UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

Organic Chemistry: Synthesis, Catalysis and Flow

New Methodologies in Asymmetric Allylic Substitution and Organocascade Reactions

by

Victor Ceban

Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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NEW METHODOLOGIES IN ASYMMETRIC ALLYLIC SUBSTITUTION AND ORGANOCASCADE REACTIONS

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Asymmetric organocatalysis and organometallic catalysis are rapidly developing. The first catalytic process can be traced back in the XIX century. Since then, research in the field of catalysis grew, especially in the last decades exponentially. Four projects involving organocatalysis are described in this thesis: "Highly enantioselective addition of anthrones to MBH-carbonates", "Synergistic catalysis: Highly diastereoselective benzoxazole addition to Morita-Baylis-Hillman carbonates", "Three-component diastereoselective cascade synthesis of thiohydantoins" and "Highly diastereoselective synthesis of spiropyrazolones".

A) Asymmetric allylic substitution

Since Tsuji and Trost reported their first examples of allylic substitution catalysed by palladium salts in 1963, many examples of allylic substitution were published involving other types of transition metals. Later, in 2002, Kim *et al.* reported the first allylic substitution using a metal-free approach.
Morita-Baylis-Hillman carbonates are important scaffolds in the synthesis of more complex molecules due to the presence of numerous functional groups.
In this thesis two examples of asymmetric allylic substitution involving Morita-Baylis-Hillman (MBH) carbonates are described.

Highly enantioselective addition of anthrones to Morita-Baylis-Hillman carbonates

Anthrone derivatives are present in various natural sources and are known for their medicinal effects. We were interested in the enantioselective addition of anthrone to MBH-carbonates. The products were synthesised in very good yields

and enantioselectivity by using a $(DHQD)_2AQN$ as catalyst. Moreover, a kinetic resolution was perfomed in order to better understand the mechanistic process.

Synergistic catalysis: Highly diastereoselective benzoxazole addition to Morita-Baylis-Hillman carbonates

Catalysis is one of the most efficient strategies for identifying new chemical reactions. Usually, a catalytic pathway relies on the interaction of a single catalyst with a single reagent in order to lower the energetic barrier. In some cases, the mono-catalytic concept is not enough and other strategies are used, in particular, synergistic catalysis. This consists in the activation of the electrophile and the nucleophile by two different catalysts for reaction to occur. Based on this idea, we studied the addition of benzoxazoles to Morita-Bayllis-Hillman carbonates by the use of two different catalysts (Metal Lewis acid and Organic Lewis base). Both catalysts work in a concerted way giving the final compound in high yield and diastereoselectivity.

B) Organocascade reactions

Synthesis of complex organic molecules is a challenge for every chemist. The aim is achieveing the final product in as few steps as possible using safer, cleaner and environmentally friendly techniques. One-pot reactions emerged as a powerful tool in creating several bonds in one step. Based on this idea, we studied two reactions:

Three-component diastereoselective cascade synthesis of thiohydantoins

Thiohydantoins have interesting medicinal applications such as antibacterial, antiviral, antimutagenic, etc. Synthesising these scaffolds in one step via three-component one-pot reaction was our main focus. We developed a three-component cascade reaction for the synthesis of thiohydantoins. The reaction between α-amino esters, nitrostyrenes and aromatic isothiocyanates is efficiently promoted by organic bases to afford highly substituted thiohydantoins in moderate to good yields and diastereoselectivities.

Highly diastereoselective synthesis of spiropyrazolones

Spiro compounds are present in various natural products and are powerful active agents. We have developed a methodology for the synthesis of spiropyrazolone bearing four chiral centres. The reaction was catalysed by a secondary amine in

a Michael-aldol cascade fashion affording the product in very good yields and diastereoselectivity.

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Definitions and Abbreviations

A: Acid

AAS: Asymmetric allylic substitution

ACN: Acetonitrile

AIBN: Azobisisobutyronitrile

ALA Dehydratase: Aminolevulinate dehydratase

B: Base

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl

BINOL: 1,1'-Bi-2-naphtol

Boc: tert-Butyloxycarbonyl

CDC: Cross-dehydrogenative coupling

DABCO: 1,4-diazabicyclo[2,2,2]octane

Dba: Dibenzylideneacetone

DBU: 1,8-Diazabicycloundec-7-ene

DCM: Dichloromethane

$(DHQD)_2AQN$: Hydroquinidine(anthraquinone-1,4-diyl)diether

$(DHQD)_2PHAL$: Hydroquinidine1,4-phtalazinediyldiether

$(DHQD)_2PYR$: Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether

$(DHQ)_2AQN$: Hydroquinine anthraquinone-1,4-diyl diether

$(DHQ)_2PHAL$: Hydroquinine1,4-phtlazinediyldiether

$(DHQ)_2PYR$: Hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether

DMAP: 4-dimethylaminpyridine

DMF: Dimethylformamide

DNA: Deoxyribonucleic acid

Dr: diastereomeric ratio

Ee: enantiomeric excess

Er: enantiomeric ratio

ESI: Electrospray ionization

EWG: Electron withdrawing group

GSK: GlaxoSmithKline

HIV: Human immunodeficiency virus

HOMO: Highest occupied molecular orbital

HPLC: High-Performance Liquid Chromatography

HR-MS: High Resolutions Mass Spectrometry

β-ICPD: beta-isocupreidine

IR: Infra-red

LDA: Lithium Diisopropylamide

LUMO: Lowest unoccupied molecular orbital

M: medium (IR) or multiplet (NMR)

MBH: Morita-Baylis-Hillman

MS: Mass Spectrometry

NMR: Nuclear Magnetic Resonance

Nu: Nucleophile

P: Product

PBG Deaminase: Porphobilinogen deaminase

PCC: Pyridinium chlorochromate

PivOH: Pivalic Acid

RAMP: (*R*)-1-amino-2-methoxymethylpyrrolidine

S: Substrate, singlet (NMR) or strong (IR)

SAMP: (*S*)-1-amino-2-methoxymethylpyrrolidine

Sn: nucleophilic substitution

SOMO: Singly occupied molecular orbital

TBAF: Tetra-butylammonium fluoride

TEA: Triethylamine

THF: Tetrahydrofurane

TLC: Thin Layer Chromatography

UV: ultraviolet

W: weak

1. Introduction to catalysis

A chemical reaction is a process in which either one substance is a subject to intramolecular modifications or two and/or more substances react between themselves in order to form new products. In 1889 Svante Arrhenius introduced the collision theory which enhanced our understanding of how chemical bonds are broken and new chemical bonds are formed.[1] He explained that a reaction only occurs if molecules collide with a particular kinetic energy superior to the minimum energy required for those molecules to approach each other. He also established a reaction profile based on the potential energy and the reaction advancement (**Figure 1.1**). First, the reactants are exposed to a certain potential energy while they approach one another. Then this energy rises until a peak is reached where the molecules are highly distorted then start to decrease forming the new bonds.

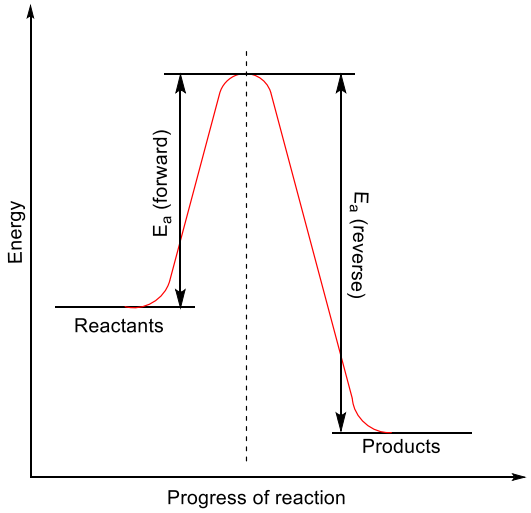


Figure 1.1 Reaction profile

The collision theory was a good start for understanding the reaction processes in atmosphere, but it was less relevant for the reaction occurring in a liquid environment. Another more complex theory was established in order to explain the processes happening in a cell environment for example. This theory is called “transition state theory” or “activated complex theory” which was thoroughly studied by Henry Eyring and Josiah Willard Gibbs (activation Gibbs energy, $\Delta G^{\ddagger}$). In this theory, the two molecules approach each other until their potential energy

has risen to the maximum where the reactants form an activated complex. At this point if the kinetic energy before collision is higher than the minimum energy required for the reaction then the old bonds will break and the new ones will form. If the kinetic energy is lower than the minimum energy required, the reaction will not occur and the reactants will be recovered. A good example of the transition state theory is the nucleophilic substitution (S_N2) reaction between bromomethane and a hydroxide (**Figure 1.2**).[2]

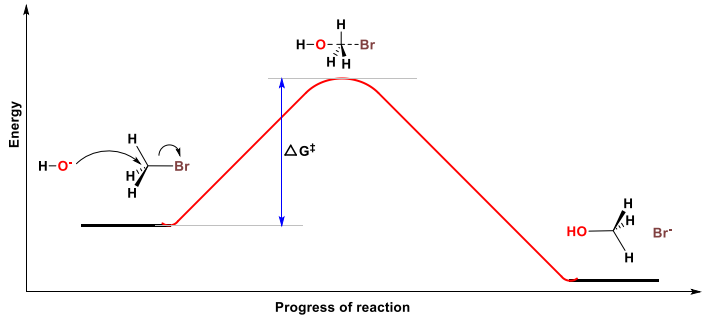


Figure 1.2: S_N2 between bromomethane and hydroxyl group

In order to progress a reaction that typically would not occur due to the high energy barrier, a chemical process called catalysis was developed (**Figure 1.3**).

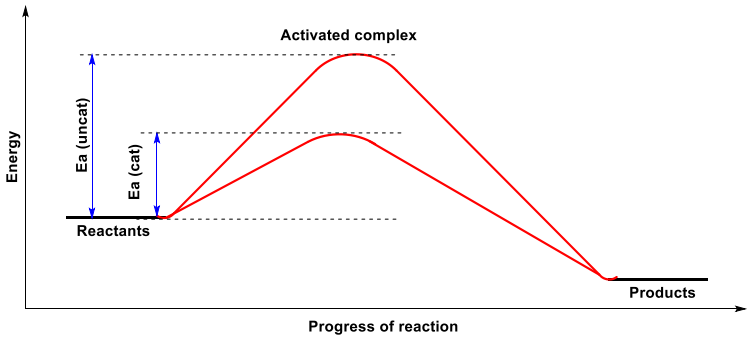


Figure 1.3: Catalysis and activation energy

Catalysis is the field in synthetic chemistry that offers the possibility of fast and selective synthesis of desired chemical molecules with reduced consumption of energy and without consumption of catalyst. The replacement of stoichiometric methodologies with catalytic alternatives is promoted by a growing environmental awareness and by the intention of chemical industry to reduce the waste production.

1.1 Catalytic asymmetric synthesis

Many compounds associated with life forms on our planet are chiral: enzymes, hormones, DNA, etc… The enantiomers of the same product typically have different biological activities. For example, the enantiomers of limonene smell differently: the *(R)*-limonene smells of oranges and *(S)*-limonene smells of lemons (**Figure 1.4**).[3]

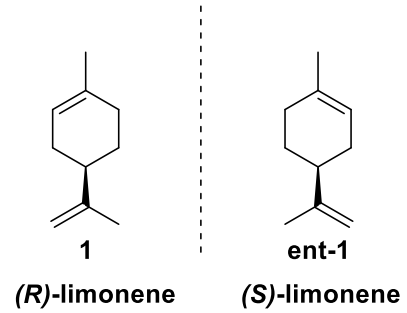


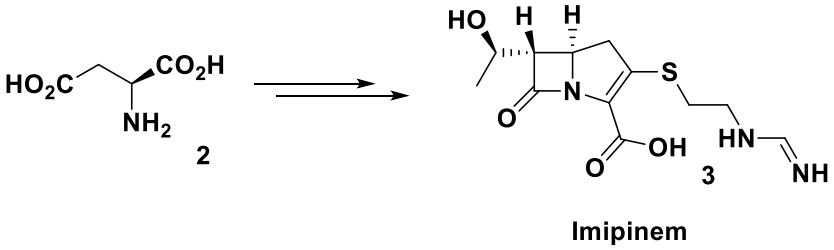
Figure 1.4: Enantiomers of limonene

A more tragic example is thalidomide, a drug prescribed for morning sickness in pregnant women. One enantiomer was beneficial while the other caused deformities in the limbs of new born children. Since then, the drug industry has researched new ways to synthesise the enantiopure active agent and tests it thoroughly for biological activity and toxicity.

The question on this matter is: How do we perform an asymmetric synthesis?

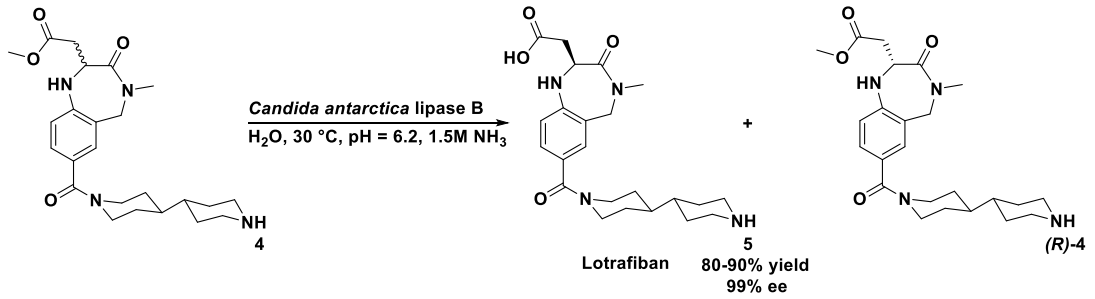
Chemists have devised with several solutions:

1) Chiral pool synthesis is a strategy in which the synthesis starts with enantiopure starting material such as amino acids or saccharides and during the synthetic process the chirality of that atom is preserved. This strategy was used for the enantioselective synthesis of Imipinem (Merck)[4] which is an intravenous *β*-lactam antibiotic. They started with L-Aspartic acid to get the final product in good yields and enantioselectivity (**Scheme 1.1**).



Scheme 1.1 Chiral pool strategy for Imipinem synthesis

2) Resolution is a strategy in which enantiomers are separated either chemically, chromatographically (HPLC) or catalytically (eg. enzymatic). A good example of using this method is the synthesis of Lotrafiban (GSK).[5] In their case, they used an enzymatic kinetic resolution obtaining the product and the *S* enantiomer of the racemic precursor (**Scheme 1.2**).



Scheme 1.2 Lotrafiban enantioselective kinetic resolution

Another example of chemical kinetic resolution will be described later in one of the projects of this thesis (**Chapter 2.2**).

3) Chiral auxiliaries: this strategy involves adding an enantiopure moiety to the reagent, creating a temporary asymmetric centre. This auxiliary will influence the outcome of the stereoselective reaction then it will be removed. The most known and widely used auxiliaries are Evans, Ellman, Oppolzer and Enders auxiliaries (**Figure 1.5**).

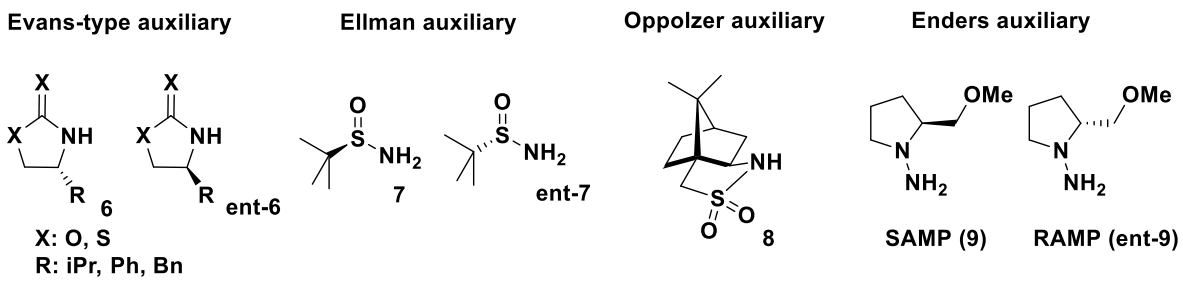
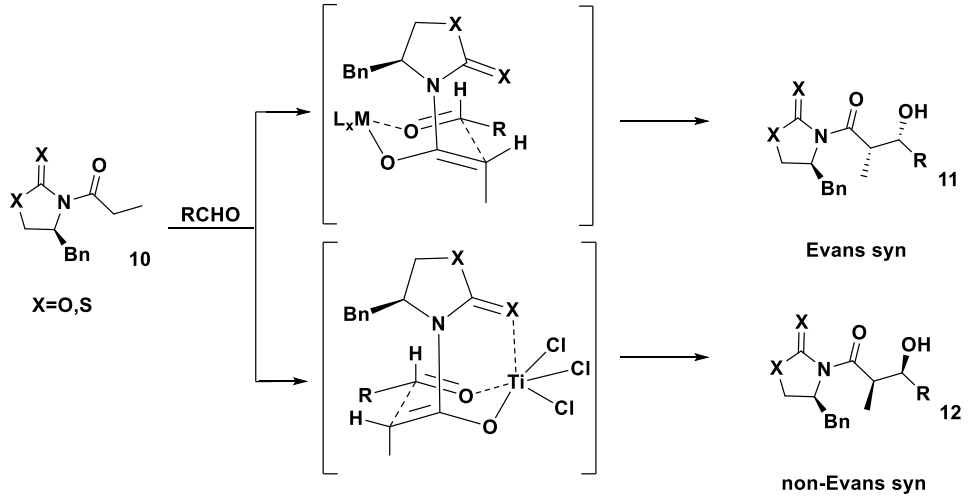


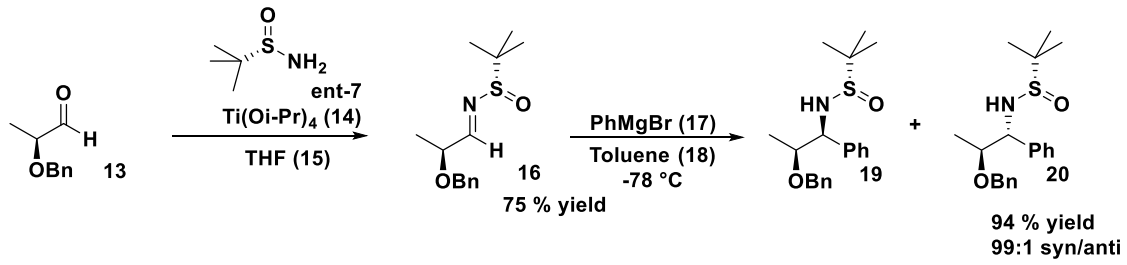
Figure 1.5 Evans/Nagao, Ellman, Oppolzer, Enders auxiliaries

The Evans (where X=O) and Nagao (where X=S) auxiliaries are usually used for the aldol reactions,[6] alkylation reactions[7] and Diels-Alder reactions (**Scheme 1.3**).[8]



Scheme 1.3 Aldol reaction via Evans/Nagao auxiliary technique[9]

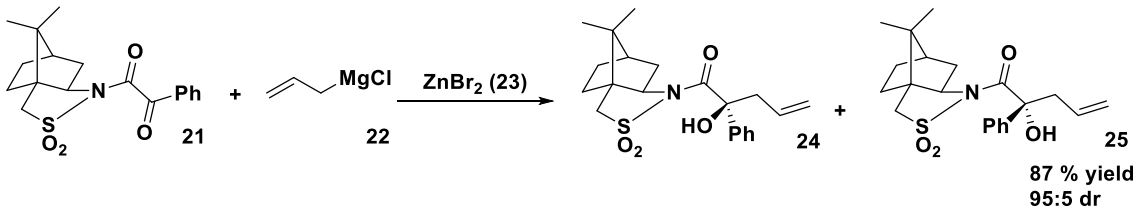
The Ellman auxiliary, *tert*-butanesulfinamide, reacts with an aldehyde or ketone forming an imine. This imine acts as an electrophile which can react with nucleophiles in order to form new C-C bonds (**Scheme 1.4**).



Scheme 1.4 Ellman auxiliary example[10]

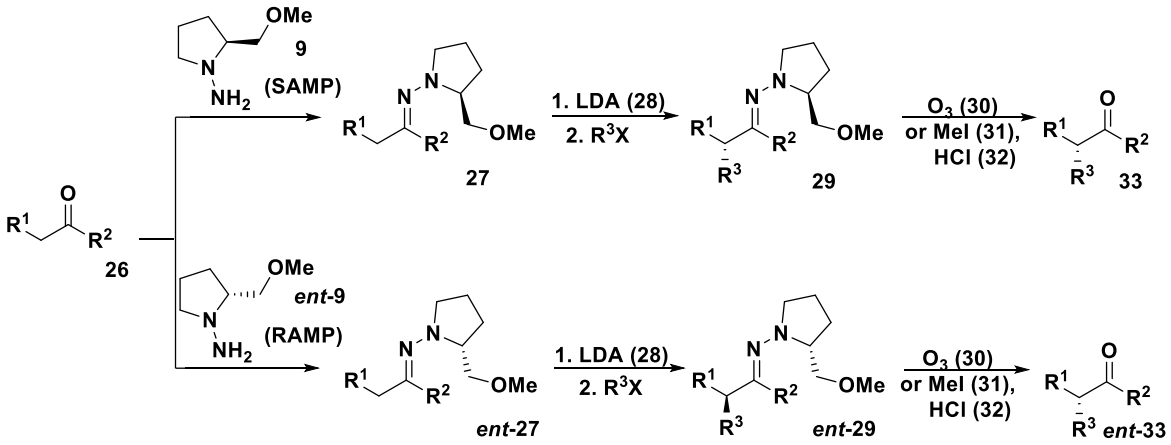
Oppolzer's camphorsultam is a chiral auxiliary which can be applied in a variety of reactions such as alkylations, allylations, reductions, cyclopropanation, Diels-Alder reactions, 1,3-dipolar cycloadditions, aldol reactions, etc...[11]

An example of Oppolzer's chiral auxiliary was reported by Jurczak and Kiegiel. They used it to do a diastereoselective allylic addition to *α*-ketoimide derived from Oppolzer's sultam. The final product was obtained in good yield and very good diastereoselectivity (**Scheme 1.5**).[12]



Scheme 1.5 Oppolzer's chiral auxiliary in allylic addition

The Enders auxiliary is a chiral hydrazine which reacts with an aldehyde or ketone forming a hydrazone. Then the *α*-position of the hydrazone is deprotonated with LDA followed by its addition to an electrophile (**Scheme 1.6**).[13]



Scheme 1.6 Enders auxiliary SAMP/RAMP

4) Enantioselective synthesis consists in creating new chiral centres by using a chiral reagent which will not be a part of the product. If the chiral reagent is in substoichiometric quantity, it is called enantioselective synthesis or asymmetric catalysis.

1.2 Organocatalysis

Almost all metabolic transformations are controlled by enzymes which are large, complex molecules and difficult to synthesise. At least half of enzyme catalysts are metal-free. Chemists are constantly searching for simple, cheap, nontoxic, easy to synthesise natural molecules which could perform a similar function as an enzyme. Organocatalysis is defined as the use of small organic molecules to catalyse organic transformations. The term “organocatalysis” was introduced by

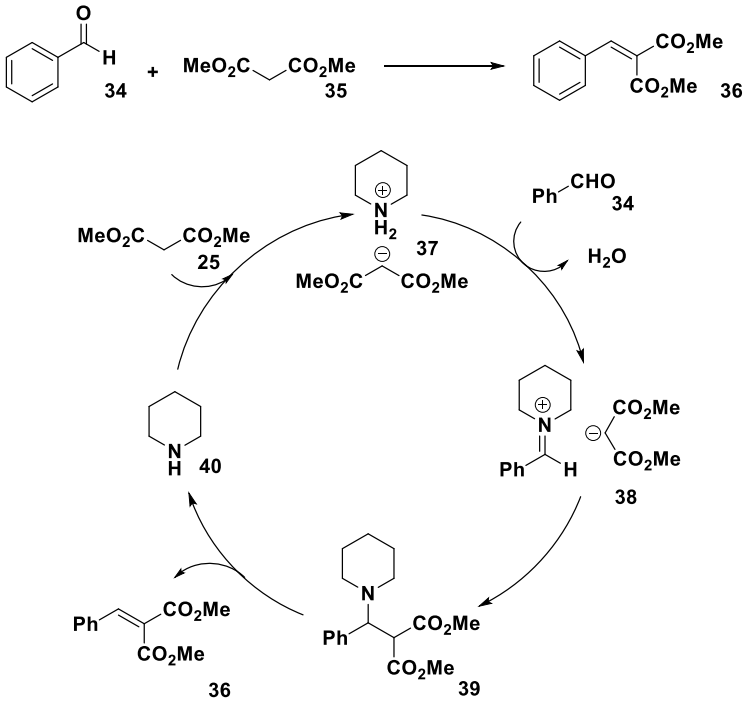
David W. C. MacMillan at the beginning of the 21st century giving the start to an exponential progress in this area over the last decade.

MacMillan describes in his article several advantages of using organocatalysis to other types of catalysis.[14] First, the majority of organic catalysts are insensitive to atmospheric oxygen and moisture which means that the reactions do not require an anhydrous medium and inert atmosphere. Second, the wide variety of organic reagents can be found and obtained from natural sources. Simple catalysts are usually cheap to prepare. Third, small organic molecules tend to be less toxic and environmentally friendly compared to catalysts having a metal in their structure.

A variety of key asymmetric carbon–carbon and carbon–heteroatom bond forming reactions (such as Diels–Alder,[15] aldol condensation, Mannich[16] and Michael[17] reactions, epoxidation,[18] nitroalkane addition to enones[19] and *α*-halogenation[20]) can be carried out by using organocatalytic methods. With the optimal conditions and by using natural or newly designed catalysts, it is possible to obtain enantiomerically pure products in high yields.[21]

1.2.1 A brief history of organocatalysis[22][23]

The first example of an organocatalytic process can be traced to the early works of Emil Knoevenagel. In 1896, he reported the aldol condensation of *β*-ketoesters or malonates with aldehydes or ketones in the presence of a primary or secondary amine, naming the catalysts as "Contactsubstanz".[24] Later, he proposed a mechanism for his reaction (**Scheme 1.7**).



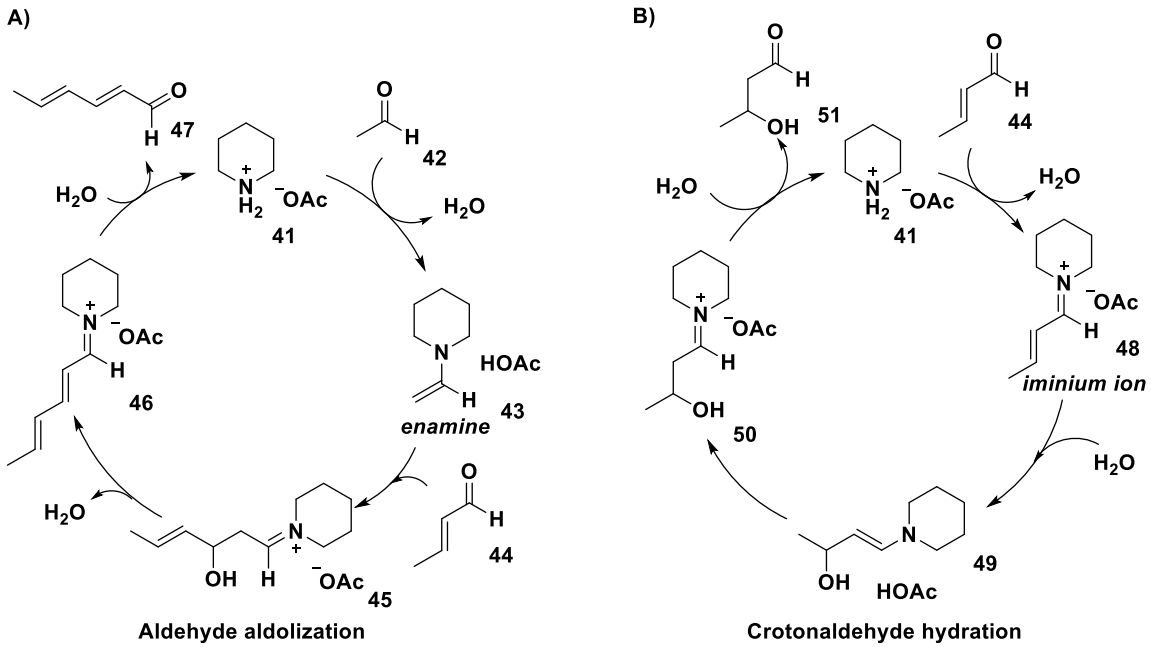
Scheme 1.7 Reaction and Mechanism of Emil Knoevenagel

Inspired by Knoevenagel's work, Henry Drysdale Dakin in 1910 published his work in which he describes the catalytic actions of amino acids, peptone and proteins.[25]

In 1930, Kuhn and Hoffer noticed that secondary amines could not only be used for the catalysis process of Knoevenagel reaction but also for the aldol condensations of aldehydes.[26] One year later, Fischer and Marshall reported a catalytic aldol addition and condensation of acetaldehyde in the presence of primary amino acids.[27]

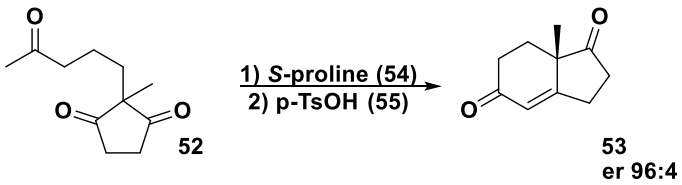
In 1936, Richard Kuhn discovered that aldol condensation of aldehydes works more effectively with piperidinium acetate (**Scheme 1.8A**).[28] Soon after that, Langenbeck and Sauerbier reported a catalytic process for a crotonaldehyde hydration with piperidinium salt (**Scheme 1.8B**).[29]

These studies influenced many scientists such as Wieland, Miescher and Woodward to work on intramolecular aldol reactions catalysed by piperidinium salts. Only in 1965, Spencer confirmed the mechanism of these reactions in which he proves that the process goes via enamine intermediates.[30]



Scheme 1.8 A) Aldehyde aldolization reported by Richard Kuhn; B) Crotonaldehyde hydration reported by Wolfgang Langenbeck

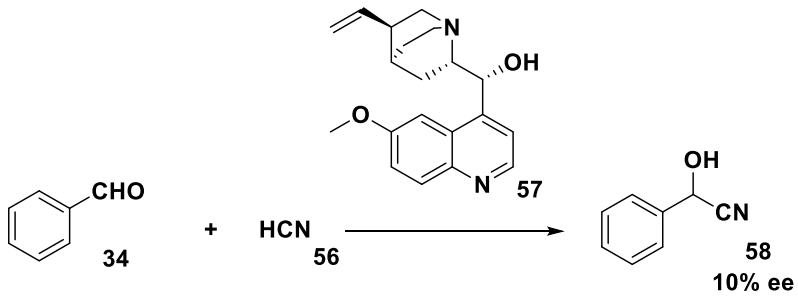
At the beginning of 1970s, Hajos and Parrish and Eder, Sauer and Wiechert reported independently the first asymmetric amine-catalysed aldolization (**Scheme 1.9**).[31]



Scheme 1.9 Hajos & Parrish reaction, 1974

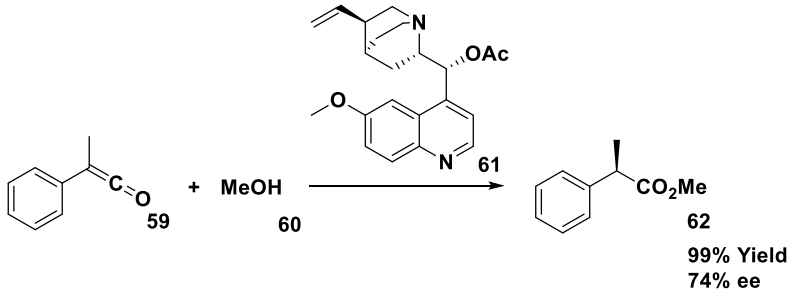
In 1981, Woodward's asymmetric synthesis of erythromycin was published in which he uses D-proline as a catalyst for an asymmetric intramolecular aldol reaction in which the ee of the two products is 12-21% ee and 20-29% ee.[32]

If we look at the history of tertiary amine catalysis, we see that in 1913 Bredig reported a cinchona-alkaloid catalytic process involving the addition of acid cyanhydric to benzaldehyde (**Scheme 1.10**).[33]



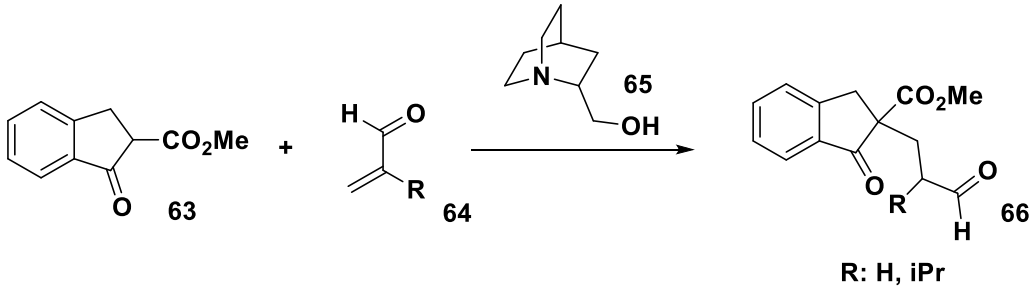
Scheme 1.10 Bredig reaction 1913

In 1960, Pracejus developed a reaction between methyl phenyl ketene and methanol catalysed by acetyl quinine with very good yields and enantioselectivity (**Scheme 1.11**).[34]



Scheme 1.11 Pracejus reaction

Inspired by Pracejus's work, Bergson and Langström reported asymmetric induction in a Michael-type reaction (**Scheme 1.12**).[35]

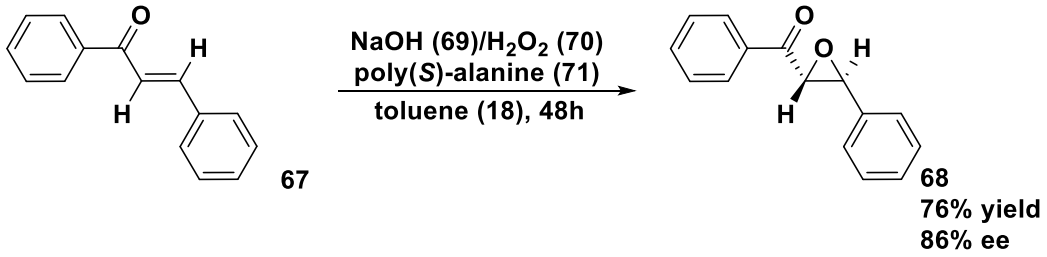


Scheme 1.12 Bergson and Langström reaction

In 1989, Kagan published a Diels-Alder cycloaddition of maleimides to anthrones catalysed by cinchona-alkaloid with up to 61% ee for the final product.

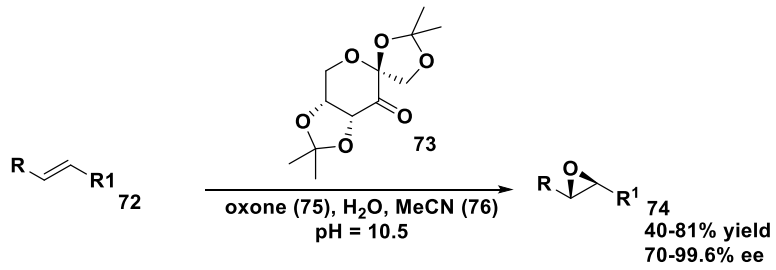
Concerning other types of asymmetric organocatalysis, in 1980 Julià and co-workers reported an epoxidation without using a transition metal (**Scheme**

1.13).[36] Further elaborations were made by Julià and Colonna in order to obtain better results in terms of yields and enantioselectivity.[37]



Scheme 1.13 Julià-Colonna epoxidation

Another epoxidation example was reported by Shi in 1996 alkene using metal-free conditions. The reaction works in high yields and enantioselectivity by using dioxiranes and oxone (**Scheme 1.14**).[38]



Scheme 1.14 Shi epoxidation

With the beginning of the new millennium a new era of organocatalysis began with the work of Benjamin List[39] and David MacMillan[40] in enamine and iminium catalysis. In this period MacMillan reported his catalysts can be used in his work for Diels-Alder reaction, Friedel-Crafts reaction,[41] Michael addition, etc.

A breakthrough in organocatalysis was the discovery in 2003 by Takemoto of the bifunctional base-thiourea catalyst,[42] also the development of phosphoric chiral Brønsted acids by Akiyama[43] and Terada.[44] Two years later, Jørgensen introduced his diphenylprolinol silyl ether catalyst[45] which was used by Hayashi for the first addition of aldehydes to nitroalkene.[46]

Today, many groups in the world are inspired from the results and the work of the afforementioned names. Researchers are developing new reactions and

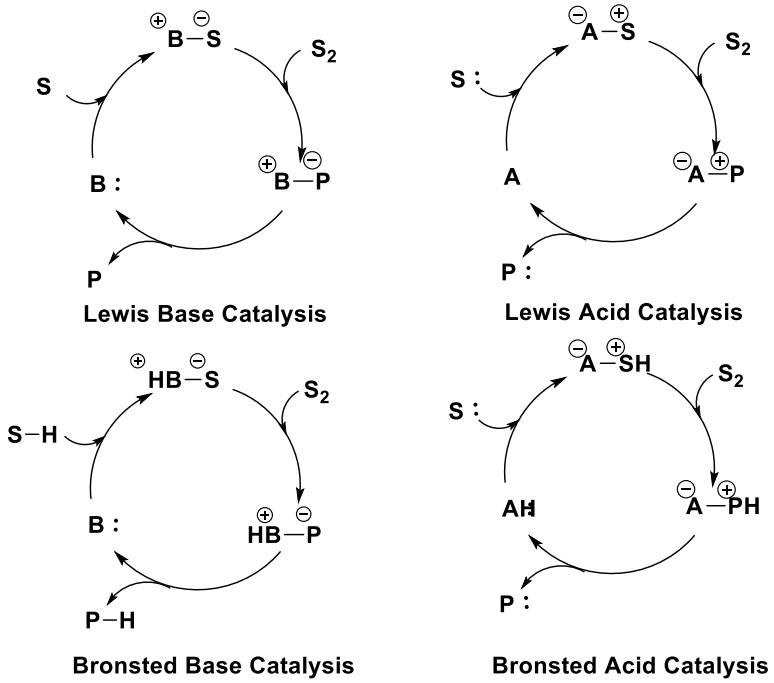
methodologies to expand the asymmetric organocatalysis to other fields of organic chemistry due to its advantages.

1.3 Activation modes in asymmetric organocatalysis

In the last decade a lot of research has been reported in the field of asymmetric organocatalysis. With the enormous body of work, new catalysts have been synthesised which allowed different modes of activations. Based on the type of the catalyst the researchers were able to identify, in most cases, the stereochemical outcome of the reaction. From a mechanistic point of view, the activation mode can be classified according to: a) the chemical nature of the organocatalyst and b) the covalent or noncovalent way of reagent-substrate interaction.[23]

1.3.1 The chemical nature of the organocatalyst classification

Organocatalysts can be classified in four groups: Lewis bases, Lewis acids, Brønsted bases and Brønsted acids.[47] The general catalytic cycles are shown in **figure 1.15**.



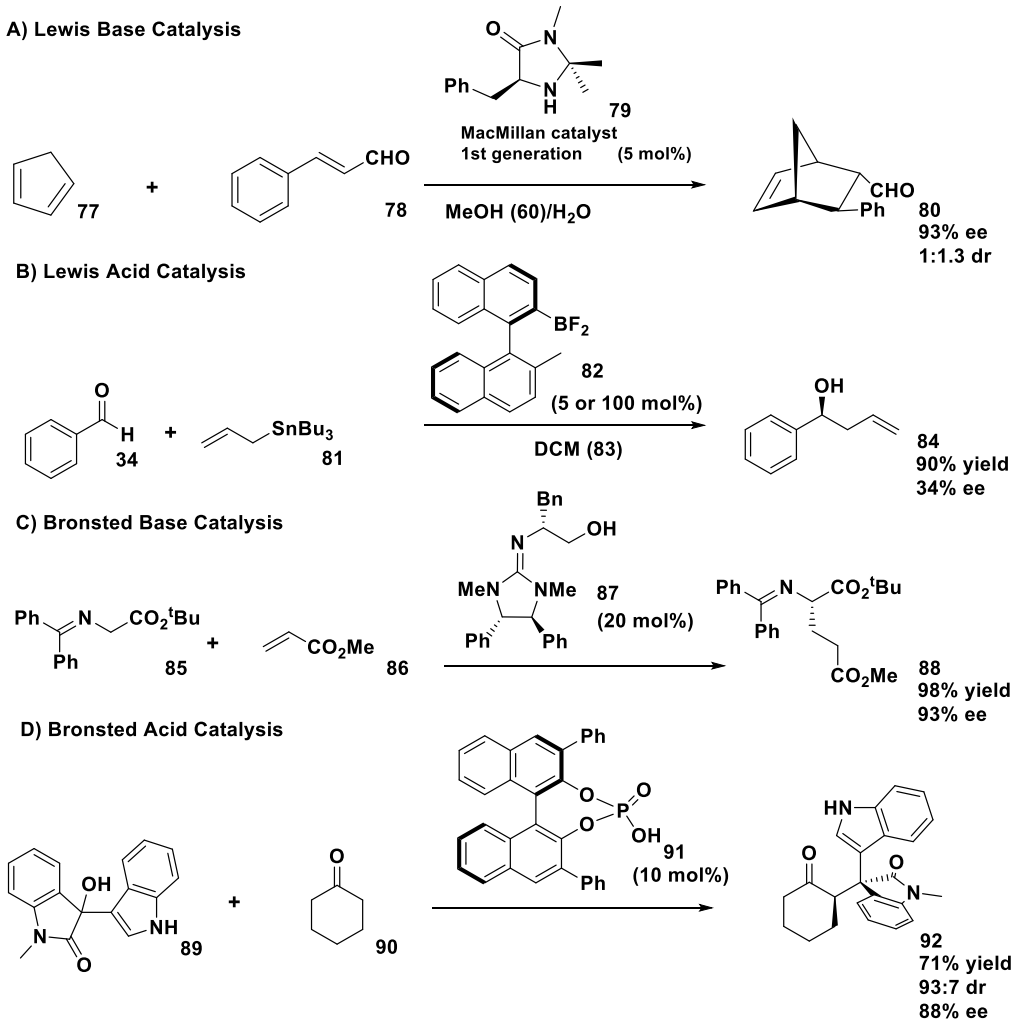
Scheme 1.15 Catalysis groups

Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle *via* a nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. A pioneering example of Lewis Base Catalysis is iminium catalysis to perform a Diels-Alders reaction. The reaction between the *α, β*-unsaturated aldehyde and secondary amine forms an activated iminium species which reacts with the diene leading to an enantioselective Diels-Alder addition (**Scheme 1.16A**).

In Lewis acid catalysis, the catalyst A activates the nucleophilic substrate (S:) forming the activated specie which reacts with the second substrate followed by the formation of the product and the release of the catalyst. An example of Lewis Acid catalysis was described by Morrison and his co-workers as binaphtylborane-catalysed allylstannation of benzaldehyde with a moderate enantioselectivity (**Scheme 1.16B**).

Brønsted base catalytic cycles are initiated *via* a (partial) deprotonation, followed by a nucleophilic attack forming the product and the catalyst recovery. An example of Brønsted base catalysis is reported by Lambert and his co-workers. They studied the reaction between glycine imine and methyl acrylate catalysed by a guanidine derivative obtaining the product in high yields and high enantioselectivity after 3 days of reaction at high concentration (**Scheme 1.16C**).

Brønsted acid catalytic cycles are initiated via a protonation of the substrate followed by the attack of the second substrate, the subsequent formation of the product and the release of catalyst. Peng and his co-workers reported an example of Brønsted acid catalysis using bi-2-naphtol-derived phosphoric acid as catalyst in performing the reaction between an indole derivative and cyclohexanone affording the product in high yields and stereoselectivity and enantioselectivity (**Scheme 1.16D**).



Scheme 1.16 Examples: A) Lewis Base Catalysis,[47] B) Lewis Acid Catalysis,[48] C) Brønsted Base Catalysis,[49] D) Brønsted Acid Catalysis.[50]

1.3.2 The covalent or noncovalent way of reagent-substrate interaction classification

This classification enumerates many more types of modes of activation:

A) Covalent organocatalysis
   1) Aminocatalysis: Enamine catalysis, iminium catalysis, dienamine catalysis, SOMO catalysis, photoredox organocatalysis, oxidative enamine catalysis,
   2) Carbene catalysis
   3) Lewis Base Organocatalysis

B) Noncovalent organocatalysis
   1) Hydrogen-bonding Activation: Hydrogen-bond donor catalysis by anion binding, Brønsted acid organocatalysis, asymmetric counteranion-directed catalysis

2) Brønsted base and bifunctional catalysis: Brønsted Base / Brønsted Acid bifunctional catalysis, Lewis Base / Brønsted Acid Bifunctional catalysis
3) Phase-Transfer and asymmetric countercation-directed catalysis

In this chapter the modes of activation used in the research of this thesis will be explained. In particular, the attention will be drawn on the enamine, iminium catalysis, Lewis base catalysis and Brønsted base catalysis.

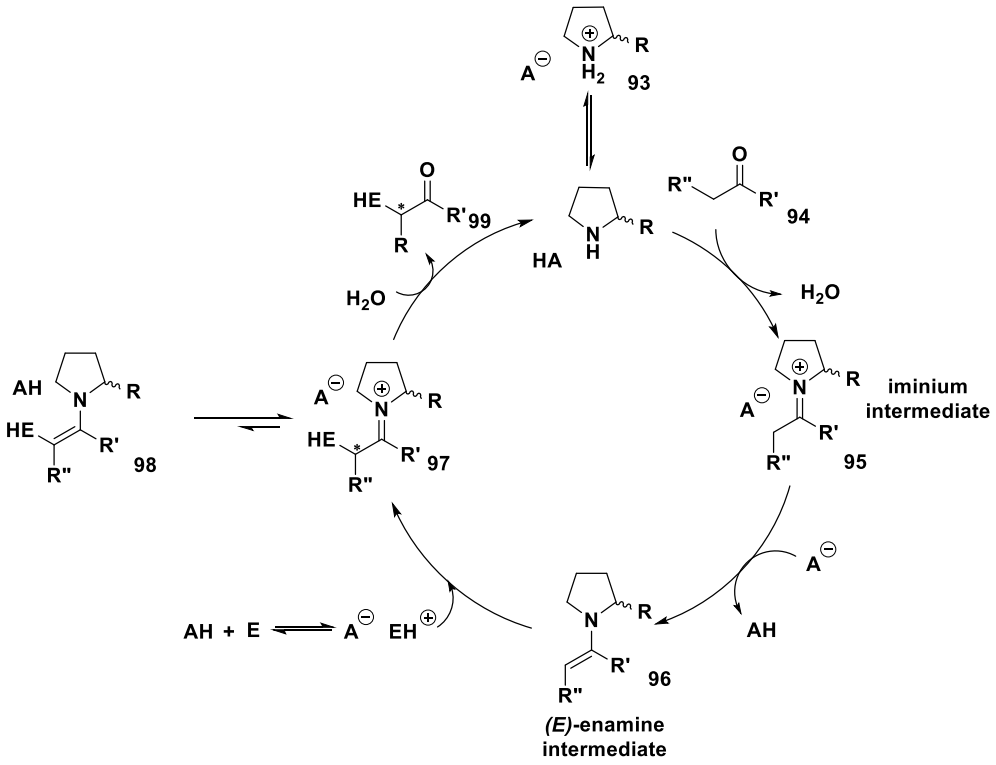
1.3.2.1 Aminocatalysis

The term of aminocatalysis was introduced by Benjamin List in 2001 in order to name the types of reactions catalysed by secondary and primary amines via enamine and iminium intermediates.[51]

1.3.2.2 Enamine catalysis

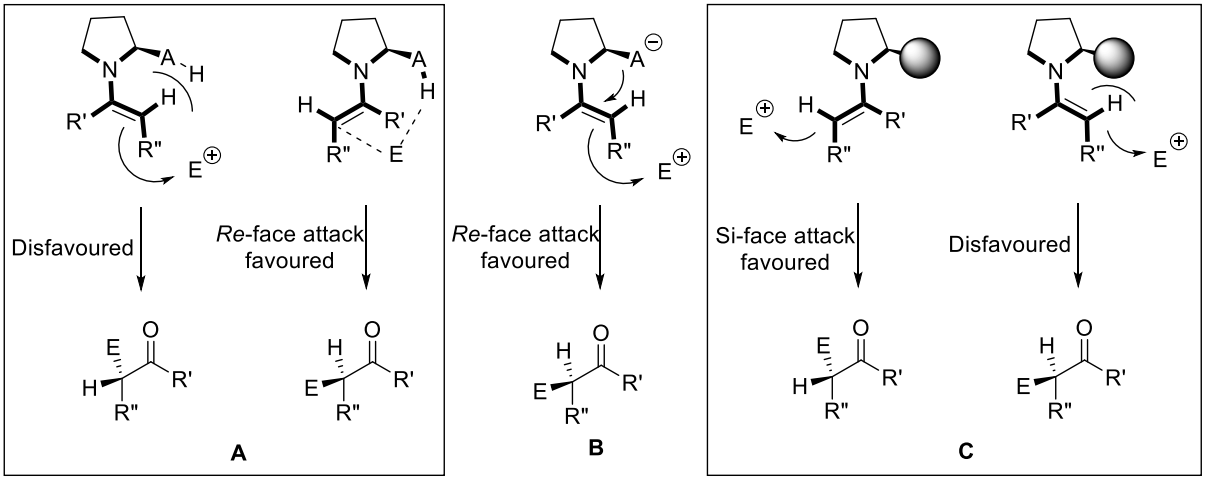
Enamine catalysis is one of the most widely used modes of activation in order to do enantioselective *α*-functionalisations of enolisable carbonyls with electrophiles.

The efficiency of this catalytic process depends on: a) the fast generation of the iminium; b) the regioselective and stereoselective transformations of the iminium into the *(E)*-enamine; c) the electrophilic attack. The general mechanism is described in the **scheme 1.17**.

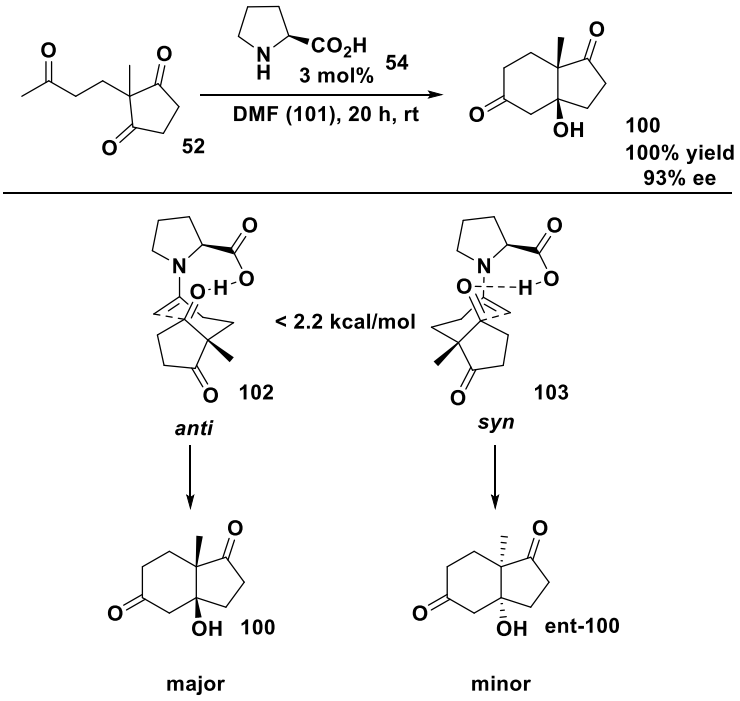


Scheme 1.17 Chiral amine catalysed α-functionalization of carbonyls

The stereoselectivity of the final product can be predicted in the case of using 2-substituted pyrrolidine catalysts. Mainly, there are three models explaining the stereochemical outcome of the reaction. If the chiral amine has a hydrogen-bond directing group, the reaction takes place via a cyclic transition state, also called List-Houk model (**Scheme 1.18A**). Another suggested model is the Seebach-Eschenmoser one. In this model the electrophile is directed by the conjugated base of the amine substituent (**Scheme 1.18B**). Finally, if the amine substituent is bulky without a hydrogen-bond directing group, the intermediate product attacks the electrophile from the less hindered face. The reaction goes via the steric model (**Scheme 1.18C**). In the case of List-Houk and steric models (**Scheme 1.18A**, **Scheme 1.18C**), the *syn*-enamine transition state is disfavoured due to the hydrogen presence in that position creating a steric repulsion.



Scheme 1.18 Transition states models: A) List-Houk model, B) Seebach-Eschenmoser model, C) Steric model

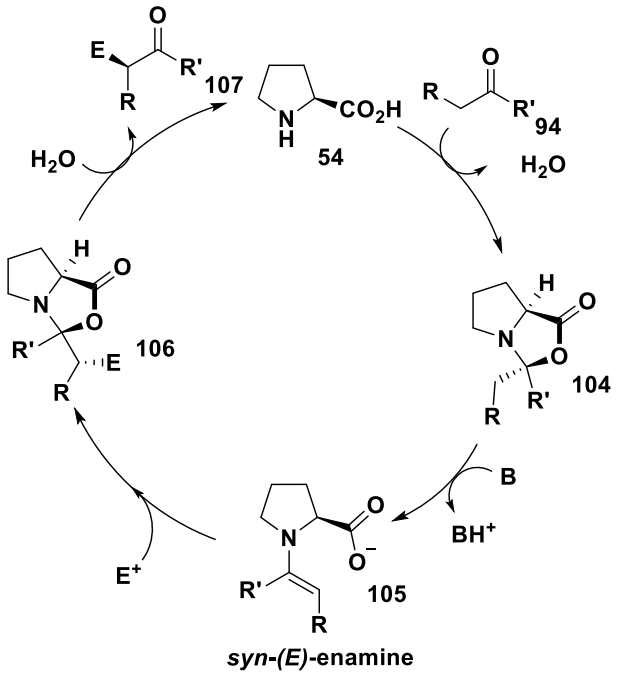


Scheme 1.19 Houk-List model for the Hajos-Parrish reaction

The most common examples of the List-Houk model are the proline catalysed reactions. Hajos and Parrish reported an intramolecular aldol reaction catalysed by L-proline in the 1970s. Later, mechanistic studies were performed in order to understand the stereochemical outcome (**Scheme 1.19**).[52] Two possible Zimmerman-Traxler transitions states were suggested, which led to two

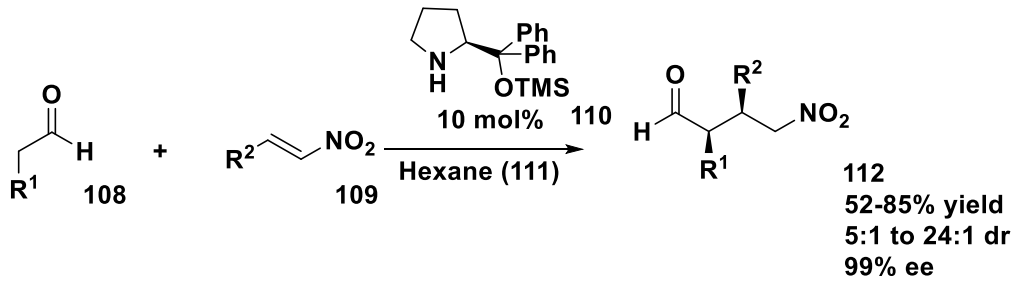
opposite enantiomers. The energy difference of 2.2 kcal/mol between the *anti* and *syn* transitions states favours the formation of the product **100**.

The second model explaining the stereochemical outcome of the reaction is the Seebach-Eschenmoser model which suggests that the conjugated base of the substituted pyrrolidine forms an oxazolidinone intermediate **104**. The oxazolidinone **104**, in the presence of a base, creates the enamine in a *syn*-conformation (intermediate **105**) which subsequentially attacks the electrophile forming the second oxazolidinone as shown in the mechanism of the **scheme 1.20**.



Scheme 1.20 Seebach-Eschenmoser model

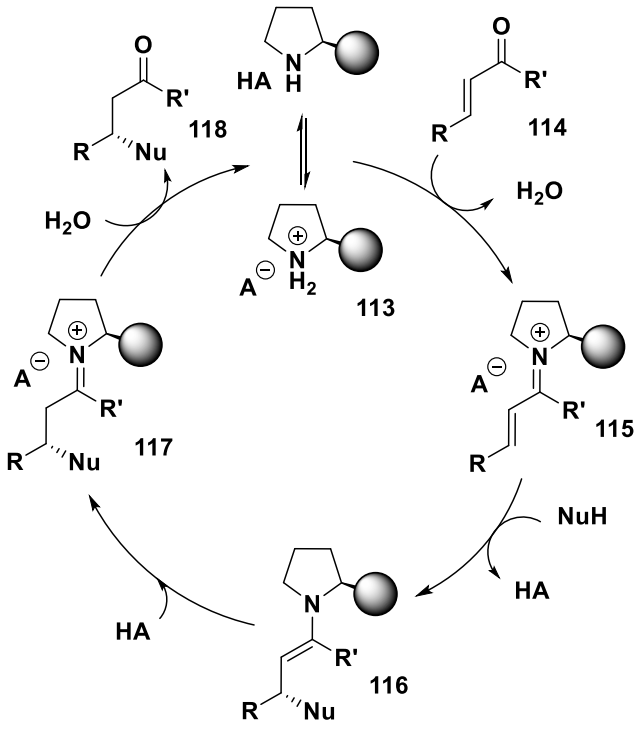
The third model is the steric one. The most well-known catalysts which follows the steric model for enamine pyrrolidine catalysis was reported independently by Jørgensen[53] and Hayashi.[46] Their diarylprolinol ether catalysts showed to be very effective in a lot of reported asymmetric electrophilic *α*-alkylations of aldehydes.[54] This system is used widely and still it is subject of research for various asymmetric organocatalytic processes (**Scheme 1.21**).



Scheme 1.21 Addition of aldehydes to *β*-nitrostyrenes

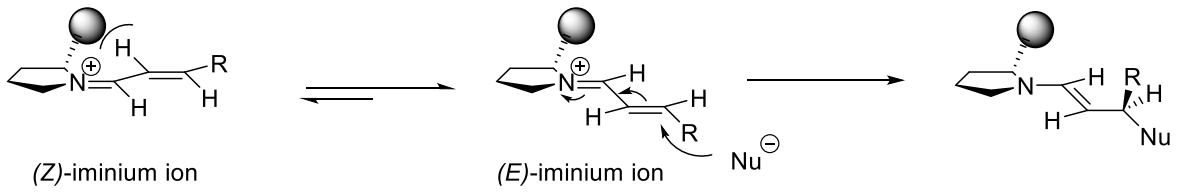
1.3.2.3 Iminium catalysis

Similar to enamine modes of activation, iminium catalysis is widely used and explored in various asymmetric organocatalytic reactions. This strategy is used for the activation of the *β*-position of *α, β*-unsaturated carbonyl substrates for 1,4-Michael addition.



Scheme 1.22 *β*-position activation of *α, β*-unsaturated carbonyl substrates via chiral amine catalysis

The typical mechanism of the activation is shown in the **scheme 1.22**. Usually the best results are obtained with secondary amine catalysts having bulky, non-hydrogen-bond directing groups following the steric model.



Scheme 1.23 *Z/E* equilibria for iminium catalysis

An important aspect that has to be mentioned is the equilibria of *Z/E* iminium transition state in iminium catalysis. The *(Z)*-iminium ion is less favoured to *(E)*-iminium ion due to the hydrogen and bulky group steric repulsion (**Scheme 1.23**).

The most well known catalysts iminium catalysts are diarylprolinol ethers (Jorgensen-Hayashi) (described in the enamine catalysis **chapter 1.3.2.2**) and the MacMillan catalysts.

MacMillan catalysts are chiral oxazolidinones salts. There are three generations of these catalysts (**Figure 1.6**). All three generations report more or less efficient results depending on the reaction for which they were used for. The first generation of MacMillan catalysts were used for Diels-Alder cycloadditions of enals, dipolar cycloadditions, Friedel-Crafts alkylations of pyrroles. An example of a Friedel-Crafts reaction via iminium catalysis was reported by MacMillan in 2001, showing the effects of the catalyst on the enantioselectivity (**Scheme 1.24**).

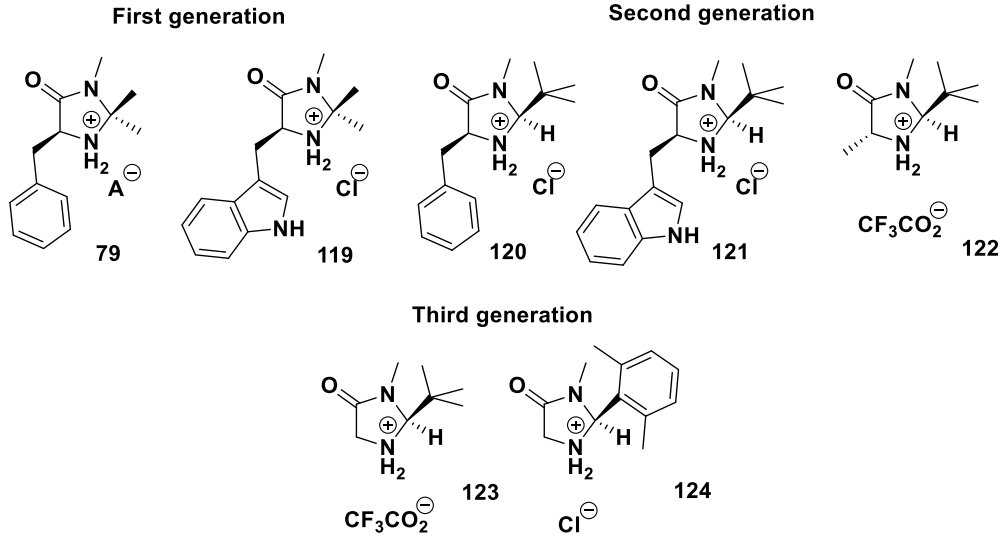
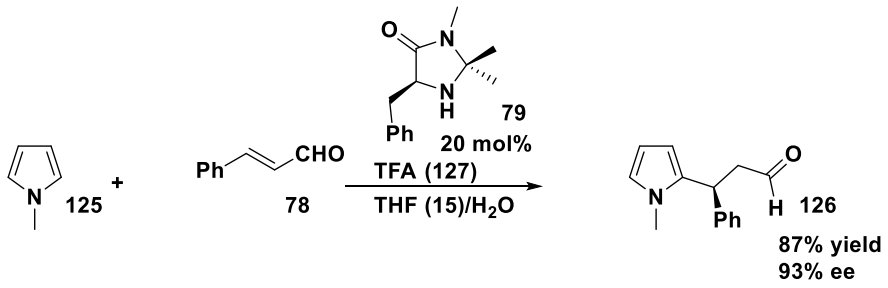


Figure 1.6 MacMillan catalysts: First generation, Second generation, Third generation



Scheme 1.24 Friedel-Crafts reaction via iminium catalysis[41]

Kinetic studies performed by MacMillan led to the synthesis of second generation imidazolidinones. It consisted in the removal of one methyl group and replacing the second with a *tert*-butyl group. The aim of these changes was to increase the *(E)*-control of the iminium ion. Finally, the third generation of imidazolidinone catalysts were synthesised by MacMillan in order to use them for the hydrogenation of *β, β*-disubtituted-*α, β*-unsaturated aldehydes.

1.3.2.4 Lewis Base Catalysis

Lewis base catalysis is a broad field and is used in different types of asymmetric processes. Typical organic asymmetric Lewis bases are the tertiary amine catalysts (cinchona-alkaloids, Sharpless catalysts) (**Figure 1.7**), sulphides and phosphines.

Some representative of Lewis base catalysed reactions are Rauhut-Currier reaction,[55] Morita-Baylis-Hillman reaction,[56] Steglich rearrangement[57] and ketene cycloaddition (**Scheme 1.25**).[58]

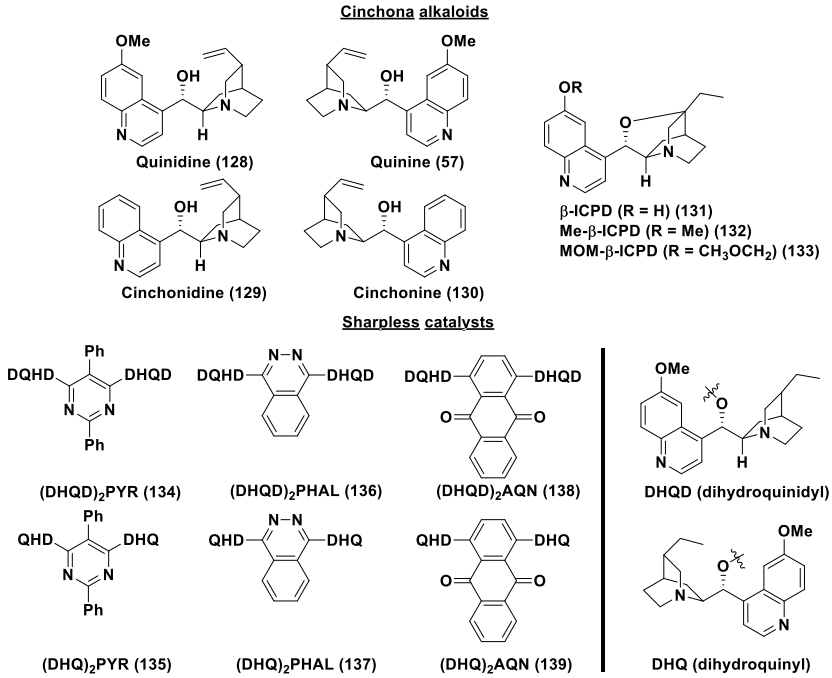
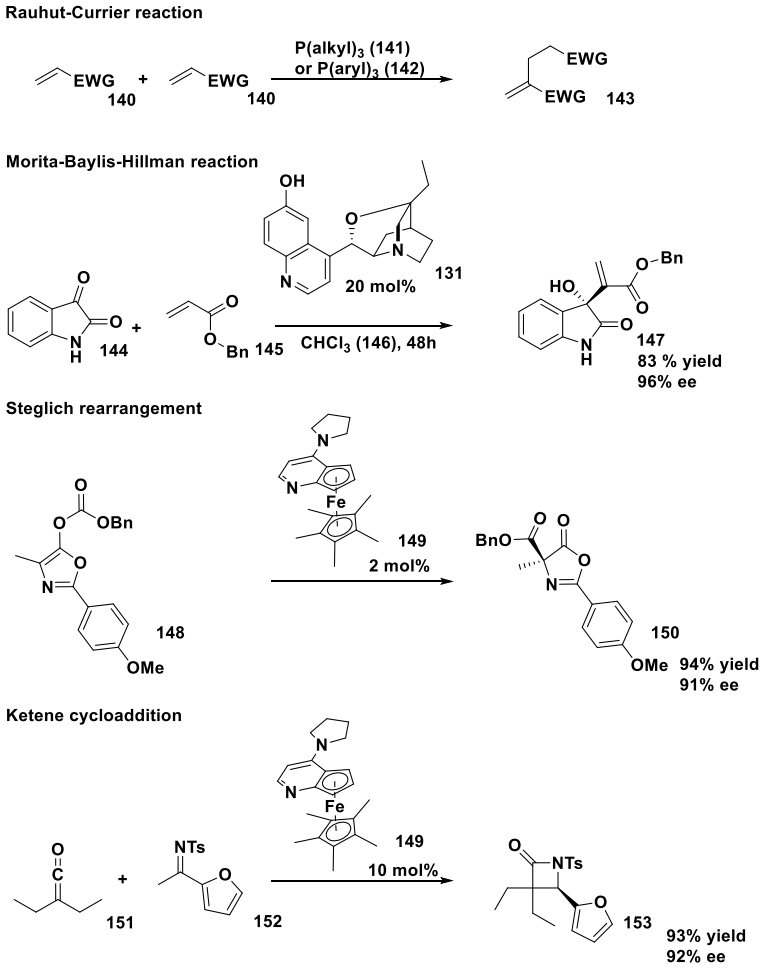


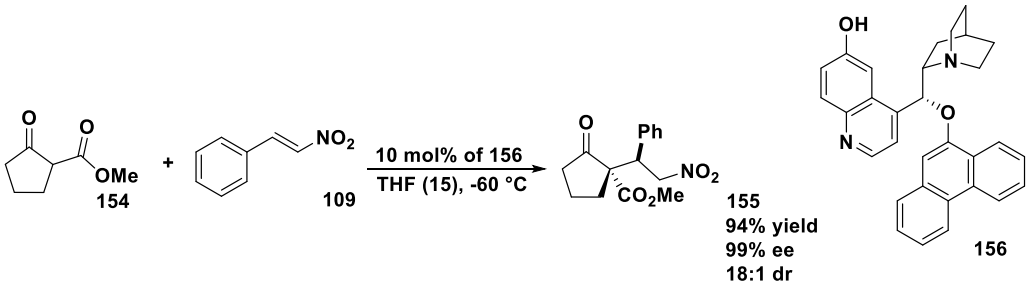
Figure 1.7 Lewis Base Catalysts



Scheme 1.25 Examples of Lewis base catalysis

1.3.2.5 Brønsted Base Catalysis

For Brønsted base catalytic process similar cinchona alkaloids can also be efficient. Tertiary amines are used as bases to deprotonate the acidic protons of the substrate. The new formed ionic pair of the anion and protonated base creates a chiral environment for an enantioselective reaction.[59] An example of Brønsted base catalysed reaction was reported by Deng *et al*. They did a keto-ester addition to nitroketene in the presence of a derivatized quinidine in excellent yield and diastereo-, enantioselectivity (**Scheme 1.26**).[60] First, the catalyst deprotonates the acidic proton situated in the α-position of the keto-ester derivative creating a chiral environment. Then, the keto-ester attacks the nitrostyrene in the β-position.

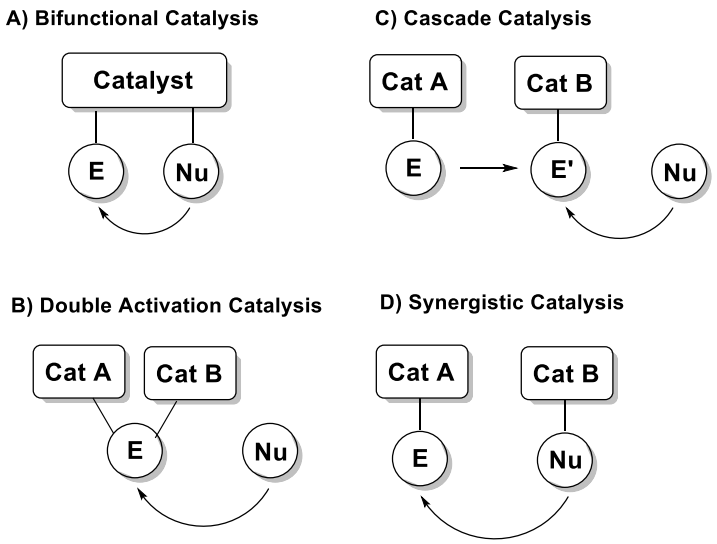


Scheme 1.26 Cinchona-alkaloid catalysed addition of keto-esters to nitroketenes

1.4 Multi-catalysis

While this mono-catalysis strategy has successfully delivered a vast number of new reactions over many decades, the concept of multi-catalysis allows access to many difficult or impossible transformations.

