UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

Department of Chemistry

Volume 1 of 1

Approach to the synthesis of pyrrolizidine and indolizidine derivatives via nitro alkyl addition to enals. New adventures in benzylic activation cyclopropanation of benzylchlorides

by

Maria Ashe

Thesis for the degree of Master of Philosophy

April_2016

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

Organic Chemistry

Thesis for the degree of Master of Philosophy

APPROACH TO THE SYNTHESIS OF PYRROLIZIDINE AND INDOLIZIDINE DERIVATIVES VIA NITRO ALKYL ADDITION TO ENALS. NEW ADVENTURES IN BENZYLIC ACTIVATION CYCLOPROPANATION OF BENZYLCHLORIDES

Maria Ashe

Organocatalysis is a rapidly developing and important part of organic chemistry allowing the development of new, environmentally friendly methodologies. In this thesis we report a diastereoselective and enantioselective cyclopropanation reaction catalysed by secondary amines.

In the first project (Chapter 2) we present an attempt at a total synthesis of pyrrolizidine and indolizidine derivatives utilising an organocatalytic approach in a key step. The proposed route could give access to diazabicyclic compounds in five or six steps starting from commercially available materials.

In the second project (Chapter 3) we present a developed methodology for organocatalytic cyclopropanation. We used benzyl chlorides decorated with electron withdrawing groups (EWG) in combination with a weak base to activate benzylic position and a range of α,β-unsaturated aldehydes to achieve the desired products with good and excellent yields, good diastereoselectivity and excellent enantioselectivity.

Table of Contents

List of Tables

List of Figures

List of Schemes

Acknowledgements

I would like to express my sincere gratitude to my supervisor Dr Ramon Rios for his support and guidance throughout the whole course of the project. His inspirational ideas and the confidence he placed in me to develop and turn them into reality have given me the courage to carry out this project, the resources and cohesive team he has brought together provided me the ideal environment, and his attention to student development has made sure that I have gained a lot of theoretical and practical knowledge from this research.

Thank you also to my co-supervisor David Harrowven, who has been generous with his deep knowledge of the subject whenever I needed.

Thank you to my group members PhD Marta Meazza, PhD Victor Ceban and PhD Luke Shirley for giving valuable advice about work and making me to feel at home and welcome in the group.

Thank you to Dr Neil Wells, Dr John Langley, Julie Herniman, Dr Andrea Mazzanti, and Mark Light for helping with the characterisation of products, without which the project could not have been completed.

Thank you to Hun Yi Shin, Hye Sung Yang, Jung Woon Yang whose work on cyclopropane opening confirmed the absolute configuration of the second diastereomer, which was essential for the project.

Thank you to Penny Spake, whose patience and help with the administrative side of my MPhil has been invaluable.

Thank you to the European regional Development Fund (ERDF) for co-funding the AI-CHEM project (No. 4061) through the INTEREG IV France (Channel)-England cross-border cooperation programme.

Definitions and Abbreviations

$[\alpha]_D$: Specific Rotation

Cbz: benzyloxycarbonyl

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM: dichloromethane

DEPT: Distortionless Enhancement by Polarization Transfer

DIPEA: *N,N*-diisopropylethylamine

dr: Diastereomeric ratio

E: Electrophile

ee: Enantiomeric excess

ESI: Electrospray ionization

EWG: Electron Withdrawing Group

HR-MS: High resolution Mass Spectrometry

LiHMDS: Lithium bis(trimethylsilyl)amide

MS: Mass Spectrometry

Nu: Nucleophile

NMR: Nuclear Magnetic Resonance

Pybox: Pyridylbis(oxazoline)

Salen: Salicylidenethanediamine

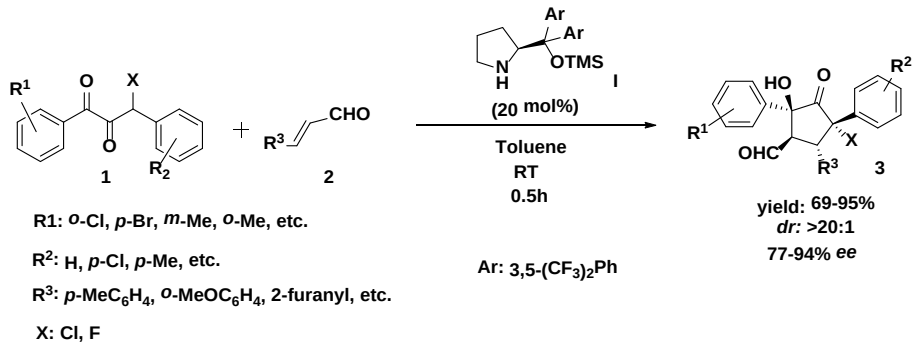
TMS: trimethylsylil

Ts: para-toluenesulfonyl

Chapter 1: Introduction

1.1 Historical overview of organocatalysis

Organocatalysis has developed as a powerful tool for synthetic chemists, alongside other well established approaches such as metal catalysis and biocatalysis. The term "organocatalysis" was coined by D.W.C. MacMillan[1] at the beginning of this century and became a starting point for some exciting progress in the area over the last decade. Organocatalysis is based on the ability of small organic molecules to catalyse organic transformations, some of which can be done in an asymmetric fashion. Nowadays the majority of asymmetric reactions rely on organometallic complexes, however organocatalysis is becoming more and more significant due to a series of advantages: a) catalysts are stable (not sensitive to moisture or air), b) they are inexpensive to make with environmentally friendly methods, c) use of organocatalysts allows the scaling up of complex procedures for industrial application with avoidance of expensive waste treatment because of environmentally friendly nature of the catalysts, d) it is ideal for synthesis of complex scaffolds through domino reactions,[1] e) it is suitable for implementation in continuous-flow systems and microreactors, which offer opportunities for more sustainable methodologies.[2] Moreover, organocatalysis can provide complex scaffolds in few steps and/or chemical transformations due its easy stereochemical prediction. For example, Alexakis and co-workers developed an organocatalytic Michael/Aldol reaction (**Scheme 1**) with high diastereo- and enantioselectivity. The presented reaction leads to the formation of interesting cyclopentanone derivatives with four contiguous stereogenic centres with good yields.[3]

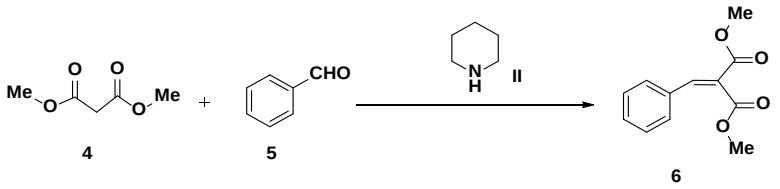


Scheme 1 Domino Michael/Aldol reaction of 3-halogeno-1,2-diones with enals.

Most organocatalysts are structurally simple molecules. This characteristic allows the construction of generalised mechanistic working models explaining or even predicting the stereochemical result of organocatalyzed reactions. The advantages of a metal-free environment,

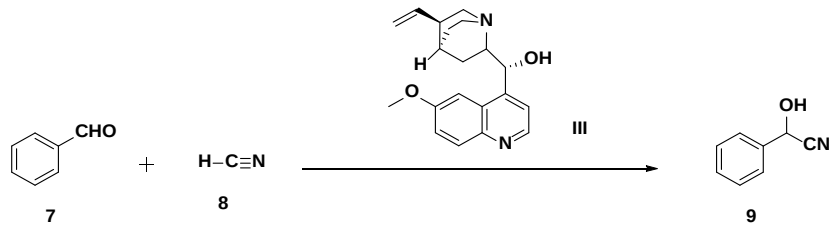
mild and simple reaction conditions have made organocatalysis the “third pillar” of enantioselective catalysis, alongside with metal- and biocatalysis.[4]

Historically the use of small organic molecules as organocatalysts can be traced back to the 19th century. However, it took a long time for asymmetric organocatalysis to establish itself as an important synthetic concept. For many years the organometallic approach was seen as a superior, more efficient and broader option than organocatalysis.



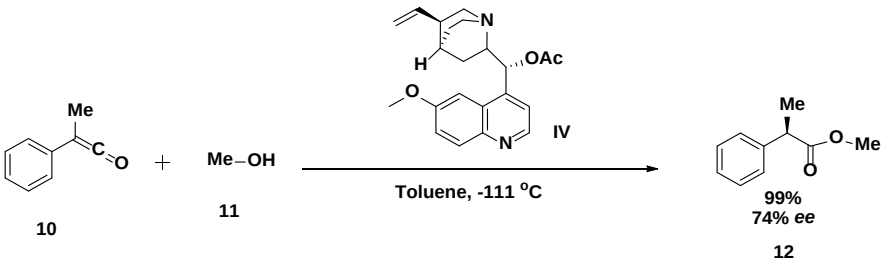
Scheme 2 An example of a reaction described by Knoevenagel

Benjamin List highlights fourteen key points in the development of organocatalysis.[5] Taking this into account for an historical perspective on elaboration of organocatalysis, only a few milestones will be reported. The use of small molecules as catalysts can be traced back to the earliest works of Emil Knoevenagel (**Scheme 2**).[5] Later, Dakin investigated the catalytic activity of primary amino acids applied to Knoevenagel condensation. That research represents a wide range of reaction substrates and catalysts.[6] However, conceptually ground-breaking development on organocatalytic approach was done by Bredig, who disclosed the addition of hydrocyanic acid (HCN) **8** to benzaldehyde **7** catalysed by cinchona alkaloids (**III)**. However, mandelonitrile **9** was obtained with less than 10% *ee* (**Scheme 3**).[1]



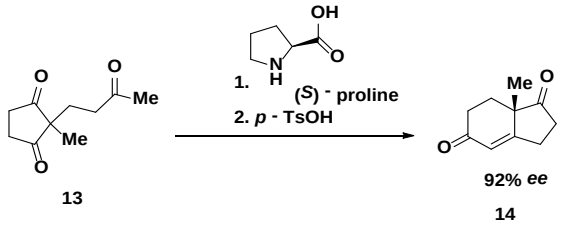
Scheme 3 Reaction between hydrogen cyanide and benzaldehyde reported by Bredig

The works of Bredig inspired further developments in the area. Reaction of methanol **11** with ketene **10** presented by Pracejus exhibited a good level of enantioselectivity as well as yield. The catalyst used for the addition was *o*-acetyl quinine **IV** (**Scheme 4**).[1]



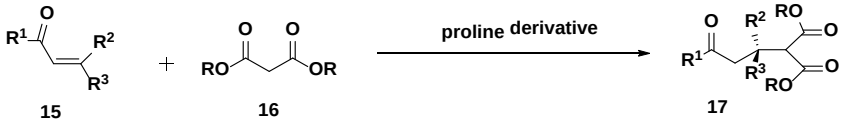
Scheme 4 Addition reported by Pracejus

A few decades later Kuhn and Hoffer discovered that secondary amines can catalyse self- and cross-aldol condensations of aldehydes as well as Knoevenagel reaction, which is still important for chemical industry. Later, more developments in the field were done by Fisher and Marshal (1931) (utilisation of catalytic properties of primary amino acids in aldol and condensation reactions of acetaldehyde), Kuhn (1936), Langerbec (1937) and Spence (1965). These works led to several chemists in 1970s (Hajos, Parrish, Eder, Sauer and Wiechert) independently focussing their attention on the development of the first amine-catalysed, asymmetric aldolisation, which became the first asymmetric intramolecular aldol reaction. The reaction was catalysed by proline which showed the utility of amino acids in aldol reactions (**Scheme 5**). Unfortunately, neither of the groups explained or mentioned the mechanism for the reaction.[1,5]



Scheme 5 Amine-catalysed aldol reaction reported by Hajos and Parish

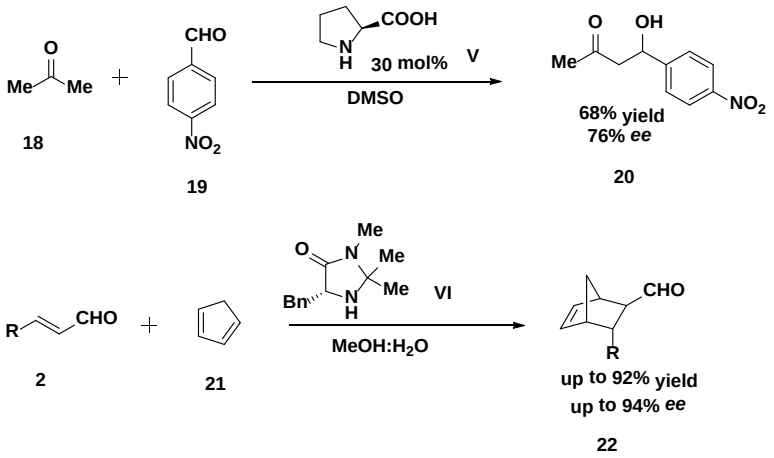
In the 1990s a new highlight in organocatalysis was described by Yamaguchi's and Taguchi's groups. They explored enantioselective Michael additions of some malonates to enones and enals in the presence of proline derivatives, suggesting an iminium ion activation mechanism. For example, a reaction reported by Taguchi is presented in **Scheme 6**.[7,8]



Scheme 6 Reaction developed by Yamaguchi and Taguchi

However, the real "renaissance"[1] of organocatalysis only started at the beginning of the 21st century with the works of List[9,10] and MacMillan[11] (**Scheme 7**). These works represent development in the areas of enamine and iminium catalysis respectively. The rediscovery of

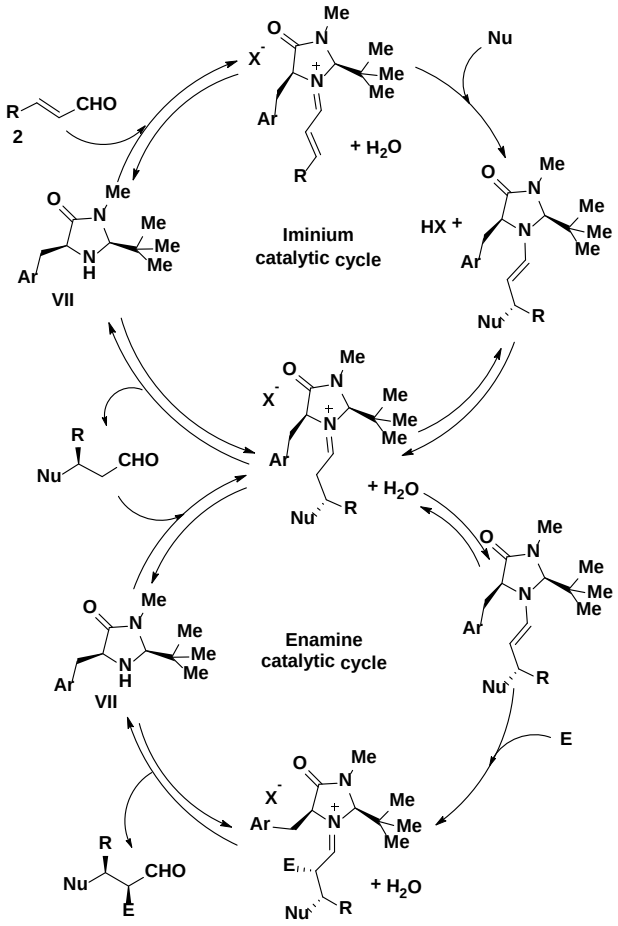
proline as a catalyst in an aldol reaction as well as iminium catalysis applied to the Diels-Alder reaction highlight the emergence of organocatalysis as an important synthetic tool alongside metal- and biocatalysis.[12]



Scheme 7 Reactions reported by List and MacMillan in 2000

After the millennium many new methodologies were developed and it is hard to choose the most important. However, a few examples can be named: bifunctional thiourea catalyst developed by Takemoto (2003),[13] the first organocascade reaction reported by MacMillan (2005) (**Scheme 8**),[14] Jorgensen developed an epoxidation of enals.[15] The first reported addition of aldehydes to nitroalkenes by Hayashi (2005),[16] enantioselective Michael-alkylation developed by Rios and Cordova,[17] and several months later reported by Wang (2007) giving access to chiral cyclopropanes.[18] The same year Rios and Cordova (2007) reported an enantioselective organocatalytic azaridination of α,β-unsaturated aldehydes,[19] different types of organocatalytic additions were reported by Rios,[12,13,14] and many more examples can be found in literature reviews.[4,22–24]

Moreover, new developments joining organocatalysis and metal catalysis in one-pot reactions opened new possibilities for further exploration of novel synthetic methods. All these works built the foundation for organocatalysis as we know it today.



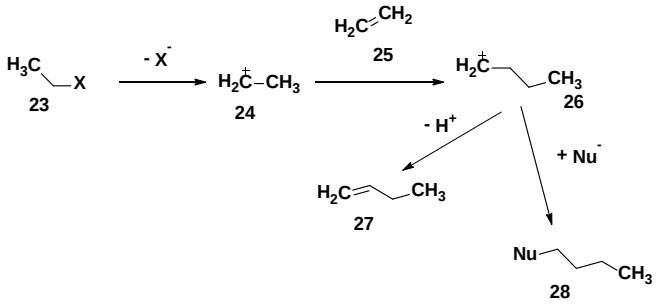
Scheme 8 Mechanism of a cascade reaction developed by MacMillan in 2005

1.2 Cascade, domino and tandem reactions

The design and development of varied complex molecules is one of the goals in organic synthesis. Synthetic organic chemists of our time are facing the challenge of developing clean, energy efficient and atom economic methodologies for the transformation of feedstock chemicals into highly valuable pharmaceutical products. Among many reaction types, carbon-carbon bond formation is regarded as of high importance in organic synthesis.[1] At the same time, chirality is also highly valued due to the fact that all physiological and pharmacological properties depend upon it. A chiral receptor can interact only with a molecule of a proper absolute configuration. Moreover, the use of chiral drugs in enantiopure forms is required as standard for nearly every new chemical entity, and the development of new synthetic methodologies is a main goal for pharmaceutical companies.[25]

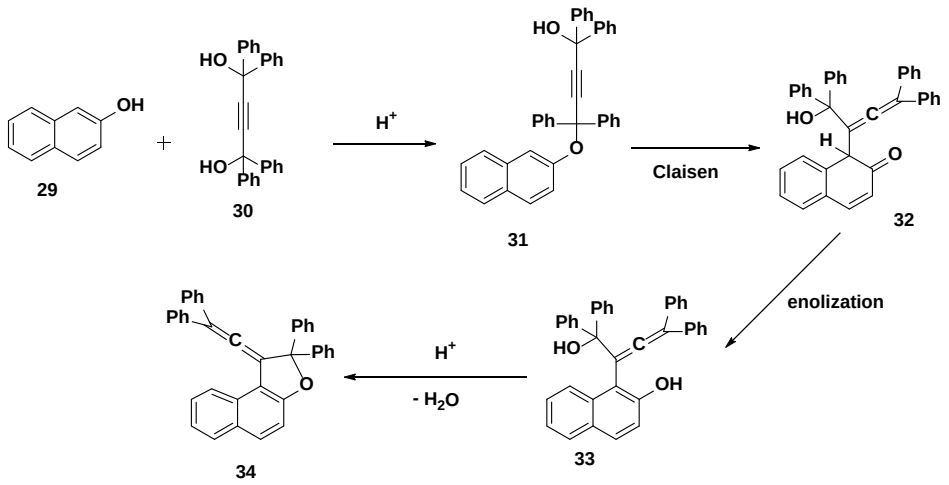
Cascade, tandem or domino reactions are types of reaction, which allow several bond formation steps to be done in a single operation. These approaches have attracted a lot of attention in

recent years because they address fundamental synthetic issues related to atom efficiency.[21] Tietze described domino reaction as “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 subsequent reactions result as a consequence of the functionality formed in the previous step”.[26] Domino reactions are often called cascade or tandem reactions, however Teitze highlights that term cascade reaction sometimes has a broader meaning.[27] In the same work, Tietze proposed a classification of domino reactions in accordance with the mechanism of the first step as radical, pericyclic, anionic, cationic, photochemical and transition-metal induced transformations. He acknowledged a possibility of several steps as well as mixing of different mechanisms. Homo-domino reaction consists of a combination of reactions with the same mechanism. On the other hand a combination of different reaction mechanisms is called a hetero-domino reaction. Tietze acknowledges an existence of more than one step domino reaction; they may include two, three or even four steps.[26] In this section, I would like to give just a brief overview of different types of domino reactions with a few examples.



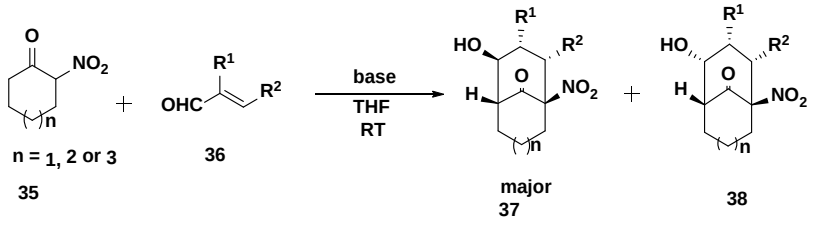
Scheme 9 Example of a cationic – cationic domino reaction

Cationic domino reactions have formation of a carbocation formally or in reality in the primary step. This carbocation then reacts with a nucleophile leading to formation of another carbocation, which engages in further cationic-cationic transformation. The final step of the process will be trapping of that carbocation with a nucleophile or loss of a proton (**Scheme 9**).[27] For example, rearrangement reactions with formation of several cationic species (**Scheme 9**). Another example worth note is the acid-catalysed cyclisation (**Scheme 10**) recently reported by Coelho and co-workers, which they used to access conjugate indenes and inden-2-ones.[28]



Scheme 10 Acid catalysed cascade reaction

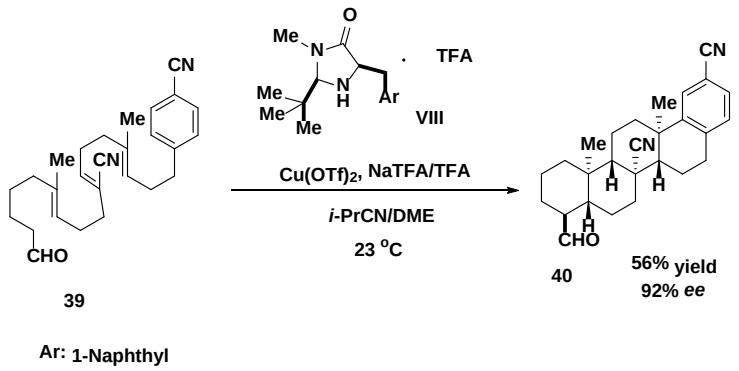
Anionic domino reactions have a formation of a nucleophile or an anion in the primary step. In many cases formation of a carbanion goes through deprotonation of a CH group with the following reaction between the formed carbanion with an electrophile resulting in the formation of a new anionic species. The latter can get involved in another anionic cycle leading to anionic-anionic process or be transformed into a species with multiple functionalities giving an opportunity for anionic-pericyclic sequence.[27] For example, Menendez reported an approach to highly functionalised bicyclo[n.3.1]alkane motives based on an anionic domino reaction (**Scheme 11**). Reported methodology utilises a base-promoted Michael-aldol reaction between α,β – unsaturated aldehydes **36** and cyclo-α-nitro ketones **35** giving access to a variety of bicycle[n.3.1]alkanone systems with seven different ring sizes (n=3-9), several stereocentres and in good yields.[29]



Scheme 11 Synthesis of derivatives of the bicycle[3.3.1]-nonane, -[4.3.1]decane and – [5.3.1]undecane systems in one-pot reaction

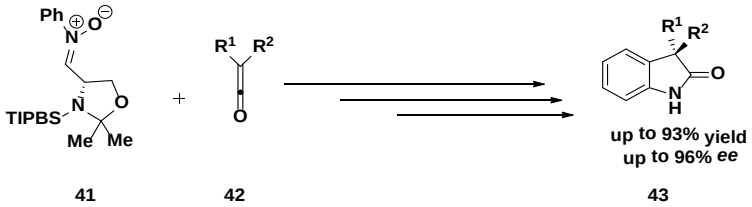
Radical domino reactions have a formation of a radical in the primary step. It can be combined with a subsequent pericyclic, cationic, anionic or radical transformation. A lot of research has been done in the area despite the difficulties presented by the very reactive nature of the radical species.[26,27,30] Here just one example is going to be mentioned to illustrate that type of cascade. MacMillan's group reported the first organocatalytic enantioselective approach to access steroidal and terpenoidal frameworks via SOMO (Singly Occupied Molecular Orbital) catalysis. It is

very important to mention that in the presented work the reaction can be conducted at room temperature resulting in formation of several stereogenic centres, quaternary carbons and C-C bonds with more than 90% *ee* and good yield (**Scheme 12**).[30,31]



Scheme 12 Example of an enantioselective polycyclization via SOMO catalysis

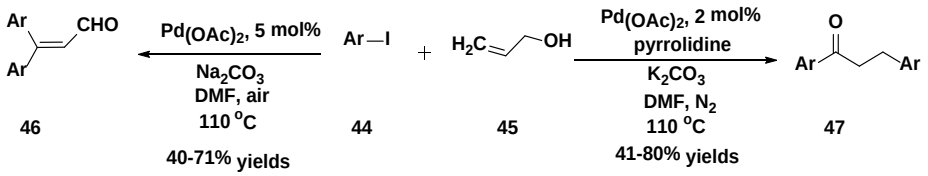
Pericyclic domino reactions are one of most common, well used and efficient tools of the synthetic organic chemist. A review reported by Barriault and group highlights recent developments in the implementation of cascade pericyclic reaction to total synthesis to directly target specific natural or biomimetic products.[32] The usefulness of that type of tandem reaction is based on the possibility of combining it with other types of cascades. To illustrate this variation of cascade reactions a paper reported by Smith and co-workers will be used.[33] The group developed a method to access 3-alkyl-3-aryloxindoles through an asymmetric pericyclic cascade of alkylarylketenes with *L*-serine derived *N*-arylnitrones in yields up to 93% and with enantioselectivity up to 98% (**Scheme 13**). Furthermore, to demonstrate the potential of this methodology they demonstrated preparation of the enantiomer of a Roche anti-cancer agent in three steps and with excellent enantioselectivity (96% *ee*).[33]



Scheme 13 Generalised example of asymmetric oxindole synthesis

Transition-metal catalysed domino reactions play an important role in organic synthesis.[26,27] Herein, we report just one example to illustrate the use of metal catalysis to form complex molecules. Hang and co-workers reported that palladium acetate ($Pd(OAc)_2$) can catalyse a triple domino transformation of various aryl iodides with propanol. The tandem transformation starts with Heck-isomerisation following by Saegusa and then finishes with a Heck reaction giving the desired products 3,3-diaryl propenals in yields from 40% to 71% (**Scheme 14**). In the same work

they reported another domino process involving triple transition metal catalysis with aminocatalysis or double transition metal catalysis and the mediation of the secondary amine. The reaction can be performed with a range of substituents on the aromatic ring giving good and moderate yields (**Scheme 14**).[34]



Scheme 14 Transition metal catalysed domino reactions for selective 3,3 or 1,3 diarylations of propanol with aryl halides

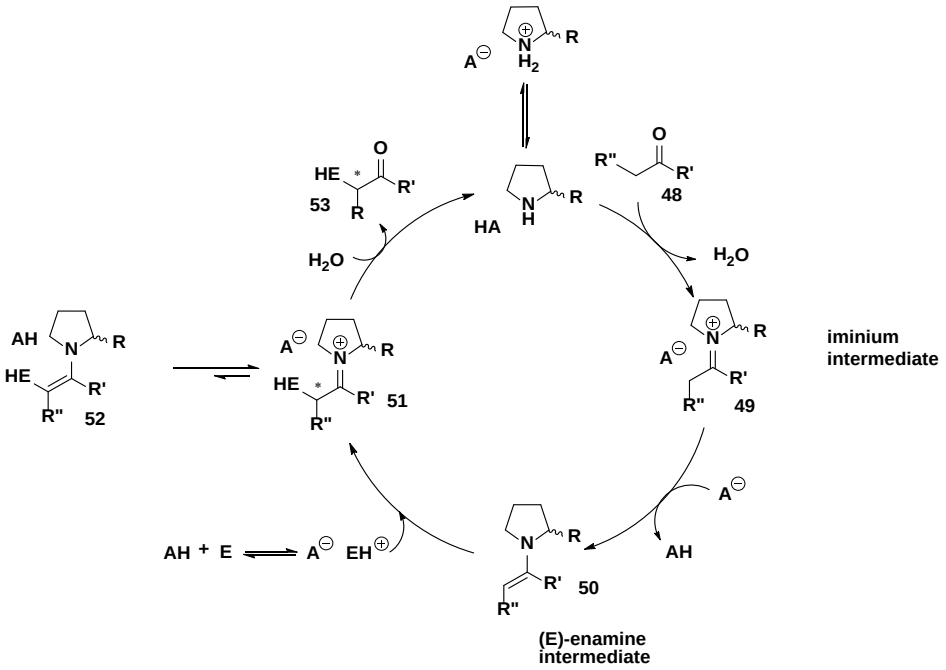
The classification reported above was developed in the 1990s whereas a proper development of organocatalysis began with the works of List and MacMillan in 2000.[9][11] However, an early attempt to find a related group for iminium catalysis led Teitze to place it in the section of anionic-pericyclic and related domino reactions.[26] Since then, organocatalysis has developed into an independent and important tool in organic chemistry. Nowadays organocatalysis can be classified using a mechanistic approach proposed by List and is described in more detail in the next section.[35]

Although, as has been shown, the area of cascade reactions is broad and complex, in this project the main focus will be on the development of novel organocatalytic domino reactions.

