concept developed in Chapter 4 to a cascade reaction for the synthesis of cyclopropanes and to push the boundaries of synergistic catalysis joining together 3 catalytic cycles for the formation of 2 new C-C bonds.
3. Azaarenes

Our research group has developed different organocatalytic methodologies for the enantioselective synthesis of useful and valuable products. For example the organocatalytic synthesis of piperidines for the synthesis of (-)-Paroxetine 147 (Scheme 35).[72]

![Scheme 35. Synthesis of piperidines](image)

Rios and co-workers developed a reaction between protected 2-hydroxymalonates 148 and MBH carbonates 139 for the synthesis of α-methylene-γ-lactone 151,[73] obtained in excellent yields and enantioselectivities (Scheme 36).

![Scheme 36. Rios’ synthesis of α-methylene-γ-lactone](image)

Other representative examples are the enantioselective addition of pyrazolones 152 to maleimides 153 (Scheme 37).[74]
Recently we became interested in the development of new methodologies for the synthesis of azaarene derivatives.

The synthesis of natural products or metabolites with biological activities has always been an important part of organic chemistry. Despite the advances obtained so far, the synthesis of natural products still requires multiple reaction steps and purifications. For these reasons it is important to study and develop new stereoselective methodologies that can avoid the use of protecting groups and simplify the reactions and the purifications.

The synthesis of azaarenes has attracted a lot of attention due to their importance as they are ubiquitous structures in biologically active pharmaceuticals, agrochemicals and natural products, as shown in Figure 9. Azaarenes are used for the treatment of diabetes as inhibitors of dipeptidyl peptidase 4 (DPP-4) 155,[75] for the treatment of schizophrenia as GlyT-1 inhibitor 156,[76] as fungicide 157,[77] as inotropic agent 158,[78] as psychoactive drug 159,[79]

Scheme 37. Addition of pyrazolones and oxazolones to maleimides

\[ \text{Scheme 37: Addition of pyrazolones and oxazolones to maleimides} \]
Figure 9. Examples of biologically active azaarenes

During the last few decades approaches for the synthesis of azaarenes using chiral auxiliaries, employing transition metal catalysts, or using organolithium reagents to deprotonate the acidic proton of the azaarene, have been studied. These methodologies require the use of harsh conditions such as high temperatures, thus presenting problems of compatibility with some functional groups.

3.1 Synthesis of azaarenes: alkylazaarenes as pronucleophiles

The majority of the methodologies reported in literature for the synthesis of azaarenes are non-asymmetric and mainly based on the direct C-H activation and functionalisation using transition metal catalysts.

Some examples of synthesis of azaarenes are the following:\textsuperscript{[80]}

\textbf{Azaarenes addition to N=N bonds:} Guo and Qu reported a Cu(II) catalysed racemic amination of 2-alkylazaarenes 160. They obtained the products with good yields but using high temperatures (\textbf{Scheme 38}).\textsuperscript{[81]}

\[ \text{DPP4-inhibitor 155} \]
\[ \text{GlyT-1 inhibitor 156} \]
\[ \text{fungicide 157} \]
\[ \text{inotropic agent 158} \]
\[ \text{psychoactive drug 159} \]
Azaarenes addition to C=N bonds: Rueping and Huang studied the addition of azaarenes 398 to N-sulfonyl aldimines 162 catalysed by copper 261 and palladium 164 salts respectively (Scheme 39).\textsuperscript{[82,83]} The final products 165 are racemic and the reactions still require the use of high temperatures.

**Scheme 39.** Rueping’s and Huang’s racemic addition of azaarenes to N-sulfonyl aldimines

Azaarenes addition to C=O bonds: Li\textsuperscript{[84]} and Fossey\textsuperscript{[85]} reported the addition of 2-methylazaarenes to isatines 167 and ethyl glyoxylates 171 respectively, using high temperatures (Scheme 40).
Scheme 40. Li’s and Fossey’s addition of 2-methylazaarenes to isatines and ethyl glyoxylates

Azaarenes addition to C=C bonds: Huang and co-workers have developed the addition of 2-alkylazaarenes to methylenemalononitriles, using ytterbium salts as catalysts, achieving the products in good yields. Matsunaga and Kanai studied the direct addition of alkylazaarenes to C=C double bonds of enones 174 catalysed by Lewis acid (Scheme 41).

Scheme 41. Matsunaga’s addition of alkylazaarenes to C=C double bonds of enones

All these methodologies are non-asymmetric and require high temperatures.

Recently, some enantioselective methodologies have been developed. In 2012 Lam and co-workers reported the enantioselective addition of alkylazaarenes 178 to N-Boc imines using Pd(II) salts 164 as catalysts and in 2013 an enantioselective nickel-catalysed Michael addition of 2-acetylazaarenes 182 to nitroalkenes 183. The choice of ligand (in this case bisoxazolines 180) becomes crucial to obtain good enantioselectivities (Scheme 42).
Melchiorre and co-workers reported the only organocatalysed methodology for the synthesis of azaarenes. They developed a methodology for the addition of (4-nitrobenzyl)pyridine 186 to enals 80 catalysed by chiral secondary amines 103 (Scheme 43). The products 187 are obtained with good yields and enantioselectivities but low diastereoselectivities.[58]

Scheme 43. Melchiorre’s first organocatalytic synthesis of azaarenes

While working on the development of the project reported in Chapter 4, another work in the organocatalytic synthesis of azaarenes was reported by Wang and co-workers.[90] They described the enantioselective Michael addition of 4-methyl-3-nitropyridine 188 to α,β-unsaturated aldehydes 80, catalysed by a chiral secondary amine 189 (Scheme 44). The final products 190 are obtained with good yields and excellent enantioselectivities (> 90% ee).
3.2 Strategies for the activation of alkyl-azaarenes

There are different methods for the activation of these compounds to allow enantioselective reaction. They all use the ability of the C=N of the azaarenes to acidify the protons in α position of the 2-alkylaazaarenes 191, enabling the formation of an azaallyl anion\cite{91} 192 that can act as a nucleophile in the addition to a π electrophile 193. The α-deprotonation of 2-alkylaazaarenes can be compared to the enolisation of carbonyl compounds (Scheme 45).

The main limitation in the development of these reactions is the low acidity of the 2-alkylaazaarenes compared with the carbonyl compounds, so there is the need to find a way to activate the 2-alkylaazaarenes, increasing the acidity of the methylene position.

(A) Activation with an electron withdrawing group (EWG) in the alkyl chain.

By adding an EWG at the α-carbon of the alkyl chain, the two hydrogens of the alkyl chain become more acidic (Figure 10). In this way the CH₂ can be deprotonated more easily and the azaarene becomes a better nucleophile.
We envisaged that incorporation of electron-withdrawing groups (such as nitro, cyano, and ester) into an azaarene 132 would decrease the pKa, increasing the acidity of the α-protons of a pendant alkyl substituent by stabilisation of the conjugate base through conjugation (Figure 11). This extended conjugation will allow deprotonation of azaarenes in milder conditions (using weaker bases and lower temperatures). For this reason this will be more compatible with the organocatalytic activation step of the enal and hence more suited to obtain higher stereoselectivities. Moreover, the use of these functional groups would provide highly useful functional handles for subsequent elaboration of the products.

(C) Activation with a metal Lewis acid that coordinates with the N-atom.

The equilibrium between the 2-alkylaazaarene and its enamine counterpart could be easily shifted once the acidity of the benzylic proton had been enhanced by a suitable metal catalyst. Moreover, a Lewis acid could coordinate with the nitrogen atom of the C=N double bond on the heteroaryl ring and could increase the acidity of the α-carbon position, facilitating the deprotonation (Figure 12).
We decided to study the stereoselective addition of azaarenes to α,β-unsaturated aldehydes. In order to achieve this goal we plan to use a synergistic approach (as explained in Chapter 1) that consist in the activation of the azaarene with a transition metal salt and the activation of the enal with a chiral secondary amine catalyst.

**Figure 12. Activation of benzoxazoles with a Lewis acid**
4. Synergistic catalysis: enantioselective addition of alkylbenzoxazoles to enals

4.1 Michael addition

4.1.1 Introduction

The Michael addition is a 1,4-addition (conjugate addition) of a nucleophile to an activated π system. The nucleophile (Michael donor) derives from the deprotonation of a CH-activated compound for example aldehydes, ketones, nitriles, β-dicarbonyl compounds or from the deprotonation of heteroatoms. If the EWG present in the Michael donor is strong enough, it is possible to use relatively weak bases (e.g., Et₃N). The Michael acceptor is an alkene or alkyne activated by an EWG.

Komnenos, in 1883, published the first example of a carbon nucleophile adding to an electron-deficient double bond[92] with the addition of the anion of diethyl malonate to ethylidene malonate. In 1887 Michael systematically studied the reaction of stabilised anions with α,β-unsaturated systems[93,94] and reported the addition of diethyl malonate 95 to the double bond of ethyl cinnamate 198 in the presence of a base to afford a pentanedioic acid diester 199. Some years later Michael reported that also electron deficient triple bonds 200 can work as Michael acceptors with diethyl malonate as Michael donors (Scheme 46).[95]

![Scheme 46](image)

Scheme 46. First examples of Michael additions reported by Michael in 1887 and 1894

Evans auxiliary was efficiently used by Wu and co-workers to promote a 1,4-Michael addition of allyltrimethylsilanes 203 to α,β-unsaturated carbonyl compounds.[96] After
the addition of the oxazolidinone auxiliary, an $N$-acylamide 202 is formed and the subsequent Michael addition is promoted by TiCl$_4$ as Lewis acid, obtaining the allylation products 204 with good yields and diastereoselectivities (Scheme 47).

Scheme 47. Wu’s 1,4-Michael addition of allyltrimethylsilanes to $\alpha,\beta$-carbonyl compounds

Several transition metal-catalysed Michael addition reactions have been developed. One nice example was reported by Jørgensen et al. with the addition of O-benzylhydroxylamines 206 to $\alpha,\beta$-unsaturated carbonyl compounds using chiral Lewis acids (TiX$_2$-TADDOL 207 or TiCl$_2$-BINOL 208) as catalysts (Scheme 48).$^{[97]}$

Scheme 48. Jørgensen’s metal catalysed Michael addition addition of O-benzylhydroxylamines to $\alpha,\beta$-unsaturated carbonyl compounds

After the development of organocatalysis since 2000, the organocatalytic asymmetric Michael addition has gained a lot of success.$^{[98–101]}$

For the purpose of this thesis only the enantioselective organocatalytic Michael addition to $\alpha,\beta$-unsaturated aldehydes as Michael acceptor will be covered.
4.1.2 Enantioselective organocatalytic Michael addition with α,β-unsaturated aldehydes as Michael acceptor

The catalytic cycle involving the formation of the iminium ion and the activation of the enal as a Michael acceptor is explained in Scheme 25 and Scheme 29.

After the formation of the iminium ion, due to the high reactivity, the competitive 1,2-addition could be a major limitation of this reaction. In this regards, MacMillan et al. in 2003 reported the first enantioselective organocatalytic Mukaiyama-Michael reaction for the synthesis of γ-butenolide products 214 through the addition of chiral imidazolidinones 215 to α,β-unsaturated aldehyde 80a. The same reaction reported in literature (Mukaiyama-aldol) uses metal salts to promote the 1,2-addition. While MacMillan proved that iminium organocatalysis using chiral imidazolidinones promotes the 1,4-addition due to the bulkiness of the catalyst (Scheme 49).

![Scheme 49. 1,4-addition of chiral imidazolidinones to α,β-unsaturated aldehydes](image)

An important reaction based on iminium chemistry is the use of enals as Michael acceptors in the reaction with nitroalkanes as Michael donors, as a strategy to synthesise γ-nitro aldehyde compounds 217. For example the works of Hayashi et al. (Scheme 50) and Wang et al. that use diphenylprolinol silyl ether 103 as a catalyst and benzoic acid 191 as additive, or the work of Ye and Liang et al. using
LiOAc as additive, allow to obtain the final products with excellent enantioselectivities and good yields. This reaction was used in the enantioselective synthesis of the drug Baclofen 218.

Scheme 50. Hayashi’s Michael addition of nitroalkanes to α,β-unsaturated aldehydes

In the same year Jørgensen and co-workers\[106\] reported the first organocatalytic asymmetric addition of malonates 95 to aromatic α,β-unsaturated aldehydes 80. The products 219 were obtained in high yields and excellent enantioselectivities. Later on Liang, Ye and co-workers\[107\] found that the reaction proceed faster with the use of a base additive 262 (Scheme 51). This reaction is useful for the synthesis of the drugs (-)-Paroxetine and (-)-Femoxetine. Another enantioselective organocatalytic Michael addition applied for the synthesis of (-)-Paroxetine 147 was reported by Rios, Moyano, Vesely et al. through the addition of amidomalonates to α,β-unsaturated aldehydes (Scheme 35),\[72\]

Scheme 51. Asymmetric addition of malonates to aromatic α,β-unsaturated aldehydes
In 2009 Melchiorre and co-workers\textsuperscript{[108]} reported the first asymmetric conjugate addition of oxindoles 221 to α,β-unsaturated aldehydes 80 (Scheme 52). With the use of diarylprolinol, proline or MacMillan catalyst the product was obtained with good enantioselectivity but without diastereoselectivity. For this reason they developed a new bifunctional chiral thiourea catalyst 222 to increase the diastereoselectivity.

\begin{center}
\textbf{Scheme 52.} Melchiorre’s addition of oxindoles to α,β-unsaturated aldehydes
\end{center}

\begin{center}
\begin{align*}
\text{R}^1, \text{R}^2 &= \text{H, Me, Bn} \\
\text{R}^1, \text{R}^2 &= \text{H, Me, Bn} \\
\text{PhCOOH} 191 \text{ (50 mol\%)} &\text{ toluene, rt, 5 days} \\
\text{yield: 47-85% major dia} &\\
\text{dr: 7:1/19:1} &\\
\text{ee: 73-99%} &
\end{align*}
\end{center}

Jørgensen et al.\textsuperscript{[109]} reported the addition of oxazolones 224 to enals 80 obtaining the products 225 with moderate to good diastereoselectivity and excellent enantioselectivity (Scheme 53). Oxazolones are important reagents for the synthesis of chiral quaternary amino acids and their derivatives.

\begin{center}
\textbf{Scheme 53.} Jørgensen’s addition of oxazolones to enals
\end{center}

\begin{center}
\begin{align*}
\text{R}^1 &= \text{Ar, Me, Et, n-Pr} \\
\text{R}^2, \text{R}^3 &= \text{\textmu-Pr, Me, Ph, Bn, CH}_2\text{Ph} \\
\text{Ar} &= 3,5-(\text{CF}_3)_2\text{C}_6\text{H}_3 \\
\text{yield: 36-88\%} &\\
\text{dr: 1:1/20:1} &\\
\text{ee: 83-96\%} &
\end{align*}
\end{center}

Recent developments report the use of β-carbonyl heteroaryl sulfones as nucleophiles in the addition to enals. Jørgensen and co-workers\textsuperscript{[110]} reported the Michael addition of β-keto sulfones 226 to α,β-unsaturated aldehydes 80 catalysed by diphenylprolinol silylether 220, obtaining the final products 228 in good yields and excellent enantioselectivities (Scheme 54).
Scheme 54. Jørgensen’s addition of β-keto sulfones to α,β-unsaturated aldehydes
4.2 Project aim

The aim of the project is to develop an enantioselective synthesis of alkylazaarenes. In particular to study the activation of 2-alkylazaarenes as nucleophiles to a Michael addition with α,β-unsaturated aldehydes, through the application of the synergistic catalysis concept.

As stated in the introduction in Chapter 1, azaarenes are common structures in biologically active molecules such as pharmaceuticals, agrochemicals and natural products. In spite of their huge importance only few enantioselective methodologies for their synthesis have been developed so far. We have been inspired by Lam and co-workers\(^\text{[88]}\) that reported the addition of alkyl-azaarenes to nitrostyrenes catalysed by Pd-bisoxazoline complexes with excellent results (Scheme 42, Chapter 3).

We planned to activate the benzylic position of the alkyl-azaarenes (a) placing an EWG on the aromatic ring and (b) adding a metal Lewis acid that would work as a catalyst, by coordination with the nitrogen atom. Only the combination of these two strategies can decrease the pKa of the α protons in the methylene position, facilitating the deprotonation in the presence of a weak base, such as a tertiary amine. After the deprotonation, the formation of the enolate form, stabilised through conjugation thanks to the nitro group, would make the benzoxazole a suitable nucleophile.

In Figure 13 are schematised the strategies of activation of azaarenes that we planned to use in the project.

![Figure 13. Modes of activation of azaarenes](image)

Recently, our research group demonstrated the feasibility of this synergistic approach reporting the addition of alkylbenzoxazoles to MBH carbonates\(^\text{[70]}\) based on synergistic
approach in a diastereoselective fashion (Scheme 33 and Scheme 55). The benzoxazole 132 is activated with AgOAc 230 that acts as a metal Lewis acid while the MBH 139 is activated by DABCO 138 and the final products 231 are obtained with good to excellent yields, completely diastereoselective.

Scheme 55. Highly diastereoselective benzoxazole addition to Morita-Baylis-Hillman carbonates
4.3 Research hypothesis and proposed mechanism

In Scheme 56 is presented the proposed mechanism for the reaction described in the project aim.

As is shown in Scheme 56, we envisioned that the metal Lewis acid could interact with the alkyl benoxazole 132a coordinating to the nitrogen and increasing the acidity of the α-carbon hydrogens 232. After treatment with the base, it forms a suitable nucleophile 233 that can react with the electrophile 236. The enal 80b reacts with the secondary amine of the organic catalyst 103 to form the activated iminium species 236. The catalyst efficiently shields one face of the enal, so the benoxazole is mostly
forced to attack the opposite face. The activated benzoxazole attacks the β position of the aldehyde and releases the metal catalyst. After the addition took place, hydrolysis of the compound 234 leads to the product 235a and releases the organic catalyst.

We studied the addition reaction between alkyl-benzoxazoles and enals as presented in section 4.2. To our delight the reaction between 132a and 80b rendered the final compound 235a by using a mixed activation of the azaarene via Lewis acid metal coordination catalysis and the activation of the enal using an organocatalyst (Scheme 57). The product 235a was obtained in low yield and selectivity and the reaction was difficult to reproduce in the same conditions.

As this reaction is difficult to monitor and follow by TLC, due to spots overlapping, we checked the reaction by the NMR of the crude. The first reaction was performed in deuterated chloroform in order to easily check the crude by NMR and follow the progress of the reaction. From the integration of the aldehyde signals it is possible to observe the formation of the final product and calculate the reaction conversion. In fact the signal of the starting aldehyde is a doublet while the signal of the final product is a characteristic triplet with a small coupling constant.

Scheme 57. First reaction tested
4.4 Results and discussions

4.4.1 Synthesis of the starting materials

4.4.1.1 Synthesis of the benzoxazoles

Most of the azaarenes were synthesised following the procedure reported in the article of Lam and co-workers\cite{88} as shown in Scheme 58.

Scheme 58. Synthesis of the benzoxazoles as starting materials

![Scheme 58](image)

The mechanism of the reaction between an aminoalcohol 237 and triethoxyalkane 238 is depicted in Scheme 59.

Scheme 59. Mechanism of benzoxazoles’ synthesis from triethoxyalkane

![Scheme 59](image)

The mechanism starts with the attack of the amine to the triethoxyalkane with the elimination of EtOH. Then the reaction can follow two pathways: (a) elimination of ethanol and formation of the iminoether 240 followed by the nucleophilic attack of the phenolic OH with elimination of another molecule of EtOH; (b) nucleophilic attack of

\footnote{The azaarenes 132 and aldehydes 80 were synthesised by me, India Willans and Michael Potter, project students that I supervised, and azaarenes 132h and 132j by Victor Ceban.}
the OH with elimination of EtOH 242, followed by a second elimination of EtO⁻ and formation of the double bond.

The results obtained in the synthesis of the starting benoxazoles are presented in Figure 14, with isolated yields ranging from 73 to 95%.

![Figure 14](image1.png)

**Figure 14.** Results obtained in the synthesis of benoxazoles with triethoxyalkanes

Benoxazoles 132i and 132j are synthesised according to the route reported in Scheme 60.

![Scheme 60](image2.png)

**Scheme 60.** Mechanism of benoxazoles’ synthesis from acids

The acid 243 reacts with PPA (polyphosphoric acid) 244 forming a mixed anhydride 245 that reacts with 2-amino-5-nitrophenol 237a to give the corresponding amide 246. This
intermediate cyclises with elimination of water to render the desired benzoxazole 132. The results are presented in Figure 15.

![Figure 15. Results obtained in the synthesis of benzoxazoles with acid](image)

### 4.4.1.2 Synthesis of the aldehydes

Cinnamaldehyde 80b and crotonaldehyde 80a are commercially available, while the other α,β-unsaturated aldehydes were synthesised. This was achieved through a Wittig reaction leading to the $E$ form of the aldehydes (Scheme 61).

![Scheme 61. General scheme of the synthesis of starting aldehydes](image)

The mechanism of the reaction is presented in Scheme 62: the first step is the attack of the carbonyl group of the benzaldehye 63 by the carbanion of the phosphonium ilyde 251. Then the negatively charged oxygen attacks the positively charged phosphorous, forming a four-membered ring oxaphosphetane intermediate 252. This intermediate goes through an elimination reaction, rendering the alkene 80 and the phosphine oxide 267 as products.
The Wittig reaction is stereoselective and all the aldehydes were obtained in the \( E \) form and this depends from the nature of the substituent on the carbon atom of the ylide. The (triphenylphosphoranyldiene)acetaldehyde 251 is an ylide stabilised through conjugation thanks to the carbonyl group substituent: an \( E \)-selectivity is observed when a stabilised ylide is used in the Wittig reaction (Scheme 63). The stereochemistry is determined by the intermediate oxaphosphetane 253 that, in the case of stabilised ylides, is \( \text{anti} \). The reason is that the stabilised ylide is less reactive and more stable and makes the formation of the oxaphosphetane reversible. The \( \text{anti} \)-oxaphosphetane is the more thermodynamically stable diastereomer due to the bulkier substituents being on the opposite side of the four-member ring.

Scheme 63. Rationalisation of the formation of \( E \)-alkene with stabilised ylides

The results obtained in the synthesis of the starting aldehydes are presented in Table 1, with yields ranging from 50 to 72%.
Table 1. Results obtained in the synthesis of enals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Number</th>
<th>R</th>
<th>Yield(^{[a]}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80c</td>
<td>2-Br</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>80d</td>
<td>3-Br</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>80e</td>
<td>4-Cl</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>80f</td>
<td>3-Cl</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>80g</td>
<td>4-CN</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>80h</td>
<td>4-Br</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>80i</td>
<td>4-NO(_2)</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>80j</td>
<td>4-F</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>80k</td>
<td>4-Me</td>
<td>65</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Yields are of pure isolated products

Then, to be able to avoid the epimerisation of the final product 235a, we synthesised a disubstituted enal 258, following the procedure reported in literature\(^{[11]}\) as depicted in Scheme 64. The first step is a Wittig reaction, followed by reduction of the ester 256 to alcohol 257 with di-isobutyl aluminium hydride and finally the oxidation of the alcohol to aldehyde by manganese dioxide. A mixture of \(E\) and \(Z\) aldehydes was obtained, but this is not an issue because the iminium intermediate formed between the aldehyde and the organic catalyst is more stable as the \(trans\) isomer, so that all the activated aldehydes will be in the \(E\) form.
Scheme 64. Synthesis of disubstituted aldehyde in β position
4.4.2 Optimisation of the reaction conditions

Interested by the result obtained, we worked on the optimisation of the reaction screening different solvents, metal Lewis acids, bases and organocatalysts.

4.4.2.1 Derivatisation

As the product 235a is not stable (degradation occurred after 48 hours even if it is kept in the fridge) we decided to derivatise it. Moreover the aldehyde is not stable even in the HPLC columns. For these reasons, we needed a derivatisation reaction that was possible to apply directly on the crude reaction mixture. The first reaction tried was a reduction of the aldehyde to alcohol. Only traces of the desired product were obtained, plus a mixture of by-products comprising the reduced form of the nitro group: this is due to the presence of Pd(OAc)$_2$ in the reaction mixture. The Wittig reaction suited well for our purpose: it is easy to perform on the crude product of the Michael addition step, after solvent evaporation, by adding DCM and methyl (triphenylphosphoranylidene)acetate 255 (Scheme 65). After 48 hours the product 235a is completely converted in the product 259a in quantitative yield.

Scheme 65. Wittig derivatisation

4.4.2.2 Screening of solvents

Table 2 collects the results obtained from the screening of solvents. The reaction was performed using 50 mol% of trimethylamine 260, 20 mol% of the organic Jorgensen-Hayashi catalyst 103 and employing Pd(OAc)$_2$ 164 as the Lewis acid catalyst in 20 mol% or 10 mol% equivalents. Entries 1 to 8 were performed to check the conversion and dr on the crude NMR, without purification of the product 235a. All the reactions were carried out at 45 °C.
Table 2. Screening of solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>dr (^{[a]})</th>
<th>(ee) dia1 % (^{[b]})</th>
<th>(ee) dia2 % (^{[b]})</th>
<th>Conversion % (24 h) (^{[a]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>Pd(OAc)(_2) 20%</td>
<td>EtOAc</td>
<td>1.2:1</td>
<td>---</td>
<td>---</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>Pd(OAc)(_2) 20%</td>
<td>DMF</td>
<td>1:1</td>
<td>---</td>
<td>---</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>Pd(OAc)(_2) 20%</td>
<td>1,4-dioxane</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>No conversion</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>Pd(OAc)(_2) 20%</td>
<td>DMSO</td>
<td>1:1</td>
<td>---</td>
<td>---</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>Pd(OAc)(_2) 20%</td>
<td>CHCl(_3)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>No conversion</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>Pd(OAc)(_2) 20%</td>
<td>toluene</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>No conversion</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>Pd(OAc)(_2) 20%</td>
<td>CH(_3)CN</td>
<td>1:1</td>
<td>nd</td>
<td>nd</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>Pd(OAc)(_2) 20%</td>
<td>THF</td>
<td>1:1</td>
<td>nd</td>
<td>nd</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>Pd(OAc)(_2) 10%</td>
<td>EtOAc</td>
<td>2:1</td>
<td>53</td>
<td>47</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>Pd(OAc)(_2) 10%</td>
<td>DMF</td>
<td>1.2:1</td>
<td>rac</td>
<td>rac</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>Pd(OAc)(_2) 10%</td>
<td>DMSO</td>
<td>1.2:1</td>
<td>rac</td>
<td>rac</td>
<td>72</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>Pd(OAc)(_2) 10%</td>
<td>CH(_3)CN</td>
<td>1.3:1</td>
<td>rac</td>
<td>rac</td>
<td>85</td>
</tr>
<tr>
<td>13</td>
<td>40</td>
<td>Pd(OAc)(_2) 10%</td>
<td>THF</td>
<td>1.4:1</td>
<td>rac</td>
<td>rac</td>
<td>74</td>
</tr>
<tr>
<td>14</td>
<td>40</td>
<td>Pd(OAc)(_2) 10%</td>
<td>DCM</td>
<td>1.3:1</td>
<td>5</td>
<td>6</td>
<td>70 (20h)</td>
</tr>
</tbody>
</table>
The results show that there was no conversion in CHCl₃, dioxane and toluene (Table 2, entries 3, 5 and 6). The reaction in EtOAc, DMF, DMSO, CH₃CN (Table 2, entries 1, 2, 4 and 7) had a good conversion after 24 hours but the reactions in DMF, DMSO and CH₃CN at 45 °C gave only by-products due to the degradation of the starting materials. The reaction in THF (Table 2, entry 8) had a low conversion. From these first 8 entries, EtOAc seemed to be the best solvent giving a slightly better diastereoselectivity of 2:1 compared to the 1:1 of the other solvents tested.

Then we checked the enantioselectivity of the derivatised product 259a. The reactions were performed at 40 °C (Table 2, entries 9-14). The reactions in DMF, DMSO, CH₃CN, THF and DCM after 24 hours presented a good conversion, between 67% and 85% (Table 2, entries 10-14) but low diastereoselectivity (less than 2:1) and low ee (racemics or lower than 10%). With EtOAc (Table 2, entry 9) the reaction has a dr of 2:1 and an ee of 53% and 47%. EtOAc seemed to be the only solvent that, in these conditions, gave low diastereoselectivity and moderate enantioselectivity. We tried the reaction in CH₃CN at 50 °C (Table 2, entry 15) but it only rendered degradation products after 24 hours. We believe that the reaction is temperature sensitive: at room temperature the conversion is low but at temperatures higher than 45 °C only the degradation of the starting materials was observed.
4.4.2.3  Screening of metal Lewis acids

We proceeded in the optimisation by screening different metal Lewis acids as listed in Table 3.

Table 3. Screening of metals

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Metal catalysts</th>
<th>Base</th>
<th>Solvent</th>
<th>dr</th>
<th>ee dia1</th>
<th>ee dia2</th>
<th>Conversion % (20 h) [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>(CF₃SO₃)₂Cu (II) 20% 261</td>
<td>TEA 50%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>(CF₃SO₃)₃Yb (III) 20% 176</td>
<td>TEA 50%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>no conversion</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>CuCl₂ (II) 20% 263</td>
<td>TEA 50%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>Cu(OAc)₂ (II) 20% 264</td>
<td>TEA 50%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>no conversion</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>CH₃COOAg 20% 130</td>
<td>TEA 50%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>PdCl₂ (II) 20% 266</td>
<td>TEA 50%</td>
<td>EtOAc</td>
<td>1:1</td>
<td>22</td>
<td>13</td>
<td>9 (45 after 4 days)</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>Co/Ti 20 % 265</td>
<td>TEA 50%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>degradation</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>Ni(OAc)₂*4H₂O (III) 5% 184</td>
<td>TEA 10%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>traces</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>K₂PdCl₄ (II) 5% 268</td>
<td>TEA 10%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>no conversion</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>K₂PtCl₆ (II) 5% 269</td>
<td>TEA 10%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>no conversion</td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>HAuCl₄ * H₂O (III) 5% 270</td>
<td>TEA 10%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>no conversion</td>
</tr>
<tr>
<td>Entry</td>
<td>T (°C)</td>
<td>Metal catalysts</td>
<td>Base</td>
<td>Solvent</td>
<td>dr [a]</td>
<td>ee dia1 % [b]</td>
<td>ee dia2 % [b]</td>
<td>Conversion % (20 h) [a]</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>-----------------</td>
<td>----------</td>
<td>---------</td>
<td>--------</td>
<td>--------------</td>
<td>--------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>AgOAc 10% 230</td>
<td>TEA 5%</td>
<td>toluene</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>no conversion</td>
</tr>
<tr>
<td>13</td>
<td>35</td>
<td>AgOAc 5% 230, Pd(OAc)$_2$ 5% 164</td>
<td>TEA 50%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>degradation</td>
</tr>
</tbody>
</table>

[a] dr and conversions are calculated from the crude NMR comparing the aldehydes signals of 80b and 235a
[b] ee are calculated on product 259a through HPLC analysis (column IE; 90:10 hexane:IPA; 1 ml/min; 230 nm)

As presented in the table above, most of the metals tested did not give any conversion at all (Table 3, entries 2, 4, 9, 10, 11, 12 and 13) or gave only degradation products (Table 3, entries 7 and 13). With some of the metals, the crude NMR showed traces of the desired aldehydes (Table 3, entries 1, 3, 5 and 8) after 20 hours. Prolonged reaction time did not lead to conversion improvement. The only metal Lewis acid that showed an improved conversion after 4 days was PdCl$_2$ 266 (Table 3, entry 6). The dr and the ee were not good, as we mainly obtained racemic products. From those results the only Lewis acid that gave acceptable conversions and enantioselectivity is Pd(OAc)$_2$ 164 (Table 2, entry 9).

4.4.2.4 Screening of different loading of Pd(OAc)$_2$

The subsequent step was to screen different loading of Pd(OAc)$_2$ 164 as reported in Table 4. The reactions were performed using 20 mol% of the organic catalyst 103, 50 mol% of triethylamine 260 as the base and EtOAc as the solvent at 40 °C.
The reaction requires the presence of Pd(OAc)$_2$ as it did not give any conversion without the presence of the Lewis acid (Table 4, entry 1). The reaction worked well with 5 mol% as well as with 1 mol% of the catalyst (Table 4, entries 2 and 3). This is the demonstration that the synergistic catalysis is necessary to make the reaction work. The reaction with 1 mol% of metal catalyst is however too slow, an acceptable conversion is reached only after 7 days. The best loading of Pd(OAc)$_2$ resulted to be 5 mol%, as it gave a comparable enantioselectivity as using 10 mol% of it (Table 5, entry 5), but producing less metal waste.
4.4.2.5 Screening of bases and of different loading of base

We also tested different bases and different loading of them as shown in Table 5.

**Table 5. Screening of bases**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Organic catalyst 20% (R)</th>
<th>Metal</th>
<th>Base</th>
<th>Solvent</th>
<th>$d_r^{[a]}$</th>
<th>ee dia1 % [b]</th>
<th>ee dia2 % [b]</th>
<th>Conversion % [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMS</td>
<td>Pd(OAc)$_2$ 10%</td>
<td>quinine 64 10%</td>
<td>EtOAc</td>
<td>---</td>
<td>----</td>
<td>----</td>
<td>No conversion</td>
</tr>
<tr>
<td>2</td>
<td>TMS</td>
<td>Pd(OAc)$_2$ 10%</td>
<td>quinidine 65 10%</td>
<td>EtOAc</td>
<td>---</td>
<td>----</td>
<td>----</td>
<td>No conversion</td>
</tr>
<tr>
<td>3</td>
<td>TMS</td>
<td>Pd(OAc)$_2$ 10%</td>
<td>DIPEA 28 50% 10%</td>
<td>EtOAc</td>
<td>2:1</td>
<td>43</td>
<td>54</td>
<td>75 (46 h)</td>
</tr>
<tr>
<td>4</td>
<td>TMS</td>
<td>Pd(OAc)$_2$ 20%</td>
<td>DABCO 138 50% 10%</td>
<td>DCM</td>
<td>---</td>
<td>----</td>
<td>----</td>
<td>No conversion</td>
</tr>
<tr>
<td>5</td>
<td>TMS</td>
<td>Pd(OAc)$_2$ 10%</td>
<td>TEA 260 20%</td>
<td>EtOAc</td>
<td>1.5:1</td>
<td>26</td>
<td>---</td>
<td>75 (42 h)</td>
</tr>
<tr>
<td>6</td>
<td>TMS</td>
<td>Pd(OAc)$_2$ 10%</td>
<td>TEA 260 10%</td>
<td>EtOAc</td>
<td>1.2:1</td>
<td>41</td>
<td>21</td>
<td>55 (42 h)</td>
</tr>
<tr>
<td>7</td>
<td>TMS</td>
<td>Pd(OAc)$_2$ 10%</td>
<td>TEA 260 5%</td>
<td>EtOAc</td>
<td>1.2:1</td>
<td>38</td>
<td>19</td>
<td>63 (42 h)</td>
</tr>
<tr>
<td>8[c]</td>
<td>TBDMS 271</td>
<td>Pd(OAc)$_2$ 10%</td>
<td>---</td>
<td>CH$_3$CN</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>No conversion</td>
</tr>
</tbody>
</table>
The reaction did not work with quinine 64, quinidine 65 and DABCO 138 (Table 5, entries 1, 2 and 4) probably because they can chelate the metal catalyst. The reaction worked well using DIPEA 28 (Table 5, entry 3) and it gave a slightly better dr and ee compared to the reaction performed using the same amount of TEA 260 (Table 5, entry 6). The reaction gave a worse enantioselectivity using 20 mol% or only 5 mol% of TEA (Table 5, entries 5 and 7). The reaction does not work in the absence of the base (Table 5, entry 8).

4.4.2.6 Synthesis of organic catalysts

As the enantioselectivities obtained with the commercial Jorgensen-Hayashi catalyst were not excellent, we decided to synthesise more bulky catalysts starting from the commercial (S)-diphenyl(pyrrolidin-2-yl)methanol by reaction with triflates or chloro silanes to obtain the derivatised products 189, 271, 273, following the procedures reported in literature (Scheme 66).[112]
Scheme 66. Synthesis of the organic catalysts
4.4.2.7 Screening of organic catalyst and temperature

Then we tested different organic catalysts and different conditions as shown in Table 6.

**Table 6. Screening of organic catalysts and temperature**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ald. (eq)</th>
<th>T (°C)</th>
<th>Organic catalyst 20% (R²)</th>
<th>Pd(OAc)₂</th>
<th>Base/Acid</th>
<th>Solv</th>
<th>dr[a]</th>
<th>ee dia1 % [b]</th>
<th>ee dia2 % [b]</th>
<th>Conversion % [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>45</td>
<td>pyrrolidine 274</td>
<td>20</td>
<td>TEA 50%</td>
<td>DCM</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>no conversion</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>rt-40</td>
<td>TMS 103</td>
<td>---</td>
<td>PhCO₂H</td>
<td>DMSO</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>traces after adding base</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>45</td>
<td>TMS (CF₃) 220</td>
<td>5</td>
<td>TEA 5%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>no conversion</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>45</td>
<td>TES 189</td>
<td>5</td>
<td>TEA 5%</td>
<td>EtOAc</td>
<td>1.2:1</td>
<td>61</td>
<td>19</td>
<td>80 (4 days)</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>25</td>
<td>TMS 103</td>
<td>5</td>
<td>TEA 5%</td>
<td>EtOAc</td>
<td>1.8:1</td>
<td>71</td>
<td>61</td>
<td>17 (24 h) / 87 (4 days)</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>50</td>
<td>TMS 103</td>
<td>5</td>
<td>TEA 5%</td>
<td>EtOAc</td>
<td>1.1:1</td>
<td>35</td>
<td>10</td>
<td>61 (24 h)</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>45</td>
<td>TBDMS</td>
<td>5</td>
<td>TEA 5%</td>
<td>EtOAc</td>
<td>1.2:1</td>
<td>9</td>
<td>1</td>
<td>66 (4 days)</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>25</td>
<td>TES 189</td>
<td>5</td>
<td>TEA 10%</td>
<td>EtOAc</td>
<td>1.6:1</td>
<td>86</td>
<td>50</td>
<td>51 (3 days)</td>
</tr>
<tr>
<td>Entry</td>
<td>Ald. (eq)</td>
<td>T (°C)</td>
<td>Organic catalyst 20% (R²)</td>
<td>Pd(OAc)$_2$ %</td>
<td>Base/Acid</td>
<td>Solv</td>
<td>dr[a]</td>
<td>ee dia1 % [b]</td>
<td>ee dia2 % [b]</td>
<td>Conversion % [a]</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>--------</td>
<td>---------------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>------</td>
<td>--------</td>
<td>---------------</td>
<td>---------------</td>
<td>----------------</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>25</td>
<td>TBDMS 271</td>
<td>5</td>
<td>TEA 10%</td>
<td>EtOAc</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>no conversion</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>25</td>
<td>trihexylsilyl 273</td>
<td>5</td>
<td>TEA 10%</td>
<td>EtOAc</td>
<td>1:1</td>
<td>44</td>
<td>4</td>
<td>70 (5days)</td>
</tr>
<tr>
<td>11</td>
<td>1.5</td>
<td>25</td>
<td>TES 189</td>
<td>5</td>
<td>DIPEA 50%</td>
<td>DCM</td>
<td>1.5:1</td>
<td>82</td>
<td>55</td>
<td>66 (3 days)</td>
</tr>
<tr>
<td>12</td>
<td>1.5</td>
<td>25</td>
<td>TES 189</td>
<td>5</td>
<td>DIPEA 50%</td>
<td>EtOAc</td>
<td>1.3:1</td>
<td>77</td>
<td>42</td>
<td>81 (3 days)</td>
</tr>
<tr>
<td>13</td>
<td>1.5</td>
<td>25</td>
<td>TES 189</td>
<td>5</td>
<td>DIPEA 50%</td>
<td>EtOAc</td>
<td>1.2:1</td>
<td>26</td>
<td>14</td>
<td>71 (7 days)</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>25</td>
<td>TBDMS 271</td>
<td>5</td>
<td>DIPEA 50%</td>
<td>CN$_3$CN</td>
<td>1.3:1</td>
<td>88</td>
<td>68</td>
<td>45 (1 day)</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>25</td>
<td>TES 189</td>
<td>5</td>
<td>DIPEA 50%</td>
<td>EtOAc</td>
<td>1.2:1</td>
<td>26</td>
<td>14</td>
<td>&gt;71 (7 days)</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>4</td>
<td>TBDMS 271</td>
<td>5</td>
<td>TEA 50%</td>
<td>CH$_3$CN</td>
<td>1:1</td>
<td>68</td>
<td>26</td>
<td>&gt;70 (6 days)</td>
</tr>
<tr>
<td>17</td>
<td>2</td>
<td>30</td>
<td>TBDMS 271</td>
<td>5</td>
<td>TEA 50%</td>
<td>CH$_3$CN</td>
<td>1.3:1</td>
<td>88</td>
<td>68</td>
<td>full (40 h)</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>30</td>
<td>---</td>
<td>5</td>
<td>TEA 50%</td>
<td>CH$_3$CN</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>complex mixtures</td>
</tr>
</tbody>
</table>

[a] dr and conversions are calculated from the crude NMR comparing the aldehydes signals of 80b and 235a
[b] ee are calculated on product 259a through HPLC analysis (column IE; 90:10 hexane:IPA; 1 ml/min; 230 nm)

When we performed the reaction using pyrrolidine 274, as the organic catalyst, in order to obtain more easily the racemic compound, the NMR of the crude showed no conversion (Table 6, entry 1). To prove the need of the synergistic catalysis activation, we tested the reaction in the same conditions reported by Wei Wang’s and co-workers, where they presented an addition of α,β-unsaturated aldehydes to dinitrotoluene and to nitropyridines. In this case we did not use Pd(OAc)$_2$ and instead of the base we used benzoic acid according to Wang’s conditions (Table 6, entry 2). The NMR of the crude showed traces of conversion only after the addition of TEA.
Then we tested the reaction using different organic catalysts: the reaction with the commercial catalyst \((R)-\alpha,\alpha\text{-bis}[3,5\text{-bis(trifluoromethyl)phenyl}]\text{-2-pyrrolidinemethanol trimethylsilyl ether 220 (Table 6, entry 3)}\) did not work and no conversion was observed in the NMR of the crude. Among the three catalysts synthesised, the \((R)-2-((\text{trihexylsilyl})\text{oxy})\text{pyrrolidine 273 gave low selectivities (Table 6, entry 10)}\) and \((S)-2-((\text{tert-butyl}dime\text{thylsilyl})\text{oxy})\text{diphenylmethyl} \text{pyrrolidine 271 in EtOAc did not show any conversion at 25 °C (Table 6, entry 9). With the cataysts 271 the reaction worked only by heating at 45 °C (Table 6, entry 7). The reaction worked well with the (S)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine 189 especially at room temperature (Table 6, entries 4, 8 and 15). These results confirmed the fact that the reaction is temperature sensitive: with higher temperatures the reaction proceeds faster but the enantioselectivity decreases. The same reduction of enantioselectivity occurs with longer reaction times (Table 6, entry 12 and 13). When the reaction was left stirring for more than 7 days an epimerisation and degradation of the final compound occurred. We tested again the reaction in DCM and it showed good results since the reaction was faster and less epimerisation occurred (Table 6, entry 11). Then we tested again the reaction with OTBDMS the bulkiest catalyst that, in theory, should give the best enantioselectivity. We used CH\(_3\)CN as the solvent, as it showed the best conversion in this reaction (Table 2, entries 7 and 12) and we obtained good enantioselectivities (Table 6, entry 14). The next reactions were performed using TEA 260, the base that gave the fastest reaction as we need a good ee but also an acceptable conversion and yield in a short period of time to prevent further epimerisation. The reaction was also tested at 4 °C but, since it took 6 days to give an acceptable conversion, the enantioselectivities obtained were lower (Table 6, entry 16). When the reaction was tested without the organic catalyst (Table 6, entry 18) a complex mixtures was seen in the NMR of the crude, confirming in this way the synergistic aspect of the reaction.

After this extensive screening, in our hands, the best conditions are the use of CH\(_3\)CN as the solvent, at 30-35 °C, 20 mol% of amine organocatalyst, 5 mol% of Pd(OAc)\(_2\) 164 and 50 mol% of Et\(_3\)N 260. TBDMS 271 derivative is the secondary amine that gives the best stereoselectivities (Table 6, entry 17).
We also tested two ligands for Pd(OAc)$_2$, phenantroline and 2,2-bipyridyl, in order to better solubilise the metal catalyst. The crude NMR of the first reaction showed only traces of conversion while with 2,2-bipyridyl we had 60% of conversion only after 10 days.

The current reaction presents some drawbacks. The reaction time becomes crucial, higher reaction times result in lower enantioselectivities: this data induces us to think that there is an epimerisation process that led to racemic mixtures. Good enantioselectivities can be obtained only if the reaction is stopped after a maximum of 40 hours by adding the Wittig reagent. Temperature also has a pivotal importance: in order to speed up the reaction, heating is required; however, high temperatures render low enantioselectivities.

4.4.3 Scope of the reaction with enals

Once we optimised the reaction, we decided to investigate the scope of the reaction in terms of the enals.
Scheme 67. Scope of the reaction with several enals. a) DIPEA as the base; b) reaction conducted at 30 °C; c) 189 as the catalyst; d) 103 as the catalyst.

