Preparation of polychlorinated isoxazoles and application to organic synthesis

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Preparation of polychlorinated isoxazoles 
and application to organic synthesis

A thesis for the degree of Doctor of Philosophy

Presented to

The Royal College of Surgeons in Ireland

By

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School of Pharmacy

Department of Pharmaceutical and Medicinal Chemistry

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Ph.D.                             2016
Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree of Doctor of Philosophy (Ph.D.), is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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The contents of the enclosed manuscript are confidential and should not be disclosed, or disseminated in any way, to any third party other than to staff or students of the Royal College of Surgeons in Ireland or an external examiner appointed for the purpose of reviewing the manuscript.
After more than three years spent in this lab I would like to thank first my supervisor Prof. Mauro F. A. Adamo for the opportunity he gave me to work in his group, following me and giving me the possibility to learn a lot from him and to spend three great years working under his supervision. Thanks Mauro.

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Abbreviations

Å  Angstrom
Ac  Acetyl
Ar  Aryl
Atm  Atmosphere
BINOL  1,1'-Bi-2-naphthol
Bn  Benzyl
Boc  tert-Butyloxycarbonyl
Bu  Butyl
Bz  Benzoyl
Cat.  Catalyst
CD  Cinchonidine
cHexane  Cyclohexane
CN  Cinchonine
CNS  Central nervous system
COD  1,5-Cyclooctadiene
COX-2  Cyclooxygenase-2
Cp  Cyclopentadienyl
CPME  Cyclopentyl methyl ether
CSP  Chiral stationary phase
δ  Chemical shift
DABCO  1,4-diazabicyclo[2.2.2]octane
DBU  1,8-Diazabicyclo[5.4.0]undec-7-ene
DCDMH  1,3-Dichloro-5,5-dimethylhydantoin
DCM  Dichloromethane
de  Diasteroisomeric excess
DEAD  Diethyl azodicarboxylate
DHODH  Dihydroorotate dehydrogenase
DHQD₂(PHAL)  Hydroquinidine 1,4 phthalazinediyl diether
DIAD  Diisopropyl azodicarboxylate
DIPEA  N,N'-Diisopropylethylamine
DMAc  Dimethylacetamide
DMAP  4-(Dimethylamino)pyridine
DME  1,2-Dimethoxyethane
DMF  Dimethylformamide
DMSO  Dimethylsulfoxide
DPPF  1,1'-Bis(diphenylphosphino)ferrocene
dr Diastereoisomeric ratio
E Electrophile
E Entgegen
EDG Electron donating group
ee Enantiomeric excess
equiv. Equivalent
epi Epimer
Et Ethyl
EWG Electron withdrawing group
FANS Nonsteroidal anti-inflammatory drugs
GABA γ-Aminobutyric acid
Het Heteroaryl
hfacac Hexafluoroacetylacetonate
HMPT Hexamethylphosphoramide
HPLC High Performance Liquid Chromatography
4-HPPD 4-Hydroxyphenylpyruvate dioxygenase
IMes 1,3-Bis(2,4,6-trimethylphenyl)-imidazolium
IPr 1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene
i-Pr Isopropyl
LDA Lithium diisopropylamide
M Molarity
m meta
MAO Monoamine oxidase
mCPBA meta-Chloroperoxybenzoic acid
MIRC Michael-initiated ring-closing reaction
Me Methyl
min Minutes
mmol Millimoles
Ms Mesyl
MS Molecular sieves
n-Bu normal-Butyl
NBS N-Bromosuccinimide
NCS N-Chlorosuccinimide
NFSI N-Fluorobenzenesulfonimide
NHC N-Heterocyclic carbene
NIS N-Iodosuccinimide
NMO N-Methylmorpholine-N-oxide
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<tr>
<td>NMR</td>
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<tr>
<td>Nu</td>
<td>Nucleophile</td>
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<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
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<td>PABA</td>
<td>4-Aminobenzoic acid</td>
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<tr>
<td>Ph</td>
<td>Phenyl</td>
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<td>PHBA</td>
<td>4-Hydroxybenzoic acid</td>
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<td>PMP</td>
<td>4-Methoxyphenyl</td>
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<td>PTC</td>
<td>Phase-transfer catalyst</td>
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<td>QD</td>
<td>Quinidine</td>
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<td>Quinine</td>
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<td>rac.</td>
<td>Racemic</td>
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<td>Ra/Ni</td>
<td>Raney Nickel</td>
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<tr>
<td>Re</td>
<td>Clockwise attack</td>
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<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>Retention factor</td>
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<td>r.t.</td>
<td>Room temperature</td>
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<td>Si</td>
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<td>Sorbitan monolaurate</td>
</tr>
<tr>
<td>T</td>
<td>Temperature</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-Butyl hydroperoxide</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>TBAB</td>
<td>Tetrabutylammonium bromide</td>
</tr>
<tr>
<td>TCICA</td>
<td>Trichloroisocyanuric acid</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflic</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
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<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>Trimethylsilyl</td>
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<td>Ts</td>
<td>Tosyl</td>
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<td>Z</td>
<td>Zusammen</td>
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Abstract

Chapter 1
Overview on isoxazoles synthesis and reactivity and on the synthetic applications of 3,5-dimethyl-4-nitroisoxazole and its derivatives.

Chapter 2
We described the electrophilic chlorination of 3,5-dimethyl-4-nitroisoxazole. The product 3-methyl-4-nitro-5-trichloromethylisoxazole was employed in transition metal-free heteroaromatic amination via a novel haloform-type reaction.

Chapter 3
We described the preparation of [2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amines and the study of their reactivity towards C-, N- and halogen-electrophiles.

Chapter 4
We described the use of 3-methyl-4-nitro-5-chloromethylisoxazole in organocatalyzed 1,2-addition to aromatic aldehydes to produce chlorohydrins and in asymmetric phase-transfer catalyzed Darzens reaction for the preparation of enantioenriched α,β-epoxiisoxazoles and glycidic esters.

Chapter 5
We described the electrophilic functionalization of 2-methyl-3-nitroindoles. We developed two methodologies for the preparation of 2-alkenyindoles and for the mono-α-chlorination to give 2-chloromethyl-3-nitroindoles.
Aim

The work behind my doctoral thesis has been focused on the study of reactivity of 3,5-dimethyl-4-nitroisoxazole. This compound shows a peculiar reactivity compared to other isoxazole derivatives due to the presence of the nitro group in 4-position. The chemical behavior of 3,5-dimethyl-4-nitroisoxazole has been extensively studied in the last decade with the development of important applications in pharmaceutical chemistry in the preparation of valuable biologically active compounds.

The investigation has been focused in the development of novel procedures for the electrophilic chlorination of 3,5-dimethyl-4-nitroisoxazole. We envisaged that the introduction of one or more chlorine atoms on the methyl group in 5-position of the nitroisoxazole core could bring to the formation of polyfunctional derivatives bearing multiple nucleophilic and electrophilic functionalities on the same molecule. The polyfunctional reactivity of these new type of isoxazole derivatives could then be exploited by means of different kind of reactions to produce important building blocks. In particular the use of 3-methyl-4-nitro-5-trichloromethylisoxazole in haloform-type reactions with different nucleophiles would produce 5-aminoisoxazoles via transition metal-free heteroaromatic amination. On the other hand, reaction of 3-methyl-4-nitro-5-chloromethylisoxazole with aldehydes and ketones would furnish α,β-epoxisoxazoles and α,β-epoxiesters through Darzens condensation. Moreover we decided to study the possibility of expanding the typical reactivity exhibited by the 4-nitroisoxazole core to other heterocyclic compounds like indoles in order to prepare valuable functionalized indoles.

Thus, the preparation of these new classes of isoxazole derivatives and their application in the development of novel chemical transformations could serve as new efficient methodologies in the synthesis of important bioactive compounds in different industrial pharmaceutical fields.
Chapter 1

Isoxazoles: synthesis and reactivity
1.0 Introduction

Isoxazoles 1.1 are an important class of five-membered aromatic heterocycles characterized by the presence of a nitrogen and an oxygen atoms in adjacent position (Figure 1). They are a part of the bigger class of the azoles, five-membered aromatic molecules containing one nitrogen atom plus at least one or more heteroatoms, like N, O, S. [1]

Figure 1. Isoxazole structure and numeration.

They were first discovered by Claisen in 1888 [2] who synthetized the 3-methyl-5-phenylisoxazole, followed some years later, in 1903, by the preparation of the parent compound of the series 1.1 by oxymation of propargylaldehyde acetal. The following important contribution to the field was given by Quilico in 1946, [3] who investigated the synthesis of the isoxazole ring by reaction of N-oxides with acetylenic compounds. From the 1950s the interest of the scientific community about their chemistry increased considerably due to their versatility in the synthesis of a wide range of natural products and heterocycles. [4] Moreover, the discovery of significant biological activities displayed by isoxazole derivatives, [5] as well as the development of important synthetic strategies relying on their chemistry, makes their study an active field of research to the present day.

Despite the fact not being widespread in nature, different compounds containing the isoxazole core have been extracted from biological sources, like algae and fungi. Some examples are muscimol 1.2, a potent CNS depressant and the natural occurring ibotenic acid 1.3, a neurotoxin widely used for studies on glutamic acid receptors, extracted from amanita muscaria (Figure 2). [6]

Figure 2. Natural occurring bioactive isoxazoles.

Over the years many synthetic and semi-synthetic isoxazole derivatives were prepared and their biological activity has been extensively studied, bearing to the discovery of important bioactive compounds, making them key components present in many synthetic
products. Their importance is demonstrated by the number of pharmaceutical and synthetic applications in which they play a fundamental role due to their peculiar chemical-physical behavior. Several studies showed isoxazole derivatives displaying a wide range of biological activities such as: selective agonists of the dopamine D4 receptor,\(^7\) GABA antagonists,\(^8\) analgesics, anti-inflammatories,\(^9\) antimicrobial, antifungal, COX-2 inhibitors,\(^10\) and anticancer agents.\(^11\) The isoxazole core is present in many drugs and pharmaceuticals as key pharmacophore capable to enforce the desired pharmacological activity due to the presence of two electronegative heteroatoms in 1,2-position, which enable the establishment of hydrogen bond interactions with a variety of receptors and enzymes unavailable to different ring systems.

Some examples of important pharmacologically active drugs containing an isoxazole core are (Figure 3): sulfamethoxazole (PABA antagonist, antibacterial) \(1.4\), oxacillin \(1.5\) and cephalosporin \(1.6\) (β-lactam antibiotics), isocarboxazide \(1.7\) (MAO inhibitor, antidepressant), anabolic steroid \(1.8\), isoxaflutole \(1.9\) (4-HPPD Inhibitor, herbicide), leflunomide \(1.10\) (DHODH inhibitor, immunosuppressant, anti-reumatic), parecoxib \(1.11\) (COX-2 inhibitor, FANS), risperidone \(1.12\) (dopamine antagonist, antipsycotic).
Moreover, from a synthetic point of view, isoxazoles exploit their utility as valuable intermediate in small molecules and natural products synthesis, due to their unique chemical behavior. Indeed, they can act as masked 1,3-dicarbonyl compounds and masked carboxylic acids as well as precursors for a variety of others heterocyclic compounds.\textsuperscript{[12]}
1.1 Synthesis of the isoxazole ring

The isoxazole ring can be constructed by several synthetic approaches. These can be classified based on the type of reaction occurring between the precursors. Condensation, 1,3-dipolar cycloaddition and cycloisomerization reactions are the most common transformations employed in their preparation (Scheme 1).

1.1.1 Condensation

The synthesis of isoxazoles by condensation is the older known, first described by Claisen in 1888. The process involves the reaction of 1,3-dicarbonyl compound 1.18 with hydroxylamine 1.19 to form oxime 1.20, followed by cyclization to isoxazoline 1.21 which after dehydration produces the symmetric isoxazole 1.22 (Scheme 2).

Scheme 1: Common synthetic methodologies for the isoxazole ring formation.
Scheme 2. Synthesis of symmetrical isoxazoles via condensation of 1,3-dicarbonyl compounds with hydroxylamine.

This methodology, although old, still has a great relevance for the synthesis of 4-unsubstituted and 4-substituted isoxazoles bearing the same substituents at 3- and 5-positions.

Unsubstituted isoxazoles and 4-monosubstituted isoxazoles 1.24 can be prepared through the reaction of tetraalkoxypropanes 1.23, with hydroxylamine (Scheme 3).[13]

![Scheme 3. Synthesis of unsubstituted and 4-monosubstituted isoxazoles.](image)

Different kind of 1,3-dicarbonyl compounds can be used in the preparation of isoxazoles by condensation such as 1,3-diketones, β-ketoesters, β-ketoaldehydes (often masked as acetals), and many examples can be found in the literature.[14]

![Figure 4. 1,3-dicarbonyl compounds utilized in the preparation of isoxazoles by condensation.](image)

The major drawbacks of these methods relying on condensation are the need of harsh reaction conditions and the low regioselectivity obtained when unsymmetrical dicarbonyl compounds are used. Different methodologies have been explored to control the regiochemistry of condensation. For example, the reaction of vinyl ketones bearing a leaving group in β-position, like dialkylamino 1.28 or alkoxy 1.29, with hydroxylamine can...
be used for the synthesis of 5-monosubstituted 1.30 and 4,5-disubstituted isoxazoles 1.31, as reported by Whitehead and Lang (Scheme 4)\textsuperscript{[15]}

\[
\begin{array}{c}
\text{Scheme 4. Synthesis of 5-monosubstituted and 4,5-disubstituted isoxazoles from } \beta- \\
\text{ethoxy and } \beta\text{-dialkylamino vinyl ketones.}
\end{array}
\]

Following a similar strategy, Omote and Steel reported the reaction of α-bromo vinyl ketones 1.32 with hydroxylamine for the selective preparation of 3-aryl-5-alkylisoxazoles 1.33 and of the regioisomer 3-alkyl-5-arylisoxazoles 1.34, depending on the reaction conditions (Scheme 5).\textsuperscript{[16]}

\[
\begin{array}{c}
\text{Scheme 5. Regioselective synthesis of 3,5-disubstituted isoxazoles from } \alpha\text{-bromo vinyl ketones.}
\end{array}
\]

In 2009, She and co-workers discovered that 3,5-disubstituted isoxazoles 1.37 could be prepared from the reaction of \(^N\)-hydroxy-p-toluene-sulfonamide 1.36 with \(^\alpha,\beta\)-unsaturated ketones 1.35 in high regioselective fashion.\textsuperscript{[17]} To explain the high regioselectivity observed they proposed the first step being the aza-Michael addition of the tosylhydroxylamine to 1.35, followed by elimination of tosylsulphinic acid, base-promoted cyclization and dehydration as last step (Scheme 6).
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Scheme 6. Regioselective synthesis of 3,5-disubstituted isoxazoles via conjugate addition/condensation.

Ila developed the regioselective synthesis of 3,5-disubstituted isoxazole 1.40 based on the condensation of hydroxylamine hydrochloride 1.38 and monothio-β-diketones 1.39 in the presence of sodium acetate (Scheme 7). The use of a mixed oxo-thioketone allows the possibility to exert control over the reaction pathway due to the higher reactivity of the thione respect to the ketone. The nitrogen atom of hydroxylamine attacks first the most electrophilic C=S double bond, followed by attack of the oxygen on the ketone forming isoxazoles 1.40 in a regioselective fashion.

Scheme 7. Regioselective synthesis of 3,5-disubstituted isoxazoles from monothio-β-diketones.

Singh reported the synthesis of 3-amino-5-substituted isoxazoles 1.43 through condensation of β-oxo-dithioesters 1.42, an amine 1.41 and hydroxylamine (Scheme 8).
**Scheme 8.** Regioselective synthesis of 3-amino-5-substituted isoxazoles from β-oxo-dithioesters.

The condensation of hydroxylamine hydrochloride with β-oxo-thioesters 1.44, as reported by Furukawa, [20] produces 3-alkoxy-5-substituted isoxazoles 1.45 in two steps (Scheme 9).

$$\begin{align*}
\text{EtO} & \quad \text{S} \quad \text{O} \quad \text{R} \\
1.44 & \\
\text{R} & = \text{Ar, alkyl}
\end{align*}$$

1) $\text{NH}_2\text{OH}\cdot\text{HCl}$
NEt$_3$
CH$_3$CN, r.t.
2) $\text{CH}_3\text{OH}/\text{H}_2\text{O}$
$p\text{H} = 3-5$
reflux

$$\begin{align*}
\text{EtO} & \quad \text{N} \quad \text{O} \quad \text{R} \\
1.45 & 
\end{align*}$$

**Scheme 9.** Regioselective synthesis of 3-ethoxy-5-substituted isoxazoles from β-oxo-thioesters.

**1.1.2 Cycloaddition**

**1.1.2.1 Thermal [4+2] cycloaddition**

1,3-Dipolar cycloaddition represents nowadays one of the most important methods for the synthesis of isoxazoles. The first example dates back to the 1930s, when Quilico reported the thermal dipolar cycloaddition between nitrile oxides and alkynes. [3] Over the years many other methodologies have been reported working both under thermal and metal-catalyzed conditions. The thermal cycloaddition of preformed nitrile oxides with different functionalized alkynes has been widely studied and many procedures have been developed, allowing the formation of boron-, [21] tin-, [22] aluminium-, [23] silicon [24] and halogen [25] substituted isoxazoles (Scheme 10).
Scheme 10. Regiospecific preparation of substituted isoxazoles via thermal 1,3-dipolar cycloaddition.
The advantage of using functionalized dipolarophiles lies in the possibility of introducing a variety of sensitive functional groups, which would be difficult to install directly on the preformed isoxazole ring. In the 1,3-dipolar cycloaddition, also known as Huisgen reaction, the nitrile oxide (dipole) and the alkyne compound (dipolarophile) react to produce the poly-substituted isoxazole in a regiospecific fashion. The mechanism involves a concerted pericyclic shift of 2 π-electrons of the dipole and 4 π-electrons of the dipolarophile (Scheme 11). The electronic effect exerted by the heteroatoms on the alkynes direct the mutual orientation of the substrates, allowing high degrees of regiospecificity.

1.1.2.2 Metal-catalyzed [4+2] cycloaddition

The first example of metal-catalyzed synthesis of isoxazole was reported by Fokin’s group in 2005 (Scheme 12). They applied the Cu(I)-catalyzed Huisgen’s 1,γ-dipolar cycloaddition to the reaction between hydroximoyl chlorides and terminal alkynes, obtaining 3,5-disubstituted isoxazole with high yields and regioselectivity (>95:5). The reaction works at room temperature and in short reaction times, while the uncatalyzed reaction requires high temperatures and furnish a mixture of 3,5- and 3,4-disubstituted isoxazoles.

They proposed a stepwise mechanism (Scheme 13) in which the active Cu(I) catalyst is formed in situ by reduction of Cu(II) with sodium ascorbate. The catalytic cycle starts with the coordination of the alkyne to the Cu(I), which increase the acidity of the terminal proton, followed by formation of the copper acetylide. In the next step the nitrile...
oxide 1.68, formed by elimination of HCl from 1.64, displaces one of the ligands and binds to the copper through the carbon proximal to the nitrogen forming species 1.69. Then the oxygen attacks the C-2 of the acetylide, forming a six-membered Cu(III) metallacycle 1.70 which undergoes ring contraction forming the isoxazolyl-copper derivative 1.71. The catalytic cycle ends with proteolysis of 1.71 that releases the isoxazole 1.66 and the Cu(I) catalyst.

Scheme 13. Proposed mechanism for the Cu(I)-catalyzed synthesis of 3,5-disubstituted isoxazoles.

In 2007, Hsung and co-workers reported the synthesis of 5-amino-substituted isoxazoles 1.74 via Cu(I)-catalyzed [4+2] dipolar cycloaddition of nitrile oxides derived from 1.72 with ynamides 1.73 as dipolarophiles.\[28\]

Fokin and et al. reported in 2008 the first Ru(II)-catalyzed [4+2] cycloaddition of alkynes 1.76 with hydroximoyl chlorides 1.75 that exhibits a complementary regioselectivity respect to the Cu(I)-catalyzed process producing 3,4-disubstituted isoxazoles 1.77. 

\[ \text{[Cp'RuCl(COD)] (10 mol%)} \quad \text{Et}_3N \text{ (1.25 equiv.)} \quad \text{DCE, r.t., 10h} \]

\[
\begin{align*}
\text{N} & \text{OH} \\
\text{R}_1 & \text{Cl} \\
\text{1.75} & \text{R}_2 \text{C} \quad \rightarrow \quad \text{R}_2 \text{C} \\
\text{1.76} & \text{1.77}
\end{align*}
\]

\[ R_1 = \text{Ar, alkyl, vinyl} \]
\[ R_2 = \text{Ar, alkyl} \]

**Scheme 15.** Ru(II)-catalyzed synthesis of 3,4-disubstituted isoxazoles.

The mechanism proposed involves initially the displacement of the COD ligand of the catalyst 1.79 by the alkyne 1.76 and the nitrile oxide 1.78 (formed in situ), producing intermediate 1.80. Oxidative coupling brings to the formation of the six membered ruthenacyle 1.81 that subsequently undergoes reductive elimination furnishing isoxazole 1.77 and restoring the ruthenium catalyst.

\[
\begin{align*}
\text{1.77} & \quad \text{1.79} \\
& \quad \text{1.76} \quad \text{1.78} \\
& \quad \text{1.79} \quad \text{1.80} \\
& \quad \text{1.81} \\
\end{align*}
\]

**Scheme 16.** Proposed mechanism for the Ru(II)-catalyzed synthesis of 3,4-disubstituted isoxazoles.
1.1.3 Cycloisomerization

The synthesis of isoxazoles via electrophilic cyclization of 1,3-disubstituted-2-alkynones has emerged in the last decade as one of the most efficient and general methods, due to the operational simplicity and mild reaction conditions. Moreover, the possibility of directly introducing heteroatoms during the ring formation makes the products easily modified by further transformations. These features allow the straightforward preparation of valuable highly functionalized isoxazoles.

The first synthesis of isoxazoles by metal-free cycloisomerization was proposed by Larock group in 2005. They reported the electrophilic cyclization of 2-alkynone-O-methyl oximes, generated by condensation of the corresponding yrones with O-methyl-hydroxylamine. The reaction can be promoted by different electrophiles like ICl, I₂, Br₂ and PhSeBr. The products were obtained in high yields and regiospecificity, with the electrophile in position of the isoxazole ring.

The reaction proceeds via a 5-endo dig cyclization process. The electrophile coordinates to the triple bond of compound 1.83, generating the halonium ion intermediate 1.85. The formation of the halonium ion activates the carbon-carbon bond toward nucleophilic attack by the oxime. Intramolecular anti-attack of the oxygen of the oxime moiety on the activated alkyne produces compound 1.86 that is readily turned into product 1.84 via SN₂ displacement by the nucleophile present in the reaction mixture.
The same group demonstrated the synthetic utility of this methodology used in combination with Pd-catalyzed Suzuki-Miyaura coupling reaction, preparing the COX-2 inhibitor valdecoxib **1.91** in three steps starting from 1-phenyl-3-methyl-2-alkyn-1-one **1.87** in 74% overall yield (Scheme 19). The reaction sequence involves the regiospecific formation of the isoxazole **1.89** via electrophilic cyclization of **1.88** with iodine monochloride. **1.89** is subsequently reacted with the commercially available benzenesulfonamide-4-boronic acid pinacol ester in a Suzuki-Miyaura cross-coupling reaction, producing the trisubstituted isoxazole **1.91**.
Scheme 19. Preparation of Valdecoxib by electrophilic cyclization/Suzuki-Miyaura coupling sequence.

In 2011 Wada reported the electrophilic cycloisomerization of $N$-alkoxycarbonyl-$O$-propargylic hydroxylamines 1.92 with NIS/BF$_3$·Et$_2$O, producing 4-halo-3,5-disubstituted isoxazoles 1.93 with complementary regiospecificity respect to Larock’s methodology (Scheme 20). [32]

![Scheme 19](image)

R$_1$ = H, Me
R$_2$ = Ar, alkyl

Scheme 20. Electrophilic cyclization of $N$-alkoxycarbonyl-$O$-propargylic hydroxylamines to 4-iodo-3,5-disubstituted isoxazoles.

After the seminal work of Larock and co-workers, various metal-catalyzed cycloisomerization procedure for the synthesis of isoxazoles have been reported. The advantage of using a metal catalyst lies in the need of milder reaction conditions and a wider functional groups tolerance, beside the possibility of obtaining 3,5-disubstituted or 3,4,5-trisubstituted isoxazoles, depending on the conditions applied. The first example of isoxazoles synthesis via metal-catalyzed cycloisomerization was reported in 2010 by Perumal, using 1,3-disubstituted-2-alkynyl-1-oximes 1.94 and AuCl$_3$ as gold(III) catalyst, obtaining 3,5-disubstituted isoxazoles 1.95 (Scheme 21). [33]

![Scheme 21](image)

R$_1$ = aryl, alkyl, H
R$_2$ = aryl, alkyl, silyl, H

Scheme 21. Gold(III)-catalyzed cycloisomerization of 1,3-disubstituted-2-alkynyl-1-oximes to 3,5-disubstituted isoxazoles.

The mechanistic proposal (Scheme 22) implies the coordination of gold(III) to the triple bond of the oxime 1.94 leading to the activated $\pi$-complex 1.96, which undergoes 5-endo dig cyclization affording intermediate 1.97. The disubstituted isoxazole 1.95 is then
produced upon protodeauration of the cyclized intermediate 1.97, restoring the gold(III) catalyst.

**Scheme 22.** Proposed mechanism for the gold(III)-catalyzed cycloisomerization of 2-alkynyl-1-oximes.

In 2014 Ryu and co-workers [34] reported the gold(I)-catalyzed cascade cycloisomerization/fluorination of 2-alkynone-O-methyl oximes 1.98 for the synthesis of 4-fluoro-3,5-disubstituted isoxazoles 1.99, using (IPr)AuCl as catalyst and selectfluor as fluorinating agent (Scheme 23).

**Scheme 23.** Gold(I)-catalyzed cascade cycloisomerization/fluorination of 2-alkynone-O-methyl oximes to 4-fluoro-3,5-disubstituted isoxazoles.

They demonstrated the first step being the gold(I)-catalyzed cycloisomerization, followed by demethylation by triflate, selectfluor-mediated oxidation to gold(III) intermediate and finally reductive elimination with the formation of the product and regeneration of the gold(I) catalyst (Scheme 24).
Following the report of gold-catalyzed methodologies for the construction of the isoxazole nucleus, other metals have been successfully employed as catalysts in the synthesis of poly-substituted isoxazoles. In 2011, Miyata reported the silver(I)-catalyzed cycloisomerization of O-benzyl-1,3-disubstituted-2-alkynyl-1-oxime ethers 1.104 for the preparation of 3,5-disubstituted isoxazoles 1.105 in the presence of phenol as the proton source (Scheme 25). [35]
Scheme 25. Synthesis of 3,5-disubstituted isoxazoles via silver(I)-catalyzed cycloisomerization/PhOH promoted benzyl cation elimination.

The mechanism (Scheme 26) involves the formation of the alkyne-silver complex 1.106, which undergoes 5-endo dig cyclization leading to oxonium intermediate 1.107. PhOH-promoted elimination of the benzyl cation produces intermediate 1.108 that upon aromatization furnish the isoxazole 1.105 and restores the catalytic silver species.


The same group reported the copper(II)-catalyzed tandem cycloisomerization/1,3 migration of O-benzyl-1,3-disubstituted-2-alkynyl-1-oxime ethers 1.109 affording 3,4,5-trisubstituted isoxazoles 1.110 (Scheme 27). [36]
The authors showed the presence of an electron-donating group on the aromatic ring being fundamental for the positive outcome of the reaction. In the mechanism proposed (Scheme 28), formation of the intermediate 1.112 by cycloisomerization of the activated alkyne 1.111 occurs, followed by intramolecular 1,3-migration of the benzyl cation to give species 1.115. Formation and migration of the benzyl cation 1.114 was favored by the presence of an EDG group as well as by the interaction with the π-system of the isoxazole ring of 1.113. Finally, aromatization of 1.115 afforded the isoxazole 1.110 and regenerate the copper catalyst.

Scheme 27. Synthesis of 3,4,5-trisubstituted isoxazoles via copper(II)-catalyzed cycloisomerization/benzyl 1,3-migration.

Scheme 28. Proposed mechanism for the Cu(II)-catalyzed synthesis of 3,4,5-trisubstituted isoxazoles.
A platinum(II)-catalyzed synthesis of 3,5-disubstituted isoxazoles 1.117 and 1.119 has been proposed by Ferreira and co-workers in 2013.\textsuperscript{[37]} Interestingly, they were able to obtain both the complementary 3,5-regioisomers changing the starting material from propargylic $N$-hydroxycarbamates 1.116 (Scheme 29) to propargylic $N$-alkoxycarbonylamino ethers 1.118 (Scheme 30), while keeping the reaction conditions unchanged.

![Scheme 29](image1.png)

**Scheme 29.** Pt(II)-catalyzed cycloisomerization of propargylic $N$-hydroxycarbamates.

![Scheme 30](image2.png)

**Scheme 30.** Pt(II)-catalyzed cycloisomerization of propargylic $N$-alkoxycarbonylamino ethers.

The mechanism proposed (Scheme 31) involved a platinum(II)-catalyzed cycloisomerization as the first step affording oxonium intermediate 1.120. Proton-transfer to the methoxy group promoted the formation of the platinum carbene 1.121, which
underwent [1,2] hydrogen shift to the species \textbf{1.123}, followed by rearrangement to isoxazoline \textbf{1.124}. Finally, protonation of the exocyclic double bond of \textbf{1.124} and removal of the tert-butyl carbonate group furnished isoxazole \textbf{1.117}. A similar reaction pathway was described for the formation of the regioisomeric compound \textbf{1.119}.

\textbf{Scheme 31.} Reaction pathway for the Pt(II)-catalyzed formation of 3,5-disubstituted isoxazoles.
1.2 Overview on the reactivity of the isoxazole ring

Direct functionalization of preformed mono-, di- and tri-substituted isoxazoles has been extensively studied as useful method for the preparation of complex isoxazoles. Their reactivity can be rationalized considering that they present the typical properties of an aromatic system undergoing electrophilic substitution on the ring, especially at 4-position. The calculated π-electron density distribution of unsubstituted isoxazole shows that the electron density is higher at the 4-position, followed by 5- and 3-position on the ring. This calculations are consistent with the experimental observations showing the 4-position being the preferred site of attack for electrophilic substitution reactions. \[^{38}\]

![Diagram of isoxazole ring with electron density distribution]

**Figure 5.** Calculated π-electron density distribution of the isoxazole ring.

1.2.1 Electrophilic substitution

The susceptibility of the isoxazole ring toward electrophilic substitution resembles what could be expected from the simultaneous presence of an activating, electron-donating, oxygen atom and of a deactivating, electron-withdrawing nitrogen atom. Thus they undergo electrophilic substitution faster than pyridines, but slower than furans. The 4-position is generally the only site of attack for electrophiles. Generally alkyl chains at the 3- and 5-positions increases the reactivity of the 4-position toward electrophiles, while the presence of aryl groups may lead to a mixed reactivity, with electrophilic substitution occurring both on the isoxazole and the aryl nucleous. \[^{1}\]

Isoxazoles can be readily nitrated and halogenated at 4-position of the ring, while sulfonation and acylation afford low yields and need drastic conditions. Moreover, chloromethylation, chlorobenzylation, hydroxymethylation and formylation have been reported. \[^{14}\] The nitration of unsubstituted and substituted isoxazoles can be achieved using various nitrating reagents, like mixed nitric and sulfuric acids (Scheme 32), acetyl nitrate and trifluoroacetyl nitrate (Scheme 33). \[^{14, 39}\]
Halogenation of the 4-position of various isoxazoles can be performed with molecular chlorine and bromine, sulfonyl and thionyl chloride, t-butylhypochloride and iodinechloride\textsuperscript{[14, 40]}, although better results were obtained using \textit{N}-halosuccinimides (NCS, NBS, NIS) as recently reported.\textsuperscript{[41]}

1.2.2 Ring opening

The presence of a relatively weak N-O bond makes this site susceptible to reductive cleavage. Different computational calculations conducted proved the N-O bond having the lowest \(\pi\)-order compared to the other bonds of the molecule.\textsuperscript{[42]} The N-O bond is therefore the weakest of the ring and can be cleaved under reducing and basic conditions as demonstrated by experimental observations. The typical conditions for the N-O bond cleavage are catalytic hydrogenation and reaction with strong bases.\textsuperscript{[56]} Catalytic hydrogenolysis of the N-O bond of \textbf{1.131} occurs readily over noble-metal catalyst, like Raney/Nichel, and platinum and palladium on carbon and leads to \(\beta\)-enaminoketones \textbf{1.132}. These can be further processed to obtain 1,3-dicarbonyl compounds \textbf{1.133} through hydrolysis of the enamine moiety. Acylation of enaminoketones \textbf{1.132}, followed
by reduction with sodium borohydride and subsequent hydrolysis affords enones 1.135. On the contrary, reduction of isoxazoles 1.131 by means of sodium and ammonia furnishes β-aminoketones 1.136 that can be further modified into the isomeric enones 1.137 by acid-catalyzed elimination of the amine group (Scheme 35). Thus the isoxazole ring can be seen like a masked form of these important functional groups and have been successfully exploited in the synthesis of various bioactive and natural compounds, like vitamin B-12 and tetracycline antibiotics.

Scheme 35. Reductive cleavage of the isoxazole ring and further transformations.

The N-O bond of the isoxazole ring can be cleaved also with reaction of strong bases (Scheme 36). 3-unsubstituted isoxazoles 1.138 react with strong bases as alkoxydes, sodium amide, lithium diisopropylamide and butyllithium affording β-ketonitriles 1.140 through the formation of the α-cianoenol intermediate 1.139.