1.3 Modes of activation in organocatalysis

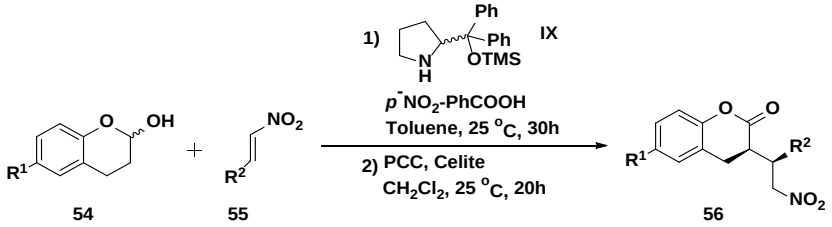
Organocatalysis is becoming a more and more important tool in contemporary organic synthesis. The structural simplicity of the majority of organocatalysts as well as variety of activation modes has been crucial for the development of mechanistic working models enabling rationalisation and in some cases prediction of stereochemical outcome of organocatalytic reactions.[1] All activation modes of organocatalysts can be described, from a mechanistic perspective proposed by List, as the covalent or noncovalent highlighting an interaction between the substrate and catalyst, and by the chemical nature of the organocatalysts (Lewis acid, Lewis base, Brønsted acid, Brønsted base).[35] It is important to mention that many organocatalysts exhibit dual properties as they can act through both covalent or noncovalent interaction or present dual acid-base properties ("bifunctional catalysts").[1] In this chapter, we will focus only on covalent organocatalysis in

particular iminium and enamine catalysis due to its significance and relevance for the research project.



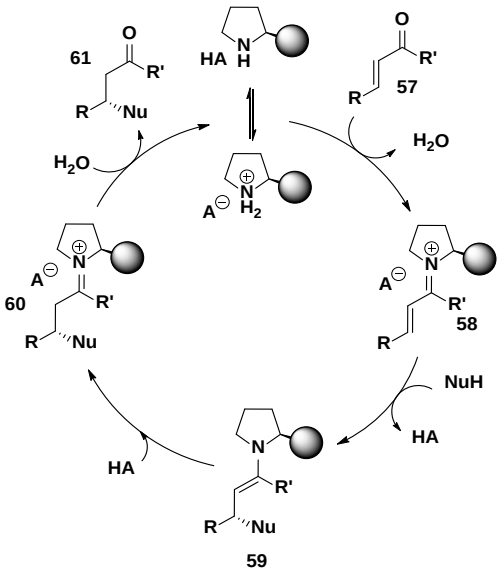
Scheme 15 General mechanism of α-functionalisation of carbonyls via the chiral-amine catalysis

Enamine catalysis represents a "standard" catalytic way for α-functionalisation of carbonyl compounds and is depicted in **Scheme 15**. The generalised enamine catalytic cycle starts with external acid (Brønsted acid AH) promoted condensation of the carbonyl **48** with amine to form an iminium ion **49**. After the iminium ion formation, one of α-acidic protons of the latter is removed by conjugate base of the AH acid leading to formation of the key nucleophilic enamine intermediate **50**. Following the reaction with an electrophile another iminium ion **51** is formed, and after hydrolysis the product **53**, the acid and the amine-catalysts are released. The liberated catalyst can then re-enter the catalytic cycle. The Brønsted acid co-catalyst can be an external acid, or protic solvent (water, alcohols), or functional groups present in the amine-catalyst (for example, carboxylic moiety of α-amino acids is often used).[1]



Scheme 16 One-pot asymmetric sequential Michael addition to access α-functionalised chroman-2-one developed by Tong

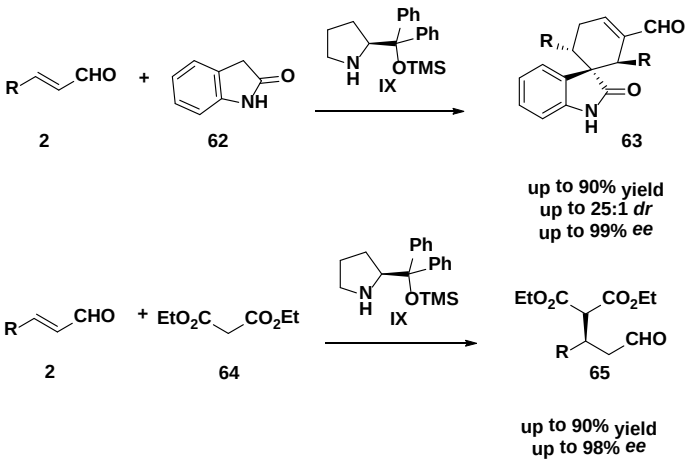
For example, Tong and co-workers recently reported an open-close strategy based on enamine catalysis applied to lactols to achieve direct access lactones **56** (**Scheme 16**). This approach gives rapid access to α-functionalised lactones with two adjacent stereogenic centers with good yields and diastereoselectivity and with excellent enantioselectivity.[36]



Scheme 17 General mechanism of β-functionalisation of α,β-unsaturated carbonyls using chiral amine-catalysis

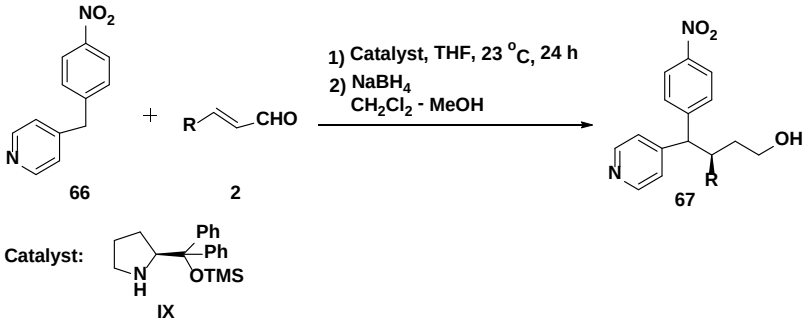
Iminium catalysis is an activation mode used as a general strategy for the asymmetric conjugate addition to β-position of α,β-unsaturated carbonyl compounds of different nucleophiles. A mechanism of aldehyde activation by a chiral pyrrolidine-catalyst is shown in **Scheme 17**. The process begins with the condensation of amine with the carbonyl **57** (promoted by acid) to form an iminium ion **58**, the latter being more electrophilic than the parental unsaturated carbonyl compound. In the next step, that more reactive intermediate undergoes addition on the nucleophile at the β-position, resulting in the formation of enamine **59** which stays in a tautomeric equilibrium with an iminium ion **60**. The following enamine hydrolysis releases both product **61** and the chiral amine-catalysts salt, which can be reused in another catalytic cycle.[1]

Iminium activation is used to create new C-C bonds. For example, different variations of addition to α,β-unsaturated carbonyls: malonates presented by Jorgensen and fluoromethyl, fluorobis(phenylsulphonyl)methane developed by Rios,[12] Cordova[37] and Wang[38]. Another example is synthesis developed by Melchiore[39] and Rios[40] to access spirocyclic compounds in one step with excellent enantioselectivity (**Scheme 18**).



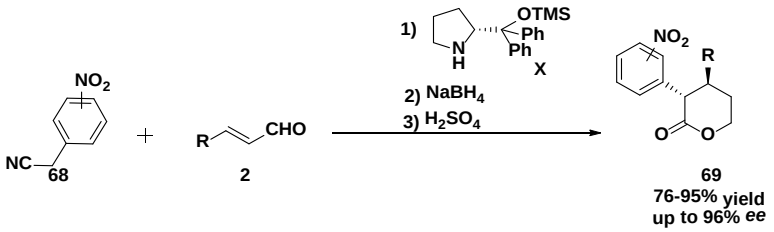
Scheme 18 Examples of nucleophilic addition

Although a lot of progress has been made in recent years in the area of organocatalysis, there are still some challenges to overcome. For example, nucleophilic addition to α,β-unsaturated carbonyls required good nucleophiles such as malonates or, generally speaking, dicarbonyl compounds possessing acidic hydrogens.



Scheme 19 Asymmetric conjugate addition nitrobenzyl pyridine to enals reported by Melchiorre

There are a limited number of examples in the literature describing addition of benzylic nucleophiles to α,β-unsaturated carbonyls. One example is reported by Melchiorre describing the addition of diarylmethylenes to β-position of enals.[41] However, the reported procedure has some limitations in terms of low diastereoselectivity and a need to have two activated aryls furnished with electron-withdrawing groups (**Scheme 19**).



Scheme 20 Addition to enals reported by Ruano

Another example, presented by Ruano on the secondary amine catalysed addition of nitroaryls to α,β-unsaturated aldehydes, benefited from good diastereo- and enantioselectivity (**Scheme 20**).[42] Rios group became interested in the activation of benzylic and pseudo-benzylic positions, resulting in the development of a complex catalytic strategy to achieve addition of azaarenes to enals with good diastereo- and enantioselectivity (**Scheme 45**).[43]

1.4 Synthesis of pyrrolizidine and indolizidine derivatives

Bicyclic *N*-heterocycle motives are found in a number of natural products such as indolizidine alkaloids, serratezomine,[44] stemona alkaloids,[45] manzamine alkaloids and nakadomorin A.[46] Bicyclic alkaloids are known to exhibit a variety of physiological and pharmacological properties. For example, (+)-epi-lupinine **71** shows *in vitro* activity against Leukaemia P-388 and lymphocytic Leukaemia L1210 (**Figure 1**).[47] Another example is lentiginosine **73**, first isolated by Elbein and co-workers in 1970 from *Astralagus lentiginous*. The interest in this compound is based on its exhibition of excellent biological activity against HIV, tumours as well as immunomodulating activity through inhibition of amyloglycosidase.[48] A rising interest in these structural moieties can be linked with them being highlighted as preferred candidates for the treatment of several diseases such as diabetes, cancer, viral infections and lysosomal disorders.[49]

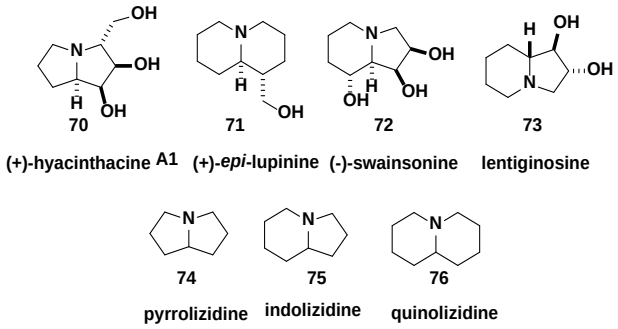
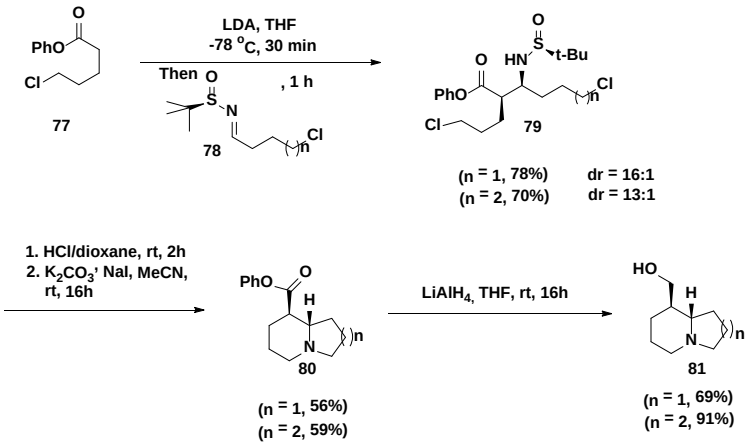


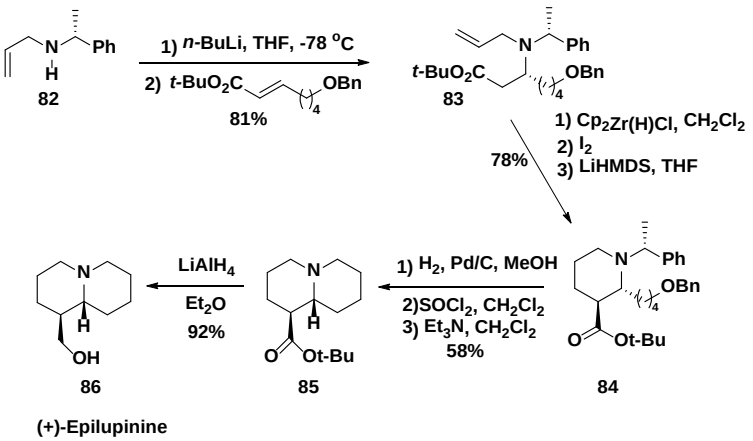
Figure 1 Examples of bicyclic *N*-heterocycles

In recent years, organic chemists have aimed to develop routes for enantioselective synthesis of compounds with izidine alkaloids motives. However, currently available synthetic ways used to build those compounds in an enantioselective fashion include tedious routes requiring the use of several protective groups, and/or chiral auxiliaries. For example, Brown and co-workers reported a strategy for the synthesis of (-)-tashiromine and (-)-epi-lupinine based on an imino-aldol reaction where imines were prepared using the Elman's auxiliary (**Scheme 21**).[47]



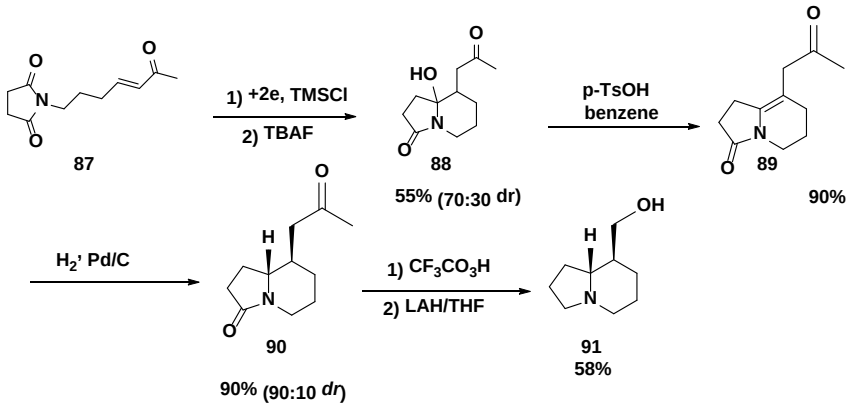
Scheme 21 Synthesis of (-)-tashirimine and (-)-*epi*-lupinine

The majority of these approaches utilise intramolecular aza-Michael reactions,[50] intramolecular nitrile oxide-alkene cycloadditions,[51] organocatalityc asymmetric Mannich cyclisation of hydroxylactams with acetals,[52] [4+2] and [2+2+2] cycloadditions,[53][54] ring closing metathesis, intramolecular Schmidt rearrangement, Staudinger-Aza-Wittig or LiHMDS-mediated ring closure.[55] All cited methodologies are based on arduous synthesis to prepare the starting materials, the utilisation of protective groups, and in some cases the use of chiral auxiliaries. For example, Ahari and co-workers reported a nine step synthesis of *epi*-lupinine (**Scheme 22**).[55]



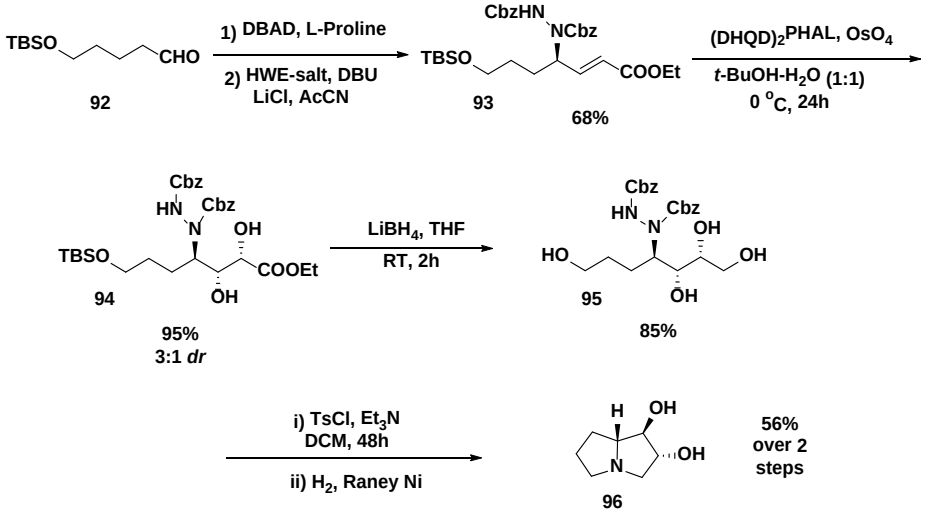
Scheme 22 Ahari's total synthesis of epi-Lupinine

Kise and co-workers recently disclosed an electroreductive intramolecular coupling of aliphatic cyclic imides with α,β-unsaturated esters and ketones leading to methyl-alkoxy exchange in silyl ketene acetals (**Scheme 23**).[56]



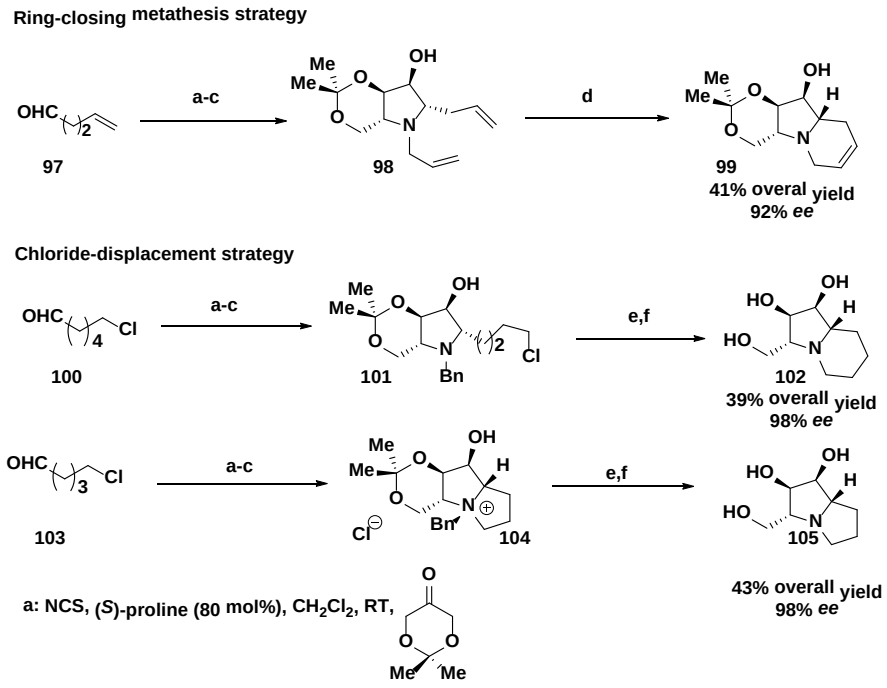
Scheme 23 A synthetic route developed by Kise

A way of utilising an organocatalytic step to access azabicyclic ring systems was reported by Kumar and co-workers. They used a proline catalysed α-amination followed by Sharpless asymmetric dihydroxylation in the key steps of the synthetic protocol. Moreover they illustrated the universality of the approach through synthesis of (-)-lentiginosine, dihydroxy pyrrolizidine, 1,2-*epi*-lentiginosine and indolizidine alkaloid coniceine. The strategy allows good stereo control and benefited from good and excellent yields throughout the procedure (**Scheme 24**).[48,57]



Scheme 24 Synthesis of dihydroxy pyrrolizidine reported by Kumar

Another example of the successful application of organocatalysts in the total synthesis of azabicyclic motives was recently presented by Britton and colleagues. They developed an impressive combination of strategies to access a variety of polyhydroxy pirrolosidines and indolizidines (**Scheme 25**) leading to desired products in moderate overall yields and excellent enantioselectivity.[49] However, the starting materials used are not commercially available.

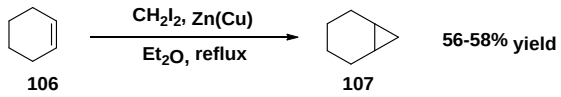


Scheme 25 Total synthesis of indolizidine and pyrrolizidine motives reported by Britton

Though the number of the developed approaches is impressive all of them require no less than 5 steps, sometimes utilising harsh conditions and do not start from commercially available materials. The aim of this work is to develop a new way to synthesise indolizidine and pyrrolidizine derivatives under mild conditions, with environmentally friendly reagents, in a few operational steps and starting from commercial materials.