MacMillan divided the multicatalysis into four different groups: *bifunctional catalysis, double activation catalysis, cascade catalysis and synergistic catalysis* (**Scheme 1.27**).[61]

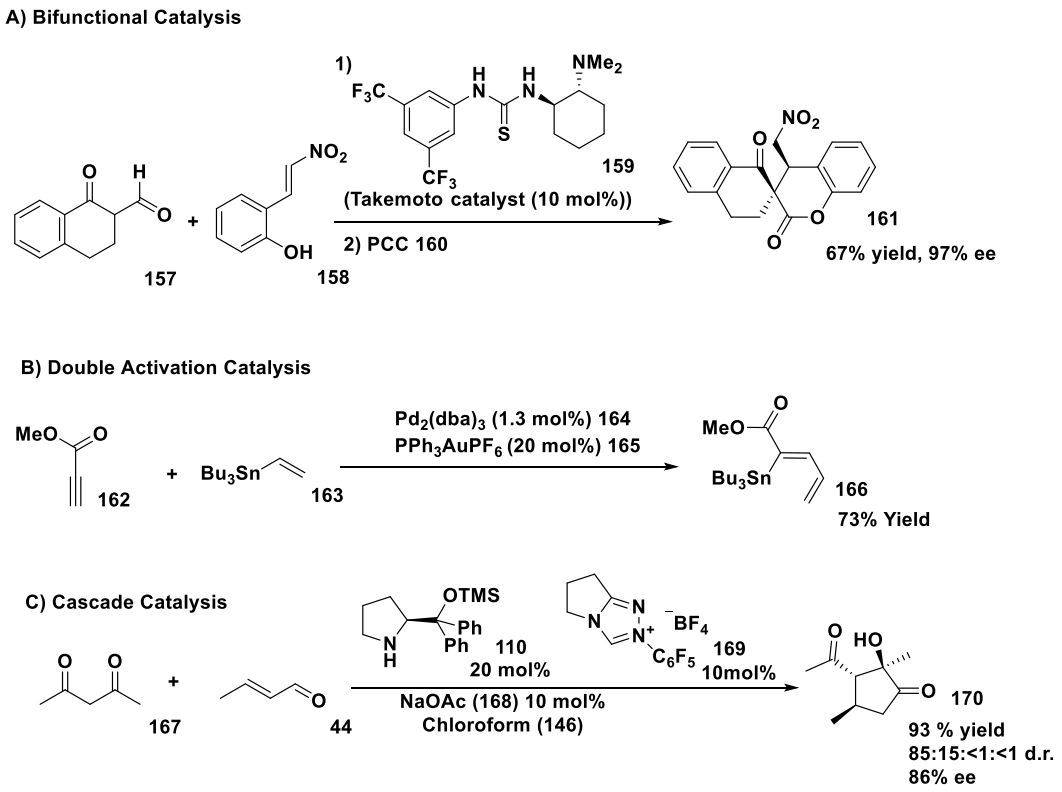


Scheme 1.27 Classification of two-catalytic systems

First, the *bifunctional catalysis* is the system where the nucleophile and the electrophile are activated by a different functional group of the same catalyst (**Scheme 1.27A**). An example of bifunctional catalysis was reported by Lee and his co-workers (**Scheme 1.28A**).[62] They studied the asymmetric domino Michael-acetalization reaction of 2-hydroxynitrostyrene and 2-oxocyclohexanecarbaldehyde in the presence of the Takemoto catalyst (bifunctional thiourea-tertiary-amine organocatalyst).

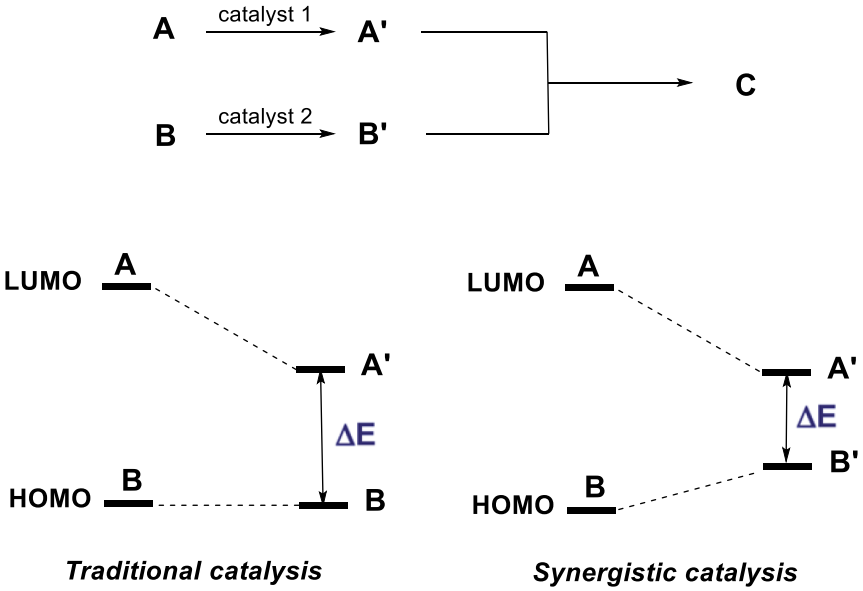
Another type of multi-catalytic system is the *double activation catalysis* where both catalysts work together in order to activate one of the reactants (**Scheme 1.27B**). Blum and her co-workers used this method in the synthesis of tri-and tetra-substituted olefins using palladium as a coupling catalyst and gold salt as a Lewis acid (**Scheme 1.28B**).[63]

Third, *cascade catalysis* is a system where both catalysts activate one of the reactant sequentially (**Scheme 1.27C**). Rovis and his co-workers obtained a functionalized cyclopentanone in high diastereoselectivity and enantioselectivity via multicatalytic secondary amine/*N*-heterocyclic carbene catalysed cascade sequence (**Scheme 1.28C**).[64]



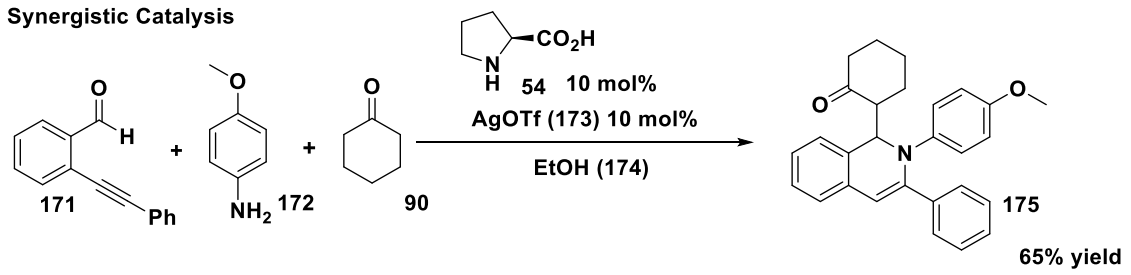
Scheme 1.28 Examples of multi-catalytic systems: A) Bifunctional Catalysis, B) Double Activation Catalysis, C) Cascade Catalysis.

Finally, *synergistic catalysis* is a process where two catalysts and two catalytic cycles work in a concerted way creating a single new bond. It involves the concurrent activation of both a nucleophile and an electrophile using distinct catalysts. This creates two reactive species, one with a higher HOMO (highest occupied molecular orbital) and the other with a lower LUMO (lowest unoccupied molecular orbital), in comparison to the respective ground state starting materials. If selected carefully, these activated species can rapidly couple, enabling chemical reactions that are impossible or inefficient via traditional mono-catalysis methods (**Scheme 1.27D**) (**Scheme 1.29**).[61]



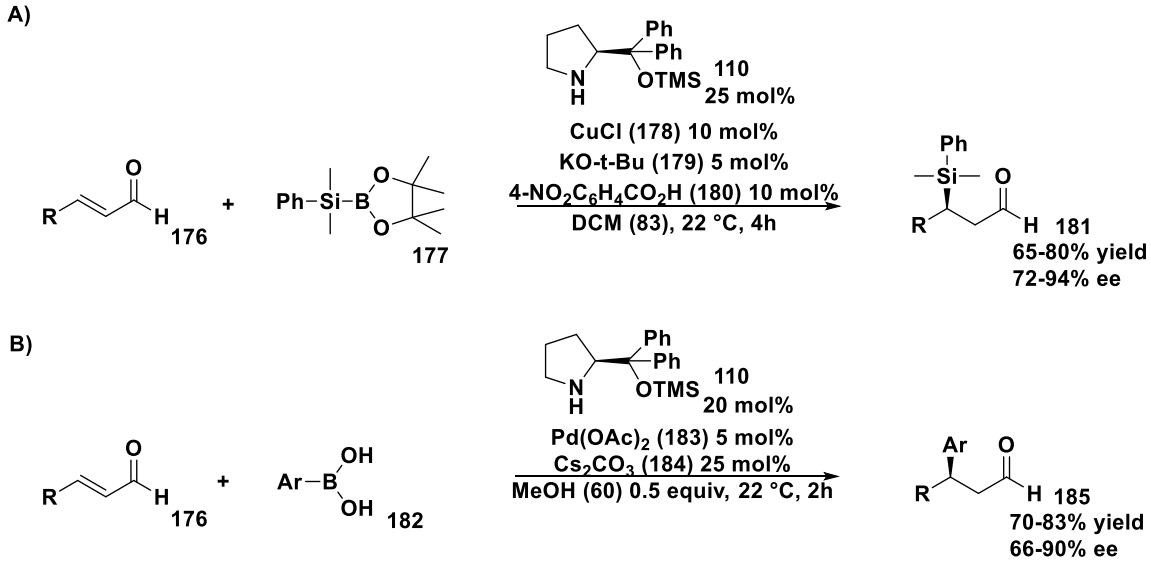
Scheme 1.29 The concept of synergistic catalysis

An example of synergistic catalytic process was reported by Wu in a multicomponent reaction of alkynylbenzaldehyde, amine and ketone catalysed by L-Proline (Lewis base) and silver triflate (Lewis acid) (**Scheme 1.30**).[65]



Scheme 1.30 Synergistic reaction reported by Wu

Other examples of synergistic catalytic systems mixing organocatalytic and organometallic processes can be found in the literature; for example, Cordova demonstrated the *β*-silylation (**Scheme 1.31A**)[66] or *β*-arylation (**Scheme 1.31B**)[67] of enals by combining iminium and Pd or Cu catalytic processes with great success.



Scheme 1.31 Synergistic systems performed by Cordova and his co-workers

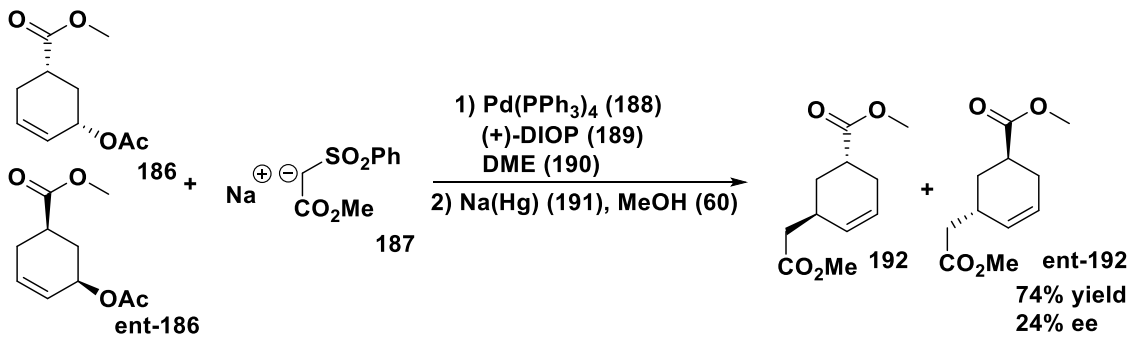
2. Asymmetric Allylic Substitution

2.1 Introduction

In 1965 Tsuji reported a reaction of π-allyl palladium chloride with nucleophiles such as ethyl malonate and acetoacetate.[68] Later on, in 1973, Trost suggested the use of phosphine as a ligand for the allylic alkylation.[69]

These first examples were the basis for the further reported synthetic transformations in which the creation of asymmetric C-C or C-heteroatom bonds was possible.

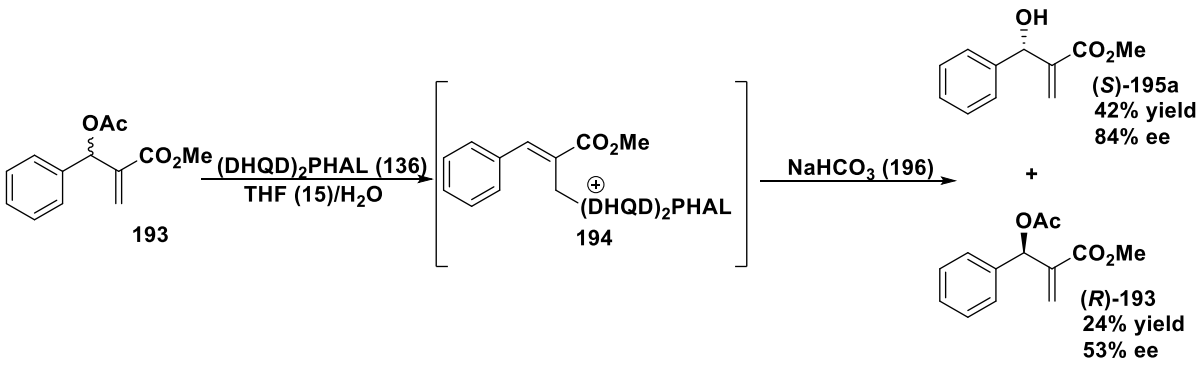
In 1977, Trost and Strege published the first enantioselective allylic substitution with a stabilised nucleophile (**Scheme 2.1**).[70] They managed to obtain the product in good yield, but low enantioselectivity.



Scheme 2.1 Trost's allylic substitution

Since then, most of allylic substitutions were made using transition metal complexes such as Cu, Ru, Mo, Ir, Rh.[71]

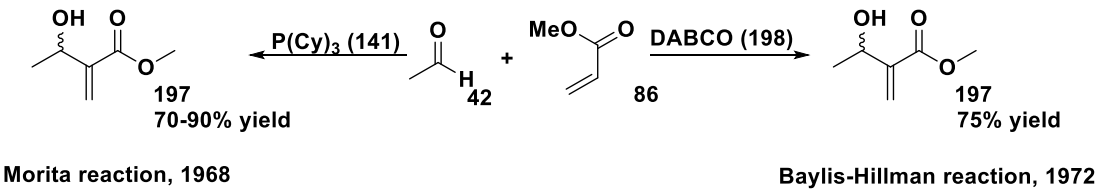
In 2002, Kim and co-workers reported the hydrolysis of Morita-Baylis-Hillman acetate with sodium bicarbonate catalysed by cinchona-alkaloid derivatives via kinetic resolution (**Scheme 2.2**).[72] Since then, many research groups focused their work into developing new strategies for asymmetric allylic substitution of Morita-Baylis-Hillman adducts via metal-free catalysis.



Scheme 2.2 Kim's hydrolysis of MBH-acetate

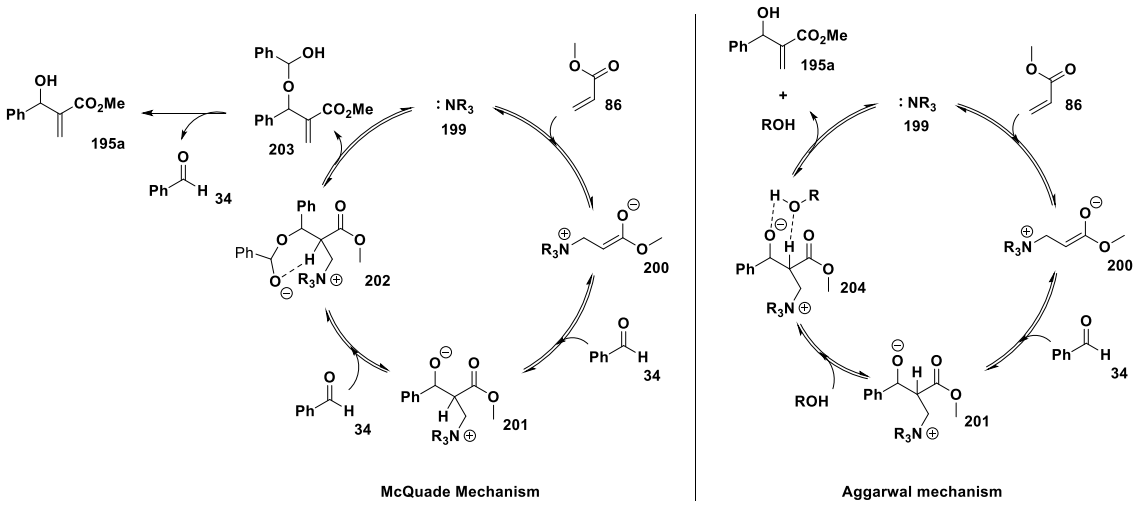
2.1.1 Morita-Baylis-Hillman reaction

The Morita-Baylis-Hillman reaction was first reported by Morita in 1968 when he published the reaction between acrylonitrile or methyl acrylate with aldehydes catalysed by tricyclohexylphosphine affording the product in very good yields (70-90%).[73] Later, in 1972 Melville Hillman and Anthony Baylis reported in a patent a similar reaction using tertiary amine in the place of a tertiary phosphine (**Scheme 2.3**).[74]



Scheme 2.3 Morita-Baylis-Hillman reaction

In 1983, mechanistic studies were reported by Hoffman and Rabe suggesting the first steps of the mechanism.[75] The mechanism starts with the Michael addition of the tertiary amine catalyst to the acrylate generating a zwitterionic species **200** (**Scheme 2.4**). The second step is an aldol addition of the aldehyde to species **200** forming the intermediate **201**. The subsequent step is a prototropic modification. For this stage kinetic and theoretical mechanistic studies were made. In 2005, two main mechanisms were suggested by McQuade *et al.* and Aggarwal *et al.* They proposed the proton transfer as the rate-determining step of the mechanism.



Scheme 2.4 Mechanistic studies of MBH reaction

McQuade *et al.* suggested that the MBH reaction is a second order kinetic and they proposed the intramolecular proton transfer via six-membered ring intermediate **202** followed by the catalyst recovery and the formation of intermediate **203** which becomes later the MBH-adduct (**Scheme 2.4**).

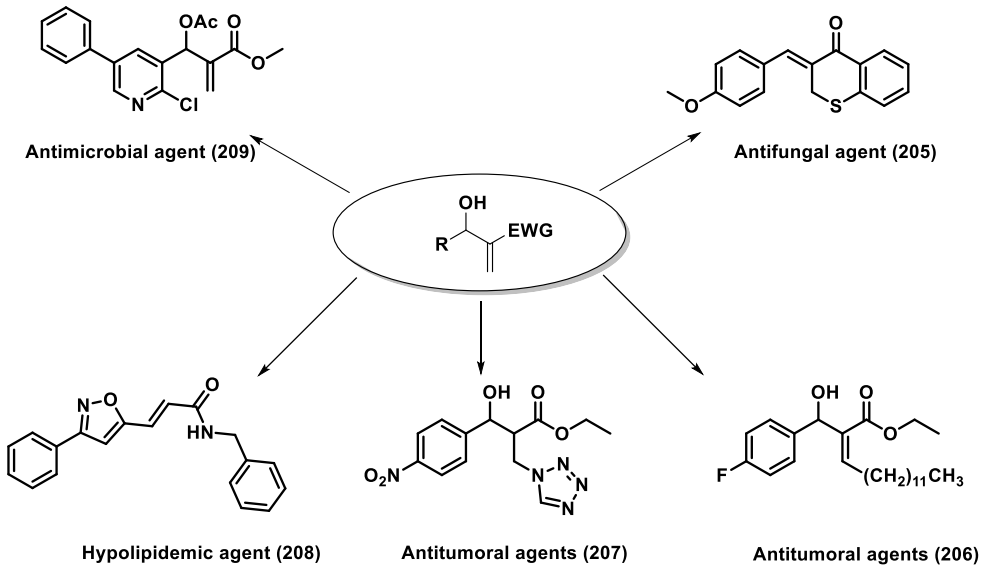
Alternatively, Aggarwal *et al.* suggested another mechanism in which the presence of a proton source is required. The protic solvent functions as the proton carrier from the carbon to the oxygen, intermediate **204** (**Scheme 2.4**).

Electrospray ionization tandem mass spectrometry of the MBH reaction was effectuated by Coelho and Ebelin.[76] They managed to intercept some of the intermediates proposed by McQuade and Aggarwal. Further investigations of this reaction showed that the equilibrium of the reaction depends on the temperature of the reaction. Cantillo and Kappe showed that the reaction between benzaldehyde and methyl acrylate at 120 °C is reversible.[77] Vasconcellos *et al.* described the reversibility by synthesising the MBH-alcohol at 0 °C in very high yields, followed by microwave irradiation 120 °C for 10 min recovering the benzaldehyde and the methyl acrylate.[78]

2.1.2 Morita-Baylis-Hillman adducts are important intermediates for synthesis of biologically active agents

Morita-Baylis-Hillman adducts have highly functionalized structures making them very good intermediates for more complex products.

A variety of biologically active agents were prepared either from MBH adducts or using the MBH reaction. Here are some examples of compounds synthesised from these intermediates (**Scheme 2.5**).[75]

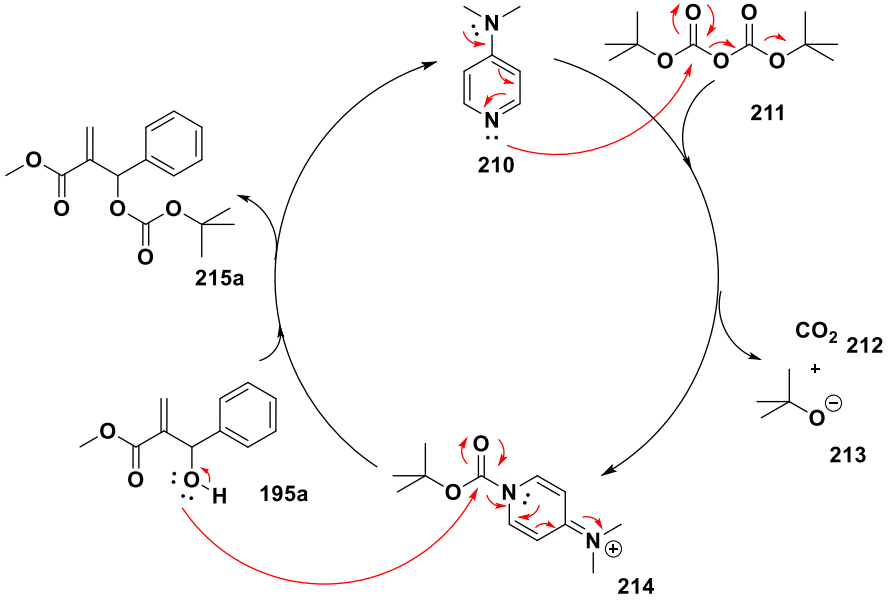


Scheme 2.5 Examples of products prepared from MBH-adducts

2.1.3 Organocatalytic methodologies using Morita-Baylis-Hillman carbonates and acetates[79]

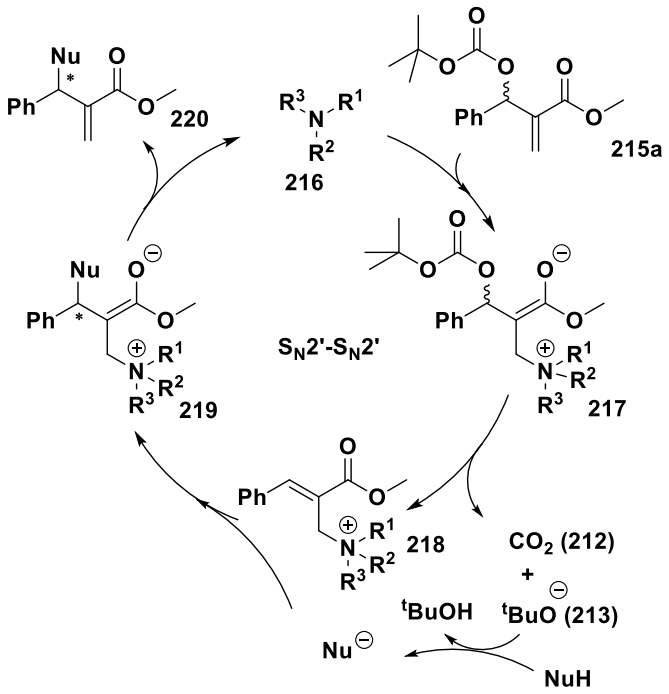
In recent years, many research groups focused their work on studying this moiety, in particular the chiral centre of the molecule which is related with an alcohol group.

First, the racemic MBH-alcohol is synthesised in the presence of an achiral tertiary amine catalyst (**Scheme 2.4**). Then, the alcohol moiety is protected with a good leaving group such as acetate or *tert*-butyloxycarbonyl. The mechanism is described in **scheme 2.6**.



Scheme 2.6 Alcohol protection mechanism with Boc

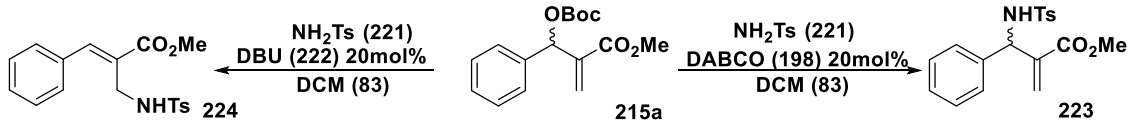
These MBH-carbonate or acetates react with nucleophiles via S_N2'-S_N2' mechanism (**Scheme 2.7**).



Scheme 2.7 S_N2'-S_N2' mechanism for AAS of MBH carbonates

The nucleophilic properties of the catalyst are an important factor for the outcome of the reaction. Orena *et al.* showed that using DBU, which has a higher

basicity and lower nucleophilicity than DABCO, can bring a S_N2'-decarboxylation mechanistic pathway instead of S_N2'-S_N2' mechanism (**Scheme 2.8**).[80]



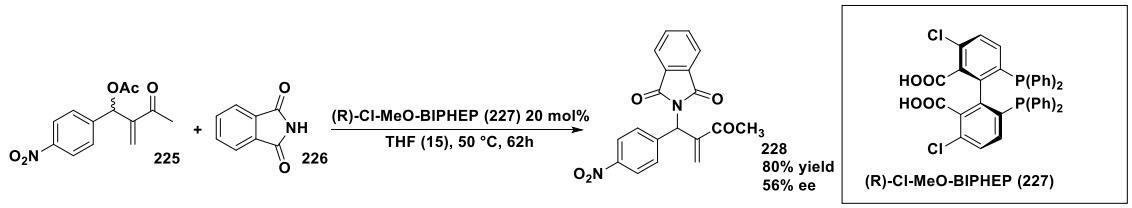
Scheme 2.8 Orena's study on influence of the catalyst

2.1.3.1 Previous works using MBH- acetates

After the first example of AAS involving MBH adducts reported by Kim in 2002, researchers were inspired to expand the work on this field.

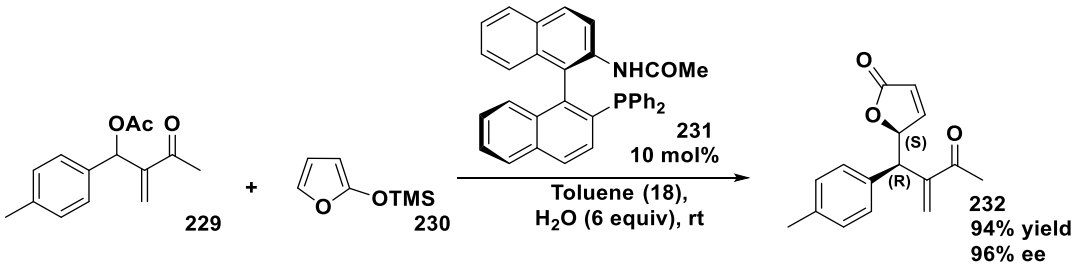
Later, Kim *et al.* also reported other examples of asymmetric allylic substitutions of MBH-acetates with different nucleophiles like phenols and secondary amines.[79]

In 2004, Krische published an enantioselective addition of phtalimide to MBH-acetate via S_N2'-S_N2' mechanism in high yields and moderate enantioselectivity (**Scheme 2.9**).[81] In 2011, Shi improved Krische's results by using a bifunctional phosphine-thiourea catalyst.[82]



Scheme 2.9 Krische's phtalimide addition to MBH-acetate

In 2008, Shi and co-workers described an enantioselective construction of *γ*-butenolides by addition of 2-trimethylsilyloxyfuran to MBH acetate.[83] The reaction was performed in high yield and very good enantioselectivity (**Scheme 2.10**).

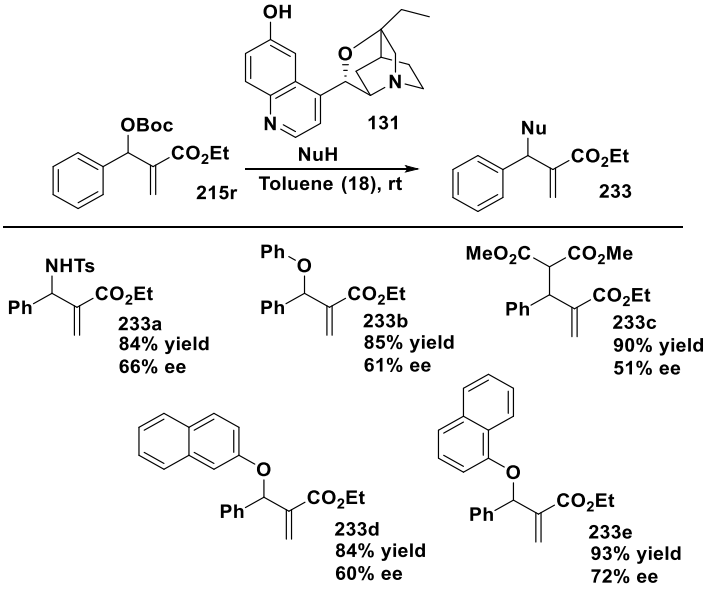


Scheme 2.10 Shi's γ-butenolide synthesis

2.1.3.2 Morita-Baylis-Hillman carbonates

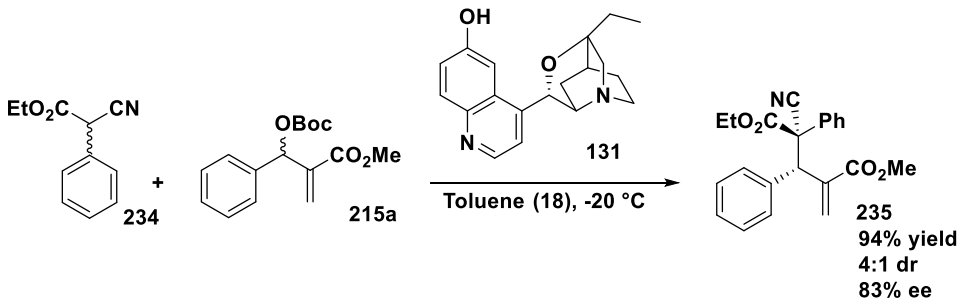
2.1.3.2.1 C-C asymmetric allylic substitution

The first examples of asymmetric allylic substitution using MBH-carbonates were described by Lu *et al.* in 2004.[84] They reported the addition of phenols, tosylamine, malonates, naphtols to MBH-carbonates with very good yields, but moderate enantioselectivity (**Scheme 2.11**).



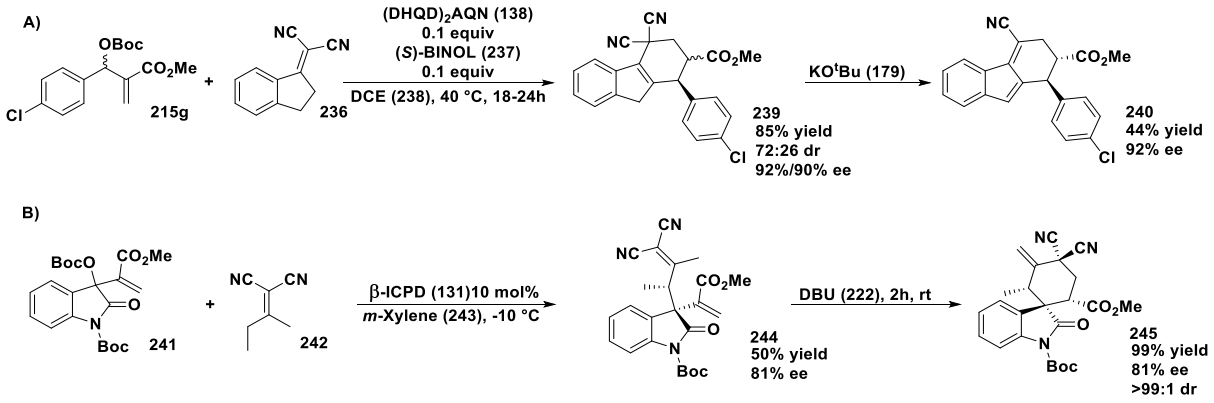
Scheme 2.11 Lu's pioneering work in AAS involving MBH-carbonate

Three years later, Hiemstra *et al.* reported the addition of cyanophenylacetate to MBH-carbonates catalysed by β-ICPD at -20 °C in high yields and enantioselectivity. The aim of this project was the synthesis of adjacent tertiary and quaternary stereocenters (**Scheme 2.12**).[85]



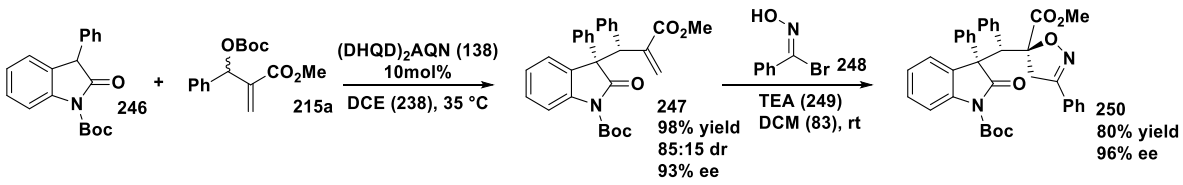
Scheme 2.12 Hiemstra et al. construction of tertiary and quaternary stereocenters

Important works in AAS involving MBH-carbonates were introduced by Chen and co-workers. One of Chen's studies was the addition of the *α,α*-cyano-olefin to MBH-carbonate followed by an intramolecular Michael addition (**Scheme 2.13A**).[86] A similar example was reported by them one year later. Chen *et al.* studied the addition of *α,α*-cyano-olefin to oxindole-MBH-carbonate followed by an intramolecular Michael addition in the presence of DBU (**Scheme 2.13B**).[87]



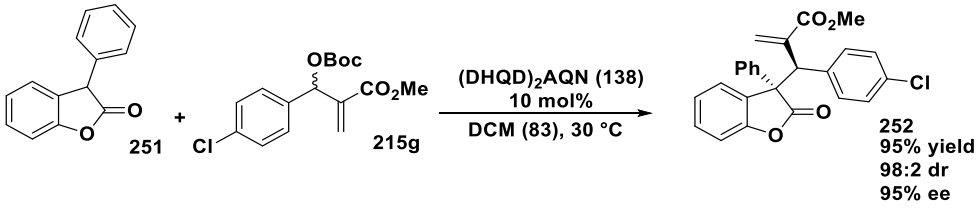
Scheme 2.13 A) *α,α*-cyano-olefin to MBH-carbonates by Chen; B) *α,α*-cyano-olefin to oxindole-MBH-carbonates by Chen

Chen and co-workers reported an oxindole addition to MBH-carbonate followed by a [3+2] cycloaddition involving benzenecarboximidoyl bromide.[88] The reaction had excellent results: high yields, high enantioselectivity and moderate diastereoselectivity (**Scheme 2.14**).



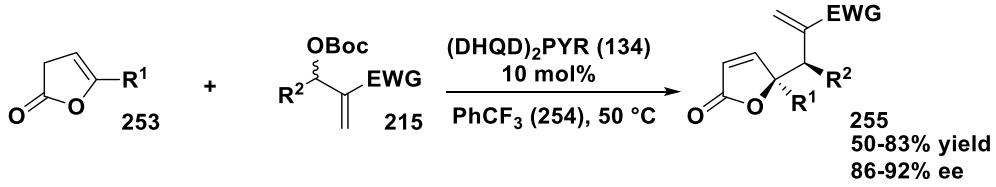
Scheme 2.14 Chen's oxindole addition to MBH-carbonates

Later, inspired by Chen's work, Li and Cheng reported the benzofuranone addition to MBH-carbonate catalysed by a Sharpless catalyst.[89] They obtained the desired product in very good yields and stereselectivity (**Scheme 2.15**).



Scheme 2.15 Li and Cheng's benzofuranone addition to MBH-carbonate

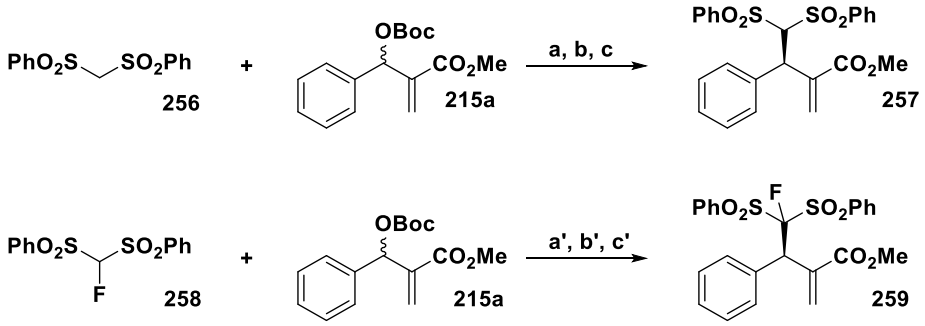
Also Chen suggested another method of addition of butenolide to MBH-carbonate compared to the one proposed by Shi (**Scheme 2.10**). While Shi's approach was via Mukaiyama-type addition, Chen used *β,γ*-butenolide as a nucleophile.[90] This methodology has the advantage in terms of atom economy. Moreover, the reaction rendered the final product in good yield and very good enantioselectivity (**Scheme 2.16**).



Scheme 2.16 Chen's butenolide addition to MBH-carbonates

An interesting metal-free methodology was reported simultaneously by Huang, Jiang, Tan (**Scheme 2.17 a, a'**)[91] and Rios group (**Scheme 2.17 b. b'**)[92] for the addition of bis(phenylsulfonyl)methane or fluoro-bis(phenylsulfonyl)methane to MBH-carbonate. Both groups used Sharpless catalysts ($(DHQD)_2AQN$ and $(DHQD)_2PHAL$ respectively) and they both obtained similar results (very good yields and enantioselectivity). In the same year, Shibata *et al.* (**Scheme 2.17 c,**

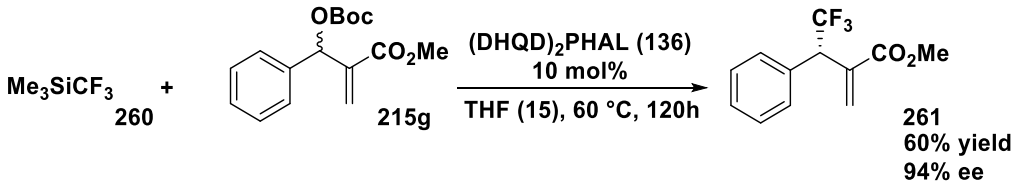
c')[93] suggested using an additive such as $FeCl_2$ which considerably increased the yield of the reaction.



a) $(DHQD)_2AQN$ 10 mol%, mesitylene, 50 °C, 43h, results: 74% yield, 95% ee; a') $(DHQD)_2AQN$ 10 mol%, Toluene, 50 °C, 13h, results: 72% yield, 99% ee; b) $(DHQD)_2PHAL$ 10 mol%, Toluene, rt, 4-5 days, results: 91% yield, 94% ee; b') $(DHQD)_2PHAL$ 10 mol%, Toluene, rt, 4-5 days, results: 80% yield, 80% ee; c) $FeCl_2$ 10 mol%, $(DHQD)_2AQN$ 10 mol%, $PhCF_3$, 40 °C, 3-4 days, results: 80% yield, 92% ee, c') $FeCl_2$ 10 mol%, $(DHQD)_2AQN$ 10 mol%, $PhCF_3$, 40 °C, 3-4 days, results: 93% yield, 94% ee.

Scheme 2.17 Bis(phenylsulfonyl)methane derivatives addition to MBH-carbonates

Also, Shibata *et al.* reported a trifluoromethylation of MBH-carbonates using the Ruppert-Prakash reagent. The product was obtained in moderate yield and excellent enantioselectivity (**Scheme 2.18**).[94]

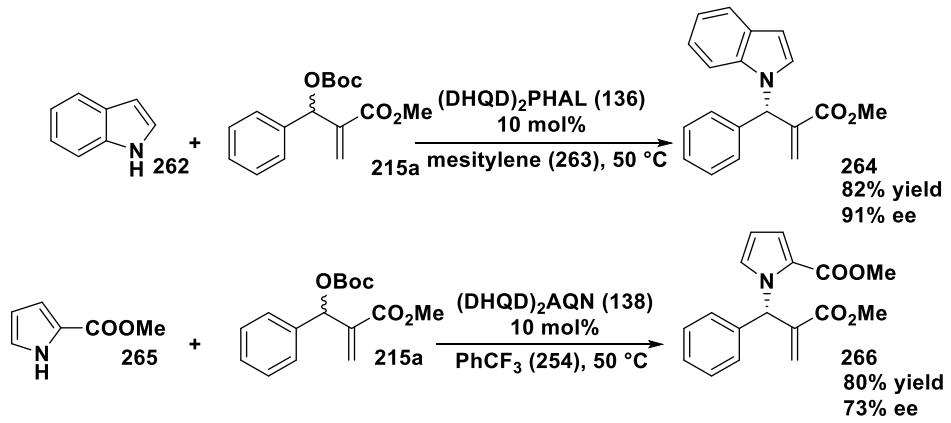


Scheme 2.18 Trifluoromethylation of MBH-carbonates

2.1.3.2.2 C-Heteroatom asymmetric allylic substitution

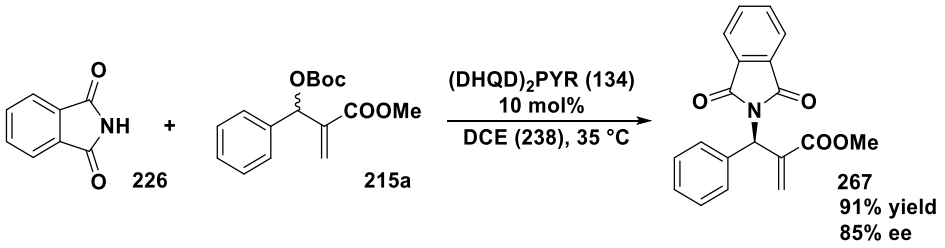
Many AAS reactions were reported for the creation of new C-heteroatom bonds.

Important work was done by Chen and co-workers. In 2009, they reported the addition of indoles and pyrroles to MBH-carbonates.[95] In this case they formed C-N bonds and the reaction rendered the final products in high yields and moderate to good enantiomeric ratio (**Scheme 2.19**).



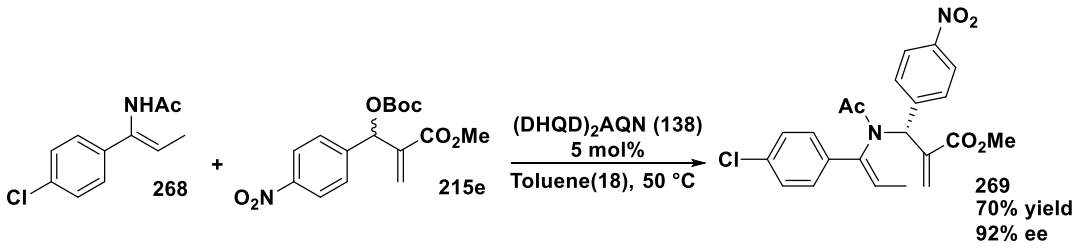
Scheme 2.19 Chen's pyrrole and indole addition to MBH-carbonates

Also, Chen *et al.* reported an addition of phtalimide to MBH-carbonates catalysed by $(DHQD)_2PYR$. After 85 hours, the final product was obtained in good yields and good enantioselectivity (**Scheme 2.20**).



Scheme 2.20 Chen's phtalimide addition to MBH-carbonates

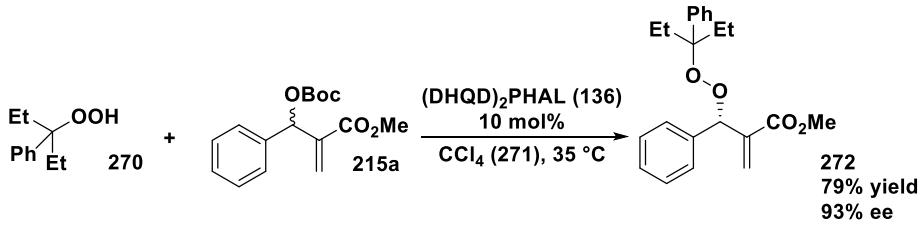
Chen and co-workers also reported the first example of enamide addition to MBH-carbonates catalysed by $(DHQD)_2AQN$.[96] The C-N bond was formed in moderate yields and good enantioselectivity (**Scheme 2.21**).



Scheme 2.21 Chen's enamine addition to MBH-carbonates

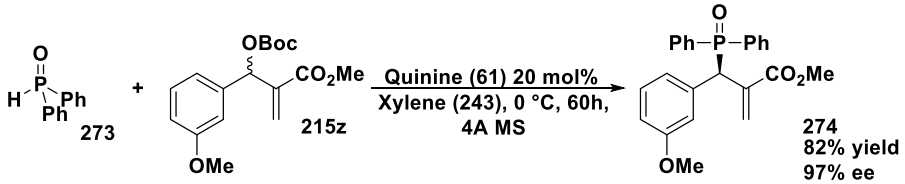
Chen and co-workers successfully managed to form C-O bond via an S_N2'-S_N2' mechanism. They achieved the addition of peroxide to MBH-carbonates

catalysed by a dimeric *cinchona* alkaloid.[97] In this case, the best catalyst appeared to be $(DHQD)_2PHAL$. They were able to form the peroxide ether in good yields and very good enantioselectivity (**Scheme 2.22**).



Scheme 2.22 Chen's peroxide addition to MBH-carbonates

While Chen *et al.* were able report many examples of C-N, C-O bond formation methods involving MBH-carbonates, Wang *et al.* succeeded to create a C-P bond by adding a phosphine to MBH-carbonates.[98] The presence of molecular sieve in this reaction is crucial for the high enantioselectivity. Without it, the reaction gains in yield, but loses considerably in enantiomeric ratio (**Scheme 2.23**).



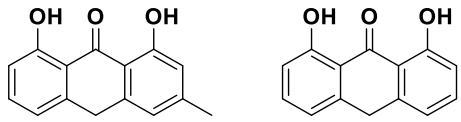
Scheme 2.23 Wang's alkyl phosphination of MBH-carbonates

In our group we successfully reported two main AAS involving MBH-carbonates. The first reaction is the anthrone addition to MBH-carbonates via S_N2'-S_N2' mechanism. The second reaction is the addition of alkyl-azaarenes to MBH-carbonates via synergistic catalysis.

2.2 Highly enantioselective addition of anthrones to MBH-carbonates

2.2.1 Introduction

More than a century ago, a dermatologist from London called Squire discovered that the Goa powder, which is extracted from legume-tree *Andira araroba,* is an effective treatment for psoriasis. Later, in 1878, Seidler and Liebermann found out that the active species of this powder is an anthrone derivative also called chrysarobin. Inspired from this discovery, in 1916 Galewsky introduced the synthetic antipsoriatic drug named cignolin, where the active agent was called later anthralin in the US and dithranol in Europe (**Figure 2.1**). 80 years of continuous research for a more effective antipsoriatic agent passed with no success in finding a better drug.[99]



Chrysarobin (275) Cignolin (276)

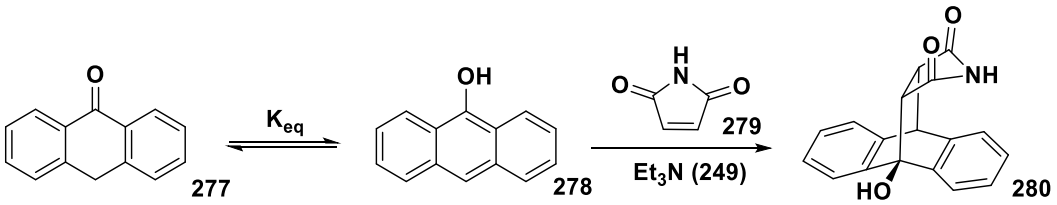
Figure 2.1 Structures of crysarobin and cignolin

Anthrones and its derivatives are important scaffolds present in various natural sources and known for their medicinal effects. They can be found in plants such as Genus Aloe,[100] Picramnia latifolia,[101] Rheum emodi (The roots of Rheum emodi (Himalayan rhubarb)) which are widely used in Ayurvedic and Asian folk medicine. The drug is administered as a stomachic, purgative, astringent, tonic, laxative in biliousness, lumbago, piles, chronic bronchitis, asthma and in certain skin diseases.[102] Also, anthrone is commonly used for the analytical determination of carbohydrates in plants.

Considering the medicinal properties of these derivatives there are not so many examples of asymmetric reactions with anthrone scaffolds described in literature.

Anthrone derivatives behave as dienes and are suitable for Diels-Alder reactions. In 1985, Mills and Beak studied the effect of the solvent over the equilibrium

constant of the tautomerisation anthrone/anthracenol. They realised that the keto form is favoured in nonpolar solvents such as toluene and the alcohol form is favoured in solvents with hydrogen acceptor atoms such as THF. In 1989, Rickborn *et al.* reported the first example of Diels-Alder reaction involving anthrone and maleimide (**Scheme 2.24**).[103] One year later, they reported reactions between anthrone and other dienophiles such as dimethyl maleate, fumaronitrile, methyl acrylate and others.[104]



Scheme 2.24 Rickborn's maleimide addition to anthrone

Later, several groups focused their research into addition of various maleimides to anthrone in an asymmetric fashion. In 2001, Yamamoto and co-workers attempted this reaction using the catalyst **A** (**Figure 2.2**) they obtained high yields (up to 99 %), but moderate enantioselectivity (up to 87 %).[105] Five years later, Tan *et al.* suggested the chiral bicyclic guanidine **B** (**Figure 2.2**) as a catalyst. This catalyst showed to be more efficient (up to 96% yield and up to 99% ee).[106] In 2010, Rios *et al.* reported a Diels-Alder reaction between anthrone and maleimides catalysed by bifunctional-thiourea **C** (**Figure 2.2**) with excellent results (up to 92% yield, up to 97% ee).[107]

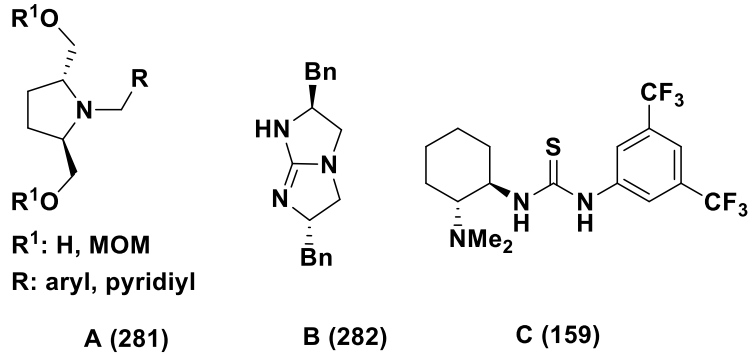
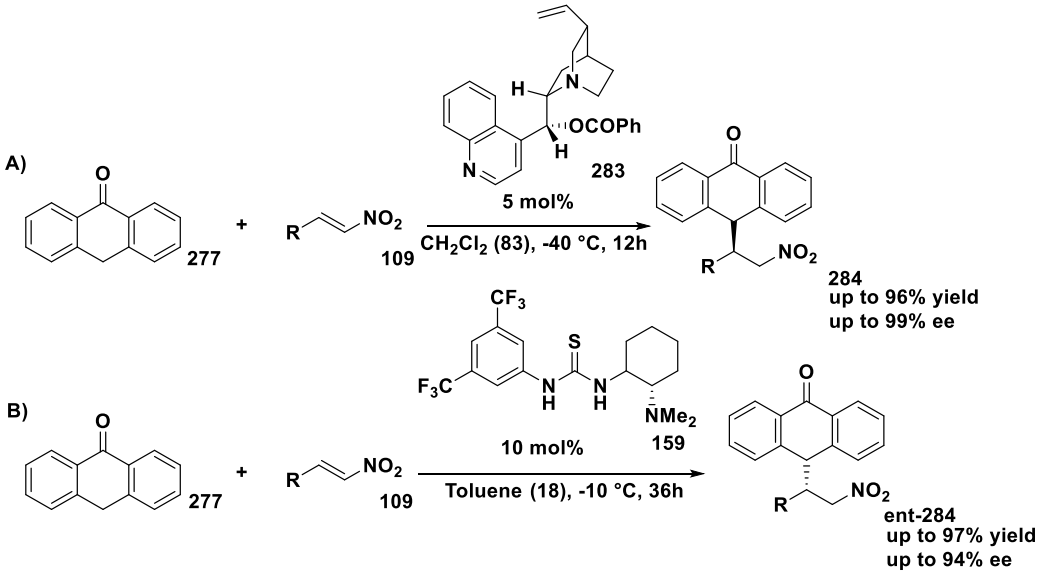


Figure 2.2 Catalysts for Diels-Alder reaction between anthrone and maleimides

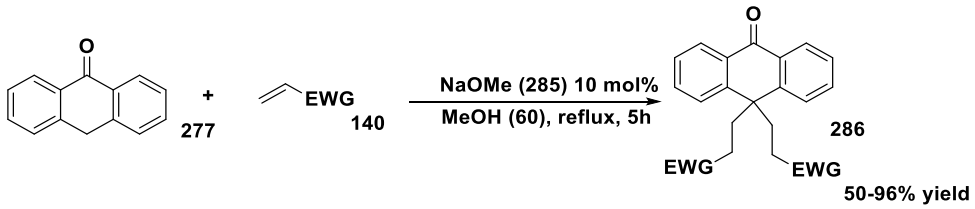
Other reactions involving anthrone are Michael additions to nitroalkenes, enones, *α,β*-unsaturated aldehydes and methyl acrylate. In 2007, Shi *et al.* reported the addition of anthrone to nitroalkene catalysed by cinchona-

alkaloid.[108] The best results were obtained by using *O*-Benzoylcupreine as a catalyst (**Scheme 2.25A**). Two years later, Yuan *et al.* attempted to do the same reaction using the bifunctional-thiourea catalyst.[109] The results were comparable with the one reported by Shi (**Scheme 2.25B**).



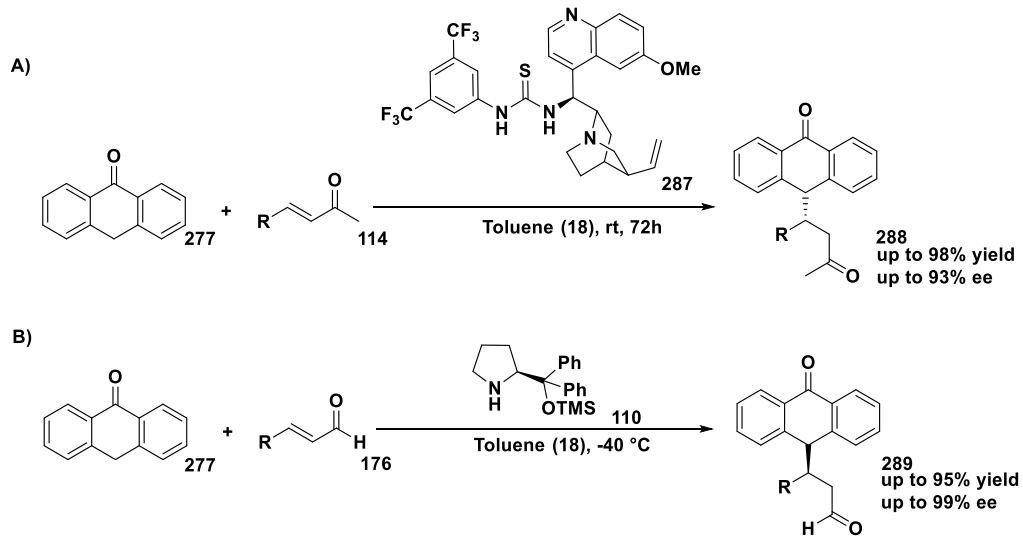
Scheme 2.25 Anthrone addition to nitroalkene

In 2004, Baik *et al.* reported a double Michael reaction with moderate to excellent yields (**Scheme 2.26**).[110]



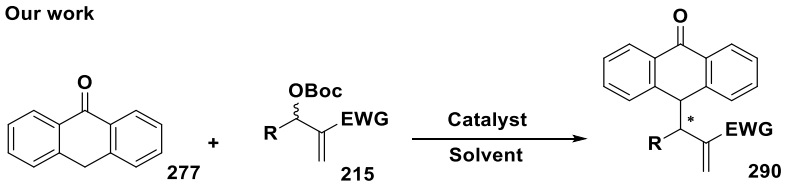
Scheme 2.26 Double Michael reaction reported by Baik

Some other examples of anthrone involved in Michael addition were reported by Ye *et al.* and Rios and co-workers. In 2010, Ye reported the addition of anthrone to enones catalysed by cinchona alkaloid derived tertiary amino–thiourea organocatalyst (**Scheme 2.27A**).[111] One year later, Rios and co-workers reported an anthrone addition to α,β-unsaturated aldehydes catalysed by diphenylprolinol derivative catalyst (**Scheme 2.27B**).[112] In both cases, the results were very good in term of yields and enantioselectivity.



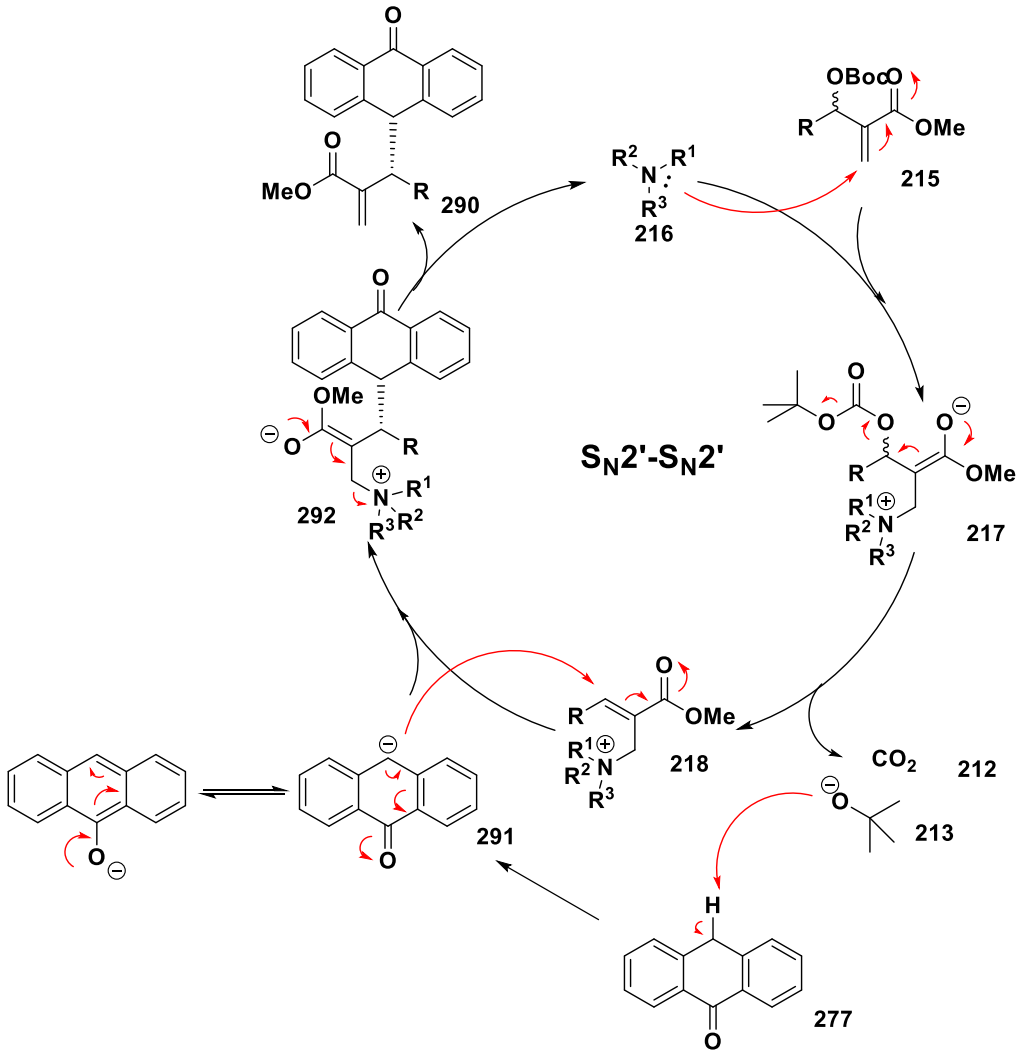
Scheme 2.27 Anthrone addition to enones and *α,β*-unsaturated aldehydes

Inspired by all these examples we wanted to study the addition of anthrone addition to MBH-carbonates via S_N2'-S_N2' mechanism in an enantioselective fashion (**Scheme 2.28**).



Scheme 2.28 Anthrone addition to MBH-carbonates

In the **scheme 2.29** the proposed mechanism was described. First, the tertiary amine attacks the MBH-carbonate in a 1,4-Michael addition fashion forming the zwitterionic species **217**. Then, we have the OBoc release in the form of CO_2 and *tert*-butoxide with the formation of the activated species **218**. The *tert*-butoxide reacts as a base and removes the hydrogen from the anthrone. The newly formed intermediate **291** attacks the activated species **218** and forms the species **292**. Finally, the product **290** is released and the catalyst is recovered.



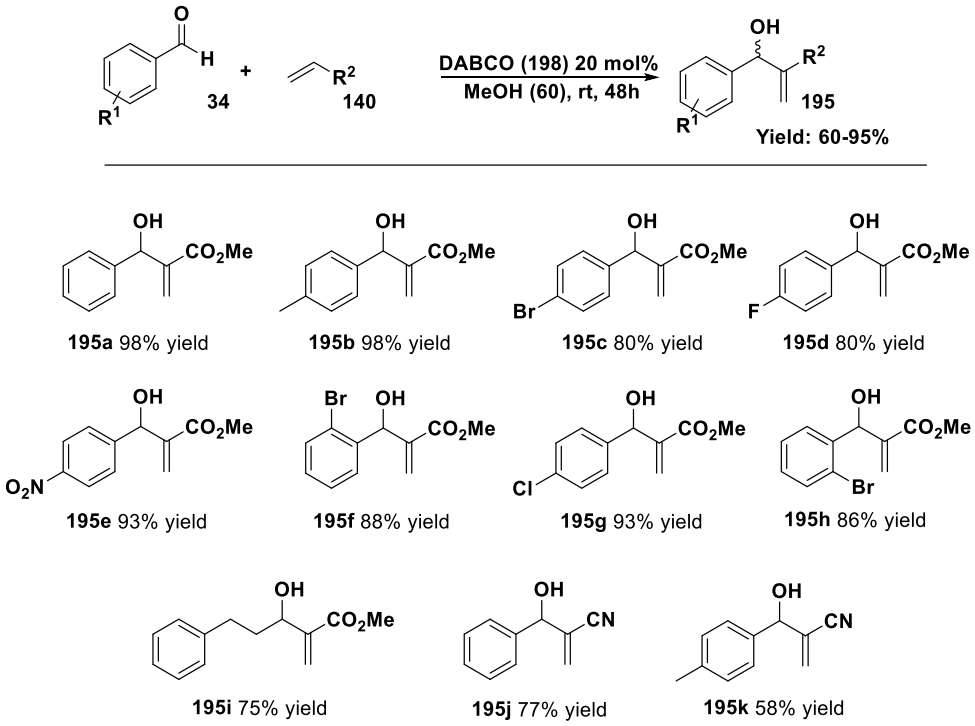
Scheme 2.29 Suggested mechanism

2.2.2 Results and discussions

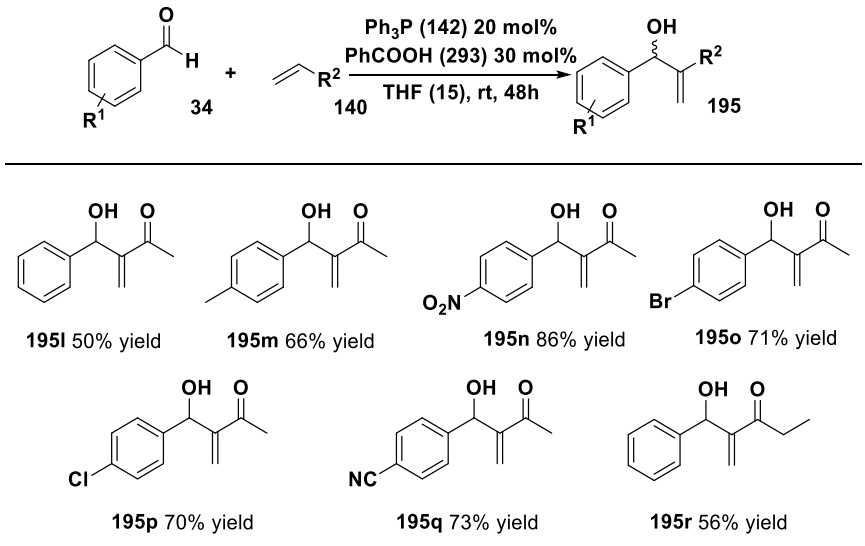
2.2.2.1 Synthesis of starting materials

MBH-alcohols were synthesised using two methods. First method involving DABCO was used for the synthesis of MBH-alcohol with ester and nitrile functional groups (**Scheme 2.30**).[85] The final products **195** were obtained in good to excellent yields. Unfortunately, this method was not effective for the synthesis of MBH-alcohols with ketone functional groups. The final product was obtained in low yields with several side products.

In order to synthesise the MBH-alcohol with ketone functional group triphenylphosphine was used instead, affording the MBH-alcohol **195** from moderate to very good yields (**Scheme 2.31**).[113]

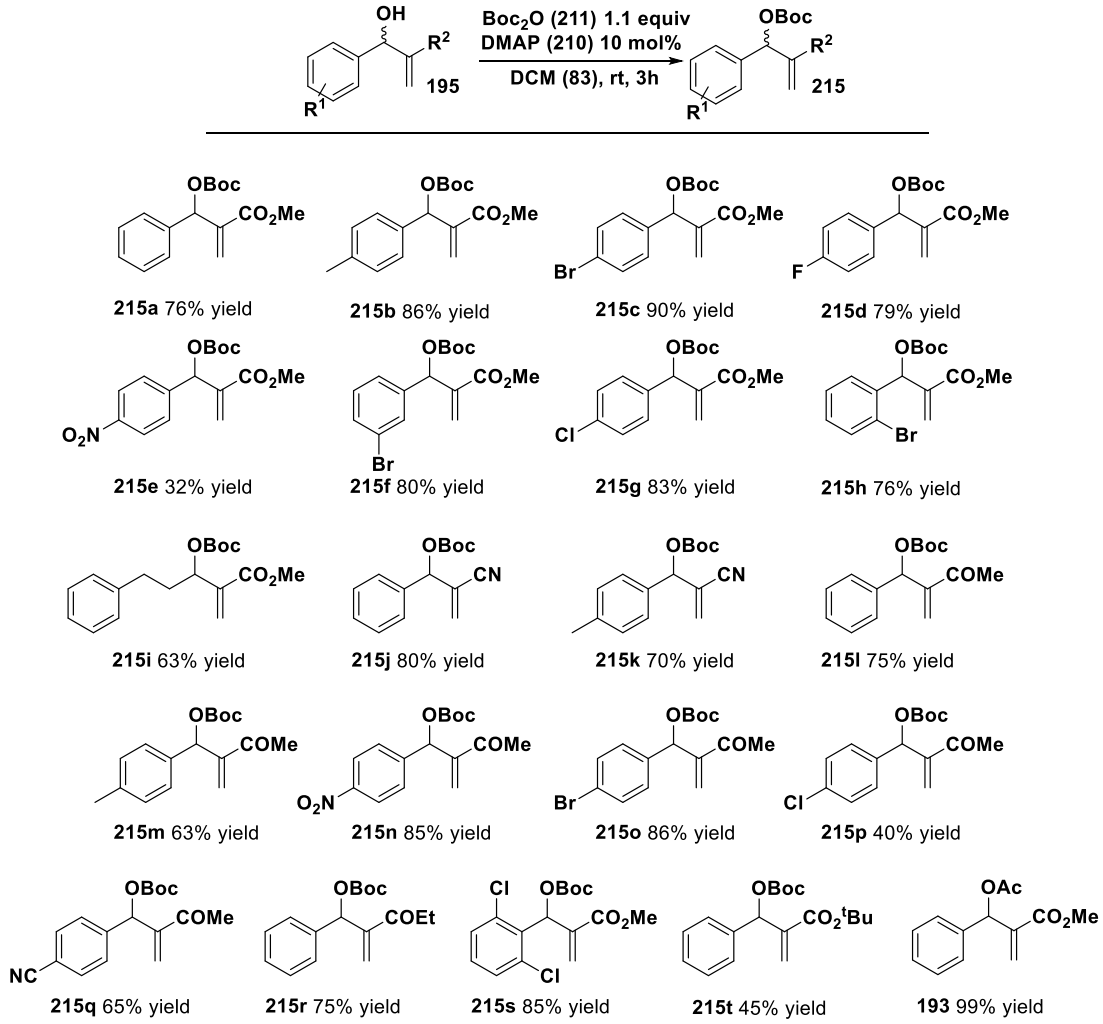


Scheme 2.30 Synthesis of MBH-alcohols



Scheme 2.31 Synthesis of MBH-alcohols with ketone functional groups

The alcohol group was activated either with an acetyl group or a *tert*-butyloxycarbonyl group. In both cases the final product is obtained in very good yields (**Scheme 2.32**).



Scheme 2.32 Synthesis of MBH-carbonates and acetate

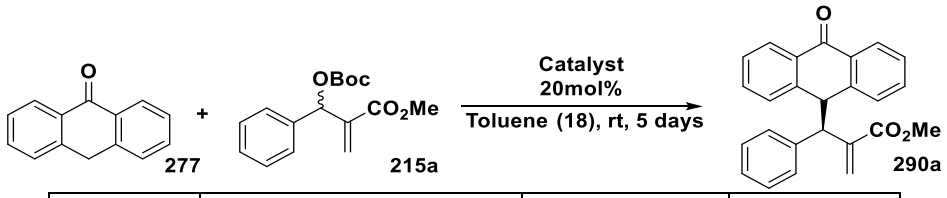
2.2.2.2 Condition screenings

Series of reactions were done analysing the effect of solvent, temperature and catalyst.

First, catalyst screening was effectuated (**Table 2.1**). Several tertiary amines were tested: cinchona-alkaloids such as *β*-ICPD, quinine, quinidine, cinchonine, cinchonidine; dimeric cinchona-alkaloids (Sharpless catalysts) such as $(DHQD)_2AQN$, $(DHQ)_2AQN$, $(DHQD)_2PHAL$, $(DHQ)_2PHAL$, $(DHQ)_2PYR$. *β*-ICPD, $(DHQ)_2PHAL$, $(DHQ)_2PYR$ showed poor enantioselectivity (**Table 2.1, entries 5, 9,**

10). Better results were obtained with quinidine, cinchonine, quinine, $(DHQ)_2AQN$, $(DHQD)_2PHAL$ (**Table 2.1, Entries 2, 3, 4, 7, 8**) with an average of 50% ee. The best enantioselective ratio was determined by using either cinchonidine or $(DHQD)_2AQN$ (**Table 2.1, entries 1, 6**).