Scheme 36. Base-promoted ring opening to β-ketonitriles.
The presence of an electrwithdrawing group in 4-position, such as a nitro group, makes the isoxazole ring susceptible of hydrolysis with sodium hydroxide at C-5, leading to the cleavage of the C-O and C=C bonds and ring-opening, revealing a carboxylic acid as demonstrated by Sarti-Fantoni (Scheme 37). The same transformation of the 3,5-disubstituted-4-nitroisoxazole core into a carboxylic acid can be performed under oxidative conditions, with potassium permanganate, and under acidic conditions with hydrochloric acid and tin chloride (see paragraph 1.3).

\[
\text{Scheme 37. Hydrolysis of activated isoxazoles.}
\]

Similarly, 3-phenyl-4-nitro-5-aminomethylisoxazole can undergo ring-opening reaction under basic conditions to produce methylamine and the nitrooxime, after hydrolysis and decarboxylation (Scheme 38).

\[
\text{Scheme 38. Alkaline hydrolysis and decarboxylation of 3-phenyl-4-nitro-5-methylamino isoxazole.}
\]

1.2.3 Metallation

3,5-disubstituted isoxazole can be selectively lithiated at 4-position affording 4-lithiumisoxazole that subsequently reacts with electrophiles obtaining various 4-substituted isoxazoles (Scheme 39).

\[
\text{Scheme 39. Direct C-4 lithiation of 3-amino-5-methyl isoxazole.}
\]
On the other hand isoxazoles bearing an alkyl chain at the 5-position undergo lithiation of the side chain preferentially (Scheme 40). The protons present at the α-position of 1.149 are relatively acidic and can be abstracted by strong bases like BuLi, LDA and NaNH₂. The intermediate carbanion 1.150 reacts with electrophiles to perform different side chain functionalizations, furnishing compounds 1.151. Notably the deprotonation occurs only on the alkyl group at the 5-position also when other alkyl groups are present at the 3- and 4-positions. On the contrary the presence of a nitro group in 4-position completely inhibits the side chain lithiation.

\[ R = \text{H, Me} \]

R = NO₂ no reaction

**Scheme 40.** Side chain lithiation of 3,5-dimethyl isoxazole.

4-metalloisoxazoles 1.153 can be more conveniently prepared via halogen-metal exchange reaction with \( n \)-butyllithium starting from 4-iodoisoxazoles 1.152 (Scheme 41). Subsequent reaction of the 4-lithiimisoxazole 1.153 with electrophiles affords trisubstituted isoxazoles 1.154.

\[ R_1 = \text{alkyl, aryl} \]
\[ R_2 = \text{alkyl, aryl} \]

E = CO₂, MeI, PhCOCl, CISnBu₃

**Scheme 41.** Lithiation of 3,5-disubstituted-4-iodo isoxazoles via halogen-metal exchange reaction.

In a similar way, reacting 4-iodoisoxazoles 1.155 with magnesium produces the corresponding 4-isoxazole magnesium iodide species 1.156 that can be subsequently reacted with electrophiles furnishing 4-functionalized isoxazoles 1.157 (Scheme 42).
1.2.4 Transition metal-catalyzed functionalization

Many examples of palladium catalyzed coupling reactions of 3,5-disubstituted-4-iodoisoxazoles 1.158 could be found in the literature for the formation of a wide range of the corresponding coupling derivatives 1.159 bearing at the 4-position aryl, heteroaryl, vinyl and acetylenyl groups (Scheme 43).[50]

Scheme 43. Palladium(0)-catalyzed cross-coupling reactions for the functionalization of 4-iodoisoxazoles.

The general mechanism for the Pd(0)-catalyzed cross-coupling reaction involves the oxidative addition of the 4-iodoisoxazole 1.158 with the palladium(0) catalyst, forming the palladium(II) complex 1.160, which undergoes transmetallation with the organometallic reagent producing the Pd(II) complex 1.161. Finally, reductive elimination occurs furnishing the 3,4,5-trisubstituted isoxazoles 1.159 and restoring the Pd(0) catalyst (Scheme 44).
In the last decade direct metal-catalyzed C-H activation of the isoxazole ring has been investigated by many groups. The advantages offered by this method lie in the possibility of avoiding the use of pre-functionalized halo-isoxazoles and no requirements of stoichiometric amount of organometallics reagents.

Scheme 44. General mechanism for the Pd(0)-catalyzed cross-coupling reaction of 4-iodoisoxazoles.

The general mechanism for the palladium(II)-catalyzed C-H activation of 3,5-disubstituted isoxazoles 1.162 involves an initial carbopalladation of the isoxazole, with the insertion of palladium into the C4-H bond and formation of the Pd(II) complex 1.164. Oxidative addition of the aryl halide species with 1.164 brings to the Pd(IV) intermediate 1.165.
which in the last step undergoes reductive elimination, affording the 3,4,5-trisubstituted isoxazole $1.162$ and regenerating the Pd(II) catalyst (Scheme 46).

Scheme 46. General mechanism for the Pd(II)-catalyzed C-H activation of 3,5-disubstituted isoxazoles.

The first example of Pd-catalyzed direct C-H activation of the 4-position of isoxazoles $1.165$ was reported by Sakai using aryl iodides and palladium on carbon as the catalyst for the preparation of compounds $1.166$ (Scheme 47). $[51]$

Scheme 47. Pd(0)-catalyzed C-H activation of 3,5-disubstituted isoxazoles with aryl iodides.

$R_1$ = Me, Ph
$R_2$ = OTs, CH$_2$OR

$X_{2}Pd^{II}$

$X_{2}Pd^{IV}$
The methodology has been later improved by Doucet and Santelli in 2009\(^{52}\) by using aryl bromides with palladium(II) chloride as catalyst under ligand-free conditions furnishing trisubstituted isoxazoles 1.168 (Scheme 48).

\[
\begin{align*}
\text{R}_1 &= \text{Me, CO}_2\text{Me, CHO} \\
\text{R}_2 &= \text{Me, Ph}
\end{align*}
\]

**Scheme 48.** Pd(II)-catalyzed C-H activation of 3,5-disubstituted isoxazoles with aryl bromides.

Doucet and co-workers further expanded the palladium-catalyzed C-H activation of 3,5-disubstituted isoxazoles \(1.169\) in 2012 by employing aryl chlorides as the coupling partners for the preparation of isoxazoles \(1.170\) (Scheme 49).\(^{53}\) In this case the use of a ferrocenyl diphosphane Sylphos \(1.171\) was necessary for the activation of the less reactive aryl chlorides.

\[
\begin{align*}
\text{R}_1 &= \text{Me} \\
\text{R}_2 &= \text{Me, Ph}
\end{align*}
\]

**Scheme 49.** Pd-catalyzed direct C-H activation of 3,5-disubstituted isoxazoles with aryl chlorides.
1.3 4-Nitroisoxazoles: reactivity and synthetic utility

3,5-dimethyl-4-nitroisoxazole 1.127 has emerged in the last decades as a powerful tool in organic chemistry. \[12\] His peculiar chemical behavior, respect to other isoxazole derivatives, arises from the presence of the nitro group in 4-position (Figure 6).

![Figure 6. Reactivity of 3,5-dimethyl-4-nitroisoxazole.](image)

The electron-withdrawing nature of the nitro group deeply affects the electronic distribution on the isoxazole ring, modifying the usual reactivity of the isoxazole core. Two most peculiar characteristics resulting from its presence can be outlined:

- The methyl group at 5-position is conjugated with the nitro group in a 1,4-conjugated system, due to the low delocalization of the π-electrons on the ring. This feature results in an increase of the acidity of the protons in α-position that can undergo deprotonation by weak organic and inorganic bases. Thus the deprotonated isoxazole can act a soft nucleophile in different types of reactions with electrophiles.

- The carbon at 5-position is the more electrophilic in the isoxazole ring and hence becomes susceptible of attack by strong nucleophiles, like hydroxyl ions, leading to ring opening with cleavage of the C-O and C=C bonds, revealing a carboxylic acid (Figure 7).

The conjugated 1,4-conjugated system of 1.127 shows to act as an ester moiety in the activation of the α-methyl group and of the C-5, tuning their reactivity. Thus, the 4-nitroisoxazole nucleus can be considered as a masked carboxylic acid or ester.

![Figure 7. 4-nitroisoxazoles as a masked carboxylic acids.](image)
These peculiar features have been exploited in the preparation of valuable compounds. The typical reaction sequence involves initially the functionalization of the α-position of 1.127 by reaction with a suitable electrophile, bringing to the formation of compound 1.174 which can be further elaborated before revealing the carboxylic acid in the final step (Scheme 50).

**Scheme 50.** Typical reaction sequence for the use of X as a carboxylic acid synthon.

1.127 can be easily synthetized in two steps in almost quantitative yields, starting from inexpensive starting materials. Acetylacetone 1.176 is first reacted with hydroxylamine hydrochloride in the presence of sodium carbonate. 3,5-dimethylisoxazole 1.126 so obtained is then subjected to nitration with sulfonitric mixture to give 1.127 (Scheme 51).

**Scheme 51.** Preparation of 3,5-dimethyl-4-nitroisoxazole.
1.3.1 Nucleophilic behavior 3,5-dimethyl-4-nitroisoxazole

The reactivity of 1.127 as a nucleophile mainly relies on Knoevenagel-like condensations with aldehydes and related compounds, and vinylogous 1,2-additions on carbonyl groups.

1.3.1.1 Knoevenagel reactions.

1.127 is known to undergo Knoevenagel condensations with different aromatic and aliphatic aldehydes to produce the corresponding styryl- derivative, as reported by Quilico and Musante. The reaction is usually performed in EtOH with catalytic amount of piperidine as a base and furnishes 3-methyl-4-nitro-5-styrylisoxazoles 1.177 as the only (E)-isomers (Scheme 52).

![Scheme 52.](image)

Although being a powerful method for the preparation of aromatic derivatives, its efficiency in reaction with aliphatic aldehydes is not always satisfactory, affording low yields of the desired condensation products with the formation of by-products. To overcome this limitation Adamo and co-workers proposed a multistep sequence to obtain aliphatic derivatives 1.179 in high yields (Scheme 53).

![Scheme 53.](image)

In the first step, alcohols 1.178 were prepared via a vinylogous Henry reaction between 1.127 and aliphatic aldehydes. Then 1.178 is dehydrated with mesyl chloride and triethylamine, furnishing compounds 1.179 in high yields and as the only (E)-isomers. It’s worth to be noted that compounds 1.177 and 1.179 are valuable synthetic building blocks and have been utilized as poly-functional scaffolds in the synthesis of important bioactive compounds (see paragraph 1.3.3).
Vetelino \cite{57} and Adamo \cite{58} showed that \textbf{1.127} reacts with dimethylamidediacetals \textbf{1.180} in DMF without need of a base furnishing \textit{[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amines} \textbf{1.181} as the only \textit{(E)}-isomers (Scheme 54). Compound \textbf{1.181} presents a peculiar reactivity that will be detailed later in the discussion (see Chapter 3).

\begin{center}
\textbf{Scheme 54.} Condensation of \textbf{1.127} with dimethylamidediacetals.
\end{center}

1.3.1.2 1,2-Addition to carbonyl compounds

In 2009, Adamo and co-workers reported the vinylogous nitroaldol (Henry) reaction of \textbf{1.127} with aromatic aldehydes. \cite{54b} The reaction produces the corresponding benzyl alcohols \textbf{1.183} in modest yield, while the use of the parent compound 3,5-diethyl-4-nitroisoaxazole \textbf{1.182} afforded the corresponding products \textbf{1.184} in higher yields (Scheme 55).

\begin{center}
\textbf{Scheme 55.} Vinylogous Henry reaction with aromatic aldehydes.
\end{center}

In 2015 Zhang and co-workers proposed the “on water” vinylogous Henry reaction of \textbf{1.127} with isatins \textbf{1.185} catalyzed by DABCO, \cite{59} obtaining the corresponding nitroaldol adducts \textbf{1.186} in excellent yields (Scheme 56).
Scheme 56. DABCO-catalyzed “on water” vinylogous Henry reaction.

The same year, Kashinath et al. reported an “on water” catalyst free vinylogous Henry reaction of 1.127 with \( p \)-nitrobenzaldehyde 1.187 (Scheme 57) and isatins 1.189 (Scheme 58).\(^{[60]}\) In both cases the authors claim the hydrogen bonding ability of water having a catalytic effect on the reactions, activating both the reagents.

Scheme 57. “On water” catalyst-free vinylogous Henry reaction of 1.127 with \( p \)-nitrobenzaldehyde.

Scheme 58. “On water” catalyst-free vinylogous Henry reaction of 1.127 with isatins.
1.3.2 Electrophilic behavior of 3,5-dimethyl-4-nitroisoxazole and its derivatives

1.3.2.1 1,4-Addition of nucleophiles to the isoxazole ring

The presence of the nitro group in 4-position of 4-nitroisoxazoles makes them susceptible to attack at the C-5 by nucleophiles. Different kind of nucleophiles can react with the 3,5-disubstituted-4-nitroisoxazole core 1.191. The attack at C-5 breaks the aromaticity of the isoxazole ring producing intermediate 1.192 that, upon protonation of the C-4 leads to the formation of isoxazolines 1.193 (Scheme 59).

Scheme 59. 1,4-addition of hard nucleophiles on the 4-nitroisoxazole core.

Tedeschi and co-workers in 1982, attempting to perform the side chain silylation of 1.127, showed that n-BuLi reacted at the C-5 of the ring producing the 3,5-dimethyl-5-butyl-4-nitro-4,5-isoxazoline 1.194 (Scheme 60).[61]

Scheme 60. Preparation of 3,5-dimethyl-5-butyl-4-nitro-4,5-isoxazoline with butyllithium.

Albertola and co-workers,[62] in a similar way, demonstrated that 1.127 is attacked at C-5 by different organolithium, Grignard and reagents furnishing the corresponding 5-disubstituted isoxazolines (Scheme 61).
Scheme 61. Preparation of 3,5-dialkyl-5-alkyl-4-nitro-4,5-isoxazoline with organolithium and Grignard reagents.

Shibata, in 2011, \[63\] proposed the first direct trifluoromethylation of isoxazoles using 4-nitroisoxazole derivatives 1.199 as substrates along with the Ruppert-Prakash reagent, under phase-transfer catalysis conditions (Scheme 62). The reaction produces valuable 5-trifluoromethylisoxazolines 1.200 with high regio- and diastereoselectivity. They demonstrated that the presence of the nitro group in 4-position is fundamental for the positive outcome of the reaction.

Scheme 62. Phase-transfer catalyzed trifluoromethylation of 4-nitroisoxazoles.

In particular conditions, soft carbon nucleophiles are capable to attack the C-5 of the 4-nitroisoxazole core, as demonstrated by Adamo and co-workers \[64\] with the synthesis of 3-methyl-4-nitro-5-syroisoxazolines 1.201 (Scheme 63). The one-pot reaction works via a tandem double 1,6-/1,4-Michael addition of bis enolizable compounds 1.202 on 1.177 prepared in situ by piperidine catalyzed reaction of 1.127 with aromatic aldehydes. \[65\]
The first 1,6-conjugate addition produces intermediate 1.203 which subsequently cyclizes to the spiroisoxazoline 1.201.

\[
\begin{align*}
\text{1.127} & \quad \text{1) ArCHO (1.0 equiv.)} \\
& \quad \text{EtOH} \\
& \quad 60 ^\circ \text{C}, 2 \text{ h} \\
\text{1.202} & \quad \text{2) } \overset{\text{O}}{\text{R}} \quad (2 \text{ equiv.}) \\
\text{1.203} & \quad \text{3) HCl dil.} \\
R = \text{H, COMe, CO}_2\text{Et}
\end{align*}
\]

Scheme 63. One-pot synthesis of spiroisoxazolines via tandem condensation/1,6-/1,4-conjugate addition.

Adamo and co-workers also reported the reduction of the 3,5-disubstituted-4-nitroisoxazoles core of 1.204 to isoxazolines 1.205 and 1.206 using sodium borohydride as reducing reagent (Scheme 64). After the addition of hydride to the C-5 of the isoxazole ring, C-4 protonation furnishes the diastereomeric isoxazolines 1.205 and 1.206. The preferential formation of compound 1.205 over 1.206 could be explained by a chelation control on the borohydride exerted by the alcohol moieties present in 1.204. Thus, the delivery of hydride occurs to the more hindered face of the isoxazole ring.

\[
\begin{align*}
\text{1.204} & \quad \text{NaBH}_4 (3.0 \text{ equiv.}) \\
& \quad \text{MeOH} \\
& \quad 0 ^\circ \text{C}, \\
\text{1.205} & \quad \text{67}-\text{79}\% \text{ yield} \\
\text{1.206} & \quad 5\text{--16}\% \text{ yield}
\end{align*}
\]

Scheme 64. Synthesis of homochiral dihydroxy-4-nitroisoxazolines.
1.3.2.2 Ring-opening reactions

1.177 and its derivatives react with NaOH in the Santi-Fantoni reaction, furnishing the corresponding carboxylic acids 1.207 after ring-opening and cleavage of the C₅-O and C₄=C₅ bonds of the isoxazole ring (Scheme 65). 5.0 Equivalents of 1M NaOH in refluxing THF affords the products after 1-2 hours. The reaction was first reported by Santi-Fantoni in 1977 [67] and then has been applied as a general methodology for the use of 1.177 as a masked carboxylic acid. [56, 68]

\[
\begin{align*}
\text{NO}_2 & \quad \text{N} \\
\text{O} & \quad \text{Ar}
\end{align*}
\]

1.177

\[
\begin{align*}
\text{1) NaOH 1M (5 equiv.)} & \quad \text{THF} \\
\text{80 °C, 1-2 h} & \quad \text{2) HCl 1M} \\
\text{r.t.} & \quad \text{HOOC} \\
\text{1.207} & \quad \text{Ar}
\end{align*}
\]

Scheme 65. Preparation of cinnamic acids via basic hydrolysis of 1-177.

The mechanism involves the consecutive attack of two hydroxyl ions at the C-5 of the isoxazole ring (Scheme 66). The attack of the first hydroxyl ion brings to the formation of intermediate 1.209 whose carbonyl is attacked by a second hydroxyl ion to 1.211, which undergoes bond cleavage leading to compounds 1.212 and 1.213. Final acidification affords carboxylic acids 1.207 and the nitroacetonoxime 1.214. The mechanism was demonstrated by studies employing enriched Na¹⁸OH for the hydrolysis, which brought to the formation of carboxylic acids bearing two ¹⁸O-labelled in the carbonyl group. [45a]
In 2011, Yuan reported an alternative methodology for the acid-promoted ring-opening of 3,5-disubstituted-4-nitroisoxazole \textsuperscript{1.215}. He demonstrated that refluxing tin chloride and hydrochloric acid in THF successfully transformed \textsuperscript{1.215} into the corresponding carboxylic acid \textsuperscript{1.216}.

\textbf{Scheme 67.} 4-nitroisoxazole ring-opening under acidic conditions.

The 4-nitroisoxazole nucleus can be converted to the corresponding carboxylic acid also under oxidative conditions, as demonstrated by Adamo and co-workers. \textsuperscript{46, 69} The
cyclopropylisoxazole 1.217 can be converted to the corresponding carboxylic acid 1.218 by treatment with potassium permanganate in a THF/acetone/H$_2$O mixture (Scheme 68). Nevertheless the mechanism of action has not been fully elucidated so far. $^{[54a]}$

![Scheme 68. 4-nitroisoxazole ring-opening under oxidative conditions.](image)

1.3.3 1,6-Conjugate addition of nucleophiles to 3-methyl-4-nitro-5-styrylisoxazoles

In the last decade 3-methyl-4-nitro-5-styrylisoxazoles 1.177 proved to be important building blocks in organic chemistry due to their peculiar reactivity. They possess two electrophilic centers that can react independently on the base of the type of nucleophile utilized. In particular they share with 1.127 the typical reactivity at the C-5 of the isoxazole ring toward hard unstabilized nucleophiles, like hydroxyl and trifluoromethyl anions, and thus can be considered α,β-unsaturated acids synths. On the other hand, they present a second electrophilic center (E$_2$) at the β-position on the exocyclic alkene.

![Figure 8. Electrophilic behavior and reactivity of 3-methyl-4-nitro-5-styrylisoxazoles.](image)

This position shows a typical Michael acceptor reactivity, reacting with soft, stabilized C-, N- and S- nucleophiles, leading to the formation of Michael adducts 1.220 (Scheme 69). The 4-nitroisoxazole moiety activates the exocyclic double bond of 1.177 towards 1,6-conjugated additions and stabilizes the carbanion 1.219 formed by delocalization of the electrons over the conjugated isoxazole system. Hence, in terms of reactivity, 1.177 can be considered as α,β-unsaturated esters equivalents.
Beside a first report in the 80s by Rao involving the reaction of 1.177 with acetylacetone and ethyl acetoacetate, no systematic studies were conducted on its reactivity with soft nucleophiles until the first decade of the XXI century. In those years Adamo and co-workers started an extensive investigation regarding the chemistry of 1.177, in order to build libraries of new heterocyclic compounds through multicomponent reactions (MCRs) based on domino Knoevenagel condensations/Michael additions reactions.

They first reported in 2002 an improved and corrected procedure for the 1,6-conjugate addition of bis-enolisable ketones 1.202 to 1.221. It was shown that reaction with catalytic amount of a secondary amine like piperidine brought to the formation of the Michael adduct 1.222 (Scheme 70).

This methodology was later improved by means of a one-pot reaction between 1.127, aromatic aldehydes and 1.202. The reaction, depending on conditions applied, can lead to 1.203 (Scheme 71) or 1.201 (Scheme 72) in good yields.
Scheme 71. One-pot Knoevenagel/1,6-conjugate addition of bis-enolisable ketones.

\[
\begin{align*}
\text{NO}_2 & \quad \text{N} \quad \text{O} \\
\text{1.127} & \quad \text{1) ArCHO (1.0 equiv.)} \\
& \quad \text{piperidine (0.1 equiv.)} \\
& \quad \text{EtOH} \\
& \quad 60 \degree C, 2 \text{ h} \\
\text{1.202} & \quad 2) \quad \text{(1.2 equiv.)} \\
& \quad \text{R} \\
\text{1.203} & \quad 60 \degree C, 6 \text{ h} \\
& \quad \text{52-84% yield} \\
R &= \text{H, COMe, CO}_2\text{Et}
\end{align*}
\]

Scheme 71. One-pot Knoevenagel/1,6-conjugate addition of bis-enolisable ketones.

Scheme 72. One-pot synthesis of spiroisoxazoline.

In 2005, \[\text{[70]}\] the same group reported the multicomponent synthesis of 3-heteroarylpropionic acids 1.223 and 1.224 through a one pot 4-MCR of 1.127 with an aromatic aldehyde, 1.176 and hydroxylamine or hydrazine, catalyzed by piperidine (Scheme 73). The methodology is based on a tandem Knoevenagel condensation/Michael addition/condensation sequence, followed by basic hydrolysis of the 3-methyl-4-nitroisoxazole ring, producing the corresponding 3-isoxazolyl- or 3-pyrazolyl-3-arylpionic acids in good to excellent yields and with a simple operational procedure.
Scheme 73. One-pot synthesis of 3-heteroarylpropionic acids via 4-MCRs.

The following year the MCR methodology was extended to the use of N-lithiated indoles 1.225 as Michael donors, allowing the preparation of 3-indolepropionic acids 1.226 and 1.227, an important class of bioactive compounds (Scheme 74).[71]

Scheme 74. One-pot synthesis of 3-indolepropionic acids via 4-MCRs.

The synthetic utility of 1.177 was also demonstrated in the preparation of novel heterocyclic compounds i.e. isoxazolopyridones 1.230 (Scheme 75). [72] Piperidine catalyzed the Michael addition of nitromethane to 1.177, prepared in situ, furnishing the γ-nitro derivative 1.228 that was transformed to the corresponding acid 1.229 under Victor-Meyer conditions. Reduction of the aromatic nitro group with tin chloride and hydrochloric acid resulted in the cyclization to isoxazole-fused pyridones 1.230.
Moreover, compounds 1.229 could be transformed into the corresponding pyrazoles 1.231 by treatment with hydrazine, following the conditions reported by Quilico and Musante,\(^{[73]}\) and subsequently cyclized to pyrazolopyridones 1.232 (Scheme 76).
Scheme 76. Modular synthesis of pyrazolopyridones.

In similar way (Scheme 77), piperidine-catalyzed conjugated addition of diethylmalonate 1.233 to *in situ* prepared 1.177, followed by acidic hydrolysis of the γ-di-ester adducts 1.234 and decarboxylation furnished the mono-acids 1.235. Tin chloride-promoted reduction of the aromatic nitro group of 1.235, afforded isoxazoloazepinones 1.236. \[74\]
Scheme 77. Modular synthesis of isoxazoloazepinones.

Also in this case it was possible to transform compounds 1.235 into the related pyrazoles 1.237 that were cyclized to the corresponding pyrazoloazepinones (Scheme 78).
Adamo and co-workers proposed in 2008 a route for the N,O-heteroatom interchange of the isoxazole ring. It was noticed that different Michael adducts gave the opposite isomers, with interchanged 3,5 substituents, upon treatment with hydroxylamine hydrochloride and sodium carbonate. This allowed the development of a procedure for the selective and consecutive functionalization of both the methyl groups of 1.127, bringing to highly functionalized isoxazoles.

The ability of the 4-nitroisoxazole core to stabilize the carbanion formed after the 1,6 conjugated addition of a nucleophile on 1.177, allows the possibility to perform a sequential Michael addition/cyclization reaction, when an opportune Michael donor is used. For example, the piperidine-catalyzed reaction of 1.177, formed in situ, and ethyl-2-...
chloroacetylacetate 1.241 brings to the formation of highly substituted cyclopropanes 1.242 and 1.243 as equimolar diastereomeric mixture (Scheme 80). \(^{[76]}\)

**Scheme 80.** Synthesis of cyclopropanes via a sequential Knoevenagel/MIRC cyclopropanation.

The reaction proceeds via a Michael initiated ring-closing mechanism (MIRC) in which the carbanion 1.244, formed after the addition of the enolate 1.244 to 1.177, displaces the chlorine through intramolecular S\(_{2}\) substitution, producing the cyclopropane ring (Scheme 81).

**Scheme 81.** Proposed mechanism for the Michael initiated ring-closing cyclopropanation.

Isoxazolyl-substituted cyclopropanes 1.247 could be similarly obtained by reaction between α-bromo styrylisoxazoles 1.246 and dimethylmalonate 1.248 using DBU as a base. The products were obtained in good to excellent yields, as the only trans-isomers (Scheme 82). \(^{[77]}\)
Scheme 82. Synthesis of cyclopropanes via 1,6-michael addition/intramolecular $S_N$2.

In this case reaction between 1.246 and 1.248 produced Michael adducts 1.250, which underwent intramolecular cyclization via $S_N$2 reaction displacing the bromine in α-position and producing cyclopropanes 1.247 (Scheme 83).

Scheme 83. Formation of cyclopropanes 1.247 via intramolecular cyclization.

Scheme 84. Preparation of α-bromo styrylisoxazoles 1.246 from 1.177.

In 2012 Adamo and co-workers reported the N-heterocyclic carbene catalyzed homoenolate addition of cinnamaldehyde 1.252 on 1.177, which further expanded the
range of C-nucleophiles utilizable in Michael addition reactions with 4-nitro-5-styrylisoxazoles. \[^{[46]}\] The reaction produced 2-isoxazolyl-3,4-diarylcylopentan-1-ones 1.253 as single diastereoisomers. 1.253 were further modified by means of α-fluorination and subsequent oxidative ring-opening of the 4-nitroisoxazole moiety, affording highly substituted cyclopentanones 1.254 (Scheme 85).

Scheme 85. NHC-catalyzed synthesis of functionalized cyclopentanones.

Over the years it has been demonstrated that the reactivity of 1.177 as Michael acceptor toward soft nucleophiles is not restricted to C-nucleophiles but S- and N-nucleophiles could successfully undergo 1,6-conjugate addition, thus increasing the chemical diversity obtainable from 1.177. Adamo and co-workers demonstrated the feasibility of the sulfa-Michael addition of sulfur nucleophiles on 1.177. In 2010 it was reported the addition of bisulfite to electrophilic olefins, including 1.177. \[^{[78]}\] The reaction proceeded via triethylamine-catalyzed 1,6-conjugate addition of aqueous sodium bisulfite to 1.177 and produces β-sulfonic acids 1.255 in excellent yields (Scheme 86).
Organic thiols also proved to be suitable Michael donor in 1,6-conjugate addition to \textbf{1.177}. Benzylthiol \textbf{1.256} showed to react with \textbf{1.177} to produce Michael adducts \textbf{1.257} in good yields, using piperidine as catalyst (Scheme 87). \cite{79}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{1.177}};
\node (b) at (2,0) {\textbf{1.256}};
\node (c) at (4,0) {\textbf{1.257}};
\draw[->] (a) -- (b);
\end{tikzpicture}
\end{center}

\textbf{Scheme 87. Sulfa-Michael addition of benzylthiol to Y.}

In 2015 Kashinat and co-workers \cite{80} reported the one-pot preparation of isoxazole-substituted tetrahydrothiophenes \textbf{1.259} via piperidine-catalyzed Knoevenagel condensation, domino sulfa-Michael/intramolecular vinylogous Henry reaction of \textbf{1.127} with 1,4-dithiane-2,5-diol \textbf{1.258} (Scheme 88).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{1.127}};
\node (b) at (2,0) {\textbf{1.259}};
\node (c) at (4,0) {\textbf{1.258}};
\draw[->] (a) -- (b);
\end{tikzpicture}
\end{center}

\textbf{Scheme 88. One-pot synthesis of isoxazole-substituted tetrahydrothiophenes \textbf{1.259}.}

The \textit{in situ} formed styrylisoxazoles \textbf{1.177} react in the second step with \textbf{1.260} derived from reaction of \textbf{1.258} with piperidine producing intermediates \textbf{1.261}, which undergo intramolecular vinylogous Henry reaction affording the cyclized products \textbf{1.259} in excellent yields (Scheme 89).
Scheme 89. Proposed mechanism for the domino sulfa-Michael/intramolecular vinylogous Henry reaction.
1.3.4 Asymmetric 1,6-conjugate additions on 3-methyl-4-nitro-5-styrylisoxazoles

The year 2009 saw a major breakthrough in the definition of 3-methyl-4-nitro-5-styrylisoxazoles as important polyfunctional scaffolds in asymmetric synthesis, with the first report of an organocatalytic asymmetric 1,6-conjugate addition on 1.177. Adamo and co-workers \[^{[68b]}\] proposed the enantioselective phase-transfer catalyzed conjugate addition of nitroalkanes to 1.177. The reaction of 1.177 with nitromethane, catalyzed by cinchonidine-derived quaternary ammonium salt 1.263, showed to proceed with excellent degrees of enantioselectivity, furnishing γ-nitroisoxazoles 1.262 in high yields (Scheme 90). Both enantiomers could be obtained using the corresponding Cinchona-derived pseudoenantiomer.

![Scheme 90. Asymmetric phase-transfer catalyzed conjugate addition of nitromethane to 1.177.](image)

Further modifications of 1.264 through alkaline hydrolysis of the isoxazole moiety revealing the acid 1.265 and reduction of the nitro group with hydrogen and Ra/Ni, produced highly valuable γ-aminoacid 1.266 without loss of enantiomeric purity. The importance of this methodology was proven with the gram scale preparation of enantiopure Baclofen 1.266, a GABA\(_B\)-receptor agonist, currently commercialized as a recemate, although only the (R)-enantiomer is biologically active (Scheme 91).
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Scheme 91. Preparation of enantiopure (R)-Baclofen.

Following this seminal report, many other examples of organocatalytic asymmetric reactions involving 1.177 have been reported, making use of phase-transfer, bifunctional and amino catalysis. In 2011, Yuan and co-workers proposed the enantioselective 1,6-conjugate addition of arylthiols 1.267 to 1.177 under bifunctional catalysis. They showed that 1.267 reacted smoothly using Takemoto’s thiourea 1.269 as catalyst, obtaining β-thioarylisoxazoles 1.268 in good to excellent yields and enantioselectivities (Scheme 92).

Scheme 92. Bifunctional thiourea-catalyzed 1,6-conjugate addition of arylthiols.

They reported a novel methodology for the isoxazole ring-opening to carboxylic acid under acidic conditions, using tin chloride and hydrochloric acid, to overcome the elimination of the arylthiol group produced by the use of the classical basic hydrolysis. This procedure was utilized for the transformation of product 1.270 into β-thioarylcarboxylicacid 1.271 on gram scale, which could be further processed to obtain important benzothiazepines, like S-(+)-thiazesim 1.272 (Scheme 93).
Scheme 93. Tin chloride-promoted isoxazole ring-opening and preparation of (S)-Thiazesim.

The same group expanded the use of bifunctional thiourea catalysis reporting the 1,6-conjugate addition of anthrone $\text{1.273}$ to $\text{1.177}$, $^{[81]}$ Different Michael adducts $\text{1.274}$ were obtained in very high yields with good to excellent enantioselectivities using thiourea $\text{1.275}$ as catalyst (Scheme 94).
In 2012 [69a] Adamo and co-workers reported the phase-transfer catalyzed enantioselective cyclopropanation of 1.177, by reaction with dimethyl 2-bromomalonate 1.276, using the quinidine-derived quaternary ammonium salt 1.278 as catalyst and aqueous potassium phosphate as base (Scheme 95). The reaction proceeded via a Michael-initiated ring-closing (MIRC) mechanism and furnished densely functionalized trans-cyclopropylisoxazoles 1.277 as single diastereoisomers, with excellent yields and good to excellent enantiomeric excesses.

It was demonstrated the isoxazole ring of 1.279 could be transformed into a carboxylic acid or ester 1.280 with a novel oxidative procedure, involving potassium permanganate.
as the oxidant. This step progressed without loss of enantiopurity (Scheme 96). Thus, highly substituted enantiopure cyclopropanes were obtained. The procedure was demonstrated to work at multigram scale, providing 1.280 in similar high yields and ees.

**Scheme 96.** Oxidative isoxazole ring-opening for the preparation of enantiopure cyclopropanes.

In 2013 Yuan and co-workers [82] reported the asymmetric synthesis of γ,γ’-thiopyrrolidonyl spirooxindoles 1.282 via a domino Michael addition/cyclization reaction, between 3-isothiocyanato oxindoles 1.281 and 1.177. The reaction, catalyzed by quinine 1.283, furnished the cycloadducts 1.282 with excellent yields, diastereo- and enantioselectivities (Scheme 97).

**Scheme 97.** Organocatalytic asymmetric synthesis of γ,γ’-thiopyrrolidonyl spirooxindoles.

They further modified product 1.284 by means of oxidation to 3,3’-pyrrolidonyl spirooxindole 1.285 using oxygen peroxide and formic acid. Subsequently 1.285 was...
subjected to alkaline hydrolysis of the 4-nitroisoxazole moiety that resulted in decarboxylation, affording compound 1.286 (Scheme 98).

![Scheme 98. Preparation of 3,3'-pyrrolidonyl spirooxindoles 1.285 and hydrolysis of the isoxazole moiety.](image)

**α,β-unsaturated-γ-butyrolactams 1.286** proved to be another class of Michael donors that efficiently undergo 1,6-conjugate addition with 1.177, as demonstrated by Wang in 2013. They used the bifunctional epi-quinine-derived squaramide catalyst 1.288 to perform a vinylogous 1,6-conjugate addition of 1.286 with 1.177, obtaining Michael adducts 1.287 bearing two adjacent stereogenic centers in high yields and diastereoselectivities as well as excellent enantioselectivities (Scheme 99).

![Scheme 99. Asymmetric 1,6-conjugate addition of α,β-unsaturated-γ-butyrolactams 1.286 to 1.177.](image)
In 2015, Enders and co-workers reported the use of 1.177 in the construction of polysubstituted cyclohexanes 1.291, bearing six consecutive stereocenters (Scheme 100).\textsuperscript{[84]}

The reaction runs via a three components, one-pot 1,4-/1,6-/vinylogous 1,2-addition sequence between β-dicarbonyl compounds 1.289, β-nitroalkenes 1.290 and 4-nitro-5-styrylisoxazoles 1.177, catalyzed by a quinine-derived squaramide 1.292.

Scheme 100. Multicomponent asymmetric synthesis of highly substituted cyclohexanes.