Some more information are reported in the Table 7.
### Table 7. Scope of the reaction with several enals

<table>
<thead>
<tr>
<th>Number</th>
<th>Organic Catalyst (R&lt;sup&gt;3&lt;/sup&gt;)</th>
<th>T (°C)</th>
<th>Yield [%]&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>ee dia 1 [%]&lt;sup&gt;[c]&lt;/sup&gt;</th>
<th>ee dia 2 [%]&lt;sup&gt;[c]&lt;/sup&gt;</th>
<th>Time before Wittig</th>
</tr>
</thead>
<tbody>
<tr>
<td>259a</td>
<td>TBDMS 271</td>
<td>30</td>
<td>84</td>
<td>1.3:1</td>
<td>88</td>
<td>68</td>
<td>24 h</td>
</tr>
<tr>
<td>259e</td>
<td>TBDMS 271</td>
<td>30</td>
<td>79</td>
<td>1.5:1</td>
<td>73</td>
<td>99</td>
<td>40 h</td>
</tr>
<tr>
<td>259f</td>
<td>TBDMS 271</td>
<td>30</td>
<td>96</td>
<td>1.4:1</td>
<td>27</td>
<td>19</td>
<td>2 days</td>
</tr>
<tr>
<td>259f</td>
<td>TES 189</td>
<td>30</td>
<td>60</td>
<td>1.4:1</td>
<td>78</td>
<td>67</td>
<td>24 h</td>
</tr>
<tr>
<td>259b</td>
<td>TBDMS 271</td>
<td>30</td>
<td>69</td>
<td>1.3:1</td>
<td>85</td>
<td>54</td>
<td>2 days</td>
</tr>
<tr>
<td>259c</td>
<td>TBDMS 271</td>
<td>35</td>
<td>81</td>
<td>1.1:1</td>
<td>86</td>
<td>99</td>
<td>40 h</td>
</tr>
<tr>
<td>259d</td>
<td>TBDMS 271</td>
<td>35</td>
<td>87</td>
<td>1.3:1</td>
<td>64</td>
<td>99</td>
<td>24 h</td>
</tr>
<tr>
<td>259h</td>
<td>TBDMS 271</td>
<td>35</td>
<td>69</td>
<td>1.6:1</td>
<td>84</td>
<td>53</td>
<td>24 h</td>
</tr>
<tr>
<td>259g</td>
<td>TBDMS 271</td>
<td>35</td>
<td>59</td>
<td>1.3:1</td>
<td>71</td>
<td>75</td>
<td>40 h</td>
</tr>
</tbody>
</table>

[a] Yields are of pure isolated diastereomers  
[b] dr are calculated from the crude NMR comparing the aldehydes signals  
[c] ee were determined by chiral HPLC analysis

As it is shown in Table 7 and Scheme 67, the reaction gave the final products in good yields and enantioselectivities when different aromatic enals were used. However in almost all the examples the diastereoselectivity of the reaction is very low. This could be explained by the epimerisation of the final adduct at the carbon in the α position of the azaarene, due to its high acidity in the reaction conditions. The best results were obtained with the 4-halogen substituted cinnamaldehydes, for example the fluoro derivative 259c was obtained in 81% yield 1.5:1 dr and in 86% and 99% ee. Compounds 259e and 259d (4-Br and 4-Cl derivatives respectively) were afforded in similar yields and stereoselectivities. Electron withdrawing groups in the aromatic ring gave lower enantioselectivities (259f and 259g). The reaction with the halogen in the ortho position of the aromatic ring of the aldehyde was faster and it gave good yield and enantioselectivity (259h). However the reaction with the halogen in the meta position
of the aromatic ring of the aldehyde did not work, the NMR of the crude showed only traces of the final product (259i).

As already stated before, for longer reaction times, the enantioselectivity of the final adducts dropped dramatically as shown in Table 7, entry 2 compared to Table 7, entry 3. This data suggests an epimerisation in the β-position of the aldehyde in the reaction conditions and could explain the low enantioselectivity in the compounds 259f and 259g as the electron withdrawing groups favour the epimerisation.

The epimerisation observed at longer reaction times is one of the most important challenges that we face in this reaction: in order to explain this phenomenon we propose that there is the formation of a Pd enolate with the enamine intermediate 274 that equilibrates through a β-elimination and an H insertion 275 (Scheme 68).

Scheme 68. Explanation of the epimerisation at the β-position

To avoid the epimerisation, we tested the reaction with (E)-3-phenylbut-2-enal an α,β-unsaturated aldehyde, disubstituted at the β position (Scheme 64, 258). Unfortunately this reaction did not work, most likely because of the steric hindrance.

We also expanded the scope of the reaction with aliphatic aldehydes as shown in Scheme 69, but they only rendered complex mixtures due to the aldehyde’s decomposition probably by polymerisation through a dienamine process.
4.4.4 **Scope of the reaction with azaarenes**

Then we proceeded to expand the scope of the reaction testing different azaarenes as presented in
Table 8 and Scheme 70.

Scheme 70. Scope of the reaction with different benzoxazoles and pyridines. a) TMS catalyst 103 used; b) TES catalyst 189 used; c) the reaction was performed at 45 °C

More information are reported in the
Table 8.
Table 8. Scope of the reaction with different benzoxazoles and pyridines

<table>
<thead>
<tr>
<th>Entry</th>
<th>number</th>
<th>T (°C)</th>
<th>R</th>
<th>organic cat</th>
<th>Yield [%] [a]</th>
<th>$dr^{[b]}$</th>
<th>ee dia1 [%] [c]</th>
<th>ee dia2 [%] [c]</th>
<th>Time before Wittig</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>276a</td>
<td>35</td>
<td>4-Br 80h</td>
<td>TBDMS 271</td>
<td>99</td>
<td>2.7:1</td>
<td>99</td>
<td>56</td>
<td>24 h</td>
</tr>
<tr>
<td>2</td>
<td>276f</td>
<td>45</td>
<td>4-Br 80h</td>
<td>TMS 103</td>
<td>39</td>
<td>1.4:1</td>
<td>29</td>
<td>24</td>
<td>5 days</td>
</tr>
<tr>
<td>3</td>
<td>276d</td>
<td>35</td>
<td>4-Br 80h</td>
<td>TBDMS 271</td>
<td>87</td>
<td>2:1</td>
<td>90</td>
<td>49</td>
<td>40 h</td>
</tr>
<tr>
<td>4</td>
<td>276e</td>
<td>30</td>
<td>H 80b</td>
<td>TMS 103</td>
<td>36/56</td>
<td>---</td>
<td>49</td>
<td>---</td>
<td>48 h</td>
</tr>
<tr>
<td>5</td>
<td>276b</td>
<td>35</td>
<td>H 80b</td>
<td>TBDMS 271</td>
<td>42</td>
<td>1.5:1</td>
<td>12</td>
<td>rac</td>
<td>10 days</td>
</tr>
<tr>
<td>6</td>
<td>276c</td>
<td>35</td>
<td>4-Br 80h</td>
<td>TBDMS 271</td>
<td>36</td>
<td>1:1</td>
<td>77</td>
<td>20</td>
<td>72 h</td>
</tr>
<tr>
<td>7</td>
<td>276h</td>
<td>35</td>
<td>4-Cl 80e</td>
<td>TES 189</td>
<td>59</td>
<td>---</td>
<td>78</td>
<td>---</td>
<td>24 h</td>
</tr>
<tr>
<td>8</td>
<td>276g</td>
<td>35</td>
<td>4-F 80j</td>
<td>TES 189</td>
<td>68/52</td>
<td>---</td>
<td>89</td>
<td>---</td>
<td>24 h</td>
</tr>
</tbody>
</table>

[a] Yields are of pure isolated diastereomers  
[b] $dr$ are calculated from the crude NMR comparing the aldehydes signals  
[c] $ee$ were determined by chiral HPLC analysis on the product isolated from flash column chromatography

To generate more complex scaffold that can be further derivatised, we tested a benzoxazole bearing a nitro group and a chlorine as substituents on the aromatic ring (276a); the product was obtained with excellent yields and enantioselectivities in the major diastereomer and good diastereoselectivities. Then we investigated the effect of the substituents on the alkyl chain of the benzoxazole. Larger substituents (n-butyl, 276d) can be used and render the final product in good yield and $ee$ and moderate $dr$, while smaller substituents (Me, 276e) made the reaction slower when the bulky catalyst (S)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine 271 was used, therefore the catalyst 103 was used. Next, we tested two benzoxazoles with the nitro group in positions 5 or 4 and both products 276b and 276c were obtained in moderate yields and with moderate to low stereoselectivity. These not so good results can be attributed to the steric effect of the nitro group that cause difficulty in the coordination of the Pd to the nitrogen atom of the benzoxazole ring. The reaction with
the enal and the 2-ethyloxazolo[4,5]pyridine gave the final product 276f in moderate yields and selectivities. The reaction also works with 4-methyl pyridine, with the final products 276g and 276h obtained in moderate yields and good ee. In the case of the pyridines, the catalyst (R)-2-((trihexylsilyl)oxy)pyrrolidine 189 was used.

The following benzoxazoles (Figure 16) did not undergo any conversion or, in the case of 2-isopropyl-6-nitrobenzoxazole 132i, only traces of product were observed. As 132i did not work, it is not surprising that also 2-(difluoromethyl)-6-nitrobenzoxazole 132j did not work. In fact a fluorine atom stabilises a carbocation in the α position by resonance effect but it destabilises a carbocation in the β position. On the contrary, a fluorine atom stabilises a β carbanion, by the inductive effect, and destabilises an α carbanion. Although α-F could, in theory, stabilise by the inductive effect, its opposing electron-pair repulsion predominates and the carbanion stability is determined by the degree of this repulsion, which increases in the order Br > Cl > F.

The reaction with the benzoxazoles 132g, 132k, 132h and 132l did not proceed because the methylene hydrogens are not sufficiently acidic without the contribution of the nitro group to the carbanion stabilisation through the delocalisation of the negative charge formed by the base. This demonstrates that the presence of an EWG on the aromatic ring of the azarene is crucial for the reactivity and it shows a limitation of the reaction reported in this chapter.

![Figure 16](image)

**Figure 16.** Azaarenes that did not react with the enals
4.4.5 Relative and absolute configuration

In order to determine the stereochemistry of the compounds obtained, an X-ray diffraction study of the minor isomer of 259f was performed.\(^2\) The relative stereochemistry was obtained, as shown in Figure 17.

![Figure 17. Crystal structure of product 259f. For more information about the crystal see Chapter 6](image)

The absolute configuration cannot be assigned reliably, based on anomalous dispersion effect since the molecule does not possess any heavy element. However, the relative configuration can be assigned as \(S^*\), \(R^*\) on C108 and C110. The analysis of the crystal shows that the compound 259f tends to crystallise as a racemic form. For this reason, it could be difficult to obtain an enantiomeric crystal.

It has to be noted that the Michael addition products derived from the pyridines are stable after isolation (Scheme 71).

\(^2\) The X-ray analysis was done by Dr Mateusz B. Pitak and Dr. Simon Coles
The absolute configuration of these compounds was determined by comparison of the compound 235d with the same compound reported by Wang and co-workers. Using the same (S)-secondary amine catalyst, the product obtained had the same specific rotation as reported in Wang’s paper. Assuming that our reaction follows a homogeneous mechanism, we could assign the absolute configuration of the stereocenter in the β position of the aldehyde. With the information obtained from the X-ray we could assign the absolute configuration to all the compounds synthesised.

4.5 Conclusion

In conclusion we developed a chiral synthesis of alkylazaarenes through an addition reaction of azaarenes to enals. We proposed one of the first examples of synergistic catalysis in which one of the catalysts is a secondary amine and the other is a metal Lewis acid. We obtained the final products in good yields, enantioselectivity ranging from low to excellent, based on the substrate, but low diastereoselectivity.
5. Synergistic catalysis: *cis*-cyclopropanation of benzoxazoles

5.1 One-pot reactions

In the last decades there has been growing importance of environmental issues related to synthetic chemistry. The most important problems addressed are the handling of waste, the search for environmentally tolerable procedures, atom economy related to the increase of the efficiency of the procedures. Most of the synthesis of pharmaceutical products require multistep synthesis and this means the use of solvents, reagents and energy for each step and especially for the work-up or the purification of the intermediate product after each step.\cite{113,114} The traditional method in organic synthesis is the formation of a single bond in each step. In Nature, though, most of the reactions are one-pot reactions or multistep synthesis,\cite{115} for example the reactions catalysed by the enzymes in the human body. In the search for greener procedures, synthetic chemists developed one-pot synthesis.

There are different types of one-pot reaction: telescoping, multicomponent, cascade/domino/tandem.

5.1.1 Telescoping reactions

A telescopic reaction is a synthetic route where the reagents are added one at a time, without doing the work-up after each step. One example is reported by Cameron, Hoerrner and co-workers for the synthesis of 7-hydroxyquinoline 282 (Scheme 72).\cite{116}
Scheme 72. Telescopic reaction for the synthesis of 7-hydroxyquinoline

One simple example of this reaction can be considered the Michael addition/Wittig reaction presented in Chapter 4, as the Wittig reagent was added to the reaction mixture without the need to purify the Michael addition product.

5.1.2 Multicomponent reactions

Multicomponent reactions convert more than two simple reagents in one complex final product. These reactions meet the request of atom economy of green chemistry, avoiding the necessity of protecting groups and the isolation of the intermediates. Some of the most famous reactions of this type are the Hantzsch pyridine synthesis,[117] Ugi,[118] Mannich,[119] Passerini[120] and Biginelli[121] reactions (Scheme 73).
5.1.3 Domino/Cascade/Tandem reactions

In the last decades there has been a huge development of cascade reactions\textsuperscript{[122–124]} and reviews have been written on this topic.\textsuperscript{[123,125]} Citing Tietze, as he defines in his review: “a domino reaction is a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step”. Domino reactions can be classified in: anionic, cationic, radical, pericyclic and transition metal induced.
5.1.3.1 Anionic domino reaction

The anionic domino reaction is the most common in literature, especially when combining two Michael/Michael reactions. The first step is the attack of an anion or a nucleophile to an electrophilic position. A lot of natural products have been synthesised in this way, for example Evans et al. published the synthesis of Salvinorin A 303 (Scheme 74), a diterpene that acts as an agonist on the k opioid receptors.

![Scheme 74. Evans’ synthesis of Salvinorin A through an anionic Michael/Michael cascade reaction](image)

5.1.3.2 Cationic domino reaction

The cationic domino reactions are characterised by the formation of a carbocation that reacts with a nucleophile, generating another carbocation that undergoes the same transformation until the carbocation is trapped by a nucleophile.

One example of this reaction is reported by Blaauw and co-workers as the key step in the synthesis of N-heterocyclic scaffolds and applied for the total synthesis of (-)-Dysibetaine PP (Scheme 75). The final products 306 were obtained in good yields and diastereoselectivities ranging from good to excellent based on the nature of the substituent R.
5.1.3.3  **Radical domino reaction**

The radical domino reactions have been applied to the synthesis of polycyclic compounds and, in most cases, they are one-component intramolecular reactions.

One application of this reaction is presented by Takahashi and co-workers for the formation of the C and D rings of the steroids, obtaining the product 311 in good yield and stereoselectivity (Scheme 76).[128]

5.1.3.4  **Pericyclic domino reaction**

Pericyclic reactions are very useful transformations in organic chemistry, for example the Diels-Alder reactions, sigmatropic and electrocyclic reactions. Combining two or more of these reactions can amplify the effect and they have been used for the
synthesis of many natural products.\textsuperscript{[129]} Most of the pericyclic domino reactions include a Diels-Alder at least in the first step.

Winkler and co-workers reported an example of this type of reaction even if it is not strictly a domino reaction as the solvent and Lewis acid have to be changed for the two cycloadditions. The first step is a cycloreversion followed by two [4+2] Diels-Alder, the first intermolecular and the second intramolecular (Scheme 77).\textsuperscript{[130]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme77.png}
\caption{Winkler’s pericyclic Diels-Alder domino reaction}
\end{figure}

\subsection{5.1.3.5 Transition metal catalysed domino reaction}

The transition metal-catalysed domino reactions are of increasing interest in organic chemistry. Several Pd catalysed domino reactions were already present in literature before the term ‘cascade’ or ‘domino’ were coined, representing some domino Heck reactions.\textsuperscript{[131,132]}

One more recent example is the enantioselective Heck reaction followed by an intramolecular aza-Michael addition reported by Pfeffer \textit{et al.} for the synthesis of 1,3-disubstituted terahydroisoquinolines 320 (Scheme 78).\textsuperscript{[133]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme78.png}
\caption{Pfeffer’s Pd catalysed domino reaction}
\end{figure}
5.1.3.6 Enzymatic domino reaction

In this type of reaction a multienzyme cocktail is used to catalyse different reactions. One example is the synthesis of Precorrin 322 starting from aminolevulinic acid and using eight different enzymes (Scheme 79).\[134\]

Scheme 79. Synthesis of Precorrin through an enzymatic domino reaction

5.1.3.7 Organocatalytic enantioselective domino reactions

Since the advent of organocatalysis is 2000, efforts have been put to apply the concept of domino reaction\[122,135\] to organocatalysis, thus maximising the advantages from a green chemistry point of view. The general scheme of iminium-enamine activation was already presented and explained in Chapter 1, Scheme 29.

As stated by the Horeau principle,\[136\] the combination of sequential asymmetric reactions will render the final product in higher enantioselectivity compared to the product obtained by the single transformations. An example is reported in Figure 18: assuming, for example, that the first and second catalytic cycles each gave 86% ee, if they are performed in a cascade reaction the final product will be obtained with 7:1 dr and 99% ee.
Enders proposed one of the first enantioselective triple organocascade reaction for the synthesis of tetra-substituted cyclohexene carbaldehydes.[137] This reaction proceeds through a Michael/Michael/aldol reaction rendering the products 324 with moderate yields but excellent enantioselectivity (Scheme 80).

Scheme 80. Enders’ Michael/Michael/aldol enantioselective cascade reaction

More examples of cascade reactions for the synthesis of cyclopropanes will be presented in the next section of this Chapter.

Recently our research group developed a highly diastereoselective synthesis of spiropyrazolones 327[138] and an enantioselective synthesis of spiroindoles 110[57] (Scheme 81).
Scheme 81. Rios’ cascade reactions for the synthesis of spiropyrazolones and spiroxindoles
5.2 Cyclopropanes

The synthesis of chiral cyclopropanes has always attracted the attention of the organic chemists\cite{139,140} due to the fact that they are often found in natural products and biologically active compounds. Cyclopropanes can be found in nature for example in terpenes, pheromones, fatty acid metabolites, amino acids\cite{141-147} Natural occurring and synthetic cyclopropanes also show pharmaceutical activities for example as antidepressants 329,\cite{148} HIV-inhibitor\cite{149} antipsychotics\cite{146} and marine lactones 328.\cite{150} The pyrethrins from the Chrysanthemum flowers 330 are potent insecticide and represented lead compounds for the synthetic pyrethroid, the most important class of insecticide on the market (Figure 19).\cite{151} Moreover the cyclopropanes are useful intermediates than can undergo ring-opening and ring-expansion reactions to form differently substituted products.\cite{152-158}

\begin{align*}
&\text{X} = \text{-CH}_2\text{CH}_2\text{-} \\
&(\text{cis-C} = \text{H}) \quad \text{(Halicholactone)} \\
&(\text{trans-C} = \text{H}) \quad \text{(Neohalicholactone)}
\end{align*}

\text{Figure 19. Examples of interesting cyclopropanes}

The most common method to synthesise cyclopropanes is the Simmons-Smith reaction, the cyclopropanation with diazomethane and the Michael initiated ring closure catalysed by transition metals or organocatalysts.

5.2.1 Simmons-Smith reaction

In 1958 Simmons and Smith developed a cyclopropanation reaction using diiodomethane 332 in the presence of zinc-copper to convert unfunctionalised alkenes 335.\cite{159,160} This reaction is a concerted process, through a [2+1] methylene transfer via
a three-centred transition state 336 as shown in Scheme 82. The reaction is
diestereospecific and it retains the configuration of the starting alkene; if the
diiodomethane is substituted there is a preference for the cis configuration of the final
product 337. There have been several modifications to prepare the starting reagent,
for example the use of diethylzinc 331 and diiodomethane (Furukawa modification,
Scheme 82).\[161,162\]

\[
\begin{align*}
\text{Et}_2\text{Zn} + \text{CH}_2\text{I}_2 & \rightarrow \text{EtZnCH}_2\text{I} + \text{EtI} \\
\text{EtZnCH}_2 + R^1 \cdots R^3 & \rightarrow \begin{array}{c}
\text{Et-} \\
\text{Zn} \\
\text{I} \\
\text{C} \\
\text{H}_2 \\
\text{C} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4
\end{array} - \text{EtZnI} \\
& \rightarrow R^1 \cdots R^4
\end{align*}
\]

Scheme 82. Furukawa modification of Simmons Smith cyclopropanation and mechanism

The asymmetric version of the Simmons Smith cyclopropanation can be achieved
through the use of chiral auxiliaries or chiral catalysts.

### 5.2.1.1 Chiral auxiliaries

When the alkene has one functional group containing a heteroatom, a directing effect
happens and the attack of the alkylidene takes place from the less hindered face of the
double bond. One example is reported by Bull et al. that uses an oxazolidinone ligand,
and the directing effect of the hydroxyl group in the allylic position allows the
formation of the syn cyclopropane 339 (Scheme 83).\[163\]

\[
\begin{align*}
\text{Bn} & \quad \text{O} \quad \text{C} \quad \text{OH} \\
\text{338} & \quad \text{Et}_2\text{Zn} 331 \quad \text{CH}_2\text{I}_2 332 \\
& \rightarrow \begin{array}{c}
\text{Bn} \\
\text{O} \\
\text{C} \\
\text{OH} \\
n\text{-Hept}
\end{array} \\
& \rightarrow \begin{array}{c}
\text{Bn} \\
\text{O} \\
\text{C} \\
\text{OH} \\
n\text{-Hept}
\end{array}
\end{align*}
\]

Scheme 83. Bull’s cyclopropanes synthesis with hydroxyl as directing group

### 5.2.1.2 Chiral ligands

Another way to achieve an asymmetric cyclopropanation is the use of stoichiometric
chiral additives as in the asymmetric modification described by Charette et al. in
They reported the cyclopropanation of allylic alcohols 340 with dioxaborolane ligands 341 (Scheme 84) obtaining the products in high yields and enantioselectivity. The chiral ligand is based on the presence of a boron atom that forms a complex with the acidic halomethylzinc reagent.

Scheme 84. Charette’s asymmetric cyclopropanation of allylic alcohols with dioxaborolane ligands

5.2.1.3 Chiral catalysts

Several catalytic systems have been published for the asymmetric Simmons-Smith cyclopropanation, though most of the catalysts have to be used in stoichiometric amounts. Again Charette reported a nice example using a chiral phosphoric acid 346 derived from a disubstituted BINOL derivative.$^{[165]}$ This allows the formation of an intermediate chiral zinc phosphate that would allow the cyclopropanation of protected allylic alcohols 345 (Scheme 85).

Scheme 85. Charette’s cyclopropanation of allylic alcohols with chiral phosphoric acid
5.2.2 Cyclopropanation with diazomethane

Diazomethane 349 reacts with olefins 348 to render cyclopropanes 352. The first step is a 1,3-cycloaddition to form a pyrazoline 350 and the second step is a denitrogenation, by thermal or photochemical decomposition (Scheme 86).\[^{[166,167]}\]

![Scheme 86. Cyclopropanation with diazomethane and olefins](image)

A safer way to use the diazocompounds is in combination with transition-metal catalysts 355, for example the work of Noyori and Nozaki (Scheme 87).\[^{[168]}\]

![Scheme 87. Noyori's synthesis of cyclopropanes](image)

The mechanism of these reactions (Scheme 88) goes through a carbenoid formation: the metal catalyst interacts with the diazo compound 358 to form a metallocarbene complex 359 and then the carbene is transferred to the alkene 335. The enantiocontrol is due to the careful choice of chiral ligand for the metal catalyst.
Scheme 88. Mechanism of the transition-metal catalysed decomposition of diazoalkenes

Fu et al. reported a copper(I) catalysed cyclopropanation of olefins 353 and diazocompounds 354 using a novel bidentate chiral ferrocene ligand 359 (Scheme 89).\textsuperscript{[169]}

\[ \text{COOAr} \quad R = \text{Ar, } n\text{-hexyl, Et}_3\text{Si} \]

Scheme 89. Fu’s cyclopropanation with bidentate chiral ferrocene copper ligand

5.2.3 Michael Initiated Ring Closure

Michael initiated ring closure (MIRC) involves a conjugate addition of a nucleophile to an alkene to produce an enolate that undergoes an intramolecular ring closure.

A good example of this methodology was reported by Aggarwal et al. using the sulfoxonium ylides 365 synthesised by Corey and Chaykovsky\textsuperscript{[170]} in 1962. Aggarwal and co-workers developed an asymmetric cyclopropanation of electron deficient alkenes 362 catalysed by a chiral sulphide 361, obtaining the final products 367 in moderate yields and excellent enantioselectivities (yield: 14-60%; dr: 4:1; ee: >97\%) (Scheme 90).\textsuperscript{[171]}

96
Scheme 90. Mechanism of Aggarwal’s asymmetric cyclopropanation of alkenes mediated by a chiral sulphide

Organocatalytic versions using ylides were later proposed by MacMillan and Gaunt. MacMillan et al. presented the amine-catalysed cyclopropanation of α,β-unsaturated aldehydes 80 by β-oxosulphonium ylides 122, using a 2-carboxylic acid dihydroindole catalyst 123, as previously reported in the Scheme 31, Chapter 1. MacMillan et al. presented the amine-catalysed cyclopropanation of α,β-unsaturated aldehydes 80 by β-oxosulphonium ylides 122, using a 2-carboxylic acid dihydroindole catalyst 123, as previously reported in the Scheme 31, Chapter 1.[65] Gaunt et al. presented an enantioselective cyclopropanation of an α-bromo carbonyl compound 369 and electron poor alkenes 370 via ammonium ylides using chiral tertiary amines 372 and 373 as catalysts (Scheme 91).[172]

Scheme 91. Gaunt’s cyclopropanation via ammonium ylides

With the advent of organocatalysis, several MIRC domino reactions catalysed by diphenylprolinol catalysts have been developed. An example is the nitrocyclopropanation reported by Cordova et al.[173] and Yan et al.[174] through the
reaction of bromonitromethane 374 with α,β-unsaturated aldehydes 80 as shown in the Scheme 92.

**Scheme 92.** Nitrocyclopropanation of 1-bromonitroalkanes with α,β-unsaturated aldehydes

Other examples of organocascade reactions leading to the formation of cyclopropanes were reported by Cordova et al.,[175,176] Wang et al.[177] and Rios et al.[178] They use enals 80 as electrophiles, activated by the secondary amine catalyst 103, and bromomalonates 376 or bromoketoesters 378 as nucleophiles respectively (Scheme 93).

**Scheme 93.** Cyclopropanation of enals with malonates and ketoesters
In 2011 Lattanzi and co-workers and Pesciaioli and co-workers developed an organocatalytic enantioselective synthesis of spirocyclopropanes through a MIRC reaction. In particular Lattanzi\cite{179} reported the cyclopropanation of 2-arylidene-1,3-izandiones 380 with bromomalonates 376, using diphenylprolinol 381 as catalyst and Pesciaioli\cite{180} reported the cyclopropanation of N-Boc protected oxindoles 383 with bromonitroalkane 374 using a quinine derivative 385 as catalyst (Scheme 94).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_94.png}
\caption{Organocatalytic enantioselective synthesis of spirocyclopropanes}
\end{figure}

In 2015 Cobb and co-workers explored an asymmetric cyclopropanation of conjugated cyanosulfones 386 with bromomalonates 376 catalysed by a derivatised cupreine catalyst 388, obtaining highly functionalised cyclopropanes 387 in good yields and enantioselectivities (Scheme 95).\cite{181}
Scheme 95. Cobb’s cyclopropanation of conjugated cyanosulfones with bromomalonates

R = Ar, Py, thiophene

yield: 73-99%
n ee: 90-99%
5.3 Project aim

Despite the advantages and progress of synergistic catalysis presented in Chapter 1, 3 and 4, there are still some limitations as, for example, the fact that only one C-C bond is formed using two catalytic cycles. This fact makes the process expensive from an atom economy point of view as there is the need to use two catalysts to create only one new bond. This drawback attracted our interest, together with the idea to study a way to improve the results obtained in the previous project (Chapter 4) and to obtain higher diastero- and enantioselectivities.

For this reasons, the aim of this second project is to expand the synergistic catalysis approach, presented in Chapter 4, to a cascade reaction. Inspired by the previous experience in our research group in the synthesis of cyclopropanes and interested to explore the possibility to combine a metal Lewis acid and an organocascade reaction in a synergistic approach, we designed a cascade reaction that could trap the enamine is situ, forming two C-C bonds with three catalytic cycles, pushing the boundaries of synergistic catalysis.

5.4 Research hypothesis and proposed reaction mechanism

We decided to study the reaction of chloromethylenebenzoxazoles with enals to obtain formyl cyclopropanes in a highly enantioselective fashion. The choice of the chloromethylenebenzoxazoles is related to the need to have a compound that could act as a nucleophile at the start of the reaction (Figure 20, 389) and subsequently as an electrophile with the loss of chlorine anion as a leaving group (Figure 20, 390).

![Figure 20. Chloromethylenebenzoxazole acting as nucleophile (389) and then as electrophile (390)](image)

One of the three catalytic cycles is the activation of a chloromethylenebenzoxazole by a metal Lewis acid, the second cycle is the activation of the enal by the secondary
amine catalyst through an iminium activation while the third cycle is still promoted by the organocatalyst, but this time, through the enamine catalysis (Figure 21).

Figure 21. New synergistic approach: two catalysts, three catalytic cycles and the formation of two new C-C bonds

To prove the viability of this approach, we tested the reaction of addition of 2-(chloromethyl)-6-nitrobenzoxazole 391a with cinnamaldehyde 80b as shown in Scheme 96 and, to our delight, the final product 392 was obtained in moderate yield.

Scheme 96. First reaction tested for the addition of 2-(chloromethyl)-6-nitrobenzoxazole with cinnamaldehyde

The proposed reaction mechanism is shown in Scheme 97.
As suggested by Lam,\textsuperscript{[88]} Pd interacts with the alkylbenzoxazole 391a by coordinating to the nitrogen, thus increasing the acidity of the protons in the methylene position. After treating the metallated alkylbenzoxazole 393 with a base, a nucleophile 389, suitable to react with the electrophile, was obtained. In the other catalytic cycle, the enal 80b reacts with the secondary amine organocatalyst 103 to form the corresponding activated iminium form 236. The (S)-catalyst efficiently shields one face of the enal. Then the coordination between the Pd enolate and the double bond of the imine occurs to form the intermediate 394. After the addition of the intermediate to the \( \beta \)-position of the iminium intermediate, the enamine intermediate 396 reacts intramolecularly with the alkyl halide through a 3-exo-tet cyclisation to form the cyclopropane ring. Hydrolysis of compound 397 affords the final product 392a and releases the catalyst, thus completing the catalytic cycle.

Some stereochemical considerations have to be done. As shown in the Scheme 97, we suggest the formation of an intermediate Pd enolate 394: the coordination of the Pd to

\textbf{Scheme 97.} Proposed mechanism for the cyclopropanation
the double bond of the iminium intermediate 236 happens on the $Si$-face, as the bulky substituents of the organic catalyst efficiently shield the $Re$-face. The azaallyl ligand in the intermediate 394 possess an $E$-stereochemistry to minimise the steric interactions between the Cl substituent and the iminium. This is the crucial step for the determination of the stereochemistry: the nucleophilic attack on the $\beta$ position of the aldehyde happens on the $Si$-face with the formation of a 6 membered ring intermediate 395 with the new Pd enolate formed in the $\alpha$ position of the iminium. Then an intramolecular alkylation between the Pd enolate and the methylene chloride, followed by an inversion of the configuration, renders the product 397 with the cis configuration between the two aromatic substituents.

5.5 Results and discussions

5.5.1 Synthesis of the starting materials

The azaarenes 391 were synthesised following the procedure presented in the article of Lam and co-workers\(^{[88]}\) using differently substituted 2-aminophenol 397 and 2-chloro-1,1,1-triethoxyethane 398 as shown in Scheme 98. The mechanism is the same as the one reported in Chapter 4, Scheme 59.

![Scheme 98. Synthesis of the chloromethylenebenzoxazoles as starting materials](image)

The results obtained in the synthesis of the starting chloro-alkylbenzoxazoles are presented in Figure 22, with yields ranging from 54 to 95%.
The α,β-unsaturated aldehydes 80 were synthesised through a Wittig reaction leading to the $E$ form of the aldehydes as already shown in Chapter 4, Scheme 61 and Scheme 62.³

5.5.2 Optimisation of the reaction conditions

It has to be noted that the final cyclopropane 392 is stable so there is no need to further derivatise as required in the project presented in Chapter 4.

Spurred by the result obtained, we studied the optimisation of the reaction screening different solvents, metal Lewis acids, bases and organocatalysts.

³ The azaarenes 391 and aldehydes 80 were synthesised by me and Cameron Ross, a summer project students that I supervised.
5.5.2.1 Screening of solvents

Table 9. Screening of solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion % (24 h)</th>
<th>dr (crude)[a]</th>
<th>ee major dia (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOAc</td>
<td>52</td>
<td>2.1 : 1.7 : 1</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$CN</td>
<td>59</td>
<td>4 : 3.2 : 1</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>33</td>
<td>3.5 : 2.4 : 1</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>97</td>
<td>2 : 1</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>57</td>
<td>2 : 1.2 : 1</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>6</td>
<td>CHCl$_3$</td>
<td>29</td>
<td>2.4 : 1.6 : 1</td>
<td>&gt; 70</td>
</tr>
</tbody>
</table>

[a] dr are calculated from the crude NMR comparing the aldehydes signals [b] ee were determined by chiral HPLC analysis

At first a screening of solvents was performed as shown in Table 9. With all the solvents tested, three diastereomers were present in the crude NMR after 24 hours except with MeOH (Table 9, entry 4). MeOH was not chosen as a solvent for the next reactions as the crude NMR was less clean than with the other solvents and showed a degradation of the reagents. Mostly degradation of the reagents was seen in the reaction performed in DMF (Table 9, entry 3). In CDCl$_3$ (Table 9, entry 6) the conversion was too low after 24 hours. The best solvent was found to be CH$_3$CN (Table 9, entry 2) as regards the diastereoselectivity, compared to EtOAc and DCM (Table 9, entries 1 and 5).
5.5.2.2 Screening of organic catalysts

Table 10. Screening of organic catalysts

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion % (24 h)</th>
<th>dr (crude)[a]</th>
<th>ee major dia (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Catalyst 103" /></td>
<td>59</td>
<td>4 : 3.2 : 1</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Catalyst 189" /></td>
<td>82</td>
<td>2.5 : 1.1 : 1</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Catalyst 220" /></td>
<td>traces</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Catalyst 71" /></td>
<td>traces</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Catalyst 272" /></td>
<td>--</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Catalyst 213" /></td>
<td>traces</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td>No organic catalyst</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

[a] dr are calculated from the crude NMR comparing the aldehydes signals
[b] ee were determined by chiral HPLC analysis

Then a screening of organic catalysts was performed (Table 10). Entries 3, 4, 5 and 6, Table 10, did not show any conversion or traces of the product in the NMR of the crude. The lack of reactivity observed with trifluoromethyl-substituted diarylprolinol 220 (Table 10, entry 3) is in agreement with Hayashi’s findings. Diarylprolinol catalysts lower the LUMO of the iminium ion intermediate facilitating the Michael addition but the formation of the iminium ion in absence of an acid co-catalyst is possible, at acceptable rate, only with the more basic/nucleophilic diphenylprolinols.

Good results were obtained with the commercial Jorgensen-Hayashi catalyst 103 (Table 10, entry 1) and with the modified version of it with a bulkier substituent 189.
(Table 10, entry 2). The conversion with the last catalyst is better, however the
disatereoselectivity is worse so that the commercial catalyst was chosen as the best
organic catalyst. To prove the need of the organic catalyst the reaction was performed
without any secondary amine (Table 10, entry 7) and from the NMR of the crude no
formation of the products was seen.

5.5.2.3 Screening of bases

Table 11. Screening of bases

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conversion % (24 h)</th>
<th>dr (crude)[a]</th>
<th>ee major dia (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TEA 260</td>
<td>59</td>
<td>4 : 3.2 : 1</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>DIPEA 28</td>
<td>full</td>
<td>1.6 : 0.8 : 1</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>2,6-lutidine 398</td>
<td>93</td>
<td>4.1 : 2.4 : 1</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Cs$_2$CO$_3$ 368</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>DABCO 138</td>
<td>34</td>
<td>2.5 : 1.1 : 1</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>6</td>
<td>No base</td>
<td>29</td>
<td>2.4 : 1 : 1</td>
<td>---</td>
</tr>
</tbody>
</table>

[a] dr are calculated from the crude NMR comparing the aldehydes signals
[b] ee were determined by chiral HPLC analysis

Table 11 shows the screening of bases that was performed using the best solvent and
organic catalyst found before. The best results were obtained with 2,6-lutidine 398
(Table 11, entry 3): the conversion is better than with TEA 260 (Table 11, entry 1) with
a similar dr from the NMR of the crude. The reaction with DIPEA 28 (Table 11, entry 2)
gave full conversion but the dr is worse. With an inorganic base 368 (Table 11, entry 4)
the reaction did not work, while with DABCO 138 (Table 11, entry 5) the conversion
and dr are worse compared to the first three entries. The reaction was tested without
any base (Table 11, entry 6), rendering only 29% conversion after 24 hours, with some degradation of the starting aldehyde. So we prove the need of a base and the best was found to be 2,6-lutidine.

5.5.2.4 Screening of metal Lewis acids

Table 12. Screening of metal Lewis acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Conversion % (24 h)</th>
<th>dr (crude)[a]</th>
<th>ee major dia (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$ 164</td>
<td>full</td>
<td>1.6:0.8:1</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>AgOBz 399</td>
<td>92</td>
<td>2:1:1</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>AgOAc 230</td>
<td>79</td>
<td>2.7:1.3:1</td>
<td>&gt;90</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)$_2$ 264</td>
<td>61</td>
<td>1.7:0.6:1</td>
<td>&gt;90</td>
</tr>
<tr>
<td>5</td>
<td>Yb(SO$_3$CF$_3$)$_2$ 176</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>Cu(SO$_3$CF$_3$)$_2$ 261</td>
<td>50</td>
<td>2.5:2.2:1</td>
<td>&gt;90</td>
</tr>
<tr>
<td>7</td>
<td>PdCl$_2$ 266</td>
<td>29</td>
<td>1:0.6:1</td>
<td>&gt;90</td>
</tr>
<tr>
<td>8</td>
<td>No Lewis Acid</td>
<td>traces</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

[a] dr are calculated from the crude NMR comparing the aldehydes signals  
[b] ee were determined by chiral HPLC analysis

Next, different metal Lewis acids were tested using acetonitrile as the solvent and DIPEA 28 as the base (Table 12). The best results were obtained with AgOAc 230 and Pd(OAc)$_2$ 164 (Table 12, entries 1 and 3), both of them showing good conversion and good selectivities: in particular Pd(OAc)$_2$ rendered a better enantioselectivity while AgOAc rendered a better diastereoselecivity. Nevertheless, comparing with those of the previous table, these results are worse than the ones obtained with 2,6-lutidine
and Pd(OAc)$_2$. The reaction with Yb(SO$_3$CF$_3$)$_2$ 176 (Table 12, entry 5) did not work as a degradation of the starting materials occurred. With the other Lewis acid tested, the reaction worked but all of them showed worse results compared to AgOAc and Pd(OAc)$_2$. With AgOBz 399 (Table 12, entry 2) low enantioselectivity was obtained, with Cu(OAc)$_2$ 264, Cu(SO$_3$CF$_3$)$_2$ 261 and PdCl$_2$ 266 (Table 12, entries 4, 6 and 7) lower conversions and dr were obtained. When the reaction was performed without any Lewis acid (Table 12, entry 8) no conversion was observed in the NMR of the crude. This demonstrated the need of both catalysts and consequentially confirms the mechanism of the synergistic catalysis.

5.5.2.5 Screening of temperatures

Table 13. Screening of temperatures

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Conversion %</th>
<th>dr (crude)$^{[a]}$</th>
<th>ee major dia (%)$^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>63 (24 h)</td>
<td>1.7 : 1.1 : 1</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>61 (60 h)</td>
<td>2 : 0.8 : 1</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>3</td>
<td>rt</td>
<td>full (24h)</td>
<td>1.6 : 0.8 : 1</td>
<td>&gt; 95</td>
</tr>
</tbody>
</table>

$^{[a]}$ dr are calculated from the crude NMR comparing the aldehydes signals

$^{[b]}$ ee were determined by chiral HPLC analysis

The reaction was tested at higher and lower temperatures as shown in Table 13. In both cases the conversion was lower than at room temperature (Table 13, entry 3). In the first case (Table 13, entry 1) the heating probably caused some degradation of the catalyst. In the second case (Table 13, entry 2) the low temperature is the cause of the lower reaction rate.
5.5.2.6 Screening of metal Lewis acids with 2,6-lutidine as a base

Table 14. Screening of metal Lewis acids with 2,6-lutidine as base

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Conversion % (24 h)</th>
<th>dr (crude)[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$ 164</td>
<td>full</td>
<td>5.2 : 2.6 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)$_2$ 264</td>
<td>traces-degradation</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>AgOAc 230</td>
<td>full (NMR less clean than with Pd)</td>
<td>2.2 : 1.4 : 1</td>
</tr>
</tbody>
</table>

[a] dr are calculated from the crude NMR comparing the aldehydes signals

As 2,6-lutidine was found to be the most suitable base, the best Lewis acids found with DIPEA 28 were tested again with 2,6-lutidine 398 as presented in Table 14. Cu(OAc)$_2$ 264 gave only traces of the final products (Table 14, entry 2), due to the degradation of the starting materials. Compared to AgOAc 230 (Table 14, entry 3), Pd(OAc)$_2$ 164 gave a better conversion, a cleaner NMR of the crude and especially a better diastereoselectivity (Table 14, entry 1).

We found that the best reaction conditions were the use of one equivalent of benzoxazole 391, two equivalents of aldehyde 80, Pd(OAc)$_2$ 164 (5 mol%) as metal Lewis acid, Jorgensen-Hayashi catalyst 103 (20 mol%) as secondary amine, 2,6-lutidine 398 (1 equivalent) as the base and CH$_3$CN as the solvent.

Then we proceeded to study the scope of the reaction testing different enals and differently substituted benzoxazoles. In all the examples reported, the major diastereomer could be easily isolated after column chromatography, while the two minor diastereomers are often an inseparable mixture.
## 5.5.3 Scope of the reaction with enals

Table 15. Scope of the reaction with several enals

<table>
<thead>
<tr>
<th>Product</th>
<th>Aldehyde (R)</th>
<th>Yield[a] (%)</th>
<th>(\text{dr}[b])</th>
<th>(ee) major (%)[c]</th>
<th>(ee) minor (%)[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>392a</td>
<td>H 80b</td>
<td>89</td>
<td>4.5 : 1.2 : 1</td>
<td>96 (R catalyst)</td>
<td>99 (S catalyst)</td>
</tr>
<tr>
<td>392b</td>
<td>4-Br 80h</td>
<td>70</td>
<td>7 : 2.2 : 1</td>
<td>97 (R catalyst)</td>
<td>98 (S catalyst)</td>
</tr>
<tr>
<td>392c</td>
<td>4-Cl 80e</td>
<td>74</td>
<td>2:1</td>
<td>98 (R catalyst)</td>
<td>97 (S catalyst)</td>
</tr>
<tr>
<td>392d</td>
<td>4-NO(_2) 80i</td>
<td>79</td>
<td>14 : 5.6 : 1</td>
<td>&gt;99 (R catalyst)</td>
<td>81 (R catalyst)</td>
</tr>
<tr>
<td>392e</td>
<td>4-CN 80g</td>
<td>89</td>
<td>4.8 : 3 : 1</td>
<td>&gt;99 (R catalyst)</td>
<td>&gt;99 (S catalyst)</td>
</tr>
<tr>
<td>392f</td>
<td>4-F 80j</td>
<td>86</td>
<td>6.6 : 2.6 : 1</td>
<td>98 (R catalyst)</td>
<td>98 (S catalyst)</td>
</tr>
<tr>
<td>392g</td>
<td>4-Me 80k</td>
<td>66</td>
<td>5.3 : 1.6 : 1</td>
<td>99 (R catalyst)</td>
<td>99 (S catalyst)</td>
</tr>
<tr>
<td>392h</td>
<td>2-Br 80c</td>
<td>81</td>
<td>13.4 : 2.3 : 1</td>
<td>&gt;99 (R catalyst)</td>
<td>&gt;99 (S catalyst)</td>
</tr>
<tr>
<td>392i</td>
<td>OHC(\longrightarrow)COOEt 80m</td>
<td>85</td>
<td>&gt; 15:1</td>
<td>81 (R catalyst)</td>
<td>-----</td>
</tr>
<tr>
<td>392j</td>
<td>OHC(\longrightarrow)Me 80a</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

[a] yields are from the sum of the isolated diastereomers after column chromatography

[b] \(\text{dr}\) are calculated from the isolated diastereomers after column chromatography

[c] \(ee\) were determined by chiral HPLC analysis
In Table 15 is presented the study of the scope of the reaction testing several enals. All the products were obtained in good to excellent yields with moderate to good diastereoselectivities and excellent enantioselectivities regarding the major diastereomer. We tested different substituents on the aromatic ring of the enal. Employing aryl compounds substituted with halogens in the para position (4-Br, 4-Cl and 4-F) the products 392b, 392c and 392f respectively, were obtained in good yields and dr (86-70% yield, 3:1 dr, up to 99% ee). When the Br is in the ortho position 392h, even if the aldehyde was sterically hindered, the reaction worked with good yields, ee and dr. When electron-withdrawing substituents were present (4-NO₂ and 4-CN) the products 392d and 392e were obtained in good yields (79-63%), good dr and excellent ee (> 99%).

Then we tested the aldehyde derived from the glioxylate 80m, obtaining the final product 392i in good yield and excellent diastereoselectivity (only one diastereomer) but with lower enantioselectivity. The reason for the epimerisation is explained in Figure 23: on the carbon bearing the ester group, the proton is more acidic compared to the other cyclopropanes synthesised. As in the reaction mixture is present a base, this could deprotonate this position and an epimerisation would occur rendering the more stable cis product 401, stabilised by the coordination of Pd with the nitrogen atom of the benzoazole ring and the carbonyl of the ester group.

![Proposed epimerisation of the minor diastereomer of the product 392i](image)

**Figure 23.** Proposed epimerisation of the minor diastereomer of the product 392i
One of the limits of the reaction is that it is not suitable for aliphatic aldehydes as it gave only complex mixtures in the crude.