Table 2.1 Anthrone-MBH-carbonate catalyst screening



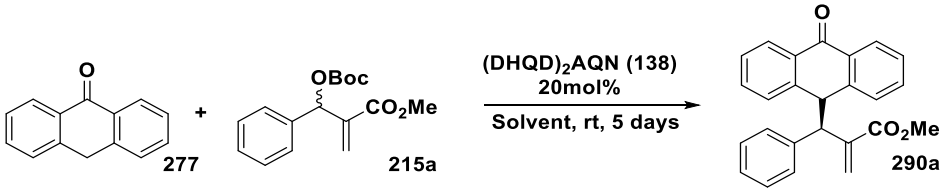
Entry	Catalyst	Conversion[a]	ee[b]
1	Cinchonidine **129**	66 %	80 %
2[c]	Quinidine **128**	88 %	-42 %
3[c]	Cinchonine **130**	15 %	-58 %
4[c]	Quinine **57**	83 %	60 %
5[c]	β-ICPD **131**	100 %	-32 %
6	$(DHQD)_2AQN$ **138**	48 %	82 %
7	$(DHQ)_2AQN$ **139**	25 %	-46 %
8	$(DHQD)_2PHAL$ **136**	50 %	54 %
9	$(DHQ)_2PHAL$ **137**	25 %	-6 %
10	$(DHQ)_2PYR$ **135**	46 %	-38 %

a) The conversion was calculated from crude ^{1}H-NMR analysis;
b) Enantiomeric ratio was determined by HPLC analysis with chiral column;
c) The reactions were effectuated by our project student Greg Gallagher.

Then solvent screening was done. From the obtained results it was noticed that the solvent does not considerably affect the enantioselectivity, but has a great influence on the conversion. In the case where toluene, tetrahydrofuran, ethyl trifluorotoluene or *p*-xylene were used (**Table 2.2, entries 2, 3, 4, 7**) the reaction does not go to completion even after 5 days. Better results were obtained by

effectuating the reaction in dichloromethane, acetonitrile or ethyl acetate (**Table 2.2, entries 1, 5, 6**).

Table 2.2 Anthrone-MBH-carbonate solvent screening

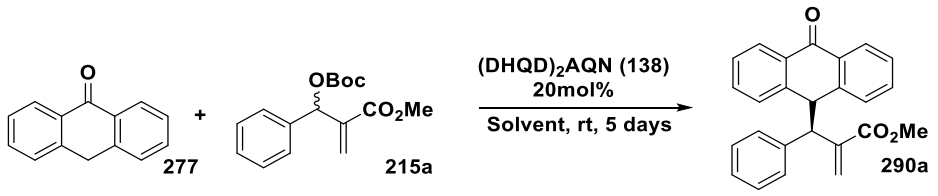


Entry	Solvent	Conversion[a]	ee[b]
1[c]	MeCN **76**	100 %	80 %
2	Toluene **18**	48 %	82 %
3	THF **15**	60 %	84 %
4	*p*-Xylene **294**	20 %	86 %
5	CH_2Cl_2 **83**	100 %	86 %
6	EtOAc **295**	92 %	82 %
7	$PhCF_3$ **254**	84 %	86 %

a) The conversion was calculated from crude ^{1}H-NMR analysis;
b) Enantiomeric ratio was determined by HPLC analysis with chiral column;
c) The reactions were effectuated by our project student Greg Gallagher.

Finally, the reaction was tested at different temperatures (**table 2.3**). By decreasing the temperature to 0 ˚C the enantioselectivity increased by 2% ee.

Table 2.3 Anthrone-MBH-carbonate temperature screening



Entry	Solvent	Temperature	Conversion[a]	ee[b]
1	CH_2Cl_2 **83**	0 ˚C	100 %	88 %
2	CH_2Cl_2 **83**	rt	100 %	86 %
3	Toluene **18**	50 C	81 %	78 %

a) The conversion was calculated from crude ^{1}H-NMR analysis;
b) Enantiomeric ratio was determined by HPLC analysis with chiral column;
c) The reactions were effectuated by our project student Greg Gallagher.

The reaction was also tested with MBH-acetate **193**. The results were similar with the reaction made with MBH-carbonate **215a**.

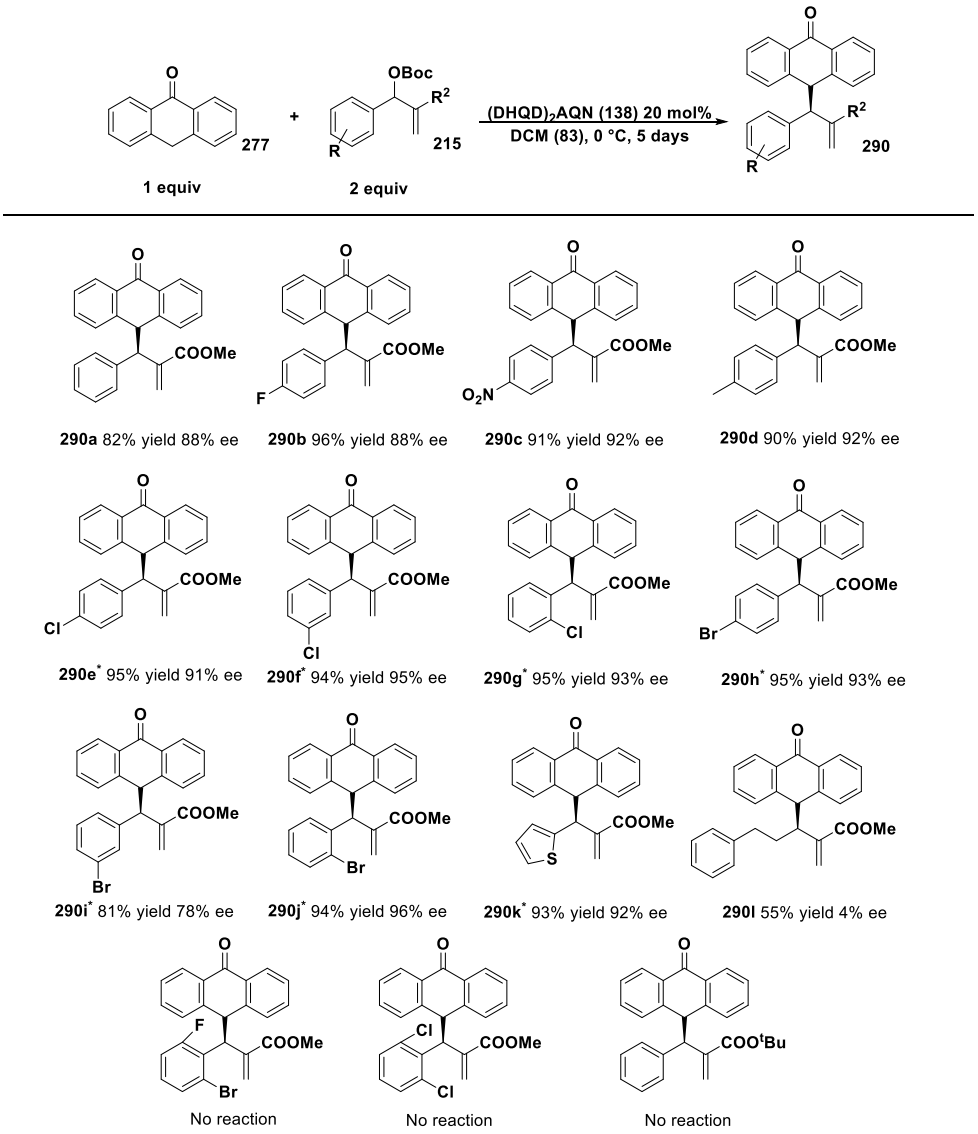
2.2.2.3 Reaction scope

Once the best conditions for the reaction were established, the scope of the reaction was expanded to different types of MBH-carbonates.

First, the scope of reaction was focused on different types of aromatic MBH-carbonates. Very good results in terms of enantioselectivity and yields were obtained for products with 4-methyl, 4-nitro, halide groups such as 4-Cl, 3-Cl, 2-Cl, 4-F, 4-Br, 2-Br (**Scheme 2.33**). Lower conversion and enantioselectivity was noticed in the case of 3-Br derivative.

A limitation for this reaction was the presence of the bulky and aliphatic groups. In the case of aliphatic derivatives moderate yield and very low enantioselectivity was obtained. In the case of bulky aromatic groups such as 2,6-Cl, di-ortho-F, Br

derivative and *tert*-butyl moiety on the ester functional group the reaction does not occur.

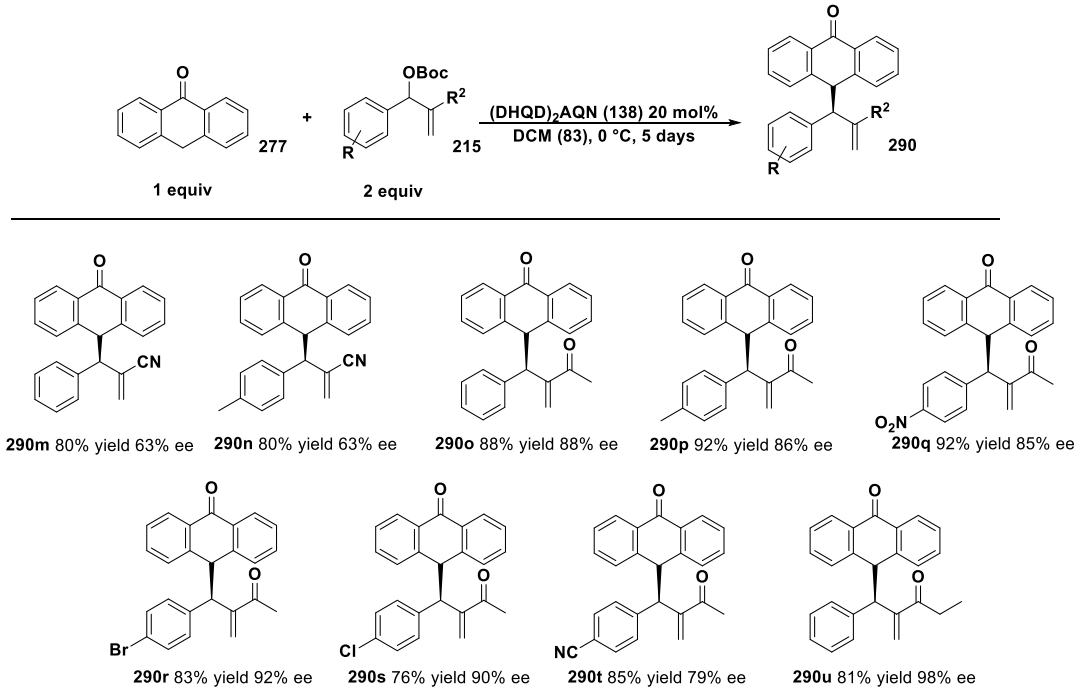


*The products were synthesised by Dr Jirí Tauchman

Scheme 2.33 Reaction scope with ester group

Later, the reaction scope was explored further by using other types of MBH-carbonates with ketone and nitrile functional groups instead of ester group (**Scheme 2.34**). A couple of reagents with nitrile functional group were tested. The obtained yields and enantioselectivities were lower than expected (**Scheme 2.34**, **290m**, **290n**).

Afterwards, the MBH-carbonate scaffolds with ketone functional groups were tried (**Scheme 2.34**, **290o-290u**). The obtained results were comparable to the ones reported earlier with MBH-carbonate scaffolds (**Scheme 2.33**, **290a-290k**).

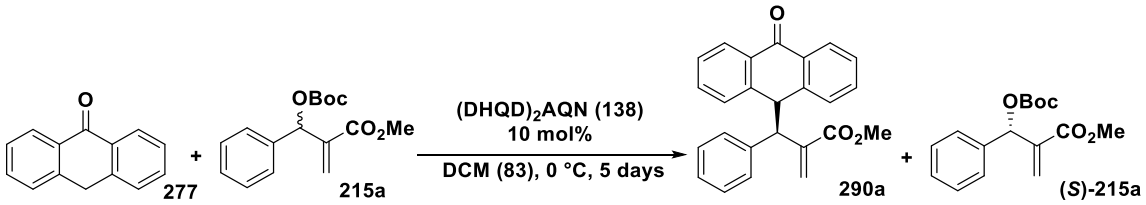


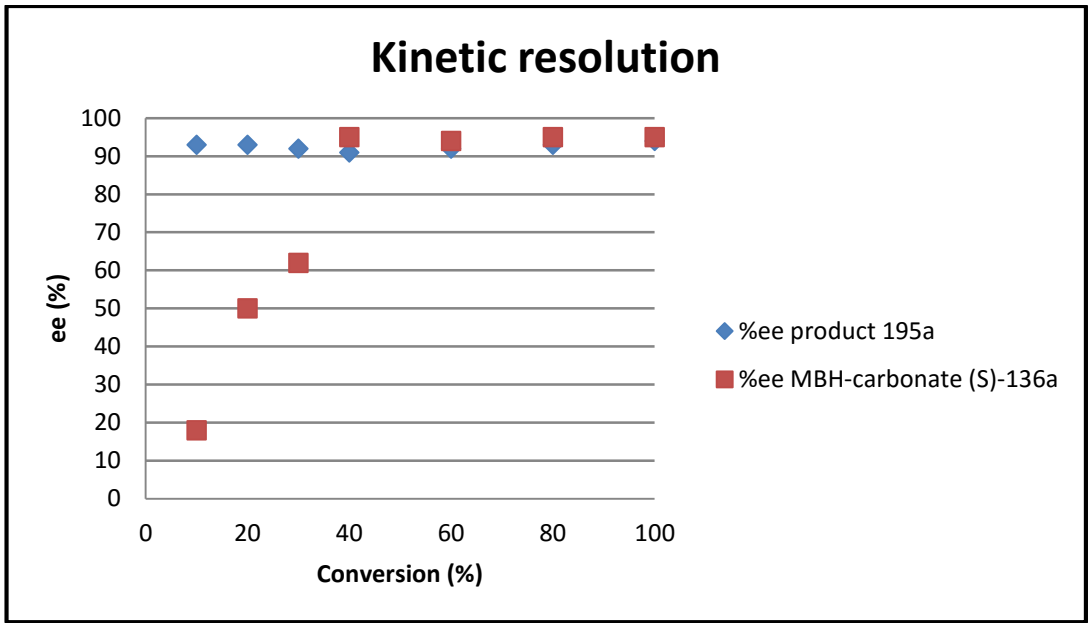
Scheme 2.34 Reaction scope involving nitrile and ketone groups

2.2.2.4 Reaction mechanism and kinetic resolution

In order to understand and to determine the mechanism of the reaction series of analyses were effectuated based on conversion and enantioselectivity of starting and final products.

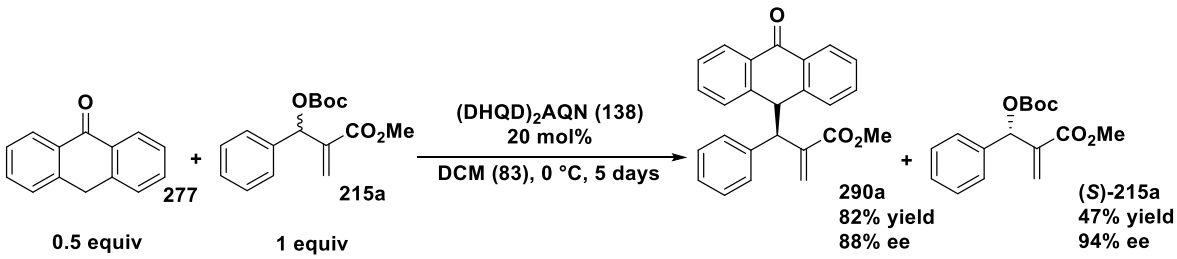
It was noticed that the enantiopurity of starting MBH-carbonate increases with the conversion and the enantiomeric excess of the final product remains constant.





Scheme 2.35 Kinetic resolution

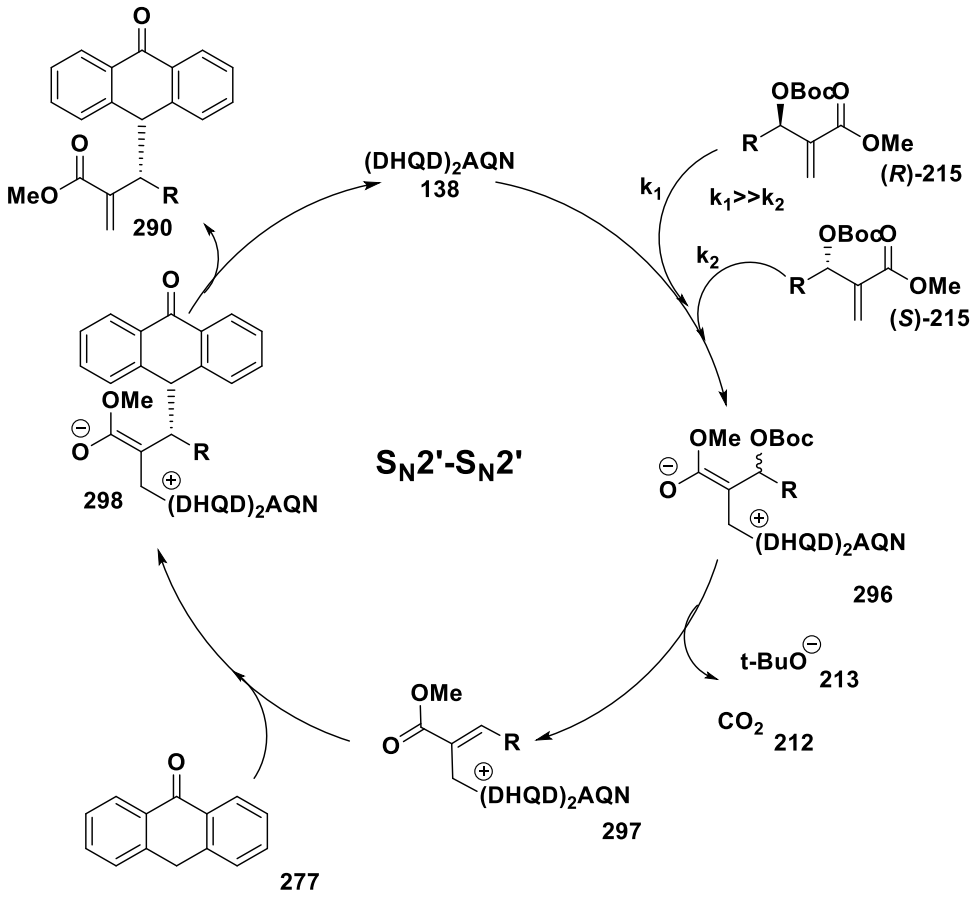
The preparative kinetic resolution showed that by reacting 0.5 equiv of anthrone with 1 equiv of MBH-carbonate it was obtained 82% yield and 88% ee of the final product and **(*S*)-215a** was recovered with 47% yield and 94% ee (**Scheme 2.36**).



Scheme 2.36 Preparative kinetic resolution Anthrone-MBH-carbonate reaction

Based on these results the following S_N2'-S_N2' mechanism was proposed (**Scheme 2.37**). First, the racemic MBH-carbonate reacts with the tertiary amine catalyst. Based on the kinetic resolution we believe that the (*R*)-enantiomer reacts at a faster rate with the catalyst then the (*S*)-enantiomer ($k_1 >> k_2$). Consequently, the intermediate **297** is formed resulting in the release of *tert*-butoxide and carbon

dioxide. It is important to mention here that both **(*R*)-215** and **(*S*)-215** lead to the same intermediate **297**. Then the intermediate **297** reacts with the anthrone followed by the recovery of the catalyst and the formation of the final product.



Scheme 2.37 Suggested mechanism

The absolute configuration was determined by single crystal X-ray analysis. The X-ray crystallography analysis shows that by using $(DHQD)_2AQN$ we obtain the (*R)* - enantiomer (**Figure 2.3**) with a Flack parameter value of 0.003.

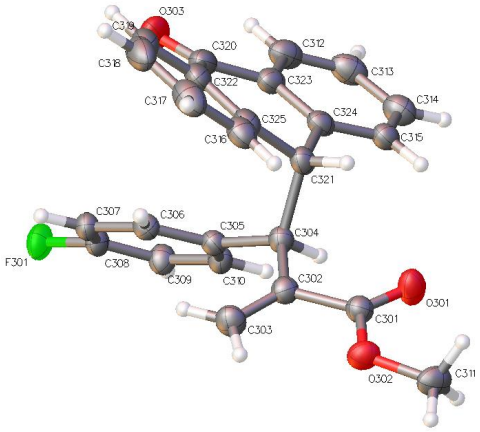
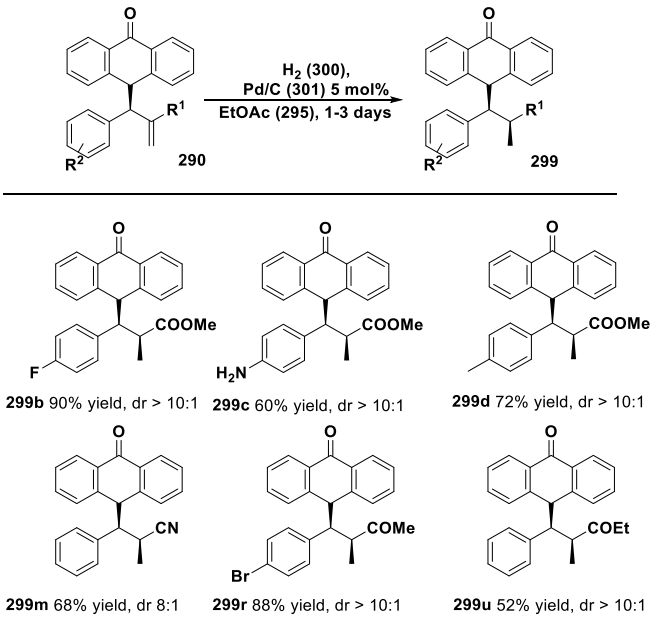


Figure 2.3 X-ray data analysis of a single crystal **290b.** Displacement ellipsoids – 50% probability level (Flack parameter 0.003)

2.2.2.5 Hydrogenation of anthrone-MBH derivatives

In order to study further the reactivity of final products **290**, the hydrogenation of anthrone-MBH adducts were performed in very good to excellent yield and diastereoselectivity (**Scheme 2.38**).



Scheme 2.38 Hydrogenation results

In the case of product **299c,** the starting material **290c** was very reactive and in several hours the hydrogenation of the double bond together with nitro group occurred. In the other examples no side reactions were detected.

X-ray single crystal analysis of the product **299r** showed that after hydrogenation (*S*, *S*)-enantiomer (**Figure 2.4**) was obtained with a Flack parameter value of 0.036.

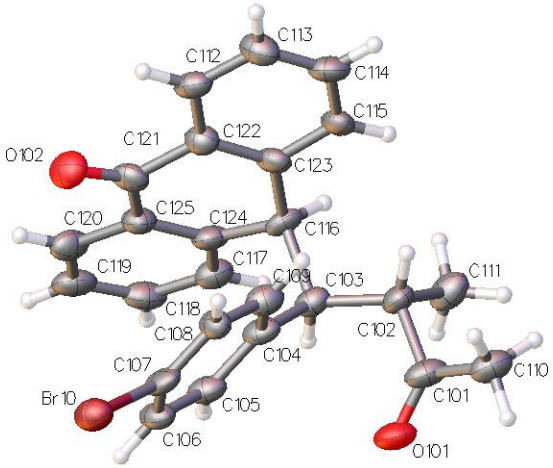


Figure 2.4 X-Ray single crystal analysis of **299r**. Displacement ellipsoids – 50% probability level (Flack parameter 0.036)

2.2.3 Conclusion

An asymmetric allylic substitution of anthrone and MBH-carbonates with excellent yields and stereoselectivity was achieved. Further analyses were done in order to understand better the mechanism. Finally, the derivatization of some of the anthrone-MBH adducts **290** by hydrogenating the double bond was done obtaining the final products in excellent yield and diastereoselectivity.

2.3 Highly diastereoselective benzoxazole addition to Morita-Baylis-Hillman carbonates

2.3.1 Introduction

Alkyl-azaarene derivatives are very important scaffolds in pharmaceutical industry and agrochemistry, and are present in various natural products. Alkyl-azaarenes derivatives showed various biological activities, such as anti-tuberculosis, psychoactive,[114] anti-schizophrenia,[115] anti-inflammatory,[116] fungicide,[117] etc. (**Figure 2.5**).

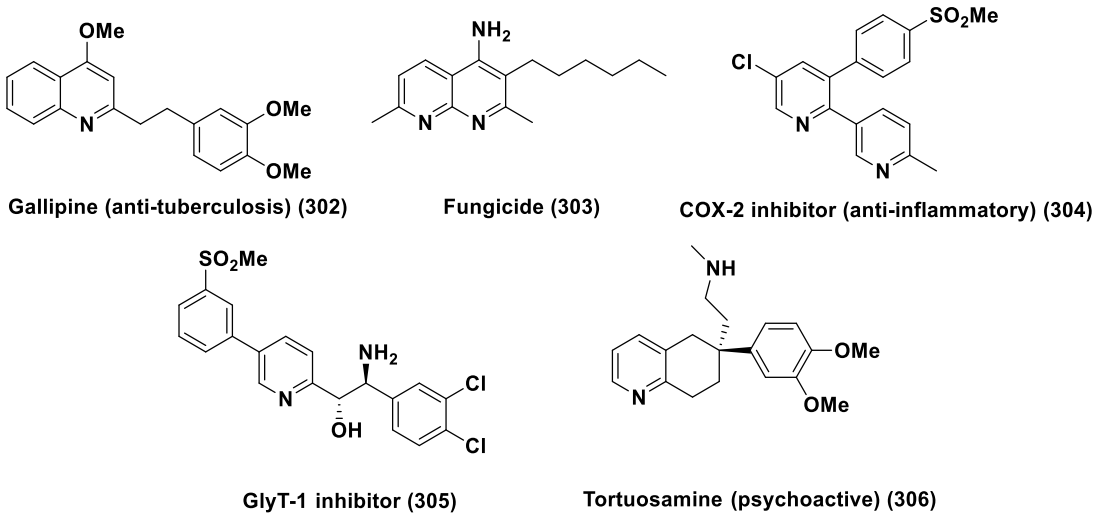
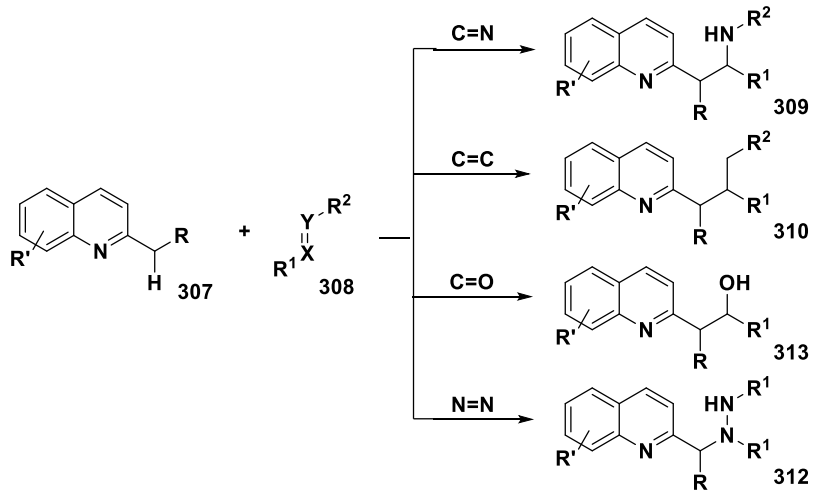


Figure 2.5 Biologically active alkyl-azaarene derivatives

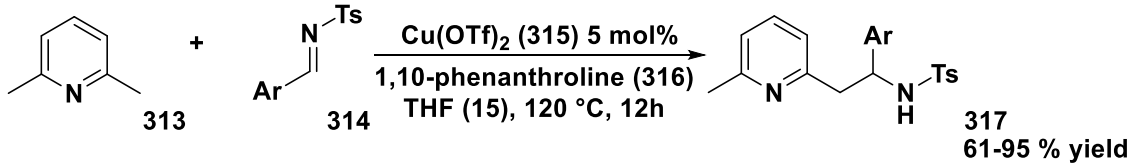
Direct activation of C(sp^3)-H of alkyl-azaarene derivatives have been developed. Here are several examples of addition of alkyl-azaarene to various electrophiles (**Scheme 2.39**).



Scheme 2.39 C(sp^3)-H functionalization of alkyl-azaarene derivatives

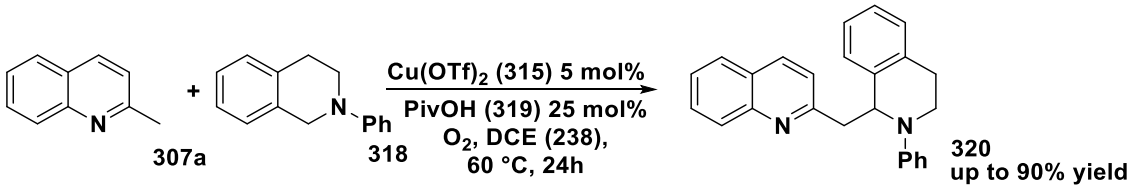
2.3.1.1 Alkyl-azaarene addition to C=N bond

In 2011, Rueping *et al.* reported the addition of alkyl-azaarene derivatives to N-sulfonyl aldimines via Mannich reaction. The best Metal Lewis acid used for the reaction is the copper triflate (**Scheme 2.40**).[118]



Scheme 2.40 Rueping's alkyl-azaarenes to N-sulfonyl aldimines

Three years later, Yang and co-workers published an addition of alkyl-azaarenes to tetrahydroisoquinoline via cross-dehydrogenative-coupling (CDC) and copper/Brønsted acid synergistic catalysis (**Scheme 2.41**).[119]

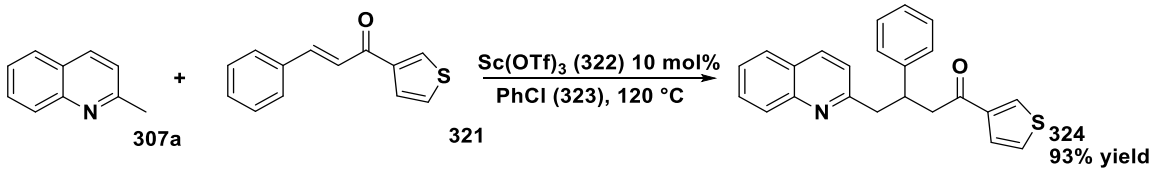


Scheme 2.41 Yang's CDC involving tetrahydroisoquinoline and azaarene

2.3.1.2 Alkyl-azaarene addition to C=C bond

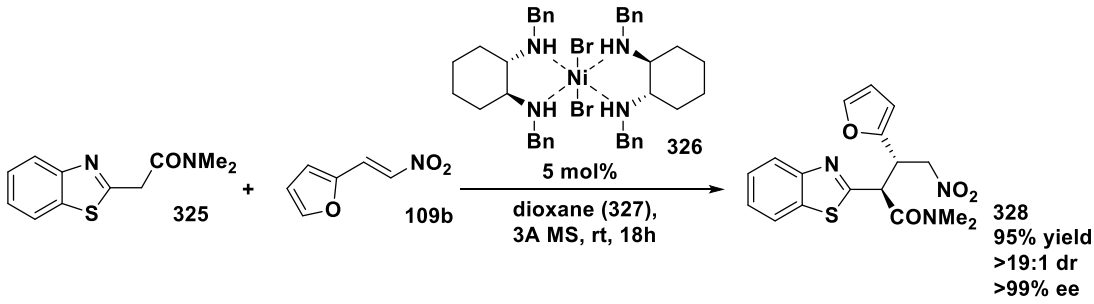
In 2011, Matsunaga and Kanai reported a Lewis acid catalysed azaarene addition to enones. The best results were obtained by using scandium or yttrium salts

(**Scheme 2.42**).[120] In 2014, Wong *et al.* reported the same reaction catalysed by cobalt salt with comparable results.[121]



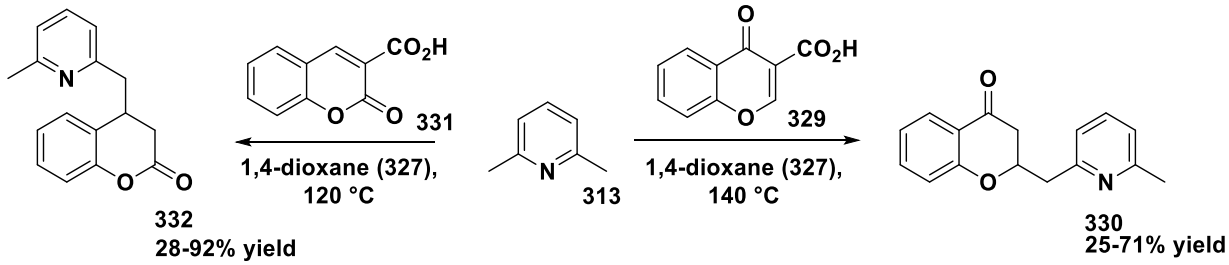
Scheme 2.42 Matsunaga and Kanai's alkyl-azaarene addition to enone

In 2012, Lam and co-workers reported a highly enantioselective and diastereoselective alkyl-azaarene addition to nitrostyrene catalysed by a nickel chiral complex (**Scheme 2.43**).[122]



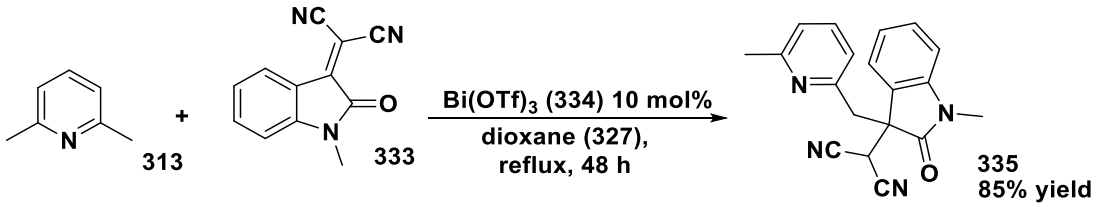
Scheme 2.43 Lam's alkyl-azaarene addition to nitrostyrene

In 2014, several examples of the addition of alkyl-azaarenes to a C=C bond were reported. Xiao and co-workers reported two similar azaarene additions to 4-oxo-4H-chromene-3-carboxylic acid[123] and coumarin-3-carboxylic acid[124] respectively, followed by a decarboxylation (**Scheme 2.44**). In both cases they obtained moderate yields (30-85 %).



Scheme 2.44 Xiao's azaarene addition to coumarin derivatives

In the same year, Huang *et al.* reported the C-H functionalization of azaarene by using $Bi(OTf)_3$. They did the addition of azaarene to oxindole derivatives with moderate to excellent yields (**Scheme 2.45**).[125]

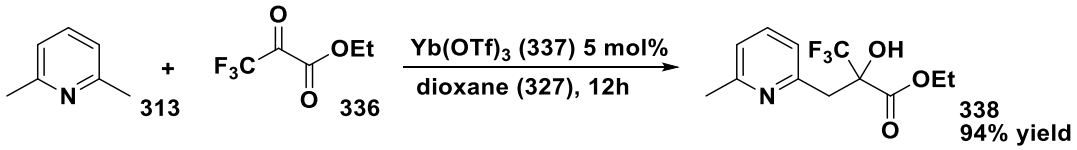


Scheme 2.45 Huang's azaarene addition to oxindole derivative

2.3.1.3 Alkyl-azaarene addition to C=O bond

Another example of $C(sp^3)$ functionalization is the alkylazaarenes addition to carbonyl group.

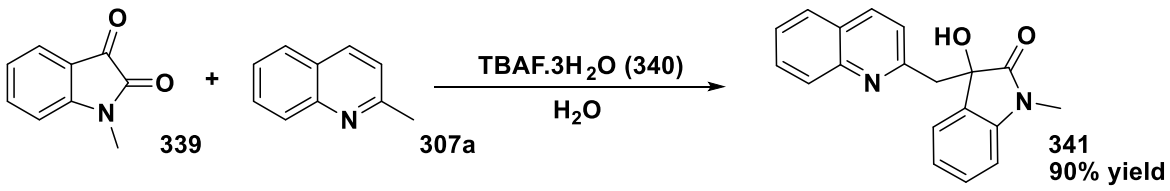
In 2012, Shaikh *et al.* reported an addition of alkylazaarene to α-trifluoromethyl carbonyl derivatives in very good yields (**Scheme 2.46**).[126]



Scheme 2.46 Shaikh's alkylazaarene addition to carbonyl

Two years later, Uozumi and co-workers suggested iron salts as catalyst. They obtained comparable results with the one reported by Shaikh.[127]

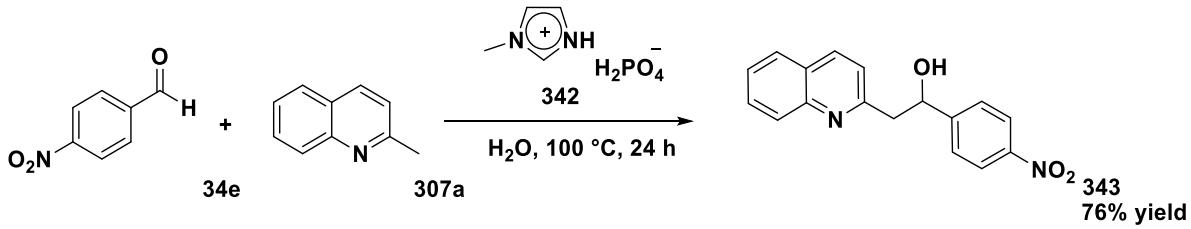
In 2013, Singh and co-workers published an alkylazaarene addition to isatin derivative catalysed by TBAF in water (**Scheme 2.47**).[128]



Scheme 2.47 Singh's alkylazaareneaddition to isatin

An interesting approach in addition of azaarene derivative to aldehyde was reported by Wang and co-workers. They used acid ionic liquids as catalysts.

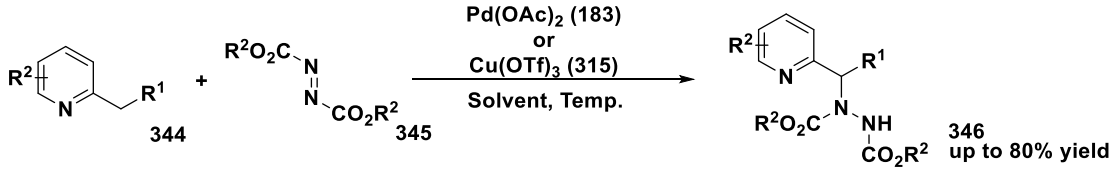
Similar to other examples described earlier the yields go up to 90% (**Scheme 2.48**).[129]



Scheme 2.48 Wang's azaarene addition to benzaldehydes

2.3.1.4 Alkyl-azaarene addition to N=N bond

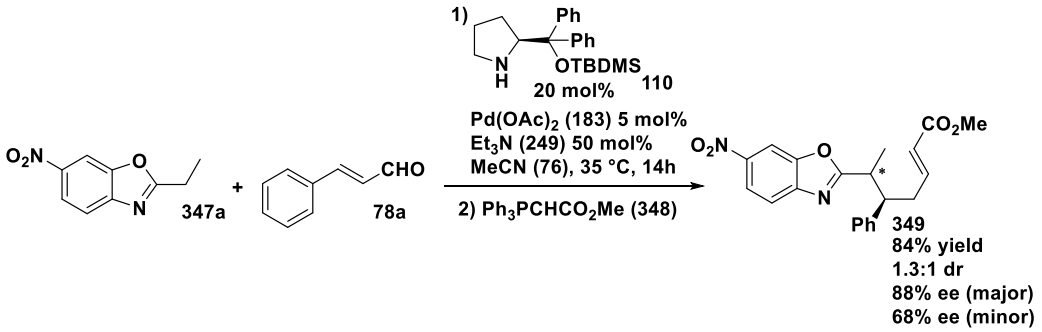
Additional examples of azaarene addition to azodicarboxylate esters have been reported in the recent years. The first example was reported by Qu and Guo in 2012. In their case the reaction was catalysed by palladium acetate if the reagent was a quinolone derivative and copper triflate if the reagent is pyridine derivative.[130] The second example was reported two years later by Huang and coworkers. They used a copper salt as catalyst.[131] In both cases the results were similar up to 80 % yield (**Scheme 2.49**).



Scheme 2.49 Qu and Guo, and Huang's azaarene addition to azodicarboxylate esters

2.3.1.5 Our work

Recently, our group reported two examples of alkyl-azaarene addition to enals (**Scheme 2.50**)[132] and MBH-carbonates[133] respectively via synergistic catalysis.



Scheme 2.50 Benzoxazole addition to enals

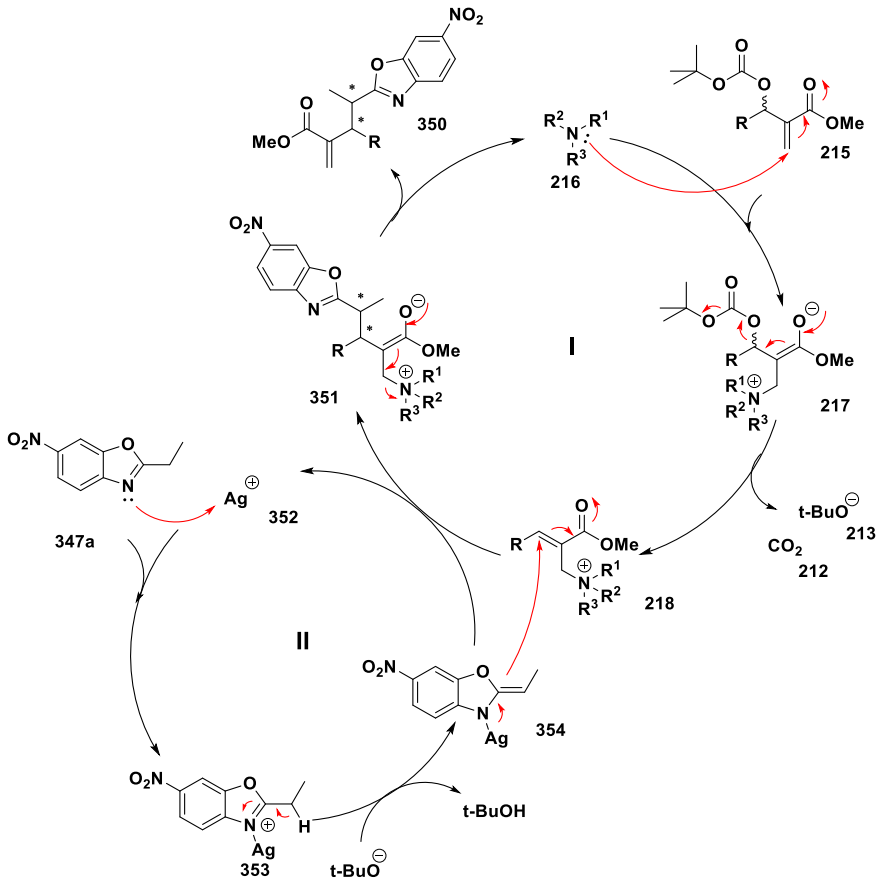
In this thesis we will describe more in details the addition of benzoxazole to MBH-carbonates.

MBH-carbonates appear to be good electrophiles when they react with strong nucleophiles such as malonates, amines and alcohols, but they seem to be less reactive or unreactive in the case of nucleophiles such as alkyl azaarenes. To make the alkylazaarene more nucleophilic we needed to activate that particular position with the help of a metal Lewis acid.

Inspired by the synergistic catalysis principle, we studied the addition of alkyl azaarenes to MBH carbonates using two types of catalysts (metal Lewis acid and organic Lewis base) (**Scheme 2.51**).

Scheme 2.51 Benzoxazole addition to MBH-carbonates via synergistic catalysis

The proposed mechanism of this reaction is described in **scheme 2.52**.



Scheme 2.52 Proposed mechanism for the synergistic reaction

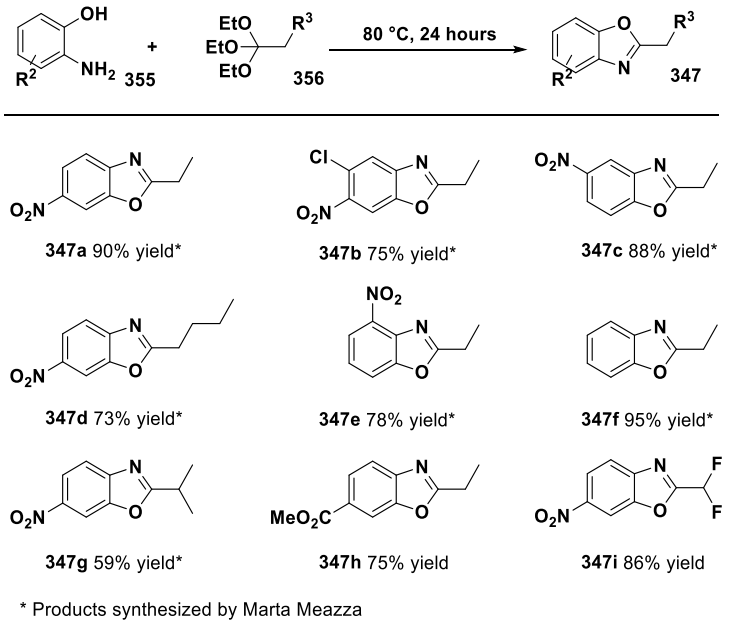
The first catalytic cycle (**I**) corresponds to a S_N2'-S_N2'.[134] The lone pair of the tertiary amine (organic Lewis base) attacks the MBH-carbonates in the *β*-position, like in a 1,4-Michael addition, forming a zwitterion (**217**). Then, an *α,β*-unsaturated ester (**218**) is formed by eliminating the -OBoc with the creation of carbon dioxide and *tert*-butoxide. The *tert*-butoxide will be part of the second catalytic cycle as a base. The intermediate **218** reacts with the activated benzoxazole **354** creating a new C-C bond between MBH moiety and benzoxazole, followed by the release of the catalyst (organic Lewis base) and the MBH-benzoxazole adduct formation (**350**).

The second catalytic cycle (**II**) corresponds to the activation of benzoxazole with silver acetate (metal Lewis acid). The lone pair of the nitrogen attacks the silver cation forming the intermediate **353** followed by the attack of *tert*-butoxide, formed in the first catalytic cycle, in order to create the active benzoxazole (**354**).

2.3.2 Results and Discussions

2.3.2.1 Synthesis of starting material

The starting benzoxazoles were synthesised following procedures described in the literature.[135] They were made by the addition of orthoformate **356** to the 2-hydroxyaniline **355** at 80 °C (**Scheme 2.53**). In all the examples, the benzoxazole was obtained in good yields.



Scheme 2.53 The starting benzoxazoles

The MBH-carbonates were synthesised following procedures described in **chapter 2.2.2.1** of this thesis.

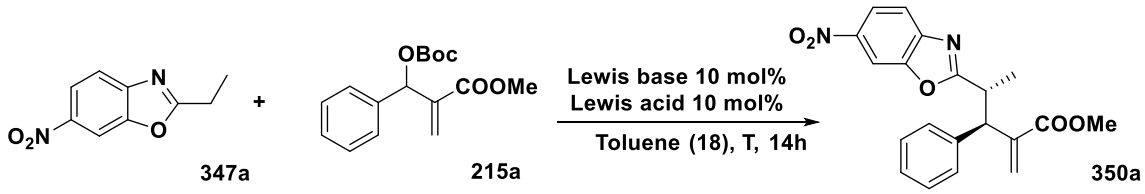
2.3.2.2 Condition screenings

First, the addition of MBH carbonate **215a** to benzoxazole **347a** in the presence of either a metal Lewis acid or a Lewis base was investigated (**Table 2.4, entries 1, 2**). In both cases the reaction does not occur.

Following the concept of synergistic catalysis, both types of synergistic catalysis were used. It was noticed that the nature of the metal used in the reaction has an influence on conversion and diastereoselectivity (**Table 2.4, entries 4-9**). Palladium salts such as $Pd(OAc)_2$ and $PdCl_2$ gave a good conversion but low diastereoselectivity. Also, copper and ytterbium salts such as $Cu(OAc)_2$, $Yb(OTf)_3$, $Cu(OTf)_2$ gave poor conversion and diastereoselectivity.

Good results were noticed by using silver salts. Different types of silver salts were tested. In all the cases only one diastereomer was created with high conversion (**Table 2.4, entries 4, 10, 11**).

Table 2.4 Catalyst screening

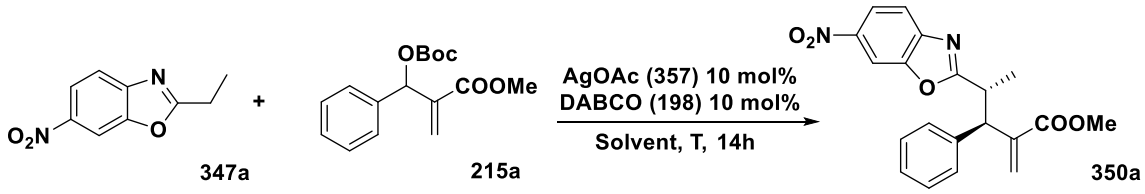


Entry	Lewis acid	Lewis base	T	Conv.[b]	dr[b]
1[c]	AgOAc **357**	-	rt	n.r.	-
2[c]	-	DABCO **198**	rt	n.r.	-
3[c]	AgOAc **357**	DMAP **210**	rt	<3%	n.d.
4[f]	AgOAc **357**	DABCO **198**	50 °C	50%	15:1
5[e]	$Pd(OAc)_2$ **183**	DABCO **198**	50 °C	71%	2:1
6	$PdCl_2$ **358**	DABCO **198**	50 °C	50%	2:1
7	$Cu(OAc)_2$ **359**	DABCO **198**	50 °C	<3%	n.d.
8	$Yb(OTf)_3$ **337**	DABCO **198**	50 °C	9%	2.5:1
9	$Cu(OTf)_2$ **315**	DABCO **198**	50 °C	9%	4:1
10	AgOBz **360**	DABCO **198**	50 °C	43%	8:1
11[c,f]	$AgSbF_6$ **361**	DABCO **198**	rt	100%	15:1

a) Procedure: In a small vial, 1.0 equiv. of benzoxazole, 2.0 equiv. of MBH-carbonate, 10 mol% Lewis Acid, 10 mol% Lewis base. The reaction was stirred at the indicated temperature T for 14 hours.
b) Determined by ^{1}H-NMR analysis of the crude.
c) Reaction was carried with 4 equiv. of MBH carbonate **215c.**
d) Reaction was stirred for 3 days at 0°C with 4 equiv. of MBH-carbonate **215a** in order to have 100% conversion.
e) The reaction was effectuated by Dr Piotr Putaj.
f) Only one diastereomer was seen in the ^{1}H-NMR analysis.

During solvent screening study, a range of solvents were tested. The nature of the solvent is important for the outcome of the reaction. Polar aprotic solvents such as DMF, EtOAc, THF, MeCN showed a lower conversion and diasteroselectivity (**Table 2.5, entries 2, 5, 6, 7**). Chlorinated solvents such as DCM and chloroform together with protic solvent such as methanol didn't show any conversion (**Table 2.5, entries 3, 4**). The best solvent for this reaction appeared to be toluene (**Table 2.5, entry 1**). In this solvent the reaction goes to completion with high diastereoselectivity.

Table 2.5 Solvent screening



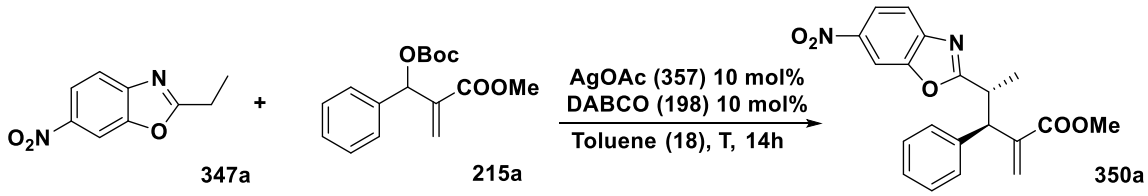
347a 215a 350a

Entry	Solvent	T	Conv.[b]	dr[b]
1[c]	Toluene **18**	50 °C	50%	15:1
2	DMF **101**	50 °C	50%	1:1
3	$CHCl_3$ **146**	50 °C	n.r.	-
4	DCM **83**	rt	n.r.	-
5	EtOAc **295**	rt	26%	3:1
6	THF **15**	50 °C	25%	5:1
7	MeCN **76**	rt	30%	2:1
8	MeOH **60**	rt	traces	nd

a) Procedure: In a small vial, 1.0 equiv. of benzoxazole, 2.0 equiv. of MBH-carbonate, 10 mol% Lewis Acid, 10 mol% Lewis base. The reaction was stirred at the indicated temperature T for 14 hours.
b) Determined by ^{1}H-NMR analysis of the crude.
c) Only one diastereomer was seen in the ^{1}H-NMR analysis.

During the reaction the cleavage of the Boc protecting group and the formation of MBH-alcohol were observed. We think this is due to the presence of the metal Lewis acid, as for the Boc cleavage acidic conditions are needed. The competition between the Boc cleavage and the MBH-benzoxazole formation was noticed.

Table 2.6 Temperature screening



Entry	Temperature	Conv.[b]	Dr[b,d]
1	50 °C	100%	15:1
2[b]	rt	100%	15:1
3[c]	0 °C	13%[d]	15:1

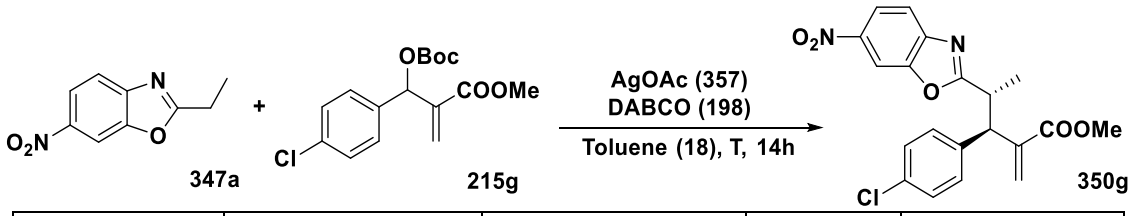
a) Determined by ^{1}H-NMR analysis of the crude.
b) Reaction was carried with 4 equiv. of MBH carbonate **136c.**
c) Reaction was stirred for 3 days at 0°C with 4 equiv. of MBH-carbonate **136a** in order to have 100% conversion.
d) Only one diastereomer was seen in the ^{1}H-NMR analysis.

The screening of several different conditions such as temperature and equivalents of MBH-carbonate were carried out. In order to have full conversion the reaction has to be performed at 0 °C for 3 days, with 4 equivalents of MBH-carbonate **215a**. It appears that by decreasing the temperature the Boc cleavage is decreased and the formation of the final compound is favoured (**350a**).

Also, the mono-substituted MBH-carbonates (**215b-g, 215i**) appear to be more reactive at room temperature. In this case the reaction between the MBH-carbonate and the benzoxazole occurs faster than the Boc cleavage.

Several tests were made in order to find the optimal catalyst amount needed to have the final compound in good yield without decreasing the diastereoselectivity (**Table 2.7**).

Table 2.7 MBH-carbonate-benzoxazole catalyst amount screening[a]



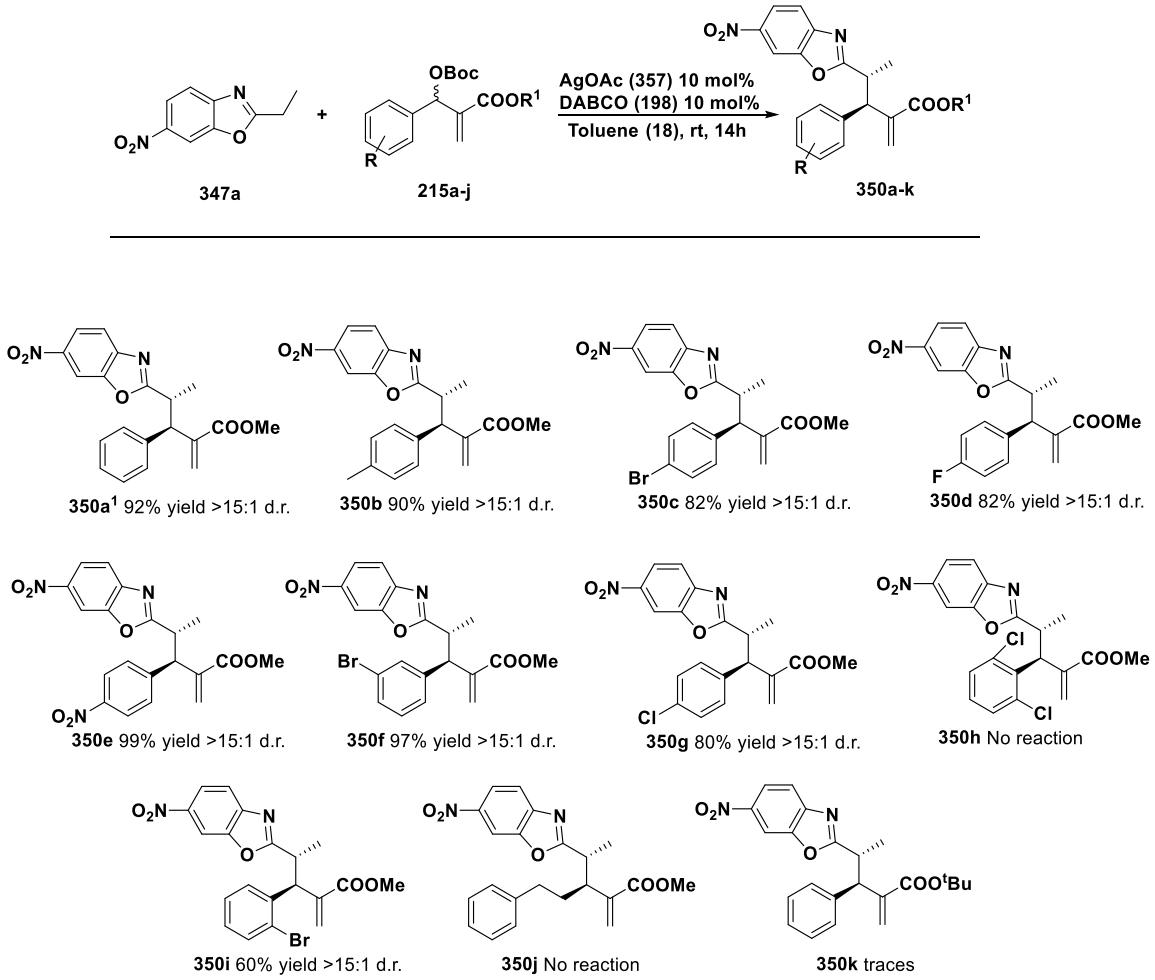
Entry	AgOAc (mol%)	DABCO (mol%)	Conv.[b]	dr[b]
1	20	10	100%	15:1
2	10	10	100%	15:1
3	5	10	62%	15:1
4	1	10	35%	15:1
5	5	5	50%	15:1
6	1	1	20%	15:1
7	10	5	traces	-

a) In a small vial, 1.0 equiv. of benzoxazole, 4 equiv. of MBH-carbonate were added in 1 ml toluene in the presence of Metal Lewis acid and Organic Lewis base. The reaction was stirred at room temperature for 14 hours.
b) Determined by ^{1}H-NMR analysis of the crude mixture

Catalyst loading does not affect the diastereoselectivity of the final compound. However, we noticed that the conversion is directly proportional with the catalyst loading. The optimal catalyst loading was found to be 10 mol% of AgOAc and 10 mol% of DABCO. When a decreased amount of catalyst was added, the full conversion was not achieved after 14 hours. Leaving the mixtures stirring for longer than 14 hours did not solve the problem. We noticed only MBH-carbonate alcohol deprotection and the quantity of final compound remained unchanged.

2.3.2.3 Reaction scope

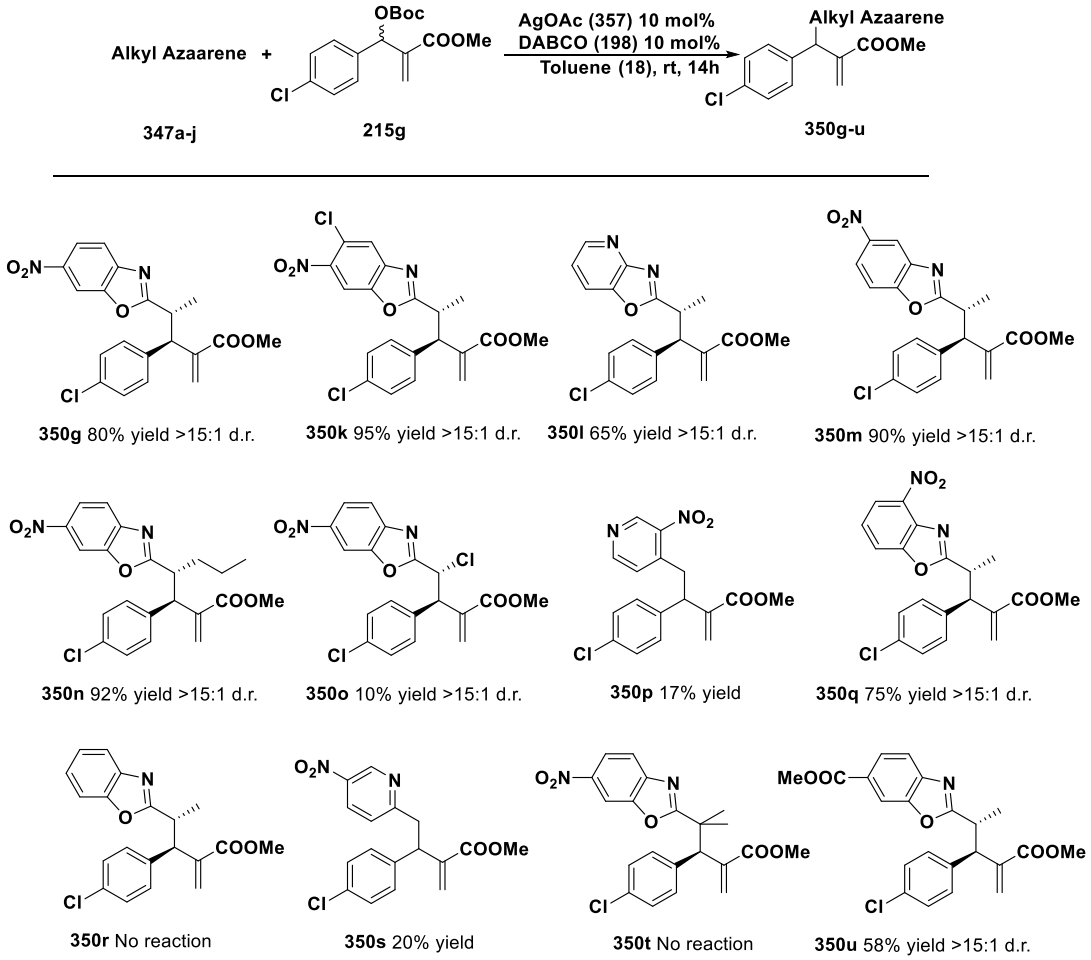
Once the optimal conditions were identified, the scope of the reaction was examined.



Scheme 2.54 Reaction scope using MBH-carbonate

First, the reaction scope was focused on the MBH-carbonate derivatives. As shown in **scheme 2.54**, the reaction provides the final adducts in good yields and high diastereoselectivity. There are some examples in which the reaction does not occur. For example, the di-ortho-substituted MBH-carbonates (**350h**) and aliphatic MBH-carbonates (**350j**) are not reactive under these conditions. We believe this is due to the absence of conjugated system between the aromatic cycle and the double-bonds of the intermediate **218** (**Scheme 2.52**). In the case of the di-ortho-substituted MBH-carbonates, the substituents in the ortho position obstruct the aryl group being in the same plan with the double-bond. In the case of aliphatic groups, the π-system is missing. The *tert*-butyl ester

substituent of MBH-carbonate derivative only gave traces of **350k**, likely due to the higher steric hindrance. A decrease in yield was noticed in the case of 2-bromo substituted MBH-carbonate (**350i**), probably also due to the bulky effect of the bromine.



Scheme 2.55 Reaction scope using alkyl azaarenes

The scope of the reaction was studied using different azaarenes as shown in **scheme 2.55**. Different substituents in the benzoxazole ring were examined. An electron-withdrawing group was found to be necessary for reactivity. The nitro substituents (**350g, 350m, 350n, 350q**) provided adduct in high yields and high diastereoselectivity. The benzoxazole with an ester group gave the final compound (**350u**) in relatively good yields and high diastereoselectivity. Unfortunately, the reaction did not occur when no electron-withdrawing group was present on the aromatic ring (**350r**). Next, the scope of the reaction was studied using benzoxazole bearing different alkyl chains. Increasing the length of the alkyl group does not affect the formation of the final compound (**350n**). However, the use of tertiary carbons in the *α*-position makes the benzoxazole

unreactive. The benzoxazole derivative with a chlorine on the alkyl chain gave the final product **350o** in poor yields but high diastereoselectivity. Further on, the oxazolopyridine with MBH-carbonate was tested. Relatively good yields with the same diastereoselectivity as in other examples were obtained. Pyridine derivatives were also applicable to the reaction. However, the results are not as good as expected (**350p, 350s**).

The relative configuration of the products was determined by X-ray diffraction analysis of a single crystal of **350i** (**Figure 2.6**). The major diastereomer has an *anti* relative configuration. Based on this configuration we suppose that the transition state has the aromatic ring of the benzoxazole and aryl substituent of the MBH-carbonate on opposite directions (**Figure 2.7**).

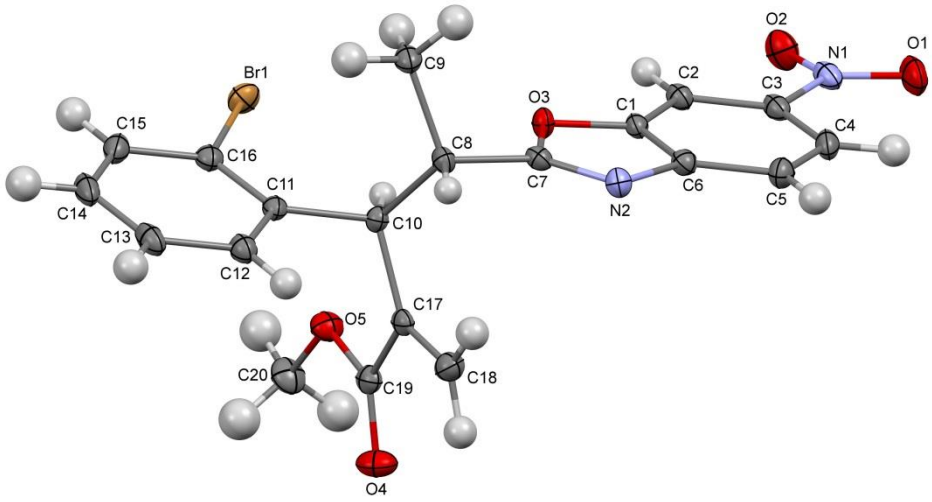


Figure 2.6 Single crystal X-ray diffraction of compound **350i**. Displacement ellipsoids – 50% probability level (X-ray analysis was effectuated by Dr Mateusz Pitak)

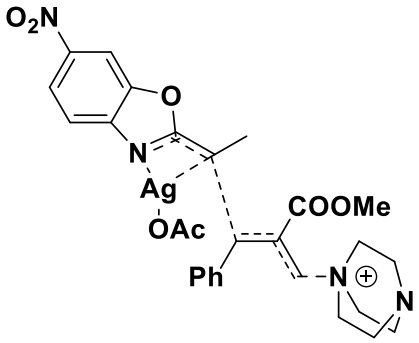


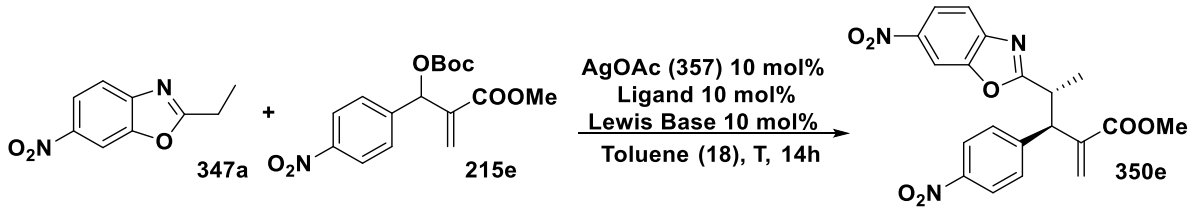
Figure 2.7 Proposed transition state

2.3.2.4 Enantioselective studies

Enantioselectivity studies were done. First several tertiary amine catalysts such as cinchonidine, quinine, cinchonine, quinidine, *β*-ICPD, $(DHQD)_2PHAL$, $(DHQ)_2PHAL$, $(DHQD)_2AQN$)) were tested under similar optimized conditions (toluene, room temperature, 14 hours, 10 mol% of metal Lewis acid, 10 mol% of Lewis base catalyst). None of the mentioned tertiary amine catalysts gave the final product, with the exception of *β*-ICPD. The increase in temperature up to 70 °C didn't show any result.

In the case of *β*-ICPD the final adduct was obtained moderate yield with high diastereoselectivity, but low enantioslectivity (**Table 2.8, entry 1**). Then the temperature was decreased to 0 °C, but no changes occurred except that the reaction was slower (**Table 2.8, entry 2**). (*R*)-BINAP was also tested. The catalyst gave full conversion, high diastereoselectivity, but poor enantioslectivity. Finally, by using both the chiral phosphine and *β*-ICPD the reaction did not occur.

Table 2.8 Catalyst screening[a]



Entry	Lewis acid	Ligand	T	Conv.[b]	d.r.[b]	Yield	e.r.[c]
1	β-ICPD **131**	-	rt	100%	15:1	54%	26:74
2	β-ICPD	-	0	76%	15:1	-	25:75
3	β-ICPD	(*R*)-BINAP **(*R*)-362**	rt	0%	-	-	-
3	β-ICPD	(*S*)-BINAP **(*S*)-362**	rt	0%	-	-	-
4	DABCO	(*R*)-BINAP **(*R*)-362**	rt	100%	15:1	-	65:35

a) In a small vial, 1.0 equiv. of benzoxazole, 4 equiv. of MBH-carbonate were added in 1 ml toluene in the presence of Metal Lewis acid and Organic Lewis base. The reaction was stirred at room temperature for 14 hours.
b) Determined by ^{1}H-NMR analysis of the crude mixture
c) The analysis was made with Chiral HPLC (Chiralpak IE, i-PrOH/Hexane=10:90, 254nm, 1ml/min): retention time 42.9 min, 60.0 min.

2.3.3 Conclusion

In summary a new reaction based on synergistic catalysis between alkyl azaarenes and MBH carbonates was developed. The reaction provides the final compounds in good yields and high diastereoselectivity. Mechanistic studies, synthetic applications, development of a chiral version based on this concept are still ongoing. Another range of chiral amines and phosphines will be tested.

3. New methodologies in organocascade reactions

3.1 Introduction

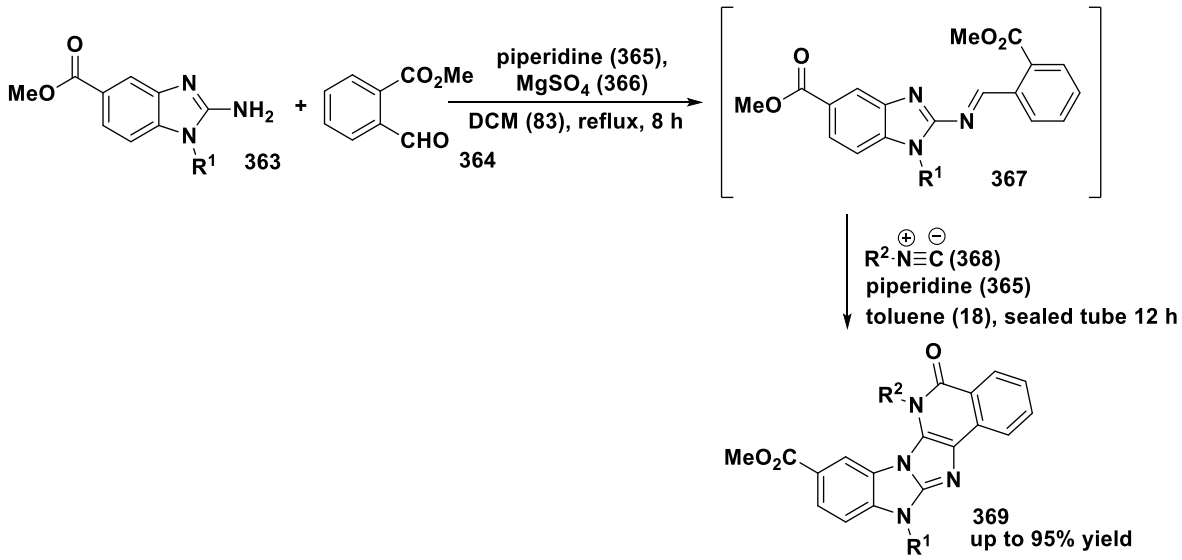
In past years work load in organic chemistry has grown at an exponential rate. Aproximately 15 000 compounds are registered every day. With the growing number of new synthesised chemicals and new reported procedures, the importance of environmental issues increases considerably. Major problems in chemistry are the increase in efficiency, finding more environmentally tolerable procedures, atom economy and efficient waste handling with the preservation of natural resources.