The sequence is initiated by a 1,4-Michael addition of 1.289 on 1.290 forming the Michael adduct 1.293 that subsequently undergoes a domino 1,6-/vinylogous 1,2 addition with the 4-nitro-5-styrylisoxazole, in the presence of catalytic amount of DBU, producing 1.291 (Scheme 101). The products were obtained in good yields and with excellent enantioselectivities as single diastereoisomers. The authors demonstrated the possibility to run the reaction on a multigram scale, without loss of yield and enantiomeric induction.
Adamo and co-workers proposed in 2015 the 1,6-conjugate addition of α-isocyanoesters 1.295 to 1.177,\[^{69b}\] thus further expanding the range of Michael nucleophiles exploitable in this kind of reaction. It was demonstrated that 1.295 could effectively undergo organocatalytic enantioselective addition to 1.177 with a cinchonidine-derived quaternary ammonium salt 1.298 as phase-transfer catalyst. The mild reaction conditions allowed an excellent stereocontrol with concomitant suppression of a potential second Michael addition, obtaining Michael adducts 1.296 in excellent yields as a 1:1 diastereoisomeric mixture. 1.296 were further processed by DIPEA-catalyzed intramolecular cyclization to produce 2,3-dihydropyrroles 1.297 as single diastereoisomers with excellent enantioselectivities (Scheme 102).
Scheme 102. Asymmetric phase-transfer catalyzed addition of isocyanoacetate for the preparation of enantiopure 2,3-dihydropyrroles.

The authors showed the synthetic potential of the protocol with the preparation of enantiopure pyrrolidine dicarboxylate 1.301. The sequence involved the reduction of dihydropyrrole 1.298 to pyrrolidine 1.299, followed by N-Boc protection and oxidative ring-opening of the isoxazole moiety, revealing the correspondent carboxylate 1.301 (Scheme 103).
In 2013 a palladium-catalyzed hydrophosphination of 1.177 with diphenylphosphine 1.302 was proposed by Leung. This methodology used a palladacycle 1.304 as the catalyst in the presence of triethylamine to produce tertiary phosphines 1.303 in excellent yields and good to excellent enantioselectivities.

**Scheme 103.** Preparation of poly-substituted enantiopure pyrrolidines.

**Scheme 104.** Palladium-catalyzed hydrophosphination of 1.177.
1.3.5 Miscellaneous asymmetric transformation involving 4-nitro-5-styrylisoxazoles

Adamo and co-workers demonstrated the possibility of stereoselectively oxidizing the exocyclic alkene of 1.177 applying the Sharpless asymmetric dihydroxylation methodology using osmium tetroxide and dimeric dihydroquinidine-derived quaternary ammonium salt 1.305 as catalyst (Scheme 105).

Scheme 105. Sharpless asymmetric dihydroxylation of 1.177.

The reaction produced homochiral α,β-dihydroxy-4-nitroisoxazoles 1.204 with excellent yields and enantioselectivities, that were subsequently subjected to reduction with sodium borohydride to form the correspondent isoxazolines 1.205 and 1.206 (see Paragraph 1.3.2.1).

Scheme 106. Diastereoselective preparation of isoxazolines.

The attack of the metal hydride at C-5 occurred preferentially on the more hindered face of the isoxazole ring, due to a chelation control exerted by the alcohol groups, bearing to
a good control of the diastereoselectivity. Isoxazolines 1.205 were further modified by reductive ring-opening of the N-O isoxazole bond, producing enantiopure iminoalcohols 1.306 bearing four consecutive stereogenic centers in good yields (Scheme 107).

![Scheme 107. Preparation of enantiopure iminoalcohols via reductive ring-opening of the N-O isoxazole bond.](image)

In 2014 Jorgensen and co-workers\(^{[68c]}\) showed that 1.177 can undergo asymmetric [4+2]-cycloaddition reactions with enals 1.307, under trienamine activation, bringing to the formation of poly-substituted cyclohexenes 1.308 bearing three adjacent stereogenic centers (Scheme 108). The reaction, catalyzed by the bulky triphenylsilyl protected diphenyl prolinol 1.309, furnished the cycloadducts 1.308 in good yields and diastereomeric ratios and excellent enantioselectivities.

![Scheme 108. Proline catalyzed asymmetric [4+2]-cycloaddition of enals with 1.177.](image)

The synthetic utility of the methodology were demonstrated reducing aldehyde 1.310 to 1.311 and hydrolysing the isoxazole moiety under basic conditions followed by in situ modification to lactam 1.312 or ester 1.313, without loss of enantiopurity (Scheme 109).
Scheme 109. Preparation of enantiopure hydroxyesters and lactams.
1.4 References


Chapter 2

Transition metal-free amination of aromatic heterocycles via a new haloform-type reaction
2.1 Electrophilic chlorination of active methylene compounds

α-Chlorocarbonyl derivatives 2.1 (Scheme 1) are an important class of intermediates in organic synthesis. Their synthetic application takes advantage of the multiple nucleophilic and electrophilic functionalities of these products. In particular, mono halogenated compounds 2.1 bear two electrophilic centers, namely the carbonyl and the α-carbon, or a nucleophilic one that could be generated upon α-deprotonation to the enolate 2.2.

Scheme 1. Reactivity of α-chlorocarbonyl compounds.

These moieties can be selectively carried through a broad range of reactions allowing the preparation of valuable functionalized compounds (Scheme 2). The halogen atom undergoes substitutions via $S_N2$ mechanism with C-, N-, O-, and S-nucleophiles producing α-substituted carbonyl compounds 2.3 as well as heterocycles. Hard carbon nucleophiles such as organolithium reagents react with 2.1 through selective addition to the carbonyl carbon providing 1,2-chlorohydrins 2.4 that can be further transformed into epoxides 2.5, olefins 2.6, and heterocycles. Moreover, the presence of acidic α-protons next to a leaving group on the α-carbon makes them suitable reagents for tandem ring-closing reactions to produce cyclopropanes 2.7 and epoxides 2.8. Two representative examples are Michael initiated ring-closing reaction (MIRC) and Darzens epoxidation (see Chapter 4).
Considering the nucleophilic behavior of the α-position of carbonyl derivatives, electrophilic chlorination is a convenient method for the introduction of a chlorine atom. The reaction proceeds through enolate that attacks the electrophilic chlorine furnishing the α-halo derivatives. Acid or basic catalysis can be applied to fasten the halogenation and to control the outcome and the substitution pattern arising from the reaction (Scheme 3).
Scheme 3. Acid- and base-catalyzed electrophilic chlorination of carbonyl compounds.

Substrates bearing two or three acidic hydrogens in α-position 2.9 can be mono-halogenated using acid catalysis to produce 2.15 only. On the other hand, the use of basic catalysis usually leads to poly-chlorinated 2.18, as the second halogenation is usually faster.\(^{12}\) This effect arises from the electron-withdrawing power of the first chlorine introduced that increases the acidity of the remaining α-protons. Hence, the C\(\text{HClR}_1\) group in 2.15 becomes more acidic than the CH\(_2\)R\(_1\) in 2.9 and undergoes enolization more rapidly. Therefore under basic conditions, mono-chloro products 2.15 are indeed not isolated but the reaction furnishes the α,α-dichloro derivatives 2.18.
2.1.1 Electrophilic chlorinating reagents

The first report of a $\alpha$-halocarbonyl compound dates back to the 1859 when Fittig described the preparation of 1,1-dichloroacetone 2.20 by action of chlorine gas on acetone (Scheme 4). \[13\]

\[
\begin{array}{c}
\text{O} \\
2.19 \\
\text{Cl}_2 \\
\text{Cl} \\
2.20
\end{array}
\]

Scheme 4. Preparation of 1,1-dichloroacetone.

In 1871, the first preparation of an $\alpha$-chloroaldehyde 2.22 was reported by Schroder, who reacted 3-methylbutanal 2.21 with chlorine gas (Scheme 5). \[14\]

\[
\begin{array}{c}
\text{O} \\
2.21 \\
\text{Cl}_2 \\
\text{Cl} \\
2.22
\end{array}
\]

Scheme 5. Preparation of 2-chloro-3-methylbutanal.

Since then a wide variety of electrophilic chlorinating reagents have been developed and successfully employed in the preparation of $\alpha$-chloroketones and aldehydes via electrophilic chlorination. \[15\] There are no general methods to be applied to all substrates, thus the choice of the chlorinating reagent depends on the structure of the ketone as well as the degree of chlorination desired. The use of chlorine gas affords both mono- or poly-substituted products depending on the reaction conditions. For example, acetophenone 2.23 is predominantly mono-chlorinated to provide 2.24 at the alkyl chain by chlorine in acetic acid at low temperatures (Scheme 6). \[16\] When the reaction is conducted at 60 °C the $\alpha,\alpha$-dichloro derivative 2.25 is produced, \[17\] which can be further transformed into the $\alpha,\alpha,\alpha$-trichloro acetophenone 2.26 in the presence of sodium acetate. \[18\]
Scheme 6. Mono-, bis- and trichlorination of acetophenone with chlorine.

Alifatic acyclic and cyclic as well as aromatic ketones 2.27 are exaustively halogenated at the α-position by reaction with chlorine in DMF at 100 °C (Scheme 7).\(^{[19]}\)

Scheme 7. Exhaustive chlorination of acyclic and cyclic ketones.

A similar procedure has been reported for the preparation of alifatic α,α-dichloroaldehydes 2.30 (Scheme 8).\(^{[20]}\)

Scheme 8. Electrophilic chlorination of aliphatic aldehydes with chlorine gas.

The use of chlorine gas, a very efficient electrophilic chlorinating reagent, in a polar aprotic solvent like DMF brings to the complete chlorination of the protons in α-position of both ketones and aldehydes. This feature is due to the increase of the acidity of the methylene group during the reaction. In fact, after the introduction of the first chlorine atom the residual proton becomes more acidic because of the electronegativity of the chlorine, bringing to a rapid introduction of a second halogen.
Sulfuryl chloride 2.31 is an effective chlorinating agent that easily reacts with α-hydrogens at room temperature without the need of a catalyst. For unsymmetrical ketones, halogenation occurs preferentially at the more substituted α-carbon in the order methyne>methylene>methyl, although the formation of mixtures of products is frequently obtained. In the case of cyclohexanone 2.32 (Scheme 9), only 2,2-dichlorocyclohexanone 2.33 is formed upon reaction with two equivalents of SO₂Cl₂ that can rearrange to compound 2.34 under acidic conditions (Scheme 9).

**Scheme 9.** Electrophilic chlorination of cyclohexanone with sulfuryl chloride.

The reaction of sulfuryl chloride with aliphatic aldehydes 2.35 selectively produces the mono chlorinated α-chloro derivatives 2.36 (Scheme 10).

**Scheme 10.** Mono-chlorination of aliphatic aldehydes with sulfuryl chloride.

Selenium oxychloride 2.37 has been reported to be a selective mono-chlorinating reagent for alkyl and aryl ketones 2.38. The reaction proceeds through the formation of a dichloro organoselenium intermediate 2.39 that is subsequently thermally decomposed to yield α-chloroketones 2.40 (Scheme 11).

**Scheme 11.** Mono-chlorination of aliphatic and aromatic ketones with selenium oxychloride.

It has to be noted that the methodologies described so far for the electrophilic chlorination involved the use of hazardous reagents. In particular reagents like chlorine gas and sulfuryl chloride are both corrosive and toxic. Moreover selenium-based compounds like
selenium oxychloride show an acute toxicity to every form of life and their use should be limited as much as possible. Due to the danger and the handling difficulties associated with the use of these chlorinating reagents, in the last decades the scientific community moved its attention to the development of novel chlorination procedures employing safer and more environmental benign chemicals.

Other suitable reagents for the selective mono-α-chlorination of aryl and alkyl ketones are copper(II) chloride 2.43 (Scheme 12) \(^{[24]}\) and trichloroisocyanuric acid 2.46 (Scheme 13) (TCICA). \(^{[25]}\)

![Scheme 12. Copper(II)-chloride promoted mono-chlorination of ketones.](image1)

![Scheme 13. Mono-chlorination of ketones with trichloroisocyanuric acid.](image2)

The use of trimethyl chlorosilane 2.49 in combination with dimethylsulfoxide and tetraethylammonium bromide has been reported for the selective mono-chlorination of alkyl and arylketones 2.47, furnishing derivatives 2.48 in good to excellent yields (Scheme 14). \(^{[26]}\)
Scheme 14. Mono-chlorination of ketones with trimethyl chlorosilane.

*N*-chlorosuccinimide 2.50, widely used in radical halogenation of different substrates, has been reported to be poorly effective in chlorination of ketones under radical conditions, giving rise to mixtures of poly-chlorinated products. However it was proven to be an effective electrophilic chlorinating reagent for the α,α-dichlorination of β-ketoamides 2.51, providing α,α-dichloro-β-ketoamides 2.52 or α,α-dichloroamides 2.53 depending on the reaction conditions (Scheme 15).

Scheme 15. Preparation of α,α-dichloro-β-ketoamides and α,α-dichloroamides with *N*-chlorosuccinimide.

In the last decade, different organocatalytic procedures, involving chiral amines 2.56, 2.57, 2.58 and Cinchona-derived 2.59 catalysts, have been reported employing NCS to perform asymmetric electrophilic chlorination of carbonyl compounds, including ketones, aldehydes, and β-ketoesters (Scheme 16).
Metal hypochlorites are another class of highly efficient electrophilic chlorinating reagent, being able to react completely with all the α-hydrogens present in the carbonyl substrate. Methyl ketones readily undergo haloform reaction with sodium hypochlorite in aqueous alkaline solution. The intermediate trichloromethyl ketones are not isolated due to the rapid hydrolysis to carboxylic acid and chloroform.

### 2.1.2 The haloform reaction

The haloform reaction is defined as the metal hypohalides-promoted transformation of methyl ketones into the corresponding carboxylic acids and haloforms (Scheme 17).

\[
\text{RCHO} \xrightarrow{\text{1) MOX, NaOH}} \text{RCOOH} + \text{CHX}_3
\]

\[\text{R = alkyl, aryl} \quad \text{X = Cl, Br, I}\]

**Scheme 17.** The haloform reaction.

The reaction is performed in alkaline solution and involves the electrophilic halogenation of the enolate to the α,α,α-trihalo derivative. This derivative is not isolated under these conditions because the hydroxide anion rapidly carries out a nucleophilic attack on the
carbonyl of 2.65, with concomitant elimination of trihalomethyl anion that is re-protonated to haloform 2.62 (Scheme 18).

![Scheme 18. Mechanism of the haloform reaction.](image)

The first report of the haloform reaction dates back to 1822, when Serullas accidentally discovered that iodine and sodium hydroxide converted ethanol into iodoform. In 1831 Guthrie and Liebig independently prepared chloroform for the first time, the first treating ethanol with sodium hypochlorite, while the latter reacting trichloroacetaldehyde with sodium hydroxide. Later, in 1834 bromoform was prepared by Dumas by the action of sodium hypobromite on ethanol. He also confirmed the composition of the haloforms and gave them the actual name, which refers to the fact that they yielded formic acid on hydrolysis. Many chemists studied this reaction in the following decades, obtaining sometime contrasting results. Beside these reports, no systematic studies of the reaction were made until 1870, when Lieben showed that “iodoform test” was given by a wide variety of compounds. He first proposed a general rule that correlated the reaction with the molecular structure of the substrate. He noticed that the haloform reaction occurred on compounds bearing a methyl ketone group as well as compounds that, under the conditions of the reaction, were oxidized to derivatives containing that structural unit. After Lieben’s general rule, during the IXX century the reaction was extensively used in qualitative organic analysis for the identification of water soluble alcohols and ketones. Therefore, it has been extensively used in the structural determination of different organic compounds, especially in the structural studies of mono and dicyclic terpenes. It also proved to be a useful tool in the industrial production of the haloforms, which were synthetized treating ethanol or acetone with hypohalites until the first decades of the XX century.

During the XX century the scientific interest about the haloform reaction decreased considerably, because of its poor versatility and synthetic utility in the preparation of valuable compounds, considering that the classical alkaline conditions invariably transformed the intermediate trichloromethyl ketones 2.65 into the acids 2.61. The investigations focused on the synthesis and isolation of stable trichloromethyl ketones 2.65. Aston reported the preparation of trichloroketones 2.65 through a two steps route. The first step involved the preparation of di-halo ketones 2.66 with chlorine in acetic acid, followed by the introduction of the third chlorine atom under pH controlled conditions using of sodium acetate buffer, to avoid the hydrolysis to the acid (Scheme 19).
The first useful synthetic applications of a haloform-type reaction were published by Nome et al. in 1987, reporting the use of 2,2,2-trichloro-1-arylethanones 2.67 as efficient benzoylating reagents for amines \[^{[40]}\] and 1,1,1-trichloropropanone 2.68 as acetylation agent.\[^{[41]}\] The reaction involves a nucleophilic acyl substitution by the amine, with elimination of chloroform and formation of amides 2.68/2.69 (Scheme 20).

In 2009, Wu and co-workers reported the direct transformation of various methyl ketones 2.70 into the corresponding primary amides 2.72 using an iodine-NH\(_4\)OH system (Scheme 21).\[^{[42]}\] The reaction proceeds through the formation of the triiodoketones 2.71, which subsequently undergo aminolysis with formation of amides 2.72 and iodoform 2.73.

In 2013 Togo and co-workers described the transformation of aryl bromides 2.74 into aromatic esters 2.78 and amides 2.79 by formation of aryl trichloromethyl ketones 2.76 as key intermediates (Scheme 22).

**Scheme 19.** Preparation of stable trichloromethyl ketones.

**Scheme 20.** Trichloromethyl ketones as benzoylating and acylating agents for amines.

**Scheme 21.** Preparation of aryl amides from ketones via iodoform reaction with ammonium hydroxide.

**Scheme 22.** Transformation of aryl bromides into aromatic esters and amides.
Scheme 22. Synthesis of aryl trichloromethyl ketones from bromo arenes.

2.76 were prepared by reaction of the aryl Grignard compounds derived from 2.74 with trichloroacetaldehyde 2.77 (Chloral), followed by in situ oxidation of intermediates 2.75 with tert-butyl hypochlorite to α,α,α-trichloroketones.\(^{[43]}\) 2.76 was then transformed into the corresponding ester 2.78 or amide 2.79 by reaction with alcohols and amines (Scheme 23).

Scheme 23. Preparation of aromatic esters and amides from trichloromethyl ketones.

2.1.3 Aromatic amination

Aromatic amines are found ubiquitously in both natural and synthetic organic compounds.\(^{[44]}\) Their preparation by direct amination of an aromatic or heteroaromatic ring plays a fundamental role in organic synthesis due to the possibility of preparing an enormous...
variety of valuable compounds that shows their utility in a number of scientific fields, from medicinal chemistry to material science. For this reason the aromatic amination has been widely studied in the last century and is still a primary topic in the investigation of new synthetic methodologies. The reaction can be performed under either catalyzed or catalyst-free conditions. The classical uncatalyzed procedures involving nucleophilic aromatic substitutions and vicarious nucleophilic substitutions usually requires harsh reaction conditions as elevate temperature and the use of very reactive and unstable reagents. Different transition metal catalyzed methodologies are present in literature. One of the first examples is the Ullman-type reaction that uses copper(I) as the catalyst for the reaction between aryl halides and N-nucleophiles (Scheme 24).

The major drawback of this procedure is the need of high temperatures and stoichiometric amount of catalyst.

![Scheme 24. Ullmann-type aromatic amination.](image)

The mechanism involves first a base-promoted coordination of the amine to copper(I) forming intermediate that undergoes oxidative addition onto the aryl halide producing the copper(III) species. Finally, reductive elimination furnishes the aryl amine and restore the active Cu(I) (Scheme 25).
Scheme 25. Mechanism for the Cu(I)-catalyzed amination of aryl halides.

The Chan-Lam coupling developed at the end of 1990s, showed an important improvement in the copper catalyzed amination.\[51\] The reaction between aryl boronic acids 2.85 and different amines proceeds at room temperature with a stoichiometric amount of Cu(OAc)$_2$ and a base, usually pyridine or triethylamine. The reaction has been reported to work also under catalytic conditions in the presence of oxygen or another oxidant that reoxidize the Cu(0) to Cu(II) at the end of the cycle (Scheme 26).\[52\]

Scheme 25. Mechanism for the Cu(I)-catalyzed amination of aryl halides.

![Mechanism Diagram]


The mechanism starts with the base-promoted coordination of the amine to Cu(II) producing intermediate 2.89 which undergoes transmetalation with the aryl boronic acid to the Cu(II) species 2.90. Reductive elimination furnishes products 2.87 and Cu(0) that is reoxidized to the active Cu(II) species by oxygen or another oxidant and restart the cycle (Scheme 27).
Scheme 27. Mechanism for the Cu(II)-catalyzed amination of aryl boronic acids.

The palladium catalyzed synthesis of aryl amines, also known as the Buchwald-Hartwig cross-coupling reaction, is one of the most powerful tools available for the amination of arenes. This methodology was developed simultaneously in the mid of 1990s by Buchwald’s and Hartwig’s groups and has been improved during the following decade. An aryl halide or triflate is reacted with various primary and secondary amines in presence of a strong base and a Pd(0) catalyst and a phosphine ligand (Scheme 28).

Usually high temperatures (100°C) are required, although the development of new fine-tuned ligands allows the reaction to proceed at lower temperatures with wide functional groups tolerance.

Mono- (2.95/2.96) and bidentate (2.97/2.98) phosphine ligands have been employed in the reaction, the latter showing a better reactivity and allowing the broadening of the scope to primary amines respect to the mono-dentate ones. Moreover, mechanistic studies showed that the use of bidentate ligands suppress \( \beta \)-elimination to occur from intermediate 1.102 leading to the formation of imines side products. \cite{56}
The mechanism, when bidentate ligands are used, involves the oxidative addition of the Pd(0) into the aryl-X bond forming the Pd(II) intermediate 2.100, which undergoes complexation of the base to 2.101 with elimination of NaX. Then the amine displaces the base from the Pd-complex producing intermediate 2.102 that undergoes reductive elimination with formation of the coupled product 2.94 and regeneration of the Pd(0)-ligand complex 2.99 (Scheme 29).[^57]

It should be noted that while the Pd(0) Buchwald-Hartwig reaction could be efficiently employed for the amination of variously substituted aromatic substrates and six membered ring heteroaromatic nuclei, the amination of 5-membered heterocycles holding one or two heteroatoms is still an outstanding synthetic problem.
2.2 Results and discussion

2.2.1 Synthesis of 3-methyl-4-nitro-5-trichloromethylisoxazole

As a part of our interest in extending the synthetic utility of 3,5-dimethyl-4-nitro-isoxazole 2.103, we decided to start a novel investigation on halogenations of 2.103. In particular, we became interested in the chlorination of the methyl group at C-5 and in the subsequent exploration of the reactivity of the products obtained. Considering the similar chemical behavior of the 4-nitro-isoxazole core of 2.103 with a carbonyl system (see Chapter 1) we decided develop a study to obtain 3-methyl-4-nitro-5-chloromethylisoxazole 2.104. We envisaged compound 2.104 could behave similarly to his parent compounds α-chloroketones 2.1, undergoing ring-closing reactions like Darzens epoxidation and Michael initiated ring closing cyclopropanation (Scheme 30).

The chlorination 2.103 has not been reported in literature, while it’s possible to find some procedures for the bromination of its analogues 2.109 bearing carboxylates, cyano or aryl substituents at C-4 (Scheme 31). The mono and di-bromination is performed under free-radical conditions, using N-bromosuccinimide (NBS) or molecular bromine as bromine radical sources. A major drawback of this procedure is the lack of control on the chemo- and regioselectivity, obtaining poly-brominated derivatives.
At the onset of the study we tried to perform the chlorination of \textbf{2.103} under radical conditions (Table 1). Different radical chlorinating reagents were tested, like \textit{N}-chlorosuccinimide 2.50, 1,3-dichloro-5,5-dimethylhydantoin 2.112 (DCDMH) and sulphuryl chloride 2.31, using benzoyl peroxide 2.113 as the radical initiator. However, in all the cases just starting material \textbf{2.103} was recovered, even when utilizing an excess of chlorinating reagent and prolonged reaction times. The use of sulphuryl chloride without a radical initiator, as source of molecular chlorine, was also proved to be ineffective, demonstrating the remarkably unreactivity of \textbf{2.103} towards halogenation under free-radical conditions.

\textbf{Table 1}. Conditions screened for the free-radical chlorination of \textbf{2.103}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chlorinating reagent (equiv.)</th>
<th>Radical initiator (equiv.)</th>
<th>Solvent</th>
<th>(T) (°C)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NCS (1.0)</td>
<td>2.113 (0.1)</td>
<td>CCl(_4)</td>
<td>90 °C</td>
<td>24 h</td>
</tr>
<tr>
<td>2</td>
<td>NCS (3.0)</td>
<td>2.113 (0.5)</td>
<td>CCl(_4)</td>
<td>120 °C</td>
<td>72 h</td>
</tr>
<tr>
<td>3</td>
<td>DCDMH (1.0)</td>
<td>2.113 (0.1)</td>
<td>CCl(_4)</td>
<td>90 °C</td>
<td>24 h</td>
</tr>
<tr>
<td>4</td>
<td>DCDMH (3.0)</td>
<td>2.113 (0.5)</td>
<td>CCl(_4)</td>
<td>120 °C</td>
<td>72 h</td>
</tr>
<tr>
<td>5</td>
<td>SO(_2)Cl(_2) (1.2)</td>
<td>2.113 (0.5)</td>
<td>CHCl(_3)</td>
<td>60 °C</td>
<td>24 h</td>
</tr>
<tr>
<td>6</td>
<td>SO(_2)Cl(_2) (20.0)</td>
<td>2.113 (0.5)</td>
<td>-</td>
<td>60 °C</td>
<td>24 h</td>
</tr>
<tr>
<td>7</td>
<td>SO(_2)Cl(_2) (1.2)</td>
<td>-</td>
<td>CHCl(_3)</td>
<td>60 °C</td>
<td>24 h</td>
</tr>
</tbody>
</table>
Hence we decided to perform the reaction under electrophilic chlorinating conditions, exploiting the acidity of the methyl group at C-5 of the isoxazole ring. NCS was chosen as source of chloronium ions and different bases were tested. We first performed the reaction with 1.2 equivalents of NCS and 1.2 equivalents of triethylamine at room temperature in DCM, obtaining, after 18 hours, a new product that was identified as 2.114 in 22% yield with unreacted starting material (Scheme 32). The mechanism of formation of 2.114 will be detailed later in the discussion. Unfortunately, the desired product 2.104 could not be detected in the reaction mixture.

Scheme 32. Electrophilic chlorination of 2.103 with NCS and triethylamine.

Thus we tested different bases, starting from 1,4-diazabicyclo[2.2.2]octane 2.115 (DABCO). Performing the reaction with 1.2 equivalents of NCS and 1.2 equivalents of DABCO in DCM for 18 hours furnished a single product that was identified as the 3-methyl-4-nitro-5-trichloromethylisoxazole 2.117 in 30% yield (Table 2, entry 1). Interestingly, compounds 2.104 and 2.116 could not be detected in the reaction mixture, even quenching the reaction after short times. The preparation of 2.117 was optimized using 3.5 equivalents of NCS, 1 equivalent of DABCO in DCM, at 25 °C for 6 hours, obtaining 2.117 in 93% yield (Table 2, entry 2). The use of an inorganic base like K$_2$CO$_3$ (Table 2, entry 3) furnished as well compound 2.117, although in longer reaction time compared to DABCO. Also in this case the mono- and di-chlorinated products were not detected.
Table 2. Optimization of the trichlorination reaction of 2.100.

<table>
<thead>
<tr>
<th>Entry</th>
<th>NCS (equiv.)</th>
<th>Base (equiv.)</th>
<th>Time (h)</th>
<th>2.104 (%) yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2.116 (%) yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2.117 (%) yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1.2)</td>
<td>DABCO (1.2)</td>
<td>18 h</td>
<td>-</td>
<td>-</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>(3.5)</td>
<td>DABCO (1.0)</td>
<td>6 h</td>
<td>-</td>
<td>-</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td>(1.2)</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (1.2)</td>
<td>18 h</td>
<td>-</td>
<td>-</td>
<td>27%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields.

The exclusive formation of 2.117 can be explained considering the acidity of the C-5 methyl group of 2.103 as well as the electrophilic mechanism involved in the reaction. Electrophilic chlorination is a base-promoted process. After the first chlorine atom is introduced, its electronegativity increases the acidity of the remaining methylene group, fasten the subsequent deprotonation and stabilizing the formation of the anion that will undergo a second and third chlorination at faster rates than the first one. Noteworthy, only the C-5 methyl underwent halogenation, leaving the C-3 one untouched.
2.2.2 Transition metal-free heteroaromatic amination via haloform-type reaction

Considering the similar reactivity of the 4-nitro-isoxazole core to a carbonyl we envisaged compound 2.117 could behave as a trichloromethyl ketone 2.118 in haloform-type reactions. Thus we decided to screen its reactivity towards different types of nucleophiles.

![Figure 1. Similarity between 2.117 and 2.118.](image)

First we reacted 2.117 with excess of aniline 2.119 at 60 °C. After 18 hours it was noted the disappearance of the starting material and the formation of two new products that were identified as 2.120 and 2.121 in 79% and 10% yield respectively (Table 3, entry 1). It should be noted that 2.120 arising from a haloform reaction is the first example of carbonyl-less variant of this reaction that leads to important aminated 5-membered heterocycles. Thus we set up a screening of reaction conditions to optimize the aromatic amination (Table 3). It was noted that at room temperature the reaction proceeded slowly (Table 3, entry 2-7). THF revealed to be the solvent of choice using 2.5 equiv. of amine at 50 °C for 12 hours (Table 3, entry 11). In order to increase the yield and considering the addition-elimination mechanism involved in the haloform reaction, we decided to explore the effect of the addition of an inorganic base. Delightfully, addition of 2 equiv. of K₂CO₃ furnished the desired product 2.120 in 89% yield, without formation of byproduct 2.121 (Table 3, entry 12). Noteworthy product 2.120 was obtained in pure form just after a work-up, without need of column chromatography. The reaction was further optimized decreasing the amount of 2.119 and potassium carbonate to stoichiometric amounts, obtaining 2.120 in 94% yield.

Table 3. Optimization of the aromatic amination of 2.117 with aniline.
With optimized conditions in hands (Scheme 33), we developed the scope of the methodology reacting different aromatic (Table 4), primary (Table 5) and secondary aliphatic amines (Table 6) with 2.117.

Scheme 33. Optimized reaction conditions for the haloform-type amination.
### Table 4. Scope of the amination reaction with primary aromatic amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>(%) yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="" alt="benzylamine" /></td>
<td><img src="" alt="product_1" /></td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td><img src="" alt="aniline" /></td>
<td><img src="" alt="product_2" /></td>
<td>97%</td>
</tr>
<tr>
<td>3</td>
<td><img src="" alt="anisole" /></td>
<td><img src="" alt="product_3" /></td>
<td>92%</td>
</tr>
<tr>
<td>4</td>
<td><img src="" alt="4-chloroaniline" /></td>
<td><img src="" alt="product_4" /></td>
<td>94%</td>
</tr>
<tr>
<td>5</td>
<td><img src="" alt="2-bromoaniline" /></td>
<td><img src="" alt="product_5" /></td>
<td>76%</td>
</tr>
<tr>
<td>6</td>
<td><img src="" alt="2-iodoaniline" /></td>
<td><img src="" alt="product_6" /></td>
<td>61%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields.
Table 5. Scope of the amination reaction with primary alifatic amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>(%) yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{CH}_2\text{CH}_2\text{NH}_2$</td>
<td><img src="image" alt="Product 2.132" /></td>
<td>87%</td>
</tr>
<tr>
<td>2</td>
<td>$\text{CH}_3\text{CH}_2\text{NH}_2$</td>
<td><img src="image" alt="Product 2.133" /></td>
<td>97%</td>
</tr>
<tr>
<td>3</td>
<td>$\text{CH}_3\text{NH}_2$</td>
<td><img src="image" alt="Product 2.134" /></td>
<td>99%</td>
</tr>
<tr>
<td>4</td>
<td>$\text{CH}_2\text{CH}_2\text{NH}_2$</td>
<td><img src="image" alt="Product 2.135" /></td>
<td>99%</td>
</tr>
<tr>
<td>5</td>
<td>$\text{C}_2\text{H}_4\text{NH}_2$</td>
<td><img src="image" alt="Product 2.136" /></td>
<td>99%</td>
</tr>
<tr>
<td>6</td>
<td>$\text{C}_6\text{H}_5\text{NH}_2$</td>
<td><img src="image" alt="Product 2.137" /></td>
<td>95%</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields.
Table 6. Scope of the amination reaction with secondary alifatic amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>(%) yield\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Amine 2.144" /></td>
<td><img src="image" alt="Product 2.150" /></td>
<td>99%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Amine 2.145" /></td>
<td><img src="image" alt="Product 2.151" /></td>
<td>97%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Amine 2.146" /></td>
<td><img src="image" alt="Product 2.152" /></td>
<td>98%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Amine 2.147" /></td>
<td><img src="image" alt="Product 2.153" /></td>
<td>81%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Amine 2.148" /></td>
<td><img src="image" alt="Product 2.154" /></td>
<td>97%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Amine 2.149" /></td>
<td><img src="image" alt="Product 2.155" /></td>
<td>95%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated yields.

The reaction proved to work well both with aromatic and aliphatic amines, producing the corresponding 5-aminooxazoles in excellent yields. Two exceptions were compounds 2.130 and 2.131 (Table 4, entries 5 and 6) that showed reduced yields, probably due to a steric effect exerted by the halogen groups present in orto-position on the aromatic ring. In fact when compared with the corresponding para-bromo 2.128 and para-chloro 2.129 derivatives (Table 4, entries 3 and 4) it’s unlikely that the electronic deactivation produced by the halogen in orto-position would have a much important effect than in para-position.
The reaction mechanism was investigated by performing the reaction between 2.117 and 2.134 in deuterated toluene and analyzing the crude mixture after 2 hours by $^1$H-NMR. The spectra recorded in deuterated toluene showed the presence of the chloroform peak (toluene $d_8$, $\delta = 6.10$ ppm), thus confirming that chloroform is produced during the reaction (Figure 2).

![Figure 2. $^1$H-NMR study showing the formation of CHCl$_3$.](image)

On the base of these findings, the reaction mechanism can be described as a nucleophilic aromatic substitution ($S_N$Ar) consisting of a two steps addition/elimination sequence (Scheme 34). The amine attacks the C-5 of 2.117 forming the non-aromatic isoxazoline 2.156. Deprotonation of 2.156 and subsequent elimination of the trichloromethyl anion restores the aromaticity of the system furnishing the 5.aminoisoxazole. The role of potassium carbonate remains unclear, because the trichloromethyl anion should be able perform the deprotonation of the amine. Moreover, K$_2$CO$_3$ has a poor solubility in THF, so that only a small part is dissolved in the reaction mixture.
To understand the mechanism of formation of compound 2.114, 2.117 was subjected to reaction with triethylamine under the optimized conditions (Scheme 35).