### 5.5.4 Scope of the reaction with benzoxazoles

Table 16. Scope of the reaction with several benzoxazoles

<table>
<thead>
<tr>
<th>Product</th>
<th>Benzoxazole</th>
<th>R</th>
<th>Yield$^a$ (%)</th>
<th>dr$^b$</th>
<th>ee major (%)$^c$</th>
<th>ee minor (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>392a</td>
<td><img src="image" alt="Benzoxazole" /></td>
<td>H 80b</td>
<td>89</td>
<td>4.5 : 1.2 : 1</td>
<td>96 (R cat.)</td>
<td>99 (S cat.)</td>
</tr>
<tr>
<td>402a</td>
<td><img src="image" alt="Benzoxazole" /></td>
<td>H 80b</td>
<td>68</td>
<td>10.5 : 3.3 : 1</td>
<td>&gt;99 (R cat.)</td>
<td>&gt;99 (S cat.)</td>
</tr>
<tr>
<td>402g</td>
<td><img src="image" alt="Benzoxazole" /></td>
<td>H 80b</td>
<td>traces</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>402b</td>
<td><img src="image" alt="Benzoxazole" /></td>
<td>H 80b</td>
<td>78</td>
<td>4.5 : 1.9 : 1</td>
<td>98 (R cat.)</td>
<td>98 (S cat.)</td>
</tr>
<tr>
<td>402c</td>
<td><img src="image" alt="Benzoxazole" /></td>
<td>H 80b</td>
<td>55</td>
<td>6.2 : 1.3 : 1</td>
<td>99 (R cat.)</td>
<td>98 (S cat.)</td>
</tr>
<tr>
<td>402d</td>
<td><img src="image" alt="Benzoxazole" /></td>
<td>H 80b</td>
<td>51</td>
<td>2.3 : 1.6 : 1</td>
<td>&gt;99 (R cat.)</td>
<td>&gt;99 (S cat.)</td>
</tr>
<tr>
<td>402e</td>
<td><img src="image" alt="Benzoxazole" /></td>
<td>4-Br 80h</td>
<td>85</td>
<td>8.1 : 4.8 : 1</td>
<td>98 (R cat.)</td>
<td>97 (S cat.)</td>
</tr>
</tbody>
</table>
In Table 16 is presented the study of the scope of the reaction testing several benzoxazoles. With the 5-Cl,6-NO₂ substituted benzoxazole 391b, the products 402a, 402e and 402f were obtained in good yields, dr and excellent ee (91-99%). When benzoxazoles with the nitro group in different position of the aromatic ring 391c and 391e were tested, lower yields but good dr and excellent ee were observed (402c and 402d). When an ester group is present in position 6 391d, the final product 402b was obtained in excellent yield and ee and good dr.

The limitation of the reaction is that the presence of an electron-withdrawing group on the benzoxazole ring is crucial for the reactivity, as previously noted in Chapter 4. In fact the reaction with the unsubstituted benzoxazole 391f did not give any product (Table 16, compound 402g).
5.5.5 Relative and absolute configuration

The relative configuration of the minor diastereomer was determined by X-ray crystallography as shown in Figure 24.\(^4\)

![Figure 24. X-ray structure of compound 392d](image)

The absolute configuration of the minor diastereomer and the relative and absolute configuration of the major diastereomer were determined by 2D-NMR and by TD-DFT simulation of the Electronic Circular Dichroism (ECD) spectra.\(^5\) The absolute configuration was determined to be 1\(R\),2\(R\),3\(S\) for the major diastereomer 392d (using (S)-301 as catalyst) and 1\(R\),2\(R\),3\(R\) for the minor diastereomer 392d’ (using (R)-301 as catalyst). (See Chapter 6 for a detailed explanation)

The major diastereomers have a cis configuration between the aryl substituent and the benzoxazole. This adds an even more important value to the methodology described in this chapter as the synthesis of cis diaromatic cyclopropanes via an intermolecular reaction is very challenging. Only Katzuki \textit{et al.}\textsuperscript{[183]} and Mezzetti \textit{et al.}\textsuperscript{[184]} reported the enantioselective synthesis of cis-cyclopropanes using iridium and ruthenium catalysts 403 and 404 respectively in the reaction of styrenes 353 with diazoacetates 354 (Scheme 99).

\(^{4}\) The X-ray analysis was done by Dr Mark E. Light

\(^{5}\) The NMR analysis and TD-DFT simulation of the Electronic Circular Dichroism (ECD) spectra were done by Professor Andrea Mazzanti
The methodology reported in this chapter can be considered stereocomplementary to the organocatalytic cyclopropanation of MacMillan et al.\textsuperscript{[65]} They reported the cyclopropanation of enals 80 catalysed by a secondary amine organocatalyst 123 mediated by a sulphur ylide 122, obtaining the final \textit{trans}-trisubstituted cyclopropanes 124 in good yields and excellent diastero- and enantioselectivities (\textbf{Scheme 100}).

\textbf{Scheme 100.} MacMillan’s enantioselective synthesis of \textit{trans}-trisubstituted cyclopropanes
5.6 Conclusion

In conclusion we demonstrated that the concept of synergistic catalysis, presented in Chapter 4, can be applied to a cascade reaction. We developed an organocascade highly enantioselective cyclopropanation of enals with chloroalkylbenzoxazoles, using a metal Lewis acid to activate the benzoxazole and a secondary amine catalyst to activate the enals with a cascade iminium and then enamine activation. The final products were obtained in good yields, moderate to good diastereoselectivity and excellent enantioselectivity in the major diastereomer. Moreover the major diastereomer has a \textit{cis} configuration that is otherwise difficult to obtain and gives more importance to the methodology reported in this chapter.
6. Experimental section

Thin layer chromatography (TLC) was performed on Merck TLC Silicagel 60 F_{254}. Product spots were visualized by UV-light at 254 nm. Column chromatography was effectuated using silica gel (Geduran Si60, 40-63 µm). Melting points were measured with a Gallenkamp Electrothermal apparatus and are uncorrected. Infra-red spectra were recorded on a Nicolet 380 FT-IR; the IR analysis were performed with the compounds dissolved in CHCl₃. ¹H-NMR, ¹³C-NMR, ¹⁹F-NMR, 2D-NMR were recorded with a Bruker DPX400 NMR. High resolution mass spectra were recorded using a MaXis (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a Time of Flight (TOF) analyser. Optical rotations were performed on an Optical Activity PolAAr 2001 machine. The HPLC analysis were performed on a Perkin Elmer Flexar HPLC and an Agilent 1220 Infinity LC system HPLC.
6.1 Synergistic catalysis: enantioselective addition of alkylbenzoxazoles to enals

6.1.1 Synthesis of the starting materials: α,β-unsaturated aldehydes (80)

The starting aldehydes were synthesised through a Wittig reaction, following the procedure described in literature. In a 250 mL round bottom flask a substituted benzaldehyde derivative 63 (2 equiv) and (triphenylphosphoranyldiene)acetaldehyde 250 (1 equiv) were stirred in anhydrous toluene at 45 °C in an atmosphere of argon. Yields were obtained after column chromatography.

The aldehydes 80a and 80b are commercially available (Sigma-Aldrich).

The H-NMR of the aldehydes 80k, 80e, 80i are consistent with the ones provided in literature.[185]

The H-NMR of the aldehydes 80j and 80f are consistent with the ones provided in literature.[186]

The H-NMR of the aldehyde 80h is consistent with the one provided in literature.[187]

The H-NMR of the aldehyde 80g is consistent with the one provided in literature.[188]

The H-NMR of the aldehyde 80c is consistent with the one provided in literature.[189]

6.1.2 Synthesis of the starting materials: azaarenes

The starting benzoxazoles were synthesised following the procedure described in literature.[88]

2-ethyl-6-nitrobenzoxazole (132a), 2-methyl-6-nitrobenzoxazole (132c) are commercially available (Acros and Sigma-Aldrich).

The H-NMR of 2-ethyl-6-nitrobenzoxazole (132a), 2-methyl-6-nitrobenzoxazole (132c) are consistent with the ones provided in literature.[190]
The $^1$H-NMR of 2-ethylbenzoxazole (132g) is consistent with the one provided in literature.[191]

The $^1$H-NMR of 2-ethyl-4-nitrobenzoxazole (132d), 2-butyl-6-nitrobenzoxazole (132e) and methyl 2-ethylbenzoxazole-6-carboxylate (132h) are consistent with the ones provided in literature.[88]

The $^1$H-NMR of 2-ethyl-5-nitrobenzoxazole (132c) is consistent with the one provided in literature.[192]

5-chloro-2-ethyl-6-nitrobenzoxazole (132b)

A mixture of 2-amino-4-chloro-5-nitrophenol (5 g, 26.4 mmol, 1 equiv) and triethyl orthopropionate (5.8 mL, 29.0 mmol, 1.1 equiv) was stirred at 50 °C for 48 hours. The crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 4.5 g of a yellow solid. The yield is 75%.

**mp:** 83-85 °C

**IR:** 3106, 3035, 2992, 1560, 1523, 1446, 1324, 1255, 1209, 822 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.07 (s, 1H, Het), 7.82 (s, 1H, Het), 3.04 (q, $J = 7.6$ Hz, 2H, CH$_2$), 1.48 (t, $J = 7.6$ Hz, 3H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.6 (Cq), 148.3 (Cq), 145.2 (Cq), 144.5 (Cq), 123.4 (Cq), 122.1 (CH), 108.4 (CH), 22.4 (CH$_2$), 10.6 (CH$_3$).

**HRMS (ESI+)** Exact mass calculated for C$_9$H$_8$Cl$_3$N$_2$O$_3$ [M+H]$^+$: 227.0218, found: 227.0217.
**2-isopropyl-6-nitrobenzoxazole (132i)**

![Chemical Structure]

In a round bottom flask charged with 2-amino-5-nitrophenol (3.0 g, 19.5 mmol, 1 equiv) isobutyric acid (1.8 mL, 19.5 mmol, 1 equiv) and polyphosphoric acid (38 g, 390 mmol, 20 equiv) were added. The reaction mixture was stirred for 7 hours at 50 °C. Then the mixture was cooled at room temperature and a solution of sodium hydroxide was added until the mixture had a basic pH. The solid formed was filtered and washed with ice-water to afford 2.4 g of a brown solid. The yield is 59%.

**mp:** 86-87 °C

**IR:** 3107, 2970, 1568, 1520, 1344, 1276, 1139, 1088, 886, 818 cm⁻¹.

**¹H NMR (400 MHz, CDCl₃)** δ 8.41 (d, J = 2.1 Hz, 1H, Het), 8.29 (dd, J = 8.7, 2.1 Hz, 1H, Het), 7.78 (d, J = 8.7 Hz, 1H, Het), 3.40 – 3.26 (m, 1H, CH₃), 1.51 (d, J = 7.0 Hz, 6H, CH₃).

**¹³C NMR (101 MHz, CDCl₃)** δ 176.2 (Cq), 149.9 (Cq), 146.7 (Cq), 144.9 (Cq), 120.3 (CH), 119.5 (CH), 107.0 (CH), 29.2 (CH), 20.1 (CH₃).

**HRMS (ESI+)** Exact mass calculated for C₁₀H₁₁N₂O₃ [M+H]⁺: 207.0764, found: 207.0764.

**2-(difluoromethyl)-6-nitrobenzoxazole (132j)**

![Chemical Structure]

In a round bottom flask charged with 2-amino-5-nitrophenol (3.6 g, 23.36 mmol, 1 equiv) 2,2-difluoroacetic acid (2.24 g, 23.36 mmol, 1 equiv) and polyphosphoric acid (45 g, 467 mmol, 20 equiv) were added. The reaction mixture was stirred for 24 hours at 80 °C. Then the mixture was cooled at room temperature and a solution of sodium hydroxide was added until the mixture had a basic pH. The solid formed was filtered and washed with ice-water to afford 4.3 g of a brown solid. The yield is 86%.
mp: 102-104 °C

IR: 3105, 1526, 1354, 1304, 1255, 1109, 1056, 844, 835 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): 8.51 (d, J = 2.0 Hz, 1H, Het), 8.34 (dd, J = 8.8 Hz, J = 2.1 Hz, 1H, Het), 7.92 (d, J = 8.9 Hz, 1H, Het), 6.93-6.65 (t, J = 52.2 Hz, 1H, CH).

¹⁹F-NMR (CDCl₃, 300 MHz): –119.9 ppm.

¹³C NMR (101 MHz, CDCl₃) δ 149.8 (Cq), 144.62 (Cq), 121.85 (CH), 121.36 (CH), 109.02 (Cq), 108.38 (CH), 106.61 (CH), 104.20 (Cq).


6.1.3 Synthesis of the catalysts: derivatives of the Jorgensen-Hayashi catalyst

The catalysts were synthesised following the procedure described in literature. The ¹H-NMR of the catalysts are consistent with the ones provided in literature.
6.1.4 Synthesis of 3-(6-nitrobenzoxazol-2-yl)-2-phenylbutanal (235a)

Scheme 101. General scheme of the Michael addition step

In a vial the following reagents were sequentially added: (S)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (20 mol% equiv, 17 mg, 0.052 mmol), cinnamaldehyde (34 mg, 0.260 mmol, 1 equiv), 2-ethyl-6-nitrobenzoxazole (50 mg, 0.260 mmol, 1 equiv), Pd(OAc)$_2$ (5 mol% equiv, 3 mg, 0.013 mmol) and TEA (50% equiv, 13 mg, 0.130 mmol) and finally EtOAc (0.5 mL). The reaction mixture was stirred at 40 °C for 3 days and then concentrated in vacuo. The crude was purified by flash column chromatography (hexane/EtOAc 10:1) to obtain the desired product.

**Diastereomer 1** (major): $^1$H-NMR (400 MHz, CDCl$_3$) δ 9.52 (t, $J = 1.6$ Hz, 1H, CHO), 8.46 (d, $J = 2.1$ Hz, 1H, Het), 8.33 (dd, $J = 8.8$, 2.1 Hz, 1H, Het), 7.81 (d, $J = 8.8$ Hz, 1H, Het), 7.39-7.23 (m, 5H, Ph), 3.75 (m, 1H, CHPh), 3.47 (dq, $J = 14.0$, 7.0 Hz, 1H, CHCH$_3$), 2.93 (ddddd, $J = 17.0$, 8.7, 1.8 Hz, 1H, CH$_2$), 2.80 (dddd, $J = 17.0$, 5.6, 1.5 Hz, 1H, CH$_2$), 1.29 (d, $J = 7.0$ Hz, 3H, CH$_3$).

**Diastereomer 2** (minor): $^1$H-NMR (400 MHz, CDCl$_3$) δ 9.62 (t, $J = 1.5$ Hz, 1H, CHO), 8.28 (d, $J = 2.1$ Hz, 1H, Het), 8.19 (dd, $J = 8.7$, 2.1 Hz, 1H, Het), 7.66 (d, $J = 8.7$ Hz, 1H, Het), 7.17-7.00 (m, 5H, Ph), 3.82-3.75 (m, 1H, CHPh), 3.48 (dq, $J = 13.9$, 7.0 Hz, 1H, CHHet), 3.07-2.89 (m, 2H, CH$_2$), 1.41 (d, $J = 7.0$ Hz, 3H, CH$_3$).

The instability of this final compound did not allow further characterisation. The derivatised products were fully characterised in the next section.
6.1.5 **General procedure**

Scheme 102. General scheme of the Michael addition and subsequent Wittig derivatisation

In a vial the following reagents were sequentially added: the organic catalyst (20 mol% equiv), α,β-unsaturated aldehyde (2 equiv), azaarene (1 equiv), Pd(OAc)$_2$ (5 mol% equiv) and CH$_3$CN (1 mL). To the crude solution was finally added TEA (50 mol% equiv). The reaction mixture was stirred at the temperature and time reported in Table 7 and
Table 8 and then concentrated in vacuo. In a vial were then added: the crude obtained after the first reaction, an excess of methyl triphenylphosphoranylidene acetate (>3 equiv) and DCM as the solvent. The reaction mixture was stirred at rt for 48 hours and then concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc) to obtain the desired product.
methyl (E)-6-(6-nitrobenzoxazol-2-yl)-5-phenylhept-2-enoate (259a)

![Chemical Structure](image)

The reaction was performed following the general procedure adding: the organic catalyst ((S)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (19 mg, 0.052 mmol, 20 mol% equiv), cinnamaldehyde (69 mg, 0.520 mmol, 2 equiv), 2-ethyl-6-nitrobenzoxazole (50 mg, 0.260 mmol, 1 equiv), Pd(OAc)$_2$ (3 mg, 0.013 mmol, 5 mol% equiv) and CH$_3$CN (1 mL). To the crude solution DIPEA (17 mg, 0.130 mmol, 50 mol% equiv) was finally added. The first reaction was stirred for 24 hours before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 83 mg of the desired products as a yellow oil. Yield: 84%.

The diastereomeric ratio was determined by the crude NMR: 1.3:1

**Diastereomer 1** (major):

methyl (5R,6R,E)-6-(6-nitrobenzoxazol-2-yl)-5-phenylhept-2-enoate

![Chemical Structure](image)

**IR (CHCl$_3$, liquid film):** 2924, 2854, 2168, 1720 (ester), 1655, 1562, 1524 (aromatic NO$_2$), 1454, 1435, 1346 (aromatic NO$_2$), 1269, 1165, 1041, 825 cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 8.36 (d, $J = 2.1$ Hz, 1H, Het), 8.24 (dd, $J = 8.8, 2.1$ Hz, 1H, Het), 7.71 (d, $J = 8.8$ Hz, 1H, Het), 7.32 – 7.06 (m, 5H, Ph), 6.55 (ddd, $J = 15.4, 7.7, 6.8$ Hz, 1H, =CHCH$_2$), 5.49 (dt, $J = 15.6, 1.3$ Hz, 1H, =CHCO$_2$Me), 3.48 (s, 3H, OCH$_3$), 3.37 (dq, $J = 9.8, 6.9$ Hz, 1H, CHCH$_2$), 3.26 – 3.14 (m, 1H, CHCH$_2$), 2.53 (ddddd, $J = 15.3, 8.4, 6.7, 1.5$ Hz, 1H, CH$_2$), 2.46 – 2.33 (m, 1H, CH$_2$), 1.17 (d, $J = 6.7$ Hz, 3H, CH$_3$).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 173.2 (Cq), 165.3 (Cq), 148.6 (Cq), 145.4 (Cq), 144.6 (CH), 144.2 (Cq), 139.5 (Cq), 127.9 (CH), 126.9 (CH), 126.4 (CH), 121.5 (CH), 119.5 (CH), 118.8 (CH), 106.2 (CH), 50.3 (CH$_3$), 48.7 (CH), 39.2 (CH), 36.3 (CH$_2$), 16.0 (CH$_3$).
The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm): \( t_r \) (major) = 29.5, \( t_r \) (minor) = 33.6, 88% ee.

\[ [\alpha]_{D}^{20} = -1.1^\circ \ (c = 0.75, \text{CHCl}_3) \]

**MS (ESI+) m/z**: 381.1 [M+H]+; HRMS (ESI+) Exact mass calculated for C\textsubscript{21}H\textsubscript{21}N\textsubscript{2}O\textsubscript{5} [M+H]+: 381.1445, found: 381.1445.

**Diastereomer 2 (minor):**

methyl (5\textit{R},6\textit{S},\textit{E})-6-(6-nitrobenzoxazol-2-yl)-5-phenylhept-2-enoate

**IR (CHCl\textsubscript{3}, liquid film):** 2924, 2854, 2172, 1720 (ester), 1659, 1562, 1524 (aromatic NO\textsubscript{2}), 1454, 1435, 1346 (aromatic NO\textsubscript{2}), 1269, 1161, 1038, 825 cm\textsuperscript{-1}.

\(^1\text{H}-\text{NMR (400 MHz, CDCl}_3\text{)} \delta 8.26 (d, \text{J} = 2.1 \text{ Hz}, 1\text{H, Het}), 8.18 (dd, \text{J} = 8.8, 2.1 \text{ Hz}, 1\text{H, Het}), 7.64 (d, \text{J} = 8.8 \text{ Hz}, 1\text{H, Het}), 7.18 – 6.95 (m, 5\text{H, Ph}), 6.69 (dt, \text{J} = 15.5, 7.2 \text{ Hz}, 1\text{H, =CHCH}_2\text{), 5.73 (dt, \text{J} = 15.6, 1.3 \text{ Hz}, 1\text{H, =CHCO}_2\text{Me), 3.56 (s, 3\text{H, OCH}_3\text{), 3.50 – 3.38 (m, 1\text{H, CHCH}_3\text{), 3.29 (dt, \text{J} = 9.2, 6.1 \text{ Hz}, 1\text{H, CHCH}_2\text{), 2.81 – 2.60 (m, 2\text{H, CH}_2\text{), 1.43 (d, \text{J} = 7.0 \text{ Hz}, 3\text{H, CH}_3\text{).}}}}

\(^{13}\text{C}-\text{NMR (101 MHz, CDCl}_3\text{)} \delta 173.5 (\text{Cq), 166.5 (Cq), 149.5 (Cq), 146.3 (Cq), 146.0 (CH), 145.0 (Cq), 140.1 (Cq), 128.6 (CH), 127.9 (CH), 127.3 (CH), 123.0 (CH), 120.4 (CH), 119.6 (CH), 107.0 (CH), 51.4 (CH), 48.9 (CH), 40.1 (CH), 34.3 (CH), 15.2 (CH)_3\text{).}}}

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 90:10, flow rate 1.0 mL/min, \( \lambda = 230 \text{ nm): } t_r \) (major) = 34.0, \( t_r \) (minor) = 31.3, 68% ee.

\[ [\alpha]_{D}^{20} = -3.9^\circ \ (c = 0.50, \text{CHCl}_3) \]
**MS (ESI+) m/z:** 381.1 [M+H]+; **HRMS (ESI+)** Exact mass calculated for C_{21}H_{21}N_{2}O_{5} [M+H]+: 381.1445, found: 381.1441.

**methyl (E)-6-(6-nitrobenzoxazol-2-yl)-5-(p-tolyl)hept-2-enoate (259b)**

The reaction was performed following the general procedure adding: the organic catalyst (S)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (38 mg, 0.104 mmol, 20 mol% equiv), (E)-3-(p-tolyl)acrylaldehyde (152 mg, 1.040 mmol, 2 equiv), 2-ethyl-6-nitrobenzoxazole (100 mg, 0.520 mmol, 1 equiv), Pd(OAc)$_2$ (6 mg, 0.026 mmol, 5 mol% equiv) and CH$_3$CN (1 mL). To the crude solution was finally added TEA (26 mg, 0.260 mmol, 50 mol% equiv). The first reaction was stirred for 48 hours at 30 °C before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 10:1) to obtain 141 mg of the desired product as a yellow oil. Yield: 69%. The diastereomeric ratio was determined by the crude NMR: 1.3:1

**Diastereomer 1**, major:

methyl (5R,6R,E)-6-(6-nitrobenzoxazol-2-yl)-5-(p-tolyl)hept-2-enoate

**IR (CHCl$_3$, liquid film):** 2978, 2947, 1720 (ester), 1655, 1562, 1524 (aromatic NO$_2$), 1435, 1342 (aromatic NO$_2$), 1269, 1119, 1041 cm$^{-1}$.

**$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$**

8.35 (d, $J = 2.1$ Hz, 1H, Het), 8.22 (dd, $J = 8.7$, 2.1 Hz, 1H, Het), 7.70 (d, $J = 8.8$ Hz, 1H, Het), 7.06 (d, $J = 7.9$ Hz, 2H, Ar), 6.97 (d, $J = 8.1$ Hz, 2H, Ar), 6.55 (ddd, $J = 15.4$, 7.8, 6.8 Hz, 1H, =CHCH$_2$), 5.49 (dt, $J = 15.5$, 1.4 Hz, 1H, =CHCO$_2$Me),
3.47 (s, 3H, OCH₃), 3.33 (dq, J = 9.6, 6.9 Hz, 1H, CHCH₃), 3.16 (td, J = 9.1, 5.7 Hz, 1H, CHCH₂), 2.51 (dddd, J = 15.4, 8.5, 6.7, 1.5 Hz, 1H, CH₂), 2.38 (dddd, J = 15.4, 7.9, 6.1, 1.5, 1H, CH₂), 2.25 (s, 3H, CH₃Ar), 1.16 (d, J = 6.9 Hz, 3H, CH₃).

$^{13}$C-NMR (101 MHz, CDCl₃) δ 174.3 (Cq), 166.3 (Cq), 149.6 (Cq), 146.4 (Cq), 145.8 (CH), 145.1 (Cq), 137.3 (Cq), 136.98 (Cq), 129.6 (CH), 127.8 (CH), 122.4 (CH), 120.5 (CH), 119.7 (CH), 107.2 (CH), 51.3 (CH₃), 49.3 (CH), 40.2 (CH₂), 37.4 (CH₂), 21.1 (CH₃), 16.9 (CH₃).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 29.5, tᵣ (minor) = 32.6, 85% ee.

$[\alpha]_D^{20} = -1.8^\circ$ (c = 1.29, CHCl₃)


Diastereomer 2, minor:

methyl (5R,6S,E)-6-(6-nitrobenzoxazol-2-yl)-5-(p-tolyl)hept-2-enoate

IR (CHCl₃, liquid film): 2982, 2947, 1720 (ester), 1659, 1562, 1524 (aromatic NO₂), 1435, 1346 (aromatic NO₂), 1269, 1119, 1041 cm⁻¹.

$^1$H-NMR (400 MHz, CDCl₃) δ 8.57 (d, J = 2.1 Hz, 1H, Het), 8.47 (dd, J = 8.8, 2.1 Hz, 1H, Het), 7.94 (d, J = 8.8 Hz, 1H, Het), 7.23 (d, J = 8.0 Hz, 2H, Ar), 7.16 (d, J = 8.1 Hz, 2H, Ar), 6.99 (dt, J = 15.5, 7.2 Hz, 1H, CHCH₂), 6.03 (dt, J = 15.6, 1.2 Hz, 1H, CHCO₂Me), 3.86 (s, 3H, OCH₃), 3.72 (dt, J₁ = J₂ = 6.9 Hz, 1H, CHCH₃), 3.55 (dt, J = 9.3, 6.0 Hz, 1H, CHCH₂), 3.06 – 2.89 (m, 2H, CH₂), 2.48 (s, 3H, CH₃Ar), 1.71 (d, J = 7.0 Hz, 3H, CH₃).
$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 173.6 (Cq), 166.5 (Cq), 149.5 (Cq), 146.3 (Cq), 146.2 (CH), 145.0 (Cq), 137.0 (Cq), 136.8 (Cq), 129.3 (CH), 127.8 (CH), 122.9 (CH), 120.4 (CH), 119.6 (CH), 107.0 (CH), 51.4 (CH$_3$), 48.5 (CH), 40.2 (CH), 34.4 (CH$_2$), 21.0 (CH$_3$), 15.1 (CH$_3$).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm): t$_r$ (major) = 31.2, t$_r$ (minor) = 29.5, 54% ee.

$[\alpha]_D^{20} = -12.2^o$ (c = 0.51, CHCl$_3$)

**MS (ESI+) m/z:** 395.1 [M+H]$^+$; **HRMS (ESI+)** Exact mass calculated for C$_{22}$H$_{23}$N$_2$O$_5$ [M+H]$^+$: 395.1601, found: 395.1606.

methyl (E)-5-(4-fluorophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate (259c)

![Chemical structure](image)

The reaction was performed following the general procedure adding: the organic catalyst (S)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (38 mg, 0.104 mmol, 20 mol% equiv), (E)-3-(4-fluorophenyl)acrylaldehyde (234 mg, 1.560 mmol, 2 equiv), 2-ethyl-6-nitrobenzoxazole (100 mg, 0.520 mmol, 1 equiv), Pd(OAc)$_2$ (6 mg, 0.026 mmol, 5 mol% equiv) and CH$_3$CN (1 mL). To the crude solution was finally added TEA (26 mg, 0.260 mmol, 50 mol% equiv). The first reaction was stirred for 40 hours at 35 °C before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 168 mg of the desired product as yellow oil. Yield: 81%. The diastereomeric ratio was determined by the crude NMR: 1.1:1
Diastereomer 1:

methyl (5R,6R,E)-5-(4-fluorophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate

IR (CHCl₃, liquid film): 2922, 2852 (stretch HC=C), 1721 (stretch C=O, ester), 1564, 1526 (aromatic NO₂), 1437, 1346 (aromatic NO₂), 1269 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 8.61 (d, J = 2.0 Hz, 1H, Het), 8.49 (dd, J = 8.8, 2.0 Hz, 1H, Het), 7.97 (d, J = 8.8 Hz, 1H, Het), 7.33 (dd, J = 8.5, 5.4 Hz, 2H, Ar), 7.23 – 7.19 (m, 2H, Ar), 6.80 (dt, J = 15.5, 7.4 Hz, 1H, =CHCH₂), 5.76 (d, J = 15.6 Hz, 1H, =CHCO₂Me), 3.74 (s, 3H, OCH₃), 3.59 (dq, J = 9.7, 6.9 Hz, 1H, CHCH₃), 3.47 (td, J = 9.1, 5.7 Hz, 1H, CHCH₂), 2.83 – 2.60 (m, 2H, CH₂), 1.42 (d, J = 6.9 Hz, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 173.9 (Cq), 166.2 (Cq), 162.0 (J = 246.0 Hz, Cq), 149.6 (Cq), 146.3 (Cq), 145.3 (CH), 145.2 (Cq), 136.1 (J = 3.3 Hz, Cq), 129.4 (J = 7.9 Hz, CH), 122.7 (CH), 120.6 (CH), 119.8 (CH), 115.9 (J = 21.3 Hz, CH), 107.2 (CH), 51.4 (CH₃), 48.9 (CH), 40.2 (CH), 37.3 (CH₂), 16.9 (CH₃).

¹⁹F NMR (376 MHz, CDCl₃) δ -114.92.

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 93:7, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 38.5, tᵣ (minor) = 43.1, 86% ee.

[α]D¹⁹ = -6.3° (c = 0.8, CHCl₃)

MS (ESI⁺) m/z: 399.1 [M+H]⁺

Diastereomer 2:

methyl (5R,6S,E)-5-(4-fluorophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate

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\text{H}
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IR (CHCl\textsubscript{3}, liquid film): 2921, 2852 (stretch HC=\text{C}), 1721 (stretch C=O, ester), 1564, 1526 (aromatic NO\textsubscript{2}), 1437, 1345 (aromatic NO\textsubscript{2}), 1269 cm\textsuperscript{-1}

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} \delta 8.51 (d, J = 2.0 Hz, 1H, Het), 8.42 (dd, J = 8.8, 2.1 Hz, 1H, Het), 7.88 (d, J = 8.8 Hz, 1H, Het), 7.20 (dd, J = 8.5, 5.4 Hz, 2H, Ar), 7.08 - 7.04 (m, 2H, Ar), 6.91 (dt, J = 14.9, 7.2 Hz, 1H, =CHCH\text{\textsubscript{2}}), 5.96 (d, J = 15.6 Hz, 1H, =CHCO\text{\textsubscript{2}}Me), 3.81 (s, 3H, OCH\textsubscript{3}), 3.66 (dq, J = 13.09, 7.0 Hz, 1H, CHCH\text{\textsubscript{3}}), 3.56 – 3.46 (m, 1H, CHCH\text{\textsubscript{2}}), 3.05 – 2.94 (m, 1H, CH\text{\textsubscript{2}}), 2.92 – 2.79 (m, 1H, CH\text{\textsubscript{2}}), 1.67 (d, J = 7.0 Hz, 3H, CH\text{\textsubscript{3}}).

\textbf{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})} \delta 173.2 (Cq), 166.4 (Cq), 161.8 (J = 246.0 Hz, Cq), 149.5 (Cq), 146.2 (Cq), 145.6 (CH), 145.0 (Cq), 135.8 (J = 3.3 Hz, Cq), 129.4 (J = 8.0 Hz, CH), 123.2 (CH), 120.5 (CH), 119.7 (CH), 115.5 (J = 21.3 Hz, CH), 107.0 (CH), 51.5 (CH\text{\textsubscript{3}}), 48.3 (CH), 40.2 (CH), 34.6 (CH\text{\textsubscript{2}}), 15.5 (CH\text{\textsubscript{3}}).

\textbf{\textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3})} \delta –115.08.

The enantiomeric excess was determined by \textbf{HPLC} using a Chiralpak IE column (hexane/iPrOH = 93:7, flow rate 1.0 mL/min, \(\lambda = 230\) nm): \(t_r\) (major) = 40.4, \(t_r\) (minor) = 42.3, 99% ee.

\([\alpha]_D^{19} = -1.65^\circ\) (c = 1, CHCl\textsubscript{3})

\textbf{MS (ESI+) m/z:} 399.1 [M+H]\textsuperscript{+}; \textbf{HRMS (ESI+)} Exact mass calculated for C\textsubscript{21}H\textsubscript{20}FN\textsubscript{2}O\textsubscript{5} [M+H]\textsuperscript{+}: 399.1351, found: 399.1349; Exact mass calculated for C\textsubscript{21}H\textsubscript{19}FN\textsubscript{2}NaO\textsubscript{5} [M+Na]\textsuperscript{+}: 421.1170, found: 421.1169.
The reaction was performed following the general procedure adding: the organic
catalyst (S)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (38 mg, 0.104
mmol, 20 mol% equiv), (E)-3-(4-chlorophenyl)acrylaldehyde (173 mg, 1.040 mmol, 2
equiv), 2-ethyl-6-nitrobenzoxazole (100 mg, 0.520 mmol, 1 equiv), Pd(OAc)$_2$ (6 mg,
0.026 mmol, 5 mol% equiv) and CH$_3$CN (1 mL). To the crude solution was finally added
TEA (26 mg, 0.260 mmol, 50 mol% equiv). The first reaction was stirred for 24 hours at
35 °C before performing the Wittig. The final crude was purified by flash column
chromatography (hexane/EtOAc 10:1) to obtain 187 mg of the desired product as
orange oil. Yield: 87%. The diastereomeric ratio was determined by the crude NMR:
1.3:1

Diastereomer 1, major:

methyl (5R,6R,E)-5-(4-chlorophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate

IR (CHCl$_3$, liquid film): 2924 (stretch HCC=C), 1721 (stretch C=O, ester), 1564, 1526
(aromatic NO$_2$), 1436, 1345 (aromatic NO$_2$), 1269 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.37 (d, $J = 1.7$ Hz, 1H, H$_2$), 8.24 (dd, $J = 8.8$, 1.7 Hz, 1H,
H$_5$), 7.72 (d, $J = 8.8$ Hz, 1H, H$_4$), 7.25 (d, $J = 8.3$ Hz, 2H, H$_3'$), 7.04 (d, $J = 8.3$ Hz, 2H, H$_2'$),
6.53 (dt, $J = 15.2$, 7.3 Hz, 1H, H$_3$), 5.51 (d, $J = 15.6$ Hz, 1H, H$_2$), 3.50 (s, 3H, OCH$_3$), 3.33
(dq, J = 14.0, 6.9 Hz, 1H, H₆), 3.21 (td, J = 9.1, 5.7 Hz, 1H, H₅), 2.49 (ddd, J = 14.7, 7.5 Hz, 1H, H₄), 2.40 (ddd, J = 14.7, 7.1 Hz, 1H, H₄), 1.17 (d, J = 6.9 Hz, 3H, CH₃).

**¹³C NMR (101 MHz, CDCl₃) δ** 173.8 (C₂), 166.2 (C₁), 149.6 (C₇₄), 146.3 (C₃₄), 145.2 (C₆), 145.1 (C₃), 138.9 (C₄′), 133.2 (C₅′), 129.3 (C₃′ or C₅′), 128.9 (C₂), 120.6 (C₅), 117.3 (C₄), 107.3 (C₂), 51.4 (OCH₃), 49.0 (C₅), 40.1 (C₆), 37.1 (C₄), 16.9 (C₇).

The enantiomeric excess was determined by **HPLC** using a Chiralpak IE column (hexane/iPrOH = 95:5, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 58.7, tᵣ (minor) = 69.0, 64% ee.

[α]D²⁰ = −8.3° (c = 1.2, CHCl₃)

**MS (ESI+) m/z:** 415.0 [M+H]⁺; **HRMS (ESI+)** Exact mass calculated for C₂₁H₁₉ClNaO₅Na [M+Na]⁺: 437.08747, found: 437.08850; Exact mass calculated for C₂₁H₁₉ClKN₂O₅ [M+K]⁺: 453.06141, found: 453.06224.

**Diastereomer 2:**

methyl (5R,6S,E)-5-(4-chlorophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate

![Chemical Structure](image)

**IR (CHCl₃, liquid film):** 2950 (stretch HC=C), 1722 (stretch C=O, ester), 1562, 1526 (aromatic NO₂), 1436, 1345 (aromatic NO₂), 1269 cm⁻¹

**¹H NMR (400 MHz, CDCl₃) δ** 8.59 (s, 1H, Het), 8.50 (d, J = 8.7 Hz, 1H, Het), 7.95 (d, J = 8.7 Hz, 1H, Het), 7.42 (d, J = 7.8 Hz, 2H, Ar), 7.24 (d, J = 7.9 Hz, 2H, Ar), 6.97 (dt, J = 7.1, 15.1 Hz, 1H, =CHCH₂), 6.03 (d, J = 15.6 Hz, 1H, =CHCO₂Me), 3.88 (s, 3H, OCH₃), 3.7 (dt, J = 6.7, 13.8 Hz, 1H, CHCH₃), 3.63 – 3.54 (m, 1H, CHCH₂), 3.11 – 3.00 (m, 1H, CH₂), 2.99 – 2.87 (m, 1H, CH₂), 1.73 (d, J = 6.9 Hz, 3H, CH₃).
\(^{13}\text{C}\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 173.1 (Cq), 166.4 (Cq), 149.5 (Cq), 146.2 (Cq), 145.4 (CH), 145.1 (Cq), 138.6 (Cq), 133.1 (Cq), 129.3 (CH), 128.8 (CH), 123.4 (CH), 120.5 (CH), 119.7 (CH), 107.1 (CH), 51.5 (CH\(_3\)), 48.3 (CH), 40.0 (CH), 34.4 (CH\(_2\)), 15.4 (CH\(_3\)).

The enantiomeric excess was determined by HPLC using a Chiralpak IB column (hexane/iPrOH = 95:5, flow rate 1.0 mL/min, \(\lambda = 230\) nm): \(t_r\) (major) = 30.3, \(t_r\) (minor) = 27.1, 98\% ee.

\([\alpha]_D^{20} = -9.9^\circ\) (c = 1.1, CHCl\(_3\))

**MS (ESI\(^+\))** m/z: 415.0 [M+H]\(^+\); HRMS (ESI\(^+\)) Exact mass calculated for C\(_{21}\)H\(_{19}\)Cl\(^{35}\)N\(_2\)NaO\(_5\) [M+Na]\(^+\): 437.08747, found: 437.08842; Exact mass calculated for C\(_{21}\)H\(_{19}\)Cl\(^{35}\)KN\(_2\)O\(_5\) [M+K]\(^+\): 453.06141, found: 453.06249.

**methyl (E)-5-(4-bromophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate (259e)**

![methyl (E)-5-(4-bromophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate (259e)](image)

The reaction was performed following the general procedure adding: the organic catalyst (S)-2-((((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (38 mg, 0.104 mmol, 20 mol% equiv), (E)-3-(4-bromophenyl)acrylaldehyde (329 mg, 1.560 mmol, 2 equiv), 2-ethyl-6-nitrobenzoxazole (100 mg, 0.520 mmol, 1 equiv), Pd(OAc)\(_2\) (6 mg, 0.026 mmol, 5 mol% equiv) and CH\(_3\)CN (1 mL). To the crude solution was finally added TEA (26 mg, 0.260 mmol, 50 mol% equiv). The first reaction was stirred for 40 hours at 30 °C before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 188 mg of the desired product as yellow oil. Yield: 79\%. The diastereomeric ratio was determined by the crude NMR: 1.5:1.
Diastereomer 1, major:

methyl (5R,6R,E)-5-(4-bromophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate

IR (CHCl₃, liquid film): 3105, 2924, 2854, 1729 (ester), 1659, 1562, 1524 (aromatic NO₂), 1435, 1346 (aromatic NO₂), 1315, 1269 cm⁻¹

¹H-NMR (400 MHz, CDCl₃) δ 8.37 (d, J = 2.0 Hz, 1H, Het), 8.24 (dd, J = 8.8, 2.0 Hz, 1H, Het), 7.72 (d, J = 8.8 Hz, 1H, Het), 7.40 (d, J = 8.3 Hz, 2H, Ar), 6.99 (d, J = 8.3 Hz, 2H, Ar), 6.53 (dt, J = 7.4, 15.2, 1H, =C(CH₂)₂), 5.51 (bd, J = 15.6 Hz, 1H, =CHO₂Me), 3.50 (s, 3H, OCH₃), 3.33 (dq, J = 8.9, 6.9 Hz, 1H, CH(CH₃)₂), 3.20 (td, J = 9.2, 5.7 Hz, 1H, CHCH₂), 2.55 – 2.35 (m, 2H, CH₂), 1.17 (d, J = 8.5 Hz, 3H, CH₃).

¹³C-NMR (101 MHz, CDCl₃) δ 173.7 (Cq), 166.2 (Cq), 149.6 (Cq), 146.3 (Cq), 145.2 (Cq), 145.0 (CH), 139.4 (Cq), 132.1 (CH), 129.6 (CH), 122.9 (CH), 121.3 (Cq), 120.6 (CH), 119.9 (CH), 107.3 (CH), 51.4 (CH₃), 49.1 (CH), 40.0 (CH), 37.1 (CH₂), 16.9 (CH₃).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 32.1, tᵣ (minor) = 36.0, 73% ee.

[α]D²⁰ = −7.6° (c = 1.75, CHCl₃)

Diastereomer 2, minor:

methyl (5R,6S,E)-5-(4-bromophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate

IR (CHCl₃, liquid film): 3105, 2924, 2854, 1720 (ester), 1659, 1562, 1520 (aromatic NO₂), 1435, 1346 (aromatic NO₂), 1435, 1315, 1269 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃) δ 8.28 (d, J = 2.0 Hz, 1H, Het), 8.19 (dd, J = 8.8, 2.0 Hz, 1H, Het), 7.65 (d, J = 8.8 Hz, 1H, Het), 7.27 (d, J = 8.4 Hz, 2H, Ar), 6.88 (d, J = 8.4 Hz, 2H, Ar), 6.65 (dt, J = 15.2, 7.1, 1H, =CHCH₂), 5.72 (d, J = 15.6 Hz, 1H, =CHCO₂Me), 3.58 (s, 3H, OCH₃), 3.42 (dq, J₁ = J₂ = 6.8 Hz, 1H, CHCH₃), 3.31 – 3.22 (m, 1H, CHCH₂), 2.79 – 2.69 (m, 1H, CH₂), 2.67 – 2.56 (m, 1H, CH₂), 2.42 (d, J = 7.0 Hz, 3H, CH₃).

¹³C-NMR (101 MHz, CDCl₃) δ 173.0 (Cq), 166.4 (Cq), 149.5 (Cq), 146.2 (Cq), 145.3 (Cq), 145.1 (CH), 139.2 (Cq), 131.8 (CH), 129.6 (CH), 123.4 (CH), 121.2 (Cq), 120.5 (CH), 119.8 (CH), 107.1 (CH), 51.5 (CH₃), 48.4 (CH), 39.9 (CH), 34.4 (CH₂), 15.4 (CH₃).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 95:5, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 23.6, tᵣ (minor) = 22.5, 99% ee.

[α]D²⁰ = −20.3° (c = 1.38, CHCl₃)

methyl (E)-6-(6-nitrobenzozazol-2-yl)-5-(4-nitrophenyl)hept-2-enoate (259f)

The reaction was performed following the general procedure adding: the organic catalyst (S)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (38 mg, 0.104 mmol, 20 mol% equiv), (E)-3-(4-nitrophenyl)acrylaldehyde (184 mg, 1.040 mmol, 2 equiv), 2-ethyl-6-nitrobenzoxazole (100 mg, 0.520 mmol, 1 equiv), Pd(OAc)$_2$ (6 mg, 0.026 mmol, 5 mol% equiv) and CH$_3$CN (1 mL). To the crude solution was finally added TEA (26 mg, 0.260 mmol, 50 mol% equiv). The first reaction was stirred at 30 °C for 24 hours before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 133 mg of the desired product as an orange oil (major diastereomer) and orange solid (minor diastereomer). Yield: 60%. The diastereomeric ratio was determined by the crude NMR: 1.4:1

**Diastereomer 1**, major:

methyl (5R,6R,E)-6-(6-nitrobenzoxazol-2-yl)-5-(4-nitrophenyl)hept-2-enoate

**IR (CHCl$_3$, liquid film):** 2954, 2924, 2854, 2360, 2341, 1720 (ester), 1601, 1562, 1524 (aromatic NO$_2$), 1435, 1346 (aromatic NO$_2$), 1269 cm$^{-1}$.

**$^1$H-NMR (400 MHz, CDCl$_3$)** $\delta$ 8.37 (d, $J = 1.8$ Hz, 1H, Het), 8.25 (dd, $J = 8.8, 1.1$ Hz, 1H, Het), 8.15 (d, $J = 8.5$ Hz, 2H, Ar), 7.73 (d, $J = 8.8$ Hz, 1H, Het), 7.31 (d, $J = 8.7$ Hz, 2H, Ar), 6.53 (dt, $J = 15.4, 7.3$ Hz, 1H, =CHCH$_2$), 5.53 (d, $J = 15.6$ Hz, 1H, =CHCO$_2$Me), 3.50 (s, 3H, OCH$_3$), 3.48 – 3.36 (m, 2H, CHCH$_3$, CHCH$_2$), 2.61 – 2.45 (m, 2H, CH$_2$), 1.19 (d, $J = 6.3$ Hz, 3H, CH$_3$).
\(^{13}\)C-NMR (101 MHz, CDCl\(_3\)) \(\delta\) 173.0 (Cq), 166.0 (Cq), 149.6 (Cq), 148.0 (Cq), 147.3 (Cq), 146.2 (Cq), 145.3 (Cq), 144.2 (CH), 129.0 (CH), 124.2 (CH), 123.4 (CH), 120.7 (CH), 120.0 (CH), 107.3 (CH), 51.5 (CH\(_3\)), 49.3 (CH), 39.8 (CH), 36.8 (CH\(_2\)), 16.9 (CH\(_3\)).

The enantiomeric excess was determined by HPLC using a Chiralpak IC column (hexane/iPrOH = 70:30, flow rate 1.0 mL/min, \(\lambda = 230\) nm): \(t_r\) (major) = 70.7, \(t_r\) (minor) = 76.9, 78% ee.