1.5 Synthesis of cyclopropanes

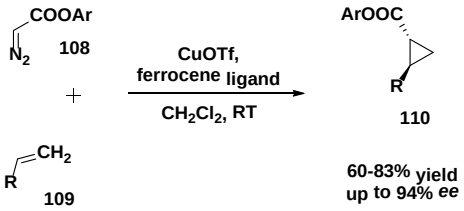
The cyclopropane moiety is interesting to synthetic organic chemists, physical organic chemists and medicinal chemists due to the vast variety of properties exhibited by molecules containing the cyclopropane subunit. For example, these compounds are conformationally constrained due to a limited degree of freedom, which leads to noticeable steric, stereoelectronic and directing effects making them universal models for the study of region-, diastereo- and enantioselectivity. At the same time, the presence of the moiety in various biologically active compounds such as terpenes, pheromones, fatty acids metabolites and some amino acids has made them a target of interest for synthetic chemists.[58]



Scheme 26 Example of Simmons-Smith cyclopropanation

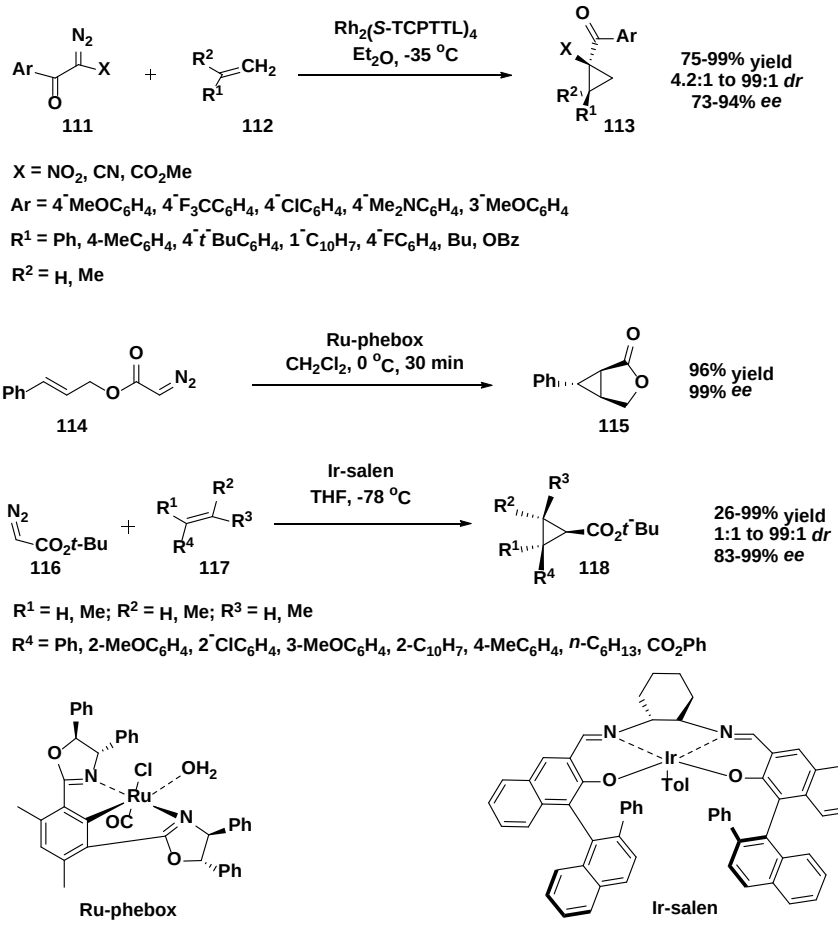
There are a variety of ways to achieve cyclopropanes reported in literature. Simmons and Smith carried out pioneering work in the field. Their work is based on activated zinc catalysed cyclopropanation between diiodomethane and alkenes affording desired products in high yields. The success of the reaction is based on its high tolerance of a variety of functional groups, broad substrate variations and stereoselectivity in respect to alkene geometry (**Scheme 26**).[58,59]

Though the field of transition metal-catalysed cyclopropanations is vast, just a few examples will be mentioned here to give a brief overview of synthetic approaches to achieve cyclopropane moiety. For example, in 2000 Rios and Fu reported a copper (I) catalysed cyclopropanation (**Scheme 27**). They used a range of olefins with aryl, alkyl and silyl groups affording the desired cyclopropane moiety in good to excellent yields, excellent diastereo- and enantioselectivity.[60]



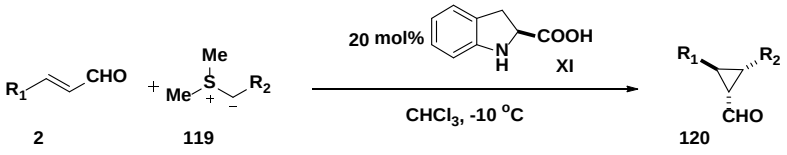
Scheme 27 Catalytic enantioselective cyclopropanation of olefins developed by Rios and Fu

Other common metalocatalytic methods to form the cyclopropane moiety include the use of catalysts containing ruthenium, palladium, rhodium and cobalt. Some of the examples are depicted in **Scheme 28**. Moreover, a review conducted by Bartoli, Bencivenni and Dalpozzo in 2013 gives a more comprehensive overview of the asymmetric cyclopropanation.[58] In 2015 Qian and Zhang published a valuable review on gold-catalysed cyclopropanation, structuring their review by the type of carbenoid precursors.[61] All of this literature demonstrates a significant interest in the development of new synthetics methodologies to form a cyclopropane subunit.



Scheme 28 Examples of transition metal catalysed cyclopropanations

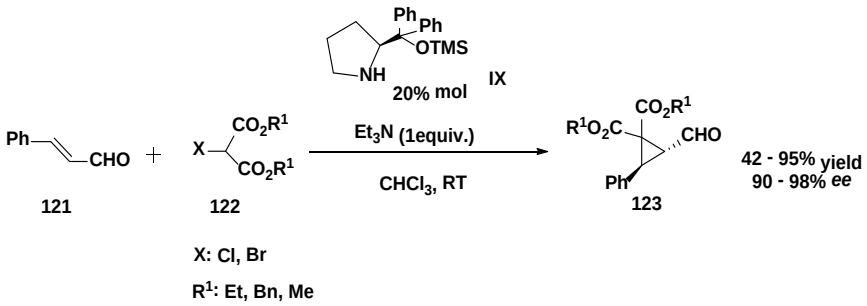
On the other hand, some organocatalytic methods to achieve cyclopropane moiety have been developed. In 2004 MacMillan and Kunz reported enantioselective cyclopropanation through utilisation of iminium catalysts. They developed a highly efficient protocol allowing access to enantioenriched cyclopropanes using stabilized ylide with 2-carboxylic acid dihydroindole catalyst (**Scheme 29**). The proposed approach gives access to cyclopropanes with excellent diastereoselectivity and enantioselectivity, and with moderate and good yields.[62]



entry	R_1	R_2	% yield	*dr*	% *ee*
1	Propyl	COPh	85	30:1	95
2	$CH_2OAllyl$	COPh	77	21:1	91
3	Me	COPh	67	>19:1	90
4		COPh	74	24:1	96
5	Propyl	COPh*p*-Br	67	72:1	92

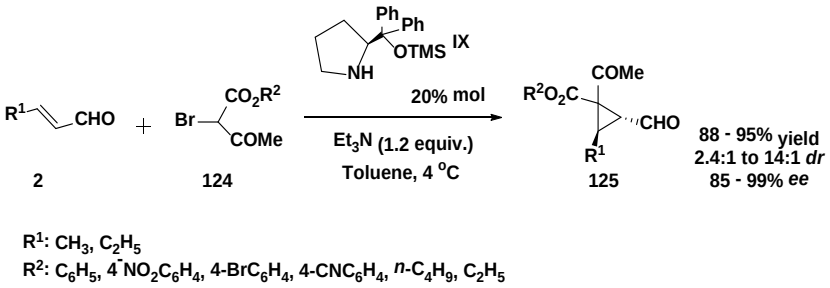
Scheme 29 Some examples of organocatalytic ylide-cyclopropanation

Cordova and co-workers and a few months later Wang and co-workers reported a one-pot organocatalytic domino reaction leading to formation of cyclopropanes (**Scheme 30**). They used bromomalonate and a range of enals to afford cyclopropanes in enantioselective fashion.[18,63]



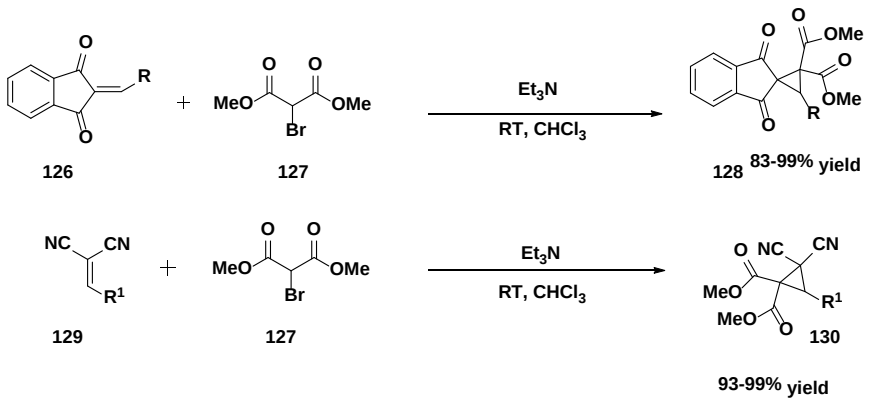
Scheme 30 Cordova's cyclopropanation

Later Rios and co-workers reported a highly stereo-controlled asymmetric organocatalytic cyclopropanation (**Scheme 31**), thereby expanding the reaction with the use of bromo-keto-esters generating three consecutive stereocentres in a highly enantioselective fashion.[21]



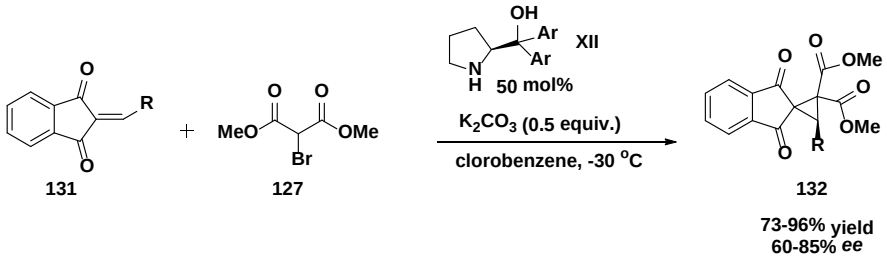
Scheme 31 Cyclopropanation reaction between enals and 2-bromo-3-keto-esters

In 2011, Lattanzi's group reported an approach to spirocyclopropanes. They investigated a Michael - initiated ring-closing reaction using a commercially available α-monohalogenated active methylene compounds and 2-arylidene-1,3-indandiones or 2-arylidene malononitriles in the presence of triethylamine leading to densely functionalized cyclopropanes (**Scheme 32**).[64]



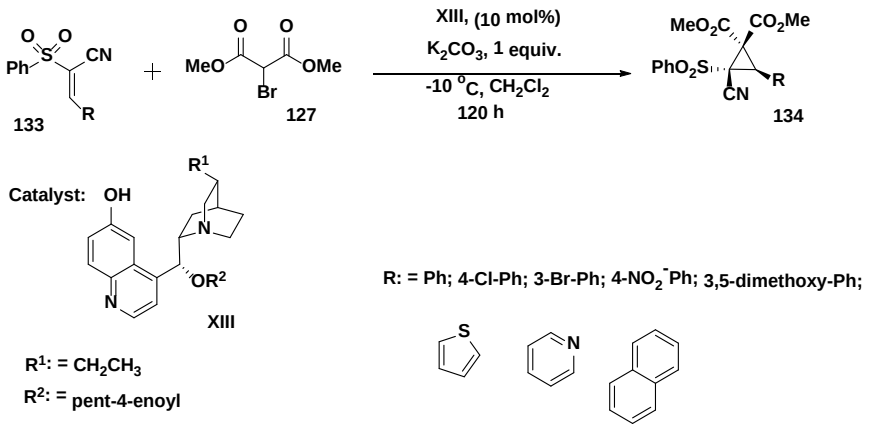
Scheme 32 Triethylamine-catalysed cyclopropanation of 2-arylidene-1,3-indandiones and 2-arylidene malononitriles with dimethylbromomalonate

In the same work they disclosed an asymmetric route to spirocyclopropanes from dimethylbromomalonate and 2-arylidene-1,3-indandiones, using a commercial α,α-L-diarylprolinol as an organocatalyst in co-operation with K_2CO_3 as additive. The products were obtained in good yields with moderate to good enantioselectivity (**Scheme 33**).[64]



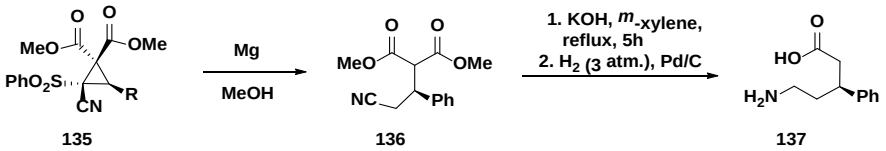
Scheme 33 An asymmetric cyclopropanation reported by Lattanzi

Cobb's group explored the utility of the Michael-initiated ring closure cyclopropanation with bromomethylmalonate, leading to a highly functionalized product containing a quaternary stereogenic centre, moreover, the latter can be used in a variety of transformations to result in synthetically useful products. The synthesis is based on the use of a novel bifunctional cupreine organocatalyst. The presented cyclopropanation (**Scheme 34**) gives total diastereocontrol, good yields and from moderate to good enantioselectivity.[65]



Scheme 34 Asymmetric cyclopropanation of conjugate cyanosulfones

The authors not only reported a way to access asymmetric cyclopropanes but also expanded the methodology to access δ^3-amino acids. The reported methodology gives rapid access to δ^3-amino acids through radical desulfonisation-ring opening initiated by magnesium (**Scheme 35**).[65]



Scheme 35 Magnesium-initiated ring-opening to form a δ^3-amino acid precursor

Although the range of methodologies reported in literature is impressive, often they require quite active nucleophiles such as malonates, or alternatively the presence of transition metal-catalysts or chiral auxiliaries; therefore there is still room for improvement. For example, in the development of new methodologies with weaker nucleophiles with benzylic and pseudo-benzylic protons.

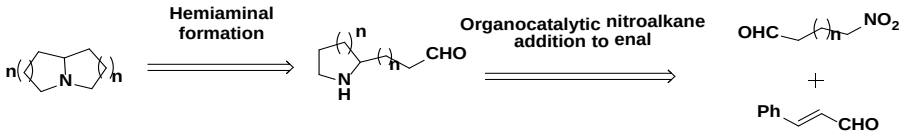
Chapter 2: Approach to the synthesis of pyrrolizidine and indolizidine derivatives via nitro alkyl addition to enals

2.1 Introduction

Pyrrolizidine and indolizidine structural motives are often found as a key moiety in numerous alkaloids, with a wide scope of biological and pharmacological properties (**Figure 1**). The combination of their low abundance in nature and potent biological activity means that over the years these azabicyclic ring systems have remained an area of high synthetic effort. As a result a wide range of synthetic methods were developed towards a variety of inzidines (indolizidine **75**, quinolizidine **76** and pyrrolizidine **74**).[57] Some synthetic strategies were presented in **Chapter 1.4**. Herein we are going to report a new route to achieve pyrrolizidine and indolizidine motives based on organocatalysis.

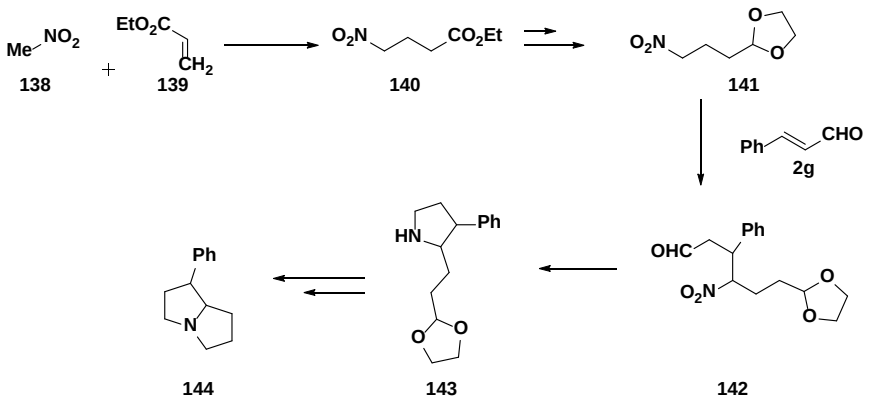
2.2 Project aims

Based on the importance of izidine motives in drug development, the aim of this project is to develop a new short pathway for enantioselective synthesis of pyrrolizidine and indolizidine derivatives utilising an organocatalytic approach, followed by heterocyclic ring formation. The structure evaluation leads to the following retrosynthesis (**Scheme 36**).



Scheme 36 Retrosynthesis of azobicyclic compounds

The analysis of the retrosynthesis resulted in the proposal of possible total synthesis with cheap and commercially available starting materials (**Scheme 37**).



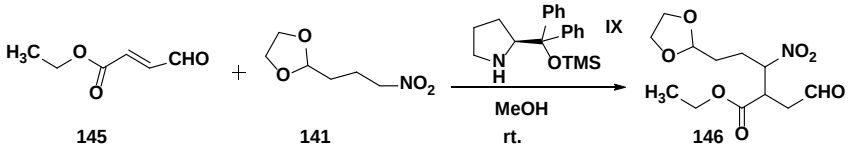
Scheme 37 Total synthesis of azobicyclic compounds

2.3 Results and discussion

Michael reaction of nitroalkanes with α,β-unsaturated aldehydes

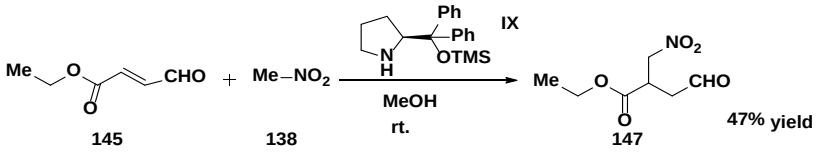
Reactions of nitroalkanes with α,β-unsaturated ketones, esters, amides and α,β-unsaturated aldehydes have been reported in literature. Hayashi and co-workers developed a procedure for reaction of α,β-unsaturated aldehydes with nitro alkanes. They used cinnamaldehyde and nitro methane as a model leading to the desired product in good yield and enantioselectivity.[66]

The asymmetric Michael addition of 2-(3-nitropropyl)-1,3-dioxolane **141** to ethyl 4-oxobut-2-enoate **145** might presented some difficulty in the laboratory, possibly due to low activity of the chosen α,β-unsaturated aldehyde and potential reactivity problems for the nitro compound (**Scheme 38**). The reaction has not been tried and the research started with use of more active alternative such as nitromethane **138**.



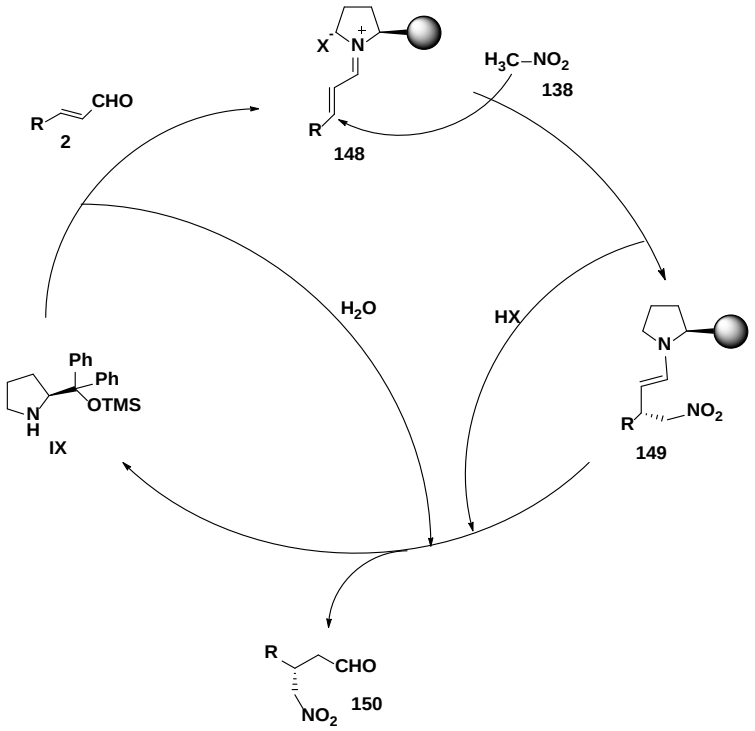
Scheme 38 Michael addition of 2-(3-nitropropyl)-1,3-dioxolane to ethyl 4-oxobut-2-enoate

By changing the nitroalkane to nitromethane **138**, the reaction occurred in 6 days to completion, which suggested low reactivity of the selected α,β-unsaturated aldehyde **145** in comparison with Hayashi's report of only a few hours (**Scheme 39**).



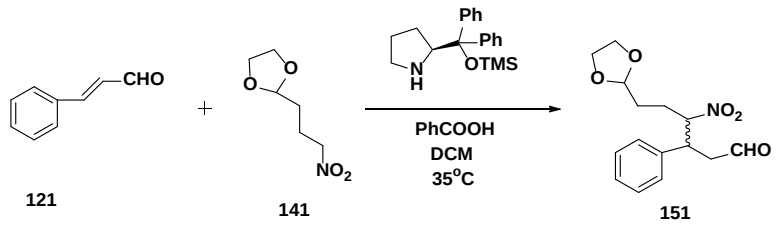
Scheme 39 Reaction of ethyl 4-oxobut-2-enoate with nitromethane

The mechanism of iminium activation begins with Brønsted acid-initiated condensation (in our case it is methanol (protic solvent)) of the α,β-unsaturated aldehyde with the amine leading to formation of an unsaturated iminium ion. The intermediate then undergoes an addition of a nucleophile (nitromethane in this case) at the β-position, resulting in β -functionalised enamine further protonation followed by hydrolysis leading to product and release of the catalyst (**Scheme 40**).[1]



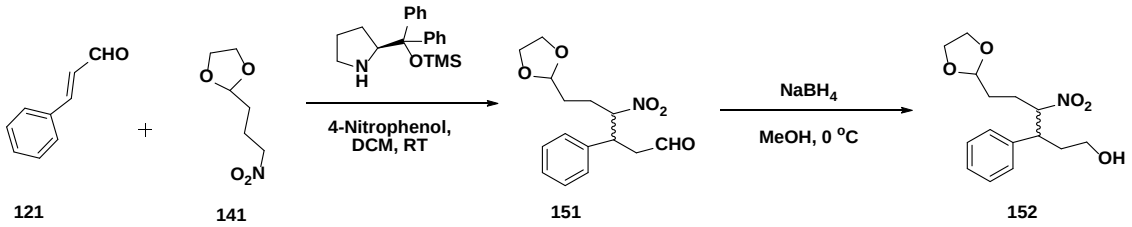
Scheme 40 Iminium activation mechanism

In parallel the reactivity of 2-(3-nitropropyl)-1,3-dioxalane was checked with cinnamaldehyde. The reaction took 12 days, although it required a temperature slightly higher than room temperature. The degradation of starting materials explains the low reaction yield (19%).



Scheme 41 Reaction of cinnamaldehyde with 2-(3-nitropropyl)-1,3-dioxolane

Based on analysis of acquired results, the need for better activation of α,β-unsaturated aldehyde can be met through the addition of acidic co-catalysts. The related studies on use of 4-nitrophenol as a co-catalyst were done by Pikho and co-workers who found that it can accelerate the rate of the reaction.[67] Based on these findings Reitel and co-workers applied that approach to synthesis of β- and γ-amino acids by organocatalytic conjugate addition of cyclopropylacetaldehyde derivatives to nitro olefins.[68][22] Inspired by these results the trial of 4-nitrophenol as a co-catalyst became an obvious choice. An increase of the reaction rate was observed allowing the reaction completion in six days at room temperature with a lower number of by-products formed (**Scheme 42**). As was expected the reaction yield increased giving two diastereomers in 45% and 31% yields respectively, with overall yield for the reaction at 76%.

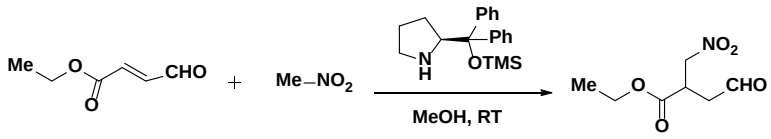


Scheme 42 Improved conditions for reaction of cinnamaldehyde with 2-(3-nitropropyl)-1,3-dioxolane

The resulting diasteriometric ratio determined by NMR resulted in 1.5:1. At this step the determination of enantiomeric excess was identified as very important for success for the project. Unfortunately the results obtained weren't encouraging as 50% *ee* was achieved for major diastereomer. However, the minor diastereomer gave better results for enantiomeric excess as 96%. The *dr* and *ee* data showed that in the proposed total synthesis we can achieve some control over one of the two formed chiral centres.

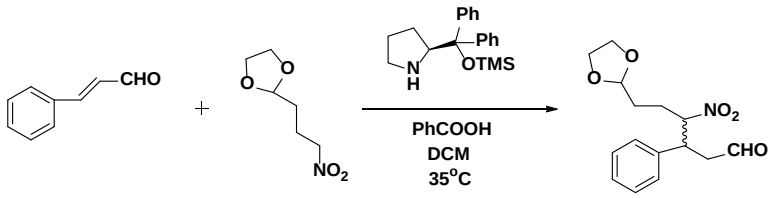
2.4 Experimental data

Synthesis 1



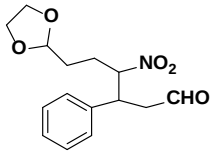
The following compounds were added into a vial in the described sequence: (*S*)-2-(diphenyl (trimethylsilyl) oxy) methyl) pyrroline (10 mol%, 0.1 equiv., 19.5 mg, 0.06 mmol), ethyl-(*E*)-4-oxobut-2-enoate (1 equiv., 75 mg, 0.6 mmol), nitromethane (3 equiv., 109.9 mg, 1.8 mmol) and finally methanol. The resulting solution was stirred at room temperature for 6 days. After completion of the reaction the solvent was extracted *in vacuo* and the crude produced was subjected to column chromatography on a silica gel (1:10 – 1:1 ethyl acetate: hexane) to obtain the desired product. Yield 47%, 53.2 mg, 0.2812 mmol.

Synthesis 2



The following compounds were added into a vial in the described sequence: (*S*)-2-(diphenyl (trimethylsilyl) oxy) methyl) pyrroline (10 mol%, 0.1 equiv., 12.3 mg, 0.0378 mmol), cinnamaldehyde (1 equiv., 50 mg, 0.378 mmol), 2-(3-nitropropyl)-1,3-dioxolane (3 equiv., 183 mg, 1.135 mmol), benzoic acid (20% equiv., 9.2 mg, 0.0756 mmol) and dichloromethane (1.5 ml). The resulting solution was stirred at 35 ^{o}C for 12 days. After reaction completion, the reaction was concentrated *in vacuo* and the product was isolated by flash chromatography (1:5 ethyl acetate: hexane). Yield 19%, 21 mg, 0.0716 mmol. (The relative and absolute configuration of two diastereomeres have not been determined).