The usual procedure in organic synthesis focuses on creating one particular bond. Keeping in mind all the environmental issues, chemists are on the quest to find procedures in which more than one bond can be formed. These transformations were called one-pot reactions. They were defined as processes with multiple reactions (more than two bonds formed) performed in one flask with no intermediate work-up. Several types of one-pot reactions currently exist: telescoping, tandem, multicomponent, domino, cascade.[136] Each type of transformation has its own advantages, but they are joined by the same idea: synthesis of complex molecules in as few steps as possible using cleaner, safer and environmentally friendly techniques.

3.1.1 Telescoping reaction

Telescoping reaction is a process in which the reagents are added to a flask one at a time without work-up between each step. This transformation is also called a sequential one-pot process.

A good example of telescoping approach was reported by Sun and co-workers. They synthesised polyheterocycles derivatives in one-pot reaction in very good yields (**Scheme 3.1**).[137]

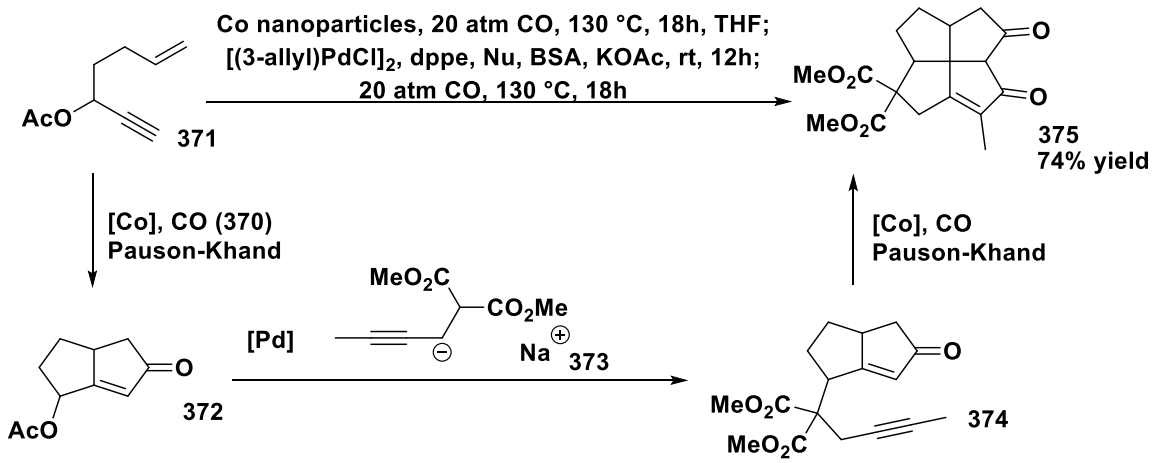


Scheme 3.1 Sun's polyheterocyclic synthesis via telescoping reaction

3.1.2 Tandem reaction

Another example of one-pot reactions is the tandem reaction. This process describes "coupled catalyses in which sequential transformation of the substrate occurs via two (or more) mechanistically distinct processes. Two of the accepted meanings for the word tandem were suggested: a) an arrangement of two mechanisms working in cooperation; b) one after the other."[138]

An example of tandem reaction was reported by Chung and co-workers in 2002. The tandem process is considered after the addition of palladium salt. They obtained the fenestrane in good yield (**Scheme 3.2**).[139]

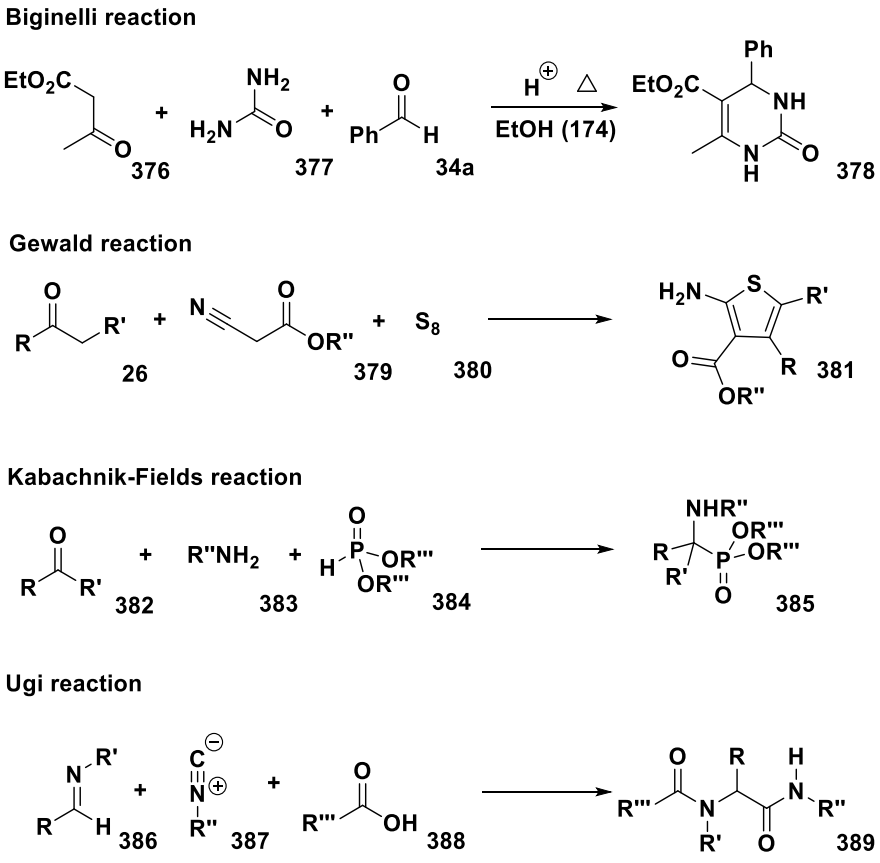


Scheme 3.2 Chung's tandem alyllic alkylation-Pauson-Khand catalysis

3.1.3 Multicomponent reactions

The multicomponent process is defined as a reaction involving at least 3 substrates, where all or the majority of atoms contribute to the formation of the new product. In these types of processes, the reagents do not react simultaneously, but in a sequence of steps. The irreversible step drives the equilibrium towards the formation of the product.[140]

Many examples of multicomponent reactions were developed. Some known examples of multicomponent reactions are: Mannich reaction,[141] Biginelli reaction,[142] Gewald reaction,[143] Hantsch dihydropyridine synthesis,[144] Kabachnik-Fields reaction,[145] Ugi reaction (**Scheme 3.3**).[146]



Scheme 3.3 Examples of multicomponent reactions

3.1.4 Domino reactions

Tietze defined the 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 the subsequent reactions result as a consequence of the functionality formed in the previous step."[136] Tietze described some astuces regarding the domino reactions: a) it is not a domino reaction if the substrate has different functional groups which undergo a transformation independently in the same pot; b) the formation of a carbocation or carbanion in a preliminary stage it is not considered as a reaction step.

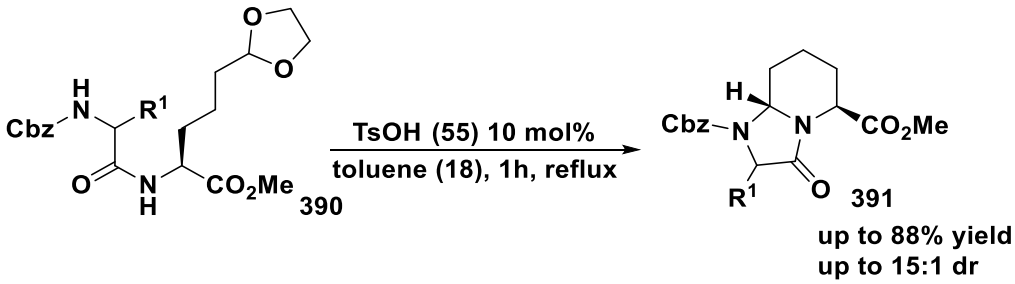
Also, Tietze classified the domino reactions into eight types according to the process mechanism involved in the process: cationic, anionic, radical, pericyclic, photochemical, carbenoid domino reaction, transition metal-catalysed, enzymatic domino reaction.

3.1.4.1 Cationic domino reaction

Cationic domino reactions represent one of the oldest known types of domino reactions. In these processes, a carbocation is formed either by elimination or by addition of a positive moiety such as a proton usually in the presence of a Brønsted or Lewis acid. This is followed by a nucleophile addition to form a new carbocation which is subject to one or more further transformations in a cationic process. The final step is the stabilisation of the positive charge by a nucleophile addition or by elimination of a proton.[147]

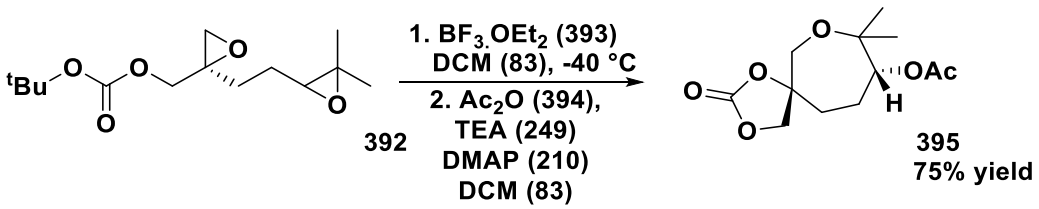
In general, the carbocations are formed from epoxides, water elimination, alkene; from an alcohol, acetal, reaction of carbonyl and imine with Lewis or Brønsted acid.

A nice example of cationic domino reaction was reported by Blaauw and co-workers in 2005. In their quest for the synthesis of (−)-Dysibetaine PP, they used cationic domino reaction as a very powerful tool for the synthesis of the researched molecule (**Scheme 3.4**).[148]



Scheme 3.4 Blaauw's cationic domino reaction for the synthesis of (−)-Dysibetaine PP

Another example of a cationic domino reaction was reported by McDonald *et al.* in 1985. They synthesised a bicyclic compound via epoxide opening catalysed by a Lewis acid (**Scheme 3.5**).[149]

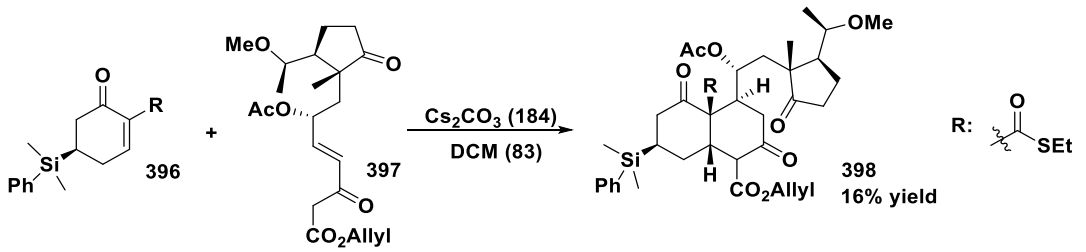


Scheme 3.5 McDonald's cationic domino reaction

3.1.4.2 Anionic domino reaction

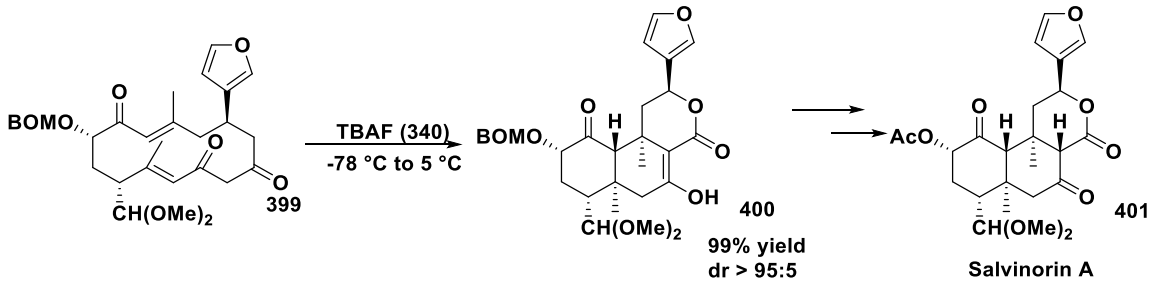
Anionic domino reactions are the most often encountered domino processes. The majority of these processes involve a Michael addition. Usually, the first step is the attack of either a real anion or a neutral nucleophile onto an electrophilic position, followed by a succession of transformations which ends up either by the addition of positive or elimination of a negative moiety.

In 2004, Deslongchamps *et al.* reported a double Michael addition as an anionic domino process. The reaction afforded the desired product, but with low yields (**Scheme 3.6**).[150]



Scheme 3.6 Deslongchamps's synthesis of highly functionalized 14-*β*-Hydroxysteroids

Another example was reported by Evans *et al.* in their research for the asymmetric synthesis of Salvinorin A. They were able to synthesise the precursor of Salvinorin A in excellent yields and enantioselectivity (**Scheme 3.7**).[151]

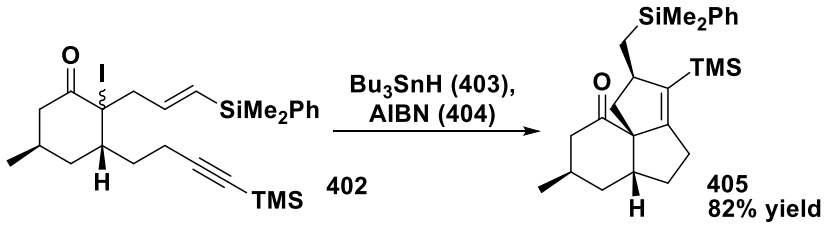


Scheme 3.7 Evans's pathway towards Salvinorin A synthesis

3.1.4.3 Radical domino reaction

Radical domino reactions are considered to be series of rapid intramolecular cyclizations of olefins and alkynes. Radical domino processes appear to be powerful for additions, fragmentations, ring-expansions, and rearrangements.[152]

A nice application of radical domino process was reported by Sha and co-workers in their research for the synthesis of (+)-Paniculatine. They managed to perform the radical cyclisation obtaining the product in very good yields (**Scheme 3.8**).[153]

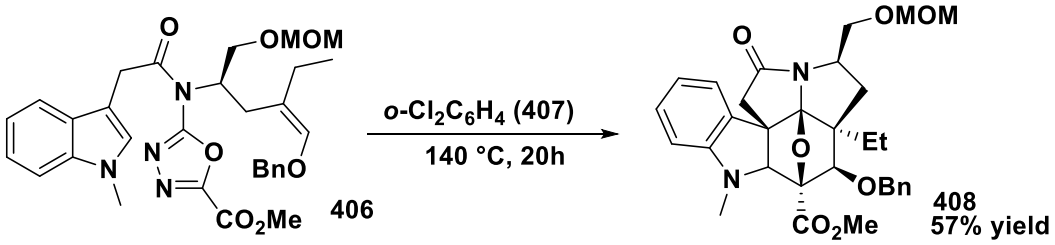


Scheme 3.8 Sha's radical domino reaction for the synthesis of (+)-Paniculatine

3.1.4.4 Pericyclic domino reaction

Pericyclic reactions are very important transformations in organic synthesis. There are many examples of pericyclic reactions such as Diels-Alder reaction, cycloadditions, Claisen and Cope rearrangements.

An example of a pericyclic reaction was reported by Boger and co-workers in 2010. Towards the synthesis of Vindorosine they developed this process in order to create the skeleton of the molecule (**Scheme 3.9**).[154]

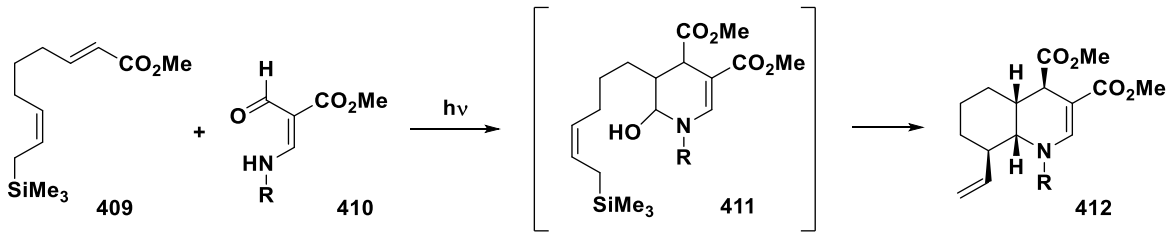


Scheme 3.9 Boger's pericyclic reaction for synthesis of Vindorosine

3.1.4.5 Photochemical domino reaction

A big interest in organic chemistry is the development of new synthetic routes which highly efficient and avoid the use of toxic reagents and solvents. Photochemically induced reactions are a new approach to this matter.

Some examples of photochemical domino reaction were reported by Tietze and co-workers in their research for the synthesis of pyrido[1,2-a]azepines and quinolizidines (**Scheme 3.10**).[155]

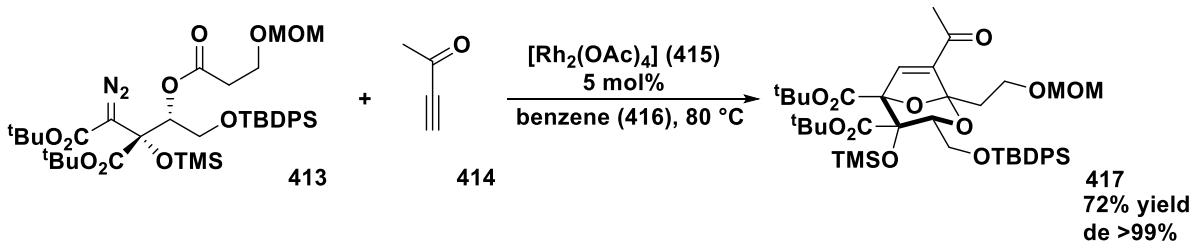


Scheme 3.10 Photochemically induced reaction by Tietze

3.1.4.6 Carbenoid domino reaction

Carbenoids can react with different functional groups, by forming reactive intermediates, such as ylides, giving the possibility to synthesise more complex molecules. The ylide/1,3-dipolar cycloaddition merges as a powerful tool for the synthesis of heterocycles.

An example of this reaction was reported by Hashimoto *et al*. in 2006. They used rhodium salt for the carbonyl ylide formation followed by a 1,3-dipolar addition affording the final product as a single diastereomer in excellent yields (**Scheme 3.11**).[156]

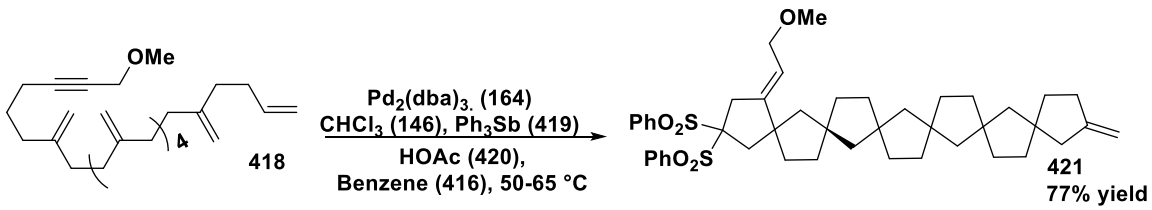


Scheme 3.11 Hashimoto's carbenoid domino reaction

3.1.4.7 Transition metal-catalysed domino reaction

The presence of transition metals in organic chemical transformations has increased considerably. In particular, palladium showed to be a very useful transition metal in many coupling reactions (Suzuki, Heck, Sonogashira, Negishi, etc.). Also it found its use in the domino processes.

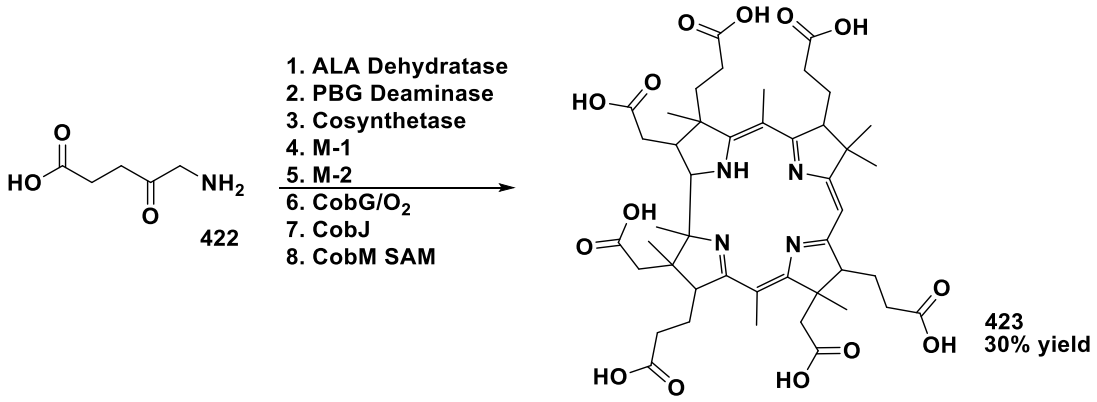
A very beautiful example of transition metal catalysed domino reaction was reported by Trost and Shi in 1993. They studied the synthesis of polyspiranes via zipper domino process using palladium as a catalyst (**Scheme 3.12**).[157]



Scheme 3.12 Trost *et al.* synthesis of polyspiranes

3.1.4.8 Enzymatic domino reaction

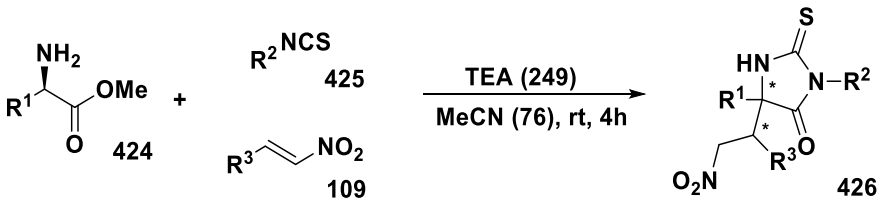
An interesting fashion of domino reaction is the use of enzymatic cocktails as catalysts. A multienzyme catalysed reaction was reported by Scott *et al.* in their quest for the synthesis of vitamin B12 (**Scheme 3.13**).[158]



Scheme 3.13 Scott's synthesis of precorrin towards the synthesis of vitamin B12

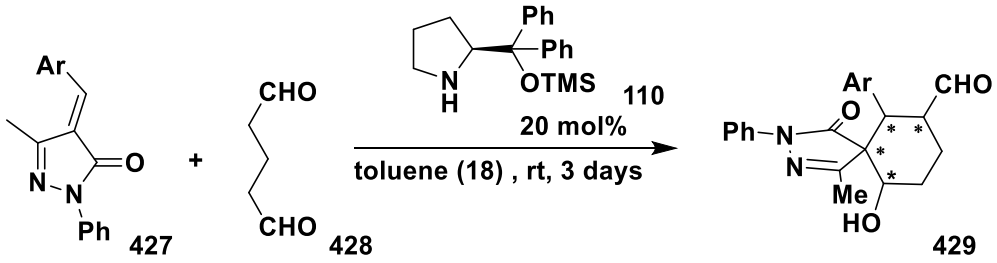
3.1.5 Our work

The following sections will give detailed accounts on our work. First project is a three-component reaction for the synthesis of thiohydantoin derivative (**Scheme 3.14**).[159]



Scheme 3.14 Thiohydantoin synthesis

The second project is the synthesis of spiropyrazolones via a cascade reaction (**Scheme 3.15**).[160]



Scheme 3.15 Spiropyrazolone synthesis

3.2 Three-component diastereoselective cascade synthesis of thiohydantoins

3.2.1 Introduction

Thiohydantoins[161] are very interesting compounds owing to their wide applications, for example, as hypolipidemic,[162] antithyrodial,[163] antibacterial,[164] antiviral (HIV and tuberculosis),[165] anticarcinogenic,[166] antimutagenic,[167] anti-ulcer, anti-inflammatory agents and as pesticides (**Figure 3.1**). However, thiohydantoins have a reputation of being unselective compounds that appear as 'frequent hitters' in screening campaigns. This behaviour has been the subject of controversial debate in the medicinal chemistry community: some consider that they are promiscuous binders with an insignificant value in drug discovery, while others consider that they are privileged scaffolds that could allow quick identification of hits and could be developed further. If thiohydantoins are considered to be privileged scaffolds, organic chemists need to develop new methodologies that offer easy access to these structures in order to build large libraries of compounds that will lead to more selective hits.

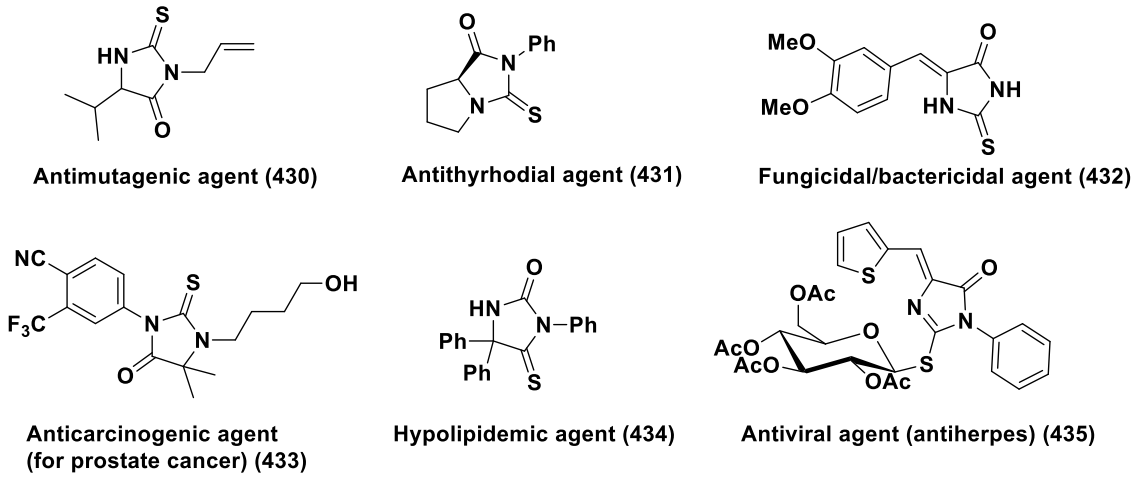
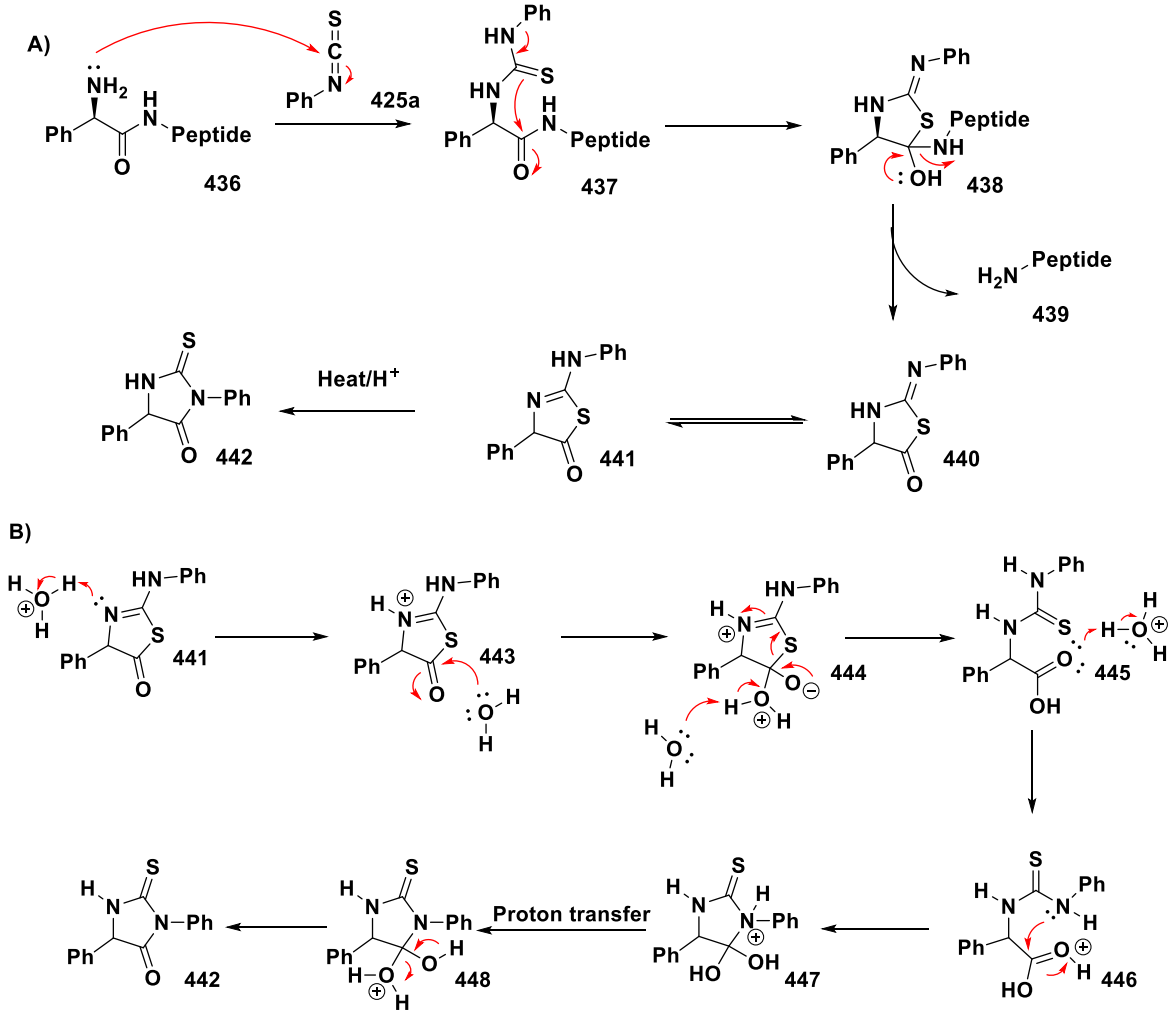


Figure 3.1 Examples of thiohydantoin application

Despite the obvious interest in the synthesis of these compounds, only a few methods in the literature for their synthesis have been found. One of the most important methodologies is the Edman degradation, which was developed by Pehr Edman for sequencing amino acids in a peptide. In this method, the terminal amino acid residue is labelled and then cleaved from the peptide

without disrupting the peptide bonds between other amino acid residues (**Scheme 3.16**).[168]

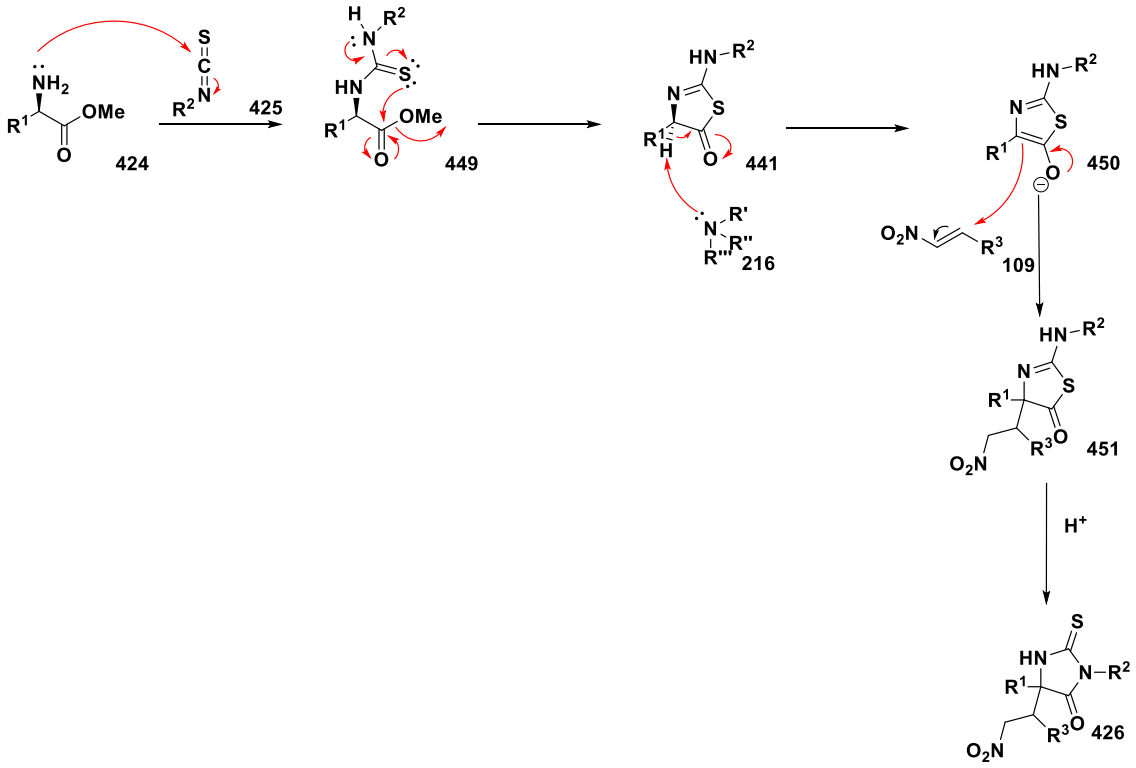


Scheme 3.16 A) Edman degradation; B) Rearrangement mechanism in Edman degradation

The mechanism of Edman degradation is described in the s**cheme 3.16**. First, the primary amine of the terminal aminoacid attacks the carbon of the isothiocyanate functional group. Then, an intramolecular transformation takes place in order to form the intermediate **438** followed by the elimination of the peptide and the formation of thiazolidinone derivative **440**. The last one is in equilibria with the **441**, which is a tautomer of **440**. At this point we have a rearrangement in the presence of heat or a catalytic amount of acid and water (**Scheme 3.16B**). First, the thiazolone's nitrogen gets protonated. Then, water attacks the carbon of the thionoester functional group forming intermediate

444. Next, series of transformations lead intermediate **444** to become **445**. In the presence of the catalytic amount of acids which protonates the oxygen of the carboxylic acid group, an intramolecular transformation occurs forming intermediate **447**. After an intramolecular proton transfer intermediate **448** is obtained. Finally, water and a proton are released forming thiohydantoin derivative **442**.

Based on Edman degradation methodology a three component reaction using the *β*-nitrostyrene as a nucleophile was studied. The proposed mechanism for this one-pot reaction is described in **scheme 3.12**.[169]



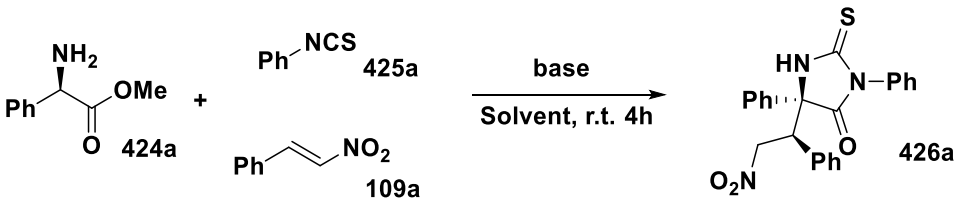
Scheme 3.17 Proposed mechanism of three component thiohydantoin synthesis

The amine group of *α*-amino ester **424** attacks the carbon of the isothiocyanate group **425** followed by ring closure and the elimination of the methoxy group forming thiazolone **441**. The tertiary amine catalyst attacks the acidic proton situated in the *α*-position of the thionoester group. At this point the stereocentre is destroyed. Intermediate **450** shows to be a good nucleophile and attacks the *β*-position of the nitrostyrene **109** forming **451**. Finally, rearrangement of intermediate **451** happens in acidic conditions as described in **scheme 3.16B** to give the final product **426**.

3.2.2 Results and Discussion

3.2.2.1 Condition screenings

Table 3.1 Thiohydantoin reaction screening[a]



Entry	Base	Solvent	NMR conversion	dr[c]
1	Et_3N **249**	MeCN	100%	10:1
2[e]	DABCO **198**	MeCN	100%	6:1
3[e]	Quinine **57**	MeCN	100%	6:1
4	Et_3N **249**	Toluene	100%	5:1
5	Et_3N **249**	CH_2Cl_2	100%	6:1
6	Et_3N **249**	$CHCl_3$	100%	7.5:1
7	Et_3N **249**	EtOAc	100%	3:1
8[e]	Takemoto catalyst **159**	MeCN	100%	10:1
9	-	MeCN	-	-
10[d]	Et_3N **249**	MeCN	100%	10:1

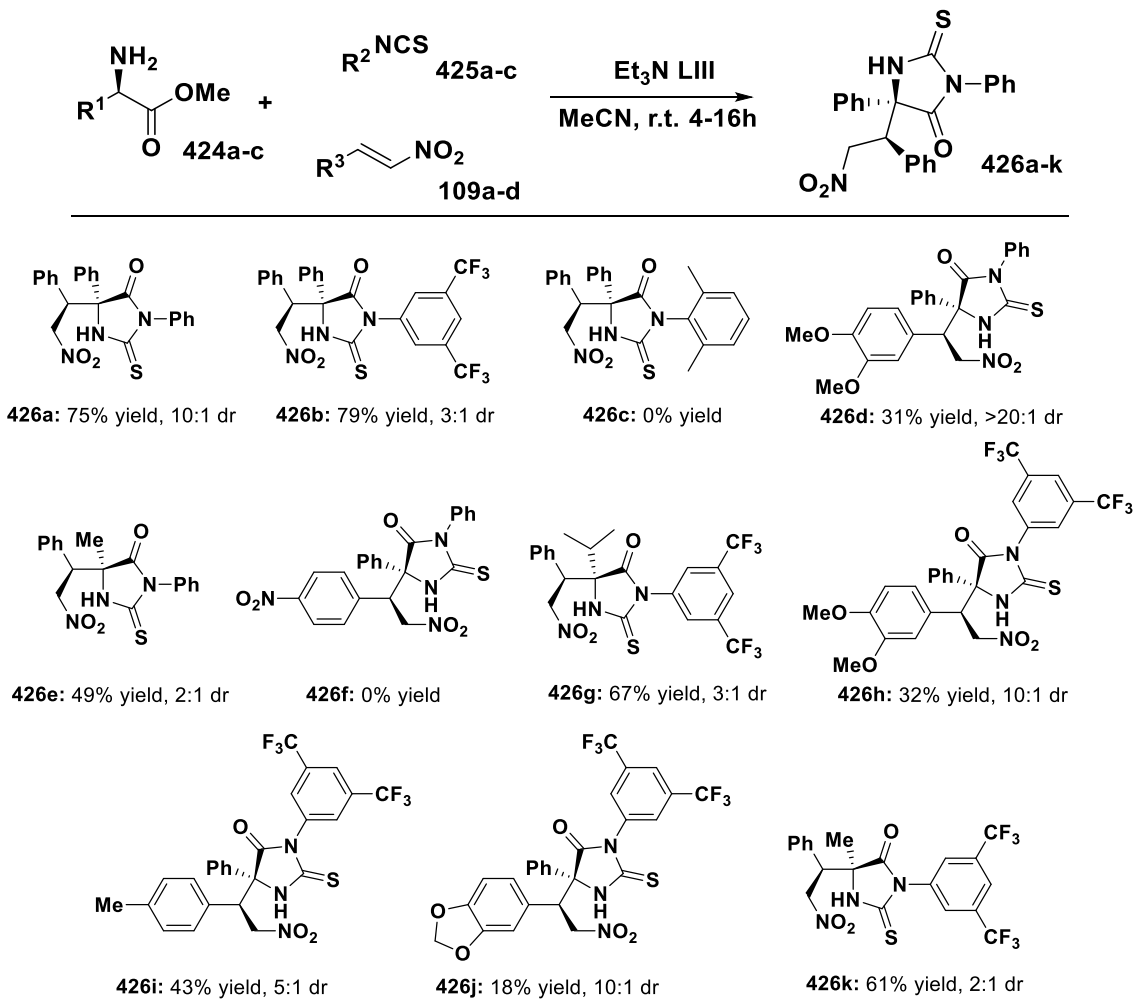
a) In a small vial, 1.0 equiv. of aminoester, 1.1 equiv. of isothiocyanate, and 1.1 equiv. of nitrostyrene were added in 1 mL of the corresponding solvent in the presence of base (20 mol %). The reaction was stirred at room temperature for 4 h.
b) Determined by ^{1}H-NMR analysis of the crude mixture (disappearance of characteristic peak of α-hydrogen of the amino ester and appearance of thiohydantoin characteristic peaks).
c) Determined by ^{1}H-NMR analysis of the crude mixture.
d) Reaction carried out with 1.1 equiv. of Et_3N and aminoester as a hydrochloride salt.
e) Reactions were carried by our project student Kane Hands.

Preliminary experiments into the multicomponent reaction between phenyl glycine methyl ester (**424a**), phenyl isocyanate (**425a**) and nitrostyrene (**109a**) with different bases and solvents were investigated. The reaction afforded the predicted disubstituted thiohydantoins in good yields and moderate to good diastereoselectivities (**Table 3.1**).

As shown in **table 3.1**, the best reaction conditions are as follows: base, Et_3N; solvent: acetonitrile. The use of DABCO and quinine as a base afforded thiohydantoin **426a** in lower diastereoselectivities and in a racemic form (**Table 3.1, entries 2, 3**). The use of other solvents such as toluene, dichloromethane, chloroform, or ethyl acetate afforded the corresponding products with lower diastereoselectivities and as more complex crude mixtures (**Table 3.1, entries 4–7**). Takemoto's catalyst afforded a similar diastereoselectivity to Et_3N (10:1 dr) with almost negligible enantioselectivity (10% ee) (**Table 3.1, entry 8**). However, when the reaction was carried out in the absence of a base, a complex mixture was obtained without the desired product (**Table 3.1, entry 9**). The reaction was also tested with the hydrochloride salt of the *α*-amino ester using 1.1 equiv. of Et_3N and a similar result to **entry 1** was obtained (**Table 3.1, entry 10**).

3.2.2.2 Reaction scope

The results of the experiments are summarized in **scheme 3.18**. First, different isothiocyanate compounds were tested. A higher reactivity of the formed intermediate was noticed if an electron-withdrawing group in the meta position of the aryl from the isothiocyanate is used (**426b, 426g**). The reaction gave the product in high yield but poor stereoselectivity compared to the similar reaction performed with phenyl thiocyanate (**426a**). By using the 2,6-dimethylisothiocyanate the reaction did not occur (**426c**). We suppose this is caused by the bulky effect of the methyl groups in the ortho position. Moreover, the methyl groups have an electron-donating inductive effect on the formed heterocycle which makes the hydrogen less acidic, thus less reactive.



Scheme 3.18 Thiohydantoin reaction scope

Several nitrostyrenes were tested and the results shows that those containing electron-donating substituents afforded poor yields and better diastereoselectivities (**426d** and **426j**), while the highly reactive *p*-nitronitrostyrene afforded a complex mixture (**426f**).

Different *α*-aminoesters were also evaluated. The adducts containing aromatic substituents afforded better yields than those containing aliphatic substituents in *α*-position with slightly poorer diastereoselectivities (**426e**, **426k**).

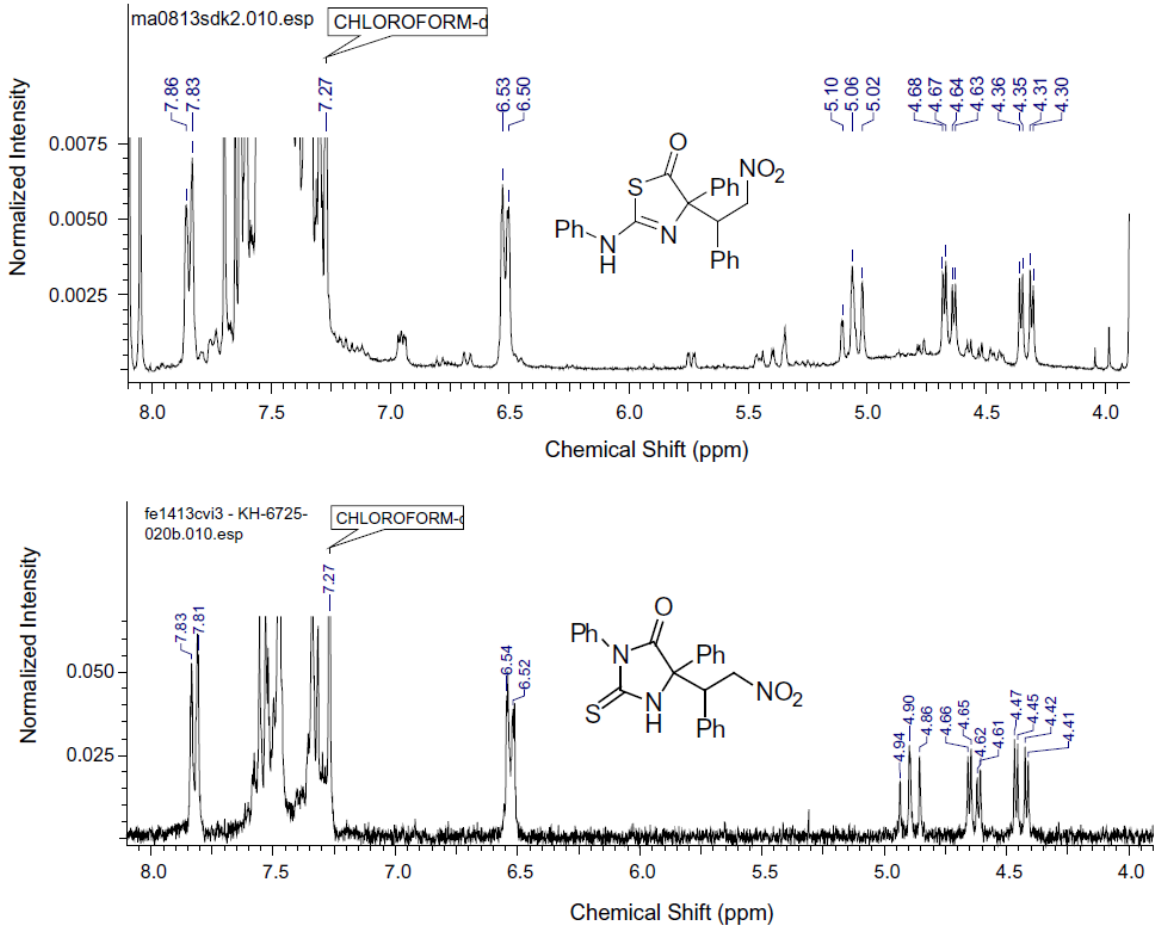
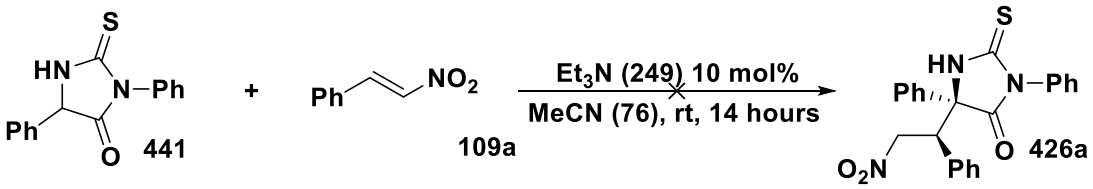


Figure 3.2 ^{1}H-NMR spectra of the crude reaction (upper) and compound **426a** (lower)

The mechanism proposed in **scheme 3.17** was confirmed by ^{1}H-NMR analysis of the crude reaction mixture and final product. In **figure 3.2**, the ^{1}H-NMR spectrum of the crude reaction mixture (upper spectrum) after the nitrostyrene addition is compared to the ^{1}H NMR spectrum of **426a** after purification by column chromatography (lower spectrum). The characteristic peaks situated between 4.00 and 5.00 ppm appear to be slightly shielded in the post column NMR compared to the crude NMR. From these analytical results, we believe that the intermediate **441** is the nucleophile, and the rearrangement that led to the final thiohydantoin product took place after the addition of the nitrostyrene being catalysed by the mildly acidic conditions of silica gel during the column chromatography.

While conducting the reaction under the optimal conditions the formation of a white solid was noticed, which showed to be the intermediate **441**.

The reaction of thiohydantoin **442** with nitrostyrene **109a** was tested as described in the **scheme 3.19**. A complex mixture of products was seen in the crude ^{1}H-NMR analysis, but the compound **426a** was not found. We believe that the thiohydantoin **442** is less nucleophilic compared to the intermediate **441** (**Scheme 3.16**) due to the formation of the aromatic thiazole system in the presence of the tertiary amine catalyst.



Scheme 3.19 Addition of thiohydantoin to nitrostyrene

In order to establish the stereochemistry of the nitro compounds obtained, an X-ray diffraction study of the major isomer of **426a** was performed. As shown in **figure 3.3**, the crystal structure of this compound confirms the previously assigned regiochemistry and shows an *anti* relative configuration.

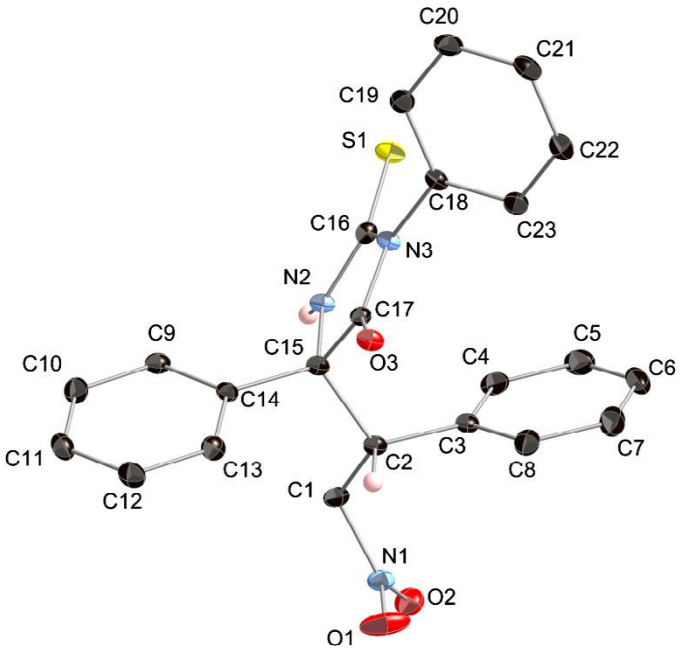


Figure 3.3 X-ray diffraction of the major isomer. Displacement ellipsoids – 35% probability level (Effectuated by Dr Mark E. Light)

3.2.3 Conclusion

In summary, a new three-component cascade reaction for the synthesis of thiohydantoins was developed. The reaction is promoted using a base, affording the final products in moderate to good yields and diastereoselectivities. We are considering continuing this project concentrating on mechanistic studies, synthetic applications, also new methodologies for the enantioselective version of our compound. In order to do this, we will test different types of tertiary amine catalysts or/and bifunctional catalysts such as thiourea-tertiary amine catalysts.

3.3 Highly diastereoselective synthesis of spiropyrazolones

3.3.1 Introduction

Spiro compounds are important scaffolds which are present in various natural products such as (-)-sibirine, *β*-vetivone, acerenone B, Shizuca-acordienol,[170] or biologically active agents such as Aldactone (diuretic, antihypertensive) and Cipargamin (antimalarial agent) (**Figure 3.4**).[171]

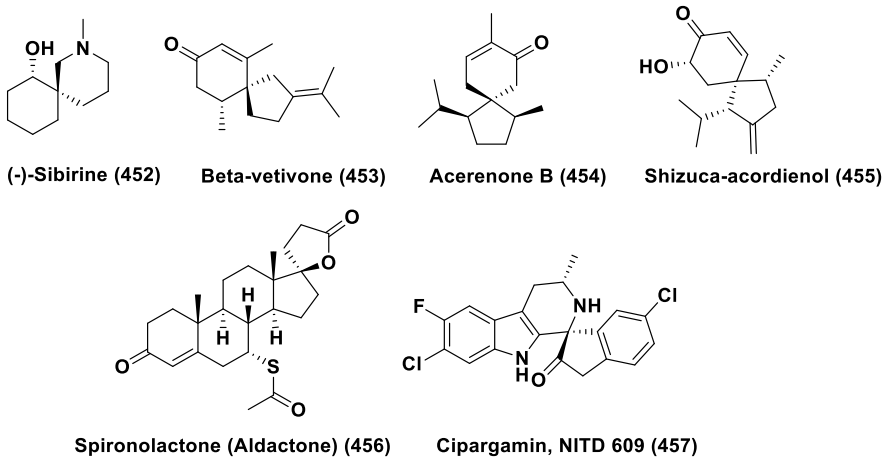
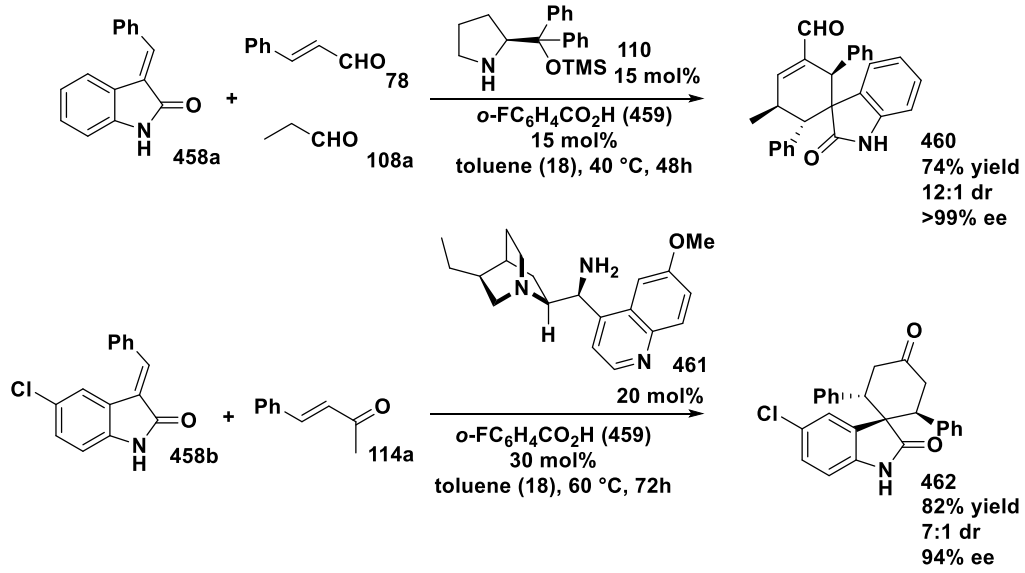


Figure 3.4 Some spiro natural products and active agents

The "spiro" term was proposed by Adolf von Baeyer in 1900 in order to define the molecules in which the rings are connected via one quaternary atom (spiroatom).[172]

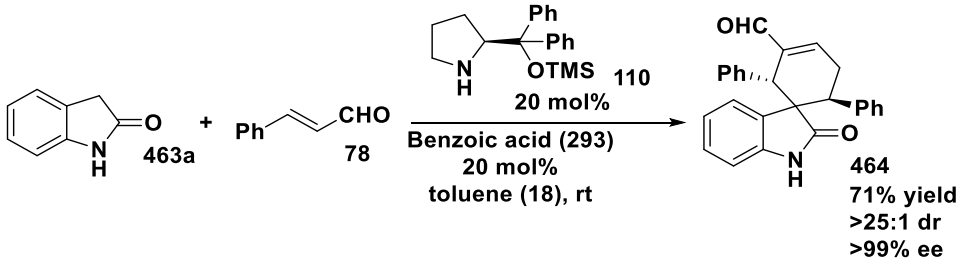
One of the first examples of spiro compound synthesis in an enantioselective fashion was reported by Tamao *et al.* in 1996. In this article they described a spirocyclization silanes in the presence of catalytic amount of rhodium complexes.[173] Recently, many research groups focused their work on the research of new methodologies for the synthesis of spiro compounds (spirooxindoles, spirooxazolones, spiropyrazolones, etc…).

In 2009, Melchiorre and co-workers reported one tandem reaction and another three-component reaction (Michael-Michael-aldol reaction) towards the synthesis of spirooxindoles. In both cases they obtained excellent results in terms enantioselectivity and yields (**Scheme 3.20**).[174]



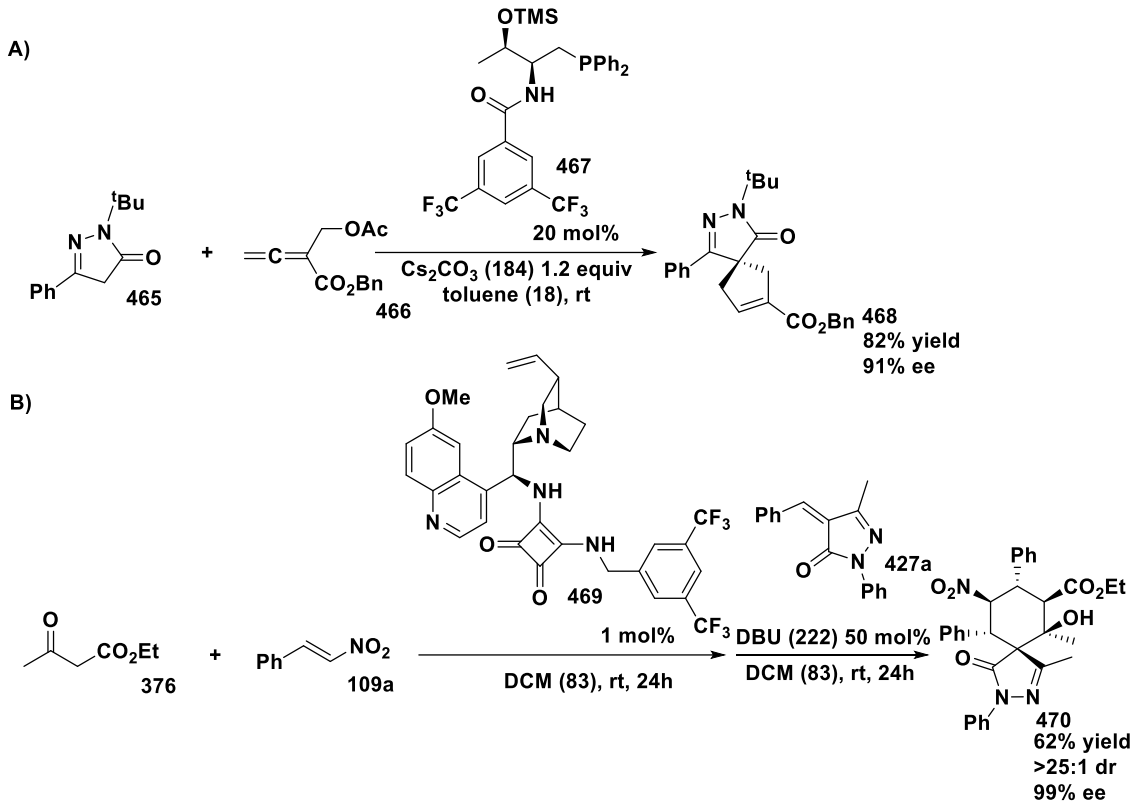
Scheme 3.20 Melchiorre's spirooxindole enantioselective synthesis

One year later, Rios *et al.* reported another example of Michael-Michael-aldol reaction involving *α,β*-unsaturated aldehyde and oxindoles, pyrazolone, oxazolones, etc...[175] All the examples described in the article showed excellent enantioselective results (**Scheme 3.21**).



Scheme 3.21 Rios's spirooxindole synthesis

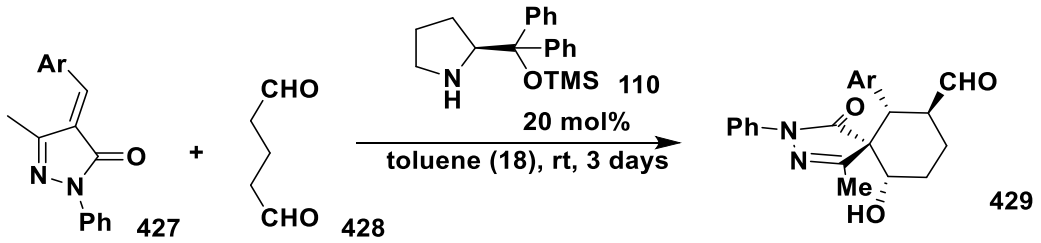
Recently, Lu and co-workers described the enantioselective synthesis of spiropyrazolones through phosphine-catalysed [4+1] annulation. The reaction provided the product in very good yields and enantioselectivity (**Scheme 3.22A**).[176] At the same time, Enders and co-workers reported a beautiful spiropyrazolones synthesis creating six asymmetric centers. They obtained excellent results in yields, diastereoselectivity and enantioselectivity (**Scheme 3.22B**).[177]



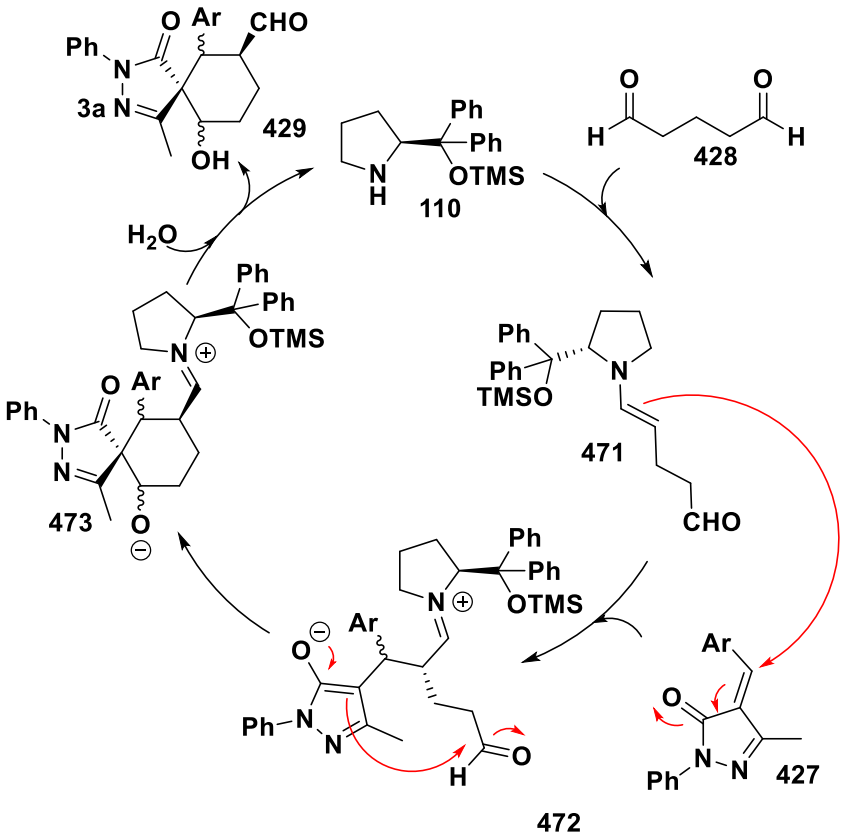
Scheme 3.22 A) Lu's spiropyrazolone synthesis via [4+1] annulation;
B) Enders's three-component spiropyrazolone synthesis

3.3.2 Our work

Inspired by the previous work we envisioned a spiropyrazolone synthesis starting with pyrazolone derivative and dialdehyde catalysed by a secondary amine (**Scheme 3.23**).



Scheme 3.23 Our work



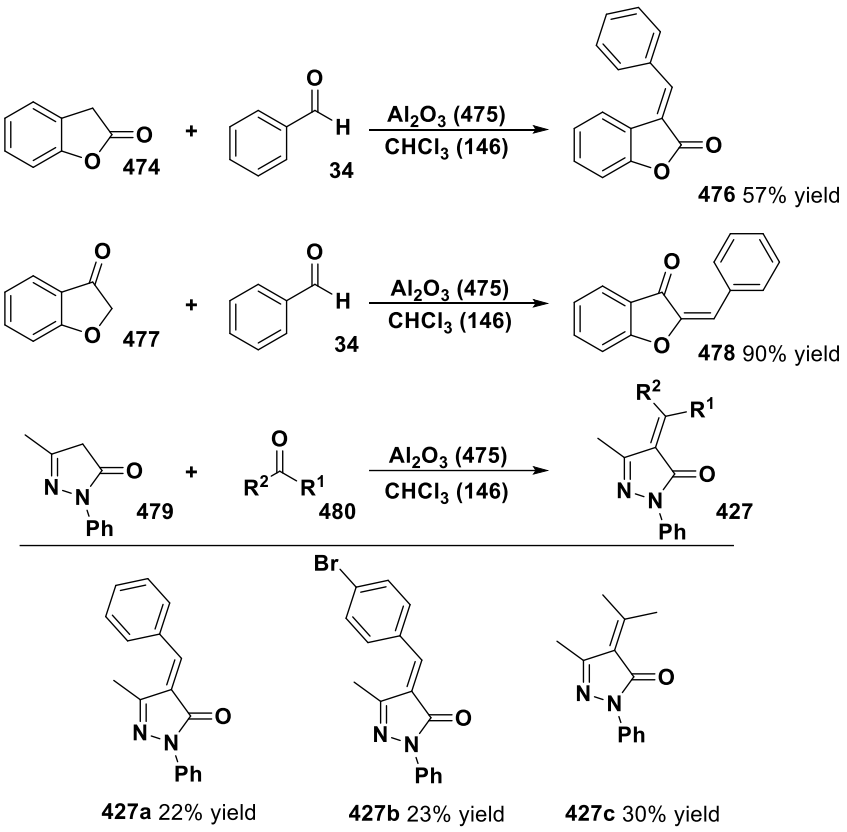
Scheme 3.24 Suggested mechanism

The suggested mechanism for this reaction is shown in the **scheme 3.24**. The catalytic cycle starts with enamine formation between secondary amine **110** and the dialdehyde **428**. Then, the enamine reacts with the pyrazolone derivative. The catalyst shields the *Re*-face of the enamine making the attack to take place on the *Si*-face. The enolate group formed in the pyrazolone ring reacts with the other aldehyde group via intramolecular aldol reaction. Finally, the hydrolysis of the intermediate **473** renders the final product **429** and regenerates catalyst **110**.

3.3.3 Results and discussions

3.3.3.1 Synthesis of starting material

The unsaturated precursors for the synthesis of the spiro compounds were made by using the starting material pyrazolone or benzofuranone and the corresponding aldehyde or ketone in the presence of aluminium oxide. While in the case of benzofuranones good yields were obtained, in the case of pyrazolones the final products were synthesised in poor yields (**Scheme 3.25**).



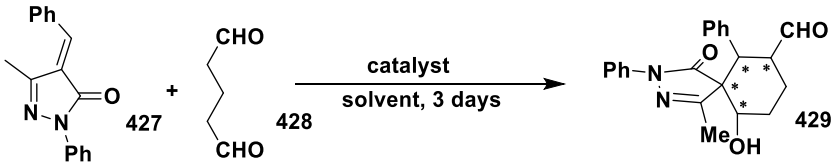
Scheme 3.25 Synthesis of starting material

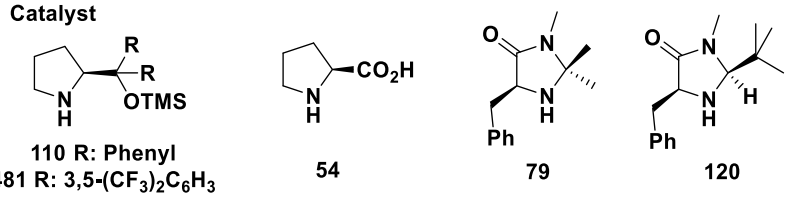
3.3.3.2 Condition screenings

First, the reaction was stirred for 3 days in chloroform catalysed by Jørgensen-Hayashi catalyst **110** (**Table 3.2, entry 5**). A full conversion, good diastereoselectivity, but very low enantioselectivity was noticed.

Then we tested several solvents, catalysts and temperatures (**Table 3.2**).

Table 3.2 Conditions screening[a]





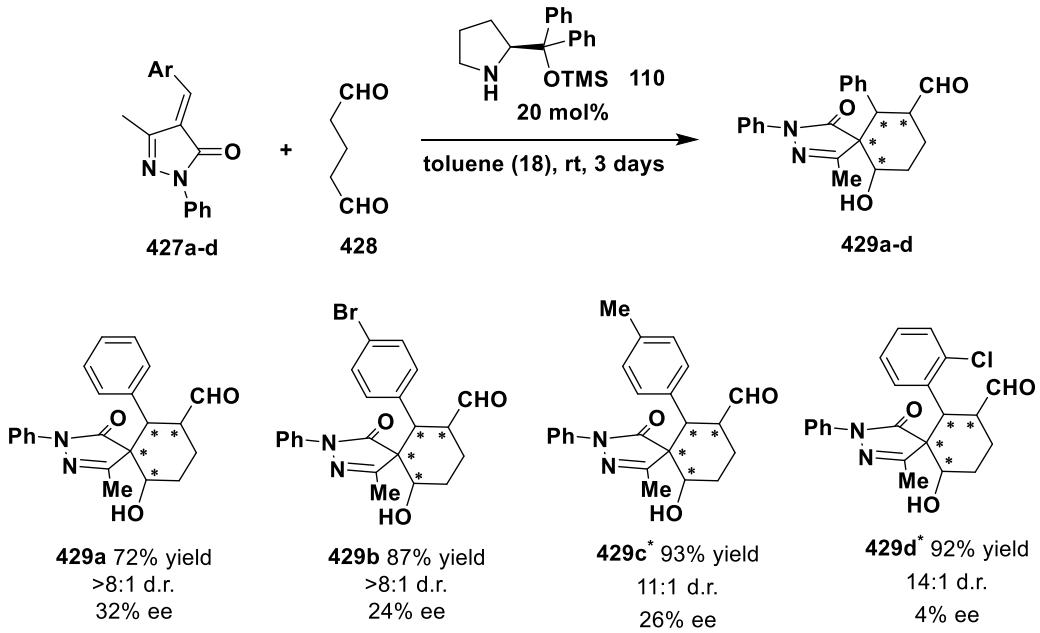
Entry	Solvent	Catalyst	Conversion[b]	Dr[b]	ee[c]
1	DCM **83**	**110**	100 %	7:1	32 %
2	Toluene **18**	**110**	100 %	10:1	32 %
3	*p*-Xylene **482**	**110**	100 %	10:1	6 %
4	AcOEt **295**	**110**	100 %	10:1	26 %
5	$CHCl_3$ **146**	**110**	100 %	5:1	6 %
6	THF **15**	**110**	100 %	5:1	4 %
7[d]	Toluene **18**	**110**	100 %	10:1	2 %
8	Toluene **18**	**481**	n.r.	-	-
9	Toluene **18**	**54**	n.r.	-	-
10	Toluene **18**	**79**	n.r.	-	-
11	Toluene **18**	**120**	n.r.	-	-
12[e]	Toluene **18**	**110**	100 %	2:1	32

a) For reaction conditions see general procedure;
b) Determined by ^{1}H-NMR analysis of the crude reaction;
c) Determined by chiral HPLC analysis of the crude mixture;
d) 20 mol% of benzoic acid was added;
e) The reaction was carried at -20 °C.

Several solvents were tested (**Table 3.2, entries1-6**). In all cases full conversion, but low enantioselectivity was obtained. While solvents such as chloroform, tetrahydrofuran and dichloromethane gave a moderate diastereoselectivity, solvents such as toluene, *p*-xylene and ethyl acetate gave very good diastereoselectivity. In our quest to find conditions to improve the enantioselectivity several types of secondary amine catalysts were tested (**Table 3.2, entries 7-11**). The reaction did not occur if catalyst **481**, L-proline (**54**), or first and second generation MacMillan catalyst (**79, 120**) were used. The addition of a catalytic amount of additive such as benzoic acid did not influence the results previously obtained. The decrease in temperature reduced the diastereoselectivity without improving the enantioselectivity (**Table 3.2, entry 12**).