The formation of the product 2.114 began after few minutes of reaction, as demonstrated by $^1$H-NMR analysis of the crude mixture and in 4 hours conversion of the starting material was complete. 2.114 was obtained in 69% yield after column chromatography and no starting material or by-products were detected. This experiment showed that 2.103 was effectively trichlorinated by NCS and triethylamine to 2.117, but it underwent a further reaction with Et$_3$N furnishing compound 2.114. A plausible mechanism to explain the formation of 2.114 involves the radical oxidation of triethylamine by the action of the trichloromethyl radical 2.159 (Scheme 36). This could be formed by a homolytic cleavage of the isoxazole-CCl$_3$ bond of 2.117. 2.159 oxidizes the nitrogen atom of Et$_3$N abstracting an electron and forming a trichloromethyl anion 2.161. The CCl$_3$ anion deprotonates the α-position of the positive radical 2.162 generating the iminium ion radical 2.163 that subsequently turns into the enamine radical 2.164 by losing a proton from the β-position.
Finally, 2.164 reacts with the isoxazole radical formed in the first step furnishing the product 2.114 as the only (E)-isomer. It has to be noted that the oxidation of tertiary amine by means of different oxidating agents is reported in literature and is utilized as a useful tool for the functionalization of the α-position of amines with various nucleophiles. [59]

Scheme 36. Proposed reaction mechanism for the formation of 2.114 by radical oxidation of Et₃N.

With the intent to determine if a radical pathway was involved in the formation of 2.114, we performed the reaction of 2.117 with triethylamine in the presence of a radical inhibitor, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) 2.165. However, this experiment didn’t clarify the mechanism since also in this case 2.177 was obtained although in slightly reduced yield (Scheme 37).

Scheme 37. Control reaction in the presence of TEMPO.

Encouraged by the efficiency of the haloform-type reaction between 2.117 and amines we expanded the scope employing different O- and S-nucleophiles. Aliphatic and aromatic alcohols were tested under the same reaction conditions (Table 7). Unfortunately, the desired substitution products were not obtained, while the substrate 2.117 underwent extensive degradation. Aromatic and aliphatic thiols failed as well in furnishing 5-thioisoxazoles under the optimized reaction conditions with complete recovery of unreacted 2.117. Increasing the equivalents of nucleophile and rising the temperature by
changing the solvent to cyclopentylmethyl ether did not lead to better results and also in this cases no substitution products were isolated.

Table 7. Haloform-type reaction of 2.117 with O- and S-nucleophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.166 (1.1)</td>
<td>THF</td>
<td>50 °C</td>
</tr>
<tr>
<td>2</td>
<td>2.167 (1.1)</td>
<td>THF</td>
<td>50 °C</td>
</tr>
<tr>
<td>3</td>
<td>2.168 (1.1)</td>
<td>THF</td>
<td>50 °C</td>
</tr>
<tr>
<td>4</td>
<td>2.169 (1.1)</td>
<td>THF</td>
<td>50 °C</td>
</tr>
<tr>
<td>5</td>
<td>2.166 (3.0)</td>
<td>CPME</td>
<td>100 °C</td>
</tr>
<tr>
<td>6</td>
<td>2.167 (3.0)</td>
<td>CPME</td>
<td>100 °C</td>
</tr>
<tr>
<td>7</td>
<td>2.168 (3.0)</td>
<td>CPME</td>
<td>100 °C</td>
</tr>
<tr>
<td>8</td>
<td>2.169 (3.0)</td>
<td>CPME</td>
<td>100 °C</td>
</tr>
</tbody>
</table>

We further investigated the chemical behavior of 2.117 reacting it with hard C-nucleophiles. Reaction of 2.117 with n-butyllithium in anhydrous Et₂O at -20 °C did not give the desired substitution product 2.170, but just complete recovery of the starting material (Scheme 38).
Hence we tested different Grignard reagents. Reacting 2.117 with phenylmagnesium bromide 2.171 anhydrous THF furnished, after aqueous work up, compound 2.172 in 93% isolated yield (Scheme 39). The dichloromethylisoxazole derivative is likely to be formed via transmetalation with the Grignard reagent, followed by hydrolysis during the acidic work-up. Despite not being the desired substitution reaction, this method finds utility in the preparation of 2.172 that, as described before, cannot be obtained by direct electrophilic halogenation of 2.117.

Scheme 39. Preparation of 3-methyl-4-nitro-5-dichloromethylisoxazole by reaction of 2.117 with phenylmagnesium bromide.

On the other hand, reaction of 2.117 with an excess of phenylethynylmagnesium bromide 2.173 in anhydrous THF produced compound 2.174, in which the Grignard reagent performs S_N2 nucleophilic substitution and transmetalation on the trichloromethyl group, producing the α-chloro-α-alkynyl derivative (Scheme 40).

Scheme 40. Preparation of 2.174 by reaction of 2.117 with phenylethynylmagnesium bromide.
2.3 Conclusions

In conclusion, we developed a procedure for the electrophilic trichlorination of 3,5-dimethyl-4-nitro-isoxazole 2.103. This involves the use of NCS as electrophilic chlorinating agent and DABCO as base and provided the product 3-methyl-4-nitro-5-trichloromethylisoxazole 2.117 in excellent yield. The reactivity of 2.117 towards different N-O-S- and C-nucleophiles was studied, bringing to the development of a new methodology for the transition-metal free amination of 3-methyl-4-nitro-5-trichloromethylisoxazole 2.117 based on a novel aromatic haloform-type reaction. The reaction proceeded smoothly with stoichiometric amounts of various primary and secondary amines in the presence of 1 equivalent of K$_2$CO$_3$ in THF at 50°C. Remarkably the products 3-methyl-4-nitro-5-amino-isoxazoles were obtained in almost quantitative yields and in pure form without need of column chromatography. This new methodology proved to be a new valuable tool for aromatic amination due to the mild conditions required, the use of stoichiometric amounts of reagents, and the high yields obtained, without need of purification. Moreover, this is the first example of a haloform-type reaction applied to a heteroaromatic ring. Hence, it could be used as a valid alternative to transition metal catalyzed amination of aromatic rings, considering that it does not involve the use of metal catalyst and harsh conditions, in the perspective of expanding its use to different aromatic compounds bearing a methyl-NO$_2$ conjugated system.
2.4 References.

[49] aF. Ullmann, J. Bielecki, Berichte der deutschen chemischen Gesellschaft 1901, 34, 2174-2185; bF. Ullmann, Berichte der deutschen chemischen Gesellschaft
Chapter 2


Chapter 3

Preparation and reactivity of [2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amines
3.1 β-Enaminoesters

β-Enaminoesters 3.1 are a class of key intermediates in organic synthesis, used as 3-carbons building blocks for the preparation of β-aminoesters 3.2, β-aminoacids 3.3, γ-aminoalcohols 3.4, heterocycles and alkaloids (Scheme 1).

Scheme 1. β-Enaminoesters as polyfunctional scaffolds.

Over the years compounds 3.1 have been used as starting materials for the synthesis of heterocyclic moieties as pyridines, pyrimidines, pyroles, pyrrolidines, indoles, pyrazoles, isoxazoles, and oxadiazoles. They also found application as intermediates for the synthesis of a variety of biologically active compounds such as antibacterial, anticonvulsant, anti-inflammatory and antitumor agents (Figure 1).

Figure 1. Biologically active β-enaminones.
Considering the vast amount of applications it is not surprising that these compounds are still actively studied.

### 3.1.1 Synthesis of β-enaminoesters

Several methodologies have been reported for the preparation of β-enaminoesters including condensation of active methylene compounds with dialkylamidodiacetals,\(^7\) direct condensation of amines with β-ketoesters and its modification using Lewis acid catalysis,\(^8\) addition of amines to alkynes,\(^9\) addition of ester enolates to nitriles,\(^10\) addition of ester enolates to tosyl imines,\(^11\) Reformatsky reaction of zinc ester enolates with dialkylformamides,\(^12\) and propargylic hydroxilamines rearrangement.\(^13\)

The condensation of active methylenes compounds 3.9 with \(N,N\)-dimethylformamide diacetals 3.10 has been used since the 1960s as an efficient method for the preparation of α-substituted or α-unsubstituted β-enaminoesters 3.11, although harsh reaction conditions were usually required (Scheme 2).\(^14\)

![Scheme 2. Synthesis of β-enaminoesters by condensation with DMF-diethylacetal.](image)

The direct addition of amines to β-dicarbonyl compounds 3.12 is the most used method for the preparation of enaminones. The uncatalyzed version requires harsh reaction conditions and suffers of low control over the stereochemical outcome with formation of mixture of \(E/Z\)-isomers. The reaction entails reacting β-dicarbonyl compounds 3.12 with amines in refluxing benzene with azeotropic removal of the water formed (Scheme 3).\(^15\)

![Scheme 3. Uncatalyzed addition of amines to β-dicarbonyl compounds.](image)
To avoid using harsh reaction conditions and to overcome the lack of stereocontrol, variants using Lewis acid catalysis have been developed. Bartoli and co-workers reported the zinc perchlorate catalyzed synthesis of alkyl 3-(dialkylamino)propenoates 3.15 by reaction of $\beta$-ketoesters 3.14 with mono- and di-substituted amines (Scheme 4). The reaction worked at room temperature in DCM providing $\beta$-enaminoesters 3.15 in excellent yields as the single (Z)-isomer.

![Scheme 4. Zn(ClO$_4$)$_2$ catalyzed preparation of (Z)-$\beta$-enaminoesters.](image)

Other Lewis acids have been reported to efficiently catalyze the enamination of $\beta$-ketoesters including bismuth trifluoroacetate (Scheme 5) and $^{[16]}$ scandium triflate (Scheme 6). $^{[17]}$ Both these methodologies provided compounds 3.17 and 3.19 in high isolated yields.

![Scheme 5. Enamination of $\beta$-dicarbonyl compounds 3.16 in water catalyzed by Bi(TFA)$_3$.](image)

![Scheme 6. Synthesis of (Z)-$\beta$-enaminoesters under solvent-free condition with Sc(OTf)$_3$.](image)

The zinc-mediated reaction of an enolizable $\alpha$-haloester 3.20 with a nitrile 3.21, also known as Blaise reaction, is an important procedure for the preparation of (Z)-$\beta$-enaminoesters 3.22 (Scheme 7). $^{[10a]}$ The reaction furnishes, after work-up with potassium carbonate, $\beta$-enaminoesters 3.22 as (Z)-isomers. It was demonstrated that
performing the reaction under sonochemical conditions allowed faster activation of the zinc dust. \[18\]

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{\textbf{3.20}} & \quad \text{Br} \\
\text{\textbf{R}}_\text{O\textbf{R}_1} & \\
1) \text{R}_2^\cdot\text{CN} & \text{3.21} \\
\text{Zn (5.0 equiv.)} & \\
\text{THF, reflux} & \\
2) \text{K}_2\text{CO}_3 & \text{50\% aq.} \\
\text{\textbf{R}} & \quad \text{O} \\
\text{\textbf{R}}_\text{O\textbf{R}_1} & \\
\end{align*}
\]

**Scheme 7.** Synthesis of Z-β-enaminoesters via Blaise reaction.

(Z)-β-enaminoesters \textbf{3.25} were efficiently prepared by reaction of electron deficient alkynes \textbf{3.23} and substituted anilines \textbf{3.24} under Ag(I) catalysis (Scheme 8). \[19\]

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{\textbf{3.23}} & \quad \text{OR}_1 \\
\text{\textbf{R}}_\text{O\textbf{R}_1} & \\
\text{AgNTf}_2 & (5 \text{ mol\%}) \\
\text{toluene} & \text{60 °C} \\
\text{\textbf{R}} & \quad \text{NH} \\
\text{\textbf{3.24}} & \quad \text{Tf} \\
\text{\textbf{R}}_\text{R}_2 & \quad \text{O} \\
\text{\textbf{3.25}} & \quad \text{OR}_1 \\
\end{align*}
\]

**Scheme 8.** Silver-catalyzed amination of electron deficient alkynes.

Recently, Jiang and co-workers reported the palladium(II)-catalyzed oxidative coupling between acrylates \textbf{3.26} and primary aromatic amines \textbf{3.27} to produce (Z)-β-enaminoesters \textbf{3.28}. This reaction showed a remarkable functional groups tolerance, providing a large scope of compound \textbf{3.28} (Scheme 9). \[20\]

\[
\begin{align*}
\text{\textbf{3.26}} & \quad \text{R} \\
\text{\textbf{3.27}} & \quad \text{NH}_2 \\
\text{Pd(OAc)}_2 & (5 \text{ mol\%}) \\
\text{LiBr (4.0 equiv.)} & \\
\text{O}_2 & \\
\text{THF} & \text{50 °C} \\
\text{\textbf{R}}_\text{R}_1 & \quad \text{NH} \\
\text{\textbf{3.28}} & \quad \text{O} \\
\text{\textbf{R}}_\text{R}_1 & \\
\end{align*}
\]

**Scheme 9.** Pd(II)-catalyzed synthesis of (Z)-β-enaminoesters.

The proposed mechanism involves the initial coordination of Pd(II) to the olefin to give complex \textbf{3.30} that undergoes nucleophilic attack by the amine producing intermediate \textbf{3.31}. β-Hydride elimination from complex \textbf{3.31} furnishes products \textbf{3.28} and the
hydridopalladium(II) species 3.32, which undergoes reductive elimination affording Pd(0). Finally Pd(0) is reoxidize to the active Pd(II) by oxygen (Scheme 10).

Scheme 10. Proposed mechanism for the palladium(II)-catalyzed oxidative coupling.

Gao and coworkers proposed the zinc-mediated reaction of α-haloesters 3.33 with N,N-dialkylformamides 3.34 (Reformatsky reaction). Condensation of the organozinc enolate with the amide, followed by water elimination provided the correspondent β-enaminoesters 3.35 as the single (E)-isomer (Scheme 11).

Scheme 11. Reformatsky reaction between α-haloesters and N,N-dialkylformamides.

The reaction of ketene acetals 3.38 with Vilsmeier reagent 3.37, prepared by reaction of N,N-dimethylformamide 3.36 with thionylchloride, has been reported by Bates [21] to produce β-enaminoesters 3.39 as single (E)-isomers (Scheme 12).
3.1.2 Reactivity of β-enaminoesters

β-Enaminoesters 3.40 are polyfunctional reagents possessing both electrophilic and nucleophilic properties (Figure 2).

3.1.2.1 Reactions with nucleophiles.

Besides the ester moiety, the C-3 represents the electrophilic center reacting with nucleophiles as a typical Michael acceptor. After the addition of the nucleophile, elimination of the N,N-dialkyl group can occur, bringing to β-substituted-α,β-unsaturated esters 3.44 (Scheme 13). Alkyl 3-(dimethylamino)propenoates 3.42 react with a variety of N-, C- and O-nucleophiles, which lead to substitution of the dialkylamino moiety. The reaction proceeds through an addition/elimination mechanism through intermediate 3.43.

[2] Primary and secondary aliphatic, aromatic and heteroaromatic amines 3.45/3.46 provide the corresponding substitution products. Carbon nucleophiles as 1,3-dicarbonyl 3.47, 3-unsubstituted indoles 3.48 and cyanide anions 3.49 also react with 3.42 at C-3 providing the substitution product 3.44 after elimination of dimethylamine 3.50.
3.1.2.2 Reactions with electrophiles

3.42 Exhibits the typical nucleophilic enamine reactivity, although their reactivity is limited by the presence of the ester. Hence, compounds 3.22 reacts with electrophiles at C-2. The addition to electrophiles is usually followed by deprotonation of the α-carbon of 3.43, restoring the enamine functionality and producing α-substituted esters 3.44 (Scheme 15).

Scheme 13. β-Enaminoesters reactivity towards N-, C-nucleophiles.

Hydrolysis of 3.42 generated the corresponding aldehydes in the form of β-hydroxy-α,β-unsaturated esters 3.51 (Scheme 14).

Scheme 14. β-Enaminoesters reactivity towards O-nucleophiles.

Scheme 15. β-Enaminoesters reactivity towards electrophiles.
3.42 reacts with different types of $C$- and $N$-electrophiles. Reaction with nitrous acid produces oximes 3.47 upon elimination of dimethylformamide from intermediate 3.46 (Scheme 16).

Scheme 16. Preparation of oximes from 3.45.

Different groups reported enamine 3.48 as a Michael donor in conjugated 1,4-addition to electron deficient olefins such as alkyl vinyl ketones 3.49 [24] acrylates 3.50 (Scheme 17), [25] or acryloyl chloride 3.51 (Scheme 18). [26]

Scheme 17. 1,4-conjugate addition of $\beta$-enaminoesters to acrylates.

Stille reported the formation of $\delta$-lactam 3.55 via tandem 1,4-addition/aza-annulation between $\beta$-enaminoester 3.53 and acryloyl chloride 3.54 (Scheme 18). [26]

Scheme 18. Synthesis of $\delta$-lactams via tandem 1,4-addition/aza-annulation of $\beta$-enaminoesters with acryloyl chloride.
3.1.2.3 Synthesis of heterocycles from β-enaminoesters

Nucleophilic and electrophilic nature of β-enaminoesters have found application as starting material for the synthesis of heterocyclic compounds.\(^{[27]}\) Starting from both (E)- or (Z)-isomer it was possible to produce a wide range of functionalized heterocycles such as pyrroles,\(^{[28]}\) pyrrolidines,\(^{[29]}\) pyrimidines,\(^{[30]}\) pyrazoles,\(^{[31]}\) isoxazoles,\(^{[32]}\) pyridines,\(^{[28a, 33]}\) pyridones and\(^{[34]}\) indoles.\(^{[28d, 35]}\)

For example, substituted pyrroles 3.58 were prepared by reacting (Z)-β-enaminoesters 3.56 and nitroolefins 3.57, as reported by Guan (Scheme 19).\(^{[28b]}\)

![Scheme 19. Synthesis of substituted pyrroles by reaction of 3.56 with nitroolefins.](image)

Park and co-workers\(^{[28c]}\) described the synthesis of poly-substituted pyrroles via a copper(II)-catalyzed reaction between β-enaminoesters 3.59 and α-diazo oxime ethers 3.60. The dihydropyrroles 3.61 initially formed underwent acid-catalyzed elimination of 3.51 to provide pyrroles 3.62 (Scheme 20).

![Scheme 20. Cu(II)-catalyzed synthesis of poly-substituted pyrroles.](image)

The mechanism involves nucleophilic addition of enamines 3.59 to the electrophilic carbenoids 3.63, to form zwitterionic intermediates 3.64. Metallotropic shift to N-
metalated species \(3.65\), followed by intramolecular nucleophilic addition to iminium ion \(3.64\) produces dihydropyrroles \(3.61\) (Scheme 21).

\[
\begin{align*}
\text{Scheme 21. Proposed mechanism for the Cu(II)-catalyzed synthesis of poly-substituted dihydropyrroles.}
\end{align*}
\]

\((Z)\)-\(\beta\)-enaminoesters \(3.66\) were used as starting materials for the Pd(II)-catalyzed synthesis of poly-substituted indoles \(3.67\), as demonstrated by Glorius.\(^{[35]}\) The reaction proceeds via intramolecular oxidative coupling catalyzed by palladium acetate and produces 3-carboxylateindoles \(3.67\).

\[
\begin{align*}
\text{Scheme 22. Preparation of substituted indoles by Pd(II)-catalyzed intramolecular oxidative coupling.}
\end{align*}
\]

\(R = \text{alkyl, aryl}\)
\(R_1 = \text{Me, halogen, CO}_2\text{R, CN}\)
\(R_2 = \text{Et, tBu}\)
The proposed mechanism starts with an electrophilic palladation of the nucleophilic enamine 3.66 followed by deprotonation with formation of the intermediate 3.68. Base-assisted deprotonation promotes C-H activation of the aromatic ring producing the species 3.69. Reductive elimination from 3.69 gives indoles 3.67 and Pd(0) that is reoxidized to Pd(II) by copper acetate (Scheme 23).

![Scheme 23. Proposed mechanism for the Pd(II)-catalyzed oxidative coupling.](image)

3.1.2.4 β-Enaminoesters reduction

β-Enaminoesters 3.1 undergo reduction with different reductive reagents and in this contest they exert the role of precursors of important scaffolds in organic chemistry such as β-aminoesters, [36] β-aminoacids [37] and γ-aminoalcohols. Treatment of 3.70 with sodium triacetoxyborohydride 3.71 allows the chemoselective reduction of the enamine moiety without affecting the ester group, producing β-aminoesters 3.72 (Scheme 24). On the other hand, reduction with sodium in an isopropyl alcohol/tetrahydrofuran mixture brings to complete reduction of both the enamine and the ester functionalities, obtaining γ-aminoalcohols 3.73.
Scheme 24. Chemoselective reduction of β-enaminoesters to β-aminoesters and γ-aminoalcohols.
3.2 Results and discussion

As a part of our research program focused on the use of 3,5-dimethyl-4-nitroisoxazole \( \text{3.74} \) as precursor for the preparation of polyfunctional scaffolds, we became interested in the synthesis and investigation of the reactivity of dimethyl-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amine \( \text{3.75} \). It is known that \( \text{3.75} \) can be prepared in one step by reaction of \( \text{3.74} \) with \( \text{3.10} \) to give the condensation product in excellent yield, as the single (\( E \))-isomer (Figure 3). \([38]\)

![Figure 3. Retrosynthesis of (\( E \))-N,N-dimethyl-2-(3-methyl-4-nitroisoxazol-5-yl)-ethenamine 3.75.](image)

Compound \( \text{3.75} \) bears structural similarities both with \( \beta \)-enaminoester \( \text{3.76} \) and styrylisoxazoles \( \text{3.77} \) (Figure 4).

![Figure 4. Structural similarity between \( \text{3.75} \), \( \beta \)-enaminoesters \( \text{3.76} \) and 3-methyl-4-nitro-5-styrylisoxazole \( \text{3.77} \).](image)

\( \text{3.76} \) displays a polyfunctional chemical behavior (Scheme 25) reacting both with electrophiles at \( \alpha \)-carbon and nucleophiles at \( \beta \)-carbon (see Paragraph 3.1.2).

![Scheme 25. Reactivity of \( \beta \)-enaminoesters 1.11 toward electrophiles and nucleophiles.](image)

However, compound \( \text{3.75} \) also contains the 4-nitroisoxazole core which is known to increase the electrophilicity of the exocyclic conjugated alkene in compound \( \text{3.77} \).
Adamo’s group developed the synthesis of 3-methyl-4-nitro-5-styrlyisoxazoles 3.77 and brought on an intensive study on their behavior as Michael acceptors.\textsuperscript{[39]} It was demonstrated that 3.77 underwent organocatalyzed 1,6-conjugate addition with different soft nucleophiles providing the corresponding nitroadducts,\textsuperscript{[40]} cyclopropanes\textsuperscript{[41]} and pyrrolidines,\textsuperscript{[42]} spirooxindoles,\textsuperscript{[43]} cyclohexanes\textsuperscript{[44]} in high yields and enantioselectivities (Scheme 26).

![Scheme 26. Reactivity of 3-methyl-4-nitro-5-styrlyisoxazoles 3.77 toward soft nucleophiles.](image)

Therefore, in principle, compound 3.75 could be considered as either a nucleophilic or an electrophilic synthon. In order to establish its chemical behavior, we decided to study its reactivity towards common nucleophiles and electrophiles.

(E)-N,N-dimethyl-2-(3-methyl-4-nitroisoxazol-5-yl)-ethenamine 3.75 was synthetized by condensation of 3.74 with 3.10 (Scheme 27). This reaction provided compound 3.75 in 92% yield.

![Scheme 27. Synthesis of (E)-N,N-dimethyl-2-(3-methyl-4-nitroisoxazol-5-yl)-ethenamine 3.75.](image)

At the onset of this study, we screened 3.75 as a Michael acceptor against common soft enolisable nucleophiles i.e. nitromethane 3.82, dimethylmalonate 3.83, benzylthiol 3.84 and indole 3.85 (Scheme 28). The reactions were carried out under Lewis acid and basic catalysis. In these experiments, compound 3.75 was recovered unreacted, even after several hours of reflux.
Scheme 28. Screening of reactivity of 3.75 towards different nucleophiles.

We also screened its reactivity towards hard nucleophiles, like Grignard reagent and n-buthyllithium but in these cases complex and unidentified reaction mixtures were obtained. This can be rationalized considering the high electrophilicity of the isoxazole C-5, which likely reacted with the organo-metal reagents, leading therefore to uncontrolled fragmentation.

Considering the remarkable unreactivity of 3.75 towards C- and S-nucleophiles, we investigated its reactivity with N-nucleophiles. Reaction with secondary amines occurred easily, generating the corresponding N-substituted products 3.91-3.95 in high yields, through an addition/elimination mechanism (Table 1). The reaction was optimized using 5.0 equivalents of cyclic amines and refluxing it for 5 hours in toluene. The desired enamines were obtained exclusively as the (E)-isomers, in high yields and in pure form after evaporation of the reaction mixture under high vacuum.

**Table 1.** Synthesis of 1-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amines 1.13a-f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>(% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><a href="#">3.86</a></td>
<td>95</td>
</tr>
</tbody>
</table>
Subsequently we moved on investigating the nucleophilic behavior of 3.75 and its derivatives. Enamines 3.75 and 3.91-3.92 were reacted with N-electrophiles diethyl azodicarboxylate (DEAD) 3.96 and diisopropyl azodicarboxylate (DIAD) 3.97. The reaction was first performed with 2.1 equivalents of DEAD in acetonitrile at room temperature, but after 24 hours just starting material was recovered from the reaction mixture. Increasing the temperature to reflux the reaction progressed to a full conversion after 24 hours. The products were isolated in high yields as 1:1 mixture of (E)- and (Z)-isomers (Table 2).
Table 2. Reaction of selected enamines with DEAD or DIAD.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product (%) Yield (E/Z Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-NMe₂ 3.75 3.98 75 1:1</td>
</tr>
<tr>
<td>2</td>
<td>3.91 DEAD 3.99 88 1:1</td>
</tr>
<tr>
<td>3</td>
<td>3.92 DEAD 3.100 89 1:1</td>
</tr>
<tr>
<td>4</td>
<td>-NMe₂ 3.75 DIAD 3.101 92 1:1</td>
</tr>
<tr>
<td>5</td>
<td>3.91 DIAD 3.102 89 1:1</td>
</tr>
</tbody>
</table>

*Isolated yields.

Compounds 3.98-3.102 could not be separated by column chromatography as single (E)- and (Z)-isomers. However it was possible to crystallize the (Z)-isomer of 3.100 and obtain an X-ray diffraction thereby confirming its structure (Figure 5).
Interestingly, a pure sample of (Z)-3.100 established equilibrium with its (E)-isomer when in solution, forming rapidly a 1:1 (E/Z) mixture. It is possible that the presence of the hydrazine moiety could favor the resonance form (Z)-3.100', thus allowing rotation along the enamine bond and consequent (Z) to (E) inter-conversion (Scheme 29).

Scheme 29. Inter-conversion of (Z)-3.100 to (E)-3.100 in solution.
The reactivity of 3.92 as nucleophile was further investigated by reaction with different acyl chlorides. In order to find the best conditions the reaction between compound 3.92 and propionyl chloride 3.102 was chosen as model. Different reaction conditions were screened, changing equivalents of acyl chloride, base, solvent and temperature (Table 3).

**Table 3. Conditions screened for the acylation of 3.92.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>3.102 (equiv.)</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>3.103 (%) Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(4.0)</td>
<td>-</td>
<td>Et(_2)O</td>
<td>reflux</td>
<td>-(^b)</td>
</tr>
<tr>
<td>2</td>
<td>(4.0)</td>
<td>-</td>
<td>MeCN</td>
<td>reflux</td>
<td>-(^c)</td>
</tr>
<tr>
<td>3</td>
<td>(4.0)</td>
<td>-</td>
<td>THF</td>
<td>45 (^\circ)</td>
<td>-(^b)</td>
</tr>
<tr>
<td>4</td>
<td>(3.0)</td>
<td>Et(_3)N (3.0)</td>
<td>THF</td>
<td>45 (^\circ)</td>
<td>-(^b)</td>
</tr>
<tr>
<td>5</td>
<td>(4.0)</td>
<td>-</td>
<td>THF</td>
<td>reflux</td>
<td>-(^c)</td>
</tr>
<tr>
<td>6</td>
<td>(2.0)</td>
<td>-</td>
<td>THF</td>
<td>reflux</td>
<td>26%</td>
</tr>
<tr>
<td>7</td>
<td>(2.0)</td>
<td>-</td>
<td>CPME</td>
<td>75 (^\circ)</td>
<td>-(^b)</td>
</tr>
<tr>
<td>8</td>
<td>(2.0)</td>
<td>K(_2)CO(_3) (2.0)</td>
<td>CPME</td>
<td>75 (^\circ)</td>
<td>-(^b)</td>
</tr>
<tr>
<td>9</td>
<td>(2.0)</td>
<td>DMAP (1.0)</td>
<td>EtOAc</td>
<td>75 (^\circ)</td>
<td>8 %</td>
</tr>
<tr>
<td>10</td>
<td>(2.0)</td>
<td>DMAP (1.0)</td>
<td>DMF</td>
<td>75 (^\circ)</td>
<td>40%</td>
</tr>
<tr>
<td>11</td>
<td>(3.0)</td>
<td>DMAP (1.5)</td>
<td>DMF</td>
<td>75 (^\circ)</td>
<td>71%</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields. \(^b\) 3.92 recovered unreacted. \(^c\) Degradation of 3.92.

It was noted that prolonged reaction times brought to degradation of both the product and the starting material, probably due to hydrolysis of the enamine moiety in solution with formation of undefined decomposition products.
With optimized conditions in hand, we expanded the scope of the acylation to enamine 3.75 and acetyl chloride (Scheme 30).

Interestingly, in contrast with N-electrophiles, reaction with C-electrophiles furnished the desired products as single (E)-isomers, thus demonstrating the capability of 3.75 and 3.92 to be acylated in stereoselective fashion. Structure of compound 3.104 was confirmed by X-ray diffraction (Figure 6).

Scheme 30. Acylation of compounds 3.75 and 3.92.

Afterwards we studied the ring-opening of the isoxazole moiety of selected compounds derived from reaction of 3.92 with C- and N-electrophiles. Two established methodologies for the conversion of the 4-nitroisoxazole core into a carboxylate were tested: (i) the alkaline promoted hydrolysis, using 5.0 equivalents of 1M NaOH in refluxing THF \[^{45}\] and (ii) the oxidative ring-opening by reaction with 6.0 equivalents of KMnO\(_4\) in

Figure 6. X-Ray diagram of compound 3.104.
THF/aceton/\textit{H}_2\textit{O}. In all the cases it was not possible to isolate the desired acids \textit{3.106} and \textit{3.107}, but just undefined degradation products were obtained (Scheme 31).

\textbf{Scheme 31.} Isoxazole ring-opening conditions.

Hypothesizing a remarkable instability derived from the presence on the same molecule of both enamine and carboxylate moieties, we tried to convert \textit{in situ} the carboxylic group revealed by the isoxazole ring-opening into a methyl ester using trimethylsilyldiazomethane \textit{3.108} in DCM/MeOH. Also in this case the desired product \textit{3.107} was not obtained (Scheme 32).

\textbf{Scheme 32.} Alkaline isoxazole ring-opening followed by \textit{in situ} esterification.

We further investigated the reactivity of compounds \textit{3.75} by studying the hydrolysis of the enamine moiety. The reaction of \textit{3.75} with 5 equivalents of 1M HCl in THF at 60 °C furnished, after 30 minutes, almost total conversion to the corresponding aldehyde \textit{3.109} (Scheme 33). Although \textit{3.109} was identified by \textit{1}H-NMR it wasn’t possible to isolate due to its rapid decomposition.
Scheme 33. Hydrolysis of enamine 3.75 to the unstable aldehyde 3.109.

On the contrary, reaction of compound 3.105 under the same reaction conditions, furnished compound 3.110 in 71% yield in pure form after a simple work-up (Scheme 34).

Scheme 34. Enamine hydrolysis of 3.105.

Formation of compound 3.110 can be explained by a two steps mechanism in which the enamine 3.105 first undergoes acid-promoted hydrolysis to the corresponding aldehyde 3.111, followed by decarbonylation (Scheme 35).

Scheme 35. Proposed reaction pathway for the formation of compound 3.110.

Once it was established that compound 3.75 displayed the typical enamine reactivity, we decide to investigate its chemical behavior in electrophilic halogenation. Hence, 3.75 was reacted with 1.0 equivalents of NCS in DCM, in an attempt to prepare compound 3.113. 3.75 was completely converted to compound 3.113 after 2 hours at room temperature, as demonstrated by 1H-NMR analysis of the crude mixture. Purification on silica gel provided a mixture of compounds 3.113 and 3-methyl-4-nitro-5-chloromethylisoxazole 3.114 in a 67:33 ratio (Scheme 36).
The purification of 3.113 was attempted by column chromatography on silica gel and alumina. However none of these methods provided 3.113 in pure form. Hence, we optimized a procedure for the preparation of 3.114. This involved electrophilic chlorination of 3.113, followed by in situ treatment of the crude reaction mixture with silica gel and hydrochloric acid. This method produced 3.114 in 94% isolated yield after column chromatography (Scheme 37).

The formation of compound 3.114 could be explained by a two steps mechanism, in which the enamine moiety of 3.113 first undergoes acid-mediated hydrolysis with formation of intermediate 3.115. This, in turn, undergoes decarbonylation that is likely to be favored by the ability of the 4-nitroisoaxazole core to stabilize incipient negative charges (Scheme 38).
It has to be noted, that any attempts to prepare compound 3.114 via direct electrophilic chlorination of the parent compound 3,5-dimethyl-4-nitroisoxazole 3.74 led exclusively to the formation of 3-methyl-4-nitro-5-trichloromethylisoxazole (see Chapter 2). Thus this procedure constitutes an excellent method for the preparation of 3.114 in high yields.

### 3.3 Conclusions

In conclusion we have investigated the chemical behavior of (E)-N,N-dimethyl-2-(3-methyl-4-nitroisoxazol-5-yl)-ethenamine 3.75 and tested its reactivity as electrophile and nucleophile. This study showed that compound 3.75 behaves primarily as an activated enamine rather than a Michael acceptor, in spite of the counter effect exerted by the conjugated nitro group that should increase the electrophilic nature of the exocyclic double bond. 3.75 showed to be unreactive towards C- and S-nucleophiles, while it reacted smoothly with secondary amines to give the corresponding enamines 3.91-3.95. The typical enamine reactivity was demonstrated by reaction with different C- and N-electrophiles such as acyl chlorides and azo compounds. A one-pot procedure consisting in a tandem electrophilic halogenation/hydrolysis/decarbonylation sequence allowed the preparation of 3-methyl-4-nitro-5-chloromethylisoxazole 3.114 and 3-methyl-4-nitro-5-bromomethylisoxazole in excellent yields.
3.4 References


Chapter 4

Organocatalytic Darzens reaction with 3-methyl-4-nitro-5-chloromethylisoxazole
4.1 Small molecules organocatalysis

Organocatalysis has emerged in the last decades as a powerful tool for the enantioselective construction of asymmetric organic frameworks.\(^1\) It is defined as the acceleration of an organic transformation by the use of a catalytic amount of small organic molecules not containing metal species. The prominent role it gained over classical metal-based catalysis is mainly due to low cost of the catalysts and operational simplicity of the methodologies employed.\(^2\) Organocatalysts are commonly derived from enantiopure natural occurring sources such as aminoacids, carbohydrates and alkaloids. Moreover they are characterized by a peculiar stability under different conditions as well as non-toxic properties making them environmental-friendly substrates.