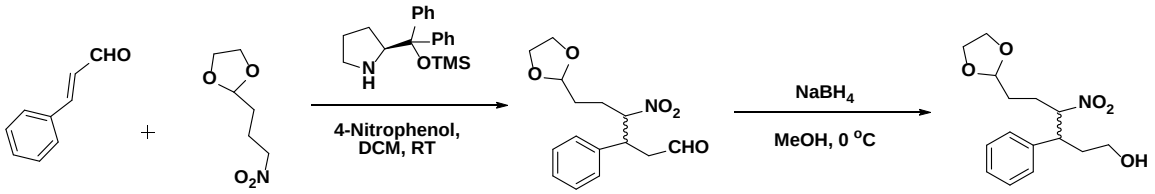
6-(1,3-dioxolan-2-yl)-4-nitro-3-phenylhexanal



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 4.80 (dt, *J* = 8.2, 7.2 Hz, 1H), 4.74 (d, *J* = 3.4 Hz, 1H), 3.87 – 3.68 (m, 6H), 2.71 (dd, *J* = 17.4, 3.4 Hz, 1H), 1.62 – 1.53 (m, 3H).

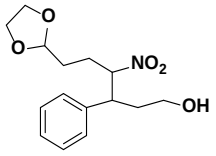
^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (CHO), 137.8 (Cq), 129.3 (2CH), 128.2 (2CH), 103.1 (CH), 92.4 (CH), 64.9 (CH_2), 64.9 (CH_2), 46.4 (CH), 43.7(CH), 29.7 (CH_2), 29.5 (CH_2), 26.0 (CH_2).

Synthesis 3



In a vial (2 ml), 2-(3-nitropropyl)-1,3-dioxolane (3 equiv., 183 mg, 1.1350 mmol), cinnamaldehyde (1 equiv., 50 mg, 0.3780 mmol), (*S*)-2-(diphenyl (trimethylsilyl) oxy) methyl) pyrroline (10% equiv., 12.3 mg, 0.0378 mmol) and 4-nitrophenol (20% equiv., 9.2 mg, 0.0756 mmol) were dissolved in dichloromethane (0.5 ml). The resulting solution was stirred at room temperature for 6 days. After reaction completion the solution was diluted with methanol (1.5 ml), and cooled to 0 °C. $NaBH_4$ (1.5 equiv., 26.4 mg, 0.6990 mmol) was added, and the resulting mixture was stirred for 2 hours at room temperature. The reaction was quenched with a saturated aqueous NH_4Cl solution (2ml), then the mixture was diluted with water (3 ml), extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography using a mixture of hexane/ethyl acetate (7:1 - 2:1). Yield 75%, 103.4 mg, 0.3501 mmol. The diastereomeric ratio was determined from the crude by NMR spectroscopy: 1.5:1.

6-(1,3-dioxolan-2-yl)-4-nitro-3-phenylhexan-1-ol



Diastereomer 1, major:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 4H), 7.25 (d, *J* = 8.2 Hz, 1H), 4.97 (t, *J* = 4.3 Hz, 1H), 4.88 (dt, *J* = 13.7, 5.7 Hz, 1H), 4.08 – 3.97 (m, 2H), 3.95 – 3.87 (m, 2H), 3.66 – 3.57 (m, 1H), 3.43 (dd, *J* = 20.0, 4.1 Hz, 2H), 2.24 – 2.13 (m, 2H), 1.96 (ddd, *J* = 17.9, 11.3, 6.0 Hz, 1H), 1.83 – 1.74 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2 (Cq), 126.7 (2CH), 126.0 (2CH), 125.7 (CH), 101.1 (CH), 91.0 (CH), 62.9 (CH_2), 62.9 (CH_2), 57.8 (CH), 43.9 (CH), 31.9 (CH_2), 27.7 (CH_2), 23.5 (CH_2).

The enantiomeric excess was determined by HPLC using a Chiralpak OZ-H column (hexane/*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 210 nm): t_r (S catalyst) = 30.2 min, t_r (R catalyst) = 24.7 min, 50% (S catalyst)/ 25% (R catalyst) *ee*.

Diastereomer 2, minor:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 – 7.31 (m, 4H), 7.22 (s, 1H), 4.85 (d, *J* = 9.8 Hz, 1H), 4.82 – 4.77 (m, 1H), 3.91 – 3.77 (m, 5H), 3.56 – 3.48 (m, 1H), 3.34 (td, *J* = 10.5 Hz, 4.0 Hz, 2H), 2.03 – 1.83 (m, 3H), 1.69 – 1.56 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.3 (Cq), 129.1 (2CH), 128.3 (2CH), 127.8 (CH), 103.2 (CH), 93.4 (CH), 64.9 (CH_2), 64.9 (CH_2), 59.8 (CH), 46.4 (CH), 35.4 (CH_2), 29.7 (CH_2), 26.3 (CH_2).

The enantiomeric excess for minor diastereomer was determined by HPLC using a Chiralpak OZ-H column (hexane/*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 210 nm): t_r (S catalyst) = 20.3 min, t_r (R catalyst) = 21.0 min, 96% (S catalyst)/ 86% (R catalyst) *ee*.

2.5 Conclusion

Evaluating the results of the presented steps we decided to stop the development of the total synthesis due to low diastereoselectivity and what is more important poor enantioselectivity. As was described at the introduction there are methods developed by other groups which give better results. Admitting our unsuccessful attempt a decision was made to focus attention on a development of new cyclopropanation methodology based on previous successful work within Rios's research group.

Chapter 3: Benzylic activation cyclopropanation of benzylchlorides

3.1 Introduction

Cyclopropane motive is an interesting and valuable synthetic intermediate, especially if functionalised with suitable arrangement between electron-donating and electron-withdrawing groups, then it can undergo different electrophilic, pericyclic or nucleophilic reactions.[69] At the same time the cyclopropane moiety is common in a variety of biologically active compounds and natural products.[70]

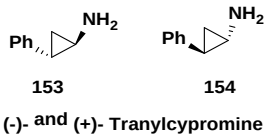


Figure 2 The enantiomers of Tranylcypromine

Compounds containing a cyclopropane fragment have always fascinated organic chemists.[25] A cyclopropane fragment is found in different naturally occurring compounds such as pheromones, unusual amino acids, despite its highly strained configuration.[71][72] This wide variety of cyclopropane-containing compounds has inspired chemists to search for new synthetic methods. Among the biological activities of naturally occurring and synthetic cyclopropane derivatives are: inhibition of enzymes, antifungal, antimicrobial, herbicidal, antitumor and others.[25] For example, cyclopropane functionality is present in anti-HIV agents, the antidepressant tranylcypromine (**Figure 2**),[73] inhibitor of papain, cysteine protease, [74] and Dopa decarboxylase (DDC) (**Figure 3**),[75] marine lactones (**Figure 4**)[76] and potential antipsychotic agents.[77]

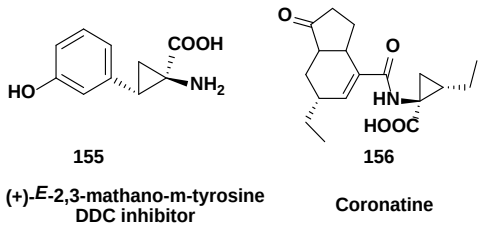
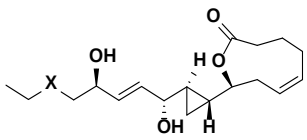


Figure 3 Cyclopropane containing amino-acids

Thousands of compounds containing a cyclopropane fragment have been synthesised and described in literature.[25] A cyclopropane is a highly strained system,[71] which can undergo various synthetically useful ring opening reactions.[25][65] Indeed, all those properties and their

prevalence in nature make the cyclopropane system a very desirable target for the development of new synthetic methodologies.



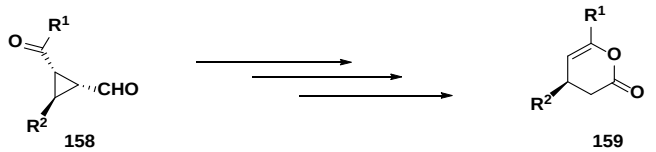
157

X = -CH2CH2- (Halicholactone)
cis-CH=CH- (Neohalocholactone)

Figure 4 Examples of marine lactones containing a cyclopropane fragment

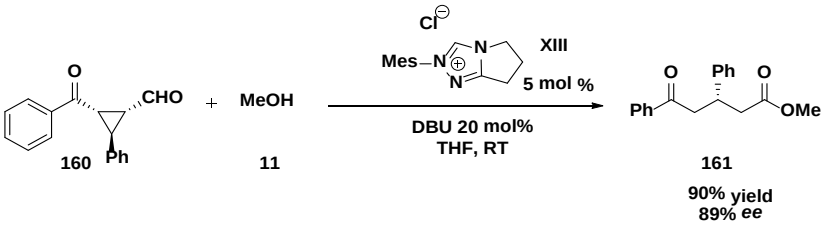
On the other hand cyclopropane subunit is a valuable synthetic building block for synthetic chemists. Comparing cyclopropane moiety, for example with bigger ring systems or their linear counterparts, they are synthetically more useful due to their high π character and angle strain. One of the uses of cyclopropane motives is in ring-opening reactions with following inter- or intramolecular transformations. Herein a few examples of cyclopropane ring-opening reactions are described to demonstrate their synthetic importance.

For example, an *umpolung* reaction useful for manipulation with functional groups. This reaction can be promoted by *N*-heterocyclic carbenes (NHCs) which in the case of cyclopropanes bearing an aldehyde group can act as a catalysts. You etal. developed intramolecular tandem redox lactonization of 2-acyl-1-formylcyclopropanes with NHC catalysts (**Scheme 43**). The desired 3,4-dihydro-*α*-pyrones were formed in moderate and excellent yields.[69]



Scheme 43 NHC-catalysed ring-expansion of formylcyclopropanes reported by You

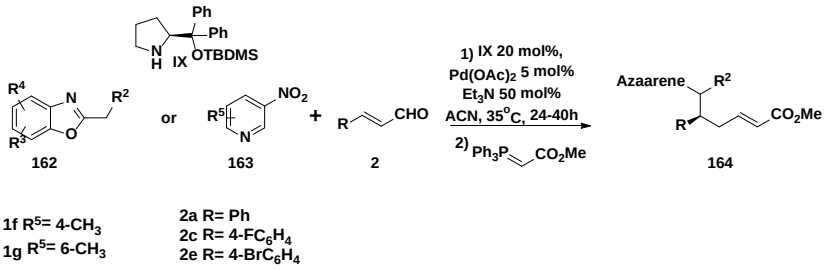
Another example of cyclopropane ring opening reaction can be conversion of chiral formylcyclopropanes to the corresponding acyclic ester under mild conditions using *N*-heterocyclic carbenes. This reaction was developed by Bode and co-workers and one example is presented in **Scheme 44**.[78]



Scheme 44 Cyclopropane ring opening reaction reported by Bode

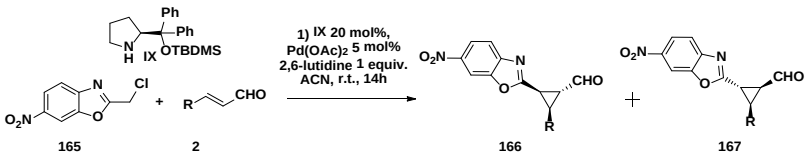
Based on chemical universality and biological activity of compound containing cyclopropane moiety Rios's research group became interested in the development of new organocatalytic cyclopropanation methodologies.

In Rios's research group interested in the activation of benzylic and pseudo-benzylic positions. Previously the research group developed a catalytic stereoselective synthesis of chiral azaarenes (**Scheme 45**) using synergistic catalysis, a simultaneous activation of an electrophile and nucleophile in separate catalytic cycles. The first cycle led to activation of α-carbon of benzoxazole through coordination of the metal Lewis acid to the nitrogen, thus increasing the acidity of α-carbon. In the second cycle an enal was activated with the use of secondary amine catalysis. The nucleophile (benzoxazole) was furnished with an electron-withdrawing group in the benzoxazole ring to increase the acidity of the α-CH, thereby increasing reactivity.[43]



Scheme 45 Addition of aza-arenes to enals

Shortly after, the possibility to access cyclopropane was investigated by Marta Meazza (**Scheme 46**).[79] The activation of alkylbenzoxazole **165** was performed with the metal Lewis acid activation mentioned earlier. Moreover, the use of synergistic catalysis led to the desired products (**166** and **167**) in good yields and enantioselectivity. An isolated major diastereomer has a cis configuration between the benzoxazole and the aromatic ring.[79]



R: Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 2-BrC_6H_4, 4-CNC_6H_4, 4-FC_6H_4, Me, CO_2Et

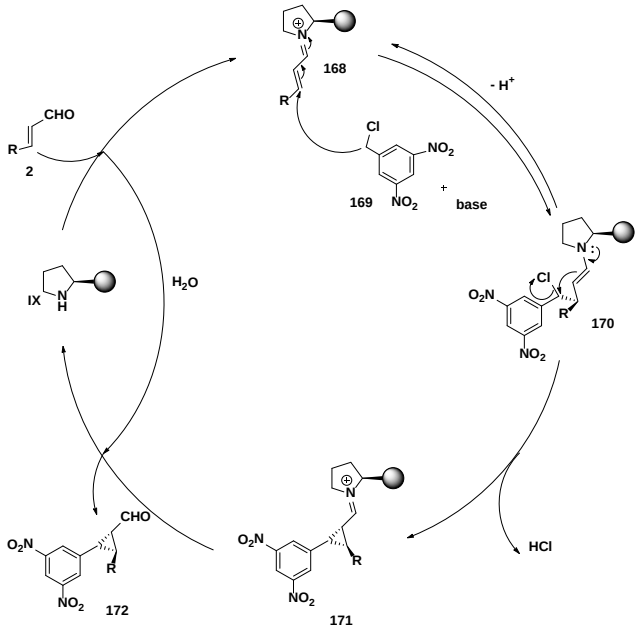
Scheme 46 Enantioselective cis cyclopropanation of enals

3.2 Project aims

Taking into account previous research done in Rios's research group and being interested in studying the activation of "pure" benzylic positions, it was envisioned a possibility to use another approach which could lead to easy access to cyclopropanes via Michael addition-*α*- alkylation cascade using benzylhalides and enals.

3.3 Research hypothesis

The benzylhalides need to be decorated with several electron withdrawing groups on the aryl ring which after deprotonation will give a suitable nucleophile. As a result of increased acidity of benzylic hydrogens, the use of a weak base is needed to initiate a cascade reaction with the electrophile. The reaction driving force which leads to synthesis of benzylic cyclopropanes will be an irreversible intramolecular alkylation. The possibility of using aryl methane derivatives, usually known as poor nucleophiles, in organocatalytic Michael addition to α,β-unsaturated aldehydes was reported by Wang.[80] The dramatic increase of their nucleophilicity was achieved through the introduction of two nitro groups in ortho- and/or para- positions on the aromatic ring, which created strong resonance and electro-induction effects. The choice of nitro group allows their further transformations to other functional groups, for example, reduction. Although benzyl chlorides are generally considered as electrophiles, it could be possible to use them as nucleophiles by decorating them with strong electron withdrawing groups, such as $–NO_2$, in combination with a weak base.

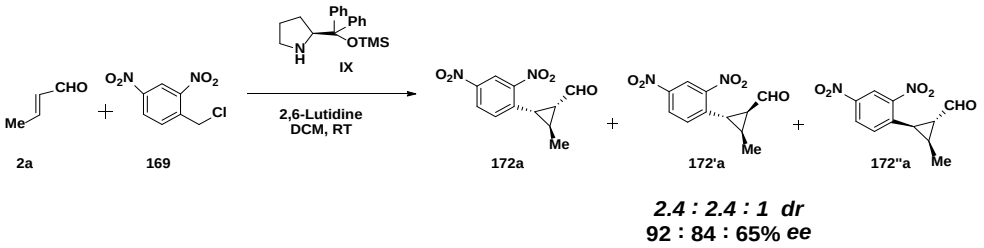


Scheme 47 Mechanism of the cyclopropanation

The mechanism of the reaction starts with an organocatalytic enal (**2**) activation (**Scheme 47**). The catalyst (**IX**), in this case *S*, forms an iminium ion with α,β-unsaturated aldehyde. The bulkier group of the catalyst is shielding one face of the enal directing the nucleophilic attack on the iminium (**168**) at this stage. The addition of nucleophile (**169**) via Michael addition, is followed by an intramolecular reaction of enamine (**170**) with the alkyl halide in the 3-exo-tet cyclisation to form the cyclopropane ring in the compound **171**. After the hydrolysis of **171** the product **172** is achieved with a simultaneous release of the catalyst, thereby completing the catalytic cycle.

3.4 Results and discussion

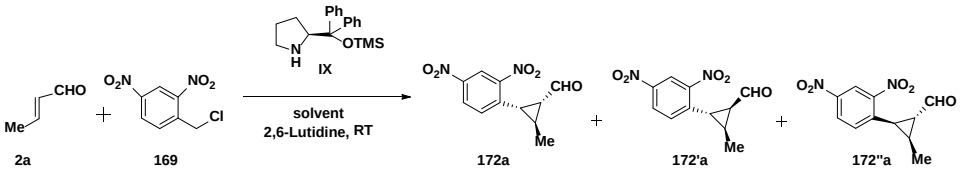
To test the hypothesis, crotonaldehyde and 2,4-dinitrobenzyl chloride were chosen because of their commercial accessibility and reactivity. The first trial conditions are presented in **Scheme 48**. The reaction proceeded forming three diastereomers but did not go to completion. Two diastereomers were separated in low yield (47%, 11 mg total weight of both diastereomers together) but with good enantioselectivity (92% *ee* for first (major) diastereomer, 84% *ee* for second diastereomer, 65% *ee* for the third diastereomer). The success of the first attempt motivated us to develop optimal reaction conditions through the trial of different solvents, bases, catalysts and temperatures.



Scheme 48 Trial conditions for the cyclopropanation

Screening of solvents

Following confirmation that the reaction was successful the need to find optimal conditions was identified. For this purpose, a reaction between 2,4-dinitrobenzyl chloride and crotonaldehyde was chosen for solvent screening (**Scheme 49**). The product structure was determined by NOESY NMR.



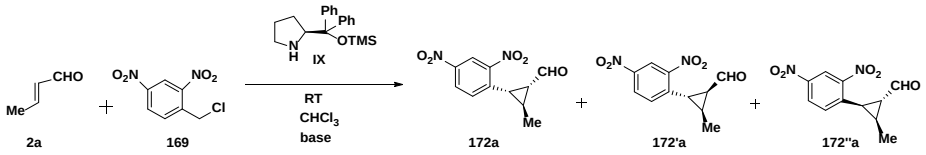
Scheme 49 Reaction used for the screening of solvents

Chloroform was identified as the best solvent due to good diastereoselectivity and enantioselectivity data (Entry 1, **Table 1**).

Table 1 Solvent screening.

Entry	Solvent	*d.r.* 172a : 172'a : 172''a	*ee*, % 172a : 172'a : 172''a	Conversion, %			
				21h	1d	2d	6d
1	Chloroform	4 : 2 : 1	99/77/67	47	-	57	71
2	Toluene	7 : 8 : 1	94/87/40	29	-	42	n/a
3	Acetonitrile	2 : 2 : 1	93/74/76	36	-	43	n/a
4	DMSO	-	-	-	none	n/a	n/a
5	Dichloromethane	2.4 : 2.4 : 1	92/84/65	-	62	n/a	n/a

The long reaction time highlighted a need for further modernisation. It is very important to mention that the reaction was conducted in the dark, using aluminium foil to avoid light. As in light the Cl-dinitrobenzyl compounds form a radical species, as shown by Melchiorre[81] and MacMillan.[82]



Scheme 50 Screening of bases

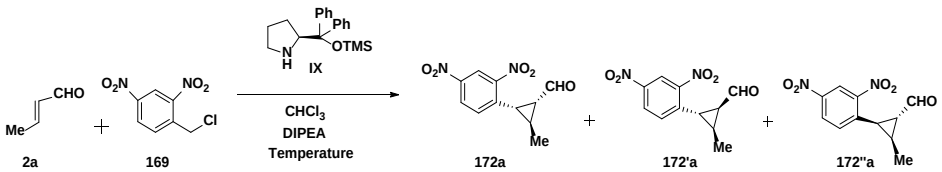
Screening of bases

The next step was to find an optimal base (**Table 2**). We checked three organic and one inorganic base. As was shown in a similar cyclopropanation the presence of a base is crucial for trapping HCl which forms as a by-product in the reaction. The reaction was checked after one day. The reaction conditions are presented in the **Scheme 50**. All the bases tested showed good results. However, reaction with DIPEA caused no side product to be formed as well as full conversion (Entry 3, **Table 2**). The bad result with potassium carbonate (Entry 4, **Table 2**) can be explained by low solubility of the latter in organic solvents, as potassium or sodium acetate might have been a better choice.

Table 2 Screening of bases

Entry	**Base**	***d.r.*** **172a : 172'a : 172''a**	***ee*, %** **172a : 172'a : 172''a**	**Conversion, %** **1d**
1	2,6-Lutidine	4 : 2 : 1	98/92/69	54
2	Trimethylamine	3 : 2 : 1	99/82/69	71
3	*N,N*-Diisopropylethylamine	3 : 2 : 1	99/77/ 71	100
4	Potassium Carbonate	3 : 2 : 1	99/91/71	72

Temperatures screening

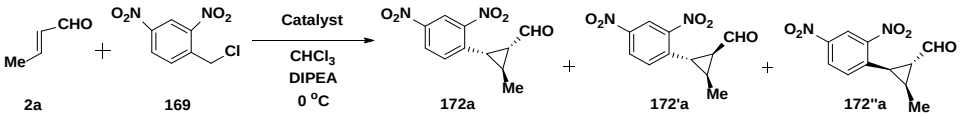


Scheme 51 Screening of temperature

The next step was the screening of temperatures (**Scheme 51**). We found that at 0 °C the stereoselectivity can be increased without the loss of activity. Running the reaction at -20 °C didn't give significant improvements and the results were similar to those achieved at 0 °C (Entry 2 and 3, **Table 3**). For that reason 0 °C was chosen to be the optimal temperature as it can be achieved and controlled easier then -20 °C.

Table 3 Screening of temperatures

Entry	Temperature	*d.r.* **172a : 172'a : 172''a**	*ee*, % **172a : 172'a : 172''a**	Conversion, %
1	RT	3 : 2 : 1	99/77/71	100%, after 3h
2	0 °C	3 : 2.5 : 1	99/81/66	100%, (3h)
3	-20 °C	2 : 2.5 : 1	99/82/40	100%, (3h)



Scheme 52 Catalysts screening

<u>Screening of catalysts</u>

The following step was a screening of different catalysts (**Scheme 52**). We found that proline gave an excellent conversion; unfortunately it was accompanied by poor enantioselectivities (entry 1, **Table 4**). To our surprise there was no real reaction with MacMillan second generation catalyst (entry 3, **Table 4**) with only slight traces of the final products observed.

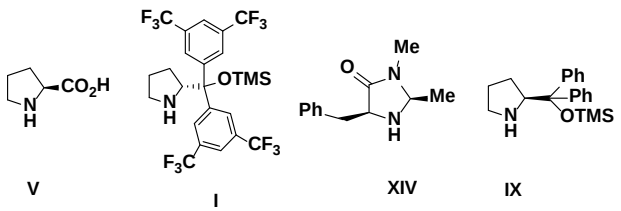
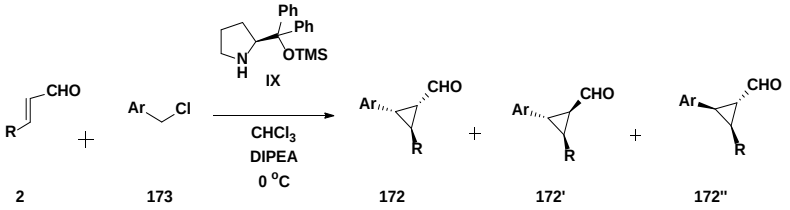


Figure 5 Catalysts used for screening

Table 4 Catalyst screening

Entry	Catalyst	*d.r.* 172a : 172'a : 172''a	*ee*, % 172a : 172'a : 172''a	Conversion, %
1	**V**	2 : 2 : 1	59/44/21	100%
2	**I**	2.4 : 2.2 : 1	99/71/32	27%
3	**XIV**	_	-	none
4	**IX**	3 : 2.5 : 1	99/81/66	100% (3h)

To conclude, we checked several variables affecting the reaction and found that the following conditions were the best: chloroform as solvent at 0 °C, catalyst **IX** (**Figure 5**), DIPEA as a base.

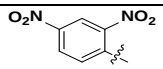
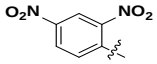
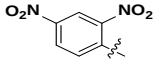
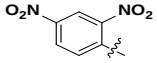
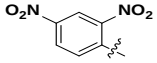
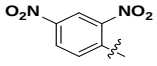
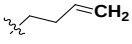
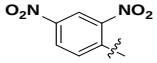
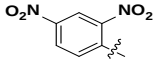
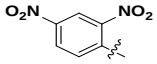
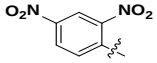
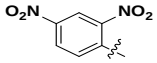
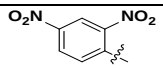
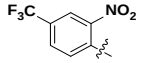
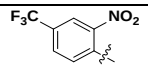
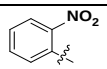
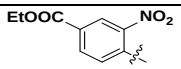


Scheme 53 Scope of the cyclopropanation

Having optimised the reaction conditions we focused our attention on study of the reaction scope (**Scheme 53**). The results of which are presented in **Table 5**.

We tested a range of aromatic and aliphatic α,β-unsaturated aldehydes as well as expanding a diversity of strong electron-withdrawing groups in the aromatic ring of benzyl chlorides. In the case of reaction between benzyl chloride **167** and aliphatic enals the desired products were obtained in high yields (up to 99%), good diastereo- and enanteoselectivities for the major product (entry 1-6, **Table 5**). In addition, we explored the influence of the electronic properties of the substituents present on the aromatic ring of α,β-unsaturated aldehydes on both reactivity and selectivity of the reaction. It was found that the presence of an electron donating group, such as –Me group, led to better diastereoselectivity in comparison with strong electron withdrawing groups, for example –CN and $–NO_2$ groups (entry 10-12, **Table 5**).