\([\alpha]_D^{20} = -3.4^\circ\) (c = 1.53, CHCl\(_3\))

**MS (ESI+) m/z:** 426.0 [M+H]\(^+\); **HRMS (ESI+) Exact mass calculated for** C\(_{21}\)H\(_{20}\)N\(_3\)O\(_7\) [M+H]\(^+\): 426.1296, found: 426.1288; **Exact mass calculated for** C\(_{21}\)H\(_{19}\)N\(_3\)NaO\(_7\) [M+Na]\(^+\): 448.1115, found: 448.1107.

Diastereomer 2, minor:

methyl (5\(R\),6\(S\),E)-6-(6-nitrobenzoxazol-2-yl)-5-(4-nitrophenyl)hept-2-enoate

\[\text{mp: 151 °C}\]

**IR (CHCl\(_3\), liquid film):** 2955, 2924, 2854, 2361, 2341, 1720 (ester), 1601, 1562, 1524 (aromatic NO\(_2\)), 1439, 1346 (aromatic NO\(_2\)), 1269 cm\(^{-1}\).

\(^{1}\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.28 (d, \(J = 2.0\) Hz, 1H, Het), 8.19 (dd, \(J = 8.8, 2.1\) Hz, 1H, Het), 8.02 (d, \(J = 8.8\) Hz, 2H, Ar), 7.64 (d, \(J = 8.8\) Hz, 1H, Het), 7.20 (d, \(J = 8.0\) Hz, 2H, Ar), 6.64 (dt, \(J = 15.4, 7.2\) Hz, 1H, =CHCH\(_3\)), 5.73 (bd, \(J = 15.6\) Hz, 1H, =CHCO\(_2\)Me), 3.58 (s, 3H, OCH\(_3\)), 3.54 – 3.39 (m, 2H, CHCH\(_3\), CHCH\(_2\)), 2.89 – 2.77 (m, 1H, CH\(_2\)), 2.73 – 2.61 (m, 1H, CH\(_2\)), 1.47 (d, \(J = 6.8\) Hz, 3H, CH\(_3\)).

\(^{13}\)C-NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.4 (Cq), 166.2 (Cq), 149.5 (Cq), 147.9 (Cq), 147.2 (Cq), 146.0 (Cq), 145.2 (Cq), 144.4 (CH), 128.9 (CH), 123.89 (CH), 123.86 (CH), 120.6 (CH), 119.9 (CH), 107.1 (CH), 51.6 (CH\(_3\)), 48.7 (CH), 39.7 (CH), 34.4 (CH\(_2\)), 15.8 (CH\(_3\)).
The enantiomeric excess was determined by HPLC using a Chiralpak IC column (hexane/iPrOH = 70:30, flow rate 1.0 mL/min, λ = 230 nm): \( t_r \) (major) = 68.1, \( t_r \) (minor) = 56.0, 99%.

\[ [\alpha]_{D}^{20} = -2.5° \quad (c = 1.55, \text{CHCl}_3) \]

**MS (ESI+) m/z**: 426.1 \([M+H]^+\); **HRMS (ESI+)** Exact mass calculated for \( C_{21}H_{20}N_3O_7 \) \([M+H]^+\): 426.1296, found: 426.1296.

**methyl (E)-5-(4-cyanophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate (259g)**

The reaction was performed following the general procedure adding: the organic catalyst \((S)-2-(((\text{tert}-\text{butyldimethylsilyl})\text{oxy})\text{diphenylmethyl})\text{pyrrolidine} \quad (38 \text{ mg}, 0.104 \text{ mmol}, 20 \text{ mol% equiv}), \quad (E)-4-(3-\text{oxoprop-1-en-1-yl})\text{benzonitrile} \quad (163 \text{ mg}, 1.040 \text{ mmol}, 2 \text{ equiv}), \quad 2-\text{ethyl-6-nitrobenzoxazole} \quad (100 \text{ mg}, 0.520 \text{ mmol}, 1 \text{ equiv}), \quad \text{Pd(OAc)}_2 \quad (6 \text{ mg}, 0.026 \text{ mmol}, 5 \text{ mol% equiv})\) and \( \text{CH}_3\text{CN} \quad (1 \text{ mL}). \) To the crude solution was finally added \( \text{TEA} \quad (26 \text{ mg}, 0.260 \text{ mmol}, 50 \text{ mol% equiv}). \) The first reaction was stirred for 40 hours at 35 °C before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 10:1) to obtain 124 mg of the desired product as dark orange oil. Yield: 59%. The diastereomeric ratio was determined by the crude NMR: 1.3:1

**Diastereomer 1:**

**methyl (5R,6R,E)-5-(4-cyanophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate**
IR (CHCl$_3$, liquid film): 2951 (stretch $HC=C$), 2928, 2229 (stretch C=N), 1720 (stretch C=O, ester), 1562, 1524 (aromatic NO$_2$), 1435, 1346 (aromatic NO$_2$), 1269 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.70 (s, 1H, Het), 8.58 (d, $J = 8.8$ Hz, 1H, Het), 8.06 (d, $J = 8.7$ Hz, 1H, Het), 7.92 (d, $J = 7.8$ Hz, 2H, Ar), 7.58 (d, $J = 7.6$ Hz, 2H, Ar), 6.85 (dt, $J = 14.9$, 7.2 Hz, 1H, =CHCH$_2$), 5.85 (d, $J = 15.6$ Hz, 1H, =CHCO$_2$Me), 3.84 (s, 3H, OCH$_3$), 3.78 – 3.61 (m, 2H, CH$_2$CH$_3$, CH$_2$CH$_2$), 2.91 – 2.74 (m, 2H, CH$_2$), 1.51 (d, $J = 6.5$ Hz, 3H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.1 (Cq), 166.0 (Cq), 149.6 (Cq), 146.2 (Cq), 146.0 (Cq), 145.3 (Cq), 144.3 (CH), 132.8 (CH), 128.9 (CH), 123.3 (CH), 120.7 (CH), 120.0 (CH), 118.4 (Cq), 111.6 (Cq), 107.3 (CH), 51.5 (CH$_3$), 49.6 (CH), 39.8 (CH), 36.8 (CH$_2$), 16.9 (CH$_3$).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 75:25, flow rate 1.0 mL/min, $\lambda = 230$ nm): $t_r$ (major) = 49.0, $t_r$ (minor) = 57.7, 71% ee.

[$\alpha$]$_D^{19}$ = $-10.4^\circ$ (c = 1, CHCl$_3$)

MS (ESI$^+$) $m/z$: 406.0 [M+H]$^+$; HRMS (ESI$^+$) Exact mass calculated for C$_{22}$H$_{20}$N$_3$O$_5$ [M+H]$^+$: 406.1397, found: 406.1393.

Diastereomer 2:

methyl (5R,6S,E)-5-(4-cyanophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate

IR (CHCl$_3$, liquid film): 2951 (stretch $HC=C$), 2928, 2229 (stretch C=N), 1720 (stretch C=O, ester), 1658, 1562, 1527 (aromatic NO$_2$), 1435, 1342 (aromatic NO$_2$), 1269 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.19 (d, $J = 2.1$ Hz, 1H, Het), 8.11 (dd, $J = 8.8$, 2.1 Hz, 1H, Het), 7.56 (d, $J = 8.8$ Hz, 1H, Het), 7.36 (bd, $J = 8.3$ Hz, 2H, Ar), 7.05 (bd, $J = 8.3$ Hz, 2H, Ar), 6.54 (dt, $J = 15.4$, 7.3 Hz, 1H, =CHCH$_2$), 5.63 (dt, $J = 15.7$, 1.4 Hz, 1H, =CHCO$_2$Me),
3.49 (s, 3H, OCH₃), 3.41 – 3.33 (m, 1H, CHCH₃), 3.28 (ddd, J = 9.8, 7.1, 5.2 Hz, 1H, CHCH₂), 2.76 – 2.66 (m, 1H, CH₂), 2.61 – 2.50 (m, 1H, CH₂), 1.36 (d, J = 7.0 Hz, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 172.5 (Cq), 166.2 (Cq), 149.5 (Cq), 146.0 (Cq), 145.8 (Cq), 145.2 (Cq), 144.5 (CH), 132.4 (CH), 128.8 (CH), 123.8 (CH), 120.6 (CH), 119.8 (CH), 118.4 (Cq), 111.4 (Cq), 107.1 (CH), 51.6 (CH₃), 49.0 (CH), 39.7 (CH), 34.3 (CH₂), 15.6 (CH₃).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 74.8, tᵣ (minor) = 70.6, 75% ee.

[α]D₁⁹ = -0.8° (c = 1, CHCl₃)


**methyl (E)-5-(2-bromophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate (259h)**

![Chemical Structure](image)

The reaction was performed following the general procedure adding: the organic catalyst (S)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (38 mg, 0.104 mmol, 20 mol% equiv), (E)-3-(2-bromophenyl)acrylaldehyde (329 mg, 1.560 mmol, 2 equiv), 2-ethyl-6-nitrobenzoxazole (100 mg, 0.520 mmol, 1 equiv), Pd(OAc)₂ (6 mg, 0.026 mmol, 5 mol% equiv) and CH₃CN (1 mL). To the crude solution was finally added TEA (26 mg, 0.260 mmol, 50 mol% equiv). The first reaction was stirred for 24 hours at 35 °C before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 10:1) to obtain 165 mg of the desired product as dark yellow oil. Yield: 69%. The diastereomeric ratio was determined by the crude NMR: 1.6:1
Diastereomer 1:

methyl (5R,6R,E)-5-(2-bromophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate

IR (CHCl₃, liquid film): 2949 (stretch HC=C), 1721 (stretch C=O, ester), 1564, 1525 (aromatic NO₂), 1436, 1345 (aromatic NO₂), 1269 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, J = 2.0 Hz, 1H, Het), 8.54 (dd, J = 8.8, 2.0 Hz, 1H, Het), 8.03 (d, J = 8.8 Hz, 1H, Het), 7.84 (d, J = 8.0 Hz, 1H, Ar), 7.56 (t, J = 7.5 Hz, 1H, Ar), 7.46 – 7.41 (m, 1H, Ar), 7.40 – 7.34 (m, 1H, Ar), 6.85 (dt, J = 15.0, 7.2 Hz, 1H, =CHCH₂), 5.77 (d, J = 15.6 Hz, 1H, =CHCO₂Me), 4.37 - 4.15 (m, 1H, CHCH₂), 3.77 (s, 3H, OCH₃), 3.76 – 3.65 (m, 1H, CHCH₃), 2.86 – 2.67 (m, 2H, CH₂), 1.53 (d, J = 6.9 Hz, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 173.6 (Cq), 166.2 (Cq), 149.7 (Cq), 146.4 (Cq), 145.2 (Cq), 144.9 (CH), 140.0 (Cq), 133.5 (CH), 128.8 (CH), 128.1 (CH), 127.5 (CH), 126.0 (Cq), 122.7 (CH), 120.5 (CH), 119.9 (CH), 107.3 (CH), 51.3 (CH₃), 46.9 (CH), 40.1 (CH), 36.8 (CH₂), 17.1 (CH₃).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 93:7, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 38.3, tᵣ (minor) = 43.0, 85% ee.

[α]D¹⁹ = -12.8° (c = 1, CHCl₃)

Diastereomer 2:

methyl (5R,6S,E)-5-(2-bromophenyl)-6-(6-nitrobenzoxazol-2-yl)hept-2-enoate

![Chemical Structure]

IR (CHCl₃, liquid film): 2924 (stretch HC=O), 1722 (stretch C=O, ester), 1563, 1525 (aromatic NO₂), 1436, 1345 (aromatic NO₂), 1269 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, J = 1.8 Hz, 1H, Het), 8.19 (dd, J = 8.8, 2.0 Hz, 1H, Het), 7.67 (d, J = 8.8 Hz, 1H, Het), 7.47 (d, J = 7.9 Hz, 1H, Ar), 7.16 (d, J = 7.4 Hz, 1H, Ar), 7.08 – 6.95 (m, 2H, Ar), 6.65 (dt, J = 15.2, 7.1 Hz, 1H, =CHCH₂), 5.68 (d, J = 15.7 Hz, 1H, =CHCO₂Me), 4.11 – 3.99 (m, 1H, CHCH₂), 3.59 – 3.56 (m, 1H, CHCH₃), 3.53 (s, 3H, OCH₃), 2.68, 2.65 (m, 2H, CH₂), 1.40 (d, J = 7.1 Hz, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 173.3 (Cq), 166.3 (Cq), 149.7 (Cq), 146.3 (Cq), 145.2 (CH), 145.1 (Cq), 139.2 (CH), 133.5 (CH), 128.7 (CH), 128.6 (Cq), 127.5 (CH), 125.4 (Cq), 123.2 (CH), 120.4 (CH), 119.7 (CH), 107.2 (CH), 51.4 (CH₃), 46.0 (CH), 38.1 (CH), 32.8 (CH₂), 13.7 (CH₃).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 93:7, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 30.2, tᵣ (minor) = 33.1, 53% ee.

[α]D¹⁹ = −69.3° (c = 0.3, CHCl₃)

methyl (E)-5-(4-bromophenyl)-6-(5-chloro-6-nitrobenzoxazol-2-yl)hept-2-enoate (276a)

The reaction was performed following the general procedure adding: the organic catalyst (5)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (32 mg, 0.088 mmol, 20 mol% equiv), (E)-3-(4-bromophenyl)acrylaldehyde (186 mg, 0.882 mmol, 2 equiv), 5-chloro-2-ethyl-6-nitrobenzoxazole (100 mg, 0.441 mmol, 1 equiv), Pd(OAc)_2 (5 mg, 0.022 mmol, 5 mol% equiv) and CH_3CN (1 mL). To the crude solution was finally added TEA (23 mg, 0.221 mmol, 50 mol% equiv). The first reaction was stirred for 24 hours at 35 °C before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 6:1) to obtain 216 mg of the desired product as orange oil. Yield: 99% (122 mg dia1 and 94 mg dia2). The diastereomeric ratio was determined by the crude NMR: 2.7:1

**Diastereomer 1**, major:

methyl (5R,6R,E)-5-(4-bromophenyl)-6-(5-chloro-6-nitrobenzoxazol-2-yl)hept-2-enoate

IR (CHCl_3, liquid film): 2987 (stretch HC=C), 2360, 1720 (stretch C=O, ester), 1560, 1534, 1446, 1348 (aromatic NO_2).

^1H NMR (400 MHz, CDCl_3) δ 8.06 (s, 1H, Het), 7.81 (s, 1H, Het), 7.44 (d, J = 8.3 Hz, 2H, Ar), 7.04 (d, J = 8.4 Hz, 2H, Ar), 6.57 (dt, J = 15.0, 7.3 Hz, 1H, =CHCH_2), 5.55 (bd, J = 15.6 Hz, 1H, =CHCO_2Me), 3.56 (s, 3H, OCH_3), 3.37 (dq, J = 9.3, 6.9 Hz, 1H, CHCH_3), 3.23 (td, J = 8.9, 6.1 Hz, 1H, CHCH_2), 2.61 – 2.37 (m, 2H, CH_2), 1.21 (d, J = 6.9 Hz, 3H, CH_3).
\[^{13}\text{C}\text{ NMR (101 MHz, CDCl}_3\text{)}\ \delta\text{ }174.2\text{ (Cq), 166.1 (Cq), 147.9 (Cq), 145.0 (CH), 144.7 (Cq), 139.4 (Cq), 132.1 (CH), 131.7 (Cq), 129.6 (CH), 123.5 (Cq), 122.8 (CH), 122.4 (CH), 121.3 (Cq), 108.7 (CH), 51.4 (CH\_3), 49.0 (CH), 39.9 (CH), 37.1 (CH\_2), 16.8 (CH\_3).\]

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, \(\lambda = 254\) nm): \(t_r\) (major) = 17.1, \(t_r\) (minor) = 14.6, 99% ee.

\([\alpha]_D^{19} = -3.7^\circ\text{ (c = 4, CHCl}_3\text{)}\]

\(^{\text{MS (ESI+)}\ m/z: 494.7\ [M+H]^+; HRMS (ESI+)\text{ Exact mass calculated for C}_{21}\text{H}_{19}\text{Br}_{79}\text{Cl}_{35}\text{N}_2\text{O}_5\ [M+H]^+: 493.0160, found: 493.0154.}\]

Diastereomer 2, minor:

methyl (5R,6S,E)-5-(4-bromophenyl)-6-(5-chloro-6-nitrobenzoxazol-2-yl)hept-2-enoate

\(^{1}\text{H NMR (400 MHz, CDCl}_3\text{)}\ \delta\text{ }8.00\text{ (s, 1H, Het), 7.76 (s, 1H, Het), 7.34 (d, J = 8.4 Hz, 2H, Ar), 6.93 (d, J = 8.4 Hz, 2H, Ar), 6.70 (dt, J = 14.8, 7.2 Hz, 1H, =CHCH}_2\text{), 5.78 (bd, J = 15.6 Hz, 1H, =CHCO}_2\text{Me), 3.64 (s, 3H, OCH}_3\text{), 3.47 (p, J = 7.0 Hz, 1H, CHCH}_3\text{), 3.30 (ddd, J = 9.5, 7.0, 5.4 Hz, 1H, CHCH}_2\text{), 2.79 (ddd, J = 12.5, 6.8, 1.1 Hz, 1H, CH}_2\text{), 2.73 – 2.59 (m, 1H, CH}_2\text{), 1.47 (d, J = 7.0 Hz, 3H, CH}_3\text{).}\]

\(^{13}\text{C NMR (101 MHz, CDCl}_3\text{)}\ \delta\text{ }173.6\text{ (Cq), 166.3 (Cq), 147.8 (Cq), 145.2 (CH), 144.6 (Cq), 139.1 (Cq), 131.8 (CH), 129.6 (CH), 129.2 (Cq), 123.5 (Cq), 123.4 (CH), 122.3 (CH), 121.3 (Cq), 108.5 (CH), 51.5 (CH\_3), 48.4 (CH), 39.8 (CH), 34.4 (CH\_2), 15.5 (CH\_3).}\]
The enantiomeric excess was determined by HPLC using a Chiralpak IA column (hexane/iPrOH = 75:25, flow rate 1.0 mL/min, λ = 254 nm): \( t_r \) (major) = 9.5, \( t_r \) (minor) = 11.1, 56% ee.

\[ [\alpha]_D^{19} = -18.5^\circ \quad (c = 1.9, \text{CHCl}_3) \]

**HRMS (ESI+)**  Exact mass calculated for \( C_{21}H_{19}Br^{79}Cl^{35}N_2O_5 \) [M+H]+: 493.0160, found: 493.0148.

methyl (E)-5-(4-bromophenyl)-6-(oxazolo[4,5-β]pyridin-2-yl)hept-2-enoate (276f)

The reaction was performed following the general procedure adding: the organic catalyst 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (22 mg, 0.067 mmol, 20 mol% equiv), (E)-3-(4-bromophenyl)acrylaldehyde (142 mg, 0.674 mmol, 2 equiv), 2-ethyloxazolo[4,5-b]pyridine (50 mg, 0.337 mmol, 1 equiv), Pd(OAc)$_2$ (4 mg, 0.017 mmol, 5 mol% equiv) and CH$_3$CN (1 mL). To the crude solution was finally added TEA (17 mg, 0.169 mmol, 50 mol% equiv). The first reaction was stirred for 4 days at 40 °C and 24 hours at 50 °C before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 55 mg of the desired products as yellow oil. Yield: 39%. The diastereomeric ratio was determined by the crude NMR: 1.4:1

**Diastereomer 1:**
methyl (5R,6R,E)-5-(4-bromophenyl)-6-(oxazolo[4,5-β]pyridin-2-yl)hept-2-enoate
IR (CHCl₃, liquid film): 2983 (stretch HC=C), 1720 (stretch C=O, ester), 1560, 1408, 1259 (aromatic NO₂).

¹H NMR (400 MHz, CDCl₃) δ 8.69 (dd, J = 4.9, 1.3 Hz, 1H, Het), 7.93 (dd, J = 8.1, 1.3 Hz, 1H, Het), 7.58 (d, J = 8.4 Hz, 2H, Ar), 7.41 (dd, J = 8.1, 4.9 Hz, 1H, Het), 7.19 (d, J = 8.4 Hz, 2H, Ar), 6.72 (dt, J = 15.3, 7.3 Hz, 1H, =CHCH₂), 5.70 (d, J = 15.6 Hz, 1H, =CHCO₂Me), 3.70 (s, 3H, OCH₃), 3.55 – 3.47 (m, 1H, CH₃CH₂), 3.40 (td, J = 9.2, 5.3 Hz, 1H, CHCH₂), 2.73 – 2.55 (m, 2H, CH₂), 1.35 (d, J = 6.9 Hz, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 171.9 (Cq), 166.3 (Cq), 155.6 (Cq), 146.5 (CH), 145.4 (CH), 142.7 (Cq), 139.7 (Cq), 132.0 (CH), 129.7 (CH), 122.8 (CH), 121.1 (Cq), 120.0 (CH), 118.2 (CH), 51.4 (CH₃), 49.0 (CH), 40.1 (CH), 37.1 (CH₂), 17.1 (CH₃).

The enantiomeric excess was determined by HPLC using a Chiralpak ID column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 32.8, tᵣ (minor) = 37.2, 29% ee.

[α]D₁⁰ = –0.72° (c = 0.88, CHCl₃)


Diastereomer 2:

methyl (5R,6S,E)-5-(4-bromophenyl)-6-(oxazolo[4,5-B]pyridin-2-yl)hept-2-enoate

IR (CHCl₃, liquid film): 2921 (stretch HC=C), 2361, 1720 (stretch C=O, ester), 1557, 1408, 1260 (aromatic NO₂).

¹H NMR (400 MHz, CDCl₃) δ 8.63 (d, J = 4.8 Hz, 1H, Het), 7.83 (dd, J = 8.1, 1.3 Hz, 1H, Het), 7.45 (d, J = 8.4 Hz, 2H, Ar), 7.35 (dd, J = 8.1, 4.9 Hz, 1H, Het), 7.10 (d, J = 8.4 Hz, 2H, Ar), 6.85 (dt, J = 14.9, 7.2 Hz, 1H, =CHCH₂), 5.91 (d, J = 15.6 Hz, 1H, =CHCO₂Me),
3.77 (s, 3H, OCH$_3$), 3.60 (dd, $J = 9.0$, 4.8 Hz, 1H, CHCH$_3$), 3.51 – 3.44 (m, 1H, CHCH$_2$),
3.00 – 2.89 (m, 1H, CH$_2$), 2.87 – 2.76 (m, 1H, CH$_2$), 1.60 (d, $J = 7.0$ Hz, 3H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.3 (Cq), 166.5 (Cq), 155.5 (Cq), 146.4 (CH), 145.7 (CH),
142.5 (Cq), 139.4 (Cq), 131.7 (CH), 129.8 (CH), 123.2 (CH), 121.0 (Cq), 119.9 (CH), 118.0
(CH), 51.5 (CH$_3$), 48.2 (CH), 39.9 (CH), 34.2 (CH$_2$), 15.3 (CH$_3$).

The enantiomeric excess was determined by HPLC using a Chiralpak ID column
(hexane/iPrOH = 80:20, flow rate 1.0 mL/min, $\lambda = 230$ nm): $t_r$ (major) = 31.1, $t_r$ (minor) = 41.3, 24% ee.

$[\alpha]_{D}^{19} = +14^\circ$ (c = 0.2, CHCl$_3$)

**MS (ESI+) m/z:** 416.7 [M+H]$^+$; **HRMS (ESI+)** Exact mass calculated for C$_{20}$H$_{20}$Br$_7$N$_2$O$_3$

methyl (E)-5-(4-bromophenyl)-6-(6-nitrobenzoxazol-2-yl)non-2-enoate (276d)

![Structure](image)

The reaction was performed following the general procedure adding: the organic
catalyst (S)-2-(((tert-butyl(dimethyl)silyl)oxy)diphenylmethyl)pyrrolidine (15 mg, 0.041
mmol, 20 mol% equiv), (E)-3-(4-bromophenyl)acrylaldehyde (86 mg, 0.410 mmol, 2
equiv), 2-butyl-6-nitrobenzoxazole (100 mg, 0.205 mmol, 1 equiv), Pd(OAc)$_2$ (2 mg,
0.010 mmol, 5 mol% equiv) and CH$_3$CN (1 mL). To the crude solution was finally added
TEA (10 mg, 0.103 mmol, 50 mol% equiv). The first reaction was stirred for 40 hours at
35 °C before performing the Wittig. The final crude was purified by flash column
chromatography (hexane/EtOAc 10:1) to obtain 87 mg of the desired product as yellow
oil. Yield: 87%. The diastereomeric ratio was determined by the crude NMR: 2:1
Diastereomer 1, major:

methyl (5R,6R,E)-5-(4-bromophenyl)-6-(6-nitrobenzoxazol-2-yl)non-2-enoate

IR (CHCl₃, liquid film): 2955, 2946, 2850 (stretch HC=C), 1720 (stretch C=O, ester), 1562, 1527 (aromatic NO₂), 1435, 1346 (aromatic NO₂), 1269 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.43 (d, J = 2.0 Hz, 1H, Het), 8.31 (dd, J = 8.8, 2.1 Hz, 1H, Het), 7.79 (d, J = 8.8 Hz, 1H, Het), 7.47 (dd, J = 8.7, 2.0 Hz, 2H, Ar), 7.07 (d, J = 8.4 Hz, 2H, Ar), 6.53 (dt, J = 15.4 , 7.4, 1H, =CHCH₂), 5.49 (dt, J = 15.5, 1.4 Hz, 1H, =CHCO₂Me), 3.53 (s, 3H, OCH₃), 3.26 (dt, J = 15.4, 10.3, 4.4 Hz, 2H, CH₂CH₂, CH₂CH₂), 2.54 – 2.44 (m, 1H, CH₂CHAR), 2.38 – 2.29 (m, 1H, CH₂CHAR), 1.71 (tdd, J = 14.3, 9.7, 7.0 Hz, 1H, CH₂CH₂CH₃), 1.46 – 1.35 (m, 1H, CH₂CH₂CH₃), 1.14 – 1.02 (m, 2H, CH₂CH₃), 0.75 (t, J = 7.3 Hz, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 173.1 (Cq), 166.1 (Cq), 149.6 (Cq), 146.2 (Cq), 145.2 (Cq), 145.0 (CH), 140.1 (Cq), 132.2 (CH), 129.5 (CH), 122.7 (CH), 121.2 (Cq), 120.6 (CH), 119.8 (CH), 107.3 (CH), 51.3 (CH₃), 48.7 (CH), 46.0 (CH), 37.5 (CH₂), 34.1 (CH₂), 20.4 (CH₂), 13.6 (CH₃).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 70:30, flow rate 1.0 mL/min, λ = 254 nm): tᵣ (major) = 9.5, tᵣ (minor) = 6.6, 90% ee.

[α]D¹⁹ = −2.6 (c = 0.5, CHCl₃)

MS (ESI+) m/z: 488.8 [M+H]+; HRMS (ESI+) Exact mass calculated for C₂₃H₂₄Br⁷⁹N₂O₅ [M+H]+: 487.0863, found: 487.0855.
Diastereomer 2, minor:

methyl (5R,6S,E)-5-(4-bromophenyl)-6-(6-nitrobenzoxazol-2-yl)non-2-enoate

![Chemical structure](image)

**IR (CHCl₃, liquid film):** 2958, 2924, 2854 (stretch HC=), 1720 (stretch C=O, ester), 1562, 1523 (aromatic NO₂), 1435, 1346 (aromatic NO₂), 1269 cm⁻¹.

**¹H NMR (400 MHz, CDCl₃) δ:**
- 8.33 (d, J = 2.1 Hz, 1H, Het), 8.25 (dd, J = 8.8, 2.1 Hz, 1H, Het), 7.69 (d, J = 8.7 Hz, 1H, Het), 7.32 – 7.27 (m, 2H, Ar), 6.92 – 6.85 (m, 2H, Ar), 6.72 (dt, J = 15.5, 7.2 Hz, 1H, =CHCH₂), 5.79 (dt, J = 15.7, 1.3 Hz, 1H, =CHCO₂Me), 3.67 (s, 3H, OCH₃), 3.38 (ddd, J = 10.3, 7.8, 4.4 Hz, 1H, CHCH₂), 3.31 – 3.21 (m, 1H, CH₂CH₂CH₃), 3.01 – 2.79 (m, 1H, CHCH₂), 2.69 – 2.58 (m, 1H, CHCH₂), 2.00 – 1.79 (m, 2H, CH₂CH₂CH₃), 1.30 – 1.18 (m, 2H, CH₂CH₃), 0.90 (t, J = 7.3 Hz, 3H, CH₃).

**¹³C NMR (101 MHz, CDCl₃) δ:**
- 172.4 (Cq), 166.4 (Cq), 149.4 (Cq), 146.1 (Cq), 145.3 (CH), 145.0 (Cq), 139.2 (Cq), 131.7 (CH), 129.6 (CH), 123.4 (CH), 121.1 (Cq), 120.5 (CH), 119.7 (CH), 107.0 (CH), 51.5 (CH₃), 48.0 (CH), 45.7 (CH), 35.4 (CH₂), 33.0 (CH₂), 20.7 (CH₂), 13.8 (CH₃).

The enantiomeric excess was determined by **HPLC** using a Chiralpak IA column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm): tᵣ (major) = 8.4, tᵣ (minor) = 13.1, 49% ee.

[α]D₁⁹ = -5.4 (c = 0.6, CHCl₃)

**MS (ESI+) m/z:** 488.7 [M+H]+; **HRMS (ESI+)** Exact mass calculated for C₂₃H₂₄Br⁷⁹N₂O₅ [M+H]+: 487.0863, found: 487.0872.
(S)-4-(6-nitrobenzoxazol-2-yl)-3-phenylbutanal (235e) (1st step)

In a vial were added in this sequence: (S)-2-(diphenyl(trimethyl)oxy)methyl)pyrrolidine (18 mg, 0.056 mmol, 20 mol% equiv), cinnamaldehyde (37 mg, 0.281 mmol, 1 equiv), 2-methyl-6-nitrobenzoxazole (50 mg, 0.281 mmol, 1 equiv), Pd(OAc)$_2$ (13 mg, 0.056 mmol, 20 mol% equiv) and Et$_3$N (14 mg, 0.141 mmol 50 mol% equiv) and finally CH$_3$CN (0.5 mL). The reaction mixture was stirred at 30 °C for 24 hours and then concentrated in vacuo. The crude was purified by flash column chromatography (hexane/EtOAc 4:1) to obtain 31 mg of the desired product. Yield: 36%

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.71 (t, $J = 1.4$ Hz, 1H, CHO), 8.37 (d, $J = 1.9$ Hz, 1H, Het), 8.26 (dd, $J = 8.8$, 2.1 Hz, 1H, Het), 7.73 (d, $J = 8.9$ Hz, 1H), 7.31 – 7.21 (m, 5H, Ph), 4.05 – 3.93 (m, 1H, CHPh), 3.35 (dd, $J = 7.5$, 4.5 Hz, 2H, CH$_2$Het), 3.04 – 2.95 (m, 2H, CH$_2$CHO).

methyl (R,E)-6-(6-nitrobenzoxazol-2-yl)-5-phenylhex-2-enoate (276e) (2nd step)

To (S)-4-(6-nitrobenzoxazol-2-yl)-3-phenylbutanal was added methyl(triphenylphosphoranilidene) acetate (141 mg, 0.422 mmol, 1.5 equiv) and DCM (0.5 mL) as a solvent. The crude was purified by flash column chromatography (hexane/EtOAc 3:1) to obtain the desired product as yellow oil. Yield: 56%.

IR (CHCl$_3$, liquid film): 2951, 2920, 2850 (stretch HC=C), 1720 (stretch C=O, ester), 1570, 1527 (aromatic NO$_2$), 1435, 1346 (aromatic NO$_2$), 1269 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.35 (d, $J = 2.1$ Hz, 1H, Het), 8.26 (dd, $J = 8.8$, 2.1 Hz, 1H, Het), 7.72 (d, $J = 8.8$ Hz, 1H, Het), 7.36 – 7.17 (m, 5H, Ph), 6.88 – 6.74 (m, 1H, =CHCH$_2$),
5.80 (d, J = 15.6 Hz, 1H, =CHCO₂Me), 3.65 (s, 3H, OCH₃), 3.62 – 3.46 (m, 1H, CH₇H₅), 3.32 (dd, J = 7.6, 3.8 Hz, 2H, CH₂Het), 2.69 (td, J = 7.2, 1.3 Hz, 2H, CH₂CH).

**¹³C NMR (101 MHz, CDCl₃)** δ 169.9 (Cq), 166.4 (Cq), 149.8 (Cq), 146.5 (Cq), 145.4 (CH), 145.1 (Cq), 141.7 (Cq), 128.9 (CH), 127.4 (CH), 127.1 (CH), 123.3 (CH), 120.4 (CH), 119.6 (CH), 107.0 (CH), 51.5 (CH₃), 42.9 (CH), 38.6 (CH₂), 35.4 (CH₂).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 29.7, tᵣ (minor) = 26.5, 49% ee.

$$[α]_{D}^{19} = +8.33^\circ$$ (c = 0.33, CHCl₃)

**MS (ESI⁺) m/z:** 367.0 [M+H]⁺; **HRMS (ESI⁺)** Exact mass calculated for C₂₀H₁₉N₂O₅ [M+H]⁺: 367.1288, found: 367.1281.

**methyl (E)-6-(5-nitrobenzoxazol-2-yl)-5-phenylhept-2-enoate (276b)**

The reaction was performed following the general procedure adding: the organic catalyst (S)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (38 mg, 0.260 mmol, 20 mol% equiv), cinnamaldehyde (137 mg, 1.040 mmol, 2 equiv), 2-ethyl-5-nitrobenzoxazole (100 mg, 0.520 mmol, 1 equiv), Pd(OAc)₂ (6 mg, 0.026 mmol, 5 mol% equiv) and CH₃CN (1 mL). To the crude solution was finally added TEA (26 mg, 0.260 mmol, 50 mol% equiv). The first reaction was stirred at 35 °C for 10 days before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 84 mg of the desired product as yellow oil. Yield: 42%. The diastereomeric ratio was determined by the crude NMR: 1.5:1
Diastereomer 1, major:

methyl (5R,6R,E)-6-(5-nitrobenzoxazol-2-yl)-5-phenylhept-2-enoate

IR (CHCl₃, liquid film): 2955, 2923, 2854 (stretch HC=CH), 1720 (stretch C=O, ester), 1527 (aromatic NO₂), 1454, 1439, 1346 (aromatic NO₂) cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, J = 2.1 Hz, 1H, Het), 8.31 (dd, J = 8.9, 2.3 Hz, 1H, Het), 7.62 (d, J = 8.8 Hz, 1H, Het), 7.36 – 7.30 (m, 3H, Ph), 7.18 (dd, J = 5.3, 3.1 Hz, 2H, Ph), 6.62 (ddd, J = 15.5, 7.8, 6.8 Hz, 1H, =CHCH₂), 5.56 (dt, J = 15.6, 1.3 Hz, 1H, =CHCO₂Me), 3.54 (s, 3H, OCH₃), 3.42 (dq, J = 9.6, 7.0 Hz, 1H, CHCH₃), 3.26 (td, J = 9.1, 5.8 Hz, 1H, CH₂), 2.60 (ddddd, J = 15.4, 8.5, 6.7, 1.5 Hz, 1H, CH₂), 2.52 – 2.43 (m, 1H, CH), 1.23 (d, J = 6.9 Hz, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 172.5 (Cq), 166.3 (Cq), 154.0 (Cq), 145.7 (CH), 145.3 (Cq), 141.6 (Cq), 140.5 (Cq), 128.9 (CH), 127.9 (CH), 127.4 (CH), 122.5 (CH), 121.0 (CH), 116.3 (CH), 110.8 (CH), 51.3 (CH₃), 49.6 (CH), 40.1 (CH), 37.4 (CH₂), 17.0 (CH₃).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 48.3, tᵣ (minor) = 52.2, 12% ee.

[α]D²⁰ = −2.8 (c = 0.5, CHCl₃)

MS (ESI⁺) m/z: 381.1 [M+H]⁺; HRMS (ESI⁺) Exact mass calculated for C₂₁H₂₁N₂O₅ [M+H]⁺: 381.1445, found: 381.1449.
Diastereomer 2, minor:
methyl (5R,6S,E)-6-(5-nitrobenzoxazol-2-yl)-5-phenylhept-2-enoate

IR (CHCl₃, liquid film): 2954, 2924, 2850 (stretch HC=), 1720 (stretch C=O, ester), 1531 (aromatic NO₂), 1457, 1439, 1346 (aromatic NO₂) cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.51 (d, J = 2.2 Hz, 1H, Het), 8.25 (dd, J = 8.9, 2.3 Hz, 1H, Het), 7.51 (d, J = 8.9 Hz, 1H, Het), 7.23 – 7.16 (m, 3H, Ph), 7.08 – 7.04 (m, 2H, Ph), 6.76 (dt, J = 15.5, 7.2 Hz, 1H, =CHCH₂), 5.80 (dt, J = 15.7, 1.4 Hz, 1H, =CHCO₂Me), 3.63 (s, 3H, OCH₃), 3.49 (p, J₁ = J₂ = 6.9 Hz, 1H, CHCH₃), 3.39 – 3.31 (m, 1H, CHCH₂), 2.86 – 2.69 (m, 2H, CH₂), 1.49 (d, J = 7.0 Hz, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 171.8 (Cq), 166.5 (Cq), 153.9 (Cq), 146.0 (CH), 145.2 (Cq), 141.4 (Cq), 140.2 (Cq), 128.6 (CH), 127.9 (CH), 127.2 (CH), 123.0 (CH), 120.8 (CH), 116.2 (CH), 110.5 (CH), 51.4 (CH₃), 48.9 (CH), 40.0 (CH), 34.3 (CH₂), 15.2 (CH₃).

The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/iPrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm): tᵣ (major) = 48.6, tᵣ (minor) = 50.5, 31% ee.

[α]D²⁰ = -1.2 (c = 0.3, CHCl₃)

MS (ESI⁺) m/z: 381.1 [M+H]⁺; HRMS (ESI⁺) Exact mass calculated for C₂₁H₂₁N₂O₅ [M+H]⁺: 381.1445, found: 381.1450.
methyl (E)-5-(4-bromophenyl)-6-(4-nitrobenzoxazol-2-yl)hept-2-enoate (276c)

![Chemical Structure](image)

The reaction was performed following the general procedure adding: the organic catalyst (S)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (38 mg, 0.260 mmol, 20 mol% equiv), cinnamaldehyde (220 mg, 1.560 mmol, 3 equiv), 2-ethyl-4-nitrobenzoxazole (100 mg, 0.520 mmol, 1 equiv), Pd(OAc)$_2$ (6 mg, 0.026 mmol, 5 mol% equiv) and CH$_3$CN (1 mL). To the crude solution was finally added TEA (26 mg, 0.260 mmol, 50 mol% equiv). The first reaction was stirred at 35 °C for 10 days before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 10:1) to obtain 84 mg of the desired product as yellow oil. Yield: 36%. The diastereomeric ratio was determined by the crude NMR: 1:1

**Diastereomer 1:**

methyl (5$R$,6$R$,E)-5-(4-bromophenyl)-6-(4-nitrobenzoxazol-2-yl)hept-2-enoate

![Chemical Structure](image)

**IR (CHCl$_3$, liquid film):** 2924 (stretch, HC=C), 1720 (stretch, C=O, ester), 1528, 1487, 1435, 1342 (aromatic NO$_2$) cm$^{-1}$.

**$^1$H NMR (400 MHz, CDCl$_3$) δ** 8.21 (dd, $J = 8.2$, 0.6 Hz, 1H, Het), 7.85 (dd, $J = 8.1$, 0.7 Hz, 1H, Het), 7.49 (d, $J = 8.4$ Hz, 3H, Ar, Het), 7.10 (d, $J = 8.4$ Hz, 2H, Ar), 6.56 (dt, $J = 15.2$, 7.6 Hz, 1H, =CHCH$_2$), 5.54 (d, $J = 15.6$ Hz, 1H, =CHCO$_2$Me), 3.55 (s, 3H, OCH$_3$), 3.53 (dd, $J = 7.0$, 3.3 Hz, 1H, CHCH$_3$), 3.27 (td, $J = 9.4$, 5.7 Hz, 1H, CHCH$_2$), 2.62 – 2.51 (m, 1H, CH$_2$), 2.48 – 2.38 (m, 1H, CH$_2$), 1.25 (d, $J = 7.0$ Hz, 3H, CH$_3$).
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.4 (Cq), 165.2 (Cq), 151.2 (Cq), 144.1 (CH), 138.7 (Cq), 138.1 (Cq), 134.7 (Cq), 131.1 (CH), 128.6 (CH), 123.4 (CH), 121.7 (CH), 120.2 (Cq), 119.8 (CH), 115.7 (CH), 50.3 (CH$_3$), 48.1 (CH), 39.2 (CH), 36.5 (CH$_2$), 16.2 (CH$_3$).

The enantiomeric excess was determined by HPLC using a Chiralpak ID column (hexane/iPrOH = 90:10, flow rate 1.0 mL/min, $\lambda$ = 254 nm): $t_r$ (major) = 47.1, $t_r$ (minor) = 39.0, 77% ee.

$[\alpha]_{D}^{20} = -29.2$ (c = 0.12, CHCl$_3$)

HRMS (ESI+) Exact mass calculated for C$_{21}$H$_{20}$Br$_7$N$_2$O$_5$ [M+H]$^+$: 459.0550, found: 459.0561.

Diastereomer 2:

methyl (5R,6S,E)-5-(4-bromophenyl)-6-(4-nitrobenzoxazol-2-yl)hept-2-enoate

IR (CHCl$_3$, liquid film): 2949 (stretch, HC=C), 1720 (stretch, C=O, ester), 1528, 1488, 1435, 1342 (aromatic NO$_2$) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.14 (d, $J$ = 8.2 Hz, 1H, Het), 7.74 (d, $J$ = 8.1 Hz, 1H, Het), 7.43 (t, $J$ = 8.2 Hz, 1H, Het), 7.33 (d, $J$ = 8.4 Hz, 2H, Ar), 7.00 (d, $J$ = 8.4 Hz, 2H, Ar), 6.72 (dt, $J$ = 15.0, 7.2 Hz, 1H, =CHCH$_2$), 5.79 (d, $J$ = 15.6 Hz, 1H, =CHCO$_2$Me), 3.65 (s, 3H, OCH$_3$), 3.63 – 3.57 (m, 1H, CHCH$_3$), 3.38 (ddd, $J$ = 9.7, 7.5, 5.1 Hz, 1H, CHCH$_2$), 2.89 – 2.79 (m, 1H, CH$_2$), 2.75 – 2.63 (m, 1H, CH$_2$), 1.53 (d, $J$ = 7.0 Hz, 3H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.5 (Cq), 166.2 (Cq), 152.2 (Cq), 145.1 (CH), 139.8 (Cq), 139.1 (Cq), 135.7 (Cq), 132.1 (CH), 129.6 (CH), 124.4 (CH), 122.8 (CH), 121.3 (Cq), 120.9 (CH), 116.7 (CH), 51.4 (CH$_3$), 49.1 (CH), 40.2 (CH), 37.5 (CH$_2$), 17.2 (CH$_3$).
The enantiomeric excess was determined by **HPLC** using a Chiralpak ID column (hexane/iPrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm): t_r (major) = 38.3, t_r (minor) = 52.1, 20% ee.

\[\alpha\]_{D}^{20} = -15.0 (c = 0.06, CHCl_3)

**HRMS (ESI+)** Exact mass calculated for C_{21}H_{20}Br^{79}N_{2}O_{5} \text{[M+H]}^+: 459.0550, found: 459.0561.

**methyl (R,E)-5-(4-chlorophenyl)-6-(4-nitropyridin-3-yl)hex-2-enoate (276h)**

![Chemical Structure](image)

The reaction was performed following the general procedure adding: the organic catalyst (S)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (18 mg, 0.181 mmol, 20 mol% equiv), \(E\)-3-(4-chlorophenyl)acrylaldehyde (121 mg, 0.724 mmol, 2 equiv), 4-methyl-3-nitropyridine (50 mg, 0.362 mmol, 1 equiv), Pd(OAc)_2 (4 mg, 0.018 mmol, 5 mol% equiv) and CH_3CN (1 mL). To the crude solution was finally added TEA (18 mg, 0.181 mmol, 50 mol% equiv). The first reaction was stirred at 35 °C for 24 hours before performing the Wittig. The final crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 77 mg of the desired product as yellow oil. Yield: 59%.

**IR (CHCl_3, liquid film):** 2949 (stretch HC=C), 1717 (stretch C=O, ester), 1600, 1526, 1492, 1350 (aromatic NO_2) cm\(^{-1}\).

**^1H NMR (400 MHz, CDCI_3)** \(\delta\) 9.08 (s, 1H, Het), 8.51 (d, \(J = 5.0\) Hz, 1H, Het), 7.22 (d, \(J = 8.2\) Hz, 2H, Ar), 6.97 (d, \(J = 8.3\) Hz, 2H, Ar), 6.85 (d, \(J = 5.1\) Hz, 1H, Het), 6.76 (dt, \(J = 15.3, 7.2\) Hz, 1H, =CHCH_2), 5.79 (d, \(J = 15.6\) Hz, 1H, =CHCO_2Me), 3.68 (s, 3H, OCH_3), 3.44 (dd, \(J = 12.0, 3.9\) Hz, 1H, CHAr), 3.17 – 3.01 (m, 2H, CH_2Het), 2.65 (t, \(J = 7.0\) Hz, 2H, CH_2CH).
\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.4 (Cq), 152.7 (CH), 146.1 (CH), 145.8 (Cq), 145.2 (CH), 143.50 (Cq), 139.8 (Cq), 133.1 (Cq), 129.0 (CH), 128.8 (CH), 126.6 (CH), 123.5 (CH), 51.5 (CH\(_3\)), 45.0 (CH), 39.3 (CH\(_2\)), 38.6 (CH\(_2\)).

The enantiomeric excess was determined by \textbf{HPLC} using a Chiralpak IA column (hexane/iPrOH = 90:10, flow rate 1.0 mL/min, \(\lambda = 254\) nm): \(t_r\) (major) = 19.3, \(t_r\) (minor) = 21.9, 78\% ee.

\([\alpha]_D^{19} = -27.5^\circ\) (c = 1.5, CHCl\(_3\))

\textbf{MS (ESI+)} \textbf{m/z}: 361.9 [M+H]\(^+\); \textbf{HRMS (ESI+)} Exact mass calculated for C\(_{18}\)H\(_{18}\)Cl\(_{35}\)N\(_2\)O\(_4\) [M+H]\(^+\): 361.0950, found: 361.0955.