3.3.3.3 Reaction scope

With the conditions we found to be optimal for this reaction we studied the scope of the reaction.



*The reaction was carried by Dr Temitope O. Olomola

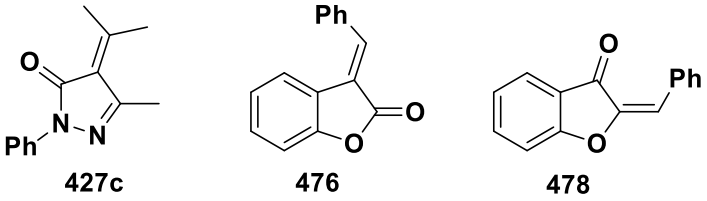
Scheme 3.26 Reaction scope

As shown in **scheme 3.26**, the reaction occurs and has comparable results. In all examples the product was obtained in very good yields. In terms of

diastereoselectivity an improvement can be noticed when the halogen substituent is in the ortho position (**Scheme 3.26, 429d**). While very good diastereoselectivity was obtained, a considerable loss in enantioselectivity was observed.

Performing the reaction with succinaldehyde instead of glutaraldehyde was with no success. After 15 hours, only decomposition of the materials and no trace of final product was seen in the crude HNMR analysis.

Other starting materials were tested (**Figure 3.5**), but no product was found.



427c 476 478

Figure 3.5 Other reagents

Despite all our attempts to synthesise the product in an enantioselective fashion we did not succeed to obtain a good enantiomeric ratio.

The relative configuration of the major diastereomer was identified by single crystal X-ray analysis of compound **300d**. From the X-ray analysis it was determined that all the substituents of the six-membered ring are situated in the equatorial position **figure 3.6**.

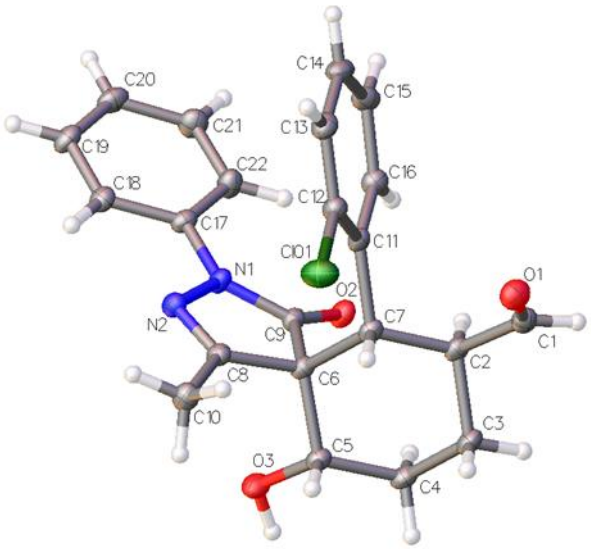
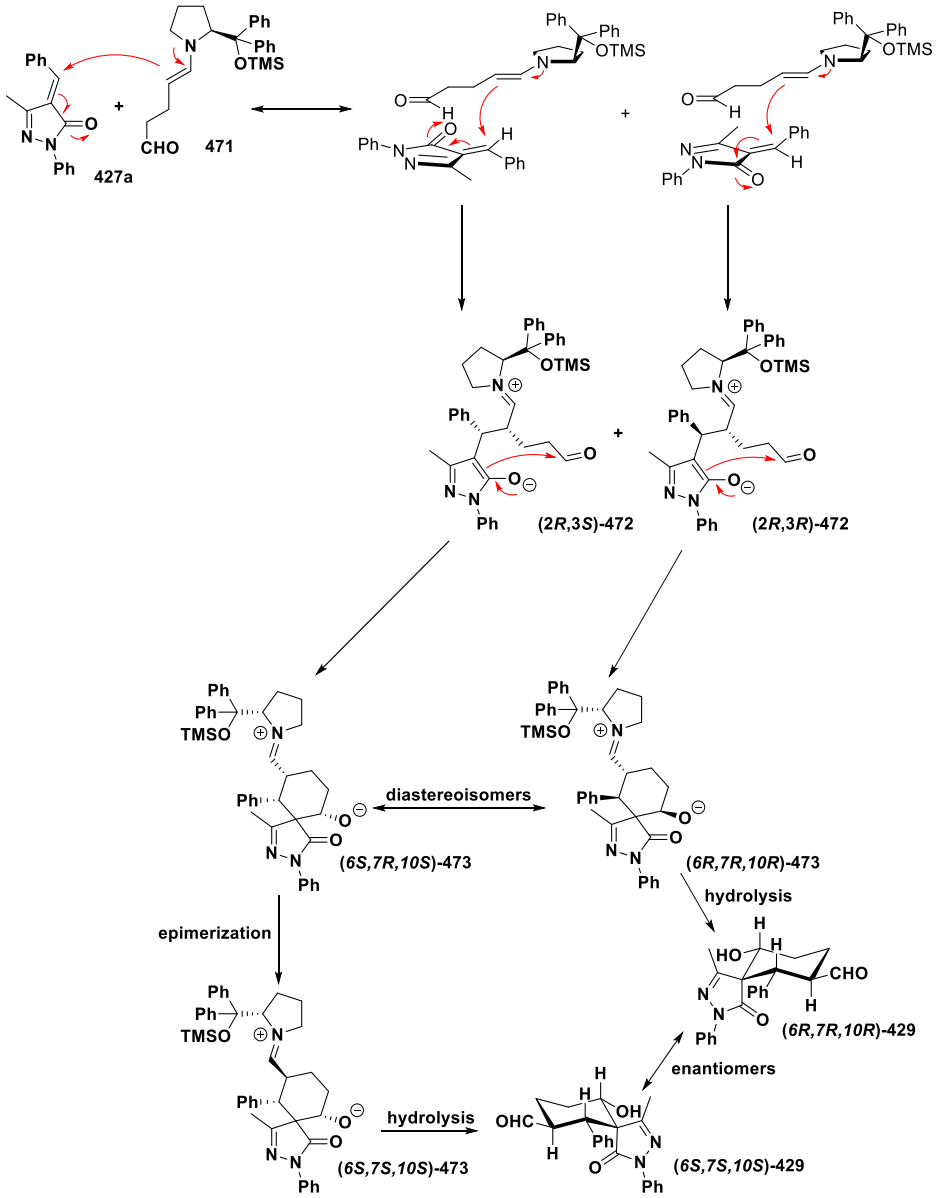


Figure 3.6 X-ray structure of compound **429d**. The displacement ellipsoids are drawn at the 50 % probability level.



Scheme 3.27 Possible explanation for the low enantioselectivity

Based on the obtained relative configuration of the compound **429d**, an explanation was suggested for this considerable lost in enantioselectivity (**Scheme 3.27**). We believe that the Michael addition in the alpha position of the aldehyde is highly stereoselective due to the direct control of the secondary amine catalyst. From this mechanistic step two diastereomers are obtained (**Scheme 3.27, 472**). Then, an intramolecular aldol reaction occurs which thermodynamically favours the equatorial position of the newly formed asymmetric centres (phenyl and hydroxyl group) (**Scheme 3.27, 473**). Next, epimerization of the enamine takes place favouring the *trans* configuration with

regards to the phenyl group, having all the substituents in the equatorial position of cyclohexane ring which is thermodynamically stable.

3.3.4 Conclusion

In conclusion, a new methodology for the synthesis of spiropyrazolone via a Michael-aldol reaction was developed. The products obtained in very good yields, good diastereoselectivity, but low enantioselectivity.

4. Experimental Part

4.1 General

Thin layer chromatography (TLC) was performed on Merck TLC Silicagel 60 F_{254}. Product spots were visualized by UV-light at 254nm, and developed with potassium permanganate. Column chromatography was effectuated using silica gel (Geduran Si60, 40-63µm).

Infra-red spectra were recorded on a Nicolet 280 FT-IR and Nicolet AVATAR 370 FT IR using KBr pellets.

^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR were recorded with Bruker AV300, Bruker DPX400 and Bruker AVANCE III 600. 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).

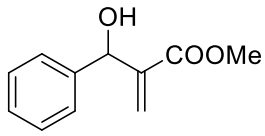
High resolution mass spectra were recorded using Esquire 3000 (Bruker; low resolution) or an LTQ Orbitrap XL instrument (Thermo Fisher Scientific; high resolution) and MaXis (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a Time of Flight (TOF) analyser.

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.

4.2 Synthesis of Morita-Baylis-Hillman derivatives

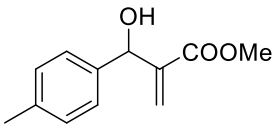
MBH-alcohols

Methyl 2-(hydroxy(phenyl)methyl)acrylate (195a)[85]



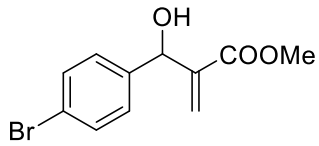
To a round bottom flask charged with methanol (0.75 equiv., 1.5 ml) was added the benzaldehyde (1 equiv, 5 g, 47 mmol) and methyl acrylate (1.2 equiv, 4.85 g (5.10 ml), 56 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv, 3.14 g, 28 mmol) was added. The solution was stirred for 72 hours and purified by column chromatography (hexane/EtOAc, 2:1). The product yield is 98%. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.37-7.23 (m, 5H, Ar<u>H</u>), 6.36 (s, 1H, C=C<u>H</u>$_2$), 5.86 (s, 1H, C=C<u>H</u>$_2$), 5.57 (s, 1H, C<u>H</u>-OH), 3.74 (s, 3H, COOC<u>H</u>$_3$), 3.61 (brs, 1H, CH-O<u>H</u>). The spectroscopical data matched with the previous reported in the literature.

methyl 2-(hydroxy(*p*-tolyl)methyl)acrylate (195b)[178]



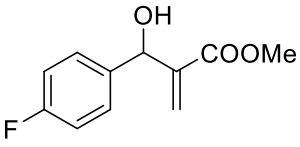
To a round bottom flask charged with methanol (0.75 equiv, 1.5 ml) was added the p-tolylaldehyde (1 equiv, 5 g, 47 mmol) and methyl acrylate (1.2 equiv, 4.85 g (5.10 ml), 56mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv, 3.14 g, 28 mmol) was added. The solution was stirred for 72 hours and purified by column chromatography (hexane/EtOAc, 2:1). The product yield is 98%. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.28 (d, *J* = 6.1 Hz, 2H, Ar<u>H</u>), 7.17 (d, *J* = 7.5 Hz, 2H, Ar<u>H</u>), 6.35 (s, 1H, C=C<u>H</u>$_2$), 5.87 (s, 1H, C=C<u>H</u>$_2$), 5.56 (s, 1H, C<u>H</u>-OH), 3.75 (s, 3H, COOC<u>H</u>$_3$), 2.92 (brs, 1H, CH-O<u>H</u>), 2.36 (s, 3H Ar-C<u>H</u>$_3$). The spectroscopical data matched with the previous reported in the literature.

methyl 2-((4-bromophenyl)(hydroxy)methyl)acrylate (195c)[178]



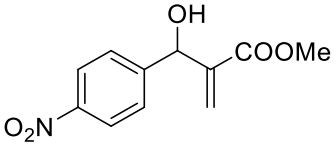
To a round bottom flask charged with methanol (0.75 equiv, 1 ml) was added the p-bromobenzaldehyde (1 equiv, 4 g, 22 mmol) and methyl acrylate (1.2 equiv, 2.20 g (2.3 ml), 26 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv., 1.21 g, 11 mmol) was added. The solution was stirred for 72 hours and purified by column chromatography (hexane/EtOAc, 4:1). The product yield is 80%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.50 (d, *J* = 8.4 Hz, 2H, ArH), 7.28 (d, *J* = 8.4 Hz, 2H, ArH), 6.36 (s, 1H, C=CH_2), 5.84 (s, 1H, C=CH_2), 5.54 (s, 1H, CH-OH), 3.76 (s, 3H, COOCH_3), 3.06 (d, *J* = 5.5 Hz, 1H, CH-OH). The spectroscopical data matched with the previous reported in the literature.

methyl 2-((4-fluorophenyl)(hydroxy)methyl)acrylate (195d)[178]



To a round bottom flask charged with methanol (0.75 equiv, 1 ml) was added the p-fluorobenzaldehyde (1 equiv, 4 g, 22 mmol) and methyl acrylate (1.2 equiv, 2.20 g (2.3 ml), 26 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv, 1.21 g, 11 mmol) was added. The solution was stirred for 72 hours and purified by column chromatography (hexane/EtOAc, 4:1). The product yield is 80%. ^{1}**H NMR** (400 MHz, $CDCl_3$): 7.40-7.31 (m, 2H, ArH), 7.05 (t, *J* = 8.4 Hz, 2H, ArH), 6.35 (s, 1H, C=CH_2), 5.85 (s, 1H, C=CH_2), 5.56 (s, 1H, CH-OH), 3.65 (s, 3H, COOCH_3), 3.05 (brs, 1H, CH-OH). The spectroscopical data matched with the previous reported in the literature.

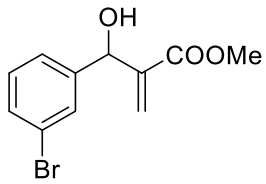
methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate (195e)[179]



To a round bottom flask charged with methanol (0.75 equiv, 1 ml) was added the p-nitrobenzaldehyde (1 equiv, 5 g, 33 mmol) and methyl acrylate (1.2 equiv, 3.42 g (3.6 ml), 40 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv., 1.86 g, 17 mmol) was added. The solution was stirred for 72 hours and purified by column chromatography (hexane/EtOAc, 4:1). The product yield is 93 %. ^{1}**H NMR** (300 MHz, $CDCl_3$): 8.21 (d, *J* = 8.8 Hz, 2H, ArH), 7.58 (d, *J* = 8.7 Hz, 2H, ArH), 6.41 (s, 1H, C=CH_2), 5.89 (s, 1H, C=CH_2),

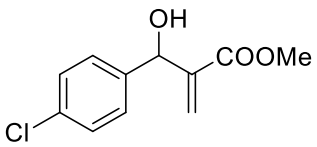
5.65 (s, 1H, C<u>H</u>-OH), 3.75 (s,3H, COOC<u>H</u>$_3$). The spectroscopical data matched with the previous reported in the literature.

<u>methyl 2-((3-bromophenyl)(hydroxy)methyl)acrylate (195f)</u>[85]



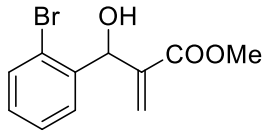
To a round bottom flask charged with methanol (0.75 equiv, 1 ml) was added the m-bromobenzaldehyde (1 equiv, 4 g, 22 mmol) and methyl acrylate (1.2 equiv, 2.20 g (2.3 ml), 26 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv., 1.21 g, 11 mmol) was added. The solution was stirred for 72 hours and purified by column chromatography (hexane/EtOAc, 4:1). The product yield is 88%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.56 (t, *J* = 1.8 Hz, 1H, Ar<u>H</u>), 7.43 (ddd, *J* = 1.5, 1.8, 7.7 Hz, 1H, Ar<u>H</u>), 7.34 (bd, *J* = 7.7 Hz, 1H, Ar<u>H</u>), 7.27-7.20 (t, *J* = 7.7 Hz, 1H, Ar<u>H</u>), 6.38 (s, 1H, C=C<u>H</u>$_2$), 5.86 (s, 1H, C=C<u>H</u>$_2$), 5.54 (d, *J* = 4.8 Hz, 1H, C<u>H</u>-OH), 3.77 (s, 3H, COOC<u>H</u>$_3$), 3.10 (d, *J* = 5.5 Hz, 1H, CH-O<u>H</u>). The spectroscopical data matched with the previous reported in the literature.

<u>methyl 2-((4-chlorophenyl)(hydroxy)methyl)acrylate (195g)</u>[178]



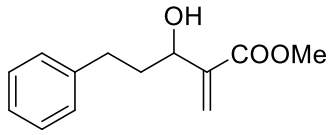
To a round bottom flask charged with methanol (0.75 equiv, 2 ml) was added the p-chlorobenzaldehyde (1 equiv, 10 g, 71 mmol) and methyl acrylate (1.2 equiv, 7.3 g (7.7 ml), 85 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv., 3.98 g, 35.3 mmol) was added. The solution was stirred for 72 hours and purified by column chromatography (hexane/EtOAc, 2:1). The product yield is 93%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.36-7.32 (m, 4H, Ar<u>H</u>), 6.37 (s, 1H, C=C<u>H</u>$_2$), 5.85 (s, 1H, C=C<u>H</u>$_2$), 5.55 (s, 1H, C<u>H</u>-OH), 3.76 (s, 3H, COOC<u>H</u>$_3$), 3.06 (d, *J* = 4.0 Hz, 1H, CH-O<u>H</u>). The spectroscopical data matched with the previous reported in the literature.

methyl 2-((2-bromophenyl)(hydroxy)methyl)acrylate (195h)[178]



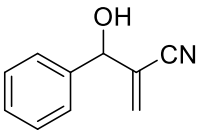
To a round bottom flask charged with methanol (0.75 equiv, 1 ml) was added the o-bromobenzaldehyde (1 equiv, 1 g, 5.4 mmol) and methyl acrylate (1.2 equiv, 558 mg (0.600 ml), 6.5 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv, 300 mg, 2.7 mmol) was added. The solution was stirred for 72 hours and purified by column chromatography (hexane/EtOAc, 2:1). The product yield is 86%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.58 (d, *J* = 7.9 Hz, 2H, ArH), 7.37 (dt, *J* = 1.1, 7.5 Hz, 1H, ArH), 7.24-7.16 (m, 1H, ArH), 6.37 (s, 1H, C=CH_2), 5.96 (d, *J* = 4.5 Hz, 1H, CH-OH), 5.58 (s, 1H, CH-OH), 3.81 (s, 3H, COOCH_3), 3.23 (d, *J* = 4.5 Hz, 1H, CH-OH). The spectroscopical data matched with the previous reported in the literature.

methyl 3-hydroxy-2-methylene-5-phenylpentanoate (195i)[180]



To a round bottom flask charged with methanol (0.75 equiv, 1 ml) was added the 3-phenylpropanal (1 equiv, 5 g, 37 mmol) and methyl acrylate (1.2 equiv, 3.86 mg (4.1 ml), 45 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv, 2.1 g, 19 mmol) was added. The solution was stirred for 120 hours and purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 75%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.35-7.15 (m, 5H, ArH), 6.26 (s, 1H, C=CH_2), 5.84 (s, 1H, C=CH_2), 4.45 (dd, *J* = 5.1, 7.7 Hz, 1H, CHOH), 3.78 (s, 3H, COOCH_3), 2.90-2.65 (m, 3H, CHOH, CH_2), 2.05-1.93 (m, 2H, CH_2). The spectroscopical data matched with the previous reported in the literature.

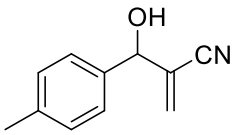
2-(hydroxy(phenyl)methyl)acrylonitrile (195j)[85]



To a round bottom flask charged with methanol (2 ml) was added the benzaldehyde (1 equiv, 3 g, 28 mmol) and acrylonitrile (1.2 equiv, 1.8 g (1.3 ml), 34 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv., 1.58 g, 14 mmol) was added. The solution was stirred for 48 hours and purified by column chromatography (hexane/EtOAc, 4:1). The product yield is 77 %. ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 5H, ArH), 6.12 (d, *J* = 1.5 Hz, 1H, C=CH_2), 6.04 (d, *J* = 1.0 Hz, 1H, C=CH_2), 5.31

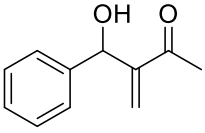
(s, 1H, CHOH), 2.44 (s, 1H, CHOH). The spectroscopical data matched with the previous reported in the literature.

2-(hydroxy(*p*-tolyl)methyl)acrylonitrile (195k)[181]



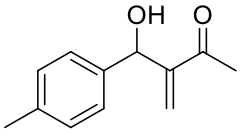
To a round bottom flask charged with methanol (2 ml) was added the 4-methylbenzaldehyde (1 equiv, 1 g, 8.3 mmol) and acrylonitrile (2 equiv, 883 mg g, 16.6 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv, 466 mg g, 4.2 mmol) was added. The solution was stirred for 48 hours and purified by column chromatography (hexane/EtOAc, 5:1). The product yield is 58 %. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 12.6 Hz, 2H, ArH), 7.20 (d, *J* = 8.0 Hz, 2H, ArH), 6.11 (d, *J* = 1.5 Hz, 1H, C=CH$_2$), 6.02 (d, *J* = 1.0 Hz, 1H, C=CH$_2$), 5.27 (d, *J* = 3.5 Hz, 1H, CHOH), 2.35 (s, 3H, Ar-CH$_3$). The spectroscopical data matched with the previous reported in the literature.

3-(hydroxy(phenyl)methyl)but-3-en-2-one (195l)[113]



To a round bottom flask charged with methanol (2 ml) was added the benzaldehyde (1 equiv, 3 g, 28 mmol), but-3-en-2-one (1.2 equiv, 2.4 g (1.7 ml), 34 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv, 1.58 g, 14 mmol) was added. The solution was stirred for 72 hours and purified by column chromatography (hexane/EtOAc, 6:1). The product yield is 50 %. ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H, ArH), 6.20 (s, 1H, C=CH$_2$), 5.98 (d, *J* = 1.1 Hz, 1H, CHOH), 5.62 (s, 1H, C=CH$_2$), 3.12 (s, 1H, CHOH), 2.34 (s, 3H, COCH$_3$). The spectroscopical data matched with the previous reported in the literature.

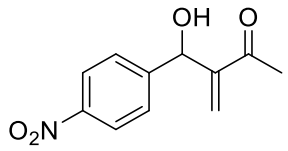
3-(hydroxy(*p*-tolyl)methyl)but-3-en-2-one (195m)[113]



To a round bottom flask charged with methanol (2 ml) was added the 4-methylbenzaldehyde (1 equiv, 3 g, 25 mmol), but-3-en-2-one (1.2 equiv, 2.1 g (1.5 ml), 30 mmol). To the mixture, 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv, 1.4 g, 12.5 mmol) was added. The solution was stirred for 72 hours and purified by column chromatography (hexane/EtOAc, 6:1).The product yield is 66 %. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.5 Hz, 2H, ArH), 7.15 (d, *J* = 8.0 Hz, 2H, ArH), 6.55 (s, 1H, C=CH$_2$), 6.23 (s, 1H, C=CH$_2$), 6.14 (d, *J* = 1.2 Hz, 1H, CHOH), 2.34 (s, 3H,

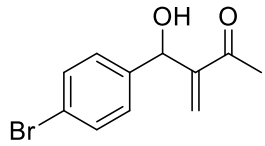
COC<u>H</u>$_3$), 2.33 (s, 3H, ArC<u>H</u>$_3$). The spectroscopical data matched with the previous reported in the literature.

3-(hydroxy(4-nitrophenyl)methyl)but-3-en-2-one (195n)[113]



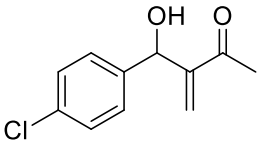
To a round bottom flask charged with THF (2 ml) was added the 4-nitrobenzaldehyde (1 equiv, 1 g, 6.5 mmol), but-3-en-2-one (3 equiv, 1.4 g (1 ml), 20 mmol). To the mixture, triphenylphosphine (0.2 equiv, 340 mg, 1.3 mmol) and benzoic acid (0.3 equiv, 240 mg, 1.95 mmol) was added. The solution was stirred for 48 hours and purified by column chromatography (hexane/EtOAc, 5:1). The product yield is 86 %. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>), 7.56 (d, *J* = 8.7 Hz, 2H, Ar<u>H</u>), 6.26 (s, 1H, C=C<u>H</u>$_2$), 6.03 (d, *J* = 0.8 Hz, 1H, C<u>H</u>OH), 5.68 (s, 1H, C=C<u>H</u>$_2$), 3.35 (brs, 1H, CHO<u>H</u>), 2.36 (s, 3H, COC<u>H</u>$_3$). The spectroscopical data matched with the previous reported in the literature.

3-((4-bromophenyl)(hydroxy)methyl)but-3-en-2-one (195o)[113]



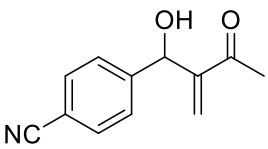
To a round bottom flask charged with THF (2 ml) was added the 4-bromobenzaldehyde (1 equiv, 5 g, 27 mmol), but-3-en-2-one (3 equiv, 5.7 g (4 ml), 81 mmol). To the mixture, triphenylphosphine (0.2 equiv, 1.4 g, 5.4 mmol) and benzoic acid (0.3 equiv, 1 g, 8.1 mmol) was added. The solution was stirred for 14 hours and purified by column chromatography (hexane/EtOAc, 5:1). The product yield is 71 %. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H, Ar<u>H</u>), 7.24 (d, *J* = 8.5 Hz, 2H, Ar<u>H</u>), 6.20 (s, 1H, C=C<u>H</u>$_2$), 5.97 (s, 1H, C=C<u>H</u>$_2$), 5.56 (d, *J* = 4.9 Hz, 1H, C<u>H</u>OH), 3.14 (d, *J* = 5.2 Hz, 1H, CHO<u>H</u>), 2.34 (s, 3H, COC<u>H</u>$_3$). The spectroscopical data matched with the previous reported in the literature.

3-((4-chlorophenyl)(hydroxy)methyl)but-3-en-2-one (195p)[113]



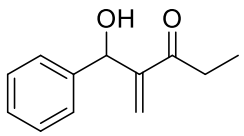
To a round bottom flask charged with THF (2 ml) was added the 4-bromobenzaldehyde (1 equiv, 2 g, 14 mmol), but-3-en-2-one (3 equiv, 3 g (2.2 ml), 43 mmol). To the mixture, triphenylphosphine (0.2 equiv, 750 mg, 2.9 mmol) and benzoic acid (0.3 equiv, 524 mg, 4.3 mmol) was added. The solution was stirred for 48 hours and purified by column chromatography (hexane/EtOAc, 5:1). The product yield is 70 %. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 4H, Ar$\underline{H}$), 6.20 (s, 1H, C=C$\underline{H}_2$), 5.97 (d, *J* = 1.0 Hz, 1H, C$\underline{H}$OH), 5.58 (s, 1H, C=C$\underline{H}_2$), 3.16 (s, 1H, CHO$\underline{H}$), 2.34 (s, 3H, COC$\underline{H}_3$). The spectroscopical data matched with the previous reported in the literature.

4-(1-hydroxy-2-methylene-3-oxobutyl)benzonitrile (195q)[182]



To a round bottom flask charged with THF (2 ml) was added the 4-bromobenzaldehyde (1 equiv, 2 g, 15 mmol), but-3-en-2-one (3 equiv, 3.2 g (2.3 ml), 46 mmol). To the mixture, triphenylphosphine (0.2 equiv, 800 mg, 3 mmol) and benzoic acid (0.3 equiv, 560 mg, 4.6 mmol) was added. The solution was stirred for 14 hours and purified by column chromatography (hexane/EtOAc, 5:1). The product yield is 73 %. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H, Ar$\underline{H}$), 7.49 (d, *J* = 8.3 Hz, 2H, Ar$\underline{H}$), 6.25 (s, 1H, C=C$\underline{H}_2$), 6.02 (s, 1H, C=C$\underline{H}_2$), 5.62 (s, 1H, C$\underline{H}$OH), 3.40 (brs, 1H, CHO$\underline{H}$), 2.35 (s, 3H, COC$\underline{H}_3$). The spectroscopical data matched with the previous reported in the literature.

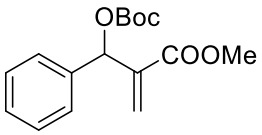
2-(hydroxy(phenyl)methyl)pent-1-en-3-one (195r)[183]



To a round bottom flask charged with THF (2 ml) was added the benzaldehyde (1 equiv, 1 g, 9.4 mmol) pent-1-en-3-one (3 equiv, 2.3 g, 28 mmol). To the mixture, triphenylphosphine (0.2 equiv, 492 mg, 2 mmol) and benzoic acid (0.3 equiv, 344 mg, 2.8 mmol) was added. The solution was stirred for 48 hours and purified by column chromatography (hexane/EtOAc, 5:1). The product yield is 56 %. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H, Ar$\underline{H}$), 6.17 (s, 1H, C=C$\underline{H}_2$), 5.93 (d, *J* = 1.0 Hz, 1H, C$\underline{H}$OH), 5.61 (s, 1H, C=C$\underline{H}_2$), 3.15 (s, 1H, CHO$\underline{H}$), 2.71 (m, 2H, COC$\underline{H}_2$CH$_3$), 1.05 (t, *J* = 7.3 Hz, 3H, COCH$_2$C$\underline{H}_3$). The spectroscopical data matched with the previous reported in the literature.

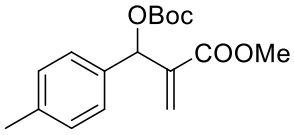
MBH-carbonates

methyl 2-(((*tert*-butoxycarbonyl)oxy)(phenyl)methyl)acrylate (215a)[85]



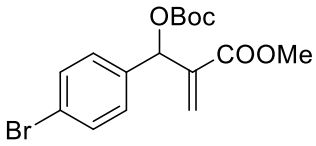
To a round bottom flask charged with DCM (0.6 M) was added the methyl 2-(hydroxy(phenyl)methyl)acrylate (1 equiv, 4 g, 21 mmol), Boc_2O (1.1 equiv, 5.02 g, 23 mmol) and 4-dimethylaminopyridine (10 mol%, 256 mg, 2.1mmol). The solution was stirred for 3 hours. The product was purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 76%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.45-7.25 (m, 5H, Ar<u>H</u>), 6.49 (s, 1H, C=C<u>H</u>$_2$), 6.42 (s, 1H, C=C<u>H</u>$_2$), 5.93 (s, 1H, C<u>H</u>OBoc), 3.73 (s, 3H, COOC<u>H</u>$_3$), 1.47 (s, 9H, OCOOC(C<u>H</u>$_3$)$_3$). The spectroscopical data matched with the previous reported in the literature.

methyl 2-(((*tert*-butoxycarbonyl)oxy)(*p*-tolyl)methyl)acrylate (215b)[178]



To a round bottom flask charged with DCM (0.6 M) was added the methyl 2-(hydroxy(p-tolyl)methyl)acrylate (1equiv, 1 g, 4.9 mmol), Boc_2O (1.1 equiv, 1.2 g, 5.4 mmol) and 4-dimethylaminopyridine (10 mol%, 59 mg, 0.49 mmol). The solution was stirred for 4 hours. The product was purified by column chromatography (hexane/EtOAc, 4:1). The product yield is 86%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.28 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>), 7.16 (d, *J* = 8.1 Hz, 2H, Ar<u>H</u>), 6.46 (s, 1H, C=C<u>H</u>$_2$), 6.40 (s, 2H, C=C<u>H</u>$_2$), 5.93 (s, 1H, C<u>H</u>OBoc), 3.72 (s, 3H, COOC<u>H</u>$_3$), 2.35 (s, 3H, ArC<u>H</u>$_3$), 1.48 (s, 9H, OCOOC(C<u>H</u>$_3$)$_3$). The spectroscopical data matched with the previous reported in the literature.

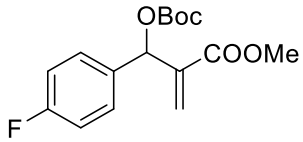
methyl 2-((4-bromophenyl)((*tert*-butoxycarbonyl)oxy)methyl)acrylate (215c)[178]



To a round bottom flask charged with DCM (0.6 M) was added the methyl 2-((4-bromophenyl)(hydroxy)methyl)acrylate (1equiv, 2 g, 7.4 mmol), Boc_2O (1.1 equiv, 1.78g, 8.15 mmol) and 4-dimethylaminopyridine (10 mol%, 90 mg, 0.74 mmol). The solution was stirred for 3 hours. The product was purified by column chromatography (hexane/EtOAc, 5:1). The product yield is 90%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.48 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>), 7.29 (d, *J* = 8.8

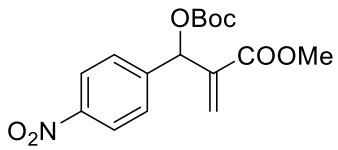
Hz, 2H, Ar<u>H</u>), 6.44 (s, 1H, C=C<u>H</u>$_2$), 6.43 (s, 1H, C=C<u>H</u>$_2$), 5.96 (s, 1H, C<u>H</u>OBoc), 3.73 (s, 3H, COOC<u>H</u>$_3$), 1.48 (s, 9H, OCOOC(C<u>H</u>$_3$)$_3$). The spectroscopical data matched with the previous reported in the literature.

<u>methyl 2-(((*tert*-butoxycarbonyl)oxy)(4-fluorophenyl)methyl)acrylate (215d)</u>[178]



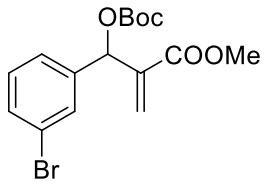
To a round bottom flask charged with DCM (0.6 M) was added the methyl 2-((4-fluorophenyl)(hydroxy)methyl)acrylate (1 equiv, 1 g, 4.8 mmol), Boc$_2$O (1.1 equiv, 1.15 g, 5.3 mmol) and 4-dimethylaminopyridine (10 mol%, 58 mg, 0.48 mmol). The solution was stirred for 4 hours. The product was purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 79%. ^{1}**H NMR** (300 MHz, CDCl$_3$): 7.40 (dd, *J* = 5.5, 8.8 Hz, 2H, Ar<u>H</u>), 7.03 (t, *J* = 8.8 Hz, 2H, Ar<u>H</u>), 6.46 (s, 1H, C=C<u>H</u>$_2$), 6.42 (s, 1H, C=C<u>H</u>$_2$), 5.98 (s, 1H, C<u>H</u>OBoc), 3.73 (s, 3H, COOC<u>H</u>$_3$), 1.48 (s, 9H, OCOOC(C<u>H</u>$_3$)$_3$). The spectroscopical data matched with the previous reported in the literature.

<u>methyl 2-(((*tert*-butoxycarbonyl)oxy)(4-nitrophenyl)methyl)acrylate (215e)</u>[85]



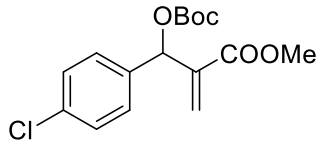
To a round bottom flask charged with DCM (0.6 M) was added the methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate (1equiv, 4g, 17 mmol), Boc$_2$O (1.1 equiv, 4.08 g, 19 mmol) and 4-dimethylaminopyridine (10 mol%, 207 mg, 1.7 mmol). The solution was stirred for 3 hours. The product was purified by column chromatography (hexane/EtOAc, 4:1). The product yield is 32%. ^{1}**H NMR** (300 MHz, CDCl$_3$): 8.23(d, *J* = 8.67 Hz, 2H, Ar<u>H</u>), 7.62 (d, *J* = 8.67 Hz, 2H, Ar<u>H</u>), 6.54 (s, 1H, C=C<u>H</u>$_2$), 6.48 (s, 1H, C=C<u>H</u>$_2$), 6.04 (s, 1H, C<u>H</u>OBoc), 3.75 (s, 3H, COOC<u>H</u>$_3$), 1.48 (s, 9H, OCOOC(C<u>H</u>$_3$)$_3$). The spectroscopical data matched with the previous reported in the literature.

methyl 2-((3-bromophenyl)((*tert*-butoxycarbonyl)oxy)methyl)acrylate (215f)[85]



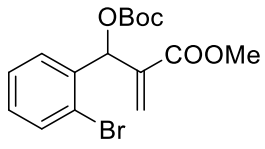
To a round bottom flask charged with DCM (0.6 M) was added the methyl 2-((3-bromophenyl)(hydroxy)methyl)acrylate (1equiv, 1 g, 3.7 mmol), Boc_2O (1.1 equiv, 890 mg, 4.1 mmol) and 4-dimethylaminopyridine (10 mol%, 45 mg, 0.37 mmol). The solution was stirred for 2 hours. The product was purified by column chromatography (hexane/EtOAc, 5:1). The product yield is 80%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.56 (dd, *J* = 1.5, 1.9 Hz, 1H, Ar<u>H</u>), 7.46 (ddd, *J* = 1.1, 1.9, 7.9 Hz, 1H, Ar<u>H</u>), 7.36 (ddd, *J* = 1.1, 1.5, 7.9 Hz, 1H, Ar<u>H</u>), 7.26-7.19 (m, 1H, Ar<u>H</u>), 6.45 (s, 2H, C=C<u>H</u>$_2$), 5.97 (s, 1H, C<u>H</u>OBoc), 3.75 (s, 3H, COOC<u>H</u>$_3$), 1.49 (s, 9H, OCOOC(C<u>H</u>$_3$)$_3$). The spectroscopical data matched with the previous reported in the literature.

methyl 2-(((*tert*-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (215g)[178]



To a round bottom flask charged with DCM (0.6 M) was added the methyl 2-((4-chlorophenyl)(hydroxy)methyl)acrylate (1 equiv, 1 g, 4.45 mmol), Boc_2O (1.1 equiv, 1.06 g, 4.9 mmol) and 4-dimethylaminopyridine (10 mol%, 54 mg, 0.45 mmol). The solution was stirred for 3 hours. The product was purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 83%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.34(d, *J* = 2.6 Hz, 4H, Ar<u>H</u>), 6.45 (s, 1H, C=C<u>H</u>$_2$), 6.42 (s, 1H, C=C<u>H</u>$_2$), 5.96 (s, 1H, C<u>H</u>OBoc), 3.73 (s, 3H, COOC<u>H</u>$_3$), 1.48 (s, 9H, OCOOC(C<u>H</u>$_3$)$_3$). The spectroscopical data matched with the previous reported in the literature.

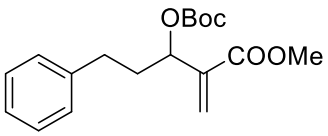
methyl 2-((2-bromophenyl)((*tert*-butoxycarbonyl)oxy)methyl)acrylate (215h)[180]



To a round bottom flask charged with DCM (0.6 M) was added the methyl 2-((2-bromophenyl)(hydroxy)methyl)acrylate (1 equiv, 1.2 g, 4.45 mmol), Boc_2O (1.1 equiv, 1.07 g, 4.9 mmol) and 4-dimethylaminopyridine (10 mol%, 55 mg, 0.45 mmol). The solution was stirred

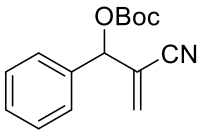
for 3 hours. The product was purified by column chromatography (hexane/EtOAc, 2:1). The product yield is 76%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.60 (dd, *J* = 1.1, 7.9 Hz, 1H, ArH), 7.42 (dd, *J* = 1.7, 7.8 Hz, 1H, ArH), 7.35 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1H, ArH), 7.22 (ddd, *J* = 1.7, 7.7, 7.8 Hz, 1H, ArH), 6.87 (s, 1H, C=CH_2), 6.50 (s, 1H, C=CH_2), 5.65 (s, 1H, CHOBoc), 3.78 (s, 3H, COOCH_3), 1.50 (s, 9H, OCOOC(CH_3)$_3$). The spectroscopical data matched with the previous reported in the literature.

methyl 3-((*tert*-butoxycarbonyl)oxy)-2-methylene-5-phenylpentanoate (215i)[180]



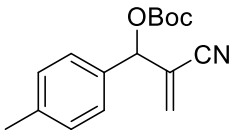
To a round bottom flask charged with DCM (0.6 M) was added methyl 3-hydroxy-2-methylene-5-phenylpentanoate (1equiv, 2 g, 9.13 mmol), Boc_2O (1.1 equiv, 2.19 g, 10 mmol) and 4-dimethylaminopyridine (10 mol%, 111 mg, 0.91 mmol). The solution was stirred for 3 hours. The product was purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 63%. ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.35-7.15 (m, 5H, ArH), 6.34(s, 1H, C=CH_2), 5.89 (s, 1H, C=CH_2), 5.48 (dd, *J* = 4.4, 8.1 Hz, 1H, CHOBoc), 3.78 (s, 3H, COOCH_3), 2.85-2.65 (m, 2H, CH_2), 2.17-1.92 (m , 2H, CH_2), 1.51 (s, 9H, OCOOC(CH_3)$_3$). The spectroscopical data matched with the previous reported in the literature.

***tert*-butyl (2-cyano-1-phenylallyl) carbonate (215j)**[85]



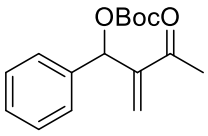
To a round bottom flask charged with DCM (0.6 M) was added 2-(hydroxy(phenyl)methyl)acrylonitrile (1equiv, 3.7 g, 23 mmol), Boc_2O (1.1 equiv, 5.54 g, 25.4 mmol) and 4-dimethylaminopyridine (10 mol%, 281 mg, 2.3 mmol). The solution was stirred for 2 hours. The product was purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 80%. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 5H, ArH), 6.10 (s, 1H, C=CH_2), 6.08 (s, 1H, C=CH_2), 6.04 (d, 1H, CHOBoc), 1.48 (s, 9H, OCOOC(CH_3)$_3$). The spectroscopical data matched with the previous reported in the literature.

***tert*-butyl (2-cyano-1-(*p*-tolyl)allyl) carbonate (215k)**[85]



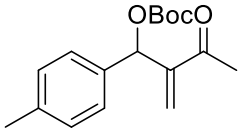
To a round bottom flask charged with DCM (0.6 M) was added 2-(hydroxy(p-tolyl)methyl)acrylonitrile (1equiv, 0.5 g, 2.9 mmol), Boc_2O (1.1 equiv, 693 mg, 3.2 mmol) and 4-dimethylaminopyridine (20 mol%, 70 mg, 0.58 mmol). The solution was stirred for 14 hours at 0 ˚C. The product was purified by column chromatography (hexane/EtOAc, 5:1). The product yield is 70 %. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 2H, ArH), 7.21 (d, *J* = 8.0 Hz, 2H, ArH), 6.07 (s, 2H, C=CH_2), 6.03 (s, 1H, CHOBoc), 2.36 (s, 3H, ArCH_3), 1.47 (s, 9H, OCOOC(CH_3)$_3$). The spectroscopical data matched with the previous reported in the literature.

***tert*-butyl (2-methylene-3-oxo-1-phenylbutyl) carbonate (215l)**[184]



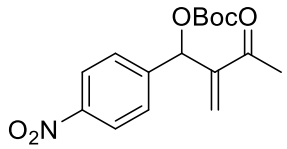
To a round bottom flask charged with DCM (0.6 M) was added 3-(hydroxy(phenyl)methyl)but-3-en-2-one (1equiv, 0.5 g, 2.8 mmol), Boc_2O (1.1 equiv, 680 mg, 3.1 mmol) and 4-dimethylaminopyridine (10 mol%, 34 mg, 0.28 mmol). The solution was stirred for 14 hours at 0 ˚C. The product was purified by column chromatography (hexane/EtOAc, 4:1). The product yield is 75 %. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.42-7.26 (m, 5H, ArH), 6.54 (s, 1H, C=CH_2), 6.24 (s, 1H, C=CH_2), 6.12 (s, 1H, CHOBoc), 2.32 (s, 3H, COCH_3), 1.46 (s, 9H, OCOOC(CH_3)$_3$). The spectroscopical data matched with the previous reported in the literature.

***tert*-butyl (2-methylene-3-oxo-1-(*p*-tolyl)butyl) carbonate (215m)**[185]



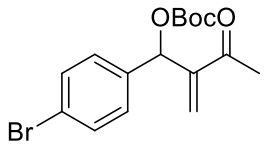
To a round bottom flask charged with DCM (0.6 M) was added 2-(hydroxy(phenyl)methyl)acrylonitrile (1equiv, 1 g, 5.3 mmol), Boc_2O (1.1 equiv, 1.3 g, 5.8 mmol) and 4-dimethylaminopyridine (10 mol%, 64 mg, 5.3 mmol). The solution was stirred for 2 hours. The product was purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 63%. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 2H, ArH), 7.12 (d, *J* = 8.0 Hz, 2H, ArH), 6.53 (s, 1H, C=CH_2), 6.20 (s, 1H, C=CH_2), 6.12 (s, 1H, CHOBoc), 2.31 (s, 3H, COCH_3), 2.30 (s, 3H, ArCH_3), 1.45 (s, 9H, OCOOC(CH_3)$_3$). The spectroscopical data matched with the previous reported in the literature.

***tert*-butyl (2-methylene-1-(4-nitrophenyl)-3-oxobutyl) carbonate (215n)**[185]



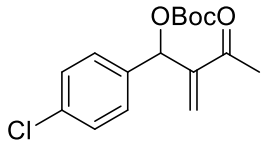
To a round bottom flask charged with DCM (0.6 M) was added 3-(hydroxy(4-nitrophenyl)methyl)but-3-en-2-one (1equiv, 500 mg, 2.3 mmol), Boc_2O (1.1 equiv, 540 mg, 2.5 mmol) and 4-dimethylaminopyridine (10 mol%, 28 mg, 0.23 mmol). The solution was stirred for 2 hours. The product was purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 85%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H, ArH), 7.58 (d, *J* = 8.7 Hz, 2H, ArH), 6.59 (s, 1H, C=CH_2), 6.29 (s, 1H, C=CH_2), 6.24 (s, 1H, CHOBoc), 2.33 (s, 3H, COCH_3), 1.45 (s, 9H, OCOOC(CH_3)$_3$). The spectroscopical data matched with the previous reported in the literature.

1-(4-bromophenyl)-2-methylene-3-oxobutyl *tert*-butyl carbonate (215o)[185]



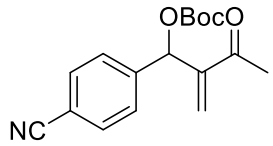
To a round bottom flask charged with DCM (0.6 M) was added 3-((4-bromophenyl)(hydroxy)methyl)but-3-en-2-one (1equiv, 500 mg, 2.3 mmol), Boc_2O (1.1 equiv, 540 mg, 2.5 mmol) and 4-dimethylaminopyridine (10 mol%, 28 mg, 0.23 mmol). The solution was stirred for 14 hours at 0 °C. The product was purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 86 %. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2H, ArH), 7.27 (d, *J* = 8.0 Hz, 2H, ArH), 6.49 (s, 1H, C=CH_2), 6.23 (s, 1H, C=CH_2), 6.16 (s, 1H, CHOBoc), 2.31 (s, 3H, COCH_3), 1.45 (s, 9H, OCOOC(CH_3)$_3$). The spectroscopical data matched with the previous reported in the literature.

***tert*-butyl (1-(4-chlorophenyl)-2-methylene-3-oxobutyl) carbonate (215p)**[185]



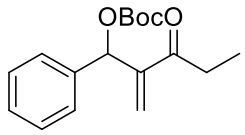
To a round bottom flask charged with DCM (0.6 M) was added 3-((4-chlorophenyl)(hydroxy)methyl)but-3-en-2-one (1equiv, 1 g, 4.8 mmol), Boc_2O (1.1 equiv, 1.4 g, 5.2 mmol) and 4-dimethylaminopyridine (20 mol%, 116 mg, 0.95 mmol). The solution was stirred for 14 hours at 0 °C. The product was purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 40 %. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 4H, ArH), 6.50 (s, 1H, C=CH_2), 6.23 (s, 1H, C=CH_2), 6.15 (s, 1H, CHOBoc), 2.31 (s, 3H, COCH_3), 1.45 (s, 9H, OCOOC(CH_3)$_3$). The spectroscopical data matched with the previous reported in the literature.

***tert*-butyl (1-(4-cyanophenyl)-2-methylene-3-oxobutyl) carbonate (215q)**[186]



To a round bottom flask charged with DCM (0.6 M) was added 4-(1-hydroxy-2-methylene-3-oxobutyl)benzonitrile (1equiv, 1 g, 5 mmol), Boc_2O (1.1 equiv, 540 mg, 2.5 mmol) and 4-dimethylaminopyridine (10 mol%, 28 mg, 0.23 mmol). The solution was stirred for 14 hours at 0 °C. The product was purified by column chromatography (hexane/EtOAc, 4:1). The product yield is 65 %. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.4 Hz, 2H, Ar<u>H</u>), 7.51 (d, *J* = 8.3 Hz, 2H, Ar<u>H</u>), 6.54 (s, 1H, C=C<u>H</u>$_2$), 6.27 (s, 1H, C=C<u>H</u>$_2$), 6.21 (s, 1H, C<u>H</u>OBoc), 2.32 (s, 3H, COC<u>H</u>$_3$), 1.45 (s, 9H, OCOOC(C<u>H</u>$_3$)$_3$). The spectroscopical data matched with the previous reported in the literature.

***tert*-butyl (2-methylene-3-oxo-1-phenylpentyl) carbonate (215r)**[187]



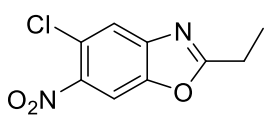
To a round bottom flask charged with DCM (0.6 M) was added 2-(hydroxy(phenyl)methyl)pent-1-en-3-one (1equiv, 1 g, 5 mmol), Boc_2O (1.1 equiv, 540 mg, 2.5 mmol) and 4-dimethylaminopyridine (10 mol%, 28 mg, 0.23 mmol). The solution was stirred for 14 hours at 0 °C. The product was purified by column chromatography (hexane/EtOAc, 4:1). The product yield is 75 %. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H, Ar<u>H</u>), 6.56 (s, 1H, C=C<u>H</u>$_2$), 6.21 (s, 1H, C=C<u>H</u>$_2$), 6.08 (s, 1H, C<u>H</u>OBoc), 2.68 (ddd, *J* = 48.3, 17.5, 7.3 Hz, 2H, COC<u>H</u>$_2$CH$_3$), 1.45 (s, 9H, OCOOC(C<u>H</u>$_3$)$_3$), 1.04 (t, *J* = 7.3 Hz, 3H, COCH$_2$C<u>H</u>$_3$). The spectroscopical data matched with the previous reported in the literature.

Synthesis of benzoxazoles

The following starting benzoxazoles described in literature were synthesised by Marta Meazza.[135] 2-ethyloxazolo-4,5-pyridine (**347j**) and 2-methylbenzoxazole (**347k**) are commercially available (Acros and Sigma-Aldrich respectively). The ^{1}H NMR spectra of 2-ethyl-6-nitrobenzoxazole (**347a**), 2-methyl-6-nitrobenzoxazole (**347l**) is consistent with the ones provided in literature.[188] The ^{1}H NMR of 2-ethylbenzoxazole (**347f**) is consistent with the one provided in literature.[189] The ^{1}H NMR of 2-ethyl-4-nitrobenzoxazole (**347e**), 2-butyl-6-nitrobenzoxazole (**347d**) and 2-ethylbenzoxazol-6-yl acetate (**347h**) are consistent with the ones

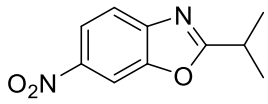
provided in literature.[135] The ^{1}H NMR of 2-ethyl-5-nitrobenzoxazole (**347c**) is consistent with the one provided in literature.[190]

5-chloro-2-ethyl-6-nitrobenzoxazole (347b) (Synthesised by Marta Meazza)



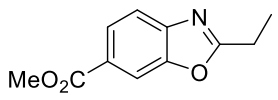
A mixture of 2-amino-4-chloro-5-nitrophenol (5 g, 26.4 mmol, 1 equiv) and triethyl orthopropionate (5.8 ml, 29.0 mmol, 1.1 equiv) was stirred at 50 °C for 48 hours. The crude was purified by flash column chromatography (hexane/EtOAc 5:1) to obtain 4.5 g of a yellow solid. The yield is 75 %. **mp:** 83-85 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** σ 8.07 (s, 1H), 7.82 (s, 1H), 3.04 (q, *J* = 7.6 Hz, 2H), 1.48 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** σ 173.6 (Cq), 148.3 (Cq), 145.2 (Cq), 144.5 (Cq), 123.4 (Cq), 122.1 (CH), 108.4 (CH), 22.4 (CH_2), 10.6 (CH_3). **HR MS (ESI+)** Exact mass calculated for $C_9H_8{}^{35}ClN_2O_3$ $[M+H]^+$: 227.0218, found: 227.0217. **IR:** 3106 (w), 3035 (w), 2992 (w), 1560 (m), 1523 (s), 1446 (m), 1324 (s), 1255 (m), 1209 (m), 822 (s).

2-isopropyl-6-nitrobenzoxazole (347g) (Synthesised by Marta Meazza)



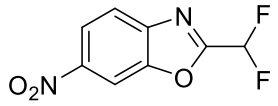
To a round bottom flask charged with 2-amino-5-nitrophenol (3.0 g, 19.5 mmol, 1 equiv) was added isobutyric acid (1.8 ml, 19.5 mmol, 1 equiv) and polyphosphoric acid (38 g, 390 mmol, 20 equiv). The reaction mixture was stirred for 7 hours at 50 °C. Then the mixture was cooled at room temperature and a solution of sodium hydroxide was added until the mixture had a pH superior to 7. The formed solid was filtered and washed with ice-water to afford 2.4 g of a brown solid. The yield is 59 %. **mp:** 86-87 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** σ 8.41 (d, *J* = 2.1 Hz, 1H), 8.29 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 3.40 – 3.26 (m, 1H), 1.51 (d, *J* = 7.0 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** σ 176.2 (Cq), 149.9 (Cq), 146.7 (Cq), 144.9 (Cq), 120.3 (CH), 119.5 (CH), 107.0 (CH), 29.2 (CH), 20.1 (CH_3). **HR MS (ESI+)** Exact mass calculated for $C_{10}H_{11}N_2O_3$ $[M+H]^+$: 207.0764, found: 207.0764. **IR:** 3107 (w), 2970 (w), 1568 (m), 1520 (s), 1344 (s), 1276 (m), 1139 (m), 1088 (m), 886 (m), 818 (m).

methyl 2-ethylbenzo[d]oxazole-6-carboxylate (347h)[135]



A mixture of methyl 4-amino-3-hydroxybenzoate (1 g, 5.98 mmol, 1 equiv.) and triethyl orthopropionate (1.16 g, 6.58 mmol, 1.1 equiv.) was stirred at 80 °C for 3 hours then cooled to room temperature. The precipitate was filtered and washed with ice-water in order to obtain a yellow solid. The mass is 914 mg. The yield is 75%. **MS** (ESI+) *m/z*: 205.9374 $[M+H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$): 8.10 (dd, *J* = 0.5, 1.5 Hz, 1H, ArH), 7.97 (dd, *J* = 1.6, 8.4 Hz, 1H, ArH), 7.62 (dd, *J* = 0.4, 8.3 Hz, 1H, ArH), 3.88 (s, 3H, $COOCH_3$), 2.97-2.89 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 1.40 (t, *J* = 7.6 Hz, 3H, CH_2CH_3). **^{13}C NMR** ($CDCl_3$, 100 MHz): 171.0 (q), 166.7 (q), 150.5 (q), 145.4 (q), 126.7 (q), 125.9 (CH), 119.1 (CH), 112.0 (CH), 52.3 (CH_3), 22.3 (CH_2), 10.7 (CH_3). The spectroscopical data matched with the previous reported in the literature.

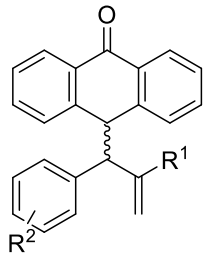
2-(difluoromethyl)-6-nitrobenzo[d]oxazole (347i)



To a round bottom flask charged with 2-amino-5-nitrophenol (3.6 g, 23.36 mmol, 1equiv) was added 2,2-difluoroacetic acid (2.24 g, 23.36 mmol, 1 equiv) and polyphosphoric acid (45 g, 467,2 mmol, 20 equiv). The reaction mixture was stirred for 24 hours at 80°C. Then the mixture was cooled at room temperature and a solution of sodium hydroxide was added until the mixture had a pH superior to 7. The formed solid was filtered and washed with ice-water to afford a brown solid. The mass is 4.3 g. The yield is 86%. **mp:** 102-104 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): 8.51 (d, *J* = 2.0 Hz, 1H, ArH), 8.34 (dd, *J* = 2.1, 8.8 Hz, 1H, ArH), 7.92 (d, *J* = 8.9 Hz, 1H, ArH), 6.93-6.65 (t, *J* = 52.2 Hz, 1H, CHF_2). **^{19}F-NMR** ($CDCl_3$, 300 MHz): -119.9 ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.8 (q), 144.6 (q), 141.9 (q), 121.8 (CH), 121.4 (CH), 108.4 (CH), 106.6 (CH), 104.2 (q). **IR** (cm^{-1}) 3105 (w), 1526 (m), 1354 (s), 1304 (w), 1255 (m), 1109 (m), 1056 (s), 844 (m). 835 (m). **MS** (ESI+) *m/z*: 215.0708 $[M+H]^+$. **HR MS (ESI+)** Exact mass calculated for $C_8H_5F_2N_2O_3$ $[M+H]^+$: 215.0724, found: 215.0719.

4.3 Highly enantioselective anthrone addition to MBH-carbonates

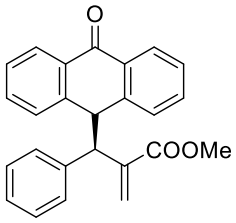
4.3.1 General procedure for the synthesis of racemic products



To a solution of anthrone (1equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added the appropriate MBH-carbonate (2 equiv, 0.2 mmol), 1,4-diaza-bicyclo[2.2.2]octane (20 mol%, 2 mg, 0.02 mmol).The reaction was stirred for 3 days at room temperature. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc).

4.3.2 General procedure for the synthesis of chiral products

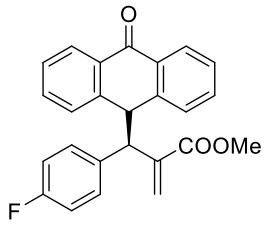
methyl (*R*)-2-((10-oxo-9,10-dihydroanthracen-9-yl)(phenyl)methyl)acrylate (290a)



To a solution of anthrone (1equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate (2 equiv, 58 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 30 mg of desired product. The product yield is 82 % as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$): σ 8.15 (dd, *J* = 7.5, 1.6 Hz, 1H, ArH), 7.97 (dd, *J* = 7.8, 1.0 Hz, 1H, ArH), 7.63 (d, *J* = 7.6 Hz, 1H, ArH), 7.55 (td, *J* = 7.5, 1.3 Hz, 1H, ArH), 7.46 (ddd, *J* = 9.0, 7.3, 1.6 Hz, 2H, ArH), 7.38 – 7.31 (m, 1H, ArH), 7.25 – 7.19 (m, 1H, ArH), 7.09 (t, *J* = 7.4 Hz, 1H, ArH), 6.96 (t, *J* = 7.7 Hz, 2H, ArH), 6.32 (s, 1H, C=CH_2), 6.30 (d, *J* = 7.3 Hz, 2H, ArH), 5.37 (d, *J* = 1.1 Hz, 1H, C=CH_2), 4.96 (d, *J* = 4.6 Hz, 1H, CH_2=C-CH-CH), 4.48 (d, *J* = 4.5 Hz, 1H, CH_2=C-CH-CH), 3.89 (s, 3H, COOCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 184.3 (q), 168.0 (q), 144.0 (q), 141.3 (q), 140.2 (q), 135.8 (q), 134.1 (q), 132.9 (q), 132.4 (CH), 131.5 (CH), 130.0 (CH), 129.1(CH), 128.4 (CH_2), 128.3 (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 126.9 (CH), 126.6 (CH), 58.4 (CH_3), 52.4 (CH), 46.8 (CH). **MS** (ESI+) *m/z* 369.18 ([M + H]$^+$). **HR MS** (m/z) for $[C_{25}H_{21}O_3]^+$ calculated $[M+H]^+$ 369.1485,

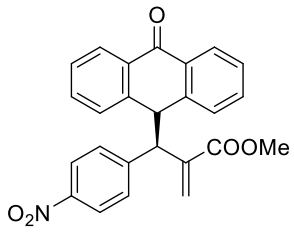
measured $[M+H]^+$ 369.1489. **IR** (cm^{-1}): 3064 (=C-H, stretch), 3029 (=C-H, stretch), 1715 (C=O, stretch), 1666 (C=O, stretch), 1600 (C=C, stretch), 1313 (C-O ester, stretch). $[\alpha]_D^{19}$ = +48.4 (c = 1.5, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak IC column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 14.2 min, t_{r2} = 16.9 min; 88 % ee.

methyl (*R*)-2-((4-fluorophenyl)(10-oxo-9,10-dihydroanthracen-9-yl)methyl)acrylate (290b)



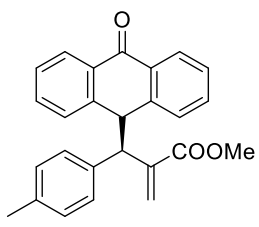
To a solution of anthrone (1equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-fluorophenyl)methyl)acrylate (2 equiv, 60 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 37 mg of a light yellow solid. The product yield is 96 %. **Mp** 181 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.16 (dd, *J* = 7.5, 1.6 Hz, 1H, ArH), 7.99 (dd, *J* = 7.8, 1.0 Hz, 1H, ArH), 7.65 (d, *J* = 7.6 Hz, 1H, ArH), 7.57 (m, 1H, ArH), 7.53 – 7.42 (m, 2H, ArH), 7.39 – 7.32 (m, 1H, ArH), 7.21 (d, *J* = 7.5 Hz, 1H, ArH), 6.65 (dd, *J* = 8.7 Hz, 2H, ArH), 6.32 (s, 1H, C=CH_2), 6.28 – 6.19 (m, 2H, ArH), 5.31 (d, *J* = 1.3 Hz, 1H, C=CH_2), 4.94 (d, *J* = 4.6 Hz, 1H, CH_2=C-CH-CH), 4.46 (d, *J* = 4.5 Hz, 1H, CH_2=C-CH-CH), 3.91 (s, 3H, COOCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 184.1 (q), 167.9 (q), 143.9 and 140.9 (q, d, J_{CF} = 301 Hz), 140.3 (q), 134.0 (q), 132.8 (q), 132.7 (q), 132.6 (CH), 131.6 (CH), 131.48 (CH), 131.4 (q), 131.4 (CH), 129.1 (CH), 128.3 (CH), 128.2 (CH_2) 127.6 (CH), 127.1 (CH), 127.0 (CH), 126.8 (CH), 114.8 (CH), 114.6 (CH), 57.8 (CH_3), 52.5 (CH), 46.6 (CH). **^{19}F NMR** (376 MHz, $CDCl_3$) σ -114.7. **MS** (ESI+) *m/z* 387.19 ($[M + H]^+$). **HR MS** (m/z) for $[C_{25}H_{20}FO_3]^+$ calculated $[M+H]^+$ 387.1391, measured $[M+H]^+$ 387.1387. **IR** (cm^{-1}): 3069 (=C-H, stretch), 3029 (=C-H, stretch), 1715 (C=O, stretch), 1666 (C=O, stretch), 1600 (C=C, stretch), 1314 (C-O ester, stretch). $[\alpha]_D^{19}$ = +16.7 (c = 1.9, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak IC column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 12.2 min, t_{r2} = 13.4 min; 88 % ee.

methyl (*R*)-2-((4-nitrophenyl)(10-oxo-9,10-dihydroanthracen-9-yl)methyl)acrylate (290c)



To a solution of anthrone (1equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-nitrophenyl)methyl)acrylate (2 equiv, 60 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 37 mg of a yellow solid. The product yield is 91 %. **Mp** 185 ˚C. ^{1}**H NMR** (400 MHz, $CDCl_3$) σ 8.20 – 8.13 (m, 1H, ArH), 7.99 (dd, *J* = 7.8, 0.9 Hz, 1H, ArH), 7.83 (d, *J* = 8.8 Hz, 2H, ArH), 7.64 (d, *J* = 7.5 Hz, 1H, ArH), 7.58 (m, 1H, ArH), 7.54 – 7.44 (m, 2H, ArH), 7.44 – 7.34 (m, 1H, ArH), 7.20 (dd, *J* = 6.0, 2.8 Hz, 1H, ArH), 6.52 (d, *J* = 8.8 Hz, 2H, ArH), 6.36 (s, 1H, C=CH_2), 5.30 (d, *J* = 1.3 Hz, 1H, C=CH_2), 5.02 (d, *J* = 5.0 Hz, 1H, CH_2=C-CH-CH), 4.56 (d, *J* = 4.9 Hz, 1H, CH_2=C-CH-CH), 3.91 (s, 3H, COOCH_3). ^{13}**C NMR** (101 MHz, $CDCl_3$) σ 184.0 (q), 167.4 (q), 147.0 (q), 143.8 (q), 143.2 (q), 140.4 (q), 139.3 (q), 133.8 (q), 132.8 (CH), 132.6 (q), 131.7 (CH), 130.7 (CH), 129.1 (CH), 128.6 (CH_2), 128.2 (CH), 127.9 (CH), 127.5 (CH), 127.4 (CH), 127.1 (CH), 122.9 (CH), 58.6 (CH_3), 52.6 (CH), 46.3 (CH). **MS** (ESI+) *m/z* 414.24 ($[M + H]^+$). **HR MS** (m/z) for $[C_{25}H_{20}NO_5]^+$ calculated $[M+H]^+$ 414.1336, measured $[M+H]^+$ 414.1339. **IR** (cm^{-1}): 3075 (=C-H, stretch), 3029 (=C-H, stretch), 1713 (C=O, stretch), 1665 (C=O, stretch), 1600 (C=C, stretch), 1520 (N-O, asymmetric stretch), 1346 (N-O, symmetric stretch), 1313 (C-O ester, stretch). $[\alpha]_D^{19}$ = +34.5 (c = 1.9, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak IB column [hexane/*i*PrOH = 95:5]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 14.9 min, t_{r2} = 16.0 min; 92 % ee.

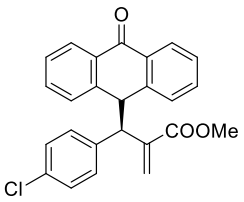
methyl (*R*)-2-((10-oxo-9,10-dihydroanthracen-9-yl)(*p*-tolyl)methyl)acrylate (290d)



To a solution of anthrone (1equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(p-tolyl)methyl)acrylate (2 equiv, 60 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was

followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 30 mg of a yellow oil. The product yield is 90 %. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.15 (dd, *J* = 7.5, 1.6 Hz, 1H, Ar<u>H</u>), 7.99 (dd, *J* = 7.8, 1.1 Hz, 1H, Ar<u>H</u>), 7.63 (d, *J* = 7.6 Hz, 1H, Ar<u>H</u>), 7.55 (td, *J* = 7.6, 1.4 Hz, 1H, Ar<u>H</u>), 7.52 – 7.40 (m, 2H, Ar<u>H</u>), 7.37 – 7.31 (m, 1H, Ar<u>H</u>), 7.25 – 7.20 (m, 1H, Ar<u>H</u>), 6.77 (d, *J* = 7.9 Hz, 2H, Ar<u>H</u>), 6.30 (s, 1H, C=C<u>H</u>$_2$), 6.19 (d, *J* = 8.1 Hz, 2H, Ar<u>H</u>), 5.34 (d, *J* = 0.8 Hz, 1H, C=C<u>H</u>$_2$), 4.93 (d, *J* = 4.6 Hz, 1H, CH_2=C-CH-C<u>H</u>), 4.46 (d, *J* = 4.4 Hz, 1H, CH_2=C-C<u>H</u>-CH), 3.88 (s, 3H, COOC<u>H</u>$_3$), 2.19 (s, 3H, ArC<u>H</u>$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 184.4 (q), 168.0 (q), 144.1 (q), 141.4 (q), 140.5 (q), 136.8 (q), 134.0 (q), 132.9 (q), 132.7 (q), 132.4 (CH), 131.5 (CH), 129.8 (CH), 129.2 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH_2), 127.4 (CH), 127.0 (CH), 126.9 (CH), 126.6 (CH), 58.0 (CH_3), 52.3 (CH), 46.8 (CH), 21.0 (CH_3). **MS** (ESI-) *m/z* 381.52 ([M - H]$^+$). **HR MS** (m/z) for $[C_{26}H_{23}O_3]^+$ calculated $[M+H]^+$ 383.1642, measured $[M+H]^+$ 383.1650. **IR** (cm^{-1}): 3056 (=C-H, stretch), 3026 (=C-H, stretch), 1715 (C=O, stretch), 1666 (C=O, stretch), 1600 (C=C, stretch), 1314 (C-O ester, stretch). **$[\alpha]_D^{19}$** = +60.4 (c = 1.5, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak IC column [hexane/*i*PrOH = 97:3]; flow rate 1.0 mL/min; 254 nm; t_{r1} = 27.3 min, t_{r2} = 30.9 min; 92 % ee.

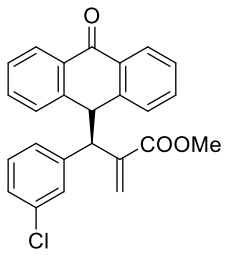
<u>methyl (*R*)-2-((4-chlorophenyl)(10-oxo-9,10-dihydroanthracen-9-yl)methyl)acrylate</u> (290e) (synthesised by Dr Jirí Tauchman)



To a solution of anthrone (1 equiv, 49 mg, 0.25 mmol) in dichloromethane (0.25 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (2 equiv, 165 mg, 0.50 mmol), $(DHQD)_2AQN$ (20 mol%, 43 mg, 0.05 mmol). The reaction was stirred for 7 days at 0 °C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was concentrated in vacuo and purified by column chromatography (20:1 Hexane/EtOAc) to obtain 96 mg of a dark yellow oil. The product yield is 95 % . **^{1}H NMR** (600 MHz, $CDCl_3$): σ 8.16 (d, *J* = 7.5 Hz, 1 H, Ar<u>H</u>), 8.01 (d, *J* = 7.6 Hz, 1 H, Ar<u>H</u>), 7.62 (d, *J* = 7.7 Hz, 1 H, Ar<u>H</u>), 7.56 (td, *J* = 7.4, 1.1 Hz, 1 H, Ar<u>H</u>), 7.52–7.41 (m, 2 H, Ar<u>H</u>), 7.36 (t, *J* = 7.4 Hz, 1 H, Ar<u>H</u>), 7.20 (d, *J* = 7.4 Hz, 1 H, Ar<u>H</u>), 6.94 (d, *J* = 8.4 Hz, 2 H, Ar<u>H</u>), 6.31 (s, 1 H, C=C<u>H</u>$_2$), 6.25

(d, *J* = 8.4 Hz, 2 H, ArH), 5.29 (s, 1 H, C=CH$_2$), 4.94 (d, *J* = 4.8 Hz, 1 H, CH$_2$=C-CH-CH), 4.44 (d, *J* = 4.6 Hz, 1 H, CH$_2$=C-CH-CH), 3.89 (s, 3 H, COOCH$_3$). **^{13}C NMR** (151 MHz, $CDCl_3$): σ 184.3 (q), 167.9 (q), 143.8 (q), 141.1 (q), 140.2 (q), 134.7 (q), 134.0 (q), 133.4 (q), 132.9 (CH), 132.7 (q), 131.8 (CH), 131.3 (CH), 129.3 (CH), 128.5 (CH), 128.4 (CH_2), 128.1 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 58.1 (CH_3), 52.6 (CH), 46.6 (CH). **MS** (ESI+) *m/z* 425 ([M + Na]$^+$). **HR MS** (ESI+) calc. for $[C_{25}H_{19}O_3{}^{35}ClNa]^+$ [M + Na]$^+$ 425.0915, found 425.0915. IR (KBr): 3068, 3028, 2952, 1723, 1665, 1627, 1598, 1491, 1462, 1435, 1359, 1312, 1289, 1242, 1195, 1171, 1148, 1135, 1092, 1015, 964, 932, 847, 815, 785, 726, 689, 633 cm^{-1}. **[α]$_D$** = +54.0 (*c* = 1.0, $CHCl_3$). The enantiomeric excess (90%) was determined by **HPLC** analysis with an IA column (*n*-heptane/*i*-PrOH 80:20, 1 mLmin^{-1}, λ = 190 nm): t_R = 5.8 (major), 6.4 (minor) min.