Table 5 Results of the optimised cyclopropanation reaction

Entry	Ar	R, 2a – 2k	Product	Total yield[1], %	*dr*[2] 172 : 172' : 172''	*ee*, % 172 : 172' : 172''
1		Me **2a**	**172a**	61	3 : 2.5 : 1	98:73:60
2		Et **2b**	**172b**	68	3 : 2 : 1	99:96:nd
3		*n*-Pr **2c**	**172c**	82	4 : 2 : 1	99:93:54
4		*n*-C_7H_{15} **2d**	**172d**	99	6 : 2 : 1	96:92:56
5		CO_2Et **2e**	**172e**	56	1 : 1 : 1	76:43:80
6		 **2f**[3]	**172f**	66	5 : 1.5 : 1	99.8:92:67
7		Ph **2g**	**172g**	78	3 : 2 : 1	97:94:96
8		4-Cl-C_6H_4 **2h**	**172h**	86	2 : 1.3 : 1	99:96:97
9[4]		4-Br-C_6H_4 **2i**	**172i**	71	2 : 2 : 1	99:94:98
10		4-CN-C_6H_4 **2j**	**172j**	80	2 : 2 : 1	86:62:nd
11		4-NO_2-C_6H_4 **2k**	**172k**	67	6 : 3 : 1	99:96:nd
12		4-Me-C_6H_4 **2l**	**172l**	80	13 : 12 : 1	98:85:96
13*		Ph **2g**	**172m**	47	2 : 1.5 : 1	99:96:90
14*		4-NO_2-C_6H_4 **2k**	**172n**	52	4 : 2 : 1	85:74:79
15		Ph **2g**	**172o**	-	-	-
16		Ph **2g**	**172p**	traces	-	-

[1] The total isolated yield of three diastereomers

[2] An NMR spectroscopy of a crude was used to determine diastereomeric ratio

[3] Enal was made by Shin and Yang (PhD students from Sungkyunkwan University, Suwon, Korea)

[4] Reaction was completed by PhD student Marta Meazza

* Reaction was done at 60 °C

Moreover, in order to expand a scope of substrates, benzyl chlorides with different nature of the substituents on the aromatic ring were checked. It was found that the presence of only one electron withdrawing group does not help to activate the benzylic proton enough for reaction to occur (entry 15, **Table 5**). The presence of weaker electron withdrawing group (-CF_3) required a change in the reaction conditions. This resulted in increase of the reaction temperature and the desired cyclopropanes being obtained in good yields and diastereoselectivity, with moderate and excellent enantioselectivity (entry 13-14, **Table 5**). Moderately strong EWG (-COOEt) led only to formation of traces of cyclopropane in the crude mixture (entry 16, **Table 5**). Introduction of a halogen substituent on the aromatic ring of the aldehyde resulted in the similar diastereoselectivity and enantioselectivity (entry 8-9, **Table 5**).

3.5 Determination of absolute and relative configurations

The absolute configuration of major diastereomer was determined by single crystal X-ray diffraction analysis of **172k** and **172i** (**Figure 6**, **Figure 10**).

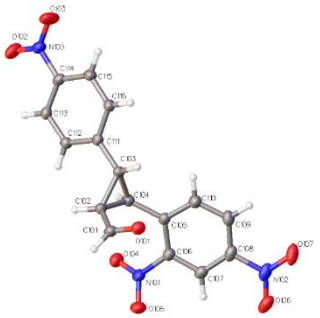


Figure 6 X-ray structure of **172k** major diastereomer made with *R*-catalyst

The relative configuration of the other diastereomers was ascertained by ^{1}HNMR analysis of the isolated compounds **172d, 172'd** and **172''d**. (The NMR data were collected using deuterated acetonitrile). However, all NMR data used for routine characterisation of cyclopropanes were done using $CDCl_3$ and acquired on Bruker 400 MHz NMR spectrometer. The coupling constants reported for both solvents does not much each other. This inconsistency in the data might be explained through solvent dependence of coupling constant. Several theories were developed other the years to explain that phenomenon. For example, one of the most frequently cited explanations is intermolecular interactions between solute and solvent molecules (such as electrostatic effects) as observed changes often correlate with some function of the dielectric

constant of the latter.[83–87] More information on solvent dependence of coupling constants can be found in a review published by Barfield and Johnston.[85]

In cyclopropanes dihedral angles are rigidly fixed by the geometry of the ring system. Based on the Karplus or Bother-By equation we can determine the size of the coupling constant based on the dihedral angle between the two coupled hydrogens. As shown in **Figure 7**, we can determine the intensity of the coupling constants of all the possible diastereomers of the reaction.

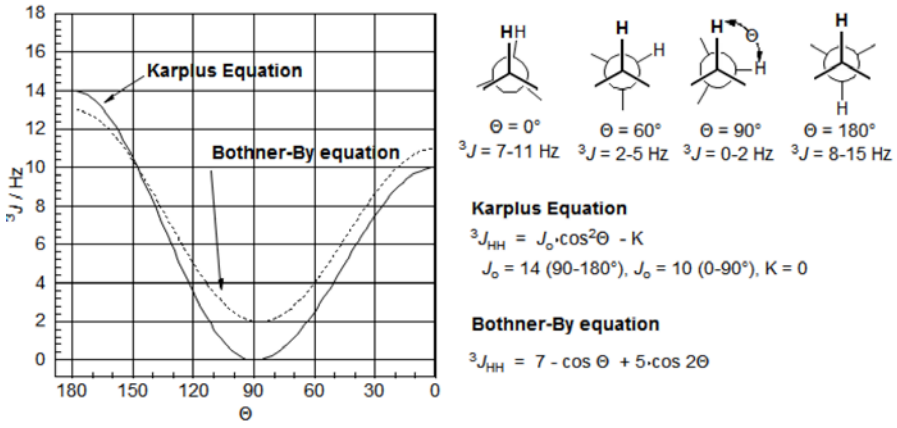


Figure 7 Karplus and Bother-By equations[5]

Based on this, we analysed the ^{1}H NMR of each diastereomer. In all the compounds the most deshielded hydrogen will be H_7, and the most shielded will be H_8. In the spectra of the major diastereomer we can determine the following coupling constants: H_9-H_8 4.9Hz, H_9-H_7 9Hz, H_8-H_7 7.5 Hz, that correspond to the X-Ray structure.[5]

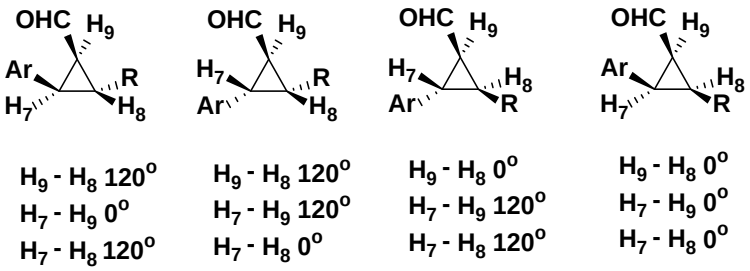
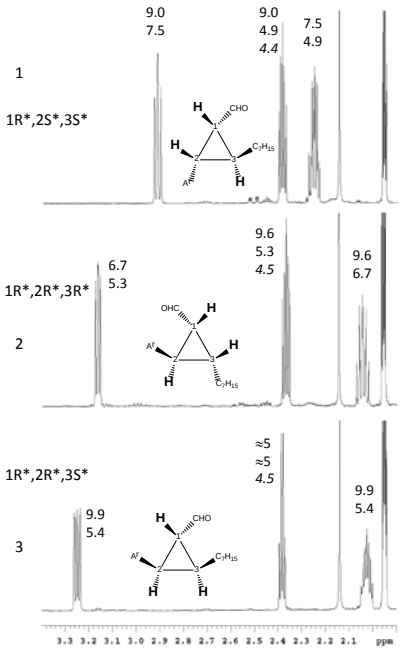


Figure 8 Dihedral angles for each possible diastereomer of cyclopropane[3]

In the second diastereomer, the coupling constants are: H_9-H_8 9.6, H_9-H_7 5.3Hz, H_8-H_7 6.7 Hz. That indicates a *cis* relationship between H_9 and H_8 (0° big coupling constant) and a *trans* relationship between H_7 and H_9 or H_8 (120° smaller coupling constant). In the minor diastereomer, the coupling constants are: H_9-H_8 5.4, H_9-H_7 5.4Hz, H_8-H_7 9.9 Hz. That indicates a *cis* relationship between H_7 and H_8 (0° big coupling constant) and a *trans* relationship between H_9 and H_7 or H_8 (120° smaller coupling constant); as summarized in **Figure 8** and **Figure 9**.[5]



J value H_3- C_7H_{15} omitted. Italics indicates couplings with CHO

Figure 9 Summarised J values for all three diastereomers (600 MHz in CD_3CN)[5]

In order to determine the absolute configuration of the compound **172'g** and at the same time to demonstrate the possible application of the developed methodology to a synthesis of synthetically interesting compounds, we investigated a ring-opening for compounds **172g** and **172'g**. As mentioned in the introduction, cyclopropanes are important intermediates for different types of synthetic transformations, one of which is ring-opening reaction giving access to a range of interesting products.

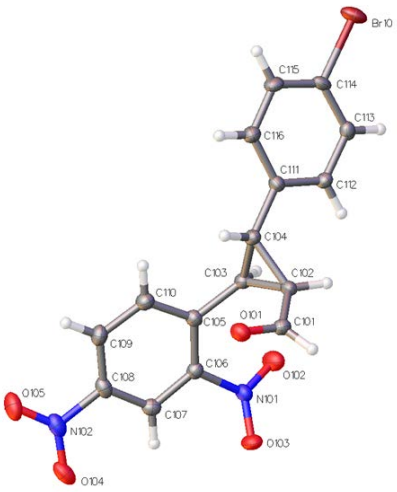
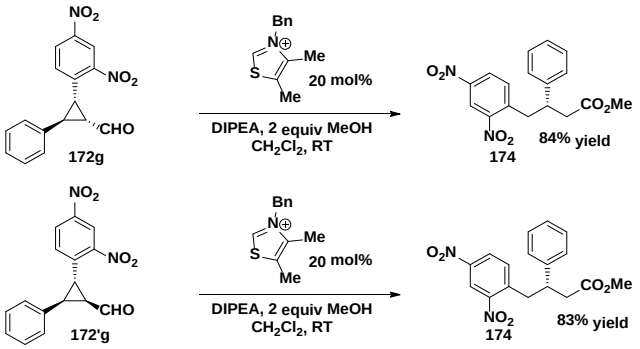


Figure 10 X-ray structure of **172i** major diastereomer made with *S*-catalyst

[5] NMR spectra for determination of relative configuration were completed by Dr Andrea Mazzanti, University of Bologna

A ring opening reaction was done using NHC X as a catalysts in methanol for compounds **172g** and **172'g**. The reaction went with totally regioselective control giving the desired product (**Scheme 54**)[6]. Then we compared the optical rotation for products of both ring-opening reactions and to our delight found that it was the same, confirming the absolute configuration of the compound **174**.



Scheme 54 A ring opening-reaction performed by Shin and Yang[7]

This reaction represents the first example, to the best of our knowledge, of totally regioselective ring opening of formyl cyclopropanes bearing two different aryl groups. At the same time it is a nice alternative to the addition of α,β-unsaturated esters to benzyl compounds affording final products in good yields and excellent enantioselectivities.

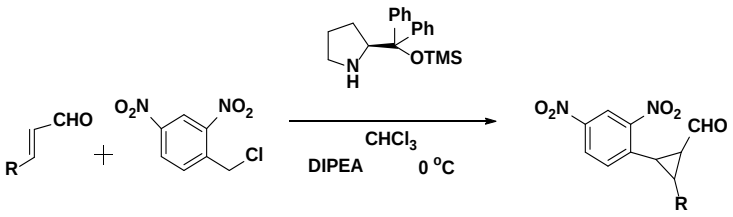
3.6 Conclusion

In summary, we developed a new methodology to access cyclopropane moiety in good to excellent yields, and with moderate diastereoselectivity and excellent enantioselectivity. The presented method benefits from the wide range of the α,β-unsaturated aldehydes used. However, benzylic compounds furnished with less electron withdrawing groups or less strong electron withdrawing groups did not exhibit a good reactivity for the reactions as the benzylic position was not well activated.

[6]The reaction for determination of the absolute configuration of the compound **172g** was done by Shin and Yang
[7] PhD student at the Department of Energy Science, Sungkyunkwan University, Suwon, Korea

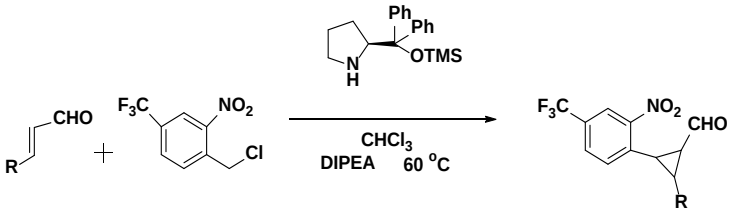
Chapter 4: Experimental data for cyclopropanation

General procedure 1



In a vial, were added (*S*)-α,α-diphenylprolinol trimethylsilyl ether (20 mol%, 0.2 equiv., 30 mg, 0.0923 mmol) and 2,4-dinitrobenzylchloryde (1 equiv., 100 mg, 0.4617 mmol) were dissolved in chloroform (1 ml). The vial was covered with aluminium foil and the resulting solution was cooled to 0 °C. After 15 minutes, the enal (2 equiv., 1.8468 mmol) and the base *N,N*-diisopropylethylamine (1.1 equiv., 66 mg, 0.5079 mmol) were added. The resulting solution was stirred at 0 °C for 3 hours. After the reaction was completed, the crude was purified by flash column chromatography (Hexane/EtOAc) to obtain the desired cyclopropane.

General procedure 2

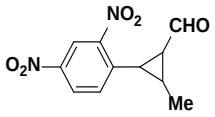


In a vial, were added (*S*)-α,α-diphenylprolinol trimethylsilyl ether (20% equiv., 27 mg, 0.084 mmol) and 2-nitro-4-(trifluoromethyl)benzylchloride (1 equiv., 100 mg, 0.417 mmol) were dissolved in chloroform (1 ml). The vial was covered with aluminium foil and then the enal (2 equiv., 1.668 mmol) and the base *N,N*-diisopropylethylamine (1.1 equiv., 59 mg, 0.459 mmol) were added. The resulting solution was stirred at 60 °C for 24 hours. After the reaction was completed, the crude was purified by flash column chromatography (Hexane/EtOAc) to obtain the desired cyclopropane.

Notes:

- Thin layer chromatography (TLC) was performed using Merck TLC Silicagel 60 F_{254}. Product spots were visualized by UV-light at 254 nm.
- Column chromatography was done using silica gel (Geduran Si60, 40-63µm).
- Infra-red spectra were recorded on Nicolet 280 FT-IR; the IR analyses were performed as a liquid IR with the compounds dissolved in $CHCl_3$.
- ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, DEPT were recorded with a Bruker DPX400 NMR. Chemical shifts (σ/ppm) are given relative to the residual peak of the NMR solvent ($CDCl_3$: σ_H = 7.26 ppm, σ_C = 77.16 ppm).
- High resolution mass spectra were recorded using a MaXis (Bruker daltonics, Bremen, Germany) mass spectrometer equipped with a Time of Flight (TOF) analyser.
- Chiral HPLC was performed with an LCP 5020 Ignos liquid chromatography pump with an LCD 5000 spectrophotometric detector with Daicel Chiralpak® columns also with Perkin Elmer HPLC with Daicel Chiralpak® columns.

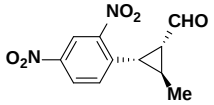
2-(2,4-Dinitrophenyl)-3-methylcyclopropane-1-carbaldehyde (172a)



The reaction was performed following the general procedure **1**. The crude was purified by column chromatography 1:10 (hexane/ EtOAc) to obtain 70 mg of the desired product. The product consists of three diasteriomers where the first diastereomer was isolated as yellow oil. Yield: 61%. The diastereomeric ratio was determined by NMR of the crude: 3:2.5:1.

Diastereomer 1, major:

(1*R*,2*S*,3*S*)-2-(2,4-dinitrophenyl)-3-methylcyclopropane-1-carbaldehyde



IR: 3105 (C-H stretch aromatic), 2866 (C-H stretch aldehyde), 1702 (C=O stretch aldehyde), 1604, 1530 (aromatic NO_2), 1461, 1346 (aromatic NO_2), 1152, 1087, 1044, 938, 909, 854, 835, 737 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.43 (d, *J* = 2.8 Hz, 1H), 8.71 (d, *J* = 2.3 Hz, 1H), 8.36 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 2.86 (dd, *J* = 8.1, 8.0 Hz, 1H), 2.46 (ddd, *J* = 8.0, 4.8, 2.8 Hz, 1H), 2.18 (dd, *J* = 8.0, 4.8 Hz, 1H), 1.38 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.1 (CHO), 150.1 (Cq), 146.8 (Cq), 138.8 (Cq), 133.6 (CH), 126.7 (CH), 119.9 (CH), 38.0 (CH), 34.2 (CH), 24.2 (CH), 17.5 (CH_3).

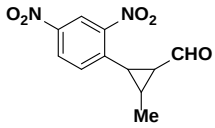
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 21.4 min., t_r (*R* catalyst used) = 24.6 min., 98% (*S* catalyst used) *ee*.

$[\alpha]_D^{26}$ = - 90.8° (c = 0.6, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{26}$ = 49.5° (c = 1.1, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{11}H_{10}N_2O_5$ $[M+Na]^+$: 273.0482, found: 273.0480.

<u>Mixture of two minor diastereomers</u>:



IR: 3105 (C-H stretch aromatic), 2866 (C-H stretch aldehyde), 1702 (C=O stretch aldehyde), 1604, 1530 (aromatic NO_2), 1461, 1346 (aromatic NO_2), 1152, 1087, 1044, 938, 909, 854, 835, 737 cm^{-1}

Minor 1 (**172'a**) diastereomer – H'; minor 2 (**172''a**) diastereomer – H.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.69 (d, *J* = 3.9 Hz, 1H'), 9.45 (d, *J* = 4.2 Hz, 1H), 8.82 (d, *J* = 2.3 Hz, 1H), 8.76 (d, *J* = 2.3 Hz, 1H'), 8.41 (dd, *J* = 8.5, 2.3 Hz, 1H), 8.36 (dd, *J* = 8.6, 2.3 Hz, 1H'), 7.59 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 1H'), 3.28 (dd, *J* = 9.8, 5.5 Hz, 1H), 3.18 (dd, *J* = 6.2, 5.9 Hz, 1H'), 2.36 (ddd, *J* = 9.2, 5.5, 4.1 Hz, 1H), 2.20 – 2.14 (m, 1H), 2.11 (ddd, *J* = 8.6, 5.9, 3.9 Hz, 1H'), 1.96 – 1.84 (m, 1H'), 1.43 (d, *J* = 6.3 Hz, 3H'), 0.88 (d, *J* = 6.2 Hz, 3H).

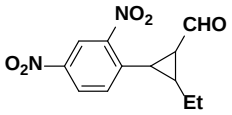
Minor1 – C'; minor2 – C.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.3 (CHO), 197.9 (C'HO), 150.1 (Cq), 146.6 (Cq'), 141.3 (Cq'), 138.2 (Cq'), 134.7 (Cq), 133.2 (CH), 131.2 (Cq), 130.0 (C'H), 127.2 (C'H), 127.0 (CH), 120.3 (CH), 120.3 (C'H), 37.2 (CH), 36.4 (C'H), 29.8 (C'H), 29.6 (CH), 27.5 (C'H), 23.8 (CH), 12.9 (CH_3), 12.7 ($C'H_3$).

The enantiomeric excess of product **172'a** was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 29.7 min., t_r (*R* catalyst used) = 27.3 min., 73% (*S* catalyst used) *ee*.

The enantiomeric excess of product **172''a** was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 43.4 min., t_r (*R* catalyst used) = 37.0 min., 60% (*S* catalyst used) *ee*.

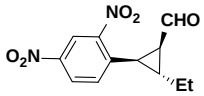
2-(2,4-Dinitrophenyl)-3-ethylcyclopropane-1-carbaldehyde (172b)



The reaction was performed following the general procedure **1**. The crude was purified by column chromatography 1:10 (hexane/ EtOAc) to obtain 83.3 mg of the desired product as yellow oil. Yield: 68%. The diastereomeric ratio was determined by NMR of the crude: 3:2:1.

<u>Diastereomer 1, major:</u>

(1*S*,2*R*,3*R*)-2-(2,4-dinitrophenyl)-3-ethylcyclopropane-1-carbaldehyde



IR: 3099 (C-H stretch aromatic), 2853 (C-H stretch aldehyde), 1701 (C=O stretch aldehyde), 1605, 1530 (aromatic NO_2), 1463, 1346 (aromatic NO_2), 1150, 1067, 991, 907, 835, 738 cm^{-1}

^1H NMR (400 MHz, CDCl3) δ = 9.45 (d, *J* = 2.7 Hz, 1H), 8.72 (d, *J* = 2.3 Hz, 1H), 8.37 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 2.88 (dd, *J* = 8.2, 8.0 Hz, 1H), 2.49 (ddd, *J* = 8.0, 4.9, 2.7 Hz, 1H), 2.19 – 2.11 (m, 1H), 1.72 – 1.54 (m, 1H), 1.09 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 198.0 (CHO), 150.1 (Cq), 146.8 (Cq), 139.0 (Cq), 133.6 (CH), 126.8 (CH), 119.9 (CH), 36.8 (CH), 33.1 (CH), 31.6 (CH), 25.6 (CH_2), 13.0 (CH_3).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): 99% *ee*.

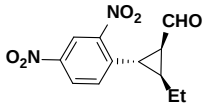
$[\alpha]_D^{21}$ = -61.9° (c = 1.2, CHCl3) (***S* catalyst used**)

$[\alpha]_D^{21}$ = 58.9° (c = 1.3, CHCl3) (***R* catalyst used**)

HRMS (ESI+) Exact mass calculated for $C_{12}H_{12}N_2O_5$ [M+Na]+: 287.0638, found: 287.0634.

Diastereomer 2, minor:

(1*S*,2*S*,3*S*)-2-(2,4-dinitrophenyl)-3-ethylcyclopropane-1-carbaldehyde



IR: 3099 (C-H stretch aromatic), 2853 (C-H stretch aldehyde), 1701 (C=O stretch aldehyde), 1605, 1530 (aromatic NO_2), 1463, 1346 (aromatic NO_2), 1150, 1067, 991, 907, 835, 738 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.66 (d, *J* = 4.0 Hz, 1H), 8.75 (d, *J* = 2.3 Hz, 1H), 8.36 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 3.24 (dd, *J* = 5.9, 5.8 Hz, 1H), 2.33 (ddd, *J* = 9.1, 4.9, 4.2 Hz, 1H), 1.87 (ddt, *J* = 13.7, 8.9, 6.8 Hz, 2H), 1.72 – 1.62 (m, 1H), 1.02 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.6 (CHO), 150.1 (Cq), 146.5 (Cq), 141.4 (Cq), 129.9 (CH), 127.2 (CH), 120.3 (CH), 36.4 (CH), 35.3 (CH), 29.0 (CH), 20.9 (CH_2), 13.9 (CH_3).

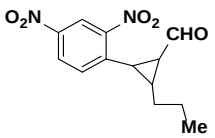
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/iPrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): 96% *ee*.

$[\alpha]_D^{21}$ = 27.6° (c = 0.5, $CHCl_3$) **(*S* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{12}H_{12}N_2O_5$ $[M+Na]^+$: 287.0638, found: 287.0640.

Diastereomer 3 minor hasn't been separated.

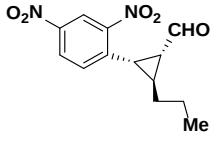
2-(2,4-Dinitrophenyl)-3-propylcyclopropane-1-carbaldehyde (172c)



The reaction was performed following the general procedure **1**. The crude was purified by column chromatography 1:7 (hexane/ EtOAc) to obtain 105 mg of the desired product as yellow oil. Yield: 82%. The diastereomeric ratio was determined by NMR of the crude: 4:2:1.

Diastereomer 1, major:

(1*R*,2*S*,3*S*)-2-(2,4-dinitrophenyl)-3-propylcyclopropane-1-carbaldehyde



IR: 3097 (C-H stretch aromatic), 2960 (C-H ctretch alkyl), 2873 (C-H stretch aldehyde), 1701 (C=O stretch aldehyde), 1604, 1530 (aromatic NO_2), 1465, 1346 (aromatic NO_2), 1151, 1067, 1001, 912, 835, 738 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.44 (d, *J* = 2.7 Hz, 1H), 8.71 (d, *J* = 2.2 Hz, 1H), 8.37 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 2.88 (dd, *J* = 8.1, 7.9 Hz, 1H), 2.48 (ddd, *J* = 7.9, 4.9, 2.9 Hz, 1H), 2.22 – 2.14 (m, 1H), 1.62 – 1.48 (m, 4H), 0.97 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.0 (CHO), 150.1 (Cq), 146.8 (Cq), 139 (Cq), 133.5 (CH), 126.8 (CH), 119.9 (CH), 37.0 (CH), 34.4 (CH_2), 33.2 (CH), 29.7 (CH), 22.1 (CH_2), 13.8 (CH_3).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 15.1 min., t_r (*R* catalyst used) = 16.2 min., 93% (*S* catalyst used)/ 99% (*R* catalyst used) *ee*.

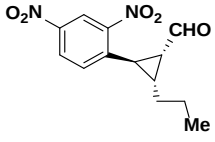
$[\alpha]_D^{21}$ = - 106.5° (c = 0.9, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{21}$ = 104.3° (c = 0.9, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{13}H_{14}N_2O_5$ $[M+Na]^+$: 301.0824, found: 301.0792.