\((S)-3-(4-fluorophenyl)-4-(4-nitropyridin-3-yl)butanal (235d) \text{ (1\textsuperscript{st} step)}\)

\[
\begin{align*}
\text{In a vial were added in this sequence:} \\
\text{(S)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (26 mg, 0.072 mmol, 20 mol\% equiv), (E)-3-(4-fluorophenyl)acrylaldehyde (109 mg, 0.724 mmol, 2 equiv), 4-methyl-3-nitropyridine (50 mg, 0.362 mmol, 1 equiv), Pd(OAc)\(_2\) (4 mg, 0.018 mmol, 5 mol\% equiv) and TEA (18 mg, 0.181 mmol, 50 mol\% equiv) and finally CH\(_3\)CN (0.5 mL). The reaction mixture was stirred at 35 \degree C for 24 hours and then concentrated \textit{in vacuo}. The crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 69 mg of the desired product. Yield: 61\%. The \(^1\)H-NMR is consistent with the one provided in literature.}^{[90]} \\
\text{[}\alpha\text{]}_{D}^{18} = -4.65 \ (\text{c = 0.01, DCM})
\end{align*}
\]
methyl \((R,E)-5\)-(4-fluorophenyl)-6-(4-nitropyridin-3-yl)hex-2-enoate (276g) (2\textsuperscript{nd} step)

\[
\begin{align*}
\text{NO}_2 & \quad \text{COOMe} \\
\text{F} & \quad \text{C} \equiv \text{C} \\
\text{H} & \quad \text{C} \equiv \text{N} \\
\end{align*}
\]

To (S)-3-(4-fluorophenyl)-4-(4-nitropyridin-3-yl)butanal was added an excess of methyl(triphenyl-phosphoranilidene) acetate and DCM (0.5 mL) as a solvent. The crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 40 mg of the desired product as yellow oil. Yield: 52%.

**IR (CHCl\textsubscript{3}, liquid film):** 2951 (stretch HC=C), 2361, 1718 (stretch C=O, ester), 1602, 1527, 1509, 1350 (aromatic NO\textsubscript{2}) cm\textsuperscript{-1}.

**\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})** \(\delta\) 9.27 (s, 1H, Het), 8.70 (d, \(J = 5.1\) Hz, 1H, Het), 7.22 – 7.09 (m, 4H, Ar), 7.04 (d, \(J = 5.1\) Hz, 1H, Het), 6.97 (dt, \(J = 15.0, 7.3\) Hz, 1H, =CHCH\textsubscript{2}), 5.99 (d, \(J = 15.6\) Hz, 1H, =CHCO\textsubscript{2}Me), 3.88 (s, 3H, OCH\textsubscript{3}), 3.63 (dd, \(J = 12.1, 4.0\) Hz, 1H, CHAr), 3.36 – 3.20 (m, 2H, CH\textsubscript{2}Het), 2.85 (t, \(J = 6.7\) Hz, 2H, CH\textsubscript{2}CH).

**\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})** \(\delta\) 166.4 (Cq), 161.8 (d, \(J = 246\) Hz, Cq), 152.7 (CH), 146.1 (CH), 145.9 (Cq), 145.4 (CH), 143.6 (Cq), 137.0 (d, \(J = 3.3\) Hz, Cq), 129.0 (d, \(J = 8.0\) Hz, CH), 126.6 (CH), 123.4 (CH), 115.7 (d, \(J = 21.3\) Hz, CH), 51.5 (CH\textsubscript{3}), 44.9 (CH), 39.5 (CH\textsubscript{2}), 38.8 (CH\textsubscript{2}).

**\textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3})** \(\delta\) –115.04.

The enantiomeric excess was determined by HPLC using a Chiralpak IA column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, \(\lambda = 254\) nm): \(t_R\) (major) = 9.6, \(t_R\) (minor) = 34.3, 89\% ee.

\([\alpha]_D^{19} = +8.5^\circ\) (c = 1.7, CHCl\textsubscript{3})

**MS (ESI+) m/z:** 345.1 [M+H]+; **HRMS (ESI+)** Exact mass calculated for C\textsubscript{18}H\textsubscript{18}FN\textsubscript{2}O\textsubscript{4} [M]+: 345.1245, found: 345.1255.
Single-crystal X-Ray diffraction data of 259f were collected at 100 K on Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn 724+ detector mounted at the window of an FR-E+ Superbright MoKα rotating anode generator with HF Varimax optics. Unit cell parameters were refined against all data. An empirical absorption correction was carried out using CrystalClear software (CrystalClear-SM Expert 3.1ba16 (Rigaku, 2012)). The crystal structure of 259f was solved by charge flipping methods and refined on Fo² by full-matrix least-squares refinements using programs of the SHELX-2013 software. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined using a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (Ueq) of the parent atom.

Crystal data for 259f: C21H19N3O7, Mr = 425.39, light brown lath, 0.20 × 0.03 × 0.01 mm³, Monoclinic, C2, a = 17.969(2), b = 11.0559(15), c = 19.839(3) Å, β = 90.528(6)°, V = 3941.0(9) Å³, Z = 8, Z’ = 2, Dc = 1.434g cm⁻³, μ = 0.110 mm⁻¹, T = 100 K, 25946 collected reflections, 8604 unique reflections (Rint = 0.0895), 4448 reflections with F²> 2σ, R(F²>2σ) = 0.0596, wR2 = 0.1285, GoF = 0.893. Crystallographic data (excluding structure factors) for the structure 259f have been deposited with the Cambridge Crystallographic Data Centre with CCDC number 1001853. Copies of the
data can be obtained, free of charge, on application to Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
6.2  Synergistic catalysis: cis-cyclopropanation of benzoxazoles

6.2.1  Synthesis of the starting material: benzoxazoles (391)

**General procedure:**

In a round bottom flask, equipped with a condenser, were added 1 equivalent of aminophenol (237) followed by 1,1 equivalents of 2-chloro-1,1,1-triethoxyethane (398). The reaction mixture is stirred and heated. The reaction is followed by TLC. After the reaction is completed, the crude is purified by recrystallization or by flash column chromatography (n-hexane/EtOAc) to obtain the desired benzoxazole.

2-(chloromethyl)-6-nitrobenzoxazole (391a)

![Structural formula of 2-(chloromethyl)-6-nitrobenzoxazole](image)

The reaction was performed following the general procedure adding 2-amino-5-nitrophenol (712 mg, 4.623 mmol, 1 equiv) and 2-chloro-1,1,1-triethoxyethane (1 g, 5.085 mmol, 1.1 equiv). The reaction mixture was stirred at 100 °C for 4 hours. The crude was purified by recrystallization with EtOH/H₂O to obtain 584 mg of the desired product as dark orange solid. Yield: 59%.

**¹H NMR (400 MHz, CDCl₃)** δ 8.49 (s, 1H, Het), 8.35 (d, J = 8.6 Hz, 1H, Het), 7.87 (d, J = 8.7 Hz, 1H, Het), 4.81 (s, 2H, CH₂).

**¹³C NMR (101 MHz, CDCl₃)** δ 165.4 (Cq), 150.3 (Cq), 145.9 (Cq), 145.9 (Cq), 120.9 (CH), 120.7 (CH), 107.7 (CH), 35.9 (CH₂).

**HRMS m/z (ESI+)** Exact mass calculated for C₈H₆ClN₂O₃ [M+H]^⁺: 213.0061, found: 213.0062.
5-chloro-2-(chloromethyl)-6-nitrobenzoxazole (391b)

The reaction was performed following the general procedure adding 2-amino-4-chloro-5-nitrophenol (1.66 g, 8.801 mmol, 1 equiv) and 2-chloro-1,1,1-triethoxyethane (1.9 g, 9.681 mmol, 1.1 equiv). The reaction mixture was stirred at 100 °C for 19 hours. The crude was purified by recrystallization with EtOH/H₂O to obtain 1.715 g of the desired product as dark brown solid. Yield: 79%.

¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H, Het), 7.94 (s, 1H, Het), 4.80 (s, 2H, CH₂).

¹³C NMR (101 MHz, CDCl₃) δ 165.9 (Cq), 148.5 (Cq), 145.6 (Cq), 144.3 (Cq), 124.0 (Cq), 123.2 (CH), 109.0 (CH), 35.7 (CH₂).

HRMS m/z (ESI⁺) Exact mass calculated for C₈H₅Cl₃N₂O₃ [M+H]⁺: 246.9672, found: 246.9671.

2-(chloromethyl)-5-nitrobenzoxazole (391c)

The reaction was performed following the general procedure adding 2-amino-4-nitrophenol (712 mg, 4.623 mmol, 1 equiv) and 2-chloro-1,1,1-triethoxyethane (1 g, 5.085 mmol, 1.1 equiv). The reaction mixture was stirred at 80 °C for 12 hours. The residual solvent was evaporated under vacuum to obtain 686 mg of the desired product as brown solid. Yield: 70%.

¹H NMR (400 MHz, CDCl₃) δ 8.65 (d, J = 1.9 Hz, 1H, Het), 8.37 (dd, J = 9.0, 2.1 Hz, 1H, Het), 7.69 (d, J = 9.0 Hz, 1H, Het), 4.80 (s, 2H, CH₂).

¹³C NMR (101 MHz, CDCl₃) δ 164.0 (Cq), 154.5 (Cq), 145.6 (Cq), 141.2 (Cq), 122.0 (CH), 117.1 (CH), 111.3 (CH), 35.9 (CH₂).
**HRMS m/z (ESI+)** Exact mass calculated for C₈H₆Cl³¹N₂O₃ [M+H]⁺: 213.0061, found: 213.0062.

**methyl 2-(chloromethyl)benzoxazole-6-carboxylate (391d)**

![methyl 2-(chloromethyl)benzoxazole-6-carboxylate](image)

The reaction was performed following the general procedure adding methyl 4-amino-3-hydroxybenzoate (980 mg, 5.862 mmol, 1 equiv) and 2-chloro-1,1,1-triethoxyethane (1.27 g, 6.448 mmol, 1.1 equiv). The reaction mixture was stirred at 100 °C for 19 hours. The crude was purified by recrystallization with EtOH/H₂O to obtain 1.250 g of the desired product as light brown solid. Yield: 95%.

**¹H NMR (400 MHz, CDCl₃)** δ 8.24 (d, J = 1.0 Hz, 1H, Het), 8.09 (dd, J = 8.4, 1.4 Hz, 1H, Het), 7.77 (d, J = 8.4 Hz, 1H, Het), 4.78 (s, 2H, CH₂), 3.96 (s, 3H, OCH₃).

**¹³C NMR (101 MHz, CDCl₃)** δ 166.3 (Cq), 163.5 (Cq), 150.8 (Cq), 144.6 (Cq), 128.1 (Cq), 126.5 (CH), 120.2 (CH), 112.6 (CH), 52.5 (CH₃), 36.2 (CH₂).

**HRMS m/z (ESI+)** Exact mass calculated for C₁₀H₈Cl³¹NO₃ [M+H]⁺: 226.0265, found: 226.0269.

**2-(chloromethyl)-4-nitrobenzoxazole (391e)**

![2-(chloromethyl)-4-nitrobenzoxazole](image)

The reaction was performed following the general procedure adding 2-amino-3-nitrophenol (1.355 g, 8.791 mmol, 1 equiv) and 2-chloro-1,1,1-triethoxyethane (1.9 g, 9.670 mmol, 1.1 equiv). The reaction mixture was stirred at 100 °C for 12 hours. The crude was purified by recrystallization with EtOH/H₂O to obtain 720 mg of the desired product as light brown solid. Yield: 93%.
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.25 (d, $J = 8.2$ Hz, 1H, Het), 7.94 (d, $J = 8.2$ Hz, 1H, Het), 7.59 (t, $J = 8.2$ Hz, 1H, Het), 4.88 (s, 2H, CH$_2$).

The $^1$H-NMR is consistent with the one provided in literature.[196]

2-(chloromethyl)benzoxazole (391f)

\[
\text{\begin{tikzpicture}
  \draw (0,0) rectangle (1,1);
  \draw[fill=white] (0.5,0.5) circle (0.1);
  \draw[fill=white] (0.5,0.5) circle (0.1);
  \draw (0.5,0.5) -- (0.8,0.8);
  \draw (0.5,0.5) -- (0.2,0.2);
  \draw (0.5,0.5) -- (0.8,0.2);
  \draw (0.5,0.5) -- (0.2,0.8);
  \node at (0.5,0.5) {Cl};
\end{tikzpicture}}
\]

The reaction was performed following the general procedure adding 2-aminophenol (640 mg, 5.865 mmol, 1 equiv) and 2-chloro-1,1,1-triethoxyethane (1.27 g, 6.451 mmol, 1.1 equiv). The reaction mixture was stirred at 80 °C for 20 hours. The crude was purified by flash column chromatography ($n$-hexane/EtOAc 5:1) to obtain 490 mg of the desired product as light orange oil. Yield: 54%.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.75 (dd, $J = 6.7$, 2.4 Hz, 1H, Het), 7.56 (dd, $J = 6.9$, 2.2 Hz, 1H, Het), 7.43 – 7.32 (m, 2H, Het), 4.76 (s, 2H, CH$_2$).

The $^1$H-NMR is consistent with the one provided in literature.[197]
6.2.2 Synthesis of the starting material: α,β-unsaturated aldehydes (80)

The starting aldehydes were synthesised through a Wittig reaction, following the procedure described in literature. In a round bottom flask a substituted benzaldehyde derivative 63 (2 equiv) and (triphenylphosphoranyldiene)acetaldehyde 250 (1 equiv) were stirred in anhydrous toluene under reflux at 50 °C under argon. The crude mixture was purified by a flash column chromatography.

The aldehydes 80a and 80b are commercially available (Sigma-Aldrich).

The ¹H-NMR of the aldehydes (E)-3-(4-bromophenyl)acrylaldehyde (80h), (E)-3-(p-tolyl)acrylaldehyde (80k) and (E)-3-(4-chlorophenyl)acrylaldehyde (80e) are consistent with the ones provided in literature.[185]

The ¹H-NMR of the aldehydes (E)-3-(4-nitrophenyl)acrylaldehyde (80i) and (E)-3-(2-bromophenyl)acrylaldehyde (80c) are consistent with the ones provided in literature.[186]

The ¹H-NMR of the aldehyde (E)-3-(4-fluorophenyl)acrylaldehyde (80j) is consistent with the ones provided in literature.[187]

The ¹H-NMR of the aldehyde (E)-4-(3-oxoprop-1-en-1-yl)benzonitrile (80g) is consistent with the ones provided in literature.[198]

The ¹H-NMR of the aldehyde ethyl (E)-4-oxobut-2-enoate (80m) is consistent with the ones provided in literature.[199]

The ¹H-NMR of the aldehyde (E)-3-(3-bromophenyl)acrylaldehyde (80d) is consistent with the ones provided in literature.[200]
6.2.3 General procedure for the synthesis of cyclopropanes (392, 402)

In a closed vial were added in this sequence: the organic catalyst 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (20 mol% equiv), α,β-unsaturated aldehyde (2 equiv), azaarene (1 equiv), Pd(OAc)$_2$ (5 mol% equiv) and CH$_3$CN (1 mL). To the reaction mixture, was finally added 2,6-lutidine (1 equiv). The reaction mixture was stirred at room temperature and then concentrated in vacuo. The crude was purified by flash column chromatography (n-hexane/EtOAc) to obtain the desired product.

The stereochemistry of the final compounds was ascertained by X-ray and circular dichroism studies carried out by Andrea Mazzanti. In Figure 25 is drawn the absolute configuration of the cyclopropanes synthesised.

![Figure 25. Stereochemistry of the products for each enantiomer of the catalyst](image-url)
6.2.4 Final products characterisation

**Compound 392a**

The reaction was performed following the general procedure adding: 2-(diphenyl(trimethylsilyl)oxy)methyl)pyrrolidine (306 mg, 0.941 mmol, 20 mol% equiv), cinnamaldehyde (1.243 g, 9.408 mmol, 2 equiv), 2-(chloromethyl)-6-nitrobenzoxazole (1 g, 4.704 mmol, 1 equiv), Pd(OAc)$_2$ (53 mg, 0.235 mmol, 5 mol% equiv), CH$_3$CN (10 mL) and 2,6-lutidine (504 mg, 4.704 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 10:1) to obtain 1.289 g of the desired products as dark yellow oil. Yield: 89%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. 

**dr:** 4.5:1.2:1

(1$R$,2$R$,3$S$)-2-(6-nitrobenzoxazol-2-yl)-3-phenylcyclopropane-1-carbaldehyde

**IR (CHCl$_3$, liquid film):** 2922, 2851, 1709 (CHO), 1570 (aromatic NO$_2$), 1525, 1345 (aromatic NO$_2$), 758 cm$^{-1}$.

**$^1$H NMR (400 MHz, CDCl$_3$)** $\delta$ 9.89 (d, $J = 2.8$ Hz, 1H, CHO), 8.24 – 8.18 (m, 2H, Het), 7.64 (d, $J = 8.6$ Hz, 1H, Het), 7.24 – 7.16 (m, 5H, Ph), 3.57 (ddd, $J = 5.6$, 5.6, 2.8 Hz, 1H, CHCHO), 3.41 (bd, $J = 5.5$ Hz, 2H, CHHet, CHPh).

**$^{13}$C NMR (101 MHz, CDCl$_3$)** $\delta$ 197.4 (CHO), 166.7 (Cq), 150.0 (Cq), 146.3 (Cq), 145.2 (Cq), 133.0 (Cq), 128.8 (CH), 128.7 (CH), 128.0 (CH), 120.7 (CH), 119.7 (CH), 107.0 (CH), 34.9 (CH), 34.5 (CH), 26.24 (CH).

The enantiomeric excess was determined by **HPLC** using a Chiralpak IA column (hexane/iPrOH = 85:15, flow rate 1.0 mL/min, $\lambda$ = 210 nm): $t_r$ (S) = 16.1, $t_r$ (R) = 17.0, 96% (R) and 99% (S) ee.
\([\alpha]_D^{22} = -107.6^\circ \ (c = 0.1, \text{CHCl}_3) \ (S \text{ catalyst})

HRMS \ m/z \ (ESI+) \ Exact \ mass \ calculated \ for \ C_{17}H_{13}N_2O_4 \ [M+H]^+: \ 309.0870, \ found: 309.0872.

\((1R,2R,3R)-2-(6-nitrobenzoxazol-2-yl)-3-phenylcyclopropane-1-carbaldehyde

\[
\begin{array}{c}
\text{minor}
\end{array}
\]

\(^1H \text{ NMR (400 MHz, CDCl}_3) \ \delta \ 9.16 \ (d, J = 5.0 \text{ Hz, } 1\text{H},-\text{CHO}), \ 8.43 \ (d, J = 2.1 \text{ Hz, } 1\text{H},H^3), \ 8.32 \ (dd, J = 8.8, 2.1 \text{ Hz, } 1\text{H}, H^1), \ 7.77 \ (d, J = 8.8 \text{ Hz, } 1\text{H}, H^6), \ 7.38 \ (m, J = 4.4 \text{ Hz, } 5\text{H, Ph}), \ 3.66 \ (m, 2\text{H}, H^{12}, H^{11}), \ 3.08 \ (m, 1\text{H}, H^{10}).

\(^{13}C \text{ NMR (101 MHz, CDCl}_3) \ \delta \ 197.2 \ (C^{16}, \ Cq), \ 166.5 \ (Cq), \ 149.8 \ (Cq), \ 146.1 \ (Cq), \ 145.0 \ (Cq), \ 132.8 \ (Cq), \ 128.7 \ (CH), \ 128.5 \ (CH), \ 127.9 \ (CH), \ 120.6 \ (C^{1}), \ 119.5 \ (C^{6}), \ 106.9 \ (C^{3}), \ 34.8 \ (C^{11}), \ 34.3 \ (C^{12}), \ 26.1 \ (C^{10}).

Proton and carbon were assigned using the COSY and HMBC NMR analysis.

\([\alpha]_D^{21} = +21.4^\circ \ (c = 0.4, \text{CHCl}_3) \ (R \text{ catalyst})

Mixture of minor and minor’: 

\(^1H \text{ NMR (400 MHz, CDCl}_3) \ \delta \ 9.69 \ (d, J = 5.7 \text{ Hz, } 1\text{H}'), \ 9.16 \ (d, J = 5.0 \text{ Hz, } 1\text{H}), \ 8.41 \ (d, J = 2.1 \text{ Hz, } 2\text{H}), \ 8.30 \ (dd, J = 8.8, 2.0 \text{ Hz, } 1\text{H} + \text{1H'}), \ 7.77 \ (dd, J = 8.8, 4.7 \text{ Hz, } 1\text{H} + \text{1H'}), \ 7.43 – 7.23 \ (m, 11\text{H Ar}), \ 3.77 \ (t, J = 6.3 \text{ Hz, } 1\text{H'}), \ 3.72 – 3.63 \ (m, 2\text{H}), \ 3.20 \ (dd, J = 8.9, 6.5 \text{ Hz, } 1\text{H'}), \ 3.09 \ (dt, J = 9.7, 5.0 \text{ Hz, } 1\text{H}), \ 2.80 \ (dt, J = 8.9, 5.9 \text{ Hz, } 1\text{H'}).

\(^{13}C \text{ NMR (101 MHz, CDCl}_3) \ \delta \ 197.0 \ (\text{CHO'}), \ 196.0 \ (\text{CHO}), \ 169.1 \ (Cq), \ 167.5 \ (Cq), \ 149.9 \ (Cq), \ 149.8 \ (Cq), \ 146.5 \ (Cq), \ 146.3 \ (Cq), \ 145.2 \ (Cq), \ 145.1 \ (Cq), \ 135.8 \ (Cq), \ 132.8 \ (Cq), \ 129.0 \ (CH), \ 129.0 \ (CH), \ 128.9 \ (CH), \ 128.1 \ (CH), \ 128.0 \ (CH), \ 126.6 \ (CH), \ 120.9 \ (CH), \ 120.9 \ (CH), \ 120.9 \ (CH),}
120.8 (CH), 119.7 (CH), 119.5 (CH), 107.1 (CH), 107.0 (CH), 39.4 (CH), 38.7 (CH), 35.2 (CH), 32.2 (CH), 26.6 (CH), 22.0 (CH).

**HRMS m/z (ESI+)** Exact mass calculated for C_{17}H_{13}N_{2}O_{4} [M+H]^+: 309.0870, found: 309.0868.

**Compound 392b**

![Compound 392b](image)

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (31 mg, 0.094 mmol, 20 mol% equiv), (E)-3-(4-bromophenyl)acrylaldehyde (198 mg, 0.940 mmol, 2 equiv), 2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.470 mmol, 1 equiv), Pd(OAc)$_2$ (5 mg, 0.024 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (50 mg, 0.470 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 127 mg of the desired products as light yellow solid. Yield: 70%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. **dr**: 7:2:2:1

**(1S,2R,3S)-2-(4-bromophenyl)-3-(6-nitrobenzooxazol-2-yl)cyclopropane-1-carbaldehyde**

![Diastereomer](image)

**IR (CHCl$_3$, liquid film):** 2926, 1714 (CHO), 1571 (aromatic NO$_2$), 1570, 1523, 1344 (aromatic NO$_2$), 760 cm$^{-1}$.

**$^1$H NMR (400 MHz, CDCl$_3$)** δ 9.88 (d, $J = 2.7$ Hz, 1H, CHO), 8.24 (d, $J = 2.1$ Hz, 1H, Het), 8.19 (dd, $J = 8.8, 2.1$ Hz, 1H, Het), 7.64 (d, $J = 8.7$ Hz, 1H, Het), 7.33 – 7.27 (m, 2H, Ar),
7.12 – 7.05 (m, 2H, Ar), 3.53 (ddd, J = 5.9, 5.3, 2.7 Hz, 1H, CHCHO), 3.38 (dd, J = 9.8, 5.2 Hz, 1H, CH), 3.32 (dd, J = 9.8, 6.0 Hz, 1H, CH).

\(^{13}\text{C NMR (101 MHz, CDCl}_3\) δ 197.1 (CHO), 166.2 (Cq), 149.9 (Cq), 146.1 (Cq), 145.2 (Cq), 132.0 (Cq), 131.7 (Cq), 130.5 (CH), 122.1 (CH), 120.8 (CH), 119.7 (CH), 107.1 (CH), 34.4 (CH), 34.2 (CH), 26.2 (CH).

The enantiomeric excess was determined by \textit{HPLC} using a Chiralpak OD-H column (hexane/iPrOH = 85:15, flow rate 1.0 mL/min, λ = 210 nm): t\text{r} (S) = 56.6, t\text{r} (R) = 43.5, 97\% (R) and 98\% (S) ee.

\([\alpha]_D^{22} = +168.0^\circ\) (c = 0.5, CHCl\(_3\)) \((R\text{ catalyst})\)

\text{mp: 116-117 °C}

\text{HRMS \textit{m/z} (ESI+)} \text{Exact mass calculated for } C_{17}H_{12}BrN_2O_4 \text{ [M+H]^+: 386.9975, found: 386.9984.}

\((1R,2R,3R)-2-(4-bromophenyl)-3-(6-nitrobenzooxazol-2-yl)cyclopropane-1-carbaldehyde\)

\text{mp: 119-120 °C}
HRMS minor m/z (ESI+) Exact mass calculated for C_{17}H_{12}Br^{79}N_{2}O_{4} [M+H]^+: 386.9975, found: 386.9982.

Mixture of minor and minor’:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.66 (d, $J = 5.5$ Hz, 1H'), 9.25 (d, $J = 4.3$ Hz, 1H), 8.40 (d, $J = 1.9$ Hz, 1H + 1H'), 8.30 (dd, $J = 8.8$, 2.1 Hz, 1H + 1H'), 7.76 (dd, $J = 8.7$, 6.1 Hz, 1H + 1H'), 7.49 (t, $J = 7.0$ Hz, 2H + 2H'), 7.24 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H'), 3.71 (t, $J = 6.2$ Hz, 1H'), 3.60 (d, $J = 6.1$ Hz, 2H), 3.12 (dd, $J = 8.7$, 6.0, 4.3 Hz, 1H + m, 1H'), 2.75 (dt, $J = 9.0$, 5.9 Hz, 1H').

Compound 392c

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (31 mg, 0.094 mmol, 20 mol% equiv), (E)-3-(4-chlorophenyl)acrylaldehyde (157 mg, 0.940 mmol, 2 equiv), 2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.470 mmol, 1 equiv), Pd(OAc)$_2$ (5 mg, 0.024 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (50 mg, 0.470 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 4:1) to obtain 120 mg of the desired products as orange solid (major dia) and yellow oil (minor dia). Yield: 74%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: 43:22:1
(1S,2R,3S)-2-(4-chlorophenyl)-3-(6-nitrobenzoxazol-2-yl)cyclopropane-1-carbaldehyde

IR (CHCl₃, liquid film): 3107, 2927, 2924, 2853, 1714 (CHO), 1570 (aromatic NO₂), 1523, 1344 (aromatic NO₂), 751 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 9.89 (d, J = 4.5 Hz, 1H, CHO), 8.25 (d, J = 2.1 Hz, 1H, Het), 8.21 (dd, J = 8.7, 2.1 Hz, 1H, Het), 7.64 (d, J = 8.7 Hz, 1H, Het), 7.16 (s, 4H, Ar), 3.56 – 3.52 (m, 1H, CH), 3.41 – 3.33 (m, 2H, CH).

¹³C NMR (101 MHz, CDCl₃) δ 197.2 (CHO), 166.3 (Cq), 149.9 (Cq), 146.1 (Cq), 145.3 (Cq), 134.0 (Cq), 131.5 (Cq), 130.2 (CH), 128.9 (CH), 120.8 (CH), 119.8 (CH), 107.1 (CH), 34.4 (CH), 34.2 (CH), 26.3 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, λ = 250 nm): tᵣ (S) = 41.0, tᵣ (R) = 28.2, 98% (R) and 97% (S) ee.

[α]D²² = +132.4° (c = 1.3, CHCl₃) (R catalyst)

mp: 86-87 °C

HRMS m/z (ESI⁺) Exact mass calculated for C₁₇H₁₂Cl₁⁵N₂O₄ [M+H]⁺: 343.0480, found: 343.0480.
(1R,2R,3R)-2-(4-chlorophenyl)-3-(6-nitrobenzoxazol-2-yl)cyclopropane-1-carbaldehyde

NMR minor diastereomer with traces of the minor':

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.26 (d, $J = 4.3$ Hz, 1H, CHO), 8.42 (d, $J = 2.1$ Hz, 1H, Het), 8.32 (dd, $J = 8.8$, 2.1 Hz, 1H, Het), 7.76 (d, $J = 8.8$ Hz, 1H, Het), 7.36 – 7.28 (m, 4H, Ar), 3.65 – 3.58 (m, 2H, CHAr, CHHet), 3.13 (ddd, $J = 8.7$, 5.7, 4.4 Hz, 1H, CHCHO).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.4 (CHO), 169.0 (Cq), 150.0 (Cq), 146.6 (Cq), 145.4 (Cq), 134.3 (Cq), 131.4 (Cq), 130.5 (CH), 129.3 (CH), 121.1 (CH), 119.8 (CH), 107.3 (CH), 38.7 (CH), 35.0 (CH), 22.4 (CH).

$[\alpha]D$_{21}^2 = +36.7^\circ$ (c = 0.2, CHCl$_3$) (R catalyst)

HRMS m/z (ESI+) Exact mass calculated for C$_{17}$H$_{12}$Cl$_3$N$_2$O$_4$ [M+H]$^+$: 343.0480, found: 343.0481.

Compound 392d

The reaction was performed following the general procedure adding: 2-(diphenyl(trimethylsilyl)oxy)methyl)pyrrolidine (31 mg, 0.094 mmol, 20 mol% equiv), (E)-3-(4-nitrophenyl)acrylaldehyde (166 mg, 0.940 mmol, 2 equiv), 2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.470 mmol, 1 equiv), Pd(OAc)$_2$ (5 mg, 0.024 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (50 mg, 0.470 mmol, 1 equiv). The crude was
purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 151 mg of the desired products as orange oil (major dia) and yellow solid (minor dia). Yield: 79%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: 14:5.6:1

(1R,2R,3S)-2-(6-nitrobenzoxazol-2-yl)-3-(4-nitrophenyl)cyclopropane-1-carbaldehyde

IR (CHCl₃, liquid film): 3109, 2924, 2852, 1714 (CHO), 1571 (aromatic NO₂), 1518, 1344 (aromatic NO₂), 735 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 9.96 (d, J = 2.4 Hz, 1H, CHO), 8.25 (d, J = 2.1 Hz, 1H, Het), 8.21 (dd, J = 8.8, 2.1 Hz, 1H, Het), 8.06 (bd, J = 8.7 Hz, 2H, Ar), 7.64 (d, J = 8.8 Hz, 1H, Het), 7.44 (bd, J = 8.7 Hz, 2H, Ar), 3.66 (ddd, J = 5.7, 5.6, 2.4 Hz, 1H, CHCHO), 3.46 (bd, J = 5.7 Hz, 2H, CHAr, CHHet).

¹³C NMR (101 MHz, CDCl₃) δ 196.6 (CHO), 165.6 (Cq), 149.9 (Cq), 147.6 (Cq), 145.9 (Cq), 145.4 (Cq), 140.5 (Cq), 129.9 (CH), 123.8 (CH), 121.0 (CH), 119.9 (CH), 107.2 (CH), 34.4 (CH), 34.1 (CH), 26.6 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/iPrOH = 55:45, flow rate 0.8 mL/min, λ = 210 nm): tᵣ (S) = 44.5, tᵣ (R) = 36.0, >99% (R and S) ee.

[α]D²¹ = −50.1° (c = 1.0, CHCl₃) (S catalyst)

HRMS m/z (ESI⁺) Exact mass calculated for C₁₇H₁₂N₃O₆ [M+H]⁺: 354.0721, found: 354.0726.
(1R,2R,3R)-2-(6-nitrobenzoxazol-2-yl)-3-(4-nitrophenyl)cyclopropane-1-carbaldehyde

![Chemical structure](image)

\(^1\text{H NMR (400 MHz, } \text{CDCl}_3\) δ 9.44 (d, \(J = 3.2\) Hz, 1H, CHO), 8.43 (d, \(J = 2.0\) Hz, 1H, Het), 8.32 (d, \(J = 8.8\) Hz, 1H, Het), 8.22 (d, \(J = 8.7\) Hz, 2H, Ar), 7.77 (d, \(J = 8.8\) Hz, 1H, Het), 7.54 (d, \(J = 8.6\) Hz, 2H, Ar), 3.71 (bd, \(J = 6.8\) Hz, 2H, CHAr, CHHet), 3.30 (ddd, \(J = 7.9, 6.7, 3.2\) Hz, 1H, CHCHO).

\(^13\text{C NMR (101 MHz, } \text{CDCl}_3\) δ 194.7 (CHO), 168.4 (Cq), 150.0 (Cq), 147.8 (Cq), 146.5 (Cq), 145.5 (Cq), 140.2 (Cq), 130.2 (CH), 124.1 (CH), 121.2 (CH), 119.9 (CH), 107.3 (CH), 38.6 (CH), 35.5 (CH), 22.7 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak IB column (hexane/iPrOH = 70:30, flow rate 1.0 mL/min, \(\lambda = 210\) nm): \(t_r\) (S) = 40.3, \(t_r\) (R) = 38.7, 81% (R) and 89% (S) ee.

\([\alpha]_D^{22} = +26.9^\circ\) (c = 0.5, CHCl\(\_3\) (R catalyst)

mp: 190 °C decomposition

HRMS \(m/z\) (ESI+) Exact mass calculated for C\(_{17}\)H\(_{12}\)N\(_3\)O\(_6\) [M+H]+: 354.0721, found: 354.0718.

**Compound 392e**

![Chemical structure](image)

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrroldidine (31 mg, 0.094 mmol, 20 mol% equiv),
(E)-4-(3-oxoprop-1-en-1-yl)benzonitrile (148 mg, 0.940 mmol, 2 equiv), 2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.470 mmol, 1 equiv), Pd(OAc)$_2$ (5 mg, 0.024 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (50 mg, 0.470 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 139 mg of the desired products as orange solid (major dia) and yellow oil (minor dia). Yield: 89%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: 4.8:3:1

$\text{4-((1S,2R,3R)-2-formyl-3-(6-nitrobenzoxazol-2-yl)cyclopropyl)benzonitrile}$

![Image of the compound](image)

IR (CHCl$_3$, liquid film): 2923, 2838, 2229 (CN), 1714 (CHO), 1571 (aromatic NO$_2$), 1523, 1345 (aromatic NO$_2$), 759 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.95 (d, $J = 2.4$ Hz, 1H, CHO), 8.27 (d, $J = 2.0$ Hz, 1H, Het), 8.23 (dd, $J = 8.7$, 2.1 Hz, 1H, Het), 7.65 (d, $J = 8.7$ Hz, 1H, Het), 7.51 (bd, $J = 8.4$ Hz, 2H, Ar), 7.37 (bd, $J = 8.3$ Hz, 2H, Ar), 3.62 (ddd, $J = 5.7$, 5.6, 2.4 Hz, 1H, CHCHO), 3.47 – 3.39 (m, 2H, CHAr, CHHet).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 196.6 (CHO), 165.7 (Cq), 149.9 (Cq), 145.9 (Cq), 145.4 (Cq), 138.5 (Cq), 132.4 (CH), 129.7 (CH), 120.9 (CH), 119.9 (CH), 118.4 (Cq), 112.0 (Cq), 107.1 (CH), 34.4 (CH), 34.2 (CH), 26.5 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak AY-H column (hexane/iPrOH = 60:40, flow rate 0.8 mL/min, $\lambda = 210$ nm): $t_r$ (S) = 33.8, $t_r$ (R) = 28.8, >99% (R and S) ee.

$[\alpha]_D^{22} = -169.2^\circ$ (c = 0.7, CHCl$_3$) ($S$ catalyst)

mp: 65 °C decomposition

HRMS $m/z$ (ESI+) Exact mass calculated for C$_{18}$H$_{12}$N$_3$O$_4$ [M+H]$^+$: 334.0822, found: 334.0814.
4-((1R,2R,3R)-2-formyl-3-(6-nitrobenzoxazol-2-yl)cyclopropyl)benzonitrile

Mixture of minor and minor':

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.69 (d, \(J = 5.3\) Hz, 1H'), 9.40 (d, \(J = 3.4\) Hz, 1H), 8.42 (bs, 1H + 1H'), 8.32 (bd, \(J = 8.8\) Hz, 1H + 1H'), 7.79 – 7.75 (m, 1H + 1H'), 7.69 – 7.65 (m, 2H + 2H'), 7.48 (d, \(J = 8.2\) Hz, 2H), 7.38 (d, \(J = 8.3\) Hz, 2H'), 3.79 (dd, \(J = 6.3, 6.2\) Hz, 1H'), 3.68 (bd, \(J = 7.1\) Hz, 2H), 3.30 – 3.19 (m, 1H + 1H'), 2.86 – 2.81 (m, 1H').

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 196.0 (CHO'), 194.8 (CHO), 168.5 (Cq), 166.5 (Cq'), 150.1 (Cq'), 150.0 (Cq), 146.5 (Cq), 146.2 (Cq'), 145.4 (Cq), 141.5 (Cq'), 138.2 (Cq), 133.0 (CH'), 132.7 (CH), 130.0 (CH), 127.6 (CH'), 121.2 (CH), 121.1 (CH'), 120.1 (CH'), 119.8 (CH), 118.39 (Cq), 118.38 (Cq'), 112.3 (Cq), 112.2 (Cq'), 107.4 (CH'), 107.3 (CH), 39.2 (CH'), 38.6(CH), 35.6(CH), 31.6 (CH'), 26.9 (CH'), 22.5 (CH).

HRMS \(m/z\) (ESI+) Exact mass calculated for C\(_{18}\)H\(_{12}\)N\(_3\)O\(_4\) [M+H]': 334.0822, found: 334.0828.

Compound 392f

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (31 mg, 0.094 mmol, 20 mol% equiv), (E)-3-(4-fluorophenyl)acrylaldehyde (141 mg, 0.940 mmol, 2 equiv), 2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.470 mmol, 1 equiv), Pd(OAc)\(_2\) (5 mg, 0.024 mmol, 5 mol% equiv), CH\(_3\)CN (1 mL) and 2,6-lutidine (50 mg, 0.470 mmol, 1 equiv). The crude
was purified by flash column chromatography (hexane/EtOAc 4:1) to obtain 132 mg of the desired products as yellow oil. Yield: 86%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: 6.6:2.6:1

\((1R,2S,3R)-2-(4-fluorophenyl)-3-(6-nitrobenzoxazol-2-yl)cyclopropane-1-carbaldehyde\)

IR (CHCl\(_3\), liquid film): 3109, 2924, 2850, 1721 (CHO), 1571 (aromatic NO\(_2\)), 1513, 1343 (aromatic NO\(_2\)), 1232 (aromatic F), 1154 (aromatic F), 757 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.89 (d, \(J = 2.7\) Hz, 1H, CHO), 8.24 (d, \(J = 1.4\) Hz, 1H, Het), 8.23 – 8.18 (m, 1H, Het), 7.64 (d, \(J = 8.7\) Hz, 1H, Het), 7.24 – 7.15 (m, 2H, Ar), 6.88 (t, \(J = 8.6\) Hz, 2H, Ar), 3.53 (ddd, \(J = 5.5, 5.5, 2.8\) Hz, 1H, CHO), 3.37 (d, \(J = 5.5\) Hz, 2H, CHAr, CHHet).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 197.2 (CHO), 166.4 (Cq), 162.4 (d, \(J = 247.3\) Hz, Cq), 149.9 (Cq), 146.1 (Cq), 145.2 (Cq), 130.6 (d, \(J = 8.3\) Hz, CH), 128.7 (d, \(J = 3.3\) Hz, Cq), 120.8 (CH), 119.7 (CH), 115.7 (d, \(J = 21.7\) Hz, CH), 107.1 (CH), 34.6 (CH), 34.1 (CH), 26.2 (CH).

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) –113.79.

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, \(\lambda = 210\) nm): \(t_r\) (S) = 24.8, \(t_r\) (R) = 18.7, 98% (R and S) ee.

\([\alpha]_D^{21} = -136.6^\circ\) (c = 1.4, CHCl\(_3\)) (S catalyst)

HRMS \(m/z\) (ESI+) Exact mass calculated for C\(_{17}\)H\(_{12}\)FN\(_2\)O\(_4\) [M+H]\(^+\): 327.0776, found: 327.0771.
(1R,2R,3R)-2-(4-fluorophenyl)-3-(6-nitrobenzoxazol-2-yl)cyclopropane-1-carbaldehyde

Mixture of minor and minor’:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.67 (d, $J = 5.6$ Hz, 1H'), 9.24 (d, $J = 4.4$ Hz, 1H), 8.43 – 8.42 (m, 1H + 1H'), 8.32 (d, $J = 8.8$, 1H + d, $J = 2.1$ Hz, 1H'), 7.78 (d, $J = 8.7$, 1H), 7.76 (d, $J = 6.2$ Hz, 1H'), 7.34 (dd, $J = 8.5$, 5.3 Hz, 2H), 7.23 (dd, $J = 5.9$, 2.8 Hz, 2H'), 7.10 – 7.03 (m, 2H + 2H'), 3.75 (dd, $J = 6.3$, 6.1 Hz, 1H'), 3.62 (m, 2H), 3.16 – 3.07 (m, 1H + 1H'), 2.77 – 2.72 (m, Hz, 1H').

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 196.9 (CHO'), 195.7 (CHO), 169.1 (Cq), 167.3 (Cq'), 163.79 (Cq'), 163.76 (Cq), 161.33 (Cq'), 161.30 (Cq), 150.1 (Cq'), 150.0 (Cq), 146.6 (Cq), 146.4 (Cq'), 145.5 (Cq'), 145.4 (Cq), 131.74 (Cq'), 131.71 (Cq'), 130.9 (CH), 130.8 (CH), 128.7 (Cq), 128.63 (CH'), 128.61 (Cq), 128.5 (CH'), 121.09 (CH), 121.06 (CH'), 120.0 (CH'), 119.7 (CH), 116.3 (CH'), 116.2 (CH), 116.1 (CH'), 115.9 (CH), 107.3 (CH'), 107.2 (CH), 39.4 (CH'), 38.7 (CH), 34.9 (CH), 31.6 (CH'), 26.7 (CH'), 22.5 (CH).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -113.43, -113.65'.

HRMS $m/z$ (ESI+) Exact mass calculated for C$_{17}$H$_{12}$FN$_2$O$_4$ [M+H]$^+$: 327.0776, found: 327.0769.
Compound 392g

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (31 mg, 0.094 mmol, 20 mol% equiv), (E)-3-(p-tolyl)acrylaldehyde (137 mg, 0.940 mmol, 2 equiv), 2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.470 mmol, 1 equiv), Pd(OAc)$_2$ (5 mg, 0.024 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (50 mg, 0.470 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 100 mg of the desired products as yellow oil. Yield: 66%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: 5.3:1.6:1

(15,2S,3R)-2-(6-nitrobenzoxazol-2-yl)-3-(p-tolyl)cyclopropane-1-carbaldehyde

IR (CHCl$_3$, liquid film): 3106, 2922, 2853, 1714 (CHO), 1571 (aromatic NO$_2$), 1522, 1344 (aromatic NO$_2$), 751, 735 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.87 (d, $J = 2.9$ Hz, 1H, CHO), 8.24 (d, $J = 1.9$ Hz, 1H, Het), 8.21 (dd, $J = 8.7$, 2.1 Hz, 1H, Het), 7.65 (d, $J = 8.7$ Hz, 1H, Het), 7.10 (d, $J = 8.0$ Hz, 2H, Ar), 6.99 (d, $J = 7.9$ Hz, 2H, Ar), 3.54 (ddd, $J = 5.6$, 5.5, 2.9 Hz, 1H, CHCHO), 3.42 – 3.31 (m, 2H, CHAr, CHHet), 2.23 (s, 3H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 197.5 (CHO), 166.8 (Cq), 150.0 (Cq), 146.3 (Cq), 145.2 (Cq), 137.8 (Cq), 129.9 (Cq), 129.4 (CH), 128.6 (CH), 120.7 (CH), 119.7 (CH), 107.1 (CH), 34.8 (CH), 34.6 (CH), 26.3 (CH), 21.2 (CH$_3$).
The enantiomeric excess was determined by **HPLC** using a Chiralpak AY-H column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, λ = 210 nm): \( t_r (S) = 22.7, t_r (R) = 21.3, 99\% \) (R and S) ee.

\[
[\alpha]_{D}^{22} = +131.3^\circ \text{ (c = 0.5, CHCl}_3) \text{ (R catalyst)}
\]

**HRMS m/z (ESI+)** Exact mass calculated for \( \text{C}_{18}\text{H}_{15}\text{N}_{2}\text{O}_{4} \) [M+H]+: 323.1026, found: 323.1024.

(1\(R\),2\(R\),3\(R\))-2-(6-nitrobenzoxazol-2-yl)-3-(p-tolyl)cyclopropane-1-carbaldehyde

![Structure](image)

Mixture of minor and minor':

Purity: 62\%, the starting benzoxazole was also present in the NMR

\(^1\text{H NMR (400 MHz, CDCl}_3\) \( \delta 9.66 \text{ (d, } J = 5.8 \text{ Hz, 1H')}, 9.14 \text{ (d, } J = 5.0 \text{ Hz, 1H)}, 8.41 \text{ (m, 1H} + 1\text{H'}), 8.31 \text{ (m, 1H} + 1\text{H'}), 7.76 \text{ (d, } J = 8.8 \text{ Hz, 1H'}), 7.75 \text{ (d, } J = 8.8 \text{ Hz, 1H'}), 7.26-7.24 \text{ (m, 2H), 7.19 – 7.11 \text{ (m, 2H} + 4\text{H'}), 3.72 \text{ (dd, } J = 6.3, 6.2 \text{ Hz, 1H'}), 3.61 \text{ (m, } J = 6.3 \text{ Hz, 2H), 3.13 \text{ (dd, } J = 8.9, 6.5 \text{ Hz, 1H'}), 3.04 \text{ (ddd, } J = 9.3, 9.3, 5.0 \text{ Hz, 1H}), 2.77 – 2.72 \text{ (m, 1H')}, 2.35 \text{ (s, 3H'), 2.34 \text{ (s, 3H}).}
\]

\(^{13}\text{C NMR (101 MHz, CDCl}_3\) \( \delta 197.3 \text{ (CHO')}, 196.2 \text{ (CHO), 171.9 (Cq), 169.4 (Cq), 152.4 \text{ (Cq), 150.0 (Cq), 146.7 (Cq), 138.2 (Cq), 132.9 (Cq), 129.9 (CH'), 129.8 (CH), 129.0 (CH), 126.7 (CH'), 121.1 (CH), 120.9 (CH'), 119.9 (CH'), 119.7 (CH), 107.3 (CH'), 107.2 (CH), 39.6 (CH'), 38.9 (CH), 35.2 (CH), 32.2 (CH'), 26.8 (CH'), 22.3 (CH), 21.30 \text{ (CH), 21.29 (CH').}
\]

**HRMS m/z (ESI+)** Exact mass calculated for \( \text{C}_{18}\text{H}_{15}\text{N}_{2}\text{O}_{4} \) [M+H]+: 323.1026, found: 323.1033.