![Image of L-Proline, D-Fructose, and Cinchona alkaloids]

**Figure 1.** Natural-occurring compounds as organocatalysts precursors.

The high degree of stereocontrol they exert in asymmetric transformations arises from their ability to form non-covalent interactions with the reactants, like hydrogen bonding and ion-pairing interactions. This feature plays a dual role in the outcome of the reaction: from one side it activates the substrates lowering the energy barrier and simultaneously directs them to react in a well-defined orientation inducing in the products the chirality held by the catalyst itself.\(^3\) Over the years two major classes of organocatalysts have been developed displaying different mechanisms of action: bifunctional and phase-transfer catalysis.

4.1.1 Bifunctional catalysis

Bifunctional asymmetric organocatalysts are small organic chiral molecules bearing two or more complementary functionalities capable of activating simultaneously both the reactants via multiple non-covalent interactions.\(^4\) The weak interactions that are established with the components of the reaction orientate them to react in an asymmetric fashion, furnishing enantioenriched products. The functionalities involved are usually a H-bond donor (OH, COOH, thiourea) and a H-bond acceptor (NR\(_3\), OR) connected together by a chiral scaffold (Figure 2).
Bifunctional asymmetric organocatalyst can be divided into three principal group, depending on the type of chiral molecule they are based on and the functionalities they present.

The cyclic aminoacid L-proline (Figure 3) has been widely use itself or as a precursor for a multitude of chiral organocatalyst.\cite{5} Many methodologies involving its use have been developed and different modifications of the proline core showed to produce efficient catalysts displaying a high catalytic activity in a wide range of transformations.\cite{6} The amino group activates the nucleophile via enamine activation or carbanion formation, while the carboxylic group acts as H-bond donor with the electrophile. The carboxylic group can be modified with different functionalities to finely tune the catalyst reactivity.

![Bifunctional organocatalyst dual activation of electrophile and nucleophile.](image)

**Figure 2.** Bifunctional organocatalyst dual activation of electrophile and nucleophile.

Cinchona alkaloids are another important class of natural occurring chiral compounds whose use have been an intensely investigated as organocatalysts.\cite{7} They are extracted from the bark of Cinchona trees and count more than thirty structurally related alkaloids.\cite{8} A major part of the extracted is constituted by four alkaloid: quinine (QN)\textsuperscript{4.8}, quinidine (QD)\textsuperscript{4.9}, cinchonine (CN)\textsuperscript{4.10} and cinchonidine (CD)\textsuperscript{4.11} forming two couples of pseudoenantiomers. (Figure 4).

![L-Proline-derived asymmetric organocatalyst.](image)

**Figure 3.** L-Proline-derived asymmetric organocatalyst.
Quinine was first isolated in 1820 by Pelletier [9] and found application as antimalarial and antiarrhythmic agent. The pioneering studies employing Cinchona alkaloids as organocatalysts conducted by Pracejus in the 1950s, [10] followed by Wynberg in 1970s, [11] demonstrated that this class of chiral Lewis bases could serve as useful catalysts for a broad spectrum of enantioselective transformations. During the following decades the interest of the scientific community about their chemistry has constantly increased and a wide variety of Cinchona alkaloids-catalyzed reactions have been reported. [12] Hence, nowadays Cinchona-derived organocatalysts are considered as one of the most privileged organic chirality inducers, efficiently catalyzing nearly all classes of organic reactions in a highly enantioselective fashion.

The key features that can be outlined for explaining their success as organocatalyst are their stability, the commercial availability and the ease of modification of their structure, making them highly tunable for different kind of reactions. The catalytic activity relies on the α,β-amino alcohol system, in which the nitrogen of the rigid quinuclidine bicycle acts as a Brønsted base, deprotonating the nucleophile, while the C-9 OH establishes H-bond interactions with the electrophile (Figure 5). Moreover other weak interactions with the reactants can arise from the presence of the C-6' OMe (H-bond) as well as the quinoline ring (π stacking).
The skeleton of *cinchona* alkaloids can be easily modified through the functionalization of five principal reactive sites of the molecule (Figure 6) in order to optimize the design of the catalyst for different applications. 1) The quinuclidine nitrogen, as well as the quinoline one, can be quaternarized to prepare chiral quaternary ammonium salts. 2) The C-9 OH can be alkylated, acylated or transformed in an amine for further derivatizations. 3) the C-6’ OMe can be demethylated or transformed in an amine. 4) The C-10 double bond can be reduced or can undergo radical reactions.

**Figure 6.** Derivatization sites of *Cinchona* alkaloids

Bifunctional thioureas 4.12-4.15 are another class of highly efficient organocatalysts capable of catalyzing a wide range of organic transformations (Figure 7). [13]
Figure 7. Thiourea-based organocatalysts.

Their mode of action involves the simultaneous activation of the nucleophile, through a general base deprotonation and the electrophile via a double H-bond donation of the thiourea moiety. The acidic thiourea moiety and the basic one work cooperatively without interfering each other. Their structure consist of a thiourea moiety connected to a chiral linker bearing an amine group and to a chiral or achiral backbone on the other side.
4.1.2 Phase-transfer catalysis

In 1971, Starks introduced the term of “phase transfer catalysis” to explain the role of tetraalkylammonium or phosphonium salt (Q+X-) in the reaction between two substrates located in different immiscible phases.\cite{15} The advantages of this methodology are its simple experimental procedures, mild reactions conditions, inexpensive and environmental friendly reagents, and the possibility of conducting large-scale preparations.\cite{16,17} These features make phase-transfer catalysis a primary synthetic tool in organic chemistry and it found widespread applications in different scientific fields. Despite the important development of phase-transfer catalysis, some mechanistic aspects still remain uncertain, due to the difficulty of investigating biphasic systems and the complex parameters involved. The representative phase-transfer reaction system is constituted by a biphasic system with an organic phase containing a compound bearing an acidic methylene or methine group and an electrophile, and an aqueous or solid phase containing an inorganic base such as alkali metal hydroxides, carbonates or phosphates. The key reactive intermediate in this type of reaction is the onium carbanion species, which reacts with the electrophile in the organic phase to afford the product.
Two mechanisms have been proposed for explaining the generation of the reactive onium carbanion species: the Starks extraction mechanism (Scheme 1) \[18\] and the Makosza interfacial mechanism (Scheme 2) \[19\].

**Scheme 1.** Starks extraction mechanism.

In the Starks extraction mechanism the phase-transfer catalyst moves back and forth across the organic and aqueous phases. The onium salt equilibrates with the inorganic base (MOH) in the aqueous phase, and extracts hydroxide into the organic phase. The onium hydroxide then abstracts hydrogen from the acidic organic compound to give the reactive intermediate $Q^+R^-$ (Scheme 1).

**Scheme 2.** Makosza interfacial mechanism.

In the Makosza interfacial mechanism the formation of the metal carbanion occurs at the interface of the organic and aqueous phase without the need of the catalyst, followed by the extraction of the formed metal carbanion species from the interface into the organic phase by the action of phase-transfer catalyst (Scheme 2).
Cinchona-derived quaternary ammonium salts are privileged organocatalysts to be used in asymmetric phase-transfer reactions. They can be divided into four generations. The N-benzyl salts belong to the first generation class. The N-9-anthracenylmethyl-O-protected alkaloids constitute the second generation, while the third includes the dimeric Cinchona-derived catalysts with spacers between two or more independent Cinchona alkaloid units. The fourth and last class comprises the electronic factor-bases Cinchona phase-transfer catalysts.

4.1.2.1 First generation: N-benzyl-Cinchona PTCs

The first successful application of Cinchona-based quaternary ammonium salts as a chiral PTC was conducted by the Merck research group in 1984 (Scheme 3). Dolling and co-workers performed the methylation of phenylindanone 4.16 using N-p-trifluoromethylbenzylcinchoninium bromide 4.18 as a catalyst under phase-transfer conditions to afford the product 4.17.

Scheme 3. Organocatalytic asymmetric phase-transfer α-alkylation.

O’Donnell and co-workers applied a similar strategy for the alkylation of N-(diphenylmethylene)glycine tert-butyl ester 4.19, using catalyst 4.21 obtaining alkylated product 4.20 with moderate enantiomeric excess. Compound 4.20 could be further hydrolyzed to afford the α-amino acid which was then recrystallized to highly enantiopure material (Scheme 4).
The origin of stereoselectivity in the *Cinchona*-catalyzed phase-transfer alkylation of \(4.19\) could be explained considering the tetrahedron identified by the four carbons bound to the bridgehead nitrogen (Figure 9). Cinchonidinium quaternary ammonium salt provides effective steric screening that can inhibit approach of the \((E)\)-enolate of the substrate to three faces F1-F3 of this tetrahedron, leaving only F4 sufficiently open to allow close contact between the enolate anion of \(4.19\) and the ammonium cation of the catalyst.
Figure 9. Origin of the stereoselectivity in Cinchona-derived quaternary ammonium salts.

Quaternary ammonium salts of Cinchona alkaloids are ideal catalyst as one face F1 of the ideal tetrahedron is blocked by the quinuclidine system itself. In addition,[25] studies on the bis-cinchona-alkaloid-catalyzed dihydroxylation of olefins by OsO₄ showed that the attachment of a bulky group such as the 9-anthracenylmethyl to the bridgehead nitrogen, leads to a quaternary ammonium structure of well-defined geometry in which a second tetrahedral face F3 is sterically inaccessible. Furthermore, the approach of the enolate via face F2 could be impeded by functionalization of the secondary hydroxyl group. The Re-face of the enolate is blocked by the quinoline ring, hence the electrophile can approach only the Si-face to afford the product 4.20.

4.1.2.2 Second generation: N-9-Anthracenylmethyl-Cinchona PTCs

Following O’Donnell’s application of Cinchona-derived quaternary ammonium salts, two independent groups developed a new class of Cinchona PTC bearing the bulky N-9-anthracenylmethyl group (Scheme 5 and 6). By introducing a larger flat substituent the F3 face became more shielded, thus improving the degree of enantioselectivity. In 1997, Lygo and co-workers reported the development of the N-9-anthracenylmethyl-Cinchona salt 4.22 and applied it to the phase-transfer alkylation of 4.19 to prepare α-amino acids with much higher enantioselectivities (Scheme 5).[26]
Scheme 5. \(N\)-9-Anthracenylmethyl-cinchonidinium salt developed by Lygo.

O- Allyl-\(N\)-9-anthracenylmethylcinchonidinium bromide 4.23 was also independently developed by Corey and co-workers.\(^{[24]}\) The phase-transfer catalyzed benzylation of 4.19 using 4.23 as the catalyst and CsOH\(\cdot\)H\(_2\)O as base at low temperatures furnished the alkylated product 4.20 with excellent enantioselectivity (Scheme 6).

Scheme 6. O- Allyl-\(N\)-9-anthracenylmethyl-cinchonidinium salt developed by Corey.
4.1.2.3 Third generation: Polymeric Cinchona PTCs

The development of catalysts bearing two independent Cinchona alkaloid units connected by spacers led to considerable increases in both the enantioselectivity and the scope of the substrates.\cite{27} In 2001, Jew and co-workers prepared the dimeric cinchonidinium-derived ammonium salts 4.24, 4.25 and 4.26, in which a phenyl is used as the spacer. Their catalytic activity was evaluated with the preparation of 4.20 via phase-transfer benzylation of 4.19 (Scheme 7).\cite{28}

\begin{equation}
\text{PhCH}_2\text{Br} \quad \text{Cat. (5 mol \%)} \quad 50\% \text{ KOH}
\end{equation}

\begin{equation}
toluene/\text{CHCl}_3 \quad -20 \, ^\circ \text{C}
\end{equation}

with 4.24 35\% ee

with 4.25 95\% ee

with 4.26 86\% ee

\textbf{Scheme 7.} Dimeric cinchonidinium-derived quaternary ammonium salts.

The increase in enantioselectivity for the \textit{meta}-dimeric catalyst 4.25 might be due to the additional steric hindrance exerted by the cinchonidine units, while in the \textit{para}-dimer the two units don’t sterically influence each other.

4.1.2.4 Fourth generation: electronic factor-based Cinchona PTCs

Since the ion-pairing of the Cinchona quaternary ammonium cation and the anionic substrate has a key role on the chiral induction, the presence of complementary polar interactions established between the substituents present on the benzyl ring and the substrate could stabilize the ion couple leading to an increase of the enantioselectivity. In 2002 Jew and co-workers began to investigate the role of the electronic factors in Cinchona PTCs. A series of \textit{N}-benzylcinchonidinium salts was prepared from
cinchonidine and benzyl bromides containing various functional groups at the ortho-, meta-, and para- positions.\textsuperscript{[29]} Their catalytic efficiencies were evaluated for the catalytic benzylation of 4.19 (Scheme 8).

\textbf{Scheme 8.} Electronic functional groups incorporated into cinchonidinium PTCs.

The main objective of this study was to evaluate whether an electronic withdrawing functional group might increase the enantioselectivity via formation of tighter ion pairs able to maintain a more rigid conformation. Data collected showed that the ortho-F derivative (89\% ee) displayed enhanced enantioselectivity compared to ortho-H (74\% ee), while meta- and para-substituted derivatives did not produce any significant difference, in spite of their electronic properties. Further studies revealed that a monofluoride at the ortho- position was critical for the enhancement of enantioselectivity, and introduction of additional F at the 3\'- and 4\'- positions gave even higher enantioselectivity.\textsuperscript{[30]}
4.2 Asymmetric epoxidation of alkenes

Epoxides are a widespread motif in nature that can be found in a wide range of compounds obtained from natural sources. Moreover they play a pivotal role in organic chemistry as important synthetic intermediates. Their reactivity, dictated by constraints of the oxirane ring, is centered on nucleophilic ring-opening reactions, making them useful and versatile building blocks in organic synthesis. The oxirane ring-opening provides a powerful route for the formation of new C-C, C-O, C-N and C-S bonds, by reaction with a wide range of nucleophiles, such as carbanions, alcohols, amines and thiols. Many examples of metal-catalyzed as well as organocatalytic processes for the epoxide ring-opening and derivatization have been developed making them useful synthetic intermediates for the preparation of poly-functionalized organic scaffolds (Scheme 9).

Scheme 9. Oxirane ring reactivity

Many examples of their use in the preparation of bioactive natural and synthetic products can be found in the literature, such as unnatural aminoacids, antibiotics, anti-malarian, and anti-cancer agents. Considering the prominent role they play in different scientific fields and the intensive use they undergo in organic chemistry, the search of methodologies for the asymmetric assembly of the epoxide moiety has gained...
much attention by the scientific community. The great efforts put in the investigation of epoxides chemistry led to the development of a variety of methodologies for the enantioselective construction of the oxirane ring, based on metal-catalyzed and organocatalytic processes.\[42\]

### 4.2.1 Metal-catalyzed epoxidation of alkenes

The pioneer work in the field of catalytic asymmetric epoxidation was presented by Sharpless and Katsuki in 1980,\[43\] with the development of a catalytic enantioselective epoxidation of allylic alcohols 4.34. The reaction is catalyzed by an *in situ* formed Ti(IV) isopropoxide/chiral diethyltartrate complex using tert-butyl hydroperoxide as the oxidizing agent (Scheme X).

\[
\text{Tl(OiPr)}_4 \text{(5 mol%) diisyl tartrate (6 mol%) TBHP (2.0 equiv.)}
\]

\[
\text{DCM, -20 °C}
\]

\[
\text{70-90% yield}
\]

\[
>90\% \text{ ee}
\]

**Scheme 9.** Sharpless epoxidation of allylic alcohols.

Different mono-, di- and tri-substituted allylic alcohols 4.34 can be oxidized to the correspondent epoxides 4.35 with excellent yields and enantioselectivities. Moreover opposite enantiomers can be obtained just switching the diethyltartrate stereochemistry.

Another important contribution in metal-catalyzed asymmetric epoxidation was provided independently by the groups of Jacobsen and Katsuki in 1990.\[44\] They reported that chiral manganese (III)-salen complexes 4.40, efficiently catalyzed the epoxidation of different unsubstituted and substituted olefins 4.38 (Scheme 10). The reaction worked with different kind of oxidants, such as sodium hypochlorite, peroxides, periodates, peracids and iodosylarenes. Noteworthy, the catalyst can be synthetized in three steps starting from enantiopure diamines and salicylaldehydes.
Despite the large scope of the Sharpless and Jacobsen epoxidation, these methodologies showed poor applicability to α,β-unsaturated systems like enones (electron poor alkenes). This limitation was overcome by Shibasaki and co-workers in 1997, with the development of a catalytic asymmetric epoxidation of enones 4.41 using lanthanoids-BINOL complexes 4.43 (Scheme 11). The authors described the use of lanthanium-(R)-BINOL with cumene hydroperoxide or alternately ytterbium-(R)-BINOL with tert-butyl hydroperoxide for the epoxidation of aromatic and aliphatic enones with excellent enantioselectivities.

Scheme 10. Manganese(III)-salen complex catalyzed epoxidation of olefins.

Scheme 11. Lanthanum-(R)-BINOL catalyzed epoxidation of enones.
4.2.2 Organocatalytic synthesis of epoxides

4.2.2.1 Sulfur ylides-mediated epoxidation of carbonyl compounds

The first example of the sulfur ylides mediated synthesis of epoxides dates back to 1962, \cite{46} when Corey and Chaykovsky reported the use of dimethylsulfoxonium methyldie 4.45 for generating epoxides upon reaction with carbonyl compounds like aldehydes and ketones 4.46 (Scheme 12). The reaction proceeds via a 1,2-addition of the dimethylsulfoxonium methyldie to the carbonyl forming the intermediate betaine 4.47, which undergoes intramolecular $S_N2$ producing the epoxide.

\begin{align*}
\text{4.44} & \xrightarrow{\text{NaH (1.0 equiv.)}} \text{DMSO} & \text{4.45} & \xrightarrow{\text{R$^\ast$R$_1$ (1.0 equiv.)}} \text{DMSO, 50 °C} & \text{4.46} & \xrightarrow{\text{R = H, alkyl, aryl}} \text{4.47} & \xrightarrow{\text{R$_1$ = alkyl, aryl}} \text{4.48}
\end{align*}

Scheme 12. Sulfur ylides-mediated epoxidation of carbonyl compounds.

The use of sulfur ylides was expanded in 1989 by Furukawa \cite{47} who reported the catalytic asymmetric epoxidation of aromatic aldehydes 4.49 with benzyl bromide 4.50, using optically active sulfonium salts 4.52 derived from camphorsulfonic acid in a liquid/solid (KOH) bifasic system (Scheme 13).

\begin{align*}
\text{4.49} & + \text{Br} & \xrightarrow{\text{sulfide (10 mol%)}} \text{KOH} & \xrightarrow{\text{MeCN, r.t.}} \text{4.50} & \xrightarrow{\text{sulfide =}} \text{4.52} & \xrightarrow{\text{50% yield}} \text{4.51} & \xrightarrow{\text{100% de}} \text{4.51} & \xrightarrow{\text{43% ee}}
\end{align*}

Scheme 13. Asymmetric epoxidation with chiral sulfonium salt.

The catalytic cycle involves initially the addition of the sulfide 4.52 to 4.50 with the formation of the sulfonium salt 4.53. Deprotonation of the latter produces the ylide 4.54 that reacts with 4.49 in a 1,2-addition, followed by intramolecular $S_N2$, forming the epoxide 4.51 and restoring the sulfide (Scheme 14).
A major improvement in terms of yields and enantioselectivities was later described by Metzner and co-workers.\textsuperscript{[48]} They performed the epoxidation between aromatic aldehydes 4.56 and benzyl bromide using catalytic amounts of enantiopure 2,5-dimethylthiolane 4.58 as sulfide source, in the presence of tetrabutylammonium iodide to fasten the first step of the catalytic cycle (benzylation of the sulfide).

\begin{align*}
\text{BnBr (2.0 equiv.)} & \quad \text{sulfide (10 mol\%)} \\
\text{NaOH (2.0 equiv.)} & \quad n\text{Bu}_4\text{NI (1.0 equiv.)} \\
R\text{CHO} & \quad \text{tBuOH/H}_2\text{O, r.t.} \\
\text{4.56} & \quad \text{4.57} \\
R = \text{aryl} & \quad 60-82\% \text{ yield} \\
\text{sulfide} = & \quad 75-85\% \text{ de} \\
\text{4.58} & \quad 64-85\% \text{ ee}
\end{align*}

\textbf{Scheme 15.} Dimethylthiolane-catalyzed asymmetric epoxidation.
Aggarwal and co-workers \(^{49}\) proposed a high diastereo- and enantioselective epoxidation by carbene transfer to aromatic aldehydes \(4.59\) catalyzed by chiral sulfides derived from camphorsulfonfyl chloride \(4.62\) (Scheme 16).

**Scheme 16.** Enantioselective epoxidation by carbene transfer to aromatic aldehydes.

In the reaction, the diazocompound \(4.63\) is formed *in situ* by a phase-transfer catalyzed Bamford-Stevens reaction of \(4.60\) with sodium hydride. Subsequently \(4.63\) is decomposed in the presence of a ruthenium complex producing the metallocarbene \(4.64\) that is then transferred to the sulfide, with the formation of sulfur ylide \(4.65\). This undergo reaction with the aldehyde to give the trans-epoxides and regenerating the sulfide that restart the catalytic cycle (Scheme 17).

**Scheme 17.** Catalytic cycle for the formation of sulfur ylides from diazo reagents.
4.2.2.2 Organocatalytic epoxidation of alkenes

Organocatalytic asymmetric epoxidation has proven over the years to be an effective way for the synthesis of chiral epoxides,\(^{[42a]}\) showing excellent results in terms of asymmetric induction through the use of a wide range of catalysts. Many efforts have been put especially in the development of asymmetric methodologies for the epoxidation of different unfunctionalized olefins, substituted olefins and electron deficient olefins such as \(\alpha,\beta\)-unsaturated ketones and \(\alpha,\beta\)-unsaturated aldehydes.

4.2.2.3 Chiral ketones-catalyzed epoxidation

Asymmetric epoxidation with chiral ketones demonstrated to be a powerful tool for the preparation of chiral epoxides using various substrates,\(^{[50]}\) particularly unfunctionalized olefins and trisubstituted olefins.\(^{[51]}\) The reaction is based on the action of an oxidant, commonly Oxone, on a chiral ketone 4.66, with the \textit{in situ} generation of a chiral dioxirane 4.69, a highly effective species for the epoxidation of olefins. Oxone facilitates the \(O\)-transfer from the ketone to the olefin via the dioxirane intermediate. After epoxidation the chiral ketone is regenerated and can start another catalytic cycle (Scheme 18).

Scheme 18. Catalytic cycle for the chiral ketone-catalyzed epoxidation of olefins.

Shi proposed in 1996 one of the first and most effective sugar-based chiral ketone catalyst (Scheme 19).\(^{[52]}\) The fructose-derived ketone 4.74, with Oxone as the oxidant,
catalyzed the epoxidation of many trans-di- and trisubstituted olefins 4.72, with excellent stereocontrol. The reaction media was kept at pH=10 to avoid decomposition of the catalyst via Baeyer-Villiger oxidation.

\[
\begin{align*}
\text{R}_1 &= \text{alkyl, aryl} & \text{41-97\% yield} \\
\text{R}_2 &= \text{H, alkyl, aryl, alkynyl, F} & \text{76-98\% ee}
\end{align*}
\]

\[
\text{Chiral ketone =}
\]

![Chiral ketone](image)

\textbf{Scheme 19.} Fructose-derived chiral ketone-catalyzed epoxidation of poly-substituted olefins.

\textbf{4.2.2.4 Iminium/enamine catalysis}

In 2005, \cite{53} Jorgensen and co-workers reported the first highly enantioselective epoxidation of α,β-unsaturated aldehydes 4.75 using diarylprolinol silyl ether catalyst 4.77 and hydrogen peroxide as the oxidant. The epoxides were obtained with high diastereo- and excellent enantioselectivity (Scheme 20).
Scheme 20. Asymmetric epoxidation of enals with pyrrolidine-derived catalyst 4.77.

The proposed mechanism starts with the formation of an iminium ion hydroxide 4.78 formed by the enal and the catalyst, which is then attacked by the hydroperoxyl anion at the β-carbon producing the enamine 4.79. This latter undergoes ring-closure producing the epoxide 4.80. Subsequent hydrolysis of the epoxy iminium ion furnishes the epoxy aldehyde 4.76 and restores the catalyst (Scheme 21).
The following year MacMillan expanded the scope of enals epoxidation by iminium/enamine catalysis, using imidazolidinone catalyst 4.84. The oxidant chosen was iminoiodinan 4.82 that by reaction with acetic acid afforded a slow release of iodosobenzene 4.85 in the reaction medium.

![Scheme 22. Chiral imidazolidinone-catalyzed epoxidation of enals.](image)

**4.2.2.5 Chiral bifunctional base catalyzed epoxidation**

Different chiral bifunctional catalyst as guanidines, amino alcohols and *cinchona*-derived thioureas have been developed for asymmetric epoxidation of electron deficient olefins. Ishikawa described the use of guanidine catalyst 4.88 for the asymmetric epoxidation of chalcone 4.86 with TBHP, to give epoxide 4.87 with good enantioselectivity (Scheme 23). The catalyst is believed to act in a bifunctional mode, by deprotonating the oxidant and simultaneously activating the enone through H-bond interaction.

![Scheme 23. Chiral guanidine-catalyzed epoxidation of enones.](image)
Lattanzi in 2005 showed that readily available α,α-diphenylprolinol 4.91 could act as catalyst for the asymmetric epoxidation of different chalcones 4.89 with tert-butyl hydroperoxide as the oxidant (Scheme 24). \[^{[56]}\]

\[
\begin{array}{c}
\text{R} = \text{aryl, Bn, alkyl} \\
\text{R}_1 = \text{aryl, Me}
\end{array}
\]

\[
\begin{array}{c}
\text{Cat. (20 mol\%)} \\
\text{TBHP (1.5 equiv.)} \\
\text{hexane, r.t.}
\end{array}
\]

\[
\begin{array}{c}
\text{60-98\% yield} \\
\text{79-92\% ee}
\end{array}
\]

Scheme 24. Diphenylprolinol-catalyzed epoxidation of chalcones.

The author stated that in this reaction catalyst 4.91 is likely to act via bifunctional, instead of iminium ion/enamine catalysis. The amine acts as a Brønsted base deprotonating the TBHP and generating a tight ion pair 4.92. Then the free hydroxyl group activates and orientates ketones 4.93, through H-bond with the carbonyl moiety, toward the attack in β-position by the alkyl peroxide anion (Scheme 25).
The same group reported the use of quinine-derived thiourea 4.97 for the epoxidation of 1,1-dicarbonyl terminal olefins 4.95 with TBHP (Scheme 26).\[57\] The products 4.96, containing a quaternary stereogenic center, were obtained in excellent yields and enantioselectivities and could be further processed to chiral aminoalcohols.

**Scheme 25.** Bifunctional prolinol-catalyzed addition of TBHP to enones.
Scheme 26. *Cinchona*-derived thiourea as bifunctional catalyst for epoxidation of 1,1-dicarbonyl terminal olefins.

**4.2.2.6 Phase-transfer catalyzed epoxidation**

Asymmetric phase-transfer catalysis (PTC) has emerged in the last decades as a powerful tool for the enantioselective construction of a wide variety of carbon-carbon and carbon-heteroatom bonds,\[^{1b, 1c, 58}\] opening access to many different enantioenriched organic compounds.\[^{1d}\] Phase-transfer catalyzed epoxidation has been studied extensively and highly effective methodologies have been developed for the epoxidation of electron deficient olefins, especially \(\alpha,\beta\)-unsaturated ketones, predominantly using chiral quaternary ammonium salts as catalysts.\[^{42, 59}\]

The reaction proceeded as a nucleophilic epoxidation *via* a Weitz-Scheffler-type mechanism, that involves a 1,4-conjugate addition of hydrogen peroxide or alkyl peroxide to alkenes that required strong basic medium, as described by Weitz and Scheffler in 1921.\[^{60}\] The mechanism involved the addition of the alkyl peroxide anion to the \(\beta\)-carbon of the enone 4.98 producing the intermediate 4.99 which undergoes ring closure by attack of the enolate to the peroxide \(\text{O-O}\) bond, furnishing epoxides 4.100 with elimination of the alkoxide.

![Diagram of the reaction mechanism](image-url)
In the asymmetric version, the chiral quaternary ammonium salt 4.101 first undergoes anion exchange with the nucleophilic epoxidizing agent, forming a tight ion pair 4.102. Thus, the catalyst brings it across the interface and directs its asymmetric approach to the enone 4.98 (Scheme 28).

The first example dates back to 1976, when Wynberg and co-workers reported the use of the quinine-derived quaternary ammonium salt 4.106 to catalyze the asymmetric epoxidation of \(\alpha,\beta\)-unsaturated ketones 4.104 (Scheme 29). [61] Although \(\alpha,\beta\)-epoxyketones 4.105 were obtained in modest enantiomeric excesses, this work firstly showed the potential usefulness of applying *Cinchona*-derived quaternary ammonium salts in asymmetric epoxidation reactions and lead the way for the following investigations.
Scheme 29. N-benzylquininium chloride-catalyzed asymmetric epoxidation of chalcones.

A remarkable improvement was obtained by Arai, Shioiri and co-workers,\[62\] who noticed that the substituents present on the $N$-benzyl moiety of the cinchonine-derived catalyst played an important role in the induction of asymmetry. In particular it was found that electron withdrawing groups in para position gave the best results, and among the substitution patterns tested, $p$-iodobenzyl derivative 4.109 was the most effective (Scheme 30).\[63\] Further investigation also demonstrated that the free hydroxy group at the C-9 of the catalyst was fundamental to obtain elevated stereocontrol.\[64\]

Scheme 30. $N$-($p$-iodobenzyl)cinchoninium bromide-catalyzed asymmetric epoxidation of chalcones.

The development of the second generation of *Cinchona*-derived quaternary ammonium salts by Lygo \[65\] and Corey \[66\] at the end of the 90s, and their application in the
asymmetric epoxidation of enones, brought to improved levels of enantiocontrol of the reaction. Lygo reported the use of \( N \)-antracenylmethyl-\( O \)-benzylchinonidinium chloride catalyst 4.112 together with sodium hypochlorite as the oxidant for the enantioselective epoxidation of various \( \alpha,\beta \)-unsaturated ketones (Scheme 31).\[^{[67]}\]

![Scheme 31. \( N \)-antracenylmethyl-\( O \)-benzylchinonidinium chloride catalyzed epoxidation of enones with sodium hypochlorite.](image)

With an accurate optimization of the reaction conditions, Corey\[^{[68]}\] succeeded to increase the yields and stereocontrol of the reaction, using the same catalyst 4.112. He demonstrated that potassium hypochlorite gave better results in combination with toluene at low temperatures (Scheme 32).
Scheme 32. *N*-antracenylmethyl-*O*-benzylcinchonidinium chloride catalyzed epoxidation of enones with potassium hypochlorite.

The author also proposed a mechanistic explanation of the high enantiocontrol observed as well as the absolute stereochemistry of the epoxides obtained. He suggested the reaction proceeding *via* a transition state in which the phenyl substituent and the carbonyl $\delta$ plane are not planar. This allows placement of the $\alpha,\beta$-unsaturated ketone in a well-defined binding mode with the catalyst (Scheme 33).

Scheme 33. Proposed transition state for the epoxidation of chalcone with catalyst 4.112.

The hypochlorite ion is in contact ion paired with the only accessible face of the quinuclidine nitrogen. In this arrangement the nucleophilic oxygen of the hypochlorite ion is in proximity of the $\beta$-carbon of the enone, thus correctly orientated for the conjugate addition on the *Re* face. After the addition, the negative charge developed at the carbonyl oxygen is stabilized by the near cation nitrogen, accelerating the reaction.

The $\alpha,\beta$-epoxy ketones 4.113 obtained was further processed by means of Baeyer-Villiger oxidation to the epoxy-ester 4.114, followed by reduction of the epoxide, producing enantioenriched $\alpha$-hydroxy esters 4.115 (Scheme 34).

Scheme 34. Preparation of enantioenriched $\alpha$-hydroxy esters.

$$\text{Ph}$$

4.113

93% ee

$\text{Ph}$

4.114

81% yield

93% ee

$\text{Ph}$

4.115

95% yield

92% ee
Jew, Park and co-workers \textsuperscript{69} tested a wide range of dimeric quaternary ammonium salt derived from \textit{Cinchona} alkaloids as catalysts for the asymmetric epoxidation of chalcones. They found catalyst 4.118 to be highly effective in the presence of Span 20 and hydrogen peroxide as the oxidant, producing the correspondent epoxides 4.117 in excellent yields and ees (Scheme35).

\[
\begin{align*}
\text{Cat. (1 mol\%)} & \quad \text{Span 20 (1 mol\%)} \\
\text{H}_2\text{O}_2 \ 30\% \ (10.0 \text{ equiv.}) & \quad \text{KOH} \ 50\% \ (1.0 \text{ equiv.}) \\
\text{iPr}_2\text{O}, \text{ r.t.}
\end{align*}
\]

Scheme 35. Epoxidation of diarylenones with dimeric catalyst 4.118.

Shibata and co-workers reported one of the few efficient epoxidation of \(\beta\)-trifluoromethyl-\(\beta,\beta\)-disubstituted enones using catalyst 4.121 and methylhydrazine 4.122/air as the oxidant. The authors suggest the active oxidant being hydrogen peroxide, created \textit{in situ} by a single electron transfer between methylhydrazine and the base, followed by reaction with molecular oxygen. Products 4.120, bearing a trifluoromethyl and an aryl group in \(\beta\)-position were obtained in excellent yields and enantioselectivities (Scheme36).
Scheme 36. Methylhydrazine-induced aerobic asymmetric epoxidation of β-trifluoromethyl-β,β-disubstituted enones.

A complementary procedure for the same type of substrates 4.122 has been proposed by Chen, using catalyst 4.124 and hydrogen peroxide as the oxidant (Scheme 37).
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Scheme 37. Phase-transfer catalyzed epoxidation of β-trifluoromethyl-β,β-disubstituted enones with hydrogen peroxide.

The author demonstrated the possibility of using product 4.125 for the preparation of enantioenriched β-trifluoromethyl-β-hydroxy ketone 4.126 through reduction with zinc and ammonium chloride (Scheme 38).


In 2004, Maruoka applied binaphtil-based spiro quaternary ammonium salt 4.129, to the enantioselective epoxidation of α,β-unsaturated ketones 4.127. The catalyst bears two diarylmethanol groups that were shown to be essential to achieve high asymmetric induction (Scheme 39).
4.2.2.7 Darzens glycidic ester synthesis

The Darzens reaction is a powerful method for the preparation of α,β-epoxy carbonyl compounds. The glycidic ester condensation was first described by Darzens at the beginning of the 20th century, involving the reaction of an α-halo ester 4.130 with an aldehyde or a ketone under basic conditions. \[^{[70]}\]

![Scheme 40. Darzens glycidic ester condensation.]

The products are α,β-epoxy esters 4.132, also called glycidic esters. α,β-Epoxy esters are poly-functional scaffolds that can be used as precursors of a variety of valuable compounds via nucleophilic ring-opening of the epoxide moiety (Scheme 41). \[^{[71]}\]
Despite the synthetic utility of α,β-epoxy esters, historically the Darzens reaction has been mainly used as a one-carbon homologation strategy for aldehydes and ketones (Scheme 42). After the condensation and the formation of the epoxide, the ester is saponified and upon acidification decarboxylation occurs with the formation of the homologate aldehyde or ketone.