Diastereomer 2, minor:

(1*R*,2*R*,3*R*)-2-(2,4-dinitrophenyl)-3-propylcyclopropane-1-carbaldehyde



IR: 3097 (C-H stretch aromatic), 2960 (C-H stretch alkyl), 2873 (C-H stretch aldehyde), 1701 (C=O stretch aldehyde), 1604, 1530 (aromatic NO_2), 1465, 1346 (aromatic NO_2), 1151, 1067, 1001, 912, 835, 738 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.65 (d, *J* = 4.1 Hz, 1H), 8.75 (d, *J* = 2.2 Hz, 1H), 8.36 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 3.23 (dd, *J* = 5.9, 5.8 Hz, 1H), 2.33 (ddd, *J* = 9.2, 5.9, 4.2 Hz, 1H), 1.94-1.77 (m, 2H), 1.69 – 1.57 (m, 1H), 1.51 – 1.33 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.7 (CHO), 150.1 (Cq), 146.5 (Cq), 141.4 (Cq), 129.8 (CH), 127.2 (CH), 120.3 (CH), 36.4 (CH), 33.3 (CH), 29.4 (CH_2), 28.9 (CH), 22.8 (CH_2), 13.7 (CH_3).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 30.6 min., t_r (*R* catalyst used) = 24.4 min., 93% (*S* catalyst used)/ 93% (*R* catalyst used) *ee*.

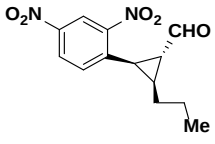
$[\alpha]_D^{21}$ = 83.4° (c = 0.7, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{21}$ = -77.8° (c = 0.6, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{13}H_{14}N_2O_5$ $[M+Na]^+$: 301.0795, found: 301.0792.

Diastereomer 3, minor':

(1*R*,2*R*,3*S*)-2-(2,4-dinitrophenyl)-3-propylcyclopropane-1-carbaldehyde



IR: 3099 (C-H stretch aromatic), 2960 (C-H stretch alkyl), 2873 (C-H stretch aldehyde), 1701 (C=O stretch aldehyde), 1604, 1530 (aromatic NO_2), 1465, 1346 (aromatic NO_2), 1151, 1067, 1001, 912, 835, 738 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.43 (d, *J* = 4.4 Hz, 1H), 8.82 (d, *J* = 2.1 Hz, 1H), 8.40 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 3.33 (dd, *J* = 9.6, 4.6 Hz, 1H), 2.22 (dd, *J* = 9.6, 4.6 Hz, 1H), 2.07 (ddd, *J* = 14.1, 9.4, 4.3 Hz, 1H), 1.39 – 1.26 (m, 4H), 0.80 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.2 (CHO), 150.7 (Cq), 147 (Cq), 138.4 (Cq), 132.8 (CH), 127 (CH), 120.4 (CH), 36.3 (CH), 29.9 (CH_2), 29.5 (CH), 29.1 (CH), 22.0 (CH_2), 13.6 (CH_3).

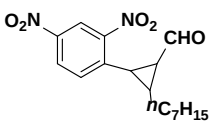
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 18.4 min., t_r (*R* catalyst used) = 31.1 min., 55% (*S* catalyst used)/ 54% (*R* catalyst used) *ee*.

$[\alpha]_D^{21}$ = - 116.5° (c = 0.2, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{21}$ = 130.8° (c = 0.2, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{13}H_{14}N_2O_5$ $[M+Na]^+$: 301.0795, found: 301.0796.

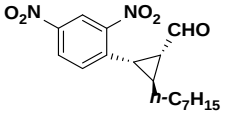
2-(2,4-Dinitrophenyl)-3-heptylcyclopropane-1-carbaldehyde (172d)



The reaction was performed following the general procedure **1**.The crude was purified by column chromatography 1:7 (hexane/ EtOAc) to obtain 153 mg of the desired product as yellow oil. Yield: 99%. The diastereomeric ratio was determined by NMR of the crude: 6:2:1.

Diastereomer 1, major:

(1*R*,2*S*,3*S*)-2-(2,4-dinitrophenyl)-3-heptylcyclopropane-1-carbaldehyde



IR: 3086 (C-H stretch aromatic), 2925 (C-H stretch alkyl), 2854 (C-H stretch aldehyde), 1699 (C=O stretch aldehyde), 1603, 1530 (aromatic NO_2), 1465, 1343 (aromatic NO_2), 1150, 1066, 909, 834, 738, 689, 642, 508 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.41 (d, *J* = 2.7 Hz, 1H), 8.70 (d, *J* = 2.1 Hz, 1H), 8.36 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 2.87 (dd, *J* = 8.2, 8.0 Hz, 1H), 2.47 (ddd, *J* = 8.0, 4.9, 2.8 Hz, 1H), 2.20 – 2.12 (m, 1H), 1.62-1.54 (m, 2H), 1.36 – 1.18 (m, 10H), 0.85 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.1 (CHO), 150.0 (Cq), 146.8 (Cq), 139.1 (Cq), 133.6 (CH), 126.8 (CH), 119.9 (CH), 37.1 (CH), 33.3 (CH), 32.4 (CH_2), 31.7 (CH_2), 29.9 (CH), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 210 nm): t_r (*S* catalyst used) = 11.7 min., t_r (*R* catalyst used) = 12.9 min., 94% (*S* catalyst used)/ 96% (*R* catalyst used) *ee*.

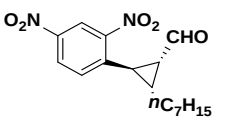
$[\alpha]_D^{22}$ = - 62.4° (c = 0.9, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{22}$ = 77.5° (c = 1.1, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{22}N_2O_5$ $[M+Na]^+$: 357.1421, found: 357.1421.

Diastereomer 2, minor:

(1*R*,2*R*,3*R*)-2-heptyl-3-(4-nitrophenyl)cyclopropane-1-carbaldehyde



IR: 3086 (C-H stretch aromatic), 2925 (C-H stretch alkyl), 2854 (c-H stretch aldehyde), 1699 (c=O stretch aldehyde), 1603, 1530 (aromatic NO_2), 1465, 1343 (aromatic NO_2), 1150, 1066, 909, 834, 738, 689, 642, 508 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.64 (d, *J*=4.1 Hz, 1H), 8.74 (d, *J* = 2.3 Hz, 1H), 8.36 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 3.23 (dd, *J* = 5.9, 5.7 Hz, 1H), 2.32 (ddd, *J* = 9.1, 5.7, 4.4 Hz, 1H), 1.93 – 1.80 (m, 2H), 1.69 – 1.54 (m, 1H), 1.34 – 1.18 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.7 (CHO), 150.1 (Cq), 146.5 (Cq), 141.4 (Cq), 129.8 (CH), 127.2 (CH), 120.3 (CH), 36.5 (CH), 33.6 (CH), 31.7 (CH_2), 29.6 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH), 27.5 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 24.4 min., t_r (*R* catalyst used) = 18.8 min., 93% (*S* catalyst used)/ 92% (*R* catalyst used) *ee*.

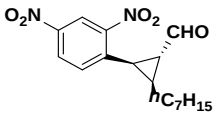
$[\alpha]_D^{22}$ = 46.8° (c = 0.4, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{22}$ = - 53.1° (c = 1.0, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{22}N_2O_5$ $[M+Na]^+$: 357.1421, found: 357.1416.

<u>Diastereomer 3, minor':</u>

(1*R*,2*R*,3*S*)-2-(2,4-dinitrophenyl)-3-heptylcyclopropane-1-carbaldehyde



IR: 3086 (C-H stretch aromatic), 2925 (C-H stretch alkyl), 2854 (C-H stretch aldehyde), 1699 (C=O stretch aldehyde), 1603, 1530 (aromatic NO_2), 1465, 1343 (aromatic NO_2), 1150, 1066, 909, 834, 738, 689, 642, 508 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.42 (d, *J* = 4.4 Hz, 1H), 8.82 (d, *J* = 2.3 Hz, 1H), 8.40 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 3.33 (dd, *J* = 9.9, 5.4 Hz, 1H), 2.22 (dd, *J* = 9.9, 4.8 Hz, 1H), 2.06 (ddd, *J* = 14.6, 9.9, 4.8 Hz, 1H), 1.32 – 1.18 (m, 12H), 0.82 (t, *J* =7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.3 (CHO), 150.7 (Cq), 146.9 (Cq), 138.4 (Cq), 132.8 (CH), 127.0 (CH), 120.4 (CH), 36.3 (CH), 31.6 (CH_2), 29.7 (CH), 29.2 (CH), 29.0 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

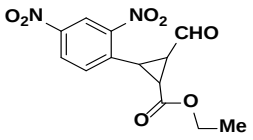
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 15.6 min., t_r (*R* catalyst used) = 22.7 min., 54% (*S* catalyst used)/ 56% (*R* catalyst used) *ee*.

$[\alpha]_D^{22}$ = - 71.5° (c = 0.3, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{22}$ = 132.6° (c = 0.61, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{22}N_2O_5$ $[M+Na]^+$: 357.1421, found: 357.1423.

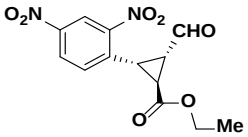
Ethyl 2-(2,4-dinitrophenyl)-3-formylcyclopropane-1-carboxylate (172e)



The reaction was performed following the general procedure **1**.The crude was purified by column chromatography 1:7 (hexane/ EtOAc) to obtain 79.3 mg of the desired product as yellow oil. Yield: 56%. The diastereomeric ratio was determined by NMR of the crude: 1:1:1.

Diastereomer 1, major:

ethyl (1*S*,2*R*,3*S*)-2-(2,4-dinitrophenyl)-3-formylcyclopropane-1-carboxylate



IR: 3092 (C-H stretch aromatic), 2922 (C-H stretch alkyl), 2852 (C-H stretch aldehyde), 1727 (C=O stretch aldehyde), 1705 (C=O stretch ester), 1604, 1530 (aromatic NO_2), 1466, 1444, 1392, 1344 (aromatic NO_2), 1286, 1183 (C-O stretch ester), 985, 910, 835, 739 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.60 (d, *J* = 1.7 Hz, 1H), 8.81 (d, *J* = 2.3 Hz, 1H), 8.42 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.51 (dd, *J* = 9.6, 6.7 Hz, 1H), 3.21 (ddd, *J* = 9.6, 4.8, 1.7 Hz, 1H), 2.92 (dd, *J* = 6.7, 4.8 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 195.5 (CHO), 169.6 (Cq), 149.8 (Cq), 147.4 (Cq), 136.2 (Cq), 133.7 (CH), 127.1 (CH), 120.3 (CH), 62.1 (CH_2), 36.1 (CH), 32.4 (CH), 28.6 (CH), 14.2 (CH_3).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 65:35, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 22.0 min., t_r (*R* catalyst used) = 42.2 min., 73% (*S* catalyst used)/ 76% (*R* catalyst used) *ee*.

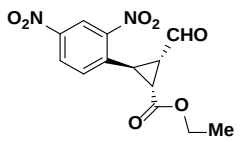
$[\alpha]_D^{23}$ = 1.4° (c = 0.4, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{23}$ = - 0.25° (c = 1.2, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{13}H_{12}N_2O_7$ $[M+Na]^+$: 331.0537, found: 331.0535.

Diastereomer 2, minor:

ethyl (1*R*,2*S*,3*S*)-2-(2,4-dinitrophenyl)-3-formylcyclopropane-1-carboxylate



IR: 3092 (C-H stretch aromatic), 2922 (C-H stretch alkyl), 2852 (C-H stretch aldehyde), 1727 (C=O stretch aldehyde), 1705 (C=O stretch ester), 1604, 1530 (aromatic NO_2), 1466, 1444, 1392, 1344 (aromatic NO_2), 1286, 1183 (C-O stretch ester), 985, 910, 835, 739 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.62 (d, *J* = 5.8 Hz, 1H), 8.90 (d, *J* = 2.3 Hz, 1H), 8.43 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 4.31 – 4.21 (m, 2H), 3.95 (dd, *J* = 6.6, 6.6 Hz, 1H), 2.55 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.40 (ddd, *J* = 9.3, 6.6, 5.8 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.5 (CHO), 168.6 (Cq), 138.3 (Cq), 130.7 (CH), 127.7 (CH), 120.8 (CH), 120.0 (Cq), 93.1 (Cq), 62.3 (CH_2), 37.0 (CH), 30.4 (CH), 28.5 (CH), 14.1 (CH_3).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 65:35, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 36.8 min., t_r (*R* catalyst used) = 29.3 min., 43% (*S* catalyst used)/ 39% (*R* catalyst used) *ee*.

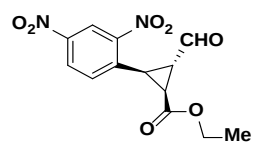
$[\alpha]_D^{23}$ = - 9.7° (c = 0.5, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{23}$ = 10.3° (c = 1.4, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{13}H_{12}N_2O_7$ $[M+Na]^+$: 331.0537, found: 331,0539.

Diastereomer 3, minor':

ethyl (1*S*,2*S*,3*S*)-2-(2,4-dinitrophenyl)-3-formylcyclopropane-1-carboxylate



IR: 3092 (C-H stretch aromatic), 2922 (C-H stretch alkyl), 2852 (C-H stretch aldehyde), 1727 (C=O stretch aldehyde), 1705 (C=O stretch ester), 1604, 1530 (aromatic NO_2), 1466, 1444, 1392, 1344 (aromatic NO_2), 1286, 1183 (C-O stretch ester), 985, 910, 835, 739 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.68 (d, *J* = 3.2 Hz, 1H), 8.81 (d, *J* = 2.3 Hz, 1H), 8.41 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 4.02 – 3.93 (m, 2H), 3.50 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.02 (ddd, *J* = 6.8, 4.6, 3.2 Hz, 1H), 2.87 (dd, *J* = 9.6, 4.6 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 195.9 (CHO), 168.1 (Cq), 150.0 (Cq), 147.3 (Cq), 136.7 (Cq), 133.6 (CH), 127.0 (CH), 120.2 (CH), 62.0 (CH_2), 35.3 (CH), 30.1 (CH), 29.4 (CH), 13.9 (CH_3).

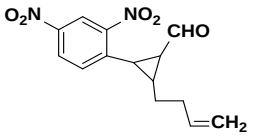
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 65:35, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 20.3 min., t_r (*R* catalyst used) = 41.8 min., 10% (*S* catalyst used)/ 80% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = - 58.0° (c = 0.5, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{23}$ = 44.1° (c = 0.7, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{13}H_{12}N_2O_7$ $[M+Na]^+$: 331.0537, found: 331.0531.

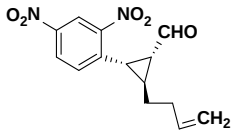
2-(But-3-en-1-yl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde (172f)



The reaction was performed following the general procedure **1**.The crude was purified by column chromatography 1:7 (hexane/ EtOAc) to obtain 44.3 mg of the desired product as yellow oil. Yield: 66%. The diastereomeric ratio was determined by NMR of the crude: 5:1.5:1.

<u>Diastereomer 1, major:</u>

(1*R*,2*S*,3*S*)-2-(but-3-en-1-yl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde



IR: 3079 (C-H stretch aromatic), 2924 (C-H stretch alkyl), 2849 (C-H stretch aldehyde), 2211, 2133, 1702 (C-H stretch aldehyde), 1640, 1603, 1530 (aromatic NO_2), 1437, 1346 (aromatic NO_2), 1150, 1066, 835, 738 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.44 (d, *J* = 2.7 Hz, 1H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.37 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 5.90 – 5.74 (m, 1H), 5.12 – 4.98 (m, 2H), 2.89 (dd, *J* = 8.2, 8.1 Hz, 1H), 2.51 (ddd, *J* = 8.1, 5.0, 2.7 Hz, 1H), 2.29 – 2.24 (m, 2H), 2.19 (dd, *J* = 8.2, 5.0 Hz, 1H), 1.80 – 1.62 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.9 (CHO), 150.0 (Cq), 146.9 (Cq), 138.8 (Cq), 137.1 (CH), 133.6 (CH), 126.8 (CH), 119.9 (CH), 116.1 (CH_2), 37.0 (CH), 33.3 (CH), 33.1 (CH_2), 31.6 (CH_2), 29.2 (CH).

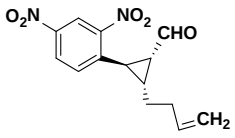
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 75:25, flow rate 1.0 mL/min, λ = 210 nm): t_r (*S* catalyst used) = 14.4 min., t_r (*R* catalyst used) = 16.4 min., 99.8% (*S* catalyst used)/ 99% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = - 119.1° (c = 1.3, $CHCl_3$) **(*S* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{14}H_{14}N_2O_5$ $[M+Na]^+$: 313.0795, found: 313.0797.

Diastereomer 2, minor:

(1*R*,2*R*,3*R*)-2-(but-3-en-1-yl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde



IR: 3079 (C-H stretch aromatic), 2924 (C-H stretch alkyl), 2849 (C-H stretch aldehyde), 2211, 2133, 1702 (C-H stretch aldehyde), 1640, 1603, 1530 (aromatic NO_2), 1437, 1346 (aromatic NO_2), 1150, 1066, 835, 738 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.68 (d, *J* =3.9 Hz, 1H), 8.76 (d, *J* = 2.4 Hz, 1H), 8.36 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 5.77 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.08 – 4.96 (m, 2H), 3.24 (dd, *J* = 6.1, 5.9 Hz, 1H), 2.34 (ddd, *J* = 9.1, 5.9, 3.9 Hz, 1H), 2.22 – 2.12 (m, 2H), 2.02 – 1.85 (m, 2H), 1.82 – 1.72 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.5 (CHO), 150.1 (Cq), 146.6 (Cq), 141.3 (Cq), 137.0 (CH), 129.9 (CH), 127.2 (CH), 120.3 (CH), 116.1 (CH_2), 36.3 (CH), 33.5 (CH_2), 32.8 (CH), 28.9 (CH), 26.5 (CH_2).

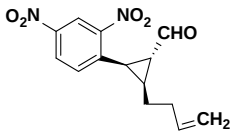
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 75:25, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 25.3 min., t_r (*R* catalyst used) = 19.6 min., 92% (S catalyst used)/ 87% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = 49.0° (c = 0.4, $CHCl_3$) **(*S* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{14}H_{14}N_2O_5$ $[M+Na]^+$: 313.0795, found: 313.0795.

Diastereomer 3, minor':

(1*R*,2*S*,3*R*)-2-(but-3-en-1-yl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde



IR: 3079 (C-H stretch aromatic), 2924 (C-H stretch alkyl), 2849 (C-H stretch aldehyde), 2211, 2133, 1702 (C-H stretch aldehyde), 1640, 1603, 1530 (aromatic NO_2), 1437, 1346 (aromatic NO_2), 1150, 1066, 835, 738 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.43 (d, *J* = 4.3 Hz, 1H), 8.82 (d, *J* = 2.4 Hz, 1H), 8.40 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 5.70 – 5.57 (m, 1H), 4.98 – 4.85 (m, 2H), 3.33 (dd, *J* = 9.8, 5.5 Hz,

1H), 2.25 – 2.23 (dd, *J* = 9.8, 4.7 Hz, 1H), 2.12 – 2.02 (m, 3H), 1.47 (ddd, *J* = 12.1, 9.8, 4.7 Hz, 1H), 0.80 – 0.68 (m, 1H).

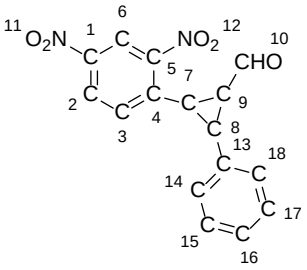
^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.1 (CHO), 147.0 (Cq), 138.2 (Cq), 136.5 (CH), 132.8 (CH), 127.0 (CH), 120.4 (CH), 120.3 (Cq), 116.1 (CH_2), 36.2 (CH), 32.9 (CH_2), 29.2 (CH), 29.1 (CH), 27.3 (CH_2).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 75:25, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 16.7 min., t_r (*R* catalyst used) = 29.0 min., 67% (*S* catalyst used)/ 71% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = - 241.0° (c = 0.1, $CHCl_3$) **(*S* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{14}H_{14}N_2O_5$ $[M+Na]^+$: 313.0795, found: 313.0801.

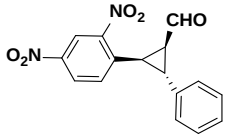
2-(2,4-dinitrophenyl)-3-phenylcyclopropane-1-carbaldehyde (172g)



The reaction was performed following the general procedure **1**.The crude was purified by column chromatography 1:5 (hexane/ EtOAc) to obtain 112 mg of the desired product as yellow oil. Yield: 78%. The diastereomeric ratio was determined by NMR of the crude: 3:2:1.

<u>Diastereomer 1, major:</u>

(1*S*,2*R*,3*R*)-2-(2,4-dinitrophenyl)-3-phenylcyclopropane-1-carbaldehyde



IR: 3099 (C-H stretch aromatic), 2853 (C-H stretch aldehyde), 1702 (C=O stretch aldehyde), 1529 (aromatic NO_2), 1458, 1345 (aromatic NO_2), 1151, 1127, 1065, 1031, 1010, 964, 919, 835, 752, 738, 698, 520 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.60 (d, *J* = 1.9 Hz, 1H, H_{10}), 8.74 (d, *J* = 2.0 Hz, 1H, H_6), 8.39 (dd, *J* = 8.5, 2.0 Hz, 1H, H_2), 7.80 (d, *J* = 8.6 Hz, 1H, H_3), 7.33 (t, *J* = 7.3 Hz, 2H, C_{14}, C_{18}), 7.27 (d, *J* = 7.1 Hz, 1H, H_{16}), 7.22 (d, *J* = 8.0 Hz, 2H, C_{15}, C_{17}), 3.40 (dd, *J* = 8.6, 8.0 Hz, 1H, H_7), 3.27 (dd, *J* = 8.0, 5.2 Hz, 1H, H_8), 2.93 (ddd, *J* = 8.6, 5.2, 2.1 Hz, 1H, H_9).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197 (CHO, C_{10}), 149.9 (Cq, C_5), 147.1 (Cq, C_1), 138.3 (Cq, C_4), 137.1 (Cq, C_{13}), 133.8 (CH, C_3), 129.0 (2CH, C_{14}, C_{18}), 127.8 (CH, C_2), 127.1 (CH, C_{16}), 126.6 (2CH, C_{15}, C_{17}), 120.1 (CH, C_6), 39.1 (CH, C_9), 34.1 (CH, C_7), 33.4 (CH, C_8).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 46.0 min., t_r (*R* catalyst used) = 52.3 min., 97% (*S* catalyst used)/ 98% (*R* catalyst used) *ee*.

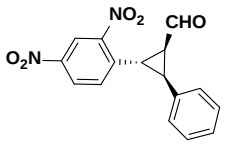
$[\alpha]_D^{26}$ = 8.9° (c = 0.7, $CHCl_3$) (***S* catalyst used**)

$[\alpha]_D^{26}$ = - 7.8° (c = 1.4, $CHCl_3$) (***R* catalyst used**)

HRMS (ESI+) Exact mass calculated for $C_{16}H_{12}N_2O_5$ $[M+Na]^+$: 335.0638, found: 335.0644.

<u>Diastereomer 2, minor:</u>

(1*S*,2*S*,3*S*)-2-(2,4-dinitrophenyl)-3-phenylcyclopropane-1-carbaldehyde



IR: 3099 (C-H stretch aromatic), 2853 (C-H stretch aldehyde), 1702 (C=O stretch aldehyde), 1529 (aromatic NO_2), 1458, 1345 (aromatic NO_2), 1151, 1127, 1065, 1031, 1010, 964, 919, 835, 752, 738, 698, 520 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.02 (d, *J* = 5.6 Hz, 1H, H_{10}), 8.82 (d, *J* = 2.1 Hz, 1H, H_6), 8.42 (dd, *J* = 8.6, 2.1 Hz, 1H, H_2), 7.55 (d, *J* = 8.6 Hz, 1H, H_3), 7.42 – 7.32 (m, 4H, H_{14}, H_{15}, H_{17}, H_{18}), 7.28 (d, *J* = 6.9 Hz, 1H, H_{16}), 3.97 (dd, *J* = 6.7, 5.6 Hz, 1H, H_7), 3.23 (dd, *J* = 9.6, 6.7 Hz, 1H, H_8), 2.55 (ddd, *J* = 10.7, 9.6, 5.6 Hz, 1H, H_9).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.2 (CHO, C_{10}), 150.2 (Cq, C_5), 146.8 (Cq, C_1), 140.5 (Cq, C_4), 133.4 (Cq, C_{13}), 130.1 (CH, C_3), 128.9 (2CH, C_{14}, C_{18}), 128.9 (2CH, C_{15}, C_{17}), 128.1 (CH, C_2), 127.5 (CH, C_{16}), 120.5 (CH, C_6), 38.3 (CH, C_9), 34.9 (CH, C_7), 26.2 (CH, C_8).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 75.3 min., t_r (*R* catalyst used) = 66.7 min., 94% (*S* catalyst used)/ 91% (*R* catalyst used) *ee*.

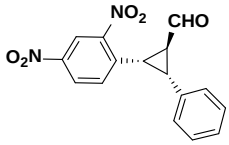
$[\alpha]_D^{26}$ = - 70.8° (c = 0.2, $CHCl_3$) (***S* catalyst used**)

$[\alpha]_D^{26}$ = 37.8° (c = 1.3, $CHCl_3$) (***R* catalyst used**)

HRMS (ESI+) Exact mass calculated for $C_{16}H_{12}N_2O_5$ $[M+Na]^+$: 335.0638, found: 335.0630.