**Compound 392h**
The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (31 mg, 0.094 mmol, 20 mol% equiv), (E)-3-(2-bromophenyl)acrylaldehyde (198 mg, 0.940 mmol, 2 equiv), 2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.470 mmol, 1 equiv), Pd(OAc)$_2$ (5 mg, 0.024 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (50 mg, 0.470 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 4:1) to obtain 147 mg of the desired products as yellow oil. Yield: 81%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: 13.4:2.3:1

**1R,2S,3R-2-(2-bromophenyl)-3-(6-nitrobenzoxazol-2-yl)cyclopropane-1-carbaldehyde**

![Structure of the compound](structure.png)

**IR (CHCl$_3$, liquid film):** 3107, 2922, 2850, 1713 (CHO), 1570 (aromatic NO$_2$), 1513, 1342 (aromatic NO$_2$), 757 cm$^{-1}$.

**$^1$H NMR (400 MHz, CDCl$_3$)** $\delta$ 9.87 (d, $J$ = 2.8 Hz, 1H, CHO), 8.22 (d, $J$ = 2.0 Hz, 1H, Het), 8.19 (dd, $J$ = 8.7, 2.1 Hz, 1H, Het), 7.59 (d, $J$ = 8.7 Hz, 1H, Het), 7.44 (d, $J$ = 7.8 Hz, 1H, Ar), 7.24 – 7.20 (m, 2H, Ar), 7.13 – 7.07 (m, 1H, Ar), 3.54 – 3.47 (m, 2H, CH), 3.40 (dd, $J$ = 8.9, 6.9 Hz, 1H, CH).

**$^{13}$C NMR (101 MHz, CDCl$_3$)** $\delta$ 196.9 (CHO), 166.8 (Cq), 149.8 (Cq), 146.3 (Cq), 145.1 (Cq), 133.6 (Cq), 132.9 (CH), 130.7 (CH), 129.7 (CH), 127.4 (CH), 126.0 (Cq), 120.7 (CH), 119.6 (CH), 107.0 (CH), 35.8 (CH), 35.6 (CH), 26.0 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/iPrOH = 70:30, flow rate 0.8 mL/min, $\lambda$ = 210 nm): $t_r$ (S) = 52.2, $t_r$ (R) = 34.0, >99% (R and S) ee.
$[\alpha]_D^{20} = -62.3^\circ$ (c = 1.0, CHCl$_3$) (S catalyst)

$[\alpha]_D^{20} = +58.7^\circ$ (c = 1.3, CHCl$_3$) (R catalyst)

**HRMS m/z (ESI+)** Exact mass calculated for C$_{17}$H$_{12}$Br$_7$N$_2$O$_4$ [M+H]$^+$: 386.9975, found: 386.9964.

(1R,2R,3R)-2-(2-bromophenyl)-3-(6-nitrobenzoxazol-2-yl)cyclopropane-1-carbaldehyde

![Chemical Structure](image)

Mainly minor diastereomer present in the NMR with traces of major diastereomer, minor’ and starting aldehyde.

**$^1$H NMR (400 MHz, CDCl$_3$)** δ 9.38 (d, $J = 3.7$ Hz, 1H, CHO), 8.44 (d, $J = 2.1$ Hz, 1H, Het), 8.32 (dd, $J = 8.7$, 2.1 Hz, 1H, Het), 7.78 (d, $J = 8.8$ Hz, 1H, Het), 7.60 (dd, $J = 7.9$, 0.8 Hz, 1H, Ar), 7.41 (d, $J = 7.2$ Hz, 1H, Ar), 7.37 – 7.33 (m, 1H, Ar), 7.24 – 7.20 (m, 1H, Ar), 3.61 (dd, $J = 6.5$, 4.9 Hz, 1H, CHhet), 3.55 (dd, $J = 9.4$, 6.7 Hz, 1H, CHar), 3.30 (ddd, $J = 9.4$, 4.6, 3.9 Hz, 1H, CHCHO).

**HRMS m/z (ESI+)** Exact mass calculated for C$_{17}$H$_{12}$Br$_7$N$_2$O$_4$ [M+H]$^+$: 386.9975, found: 386.9978.
Compound 392i

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (31 mg, 0.094 mmol, 20 mol% equiv), ethyl (E)-4-oxobut-2-enoate (198 mg, 0.940 mmol, 2 equiv), 2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.470 mmol, 1 equiv), Pd(OAc)$_2$ (5 mg, 0.024 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (50 mg, 0.470 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 4:1) to obtain 147 mg of the desired products as yellow oil. Yield: 81%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: >15

ethyl (1S,2R,3R)-2-formyl-3-(6-nitrobenzoxazol-2-yl)cyclopropane-1-carboxylate

IR (CHCl$_3$, liquid film): 3019, 2920, 2851, 1730 (CHO), 1577 (aromatic NO$_2$), 1528, 1346 (aromatic NO$_2$), 1214 (ester), 746 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.87 (d, $J = 2.0$ Hz, 1H, CHO), 8.41 (d, $J = 2.0$ Hz, 1H, Het), 8.29 (dd, $J = 8.8$, 2.1 Hz, 1H, Het), 7.78 (d, $J = 8.8$ Hz, 1H, Het), 4.06 (q, $J = 7.1$ Hz, 2H, OCH$_2$CH$_3$), 3.53 (ddd, $J = 5.9$, 5.4, 2.1 Hz, 1H, CHCHO), 3.27 (dd, $J = 9.5$, 5.9 Hz, 1H, CH), 2.82 (dd, $J = 9.5$, 5.4 Hz, 1H, CH), 1.12 (t, $J = 7.1$ Hz, 3H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.9 (CHO), 167.4 (Cq), 165.4 (Cq), 150.1 (Cq), 146.3 (Cq), 145.6 (Cq), 120.9 (CH), 120.2 (CH), 107.4 (CH), 62.1 (CH$_2$), 33.2 (CH), 29.6 (CH), 24.4 (CH), 14.1 (CH$_3$).

The enantiomeric excess was determined by HPLC using a Chiralpak AY-H column (hexane/iPrOH = 50:50, flow rate 1.0 mL/min, $\lambda$ = 210 nm): $t_r$ (S) = 31.8, $t_r$ (R) = 35.2, 81% (R) / 87% (S) ee.

$[\alpha]_D^{22} = -45.8^\circ$ (c = 0.4, CHCl$_3$) (S catalyst)
HRMS $m/z$ (ESI+): Exact mass calculated for C$_{14}$H$_{13}$N$_2$O$_6$ [M+H]+: 305.0768, found: 305.0763.

**Compound 402a**

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (26 mg, 0.081 mmol, 20 mol% equiv), cinnamaldehyde (107 mg, 0.810 mmol, 2 equiv), 5-chloro-2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.405 mmol, 1 equiv), Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (43 mg, 0.405 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 10:1) to obtain 106 mg of the desired products as yellow oil. Yield: 68%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: 10.5:3.3:1

(15,2S,3R)-2-(5-chloro-6-nitrobenzoxazol-2-yl)-3-phenylcyclopropane-1-carbaldehyde

IR (CHCl$_3$, liquid film): 3101, 2922, 2849, 1713 (CHO), 1564 (aromatic NO$_2$), 1531, 1344 (aromatic NO$_2$), 752 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.89 (d, $J = 2.7$ Hz, 1H, CHO), 7.89 (s, 1H, Het), 7.69 (s, 1H, Het), 7.22 – 7.17 (m, 5H, Ph), 3.56 (ddd, $J = 6.1, 5.1, 2.8$ Hz, 1H, CHCHO), 3.44 – 3.33 (m, 2H, , CHPh, CHHet).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 197.2 (CHO), 167.3 (Cq), 148.2 (Cq), 144.71 (Cq), 144.67 (Cq), 132.8 (Cq), 128.8 (CH), 128.7 (CH), 128.1 (CH), 123.8 (Cq), 122.2 (CH), 108.4 (CH), 35.0 (CH), 34.5 (CH), 26.1 (CH).
The enantiomeric excess was determined by **HPLC** using a Chiralpak IC column (hexane/iPrOH = 85:15, flow rate 1.0 mL/min, λ = 210 nm): \( t_r \) (S) = 30.7, \( t_r \) (R) = 33.9, >99% (R and S) ee.

\[ \alpha \]D21 = +99.6° (c = 0.4, CHCl3) (R catalyst)

**HRMS m/z (ESI+)** Exact mass calculated for C17H12Cl35N2O4 [M+H]+: 343.0480, found: 343.0472.

\((15,2S,3S)-2\)-(5-chloro-6-nitrobenzoxazol-2-yl)-3-phenylcyclopropane-1-carbaldehyde

![Chemical structure](image)

Mixture of minor and minor’:

**1H NMR (400 MHz, CDCl3)** \( \delta \) 9.57 (d, \( J = 5.5 \) Hz, 1H’), 9.06 (d, \( J = 4.9 \) Hz, 1H), 7.99 (s, 1H + 1H’), 7.73 (s, 1H’), 7.71 (s, 1H), 7.29 – 7.13 (m, 5H + 5H’), 3.63 (dd, \( J = 6.3 \), 6.3 Hz, 1H’), 3.59 – 3.48 (m, 2H), 3.05 (dd, \( J = 8.9 \), 6.5 Hz, 1H’), 2.97 (dt, \( J = 9.7 \), 4.9 Hz, 1H), 2.70 (ddd, \( J = 8.9 \), 6.2, 5.7 Hz, 1H’).

**13C NMR (101 MHz, CDCl3)** \( \delta \) 196.9 (CHO’), 195.9 (CHO), 169.9 (Cq), 168.2 (Cq’), 148.4 (Cq’), 148.3 (Cq), 145.2 (Cq), 145.0 (Cq’), 144.97 (Cq’), 144.8 (Cq), 135.8 (CH’), 132.8 (CH), 129.3 (CH’), 129.2 (CH), 129.1 (CH), 128.4 (Cq), 128.3 (Cq’), 126.8 (CH’), 124.2 (Cq), 124.4 (Cq’), 122.5 (CH’), 122.3 (CH), 108.8 (CH’), 108.7 (CH), 39.5 (CH’), 38.9 (CH), 35.6 (CH), 32.5 (CH’), 26.7 (CH’), 22.1 (CH).

The enantiomeric excess was determined by **HPLC** using a Chiralpak IC column (hexane/iPrOH = 85:15, flow rate 1.0 mL/min, λ = 210 nm): \( t_r \) (S) = 37.7, \( t_r \) (R) = 40.1, 90% (R) ee.

\[ \alpha \]D21 = −15.4° (c = 0.6, CHCl3) (S catalyst)

**HRMS m/z (ESI+)** Exact mass calculated for C17H12Cl35N2O4 [M+H]+: 343.0480, found: 343.0476.
Compound 402b

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (29 mg, 0.089 mmol, 20 mol% equiv), cinnamaldehyde (117 mg, 0.886 mmol, 2 equiv), methyl 2-(chloromethyl)benzoxazole-6-carboxylate (100 mg, 0.443 mmol, 1 equiv), Pd(OAc)$_2$ (5 mg, 0.022 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (48 mg, 0.443 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 111 mg of the desired products as yellow oil. Yield: 78%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: 4.5:1.9:1

methyl 2-((1R,2R,3S)-2-formyl-3-phenylcyclopropyl)benzoxazole-6-carboxylate

IR (CHCl$_3$, liquid film): 3061, 2952, 2847, 1717 (CHO, CO ester), 1434, 1287 (ester), 1269 (ester), 746 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.87 (d, $J = 2.9$ Hz, 1H, CHO), 8.00 (d, $J = 0.9$ Hz, 1H, Het), 7.98 (dd, $J = 8.3$, 1.5 Hz, 1H, Het), 7.58 (d, $J = 8.3$ Hz, 1H, Het), 7.24 – 7.14 (m, 5H, Ph), 3.91 (s, 3H, OCH$_3$), 3.54 (ddd, $J = 5.5$, 5.5, 2.9 Hz, 1H, CHCHO), 3.41 – 3.33 (m, 2H, CHPh, CHHet).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 197.6 (CHO), 166.5 (Cq), 164.3 (Cq), 150.4 (Cq), 144.8 (Cq), 133.2 (Cq), 128.7 (CH), 128.4 (CH), 127.7 (CH), 126.9 (Cq), 126.1 (CH), 119.2 (CH), 111.9 (CH), 52.4 (CH$_3$), 34.4 (CH), 34.3 (CH), 26.2 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak AY-H column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, $\lambda = 230$ nm): $t_r$ (S) = 21.1, $t_r$ (R) = 20.0, 98% (R) / 98% (S) ee.

$[\alpha]_D^{22} = -104.6^\circ$ (c = 0.8, CHCl$_3$) (S catalyst)
$[\alpha]_D^{22} = +105.8^\circ$ (c = 0.4, CHCl$_3$) \textbf{(R catalyst)}

**HRMS m/z (ESI+)** Exact mass calculated for C$_{19}$H$_{16}$NO$_4$ [M+H]$^+$: 322.1074, found: 322.1079.

\textbf{methyl 2-((1R,2R,3S)-2-formyl-3-phenylcyclopropyl)benzoxazole-6-carboxylate}

![Chemical Structure]

Mixture of minor and minor’ (inverted compared to the previous products as in this case the minor’ is prevalent):

**$^1$H NMR (400 MHz, CDCl$_3$)** δ 9.64 (d, $J = 6.0$ Hz, 1H’), 9.13 (d, $J = 5.2$ Hz, 1H), 8.22 – 8.18 (m, 1H + 1H’), 8.09 (d, $J = 8.4$ Hz, 1H + d, $J = 8.4$ Hz, 1H’), 7.71 (d, $J = 8.3$, Hz, 1H’), 7.70 (d, $J = 8.3$, Hz, 1H), 7.41 – 7.22 (m, 5H + 5H’), 3.97 (s, 3H + 3H’), 3.76 (dd, $J = 6.3$, 6.3 Hz, 1H’), 3.69 – 3.59 (m, 2H), 3.17 (dd, $J = 8.9$, 6.5 Hz, 1H’), 3.04 (ddd, $J = 9.7$, 5.4, 5.0 Hz, 1H), 2.73 (ddd, $J = 8.9$, 6.0, 6.0 Hz, 1H’).

**$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 197.3 (CHO’), 196.3 (CHO), 166.9 (Cq), 166.53 (Cq’), 166.50 (Cq), 165.2 (Cq’), 150.4 (Cq’), 150.3 (Cq), 145.1 (Cq), 144.9 (Cq’), 136.1 (Cq’), 133.1 (Cq), 129.0 (CH’), 129.0 (CH + CH’), 128.9 (CH), 128.0 (CH), 127.9 (CH’), 127.3 (Cq), 127.1 (Cq’), 126.6 (CH’), 126.5 (CH), 119.4 (CH’), 119.1 (CH), 112.14 (CH’), 112.07 (CH), 52.4 (CH$_3$ + CH$_3’$), 39.5 (CH’), 38.5 (CH), 34.8 (CH), 31.7 (CH’), 26.6 (CH’), 22.1 (CH).

**HRMS m/z (ESI+)** Exact mass calculated for C$_{19}$H$_{16}$NO$_4$ [M+H]$^+$: 322.1074, found: 322.1079.
Compound 402c

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (31 mg, 0.094 mmol, 20 mol% equiv), cinnamaldehyde (124 mg, 0.940 mmol, 2 equiv), 2-(chloromethyl)-5-nitrobenzoxazole (100 mg, 0.470 mmol, 1 equiv), Pd(OAc)$_2$ (5 mg, 0.024 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (50 mg, 0.470 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 3:1) to obtain 80 mg of the desired products as dark yellow oil. Yield: 55%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. $d_r$: 6.2:1.3:1

$\text{(1R,2R,3S)-2-(5-nitrobenzoxazol-2-yl)-3-phenylcyclopropane-1-carbaldehyde}$

IR (CHCl$_3$, liquid film): 3105, 2923, 2852, 1714 (CHO), 1526, 1347 (aromatic NO$_2$), 743 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.89 (d, $J = 2.8$ Hz, 1H, CHO), 8.44 (d, $J = 2.3$ Hz, 1H, Het), 8.19 (dd, $J = 8.9, 2.3$ Hz, 1H, Het), 7.42 (d, $J = 9.0$ Hz, 1H, Het), 7.23 – 7.14 (m, 5H, Ph), 3.56 (ddd, $J = 5.5, 5.4, 2.8$ Hz, 1H, CHCHO), 3.38 (d, $J = 5.5$ Hz, 2H, CHPh, CHHet).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 194.5 (CHO), 162.0 (Cq), 151.3 (Cq), 142.4 (Cq), 138.4 (Cq), 130.1 (Cq), 125.8 (CH), 125.6 (CH), 125.0 (CH), 118.1 (CH), 113.2 (CH), 107.6 (CH), 31.8 (CH), 31.4 (CH), 23.1 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/PrOH = 70:30, flow rate 1.0 mL/min, $\lambda = 210$ nm): $t_r$ (S) = 20.6, $t_r$ (R) = 19.8, 99% (R) / 98% (S) ee.

[$\alpha$]$_{D}^{22} = -41.6^\circ$ (c = 0.8, CHCl$_3$, S catalyst)
$[\alpha]_D^{22} = +36.2^\circ$ (c = 0.5, CHCl$_3$) (R catalyst)

**HRMS m/z (ESI+)** Exact mass calculated for C$_{17}$H$_{13}$N$_2$O$_4$ [M+H]$^+$: 309.0870, found: 309.0868.

(1R,2R,3R)-2-(5-nitrobenzoxazol-2-yl)-3-phenylcyclopropane-1-carbaldehyde

Mixture of minor and minor$'$:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.66 (d, $J = 5.7$ Hz, 1H'), 9.15 (d, $J = 5.0$ Hz, 1H), 8.57 (d, $J = 2.2$ Hz, 1H'), 8.55 (d, $J = 2.2$ Hz, 1H), 8.31 (dd, $J = 8.9$, 2.5 Hz, 1H + dd, $J = 8.9$, 2.5 Hz, 1H'), 7.62 (bd, $J = 8.9$ Hz, 1H + 1H'), 7.41 – 7.24 (m, 10H), 3.75 (dd, $J = 6.3$, 6.3 Hz, 1H'), 3.69 – 3.59 (m, 2H), 3.16 (dd, $J = 8.9$, 6.5 Hz, 1H'), 3.06 (ddd, $J = 9.7$, 5.0, 4.9 Hz, 1H), 2.77 (ddd, $J = 8.9$, 5.9, 5.9 Hz, 1H').

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 197.2 (CHO), 196.1 (CHO), 167.6 (Cq), 165.9 (Cq), 154.4 (Cq), 154.3 (Cq), 145.7 (2 Cq), 141.9 (Cq), 141.7 (Cq), 136.0 (Cq), 132.9 (Cq), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.3 (CH), 128.2 (CH), 126.8 (CH), 121.4 (CH), 121.2 (CH), 116.4 (CH), 116.1 (CH), 110.9 (CH), 110.8 (CH), 39.4 (CH), 38.6 (CH), 35.2 (CH), 32.1 (CH), 26.6 (CH), 22.0 (CH).

**HRMS m/z (ESI+)** Exact mass calculated for C$_{17}$H$_{13}$N$_2$O$_4$ [M+H]$^+$: 309.0870, found: 309.0877.

**Compound 402d**

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (31mg, 0.094 mmol, 20 mol% equiv),
cinnamaldehyde (124 mg, 0.940 mmol, 2 equiv), 2-(chloromethyl)-4-nitrobenzoxazole (100 mg, 0.470 mmol, 1 equiv), Pd(OAc)$_2$ (5 mg, 0.024 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (50 mg, 0.470 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 3:1) to obtain 74 mg of the desired products as dark yellow oil. Yield: 51%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: 2.3:1.6:1

(1R,2R,3S)-2-(4-nitrobenzoxol-2-yl)-3-phenylcyclopropane-1-carbaldehyde

Mixture of major (m) and minor:

**IR** (CHCl$_3$, liquid film): 3020, 2852, 1713 (CHO), 1561 (aromatic NO$_2$), 1526, 1343 (aromatic NO$_2$), 1214, 747 cm$^{-1}$.

**$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$ 9.88 (d, $J = 2.8$ Hz, 1H$^m$), 9.14 (d, $J = 5.0$ Hz, 1H), 8.20 (d, $J = 8.3$ Hz, 1H), 8.10 (d, $J = 8.2$ Hz, 1H$^m$), 7.85 (d, $J = 8.1$ Hz, 1H), 7.61 (d, $J = 8.1$ Hz, 1H$^m$), 7.49 (dd, $J = 8.2$ Hz, 1H), 7.39 – 7.15 (m, 6H$^m$ + 5H), 3.77 – 3.72 (m, 2H), 3.64 (ddd, $J = 5.6$, 5.6, 2.9 Hz, 1H$^m$), 3.50 (ddd, $J = 9.8$, 5.1 Hz, 1H), 3.44 – 3.34 (m, 1H$^m$), 3.12 (ddd, $J = 9.2$, 5.2, 5.2 Hz, 1H).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta$ 197.3 (CHO$^m$), 195.9 (CHO), 167.9 (Cq), 165.5 (Cq$^m$), 152.3 (Cq), 152.2 (Cq$^m$), 139.8 (Cq), 138.7 (Cq$^m$), 136.1 (Cq), 135.7 (Cq$^{2m}$), 132.9 (Cq$^m$), 132.8 (Cq), 129.0 (CH), 128.9 (CH), 128.7 (CH$^m$), 128.4 (CH$^m$), 128.1 (CH), 127.8 (CH$^m$), 124.4 (CH), 124.2 (CH$^m$), 121.1 (CH), 120.8 (CH$^m$), 116.4 (CH), 116.2 (CH$^m$), 38.6 (CH), 35.1 (CH), 34.7 (CH$^m$), 34.5 (CH$^m$), 26.2 (CH$^m$), 22.1 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak AY-H column (hexane/iPrOH = 70:30, flow rate 1.0 mL/min, $\lambda = 210$ nm): $t_r$ (S) = 37.7, $t_r$ (R) = 21.7, >99% (R and S) ee.

$\left[\alpha\right]_D^{22} = -5.2^\circ$ (c = 0.8, CHCl$_3$) **(S catalyst)**

$\left[\alpha\right]_D^{22} = +6.6^\circ$ (c = 0.7, CHCl$_3$) **(R catalyst)**
HRMS $m/z$ (ESI+) Exact mass calculated for C$_{17}$H$_{13}$N$_2$O$_4$ [M+H]$^+$: 309.0870, found: 309.0871.

$(1R,2R,3R)$-2-(4-nitrobenzoxazol-2-yl)-3-phenylcyclopropane-1-carbaldehyde

![Chemical Structure](image)

Mixture of major$^m$, minor, minor$'$ and traces of starting benzoxazole:

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.88 (d, $J = 2.8$ Hz, 1H$^m$), 9.73 (d, $J = 5.6$ Hz, 1H$'$), 9.14 (d, $J = 5.0$ Hz, 1H), 8.20 (d, $J = 8.3$ Hz, 1H), 8.10 (d, $J = 8.2$ Hz, 4H$^m$), 7.85 (ddd, $J = 8.1$, 4.7, 0.8 Hz, 4H $+$ $'$), 7.64 – 7.57 (m, 4H$^m$), 7.50 (td, $J = 8.2$, 3.3 Hz, 5H $+$ $'$), 7.42 – 7.13 (m, 51H), 3.85 (dd, $J = 6.3$, 6.3 Hz, 1H$'$), 3.78 – 3.72 (m, 2H), 3.64 (ddd, $J = 6.0$, 5.2, 2.9 Hz, 1H$^m$), 3.51 (dd, $J = 9.8$, 5.1 Hz, 1H$^m$), 3.45 – 3.34 (m, 1H$^m$), 3.29 (dd, $J = 8.9$, 6.6 Hz, 1H$'$), 3.12 (ddd, $J = 9.2$, 5.2, 5.2 Hz, 1H), 2.79 (ddd, $J = 8.9$, 5.9, 5.9 Hz, 1H$'$).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 197.3 (CHO$^m$), 197.1 (CHO$'$), 195.9 (CHO), 167.9 (Cq), 166.4 (Cq$'$), 165.5 (Cq$^m$), 152.3 (Cq), 152.2 (Cq$''$), 138.8 (Cq), 138.6 (Cq$^m$), 136.1 (Cq), 135.9 (Cq$'$), 135.8 (Cq), 135.7 (Cq$''$), 132.9 (Cq$''$), 132.8 (Cq), 129.0 (CH), 128.97 (CH$'$), 128.90 (CH), 128.7 (CH$^m$), 128.4 (CH$''$), 128.1 (CH), 128.0 (CH$'$), 127.8 (CH$''$), 126.6 (CH$'$), 125.7 (CH$'$), 124.6 (CH$'$), 124.4 (CH), 124.2 (CH$''$), 121.1 (CH), 120.8 (CH$''$), 117.2 (CH$'$), 116.5 (CH$'$), 116.4 (CH), 116.2 (CH$''$), 39.7 (CH$'$), 38.6 (CH), 35.9 (CH$'$), 35.1 (CH), 34.7 (CH$''$), 34.5 (CH$''$), 32.1 (CH$'$), 26.6 (CH$'$), 26.3 (CH$''$), 22.1 (CH).

HRMS $m/z$ (ESI+) Exact mass calculated for C$_{17}$H$_{13}$N$_2$O$_4$ [M+H]$^+$: 309.0870, found: 309.0871.
**Compound 402e**

![Chemical Structure](image)

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (26 mg, 0.081 mmol, 20 mol% equiv), (E)-3-(4-bromophenyl)acrylaldehyde (171 mg, 0.810 mmol, 2 equiv), 5-chloro-2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.405 mmol, 1 equiv), Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (43 mg, 0.405 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 4:1) to obtain 145 mg of the desired products as yellow oil. Yield: 85%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. \(\text{dr: } 8.1:4.8:1\)

**\((1R,2S,3R)-2-(4-bromophenyl)-3-(5-chloro-6-nitrobenzoxazol-2-yl)cyclopropane-1-carbaldehyde**

![Chemical Structure](image)

**IR (CHCl$_3$, liquid film):** 3101, 2923, 2850, 1713 (CHO), 1565 (aromatic NO$_2$), 1531, 1446, 1345 (aromatic NO$_2$), 755 cm$^{-1}$.

**$^1$H NMR (400 MHz, CDCl$_3$) \(\delta \):** 9.89 (d, $J = 2.6$ Hz, 1H, CHO), 7.92 (s, 1H, Het), 7.69 (s, 1H, Het), 7.33 (d, $J = 8.4$ Hz, 2H, Ar), 7.09 (d, $J = 8.4$ Hz, 2H, Ar), 3.53 (dd, $J = 5.6$, 5.6, 2.6 Hz, 1H, CHCHO), 3.35 (ddd, $J = 9.8$, 5.7 Hz, 2H, CHAr, CHHet).

**$^{13}$C NMR (101 MHz, CDCl$_3$) \(\delta \):** 196.8 (CHO), 166.7 (Cq), 148.1 (Cq), 144.6 (Cq), 144.4 (Cq), 131.7 (CH), 130.3 (CH), 123.8 (Cq), 123.8 (Cq), 122.2 (CH), 122.1 (Cq), 108.4 (CH), 34.2 (CH), 34.2 (CH), 25.9 (CH).
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/iPrOH = 85:15, flow rate 1.0 mL/min, λ = 210 nm): \( t_r (S) = 39.2, t_r (R) = 30.6, 98\% (R) / 97\% (S) \) ee.

\[ [\alpha]_{D}^{21} = -153.8^\circ \text{ (c = 0.6, CHCl}_3 \text{)} \] \text{(S catalyst)}

HRMS \( m/z \) (ESI+) Exact mass calculated for \( \text{C}_{17}\text{H}_{11}\text{Br}^{79}\text{Cl}^{35}\text{N}_2\text{O}_4 \) [M+H]⁺: 420.9585, found: 420.9587.

\((1R,2R,3R)-2-(4\text{-bromophenyl})-3-(5\text{-chloro-6-nitrobenzoxazol-2-yl})\text{cyclopropane-1-carbaldehyde}\)

Mixture of minor and minor’:

\(^1\text{H NMR (400 MHz, CDCl}_3 \) \( \delta 9.66 \text{ (d, } J = 5.3 \text{ Hz, 1H’), 9.26 \text{ (d, } J = 4.2 \text{ Hz, 1H), 8.09 \text{ (s, 1H + 1H’), 7.83 \text{ (s, 1H’), 7.81 \text{ (s, 1H), 7.51 \text{ (d, } J = 8.3 \text{ Hz, 2H’), 7.49 \text{ (d, } J = 8.3 \text{ Hz, 2H), 7.23 \text{ (d, } J = 8.4 \text{ Hz, 2H), 7.13 \text{ (d, } J = 8.4 \text{ Hz, 2H’), 3.69 \text{ (dd, } J = 6.3, 6.3 \text{ Hz, 1H’), 3.58 \text{ (bd, } J = 6.8 \text{ Hz, 2H), 3.15 – 3.08 \text{ (m, 1H + 1H’), 2.80 – 2.72 \text{ (m, 1H’).}} \)

\(^{13}\text{C NMR (101 MHz, CDCl}_3 \) \( \delta 196.2 \text{ (CHO’), 195.1 \text{ (CHO), 169.4 \text{ (Cq), 167.6 \text{ (Cq’), 148.1 \text{ (Cq), 144.9 \text{ (Cq), 144.7 \text{ (Cq’), 144.7 \text{ (Cq)}, 134.7 \text{ (Cq), 132.2 \text{ (CH’), 132.0 \text{ (CH), 131.6 \text{ (Cq), 130.6 \text{ (CH), 128.3 \text{ (CH’), 124.1 \text{ (Cq), 122.4 \text{ (CH’), 122.3 \text{ (Cq), 122.1 \text{ (CH), 122.0 \text{ (Cq’), 108.6 \text{ (CH’), 108.5 \text{ (CH), 39.0 \text{ (CH’), 38.5 \text{ (CH), 35.0 \text{ (CH), 31.6 \text{ (CH’), 26.4 \text{ (CH’), 22.0 \text{ (CH).}} \)

HRMS \( m/z \) (ESI+) Exact mass calculated for \( \text{C}_{17}\text{H}_{11}\text{Br}^{79}\text{Cl}^{35}\text{N}_2\text{O}_4 \) [M+H]⁺: 420.9585, found: 420.9585.
Compound 402f

The reaction was performed following the general procedure adding: 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (26 mg, 0.081 mmol, 20 mol% equiv), (E)-3-(3-bromophenyl)acrylaldehyde (171 mg, 0.810 mmol, 2 equiv), 5-chloro-2-(chloromethyl)-6-nitrobenzoxazole (100 mg, 0.405 mmol, 1 equiv), Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 5 mol% equiv), CH$_3$CN (1 mL) and 2,6-lutidine (43 mg, 0.405 mmol, 1 equiv). The crude was purified by flash column chromatography (hexane/EtOAc 4:1) to obtain 112 mg of the desired products as yellow oil. Yield: 66%. The diastereomeric ratio was calculated based on the isolated products after column chromatography. dr: 17.4:6.3:1

$^{19}$F 1H NMR (400 MHz, CDCl$_3$) $\delta$ 9.92 (d, $J = 2.5$ Hz, 1H, CHO), 7.94 (s, 1H, Het), 7.72 (s, 1H, Het), 7.44 (dd, $J = 1.7$, 1.7 Hz, 1H, Ar), 7.33 (ddd, $J = 7.7$, 1.6, 1.6 Hz, 1H, Ar), 7.14 – 7.05 (m, 2H, Ar), 3.56 (ddd, $J = 5.6$, 5.6, 2.5 Hz, 1H, CHCHO), 3.41 – 3.34 (m, 2H, CHAr, CHHet).

IR (CHCl$_3$, liquid film): 3101, 2922, 2850, 1714 (CHO), 1564(aromatic NO$_2$), 1531, 1446, 1344(aromatic NO$_2$), 754 cm$^{-1}$.

$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.92 (d, $J = 2.5$ Hz, 1H, CHO), 7.94 (s, 1H, Het), 7.72 (s, 1H, Het), 7.44 (dd, $J = 1.7$, 1.7 Hz, 1H, Ar), 7.33 (ddd, $J = 7.7$, 1.6, 1.6 Hz, 1H, Ar), 7.14 – 7.05 (m, 2H, Ar), 3.56 (ddd, $J = 5.6$, 5.6, 2.5 Hz, 1H, CHCHO), 3.41 – 3.34 (m, 2H, CHAr, CHHet).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 196.7 (CHO), 166.6 (Cq), 148.1 (Cq), 144.7 (Cq), 144.4 (Cq), 134.9 (Cq), 132.0 (CH), 131.2 (CH), 130.0 (CH), 127.2 (CH), 123.8 (Cq), 122.5 (Cq), 122.2 (CH), 108.4 (CH), 34.2 (CH), 34.1 (CH), 26.0 (CH).
The enantiomeric excess was determined by **HPLC** using a Chiralpak OD-H column (hexane/iPrOH = 70:30, flow rate 1.0 mL/min, λ = 210 nm): $t_r (S) = 38.2$, $t_r (R) = 32.9$, 91% (R) / 97% (S) ee.

$[\alpha]_D^{21} = -107.2^\circ$ (c = 1.3, CHCl$_3$) *(S catalyst)*

$[\alpha]_D^{21} = +97.9^\circ$ (c = 2.0, CHCl$_3$) *(R catalyst)*

**HRMS** $m/z$ *(ESI+) Exact mass calculated for C$_{17}$H$_{11}$Br$_{79}$Cl$_{35}$N$_2$O$_4$ [M+H]$^+$: 420.9585, found: 420.9581.

*(1R,2R,3R)-2-(3-bromophenyl)-3-(5-chloro-6-nitrobenzoxazol-2-yl)cyclopropane-1-carbaldehyde*

Mixture of minor and minor’:

**$^1$H NMR (400 MHz, CDCl$_3$)** $\delta$ 9.67 (d, $J = 5.3$ Hz, 1H’), 9.26 (d, $J = 4.3$ Hz, 1H), 8.10 (s, 1H + 1H’), 7.84 (s, 1H’), 7.82 (s, 1H), 7.54 (bs, 1H), 7.49 – 7.43 (m, 1H + 1H’), 7.41 (t, $J = 1.7$ Hz, 1H’), 7.32 – 7.17 (m, 2H + 2H’), 3.71 (dd, $J = 6.3$, 6.3 Hz, 1H’), 3.64 – 3.60 (m, 2H), 3.19 – 3.08 (m, 1H + 1H’), 2.84 – 2.76 (ddd, $J = 9.0$, 6.0, 5.4 Hz, 1H’).

**$^{13}$C NMR (101 MHz, CDCl$_3$)** $\delta$ 196.2 (CHO’), 195.0 (CHO), 169.3 (Cq), 167.5 (Cq’), 148.1 (Cq’), 148.0 (Cq), 144.9 (Cq), 144.7 (Cq), 138.0 (Cq’), 134.8 (Cq), 132.1 (CH), 131.4 (CH), 131.2 (CH’), 130.6 (CH’), 130.4 (CH), 129.8 (CH’), 127.6 (CH), 125.4 (CH’), 124.1 (Cq), 124.0 (Cq’), 123.1 (Cq’), 122.9 (Cq), 122.4 (CH’), 122.1 (CH), 108.6 (CH+CH’), 38.9 (CH’), 38.5 (CH), 34.8 (CH), 31.5 (CH’), 26.4 (CH’), 21.9 (CH).

**HRMS** $m/z$ *(ESI+) Exact mass calculated for C$_{17}$H$_{11}$Br$_{79}$Cl$_{35}$N$_2$O$_4$ [M+H]$^+$: 420.9585, found: 420.9589.
6.2.5 Crystallographic data and experimental 392d minor diastereomer obtained with (R)-catalyst

![Crystal Structure Image]

**Figure 26.** Thermal ellipsoids drawn at the 50% probability level

**Experimental.** Single clear colourless fragment-shaped crystals of (2014sot0046) were recrystallised from a mixture of TCM and hexane by slow evaporation. A suitable crystal (0.09 × 0.08 × 0.05 mm³) was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at *T* = 100(2) K during data collection. Using Olex2,[201] the structure was solved with the ShelXT (Sheldrick, 2008) structure solution program, using the Direct Methods solution method. The model was refined with version of ShelXL[202] using Least Squares minimisation.

**Crystal Data.** C₁₇H₁₁N₃O₆, *M*= 353.29, monoclinic, P2₁/c (No. 14), *a* = 9.9877(5) Å, *b* = 15.1541(7) Å, *c* = 10.2131(6) Å, *β* = 103.161(5), *α* = *γ* = 90°, *V* = 1505.20(14) Å³, *T* = 100(2) K, *Z* = 4, *Z*' = 1, *µ* (MoKα) = 0.121, 14536 reflections measured, 3884 unique (*R*int = 0.0709) which were used in all calculations. The final w*R*₂ was 0.3428 (all data) and *R*_1 was 0.1503 (I > 2(I)).
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<th><strong>2014sot0046</strong></th>
</tr>
</thead>
<tbody>
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<td>Formula</td>
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<td>$D_{\text{calc}}$ / g cm$^{-3}$</td>
<td>1.559</td>
</tr>
<tr>
<td>$\mu$ / mm$^{-1}$</td>
<td>0.121</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>353.29</td>
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<td>Colour</td>
<td>clear colourless</td>
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<td>Shape</td>
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<td>Max Size / mm</td>
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<td>Mid Size / mm</td>
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<td>$b$ / Å</td>
<td>15.1541(7)</td>
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<tr>
<td>$c$ / Å</td>
<td>10.2131(6)</td>
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<tr>
<td>$\beta$ / °</td>
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<tr>
<td>$\gamma$ / °</td>
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</tr>
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<td>Independent Refl.</td>
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<tr>
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<td>$R_{\text{int}}$</td>
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<td>Deepest Hole</td>
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</tr>
<tr>
<td>$R_1$</td>
<td>0.1503</td>
</tr>
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</table>
Experimental Extended. A clear colourless fragment-shaped crystal with dimensions $0.09 \times 0.08 \times 0.05 \text{mm}^3$ was mounted on a MITIGEN holder in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at $T = 100(2) \text{K}$. Data were measured using profile data from $\omega$-scans of $1.0^\circ$ per frame for $15.0 \text{s}$ using MoK$_\alpha$ radiation (Rotating Anode, $45.0 \text{kV, 55.0 mA}$). The total number of runs and images was based on the strategy calculation from the program CrystalClear (Rigaku). The actually achieve resolution was $\Theta = 28.699$.

Cell parameters were retrieved using the CrysAlisPro (Agilent, V1.17.1.37.31, 2014) software and refined using CrysAlisPro (Agilent, V1.17.1.37.31, 2014) on 6234 reflections, 43 of the observed reflections. Data reduction was performed using the CrysAlisPro (Agilent, V1.17.1.37.31, 2014) software which corrects for Lorentz polarisation. The final completeness is 99.60 out to $28.699$ in $\Theta$. The absorption coefficient (MU) of this material is 0.121 and the minimum and maximum transmissions are 0.56971 and 1.00000.

The structure was solved by Direct Methods using the ShelXT\cite{ShelXT} structure solution program and refined by Least Squares using version of ShelXL\cite{ShelXL}. The structure was solved in the space group P$2_1$/c ($\#14$). All non-hydrogen atoms were refined anisotropically. Hydrogens positions were calculated geometrically and refined using the riding model.

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6.2.6 Conformational analysis and absolute configuration

All the attempts to obtain good enantiopure crystals of the compounds prepared were not successful. For this reason the relative and absolute configuration was determined by a combination of conformational analysis and theoretical simulations of chiro-optical spectra. Compound 392d was selected as representative compound because good racemic crystals were obtained for the minor diastereomer (392d-minor). X-ray data allowed the determination of the relative configuration of the three stereogenic centres of the cyclopropane ring as $R^*, R^*, R^*$ (Figure 24).

Although the rigidity of the cyclopropane core reduces the number of conformations to be considered, two conformational degrees of freedom due to the rotation of the aldehyde and of the benzoazole moiety must be considered for the conformational analysis step.

The whole conformational space was explored by means of Monte Carlo searching together with the MMFF94 molecular mechanics force field as implemented in Titan 1.0.5 (Wavefunction inc.)

All the conformations found by MM search within a 10 kcal/mol window were then optimized using DFT at the B3LYP/6-31+G(d,p) level using the Gaussian 09 suite of programs. The harmonic vibrational frequencies of each optimized conformation were calculated at the same level to confirm their stability (no imaginary frequencies were observed) and to evaluate the ZPE corrected enthalpy and free energy of each conformation. After DFT minimization, four conformations were found to be enclosed in a 1 kcal/mol window as shown in Figure 27 and marked as a-d in Table 17 and Table 18.

---

Table 17. Relative energies of the four conformations of 392d-minor

The relative energies have been evaluated using ZPE-corrected enthalpies and different optimization levels: B3LYP/6-31+G(d,p) and M06-2X/6-31+G(d,p). Populations are calculated using Boltzmann distribution at 298°K.

<table>
<thead>
<tr>
<th>Conformation</th>
<th>( H^\circ ) (B3LYP)</th>
<th>( H^\circ ) (M06-2X)</th>
<th>Pop. (B3LYP)</th>
<th>Pop. (M06-2X)</th>
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<tbody>
<tr>
<td>a</td>
<td>0.74</td>
<td>1.25</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>b</td>
<td>0.48</td>
<td>0.88</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>c</td>
<td>0.63</td>
<td>0.89</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>d</td>
<td>0.00</td>
<td>0.00</td>
<td>48</td>
<td>64</td>
</tr>
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</table>

Table 18. Relative energies of the four conformations of 392d-minor

The relative energies have been evaluated using ZPE-corrected Gibbs free energies and different optimization levels: B3LYP/6-31+G(d,p) and M06-2X/6-31+G(d,p). Populations are calculated using Boltzmann distribution at 298°K.

<table>
<thead>
<tr>
<th>Conformation</th>
<th>( G^\circ ) (B3LYP)</th>
<th>( G^\circ ) (M06-2X)</th>
<th>Pop. (B3LYP)</th>
<th>Pop. (M06-2X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>0.47</td>
<td>0.61</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>b</td>
<td>0.08</td>
<td>0.28</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>c</td>
<td>0.94</td>
<td>1.00</td>
<td>8</td>
<td>9</td>
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<tr>
<td>d</td>
<td>0.00</td>
<td>0.00</td>
<td>39</td>
<td>46</td>
</tr>
</tbody>
</table>

As predictable, the four conformations correspond to the four different relative dispositions of the CHO and benoxazole group, and the relative energies (both as ZPE-corrected enthalpies or Gibbs free energies) suggested that all these conformations should be appreciably populated. To check whether a different theoretical level provided different results, the four ground states were optimised again at the M06-2X/6-31+G(d,p) level with similar results in terms of relative energies. Conformation d was always the most stable, albeit it does not correspond to that observed in the solid phase.
state, that is conformation c. In addition to that, the dihedral angle between the plane of the p-nitrophenyl ring and the cyclopropane plane calculated for conformations c and d is rather different with respect to that observed in the solid state. However, both the calculation levels yield the same results and the different dihedral angle observed in the X-ray structure could be the result of crystal lattice stabilisation. Indeed, when the geometry read from X-ray data was used as input to DFT optimization, the p-nitrophenyl ring was rotated to provide again conformation c.

![Figure 27. 3D view of the four conformations of the model compound 392d-minor](image)

6.2.6.1 Absolute configuration

The determination of the absolute configuration (AC) of chiral molecules using chiroptical techniques like optical rotation (OR), electronic circular dichroism (ECD), and vibrational circular dichroism (VCD) has gained feasibility and reliability because of the development of methods for the prediction of these properties based on density
functional theory (DFT) and on its Time-Dependent formalism (TD-DFT). In the present case the theoretical calculation of the electronic circular dichroism spectra (ECD) was selected for the absolute configuration assignment because of the presence of good UV chromophores. The ECD spectrum of 392d-minor (obtained with (R)-catalyst) was acquired in HPLC-grade acetonitrile solution (6·10⁻⁵ M) with a cell path of 0.5 cm in the 190-400 nm region by the sum of 16 scans at 50 nm/min scan rate (Figure 28). Albeit rather weak, the experimental ECD spectrum exhibits three negative Cotton effects at 321, 238 and 206 nm, a broad positive branch at 265-290 nm, as well as two weak positive branches at 222 and 194 nm.

![Figure 28](image-url)

**Figure 28.** ECD (blue trace) and UV (red trace) spectra of 392d-minor (R)-catalyst. Spectra were recorded in acetonitrile, 6·10⁻⁵ M, 0.5 cm cell path

The electronic excitation energies and rotational strengths have been calculated for the isolated molecule in the gas phase for the four conformations a-d using TD-DFT. In a preliminary test, two different basis sets (6-311++G(2d,p) and def2-TZVP) were employed to calculate the ECD spectrum of conformation d using the CAM-B3LYP functional and the two geometries provided by the B3LYP and M06-2X optimisation steps. The results are reported in Figure 29, showing that the basis sets and input geometries did not influence the calculated ECD spectrum at a great extent.
Figure 29. TD-DFT simulated spectra calculated for conformation d of 392d-minor

The spectra were calculated using the same CAM-B3LYP functional, two different basis sets (6-311++G(2d,p) and def2TZVP) and two different input geometries from B3LYP/6-31+G(d,p) and M06-2X/6-31+G(d,p) optimization. For each calculation the first 60 excited states were calculated, and the spectrum was obtained using a 0.30 eV line width at half height.

The ECD spectra of the four conformations were calculated with four different methods (functionals), to ascertain if different computational approaches provide different shapes of the simulated spectra (Figure 30).