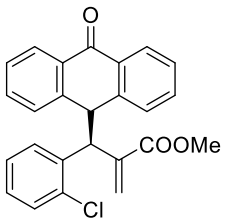
methyl (*R*)-2-((3-chlorophenyl)(10-oxo-9,10-dihydroanthracen-9-yl)methyl)acrylate (290f) (synthesised by Dr Jirí Tauchman)



To a solution of anthrone (1 equiv, 49 mg, 0.25 mmol) in dichloromethane (0.25 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(3-chlorophenyl)methyl)acrylate (2 equiv, 165 mg, 0.50 mmol), $(DHQD)_2AQN$ (20 mol%, 43 mg, 0.05 mmol). The reaction was stirred for 7 days at 0 °C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was concentrated in vacuo and purified by column chromatography (20:1 hexane/EtOAc) to obtain 95 mg of a yellow oil. The product yield is 94 %. **^{1}H NMR** (600 MHz, $CDCl_3$): σ 8.18 (dd, *J* = 7.5, 1.6 Hz, 1 H, ArH), 8.00 (dd, *J* = 7.8, 1.1 Hz, 1 H, ArH), 7.60 (d, *J* = 7.3 Hz, 1 H, ArH), 7.56 (td, *J* = 7.4, 1.3 Hz, 1 H, ArH), 7.51–7.43 (m, 2 H, ArH), 7.37 (td, *J* = 7.5, 1.2 Hz, 1 H, ArH), 7.20 (dd, *J* = 7.3, 0.9 Hz, 1 H, ArH), 7.07 (m, 1 H, ArH), 6.90 (t, *J* = 7.9 Hz, 1 H, ArH), 6.33 (s, 1 H, C=CH$_2$), 6.28 (t, *J* = 1.8 Hz, 1 H, ArH), 6.21 (d, *J* = 7.8 Hz, 1 H, ArH), 5.33 (d, *J* = 1.4 Hz, 1 H, C=CH$_2$), 4.95 (d, *J* = 4.8 Hz, 1 H, CH$_2$=C-CH-CH), 4.43 (d, *J* = 4.7 Hz, 1 H, CH$_2$=C-CH-CH), 3.88 (s, 3 H, COOCH$_3$). **^{13}C NMR** (151 MHz, $CDCl_3$): σ 184.2 (q), 167.8 (q), 143.6 (q), 141.0 (q), 139.7 (q), 138.1 (q), 134.1 (q), 133.73 (q), 132.9 (CH), 132.7 (q), 131.8 (CH), 130.2 (CH), 129.2 (CH), 129.1 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH_2), 127.8 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 58.3 (CH_3), 52.6 (CH), 46.8 (CH). **MS** (ESI+) *m/z* 425 ([M + Na]$^+$). **HR MS** (ESI+) calc. for $[C_{25}H_{19}O_3{}^{35}ClNa]^+$ [M + Na]$^+$ 425.0915, found 425.0915. **IR** (KBr): 3075, 3063, 3025, 2947, 1712, 1673,

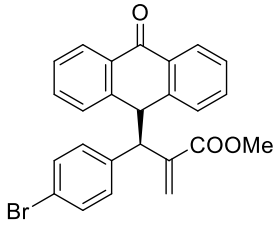
1622, 1598, 1568, 1461, 1434, 1359, 1314, 1266, 1213, 1177, 1156, 1138, 1084, 976, 955, 934, 917, 821, 806, 722, 710, 686, 635 cm^{-1}. **[α]$_D$** = +56.0 (*c* = 1.0, $CHCl_3$). The enantiomeric excess (94%) was determined by **HPLC** analysis with an IA column (*n*-heptane/*i*-PrOH 80:20, 1 $mLmin^{-1}$, λ = 190 nm): t_R = 5.5 (minor), 6.1 (major) min.

<u>methyl (*S*)-2-((2-chlorophenyl)(10-oxo-9,10-dihydroanthracen-9-yl)methyl)acrylate</u> (290g) (synthesised by Dr Jirí Tauchman)



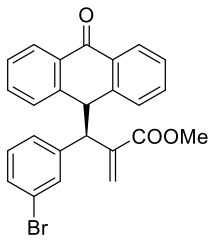
To a solution of anthrone (1 equiv, 49 mg, 0.25 mmol) in dichloromethane (0.25 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(2-chlorophenyl)methyl)acrylate (2 equiv, 165 mg, 0.50 mmol), $(DHQD)_2AQN$ (20 mol%, 43 mg, 0.05 mmol). The reaction was stirred for 7 days at 0 °C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was concentrated in vacuo and purified by column chromatography (20:1 hexane/EtOAc) to obtain 96 mg of a light yellow oil. The product yield is 95 %. **^{1}H NMR** (600 MHz, $CDCl_3$): σ 8.17 (d, *J* = 7.7 Hz, 1 H, Ar<u>H</u>), 8.08 (d, *J* = 7.7 Hz, 1 H, Ar<u>H</u>), 7.53–7.42 (m, 3 H, Ar<u>H</u>), 7.41–7.30 (m, 3 H, Ar<u>H</u>), 7.21 (d, *J* = 7.9 Hz, 1 H, Ar<u>H</u>), 7.09 (td, *J* = 7.6, 1.3 Hz, 1 H, Ar<u>H</u>), 6.96 (t, *J* = 7.6 Hz, 1 H, Ar<u>H</u>), 6.45 (d, *J* = 7.8 Hz, 1 H, Ar<u>H</u>), 6.29 (s, 1 H, C=C<u>H$_2$</u>), 5.37 (d, *J* = 5.0 Hz, 1 H, CH_2=C-CH-C<u>H</u>), 5.18 (s, 1 H, C=C<u>H$_2$</u>), 5.06 (d, *J* = 5.1 Hz, 1 H, CH_2=C-C<u>H</u>-CH), 3.79 (s, 3 H, COOC<u>H$_3$</u>). **^{13}C NMR** (151 MHz, $CDCl_3$) σ 184.7 (q), 167.6 (q), 142.5 (q), 140.0 (q), 139.1 (q), 135.2 (q), 134.7 (q), 134.0 (q), 133.2 (CH), 132.2 (q), 132.0 (CH), 131.1 (CH), 130.0 (CH), 129.5 (CH), 129.1 (CH), 128.9 (CH), 128.6 (CH_2), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.0 (CH), 52.5 (CH_3), 51.6 (CH), 45.8 (CH). **MS** (ESI+) *m/z* 425 ($[M + Na]^+$). **HR MS** (ESI+) calc. for $[C_{25}H_{19}O_3{}^{35}ClNa]^+$ $[M + Na]^+$ 425.0915, found 425.0915. **IR** (KBr): 3071, 3031, 2997, 2950, 1715, 1662, 1624, 1600, 1474, 1462, 1439, 1313, 1288, 1255, 1219, 1189, 1134, 1091, 1038, 991, 962, 934, 814, 761, 753, 740, 705, 690, 667, 636 cm^{-1}. **[α]$_D$** = +59.0 (*c* = 1.0, $CHCl_3$). The enantiomeric excess (94%) was determined by **HPLC** analysis with an IA column (*n*-heptane/*i*-PrOH 95:5, 1 $mLmin^{-1}$, λ = 190 nm): t_R = 7.9 (major), 8.5 (minor) min.

methyl (*R*)-2-((4-bromophenyl)(10-oxo-9,10-dihydroanthracen-9-yl)methyl)acrylate (290h) (synthesised by Dr Jirí Tauchman)



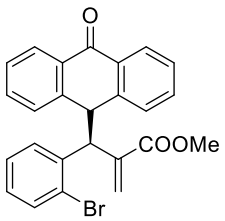
To a solution of anthrone (1 equiv, 49 mg, 0.25 mmol) in dichloromethane (0.25 mol/L) was added methyl 2-((4-bromophenyl)((tert-butoxycarbonyl)oxy)methyl)acrylate (2 equiv, 185 mg, 0.50 mmol), $(DHQD)_2AQN$ (20 mol%, 43 mg, 0.05 mmol). The reaction was stirred for 7 days at 0 °C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was concentrated in vacuo and purified by column chromatography (20:1 hexane/EtOAc) to obtain 106 mg of a yellow oil. The product yield is 95 %. **^{1}H NMR** (600 MHz, $CDCl_3$): σ 8.17 (dd, *J* = 7.7, 1.6 Hz, 1 H, ArH), 8.02 (dd, *J* = 7.7, 1.2 Hz, 1 H, ArH), 7.61 (d, *J* = 7.7 Hz, 1 H, ArH), 7.56 (td, *J* = 7.5, 1.4 Hz, 1 H, ArH), 7.51–7.42 (m, 2 H, ArH), 7.36 (td, *J* = 7.5, 1.1 Hz, 1 H, ArH), 7.20 (d, *J* = 7.4 Hz, 1 H, ArH), 7.14–7.07 (m, 2 H, ArH), 6.30 (s, 1 H, C=CH_2), 6.23–6.17 (m, 2 H, ArH), 5.28 (d, *J* = 1.4 Hz, 1 H, C=CH_2), 4.94 (d, *J* = 4.9 Hz, 1 H, CH_2=C-CH-CH), 4.43 (d, *J* = 4.8 Hz, 1 H, CH_2=C-CH-CH), 3.88 (s, 3 H, COOCH_3). **^{13}C NMR** (151 MHz, $CDCl_3$): σ 184.3 (q), 167.9 (q), 143.8 (q), 141.1 (q), 140.1 (q), 135.3 (q), 134.0 (q), 132.9 (q), 132.7 (CH), 131.8 (q), 131.6 (CH), 131.1 (CH), 129.3 (CH), 128.5 (CH), 128.4 (CH_2), 127.8 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 121.5 (CH), 58.2 (CH_3), 52.6 (CH), 46.6 (CH). **MS** (ESI+) *m/z* 469 ([M + Na]$^+$). **HR MS** (ESI+) calc. for $[C_{25}H_{19}O_3BrNa]^+$ [M + Na]$^+$ 469.0410, found 469.0410. **IR** (KBr): 3065, 3026, 2950, 1716, 1668, 1600, 1488, 1462, 1437, 1407, 1360, 1314, 1293, 1245, 1191, 1171, 1138, 1075, 1010, 952, 932, 815, 767, 720, 688, 635 cm^{-1}. **$[\alpha]_D$** = +56.0 (*c* = 1.0, $CHCl_3$). The enantiomeric excess (93%) was determined by **HPLC** analysis with an IA column (*n*-heptane/*i*-PrOH 80:20, 1 mLmin^{-1}, λ = 196 nm): t_R = 6.0 (minor), 6.6 (major) min.

methyl (*R*)-2-((3-bromophenyl)(10-oxo-9,10-dihydroanthracen-9-yl)methyl)acrylate (290i) (synthesised by Dr Jirí Tauchman)



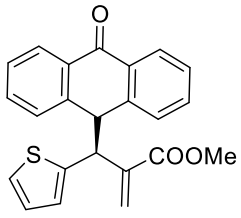
To a solution of anthrone (1 equiv, 49 mg, 0.25 mmol) in dichloromethane (0.25 mol/L) was added methyl 2-((3-bromophenyl)((tert-butoxycarbonyl)oxy)methyl)acrylate (2 equiv, 185 mg, 0.50 mmol), $(DHQD)_2AQN$ (20 mol%, 43 mg, 0.05 mmol). The reaction was stirred for 7 days at 0 °C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was concentrated in vacuo and purified by column chromatography (20:1 hexane/EtOAc) to obtain 91 mg of a yellow oil. The product yield is 81 %. **^{1}H NMR** (600 MHz, $CDCl_3$): σ 8.19 (dd, *J* = 7.7, 1.6 Hz, 1 H, ArH), 8.00 (dd, *J* = 7.7, 1.1 Hz, 1 H, ArH), 7.60 (d, *J* = 7.2 Hz, 1 H, ArH), 7.57 (td, *J* = 7.4, 1.4 Hz, 1 H, ArH), 7.45–7.51 (m, 2 H, ArH), 7.42–7.32 (m, 1 H, ArH), 7.23 (m, 1 H, ArH), 7.20 (dd, *J* = 7.4, 0.9 Hz, 1 H, ArH), 6.84 (t, *J* = 7.8 Hz, 1 H, ArH), 6.41 (t, *J* = 1.7 Hz, 1 H, ArH), 6.33 (s, 1 H, C=CH_2), 6.26 (d, *J* = 7.8 Hz, 1 H, ArH), 5.32 (d, *J* = 1.4 Hz, 1 H, C=CH_2), 4.94 (d, *J* = 4.8 Hz, 1 H, CH_2=C-CH-CH), 4.42 (d, *J* = 4.7 Hz, 1 H, CH_2=C-CH-CH), 3.89 (s, 3 H, COOCH_3). **^{13}C NMR** (151 MHz, $CDCl_3$): σ 184.2 (q), 167.8 (q), 143.6 (q), 141.0 (q), 139.7 (q), 138.4 (q), 134.1 (q), 133.1 (q), 132.9, 132.7 (q), 131.8 (CH), 130.5 (CH), 129.4 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH_2), 127.8 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 121.9 (CH), 58.3 (CH_3), 52.6 (CH), 46.8 (CH). **MS** (ESI+) *m/z* 469 ($[M + Na]^+$). **HR MS** (ESI+) calc. for $[C_{25}H_{19}O_3BrNa]^+$ $[M + Na]^+$ 469.0410, found 469.0411. **IR** (KBr): 3076, 3059, 3026, 2949, 1713, 1671, 1624, 1600, 1561, 1475, 1462, 1434, 1360, 1312, 1300, 1264, 1214, 1159, 1137, 955, 931, 816, 801, 718, 688, 634 cm^{-1}. **$[\alpha]_D$** = –25.7 (*c* = 0.7, $CHCl_3$). The enantiomeric excess (68%) was determined by **HPLC** analysis with an IA column (*n*-heptane/*i*-PrOH 80:20, 1 $mLmin^{-1}$, λ = 190 nm): t_R = 5.6 (major), 6.1 (minor) min.

<u>methyl (*S*)-2-((2-bromophenyl)(10-oxo-9,10-dihydroanthracen-9-yl)methyl)acrylate</u> (290j) (synthesised by Dr Jirí Tauchman)



To a solution of anthrone (1 equiv, 49 mg, 0.25 mmol) in dichloromethane (0.25 mol/L) was added methyl 2-((2-bromophenyl)((tert-butoxycarbonyl)oxy)methyl)acrylate (2 equiv, 185 mg, 0.50 mmol), $(DHQD)_2AQN$ (20 mol%, 43 mg, 0.05 mmol). The reaction was stirred for 7 days at 0 °C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was concentrated in vacuo and purified by column chromatography (20:1 Hexane/EtOAc) to obtain 105 mg of colourless oil. The product yield is 94 %. ^{1}**H NMR** (600 MHz, $CDCl_3$): σ 8.18 (d, *J* = 7.6 Hz, 1 H, Ar<u>H</u>), 8.09 (d, *J* = 7.6 Hz, 1 H, Ar<u>H</u>), 7.58–7.36 (m, 6 H, Ar<u>H</u>), 7.32 (d, *J* = 7.7 Hz, 1 H, Ar<u>H</u>), 7.01 (m, 2 H, Ar<u>H</u>), 6.48 (m, 1 H, Ar<u>H</u>), 6.28 (s, 1 H, C=C<u>H</u>$_2$), 5.35 (d, *J* = 5.2 Hz, 1 H, CH_2=C-CH-C<u>H</u>), 5.19 (s, 1 H, C=C<u>H</u>$_2$), 5.06 (d, *J* = 5.3 Hz, 1 H, CH_2=C-C<u>H</u>-CH), 3.79 (s, 3 H, COOC<u>H</u>$_3$). ^{13}**C NMR** (151 MHz, $CDCl_3$): σ 184.82 (q), 167.59 (q), 142.33 (q), 142.01 (q), 139.19 (q), 136.48 (q), 134.05 (q), 133.46 (q), 133.24 (CH), 132.22 (q), 132.04 (CH), 131.18 (CH), 129.68 (CH), 129.07 (CH), 128.89 (CH), 127.65 (CH_2), 127.54 (CH), 127.22 (CH), 126.97 (CH), 126.65 (CH), 126.44 (CH), 54.43 (CH_3), 52.49 (CH), 45.79 (CH). **MS** (ESI+) *m/z* 469 ($[M + Na]^+$). **HR MS** (ESI+) calc. for $[C_{25}H_{19}O_3BrNa]^+$ $[M + Na]^+$ 469.0410, found 469.0410. **IR** (KBr): 3068, 3032, 3010, 2946, 1715, 1670, 1601, 1467, 1436, 1361, 1315, 1295, 1261, 1194, 1160, 1138, 1021, 955, 944, 932, 813, 789, 758, 737, 717, 689, 661, 636 cm^{-1}. $[\alpha]_D$ = +59.0 (*c* = 1.0, $CHCl_3$). The enantiomeric excess (94%) was determined by **HPLC** analysis with an IA column (*n*-heptane/*i*-PrOH 90:10, 1 $mLmin^{-1}$, λ = 190 nm): t_R = 6.4 (major), 7.0 (minor) min.

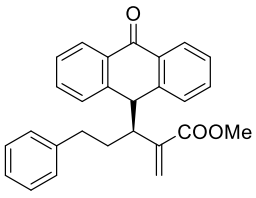
<u>methyl (*S*)-2-((10-oxo-9,10-dihydroanthracen-9-yl)(thiophen-2-yl)methyl)acrylate</u> (290k) (synthesised by Dr Jirí Tauchman)



To a solution of anthrone (1 equiv, 49 mg, 0.25 mmol) in dichloromethane (0.25 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(thiophen-2-yl)methyl)acrylate (2 equiv, 149 mg, 0.50 mmol), $(DHQD)_2AQN$ (20 mol%, 43 mg, 0.05 mmol). The reaction was stirred for 7 days at 0 °C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was concentrated in vacuo and purified by column

chromatography (20:1 hexane/EtOAc) to obtain 87 mg of a yellow oil. The product yield is 93 %. ^{1}**H NMR** (600 MHz, $CDCl_3$): σ 8.19 (dd, *J* = 7.6, 1.5 Hz, 1 H, ArH), 8.04 (dd, *J* = 7.8, 1.2 Hz, 1 H, ArH), 7.63 (d, *J* = 7.7 Hz, 1 H, ArH), 7.57 (td, *J* = 7.5, 1.4 Hz, 1 H, ArH), 7.53–7.45 (m, 2 H, ArH), 7.38 (dt, *J* = 7.5, 1.1 Hz, 1 H, ArH), 7.25 (m, 1 H, ArH), 6.99 (dd, *J* = 5.1, 0.9 Hz, 1 H, ArH), 6.70 (dd, *J* = 5.1, 3.6 Hz, 1 H, ArH), 6.38 (s, 1 H, ArH), 5.90 (d, *J* = 3.4 Hz, 1 H, C=CH_2), 5.37 (d, *J* = 1.1 Hz, 1 H, C=CH_2), 4.88 (d, *J* = 4.3 Hz, 1 H, CH_2=C-CH-CH), 4.85 (d, *J* = 4.2 Hz, 1 H, CH_2=C-CH-CH), 3.89 (s, 3 H, COOCH_3). ^{13}**C NMR** (151 MHz, $CDCl_3$): σ 184.5 (q), 167.6 (q), 143.6 (q), 140.5 (q), 139.6 (q), 138.2 (q), 134.4 (q), 133.1 (CH), 132.8 (q), 131.5 (CH), 129.7 (CH), 129.5 (CH), 128.4 (CH_2), 127.8 (CH), 127.5 (CH), 127.4 (CH), 127.0 (CH), 126.9 (CH), 126.7 (CH), 124.6 (CH), 52.9 (CH_3), 52.6 (CH), 47.6 (CH). **MS** (ESI+) *m/z* 397 ($[M + Na]^+$). **HR MS** (ESI+) calc. for $[C_{23}H_{18}O_3SNa]^+$ $[M + Na]^+$ 397.0869, found 397.0870. **IR** (KBr): 3069, 3030, 2956, 1709, 1666, 1627, 1600, 1463, 1477, 1443, 1314, 1301, 1275, 1264, 1211, 1196, 1170, 1146, 1091, 1045, 988, 951, 933, 846, 817, 771, 702, 635, 569 cm^{-1}. $[\alpha]_D$ = +73.0 (*c* = 1.0, $CHCl_3$). The enantiomeric excess (90%) was determined by **HPLC** analysis with an IA column (*n*-heptane/*i*-PrOH 80:20, 1 $mLmin^{-1}$, λ = 190 nm): t_R = 5.7 (minor), 7.0 (major) min.

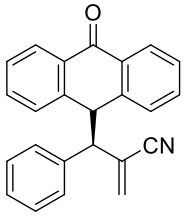
methyl (*S*)-2-methylene-3-(10-oxo-9,10-dihydroanthracen-9-yl)-5-phenylpentanoate (290l)



To a solution of anthrone (1equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added methyl 3-((tert-butoxycarbonyl)oxy)-2-methylene-5-phenylpentanoate (2 equiv, 65 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 °C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 20 mg of a yellow solid. The product yield is 55 %. **Mp** 182 °C. ^{1}**H NMR** (400 MHz, $CDCl_3$) σ 8.21 – 8.10 (m, 2H, ArH), 7.53 – 7.30 (m, 5H, ArH), 7.20 (ddd, *J* = 12.2, 7.2, 2.3 Hz, 2H, ArH), 7.13 – 7.00 (m, 4H, ArH), 6.77 (d, *J* = 6.7 Hz, 2H, ArH), 6.26 (s, 1H, C=CH_2), 4.83 (s, 1H, C=CH_2), 4.31 (d, *J* = 3.5 Hz, 1H, CH_2=C-CH-CH), 3.62 (s, 3H, COOCH_3), 3.22 (ddd, *J* = 11.4, 3.5, 3.3 Hz, 1H, CH_2=C-CH-CH), 2.35 (ddd, *J* = 14.1, 9.6, 4.5 Hz, 1H, CH_2), 2.24 – 2.12 (m, 1H,

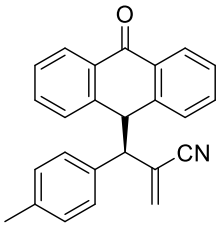
CH_2), 1.53 (m, 1H, CH_2), 1.25 – 1.16 (m, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 185.1 (q), 167.6 (q), 143.1 (q), 141.7 (q), 141.2 (q), 138.9 (q), 133.5 (q), 133.1 (q), 132.5 (CH), 131.7 (CH), 129.3 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.5 (CH_2), 127.3 (CH), 127.2 (CH), 127.1 (CH), 126.7 (CH), 125.9 (CH), 52.0 (CH_3), 49.0 (CH), 46.6 (CH), 33.1 (CH_2), 29.8 (CH_2). **MS** (ESI+) *m/z* 397.26 ([M + H]$^+$).**HR MS** (m/z) for $[C_{27}H_{25}O_3]^+$ calculated $[M+H]^+$ 397.1798, measured $[M+H]^+$ 397.1803. **IR** (cm^{-1}): 3061 (=C-H, stretch), 3026 (=C-H, stretch), 2947 (C-H, stretch), 1715 (C=O, stretch), 1665 (C=O, stretch), 1600 (C=C, stretch), 1314 (C-O ester, stretch). **$[\alpha]_D^{19}$** = +2.1 (c = 1.0, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak IC column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 21.4 min, t_{r2} = 43.5 min; 4 % ee.

(*R*)-2-((10-oxo-9,10-dihydroanthracen-9-yl)(phenyl)methyl)acrylonitrile (290m)



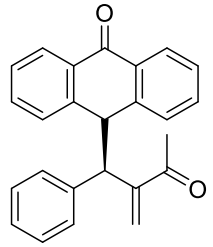
To a solution of anthrone (1 equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added tert-butyl (2-cyano-1-phenylallyl) carbonate (2 equiv, 50 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 26 mg of a beige solid. The product yield is 80 %. **Mp** 181 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.08 (ddd, *J* = 23.2, 7.7, 1.4 Hz, 2H, ArH), 7.61 (ddd, *J* = 14.1, 9.0, 4.5 Hz, 2H, ArH), 7.41 (ddd, *J* = 15.3, 7.8, 1.3 Hz, 2H, ArH), 7.35 (m, 1H, ArH), 7.23 – 7.14 (m, 2H, ArH), 7.07 (dd, *J* = 10.5, 4.8 Hz, 2H, ArH), 6.55 (d, *J* = 7.2 Hz, 2H, ArH), 5.86 (d, *J* = 0.9 Hz, 1H, C=CH_2), 5.41 (d, *J* = 1.4 Hz, 1H, C=CH_2), 4.90 (d, *J* = 6.8 Hz, 1H, CH_2=C-CH-CH), 3.64 (d, *J* = 6.8 Hz, 1H, CH_2=C-CH-CH). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 184.4 (q), 142.7 (q), 140.8 (q), 134.9 (q), 133.6 (CH_2), 133.5 (q), 132.8 (q), 132.6 (CH), 131.8 (CH), 129.1 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 124.2(q), 118.9 (q), 63.2 (CH), 47.8 (CH). **MS** (ESI+) *m/z* 336.24 ([M + H]$^+$). **HR MS** (m/z) for $[C_{24}H_{18}NO]^+$ calculated $[M+H]^+$ 336.1383, measured $[M+H]^+$ 336.1379. **IR** (cm^{-1}): 3064 (=C-H, stretch), 3030 (=C-H, stretch), 2221 (C≡N, stretch), 1665 (C=O, stretch), 1600 (C=C, stretch). **$[\alpha]_D^{19}$** = +1.7 (c = 1.3, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak ID column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 16.7 min, t_{r2} = 18.0 min; 63 % ee.

(*R*)-2-((10-oxo-9,10-dihydroanthracen-9-yl)(*p*-tolyl)methyl)acrylonitrile (290n)



To a solution of anthrone (1 equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added tert-butyl (2-cyano-1-(p-tolyl)allyl) carbonate (2 equiv, 55 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 32 mg of a white solid. The product yield is 92 %. **Mp** 183 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.09 (ddd, *J* = 21.8, 7.7, 1.4 Hz, 2H, ArH), 7.65 (d, *J* = 7.3 Hz, 1H, ArH), 7.59 (ddd, *J* = 8.5, 7.5, 1.2 Hz, 1H, ArH), 7.39 (m, 3H, ArH), 7.24 – 7.17 (m, 1H, ArH), 6.88 (d, *J* = 7.9 Hz, 2H, ArH), 6.45 (d, *J* = 8.1 Hz, 2H, ArH), 5.83 (d, *J* = 0.6 Hz, 1H, C=CH_2), 5.37 (d, *J* = 1.4 Hz, 1H, C=CH_2), 4.87 (d, *J* = 6.8 Hz, 1H, CH_2=C-CH-CH), 3.61 (d, *J* = 6.8 Hz, 1H, CH_2=C-CH-CH), 2.24 (s, 3H, ArCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 184.5 (q), 142.8 (q), 140.9 (q), 137.8 (q), 133.5 (q), 133.4 (CH_2), 132.8 (q), 132.5, 131.9 (q), 131.8 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 127.7 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 124.5 (q), 119.0 (q), 62.9 (CH), 47.7 (CH), 21.1 (CH_3). **MS** (ESI+) *m/z* 350.32 ($[M + H]^+$). **HR MS** (m/z) for $[C_{25}H_{20}NO]^+$ calculated $[M+H]^+$ 350.1539, measured $[M+H]^+$ 350.1547. **IR** (cm^{-1}): 3064 (=C-H, stretch), 3024 (=C-H, stretch), 2220 (C≡N, stretch), 1666 (C=O, stretch), 1600 (C=C, stretch). **$[\alpha]_D^{19}$** = +4.9 (c = 1.6, $CHCl_3$)**.** The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak ID column [hexane/*i*PrOH = 95:5]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 21.6 min, t_{r2} = 23.6 min; 68 % ee.

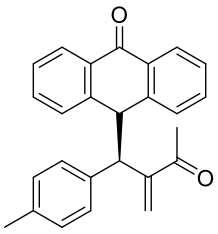
(*R*)-10-(2-methylene-3-oxo-1-phenylbutyl)anthracen-9(10H)-one (290o)



To a solution of anthrone (1 equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added tert-butyl (2-methylene-3-oxo-1-phenylbutyl) carbonate (2 equiv, 55 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1

hexane/EtOAc) to obtain 31 mg of a white solid. The product yield is 88 %. Mp 181 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.15 (dd, *J* = 7.5, 1.6 Hz, 1H, ArH), 8.00 (d, *J* = 7.7 Hz, 1H, ArH), 7.55 – 7.39 (m, 4H, ArH), 7.34 (ddd, *J* = 8.2, 5.9, 2.6 Hz, 1H, ArH), 7.20 – 7.15 (m, 1H, ArH), 7.11 (dd, *J* = 7.3 Hz, 1H, ArH), 7.02 (dd, *J* = 7.5, 7.3 Hz, 2H, ArH), 6.47 (d, *J* = 7.4, 7.2 Hz, 2H, ArH), 6.19 (s, 1H, C=CH_2), 5.51 (d, *J* = 0.8 Hz, 1H, C=CH_2), 4.92 (d, *J* = 4.9 Hz, 1H, CH_2=C-CH-CH), 4.62 (d, *J* = 4.8 Hz, 1H, CH_2=C-CH-CH), 2.39 (s, 3H, COCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 199.7 (q), 184.5 (q), 147.7 (q), 143.7 (q), 141.9 (q), 136.9 (q), 133.9 (q), 133.0 (q), 132.2 (CH), 131.5 (CH), 129.9 (CH), 129.2 (CH_2), 129.0 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 127.1 (CH), 127.08 (CH), 127.0 (CH), 126.6 (CH), 56.3 (CH), 46.9 (CH), 26.5 (CH_3). **MS** (ESI+) *m/z* 353.25 ($[M + H]^+$). **HR MS** (m/z) for $[C_{25}H_{21}O_2]^+$ calculated $[M+H]^+$ 353.1536, measured $[M+H]^+$ 353.1540. **IR** (cm^{-1}): 3064 (=C-H, stretch), 3029 (=C-H, stretch), 1665 (C=O, stretch), 1600 (C=C, stretch). **$[\alpha]_D^{19}$** = +87.2 (c = 1.5, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak ID column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 28.0 min, t_{r2} = 31.6 min; 88 % ee.

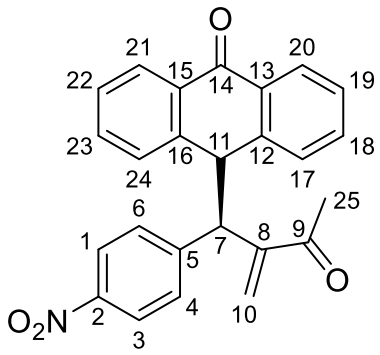
(*R*)-10-(2-methylene-3-oxo-1-(*p*-tolyl)butyl)anthracen-9(10H)-one (290p)



To a solution of anthrone (1 equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added tert-butyl (2-methylene-3-oxo-1-(p-tolyl)butyl) carbonate (2 equiv, 58 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 °C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 33 mg of a white solid. The product yield is 92 %. **Mp** 184 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.16 (dd, *J* = 7.5, 1.6 Hz, 1H, ArH), 8.01 (d, *J* = 7.6 Hz, 1H, ArH), 7.57 – 7.39 (m, 4H, ArH), 7.34 (s, 1H, ArH), 7.19 (d, *J* = 7.4 Hz, 1H, ArH), 6.83 (d, *J* = 7.9 Hz, 2H, ArH), 6.36 (d, *J* = 8.1 Hz, 2H, ArH), 6.17 (s, 1H, C=CH_2), 5.47 (s, 1H, C=CH_2), 4.89 (d, *J* = 4.9 Hz, 1H, CH_2=C-CH-CH), 4.60 (d, *J* = 4.8 Hz, 1H, CH_2=C-CH-CH), 2.38 (s, 3H, COCH_3), 2.21 (s, 3H, ArCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 199.7 (q), 184.6 (q), 148.0 (q), 143.9 (q), 142.1 (q), 136.7 (q), 133.9 (q), 133.9 (q), 133.0 (q), 132.2 (CH), 131.5 (CH), 129.7 (CH), 129.1 (CH_2), 129.0 (CH), 128.6 (CH), 128.6 (CH), 127.3 (CH), 127.0 (CH), 127.0 (CH), 126.7 (CH), 55.9 (CH), 46.9 (CH), 26.5 (CH_3), 21.0 (CH_3). **MS** (ESI+) *m/z* 367.33 ($[M + H]^+$). **HR MS** (m/z) for $[C_{26}H_{23}O_2]^+$ calculated $[M+H]^+$ 367.1693, measured $[M+H]^+$ 367.1690. **IR** (cm^{-1}):

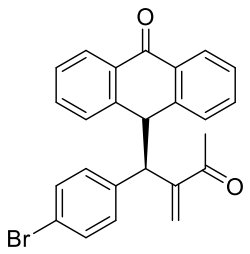
3064 (=C-H, stretch), 3027 (=C-H, stretch), 1665 (C=O, stretch), 1600 (C=C, stretch). $[\alpha]_D^{19}$ = +32.0 (c = 1.6, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak IA column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 8.5 min, t_{r2} = 12.6 min; 86 % ee.

(*R*)-10-(2-methylene-1-(4-nitrophenyl)-3-oxobutyl)anthracen-9(10H)-one (290q)



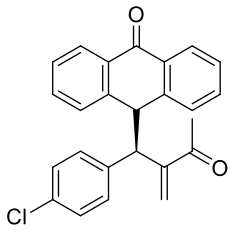
To a solution of anthrone (1 equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added tert-butyl (2-methylene-1-(4-nitrophenyl)-3-oxobutyl) carbonate (2 equiv, 64 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 °C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 33 mg of a beige solid. The product yield is 92 %. **Mp** 182 °C. ^{1}**H NMR** (400 MHz, $CDCl_3$) σ 8.23 – 8.09 (m, 1H, Ar<u>H</u>, **C20**), 8.02 (d, *J* = 7.7 Hz, 1H, Ar<u>H</u>, **C21**), 7.88 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>, **C1**, **C3**), 7.58 – 7.50 (m, 2H, Ar<u>H</u>, **C19**, **C22**), 7.50 – 7.42 (m, 2H, Ar<u>H</u>, **C18**, **C23**), 7.41 – 7.33 (m, 1H, Ar<u>H</u>, **C17**), 7.19 – 7.08 (m, 1H, Ar<u>H</u>, **C24**), 6.68 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>, **C4**, **C6**), 6.23 (s, 1H, C=C<u>H</u>$_2$, **C10**), 5.47 (s, 1H, C=C<u>H</u>$_2$, **C10**), 4.96 (d, *J* = 5.4 Hz, 1H, CH_2=C-CH-C<u>H</u>, **C11**), 4.66 (d, *J* = 5.3 Hz, 1H, CH_2=C-C<u>H</u>-CH, **C7**), 2.41 (s, 3H, COC<u>H</u>$_3$, **C25**). ^{13}**C NMR** (101 MHz, $CDCl_3$) σ 199.2 (q, **C9**), 184.3 (q, **C14**), 146.9 (q, **C5**), 145.0 (q, **C2**), 143.0 (q, **C13**), 141.1 (q, **C15**), 133.7 (q, **C12**), 132.8 (q, **C16**), 132.6 (**C21**), 131.8 (**C20**), 130.6 (**C4**, **C6**), 129.4 (CH_2, **C10**), 128.9 (**C23**), 128.3 (**C24**), 127.8 (**C17**), 127.6 (**C18**), 127.4 (**C19**), 127.1 (**C22**), 123.0 (**C1**, **C3**), 56.9 (**C11**), 46.5 (**C7**), 26.5 (**C25**). **MS** (ESI+) *m/z* 398.32 ([M + H]$^+$). **HR MS** (m/z) for $[C_{25}H_{20}NO_4]^+$ calculated $[M+H]^+$ 398.1387, measured $[M+H]^+$ 398.1391. **IR** (cm^{-1}): 3071 (=C-H, stretch), 3029 (=C-H, stretch), 1665 (C=O, stretch), 1600 (C=C, stretch), 1520 (N-O, asymmetric stretch), 1346 (N-O, symmetric stretch). $[\alpha]_D^{19}$ = +51.0 (c = 1.6, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak IE column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 37.1 min, t_{r2} = 41.5 min; 85 % ee.

(*R*)-10-(1-(4-bromophenyl)-2-methylene-3-oxobutyl)anthracen-9(10H)-one (290r)



To a solution of anthrone (1 equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added 1-(4-bromophenyl)-2-methylene-3-oxobutyl tert-butyl carbonate (2 equiv, 71 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 35 mg of a yellow solid. The product yield is 83 %. **Mp** 185 ˚C. ^{1}**H NMR** (400 MHz, $CDCl_3$) σ 8.17 (dd, *J* = 7.4, 1.7 Hz, 1H, ArH), 8.04 (d, *J* = 7.7 Hz, 1H, ArH), 7.50 (dd, *J* = 7.7, 2.5 Hz, 2H, ArH), 7.48 – 7.41 (m, 2H, ArH), 7.37 (ddd, *J* = 8.2, 5.2, 3.3 Hz, 1H, ArH), 7.20 – 7.10 (m, 3H, ArH), 6.38 (d, *J* = 8.4 Hz, 2H, ArH), 6.18 (s, 1H, C=CH_2), 5.43 (s, 1H, C=CH_2), 4.90 (d, *J* = 5.1 Hz, 1H, CH_2=C-CH-CH), 4.55 (d, *J* = 5.1 Hz, 1H, CH_2=C-CH-CH), 2.38 (s, 3H, $COCH_3$). ^{13}**C NMR** (101 MHz, $CDCl_3$) σ 199.5 (q), 184.4 (q), 147.5 (q), 143.4 (q), 141.7 (q), 136.3 (q), 133.7 (q), 132.9 (q), 132.3 (CH), 131.7 (CH), 131.4 (CH), 131.1 (CH), 129.2 (CH_2), 129.0 (CH), 128.5 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 121.2 (q), 56.1 (CH), 46.6 (CH), 26.5 (CH_3). **MS** (ESI+) *m/z* 431.30 ($[M + H]^+$). **HR MS** (m/z) for $[C_{25}H_{20}BrO_2]^+$ calculated $[M+H]^+$ 431.0641, measured $[M+H]^+$ 431.0635. **IR** (cm^{-1}): 3066 (=C-H, stretch), 3027 (=C-H, stretch), 1665 (C=O, stretch), 1600 (C=C, stretch). $[\alpha]_D^{19}$ = +51.1 (c = 1.7, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak IC column [hexane/*i*PrOH = 95:5]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 24.0 min, t_{r2} = 27.2 min; 92 % ee.

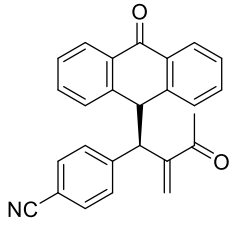
(*R*)-10-(1-(4-chlorophenyl)-2-methylene-3-oxobutyl)anthracen-9(10H)-one (290s)



To a solution of anthrone (1equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added tert-butyl (1-(4-chlorophenyl)-2-methylene-3-oxobutyl) carbonate (2 equiv, 62 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain

29 mg of a beige solid. The product yield is 76 %. **Mp** 181 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.17 (dd, *J* = 7.4, 1.7 Hz, 1H, Ar<u>H</u>), 8.03 (d, *J* = 7.7 Hz, 1H, Ar<u>H</u>), 7.52 (d, *J* = 3.7 Hz, 2H, Ar<u>H</u>), 7.45 (m, 2H, Ar<u>H</u>), 7.37 (m, 1H, Ar<u>H</u>), 7.19 – 7.12 (m, 1H, Ar<u>H</u>), 7.04 – 6.96 (m, 2H, Ar<u>H</u>), 6.42 (d, *J* = 8.5 Hz, 2H, Ar<u>H</u>), 6.18 (s, 1H, C=C<u>H</u>$_2$), 5.43 (s, 1H, C=C<u>H</u>$_2$), 4.90 (d, *J* = 5.2 Hz, 1H, CH_2=C-CH-C<u>H</u>), 4.56 (d, *J* = 5.0 Hz, 1H, CH_2=C-C<u>H</u>-CH), 2.39 (s, 3H, COC<u>H</u>$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 199.5 (q), 184.4 (q), 147.6 (q), 143.5 (q), 141.7 (q), 135.7 (q), 133.8 (q), 133.0 (q), 132.9 (q), 132.4 (CH), 131.6 (CH), 131.1 (CH), 129.2 (CH_2), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 56.1 (CH), 46.7 (CH), 26.5 (CH_3). **MS** (ESI+) *m/z* 387.25 ($[M + H]^+$). **HR MS** (m/z) for $[C_{25}H_{20}{}^{35}ClO_2]^+$ calculated $[M+H]^+$ 387.1146, measured $[M+H]^+$ 387.1150. **IR** (cm^{-1}): 3067 (=C-H, stretch), 3027 (=C-H, stretch), 1665 (C=O, stretch), 1600 (C=C, stretch). **$[\alpha]_D^{19}$** = +68.4 (c = 1.5, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak ID column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 24.0 min, t_{r2} = 29.4 min; 90 % ee.

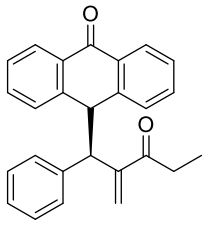
<u>(*R*)-4-(2-methylene-3-oxo-1-(10-oxo-9,10-dihydroanthracen-9-yl)butyl)benzonitrile</u> (290t)



To a solution of anthrone (1equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added tert-butyl (1-(4-cyanophenyl)-2-methylene-3-oxobutyl) carbonate (2 equiv, 60 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 32 mg of an orange solid. The product yield is 85 %. **Mp** 182 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.20 – 8.13 (m, 1H, Ar<u>H</u>), 8.03 (d, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 7.56 – 7.42 (m, 4H, Ar<u>H</u>), 7.41 – 7.35 (m, 1H, Ar<u>H</u>), 7.32 (d, *J* = 8.3 Hz, 2H, Ar<u>H</u>), 7.16 – 7.08 (m, 1H, Ar<u>H</u>), 6.63 (d, *J* = 8.3 Hz, 2H, Ar<u>H</u>), 6.21 (s, 1H, C=C<u>H</u>$_2$), 5.45 (s, 1H, C=C<u>H</u>$_2$), 4.94 (d, *J* = 5.4 Hz, 1H, CH_2=C-CH-C<u>H</u>), 4.59 (d, *J* = 5.3 Hz, 1H, CH_2=C-C<u>H</u>-CH), 2.40 (s, 3H, COC<u>H</u>$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 199.3 (q), 184.3 (q), 146.9 (q), 143.1 (q), 142.9 (q), 141.2 (q), 133.7 (q), 132.8 (q), 132.5 (CH), 131.8 (CH), 131.7 (CH), 130.5 (CH), 129.3 (CH_2), 129.0 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 127.1 (CH), 118.5 (q), 111.1 (q), 57.1 (CH), 46.5

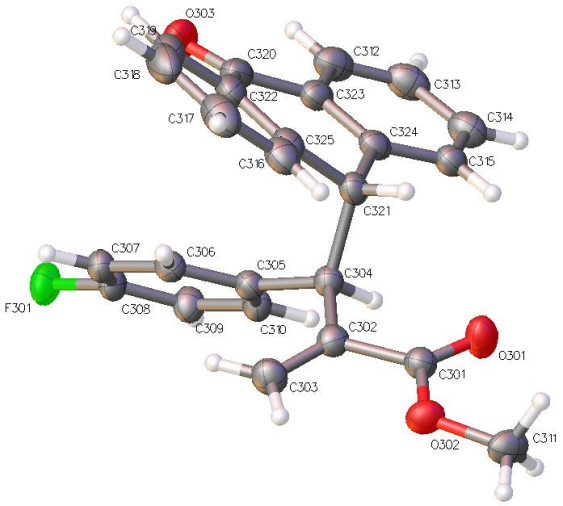
(CH), 26.5 (CH_3). **MS** (ESI+) *m/z* 378.30 ($[M + H]^+$). **HR MS** (m/z) for $[C_{26}H_{19}NO_2]^+$ calculated $[M+H]^+$ 378.1489, measured $[M+H]^+$ 378.1483. **IR** (cm^{-1}): 3068 (=C-H, stretch), 3029 (=C-H, stretch), 2228 (C≡N, stretch), 1665 (C=O, stretch), 1600 (C=O, stretch). $[\alpha]_D^{19}$ = +46.2 (c = 1.6, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak IE column [hexane/*i*PrOH = 70:30]; flow rate 0.5 mL/min; 254 nm; t_{r1}= 52.2 min, t_{r2} = 54.0 min; 79 % ee.

(*R*)-10-(2-methylene-3-oxo-1-phenylpentyl)anthracen-9(10H)-one (290u)



To a solution of anthrone (1 equiv, 19 mg, 0.1 mmol) in dichloromethane (0.1 mol/L) was added tert-butyl (2-methylene-3-oxo-1-phenylpentyl) carbonate (2 equiv, 58 mg, 0.2 mmol), $(DHQD)_2AQN$ (20 mol%, 14 mg, 0.02 mmol). The reaction was stirred for 5 days at 0 ˚C. The reaction was followed by NMR until the disappearance of starting material. The reaction mixture was purified by column chromatography (20:1 hexane/EtOAc) to obtain 29 mg of a beige solid. The product yield is 81 %. **Mp** 183 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.15 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar<u>H</u>), 8.00 (d, *J* = 7.6 Hz, 1H, Ar<u>H</u>), 7.60 – 7.38 (m, 5H, Ar<u>H</u>), 7.38 – 7.31 (m, 1H, Ar<u>H</u>), 7.18 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.11 (dd, *J* = 7.3, 7.2 Hz, 1H, Ar<u>H</u>), 7.02 (dd, *J* = 7.5, 7.3 Hz, 2H, Ar<u>H</u>), 6.48 (d, *J* = 7.6 Hz, 2H, Ar<u>H</u>), 6.18 (s, 1H, C=C<u>H</u>$_2$), 5.46 (s, 1H, C=C<u>H</u>$_2$), 4.92 (d, *J* = 4.9 Hz, 1H, CH_2=C-CH-C<u>H</u>), 4.64 (d, *J* = 4.8 Hz, 1H, CH_2=C-CH-C<u>H</u>), 2.81 (dt, *J* = 10.9, 7.3 Hz, 1H, COC<u>H</u>$_2$CH$_3$), 2.69 (dt, *J* = 10.1, 7.3 Hz, 1H, COC<u>H</u>$_2$CH$_3$), 1.12 (t, *J* = 7.3 Hz, 3H, COCH$_2$C<u>H</u>$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 202.5 (q), 184.5 (q), 147.3 (q), 143.8 (q), 142.0 (q), 137.1 (q), 133.9 (q), 133.0 (q), 132.2 (CH), 131.5 (CH), 129.9 (CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH_2), 127.3 (CH), 127.1 (CH), 127.0 (CH), 126.9 (CH), 126.6 (CH), 56.7 (CH), 47.0 (CH), 31.4 (CH_2), 8.5 (CH_3). **MS** (ESI+) *m/z* 367.16 ($[M + H]^+$). **HR MS** (m/z) for $[C_{26}H_{22}O_2]^+$ calculated $[M+H]^+$ 367.1693, measured $[M+H]^+$ 367.1701. **IR** (cm^{-1}): 3064 (=C-H, stretch), 3027 (=C-H, stretch), 2978 (C-H, stretch), 2937 (C-H, stretch), 1716 (C=O, stretch), 1665 (C=O, stretch), 1600 (C=C, stretch). $[\alpha]_D^{19}$ = +47.2 (c = 1.5, $CHCl_3$). The enantiomeric excess was determined by **HPLC** analysis using a Chiralpak ID column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; 254 nm; t_{r1}= 22.7 min, t_{r2} = 28.4 min; 98 % ee.

X-Ray single crystal analysis of the product of 290b



Displacement ellipsoids – 50% probability level

Experimental

Single crystals of $C_{25}H_{19}FO_3$ **[290b]**. A suitable crystal was selected and Mitegen mount on a Rigaku AFC11 007-HF diffractometer. The crystal was kept at 100(2) K during data collection. Using Olex2 [Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341], the structure was solved with the ShelXT [Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

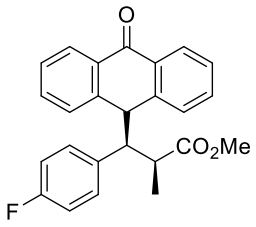
Crystal structure determination of [290b]

Crystal Data for $C_{25}H_{19}FO_3$ (M =386.40 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 11.07781(8) Å, b = 12.29676(10) Å, c = 42.1557(3) Å, V = 5742.50(8) Å^3, Z = 12, T = 100(2) K, μ(CuKα) = 0.767 mm^{-1}, *Dcalc* = 1.341 g/cm^3, 77409 reflections measured (4.192° ≤ 2Θ ≤ 137.932°), 10586 unique (R_{int} = 0.0403, R_{sigma} = 0.0152) which were used in all calculations. The final R_1 was 0.0319 (I > 2σ(I)) and wR_2 was 0.0832 (all data).

Crystal data and structure refinement for 290b.	
Identification code	2015vc001 (cv7499-67C)
Empirical formula	$C_{25}H_{19}FO_3$
Formula weight	386.40
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	11.07781(8)
b/Å	12.29676(10)
c/Å	42.1557(3)
α/°	90
β/°	90
γ/°	90
Volume/Å³	5742.50(8)
Z	12
ρ_{calc}g/cm³	1.341
μ/mm⁻¹	0.767
F(000)	2424.0
Crystal size/mm³	0.2 × 0.15 × 0.12
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	4.192 to 137.932
Index ranges	$-13 \leq h \leq 13$, $-14 \leq k \leq 14$, $-51 \leq l \leq 49$
Reflections collected	77409
Independent reflections	10586 [R_{int} = 0.0403, R_{sigma} = 0.0152]
Data/restraints/parameters	10586/0/788
Goodness-of-fit on F²	1.076
Final R indexes [I>=2σ (I)]	R_1 = 0.0319, wR_2 = 0.0829
Final R indexes [all data]	R_1 = 0.0323, wR_2 = 0.0832
Largest diff. peak/hole / e Å⁻³	0.20/-0.18
Flack parameter	0.00(3)

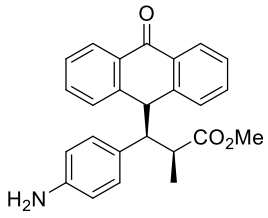
4.3.3 Hydrogenation reaction

methyl (*2S,3S*)-3-(4-fluorophenyl)-2-methyl-3-(10-oxo-9,10-dihydroanthracen-9-yl)propanoate (299b)



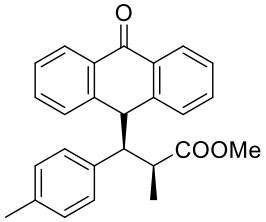
In a 2-neck round-bottom flask (RBF) methyl (R)-2-((4-fluorophenyl)(10-oxo-9,10-dihydroanthracen-9-yl)methyl)acrylate (1.0 equiv, 20 mg, 0.052 mmol) was added together with Pd/C (0.15 equiv w/w, 3 mg). EtOAc (1 ml, 0.052 mol/L) was added. The RBF was sealed and flushed twice with argon. Then the reaction mixture was flushed once with H_2. The rubber balloon was refilled with H_2 and connected to the RBF. The reaction was monitored by TLC until the reaction completion (3 days). The mixture was filtered through celite, washed with EtOAc and concentrated in vacuo. The mixture was purified by column chromatography (10:1 hexane: EtOAc) to obtain 18 mg of a yellow solid. The product yield is 90 %. **Mp** 186 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.01 (dd, *J* = 8.0, 1.3 Hz, 1H, ArH), 7.92 (d, *J* = 6.9 Hz, 1H, ArH), 7.62 (ddd, *J* = 11.7, 9.5, 4.3 Hz, 3H, ArH), 7.47 (t, *J* = 7.0 Hz, 2H, ArH), 7.43 – 7.35 (m, 1H, ArH), 6.46 (dd, *J* = 8.7 Hz, 2H, ArH), 5.76 (dd, *J* = 8.6, 5.4 Hz, 2H, ArH), 4.74 (d, *J* = 3.0 Hz, 1H, CH_3-CH-CH-CH), 3.30 – 3.23 (dd, J = 11.3, 3.1 Hz, 1H, CH_3-CH-CH-CH), 3.26 (s, 3H, $COOCH_3$), 3.15 - 3.05 (m, 1H, CH_3-CH-CH-CH), 1.79 (d, *J* = 6.7 Hz, 3H, CH_3-CH-CH-CH). **^{19}F NMR** (376 MHz, $CDCl_3$) σ -114.79. **^{13}C NMR** (101 MHz, $CDCl_3$) σ 183.1 (q), 175.3 (q), 144.2 and 140.0 (q, d, J_{CF} = 298.0 Hz), 134.7 (q), 133.6 (q), 132.7, 131.9, 131.2 (q), 131.2 (q), 127.9 (CH), 127.9 (CH), 127.7 (CH), 127.2 (CH), 127.1 (CH), 126.4 (CH), 114.1 (CH), 113.9 (CH), 59.0 (CH_3), 51.5 (CH), 43.8 (CH), 42.2 (CH), 17.3 (CH_3). **MS** (ESI+) *m/z* 389.24 ($[M + H]^+$). **HR MS** (m/z) for $[C_{25}H_{22}FO_3]^+$ calculated $[M+H]^+$ 389.1547, measured $[M+H]^+$ 389.1544. **IR** (cm^{-1}): 1735 (C=O, stretch), 1668 (C=O, stretch), 1314 (C-O ester, stretch), 1166 (C-F, stretch), 931, 836, 754, 722, 693. **$[\alpha]_D^{21}$** = -6.1 (c = 1.0, $CHCl_3$).

methyl (*2S,3S*)-3-(4-aminophenyl)-2-methyl-3-(10-oxo-9,10-dihydroanthracen-9-yl)propanoate (299c)



In a 2-neck round-bottom flask (RBF) methyl (R)-2-((4-aminophenyl)(10-oxo-9,10-dihydroanthracen-9-yl)methyl)acrylate (1.0 equiv, 20 mg, 0.054 mmol) was added together with Pd/C (0.15 equiv w/w, 3 mg). EtOAc (1 ml, 0.054 mol/L) was added. The RBF was sealed and flushed twice with argon. Then the reaction mixture was flushed once with H_2. The rubber balloon was refilled with H_2 and connected to the RBF. The reaction was monitored by TLC until the reaction completion (overnight). The mixture was filtered through celite, washed with EtOAc and concentrated in vacuo. The mixture was purified by column chromatography (5:1 hexane: EtOAc) to obtain 18 mg of a brown oil. The product yield is 60 %. ^{1}**H NMR** (400 MHz, $CDCl_3$) σ 8.02 – 7.96 (m, 1H, Ar<u>H</u>), 7.91 (d, *J* = 7.1 Hz, 1H, Ar<u>H</u>), 7.64 – 7.53 (m, 3H, Ar<u>H</u>), 7.47 – 7.41 (m, 2H, Ar<u>H</u>), 7.37 (dd, *J* = 10.8, 4.0 Hz, 1H, Ar<u>H</u>), 6.09 (d, *J* = 8.4 Hz, 2H, Ar<u>H</u>), 5.55 (d, *J* = 8.4 Hz, 2H, Ar<u>H</u>), 4.71 (d, *J* = 2.9 Hz, 1H, CH_3-CH-CH-C<u>H</u>), 3.27 (s, 3H, COOC<u>H</u>$_3$), 3.15 (dd, *J* = 11.6, 3.0 Hz, 1H, CH_3-CH-C<u>H</u>-CH), 3.09 – 3.00 (m, 1H, CH_3-C<u>H</u>-CH-CH), 1.76 (d, *J* = 6.6 Hz, 3H, C<u>H</u>$_3$-CH-CH-CH). ^{13}**C NMR** (101 MHz, $CDCl_3$) σ 195.4 (q), 175.5 (q), 144.7 (q), 144.6 (q), 143.8 (q), 140.6 (q), 134.9 (q), 132.4 (CH), 131.6 (CH), 130.2 (CH), 129.3 (q), 127.9 (CH), 127.8 (CH), 127.4 (CH), 126.9 (CH), 126.8 (CH), 126.2 (CH), 113.9 (CH), 59.2 (CH_2), 51.4 (CH), 44.2 (CH), 42.2 (CH), 17.3 (CH_3). **HR MS** (m/z) for $[C_{25}H_{23}NO_3Na]^+$ calculated $[M+Na]^+$ 408.1570, measured $[M+Na]^+$ 408.1572. **IR** (cm^{-1}): 3420 and 3365 (NH_2, stretch), 1733 (C=O, stretch), 1665 (C=O, stretch), 1315 (C-O ester, stretch), 1195, 1168, 932, 756, 695. $[\alpha]_D^{21}$ = -6.4 (c = 1.0, $CHCl_3$).

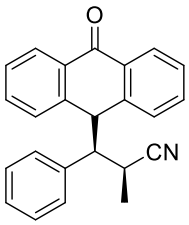
methyl (*2S,3S*)-2-methyl-3-(10-oxo-9,10-dihydroanthracen-9-yl)-3-(*p*-tolyl)propanoate (299d)



In a 2-neck round-bottom flask (RBF) methyl (R)-2-((10-oxo-9,10-dihydroanthracen-9-yl)(p-tolyl)methyl)acrylate (1.0 equiv, 25 mg, 0.065 mmol) was added together with Pd/C (0.15 equiv w/w, 3 mg). EtOAc (1 ml, 0.065 mol/L) was added. The RBF was sealed and flushed twice with argon. Then the reaction mixture was flushed once with H_2. The rubber balloon was refilled with H_2 and connected to the RBF. The reaction was monitored by TLC

until the reaction completion (2 days). The mixture was filtered through celite, washed with EtOAc and concentrated in vacuo. The mixture was purified by column chromatography (5:1 Hexane: EtOAc) to obtain 18 mg of a beige solid. The product yield is 72 %. **Mp** 184 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 7.99 (dd, *J* = 8.3, 1.2 Hz, 1H, ArH), 7.90 (d, *J* = 7.7 Hz, 1H, ArH), 7.66 – 7.55 (m, 3H, ArH), 7.44 (dd, *J* = 11.4, 4.3 Hz, 2H, ArH), 7.41 – 7.34 (m, 1H, ArH), 6.55 (d, *J* = 7.9 Hz, 2H, ArH), 5.68 (d, *J* = 8.1 Hz, 2H, ArH), 4.73 (d, *J* = 3.1 Hz, 1H, CH_3-CH-CH-CH), 3.29 – 3.20 (m, 4H, CH_3-CH-CH-CH and $COOCH_3$), 3.12 (dd, *J* = 11.6, 6.6 Hz, 1H, CH_3-CH-CH-CH), 2.12 (s, 3H, $ArCH_3$), 1.78 (d, *J* = 6.6 Hz, 3H, CH_3-CH-CH-CH). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 183.2 (q), 175.5 (q), 144.5 (q), 140.5 (q), 136.6 (q), 134.7 (q), 133.7 (q), 132.5 (CH), 132.2 (CH), 131.7 (CH), 129.0 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.0 (CH), 126.9 (CH), 126.3 (CH), 59.5 (CH_3), 51.4 (CH), 43.9 (CH), 42.2 (CH), 21.0 (CH_3), 17.3 (CH_3). **MS** (m/z) for $C_{26}H_{24}O_3$ $[M+H]^+$ 385.32. **HR MS** (m/z) for $[C_{26}H_{24}O_3Na]^+$ calculated $[M+Na]^+$ 407.1618, measured $[M+Na]^+$ 407.1615. **IR** (cm^{-1}): 3062 (=C-H aromatic, stretch), 2949 (=C-H aromatic, stretch), 1668 (C=O, stretch), 1164, 1100, 1055, 931. **$[\alpha]_D^{21}$** = -11.5 (c = 1.0, $CHCl_3$).

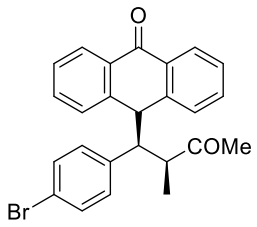
(*2S,3S*)-2-methyl-3-(10-oxo-9,10-dihydroanthracen-9-yl)-3-phenylpropanenitrile (299m)



In a 2-neck round-bottom flask (RBF) (R)-2-((10-oxo-9,10-dihydroanthracen-9-yl)(phenyl)methyl)acrylonitrile (1.0 equiv, 25 mg, 0.074 mmol) was added together with Pd/C (0.15 equiv w/w, 3 mg). EtOAc (1 ml, 0.074 mol/L) was added. The RBF was sealed and flushed twice with argon. Then the reaction mixture was flushed once with H_2. The rubber balloon was refilled with H_2 and connected to the RBF. The reaction was monitored by TLC until the reaction completion (2 days). The mixture was filtered through celite, washed with EtOAc and concentrated in vacuo. The mixture was purified by column chromatography (5:1 Hexane: EtOAc) to obtain 16 mg of a beige solid. The product yield is 68 %. **Mp** 183 ˚C. **Dr** is 8:1. **^{1}H NMR** (400 MHz, $CDCl_3$) σ 8.09 (ddd, *J* = 27.9, 7.7, 0.9 Hz, 2H, ArH), 7.82 (d, *J* = 7.6 Hz, 1H, ArH), 7.65 (td, *J* = 7.5, 1.3 Hz, 1H, ArH), 7.50 (t, *J* = 7.1 Hz, 1H, ArH), 7.32 (dd, *J* = 11.0, 4.1 Hz, 1H, ArH), 7.24 – 7.16 (m, 2H, ArH), 7.12 (t, *J* = 7.6 Hz, 2H, ArH), 6.78 (dd, *J* = 20.3, 7.4 Hz, 3H, ArH), 4.57 (d,

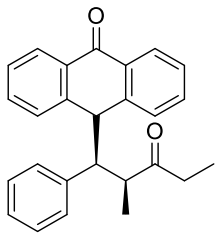
J = 8.4 Hz, 1H, CH_3-CH-CH-C<u>H</u>), 2.80 (m, 1H, CH_3-C<u>H</u>-CH-CH), 2.57 (dd, *J* = 8.3, 6.6 Hz, 1H, CH_3-CH-C<u>H</u>-CH), 1.20 (d, *J* = 7.0 Hz, 3H, C<u>H</u>$_3$-CH-CH-CH). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 185.0 (q), 142.9 (q), 142.0 (q), 136.4 (q), 133.2 (q), 132.5 (CH), 131.4 (CH), 129.0 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.7 (q), 127.5 (CH), 127.4 (CH), 122.0 (q), 61.3 (CH), 47.5(CH), 28.8 (CH), 17.3 (CH_3). **MS** (ESI+) *m/z* 338.24 ($[M + H]^+$). **HR MS** (m/z) for $[C_{24}H_{20}NO]^+$ calculated $[M+H]^+$ 338.1539, measured $[M+H]^+$ 338.1538. **IR** (cm^{-1}): 3066 and 3031 (C=CH aromatic, stretch), 2244 (C≡N, stretch), 1668 (C=O, stretch), 1170, 966, 709. **[α]$_D^{21}$** = -8.0 (c = 1.0, $CHCl_3$).

<u>10-((*1S,2S*)-1-(4-bromophenyl)-2-methyl-3-oxobutyl)anthracen-9(10H)-one</u> (299r)



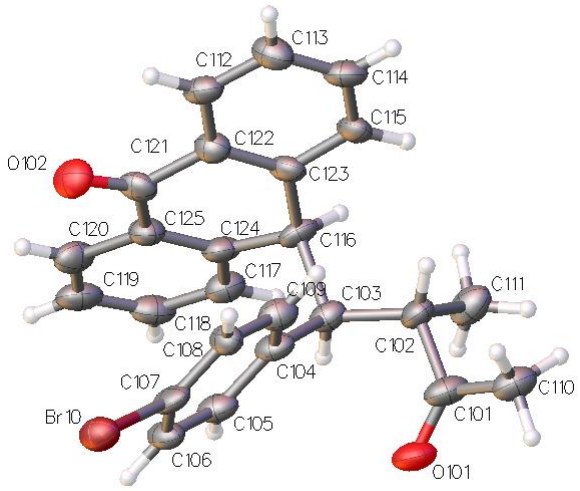
In a 2-neck round-bottom flask (RBF) (R)-10-(1-(4-bromophenyl)-2-methylene-3-oxobutyl)anthracen-9(10H)-one (4r) (1.0 equiv, 25 mg, 0.058 mmol) was added together with Pd/C (0.15 equiv w/w, 3 mg). EtOAc (1 ml, 0.058 mol/L) was added. The RBF was sealed and flushed twice with argon. Then the reaction mixture was flushed once with H_2. The rubber balloon was refilled with H_2 and connected to the RBF. The reaction was monitored by TLC until the reaction completion (2 days). The mixture was filtered through celite, washed with EtOAc and concentrated in vacuo. The mixture was purified by column chromatography (5:1 Hexane:EtOAc) to obtain 22 mg of awhite solid. The product yield is 88 %. **Mp** 185 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.6 Hz, 1H, Ar<u>H</u>), 7.93 (d, *J* = 7.8 Hz, 1H, Ar<u>H</u>), 7.64 (t, *J* = 7.4 Hz, 2H, Ar<u>H</u>), 7.57 (d, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 7.49 (dd, *J* = 12.3, 7.4 Hz, 2H, Ar<u>H</u>), 7.40 (t, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 6.89 (d, *J* = 8.3 Hz, 2H, Ar<u>H</u>), 5.65 (d, *J* = 8.2 Hz, 2H, Ar<u>H</u>), 4.74 (d, *J* = 1.3 Hz, 1H, CH_3-CH-CH-C<u>H</u>), 3.23 (m, 2H, CH_3-C<u>H</u>-C<u>H</u>-CH), 1.81 (s, 3H, COC<u>H</u>$_3$), 1.71 (d, *J* = 6.1 Hz, 3H, C<u>H</u>$_3$-CH-CH-CH). **^{13}C NMR** (101 MHz, $CDCl_3$) σ 210.5 (q), 183.0 (q), 144.0 (q), 140.1 (q), 134.9 (q), 134.7 (q), 133.5 (q), 132.8 (CH), 131.9 (CH), 130.7 (q), 130.4 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 127.2 (CH), 126.5 (CH), 121.4 (CH), 58.7 (CH_3), 48.5 (CH), 43.7 (CH), 29.3 (CH), 16.8 (CH_3). **MS** (ESI+) *m/z* 433.18 ($[M + H]^+$). **HR MS** (m/z) for $[C_{25}H_{21}BrO_2]^+$ calculated $[M+H]^+$ 433.0798, measured $[M+H]^+$ 433.0806. **IR** (cm^{-1}): 3066 (=C-H aromatic, stretch), 3027 (=C-H aromatic, stretch), 1667 (C=O, stretch), 1156, 1073, 1010, 931. **[α]$_D^{21}$** = -9.2 (c = 1.0, $CHCl_3$).

10-((*1S,2S*)-2-methyl-3-oxo-1-phenylpentyl)anthracen-9(10H)-one (299u)



In a 2-neck round-bottom flask (RBF) methyl (R)-10-(2-methylene-3-oxo-1-phenylpentyl)anthracen-9(10H)-one (5u) (1.0 equiv, 25 mg, 0.068 mmol) was added together with Pd/C (0.15 equiv w/w, 3 mg). EtOAc (1 ml, 0.068 mol/L) was added. The RBF was sealed and flushed twice with argon. Then the reaction mixture was flushed once with H_2. The rubber balloon was refilled with H_2 and connected to the RBF. The reaction was monitored by TLC until the reaction completion (3 days). The mixture was filtered through celite, washed with EtOAc and concentrated in vacuo. The mixture was purified by column chromatography (10:1 Hexane:EtOAc) to obtain 13 mg of a colourless oil. The product yield is 52 %. ^{1}**H NMR** (400 MHz, $CDCl_3$) σ 7.99 (dd, *J* = 7.8, 1.2 Hz, 1H, ArH), 7.87 (dd, *J* = 7.8, 1.0 Hz, 1H, ArH), 7.67 – 7.56 (m, 3H, ArH), 7.53 (d, *J* = 7.6 Hz, 1H, ArH), 7.46 (ddd, *J* = 7.9, 7.8, 1.1 Hz, 1H, ArH), 7.40 – 7.34 (m, 1H, ArH), 7.02 – 6.94 (m, 1H, ArH), 6.74 (t, *J* = 7.8 Hz, 2H, ArH), 5.74 (d, *J* = 7.2 Hz, 2H, ArH), 4.76 (d, *J* = 2.7 Hz, 1H, CH_3-CH-CH-CH), 3.39 – 3.19 (m, 2H), 2.33 – 2.15 (m, 1H, CH_3-CH-CH-CH), 1.99 (ddd, *J* = 18.0, 15.2, 7.9 Hz, 1H, CH_3-CH-CH-CH), 1.70 (d, *J* = 6.3 Hz, 3H, CH_3-CH-CH-CH), 0.66 (t, *J* = 7.2 Hz, 3H, $COCH_2CH_3$). ^{13}**C NMR** (101 MHz, $CDCl_3$) σ 190.7 (q), 170.1 (q), 140.6 (q), 137.8 (q), 137.6 (q), 136.7 (q), 136.2 (q), 135.5 (CH), 134.9 (CH), 133.7 (CH), 132.6 (CH), 131.7 (CH), 129.3 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 126.9 (CH), 126.2 (CH), 59.3 (CH), 47.7 (CH), 44.0 (CH_2), 35.6 (CH_3), 17.1 (CH_3). **MS** (m/z) for $C_{26}H_{24}O_2$ $[M+H]^+$ 369.29. **HR MS** (m/z) for $[C_{26}H_{24}O_2Na]^+$ calculated $[M+Na]^+$ 391.1669, measured $[M+Na]^+$ 391.1676. **IR** (cm^{-1}): 3067 (=C-H aromatic, stretch), 2927 (=C-H aromatic, stretch), 1669 (C=O, stretch), 1313, 1073, 1010, 710. $[\alpha]_D^{21}$ = -3 (c = 1.0, $CHCl_3$).

X-Ray single crystal analysis of the product of 299r



Displacement ellipsoids – 50% probability level

Experimental

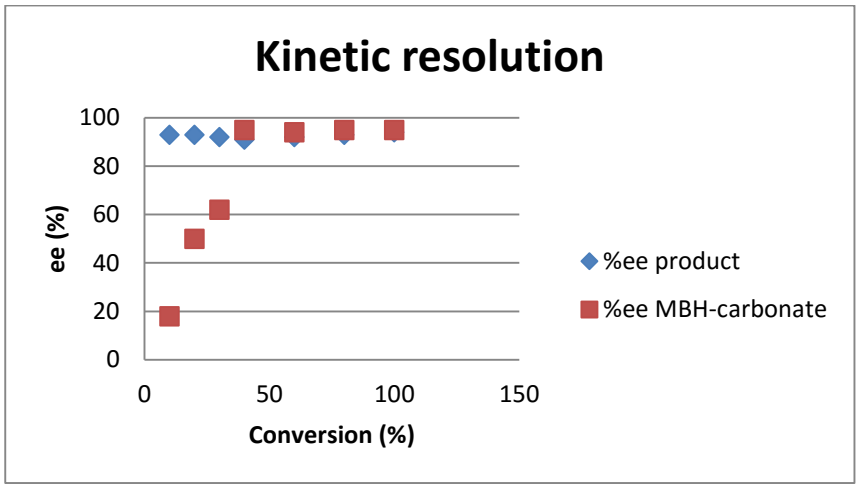
Single crystals of $C_{25}H_{21}BrO_2$ **[299r]** were diluted in minimum of chloroform and crystallyzed with hexane. A suitable crystal was selected and Mitegen mount on a Rigaku AFC11 007-HF diffractometer. The crystal was kept at 100(2) K during data collection. Using Olex2 [Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341], the structure was solved with the ShelXT [Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8] structure solution program using Direct Methods and refined with the ShelXL [Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122] refinement package using Least Squares minimisation.