Diastereomer 3, minor':

(1*S*,2*S*,3*R*)-2-(2,4-dinitrophenyl)-3-phenylcyclopropane-1-carbaldehyde



IR: 3099 (C-H stretch aromatic), 2853 (C-H stretch aldehyde), 1702 (C=O stretch aldehyde), 1529 (aromatic NO_2), 1458, 1345 (aromatic NO_2), 1151, 1127, 1065, 1031, 1010, 964, 919, 835, 752, 738, 698, 520 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.69 (d, *J* = 3.7 Hz, 1H, H_{10}), 8.61 (d, *J* = 2.1 Hz, 1H, H_6), 8.25 (dd, *J* = 8.5, 2.1 Hz, 1H, H_2), 7.43 (d, *J* = 8.6 Hz, 1H, H_3), 7.13 – 7.06 (m, 3H, H_{15}, H_{16}, H_{17}), 6.82 – 6.77 (m, 2H, H_{14}, H_{18}), 3.63 (dd, *J* = 10.2, 5.7 Hz, 1H, H_7), 3.32 (dd, *J* = 10.2, 5.1 Hz, 1H, H_8), 3.02 (ddd, *J* = 14.5, 10.2, 5.1 Hz, 1H, H_9).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.6 (CHO, C_{10}), 150.5 (Cq, C_5), 146.8 (Cq, C_1), 137.5 (Cq, C_4), 133.0 (CH, C_3), 132.8 (Cq, C_{13}), 128.6 (2CH, C_{14}, C_{18}), 127.6 (3CH, C_{15}, C_{16}, C_{17}), 126.7 (CH, C_2), 120.2 (CH, C_6), 35.4 (CH, C_9), 33.1 (CH, C_7), 31.4 (CH, C_8).

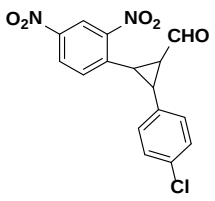
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 31.1 min., t_r (*R* catalyst used) = 41.3 min., 96% (*S* catalyst used)/ 96% (*R* catalyst used) *ee*.

$[\alpha]_D^{26}$ = - 73.9° (c = 0.8, $CHCl_3$) (***S* catalyst used**)

$[\alpha]_D^{26}$ = 70.8° (c = 1.4, $CHCl_3$) (***R* catalyst used**)

HRMS (ESI+) Exact mass calculated for $C_{16}H_{12}N_2O_5$ $[M+Na]^+$: 335.0638, found: 335.0641.

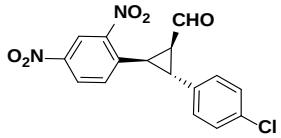
2-(4-chlorophenyl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde (172h)



The reaction was performed following the general procedure **1**.The crude was purified by column chromatography 1:5 (hexane/ EtOAc) to obtain 137 mg of the desired product as yellow oil. Yield: 86%. The diastereomeric ratio was determined by NMR of the crude: 2:1.3:1.

Diastereomer 1, major:

(1*S*,2*R*,3*R*)-2-(4-chlorophenyl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde



IR: 3099 (C-H stretch aromatic), 2854 (C-H stretch aldehyde), 1702 (C=O stretch aldehyde), 1529 (aromatic NO_2), 1496, 1435, 1397, 1345 (aromatic NO_2), 1214, 1151, 1126, 1092, 1066, 1038 – 1013 (Aryl-Cl with C-Cl stretch), 964, 918, 835, 811, 759, 739, 668 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.64 (d, *J* = 2.0 Hz, 1H), 8.79 (d, *J* = 2.3 Hz, 1H), 8.43 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 3.40 (dd, *J* = 9.1, 8.2 Hz, 1H), 3.28 (dd, *J* = 8.2, 5.2 Hz, 1H), 2.98 (ddd, *J* = 9.1, 5.2, 2.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.6 (CHO), 149.9 (Cq), 147.2 (Cq), 137.9 (Cq), 135.6 (Cq), 133.7 (CH), 133.7 (Cq), 129.2 (2CH), 127.9 (2CH), 127.1 (CH), 120.1 (CH), 38.9 (CH), 34.1 (CH), 32.5 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 55:45, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 24.4 min., t_r (*R* catalyst used) = 31.8 min., 94% (*S* catalyst used)/ 99% (*R* catalyst used) *ee*.

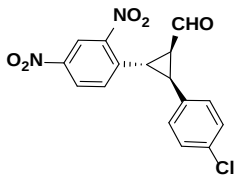
$[\alpha]_D^{23}$ = 21.1° (c = 0.7, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{22}$ = - 7.3° (c = 0.9, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{16}H_{11}ClN_2O$ $[M+Na]^+$: 369.0249, found: 369.0247.

Diastereomer 2, minor:

(1*S*,2*S*,3*S*)-2-(4-chlorophenyl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde



IR: 3099 (C-H stretch aromatic), 2854 (C-H stretch aldehyde), 1702 (C=O stretch aldehyde), 1529 (aromatic NO_2), 1496, 1435, 1397, 1345 (aromatic NO_2), 1214, 1151, 1126, 1092, 1066, 1038 – 1013 (Aryl-Cl with C-Cl stretch), 964, 918, 835, 811, 759, 739, 668 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.10 (d, *J* = 5.0 Hz, 1H), 8.81 (d, *J* = 2.3 Hz, 1H), 8.42 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.35 – 7.27 (m, 4H), 3.93 (dd, *J* = 7.0, 5.6 Hz, 1H), 3.15 (dd, *J* = 9.4, 7.0 Hz, 1H), 2.61 (ddd, *J* = 10.0, 9.4, 5.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.6 (CHO), 150.1 (Cq), 146.9 (Cq), 140.1 (Cq), 134 (Cq), 131.9 (Cq), 130.3 (3CH), 129.1 (2CH), 127.5 (CH), 120.5 (CH), 37.9 (CH), 34.5 (CH), 26.5 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 55:45, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 43.8 min., t_r (*R* catalyst used) = 39.4 min., 94% (*S* catalyst used)/ 96% (*R* catalyst used) *ee*.

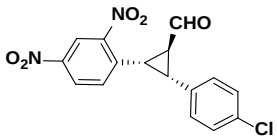
$[\alpha]_D^{22}$ = - 75.7° (c = 0.9, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{22}$ = 72.2° (c = 0.8, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{16}H_{11}ClN_2O$ $[M+Na]^+$: 369.0249, found: 369.0240.

<u>Diastereomer 3, minor':</u>

(1*S*,2*R*,3*S*)-2-(4-chlorophenyl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde



IR: 3099 (C-H stretch aromatic), 2854 (C-H stretch aldehyde), 1702 (C=O stretch aldehyde), 1529 (aromatic NO_2), 1496, 1435, 1397, 1345 (aromatic NO_2), 1214, 1151, 1126, 1092, 1066, 1038 – 1013 (Aryl-Cl with C-Cl stretch), 964, 918, 835, 811, 759, 739, 668 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.71 (d, *J* = 3.6 Hz, 1H), 8.66 (d, *J* = 2.3 Hz, 1H), 8.29 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 3.62 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.29 (dd, *J* = 10.2, 5.2 Hz, 1H), 2.99 (ddd, *J* = 14.5, 10.2, 5.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.2 (CHO), 150.4 (Cq), 147 (Cq), 137 (Cq), 133.7 (Cq), 132.8 (CH), 131.4 (Cq), 128.9 (2CH), 128.9 (2CH), 126.7 (CH), 120.4 (CH), 35.2 (CH), 32.5 (CH), 31.4 (CH).

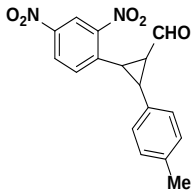
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 60:40, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 29.1 min., t_r (*R* catalyst used) = 32.6 min., 97% (*S* catalyst used)/ 97% (*R* catalyst used) *ee*.

$[\alpha]_D^{22}$ = - 56.1° (c = 0.6, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{22}$ = 56.2° (c = 0.7, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{16}H_{11}ClN_2O_5$ $[M+Na]^+$: 369.0249, found: 369.0249.

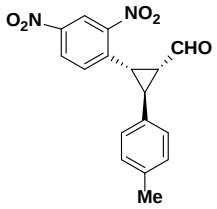
2-(2,4-Dinitrophenyl)-3-(p-tolyl)cyclopropane-1-carbaldehyde (172i)



The reaction was performed following the general procedure **1**.The crude was purified by column chromatography 1:5 (hexane/ EtOAc) to obtain 120 mg of the desired product as yellow oil. Yield: 80%. The diastereomeric ratio was determined by NMR of the crude: 13:12:1.

Diastereomer 1, major:

(1*R*,2*S*,3*S*)-2-(2,4-dinitrophenyl)-3-(p-tolyl)cyclopropane-1-carbaldehyde



IR: 3020 (C-H stretch aromatic), 2923, 2853 (C-H stretch aldehyde), 1699 (C=O stretch aldehyde), 1525 (aromatic NO_2), 1434, 1397, 1342 (aroamtic NO_2), 1215, 1150, 1127, 1065, 909, 835, 802, 752, 738, 668 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.62 (d, *J* = 2.2 Hz, 1H), 8.78 (d, *J* = 2.3 Hz, 1H), 8.42 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.21 – 7.12 (m, 4H), 3.42 (dd, *J* = 9.0, 7.5 Hz, 1H), 3.28 (dd, *J* = 7.5, 5.1 Hz, 1H), 2.97 (ddd, *J* = 9.0, 5.1, 2.3 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.2 (CHO), 149.9 (Cq), 147.0 (Cq), 138.5 (Cq), 137.6 (Cq), 134.0 (Cq), 133.8 (CH), 129.7 (2CH), 127.1 (CH), 126.5 (2CH), 120.1 (CH), 39.1 (CH), 34.1 (CH), 33.3 (CH), 21.1 (CH_3).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 60:40, flow rate 1.0 mL/min, λ = 230 nm): t_r(*S* catalyst used) = 29.2 min., t_r(*R* catalyst used) = 40.1 min., 98% (*S* catalyst used)/ 98% (*R* catalyst used) *ee*.

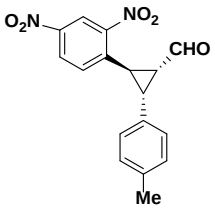
$[\alpha]_D^{22}$ = 11.3° (c = 0.6, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{22}$ = - 11.8° (c = 1.1, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{14}N_2O_5$ $[M+Na]^+$: 349.0795, found: 349.0797.

Diastereomer 2, minor:

(1*R*,2*R*,3*R*)-2-(2,4-dinitrophenyl)-3-(p-tolyl)cyclopropane-1-carbaldehyde



IR: 3020 (C-H stretch aromatic), 2923, 2853 (C-H stretch aldehyde), 1699 (C=O stretch aldehyde), 1525 (aromatic NO_2), 1434, 1397, 1342 (aroamtic NO_2), 1215, 1150, 1127, 1065, 909, 835, 802, 752, 738, 668 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.01 (d, *J* = 5.6 Hz, 1H), 8.80 (t, *J* = 2.1 Hz, 1H), 8.41 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 3.94 (dd, *J* = 7.0, 5.3 Hz, 1H), 3.20 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.52 (ddd, *J* = 9.0, 5.3, 4.0 Hz, 1H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.5 (CHO), 150.1 (Cq), 146.8 (Cq), 140.7 (Cq), 137.9 (Cq), 130.4 (Cq), 130.2 (CH), 129.6 (2CH), 128.7 (2CH), 127.5 (CH), 120.5 (CH), 38.3 (CH), 34.7 (CH), 26.3 (CH), 21.1 (CH_3).

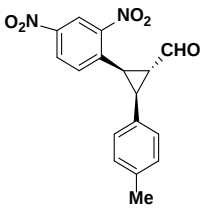
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 60:40, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 40.6 min., t_r (*R* catalyst used) = 46.4 min., 84% (*S* catalyst used)/ 85% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = 50.4° (c = 0.4, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{14}N_2O_5$ $[M+Na]^+$: 349.0795, found: 349.0803.

Diastereomer 3, minor':

(1*R*,2*R*,3*S*)-2-(2,4-dinitrophenyl)-3-(p-tolyl)cyclopropane-1-carbaldehyde



IR: 3020 (C-H stretch aromatic), 2923, 2853 (C-H stretch aldehyde), 1699 (C=O stretch aldehyde), 1525 (aromatic NO_2), 1434, 1397, 1342 (aroamtic NO_2), 1215, 1150, 1127, 1065, 909, 835, 802, 752, 738, 668 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.66 (d, *J* = 3.9 Hz, 1H), 8.62 (d, *J* = 2.4 Hz, 1H), 8.25 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 6.90 (t, *J* = 8.1 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 3.60 (dd, *J* = 10.2, 5.7 Hz, 1H), 3.28 (dd, *J* = 10.2, 5.1 Hz, 1H), 2.93 (ddd, *J* = 9.3, 5.7, 5.1 Hz, 1H), 2.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.9 (CHO), 150.4 (Cq), 146.8 (Cq), 137.7 (Cq), 137.4 (Cq), 133.0 (CH), 129.6 (Cq), 129.3 (2CH), 127.5 (2CH), 126.7 (CH), 120.2 (CH), 35.5 (CH), 33.0 (CH), 31.3 (CH), 21.0 (CH_3).

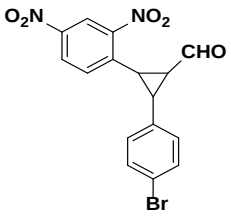
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 33.3 min., t_r (*R* catalyst used) = 39.2 min., 97% (*S* catalyst used)/ 96% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = - 86.5° (c = 0.1, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{23}$ = 83.0° (c = 0.1, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{14}N_2O_5$ $[M+Na]^+$: 349.0795, found: 349.0799.

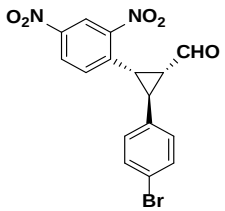
2-(4-bromophenyl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde (172j)



The reaction was performed following the general procedure **1**.The crude was purified by column chromatography 1:5 (hexane/ EtOAc) to obtain 129 mg of the desired product as yellow oil (The first diastereomer is a solid for which was obtained a crystal). Yield: 71%. The diastereomeric ratio was determined by NMR of the crude: 2:2:1.

<u>Diastereomer 1, major:</u>

(1*R*,2*S*,3*S*)-2-(4-bromophenyl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde



^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.65 (d, *J* = 2.0 Hz, 1H), 8.80 (d, *J* = 2.3 Hz, 1H), 8.44 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 3.41 (dd, *J* = 8.5, 8.1 Hz, 1H), 3.26 (dd, *J* = 8.5, 5.2 Hz, 1H), 2.99 (ddd, *J* = 8.1, 5.2, 2.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.7 (CHO), 149.9 (Cq), 147.2 (Cq), 137.9 (Cq), 136.1 (Cq), 133.7 (CH), 132.1 (2CH), 128.3 (2CH), 127.1 (CH), 121.6 (Cq), 120.2 (CH), 38.9 (CH), 34.1 (CH), 32.6 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 40.6 min., t_r (*R* catalyst used) = 56.3 min., 99% (*S* catalyst used)/ 99% (*R* catalyst used) *ee*.

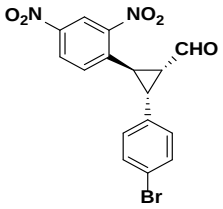
$[\alpha]_D^{22}$ = 12.3° (c = 0.8, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{22}$ = - 2.4° (c = 0.5, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{11}H_{10}N_2O_5$ $[M+Na]^+$: 412.9744, found: 412.9750.

<u>Diastereomer 2, minor:</u>

(1*R*,2*R*,3*R*)-2-(4-bromophenyl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde



^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.11 (d, *J* = 5.0 Hz, 1H), 8.83 (d, *J* = 2.3 Hz, 1H), 8.43 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 3.94 (dd, *J* = 7.3, 5.5 Hz, 1H), 3.13 (dd, *J* = 9.6, 7.3 Hz, 1H), 2.62 (ddd, *J* = 9.6, 5.5, 4.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.6 (CHO), 150.1 (Cq), 146.9 (Cq), 140.1 (Cq), 132.4 (Cq), 132.0 (2CH), 130.6 (2CH), 130.3 (CH), 127.5 (CH), 122.1 (Cq), 120.6 (CH), 37.9 (CH), 34.5 (CH), 26.4 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 55:45, flow rate 1.0 mL/min, λ = 210 nm): t_r (*S* catalyst used) = 50.0 min., t_r (*R* catalyst used) = 42.9 min., 92% (*S* catalyst used)/ 94% (*R* catalyst used) *ee*.

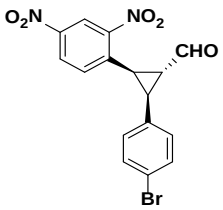
$[\alpha]_D^{22}$ = - 69.2° (c = 1.0, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{22}$ = 69.8° (c = 1.1, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{11}H_{10}N_2O_5$ $[M+Na]^+$: 412.9744, found: 412.9748.

<u>Diastereomer 3, minor':</u>

(1*R*,2*S*,3*R*)-2-(4-bromophenyl)-3-(2,4-dinitrophenyl)cyclopropane-1-carbaldehyde



^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.71 (d, *J* = 3.6 Hz, 1H), 8.67 (d, *J* = 2.3 Hz, 1H), 8.30 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.25 – 7.21 (m, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 3.63 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.28 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.01 –2.97 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.3 (CHO), 150.4 (Cq),147.0 (Cq), 137.0 (Cq), 132.8 (CH), 131.9 (Cq), 131.8 (2CH), 129.2 (2CH), 126.9(CH), 121.7 (Cq), 120.4 (CH), 35.2 (CH), 32.6 (CH), 31.5 (CH).

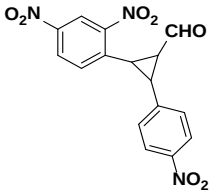
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 55:45, flow rate 1.0 mL/min, λ = 210 nm): t_r (*S* catalyst used) = 30.6 min., t_r (*R* catalyst used) = 34.0 min., 99.7% (*S* catalyst used)/ 98% (*R* catalyst used) *ee*.

$[\alpha]_D^{22}$ = - 25.9° (c = 0.4, $CHCl_3$) **(*S* catalyst used)**

$[\alpha]_D^{22}$ = 46.8° (c = 0.2, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{11}H_{10}N_2O_5$ $[M+Na]^+$: 412.9744, found: 412.9732.

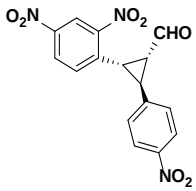
2-(2,4-dinitrophenyl)-3-(4-nitrophenyl)cyclopropane-1-carbaldehyde (172k)



The reaction was performed following the general procedure**1**.The crude was purified by column chromatography 1:6 (hexane/ EtOAc) to obtain 110.5 mg of the desired product as yellow oil. Yield: 67%. The diastereomeric ratio was determined by NMR of the crude: 6:3:1.

<u>Diastereomer 1, major:</u>

(1*R*,2*S*,3*S*)-2-(2,4-dinitrophenyl)-3-(4-nitrophenyl)cyclopropane-1-carbaldehyde



IR: 3095 (C-H stretch aromatic), 2852 (C-H stretch aldehyde), 1703 (C=O stretch aldehyde), 1602, 1518 (aromatic NO_2), 1345 (aromatic NO_2), 1151, 1111, 1065, 1012, 960, 919, 854, 835, 749, 694 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.70 (d, *J* = 1.8 Hz, 1H), 8.83 (d, *J* = 2.3 Hz, 1H), 8.46 (dd, *J* = 8.5, 2.3 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 3.51 (dd, *J* = 8.7, 7.9 Hz, 1H), 3.38 (dd, *J* = 7.9, 5.2 Hz, 1H), 3.12 (ddd, *J* = 8.7, 5.2, 1.9 Hz, 1H).

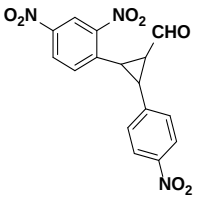
^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.0 (CHO), 149.9 (Cq), 147.4 (Cq), 147.4 (Cq), 144.6 (Cq), 137.1 (Cq), 133.7 (CH), 127.4 (2CH), 127.2 (CH), 124.3 (2CH), 120.3 (CH), 39.0 (CH), 34.6 (CH), 32.4 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 45:55, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 42.2 min., t_r (*R* catalyst used) = 51.3 min., 96% (*S* catalyst used)/ 99% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = 26.3° (c = 0.5, $CHCl_3$) **(*S* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{11}N_3O_7$ $[M+Na]^+$: 380.0489, found: 380.0480.

Mixture of two minor diastereomeres:



IR: 3095 (C-H stretch aromatic), 2852 (C-H stretch aldehyde), 1703 (C=O stretch aldehyde), 1602, 1518 (aromatic NO_2), 1345 (aromatic NO_2), 1151, 1111, 1065, 1012, 960, 919, 854, 835, 749, 694 cm^{-1}

Minor 1 (**172'k**) diastereomer – H'; minor 2 (**172''k**) diastereomer – H.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.79 (d, *J* = 3.3 Hz, 1H'), 9.29 (d, *J* = 4.0 Hz, 1H), 8.86 (d, *J* = 2.3 Hz, 1H), 8.65 (d, *J* = 2.3 Hz, 1H'), 8.46 (dd, *J* = 8.6, 2.4 Hz, 1H), 8.34 (dd, *J* = 8.5, 2.3 Hz, 1H'), 8.20 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H'), 7.58 (t, *J* = 9.1 Hz, 3H), 7.54 (d, *J* = 8.6 Hz, 1H'), 6.98 (d, *J* = 8.7 Hz, 2H'), 4.04 (dd, *J* = 7.5, 5.7 Hz, 1H), 3.72 (dd, *J* = 10.2, 6.0 Hz, 1H'), 3.40 (dd, *J* = 10.2, 4.3 Hz, 1H'), 3.22 (dd, *J* = 9.4, 7.5 Hz, 1H), 3.14 (ddd, *J* = 8.8, 6.0, 4.3 Hz, 1H'), 2.82 (ddd, *J* = 9.4, 5.7, 4.0 Hz, 1H).

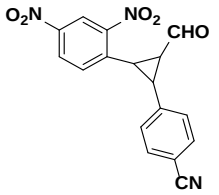
Minor 1 – C', minor 2 – C.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.6 (C'HO), 195.5 (CHO), 150.3 (Cq), 150.1 (Cq), 147.5 (C'q), 147.3 (C'q), 147.2 (C'q), 140.8 (Cq), 140.7 (C'q), 139.5 (Cq), 136.2 (C'q), 133.0 (C'H), 130.5 (C'H), 129.9 (2CH), 128.4 (2 C'H), 127.7 (CH), 127.2 (C'H), 126.4 (Cq), 124.0 (2CH), 123.8 (2 C'H), 120.7 (CH), 120.5 (CH), 37.7 (CH), 35.4 (C'H), 34. (CH), 32.7 (C'H), 32.3 (C'H), 27.0 (CH). Peak at 29.7 (CH_2) belongs 'grease'.

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 55:45, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 46.5 min., t_r (*R* catalyst used) = 49.3 min., 78% (*S* catalyst used)/ 96% (*R* catalyst used) *ee*.

The product 3 (**172''k**) comes as the same peak for *S* catalyst used and *R* catalyst used.

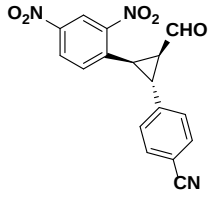
4-(2-(2,4-dinitrophenyl)-3-formylcyclopropyl)benzonitrile (172l)



The reaction was performed following the general procedure **1**. The crude was purified by column chromatography 1:6-1:4 (hexane/ EtOAc) to obtain 124.6 mg of the desired product as yellow oil. Yield: 80%. The diastereomeric ratio was determined by NMR of the crude: 2:2:1.

Diastereomer 1, major:

4-((1*R*,2*R*,3*S*)-2-(2,4-dinitrophenyl)-3-formylcyclopropyl)benzonitrile



^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.68 (d, *J* = 1.8 Hz, 1H), 8.82 (d, *J* = 2.3 Hz, 1H), 8.44 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 3.47 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.33 (dd, *J* = 7.6, 5.3 Hz, 1H), 3.07 (ddd, *J* = 9.2, 5.3, 1.8 Hz, 1H).

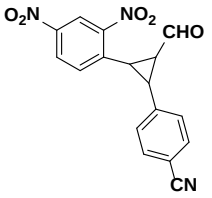
^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.1 (CHO), 149.9 (Cq), 147.3 (Cq), 142.6 (Cq), 137.2 (Cq), 133.7 (CH), 132.8 (CH), 132.6 (CH), 127.3 (CH), 127.2 (CH), 126.7 (CH), 120.3 (CH), 118.3 (Cq), 111.7 (Cq), 38.9 (CH), 34.4 (CH), 32.6 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 55:45, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 37.1 min., t_r (*R* catalyst used) = 43.6 min., 86% (*S* catalyst used)/ 74% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = - 13.9° (c = 0.6, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{11}N_3O_5$ $[M+Na]^+$: 360.0591, found: 360.0586.

Mixture of two diastereomers:



Minor 1 (**172'l**) diastereomer – H'; minor 2 (**172''l**) diastereomer – H.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.76 (d, *J* = 3.4 Hz, 1H'), 9.25 (d, *J* = 4.2 Hz, 1H), 8.85 (d, *J* = 2.3 Hz, 1H), 8.66 (d, *J* = 2.3 Hz, 1H'), 8.45 (dd, *J* = 8.6, 2.4 Hz, 1H), 8.33 (dd, *J* = 8.5, 2.4 Hz, 1H'), 7.65 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H'), 7.42 – 7.37 (m, 2H' and 2H), 6.92 (d, *J* = 8.2 Hz, 2H'), 4.01 (dd, *J* = 7.4, 5.7

Hz, 1H), 3.70 (dd, *J* = 10.2, 6.0 Hz, 1H'), 3.35 (dd, *J* = 10.2, 5.5 Hz, 1H'), 3.18 (dd, *J* = 9.6, 7.4 Hz, 1H), 3.14 (ddd, *J* = 10.2, 5.5, 3.4 Hz, 1H'), 2.77 (ddd, *J* = 9.6, 5.7, 4.2 Hz, 1H).