[209]
The spectra were calculated using four different functionals (CAM-B3LYP, BH&HLYP, M06-2X, ωB97-XD) and the same 6-311++G(2d,p) basis set. For each conformation the first 60 excited states were calculated, and the spectrum was obtained using a 0.30 eV line width at half height.

Simulations were performed using the B3LYP-optimised geometries with the hybrid functionals BH&HLYP⁸ and M06-2X,⁷ ωB97XD that include empirical dispersion⁹ and CAM-B3LYP that includes long range correction using the Coulomb Attenuating Method. Given the result of the preliminary tests, the calculations employed the B3LYP-optimised geometries and the 6-311++G(2d,p) basis set, that is computationally cheaper than def2TZVPP, still providing good accuracy.⁷⁸-⁷⁹ The rotational strengths were calculated in both length and velocity representation, the resulting values being

---

⁸ In Gaussian 09 the BH&HLYP functional has the form: 0.5*Ex_HF + 0.5*Ex_LSDA + 0.5*ΔEx_Becke88 + E_CLYP
very similar (RMS difference < 5 %). Errors due to basis set incompleteness should be therefore very small.\cite{218}

Although the spectra simulated within the same functional for the four conformation are quite different, they are nevertheless consistent with the simulation of the positive Cotton effect in the 245-270 nm region (Figure 30). This part of the UV spectrum is dominated by the two UV transitions of the \( p \)-nitrophenyl moiety (oriented on the long axis) and of the 5-nitrobenzoxazole moiety. The almost coincidence of the simulated spectra for the same conformation on varying the functional, represent a good proof of the simulations consistency.

The population-weighted spectra to be compared with the experimental spectrum were obtained using the percentages derived from ZPE corrected enthalpies (Table 17). As shown in Figure 31, the spectra simulated assuming 1\( R \),2\( R \),3\( R \) absolute configuration match well the Cotton effects at 321, 283 nm. The best simulation was obtained by the \( \omega \)B97-XD functional, but all the simulated spectra show a good agreement with the experimental one.

![Figure 31. Simulations of the experimental ECD spectrum of 392d-minor (obtained with (R)-catalyst).](image1)

\[ \text{Figure 31. Simulations of the experimental ECD spectrum of 392d-minor (obtained with (R)-catalyst).} \]
For each quadrant, the black line correspond to the experimental spectrum. The colored lines correspond to the simulations obtained using the populations derived from B3LYP/6-31+G(d,p) optimisation. The simulated spectra were vertically scaled and red-shifted by 7-14 nm to get the best match with the experimental spectrum. All the simulations are for the $1R, 2R, 3R$ absolute configuration.

6.2.6.2 Major diastereomer

Good single crystals of the major diastereomer could not be obtained and the assignment of the relative configuration was determined by NMR. The $^1$H and $^{13}$C signals were assigned by means of 2D-NMR experiments (COSY, HSQC and HMBC), and NOE spectra were acquired using the DPGSE sequence.$^{[219]}$ In the case of the major isomer of $392d$ (obtained with (S)-catalyst) ($392d$-major), the $^1$H signals of the hydrogens of cyclopropane were heavily overlapped in a variety of solvent (CDCl$_3$, DMSO, CD$_3$CN), and the compound was not chemically stable in CD$_3$OD. More resolved spectra were obtained for the parent compound $392a$ that exhibited a resolved $^1$H spectrum in CD$_3$CN (Figure 32). A close inspection of the $^1$H spectrum provided useful information about the relative disposition of the three hydrogens of the cyclopropane ring (named as H1, H2 and H3 in Figure 32).
The two vicinal \( ^3J \) coupling constants H2-H1 and H2-H3 have similar values (4.9 and 6.3 Hz, respectively), while the H1-H3 coupling constant between the two CH bearing the aromatic rings is rather large (10.0 Hz). The large value of the latter suggests that the dihedral angle between the two hydrogens is close to 0° (thus a syn relationship of the aromatic rings), while the smaller coupling constants of H1 and H3 with H2 are a clear indication of a gauche disposition of H2 with respect to H1 and H3 (thus a trans relationship of the hydrogens).

As a confirmation, the \(^1\)H spectrum of **392d-minor** showed a similar set of rate constants, but the large one (9.9 Hz) took place between H2 and H3 (see Table 19).

To have further support to the assignment based on coupling constant, DFT calculations were run to calculate the coupling constants values of the major isomer supposing the \(1R^*,2R^*,3S^*\) relative configuration. Due to the rigidity of cyclopropane, the relative disposition of the key hydrogens of the stereogenic centers are fixed independently from the different conforations of the CHO and benoxazole, and the values of the coupling constants can elucidate the relative stereochemistry.\(^{[220]}\) Before running the NMR simulations, a conformational search was run by means of Monte
Carlo searching together with the MMFF94 molecular mechanics force field. All the conformations found by MM search were then optimised using DFT at the B3LYP/6-31+G(d,p) level and their stability was checked by vibrational analysis. As for 392d-minor, four conformations were found to be enclosed in a 2 kcal/mol window as shown in Figure 33 and marked as a-d in Table 19. Again, the four conformations correspond to the four different relative dispositions of the CHO and benzoxazole group.

![Figure 33. Geometries of the four conformations of 392a-major](image)

Table 19. Relative energies of the four conformations of 392a-major

The relative energies were evaluated using ZPE-corrected enthalpies and different optimisation levels: B3LYP/6-31+G(d,p) and M06-2X/6-31+G(d,p). Populations are calculated using Boltzmann distribution at 298°K.
<table>
<thead>
<tr>
<th>Conformation</th>
<th>H° (B3LYP)</th>
<th>H° (M06-2X)</th>
<th>Pop. (B3LYP)</th>
<th>Pop. (M06-2X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>0.58</td>
<td>0.97</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>b</td>
<td>0.73</td>
<td>1.37</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>c</td>
<td>0.00</td>
<td>0.00</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>d</td>
<td>0.17</td>
<td>0.01</td>
<td>31</td>
<td>43</td>
</tr>
</tbody>
</table>

The simulations of the coupling constants were run at the B3LYP/6-311++G(2d,p) level using the GIAO method and including the Fermi contact term (Gaussian 09 keyword: spinspin, mixed). The calculated coupling constants for the $1R^*,2R^*,3S^*$ relative configuration (Table 20) are in a very good agreement with the experimental values of $392a$-major.

**Table 20.** Calculated and experimental coupling constants for the four diastereomers of $392d$.

Calculations were run at the GIAO-B3LYP/6-311++G(2d,p)//B3LYP/6-31+G(d,p) level. In parenthesis are reported the calculated J-couplings of the conformations in which the H2-C-(CO)-H dihedral is close to 180°. In italics are reported the calculated values for those conformations in which the H1-C1-Cq-O ≈ 180°. Plain text values are relative to values for those conformations in which the H1-C1-Cq-O ≈ 0°.

<table>
<thead>
<tr>
<th></th>
<th>Calcd. for</th>
<th>Calcd. for</th>
<th>Calcd. for</th>
<th>Calcd. for</th>
<th>Expl.</th>
<th>Expl.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1R*,2S*,3S*)</td>
<td>(1R*,2S*,3R*)</td>
<td>(1R*,2R*,3S*)</td>
<td>(1R*,2R*,3R*)</td>
<td>392a-major</td>
<td>392a-minor</td>
</tr>
<tr>
<td>H2-CHO</td>
<td>2.0 (6.9)</td>
<td>1.8 (6.7)</td>
<td>1.7 (6.9)</td>
<td>1.5 (7.6)</td>
<td>3.7</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>1.9 (6.5)</td>
<td>1.7 (6.9)</td>
<td>1.7 (6.9)</td>
<td>1.5 (7.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2-H1</td>
<td>9.5 (10.0)</td>
<td>9.7 (10.1)</td>
<td>4.9 (5.1)</td>
<td>5.5 (4.2)</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>9.0 (9.6)</td>
<td>9.9 (10.4)</td>
<td>4.7 (5.1)</td>
<td>5.7 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2-H3</td>
<td>10.8 (10.4)</td>
<td>5.4 (7.2)</td>
<td>6.4 (6.9)</td>
<td>11.3 (11.2)</td>
<td>6.3</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td>10.1 (10.4)</td>
<td>5.5 (6.8)</td>
<td>6.2 (6.6)</td>
<td>11.1 (11.2)</td>
<td></td>
<td></td>
</tr>
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</table>
As a check of the calculation reliability, the coupling constants were calculated also for 392d-minor, which relative configuration was known from X-ray data. Also in this case the calculated values fully matched the experimental values. It should be noted that in both compounds the experimental value of the H2-CHO coupling constant clearly results from the weighted average of two conformations where the dihedral angle H2-C-(CO)-H is close to 0° or 180° (see below). The resulting experimental value seems to suggest that both of the two conformations are populated roughly at the same extent. The full set of coupling constants were calculated also for the remaining two diastereomers due to the inversion at C2 carbon (Table 20, columns 2 and 3). In both cases the set of calculated couplings does not match the experimental data, thus confirming the previous assignment of the (1R*,2R*,3S*) relative configuration to 392a-major.

<table>
<thead>
<tr>
<th>H1-H3</th>
<th>10.3 (10.5)</th>
<th>7.2 (6.7)</th>
<th>11.2 (11.3)</th>
<th>7.4 (6.7)</th>
<th>10.0</th>
<th>6.6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.7 (10.7)</td>
<td>7.6 (7.2)</td>
<td>11.2 (11.3)</td>
<td>7.9 (6.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+a relative configuration from X-ray data
Figure 34. DPFGSE NOE spectra of 392a-major (600 MHz in CD$_3$CN).

Bottom: control spectrum. Middle trace: NOE obtained on saturation of the ortho-phenyl signal. Top trace: NOE obtained on saturation of the CHO signal.

NOE spectra were recorded to further confirm the relative configuration of the major diastereomer of 392a. These spectra, however, were thwarted by the distance constraints imposed by the cyclopropanic ring and by the partial overlapping of the key signals (H1, H2 and H3). On saturation of the CHO signal (Figure 34), comparable NOEs were observed for H1 and H3, while on saturation of the ortho hydrogens of the phenyl ring the NOE on H2 is larger than that on H3 and H1. These results again confirm the relative configuration previously assigned by the coupling constants analysis.
6.2.6.3 Absolute configuration of 392d-major

For coherence with the first assignment, the absolute configuration of the major diastereomer was performed on compound 392d-major (obtained with (S)-catalyst). The ECD spectrum was acquired in HPLC-grade acetonitrile solution (1·10⁻⁴ M) with a cell path of 0.2 cm in the 195-400 nm region by the sum of 16 scans at 50 nm/min scan rate (Figure 35). The spectrum of 392d-major is similar to the of the minor isomer, but the relative intensities of the Cotton effects are different. In this case the two branches at 310 and 270 nm seem to generate a weak exciton coupling and that at 245 nm is much more weaker than the corresponding one of the minor isomer.

![Figure 35](image-url). ECD (blue trace) and UV (red trace) spectra of 392d-major (obtained with (S)-catalyst). Spectra were recorded in acetonitrile, 1·10⁻⁴M, 0.2 cm cell path.

The four stable conformations of 392d-major were again optimised at the B3LYP/6-31+G(d,p) level starting from the geometries obtained for 392a-major. Calculations were run in the gas-phase and including two different solvents (chloroform and acetonitrile) using the PCM method. The relative energies and corresponding populations derived from Boltzmann statistics are reported in Table 21.

The electronic excitation energies and rotational strengths have been calculated for the isolated molecule in the gas phase with the four different methods (functionals)
already employed for the simulation of the ECD spectrum of the minor diastereomer (CAM-B3LYP, BH&HLYP, M06-2X, and ωB97XD). In analogy with 392d-minor, TD-DFT calculations employed the 6-311++G(2d,p) basis set, yielding the results reported in Figure 36.

Table 21. Relative energies of the four conformations of 392d-major

They were evaluated using ZPE-corrected enthalpies obtained from B3LYP/6-31+G(d,p) optimizations in gas phase and including two different solvents (CHCl₃ and CH₃CN) with the PCM method. Populations are calculated using Boltzmann distribution at 298 °K.

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<tr>
<th>Conf.</th>
<th>gas phase</th>
<th>PCM(CHCl₃)</th>
<th>PCM(CH₃CN)</th>
<th>Pop%</th>
<th>Pop%</th>
<th>Pop%</th>
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<td>0.00</td>
<td>5</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>b</td>
<td>1.12</td>
<td>0.18</td>
<td>0.08</td>
<td>11</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>c</td>
<td>0.79</td>
<td>0.21</td>
<td>0.25</td>
<td>17</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>d</td>
<td>0.00</td>
<td>0.00</td>
<td>0.37</td>
<td>67</td>
<td>32</td>
<td>17</td>
</tr>
</tbody>
</table>

Within the same conformation, the four kind of calculations provide very similar traces. However, at a variance with the minor isomer, the simulated spectra for conformations a and d are nearly opposite to that simulated for b and c. The two pairs of conformations showing opposite spectra are different because of the ≈ 180° rotation of the benzoxazole ring. A rationale of the opposite calculated traces can be found in a close analysis of the different disposition of the p-nitrophenyl ring and benzoxazole in the two conformations. (Figure 37).
Figure 36. Calculated ECD for each conformation of 392d-major with different functionals and the same 6-311++G(2d,p) basis set

Figure 37. View of the dipoles of 392d-major acting in the generation of the UV spectrum in the 250-350 nm region.
In both conformations the \(p\)-nitrophenyl ring is far away from the observer and the benzoxazole is close. The dotted arrows correspond to the UV transition of the \(p\)-nitrophenyl ring oriented along the long axis, while the full arrow are that of benzoxazole.

The dihedral angles generated by the two dipoles of along the long axes of \(p\)-nitrophenyl and benzoxazole in the two conformations yield opposite sign, thus explaining the opposite exciton coupling in the simulations. Being the ECD spectrum the weighted average of the spectra of the four conformations, the correct ratio to be used is crucial for the success of the ECD simulation (in the following discussion only conformations c and d will be considered since the spectrum of the second conformation of each pair due to CHO rotation is identical). In similar cases\(^{[215,222]}\) the conformational ratio could be evaluated by Dynamic NMR or NOE experiments, but in the present situation this approach is thwarted by the absence of any benzoxazole hydrogen in the closeness of the cyclopropane ring. To overcome this difficulties, a carefully degassed CDCl\(_3\) NMR sample was prepared in order to extend the effective radius of the NOE effect. CDCl\(_3\) was selected as solvent because of its low viscosity that allows longer T1 relaxation times. In CDCl\(_3\) the two signals of the two CH of cyclopropane bearing the aromatic rings (H1 and H3) are exactly overlapped and yield a doublet, whereas the CH(CHO) signal is a triplet of doublets due to the coupling with the two isochronous CH of cyclopropane and with the CHO. DPFGSE NOE spectra were acquired using long mixing times (4-6 s) corresponding to the T1 relaxation time of the cyclopropane hydrogens measured at ambient temperature by the inversion-recovery sequence (Figure 38).
Figure 38. DPFGSE-NOE of 392d-major recorded on saturation of the CH(CHO) signal and using 4 s mixing time.

The negative NOE at 8.08 ppm is due to transferred NOE from the NOE signal at 7.44 ppm.

On saturating the CH(CHO) signal, weak but comparable NOEs were observed on the two aromatic signals in position 4 (ortho to the oxygen of benzoxazole) and in position 7 (ortho to the nitrogen) of benzoxazole. If only one conformation were populated, NOE should be visible mainly on one signal of the benzoxazole. Taking into account only conformation c, the theoretical NOE ratio should be 88:12 in favour of the NOE on H-4. If only conformation d were populated, the observed NOE ratio should be reversed to 14:86 (ratio were calculated using the distances of the optimized structures, and using the r^6 rule). The experimental evidence of a 60:40 H-4:H-7 ratio suggests that both conformations are appreciably populated. When considering the distances extracted from calculations, the experimental NOE ratio corresponds to a 56:44 ratio in favour of the c conformation. Unfortunately the same NOE spectrum
taken in acetonitrile did not allow to see any long-range enhancement, most probably because of faster relaxation times that did not allow to develop measurable NOEs for H-4 and H-7. As from Table 21, conformation d was calculated to be the most stable in the gas phase and in chloroform, whereas conformation a is the most stable in acetonitrile. Nevertheless, the energy differences are very small and well support the NOE results obtained in chloroform. To evaluate the variations caused by the different conformational ratios, the simulations of the experimental ECD spectrum were obtained using the three different sets of relative energies reported in Table 21. From the simulations reported in Figure 39 it is evident that the simulations obtained using the relative ratio suggested by PCM calculations provide better results than that obtained using the gas-phase conformational ratio. Nevertheless, each simulation well reproduces the experimental trace, and the 1R, 2R, 3S absolute configuration can be reliably assigned to the major isomer of 392d.
Figure 39. Simulations of the experimental ECD spectrum of 392d-major.

For each graph, the black line correspond to the experimental spectrum. The colored lines correspond to the simulations obtained using the populations derived from B3LYP/6-31+G(d,p) geometry optimizations. Left column: gas-phase optimization; middle column: PCM optimization with chloroform; right column: PCM optimization with acetonitrile. The simulated spectra were vertically scaled and red-shifted by 12-18 nm to get the best match with the experimental spectrum. All the simulations are for the 1R,2R,3S absolute configuration.
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“Green chemistry: first organophotocatalytic approach to the synthesis of phosphoramidates”

by

Marta Meazza

Thesis for the degree of Doctor of Philosophy

February 2016
Photocatalysis has become lately a common strategy for the synthesis of new atom-atom bond. Light is a renewable source that should be witnessed as the future for industrial processes.

Our research group started a quest of new green procedures and, for this reason, we turned our attention to photocatalysis. The use of light as the initiator of a chemical reaction presents several advantages in terms of renewable source of energy, cost and generation of waste.

On the other hand, atom economy should be one of the main driving force in the design of new strategies for the synthesis of organic compounds. In this area, Cross Dehydrogenative Couplings have emerged as an useful approach. Formally, in CDC reactions two unfunctionalised molecules react together generating a new atom-atom bond and obtaining hydrogen as the only by-product. In this part of my thesis are described our last efforts in the green chemistry area joining the two concepts of photocatalysis and CDC reactions to generate new green protocols for the formation of atom-atom bonds.

Fascinated by the widely use of phosphoramidates as catalysts, flame retardants or even in biological applications, we focused the attention on their synthesis. All the methodologies previously reported in the literature are based on the use of halogens, phosphoryl chlorides, stoichiometric oxidants or transition metal catalysts. We studied the reaction between phosphites and amines to generate phosphoramidates in a CDC process using a photocatalytic oxidation with oxygen acting as a stoichiometric oxidant.

The reaction was catalysed by an organic dye (Rose Bengal), and the phosphoramidates were obtained in excellent yields in reasonable reaction times when irradiated with green LED light. Importantly, we developed a protocol to isolated the final products without the use of any chromatographic technique making all the process a clear example of green methodology. Moreover we designed a homemade photoreactor that improved reaction times.
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DECLARATION OF AUTHORSHIP

I, Marta Meazza

declare that the thesis entitled

“Green chemistry: first organophotocatalytic approach to the synthesis of phosphoramidates”

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

• this work was done wholly or mainly while in candidature for a research degree at this University;
• where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
• where I have consulted the published work of others, this is always clearly attributed;
• where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
• I have acknowledged all main sources of help;
• where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
• parts of this work have been published as:


Signed: ..............................................................................................................

Date: ..............................................................................................................
# Definitions and Abbreviations

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<td>2,3-Dichloro-5,6-Dicyanobenzoquinone</td>
</tr>
<tr>
<td>DG</td>
<td>Directing Group</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>dtd</td>
<td>doublet of triplets of doublets</td>
</tr>
</tbody>
</table>
E, E*  Electrophile
EDG  Electron Donating Group
equiv  equivalents
ESI+  Electrospray Ionization (positive mode)
Et  Ethyl
EtOAc  Ethyl Acetate
EWG  Electron Withdrawing Group
g  gram
h  hour
HRMS  High Resolution Mass Spectrometry
Hz  Hertz
IR  Infra Red
[IrCp*Cl2]2  (Pentamethylcyclopentadienyl)Iridium Dichloride Dimer
J  coupling constant
m  multiplet
Me  Methyl
mg  milligram
MHz  Mega Hertz
mL  millilitre
mmol  millimoles
m.p.  melting point
Mw  Microwave
\( m/z \)  mass / charge ratio

\( \mu l \)  microliter

NMR  Nuclear Magnetic Resonance

NOE  Nuclear Overhauser Effect

NSAID  Nonsteroidal Anti-Inflammatory Drug

Nu  Nucleophile

PC  Photocatalyst

Ph  Phenyl

ppm  parts per million

\( i-Pr \)  Isopropyl

\( n-Pr \)  Normal Propyl

ProTide  PROdrug + nucleoTIDE

RB  Rose Bengal

rt  room temperature

s  singlet

SOMO  Singly Occupied Molecular Orbital

SET  Single Electron Transfer

t  triplet

td  triplet of doublets

TEMPO  \((2,2,6,6\text{-Tetramethylpiperidin-1-yl})\text{oxy}l\)

Tf  Trifluoromethanesulfonyl

TFA  Trifluoroacetic Acid
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TOF</td>
<td>Time of Flight</td>
</tr>
<tr>
<td>VB</td>
<td>Valence Band</td>
</tr>
</tbody>
</table>
1. Introduction

1.1 Green chemistry

The area of green chemistry, or sustainable chemistry, is based on the development of chemical processes minimising the production of hazardous substances.\cite{1,2} Green chemistry was develop since the early 1990s and is bases on 12 principles,\cite{3} developed by Anastas and Warner:\cite{4}

1. **Prevention**: it is better to prevent waste than to treat or clean up waste after it has been created.

   Regarding the first principle, Sheldon developed the concept of E-factor\cite{5} that is the calculation of the total amount of waste in a process, considering the amount of reagents, solvents, yields and fuel used. The ideal E factor is zero and is a useful tool to compare chemical processes.

2. **Atom Economy**: synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.

   This concept, also called atom efficiency, was introduced by Trost.\cite{6} It is used to evaluate the amount of waste in a process and it does not take into account the substances that do not appear in the stoichiometric equation.

3. **Less Hazardous Chemical Syntheses**: wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. **Designing Safer Chemicals**: chemical products should be designed to affect their desired function while minimising their toxicity.

5. **Safer Solvents and Auxiliaries**: the use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. **Design for Energy Efficiency**: energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. **Use of Renewable Feedstocks**: a raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. **Reduce Derivatives**: unnecessary derivatisation (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimised or avoided if possible, because such steps require additional reagents and can generate waste.

9. **Catalysis**: catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. **Design for Degradation**: chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. **Real-time analysis for Pollution Prevention**: analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. **Inherently Safer Chemistry for Accident Prevention**: substances and the form of a substance used in a chemical process should be chosen to minimise the potential for chemical accidents, including releases, explosions, and fires.

As stated in the principle 9, catalysis is important for green chemistry as it allows the production of less waste and reduces the energy requirements. The works of the Nobel Prize winners in 2001, Sharpless, Noyori and Knowles\(^7-9\) met some of the requirement for green chemistry processes.

They were still using transition metal catalysts that produce toxic wastes, so the development of organocatalysis and biocatalysis respond even more to the request of
using less toxic catalysts. (These type of catalysis are discussed in Volume 1, Chapter 1 of this thesis)

Photocatalysis, as sub-category of photochemistry, is another step in the search for the development of greener procedures. It uses a light source (a renewable source of energy) to activate the reagents toward a chemical transformations, especially with the use of visible light sources.

For the purpose of this thesis only the visible light photochemistry and photocatalysis will be described in the next sections.

1.2 Photochemistry

Photochemistry is the study of the chemical reactions that happen under the influence of a source of light. Few reactions are reported in the 19th century using the sun as the light source.[10] Giacomo Ciamician, an Italian chemist that worked at the beginning of the 20th century, is considered the “father of photochemistry”. In particular, as the fuel was a limited source of energy, he promoted the use of the sun as an unlimited source of energy in an article called “The photochemistry of the future”.

There are two fundamental laws governing photochemistry:

- The first law of photochemistry (Grotthuss-Draper law) states that a compound must absorb the light to have sufficient energy to break or reorganise a covalent bond;
- The second law of photochemistry (Stark-Einstein law) states that only one molecule is activated for each photon absorbed by the system.

The energy supplied by each wavelength is calculated by the Planck-Einstein relation:

\[ E = \frac{hc}{\lambda} \]

Where \( h \) is the constant of proportionality or Planck constant, \( c \) is the speed of light and \( \lambda \) is the wavelength. From the equation is possible to notice that when considering the visible light (\( \lambda = 400-800 \text{ nm} \)) the \( E \) will be lower than using shorter wavelengths
near the ultraviolet (λ = 200-400 nm). Consequently UV light can more easily promote a photochemical reaction compared to visible light. A major drawback in the use of visible light is that most organic molecules are not able to absorb light at longer wavelengths. The solution is to use photosensitizers or photocatalysts.[12]

1.2.1 Photocatalysis

The photocatalysis is based on the use of a catalyst that can absorb the visible light and activate in this way the reaction. The idea came from observing plants performing the photosynthesis in which chlorophyll acts as a catalyst. Chlorophyll absorbs energy from sunlight and excites an electron from a lower to a higher state making possible the transfer of the electron to another molecule and its concurrent return to the ground state. A chain of such electron-transfer processes allows at the end the reduction of carbon dioxide and its fixation into sugars. The initial donors are water molecules that will be converted in oxygen.[13]

The photocatalytic reactions often occur at room temperature and the light source is usually a commercial light bulb: these are clear advantages towards greener procedures, compared to the use of high or low temperatures or UV lamp as source of light. Another advantage is that, as most organic molecules do not absorb the visible light, it is unlikely that side-reactions will happen.[14]

When a molecule absorbs a photon becomes excited and one electron is promoted to an unoccupied molecular orbital and if the spin does not change the two unpaired electrons have opposite spin and the molecule is in a singlet state. If the spin changes, then the two electrons have the same spin and the molecule is in a triplet state. Any of these photoexcited states is more reactive than the starting one.

In a photocatalysed reaction, a photocatalyst (PC) absorbs the light and triggers an energy transfer process or an electron transfer process.[15] In Scheme 1 is presented the scheme of a photoinduced energy transfer that can occur from a PC in either a singlet or triplet state.
The most common pathway is the photoredox catalysis, based on a single electron transfer process (SET) from the photoexcited catalyst that can act as an electron donor or electron acceptor. As shown in Scheme 2, the excited photocatalyst (PC*) can oxidise an electron donor (D) becoming an electron negative radical or it can reduce an electron acceptor (A) becoming an electron positive radical species, both happening through a single electron transfer process. This is followed by a second SET process, reacting with another electron donor or acceptor.

1.2.2 Photocatalysts

The most common type of catalysts that are activated by visible light can be classified as:

- Iridium or Ruthenium complexes
- Porphyrins or organic dyes
- Semiconductors

1.2.2.1 Iridium or Ruthenium complexes

This type of catalysts are currently the most commonly used, in particular Ru(bpy)$_3$X$_n$ 1 and Ir(ppy)$_3$ 2 shown in Figure 1.$^{16,17}$

![Figure 1. Ru(bpy)$_3$X$_n$ and Ir(ppy)$_3$](image)

Ru(bpy)$_3$X$_n$ 1 was the first to be developed and is still the most used, in particular for its reductive properties. In Scheme 3 the general mechanism of a reaction photocatalysed by Ru(bpy)$_3^{2+}$ 3 is presented. The complex absorbs a photon from the light source and becomes the excited form Ru(bpy)$_3^{2+*}$ 4 that is subsequently reduced to the Ru(I) species 5 in the presence of an electron donor (D). In the subsequent step the Ru(bpy)$_3^{3+}$ 5 acts as electron donor for different kind of substrates (A).

![Scheme 3. General mechanism of a reaction photocatalysed by Ru(bpy)$_3^{2+}$](image)

The advantages of this catalyst are the long lifetime of the photoexcited state and the chemical stability of the ground-state form.
In 2008 Yoon et al. reported one of the first examples using Ru(bpy)$_3$Cl$_2$ 1 in a synthetically useful transformation.[18] They reported the use of this complex as catalyst for the [2+2] cycloaddition of a bis(enone) 6 obtaining the final product 8 in good yield and stereoselectivity (Scheme 4).

![Scheme 4. Yoon’s [2+2] cycloaddition of a bis(enone)](image)

In the same year MacMillan et al. reported the first example of merging photoredox catalysis and asymmetric organocatalysis in the α-alkylation of aldehydes.[19] The reaction mechanism proposed by MacMillan is presented in Scheme 5. In one catalytic cycle the metal complex 1 is activated by the light and acts, at first, as an oxidant with the intermediate 18 to render the iminium intermediate 19 and then as a reductant to form an electron-deficient alkyl radical 17. This radical will react with the SOMO of the enamine intermediate 16 formed in the organocatalytic cycle by the reaction of the aldehyde 11 with the secondary amine catalyst 13. This will lead to the formation of the radical 18 that will undergo a SET process to render the iminium intermediate 19. The hydrolysis of the iminium ion releases the final aldehyde 15 and the starting catalyst 13 that will re-enter in the catalytic cycle.
Looking for more green reactions, organic chemists studied the use of organic dyes as photocatalysts. Some of the most commonly employed photocatalysts are shown in Figure 2. They are all highly conjugated molecules that can absorb a photon from visible light and have an excited state life long enough to be able to act as oxidants or reductants. Organic dyes have the advantage to be less toxic, less expensive and more stable than the corresponding metal complex photocatalysts. More details of the mechanism of activation of organic dyes will be discussed in the section relative to cross-dehydrogenative coupling reactions.
1.2.2.3 **Semiconductors**

Semiconductors are easily available, cheap and non-toxic; the most used one is TiO$_2$.

After excitation by a light source of the valence band (VB) of the semiconductor, the electrons are excited in the conductance band (CB) as an electron-hole pair. After their migration to the surface of the semiconductor, a SET can take place with an electron acceptor (A) or an electron donor (D) as shown in **Figure 3**.
1.3 Cross-Dehydrogenative Couplings

Carbon-carbon bond formations are among the most important synthetic chemistry processes. The most common methods to form C-C bonds are the transition-metal catalysed cross-coupling reactions, in particular those catalysed by Pd (Scheme 6).\textsuperscript{[20]} The disadvantage of these reactions is the need for a prefunctionalised starting material (Y), thus adding an extra step to the synthesis.

\[
\begin{align*}
X{-}\text{Ar} & \quad + \quad Y{-}\text{R} \quad \xrightarrow{\text{Pd(0)}} \quad \text{Ar}{-}\text{R} \\
X & = \text{halide}
\end{align*}
\]

Inspired by the search for greener and more sustainable procedure, Cross-Dehydrogenative Coupling (CDC) reactions were developed.\textsuperscript{[21]} This chemistry overcomes the drawbacks of the functional group chemistry, developing
methodologies that directly activate the C-H bond (Scheme 7), creating the new bond whilst eliminating a hydrogen atom from each reagent. The benefits are the production of less waste, the lower costs and the minor number of synthetic steps required. Challenges include the selective activation of one C-H over the others present in the molecule and the low reactivity of the C-H bond.

![Scheme 7. Scheme of a CDC reaction](image)

Even if examples are present in literature since 1960s, the CDC reactions have seen a huge development in the last fifteen years. This methodology has been used not only for the formation of carbon-carbon bond,[22,23] but also carbon-heteroatom bond[24] and more recently, heteroatom-heteroatom bond.[25][26]

However, CDC reactions often require the use of oxidants to generate the reactive species. In the literature, amines can go through CDC processes due to their oxidation to imines. For example tetrahydroisoquinolines 41 and 44 can react with nitromethane 42a through a CDC reaction using different oxidation approaches (Scheme 8): stoichiometric oxidants such as peroxides 47,[27] 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 48)[28] or hypervalent iodines 49,[29] transition metals 46 or photocatalysts to activate oxygen.[30]
Scheme 8. Examples of CDC reactions using stoichiometric oxidants: peroxides (a), DDQ (b), hypervalent iodines (c) and transition metals activating oxygen (d)

In recent years, light activated CDC reactions have been developed, most of them catalysed by transition metal complexes[^31] and, more recently, by organic dyes. Precisely the use of oxygen as stoichiometric oxidant, activated by photocatalysts, is the greener procedure.

Electron-rich alkylamines are the most common electrophiles used in photocatalytic CDC reactions. After the oxidation of the amines thanks to the excited photocatalyst, a radical cation 51 is formed on the amine. This intermediate can decompose in different ways (Scheme 9): (a) abstraction of the proton in α-position of the amine with the formation of an iminium ion 52 that can be attacked by a nucleophile; (b) deprotonation with the formation of a carbon radical intermediate 54; these species can react with olefins or arenes or (c) can generate an iminium ion through oxidation via a SET; (d) regeneration of the neutral amine 57 via a SET with the reduced photocatalyst.
1.3.1 CDC with metal organic dyes as catalysts

In the last years several photochemical reactions catalysed by organic dyes have been developed as the dyes are less toxic, cheaper and more stable than the metal catalysts. Tan et al. reported a CDC between a $N$-aryl-tetrahydroisoquinoline 41 and nitroalkanes 42 catalysed by Rose Bengal 20 and green LEDs as the source of light. They also reported the same reaction using acetone 58, activated by pyrrolidine/trifluoroacetic acid (TFA) as nucleophiles or a chiral version using L-proline or its derivatives 59, obtaining all the products 60 in good yields but with low enantioselectivities (Scheme 10).[^32]

![Scheme 9. Possible ways of decomposition of amine radical cation](image)

**Scheme 10.** Tan’s CDC between an $N$-aryl-tetrahydroisoquinoline and nitroalkanes catalysed by Rose Bengal and green LEDs

The proposed mechanism is presented in Scheme 11: the Rose Bengal (RB, 20) is excited by the light to form RB* 61, this form abstracts an electron from the $N$-aryl-
tetrahydroisoquinoline 41 through a SET process, forming a radical anion on the RB 62 and a radical cation on the amine 63. Then the RB radical anion 62 is re-oxidised to the starting RB by oxygen with the formation of an oxygen radical anion. This last radical anion reacts with the amine radical cation 63 with the formation of hydroperoxide anion and an iminium cation 64 that can be trapped by different nucleophiles.

**Scheme 11.** Proposed mechanism of the CDC reactions activated by organic dyes and visible light

Rueping and co-workers developed a similar CDC reaction, catalysed by green light and Rose Bengal 20 as dye, using a tetrahydroisoquinoline 44 as electrophile and a range of different nucleophiles (**Scheme 12**). They performed these reactions with a flow reactor, allowing for a more efficient, uniform and reproducible reaction.

**Scheme 12.** Rueping’s CDC reaction of tetrahydroisoquinoline as electrophile and a range of different nucleophiles

König et al. reported similar reactions but catalysed by Eosin Y 21 and green light to oxidise N-aryl-tetrahydroisoquinoline 41. The nucleophiles that attack the
intermediate iminium ion are malononitrile 67, nitroalkanes 42, dialkylphosphonates 70 and malonates 72 as shown in Scheme 13.

Scheme 13. König's CDC reactions between N-aryl-tetrahydroisoquinoline and different nucleophiles catalysed by Eosin Y and green light.
2. Objectives

Fascinated by the use of organic dyes as photocatalysts for visible light CDC atom-atom forming reactions, we planned their use in the formation of phosphorous-nitrogen bonds. The objectives of this project are the development of CDC reaction catalysed by visible light and an organic dye in the formation of a P-N bond, in particular between phosphites and amines in order to synthesise phosphoramidates in a safer and greener way, avoiding the use of toxic reagents.

Phosphoramidates attracted our interest as they are important scaffolds. To cite just a few examples, they are used as scaffolds of biological active molecules, as chiral ligands, as organocatalysts and in the ProTide technology. Despite their importance, the synthesis of phosphoramidates requires the use of harsh conditions or halides or transition metals (more information on phosphoramidates’ synthesis and their use will be presented in Chapter 3).
3. Phosphoramidates

Phosphoramidates are important structures in biologically active molecules (Figure 4) for example as constituents of antibiotics as the antifungal antibiotic phosphomidosine 74\textsuperscript{[35]} or the microcin C7 75,\textsuperscript{[36,37]} an antibiotic that inhibits the protein synthesis in vivo. Phosphoramidates’ derivatives are also used as nonsteroidal anti-inflammatory drugs (NSAID) 76, for the treatment of osteoarthritis\textsuperscript{[38]} and phosphoramidate ProTide technology\textsuperscript{[39]} has been used to bypass the rate-limiting step of the initial phosphorylation of nucleosides.

![Phosphoramidates derivatives](image)

**Figure 4.** Examples of phosphoramidates’ derivatives used in medicinal chemistry

Phosphoramidates 77 have been used as flame retardants 79\textsuperscript{[40]} and in Mass Spectrometry 82\textsuperscript{[41,42]} improving the ionisation efficiency in the electrospray ionisation. Moreover, in the last years has been reported the use of phosphoramidates’ derivatives as ligands 78 in hydroaminoalkylation reactions\textsuperscript{[43]} and, by Zhou and co-workers, as catalysts (80 and 81) for the addition of oxindoles to nitrostyrenes\textsuperscript{[44]} and for the Michael addition of fluorinated silyl enol ethers\textsuperscript{[45]} (Figure 5).
3.1 Synthesis of phosphoramidates

The most common way to synthesise phosphoramidates is through the use of phosphorous halides via the Atherton-Todd reaction between a dialkylphosphite and a primary or secondary amine in the presence of a base and carbon tetrachloride. The reaction was first reported by Atherton and Todd in 1945;[46] the proposed mechanism is based on the reaction of the dialkylphosphite 83 with CCl₄ 84 and a base with the formation of a chlorophosphate 85 as intermediate that will then react with the amine 86, rendering the final phosphoramidate 87 (Scheme 14).[47]

Other methods to synthesise phosphoramidates involve the reaction between phosphate diesters with PPh₃ and CCl₄[48] or the nucleophilic substitutions of phosphate diesters 93 by alkylamines 91 using POCl₃ 88.[49] As shown in Scheme 15, the activated intermediate is probably a phosphorochloridate 89 or a dichlorophosphoric anhydride 90.
Scheme 15. Nucleophilic substitutions of phosphate diesters by alkylamines using POCl₃

The drawback of all these methodologies is the formation and handling of toxic and unstable reagents such as the carcinogenic carbon tetrachloride and the intermediate halogenated halides. To solve this problem Breifuss et al. developed a reaction between nitroarenes 94 and phosphorous reagents 95 for the synthesis of N-arylphosphoramidates 96. In this case toxic and dangerous reagents are not used, but the phosphite has to be used in excess (6 equivalents) along with temperature of 200 °C in a microwave reactor (Scheme 16).

Scheme 16. Breifuss’ synthesis of phosphoramidates starting from nitroarenes

Other methods involve the use of organic azides or phosphoryl azides, called the Staudinger-phosphite method. Hackenber et al. reported in 2008 a reaction between azides and phosphites to give a phosphoramidate intermediate 97 that, after a rearrangement catalysed by BF₃ in benzene, renders the phosphoramidates 98 in good yields (Scheme 17).
In 2014 Chang et al. reported a synthesis of phosphoramidates 106 through the reaction of phosphoryl azides 102 and aromatic systems containing directing groups 101 catalysed by an Ir(III) complex 103, as shown in Scheme 18.\textsuperscript{[53]}

![Scheme 17. Mechanism of the Staudinger-phosphite synthesis of phosphoramidates](image)

Scheme 17. Mechanism of the Staudinger-phosphite synthesis of phosphoramidates

The methodologies reported until now are based on the prefuctionalisation of the starting material before preforming the actual reaction that will render the final phosphoramidate, leading to longer and more expensive procedures in terms of money and resources. In the last years, looking for more green procedures for the synthesis of phosphoramidates, cross-dehydrogenative couplings have been developed, also called oxidative couplings. In these cases there is no need for prefuctionalised starting materials leading to more atom economical processes.

In 2013 three different research groups published CDC reactions catalysed by copper salts. In particular Hayes et al. reported the oxidative coupling of amines 86 and phosphonates 83 using CuI 107 as catalyst and the air oxygen as the sole oxidant.\textsuperscript{[26]}

Chen, Yu and co-workers\textsuperscript{[54]} reported a CDC reaction between arylamines and dialkylyphosphites catalysed by CuBr 46 and O\textsubscript{2} and Mizuno et al.\textsuperscript{[55]} reported a CDC
reaction between amides and dialkylphosphites catalysed by Cu(OAc)$_2$ 109 and O$_2$ (Scheme 19). As shown in the proposed mechanism, these reactions use air oxygen as the sole oxidant and produce water as waste.

Scheme 19. CDC catalysed by Cu salts and O$_2$ and proposed mechanism

In the last years Prabhu et al. and Vishwakarma and Singh et al. reported the use of molecular iodine to catalyse the phosphoramidation reaction. Prabhu$^{[25]}$ used H$_2$O$_2$ as stoichiometric oxidant: iodine reacts with H$_2$O$_2$ forming the hypoiodous acid (HIO) that reacts with dialkylphosphite 83 to give phosphoryl iodide 50. This intermediate is attacked by different nucleophiles to render the final products 111 in good yields using mild conditions. Singh$^{[56]}$ used I$_2$ to perform the reaction between dialkylphosphites 83 and anilines 114.
Scheme 20. Proposed mechanism of Prabhu’s CDC reaction catalysed by I₂ and H₂O₂.
4. Organophotocatalytic synthesis of phosphoramidates

4.1 Research hypothesis and proposed reaction mechanism

Due to the importance of the phosphoramidates scaffolds (Chapter 3) and based on the increasing development of CDC reactions (Chapter 1), we planned to develop a CDC reaction for the synthesis of phosphoramidates. We envisioned that a dialkylphosphite 83 would react with an amine 86 through a SET photoredox process catalysed by an organic dye, activated by visible light (Scheme 21).

![Scheme 21. General scheme of the CDC reaction between dialkylphosphite and amines](attachment:image.png)

First we tested the reaction between 2 equivalents of \( p \)-anisidine 114a and 1 equivalent of diethylphosphite 83a as the final product 96b had already been synthesised by Hayes and co-workers.\(^{[26]}\) The reaction was performed at room temperature and checked by TLC after 48 hours, then the product was isolated (Table 1).

![Table 1. Initial tests](attachment:table.png)
From these preliminary results it was clear that only Rose Bengal 20 works in this reaction whilst the other two dyes tested did not give any product (Table 1, entries 1 and 2). The conversion obtained with CH$_3$CN and toluene is comparable (Table 1, entries 3 and 4). Green light (wavelength: 495–570 nm) is the best wavelength able to activate Rose Bengal as reported in literature and in Chapter 1 and 3.

The proposed reaction mechanism, catalysed by Rose Bengal, is outlined in Scheme 22.

Rose Bengal 20 accepts a photon from the green light to form the excited triplet state 61. The activated Rose Bengal (RB) removes one electron from the amine 86 through a
single electron transfer (SET) process, forming the amine radical cation 115 and the RB radical anion 62. The RB radical anion is re-oxidised to the ground state 20 by molecular oxygen present in the air with the formation of the anion superoxide that reacts with the dialkyphosphite 83 to form the phosphorous radical 116 and hydroperoxide anion. The phosphite radical 116 reacts with the amine radical cation 115 to render intermediate 117 that, after deprotonation, gives the final phosphoramidate 96.

4.2 Photoreactor

To perform these reactions, we have assembled the photoreactor shown in Figure 6. The photoreactor consists of a glass cylinder wrapped with a row of green LEDs and placed on a heater-stirrer apparatus. The reactions are carried out in closed vials placed inside the cylinder and put on the metal heated plate.

![Photoreactor](image)

**Figure 6.** Photo and scheme of the photoreactor used in this project
4.3 Results and discussions

After obtaining the first positive results we proceeded on the optimisation of the reaction conditions and the study of the scope of the reaction. To control when the full conversion was reached, the reactions have been checked by $^{31}$P-NMR (the starting material resonates at $\delta$ 7.31 and the final product at $\delta$ 2.38).

It has to be noted that there is no need for a column chromatography to purify the final products as we optimised an effective acid/base work up by diluting the crude in CHCl$_3$ and washing at first with 0.5 M HCl and then with saturated NaHCO$_3$ aqueous solution.

This adds considerable importance to this work as it does not require expensive, time consuming and waste generating purification, making it a greener procedure easier to up-scale in an industrial setting.

4.3.1 Optimization of the reaction conditions

4.3.1.1 Screening of organic dyes

First we tested different dyes in the conditions reported in Scheme 23.

The dyes tested are: Rose Bengal 20, Eosin Y 21, Nile red 23, Neutral red 24, Methylene blue 25, Orange II sodium salt 26, Disperse red 1 27, Mordant orange 1 28.

No conversion was observed in the NMR of the crude except with Rose Bengal.

4.3.1.2 Screening of solvents

Then we tested different solvents with and without molecular sieves, using Rose Bengal 20 as the dye and the results are presented in Table 2.
Table 2. Screening of solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Molecular Sieves</th>
<th>Conversion(^{[a]}) 24 h (%)</th>
<th>Conversion(^{[a]}) 2 days (%)</th>
<th>Conversion(^{[a]}) 3 days (%)</th>
<th>Yield(^{[b]}) (%)</th>
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</thead>
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<tr>
<td>1</td>
<td>toluene</td>
<td>no</td>
<td>17</td>
<td>51</td>
<td>full</td>
<td>54</td>
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<td>3</td>
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<tr>
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<td>86</td>
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<td>not clean</td>
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<tr>
<td>5</td>
<td>CH(_3)CN</td>
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<td>59</td>
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<tr>
<td>6</td>
<td>CH(_3)CN</td>
<td>no</td>
<td>11</td>
<td>---</td>
<td>66 (4 days)</td>
<td>95</td>
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<td>7</td>
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<td>degradation</td>
<td>---</td>
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<td>---</td>
</tr>
<tr>
<td>8</td>
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<td>no</td>
<td>product + impurities</td>
<td>---</td>
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<td>---</td>
</tr>
<tr>
<td>9</td>
<td>EtOAc</td>
<td>no</td>
<td>82</td>
<td>full</td>
<td>---</td>
<td>not clean</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Conversions are calculated from \(^{31}\)P-NMR of the crude
\(^{[b]}\) Yields are of pure isolated product

The results show that the reaction does not work with DMF and EtOH as solvents independently from the presence of molecular sieves (Table 2, entries 2, 3, 7 and 8) giving no conversion or side products. Both toluene, CH\(_3\)CN and EtOAc showed full conversion form the NMR of the crude. The fastest reaction was with EtOAc, especially without the molecular sieves, but in both cases the product isolated after the extraction was not clean (Table 2, entries 4 and 9). Toluene gave full conversion after 3 days (Table 2, entry 1) while CH\(_3\)CN required more than 4 days to achieve full conversion. In the end, the solvent chosen was CH\(_3\)CN without molecular sieves as the isolated yield was quantitative (95%, Table 2, entry 6), compared with the use of molecular sieves (59%, Table 2, entry 5) or the use of toluene (54%, Table 2, entry 1).
4.3.1.3 Screening of LEDs

A screening of different LEDs and organic dyes was done as presented in Table 3.