Crystal structure determination of [299r]

Crystal Data for $C_{25}H_{21}BrO_2$ (M =433.33 g/mol): orthorhombic, space group $C222_1$ (no. 20), a = 14.1137(4) Å, b = 14.1141(5) Å, c = 39.2592(13) Å, V = 7820.5(4) Å^3, Z = 16, T = 100(2) K, μ(CuKα) = 3.001 mm^{-1}, $Dcalc$ = 1.472 g/cm^3, 57094 reflections measured (4.502° ≤ 2Θ ≤ 137.968°), 7193 unique (R_{int} = 0.1076, R_{sigma} = 0.0386) which were used in all calculations. The final R_1 was 0.0663 (I > 2σ(I)) and wR_2 was 0.1868 (all data).

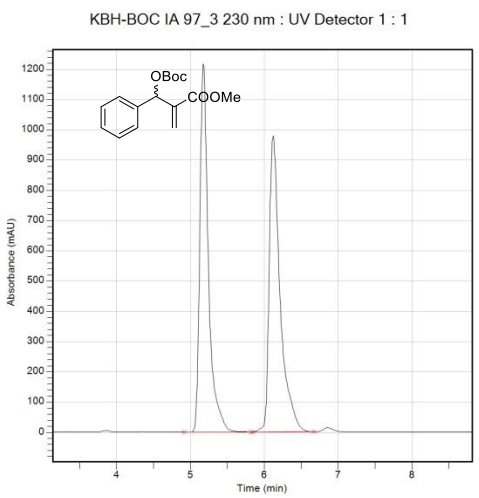
Crystal data and structure refinement for 299r.	
Identification code	2015VC003
Empirical formula	$C_{25}H_{21}BrO_2$
Formula weight	433.33
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$C222_1$
a/Å	14.1137(4)
b/Å	14.1141(5)
c/Å	39.2592(13)
α/°	90
β/°	90
γ/°	90
Volume/Å³	7820.5(4)
Z	16
ρ_{calc}g/cm³	1.472
μ/mm⁻¹	3.001
F(000)	3552.0
Crystal size/mm³	0.156 × 0.115 × 0.1
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	4.502 to 137.968
Index ranges	$-17 \le h \le 16$, $-16 \le k \le 16$, $-47 \le l \le 47$
Reflections collected	57094
Independent reflections	7193 [R_{int} = 0.1076, R_{sigma} = 0.0386]
Data/restraints/parameters	7193/512/511
Goodness-of-fit on F^2	1.122
Final R indexes [I>=2σ (I)]	R_1 = 0.0663, wR_2 = 0.1794
Final R indexes [all data]	R_1 = 0.0702, wR_2 = 0.1868
Largest diff. peak/hole / e Å⁻³	1.35/-2.32
Flack parameter	0.036(10)

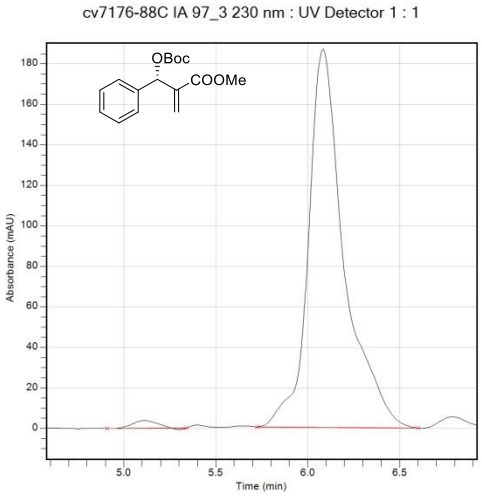
4.3.4 Kinetic resolution



These are the results from HPLC analysis which I made the graphic:

conversion	10	20	30	40	60	80	100
%ee product	93	93	92	91	92	93	94
%ee MBH-carbonate	18	50	62	95	94	95	95



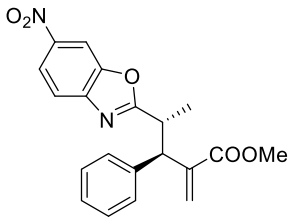


Time	Area	Area %
5.177	9,906,048.4	49.52
6.121	10,099,707.2	50.48
Total	20,005,755.5	100.00

Time	Area	Area %
5.115	14,039.4	2.56
6.100	534,132.1	97.44
Total	548,171.5	100.00

4.4 Highly diastereoselective addition of benzoxazole to MBH-carbonates

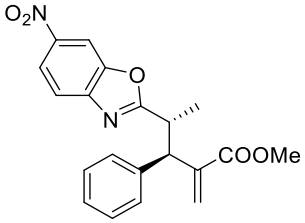
(±)methyl 2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)-3-phenylpentanoate (350a') (The reaction was effectuated by Dr Piotr Putaj)



To a solution of 2-ethyl-6-nitrobenzo[d]oxazole (1equiv, 19 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate (2 equiv, 58 mg, 0.2 mmol), $Pd(OAc)_2$ (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. D.r. is 2:1. The reaction mixture was purified by column chromatography (10:1 hexane/EtOAc). The mass of obtained oil is 18 mg. The product yield is 50%. ^{1}**H NMR** ($CDCl_3$, 300 MHz): Diastereomer 1: 8.35 (d, *J* = 2.0 Hz, 1H, ArH), 8.22 (dd, *J* = 8.8, 2.1 Hz, 1H, ArH), 7.69 (d, *J* = 8.8 Hz, 1H, ArH), 7.31-7.20 (m, 5H, ArH), 6.10 (s, 1H, C=CH_2), 5.77 (s, 1H, C=CH_2), 4.36 (d, *J* = 11.9 Hz, 1H, CH_2=C-CH-CH_3), 3.8 (m, 1H, CH_2=C-CH-CH-CH_3), 3.54 (s, 3H, COOCH_3), 1.20 (d, *J* = 6.9 Hz, 3H, CH_2=C-CH-CH-CH_3). Diastereomer 2: 8.2 (d, *J* = 2.0 Hz, 1H, ArH), 8.12 (dd, *J* = 8.8, 2.1 Hz, 1H, ArH), 7.56 (d, *J* = 8.8 Hz, 1H, ArH), 7.16-6.93 (m, 5H, ArH), 6.38 (s, 1H, C=CH_2), 5.84 (s, 1H, C=CH_2), 4.34 (d, *J* = 11.2 Hz, 1H, CH_2=C-CH-CH_3), 4.00 (m, 1H, CH_2=C-CH-CH-CH_3), 3.66 (s, 3H, COOCH_3), 1.45 (d, *J* = 6.9 Hz, 3H, CH_2=C-CH-CH-CH_3).

(±)methyl 2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)-3-phenylpentanoate (350a)

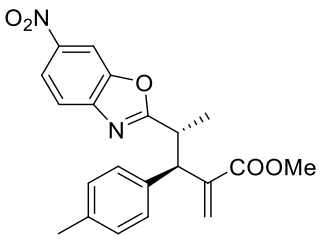
To a solution of 2-ethyl-6-nitrobenzo[d]oxazole(1 equiv, 19 mg, 0.1 mmol) in



anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate (4 equiv, 120 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (7:1 Hexane/EtOAc) to obtain 34 mg of the desired product as

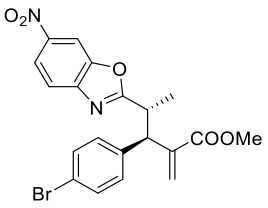
oil. The product yield is 92%. **MS** (ESI+) *m/z* 367.02 ([M + H]$^+$). **HR MS (m/z)** for $[C_{20}H_{19}N_2O_5]^+$ calculated $[M+H]^+$ 367.1288, measured $[M+H]^+$ 367.1280. **IR** (cm^{-1}): 2985, 1720, 1620, 1524, 1343, 1150. ^{1}**H NMR** ($CDCl_3$, 300 MHz): 8.41 (dd, *J* = 2.2 Hz, 1H, ArH), 8.29 (dd, *J* = 8.8, 2.2 Hz, 1H, ArH), 7.76 (d, *J* = 8.8 Hz, 1H, ArH), 7.40-7.25 (m, 5H, ArH), 6.19 (s, 1H, C=CH_2), 5.86 (d, *J* = 0.7 Hz, 1H, C=CH_2), 4.45 (d, *J* = 11.7 Hz, 1H, CH_2=C-CH-CH-CH_3), 3.90 (m, 1H, CH_2=C-CH-CH-CH_3), 3.61 (s, 3H, COOCH_3), 1.28 (d, *J* = 6.6 Hz, 3H, CH_2=C-CH-CH-CH_3). ^{13}**C NMR** ($CDCl_3$, 75 MHz): 174.2 (q), 166.4 (q), 149.7(q), 146.5 (q), 145.0 (q), 141.6 (q), 139.3 (q), 128.7 (CH), 128.6 (CH), 127.4 (CH), 124.9 (CH_2), 120.4 (CH), 119.6 (CH), 119.4 (CH), 107.2 (CH), 106.9 (CH), 52.0(CH_3), 50.7(CH), 38.2 (CH), 18.4 (CH_3).

(±)methyl 2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)-3-(*p*-tolyl)pentanoate (350b)



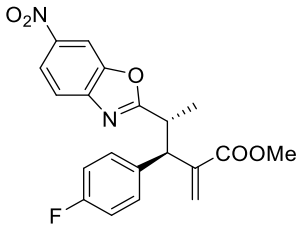
To a solution of 2-ethyl-6-nitrobenzo[d]oxazole (1 equiv, 19 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(p-tolyl)methyl)acrylate (4 equiv, 122 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (5:1 hexane/EtOAc) to obtain 43 mg of the desired product as oil. The product yield is 90%. **MS** (ESI+) *m/z*: 381.1 [M+H]$^+$. **HR MS (m/z)** for $[C_{21}H_{21}N_2O_5]^+$ calculated $[M+H]^+$ 381.1372, measured $[M+H]^+$ 381.1376. **IR** (cm^{-1}): 2985, 2950, 1720, 1626, 1524, 1343, 1149. ^{1}**H NMR** ($CDCl_3$, 300 MHz): 8.33 (d, *J* = 2.2 Hz, 1H, ArH), 8.20 (dd, *J* = 8.8, 2.2 Hz, 1H, ArH), 7.68 (d, *J* = 8.8 Hz, 1H, ArH), 7.16 (d, *J* = 8.1 Hz, 2H, ArH), 7.08 (d, *J* = 8.1 Hz, 2H, ArH), 6.08 (s, 1H, C=CH_2), 5.74 (s, 1H, C=CH_2), 4.32 (d, *J* = 12.1 Hz, 1H, CH_2=C-CH-CH-CH_3), 3.79 (m, 1H, CH_2=C-CH-CH-CH_3), 3.53 (s, 3H, COOCH_3), 2.27 (s, 3H, ArCH_3), 1.19 (d, *J* = 6.9 Hz, 3H, CH_2=C-CH-CH-CH_3). ^{13}**C NMR** ($CDCl_3$, 75 MHz): 174.3 (q), 166.5 (q), 149.7 (q), 146.5 (q), 145.0 (q), 141.7 (q), 137.0 (q), 136.2 (q), 129.4 (CH), 128.5 (CH), 124.7 (CH_2), 120.4 (CH), 119.6 (CH), 107.2 (CH), 52.0 (CH_3), 50.3 (CH), 38.2 (CH), 21.1 (CH_3), 18.4 (CH_3).

(±)methyl 3-(4-bromophenyl)-2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)pentanoate (350c)



To a solution of 2-ethyl-6-nitrobenzo[d]oxazole (1equiv, 100 mg, 0.52 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-((4-bromophenyl)((tert-butoxycarbonyl)oxy)methyl)acrylate (4 equiv, 768 mg, 2.08 mmol), silver acetate (10 mol%, 12 mg, 0.052 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 6 mg, 0.052 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (5:1 hexane/EtOAc) to obtain 188 mg of the desired product as oil. The product yield is 80%. **MS** (ESI+) *m/z* 444.01 ([M + H]$^+$). **HR MS** (m/z) for $[C_{20}H_{18}BrN_2O_5]^+$ calculated $[M+H]^+$ 445.0394, measured $[M+H]^+$ 445.0386. **IR** (cm^{-1}): 2989, 2951, 1717, 1624, 1524, 1342, 1148. **^{1}H NMR** ($CDCl_3$, 300 MHz): 8.33 (d, *J* = 2.2 Hz, 1H, ArH), 8.21 (dd, *J* = 8.8, 2.2 Hz, 1H, ArH), 7.68 (d, *J* = 7.7 Hz, 1H, ArH), 7.40 (d, *J* = 8.4 Hz, 2H, ArH), 7.16 (d, *J* = 8.4 Hz, 2H, ArH), 6.77 (s, 1H, C=CH_2), 5.76 (d, *J* = 0.7 Hz, 1H, C=CH_2), 4.33 (d, *J* = 11.7 Hz, 1H, CH_2=C-CH-CH-CH_3), 3.79 (m, 1H, CH_2=C-CH-CH-CH_3), 3.54 (s, 3H, COOCH_3), 1.19 (d, *J* = 6.9 Hz, 3H, CH_2=C-CH-CH-CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz): 173.8 (q), 166.2 (q), 149.6 (q), 146.4 (q), 145.1 (q), 141.1 (q), 138.4 (q), 131.9 (CH), 130.3 (CH), 125.2 (CH_2), 121.33 (q), 120.5 (CH), 119.7 (CH), 107.2 (CH), 52.1 (CH), 50.2 (CH), 37.9 (CH), 18.3 (CH_3).

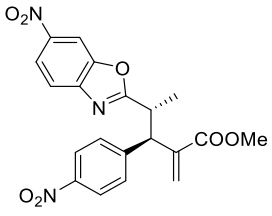
(±)methyl 3-(4-fluorophenyl)-2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)pentanoate (350d)



To a solution of 2-ethyl-6-nitrobenzo[d]oxazole (1equiv, 19 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-fluorophenyl)methyl)acrylate (4 equiv, 124 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (5:1 hexane/EtOAc) to obtain 32 mg of the desired product as oil. The product yield is 82%. **MS** (ESI+) *m/z* 384.97 ([M + H]$^+$). **HR MS** (m/z) for $[C_{20}H_{18}FN_2O_5]^+$ calculated $[M+H]^+$ 385.1194, measured $[M+H]^+$

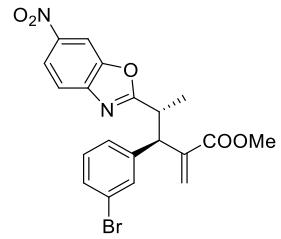
385.1200. **IR** (cm^{-1}): 2946, 1724, 1625, 1527, 1341, 1151. **^{1}H NMR** ($CDCl_3$, 300 MHz): 8.34 (d, *J* = 2.2 Hz, 1H, ArH), 8.21 (dd, *J* = 8.8, 2.2 Hz, 1H, ArH), 7.68 (d, *J* = 8.8 Hz, 1H, ArH), 7.29-7.21 (m, 2H, ArH), 7.02-6.93 (m, 2H, ArH), 6.10 (s, 1H, C=CH_2), 5.75 (d, *J* = 1.1 Hz, 1H, C=CH_2), 4.35 (d, *J* = 11.7 Hz, 1H, CH_2=C-CH-CH-CH_3), 3.84-3.71 (m, 1H, CH_2=C-CH-CH-CH_3), 3.55 (s, 3H, COOCH_3), 1.19 (d, *J* = 6.9 Hz, 3H, CH_2=C-CH-CH-CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz): 173.9 (q), 166.3 (q), 163.6 (q), 149.6 and 146.1 (q, d, J_{CF} = 247.1 Hz), 145.1 (q), 141.4 (q), 135.0 (q), 130.2 (CH), 130.1 (CH), 124.9 (CH_2), 120.5 (CH), 119.7 (CH), 115.8 (CH), 115.5 (CH), 107.2 (CH), 52.0 (CH_3), 50.0 (CH), 38.1 (CH), 18.3 (CH_3). **^{19}F NMR** ($CDCl_3$, 300 MHz): -115.2 ppm.

(±)methyl 2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)-3-(4-nitrophenyl)pentanoate (350e)



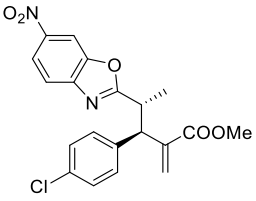
To a solution of 2-ethyl-6-nitrobenzo[d]oxazole (1 equiv, 19 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-nitrophenyl)methyl)acrylate (4 equiv, 135 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (7:1 hexane/EtOAc) to obtain 41 mg of the desired product as white solid. The product yield is 99%. **Mp** 136 °C. **MS** (ESI+) *m/z* 412.02 ($[M + H]^+$). **HR MS** (m/z) for $[C_{20}H_{18}N_3O_7]^+$ calculated $[M+H]^+$ 412.1139, measured $[M+H]^+$ 412.1146. **IR** (cm^{-1}): 2986, 2950, 1719, 1604, 1520, 1346, 1150. **^{1}H NMR** ($CDCl_3$, 300 MHz): 8.35 (d, *J* = 1.9 Hz, 1H, ArH), 8.23 (dd, *J* = 8.7, 2.3 Hz, 1H, ArH), 8.16 (d, *J* = 9.0 Hz, 2H, ArH), 7.70 (d, *J* = 8.7 Hz, 1H, ArH), 7.49 (d, *J* = 8.7 Hz, 2H, ArH), 6.19 (s, 1H, C=CH_2), 5.85 (d, *J* = 1.1 Hz, 1H, C=CH_2), 4.50 (d, *J* = 11.7 Hz, 1H, CH_2=C-CH-CH-CH_3), 3.92-3.80 (m,1H, CH_2=C-CH-CH-CH_3), 3.56 (s, 3H, COOCH_3), 1.21 (d, *J* = 7.2 Hz, 3H, CH_2=C-CH-CH-CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz): 173.1(q), 165.9 (q), 149.6 (q), 147.3 (q), 147.0 (q), 146.2 (q), 145.2 (q), 140.4 (q), 129.6 (CH), 126.2 (CH_2), 124.0 (CH), 120.6 (CH), 119.8 (CH), 107.2 (CH), 52.2 (CH), 50.6 (CH), 37.7 (CH), 18.3 (CH). **HPLC** analysis (Chiralpak IE, i-PrOH/Hexane=10:90, 254nm, 1ml/min): retention time 42.95 min, 60.03 min, enantiomeric ratio: 50:50.

(±)methyl 3-(3-bromophenyl)-2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)pentanoate (350f)



To a solution of 2-ethyl-6-nitrobenzo[d]oxazole (1equiv, 19 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-((3-bromophenyl)((tert-butoxycarbonyl)oxy)methyl)acrylate (4equiv, 148 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (7:1 hexane/EtOAc) to obtain 43 mg of the desird product as oil. The product yield is 97%. **MS** (ESI+) *m/z* 444.98 ($[M + H]^+$). **HR MS** (m/z) for $[C_{20}H_{18}BrN_2O_5]^+$ calculated $[M+H]^+$ 445.0394, measured $[M+H]^+$ 445.0397. **IR** (cm^{-1}): 2985, 2950, 1718, 1618, 1527, 1343, 1150. **^{1}H NMR** ($CDCl_3$, 300 MHz): 8.34 (d, *J* = 2.2 Hz, 1H, ArH), 8.21 (dd, *J* = 8.8, 2.2 Hz, 1H, ArH), 7.68 (d, *J = 8.8 Hz*, 1H, ArH), 7.45-7.10 (m, 4H, ArH), 6.14 (s, 1H, C=CH_2), 5.78 (s, 1H, C=CH_2), 4.33 (d, *J* = 11.7 Hz, 1H, CH_2=C-CH-CH-CH_3), 3.85-3.70 (m, 1H, CH_2=C-CH-CH-CH_3), 3.55 (s, 3H, COOCH_3), 1.20 (d, *J* = 6.9 Hz, 3H, CH_2=C-CH-CH-CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz): 173.7 (q), 166.2 (q), 149.6 (q), 146.4 (q), 145.1 (q), 141.7 (q), 140.9 (q), 131.5 (CH), 130.6 (CH), 130.3 (CH), 127.5 (CH), 125.5 (CH_2), 122.8 (q), 120.5 (CH), 119.7 (CH), 107.2 (CH), 52.1 (CH_3), 50.3 (CH), 38.0 (CH), 18.4 (CH_3).

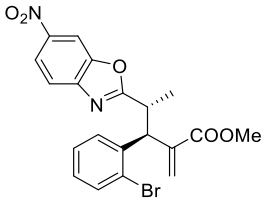
(±)methyl 3-(4-chlorophenyl)-2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)pentanoate (350g)



To a solution of 2-ethyl-6-nitrobenzo[d]oxazole (1equiv, 19 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (4 equiv, 148 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (7:1 hexane/EtOAc) to obtain 32 mg of the desired product as oil. The product yield is 80%. **MS** (ESI+) *m/z* 400.81 ($[M + H]^+$). **HR MS** (m/z) for $[C_{20}H_{18}{}^{35}ClN_2O_5]^+$ calculated $[M+H]^+$ 401.0899, measured $[M+H]^+$

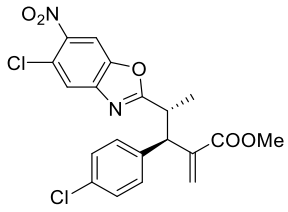
401.0902. **IR** (cm^{-1}): 2989, 2950, 1717, 1621, 1523, 1342. ^{1}**H NMR** ($CDCl_3$, 300 MHz): 8.34 (d, *J* = 2.2 Hz, 1H, ArH), 8.21 (dd, *J* = 8.8, 2.2 Hz, 1H, ArH), 7.68 (d, *J* = 8.8 Hz, 1H, ArH), 7.30-7.16 (m, 4H, ArH), 6.11 (s, 1H, C=CH$_2$), 5.76 (d, *J* = 0.7 Hz, 1H, C=CH$_2$), 4.34 (d, *J* = 11.7 Hz, 1H, CH_2=C-CH-CH-CH_3), 3.85-3.72 (m, 1H, CH_2=C-CH-CH-CH_3), 3.54 (s, 3H, COOCH$_3$), 1.19 (d, *J* = 6.6 Hz, 3H, CH_2=C-CH-CH-CH$_3$). ^{13}**C NMR** ($CDCl_3$, 75 MHz): 173.8 (q), 166.2 (q), 149.6 (q), 146.4 (q), 145.1 (q), 141.2 (q), 137.9 (q), 133.2 (q), 130.0 (CH), 128.9 (CH), 125.2 (CH_2), 120.5 (CH), 119.7 (CH), 107.2 (CH), 52.1 (CH_3), 50.2 (CH), 37.9 (CH), 18.3 (CH_3).

(±)methyl 3-(2-bromophenyl)-2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)pentanoate (350i)



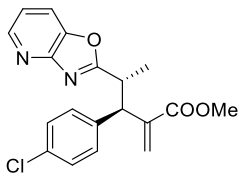
To a solution of 2-ethyl-6-nitrobenzo[d]oxazole (1equiv, 19 mg, 0. 1mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(2-bromophenyl)methyl)acrylate (4equiv, 148 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (5:1 hexane/EtOAc) to obtain 26 mg of the desired product as white solid. The product yield is 60%. **Mp** 138 °C. **MS** (ESI+) *m/z* 446.93 ($[M + H]^+$). **HR MS** (m/z) for $[C_{20}H_{18}BrN_2O_5]^+$ calculated $[M+H]^+$ 445.0394, measured $[M+H]^+$ 445.0397. **IR** (cm^{-1}): 2983, 2950, 1720, 1625, 1523, 1346, 1153. ^{1}**H NMR** ($CDCl_3$, 300 MHz): 8.38-8.33 (d, *J* = 1.8 Hz, 1H, ArH), 8.25-8.19 (dd, *J* = 8.8, 2.2 Hz, 1H, ArH), 7.71 (d, *J* = 8.8 Hz, 1H, ArH), 7.59-7.54 (dd, *J* = 7.7, 1.1 Hz, 1H, ArH), 7.34-7.21 (m ,2H, ArH), 7.10-7.03 (ddd, *J* = 8.8, 6.6, 2.2 Hz, 1H, ArH), 6.19 (s, 1H, C=CH$_2$), 5.80 (d, *J* = 0.7 Hz, 1H, C=CH$_2$), 5.00 (d, *J* = 11.7 Hz, 1H, CH_2=C-CH-CH-CH_3), 3.92-3.75 (m, 1H, CH_2=C-CH-CH-CH_3), 3.53 (s, 3H, COOCH$_3$), 1.26 (d, *J* = 6.9 Hz, 3H, CH_2=C-CH-CH-CH$_3$). ^{13}**C NMR** ($CDCl_3$, 75 MHz): 173.7 (q), 166.3 (q), 149.7 (q), 146.4 (q), 145.0 (q), 140.4 (q), 138.5 (q), 133.5 (CH), 128.8 (CH), 127.8 (CH), 126.6 (CH_2), 120.5 (CH), 119.7 (CH), 107.3 (CH), 52.0 (CH_3), 48.9 (CH), 38.7 (CH), 17.3 (CH_3).

(±)methyl 4-(5-chloro-6-nitrobenzo[d]oxazol-2-yl)-3-(4-chlorophenyl)-2-methylenepentanoate (350k)



To a solution of 5-chloro-2-ethyl-6-nitrobenzo[d]oxazole (1 equiv, 23mg, 0.1mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (4 equiv, 135 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (5:1 hexane/EtOAc) to obtain 47 mg of the desired product as white solid. The product yield is 95%. **Mp** 138 °C. **MS** (ESI+) *m/z* 434.93 ([M + H]$^+$). **HR MS** (m/z) for $[C_{20}H_{17}{}^{35}Cl_2N_2O_5]^+$ calculated $[M+H]^+$ 435.0509, measured $[M+H]^+$ 435.0509. **IR** (cm^{-1}): 2993, 2951, 1720, 1627, 1538, 1346, 1151. ^{1}**H NMR** ($CDCl_3$, 400 MHz): 8.00 (s, 1H, ArH), 7.74 (s, 1H, ArH), 7.3-7.1 (m, 4H, ArH), 6.11 (s, 1H, C=CH_2), 5.74 (s, 1H, C=CH_2), 4.31 (d, *J* = 11.6 Hz, 1H, CH_2=C-CH-CH-CH_3), 3.80-3.70 (m, 1H, CH_2=C-CH-CH-CH_3), 3.55 (s, 3H, COOCH_3), 1.18 (d, *J* = 6.9 Hz, 3H, CH_2=C-CH-CH-CH_3). ^{13}**C NMR** ($CDCl_3$, 100 MHz): 174.4 (q), 166.2 (q), 147.9 (q), 144.8 (q), 141.1 (q), 137.7 (q), 133.3 (q), 130.0 (CH), 129.0 (CH), 128.5 (q), 125.2 (CH_2), 123.5 (q), 122.3 (CH), 108.6 (CH), 52.1 (CH_3), 50.2 (CH), 37.9 (CH), 18.3 (CH_3).

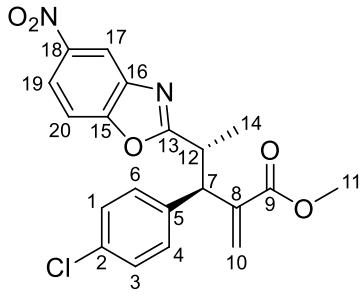
(±)methyl 3-(4-chlorophenyl)-2-methylene-4-(oxazolo[4,5-b]pyridin-2-yl)pentanoate (350l)



To a solution of 2-ethyloxazolo[4,5-b]pyridine (1equiv, 15 mg, 0.1 mmol) in anhydroustoluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (4 equiv, 135 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (4:1 hexane/EtOAc) to obtain 23 mg of the desired product as oil. The product yield is 65%. **MS** (ESI+) *m/z* 357.03 ([M + H]$^+$). **HR MS** (m/z) for $[C_{19}H_{18}{}^{35}ClN_2O_3]^+$ calculated $[M+H]^+$ 357.1000, measured $[M+H]^+$ 357.1004. **IR** (cm^{-1}): 2986, 2947, 1720, 1624, 1151. ^{1}**H NMR** ($CDCl_3$, 400 MHz): 8.57-8.53 (dd, *J* =

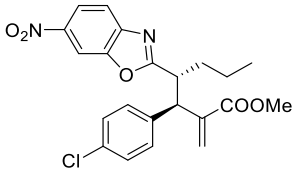
4.9. 1.5 Hz, 1H, ArH), 7.83-7.78 (dd, *J* = 8.1, 1.5 Hz, 1H, ArH), 7.37-7.25 (m, 5H, ArH), 6.21 (s, 1H, C=CH$_2$), 5.92 (d, *J* = 1.0 Hz, 1H, C=CH$_2$), 4.45 (d, *J* = 11.7 Hz, 1H, CH$_2$=C-CH-CH-CH$_3$), 3.92-3.82 (m, 1H, CH$_2$=C-CH-CH-CH$_3$), 3.63 (s, 3H, COOCH$_3$), 1.27 (d, *J* = 6.9 Hz, 3H, CH$_2$=C-CH-CH-CH$_3$). **^{13}C NMR** ($CDCl_3$, 100 MHz): 172.0 (q), 166.3 (q), 155.6 (q), 146.3 (CH), 142.7 (q), 141.0 (q), 138.2 (q), 133.1 (q), 130.0 (CH), 128.8 (CH), 125.4 (CH_2), 119.8 (CH), 118.2 (CH), 52.0 (CH_3), 50.0 (CH), 38.0 (CH), 18.3 (CH_3).

(±)methyl 3-(4-chlorophenyl)-2-methylene-4-(5-nitrobenzo[d]oxazol-2-yl)pentanoate (350m)



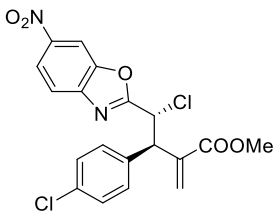
To a solution of 2-ethyl-5-nitrobenzo[d]oxazole(1equiv, 20 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (4 equiv, 135 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (4:1 hexane/EtOAc) to obtain 38 mg of the desired product as oil. The product yield is 90%. **MS** (ESI+) *m/z* 400.94 ([M + H]$^+$). **HR MS** (m/z) for [$C_{20}H_{18}{}^{35}ClN_2O_5$]$^+$ calculated [M+H]$^+$ 401.0899, measured [M+H]$^+$ 401.0889. **IR** (cm^{-1}): 2986, 2954, 1720, 1617, 1528, 1346, 1151. **^{1}H NMR** ($CDCl_3$, 300 MHz): 8.52-8.47 (d, *J* = 2.2 Hz, 1H, ArH, **C17**), 8.25-8.19 (dd, *J* = 8.8, 2.2 Hz, 1H, ArH, **C19**), 7.55-7.49 (d, *J* = 9.2 Hz, 1H, ArH, **C20**), 7.30-7.19 (m, 4H, ArH, **C1**, **C3**, **C4**, **C6**), 6.11 (s, 1H, C=CH$_2$, **C10**), 5.77 (s, 1H, C=CH$_2$, **C10**), 4.33 (d, *J* = 12.1 Hz, 1H, CH$_2$=C-CH-CH-CH$_3$, **C7**), 3.83-3.69 (m, 1H, CH$_2$=C-CH-CH-CH$_3$, **C12**), 3.54 (s, 3H, COOCH$_3$, **C11**), 1.19 (d, *J* = 7.0 Hz, 3H, CH$_2$=C-CH-CH-CH$_3$, **C14**). **^{13}C NMR** ($CDCl_3$, 75 MHz): 172.1 (q, **C13**), 166.3 (q, **C9**), 154.1 (q, **C18**), 145.2 (q, **C16**), 141.5 (q, **C15**), 141.2 (q, **C16**), 137.9 (q, **C5**), 133.2 (q, **C2**), 130.0 (CH, **C4, C6**), 128.9 (CH, **C1, C3**), 125.2 (CH_2, **C10**), 120.9 (CH, **C19**), 116.2 (CH, **C20**), 110.7 (CH, **C17**), 52.1 (CH_3, **C11**), 50.1 (CH, **C7**), 37.8 (CH, **C12**), 18.3 (CH_3, **C14**).

(±)methyl 3-(4-chlorophenyl)-2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)heptanoate (350n)



To a solution of 2-butyl-6-nitrobenzo[d]oxazole(1equiv, 22 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (4equiv, 135 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (5:1 hexane/EtOAc) to obtain 41 mg of the desired product as oil. The product yield is 92 %. **MS** (ESI+) *m/z* 429.03 ([M + H]$^+$). **HR MS** (m/z) for $[C_{22}H_{22}{}^{35}ClN_2O_5]^+$ calculated $[M+H]^+$ 429.1212, measured $[M+H]^+$ 429.1208. **IR** (cm^{-1}): 2958, 2872, 1720, 1624, 1528, 1346, 1147. **^{1}H NMR** ($CDCl_3$, 300 MHz): 8.34 (d, *J* = 1.8 Hz, 1H, Ar<u>H</u>), 8.21 (dd, *J* = 8.8, 2.2 Hz, 1H, Ar<u>H</u>), 7.68 (d, *J* = 8.8 Hz, 1H, Ar<u>H</u>), 7.29-7.20 (m, 4H, Ar<u>H</u>), 6.06 (s, 1H, C=C<u>H</u>$_2$), 5.77 (s, 1H, C=C<u>H</u>$_2$), 4.36 (d, *J* = 12.1 Hz, 1H, CH_2=C-C<u>H</u>-CH-CH_2-CH_2-CH_3), 3.74-3.61 (m,1H, CH_2=C-CH-C<u>H</u>-CH_2-CH_2-CH_3), 3.53 (s, 3H, $COOCH_3$), 1.70-1.59 (m,1H, CH_2=C-CH-CH-C<u>H</u>$_2$-CH_2-CH_3), 1.47-1.35 (m,1H, CH_2=C-CH-CH-C<u>H</u>$_2$-CH_2-CH_3), 1.10-1.00 (m, 2H, CH_2=C-CH-CH-CH_2-C<u>H</u>$_2$-CH_3), 0.69 (t, *J* = 7.0 Hz, 3H, CH_2=C-CH-CH-CH_2-CH_2-C<u>H</u>$_3$). **^{13}C NMR** ($CDCl_3$, 75 MHz): 173.1 (q), 166.2 (q), 149.6 (q), 146.3 (q), 141.2 (q), 138.1 (q), 133.2 (q), 130.0 (CH), 129.0 (CH), 125.3 (CH_2), 120.5 (CH), 119.7 (CH), 107.2 (CH), 52.0 (CH_3), 49.5 (CH), 43.5 (CH), 34.6 (CH_2), 20.4 (CH_2), 13.6 (CH_3).

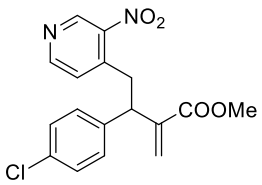
(±)methyl 4-chloro-3-(4-chlorophenyl)-2-methylene-4-(6-nitrobenzo[d]oxazol-2-yl)butanoate (350o)



To a solution of 2-(chloromethyl)-6-nitrobenzo[d]oxazole (1equiv, 21mg, 0.1mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (4 equiv, 135 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (7:1 hexane/EtOAc) to obtain 5 mg of the

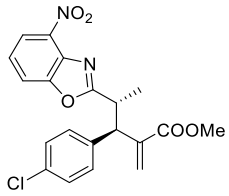
desired product as oil. The product yield is 10 %. **MS** (ESI+) *m/z* 480.93 ([M + H]$^+$). **HR MS** (m/z) for $[C_{19}H_{15}{}^{35}Cl_2N_2O_5]^+$ calculated $[M+H]^+$ 481.0280, measured $[M+H]^+$ 481.0287. **IR** (cm^{-1}): 2951, 1720, 1628, 1528, 1346, 1150. ^{1}**H NMR** ($CDCl_3$, 400 MHz): 8.41ppm (d, *J* = 2.1 Hz, 1H, Ar<u>H</u>), 8.26 (dd, *J* = 8.8, 2.1 Hz, 1H, Ar<u>H</u>), 7.78 (d, *J* = 8.8 Hz, 1H, Ar<u>H</u>), 7.33-7.26 (m, 4H, Ar<u>H</u>), 6.13 (s, 1H, C=C<u>H</u>$_2$), 5.76 (d, *J* = 11.3 Hz, 1H, CH_2=C-CH-C<u>H</u>), 5.74 (s, 1H, C=C<u>H</u>$_2$), 4.76 (d, *J* = 11.3 Hz, 1H, CH_2=C-C<u>H</u>-CH), 3.59 (s, 3H, COOC<u>H</u>$_3$). ^{13}**C NMR** ($CDCl_3$, 100 MHz): 167.0 (q), 165.5 (q), 149.8 (q), 145.9 (q), 145.6 (q), 139.2 (q), 135.7 (q), 133.9 (q), 130.1 (CH), 128.9 (CH), 127.2 (CH_2), 120.8 (CH), 120.9 (CH), 107.8 (CH), 54.3 (CH_3), 52.4 (CH), 52.0 (CH).

<u>(±)methyl 3-(4-chlorophenyl)-2-methylene-4-(3-nitropyridin-4-yl)butanoate (350p)</u>



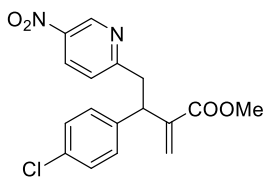
To a solution of 4-methyl-3-nitropyridine (1equiv, 14 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (4equiv, 135 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (7:1 hexane/EtOAc) to obtain 6 mg of the desired product as oil. The product yield is 17%. **MS** (ESI+) *m/z*: 347.0 $[M+H]^+$. **HR MS** (m/z) for $[C_{17}H_{16}{}^{35}ClN_2O_4]^+$ calculated $[M+H]^+$ 347,0720, measured $[M+H]^+$ 347.0715. **IR** (cm^{-1}): 2951, 1722, 1627, 1522, 1352, 1138. ^{1}**H NMR** ($CDCl_3$, 400 MHz): 9.09 (s, 1H, Pyr<u>H</u>), 8.57 (d, *J = 4.8 Hz*, 1H, Pyr<u>H</u>), 7.23 (d, *J* = 7.8 Hz, 2H, Ar<u>H</u>), 7.04 (d, *J* = 7.8 Hz, 2H, Ar<u>H</u>), 6.99 (d, *J* = 5.0 Hz, 1H, Pyr<u>H</u>), 6.39 (s, 1H, C=C<u>H</u>$_2$), 5.73 (s, 1H, C=C<u>H</u>$_2$), 4.24 (t, *J* = 7.6 Hz, 1H, CH_2=C-C<u>H</u>-CH_2), 3.67 (s, 3H, COOC<u>H</u>$_3$), 3.59 (d, *J* = 14.0, 6.0 Hz, 1H, CH_2=C-CH-C<u>H</u>$_2$), 3.45-3.37 (dd, *J* = 13.6, 9.4 Hz, 1H, CH_2=C-CH-C<u>H</u>$_2$). ^{13}**C NMR** ($CDCl_3$, 100 MHz): 166.5 (q), 152.7 (q), 145.9 (q), 143.5 (CH), 141.8 (q), 138.6 (q), 133.1 (q), 131.1 (CH), 129.3 (CH), 128.8 (CH), 126.4 (CH), 125.5 (CH_2), 52.1(CH_3), 45.9 (CH), 36.5 (CH_2).

(±)methyl 3-(4-chlorophenyl)-2-methylene-4-(4-nitrobenzo[d]oxazol-2-yl)pentanoate (350q)



To a solution of 2-ethyl-4-nitrobenzo[d]oxazole (1 equiv, 20 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (4 equiv, 135 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (4:1 hexane/EtOAc) to obtain 30 mg of the desired product as oil. The product yield is 75%. **MS** (ESI+) *m/z* 400.99 ($[M + H]^+$). **HR MS** (m/z) for $[C_{20}H_{18}{}^{35}ClN_2O_5]^+$ calculated $[M+H]^+$ 401.0899, measured $[M+H]^+$ 401.0898. **IR** (cm^{-1}): 2990, 2951, 1720, 1624, 1528, 1340, 1147. **^{1}H NMR** ($CDCl_3$, 300 MHz): 8.09 (d, *J* = 8.1 Hz, 1H, ArH), 7.75 (d, *J* = 7.7 Hz, 1H, ArH), 7.39 (dd, *J* = 8.1, 8.1 Hz, 1H, ArH), 7.28-7.17 (m, 4H, ArH), 6.11 (s, 1H, C=CH_2), 5.87 (s, 1H, C=CH_2), 4.38 (d, *J* = 12.1 Hz, 1H, CH_2=C-CH-CH-CH_3), 3.95-3.82 (m, 1H, CH_2=C-CH-CH-CH_3), 3.55 (s, 3H, COOCH_3), 1.20 (d, *J* = 7.0 Hz, 1H, CH_2=C-CH-CH-CH_3). **^{13}C NMR** ($CDCl_3$, 100 MHz): 172.5 (q), 166.3 (q), 152.3 (q), 141.0 (q), 139.0 (q), 138.1 (q), 135.8 (q), 133.2 (q), 130.0 (CH), 128.9 (CH), 125.5 (CH), 124.2 (CH_2), 120.8 (CH), 116.6 (CH), 52.1 (CH_3), 49.7 (CH), 38.1 (CH), 18.4 (CH_3).

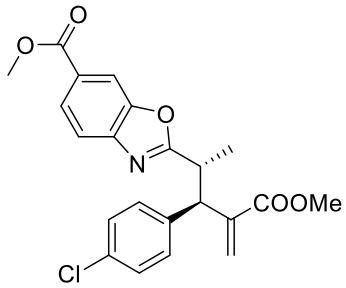
(±)methyl 3-(4-chlorophenyl)-2-methylene-4-(5-nitropyridin-2-yl)butanoate (350s)



To a solution of 2-methyl-5-nitropyridine (1 equiv, 14 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (4 equiv., 135 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (5:1 hexane/EtOAc) to obtain 7 mg of the desired product as oil. The product yield is 20%. **MS** (ESI+) *m/z* 346.99 ($[M + H]^+$). **HR MS** (m/z) for $[C_{17}H_{16}{}^{35}ClN_2O_4]^+$ calculated $[M+H]^+$ 347,0720, measured $[M+H]^+$ 347.0723. **IR** (cm^{-1}): 2951, 1717, 1631, 1524, 1352, 1145. **^{1}H NMR** ($CDCl_3$, 400

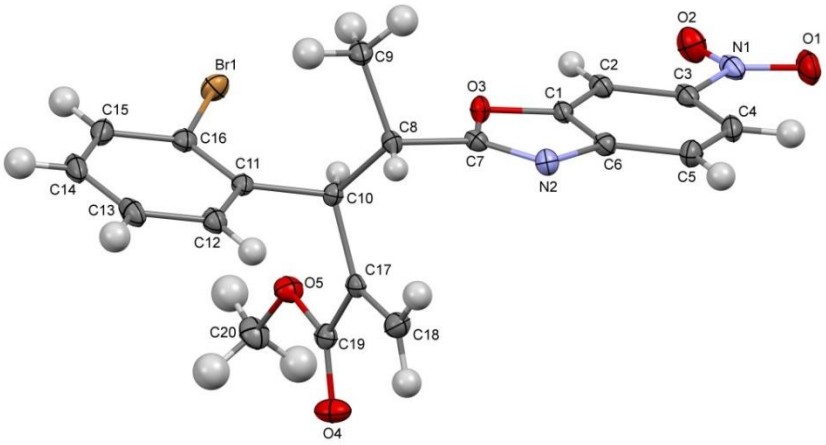
MHz): 9.02 (s, 1H, ArH), 8.50 (s, 1H, ArH), 7.15 (d, *J* = 7.8 Hz, 2H, ArH), 6.96 (d, *J* = 7.8 Hz, 2H, ArH), 6.91 (d, *J* = 4.7 Hz, 1H, ArH), 6.31 (s, 1H, C=CH$_2$), 5.65 (s, 1H, C=CH$_2$), 4.16 (t, *J* = 8.0 Hz, 1H, CH$_2$=C-CH-CH$_2$), 3.60 (s, 3H), 3.53 (dd, *J* = 12.8, 4.9 Hz, 1H, CH$_2$=C-CH-CH$_2$), 3.33 (dd, *J* = 13.5, 9.4 Hz, 1H, CH$_2$=C-CH-CH$_2$). **^{13}C NMR** ($CDCl_3$, 100 MHz): 166.5 (q), 152.7 (CH), 146.0 (CH), 143.5 (q), 141.8 (q), 138.6 (q), 133.1 (q), 129.3 (CH), 128.8 (CH), 128.4 (q), 126.3 (CH), 125.5 (CH_2), 52.1 (CH), 45.9 (CH), 36.5 (CH_2).

(±)methyl 4-(6-acetoxybenzo[d]oxazol-2-yl)-3-(4-chlorophenyl)-2-methylenepentanoate (350u)



To a solution of methyl 2-ethylbenzo[d]oxazole-6-carboxylate (1equiv, 21 mg, 0.1 mmol) in anhydrous toluene (0.1 mol/L) was added methyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (4 equiv, 135 mg, 0.4 mmol), silver acetate (10 mol%, 2 mg, 0.01 mmol), 1,4-diaza-bicyclo[2.2.2]octane (10 mol%, 1 mg, 0.01 mmol). The reaction was stirred for 14 hours. The conversion was checked by NMR. The reaction mixture was purified by column chromatography (7:1 hexane/EtOAc) to obtain 24 mg of the desired product as oil. The product yield is 58%. **MS** (ESI+) *m/z* 413.99 ($[M + H]^+$). **HR MS** (m/z) for $[C_{22}H_{21}{}^{35}ClNO_5]^+$ calculated $[M+H]^+$ 414.1103, measured $[M+H]^+$ 414.1106. **IR** (cm^{-1}): 2990, 2950, 1716, 1624, 1147, 1079. **^{1}H NMR** ($CDCl_3$, 400 MHz): 8.11 (s, 1H, ArH), 7.98 (d, *J* = 8.3 Hz, 1H, ArH), 7.61 (d, *J* = 8.3 Hz, 1H, ArH), 7.27-7.23 (d, *J* = 8.7 Hz, 2H, ArH), 7.23-7.19 (d, *J* = 8.7 Hz, 2H, ArH), 6.10 (s, 1H, C=CH$_2$), 5.77 (s, 1H, C=CH$_2$), 4.33 (d, *J* = 11.7 Hz, 1H, CH$_2$=C-CH-CH-CH$_3$), 3.88 (s, 3H, ArCOOCH$_3$), 3.79-3.69 (m, 1H, CH$_2$=C-CH-CH-CH$_3$), 3.53 (s, 3H, COOCH$_3$), 1.17 (d, *J* = 6.9 Hz, 3H, CH$_2$=C-CH-CH-CH$_3$). **^{13}C NMR** ($CDCl_3$, 100 MHz): 172.0 (q), 166.3 (q), 155.6 (q), 146.3 (q), 142.7 (q), 141.0 (q), 138.2 (q), 133.1 (q), 130.0 (CH), 128.9 (CH), 126.1 (q), 125.4 (CH_2), 119.8 (CH), 118.2 (CH), 52.4 (CH_3), 52.0 (CH_3), 50.0 (CH), 38.0 (CH), 18.3 (CH_3).

X-Ray single crystal analysis of the product of 350i



Displacement ellipsoids – 50% probability level

Single crystals of $C_{20}H_{17}BrN_2O_5$ **[350i]** were diluted in minimum of chloroform and crystallyzed with hexane. A suitable crystal was selected and Mitegen mounted.

Diffractometer: Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with VHF Varimax optics (70m focus).

Cell determination and data collection: CrystalClear-SM Expert 2.0 r11 (Rigaku, 2011).

Data reduction, cell refinement and absorption correction: CrystalClear-SM Expert 2.0 r13 (Rigaku, 2011**).**

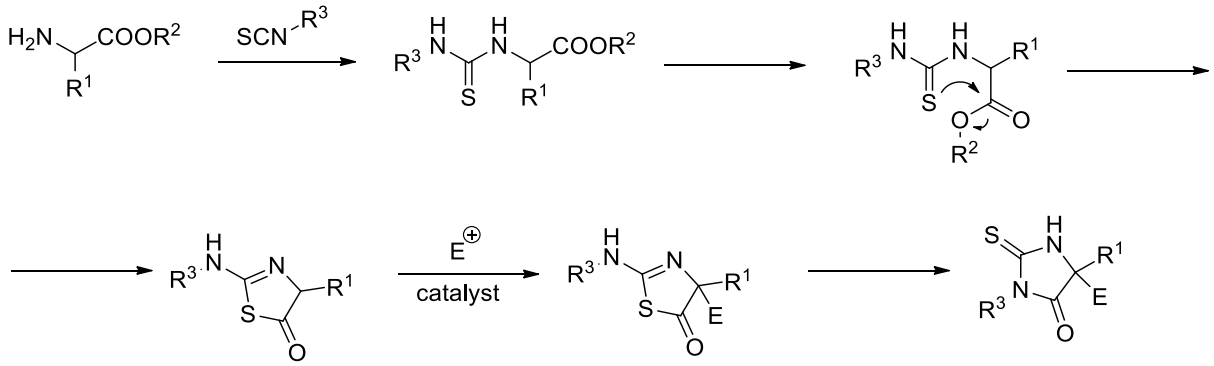
Structure solution: SHELXS97 (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

Structure refinement: SHELXL97 (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122).

Crystal data and structure refinement details	
Identification code	2013ncs0652 (CV-6903-54) 238i
Empirical formula	$C_{20}H_{17}BrN_2O_5$
Formula weight	445.26 g/mol
Temperature	100(2) K
Wavelength	0.71075 Å
Crystal system	Triclinic
Space group	*P*–1
Unit cell dimensions	a = 8.9971(4) Å α = 70.132(5)° b = 10.0949(4) Å β = 68.095(5)° c = 11.5631(8) Å γ = 80.935(6)°
Volume	915.83(9) Å^3
Z	2
Density (calculated)	1.615 Mg / m^3
Absorption coefficient	2.280 mm^{-1}
F(000)	452
Crystal	Plate; Colourless
Crystal size	0.240 × 0.200 × 0.040 mm^3
θ range for data collection	3.194 – 27.477°
Index ranges	$-11 \le h \le 11$, $-13 \le k \le 13$, $-14 \le l \le 14$
Reflections collected	12120
Independent reflections	4167 [R_{int} = 0.0244]
Completeness to θ = 25.242°	99.6 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	1.000 and 0.672
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4167 / 0 / 255

Goodness-of-fit on F^2	1.082
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0257, *wR2* = 0.0675
***R* indices (all data)**	*R1* = 0.0273, *wR2* = 0.0684
Extinction coefficient	n/a
Largest diff. peak and hole	0.455 and −0.431 e Å^{-3}

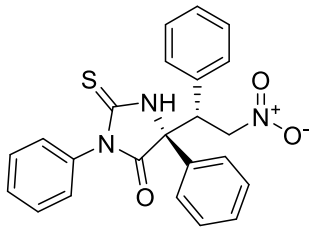
4.5 Three-component diastereoselective cascade synthesis of thiohydantoins



General procedure: To a solution of amino ester (1equiv, 0.6 mmol) in MeCN (1ml, 0.6M) was added isothiocyanate (1,2 equiv, 0.7 mmol) and β-nitrostyrene (1,2 equiv, 0.7 mmol) and triethylamine (0,2 equiv, 0.12 mmol). The solution was stirred for the indicated time and subsequently the solvent was removed by rotary evaporation. The reaction mixture was purified by column chromatography (Hexane/Acetone). The product was confirmed by MS(ESI-), IR, ^{1}H-NMR, ^{13}C-NMR, DEPT 135, ^{19}F-NMR.

Thin layer chromatography (TLC) was performed on Merck TLC Silicagel 60 F_{254}. Product spots were visualized by UV-light at 254nm, and developed with potassium permanganate. Column chromatography was effectuated using silica gel (Geduran Si60, 40-63µm. Infra-red spectra were recorded on a Nicolet 280 FT-IR. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR were recorded with Bruker AV300, Bruker DPX400. High resolution mass spectra were recorded using a MaXis (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a Time of Flight (TOF) analyser.

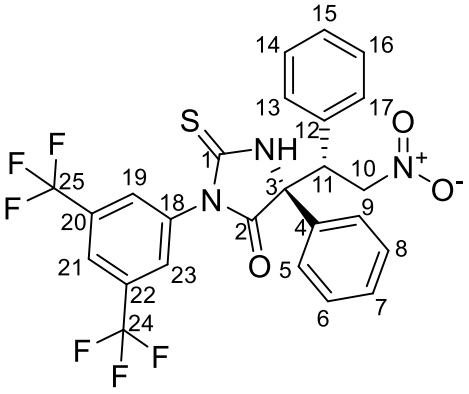
(±) 5-(2-Nitro-1-phenylethyl)-3,5-diphenyl-2-thioxoimidazolidin-4-one (426a)



Reaction time is 4 hours. Product was purified by column chromatography (hexane/acetone 9:1) to give a white solid. Yield: 75 %. **D.r.**: 10:1. **Mp** 243 °C. **MS** (ESI-) *m/z*: 416.4 $[M-H]^-$. **HR MS** (m/z) for $[C_{23}H_{18}N_3O_3S]^-$ calculated $[M-H]^-$ 416.1074, measured $[M-H]^-$ 416.1066. **IR** (cm^{-1}): 3292 (N-H, stretch), 1725 (C-O, stretch), 1554 and 1373 (N-O, stretch), 1192 (C-S, stretch). **^{1}H NMR** ($CDCl_3$, 400 MHz): 9,39 (s, 1H, NH), 7.75 (d, *J* = 7.3 Hz, 2H, ArH), 7.50-7.40 (m, 9H, ArH), 7.35-7.20 (m, 4H, ArH), 6,45 (d, *J* = 6.7

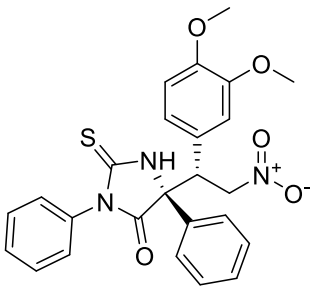
Hz, 2H, ArH), 4,80 (t, *J* =12.5 Hz, 1H, CH-CH$_2$-NO$_2$), 4.56 (dd, *J* = 11.4, 3.9 Hz, 1H, CH-CH$_2$-NO$_2$), 4.35 (dd, *J* = 12.7, 3.9 Hz, 1H, CH-CH$_2$-NO$_2$). **^{1}H NMR** (CD$_3$)$_2$SO, 400 MHz: 11.67 (s, 1H), NH), 7.79 (d, *J* = 7.3Hz, 1H,), 7.59 (t, *J* = 7.2 Hz, 2H), 7.55-7.37 (m, 6H), 7.35-7.25 (m, 3H), 6.38 (d, *J* = 6.6 Hz, 2H), 5.24 (dd, *J* = 14.5, 12.8 Hz, 1H), 4.54 (dd, *J* = 4.4, 2.6 Hz, 1H), 4.51 (t, *J* = 4.4 Hz, 1H). **^{13}C NMR** (((CD$_3$)$_2$SO, 75 MHz): 182.6 (q), 172.7 (q), 134.5 (q), 133.4 (q), 132.8 (q), 129.9 (CH), 129.8 (CH), 129.7 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.5 (CH), 126.2 (CH), 75.3 (CH$_2$), 71.8 (q), 51.7 (CH).

(±) 3-(3,5-bis(trifluoromethyl)phenyl)-5-(2-nitro-1-phenylethyl)-5-phenyl-2-thioxoimidazolidin-4-one (426b)



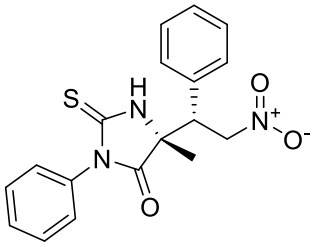
Reaction time is 4 hours. Product was purified by column chromatography (hexane/acetone 9:1) to give a brown oil. Yield: 79%. **D.r.**: 3:1. **MS** (ESI-) *m/z*: 552.1 [M-H]$^-$. **HR MS** (m/z) for [C$_{25}$H$_{16}$F$_6$N$_3$O$_3$S]$^-$ calculated [M-H]$^-$ 552.0822, measured [M-H]$^-$ 552.0822. **IR** (cm^{-1}): 3307 (N-H, stretch), 1735 (C-O, stretch), 1555 and 1374 (N-O, stretch), 1410 (C-F, stretch), 1136 (C-S, stretch). **^{1}H NMR** (CDCl$_3$, 400 MHz): 9.74 (s, 1H, NH), 7.77 (s, 1H, ArH, **C21**), 7.74 (dd, *J* = 8.4, 1.5 Hz, 2H, ArH, **C19**, **C23**), 7.52-7.36 (m, 8H, ArH, **C5**, **C6**, **C7**, **C8**, **C9**, **C13**, **C14**, **C15**, **C16**, **C17**), 6.88 (s, 2H, ArH, **C5**, **C6**, **C7**, **C8**, **C9**, **C13**, **C14**, **C15**, **C16**, **C17**), 4.85 (dd, *J* = 13.0, 11.6 Hz, 1H, CH-CH$_2$-NO$_2$, **C10**), 4.57 (dd, *J* = 11.5, 3.9 Hz, 1H, CH-CH$_2$-NO$_2$, **C11**), 4.32 (dd, *J* = 13.2, 3.9 Hz, 1H, CH-CH$_2$-NO$_2$, **C10**). **^{19}F NMR** (CDCl3, 300 MHz): -63 ppm. **^{13}C NMR** (CDCl$_3$, 75 MHz): 180.0 (q, **C1**), 169.4 (q, **C2**), 131.2 (q), 130.8 (q), 130.5 (q), 130.4 (q), 129.8 (q), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.3 (CH), 126.9 (CH), 126.8 (CH), 123.6 (CH, **C19**, **C23**), 121, 4 (CH, **C21**), 72.5 (CH$_2$, **C10**), 70.4 (q, **C3**), 50.4 (CH, **C11**).

(±) 5-(1-(3,4-dimethoxyphenyl)-2-nitroethyl)-3,5-diphenyl-2-thioxoimidazolidin-4-one (426d)



Reaction time is 5 hours. Product was purified by column chromatography (hexane/acetone 9:1) to give a yellow solid. Yield: 31%. **D.r.**: 10:1. **Mp** 242 °C. **MS** (ESI-) *m/z*: 476.1 $[M-H]^-$. **HR MS** (m/z) for $[C_{25}H_{22}N_3O_5S]^-$ calculated $[M-H]^-$ 476.1286, measured $[M-H]^-$ 476.1274. **IR** (cm^{-1}): 3321 (N-H, stretch), 1721 (C-O, stretch), 1497 and 1410 (N-O, stretch), 1237 (C-O stretch, ether), 1018 (C-S, stretch). ^{1}**H NMR** ($CDCl_3$, 400 MHz): 9.49 (d, *J* = 7.6 Hz, NH, 1H), 7.69 (d, *J* = 6.8 Hz, 2H, ArH), 7.47-7.38 (m , 5H, ArH), 7.30-7.22 (m, 4H, ArH), 6.95-6.70 (m, 4H, ArH), 6.52 (dd, *J* = 7.3, 1.4 Hz, 2H, ArH), 4.80 (dd, *J* = 12.5, 11.9 Hz, 1H, CH-CH_2-NO_2), 4.47 (dd, *J* = 11.6, 4.0 Hz, 1H, CH-CH_2-NO_2), 4.29 (dd, *J* = 13.1, 4.2 Hz, 1H, CH-CH_2-NO_2), 3.83 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3). ^{13}**C NMR** ($CDCl_3$, 75 MHz): 183.5 (q), 172.1 (q), 149.9 (q), 149.2 (q), 131.9 (q), 129.8 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 128.0 (CH), 126.1 (CH), 125.7 (CH), 125.6 (CH), 124.1 (CH), 112.4 (CH), 111.4 (CH), 75.0 (CH_2), 71.9 (q), 56.2 (CH_3), 56.1 (CH_3), 51.7 (CH).

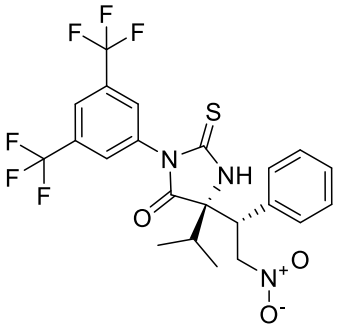
(±) 5-methyl-5-(2-nitro-1-phenylethyl)-3-phenyl-2-thioxoimidazolidin-4-one (426e)



Reaction time is 5 hours. Product was purified by column chromatography (hexane/acetone 9:1) as white solid. Yield: 49%. **D.r.**: 2:1. **Mp** 239 °C. **MS** (ESI-) *m/z*: 354.4 $[M-H]^-$. **HR MS** (m/z) for $[C_{18}H_{16}N_3O_3S]^-$ calculated $[M-H]^-$ 354.0918, measured $[M-H]^-$ 354.0920. **IR** (cm^{-1}): 3293 (NH, stretch), 1746 (C-O, stretch), 1551and 1374 (N-O, stretch), 1162 (C-S, stretch). ^{1}**H NMR** ($CDCl_3$, 400 MHz) major diastereomer: 8.62 (s, 1H, NH), 7.50-7.28 (m, 8H + 8H (of the minor diastereomer), ArH), 6.60 (dd, *J* = 4.9, 3.6 Hz, 2H, ArH), 4.91 (m, 2H, CH-CH_2-NO_2), 3.98 (dd, *J* = 9.3, 5.9 Hz, 1H, CH-CH_2-NO_2), 1.62 (s, 3H, CH_3). ^{1}**H NMR** ($CDCl_3$, 400 MHz) minor diastereomer: 7.83 (s, 1H, NH), 7.50-7.28 (m, 8H + 8H (of the major diastereomer), ArH), 7.00 (dd, *J* = 8.0, 2.1 Hz, 2H, ArH), 5.01 (dd, *J* = 13.5, 10.2 Hz, 1H, CH-CH_2-NO_2), 4.81 (dd, *J* = 13.5, 5.1 Hz, 1H, CH-CH_2-NO_2), 3.92 (dd, *J* = 10.2, 5.3 Hz, 1H, CH-CH_2-NO_2), 1.54 (s, 3H, CH_3). ^{13}**C NMR** ($CDCl_3$, 75 MHz) (minor diastereomer + major diastereomer):182.9 (q), 182.4 (q), 174.4 (q), 174.2 (q), 133.1(q), 132.9, 132.0 (q), 131.9 (q), 129.6 (CH), 129.5 (CH), 129.4 (CH), 129.3

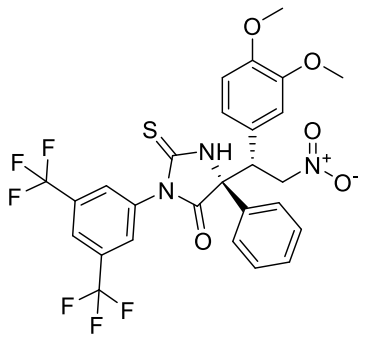
(CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 74.8 (CH_2), 74.5 (CH_2), 66.2 (q), 65.8 (q), 50.0, (CH), 49.9 (CH), 22.6 (CH_3), 20.6 (CH_3).

(±) 3-(3,5-bis(trifluoromethyl)phenyl)-5-isopropyl-5-(2-nitro-1-phenylethyl)-2-thioxoimidazolidin-4-one (426g)



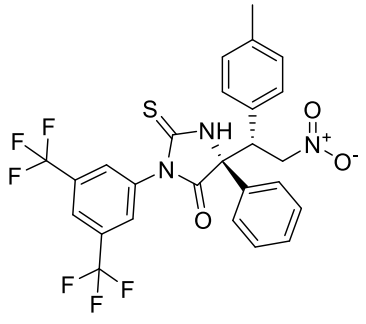
Reaction time is 24 hours. Product was purified by column chromatography (hexane/acetone, 9:1) to give a white solid. Yield: 38%. **D.r.**: 3:1. **Mp** 242 ˚C. **MS** (ESI-) *m/z*: 518.1 $[M-H]^-$. **HR MS** (m/z) for $[C_{22}H_{18}N_3O_3S]^-$ calculated $[M-H]^-$ 518.0979, measured $[M-H]^-$ 518.0968. **IR** (cm^{-1}): 3324 (NH, stretch), 1752 (C-O, stretch), 1553and 1375 (N-O, stretch), 1410 (C-F, stretch), 1162 (C-S, stretch). ^{1}**H NMR** ($CDCl_3$, 400 MHz) of major diastereomer: 8.28 (s, 1H, NH), 7.77 (s, 1H, ArH), 7.45-7.20 (m, 7H, ArH), 6.84 (s, 2H, ArH), 4.94 (t, *J* = 12.1 Hz, 1H, CH-CH_2-NO_2), 4.80 (dd, *J* = 12.7, 4.4 Hz, 1H, CH-CH_2-NO_2), 4.22 (dd, *J* = 11.0, 4.3 Hz, 1H, CH-CH_2-NO_2), 2.20 (sept, *J* = 6.7 Hz, 1H, CH_3-CH-CH_3), 1.37 (d, *J* = 7.0 Hz, 3H, CH_3-CH-CH_3), 1.08 (d, *J* = 6.6 Hz, 3H, CH_3-CH-CH_3). ^{1}**H NMR** ($CDCl_3$, 400 MHz) of minor diastereomer: 8.28 (s, 1H, NH), 7.83 (s, 1H, ArH), 7.45-7.20 (m, 7H, ArH), 7.18 (s, 1H, ArH), 5.26 (dd, *J* = 13.6, 11.4 Hz, 1H, CH-CH_2-NO_2), 4.84 (dd, *J* = 13.6, 4.4 Hz, 1H, CH-CH_2-NO_2), 3.99 (dd, *J* = 11.1, 4.3 Hz, 1H, CH-CH_2-NO_2), 2.34 (sept, *J* = 6.9 Hz, 1H, CH_3-CH-CH_3), 1.21 (d, *J* = 6.9 Hz, 3H, CH_3-CH-CH_3), 1.04 (d, *J* = 6.5 Hz, 3H, CH_3-CH-CH_3). ^{19}**F NMR** ($CDCl_3$, 300 MHz): -63 ppm. ^{13}**C NMR** ($CDCl_3$, 100 MHz): 181.9 (q), 172.1 (q), 133.4 (q), 132.7 (q), 132.6 (q), 132.1 (q), 129.6 (CH), 129.4 (CH), 129.2 (CH), 128.7 (CH), 124.4 (CH), 123.0 (CH), 120.8 (CH), 74.5 (CH_2), 73.2 (q), 47.2 (CH), 33.0 (CH), 17.6 (CH_3), 15.9 (CH_3).

(±) 3-(3,5-bis(trifluoromethyl)phenyl)-5-(1-(3,4-dimethoxyphenyl)-2-nitroethyl)-5-phenyl-2-thioxoimidazolidin-4-one (426h)



Reaction time is 24 hours. Product was purified by column chromatography (hexane/acetone, 5:1) to give a yellow solid. Yield: 32%. **D.r.**: 10:1. **Mp** 245 ˚C. **MS** (ESI-) *m/z*: 612.2 [M-H]$^-$. **HR MS** (m/z) for $[C_{27}H_{20}F_6N_3O_5S]^-$ calculated [M-H]$^-$ 612.1033, measured [M-H]$^-$ 612.1032. **IR** (cm^{-1}): 3311 (N-H, stretch), 1717 (C-O, stretch), 1515 and 1371 (N-O, stretch), 1407 (C-F, stretch), 1277 (C-O stretch, ether), 1021 (C-S, stretch). ^{1}**H NMR** ($CDCl_3$, 400 MHz): 8.94 (s, 1H, NH), 7.70 (d, *J* = 7.1 Hz, 2H, Ar<u>H</u>), 7.55-7.35 (m, 5H, Ar<u>H</u>), 6.99 (s, 2H, Ar<u>H</u>), 6.91 (dd, *J* = 8.3, 2.1 Hz, 1H, Ar<u>H</u>), 6.84 (s, 2H, Ar<u>H</u>), 4.74 (dd, *J* = 12.7, 11.0 Hz, 1H, CH-C<u>H</u>$_2$-NO_2), 4.46 (dd, *J* = 10.8, 4.2 Hz, 1H, C<u>H</u>-CH_2-NO_2), 4.38 (dd, *J* = 12.7, 4.2 Hz, 1H, CH-C<u>H</u>$_2$-NO_2), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3). ^{19}**F NMR** ($CDCl_3$, 300 MHz): -63 ppm. ^{13}**C NMR** ($CDCl_3$, 100 MHz): 181.9 (q), 171.5 (q), 150.4 (q), 149.4 (q), 133.4 (q), 132.8 (q),132.6 (q), 132.4 (q), 130.2 (CH), 130.0 (CH), 128.7 (CH), 125.5 (CH), 123.8 (CH), 123.4 (CH), 123.2 (CH), 122.1 (CH), 121.1 (CH), 112.1 (CH), 111.0 (CH), 74.8 (CH_2), 72.2 (q), 56.3 (CH_3), 55.7 (CH_3), 51.7 (CH).

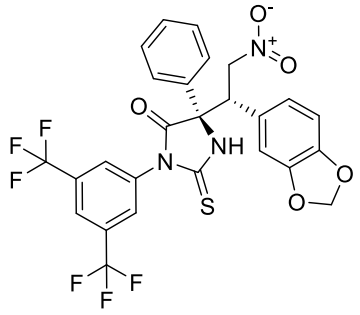
(±) 3-(3,5-bis(trifluoromethyl)phenyl)-5-(2-nitro-1-(*p*-tolyl)ethyl)-5-phenyl-2-thioxoimidazolidin-4-one (426i)



Reaction time is 24 hours. Product was purified by column chromatography (hexane/acetone 9:1) to give a brown solid. Yield: 43%. **D.r.**: 5:1. **Mp** 234 ˚C. **MS** (ESI-) *m/z*: 566.1 [M-H]$^-$. **HR MS** (m/z) for $[C_{26}H_{18}F_6N_3O_3S]^-$ calculated [M-H]$^-$ 566.0979, measured [M-H]$^-$ 566.0989. **IR** (cm^{-1}): 3297 (N-H, stretch), 1724 (C-O, stretch), 1558 and 1374 (N-O, stretch), 1410 (C-F, stretch), 1140 (C-S, stretch). ^{1}**H NMR** ($CDCl_3$, 400 MHz): 9.53 (s, 1H, NH), 7.82-6.70 (m, 12H, Ar<u>H</u>), 4.81 (t, *J* = 12.0 Hz, 1H, CH-C<u>H</u>$_2$-NO_2), 4.48 (dd, *J* = 11.5, 4.2 Hz, 1H, C<u>H</u>-CH_2-NO_2), 4.30 (dd, *J* = 12.8, 4.0 Hz, 1H, CH-C<u>H</u>$_2$-NO_2), 2.30 (s, 3H, ArC<u>H</u>$_3$). ^{19}**F NMR** ($CDCl_3$, 300 MHz): -63 ppm. ^{13}**C NMR** ($CDCl_3$, 100 MHz):182.0 (q), 171.4 (q), 140.2 (q), 133.3 (q), 132.7 (q), 132.6 (q), 132.3 (q), 130.6 (q), 130.4 (CH), 130.1 (CH), 129.9 (CH), 129.8 (CH), 129.7 (CH), 129.5

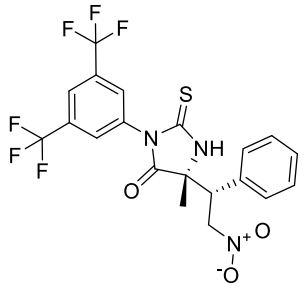
(CH), 129.2 (CH), 128.8 (CH), 128.5 (CH), 125.5 (CH), 123.9 (CH), 123.3 (CH), 121.2 (q), 74.5 (CH_2), 72.3 (q), 52.1 (CH), 20.9 (CH_3).