Different α-halo methylene compounds 4.134 able to generate a stabilized α-halo anion can take part in the condensation, like esters, ketones, nitriles, sulfonates and phosphonates (Scheme 43). \[^{[72]}\]

The mechanism involves an aldol addition of the stabilized anion 4.137 to the carbonyl 4.135, forming the two diastereoisomeric aldolate 4.138 and 4.140 that undergo ring-closure via intramolecular S_n2 reaction to the corresponding epoxides 4.139 and 4.141 (Scheme 44).
The ratio of the diastereoisomeric products is dependant on the structure of the reagents and the reaction conditions. Notably, under peculiar conditions it is possible to isolate the intermediate halohydrins.\(^{[73]}\)

\[ 4.134 \xleftrightarrow{\text{B}^-} 4.137 + 4.135 \]

\[ 4.138 \xrightarrow{\text{B}^-} 4.139 \]

\[ 4.140 \xrightarrow{\text{B}^-} 4.141 \]

**Scheme 44.** Mechanism of the Darzens condensation.

For halohydrins 4.142/4.143, the aldol addition is reversible, as demonstrated by Zimmerman (Scheme 45).\(^{[74]}\) When both diastereoisomers 4.142/4.143 are individually reacted with potassium tert-butoxide the only product observed is the cis-epoxide 4.144. This result involves that halohydrin 4.143, that cannot cyclize to epoxide 4.145 due to steric and electronic factors, undergoes a retro-aldolization/aldolization sequence. The two starting reagents formed via the retro-aldol re-condense to 4.142 that has the right conformation to cyclize to the cis-epoxide 4.144.

**Scheme 45.** Preparation of epoxide 4.144 from diastereoisomeric mixture of halohydrins 4.142/4.143.
4.2.2.8 Asymmetric Darzens epoxidation

The development of catalytic enantioselective methodologies for the Darzens reaction is challenging. The use of chiral quaternary ammonium salts would provide a method to exert efficient stereocontrol in the formation of the two stereogenic centers formed during the reaction, establishing a catalytic cycle (Scheme 46). This task has demonstrated to be difficult to achieve, considering that only few examples of catalytic enantioselective Darzens reactions have been reported over the years.

Scheme 46. Proposed mechanism for the asymmetric PTC Darzens reaction in a liquid/solid bifasic system.

The first phase-transfer catalyzed Darzens reaction has been described by Arai and Shioiri in 1998 (Scheme 47). The reaction between different aliphatic and aromatic aldehydes and phenacyl chloride, catalyzed by the cinchonine-derived quaternary ammonium salt, afforded the corresponding oxiranes in good yields with moderate to good enantioselectivities.
Scheme 47. Phase-transfer catalyzed Darzens reaction of acyclic $\alpha$-chboro-ketone 4.150.

The following year, the same group expanded the methodology to cyclic $\alpha$-chloro ketones 4.154, using similar phase-transfer conditions for the reaction with aliphatic aldehydes 4.151 (Scheme 48).\footnote{\textsuperscript{75}}

Scheme 48. Phase-transfer catalyzed Darzens reaction of cyclic $\alpha$-chboro-ketone 4.154.

A notable improvement in terms of asymmetric induction has been obtained by Deng and co-workers in 2011 (Scheme 49).\footnote{\textsuperscript{77}} Thanks to a fine tuning of the quinidine-derived quaternary ammonium salt 4.158 they were able to obtain epoxides 4.157 in high yields and enantioselectivities, reporting the first highly efficient and general applicable PTC Darzens reaction between $\alpha$-chboro ketones 4.156 and aldehydes. They demonstrated the importance of the free OH group in 6'-position as well as the phenanthracenyl group in 9-position on the catalyst.
Scheme 49. Phase-transfer catalyzed Darzens reaction of acyclic α-chloro-ketones 4.156 with catalyst 4.158.

Using similar reaction conditions they expanded the scope of the reaction to the cyclic α-chloro ketone 4.154 obtaining also in this case high degrees of enantioselection (Scheme 50).

Scheme 50. Phase-transfer catalyzed Darzens reaction of cyclic α-chloro-ketone 4.154 with catalyst 4.158.
Other examples employing chloromethyl phenyl sulfones and amides have been described by the group of Jew \cite{78} and Arai \cite{79} respectively. Interestingly α-chloro esters haven’t been reported so far as substrates for asymmetric Darzens reaction.
4.3 Results and discussion

The Darzens reaction is a powerful method for the construction of the oxirane ring and its efficiency relies on the consecutive formation of a C-C and a C-O bonds. [72] The execution of this reaction in enantioselective fashion further increases its synthetic utility, bringing to the simultaneous formation of two adjacent stereogenic centers. [77] Asymmetric organocatalyzed Darzens reactions have been reported, but the methodologies developed are limited to the use of α-chloro ketones as the halogenated partner that by reaction with aromatic or aliphatic aldehydes furnish the corresponding α,β-epoxi ketones (See Paragraph 4.2.2.8). Interestingly, the use of α-chloro esters in organocatalyzed Darzen reactions has not been reported so far. Adamo’s group extensively investigated the chemical behavior of 3,5-dimethyl-4-nitroisoxazole 4.160, demonstrating its ability to react as a masked carboxylate in a variety of chemical transformations. [80] Furthermore, the 4-nitroisoxazole core can undergo ring-opening revealing a carboxylic acid. [81] 4.160 can be easily transformed into its α-chloro derivative 4.161 as described in Chapter 3 (Scheme 51).


Considering the similarity in terms of reactivity of the 4-nitroisoxazole moiety with an ester functionality, we envisaged that 4.161 could be employed in asymmetric organocatalytic Darzens reactions for the preparation of enantioenriched α,β-epoxiisoxazoles 4.162 (Scheme 51).

Scheme 52. Darzens reaction of 4.161 with aldehydes.

At the onset of the study, we tested the ability of 4.161 to undergo Darzens reaction with benzaldehyde 4.147 following standard procedures involving the use of strong bases such as KOH in EtOH and tBuOK in tBuOH (Table 1, entry 1 and 2). In both cases the
desired epoxide 4.163 was not produced and extensive degradation of the starting material was noticed.

Table 1. General base-promoted Darzens condensation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>4.163 (%) yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>4.164 (%) yield&lt;sup&gt;b&lt;/sup&gt;</th>
<th>4.165 (%) yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH (1.0)</td>
<td>EtOH</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>tBuOK (1.0)</td>
<td>tBuOH</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N (1.0)</td>
<td>DCM</td>
<td>-</td>
<td>13%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>DABCO (1.0)</td>
<td>DCM</td>
<td>-</td>
<td>16%</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>DABCO (2.5)</td>
<td>DCM</td>
<td>-</td>
<td>-</td>
<td>8%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield.

Thus we studied the effect of nitrogen bases on the reaction. Using tertiary amines such as triethylamine or DABCO in DCM (Table 1, entry 3 and 4) brought to the formation of a new product, although in low yield, that was identified as the halohydrin 4.164. Increasing the equivalents of the base did not improve the outcome of the reaction. 4.164 was not detected in the reaction mixture, and the only product that could be isolated was identified as 4.165 with concomitant degradation of 4.161 to undefined products (Table 1, entry 5). The formation of compound 4.165 can be explained by a tandem self-condensation/Michael initiated ring-closing cyclopropanation. To confirm this hypothesis we reacted 4.161 with triethylamine obtaining compound 4.165 together with unidentified degradation products (Scheme 52).
A plausible mechanism involves firstly self-condensation of \( \text{4.161} \) to compound \( \text{4.166} \). Subsequently, another molecule of \( \text{4.161} \) performs a 1,6-conjugate addition on \( \text{4.166} \), followed by ring-closing cyclopropanation to produce \( \text{4.165} \) (Scheme 53).

The preliminary results obtained demonstrated the reactivity of compound \( \text{4.161} \) towards tandem nucleophilic addition/cyclization reactions and outlined a set of reaction conditions to be avoided for minimizing the self-condensation and degradation. Hence, we investigated Darzens condensation under organocatalytic conditions. Delightfully,
when 4.161 was reacted with 4.147 in the presence of 0.20 equivalents of quinidine 4.8 in DCM, halohydrin 4.164 was the major product formed after 120 hours (Scheme 54). Noteworthy formation of compound 4.165 was suppressed together with degradation of 4.161. This result, compared with the one obtained under general base catalysis, indicates the active role exerted by the catalyst in activating both the substrates for the reaction. Unfortunately the reaction did not provide any level of stereocontrol and 4.164 was obtained as a racemic mixture of diastereoisomers.

Scheme 54. Quinidine-catalyzed 1,2-addition of 4.161 to benzaldehyde.

Thus, we screened different bifunctional organocatalysts and solvents with the intent to improve the stereochemical outcome of the reaction (Table 2).
Table 2. Organocatalyzed formation of 4.164.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Solvent</th>
<th>4.164 (%) yield</th>
<th>dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.8</td>
<td>DCM</td>
<td>78%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>2</td>
<td>4.8</td>
<td>toluene</td>
<td>64%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>3</td>
<td>4.8</td>
<td>THF</td>
<td>88%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>4</td>
<td>4.9</td>
<td>DCM</td>
<td>78%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>5</td>
<td>4.9</td>
<td>toluene</td>
<td>53%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>6</td>
<td>4.9</td>
<td>THF</td>
<td>79%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
</tbody>
</table>

Cat. =

4.8 R = OMe quinine
4.11 R = H cinchonidine
4.9 R = OMe quinidine
4.10 R = H cinchonine

4.14

4.167

4.12
<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>4.10</td>
<td>DCM</td>
<td>80%</td>
<td>1:1</td>
<td>rac.</td>
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<tr>
<td>8</td>
<td>4.10</td>
<td>toluene</td>
<td>72%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>9</td>
<td>4.10</td>
<td>THF</td>
<td>77%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>10</td>
<td>4.11</td>
<td>DCM</td>
<td>84%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>11</td>
<td>4.11</td>
<td>toluene</td>
<td>67%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>12</td>
<td>4.11</td>
<td>THF</td>
<td>89%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>13</td>
<td>4.12</td>
<td>DCM</td>
<td>85%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>14</td>
<td>4.12</td>
<td>toluene</td>
<td>72%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>15</td>
<td>4.12</td>
<td>THF</td>
<td>93%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>16</td>
<td>4.14</td>
<td>DCM</td>
<td>85%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>17</td>
<td>4.14</td>
<td>toluene</td>
<td>77%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>18</td>
<td>4.14</td>
<td>THF</td>
<td>84%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>19</td>
<td>4.167</td>
<td>DCM</td>
<td>79%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>20</td>
<td>4.167</td>
<td>toluene</td>
<td>63%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
<tr>
<td>21</td>
<td>4.167</td>
<td>THF</td>
<td>88%</td>
<td>1:1</td>
<td>rac.</td>
</tr>
</tbody>
</table>

* Isolated yields.  
  * The diastereomeric ratio was determined by $^1$H-NMR analysis of the pure product.  
  * The ee value was determined by HPLC on a chiral stationary phase.

In all the cases 4.164 was produced in moderate to good yields as a 1:1 mixture of diastereoisomers, but no asymmetric induction was obtained. The lack of stereocontrol can be explained considering the reversibility of the reaction involved in the formation of the halohydrin. It has been reported the 1,2-addition of 4.160 to aromatic aldehydes being a reversible transformation in which the reaction reach the equilibrium depending on the reaction conditions. [82] Similarly, reaction of α-chloro esters with 4.147 to produce halohydrins has been demonstrated to be a reversible process (See Paragraph 4.2.2.7). [74]
Then we tested the reaction under phase-transfer conditions (Table 3). The reaction was performed initially in the presence of inorganic bases, such as potassium carbonate and lithium hydroxide in DCM, using TBAB as phase-transfer catalyst (Table 3, entry 1 and 2). After 72 hours a new product was isolated and identified as the epoxide 4.168, although in low yield. Noteworthy 4.168 was obtained as the only trans-isomer. Performing the reaction in toluene slowed down the reaction (Table 3, entry 3 and 4) while the use of THF brought to degradation of 4.161 (Table 3, entry 5 and 6).

Table 3. Phase-transfer catalyzed preparation of epoxide 4.168.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>4.168 (%) yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (5.0)</td>
<td>DCM</td>
<td>12%</td>
</tr>
<tr>
<td>2</td>
<td>LiOH (4.0)</td>
<td>DCM</td>
<td>14%</td>
</tr>
<tr>
<td>3</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (5.0)</td>
<td>toluene</td>
<td>5% &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>LiOH (4.0)</td>
<td>toluene</td>
<td>4% &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (5.0)</td>
<td>THF</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>LiOH (4.0)</td>
<td>THF</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup> Conversions determined by <sup>1</sup>H-NMR analysis of the crude mixture.

Disappointed by the results obtained we tested the reaction using Cinchona-derived quaternary ammonium salts 4.169 and 4.170 as catalysts using different bases and solvents (Table 4).
Table 4. Screening of conditions for the asymmetric Darzens condensation.

![Chemical structure of 4.161](image1.png)  

![Chemical structures of 4.169 and 4.170](image2.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>(% yield)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.169</td>
<td>K₂CO₃ (5.0)</td>
<td>DCM</td>
<td>48 h</td>
<td>36%</td>
<td>3%</td>
</tr>
<tr>
<td>2</td>
<td>4.169</td>
<td>LiOH (3.0)</td>
<td>DCM</td>
<td>48 h</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>3</td>
<td>4.169</td>
<td>K₃PO₄ (5.0)</td>
<td>DCM</td>
<td>72 h</td>
<td>39%</td>
<td>3%</td>
</tr>
<tr>
<td>4</td>
<td>4.169</td>
<td>NaOH 1M (1.0)</td>
<td>DCM</td>
<td>24 h</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4.169</td>
<td>NaOH 0.1M (1.0)</td>
<td>DCM</td>
<td>24 h</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.169</td>
<td>K₂CO₃ (5.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4.169</td>
<td>LiOH (3.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4.169</td>
<td>K₃PO₄ (5.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Table Entry</td>
<td>Reaction 4.169</td>
<td>Baseline 4.169</td>
<td>Reaction 4.170</td>
<td>Baseline 4.170</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>NaOH 1M (1.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>NaOH 0.1M (1.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>K₂CO₃ (5.0)</td>
<td>toluene</td>
<td>10 days</td>
<td>47%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>LiOH (3.0)</td>
<td>toluene</td>
<td>10 days</td>
<td>15%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>K₃PO₄ (5.0)</td>
<td>toluene</td>
<td>10 days</td>
<td>33%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>NaOH 1M (1.0)</td>
<td>toluene</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>NaOH 0.1M (1.0)</td>
<td>toluene</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>K₂CO₃ (5.0)</td>
<td>DCM</td>
<td>48 h</td>
<td>52%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>LiOH (3.0)</td>
<td>DCM</td>
<td>48 h</td>
<td>47%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>K₃PO₄ (5.0)</td>
<td>DCM</td>
<td>72 h</td>
<td>54%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>NaOH 1M (1.0)</td>
<td>DCM</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>NaOH 0.1M (1.0)</td>
<td>DCM</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>K₂CO₃ (5.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>LiOH (3.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>K₃PO₄ (5.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>NaOH 1M (1.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>NaOH 0.1M (1.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Compared to the TBAB-catalyzed reaction, compound 4.168 was obtained generally in higher yields (compare Table 3, entry 1 with Table 4, entry 1). This results suggest the Cinchona-derived quaternary ammonium salts acting as bifunctional catalysts in the activation of the substrates to undergo the reaction. From this initial screening some features can be outlined: (i) toluene proved to be a superior solvent compared to DCM, while the use of THF brought to degradation products. (ii) aqueous bases did not furnish the desired epoxide but only degradation of the starting material. (iii) solid inorganic bases gave the best results and among these potassium phosphate was be the most effective. (iii) catalyst 4.170, bearing a methoxy group in position C-6’ of the quinoline ring gave better results both in terms of yields and enantioselectivities respect to 4.169.

With this set of conditions in hands we screened different quinine-derived quaternary ammonium salts 4.171-4.179 (Table 5).

Table 5. Screening of quinine-derived quaternary ammonium salts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>(%) yield</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>4.170</td>
<td>K₂CO₃ (5.0)</td>
<td>toluene</td>
</tr>
<tr>
<td>27</td>
<td>4.170</td>
<td>LiOH (3.0)</td>
<td>toluene</td>
</tr>
<tr>
<td>28</td>
<td>4.170</td>
<td>K₃PO₄ (5.0)</td>
<td>toluene</td>
</tr>
<tr>
<td>29</td>
<td>4.170</td>
<td>NaOH 1M</td>
<td>toluene</td>
</tr>
<tr>
<td>30</td>
<td>4.170</td>
<td>NaOH 0.1M</td>
<td>toluene</td>
</tr>
</tbody>
</table>

a Isolated yields. b The absolute configuration was determined by comparison with literature data. c The ee value was determined by HPLC on a chiral stationary phase.
<table>
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<tr>
<th></th>
<th><img src="4.171" alt="Chemical Structure 1" /></th>
<th></th>
<th><img src="4.172" alt="Chemical Structure 2" /></th>
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<td>6</td>
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<td>(-)-15%</td>
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<tr>
<td>7</td>
<td><img src="4.177" alt="Chemical Structure" /></td>
<td>83%</td>
<td>(-)-27%</td>
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<td>8</td>
<td><img src="4.178" alt="Chemical Structure" /></td>
<td>70%</td>
<td>(-)-12%</td>
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<tr>
<td>9</td>
<td><img src="4.179" alt="Chemical Structure" /></td>
<td>76%</td>
<td>(-)-17%</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Isolated yields.  
  
  The absolute configuration was determined by comparison with literature data.  
  
  The ee value was determined by HPLC on a chiral stationary phase.

As can be seen from Table 5 yields were deeply affected by the substitution pattern on the benzyl group of the catalyst. EWG groups in ortho-position gave reduced yields (Table 5, entry 1,2,3 and 5), while EWG and EDG groups in meta- and para-position furnished higher yields (Table 5, entries 7,8 and 9). However the enantiomeric excesses were generally low. The best result was obtained using N-(3,5-bistrifluoromethyl)-benzylquininium bromide that afforded the product in 83% yield and 27% ee (Table 3, entry 7).
Finally we checked the possibility to open the 4-nitroisoxazole moiety of 4.168 to reveal the carboxylic acid. Three established procedures have been reported in the literature for the isoxazole ring-opening working under basic, acidic or oxidative conditions. Epoxides are known to easily undergo ring-opening of the oxirane functionality when reacted with nucleophiles as well as in the presence of Lewis acids. Hypothesizing a remarkable instability of 4.168 under both basic and acidic conditions we opted for the oxidative ring-opening. Delightfully, reacting 4.168 with potassium permanganate in a THF/acetonewater mixture, followed by in situ methylation with TMS-diazomethane afforded the desired glycidic ester 4.180 in 78% yield (Scheme 55).

Scheme 55. Oxidative isoxazole ring-opening/methylation.
4.4 Conclusions

In conclusion we demonstrated the ability of 3-methyl-4-nitro-5-chloromethylisoxazole \textbf{4.161} to undergo organocatalyzed 1,2-nucleophilic additions to \textbf{4.147}, showing a different reactivity depending on the kind of organocatalyst employed. In particular the use of bifunctional organocatalysts led to the formation of halohydrin \textbf{4.164} in good yields although without stereocontrol. On the other hand, under phase-transfer conditions \textbf{4.161} displayed a polyfunctional nucleophilic/electrophilic behavior, undergoing Darzens condensation to produce epoxide \textbf{4.168}. Employing the \textit{Cinchona}-derived quaternary ammonium salts \textit{N}-(3,5-bistrifluoromethyl)-benzylquininium bromide with potassium phosphate in toluene brought to the formation of enantioenriched 3-methyl-4-nitro-5-((2\textit{R},3\textit{S})-3-phenyloxiran-2-yl)isoxazole (2\textit{R},3\textit{S})-\textbf{4.168}. Moreover, we successfully opened the 4-nitroisoxazole core of \textbf{4.168} via one-pot oxidative ring-opening/esterification to produce glycidic ester \textbf{4.180}, thus demonstrating the utility of this procedure in the preparation of \textgreek{a},\textgreek{b}-epoxiesters. Further studies have to be undertaken for increasing the level of enantiocontrol of the Darzens condensation and for investigating the reactivity of the oxirane moiety of \textbf{4.168} in reaction with nucleophiles.
4.5 References


[70] aG. Darzens, Compt. Rend. 1904, 1241; bG. Darzens, Compt. Rend. 1906, 214.


Chapter 5

Electrophilic α-functionalization of 2-methyl-3-nitro-1H-indoles
5.1 Indoles

Indoles 5.1 (Figure 1) are a class of key structural components that can be found almost ubiquitously in many natural and synthetic compounds, showing a broad range of applications in different scientific fields. [1]

![Figure 1. Indole structure and numeration.](image)

First prepared by Baeyer in 1866, [2] the interest about their chemistry increased after the discovery that many alkaloids extracted from natural sources contained the indole moiety. [3] Moreover, studies conducted on different indole derivatives explained the fundamental roles they play in many biochemical processes, both in animals and plants. [4] The indole nucleus, for example, is constitutive of tryptophan 5.2, an essential aminoacid, of the neurotransmitter serotonin 5.3, of the hormone melatonin 5.4, as well of the plants hormone indole-3-acetic acid 5.6 (Figure 2).

![Figure 2. Natural-occurring bioactive indoles.](image)

The high activity displayed in biological systems led to an intense pharmaceutical research on indole derivatives during the second half of the twentieth century that brought to the development of a large number of bioactive compounds. The ability of the indole core in interacting and reversibly binding to a wide range of enzymes and receptors, made it a privileged scaffold in drug discovery. [5] Therefore, it has become one of the most important and widespread heterocyclic structural motif in medicinal chemistry and nowadays different indole-derived drugs are marketed worldwide displaying various
therapeutic properties, such as anti-inflammatory 5.6, anticancer 5.7, antihypertensive 5.8 for citing some examples (Figure 3).

![Indole-based marketed drugs]

5.1.1 Synthesis of the indole ring


![Indole-based marketed drugs]

5.6 Indomethacin 5.7 Vinblastine 5.8 Ajmalicine

Figure 3. Indole-based marketed drugs.
Chapter 5

Fischer 1883

\[
\begin{align*}
\text{N} & \quad \text{acid} \\
\text{R} & \quad \text{heat} \\
\text{N} & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
5.9 & \quad 5.10 \\
\end{align*}
\]

Bischler-Möhla 1881

\[
\begin{align*}
\text{NH} & \quad \text{acid} \\
\text{Br} & \quad \text{heat} \\
\text{R} & \\
\end{align*}
\]

\[
\begin{align*}
5.11 & \quad 5.12 \\
\text{N} & \quad \text{R} \\
5.13 & \\
\end{align*}
\]

Reissert 1897

\[
\begin{align*}
\text{NO}_2 & \quad 1) \text{base} \\
\text{CO}_2 & \quad 2) \text{H}^+ \\
\text{H} & \quad \text{CO}_2 \\
\text{R} & \\
\end{align*}
\]

\[
\begin{align*}
5.14 & \quad 5.15 \\
\text{N} & \quad \text{CO}_2 \\
5.16 & \\
\end{align*}
\]

Madelung 1912

\[
\begin{align*}
\text{O} & \quad \text{base} \\
\text{heat} \\
\text{R} & \\
\end{align*}
\]

\[
\begin{align*}
5.17 & \quad 5.18 \\
\end{align*}
\]

Cadogan-Sundberg 1965

\[
\begin{align*}
\text{NO}_2 & \quad \text{R}_3\text{P} \\
\text{hv} \\
\text{N}_3 \\
\text{R} & \\
\end{align*}
\]

\[
\begin{align*}
5.19 & \quad 5.20 \\
5.21 & \\
\end{align*}
\]

Batcho-Leimgruber 1971

\[
\begin{align*}
\text{NO}_2 & \quad \text{H}_2 \quad \text{Pd/C} \\
\text{R} & \\
\end{align*}
\]

\[
\begin{align*}
5.22 & \quad 5.23 \\
\end{align*}
\]
Scheme 1. Representative strategies for the preparation of the indole nucleus.

Considering the vast number of applications indoles find in many scientific fields, the search for new and efficient methods for their preparation and functionalization has attracted much attention over the years from the scientific community and still remains a central topic in organic chemistry.
5.1.2 Synthesis of 2-alkenyl-indoles

Alkenyl indoles 5.37 are valuable intermediates for the preparation of important polycyclic heterocycles and can be found in useful bioactive compounds (Figure 4).

![Figure 4](image)

Figure 4. (E)-2-alkenylindole structure and numeration.

The 2-alkenylindole core is an important structural component of several biologically active compounds such as fluvastatin 5.38, chartelline C 5.39, flinderole 5.40 (Figure 5).

![Figure 5](image)

Figure 5. Bioactive compounds containing the 2-alkenylindole core.

Besides the biological application, the importance of 5.37 lies in the broad synthetic applications they found in the preparation of 2-alkylindoles 5.38 and different polycyclic heterocycles 5.39 and 5.40 (Figure 6). Moreover they are important starting materials for the construction of complex indole derivatives.
Scheme 6. 2-alkenyindoles as 2-alkylindoles and polycyclic heterocycles precursors.

In the last decade their preparation has been performed mostly by functionalization of preformed indoles via transition metal-catalyzed C-H activation. [24] This route allows performing the reaction without the need of preliminary activation of the substrate, providing higher reaction economy. The major drawback arising from this approach consists in the regioselectivity between 2- and 3-position of the indole nucleus, considering that the latter is the more reactive center towards electrophiles. This problem can be overcome by employing a N-directing group that directs the insertion of the palladium specie to the less reactive 2-position. Ricci and co-workers reported the regiospecific C-2 alkenylation of N-(2-pyridylmethyl)-indole 5.41 with electrophilic olefins 5.42, catalyzed by palladium(II) dichloride in the presence of copper acetate as re-oxidant (Scheme 7). [25] The authors demonstrated the 2-pyridylmethyl group to be fundamental for the regioselectivity of the reaction, considering that the use of N-benzyl protecting group just yielded the corresponding 3-alkenyl indoles.
Scheme 7. Regiospecific C-2 alkenylation of N-(2-pyridylmethyl)-indole.

The selective C-H activation of the 2-position in $\text{5.41}$ is due to the formation of a labile palladacycle formed by the C-2 of the indole and the nitrogen of the pyridyl directing group, that directs the less reactive C-2 towards oxidative insertion. The mechanism involves a regiospecific C-2 cyclopalladation of $\text{5.41}$ facilitated by the coordination with the nitrogen of the directing group, forming the palladacycle $\text{5.44}$, which undergoes coordination with the olefin producing complex $\text{5.45}$, followed by 1,2-insertion affording intermediate $\text{5.46}$. Subsequently, β-hydride elimination yields 2-alkenylindoles $\text{5.43}$ and reductive elimination of HX generates Pd(0) that is re-oxidized by copper acetate to the active Pd(II) species (Scheme 8).
Scheme 8. Proposed mechanism for the selective C-2 alkenylation of N-(2-pyridylmethyl)-indole.

Carretero and co-workers expanded the synthetic utility of this approach employing 2-pyridylsulfone as removable directing group.\(^{26}\) This strategy allowed the preparation of N-(2-pyridyl)-sulfonyl-2-alkenyl indoles 5.48 in good yields using palladium(II) dichloride diacetonitrile as catalyst (Scheme 9).

\[
\begin{align*}
5.47 &&\quad \text{Pd(CH_3CN)_2Cl}_2 (10 \text{ mol\%}) \quad \text{Cu(OAc)}_2 (2.0 \text{ equiv.}) &\quad \rightarrow &\quad 5.49 \\
&\quad \text{DMA} \quad 110 \degree C, 24 \text{ h} \quad &\quad &\quad (2-5 \text{ equiv.}) \\
\end{align*}
\]

\[ R = \text{CO}_2\text{R}, \text{CONMe}_2, \text{PO(OMe)}_2, \text{alkyl, aryl} \]

40-85\% yield

Scheme 9. 2-pyridylsulfone directed C-2 alkenylation of indoles.

The directing group could be subsequently removed by reaction with zinc and ammonium chloride, producing the corresponding 2-alkenyl-1H-indoles 5.50 in good yields. An alternative modification involved the reaction of 5.49 with magnesium in methanol, bringing to the simultaneous elimination of the 2-pyridyl-sulfonyl directing group and hydrogenation of the alkenyl moiety, with the formation of 2-alkenyl-1H-indoles 5.51 in moderate yield (Scheme 10).

\[
\begin{align*}
5.50 &&\quad \text{Zn} \quad \text{NH}_4\text{Cl} &\quad \rightarrow &\quad 5.49 \\
&\quad \text{THF} \quad \text{r.t.} &\quad &\quad \\
5.49 &&\quad \text{Mg} \quad \text{MeOH} 0 \degree \text{C to r.t.} &\quad \rightarrow &\quad 5.51 \\
&\quad &\quad 79-83\% \text{ yield} &\quad &\quad 66-70\% \text{ yield} \\
\end{align*}
\]

Scheme 10. Removal of the 2-pyridyl-sulfonyl directing group.

A complementary procedure for the regioselective alkenylation of compounds 5.52 with olefins 5.53 has been proposed by Miura and co-workers,\(^{27}\) using a carboxylate in 3-position as the directing group. The carboxylic group directs the alkenylation on the C-2 and is removed at the end of the catalytic cycle, furnishing 2-alkenyl indoles 5.54 in moderate yields (Scheme 11).
Scheme 11. Carboxylate-directed selective C-2 alkenylation.

The mechanism involves as first step the coordination of Pd(OAc)$_2$ with the carboxylate moiety, forming a Pd(II)-carboxylate 5.55 with elimination of AcOH. The C-2 subsequently undergoes carbopalladation, giving the palladacycle 5.56, which in turn coordinates the alkene 5.53. Alkene insertion, followed by β-hydride elimination produce the hydridopalladium carboxylate 5.57. Successively, decarboxylation to the intermediate 5.58 and reductive elimination yield 2-alkenylindoles 5.54 and palladium(0) that is re-oxidized to Pd(II) by Cu(OAc)$_2$. 

R = Me, CH$_2$OMe, Ph
R$_1$ = CO$_2$R, Ph

39-62% yield
Gaunt demonstrated the feasibility of selectively obtaining 2- or 3-alkenyl-indoles through a fine tuning of the reaction conditions, without the need of directing groups.\[28]\] In particular it was shown that using palladium(II) acetate in a weakly coordinating solvent as 1,4-dioxane and acetic acid as the co-solvent, in combination with tert-butyl benzoyl peroxide as the re-oxidizing agent, favored the alkenylation to occur at the 2-position of the indole ring (Scheme 13).

Scheme 12. Proposed mechanism for the carboxylate-directed selective C-2 alkenylation.

Scheme 13. Regiospecific C-2 alkenylation of 2,3-unsubstituted-1H-indoles.
The catalytic cycle proposed (Scheme 14) involves an initial carbopalladation of the 3-position of 5.1 occurring via the intermediate 5.61. Subsequently migration to the 2-position occurs, forming the intermediate 5.64. The migration is believed to be favored by the acidic conditions that suppress the base-promoted formation of intermediate 5.62. Thus, 5.64 undergoes coordination with the alkene 5.59, followed by 1,2-insertion to 5.65 and β-elimination, producing the products 2-alkenyl-1H-indoles 5.60. Finally, reductive elimination and re-oxidation of Pd(0) close the catalytic cycle reforming the active Pd(II) species.

Scheme 14. Proposed mechanism for the regioselective 2-alkenylation of 2,3-unsubstituted-1H-indoles.
5.2 Results and discussion

With the intent of expanding the chemistry of 3,5-dimethyl-4-nitroisoxazole 5.66 to other heterocyclic compounds, we became interested in the study of the reactivity of 2-methyl-3-nitro-1H-indole 5.67. 5.67 Contains a reactive system composed of a methyl group that is made acidic by conjugation with the adjacent nitro group (Figure 6). We supposed could behave similarly to 5.66, reacting with electrophiles at the α-position and thus could serve as a versatile starting material for the derivatization of the indole ring.

Figure 6. Similarity between 5.66 and 5.67.

We started our investigation by preparing 5.67 via electrophilic nitration of the commercially available 2-methyl-1H-indole 5.68. Different procedures reported in the literature were tested, including silver nitrate and N-bromosuccinimide in refluxing acetonitrile; silver nitrate and benzoyl chloride in acetonitrile at 0 °C. However none afforded the desired product. Other classical procedures for electrophilic nitration, i.e. sulfonitric mixture cannot be applied on the indole nucleus due to the high acidity of the reaction medium that, protonating the N-H moiety, strongly deactivates the 3-position towards electrophiles (Scheme 16).

Scheme 15. Attempted conditions for the preparation of 5.67.
Thus, we decided to follow the procedure reported by Gribble \cite{32} that made use of acetyl nitrate as the electrophilic nitrating reagent. Therefore, 5.68 was first protected with di-tert-butyl dicarbonate 5.69 affording the 5.70 in almost quantitative yield (Scheme 17).

\[
\text{5.68} \xrightarrow{\text{(Boc)}_2\text{O (1.3 equiv.)} \quad \text{DMAP (1.0 equiv.)}} \quad \text{THF} \quad 30 \, ^\circ\text{C}, 18 \, \text{h}} \quad \text{5.70}
\]

97% yield

Scheme 16. Protection of 5.68 with di tert-butyl dicarbonate.

5.70 was then subjected to nitration with acetyl nitrate 5.72 (prepared \textit{in situ} by reacting acetic anhydride 5.71 with concentrated nitric acid) in acetic anhydride at \(-70^\circ\text{C}\) for 1.5 hours producing 5.73 (Scheme 18). It was noted that keeping the temperature at \(-70^\circ\text{C}\) was fundamental to obtain a good selectivity in the nitration of 3- over the 5-position. However, operating under a strict control of the reaction temperature the desired product 5.73 was obtained in 86% yield with only 4% yield of 5.74.

\[
\text{HNO}_3 + \overset{}{\text{O}}\overset{}{\text{O}} \quad \overset{}{\text{O}}\overset{}{\text{O}}^+ \quad \overset{}{\text{O}}\overset{}{\text{O}}^- \quad \text{Ac}_2\text{O} \quad -70^\circ\text{C}, 1.5 \, \text{h}} \quad \text{5.70} \quad \text{5.72} \quad \text{5.73} \quad \text{5.74}
\]

86% yield 4% yield

Scheme 17. Nitration of 5.70 with acetyl nitrate.

5.73 was straightforwardly deprotected to compound 5.67 in 87% yield by using trifluoroacetic acid in DCM at room temperature for 18 hours (Scheme 19). Via an alternative procedure employing HCl 4M in dioxane compound 5.67 was similarly obtained, albeit in reduced yields.
With the optimized condition in hands for the preparation of 5.73 we started studying its chemical behavior in reaction with different electrophiles.

### 5.2.1 Preparation of 2-alkenyl-3-nitro-1H-indoles and study of their reactivity as Michael acceptors

It is known that 3-methyl-4-nitro-5-styrylisoxazoles 5.75 can be prepared in one step by piperidine-catalyzed condensation of 3,5-dimethyl-4-nitroisoxazole 5.66 with benzaldehyde (Scheme 20).