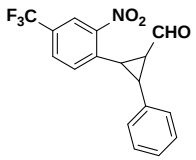
Minor1 diastereomer – C'; minor2 diastereomer – C.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.7 (C'HO), 195.7 (CHO), 150.3 (C'q), 150.1 (Cq), 147.2 (C'q), 147.1 (Cq), 139.6 (Cq), 138.8 (Cq), 138.6 (C'q), 136.3 (C'q), 133.0 (C'H), 132.5 (2CH), 132.3 (2C'H), 130.5 (CH), 129.8 (2CH), 128.3 (2C'H), 127.6 (CH), 127.2 (C'H), 120.7 (CH), 120.5 (C'H), 118.3 (Cq), 118.1 (C'q), 111.9 (Cq), 111.7 (C'q), 37.7 (CH), 35.2 (C'H), 35.1 (CH), 32.8 (C'H), 32.1 (C'H), 26.7 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 65:35, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 48.7 min., t_r (*R* catalyst used) = 45.1 min., 62% (*S* catalyst used)/ 65% (*R* catalyst used) *ee*.

The enantiomeric excess hasn't been determined for the product 3 (**172''l**).

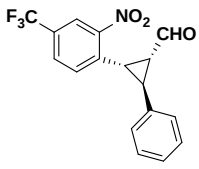
2-(2-nitro-4-(trifluoromethyl)phenyl)-3-phenylcyclopropane-1-carbaldehyde (172m)



The reaction was performed following the general procedure **2**. The crude was purified by column chromatography 1:5 (hexane/ EtOAc) to obtain 65 mg of the desired product as yellow oil. Yield: 47%. The diastereomeric ratio was determined by NMR of the crude: 2:1.5:1.

<u>Diastereomer 1, major:</u>

(1*R*,2*S*,3*S*)-2-(2-nitro-4-(trifluoromethyl)phenyl)-3-phenylcyclopropane-1-carbaldehyde



IR: 3089 (C-H stretch aromatic), 2851 (C-H stretch aldehyde), 2208, 2146, 2054, 2041, 1709 (C=O stretch aldehyde), 1354(aromatic NO_2), 1327 (CF_3 antysym stretch), 1134, 699, 644 (CF_3 attached to aromatics (CF_3 deformation)) cm^{-1}

The spectral data presented is a mixture of the product and cinnamaldehyde.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.01 (d, *J* = 5.8 Hz, 1H), 8.26 (d, *J* = 1.1 Hz, 1H), 7.84 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.37 (m, 6H), 6.71 (dd, *J* = 16.0, 7.7 Hz, 1H), 3.95 (dd, *J* = 6.7, 5.5 Hz, 1H), 3.19 (dd, *J* = 9.3, 6.7 Hz, 1H), 2.49 (ddd, *J* = 9.3, 5.5, 3.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.7 (CHO), 137.6 (Cq), 134.0 (Cq), 133.8 (Cq), 131.3 (CH), 130.8 (Cq), 129.9 (CH), 129.1 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 124.0 (CH), 122.4 (CH), 37.9 (CH), 34.4 (CH), 26.3 (CH).

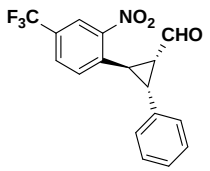
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 18.1 min., t_r (*R* catalyst used) = 13.5 min., 93% (*S* catalyst used)/ 99% (*R* catalyst used) *ee*.

$[\alpha]_D^{26}$ = - 37.3° (c = 0.5, $CHCl_3$) **(*S* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{12}F_3NO_5$ $[M+H]^+$: 336.0842, found: 336.0840.

<u>Diastereomer 2, minor:</u>

(1*R*,2*R*,3<u>R</u>)-2-(2-nitro-4-(trifluoromethyl)phenyl)-3-phenylcyclopropane-1-carbaldehyde



IR: 3089 (C-H stretch aromatic), 2851 (C-H stretch aldehyde), 2208, 2146, 2054, 2041, 1709 (C=O stretch aldehyde), 1354(aromatic NO_2), 1327 (CF_3 antysym stretch), 1134, 699, 644 (CF_3 attached to aromatics (CF_3 deformation)) cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.01 (d, *J* = 5.8 Hz, 1H), 8.26 (d, *J* = 1.1 Hz, 1H), 7.84 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.37 (ddd, *J* = 12.9, 7.4, 4.1 Hz, 5H), 3.95 (dd, *J* = 7.3, 5.5 Hz, 1H), 3.19 (dd, *J* = 9.4, 7.3 Hz, 1H), 2.49 (d_{ap}t, *J* = 9.4, 5.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.7 (CHO), 150.2 (Cq), 137.6 (Cq), 133.8 (Cq), 129.9 (CH), 129.9 (CH), 129.8 (CH), 129.5 (Cq), 129.2 (Cq), 128.9 (CH), 128.9 (CH), 127.9 (CH), 122.4 (CH), 122.4 (CH), 37.9 (CH), 34.4 (CH), 26.3 (CH).

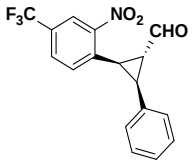
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 13.5 min., t_r (*R* catalyst used) = 11.6 min., 94% (*S* catalyst used)/ 96% (*R* catalyst used) *ee*.

$[\alpha]_D^{26}$ = - 52.9° (c = 0.4, $CHCl_3$) **(*S* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{12}F_3NO_5$ $[M+H]^+$: 336.0842, found: 336.0842.

Diastereomer 3, minor':

(1*R*,2*R*,3*S*)-2-(2-nitro-4-(trifluoromethyl)phenyl)-3-phenylcyclopropane-1-carbaldehyde



IR: 3089 (C-H stretch aromatic), 2851 (C-H stretch aldehyde), 2208, 2146, 2054, 2041, 1709 (C=O stretch aldehyde), 1354(aromatic NO_2), 1327 (CF_3 antysym stretch), 1134, 699, 644 (CF_3 attached to aromatics (CF_3 deformation)) cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.67 (d, *J* = 3.9 Hz, 1H), 8.05 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.12 – 7.05 (m, 3H), 6.77 (d, *J* = 7.8 Hz, 2H), 3.62 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.28 (dd, *J* = 10.1, 5.1 Hz, 1H), 2.94 (ddd, *J* = 9.5, 5.1, 3.9 Hz, 1H).

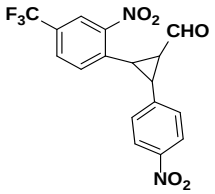
^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.0 (CHO), 150.5 (Cq), 134.5 (Cq), 133.1 (Cq), 132.8 (CH), 131.1 (Cq), 130.7 (Cq), 129.2 (CH), 129.2 (CH), 128.5 (CH), 127.6 (CH), 127.4 (CH), 122.1 (CH), 122.0 (CH), 35.7 (CH), 32.8 (CH), 31.5 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 10.7 min., t_r (*R* catalyst used) = 15.0 min., 93% (*S* catalyst used)/ 90% (*R* catalyst used) *ee*.

$[\alpha]_D^{26}$ = 70.9° (c = 0.5, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{12}F_3NO_5$ $[M+Na]^+$: 358.0661, found: 358.0668.

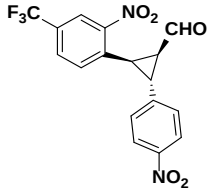
2-(2-nitro-4-(trifluoromethyl)phenyl)-3-(4-nitrophenyl)cyclopropane-1-carbaldehyde (172n)



The reaction was performed following the general procedure **2**.The crude was purified by column chromatography 1:7 (hexane/ EtOAc) to obtain 82.1 mg of the desired product as yellow oil. Yield: 52%.The diastereomeric ratio was determined by NMR of the crude: 4:2:1.

Diastereomer 1, major:

(1*S*,2*R*,3*R*)-2-(2-nitro-4-(trifluoromethyl)phenyl)-3-(4-nitrophenyl)cyclopropane-1-carbaldehyde



IR: 3083 (C-H stretch aromatic), 2851 (C-H stretch aldehyde), 1706 (C=O stretch aldehyde), 1537 (aromatic NO_2), 1346 (aromatic NO_2), 1325 (CF_3 antiasym stretch), 668 (CF_3 attached to aromatics (CF_3 deformation)) cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.61 (d, *J* = 2.2 Hz, 1H), 8.27 – 8.21 (m, 3H), 7.87 (d, *J* = 7.1 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 3.49 ($_{ap}$t, *J* = 8.3 Hz, 1H), 3.38 (dd, *J* = 7.2, 5.3 Hz, 1H), 3.06 (ddd, *J* = 9.2, 5.3, 2.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.0 (CHO), 149.9 (Cq), 147.3 (Cq), 145.0 (Cq), 134.1 (Cq), 133.2 (CH), 131.4 (Cq), 129.7 (CH), 129.7 (CH), 127.4 (CH), 124.2 (CH), 122.3 (CH), 122.2 (CH), 121.3 (Cq), 39.0 (CH), 34.6 (CH), 31.8 (CH).

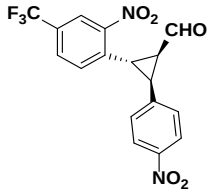
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 75:25, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 20.4 min., t_r (*R* catalyst used) = 27.7 min., 80% (*S* catalyst used)/ 85% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = - 11.0° (c = 0.5, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{11}F_3N_2O_5$ $[M+Na]^+$: 403.0512, found: 403.0507.

Diastereomer 2, minor:

(1*S*,2*S*,3*S*)-2-(2-nitro-4-(trifluoromethyl)phenyl)-3-(4-nitrophenyl)cyclopropane-1-carbaldehyde



IR: 3083 (C-H stretch aromatic), 2851 (C-H stretch aldehyde), 1706 (C=O stretch aldehyde), 1537 (aromatic NO_2), 1346 (aromatic NO_2), 1325 (CF_3 antiasym stretch), 668 (CF_3 attached to aromatics (CF_3 deformation)) cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.27 (d, *J* = 4.2 Hz, 1H), 8.29 (d, *J* = 1.2 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 7.87 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 1H), 4.05 – 3.99 (m, 1H), 3.16 (dd, *J* = 9.6, 7.5 Hz, 1H), 2.75 (ddd, *J* = 9.6, 5.5, 4.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.0 (CHO), 150.1 (Cq), 147.4 (Cq), 141.2 (Cq), 136.6 (Cq), 131.3 (Cq), 130.3 (CH), 130.1 (CH), 130.0 (CH), 129.9 (CH), 123.9 (CH), 122.6 (CH), 122.6 (CH), 121.2 (Cq), 37.5 (CH), 34.6 (CH), 27.1 (CH).

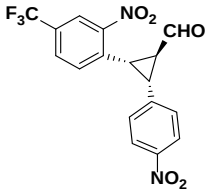
The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 230 nm): t_r (*S* catalyst used) = 23.0 min., t_r (*R* catalyst used) = 21.7 min., 75% (*S* catalyst used)/ 74% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = 66.3° (c = 0.2, $CHCl_3$) **(*R* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{11}F_3N_2O_5$ $[M+Na]^+$: 403.0512, found: 403.0503.

Diastereomer 3, minor':

(1*S*,2*S*,3*R*)-2-(2-nitro-4-(trifluoromethyl)phenyl)-3-(4-nitrophenyl)cyclopropane-1-carbaldehyde



IR: 3083 (C-H stretch aromatic), 2851 (C-H stretch aldehyde), 1706 (C=O stretch aldehyde), 1537 (aromatic NO_2), 1346 (aromatic NO_2), 1325 (CF_3 antiasym stretch), 668 (CF_3 attached to aromatics (CF_3 deformation)) cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 9.75 (d, *J* = 3.5 Hz, 1H), 8.08 (d, *J* = 1.2 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.76 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.70 (dd, *J* = 10.2, 5.9 Hz, 1H), 3.36 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.07 ($_{ap}$td, *J* = 5.9, 3.5 Hz, 1H).

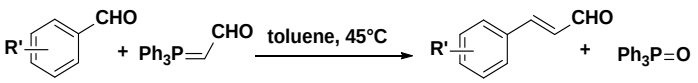
^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.0 (CHO), 150.2 (Cq), 147.1 (Cq), 141.2 (Cq), 133.3 (Cq), 132.7 (CH), 131.8 (Cq), 129.7 (CH), 129.7 (CH), 128.4 (CH), 123.7 (CH), 122.4 (CH), 122.4 (CH), 121.1 (Cq), 35.7 (CH), 32.4 (CH), 32.4 (CH).

The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 210 nm): t_r (*S* catalyst used) = 24.7 min., t_r (*R* catalyst used) = 28.5 min., 69% (*S* catalyst used)/ 79% (*R* catalyst used) *ee*.

$[\alpha]_D^{23}$ = 18.2° (c = 0.5, $CHCl_3$) **(*S* catalyst used)**

HRMS (ESI+) Exact mass calculated for $C_{17}H_{11}F_3N_2O_5$ $[M+Na]^+$: 403.0512, found: 403.0515.

Synthesis of the starting materials: α,β-unsaturated aldehydes



The starting aldehydes were synthesized trough a Wittig reaction, following the procedure described in literature.[88] In a 250 mL round bottom flask a substituted benzaldehyde derivative (2 equiv.) and (triphenylphosphoranyldiene)acetaldehyde (1 equiv.) were stirred in anhydrous

toluene under reflux at 45 °C in an atmosphere of argon. Yields were obtained following purification by column chromatography.

The ^{1}H-NMR of the aldehydes **2h, 2i** and **2l** are consistent with the ones provided in literature.[89]

The ^{1}H-NMR of the aldehydes **2j** and **2k** are consistent with the ones provided in literature.[90]

The ^{1}H-NMR of the aldehydes **2e** is consistent with the ones provided in literature.[91]

The ^{1}H-NMR of the aldehydes **2f** is consistent with the ones provided in literature.[92]

The ^{1}H-NMR of the compound (2-(3-nitropropyl)-1,3-dioxolane) **141 is** consistent with the ones provided in literature.[93]

List of References

[1] R. Rios, Ed. , *Stereoselective Organocatalysis: Bond Formation Methodologies and Activation Modes*, Wiley, Hoboken, **2013**.

[2] L. Carroccia, B. Musio, L. Degennaro, G. Romanazzi, R. Luisi, *J. Flow Chem.* **2013**, *3*, 29–33.

[3] A. Lefranc, L. Guenee, A. Alexakis, *Org. Lett.* **2013**, *15*, 2172–21775.

[4] A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703–4832.

[5] B. List, *Angew. Chemie - Int. Ed.* **2010**, *49*, 1730–1734.

[6] H. D. Dakin, *J. Biol. Chem.* **1910**, *7*, 49–55.

[7] T. Taguchi, A. Kawara, *Tetrahedron Lett.* **1994**, *35*, 8805–8808.

[8] B. M. Yamaguchi, T. Shiraishi, M. Hirama, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1176–1178.

[9] B. List, R. A. Lerner, C. F. B. Iii, N. Torrey, P. Road, L. Jolla, R. V December, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

[10] B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575.

[11] K. A. Ahrendt, C. J. Borths, D. W. C. Macmillan, R. V January, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

[12] A.-N. Alba, X. Companyo, M. Viciano, R. Rios, *Curr. Org. Chem.* **2009**, *13*, 1432–1474.

[13] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[14] Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.

[15] M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964–6965.

[16] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chemie - Int. Ed.* **2005**, *44*, 4212–4215.

[17] R. Rios, H. Sundén, J. Vesely, G.-L. Zhao, P. Dziedzic, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1028–1032.

[18] H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894.

[19] J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chemie Int. Ed.* **2007**, *46*, 778–781.

[20] Y. S. Kim, S. M. Kim, B. Wang, X. Companyó, J. Li, A. Moyano, S. Im, Z. Tošner, J. W. Yang, R. Rios, *Adv. Synth. Catal.* **2014**, *356*, 437–446.

[21] X. Companyó, A. N. Alba, F. Cárdenas, A. Moyano, R. Rios, *European J. Org. Chem.* **2009**, 3075–3080.

[22] K. Reitel, K. Lippur, I. Järving, M. Kudrjašova, M. Lopp, T. Kanger, *Synth.* **2013**, *45*, 2679–2683.

[23] F. Vetica, R. de Figueiredo, M. Orsini, D. Tofani, T. Gasperi, *Synthesis (Stuttg).* **2015**, *47*,

2139–2184.

[24] C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2431.

[25] H. Pellissier, *Tetrahedron* **2008**, *64*, 7041–7095.

[26] L. F. Tietze, *Chem. Rev. (Washington, D. C.)* **1996**, *96*, 115–136.

[27] L. F. Tietze, U. Beifuss, *Angew. Chemie - Int. Ed.* **1993**, *32*, 131–163.

[28] C. M. Sousa, J. Berthet, S. Delbaere, P. J. Coelho, *J. Org. Chem.* **2014**, *79*, 5781–5786.

[29] G. Giorgi, S. Miranda, M. Ruiz, J. Rodriguez, P. López-Alvarado, J. C. Menéndez, *European J. Org. Chem.* **2011**, 2101–2110.

[30] L. F. Tietze, *Domino Reactions: Concepts for Efficient Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, **2014**.

[31] S. Rendler, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 5027–5029.

[32] J. Poulin, C. M. Grisé-Bard, L. Barriault, *Chem. Soc. Rev.* **2009**, *38*, 3092–3101.

[33] E. Richmond, K. B. Ling, N. Duguet, L. B. Manton, N. Çelebi-Ölçüm, Y.-H. Lam, S. Alsancak, A. M. Z. Slawin, K. N. Houk, A. D. Smith, *Org. Biomol. Chem.* **2015**, *13*, 1807–1817.

[34] Z.-Q. Zhu, J.-S. He, H.-J. Wang, Z.-Z. Huang, *J. Org. Chem.* **2015**, *80*, 9354–9359.

[35] J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724.

[36] Y.-K. Liu, Z.-L. Li, J.-Y. Li, H.-X. Feng, Z.-P. Tong, *Org. Lett.* **2015**, *17*, 2022–2025.

[37] F. Ullah, G.-L. Zhao, L. Deiana, M. Zhu, P. Dziedzic, I. Ibrahem, P. Hammar, J. Sun, A. Córdova, *Chem. - A Eur. J.* **2009**, *15*, 10013–10017.

[38] S. Zhang, Y. Zhang, Y. Ji, H. Li, W. Wang, *Chem. Commun.* **2009**, 4886–4888.

[39] C. Cassani, X. Tian, E. C. Escudero-Adán, P. Melchiorre, *Chem. Commun.* **2011**, *47*, 233–235.

[40] X. Companyó, A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyano, R. Rios, *Chem. Commun.* **2010**, *46*, 6953–6955.

[41] S. Vera, Y. Liu, M. Marigo, E. Escudero-Adán, P. Melchiorre, *Synlett* **2011**, *2011*, 489–494.

[42] M. B. Cid, S. Duce, S. Morales, E. Rodrigo, J. L. G. Ruano, *Org. Lett.* **2010**, *12*, 3586–9.

[43] M. Meazza, V. Ceban, M. B. Pitak, S. J. Coles, R. Rios, *Chem. - A Eur. J.* **2014**, *20*, 16853–16857.

[44] H. Morita, M. Arisaka, N. Yoshida, J. Kobayashi, *J. Org. Chem.* **2000**, *65*, 6241–6245.

[45] D. R. Williams, K. Shamim, J. P. Reddy, G. S. Amato, S. M. Shaw, *Org. Lett.* **2003**, *5*, 3361–3364.

[46] D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633.

[47] A. C. Cutter, I. R. Miller, J. F. Keily, R. K. Bellingham, M. E. Light, R. C. D. Brown, *Org. Lett.* **2011**, *13*, 3988–3991.

[48] S. V. Kauloorkar, V. Jha, G. Jogdand, P. Kumar, *Org. Biomol. Chem.* **2014**, *12*, 4454–4460.

[49] M. Bergeron-Brlek, M. Meanwell, R. Britton, *Nat. Commun.* **2015**, *6*, 6903–6908.

[50] S. Fustero, J. Moscardó, M. Sánchez-Roselló, S. Flores, M. Guerola, C. Del Pozo, *Tetrahedron* **2011**, *67*, 7412–7417.

[51] D. Su, X. Wang, C. Shao, J. Xu, R. Zhu, Y. Hu, *J. Org. Chem.* **2011**, *76*, 188–194.

[52] T. Syntheses, D. Koley, Y. Krishna, K. Srinivas, A. A. Khan, R. Kant, *Angew. Chemie Int. Ed.* **2014**, *53*, 13196–13200.

[53] A. Srikrishna, N. C. Babu, M. S. Rao, *Tetrahedron* **2004**, *60*, 2125–2130.

[54] R. G. Thorat, S. V. Pansare, *European J. Org. Chem.* **2013**, 7282–7285.

[55] M. Ahari, A. Perez, C. Menant, J. Vasse, J. Szymoniak, *Synthesis (Stuttg).* **2008**, *10*, 2473–2476.

[56] N. Kise, Y. Inoue, T. Sakurai, *Tetrahedron Lett.* **2013**, *54*, 3281–3285.

[57] S. V. Kauloorkar, V. Jha, P. Kumar, *RSC Adv.* **2013**, *3*, 18288–18291.

[58] G. Bartoli, G. Bencivenni, R. Dalpozzo, *Synthesis (Stuttg).* **2014**, *46*, 979–1029.

[59] R. D. Smith, H. E. Simmons, *Org. Synth.* **1961**, *41*, 72–75.

[60] R. Rios, J. Liang, M. M.-C. Lo, G. C. Fu, *Chem. Commun.* **2000**, *2*, 377–378.

[61] D. Qian, J. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 677–698.

[62] R. K. Kunz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3240–3241.

[63] I. Ibrahem, G. L. Zhao, R. Rios, J. Vesely, H. Sundén, P. Dziedzic, A. Córdova, *Chem. - A Eur. J.* **2008**, *14*, 7867–7879.

[64] A. Russo, S. Meninno, C. Tedesco, A. Lattanzi, *European J. Org. Chem.* **2011**, 5096–5103.

[65] a. J. A. Cobb, L. S. Aitken, L. E. Hammond, S. Rajkumar, K. Shankland, G. D. Brown, *Chem. Commun.* **2015**, *51*, 13558–13561.

[66] H. Gotoh, D. Okamura, H. Lshikawa, Y. Hayashl, *Org. Lett.* **2009**, *11*, 4056–4059.

[67] G. Sahoo, H. Rahaman, Á. Madarász, I. Pápai, M. Melarto, A. Valkonen, P. M. Pihko, *Angew. Chemie - Int. Ed.* **2012**, *51*, 13144–13148.

[68] M. Kaasik, A. Noole, K. Reitel, I. Järving, T. Kanger, *European J. Org. Chem.* **2015**, *2015*, 1745–1753.

[69] M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804–818.

[70] D. Y.-K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631–4642.

[71] R. Faust, *Angew. Chemie - Int. Ed.* **2001**, *40*, 2251–2253.

[72] F. Gnad, O. Reiser, *Chem. Rev.* **2003**, *103*, 1603–1623.

[73] R. Csuk, M. J. Schabel, Y. Von Scholz, *Tetrahedron Asymmetry* **1996**, *7*, 3505–3512.

[74] J. S. Ravi Kumar, S. Roy, A. Datta, *Bioorganic Med. Chem. Lett.* **1999**, *9*, 513–514.

[75] M. Kaasik, A. Noole, K. Reitel, I. Järving, T. Kanger, *European J. Org. Chem.* **2015**, *8*, 1745–

1753.

[76] D. K. Mohapatra, A. Datta, *J. Org. Chem.* **1998**, *63*, 642–646.

[77] X. Zhang, K. Hodgetts, S. Rachwal, H. Zhao, J. W. F. Wasley, K. Craven, R. Brodbeck, A. Kieltyka, D. Hoffman, M. D. Bacolod, et al., *J. Med. Chem.* **2000**, *43*, 3923–3932.

[78] S. S. Sohn, J. W. Bode, *Angew. Chemie Int. Ed.* **2006**, *45*, 6021–6024.

[79] M. Meazza, M. E. Light, A. Mazzanti, R. Rios, *Chem. Sci.* **2016**, *7*, 984–988.

[80] T. Li, J. Zhu, D. Wu, X. Li, S. Wang, H. Li, J. Li, W. Wang, *Chem. - A Eur. J.* **2013**, *19*, 9147–9150.

[81] M. Silvi, E. Arceo, I. D. Jurberg, C. Cassani, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 6120–6123.

[82] H. W. Shih, M. N. Vander Wal, R. L. Grange, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 13600–13603.

[83] E. A. Carter, J. T. Hynes, *J. Phys. Chem.* **1989**, *93*, 2184–2187.

[84] E. Rahkamaa, J. Jokisaari, *Zeitschrift fuer Naturforschung, Tl. A Astrophys. Phys. und Phys. Chemie* **1968**, *23*, 2094 – 2097.

[85] M. Barfield, M. D. Johnston, *Chem. Rev.* **1973**, *73*, 53–73.

[86] K. V Mikkelsen, P. Jørgensen, *J. Chem. Phys.* **1998**, *108*, 2528–2537.

[87] D. Zaccari, V. Barone, J. E. Peralta, R. H. Contreras, O. E. Taurian, E. Diez, A. Esteban, *Int. J. Mol. Sci.* **2003**, *4*, 93–106.

[88] F. Hirayama, H. Koshio, N. Katayama, H. Kurihara, Y. Taniuchi, K. Sato, N. Hisamichi, Y. Sakai-Moritani, T. Kawasaki, Y. Matsumoto, et al., *Bioorg. Med. Chem.* **2002**, *10*, 1509–23.

[89] T.-S. Jiang, J.-H. Li, *Chem. Commun.* **2009**, 7236–7238.

[90] E. Kim, M. Koh, B. J. Lim, S. B. Park, *J. Am. Chem. Soc.* **2011**, *133*, 6642–6649.

[91] F. Cermola, *J. Chem. Res.* **2005**, *2005*, 677–681.

[92] I. Coldham, a. J. M. Burrell, H. D. S. Guerrand, N. Oram, *Org. Lett.* **2011**, *13*, 1267–1269.

[93] M. Heme, *Helv. Chim. Acta* **1994**, *77*, 579 – 585.