(±) 5-(1-(benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)-3-(3,5-bis(trifluoromethyl)phenyl)-5-phenyl-2-thioxoimidazolidin-4-one (426j)



Reaction time is 24 hours. Product was purified by column chromatography (hexane/acetone, 9:1) to give a brown solid. Yield: 18%. **D.r.**: 10:1 **Mp** 244 ˚C. **MS** (ESI-) *m/z*: 596.1 $[M-H]^-$. **HR MS** (m/z) for $[C_{26}H_{16}F_6N_3O_5S]^-$ calculated $[M-H]^-$ 596.0720, measured $[M-H]^-$ 596.0710. **IR** (cm^{-1}): 3192 (N-H, stretch), 1724 (C-O, stretch), 1490 and 1371 (N-O, stretch), 1407 (C-F, stretch), 1277 (C-O stretch, ether), 1035 (C-S, stretch). ^{1}**H NMR** ($CDCl_3$, 300 MHz): 9.37 (s, 1H, NH), 7.90 (s, 1H, Ar<u>H</u>), 7.77 (d, *J* = 8.3 Hz, 2H, Ar<u>H</u>), 7.67-7.45 (m, 5H, Ar<u>H</u>), 7.16 (s, 1H, Ar<u>H</u>), 6.98-6.85 (m, 3H, Ar<u>H</u>), 6.02 (d, *J* = 1.9 Hz, 2H, RO-C<u>H</u>$_2$-OR), 4.81 (dd, *J* = 12.8, 11.7 Hz, 1H, CH-C<u>H</u>$_2$-NO_2), 4.55 (dd, *J* = 11.3, 4.1 Hz, 1H, C<u>H</u>-CH_2-NO_2), 4.40 (dd, *J* = 12.8, 3.8 Hz, 1H, CH-C<u>H</u>$_2$-NO_2), ^{19}**F NMR** ($CDCl_3$, 300 MHz): -63 ppm. ^{13}**C NMR** ($CDCl_3$, 75 MHz): 180.0 (q), 169.6 (q), 162.5 (q), 156.2 (q), 149.2 (q), 146.9 (q), 146.4 (q), 130.8 (q), 128.2 (CH), 128.0 (CH), 127.5 (CH), 123.6 (CH), 121.1 (CH), 114.5 (CH), 107.6 (CH), 106.9 (CH), 99.9 (CH_2), 87.9 (q), 72.6 (CH_2), 49.9 (CH).

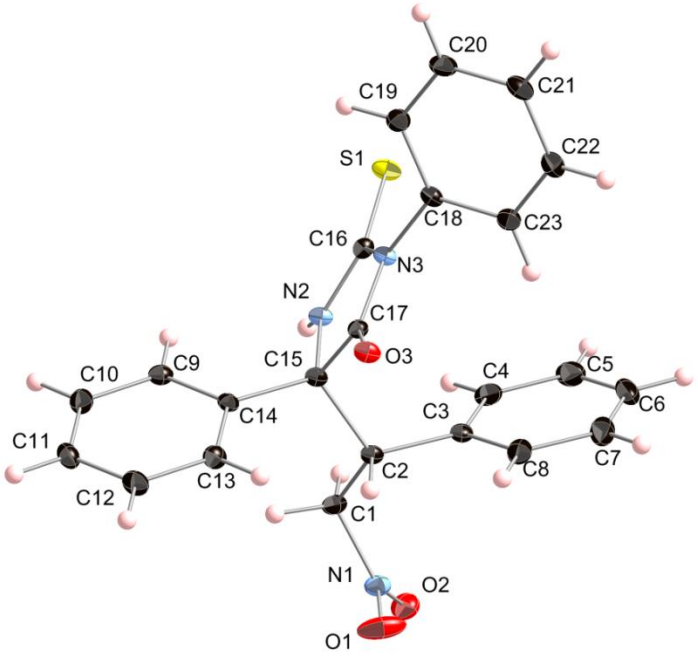
(±) 3-(3,5-bis(trifluoromethyl)phenyl)-5-methyl-5-(2-nitro-1-phenylethyl)-2-thioxoimidazolidin-4-one (426k)



Reaction time is 24 hours. Product was purified by column chromatography (hexane/acetone, 9:1) to give a beige solid. Yield: 61%. **D.r.**: 1:1. **Mp** 246 ˚C. **MS** (ESI-) *m/z*: 490.0 $[M-H]^-$. **HR MS** (m/z) for $[C_{20}H_{13}F_6N_3O_3S]^-$ calculated $[M-H]^-$ 490.0666, measured $[M-H]^-$ 490.0655. **IR** (cm^{-1}): 3324 (NH, stretch), 1752 (C-O, stretch), 1553 and 1375 (N-O, stretch), 1410 (C-F, stretch), 1162 (C-S, stretch). ^{1}**H NMR** ($CDCl_3$, 400 MHz) of diastereomer 1 and diastereomer 2: 7.86 (s, 1H, Ar<u>H</u>), 7.79 (s, 1H, Ar<u>H</u>), 7.76 (s, 1H, Ar<u>H</u>), 7.41 (s, 2H, Ar<u>H</u>), 7.39-7.30 (m, 6H, Ar<u>H</u>), 7.25-7.15 (m ,4H, Ar<u>H</u>), 7.03 (s, 2H, Ar<u>H</u>), 5.02 (dd, *J* = 13.7, 9.4 Hz, 1H, CH-C<u>H</u>$_2$-NO_2), 4.95 (dd, *J* = 13.2, 5.5 Hz, 1H, CH-C<u>H</u>$_2$-

NO_2), 4.92-4.80 (m, 2H, CH-C<u>H</u>$_2$-NO_2), 3.97 (dd, *J* = 9.5, 5.5 Hz, 1H, C<u>H</u>-CH_2-NO_2), 3.94 (dd, *J* = 10.2, 5.8 Hz, 1H, C<u>H</u>-CH_2-NO_2), 1.68 (s, 3H, C<u>H</u>$_3$), 1.61 (s, 3H, C<u>H</u>$_3$). **^{19}F NMR** ($CDCl_3$, 300 MHz): -63 ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz) of diastereomer 1 and diastereomer 2:181.2 (q), 180.6 (q), 173.5 (q), 173.5 (q), 133.3 (q), 132.8 (q), 132.6 (q), 132.6 (q), 132.4 (q), 132.3 (q), 129.7 (CH), 129.6 (CH), 129.5 (CH), 129.4 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 123.9 (CH), 123.3 (CH), 121.2 (CH), 74.5 (CH_2), 74.1 (CH_2), 66.4 (q), 66.2 (q), 50.1 (CH), 49.9 (CH), 22.2 (CH_3), 20.4 (CH_3).

X-Ray single crystal analysis of the product of 426a



Thermal ellipsoids drawn at the 35% probability level

Single crystals of $C_{23}H_{19}N_3O_3S$ **[426a]** were diluted in minimum of chloroform and crystallyzed with hexane. A suitable crystal was selected and Mitegen mounted.

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (Sheldrick, G.M. (2008). *Acta Cryst*. **A64**, 112-122). S**tructure refinement**: SHELXL2012 (G. M. Sheldrick (2012), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com).

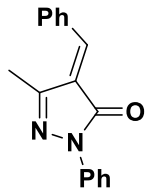
Crystal data and structure refinement details	
Identification code	**2013sot0037** (KH6725-020) **426a**
Empirical formula	$C_{23}H_{19}N_3O_3S$
Formula weight	417.47 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 10.547(3) Å b = 12.192(3) Å β = 90.411(8)° c = 16.015(4) Å
Volume	2059.3(9) Å^3
Z	4
Density (calculated)	1.347 Mg / m^3
Absorption coefficient	0.187 mm^{-1}
F(000)	872
Crystal	Plate; Orange
Crystal size	0.210 × 0.080 × 0.020 mm^3
θ range for data collection	3.044 – 27.481°
Index ranges	$-13 \le h \le 13$, $-15 \le k \le 15$, $-18 \le l \le 20$
Reflections collected	13665
Independent reflections	4707 [R_{int} = 0.0368]
Completeness to θ = 25.242°	99.6 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	1.000 and 0.808
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4707 / 0 / 275

Goodness-of-fit on F^2	1.126
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0534, *wR2* = 0.1014
***R* indices (all data)**	*R1* = 0.0652, *wR2* = 0.1060
Extinction coefficient	n/a
Largest diff. peak and hole	0.359 and −0.261 e $Å^{-3}$

4.6 Highly diastereoselective synthesis of spiropyrazolones

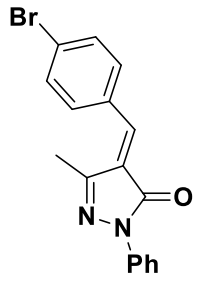
Starting material

4-benzylidene-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (427a)[191]



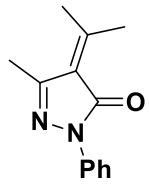
To a round bottom flask charged with chloroform (50 ml) was added 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (1equiv, 4 g, 23 mmol), benzaldehyde (1.1 equiv, 2.7 g, 25 mmol) and aluminium oxide (7 equiv, 16 g, 161 mmol). The solution was stirred for 24 hours at room temperature. The aluminium oxide was filtered, then the product was purified by column chromatography (hexane/EtOAc, 6:1). The product yield is 22 %. ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.96 (dd, *J* = 8.7, 1.1 Hz, 2H), 7.58 – 7.48 (m, 3H), 7.46 – 7.38 (m, 3H), 7.18 (dd, *J* = 11.6, 4.3 Hz, 1H), 2.37 (s, 3H). The spectroscopical data matched with the previous reported in the literature.

4-(4-bromobenzylidene)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (427b)[192]



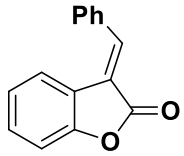
To a round bottom flask charged with chloroform (50 ml) was added 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (1equiv, 1 g, 6.3 mmol), 4-bromobenzaldehyde (1.1 equiv, 1.2 g, 5.8 mmol) and aluminium oxide (7 equiv, 4 g, 39.8 mmol). The solution was stirred for 14 hours at room temperature. The aluminium oxide was filtered, then the product was purified by column chromatography (hexane/EtOAc, 3:1). The product yield is 23 %. ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.6 Hz, 2H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.47 – 7.38 (m, 2H), 7.31 (s, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 2.36 (s, 3H). The spectroscopical data matched with the previous reported in the literature.

5-methyl-2-phenyl-4-(propan-2-ylidene)-2,4-dihydro-3H-pyrazol-3-one (427c)[193]



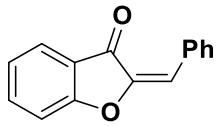
To a round bottom flask charged with acetone (200 equiv, 160 ml, 2.2 mol) was added 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (1equiv, 2 g, 11 mmol). The solution was stirred for 24 hours at room temperature. The mixture was concentrated in vacuo. The product was recrystallized in 2-propanol. The product yield is 30 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97 – 7.88 (m, 2H), 7.44 – 7.34 (m, 2H), 7.16 (ddd, *J* = 7.1, 2.3, 1.1 Hz, 1H), 2.63 (s, 3H), 2.43 (s, 3H), 2.37 (s, 3H). The spectroscopical data matched with the previous reported in the literature.

3-benzylidenebenzofuran-2(3H)-one (476)[194]



To a round bottom flask charged with chloroform (50 ml) was added benzofuran-2(3H)-one (1equiv, 1 g, 7.5 mmol), benzaldehyde (1.1 equiv, 870 mg, 8.2 mmol) and aluminium oxide (7 equiv, 5.3 g, 52 mmol). The solution was stirred for 14 hours at room temperature. The aluminium oxide was filtered, then the mixture was concentrated in vacuo to give the product in 57 % yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.76 – 7.64 (m, 3H), 7.57 – 7.44 (m, 3H), 7.38 – 7.28 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.04 (td, *J* = 7.7, 0.9 Hz, 1H). The spectroscopical data matched with the previous reported in the literature.

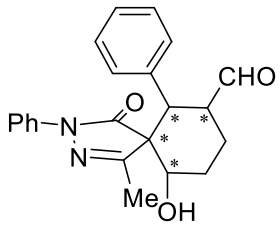
2-benzylidenebenzofuran-3(2H)-one (478)[195]



To a round bottom flask charged with chloroform (50 ml) was added benzofuran-2(3H)-one (1equiv, 200 mg, 1.5 mmol), benzaldehyde (1.1 equiv, 237 mg, 2.2 mmol) and aluminium oxide (7 equiv, 2.5 g, 10.3 mmol). The solution was stirred for 48 hours at room temperature. The aluminium oxide was filtered, then the mixture was concentrated in vacuo to give the product in 90 % yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 2H), 7.85 – 7.79 (m, 1H), 7.71 – 7.63 (m, 1H), 7.52 – 7.40 (m, 3H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 6.91 (s, 1H). The spectroscopical data matched with the previous reported in the literature.

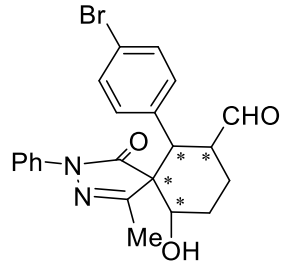
General procedure for the preparation spiropyrazolones (429): To a solution of unsaturated pyrazolone (1 equiv) in toluene was added glutaraldehyde (3 equiv) and (*S*)-2-(diphenyl ((trimethylsilyl) oxy) methyl)pyrroline (0.2 equiv). The solution was stirred for 3 days and subsequently the solvent was removed by rotary evaporation. The reaction mixture was purified by column chromatography (Hexane/AcOEt). The product was confirmed by ^{1}H-NMR.

(±)-10-hydroxy-1-methyl-4-oxo-3,6-diphenyl-2,3-diazaspiro[4.5]dec-1-ene-7-carbaldehyde (429a)



The mixture was purified by column chromatography (hexane/EtOAc, 5:1) to give a brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.59 (d, *J* = 1.9 Hz, 1H, CHO), 7.91 – 7.72 (m, 2H, ArH), 7.56 – 7.46 (m, 2H, ArH), 7.40 – 7.30 (m, 6H, ArH), 4.17 (dd, *J* = 11.9, 4.2 Hz, 1H, CHOH), 4.10 (ddd, *J* = 12.1, 3.6, 2.0 Hz, 1H, Ar-CH-CH-CHO), 3.27 (d, *J* = 12.0 Hz, 1H, Ar-CH-CH-CHO), 2.83 (m, 1H, CH_2), 2.43 – 2.36 (m, 1H, CH_2), 2.35 (s, 3H, CH_3), 2.19 – 2.11 (m, 1H, CH_2), 1.79 – 1.66 (m, 1H, CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 203.0 (CH), 172.6 (q), 160.5 (q), 137.4 (q), 135.8 (q), 128.8 (CH), 128.7 (CH), 127.9 (CH), 125.4 (CH), 119.7 (CH), 71.9 (CH), 64.0 (q), 47.5 (CH), 46.7 (CH), 27.0 (CH_2), 24.5 (CH_2), 13.6 (CH_3). **MS** (ESI+) *m/z* 363.32 ($[M + H]^+$). **HR MS** (ESI) for $[C_{22}H_{23}N_2O_3]^+$ $[M+H]^+$ calculated 363.1703, measured 363.1705. **IR** (cm^{-1}): 3399 (br), 2940 (m), 2869 (m), 1690 (s), 1596 (m), 1454 (w), 1399 (w), 1367 (m), 1299 (m), 1069 (m), 909 (s). The enantiomeric excess was determined by **HPLC** using a Chiralpak ID column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 210 nm): t_{r1}= 13.4 min, t_{r2} = 15.6 min, 32% *ee.*

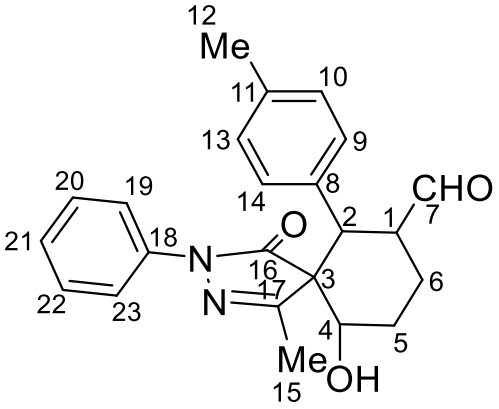
(±)-6-(4-bromophenyl)-10-hydroxy-1-methyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-ene-7-carbaldehyde (429b)



The reaction mixture was purified by column chromatography (hexane/EtOAc, 3:2) to give a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.41 (d, *J* = 1.8 Hz, 1H, CHO), 7.63 – 7.58 (m, 2H, ArH), 7.34 (m, 3H, ArH), 7.29 (d, *J* = 8.6 Hz, 2H, ArH), 7.16 (ddd, *J* = 8.5, 2.3, 1.1 Hz, 1H, ArH), 7.06 (d, *J* = 8.5 Hz, 2H, ArH), 3.97 (dd, *J* = 11.6, 4.6 Hz, 1H, CHOH), 3.89 (tdd, *J* = 12.1, 3.6, 1.8 Hz, 1H, Ar-CH-CH-CHO), 3.08 (d, *J* = 11.9 Hz, 1H, Ar-CH-CH-CHO), 2.63 (ddd, *J* = 16.1, 13.0, 4.0 Hz, 1H, CH_2), 2.22

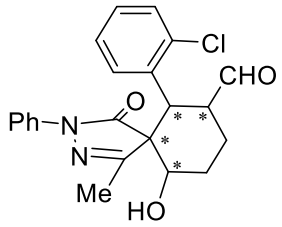
(m, 1H, CH_2), 2.14 (s, 3H, CH_3), 2.01 – 1.93 (m, 1H, CH_2), 1.53 – 1.41 (m, 1H, CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 201.3 (CH), 171.4 (q), 159.3 (q), 136.2 (q), 134.1 (q), 130.8 (q), 127.7 (CH), 124.4 (CH), 121.0 (CH), 118.5 (CH), 70.6 (CH), 62.7 (q), 45.7 (CH), 45.4 (CH), 25.7 (CH_2), 23.3 (CH_2), 12.4 (CH_3). **MS** (ESI+) *m/z* 441.19 ($[M + H]^+$). **HR MS** (ESI) for $[C_{22}H_{22}BrN_2O_3]^+$ $[M+H]^+$ calculated 441.0808, measured 441.0810. **IR** (cm^{-1}): 3412 (br), 2930 (w), 1693 (s), 1595 (m), 1491 (s), 1401 (w), 1367 (m), 1298 (m), 1075 (m), 909 (m). The enantiomeric excess was determined by **HPLC** using a Chiralpak ID column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 210 nm): t_{r1}= 11.5 min, t_{r2} = 12.7 min, 24% *ee.*

(±)-10-hydroxy-1-methyl-4-oxo-3-phenyl-6-(*p*-tolyl)-2,3-diazaspiro[4.5]dec-1-ene-7-carbaldehyde (429c)



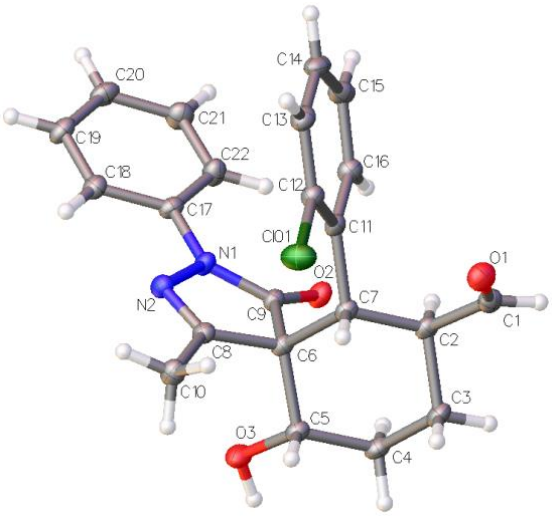
The reaction mixture was purified by column chromatography (hexane/EtOAc, 3:2) to give a white solid. **Mp** 94 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.38 (d, *J* = 2.0 Hz, 1H, C<u>H</u>O, **C7**), 7.66-7.60 (m, 2H, **C19**, **C23**), 7.37-7.30 (m, 2H, Ar<u>H</u>. **C20**, **C22**), 7.15 (t, *J* = 7.4 Hz, 1H, Ar<u>H</u>, **C21**), 7.06 (d, *J* = 8.0 Hz, 2H, Ar<u>H</u>, **C9**, **C14**), 6.96 (d, *J* = 8.0 Hz, 2H, Ar<u>H</u>, **C10**, **C13**), 3.94 (dd, *J* = 11.6, 4.6 Hz, 1H, C<u>H</u>OH, **C4**), 3.88 (tdd, *J* = 12.0, 3.6, 2.0 Hz, 1H, Ar-CH-C<u>H</u>-CHO, **C1**), 3.02 (d, *J* = 12.0 Hz, 1H, Ar-C<u>H</u>-CH-CHO, **C2**), 2.61 (ddd, *J* = 25.2, 13.3, 4.1 Hz, 1H, CH_2, **C5**), 2.22-2.16 (overlapping signals, 4H, CH_3, CH_2, **C15**, **C5**), 2.13 (s, 3H, $ArCH_3$, **C12**), 1.97-1.88 (m, 1H, CH_2, **C6**) and 1.49 (ddd, *J* = 26.1, 13.3, 4.1 Hz, 1H, CH_2, **C6**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.2 (**C7**), 172.7 (q, **C16**), 160.5 (q, **C17**), 137.8 (q, **C11**), 137.4 (q, **C18**), 132.6 (q, **C8**), 129.5 (**C10**, **C13**), 128.6 (**C20**, **C22**), 127.7 (**C9**, **C14**), 125.3 (**C21**), 119.6 (**C19**, **C23**), 71.9 (**C4**), 64.1 (q, **C3**), 47.2 (**C1**), 46.8 (**C2**), 26.9 (CH_2, **C5**), 24.4 (CH_2, **C6**), 20.9 (**C12**), 13.5 (**C15**). **MS** (ESI+) *m/z* 377.37 ($[M + H]^+$). **HR MS** (ESI) for $[C_{23}H_{25}N_2O_3]^+$ $[M+H]^+$ calculated 377.1860, measured 377.1867. **IR** (cm^{-1}): 3436 (br), 2951 (w), 1697 (s), 1596 (m), 1499 (s), 1400 (w), 1366 (m), 1298 (m), 1068 (m), 908 (m). The enantiomeric excess was determined by **HPLC** using a Chiralpak ID column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 210 nm): t_{r1}= 12.1 min, t_{r2} = 14.3 min, 26% *ee.*

(±)-6-(2-chlorophenyl)-10-hydroxy-1-methyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-ene-7-carbaldehyde (429d)



The reaction mixture was purified by column chromatography (hexane/EtOAc, 3:2) to give a pink solid. **Mp** 96 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 2.2 Hz, 1H, CHO), 7.71 (dd, *J* = 7.4, 6.3 Hz, 2H, ArH), 7.42-7.30 (m, 4H, ArH), 7.18 (t, *J* = 7.4 Hz, 1H, ArH), 7.08 (td, *J* = 7.6, 1.5 Hz, 1H, ArH), 7.02 (td, *J* = 7.6, 1.5 Hz, 1H, ArH), 4.06-3.98 (m, 1H, CHOH), 3.88 (d, *J* = 11.9 Hz, 1H, Ar-CH-CH-CHO), 3.76 (tdd, *J* = 11.9, 3.4, 2.4 Hz, 1H, Ar-CH-CH-CHO), 2.65 (ddd, *J* = 25.4, 13.3, 4.3 Hz, 1H), 2.19 (s, 3H, CH_3), 2.17-2.13 (m, 1H, CH_2), 2.11 (m, 1H, CH_2), 1.95 (ddd, *J* = 9.2, 7.5, 4.1 Hz, 1H, CH_2) and 1.59 (ddd, *J* = 25.4, 13.3, 4.1 Hz, 1H, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.1 (CH), 172.8 (q), 161.0 (q), 137.4 (q), 134.0 (q), 133.5 (q), 130.0 (CH), 129.2 (CH), 128.8 (CH), 128.5 (CH), 127.6 (CH), 125.4 (CH), 119.5 (CH), 72.2 (CH), 63.3 (q), 48.0 (CH), 41.9 (CH), 26.7 (CH_2), 24.4 (CH_2), 13.7 (CH_3). **MS** (ESI+) *m/z* 397.24 ($[M + H]^+$). **HR MS** (ESI) for $[C_{22}H_{22}ClN_2O_3]^+$ $[M+H]^+$ calculated 397.1313, measured 397.1323. **IR** (cm^{-1}): 3436 (br), 2930 (w), 1692 (s), 1595 (m), 1476 (s), 1400 (w), 1369 (m), 1298 (m), 1055 (m), 910 (m). The enantiomeric excess was determined by **HPLC** using a Chiralpak ID column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 210 nm): t_{r1}= 14.1 min, t_{r2} = 16.4 min, 3% *ee*.

X-Ray single crystal analysis of the product of 429d



Displacement ellipsoids – 50% probability level

Experimental

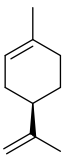
Single crystals of $C_{22}H_{21}ClN_2O_3$ **[429d]**. A suitable crystal was selected and **Mitegen Mount** on a **Rigaku AFC11 007-HF** diffractometer. The crystal was kept at 100(2) K during data collection. Using Olex2 [Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341], the structure was solved with the ShelXT [Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8] structure solution program using Direct Methods and refined with the ShelXL [Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122] refinement package using Least Squares minimisation.

Crystal structure determination of [429d]

Crystal Data for $C_{22}H_{21}ClN_2O_3$ (M =396.86 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 9.90175(13) Å, b = 8.02985(9) Å, c = 23.3685(3) Å, β = 96.4448(12)°, V = 1846.28(4) Å^3, Z = 4, T = 100(2) K, μ(CuKα) = 2.056 mm^{-1}, *Dcalc* = 1.428 g/cm^3, 24601 reflections measured (9.36° ≤ 2Θ ≤ 138.082°), 3363 unique (R_{int} = 0.0868, R_{sigma} = 0.0313) which were used in all calculations. The final R_1 was 0.0456 (I > 2σ(I)) and wR_2 was 0.1231 (all data).

Crystal data and structure refinement for 2015VC002 429d	
Identification code	2015VC002 (TO13cS)
Empirical formula	$C_{22}H_{21}ClN_2O_3$
Formula weight	396.86 g/mol
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	9.90175(13)
b/Å	8.02985(9)
c/Å	23.3685(3)
α/°	90
β/°	96.4448(12)
γ/°	90
Volume/Å³	1846.28(4)
Z	4
ρ_{calc}g/cm³	1.428
μ/mm⁻¹	2.056
F(000)	832.0
Crystal size/mm³	0.22 × 0.1 × 0.04
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.36 to 138.082
Index ranges	$-11 \le h \le 11$, $-8 \le k \le 9$, $-27 \le l \le 28$
Reflections collected	24601
Independent reflections	3363 [R_{int} = 0.0868, R_{sigma} = 0.0313]
Data/restraints/parameters	3363/0/258
Goodness-of-fit on F²	1.107
Final R indexes [I>=2σ (I)]	R_1 = 0.0456, wR_2 = 0.1228
Final R indexes [all data]	R_1 = 0.0461, wR_2 = 0.1231
Largest diff. peak/hole / e Å⁻³	0.32/-0.46

Molecular structures



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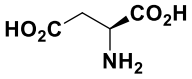

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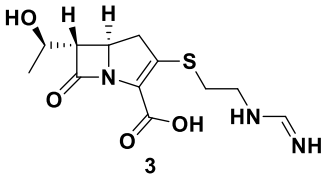

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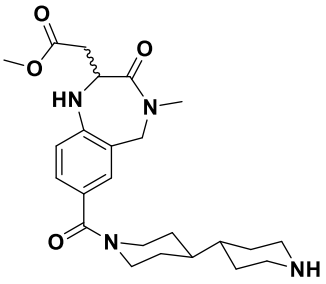

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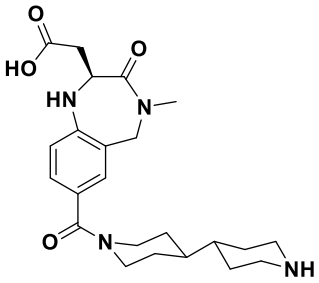

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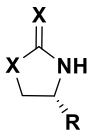

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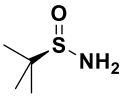

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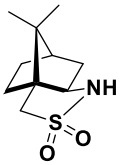

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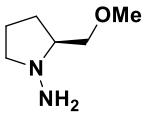

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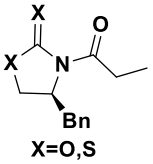

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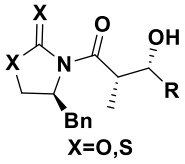

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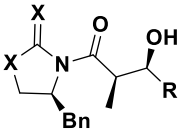

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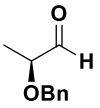

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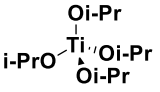

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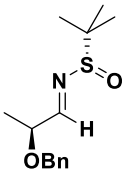

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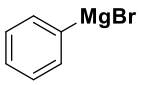

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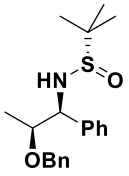

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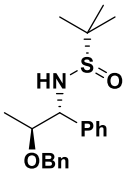

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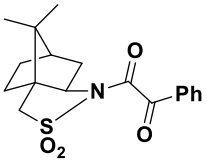

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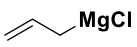

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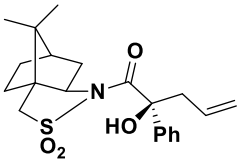

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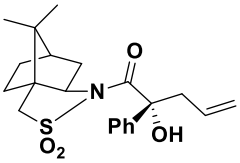

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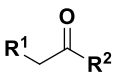

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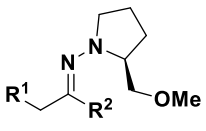

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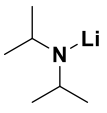

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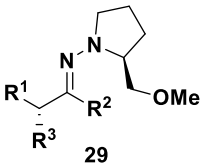

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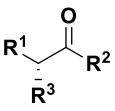

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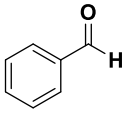

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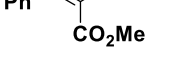

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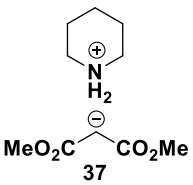

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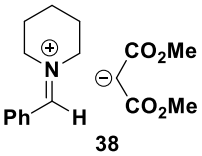

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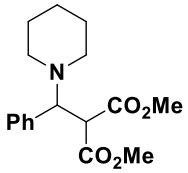

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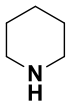

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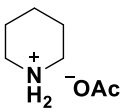

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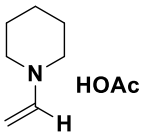

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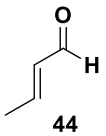

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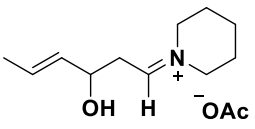

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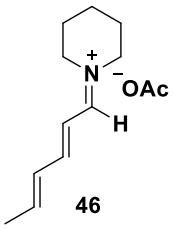

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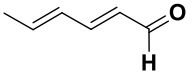

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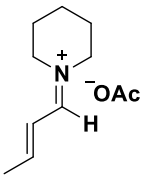

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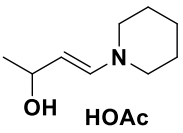

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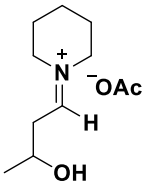

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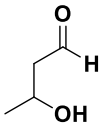

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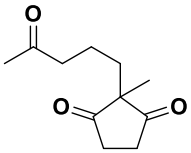

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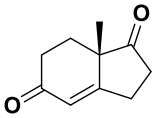

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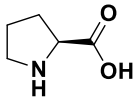

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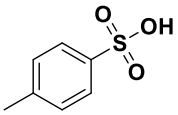

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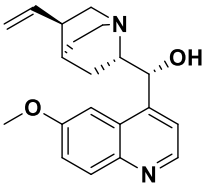

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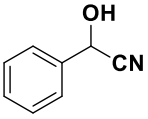

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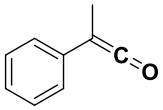

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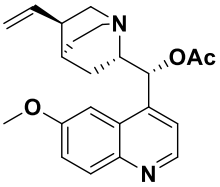

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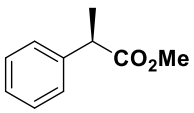

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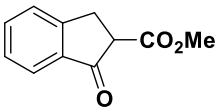

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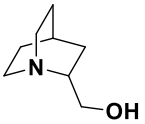

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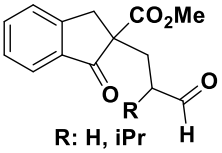

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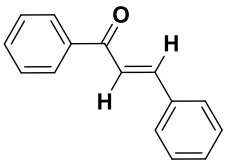

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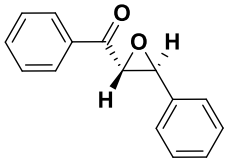

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NaOH

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H_2O_2

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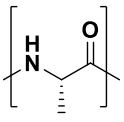

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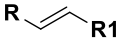

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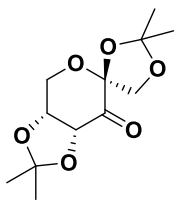

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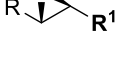

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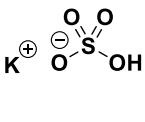

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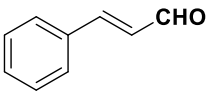

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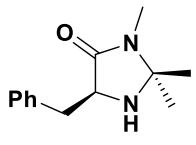

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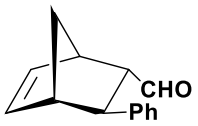

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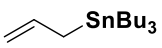

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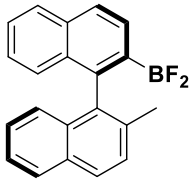

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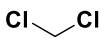

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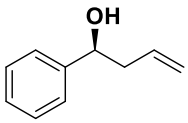

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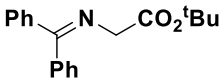

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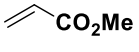

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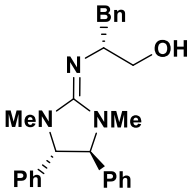

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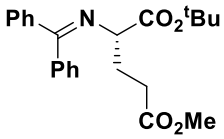

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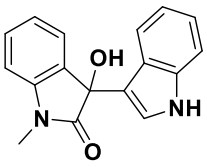

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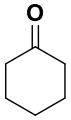

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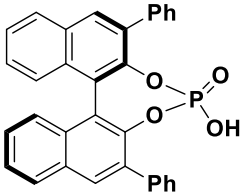

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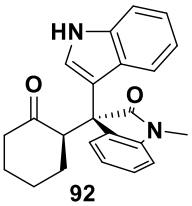

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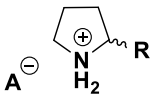

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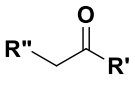

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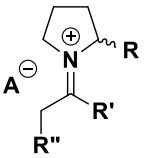

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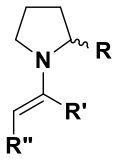

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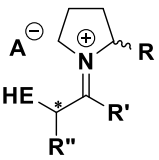

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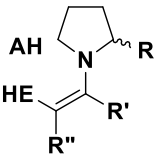

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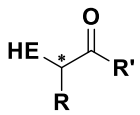

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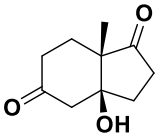

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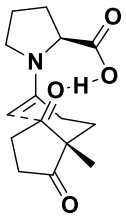

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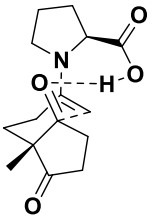

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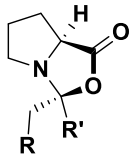

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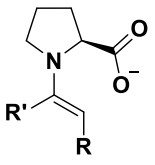

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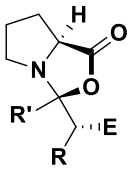

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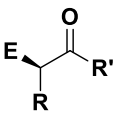

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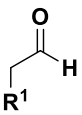

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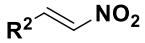

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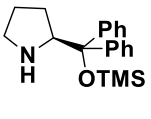

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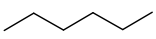

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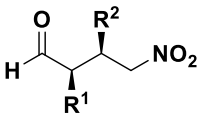

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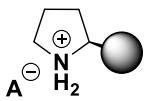

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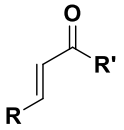

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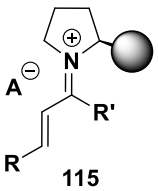

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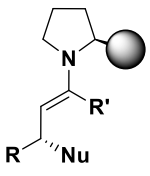

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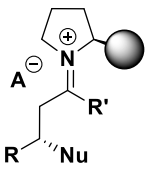

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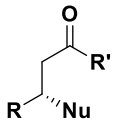

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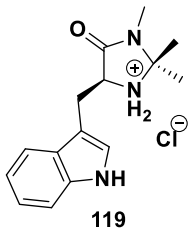

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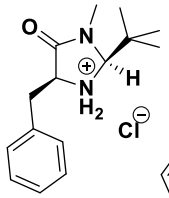

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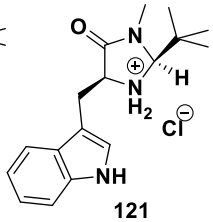

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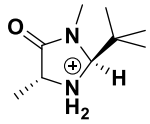

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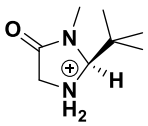

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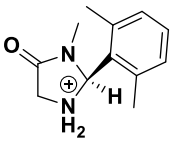

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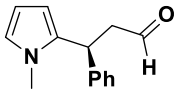

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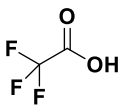

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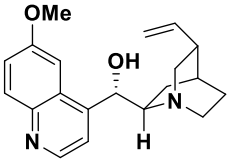
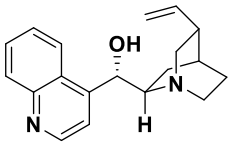
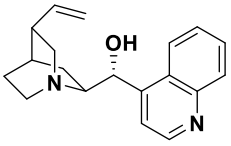


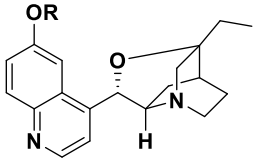
Quinidine (128)



Cinchonidine (129)

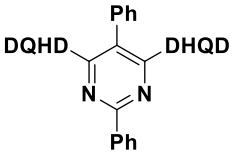


Cinchonine (130)

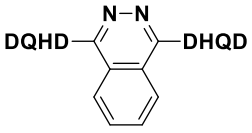


β-ICPD (R = H) (131)
Me-β-ICPD (R = Me) (132)
MOM-β-ICPD (R = CH_3OCH_2) (133)

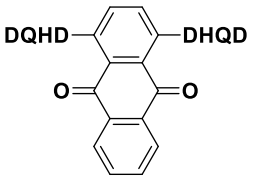
Sharpless catalysts



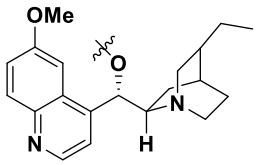
$(DHQD)_2PYR$ (134)



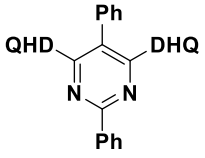
$(DHQD)_2PHAL$ (136)



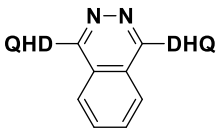
$(DHQD)_2AQN$ (138)



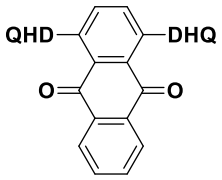
DHQD (dihydroquinidyl)



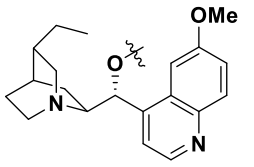
$(DHQ)_2PYR$ (135)



$(DHQ)_2PHAL$ (137)



$(DHQ)_2AQN$ (139)

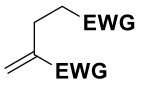


DHQ (dihydroquinyl)

140

141

142



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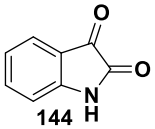

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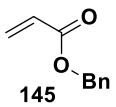

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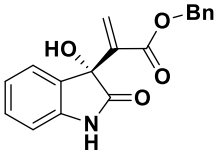

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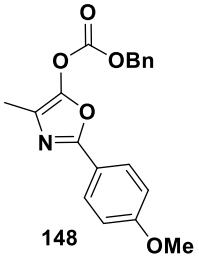

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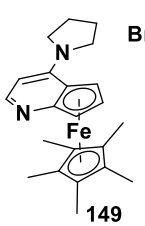

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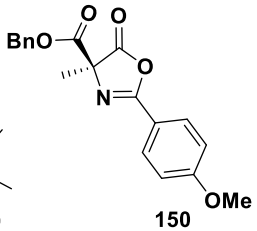

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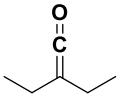

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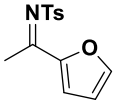

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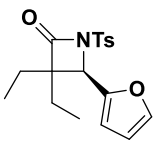

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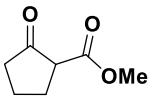

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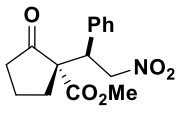

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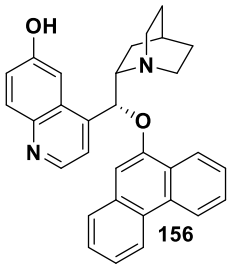

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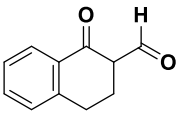

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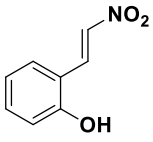

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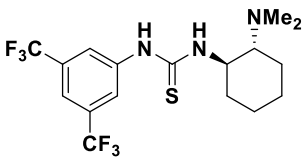

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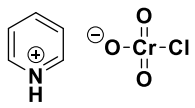

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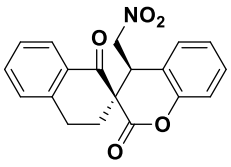

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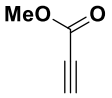

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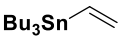


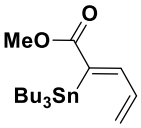
163

$Pd_2(dba)_3$

164

PPh_3AuPF_6

165



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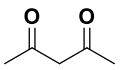
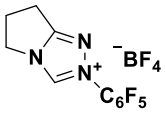


167

NaOAc



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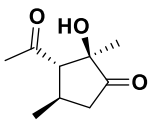

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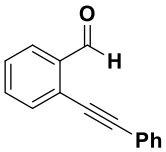

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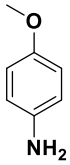


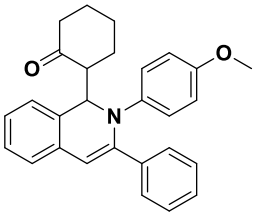
172

AgOTf

173

EtOH

174



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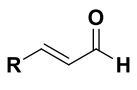

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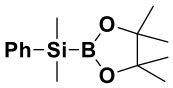


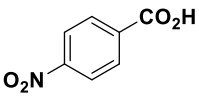
177

CuCl

178

KO-t-Bu

179



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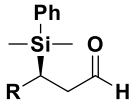

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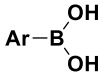


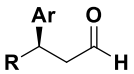
182

$Pd(OAc)_2$

183

Cs_2CO_3

184



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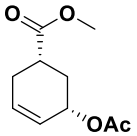

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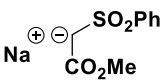
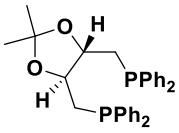


187

$Pd(PPh_3)_4$

188



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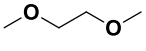

190

Na(Hg)

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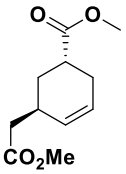

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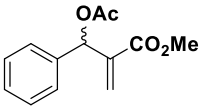

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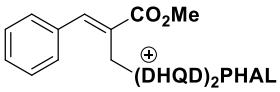

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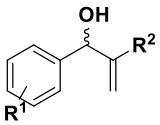

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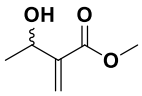

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NR3

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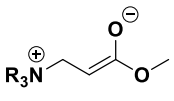

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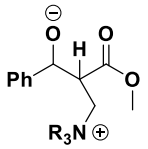

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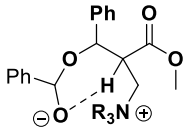

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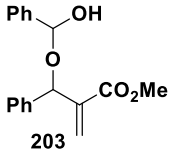

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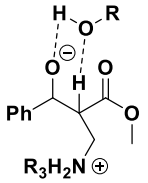

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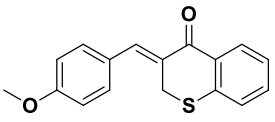

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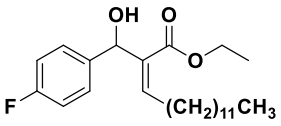

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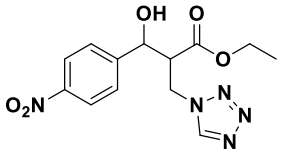

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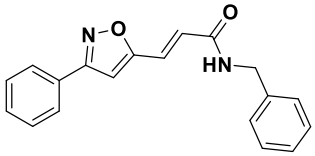

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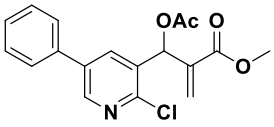

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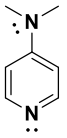

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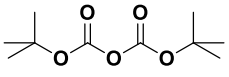

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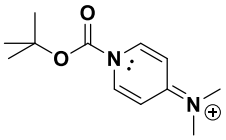

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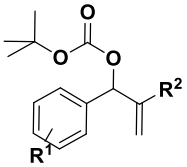

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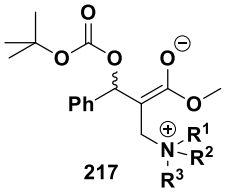

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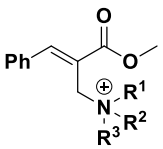

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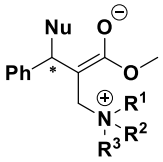

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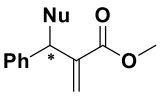

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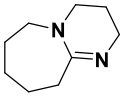

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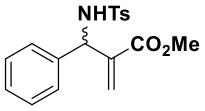

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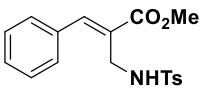

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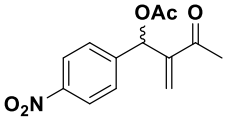

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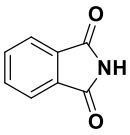

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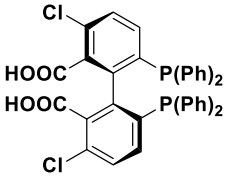

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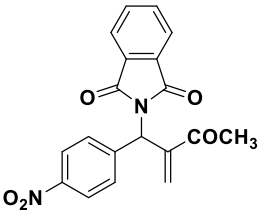

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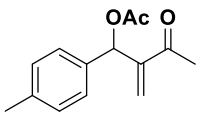

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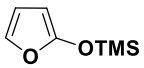

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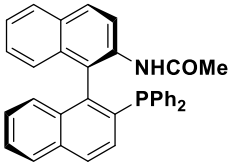

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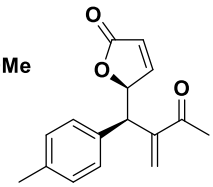

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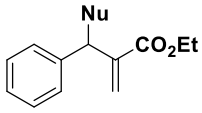

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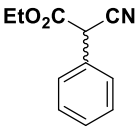

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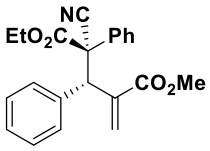

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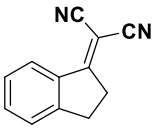

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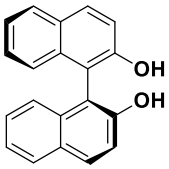

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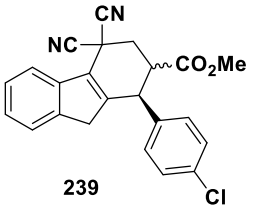

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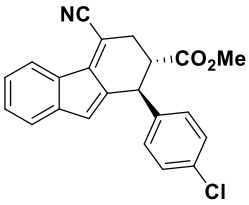

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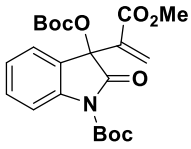

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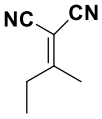

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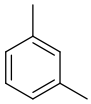

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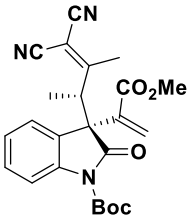

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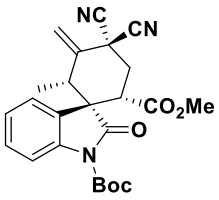

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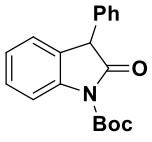

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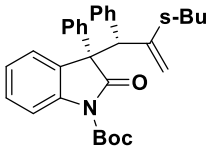

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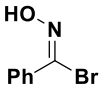

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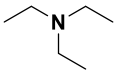

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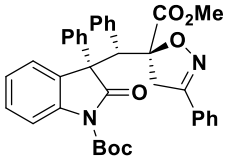

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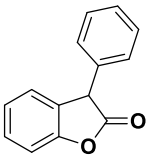

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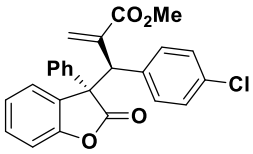

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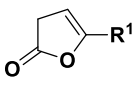

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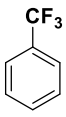

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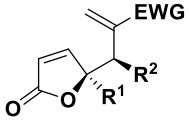

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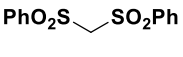

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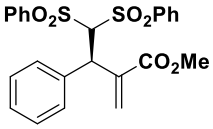

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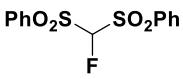

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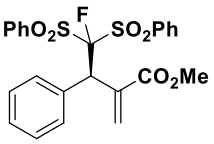

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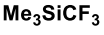

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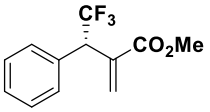

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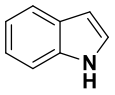

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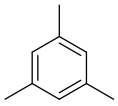

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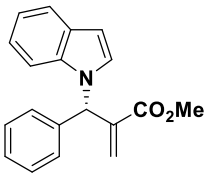

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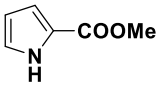

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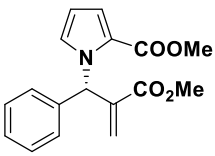

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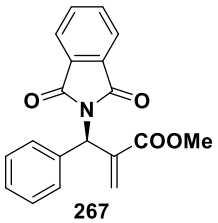

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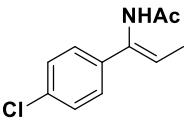

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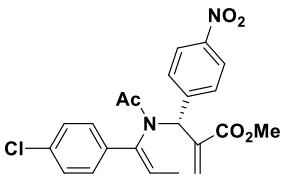

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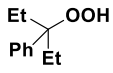

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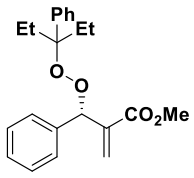

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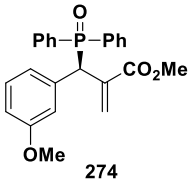

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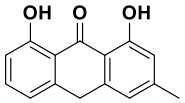

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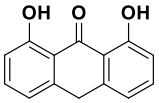

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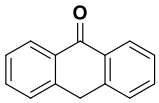

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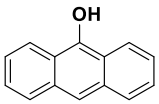

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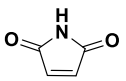

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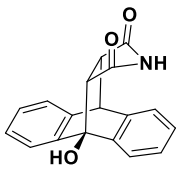

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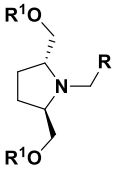

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R: aryl, pyridiyl

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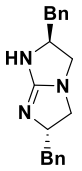

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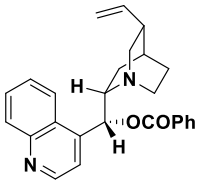

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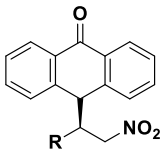

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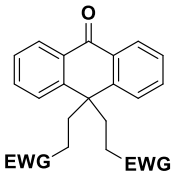

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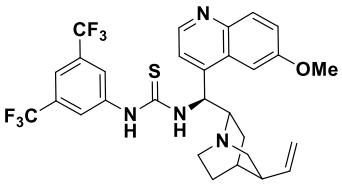

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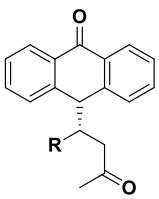

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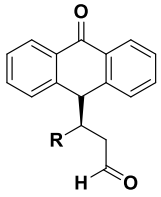

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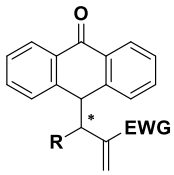

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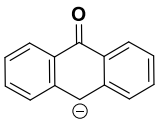

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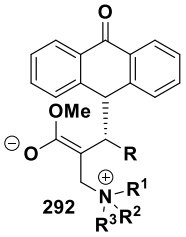

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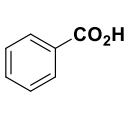

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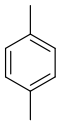

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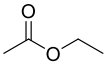

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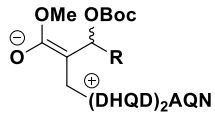

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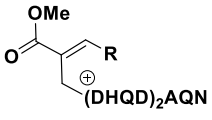

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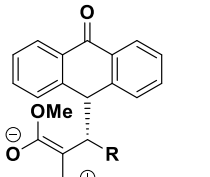

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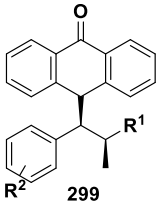

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H_2

300

Pd/C

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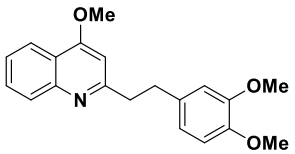

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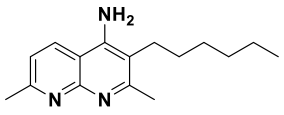

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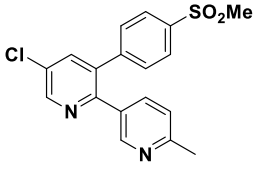

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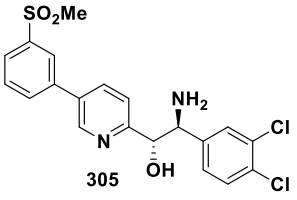

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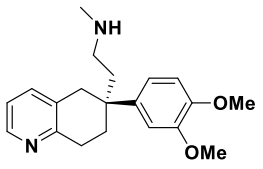

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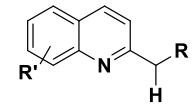

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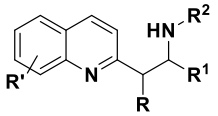

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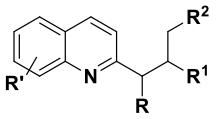

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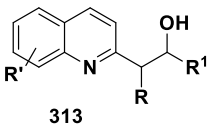

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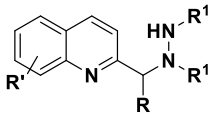

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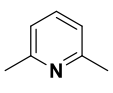

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314

Cu(OTf)$_2$

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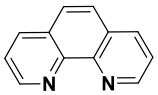

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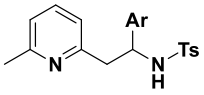

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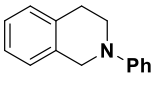

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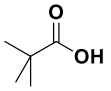

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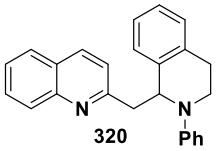

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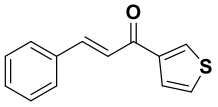

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Sc(OTf)$_3$

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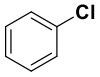

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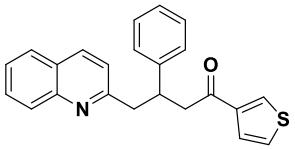

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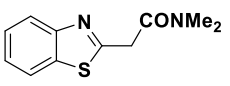

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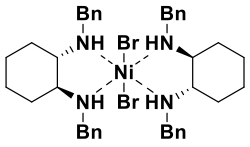

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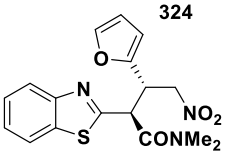

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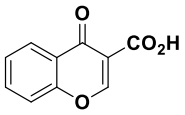

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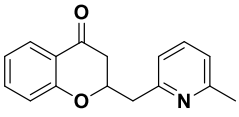

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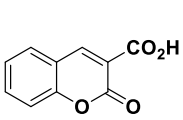

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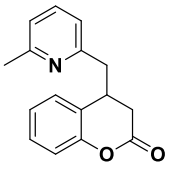

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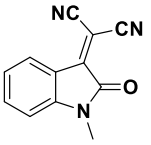

333

Bi(OTf)$_3$

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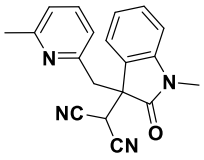

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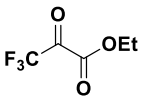

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Yb(OTf)$_3$

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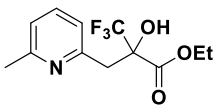

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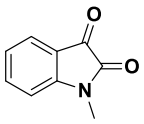

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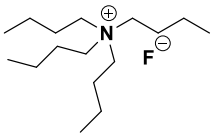

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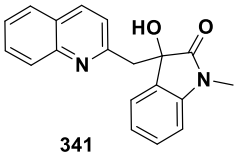

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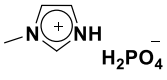

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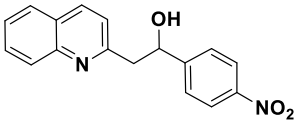

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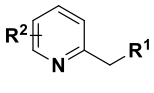

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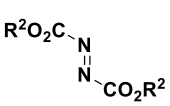

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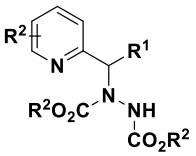

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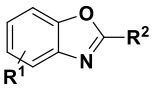

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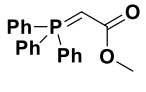

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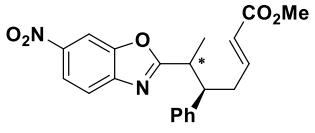

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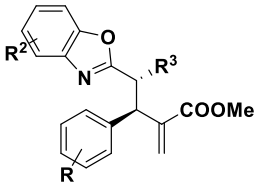

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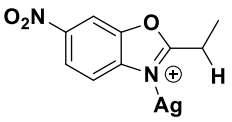

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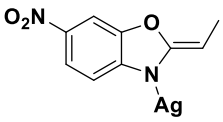

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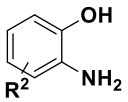

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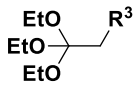

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AgOAc

357

$PdCl_2$

358

$Cu(OAc)_2$

359

AgOBz

360

$AgSbF_6$

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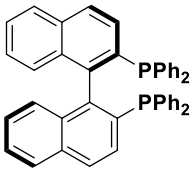

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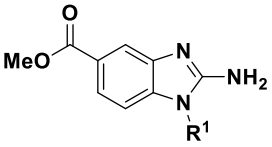

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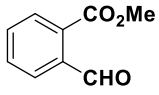

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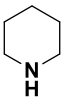

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$MgSO_4$

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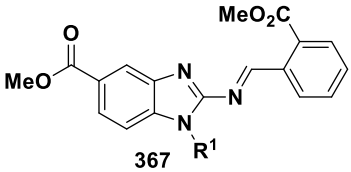

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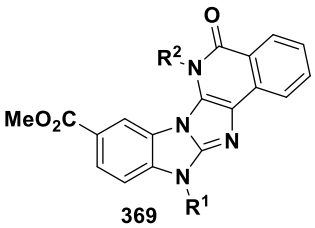

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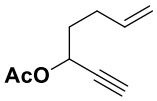

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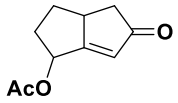

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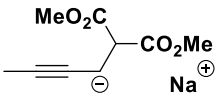

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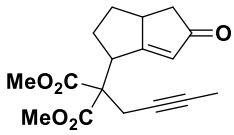

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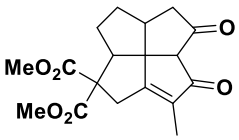

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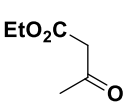

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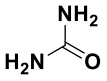

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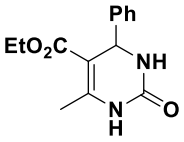

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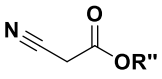

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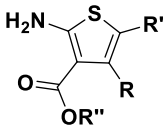

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382

$R''NH_2$

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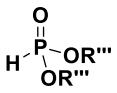

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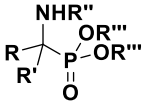

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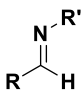

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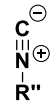

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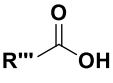

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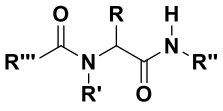

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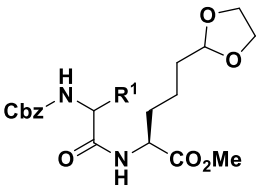

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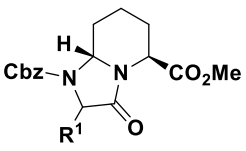

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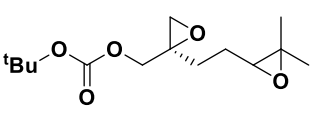

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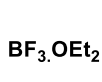

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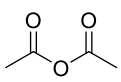

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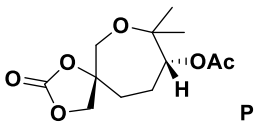

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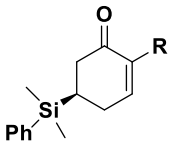

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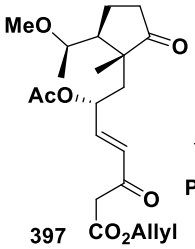

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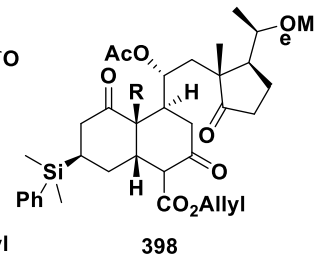

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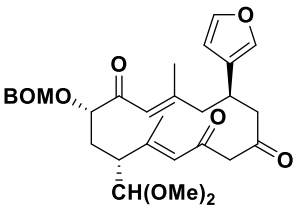

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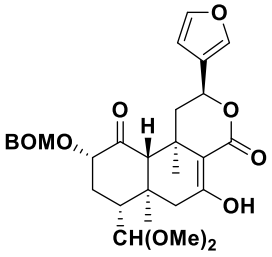

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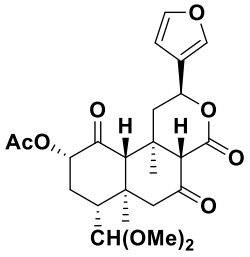

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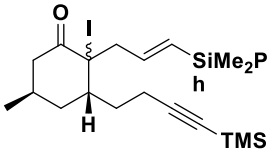

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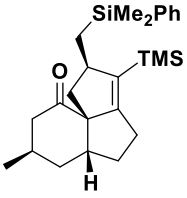

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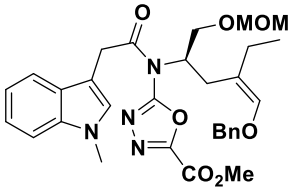

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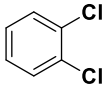

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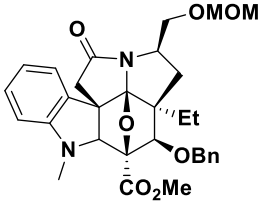

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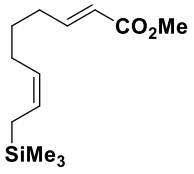

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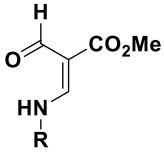

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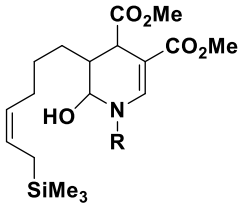

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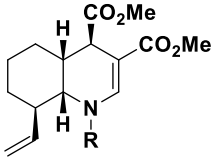

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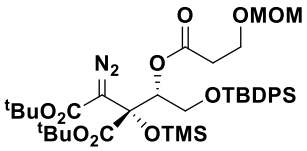

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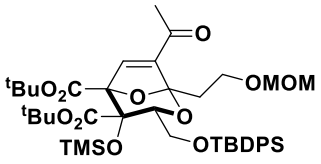

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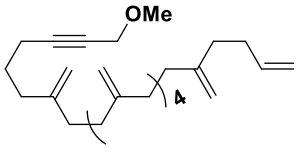

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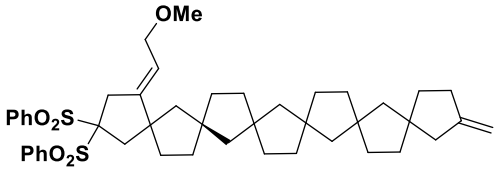

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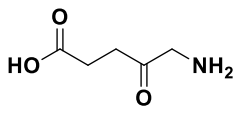

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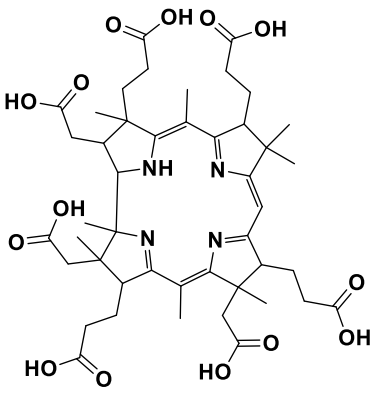

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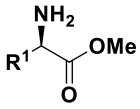

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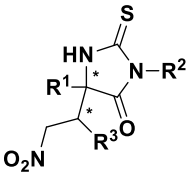

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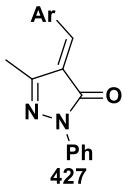

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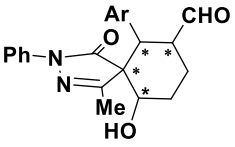

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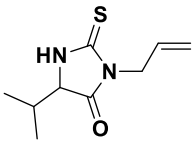

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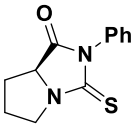

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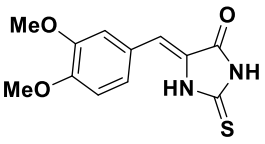

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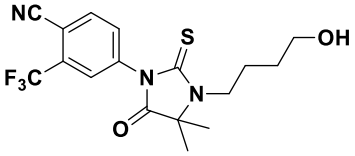

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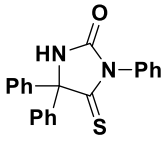

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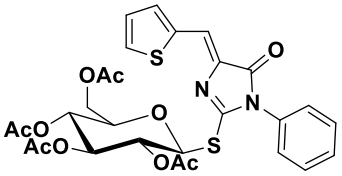

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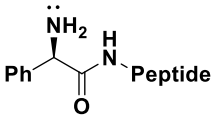

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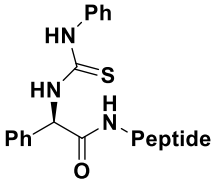

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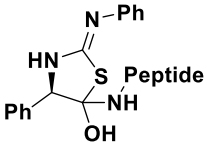

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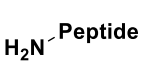

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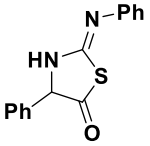

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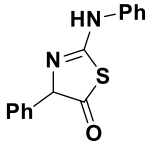

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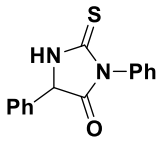

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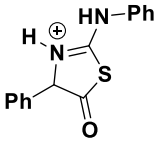

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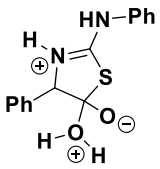

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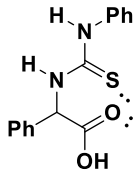

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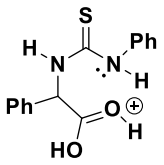

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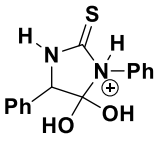

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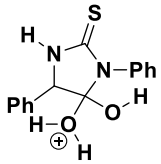

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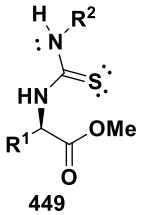

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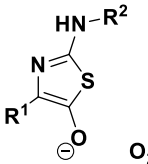

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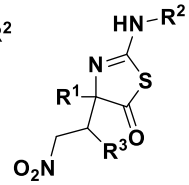

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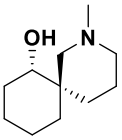

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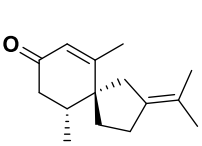

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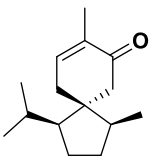

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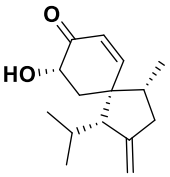

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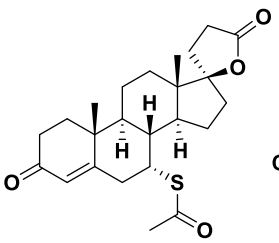

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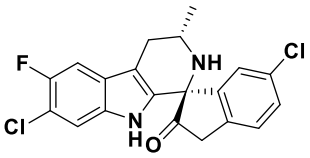

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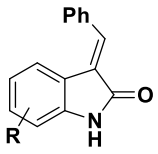

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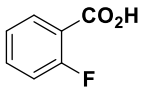

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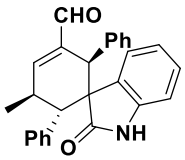

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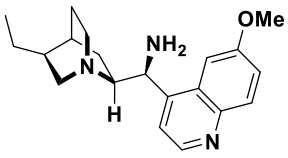

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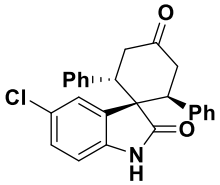

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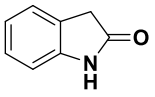

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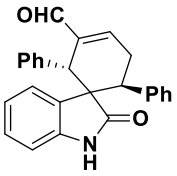

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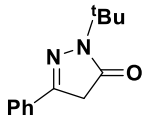

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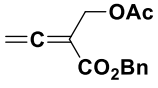

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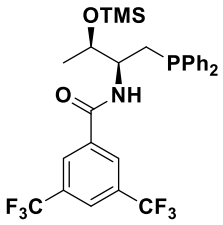

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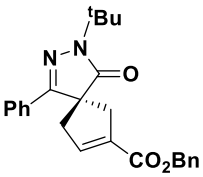

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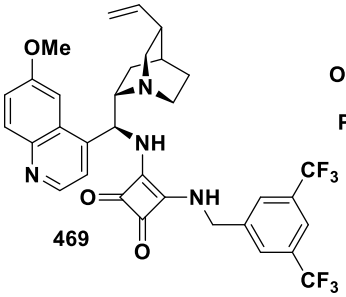

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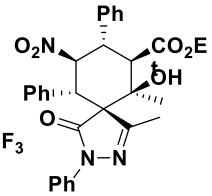

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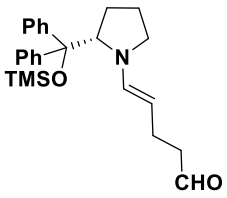

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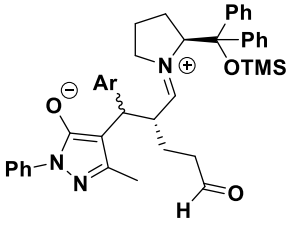

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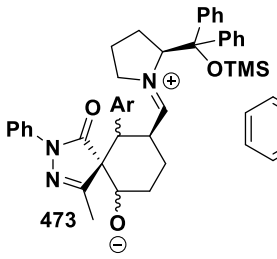

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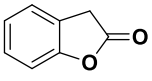

474

Al_2O_3

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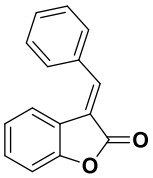

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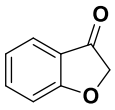

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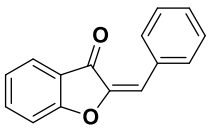

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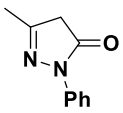

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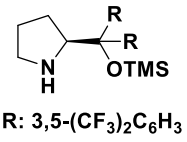

R: 3,5-$(CF_3)_2C_6H_3$

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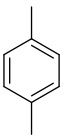

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