![Scheme 19. Preparation of 3-methyl-4-nitro-5-styrylisoxazoles.](image)

Considering the structural similarity between 5.70 and 5.66, we supposed 5.70 could show a similar chemical behavior when reacted with different aromatic aldehydes. Reacting 5.70 with benzaldehyde 5.76 following the standard conditions for the preparation of 5.75 (1.1 equiv. of PhCHO, 0.1 equiv. of piperidine, EtOH, 65 °C) brought to the formation of a new product in 55% yield that was identified as 2-styryl-3-nitro-1H-indole 5.77 (Scheme 21).

![Scheme 20. Piperidine-catalyzed condensation of 5.70 with 5.76.](image)
Interestingly, during the course of the reaction the tert-butyl carbonate protecting group was removed. This was explained as an intramolecular attack of the alkoxide, formed in the first step in 5.78, on the carbamate group producing unstable 5.79 that subsequently undergoes base-catalyzed elimination producing 5.77 as the only (E)-isomer (Scheme 22).

Scheme 21. Plausible mechanism for the tandem condensation/elimination sequence.

5.77 displays a peculiar insolubility in most organic and aqueous solvent and can be separated by the reaction mixture and obtained in pure form by simple filtration. Encouraged by this preliminary result, different conditions were screened to increase the yield of the reaction using the reaction between 5.70 and 5.76 as a model (Table 1).
Table 1. Conditions tested for the preparation of 5.77.

<table>
<thead>
<tr>
<th>Entry</th>
<th>5.76 (equiv.)</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>5.77 (%) yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>Piperidine (0.1)</td>
<td>EtOH</td>
<td>65 °C</td>
<td>8 h</td>
<td>55%</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>Piperidine (0.5)</td>
<td>EtOH</td>
<td>65 °C</td>
<td>24 h</td>
<td>56%</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>DMAP (0.5)</td>
<td>EtOH</td>
<td>65 °C</td>
<td>8 h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>Et(_3)N (0.5)</td>
<td>EtOH</td>
<td>65 °C</td>
<td>8 h</td>
<td>22%</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>Piperidine (0.5)</td>
<td>CPME</td>
<td>85 °C</td>
<td>8 h</td>
<td>53%</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>Piperidine (0.5)</td>
<td>CPME</td>
<td>85 °C</td>
<td>24 h</td>
<td>70%</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>Piperidine (0.5)</td>
<td>CHCl(_3)</td>
<td>70 °C</td>
<td>8 h</td>
<td>49%</td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>Piperidine (0.5)</td>
<td>CHCl(_3)</td>
<td>70 °C</td>
<td>24 h</td>
<td>76%</td>
</tr>
<tr>
<td>9</td>
<td>2.0</td>
<td>Piperidine (0.5)</td>
<td>CHCl(_3)</td>
<td>70 °C</td>
<td>48 h</td>
<td>85%</td>
</tr>
<tr>
<td>10</td>
<td>2.0</td>
<td>Piperidine (0.5)</td>
<td>CHCl(_3)</td>
<td>70 °C</td>
<td>72 h</td>
<td>93%</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield after filtration.

Piperidine showed to be superior to tertiary and aromatic amines (Table 1, entries 2-4). For a good outcome of the reaction it was necessary to increase the equivalents of 5.76 and prolong the reaction time (Table 1, entries 6-9). Chloroform proved to be the solvent of choice, furnishing the product N in 93% yield after 72 hours at 70 °C (Table 1, entry 10). With the optimized conditions in hands, we then studied the scope of the reaction. Different aromatic aldehydes were reacted with 5.77, obtaining the corresponding condensation products 5.90- in good to excellent yields (Table 2).
Table 2. Preparation of 2-styryl-3-nitro-1H-indoles.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>(% yield)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[5.76]</td>
<td>[5.77]</td>
<td>93%</td>
</tr>
<tr>
<td>2</td>
<td>[5.81]</td>
<td>[5.90]</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>[5.82]</td>
<td>[5.91]</td>
<td>88%</td>
</tr>
<tr>
<td>4</td>
<td>[5.83]</td>
<td>[5.92]</td>
<td>91%</td>
</tr>
<tr>
<td>5</td>
<td>[5.84]</td>
<td>[5.93]</td>
<td>65%</td>
</tr>
</tbody>
</table>
In general, aromatic aldehydes bearing electron-withdrawing groups like halogens and nitro gave the best results than electron-donating groups (Table 2, entry 5). Heteroaromatic aldehydes like 2-pyridinecarboxaldehyde furnished the desired condensation product, while 3-pyrrolidinecarboxaldehyde failed in the reaction (Table 2, entries 9 and 10).

Considering the prominent effect exerted by the nitro group in activating the exocyclic double bond in compound 5.75, we envisaged compounds could be used as a Michael acceptor in 1,6-conjugate addition reactions. Thus, we started testing different soft carbon nucleophiles in Michael addition reactions with 5.77. Nitromethane 5.99, acetylacetone 5.100 and dimethylmalonate 5.101 were chosen as the nucleophiles, as they have been reported to react with 5.75 under base-promoted and organocatalytic conditions.³³³
Reaction of nitromethane in the presence of equimolar quantities of secondary, tertiary and aromatic amines in different solvent failed to give the desired β-addition product 5.102 (Table 3). Rising the temperature did not improve the outcome of the reactions as well and in all the cases only starting material 5.75 could be detected in the crude mixture. Thus, we decided to perform the reactions under organocatalytic conditions, using the Cinchona-derived quaternary ammonium salt 5.103 and the thiourea 5.104 (Takemoto’s catalyst) as model catalysts for phase-transfer and bifunctional catalysis respectively (Table 4). Organocatalytic conditions proved as well to be ineffective in providing the desired addition products 5.102 with complete recovery of unreacted 5.75 after 48 hours.

Table 3. Base-promoted 1,6-conjugate addition of nitromethane to 5.75.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>5.102 (%) yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Piperidine (1.0)</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Piperidine (1.0)</td>
<td>DMF</td>
<td>110 °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Piperidine (1.0)</td>
<td>CHCl3</td>
<td>r.t. °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Piperidine (1.0)</td>
<td>CHCl3</td>
<td>70 °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Et3N (1.0)</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Et3N (1.0)</td>
<td>DMF</td>
<td>110 °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Et3N (1.0)</td>
<td>CHCl3</td>
<td>r.t. °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Et3N (1.0)</td>
<td>CHCl3</td>
<td>70 °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>DMAP (1.0)</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>DMAP (1.0)</td>
<td>DMF</td>
<td>110 °C</td>
<td>48 h</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 4. Organocatalytic 1,6-conjugate addition of nitromethane to 5.75.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Catalyst (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>5.102 (%) yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$ (5.0)</td>
<td>-</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$ (5.0)</td>
<td>-</td>
<td>DMF</td>
<td>110 °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$ (5.0)</td>
<td>-</td>
<td>CHCl$_3$</td>
<td>r.t. °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>K$_2$CO$_3$ (5.0)</td>
<td>-</td>
<td>CHCl$_3$</td>
<td>70 °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>K$_2$CO$_3$ (5.0)</td>
<td>-</td>
<td>toluene</td>
<td>r.t.</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>K$_2$CO$_3$ (5.0)</td>
<td>-</td>
<td>toluene</td>
<td>100 °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>K$_2$CO$_3$ (5.0)</td>
<td>5.103 (0.2)</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
<td>-</td>
</tr>
</tbody>
</table>
The same set of conditions were tested in the reaction between 5.75 and acetylacetone 5.100 (Table 5 and 6) but also in these cases the results were disappointing, with complete recovery of unreacted starting material without formation of the desired Michael adduct 5.105.

**Table 5. Base-promoted 1,6-conjugate addition of acetylacetone to 5.75.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>5.105 (%) yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Piperidine (1.0)</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Piperidine (1.0)</td>
<td>DMF</td>
<td>110 °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>Entry</td>
<td>Base (equiv.)</td>
<td>Catalyst (equiv.)</td>
<td>Solvent</td>
<td>T (°C)</td>
<td>Time (h)</td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>------------------</td>
<td>---------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>1</td>
<td>K$_2$CO$_3$ (5.0)</td>
<td>-</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$ (5.0)</td>
<td>-</td>
<td>DMF</td>
<td>110 °C</td>
<td>48 h</td>
</tr>
</tbody>
</table>

Table 6. Organocatalytic 1,6-conjugate addition of acetylacetone to 5.75.
<table>
<thead>
<tr>
<th></th>
<th>K₂CO₃ (5.0)</th>
<th>5.103 (0.2)</th>
<th>DMF</th>
<th>r.t.</th>
<th>48 h</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>CHCl₃</td>
<td>r.t. °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CHCl₃</td>
<td>70 °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>toluene</td>
<td>r.t.</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>toluene</td>
<td>100 °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>DMF</td>
<td>110 °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CHCl₃</td>
<td>r.t. °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>CHCl₃</td>
<td>70 °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>toluene</td>
<td>r.t.</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>toluene</td>
<td>100 °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>DMF</td>
<td>110 °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>CHCl₃</td>
<td>r.t. °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>CHCl₃</td>
<td>70 °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>toluene</td>
<td>r.t.</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>toluene</td>
<td>100 °C</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disappointed by the results obtained with nitromethane and acetylacetone, we decided to study the reactivity of 5.75 with dimethylmalonate 5.101. Also in this case the base-promoted conditions (Table 7) failed to furnish the desired Michael adduct 5.106, with complete recovery of 5.75 after 48 hours.

Table 7. Base-promoted 1,6-conjugate addition of dimethylmalonate to 5.75.
The use of bifunctional thiourea 5.104 as catalyst in different solvents did not lead to the formation of the addition product 5.106 (Table 8).

Table 8. Bifunctional thiourea-catalyzed 1,6-conjugate addition of dimethylmalonate to 5.75.
When the reaction was performed with the quaternary ammonium salt 5.103 in toluene, using potassium carbonate as base (Table 9, entry 11), after 24 hours at r.t. two new products were obtained, which were identified as 5.107 and 5.108. Repeating the reaction at 70 °C for 24 hours brought to slightly increased the yields (Table 9, entry 12), although a large amount of 5.75 was recovered unreacted. Performing the reaction other solvents like DMF and CHCl₃ did not afford any products. A control set of reaction without the catalyst was run and did not produce the products, thus indicating the fundamental role of the catalyst in the transformation. Increasing the reaction time to 72 hours did not improve the outcome of the reaction and similar yields were obtained (Table 9, entry 13).

Table 9. Organocatalytic 1,6-conjugate addition of dimethylmalonate to 5.75.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>5.107 (%) yield</th>
<th>5.108 (%) yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>DMF</td>
<td>110 °C</td>
<td>48 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>CHCl₃</td>
<td>r.t. °C</td>
<td>48 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>CHCl₃</td>
<td>70 °C</td>
<td>48 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>toluene</td>
<td>r.t.</td>
<td>48 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>toluene</td>
<td>100 °C</td>
<td>48 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>5.103 (0.2)</td>
<td>DMF</td>
<td>r.t.</td>
<td>48 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>5.103 (0.2)</td>
<td>DMF</td>
<td>110 °C</td>
<td>48 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>5.103 (0.2)</td>
<td>CHCl₃</td>
<td>r.t. °C</td>
<td>48 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>5.103 (0.2)</td>
<td>CHCl₃</td>
<td>70 °C</td>
<td>48 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>5.103 (0.2)</td>
<td>toluene</td>
<td>r.t.</td>
<td>24 h</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
<td>5.103 (0.2)</td>
<td>toluene</td>
<td>70 °C</td>
<td>48 h</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>13</td>
<td>5.103 (0.2)</td>
<td>toluene</td>
<td>70 °C</td>
<td>72 h</td>
<td>10</td>
<td>27</td>
</tr>
</tbody>
</table>

Catalyst = 5.103
It should be noted that in all cases a notable amount of undissolved starting material was present in the reaction mixture. Indeed, the main problem encountered in performing the reactions was the extremely low solubility of the starting material in almost any organic solvent. The only solvent that provided a slightly higher solubility was DMF, which however failed in producing compounds 5.107 and 5.108, in contrast to toluene. The formation of compounds 5.108 can be explained by a tandem 1,6-conjugate addition/decarboxylation/intramolecular cyclization sequence (Scheme 23). In the first step 5.101 performs a 1,6-conjugate addition on 5.75, producing the intermediate 5.109, which subsequently undergoes hydrolysis to the monoester 5.110 followed by decarboxylation to produce compound 5.107. Finally, intramolecular cyclization of 5.107 yields the tricyclic compound 5.108.

\[
\begin{align*}
5.107 \quad &\xrightarrow{\text{MeOH, N}_2, \text{r.t., 36 h}} 5.108 \\
\end{align*}
\]

Scheme 22. Proposed mechanism for the formation of compounds 5.107 and 5.108.

In order to better understand the mechanism of formation of the tricyclic compound 5.108, we decided to carry out the cyclization step starting from compound 5.107. We first tried to react 5.107 with sodium methoxide in methanol, \(^{[34]}\) but this procedure failed to produce the cyclized product (Scheme 24).
Scheme 23. Sodium methoxide-promoted cyclization of 5.107 to tricyclic indole 5.108.

Hence, we tried to use a set of conditions similar to the one utilized in the tandem reaction. Reacting 5.107 with 5.0 equiv. of potassium carbonate in toluene furnished the desired tricyclic compound 5.108 in 61% yield after 36 hours at room temperature, thus demonstrating 5.107 to be the precursor of 5.108 in the reaction sequence (Scheme 25).

Scheme 24. Potassium carbonate-promoted cyclization of 5.107 to tricyclic indole 5.108.

5.2.2 Conclusions

In conclusion, we have demonstrated that compound 5.73 can be successfully employed as useful precursor for the preparation of 2-alkenyl-1H-indoles 5.77, 5.90-5.97 via piperidine-catalyzed condensation with aromatic aldehydes with concomitant removal of the tert-butyl carbonate protecting group. The condensation products were obtained in good to excellent yields by an operationally simple procedure. Noteworthy the methodology does not require the use of transition metal catalysis. This feature makes it a valuable alternative to the palladium-catalyzed processes for the synthesis of 2-alkenyl-1H-indoles. We investigated the reactivity of 5.75 in 1,6-conjugate addition with soft carbon nucleophiles, demonstrating its ability to act as a Michael acceptor with the formation of the Michael adduct 5.107 and the tricyclic indole 5.108.

Considering the extremely low solubility of 2-alkenyl-1H-indoles in common organic solvents further investigations will be focused on the study of reactivity of different N-protected-2-styryl-3-nitroindoles 5.109 in 1,6-conjugate additions, for the preparation of libraries of poly-functionalized indoles 5.110 (Scheme 26).
5.2.3 Electrophilic chlorination of 2-methyl-3-nitroindole derivatives

5.2.2.1 Electrophilic chlorination of tert-butyl 2-methyl-3-nitro-1H-indole-1-carboxylate

It has been demonstrated that compound 5.66 reacts with electrophilic chlorinating reagent to produce the trichloro derivative 5.111 which undergoes substitution of the CCl$_3$ moiety by amines via an haloform-type reaction (Scheme 27), leading to the formation of 5-aminoisoxazoles 5.112 (see Chapter 2).

Considering the structural similarity between 5.66 and 5.73, we envisaged that indole 5.73 could behave similarly when subjected to electrophilic chlorination, thus allowing the preparation of the trichloro derivative 5.115. The reaction was therefore studied with different electrophilic chlorinating reagents such as N-chlorosuccinimide 5.116, 1,3-dichloro-5,5-dimethylhydantoin 5.117 and trichloroisocyanuric acid 5.118 (Scheme 28).

**Scheme 25.** N-protected-2-styryl-3-nitroindoles as Michael acceptor in 1,6-conjugate additions.

**Scheme 26.** Preparation of 5-aminoisoxazoles via electrophilic chlorination/haloform-type reaction.
Scheme 27. Electrophilic chlorination of 5.73 with common chlorinating reagents.

The reaction of 5.73 with NCS did not afford the desired trichloro derivative 5.115, even using a large excess of NCS for prolonged reaction times. In most cases the conditions tested furnished a mixture of 5.113 and 5.114, which proved to be of difficult separation (Table 10). Moreover NMR analysis of the crude mixtures revealed the presence of undefined degradation products.

<table>
<thead>
<tr>
<th>Entry</th>
<th>NCS (equiv.)</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>5.113 (%) yield</th>
<th>5.114 (%) yield</th>
<th>5.115 (%) yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.5</td>
<td>DABCO (1.0)</td>
<td>DCM</td>
<td>21%</td>
<td>22%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>DABCO (2.5)</td>
<td>DCM</td>
<td>11%</td>
<td>33%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>DABCO (0.5)</td>
<td>DCM</td>
<td>36%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
<td>DABCO (1.0)</td>
<td>THF</td>
<td>9%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5 b</td>
<td>3.5</td>
<td>DABCO (1.0)</td>
<td>MeCN</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>3.5</td>
<td>DBU (1.0)</td>
<td>DCM</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>3.5</td>
<td>K₂CO₃ (5.0)</td>
<td>THF</td>
<td>7%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Isolated yields.  
*b Reaction performed at 80 °C.

Unsatisfied by the results obtained with NCS we then screened other chlorinating reagents. TCICA proved to be unreactive under the reaction conditions tested, while DCDMH provided a higher selectivity for the reparation of the mono-chloro indole 5.113. Hence we set up a screening to optimize the preparation of compound 5.113.

Table 11. Conditions screened for the preparation of compound 5.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Cl⁺ reagent (equiv.)</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>Time</th>
<th>5.113 (%) yieldᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TCICA (3.5)</td>
<td>DABCO (1.0)</td>
<td>DCM</td>
<td>24 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>TCICA (3.5)</td>
<td>DABCO (1.0)</td>
<td>THF</td>
<td>24 h</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>TCICA (3.5)</td>
<td>DABCO (1.0)</td>
<td>MeCN</td>
<td>24 h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>DCDMH (2.1)</td>
<td>DABCO (1.0)</td>
<td>DCM</td>
<td>24 h</td>
<td>49%</td>
</tr>
<tr>
<td>5ᵇ</td>
<td>DCDMH (1.1)</td>
<td>DABCO (1.0)</td>
<td>DCM</td>
<td>24 h</td>
<td>54%</td>
</tr>
<tr>
<td>6</td>
<td>DCDMH (1.1)</td>
<td>-</td>
<td>DCM</td>
<td>24 h</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>DCDMH (1.1)</td>
<td>DIPEA (1.0)</td>
<td>DCM</td>
<td>24 h</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>DCDMH (1.1)</td>
<td>DMAP (1.0)</td>
<td>DCM</td>
<td>24 h</td>
<td>29%</td>
</tr>
<tr>
<td>9</td>
<td>DCDMH (1.1)</td>
<td>Et₃N (1.0)</td>
<td>DCM</td>
<td>3 h</td>
<td>70%</td>
</tr>
<tr>
<td>10</td>
<td>DCDMH (1.3)</td>
<td>Et₃N (1.3)</td>
<td>DCM</td>
<td>1 h</td>
<td>76%</td>
</tr>
<tr>
<td>11</td>
<td>DCDMH (1.3)</td>
<td>Et₃N (1.3)</td>
<td>THF</td>
<td>1.5 h</td>
<td>68%</td>
</tr>
<tr>
<td>12</td>
<td>DCDMH (1.3)</td>
<td>Et₃N (1.3)</td>
<td>MeCN</td>
<td>1 h</td>
<td>44%</td>
</tr>
</tbody>
</table>

ᵃ Isolated yields.

The use of DCDMH in combination with triethylamine in DCM showed to be the best conditions (Table 11, Entry 10), furnishing compound 5.113 in 76% isolated yield. Changing the solvent to THF or MeCN led to decreased yields (Table 11, entry 10-12). The nature of the base employed had a remarkable effect on the formation of the product. The use of DIPEA did not lead to any product, with just starting material was recovered after 24 hours; meanwhile DMAP furnished 5.113 in lower yield (Table 11, entry 7-8). It was noted that in absence of base the reaction furnished only starting material (Table 11, entry 6), thus demonstrating that the base has a fundamental role in the outcome of the reaction and also confirming the electrophilic mechanism involved in this transformation.
5.2.2.2 Electrophilic chlorination of 2-methyl-3-nitro-1H-indole 5.67

Considering that steric hindrance of the bulky tert-butyl carbonate group could have an important role in the introduction of more than two chlorine atoms on the α-methyl of 5.73, we decided to test the reactivity of the unprotected 2-methyl-3-nitro-1H-indole 5.67 towards electrophilic chlorination. 5.67 was first subjected to the chlorination conditions optimized for the preparation of 5.111. The result was not satisfactory since compound 5.121 was not detected in the reaction mixture, while a mixture of 5.119, 5.120 and 5.122 was isolated in low yield (Table 12, Entry 1). Increasing the reaction time afforded higher yields but again without the formation of the desired tri-chloro indole 5.121 (Table 12, entry 2). Changing the base to tertiary and aromatic amines as well as cyclic amidine DBU did not improve the reaction outcome, with the formation of low quantities of 5.119 and 5.120 (Table 12, entry 4-6).

Table 12. Electrophilic chlorination of 5.67 with NCS.

<table>
<thead>
<tr>
<th>Entry</th>
<th>NCS (equiv.)</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>5.119 (%) yielda</th>
<th>5.120 (%) yielda</th>
<th>5.121 (%) yielda</th>
<th>5.122 (%) yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(3.5)</td>
<td>DABCO (1.2)</td>
<td>DCM</td>
<td>22%</td>
<td>26%</td>
<td>-</td>
<td>17%</td>
</tr>
</tbody>
</table>
It was noted that in all the cases the starting material was completely consumed within 1 hour from the reaction onset. Further studies demonstrated that after 1 hour 5.67 was completely converted to a new product, which was identified as 1-chloro-2-methyl-3-nitroindole 5.123 or the structural isomer 2-methyl-3-chloro-3-nitroindolenine 5.124. The isolated chlorinated product exhibited a marked instability and rapidly decomposed producing a complex mixture of products. Analysis of the mixture showed the presence of 5.119 and 5.122 in combination with other unidentified degradation products. We attempted to characterize compound 5.123/5.124 by $^1$H-NMR and $^{13}$C-NMR analysis for elucidating its actual structure. In particular we pointed our attention at the changing in chemical shift of the C-3 of the indole nucleus, which in compound 5.123 is hybridized sp$^2$ while in compound 5.124 is a sp$^3$ quaternary carbon (Figure 7). However the data collected from the experiments were not exhaustive enough to unequivocally clarify the structure of the chemical species, because a marked change in the chemical shift did not occur.

Figure 7. C-3 hybridization in compounds 5.123 and 5.124.

The formation of compounds 5.119 and 5.122 from compound 5.123/5.124 likely proceeds via an intermolecular electrophilic self-chlorination (Scheme 28). Thus
compound 5.123/5.124 first undergo heterolytic bond cleavage forming compound 5.125 and a chloronium ion. 5.125 subsequently acts as a base promoting the electrophilic chlorination of another molecule of 5.67 bringing to the formation of 5.119 and 5.120. 5.122 is then formed from the hydrate 5.126 derived from the di-chloro indole 5.120.


The rationale behind the proposed mechanism derives from the experimental evidence that 5.67 is not chlorinated by different chlorinating reagents in absence of a base. At the same time radical conditions are not effective in the chlorination of the methyl group, as demonstrated in control experiments (Scheme 29)

Scheme 29. Control experiments for the chlorination of 5.67.

The formation of compounds 5.119 and 5.122 starting from 5.67 it’s a prove of its ability to act as an electrophilic chlorinating reagent and further studies have to be undertaken to deeply understanding and exploiting this chemical behavior.
5.2.4 Conclusions

In conclusion we have studied the chemical behavior of 5.67 and his derivative 5.73 in electrophilic chlorination reaction with different chlorinating reagents. During the investigation we were able to optimize a methodology for the electrophilic mono-chlorination of 5.73 using DCDMH as the electrophilic chlorinating reagent in the presence of Et₃N in DCM. Performing the chlorination using 5.67 as the substrate resulted in the obtainment of mixtures of chlorinated compounds 5.119, 5.120 together with the aldehyde 5.121. Unfortunately we were not able to obtain the tri-chloro derivatives 5.113 and 5.121 under the reaction conditions tested. Further investigations have to be carried out for studying the role of different N-protecting groups on the electrophilic chlorination reaction of 2-methyl-4-nitroindoles as well as for the use of compound 5.113 as substrate in ring-closing reactions for the preparation of epoxiindoles 5.127 and cyclopropylindoles 5.128 (Scheme 30).

Scheme 30. Preparation of cyclopropylindoles and epoxiindoles via ring-closing transformations.
5.3 References


General conclusions

Chapter 2

We developed an efficient procedure for the base-mediated electrophilic trichlorination if 3,5-dimethyl-4-nitroisoxazole using N-chlorosuccinimide as electrophilic chlorinating reagent and DABCO as the base. The trichloroisoxazole obtained was used in transition metal-free heteroaromatic amination via a novel haloform-type reaction with aromatic and aliphatic amines.

Chapter 3

We investigated the chemical behavior of (E)-N,N-dimethyl-2-(3-methyl-4-nitroisoxazol-5-yl)-ethenamine, demonstrating its ability to react with electrophiles predominantly as an activated enamine. We development a one-pot procedure for the preparation of 3-methyl-4-nitro-5-chloromethyl isoxazole involving a tandem electrophilic halogenation/hydrolysis/ decarbonylation sequence.

Chapter 4

We studied the organocatalyzed 1,2-addition of 3-methyl-4-nitro-5-chloromethyl isoxazole to benzaldehyde. The demonstrated the possibility to obtain selectively halohydrins or epoxides by changing the type of organocatalyst employed. In particular the use of bifunctional Takemoto’s catalyst furnished the halohydrin in excellent yield. On the other hand, performing the reaction under phase-transfer catalyzed conditions brought to the formation of the α,β-epoxiisoxazole via Darzens condensation.

Chapter 5

We expanded the typical reactivity showed by 3,5-dimethyl-4-nitroisoxazole to indole derivatives. 2-methyl-3-nitro-1H-indole was synthesized and applied in Knoevenagel condensation with aromatic aldehydes to prepare a novel class of heterocyclic Michael acceptors. We developed a procedure for the electrophilic monochlorination of 2-methyl-3-nitro-1H-indole derivative in the presence of 1,3-Dichloro-5,5-dimethylhydantoin and triethylamine.
General Experimental Details

General Methods

$^1$H- and $^{13}$C-NMR spectra were recorded on a Bruker 400 instrument. Chemical shifts ($\delta$) are reported in ppm relative to residual solvent signals for $^1$H and $^{13}$C NMR ($^1$H-NMR: 7.26 ppm for CDCl$_3$, 3.34 ppm for CD$_3$OD, 2.50 ppm for (CD$_3$)$_2$SO; $^{13}$C NMR: 77.16 ppm for CDCl$_3$, 49.00 ppm for CD$_3$OD, 39.52 ppm for (CD$_3$)$_2$SO. $^{13}$C-NMR spectra were acquired with $^1$H broad band decoupled mode. Coupling constants ($J$) are in Hz. Multiplicities are reported as follows: s, singlet, d, doublet, dd, doublets of doublets, t, triplet, q, quartet, m, multiplet, c, complex, and br, broad. Mass spectra were recorded on a Micro mass LCT spectrometer using electrospray (ES) ionisation techniques. Melting points were determined using a Stuart scientific melting point apparatus. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase CSP-HPLC (Daicel Chiralpak AD, Chiralcel OD and Chiralcel AS columns), using a UV detector operating at 254 nm and 210 nm. Infrared (IR) spectra were recorded as thin films between NaCl plates using a Bruker Tensor27 FT-IR instrument. Absorption maximum ($\nu_{\text{max}}$) was reported in wavenumbers (cm$^{-1}$) and only selected peaks are reported. The following abbreviations are used: w, weak, m, medium, s, strong and br, broad.

Materials

Tetrahydrofuran was freshly distilled over sodium benzophenone prior to use according to standard procedure. Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Reactions were checked for completion by TLC (EM Science, silica gel 60 F254). Flash chromatography was performed using silica gel 60 (0.040-0.063 mm, 230-400 mesh).
Experimental Section Chapter 2

3-methyl-4-nitro-5-trichloromethylisoxazole 2.117

![Structural formula of 3-methyl-4-nitro-5-trichloromethylisoxazole](image)

To a solution of 3,5-dimethyl-4-nitro-isoxazole (1 g, 7.04 mmol) in DCM (20 mL) was added DABCO (790 mg, 7.04 mmol, 1.0 equiv.). The solution was cooled to 0°C with an ice-bath and N-chlorosuccinimide (3.23 g, 24.63 mmol, 3.5 equiv.) was added in portions. The reaction mixture was brought to 25°C and stirred at this temperature for 6 hours. The mixture was filtered on Celite, washing with DCM. The filtrate was washed with saturated NH₄Cl and brine and the organic phase anhydrified on Na₂SO₄, filtered and evaporated at reduced pressure. The crude product was purified by column chromatography eluting with EtOAc / Pet Ether (1:99) to obtain 2.117.

White solid, 1.60 g, 93% yield, Rᵣ = 0.56 (EtOAc / PetEt 3:7).

¹H NMR (400 MHz, CDCl₃) δ_H = 2.60 (3H, s).

¹³C NMR (100.6 MHz, CDCl₃) δ_c = 164.1, 158.1, 128.1, 83.8, 11.7.

HRMS found: [M]⁺ 243.9216, C₅H₃N₂O₃Cl₃ requires 243.9209.

General procedure for aromatic amination

3-methyl-4-nitro-5-trichloromethylisoxazole 2.117 (100 mg, 0.407 mmol) was dissolved in THF (0.4 mL) in a test tube and K₂CO₃ (56 mg, 0.407 mmol, 1.0 equiv.) was added, followed by amine (0.448 mmol, 1.1 equiv.). The test tube was sealed and the solution was brought to 50°C and stirred at this temperature for 12 hours. The reaction mixture was partitioned between H₂O (10 mL) and DCM (10 mL), the phases separated and the aqueous phase extracted with DCM (3x10 mL). The combined organic phases were anhydrified on Na₂SO₄, filtered and evaporated at reduced pressure to obtain the pure product, without need of further purification.
(3-methyl-4-nitro-isoxazol-5-yl)-phenyl-amine 2.120

![Chemical structure](image)

Yellow solid, 84 mg, 94% yield, yellow solid, $R_f = 0.63$ (EtOAc/Pet Ether 4:6).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 9.47$ (1H, br s), 7.49-7.42 (4H, m), 7.28-7.24 (1H, m), 2.54 (3H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_C = 162.5, 156.0, 135.2, 129.9, 126.2, 120.1, 112.0, 12.0$.

HRMS found: [M]$^+$ 219.0652, C$_{10}$H$_9$N$_3$O$_3$ requires 219.0644.

(3-methyl-4-nitro-isoxazol-5-yl)-p-tolyl-amine 2.127

![Chemical structure](image)

Brown solid, 92 mg, 97% yield, $R_f = 0.60$ (EtOAc/Pet Ether 4:6).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 9.43$ (1H, br s), 7.35 (2H, d, $J = 8.4$ Hz), 7.23 (2H, d, $J = 8.4$ Hz), 2.53 (3H, s), 2.36, (3H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_C = 162.6, 156.0, 136.3, 132.6, 130.4, 120.2, 111.9, 21.1, 12.0$.

HRMS found: [M]$^+$ 233.0798, C$_{11}$H$_{11}$N$_3$O$_3$ requires 233.0800.

(4-bromo-phenyl)-(3-methyl-4-nitro-isoxazol-5-yl)-amine 2.128

![Chemical structure](image)
Yellow solid, 111 mg, 92% yield, R_f = 0.60 (EtOAc/ et Ether 4:6).

^1^H NMR (400 MHz, DMSO) \( \delta_H = 10.79 \) (1H, br s,), 7.64 – 7.62 (2H, m), 7.52 – 7.50 (2H, m), 2.42 (3H, s).

^1^C NMR (100.6 MHz, DMSO) \( \delta_c = 162.4, 155.8, 135.3, 132.0, 124.7, 118.4, 111.6, 11.7. \)

HRMS found: [M]^+ 296.9741, C_{10}H_{8}BrN_{3}O_{3} requires 296.9749.

(4-chloro-phenyl)-(3-methyl-4-nitro-isoxazol-5-yl)-amine 2.129

![Chemical Structure](attachment:image.png)

Yellow solid, 97 mg, 94% yield, R_f = 0.58 (EtOAc/Pet Ether 4:6).

^1^H NMR (400 MHz, DMSO) \( \delta_H = 10.81 \) (1H, br s,), 7.58-7.56 (2H, m), 7.51-7.49 (2H, m), 2.42 (3H, s).

^1^C NMR (100.6 MHz, DMSO) \( \delta_c = 162.4, 155.8, 134.9, 130.2, 129.1, 124.5, 111.6, 11.7. \)

HRMS found: [M]^+ 253.0251, C_{10}H_{8}ClN_{3}O_{3} requires 253.0254.

(2-bromo-phenyl)-(3-methyl-4-nitro-isoxazol-5-yl)-amine 2.130

![Chemical Structure](attachment:image.png)

Brown solid, 92 mg, 76% yield, R_f = 0.58 (EtOAc/Pet Ether 4:6).

^1^H NMR (400 MHz, CDCl_3) \( \delta_H = 10.11 \) (1H, br s), 7.96-7.94 (1H, m), 7.67-7.65 (1H, m), 7.43-7.39 (1H, m), 7.13-7.09 (1H, m), 2.56 (3H, s).

^1^C NMR (100.6 MHz, CDCl_3) \( \delta_c = 162.2, 156.0, 133.8, 133.3, 129.1, 126.9, 120.4, 114.2, 112.5, 11.9. \)

HRMS found: [M]^+ 296.9753, C_{10}H_{8}BrN_{3}O_{3} requires 296.9749.
Experimental Section Chapter 2

(2-iodo-phenyl)-(3-methyl-4-nitro-isoxazol-5-yl)-amine 2.131

![Chemical structure](image)

Black solid, 86 mg, 61% yield, R_f = 0.56 (EtOAc/Pet Ether 4:6).

^1^H NMR (400 MHz, CDCl_3) δ_H = 9.94 (1H, br s), 7.92-7.89 (1H, m), 7.45-7.43 (1H, m), 7.00-6.95 (1H, m), 2.56 (3H, s).

^1^C NMR (100.6 MHz, CDCl_3) δ_C = 162.4, 156.1, 140.0, 136.7, 130.0, 127.5, 120.5, 117.5, 90.1, 12.0.

HRMS found: [M]^+ 344.9626, C_{10}H_8N_3O_3 requires 344.9610.

(3-methyl-4-nitro-isoxazol-5-yl)-propyl-amine 2.138

![Chemical structure](image)

Yellow solid, 65 mg, 87% yield, R_f = 0.60 (EtOAc/Pet Ether 4:6).

^1^H NMR (400 MHz, CDCl_3) δ_H = 7.56 (1H, br s), 3.50 (2H, m), 2.46 (3H, s), 1.73 (2H, m), 1.01 (3H, t, J = 7.4 Hz).

^1^C NMR (100.6 MHz, CDCl_3) δ_C = 165.5, 156.3, 110.9, 44.6, 23.0, 12.0, 11.2.