Table 3. Screening of LEDs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dye</th>
<th>LED Colour</th>
<th>Conversion[^{[a]}] 48 h (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rose Bengal 20</td>
<td>Blue</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>Rose Bengal 20</td>
<td>--- (tin foil wrapped)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Rose Bengal 20</td>
<td>White</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Eosin Y 21</td>
<td>Blue</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Methylene blue 25</td>
<td>Blue</td>
<td>0</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Conversions are calculated from \(^{31}\)P-NMR of the crude

The reaction works with Rose Bengal 20 with blue and white light (Table 3, entries 1 and 3) but, in both cases, the conversions after 2 days are lower than that achieved using Rose Bengal and green light (Table 4, entry 1). The reaction does not work with Eosin Y 21 with blue light as well as with Methylene blue 25 and blue light (Table 3, entries 4 and 5). A test reaction was done without the presence of any sort of light and with the vial wrapped with tin foil (Table 3, entry 2). As expected, no conversion was seen in the crude NMR as a source of light is needed to activate the organic dyes.

4.3.1.4 Screening of Rose Bengal

Then a screening of different loadings of Rose Bengal 20 was performed and the results are shown in Table 4.
Table 4. Screening of loading of Rose Bengal

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rose Bengal (equiv %)</th>
<th>Conversion(^{[a]}) 24 h (%)</th>
<th>Conversion(^{[a]}) 2 days (%)</th>
<th>Conversion(^{[a]}) 4 days (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>8</td>
<td>56</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>7</td>
<td>37</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>3</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>----</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Conversions are calculated from \(^{31}\)P-NMR of the crude

The reaction works even with 5 mol% of Rose Bengal 20. As the reaction is too slow with 10 and 5 mol% (Table 4, entries 2 and 3), 20 mol% (Table 4, entry 1) was chosen as the best amount of the dye. As a control, the reaction was tested without the organic dye (Table 4, entry 4). No conversion was observed in the NMR of the crude, proving the need of the dye as explained in the proposed mechanism.

4.3.1.5 Conversions with different aniline’s loading

Up until this point the screenings were performed using 2 equivalents of the aniline 114b and we wanted to check if there would be any difference using different ratios of the two starting materials (Table 5).
Table 5. Study of the conversion with different aniline’s loading

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv aniline</th>
<th>Conversion(^{[a]}) 1 day (%)</th>
<th>Conversion(^{[a]}) 2 days (%)</th>
<th>Conversion(^{[a]}) 3 days (%)</th>
<th>Conversion(^{[a]}) 4 days (%)</th>
<th>Conversion(^{[a]}) 5 days (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>product + acid + SM</td>
<td>product + acid + SM</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>35</td>
<td>product + acid + SM</td>
<td>product + acid</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>40</td>
<td>75</td>
<td>full</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Conversions are calculated from \(^{31}\)P-NMR of the crude

A clean NMR of the crude was seen only using 2 equivalents of aniline 114b (Table 5, entry 3), while using 1:1 ratio (Table 5, entry 2) or 2 equivalents of diethylphosphite 83a (Table 5, entry 1) the NMR showed a slower formation of the product for the first 3 days and then the formation of the phosphoric acid as a side product without any improvement on the conversion.

The best conditions for the reaction between diethylphosphite 83 and anilines 114 are: 1 equivalent of diethylphosphite, 2 equivalents of aniline, 20 mol% of Rose Bengal and CH₃CN as the solvent.

4.3.1.6 Screening of solvents for aliphatic amines

When the reaction was tested with aliphatic amines 118, in the best conditions found, the reaction did not give full conversion and only traces of products 119 were obtained after the workup. For this reason, a screening of solvents was done using diethylphosphite 83a and benzylamine 118a.
As shown in Table 6, the reaction did not work in CHCl₃ and, when using CH₃CN or EtOAc, the NMR of the crude showed the formation of side products. The best solvent, in the case of aliphatic amines, was found to be toluene that, after 24 hours, gave 27% conversion without the formation of any by-product.

### 4.3.2 Scope of the reaction with anilines

Having the optimal conditions in hand, we studied the scope of the reaction as regards the anilines 114 and the results are presented in Scheme 24.
Scheme 24. Scope of the reaction with anilines

More information about the time needed to reach full conversion are presented in Table 7.

### Table 7. Scope of the reaction with aromatic amines

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Time full conversion[a] (days)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>96b</td>
<td>4-OMe</td>
<td>10</td>
<td>95</td>
</tr>
<tr>
<td>96d</td>
<td>2-OMe</td>
<td>7</td>
<td>59</td>
</tr>
<tr>
<td>96e</td>
<td>4-CH₃</td>
<td>5</td>
<td>97</td>
</tr>
<tr>
<td>96f</td>
<td>3-CH₃</td>
<td>7</td>
<td>99</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: CH₃CN, 70 °C, green light, 20 mol% Rose Bengal.
<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Time full conversion(^{[a]}) (days)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>96g</td>
<td>2-CH(_3) 114f</td>
<td>6</td>
<td>98</td>
</tr>
<tr>
<td>96c</td>
<td>4-F 114b</td>
<td>7</td>
<td>73</td>
</tr>
<tr>
<td>96h</td>
<td>4-Cl 114g</td>
<td>8</td>
<td>74</td>
</tr>
<tr>
<td>96i</td>
<td>4-Br 114h</td>
<td>7</td>
<td>87</td>
</tr>
<tr>
<td>96j</td>
<td>4-I 114i</td>
<td>2</td>
<td>96</td>
</tr>
<tr>
<td>96k</td>
<td>2-F 114j</td>
<td>6</td>
<td>93</td>
</tr>
<tr>
<td>96l</td>
<td>4-CN 114k</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
<td>96m</td>
<td>![NH(_2)] 114l</td>
<td>6</td>
<td>61</td>
</tr>
<tr>
<td>96n</td>
<td>3,4,5-OMe 114m</td>
<td>6</td>
<td>83</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Conversions are calculated from \(^{31}\)P-NMR of the crude

The reaction works well when an electron donating group is present on the aniline such as OMe or Me. In the case of the Me substituted anilines the products were obtained in almost quantitative yields with the substituent in *ortho*, *meta* or *para* position (96g, 96f and 96e). When the aniline was substituted with 4-OMe or with the 3,4,5-OMe, the final products 96b and 96n were obtained in quantitative yields, instead lower yields were obtained with the 2-OMe substituted aniline 96d. High yields were obtained also with all the halogenated anilines: 4-F, 4-Cl, 4-Br, 4-I, 2-F (96c, 96h, 96i, 96j and 96k). When an electron-withdrawing substituent (4-CN) or a sterically congested aniline were used, lower yields were achieved (96l and 96m).

The limitations of this methodology are the use of heteroaromatic amines and vinyl anilines. The 2-aminothiazole 96p decomposes in the reaction conditions and the 4-vinyl aniline 96o rendered complex mixtures due to its sensitive radical nature which may give oligo- or polymerisation.
4.3.3 Scope of the reaction with aliphatic amines

Then we studied the scope of the reaction with aliphatic amines 118, more challenging substrates. Rueping et al. reported a reaction between the tetrahydroisoquinoline 120 and diethylphosphite 83a, catalysed by a Ruthenium photocatalyst 1 and light.[24] They obtained the Kabachnik-Fields product 122 with a C-P bond formation. When our reaction conditions were tested, a mixture of the Kabachnik-Fields product 122 and the phosphoramidate 121 was obtained in 14:1 ratio, with a clear preference towards the K-F one (Scheme 25).

Scheme 25. Reaction with tetrahydroisoquinoline for the competition between Kabachnik-Fields product and the phosphoramidation one

When other primary aliphatic amines 118 were tested with Rose Bengal 20 as the organic dye and toluene as the solvent, the phosphoramidate products 119 were obtained with moderate yields and the results are shown in Table 8. Unfortunately, the reaction did not work with secondary amines like morpholine 123, pyrrolidine 124 and piperidine 125.

Table 8. Scope of the reaction with aliphatic amines

<table>
<thead>
<tr>
<th>Product</th>
<th>Amine</th>
<th>Time full conversion[a] (days)</th>
<th>Yield[b] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>119a</td>
<td>benzylamine 118a</td>
<td>6</td>
<td>59</td>
</tr>
<tr>
<td>119b</td>
<td>isopropylamine 118b</td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>Product</td>
<td>Amine</td>
<td>Time full conversion\textsuperscript{[a]} (days)</td>
<td>Yield\textsuperscript{[b]} (%)</td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
<td>---------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>119c</td>
<td>tert-butylamine 118c</td>
<td>4</td>
<td>53</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Conversions are calculated from \textsuperscript{31}P-NMR of the crude
\textsuperscript{[b]} Yields are of pure isolated products

The different reactivity of the amines 118a, b and c and the tetrahydroisoquinoline 41 depends on the stabilisation of tertiary 63 or primary 127 amine radical cations. In the case of the tetrahydroisoquinoline 63 there is a subsequent deprotonation at the α-position of amine radical cations by a base (e.g. superoxide anion) due to the lower pKa value of the relevant acidic protons (Scheme 26).

**Scheme 26.** Kabachnik-Fields reaction with tetrahydroisoquinoline

In the case of the other amines, the pKa value of the α-protons is higher so there is no deprotonation and the NH\textsubscript{2} radical cation 127 can react with the phosphorous radical 116 (Scheme 27).

**Scheme 27.** Rationalisation of the N-P bond formation instead of the C-P
4.3.4 Scope of the reaction with different phosphites

Then we studied the scope of the reaction with different phosphorous sources. 4-F aniline 114b was chosen as it gave one of the fastest reactions with diethylphosphite 83a. As it is shown in Scheme 28, the reaction with diphenylphosphite 83b or dibenzylphosphite 83c rendered a mixture of products.

![Scheme 28. Substrate scope with different phosphites](image)

4.3.5 Studies on the mechanism

4.3.5.1 Competition experiment

To verify the formation and stabilisation of the amine radical cation intermediate 115 (page 26), a reaction was performed with equal molar ratio of 4-anisidine 114a and 4-cyanoaniline 114k in the same vial under the optimal reaction conditions found (Scheme 29). As expected from the mechanism, the only product formed was the phosphoramidate 96b derived from 4-anisidine 114a, indicating that an electron-donating group such as OMe stabilises the amine radical cation 115.

![Scheme 29. Competition experiment between an aniline with an EWG and an EDG](image)
4.3.5.2 Recyclability test

After washing and extracting the product diethyl (4-chlorophenyl)phosphoramide 96h, the Rose Bengal 20 was extracted from the aqueous basic phase and used again to perform the same reaction. The recycled Rose Bengal showed a similar reactivity, in fact in the first cycle the product 96h was obtained with 74% yields and with 67% yield in the second cycle (Scheme 30).

![Scheme 30. Recyclability of Rose Bengal](image)

4.3.5.3 Reaction with radical scavenger

To prove that a radical intermediate is involved in the key step, the reaction was tested adding a radical scavenger. The reaction was performed, following the general procedure, using the 4-Me aniline 114d and adding 1 equivalent of TEMPO (1,2,6,6-tetramethylpiperidin-1-yl)oxy, 128 (Scheme 31).

![Scheme 31. Reaction with radical scavenger](image)

After 24 hours no conversion was seen in the crude NMR and after 4 days only 13% conversion while, in the normal conditions, full conversion should be reached after 5 days. If no radical intermediate would have been involved in the reaction mechanism, the rate of the reaction should have remained the same.
4.3.5.4 Scale-up of the reaction

Finally, in order to show the suitability of this methodology in a multigram synthesis, and a possible industrial scale-up, we tested the reaction on a five gram scale of diethylphosphite 83a (Scheme 32). The product 96j was obtained in high yield without the need of a column chromatography.

Scheme 32. Multigram reaction
5. Conclusions

In summary, we developed a new methodology for the synthesis of phosphoramidates starting from diethylphosphites and primary amines, catalysed by an organic dye and green light. The products were obtained with excellent yields. As the light is a renewable energy and Rose Bengal is a cheap and non-toxic chemical, this methodology improves the existing methodologies eliminating the use of metals or halide reagents and, in particular, the requirement of column chromatography as a purification step. For these reasons, this new reaction fulfils the requirements of the green chemistry.
6. Experimental section

Thin layer chromatography (TLC) was performed on Merck TLC Silicagel 60 F254. Product spots were visualized by UV-light at 254 nm. Column chromatography was effectuated using silica gel (Geduran Si60, 40-63 µm). Melting points were measured with a Gallenkamp Electrothermal apparatus and are uncorrected. Infra-red spectra were recorded on a Nicolet 380 FT-IR; the IR analysis were performed with the compounds dissolved in CHCl₃. ¹H-NMR, ¹³C-NMR, ¹⁹F-NMR, 2D-NMR were recorded with a Bruker DPX400 NMR. High resolution mass spectra were recorded using a MaXis (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a Time of Flight (TOF) analyser.
6.1 General procedure for the synthesis of phosphoramidates

In a closed vial were added in this sequence: the organic dye Rose Bengal (73 mg, 0.072 mmol, 20 mol% equiv), the amine (0.724 mmol, 2 equiv), the solvent (1.5 mL) and diethyl phosphate (47 µl, 0.362 mmol, 1 equiv). The reaction mixture was stirred at 70 °C in the photoreactor under green light (see table of results for reaction times). CHCl₃ was added to the crude mixture and the organic phase was washed with 0.5 M HCl (3 x 20 ml), then with saturated NaHCO₃ aqueous solution (3 x 20 ml). The organic phases were dried over MgSO₄, filtered and the solvent was evaporated under vacuo to afford the desired phosphoramidate.
6.2 Final products characterisation

diethyl (4-methoxyphenyl)phosphoramide (96b)

The reaction was performed following the general procedure using (89 mg, 0.724 mmol) of 4-methoxyaniline and CH$_3$CN as a solvent. 80 mg of black solid were obtained. Yield: 95%.

**mp:** 55-57 °C.

**IR (CHCl$_3$, liquid film):** 3175 (N-H stretch), 2982, 2905 (aliphatic C-H stretch), 1512, 1481 (aromatic C=C stretch), 1220 (P=O stretch), 1028, 974 (P-OR ester stretch) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.94 (d, $J = 8.9$ Hz, 2H, Ar), 6.82 (d, $J = 8.9$ Hz, 2H, Ar), 5.01 (d, $J = 8.5$ Hz, 1H, NH), 4.25 – 4.02 (m, 4H, CH$_2$), 3.78 (s, 3H, OCH$_3$), 1.32 (t, $J = 7.1$ Hz, 6H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 155.0 (Cq), 132.5 (Cq), 119.3 (d, $J = 6.6$ Hz, CH), 114.7 (CH), 62.8 (d, $J = 5.0$ Hz, CH$_2$), 55.6 (CH$_3$), 16.1 (d, $J = 7.2$ Hz, CH$_3$).

$^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 2.42.

**HRMS m/z (ESI+)** Exact mass calculated for C$_{11}$H$_{19}$NO$_4$P [M+H]$^+$: 260.1046, found: 260.1045.

The experimental data obtained is in accordance with the data reported in literature.$^{[26]}$
**diethyl (2-methoxyphenyl)phosphoramidate (96d)**

![Chemical Structure]

The reaction was performed following the general procedure using (89 mg, 0.724 mmol) of 2-methoxyaniline and CH$_3$CN as a solvent. 55 mg of brown oil were obtained. Yield: 59%.

**IR (CHCl$_3$, liquid film):** 3409 (N-H stretch), 2981, 2930 (aliphatic C-H stretch), 1600, 1508 (aromatic C=C stretch), 1245 (P=O stretch), 1024, 972 (P-OR ester stretch) cm$^{-1}$.

**$^1$H NMR (400 MHz, CDCl$_3$)** $\delta$ 7.20 (dd, $J = 7.5, 1.8$ Hz, 1H, Ar), 6.94 – 6.83 (m, 3H, Ar), 5.74 (d, $J = 10.2$ Hz, 1H, NH), 4.26 – 4.01 (m, 4H, CH$_2$), 3.86 (s, 3H, OCH$_3$), 1.32 (t, $J = 7.1$ Hz, 6H, CH$_3$).

**$^{13}$C NMR (101 MHz, CDCl$_3$)** $\delta$ 147.5 (d, $J = 10.1$ Hz, Cq), 129.2 (d, $J = 2.0$ Hz, Cq), 121.4 (CH), 121.1 (CH), 116.1 (d, $J = 1.2$ Hz, CH), 110.2 (CH), 62.8 (d, $J = 4.9$ Hz, CH$_2$), 55.6 (CH$_3$), 16.1 (d, $J = 7.2$ Hz, CH$_3$).

**$^{31}$P NMR (162 MHz, CDCl$_3$)** $\delta$ 2.30.

**HRMS m/z (ESI+)** Exact mass calculated for C$_{11}$H$_{19}$NO$_4$P [M+H]$^+$: 260.1046, found: 260.1047.

The experimental data obtained is in accordance with the data reported in literature.$^{[56]}$

---

**diethyl p-tolylphosphoramidate (96e)**

![Chemical Structure]

The reaction was performed following the general procedure using (80 μl, 0.724 mmol) of p-toluidine and CH$_3$CN as a solvent. 85 mg of red solid were obtained. Yield: 97%.
mp: 89-91 °C.

IR (CHCl₃, liquid film): 3191, 3163 (N-H stretch), 2981, 2929, 2868 (aliphatic C-H stretch), 1514, 1480 (aromatic C=C stretch), 1221 (P=O stretch), 1020, 969 (P-OR ester stretch) cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.06 (d, J = 8.3 Hz, 2H, Ar), 6.90 (d, J = 7.8 Hz, 2H, Ar), 5.68 (bs, 1H, NH), 4.24 – 3.99 (m, 4H, CH₂), 2.28 (s, 3H, CH₃), 1.32 (t, J = 7.1 Hz, 6H, CH₂CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 136.9 (d, J = 4.2 Hz, Cq), 131.1 (d, J = 3.7 Hz, Cq), 129.8 (CH), 117.4 (d, J = 7.1 Hz, CH), 62.7 (d, J = 4.8 Hz, CH₂), 20.6 (CH₃), 16.1 (d, J = 7.2 Hz, CH₃).

³¹P NMR (162 MHz, CDCl₃) δ 2.29.

HRMS m/z (ESI+) Exact mass calculated for C₁₁H₁₉NO₃P [M+H]⁺: 244.1097, found: 244.1098.

The experimental data obtained is in accordance with the data reported in literature.⁵⁴

diethyl m-tolyolphosphoramidate (96f)

The reaction was performed following the general procedure using (80 μl, 0.724 mmol) of m-toluidine and CH₃CN as a solvent. 88 mg of brown solid were obtained. Yield: 99%.

mp: 65-68 °C.

IR (CHCl₃, liquid film): 3173 (N-H stretch), 2982, 2907 (aliphatic C-H stretch), 1509, 1486 (aromatic C=C stretch), 1229 (P=O stretch), 1023, 974 (P-OR ester stretch) cm⁻¹.
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.13 (dd, $J = 8.1, 8.1$ Hz, 1H, Ar), 6.84 – 6.82 (m, 2H, Ar), 6.77 (d, $J = 7.6$ Hz, 1H, NH), 6.29 – 6.27 (m, 1H, Ar), 4.25 – 4.03 (m, 4H, CH$_2$), 2.31 (s, 3H, CH$_3$), 1.32 (t, $J = 7.1$ Hz, 6H, CH$_2$CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 139.7 (Cq), 139.2 (Cq), 129.1 (CH), 122.4 (CH), 118.0 (d, $J = 7.7$ Hz, CH), 114.3 (d, $J = 6.9$ Hz, CH), 62.7 (d, $J = 4.8$ Hz, CH$_2$), 21.5 (CH$_3$), 16.1 (d, $J = 7.2$ Hz, CH$_3$).

$^{31}$P NMR (162 MHz, CDCl$_3$) δ 2.55.

HRMS $m/z$ (ESI+) Exact mass calculated for C$_{11}$H$_{19}$NO$_3$P [M+H]$^+$: 244.1097, found: 244.1099.

diethyl o-tolylphosphoramidate (96g)

The reaction was performed following the general procedure using (80 μl, 0.724 mmol) of o-toluidine and CH$_3$CN as a solvent. 86 mg of brown oil were obtained. Yield: 98%.

IR (CHCl$_3$, liquid film): 3210 (N-H stretch), 2981, 2908 (aliphatic C-H stretch), 1501, 1415 (aromatic C=C stretch), 1238 (P=O stretch), 1024, 974 (P-OR ester stretch) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.21 (d, $J = 7.9$ Hz, 1H, Ar), 7.14 (t, $J = 8.0$ Hz, 2H, Ar), 6.91 (t, $J = 7.2$ Hz, 1H, Ar), 4.95 (d, $J = 8.1$ Hz, 1H, NH), 4.25 – 4.02 (m, 4H, CH$_2$), 2.24 (s, 3H, CH$_3$), 1.32 (t, $J = 7.1$ Hz, 6H, CH$_2$CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 137.7 (Cq), 130.6 (CH), 127.1 (CH), 125.1 (d, $J = 10.9$ Hz, Cq), 121.9 (CH), 117.0 (d, $J = 1.4$ Hz, CH), 62.9 (d, $J = 5.0$ Hz, CH$_2$), 17.7 (CH$_3$), 16.1 (d, $J = 7.2$ Hz, CH$_3$).

$^{31}$P NMR (162 MHz, CDCl$_3$) δ 2.22.

HRMS $m/z$ (ESI+) Exact mass calculated for C$_{11}$H$_{19}$NO$_3$P [M+H]$^+$: 244.1097, found: 244.1097.
The experimental data obtained is in accordance with the data reported in literature.\textsuperscript{[56]}

diethyl (4-fluorophenyl)phosphoramidate (96c)

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

The reaction was performed following the general procedure using (62 μl, 0.724 mmol) of 4-fluoroaniline and CH\textsubscript{3}CN as a solvent. 65 mg of black solid were obtained. Yield: 73%.

\textbf{mp:} 50-51 °C.

\textbf{IR (CHCl\textsubscript{3}, liquid film):} 3176 (N-H stretch), 3090 (aromatic C-H stretch), 2982, 2906 (aliphatic C-H stretch), 1509 (aromatic C=C stretch), 1214 (P=O stretch), 1025, 975 (P-OR ester stretch) cm\textsuperscript{-1}.

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} δ 7.03 – 6.89 (m, 4H, Ar), 6.21 (s, 1H, NH), 4.33 – 3.88 (m, 4H, CH\textsubscript{2}), 1.32 (t, J = 7.1 Hz, 6H, CH\textsubscript{3}).

\textbf{\textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3})} δ -122.68 (d, J = 12.7 Hz).

\textbf{\textsuperscript{31}P NMR (162 MHz, CDCl\textsubscript{3})} δ 2.35.

\textbf{HRMS m/z (ESI+)} Exact mass calculated for C\textsubscript{10}H\textsubscript{16}FNO\textsubscript{3}P [M+H]\textsuperscript{+}: 248.0846, found: 248.0848.

The experimental data obtained is in accordance with the data reported in literature.\textsuperscript{[56]} CAS Registry Number: 50672-18-9
diethyl (4-chlorophenyl)phosphoramidate (96h)

The reaction was performed following the general procedure using (92 mg, 0.724 mmol) of 4-chloroaniline and CH$_3$CN as a solvent. 71 mg of brown solid were obtained. Yield: 74%.

**mp:** 69.8-71.5 °C.

**IR (CHCl$_3$, liquid film):** 3161 (N-H stretch), 3063 (aromatic C-H stretch), 2981 (aliphatic C-H stretch), 1598, 1494 (aromatic C=C stretch), 1224 (P=O stretch), 1025, 977 (P-OR ester stretch) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.21 (bd, $J = 8.7$ Hz, 2H, Ar), 6.94 (bd, $J = 8.8$ Hz, 2H, Ar), 5.87 (d, $J = 8.7$ Hz, 1H, NH), 4.26 – 4.01 (m, 4H, CH$_2$), 1.32 (t, $J = 7.1$ Hz, 6H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 138.5 (Cq), 129.2 (CH), 126.6 (Cq), 118.6 (d, $J = 7.4$ Hz, CH), 62.9 (d, $J = 4.9$ Hz, CH$_2$), 16.1 (d, $J = 7.1$ Hz, CH$_3$).

$^{31}$P NMR (162 MHz, CDCl$_3$) δ 1.68.

**HRMS m/z (ESI+)** Exact mass calculated for C$_{10}$H$_{16}$Cl$_{35}$NO$_3$P [M+H]$^+$: 264.0551, found: 264.0549.

diethyl (4-bromophenyl)phosphoramidate (96i)

The reaction was performed following the general procedure using (124 mg, 0.724 mmol) of 4-bromoaniline and CH$_3$CN as a solvent. 97 mg of brown oil were obtained. Yield: 87%.
IR (CHCl$_3$, liquid film): 3185, 3153 (N-H stretch), 3056 (aromatic C-H stretch), 2981 (aliphatic C-H stretch), 1595, 1492 (aromatic C=C stretch), 1224 (P=O stretch), 1024, 976 (P-OR ester stretch) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34 (bd, $J = 8.7$ Hz, 2H, Ar), 6.92 (bd, $J = 8.8$ Hz, 2H, Ar), 6.85 (d, $J = 9.3$ Hz, 1H, NH), 4.23 – 4.01 (m, 4H, CH$_2$), 1.31 (t, $J = 7.1$ Hz, 6H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 139.1 (Cq), 132.1 (CH), 119.0 (d, $J = 7.5$ Hz, CH), 113.9 (Cq), 62.9 (d, $J = 4.9$ Hz, CH$_2$), 16.1 (d, $J = 7.1$ Hz, CH$_3$).

$^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 2.11.

HRMS m/z (ESI+) Exact mass calculated for C$_{10}$H$_{16}$Br$_7$NO$_3$P [M+H]$^+$: 308.0046, found: 308.0049.

Diethyl (4-iodophenyl)phosphoramidate (96j)

The reaction was performed following the general procedure using (159 mg, 0.724 mmol) of 4-iodoaniline and CH$_3$CN as a solvent. 120 mg of brown solid were obtained. Yield: 96%.

mp: 66-68 °C.

IR (CHCl$_3$, liquid film): 3180, 3146 (N-H stretch), 2981, 2939 (aliphatic C-H stretch), 1591, 1489 (aromatic C=C stretch), 1223 (P=O stretch), 1024, 976 (P-OR ester stretch) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.53 (d, $J = 8.6$ Hz, 2H, Ar), 6.78 (d, $J = 8.8$ Hz, 2H, Ar), 5.74 (d, $J = 8.8$ Hz, 1H, NH), 4.25 – 4.00 (m, 4H, CH$_2$), 1.32 (t, $J = 7.1$ Hz, 6H, CH$_3$).
\( ^{13} \text{C NMR (101 MHz, CDCl}_3 \) \( \delta \) 139.5 (Cq), 138.1 (CH), 119.4 (d, J = 7.2 Hz, CH), 84.1 (Cq), 63.0 (d, J = 4.9 Hz, CH\(_2\)), 16.1 (d, J = 7.1 Hz, CH\(_3\)).

\( ^{31} \text{P NMR (162 MHz, CDCl}_3 \) \( \delta \) 1.41.

HRMS \( m/z \) (ESI+) Exact mass calculated for C\(_{10}\)H\(_{16}\)INO\(_3\)P [M+H]+: 355.9907, found: 355.9914.

The same reaction was performed on 5 g scale. In a round bottom flask were added in this sequence: the organic dye Rose Bengal (5 g, 3.9 mmol, 11 mol% equiv), 4-iodoaniline (15.9 g, 72 mmol, 2 equiv), the solvent (75 mL) and diethyl phosphate (5 g, 36 mmol, 1 equiv). After the work-up, 10.5 g of brown solid were obtained. Yield: 82%.

diethyl (2-fluorophenyl)phosphoramidate (96k)

\[
\begin{align*}
\text{EtO} & \text{O} \\
\text{EtO} & \text{N} \\
\text{F} & \text{Ar}
\end{align*}
\]

The reaction was performed following the general procedure using (62 \, \mu\text{l}, 0.724 mmol) of 2-fluoroaniline and CH\(_3\)CN as a solvent. 83 mg of black foam were obtained. Yield: 93%.

IR (CHCl\(_3\), liquid film): 3182 (N-H stretch), 2983, 2919, 1619, 1243, 1214 (P=O stretch), 1025, 977 (P-OR ester stretch), 750 cm\(^{-1}\).

\( ^{1} \text{H NMR (400 MHz, CDCl}_3 \) \( \delta \) 7.31 – 7.27 (m, 1H, Ar), 7.06 (dd, J = 13.2, 5.6 Hz, 2H, Ar), 6.96 – 6.87 (m, 1H, Ar), 5.35 (d, J = 5.2 Hz, 1H, NH), 4.28 – 4.07 (m, 4H, CH\(_2\)), 1.34 (td, J = 7.1, 0.6 Hz, 6H, CH\(_3\)).

\( ^{13} \text{C NMR (101 MHz, CDCl}_3 \) \( \delta \) 155.2 (Cq), 127.9 (Cq), 124.6 (d, J = 3.8 Hz, CH), 122.0 (d, J = 7.2 Hz, CH), 118.2 (CH), 115.2 (d, J = 19.2 Hz, CH), 63.2 (d, J = 5.1 Hz, CH\(_2\)), 16.1 (d, J = 7.0 Hz, CH\(_3\)).
$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -133.29 (d, $J = 13.3$ Hz).

$^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 1.28.

HRMS $m/z$ (ESI+) Exact mass calculated for C$_{10}$H$_{16}$FNO$_3$P [M+H]$^+$: 248.0846, found: 248.0848.

diethyl (4-cyanophenyl)phosphoramidate (96I)

The reaction was performed following the general procedure using (85 mg, 0.724 mmol) of 4-aminobenzonitrile and CH$_3$CN as a solvent. 50 mg of red oil were obtained. Yield: 54%.

IR (CHCl$_3$, liquid film): 3363 (N-H stretch), 3052 (aromatic C-H stretch), 2982 (aliphatic C-H stretch), 2220 (C≡N stretch) 1514, 1477 (aromatic C=C stretch), 1228 (P=O stretch), 1024, 974 (P-OR ester stretch) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$ ) $\delta$ 7.54 (d, $J = 8.6$ Hz, 2H, Ar), 7.07 (d, $J = 8.7$ Hz, 2H, Ar), 4.26 – 4.04 (m, 4H, CH$_2$), 1.34 (t, $J = 7.0$ Hz, 6H, CH$_3$).

$^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 0.61.

HRMS $m/z$ (ESI+) Exact mass calculated for C$_{11}$H$_{18}$N$_2$O$_3$P [M+H]$^+$: 255.0893, found: 255.0892.

The experimental data obtained is in accordance with the data reported in literature.$^{[56]}$
diethyl naphthalen-1-ylphosphoramidate (96m)

The reaction was performed following the general procedure using (104 mg, 0.724 mmol) of naphthalen-1-amine and CH$_3$CN as a solvent. 62 mg of black solid were obtained. Yield: 61%.

**mp:** 103-105 °C.

**IR (CHCl$_3$, liquid film):** 3202 (N-H stretch), 2981, 2918, 2849 (aliphatic C-H stretch), 1597, 1579, 1519, 1469 (aromatic C=C stretch), 1239 (P=O stretch), 1022, 972 (P-OR ester stretch) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97 – 7.94 (m, 1H, Ar), 7.90 – 7.80 (m, 1H, Ar), 7.53 (dtd, $J = 8.1, 6.7, 1.2$ Hz, 3H, Ar), 7.44 – 7.35 (m, 2H, Ar), 5.93 – 5.67 (m, 1H, NH), 4.30 – 4.05 (m, 4H, CH$_2$), 1.31 (t, $J = 7.1$ Hz, 6H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 134.6 (Cq), 134.3 (Cq), 128.8 (CH), 126.1 (CH), 126.0 (CH), 125.3 (d, $J = 2.2$ Hz, Cq), 122.8 (CH), 120.2 (m, 2CH), 114.2 (CH), 63.0 (d, $J = 5.0$ Hz, CH$_2$), 16.1 (d, $J = 7.1$ Hz, CH$_3$).

$^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 2.65.

HRMS $m$/z (ESI+) Exact mass calculated for C$_{14}$H$_{19}$NO$_3$P [M+H]$^+$: 280.1097, found: 280.1100.
diethyl (3,4,5-trimethoxyphenyl)phosphoramidate (96n)

\[
\text{EtO}^-\text{P}^\bigg<\begin{array}{c}
\text{EtO}^-\text{P}^\bigg<\begin{array}{c}
\text{N}
\end{array}
\end{array}
\begin{array}{c}
\text{OMe}
\end{array}
\begin{array}{c}
\text{OMe}
\end{array}
\begin{array}{c}
\text{OMe}
\end{array}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\text{Ar}
\]

The reaction was performed following the general procedure using (133 mg, 0.724 mmol) of 3,4,5-trimethoxyaniline and CH\textsubscript{3}CN as a solvent. 96 mg of black foam were obtained. Yield: 83%.

**IR (CHCl\textsubscript{3}, liquid film):** 3233, 2983, 2937 (aliphatic C-H stretch), 1601, 1507 (aromatic C=C stretch), 1452, 1231 (P=O stretch), 1126, 975 (P-OR ester stretch) cm\textsuperscript{-1}.

**\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})** δ 6.26 (bs, 2H, Ar), 5.68 (bs, 1H, NH), 4.26 – 4.04 (m, 4H, CH\textsubscript{2}), 3.82 (s, 6H, OCH\textsubscript{3}), 3.79 (s, 3H, OCH\textsubscript{3}), 1.34 (t, J = 7.1 Hz, 6H CH\textsubscript{2}CH\textsubscript{3}).

**\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})** δ 153.7 (Cq), 135.8 (d, J = 3.5 Hz, Cq), 133.0 (d, J = 2.2 Hz, Cq), 95.19 (d, J = 7.4 Hz, 2CH), 62.9 (d, J = 4.8 Hz, CH\textsubscript{2}), 61.0 (CH\textsubscript{3}), 56.0 (CH\textsubscript{3}), 16.2 (d, J = 7.1 Hz, CH\textsubscript{3}).

**\textsuperscript{31}P NMR (162 MHz, CDCl\textsubscript{3})** δ 2.01, 1.96.

**HRMS m/z (ESI+)** Exact mass calculated for C\textsubscript{13}H\textsubscript{23}NO\textsubscript{6}P [M+H]\textsuperscript{+}: 320.1258, found: 320.1263.

diethyl isopropylphosphoramidate (119b)

\[
\text{EtO}^-\text{P}^\bigg<\begin{array}{c}
\text{EtO}^-\text{P}^\bigg<\begin{array}{c}
\text{N}
\end{array}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\text{CH}_2\text{CH}_3
\]

The reaction was performed following the general procedure using (106 μl, 0.724 mmol) of propan-2-amine and toluene as a solvent. 30 mg of red oil were obtained. Yield: 42%.
IR (CHCl₃, liquid film): 3020, 2182, 2042, 1214 (P=O stretch), 907 (P-OR ester stretch), 748 cm⁻¹.

³¹H NMR (400 MHz, CDCl₃) δ 4.15 – 4.00 (m, 4H, OCH₂), 3.46 – 3.28 (m, 1H, CH), 2.36 (bs, 1H, NH), 1.34 (td, J = 7.1, 0.6 Hz, 6H, OCH₂CH₃), 1.17 (dd, J = 6.4, 0.6 Hz, 6H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 62.2 (CH), 43.8 (CH), 25.3 (d, J = 5.6 Hz, CH₃), 16.2 (d, J = 7.2 Hz, CH₃).

³¹P NMR (162 MHz, CDCl₃) δ 8.09.

HRMS m/z (ESI⁺) Exact mass calculated for C₇H₁₉NO₃P [M+H]⁺: 196.1097, found: 196.1095.

**diethyl tert-butylphosphoramidate (119c)**

The reaction was performed following the general procedure using (76 µl, 0.724 mmol) of 2-methylpropan-2-amine and toluene as a solvent. 40 mg of red oil were obtained. Yield: 53%.

IR (CHCl₃, liquid film): 2917, 2848, 2153, 2052, 1558 (P=O stretch), 905 (P-OR ester stretch), 803 cm⁻¹.

³¹H NMR (400 MHz, CDCl₃) δ 4.13 – 4.01 (m, 4H, OCH₂), 2.54 (d, J = 6.0 Hz, 1H, NH), 1.34 (td, J = 7.1, 0.7 Hz, 6H, OCH₂CH₃), 1.28 (d, J = 0.6 Hz, 9H, CH₃).

³¹P NMR (162 MHz, CDCl₃) δ 7.01.


The experimental data obtained is in accordance with the data reported in literature.[²⁶]
diethyl benzylphosphoramidate (119a)

\[
\begin{align*}
\text{EtO} & \quad \text{P} \quad \text{NH} \\
\text{EtO} & \quad \text{O} \\
\end{align*}
\]

The reaction was performed following the general procedure using (79 μl, 0.724 mmol) of benzylamine and toluene as a solvent. 52 mg of red oil were obtained. Yield: 59%.

**IR (CHCl\textsubscript{3}, liquid film):** 3235 (N-H stretch), 3022, 2983 (aliphatic C-H stretch), 1644, 1453 (aromatic C=C stretch), 1214 (P=O stretch), 1026, 907 (P-OR ester stretch), 750 cm\textsuperscript{-1}.

**\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})** \(\delta\) 7.38 – 7.28 (m, 5H, Ph), 4.16 – 3.98 (m, 6H, CH\textsubscript{2} and OCH\textsubscript{2}CH\textsubscript{3}), 2.96 (bs, 1H, NH), 1.31 (t, \(J = 7.1\) Hz, 6H, CH\textsubscript{3}).

**\textsuperscript{31}P NMR (162 MHz, CDCl\textsubscript{3})** \(\delta\) 8.45.

**HRMS \(m/z\) (ESI+)** Exact mass calculated for C\textsubscript{11}H\textsubscript{19}NO\textsubscript{3}P [M+H]\textsuperscript{+}: 244.1097, found: 244.1103.

The experimental data obtained is in accordance with the data reported in literature.\textsuperscript{[26]}
List of References


Synergistic catalysis: enantioselective addition of alkylbenzoxazoles to enals
NMR benzoxazoles
NMR and HPLC final products
HPLC Traces
### Table 1

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mm-6673-06dia1 IE 03-7 230nm : UV Detector 1 : 1

mm-6673-06dia2 IE 03-7 230nm : UV Detector 1 : 1

Time | Area | Area %
--- | --- | ---
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43.486 | 3,093,168.1 | 46.75
Total | 6,616,933.7 | 100.00

Time | Area | Area %
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Time | Area | Area %
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Time | Area | Area %
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diastereomer 1: peak 2 and peak 3

diastereomer 2: peak 1 and peak 4
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**Table 1**

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**Table 2**

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**Figure 1**

- **Figure 1a**
- **Figure 1b**

**Figure 2**

- **Figure 2a**
- **Figure 2b**
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<td>1 19.321 min</td>
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<td>728.01398</td>
<td>13.62555</td>
<td>75.1126</td>
<td>1 19.334 min</td>
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<td>89.0005</td>
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<tr>
<td>2 22.158 min</td>
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<td>0.9268</td>
<td>241.21671</td>
<td>4.34142</td>
<td>24.8874</td>
<td>2 21.870 min</td>
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<td>194.91499</td>
<td>2.62380</td>
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<tr>
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</table>

**Chemical Structures**

1. \( \text{NO}_2 \text{Cl} \rightarrow \text{COOMe} \)
2. \( \text{NO}_2 \text{F} \rightarrow \text{COOMe} \)
Synergistic catalysis: syn-cyclopropanation of benzoxazoles
HPLC traces

The racemic mixtures used in the HPLC traces were prepared by mixing the product obtained using the organic catalyst with the R configuration and the product obtained using the organic catalyst with the S configuration.

![HPLC traces diagram]

Mixture of S and R: (IA, 85.15, 210, 1ml/min)

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Chiral S:

![Chiral S HPLC traces diagram]

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Chiral R:

Mixture of S and R: (OD-H, 85.15, 210 nm, 1ml/min)

Mixture of S and R: (OD-H, 85.15, 210 nm, 1ml/min)
Chiral S:

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Chiral R:

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Mixture of S and R: (OD-H, 80.20, 250 nm, 1ml/min)

Chiral S:

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Chiral R:

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Chiral R:

Mixture of S and R: (OD-H, 55.45, 210 nm, 0.8 ml/min)

Mixture of S and R: (OD-H, 55.45, 210 nm, 0.8 ml/min)
### Chiral S:

<table>
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### Chiral R:

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Mixture of S and R: (IB, 70.30, 210 nm, 1 ml/min)

Chiral S:
Chiral R:

Mixture of S and R: (AY-H, 60.40, 210 nm, 0.8 ml/min)

Mixture of S and R: (AY-H, 60.40, 210 nm, 0.8 ml/min)
Chiral S:

<table>
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Chiral R:

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<tbody>
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<td>[min]</td>
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Mixture of S and R: (OD-H, 80.20, 210 nm, 1 ml/min)

Chiral S:

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Chiral R:

Mixture of S and R: (AY-H, 80.20, 210 nm, 1 ml/min)
Chiral S:

![Chiral S graph]

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<td>4.95649e4</td>
<td>983.27905</td>
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Chiral R:

![Chiral R graph]

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<tbody>
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Mixture of S and R: (OD-H, 70.30, 210 nm, 0.8 ml/min)

Chiral S:
Chiral R:

Mixture of S and R: (AY-H, 50.50, 210 nm, 1 ml/min)

---

Mixture of S and R: (AY-H, 50.50, 210 nm, 1 ml/min)
### Chiral S:

![Chiral S Peaks](image)

<table>
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<th>Area</th>
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<th>%</th>
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<td>1</td>
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<td>598.56952</td>
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</table>

### Chiral R:

![Chiral R Peaks](image)

<table>
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<th>Type</th>
<th>Width</th>
<th>Area</th>
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<tr>
<td>1</td>
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<td>0.7819</td>
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<td>3736.24438</td>
<td>50.46899</td>
<td>90.6368</td>
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</table>
Mixture of S and R: (IC, 85.15, 210 nm, 1 ml/min)

Chiral S:
Chiral R:

Minor Mixture of S and R: (IC, 85.15, 210 nm, 1 ml/min)

<table>
<thead>
<tr>
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Minor

Mixture of S and R: (IC, 85.15, 210 nm, 1 ml/min)

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Chiral R:

- Mixture of S and R: (AY-H, 80.20, 230 nm, 1ml/min)

```
MeOOC       CHO
\      \    \\
 Ph     major
```

Mixture of S and R: (AY-H, 80.20, 230 nm, 1ml/min)
Chiral S:

Peak RetTime Type Width  Area  Height  Area %
#  [min] [min] [mAU*s] [mAU]    %
1  19.063 MM 0.6765  40.05763 9.86947e-1  0.9998
2  21.095 MM 0.8796  3966.42554 75.15952  99.0002

Chiral R:

Peak RetTime Type Width  Area  Height  Area %
#  [min] [min] [mAU*s] [mAU]    %
1  19.967 MM 0.9136  3575.64111 65.23161  99.2013
2  21.260 MM 0.5517  28.78887 6.16726e-1  0.7987
Mixture of S and R: (OD-H, 70.30, 210 nm, 1 ml/min)

Chiral S:
Chiral R:

Mixture of S and R: (AY-H, 70.30, 210 nm, 1 ml/min)

Mixture of S and R: (AY-H, 70.30, 210 nm, 1 ml/min)
### Chiral S:

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### Chiral R:

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<th>Area</th>
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Mixture of S and R: (OD-H, 70.30, 230 nm, 1 ml/min)

Chiral S:
Chiral R:

Mixture of S and R: (OD-H, 70.30, 210 nm, 1 ml/min)

Mixture of S and R: (OD-H, 70.30, 210 nm, 1 ml/min)
### Chiral S:

![Chiral S graph]

<table>
<thead>
<tr>
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<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
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### Chiral R:

![Chiral R graph]

<table>
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</tbody>
</table>
NMR starting materials

[1H-NMR spectrum]

[13C-NMR spectrum]
NMR cyclopropanes

major diastereomer:
minor diastereomer:
mixture of minor and minor':
major diastereomer:

DFT-135

H-NMR
minor diastereomer:

$^{1}H$-NMR

$^{13}C$-NMR
mixture of minor and minor' diastereomers:
major diastereomer:

$^1$H-NMR

$^{13}$C-NMR
minor diastereomer with traces of minor$^*$:
major diastereomer:

$^1$H-NMR

$^{13}$C-NMR
minor diastereomer:

1H-NMR DEPT-135
major diastereomer:
mixture of minor and minor' diastereomers:
major diastereomer:

$\text{\textsuperscript{1}H-NMR}$

$\text{\textsuperscript{13}C-NMR}$
DEPT-135

$^{19}$F-NMR
mixture of minor and minor’ diastereomers:
major diastereomer:

$^1$H-NMR

$^{13}$C-NMR
mixture of minor and minor' diastereomers:

$^1$H-NMR
major diastereomer:
minor diastereomer + traces of minor’ and major diastereomers and starting enals

Product:

1H-NMR
major diastereomer:

$^1$H-NMR

$^{13}$C-NMR
mixture of minor and minor' diastereomers:
$^{13}$C-NMR

DEPT-135
major diastereomer:

$^1$H-NMR

$^{13}$C-NMR
mixture of minor and minor' diastereomers:
major diastereomer:

$^1$H-NMR

$^{13}$C-NMR
mixture of minor and minor' diastereomers:

$^1$H-NMR

DEPT-135
mixture of major and minor diastereomers:
mixture of major minor and minor' diastereomers:

\[ ^1H\text{-NMR} \]
major diastereomer:

$^1$H-NMR

$^{13}$C-NMR
mixture of minor and minor ' diastereomers:
major diastereomer:

$^1$H-NMR

$^{13}$C-NMR
mixture of minor and minor’ diastereomers:
First pure organophotocatalytic synthesis of phosphoramidates
NMR