HRMS found: [M]^+ 185.0795, C_7H_{11}N_3O_3 requires 185.0800.

(3-methyl-4-nitro-isoxazol-5-yl)-allyl-amine 2.139

![Chemical structure](image)

Brown solid, 72 mg, 97% yield, R_f = 0.61 (EtOAc/Pet Ether 4:6).
$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 7.64$ (1H, br s), 5.95-5.87 (1H, m), 5.35-5.27 (2H, m), 4.16-4.14 (2H, m), 2.46 (3H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_C = 165.3$, 156.4, 131.7, 118.8, 111.0, 45.0, 11.9.

HRMS found: [M]$^+$ 183.0637, C$_7$H$_9$N$_3$O$_3$ requires 183.0644.

(3-methyl-4-nitro-isoxazol-5-yl)-isopropyl-amine 2.140

![Chemical Structure](image)

Yellow solid, 74 mg, 99% yield, $R_f = 0.51$ (EtOAc/Pet Ether 4:6).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 7.40$ (1H, br s), 4.15-4.06 (1H, m), 2.45 (3H, s), 1.37 (6H, d, $J = 6.4$ Hz).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_C = 164.6$, 156.2, 110.7, 46.0, 23.0, 12.0.

HRMS found: [M]$^+$ 185.0806, C$_7$H$_{11}$N$_3$O$_3$ requires 185.0800.

(3-methyl-4-nitro-isoxazol-5-yl)-sec-butyl-amine 2.141

![Chemical Structure](image)

Yellow solid, 80 mg, 99% yield, $R_f = 0.52$ (EtOAc/Pet Ether 4:6).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 7.39$ (1H, br s), 3.92-3.86 (1H, m), 2.44 (3H, s), 1.66 (2H, m), 1.32 (3H, d, $J = 6.4$ Hz), 0.96 (3H, t, $J = 7.6$ Hz)

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_C = 164.9$, 156.2, 110.7, 51.5, 29.8, 20.7, 12.0, 10.3.

HRMS found: [M]$^+$ 199.0966, C$_8$H$_{13}$N$_3$O$_3$ requires 199.0957.
(3-methyl-4-nitro-isoxazol-5-yl)-cyclobutyl-amine 2.142

Brown solid, 79 mg, 99% yield, \( R_f = 0.51 \) (EtOAc Pet Ether 4:6).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta_H = 7.65 \) (1H, br s), 4.39-4.33 (1H, m), 2.48-2.44 (2H, m), 2.44 (3H, s), 2.20-2.10 (2H, m), 1.87-1.78 (2H, m).

\(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta_c = 164.2, 156.2, 110.7, 47.7, 31.1, 15.1, 12.0. \)

HRMS found: [M]\(^+\) 197.0810, \( C_8H_{11}N_3O_3 \) requires 197.0800.

(3-methyl-4-nitro-isoxazol-5-yl)-benzyl-amine 2.143

Orange solid, 90 mg, 95% yield, \( R_f = 0.26 \) (EtOAc/Pet Ether 3:7).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta_H = 7.80 \) (1H, br s), 7.40-7.34 (5H, m), 4.70 (2H, d, \( J = 6.4 \) Hz), 2.48 (3H, s).

\(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta_c = 165.2, 156.5, 135.5, 129.3, 128.7, 128.0, 111.1, 46.8, 12.0. \)

HRMS found: [M]\(^+\) 233.0798, \( C_{11}H_{11}N_3O_3 \) requires 233.0800.

(3-methyl-4-nitro-isoxazol-5-yl)-pyrrolidine 2.150

Brown oil, 79 mg, 99% yield, \( R_f = 0.29 \) (EtOAc/Pet Ether 3:7).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta_H = 3.79-3.76 \) (4H, m), 2.45 (3H, s), 2.05-2.01 (4H, m).
$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 162.7, 158.1, 112.1, 50.6, 25.5, 13.0$. 

HRMS found: [M]$^+$ 197.0809, C$_8$H$_{11}$N$_3$O$_3$ requires 197.0800.

(3-methyl-4-nitro-isoxazol-5-yl)-piperidine 2.151

Brown oil, 83 mg, 97% yield, $R_f$ = 0.29 (EtOAc/Pet Ether 3:7).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 3.61 - 3.60$ (4H, m), 2.41 (3H, s), 1.71 (6H, br s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 164.4, 158.4, 112.6, 49.7, 25.6, 23.7, 13.2$.

HRMS found: [M]$^+$ 251.0959, C$_9$H$_{13}$N$_3$O$_3$ requires 211.0957.

(3-methyl-4-nitro-isoxazol-5-yl)-morpholine 2.152

Brown solid, 85 mg, 98% yield, brown solid, $R_f$ = 0.26 (EtOAc/Pet Ether 3:7).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 3.85 - 3.83$ (4H, m), 3.75-3.72 (4H, m), 2.46 (3H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 164.5, 158.6, 113.4, 66.4, 48.6, 13.2$.

HRMS found: [M]$^+$ 213.0759, C$_8$H$_{11}$N$_3$O$_4$ requires 213.0750.

1-(3-methyl-4-nitro-isoxazol-5-yl)2,3-dihydro-$1H$-indole 2.153

Black solid, 81 mg, 81% yield, $R_f$ = 0.49 (EtOAc/Pet Ether 3:7)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 7.42 - 7.40$ (1H, m), 7.30-7.23 (2H, m), 7.14-7.10 (1H, m), 4.31 (2H, t, $J = 8.0$ Hz), 3.29 (2H, t, $J = 8.0$ Hz), 2.53 (3H, s).
Experimental Section Chapter 2

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c =$ 160.8, 157.7, 141.3, 132.1, 127.7, 125.5, 125.1, 115.6, 114.4, 52.8, 29.1, 12.8.

HRMS found: [M]$^+$ 245.0796, C$_{12}$H$_{11}$N$_3$O$_3$ requires 245.0800.

[1-(3-methyl-4-nitro-isoxazol-5-yl)-pyrrolidin-2-yl]-methanol 2.154

Brown oil, 90 mg, 97% yield, $R_f = 0.26$ (EtOAc/Pet Ether 4:6).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_h =$ 4.55-4.52 (1H, m), 3.95-3.92 (1H, m), 3.72-3.55 (3H, m), 2.81 (1H, br s), 2.38 (3H, s), 2.13-2.10 (3H, m), 1.94-1.91 (1H, m).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c =$ 162.6, 158.0, 112.5, 62.7, 62.3, 52.2, 27.7, 24.2, 12.9.

HRMS found: [M+H]$^+$ 228.0990, C$_9$H$_{14}$N$_3$O$_4$ requires 228.0984.

1-(3-methyl-4-nitro-isoxazol-5-yl)-pyrrolidine-2-carboxylic acid 2.155

Brown oil, 93 mg, 95% yield, $R_f = 0.11$ (EtOAc/Pet Ether 4:6).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_h =$ 9.35 (1H, br s), 5.13-5.12 (1H, m), 3.94-3.78 (2H, m), 2.41 (3H, s), 2.40-2.36 (1H, m), 2.29-2.24 (1H, m), 2.07-2.03 (2H, m).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c =$ 175.7, 162.5, 158.1, 112.6, 62.3, 51.3, 30.7, 23.3, 12.9.

HRMS found: [M]$^+$ 241.0702, C$_9$H$_{11}$N$_3$O$_5$ requires 241.0699.
Procedure for the preparation of (E)-N,N-diethyl-2-(3-methyl-4-nitroisoxazol-5-yl)-ethenamine 2.114

3-methyl-4-nitro-5-trichloromethylisoxazole 2.117 (100 mg, 0.407 mmol) was dissolved in THF (0.5 mL) in a test tube and triethylamine (114 µL, 0.611 mmol, 1.5 equiv.) was added. The tube was sealed; the solution brought to 50°C and stirred at this temperature for 4 hours. The reaction mixture was partitioned between H₂O (10 mL) and DCM (10 mL), the phases separated and the organic phase washed with H₂O (10 mL). The organic phase was anhydrified on Na₂SO₄, filtered and evaporated at reduced pressure. The crude was purified by column chromatography eluting with EtOAc:Pet Ether (2:8), to obtain the pure product 2.114.

Orange solid, 63 mg, 69% yield, Rf = 0.32 (EtOAc/Pet Ether 4:6).

1H NMR (400 MHz, CDCl₃) δH = 7.66 (1H, d, J = 13.2 Hz), 5.96 (1H, d, J = 13.2 Hz), 3.39 (4H, q, J = 7.2 Hz), 2.49 (3H, s), 1.29-1.25 (6H, m).

13C NMR (100.6 MHz, CDCl₃) δC = 170.4, 156.0, 150.2, 142.5, 81.9, 51.1, 43.0, 14.9, 12.4, 11.7.

HRMS found: [M+H]⁺ 226.1190, C₁₀H₁₆N₃O₃ requires 226.1192.

Procedure for the preparation of 3-methyl-4-nitro-5-dichloromethylisoxazole 2.172

3-methyl-4-nitro-5-trichloromethylisoxazole 2.117 (700 mg, 2.852 mmol) was dissolved in anhydrous THF (3 mL) in a Schlenk tube and cooled to -78 °C. Phenylmagnesium bromide 1M in THF was added dropwise (3.42 mL, 3.420 mmol, 1.2 equiv.). The solution was brought to room temperature and reacted for 1 hour. The reaction was then quenched with saturated ammonium chloride (30 mL). The mixture was extracted with DCM (3x30 mL) and the organic phase was anhydrified on Na₂SO₄, filtered and evaporated at reduced pressure. The crude was purified by column chromatography eluting with EtOAc:Pet Ether (1:99), to obtain the pure product 2.172.

Off white solid, 559 mg, 93% yield, Rf = 0.45 (EtOAc/Pet Ether 2:8).
1H NMR (400 MHz, CDCl3) δH = 7.38 (1H, s), 2.61 (3H, s).

13C NMR (100.6 MHz, CDCl3) δc = 165.9, 156.2, 128.4, 57.7, 11.7.

HRMS found: [M]+ 209.9604, C8H4Cl2N2O3 requires 209.9599.

**Procedure for the preparation of 3-methyl-4-nitro-5-dichloromethylisoxazole 2.174**

![Chemical structure](image)

3-methyl-4-nitro-5-trichloromethylisoxazole 2.117 (100 mg, 0.407 mmol) was dissolved in anhydrous THF (1 mL) in a Schlenk tube and cooled to -78 °C. Phenylethynylmagnesium bromide 1M in THF was added dropwise (1.22 mL, 1.22 mmol, 3.0 equiv.). The solution was brought to room temperature and reacted for 48 hours. The reaction was then quenched with saturated ammonium chloride (5 mL). The mixture was extracted with DCM (3x10 mL) and the organic phase was anhydrified on Na2SO4, filtered and evaporated at reduced pressure. The crude was purified by column chromatography eluting with EtOAc:Pet Ether (5:95), to obtain the pure product 2.174.

Brown solid, 69 mg, 62% yield, Rf = 0.37 (EtOAc/Pet Ether 2:8).

1H NMR (400 MHz, CDCl3) δH = 7.48-7.46 (2H, m), 7.41-7.39 (1H, m), 7.36-7.32 (2H, m), 6.08 (1H, s), 2.19 (3H, s).

13C NMR (100.6 MHz, CDCl3) δc = 149.7, 132.4, 130.4, 128.6, 119.9, 99.7, 99.1, 94.3, 93.6, 31.1, 11.8.

HRMS found: [M+H]+ 277.0391, C13H10ClN2O3 requires 277.0380.
Experimental Section Chapter 3

Dimethyl-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amine 3.75

\[
\begin{align*}
\text{NO}_2 & \quad \text{N} \\
\text{O} & \quad \text{N}
\end{align*}
\]

To a solution of 3,5-dimethyl-4-nitroisoxazole (8.0 g, MW 142, 0.060 mol) in dry DMF (30 mL) was added diethoxymethyldimethylamine (12.4 mL, 0.070 mol, 1.15 equiv.) and the resulting reaction mixture was refluxed for 20 hours. The dark reaction mixture so obtained was allowed to reach room temperature and the solvent removed under reduced pressure to give pure dimethyl-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amine 3.75, without need of further purification.

Yellow-green solid, 7.93 g, 92% yield, \( R_f = 0.2 \) (EtOAc:Hexane 1:1).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.65 \) (1H, d, \( J = 12.8 \) Hz), 5.86 (1H, d, \( J = 12.8 \) Hz), 3.20 (3H, br s), 2.98 (3H, br s), 2.47 (3H, s).

\(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta_c = 170.2, 155.8, 152.0, 122.1, 82.1, 45.6, 37.3, 12.3. \)

HRMS found: [M+H]+ 198.0872, C\(_8\)H\(_{12}\)N\(_3\)O\(_3\) requires 198.0879.

General procedure for the preparation of compounds 3.91-3.95

To a solution of dimethyl-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amine 3.75 (543 mg, 3.0 mmol) in toluene (3 mL), amine 3.86-3.90 (5.0 equiv.) was added and the reaction mixture refluxed for 5 hours. The solvent was removed under reduced pressure to obtain compounds 3.91-3.95 without need of further purification.

3-Methyl-4-nitro-5-(2-pyrrolidin-1-yl-vinyl)-isoxazole 3.91.

\[
\begin{align*}
\text{NO}_2 & \quad \text{N} \\
\text{O} & \quad \text{N}
\end{align*}
\]

Orange solid, 636 mg, 95% yield, \( R_f = 0.6 \) (EtOAc:Hexane 1:1).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.82 \) (1H, d, \( J = 12.8 \) Hz), 5.75 (1H, d, \( J = 12.8 \) Hz), 3.57-3.54 (2H, m), 3.32-3.29 (2H, m), 2.42 (3H, s), 2.04-1.99 (2H, m), 1.96-1.91 (2H, m).
$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c$ = 168.9, 154.7, 146.9, 120.8, 82.05, 51.9, 46.2, 24.2, 23.4, 11.2.

HRMS found: [M+H]$^+$ 224.1024, C$_{10}$H$_{14}$N$_3$O$_3$ requires 224.1035.

1-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-vinyl]-piperidine 3.92

Orange solid, 703 mg, 99% yield, $R_f$ = 0.6 (EtOAc:Hexane 1:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ = 7.62 (1H, d, $J$ = 13.3 Hz), 6.00 (1H, d, $J$ = 13.3 Hz), 3.42 (4H, br s), 2.48 (3H, s), 1.71 (6H, br s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c$ = 169.7, 155.9, 150.7, 122.0, 81.4, 55.7, 46.2, 26.6, 25.0, 24.0, 12.4.

HRMS found: [M+H]$^+$ 238.1185, C$_{11}$H$_{16}$N$_3$O$_3$ requires 238.1192.

1-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-vinyl]-azepane 3.93

Yellow solid, 723 mg, 96% yield, $R_f$ = 0.4 (EtOAc:Hexane 1:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ = 7.70 (1H, d, $J$ = 13.2 Hz), 5.90 (1H, d, $J$ = 13.2 Hz), 3.52-3.49 (2H, m), 3.43-3.40 (2H, m), 2.47 (3H, s), 1.86-1.83 (2H, m), 1.77-1.76 (2H, m), 1.62-1.57 (4H, m).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c$ = 170.3, 155.9, 151.5, 121.9, 81.5, 56.7, 48.9, 30.2, 27.9, 26.9, 25.5, 12.3.

HRMS found: [M+H] 252.1337, C$_{12}$H$_{18}$N$_3$O$_3$ requires 252.1348.
1-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-vinyl]azocane 3.94

Yellow solid, 740 mg, 93% yield, $R_f = 0.6$ (EtOAc:Hexane 1:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$H = 7.64 (1H, d, $J = 13.2$ Hz), 5.90 (1H, d, $J = 13.2$ Hz), 3.43-3.39 (4H, m), 2.43 (3H, s), 1.81-1.72 (4H, m), 1.59-1.52 (6H, m).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$C = 170.1, 155.9, 151.0, 121.24, 82.3, 57.7, 48.8, 27.4, 26.1, 25.8, 25.0, 24.6, 12.3.

HRMS found: [M+H]$^+$ 266.1512, C$_{13}$H$_{20}$N$_3$O$_3$ requires 266.1505.

4-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-vinyl]-morpholine 3.95

Green solid, 688 mg, 96% yield, $R_f = 0.3$ (EtOAc:Hexane 1:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$H = 7.53 (1H, d, $J = 13.2$ Hz), 5.96 (1H, d, $J = 13.2$ Hz), 3.74-3.72 (4H, m), 3.42-3.40 (4H, m), 2.43 (3H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$C = 169.1, 154.8, 148.9, 121.0, 81.0, 65.6, 65.2, 46.2, 40.0, 10.8.

HRMS found: [M+H]$^+$ 240.0974, C$_{10}$H$_{14}$N$_3$O$_4$ requires 240.0984.

**General procedure for the reaction of selected enamines with DEAD or DIAD**

To a solution of enamine 3.75-3.91-3.92 (0.400 mmol) in acetonitrile (2 mL) was added DEAD (146 mg, 0.840 mmol, 2.1 equiv.) and the resulting solution was refluxed for 24 hours. The solvent was evaporated and the product purified by column chromatography using EtOAc: Pet Ether (1:9) to obtain desired product as a one to one mixture of (E/Z)-diastereoisomers.
(E/Z)-2-((N'-N''-hydrazinedicarboxylic acid ethyl ester)-2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-dimethyl-amine 3.98

Yellow liquid, 110 mg, 75% yield, R_f = 0.4 (EtOAc:Pet Ether 3:1).

\(^1\)H NMR (400 MHz, CDCl_3) \(\delta_H = 8.14-8.02\) (1H, m), 6.96 (1H, br s), 4.23-4.09 (4H, m), 3.37 (6H, br s), 2.48 (3H, s), 1.28-1.23 (6H, m).

\(^{13}\)C NMR (100.6 MHz, CDCl_3) \(\delta_c = 168.1, 157.5, 156.2, 155.8, 149.0, 148.6, 129.7, 123.3, 99.7, 63.7, 62.6, 61.9, 48.6, 38.3, 14.4, 14.2, 12.8.

HRMS found: [M+H]^+ 372.1509, C_{14}H_{22}N_{5}O_{7} requires 372.1519.

(E/Z)-2-((N'-N''-hydrazinedicarboxylic acid ethyl ester)-2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-pyrrolidine 3.99

Yellow liquid, 140 mg, 88% yield, R_f = 0.6 (EtOAc:Pet Ether 3:1).

\(^1\)H NMR (400 MHz, CDCl_3) \(\delta_H = 8.39-8.28\) (1H, m), 6.96-6.93 (1H, m), 4.76 (1H, br s), 4.27-4.06 (4H, m), 3.63 (2H, br s), 3.41-3.39 (1H, m), 2.42 (3H, s), 1.98-1.73 (4H, m), 1.28-1.21 (6H, m).

\(^{13}\)C NMR (100.6 MHz, CDCl_3) \(\delta_c = 167.8, 157.9, 157.6, 155.7, 146.5, 145.9, 123.1, 100.0, 64.2, 64.1, 63.8, 63.5, 62.3, 61.9, 56.1, 47.7, 26.3, 24.1, 14.7, 14.4, 14.1, 14.0, 13.0.

HRMS found: [M+H]^+ 398.1665, C_{16}H_{24}N_{5}O_{7} requires 398.1676.
(E/Z)-2-\(N'\text{-}N''\)-hydrazinedicarboxylic acid ethyl ester)-2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-piperidine 3.100

Orange oil, 146 mg, 89% yield, \(R_f = 0.5\) (EtOAc:Pet Ether 3:1).

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta_H = 8.08\text{-}7.93\) (1H, m), 6.96 (1H, br s), 4.22\text{-}4.12 (4H, m), 3.74 (4H, br s), 2.46 (3H, s), 1.70 (6H, br s), 1.25\text{-}1.22 (6H, m).

\(^{13}C\) NMR (100.6 MHz, CDCl\(_3\)) \(\delta_c = 168.4\), 157.6, 156.6, 146.9, 123.4, 98.9, 63.7, 62.0, 26.6, 23.9, 14.5, 13.0.

HRMS found: [M+H]\(^+\) 412.1815, C\(_{17}\)H\(_{26}\)N\(_5\)O\(_7\) requires 412.1832.

(E/Z)-2-\(N'\text{-}N''\)-hydrazinedicarboxylic acid isopropyl ester)-2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-dimethylamine 3.101

Yellow liquid, 147 mg, 92% yield, \(R_f = 0.3\) (EtOAc:Pet Ether 3:1).

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta_H = 8.02\text{-}7.93\) (1H, m), 6.85\text{-}6.80 (1H, m), 4.96\text{-}4.84 (2H, m), 3.39\text{-}3.15 (6H, m), 2.42 (3H, s), 1.21\text{-}1.18 (12H, m).

\(^{13}C\) NMR (100.6 MHz, CDCl\(_3\)) \(\delta_c = 168.2\), 157.5, 156.8, 156.0, 155.8, 151.9, 148.9, 148.5, 123.9, 99.7, 71.6, 69.9, 49.0, 38.7, 22.0, 21.9, 12.9.

HRMS found: [M+H] 400.1831, C\(_{16}\)H\(_{28}\)N\(_5\)O\(_7\) requires 400.1832.

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(E/Z)-2-([N'-N"-hydrazinedicarboxylic acid isopropyl ester]-2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-piperidine 3.102

Yellow liquid, 156 mg, 89% yield, R\text{f} = 0.6 (EtOAc:Pet Ether 3:1).

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta_H = 8.04\text{-}7.88 (1H, m), 6.81\text{-}6.74 (1H, m), 4.94, 4.86 (2H, m), 4.32\text{-}3.69 (4H, br s), 2.42 (3H, s), 1.67\text{-}1.58 (6H, m), 1.21\text{-}1.19 (12H, m).

\(^{13}\)C NMR (100.6 MHz, CDCl\textsubscript{3}) \(\delta_c = 169.7, 157.6, 155.7, 146.9, 119.1, 99.9, 71.5, 70.1, 69.8, 26.6, 23.9, 22.0, 21.9, 13.0.

HRMS found: [M+H]\(^+\) 440.2134, C\textsubscript{19}H\textsubscript{30}N\textsubscript{5}O\textsubscript{7} requires 440.2145.

General procedure for the reaction of enamine 3.75 and 3.92 with acyl chlorides

To a solution of enamine (0.400 mmol) in anhydrous DMF (0.6 mL) under argon atmosphere, was added DMAP (0.600 mmol, 1.5 equiv.) and the mixture was stirred until complete dissolution. An opportune acyl chloride (3.0 equiv.) was added dropwise and the reaction mixture heated at 75 °C for 18 hours. The reaction mixture was then allowed to reach room temperature, diluted with DCM (5 mL) and quenched with saturated sodium bicarbonate (7 mL). The organic layer was separated and the aqueous layer further extracted with DCM (3 x 5 mL). The combined organic phases were anhydried on sodium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography eluting with EtOAc:Pet Ether (1:9) to obtain the desired product.

(E)-2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-piperidin-1-yl-pent-1-en-3-one 3.103

![Chemical structure image]
Orange solid, 83 mg, 71% yield, $R_f = 0.5$ (EtOAc:Pet Ether 2:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 7.87$ (1H, s), 3.20 (4H, br s), 2.60 (3H, s), 2.29 (2H, q, $J = 7.2$ Hz), 1.68-1.61 (6H, m), 1.04 (3H, t, $J = 7.2$ Hz).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 195.5$, 170.3, 156.3, 154.6, 130.5, 92.8, 56.0, 49.5, 32.4, 25.8, 23.3, 12.4, 9.2.

HRMS found: [M+H$^+$] 294.1431, C$_{14}$H$_{20}$N$_3$O$_4$ requires 294.1454.

(E)-3-(3-Methyl-4-nitro-isoxazol-5-yl)-4-piperidin-1-yl-but-3-en-2-one 3.104

Orange solid, 62 mg, 55% yield, $R_f = 0.5$ (EtOAc:Pet Ether 2:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 7.87$ (1H, s), 3.53 (2H, br s), 2.77 (2H, br s), 2.60 (3H, s), 2.05 (3H, s), 1.60 (6H, br s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 192.1$, 170.0, 156.2, 154.8, 130.2, 93.3, 57.5, 48.1, 27.0, 26.5, 23.1, 12.3.

HRMS found: [M+H$^+$] 280.1291, C$_{13}$H$_{18}$N$_3$O$_4$ requires 280.1297.

(E)-2-(3-Methyl-4-nitro-isoxazol-5-yl)-dimethylamino-pent-1-en-3-one 3.105

Orange solid, 71 mg, 70% yield, $R_f = 0.4$ (EtOAc:Pet Ether 2:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 7.84$ (1H, s), 3.23 (3H, br s), 2.55 (3H, s), 2.50 (3H, br s), 2.27 (2H, q, $J = 7.2$ Hz), 0.99 (3H, t, $J = 7.2$ Hz).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 195.1$, 169.7, 156.1, 155.4, 131.1, 93.9, 47.4, 39.5, 32.2, 12.2, 9.0.
HRMS found: $[M+H]^+ 254.1133$, C$_{11}$H$_{16}$N$_3$O$_4$ requires 254.1141.

1-(3-methyl-4-nitro-isoxazol-5-yl)butan-2-one 3.110

![Chemical Structure]

To a solution of enamine 3.105 (0.256 mmol) in THF (1.5 mL) was added dropwise HCl 1N (1.3 mL) and heated at 60°C for 0.5 hours. The reaction mixture was cooled to room temperature and extracted three times with EtOAc. The combined organic phases were anhydrified on sodium sulphate, filtered and evaporated at reduced pressure to obtain pure product without need of further purification.

Brown solid, 36 mg, 71% yield, $R_f = 0.5$ (EtOAc:Pet Ether 2:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 4.30$ (2H, s), 2.66 (2H, q, $J = 7.2$ Hz), 2.57 (3H, s), 1.13 (3H, t, $J = 7.2$ Hz).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 201.4$, 168.6, 155.8, 131.2, 41.1, 36.7, 11.7, 7.6.

HRMS found: $[M+H]^+ 199.0725$, C$_8$H$_{11}$N$_2$O$_4$ requires 199.0719.

3-methyl-4-nitro-5-chloromethylisoxazole 3.114

![Chemical Structure]

To a solution of 3.75 (400 mg, 2.030 mmol) in DCM (3 mL), was added N-chlorosuccinimide (270 mg, 2.030 mmol, 1.0 equiv.) portion wise and the resulting solution stirred for two hours at room temperature. Then, silica (2.5 g) and HCl 1M (0.25 mL) were consecutively added and the solvent was evaporated under reduced pressure. The mixture was kept for two hours at 45 °C in the rotary evaporator and purified by column chromatography eluting with EtOAc:Pet Ether (1:9) to give compound 3.75.

Pale brown oil, 337 mg, 94% yield, $R_f = 0.6$ (EtOAc:Pet Ether 2:8).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 4.97$ (2H, s), 2.59 (3H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 168.1$, 156.1, 130.0, 33.31, 11.7.
HRMS found: [M]$^+$ 175.9997, C$_5$H$_5$ClN$_2$O$_3$ requires 175.9989.
Experimental Section Chapter 4.

Preparation of trans, meso-1,2,3-tris(3-methyl-4-nitroisoxazol-5-yl)cyclopropane 4.165.

To a solution of 4.161 (200 mg, 1.133 mmol) in EtOH (3.5 mL) was added triethylamine (394 μL, 2.83 mmol, 2.5 equiv.) and the mixture was heated at 50 °C for 2 hours. DCM (20 mL and HCl 1M (10 mL) were added and the mixture was extracted with DCM (3 x 20 mL). the combined organic layers were anhydrified on sodium sulphate, filtered and evaporated at reduced pressure. The crude residue was purified by column chromatography on silica gel eluting with EtOAc/Pet Ether (2:8) to give product 4.165.

Brown oil, 62 mg, 13% yield, R_f = 0.27 (EtOAc/Pet Ether 3:7).

^1H NMR (400 MHz, CDCl_3) δ_H = 4.62 (1H, t, J = 6.8 Hz), 4.26 (2H, d, J = 6.8 Hz), 2.62 (3H, s), 2.56 (6 H, s).

^13C NMR (100.6 MHz, CDCl_3) δ_c =167.2, 165.9, 156.7, 156.4, 25.9, 23.0, 11.7, 11.7.

HRMS found: [M+H]^+ 421.0735, C_{15}H_{13}N_{6}O_{9} requires 421.0744.

General procedure for the organocatalyzed synthesis of 2-chloro-2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethanol 4.164.

In a round bottomed test tube was prepared a solution of 4.161 (44 mg, 0.25 mmol) in THF (0.5 mL). Then the bifunctional organocatalyst 4.12 (21 mg, 0.05 mmol, 0.2 equiv.) and benzaldehyde (127 μL, 1.25 mmol, 5.0 equiv.) were added. The test tube was sealed and the reaction mixture stirred for 120 hours at room temperature. Saturated ammonium chloride (3 mL) was added and the reaction mixture was extracted with DCM (3 x 10 mL). The combined organic layers were anhydrified on sodium sulfate, filtered and evaporated...
at reduced pressure. The crude mixture was purified by column chromatography on silica gel eluting with EtOAc/Pet Ether (1:9) to obtain halohydrin 4.164 as a 1:1 mixture of diastereoisomers.

Off white solid, 66 mg, 93% yield $R_f = 0.23$ (DCM/Pet Ether 4:6).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 7.45-7.38$ (5H, m), 7.32-7.28 (5H, m), 5.94-5.88 (2H, m), 5.30-5.27 (2H, m), 3.01-3.00 (1H, m), 2.59 (3H, s), 2.58-2.57 (1H, m), 2.46 (3H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_C = 168.7$, 167.9, 155.9, 155.7, 138.5, 137.2, 130.8, 129.6, 129.0, 128.7, 126.9, 126.6, 76.2, 75.9, 56.2, 53.1, 11.8, 11.6.

HRMS found: [M+H]$^+$ 283.0489, C$_{12}$H$_{12}$ClN$_2$O$_4$ requires 283.0486.

**General procedure for the phase-transfer catalyzed Darzens reaction for the preparation of 3-methyl-4-nitro-5-((2R,3S)-3-phenyloxiran-2-yl)isoxazole 4.168.**

![Image of the compound](image)

A solution of 4.161 (44 mg, 0.25 mmol) in toluene (1 mL) was prepared in around bottomed test tube. Then quaternary ammonium salt 4.177 (32 mg, 0.05 mmol, 0.2 equiv.) was added followed by benzaldehyde (127 $\mu$L, 1.25 mmol, 5.0 equiv.). The mixture was stirred for 10 minutes and then potassium phosphate tribasic (265 mg, 1.25 mmol, 5.0 equiv.) was added. The test tube was sealed and the reaction mixture stirred for 10 days at room temperature. The reaction was quenched with HCl 1M (3 mL) and the reaction mixture was extracted with DCM (3 x 10 mL). The combined organic layers were anhydrided on sodium sulfate, filtered and evaporated at reduced pressure. The crude mixture was purified by column chromatography eluting with DCM/Pet Ether (8:2) to obtain epoxide (2R,3S)-4.168 as the only trans-isomer ($cis/trans = 1:99$).

White solid, 51 mg, 83% yield $R_f = 0.35$ (DCM/Pet Ether 4:6).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 7.43-7.37$ (5H, m), 4.73 (1H, d, $J = 1.7$ Hz), 4.47 (1H, d, $J = 1.7$ Hz), 2.60 (3H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_C = 168.3$, 156.1, 134.3, 129.6, 129.0, 128.6, 126.0, 61.1, 53.4, 11.6.

HRMS found: [M+H]$^+$ 247.0725, C$_{12}$H$_{11}$N$_2$O$_4$ requires 247.0719.
The ee of the product was determined by CSP-HPLC using a Chiralpak AS column (n-Hexane/EtOH 99:1, flow rate 0.5 mL/min, t_{min} = 19.91 min, t_{maj} = 21.05 min, 27% ee. [α]_D^20 = -12 (c 2.0, CHCl₃).


![Chemical structure](image)

In a 10 mL round bottom flask compound **4.168** (25 mg, 0.1 mmol) was dissolved in a THF/acetone mixture (1 mL + 1 mL). A solution of potassium permangate (95 mg, 0.6 mmol, 6.0 equiv.) in water (3 mL) was added dropwise and the resulting mixture was stirred for 3 hours covered from light. The permanganate excess was quenched with Na₂SO₃ saturated solution (8 mL) followed by acidification to pH = 3 with HCl 3M. The solution was extracted with DCM (3 x 10 mL) and the combined organic layers were evaporated at reduced pressure to 1 mL volume. Then MeOH (0.2 mL) and Et₂O (1 mL) were added, followed by TMS-diazomethane (150 μL, 0.3 mmol, 3.0 equiv.) dropwise and the solution stirred for 30 minutes at room temperature. The solvent was evaporated under reduced pressure to obtain the ester **4.180** without need of further purification.

White solid, R_F = 0.17 (DCM/Pet Ether 4:6).

^1H NMR (400 MHz, CDCl₃) δ_H = 7.40-7.34 (3H, m), 7.30-7.28 (2H, m) 4.10 (1H, d, J = 1.7 Hz), 3.83 (3H, s), 3.52 (1H, d, J = 1.7 Hz).

^13C NMR (100.6 MHz, CDCl₃) δ_c = 168.8, 135.0, 129.2, 128.8, 126.0, 58.1, 56.8, 52.8.

HRMS found: [M+H]⁺ 179.0714, C₁₀H₁₁O₃ requires 179.0708.
Experimental Section Chapter 5

Procedure for the preparation of tert-butyl 2-methyl-3-nitro-1H-indole-1-carboxylate 5.73

For generating acetyl nitrate, a solution of 70% nitric acid (0.71 mL, 11.28 mmol, 3.0 equiv.) was added dropwise to a cooled solution (0°C) of acetic anhydride (7.46 mL, 78.90 mmol, 21.0 equiv.) under nitrogen atmosphere. After the addition, the solution was stirred for 15 minutes at room temperature and used immediately after that time.

A solution of tert-butyl 2-methyl-1H-indole-1-carboxylate 5.70 (870 mg, 3.76 mmol) in acetic anhydride (18.8 mL) was prepared under nitrogen atmosphere and cooled to -70°C. The preformed acetyl nitrate was added dropwise to the solution of 5.70 at -70°C over 30 minutes and the mixture was stirred at this temperature for 1.5 hours. The reaction mixture was poured into 20 g of ice and stirred for 1 hour, cooling with an ice bath. The precipitate formed was filtered and washed several times with H2O. The filtrate was extracted with EtOAc (3 x 40 mL). The combined organic phases were washed with brine (2 x 50 mL), dried over Na2SO4 and concentrated at reduced pressure. The combined solids were purified by column chromatography eluting with EtOAc:Pet Ether (5:95) to give the product 5.73.

White solid, 892 mg, 86% yield, Rf = 0.58 (EtOAc/PetEt 2:8).

1H NMR (400 MHz, CDCl3) δH = 8.24-8.21 (1H, m), 8.07-8.05 (1H, m), 7.40-7.37 (2H, m), 3.06 (3H, s), 1.73 (9H, s).

13C NMR (100.6 MHz, CDCl3) δc = 149.3, 142.3, 133.8, 131.5, 125.9, 125.2, 121.8, 120.5, 115.1, 86.8, 28.2, 15.2.

HRMS found: [M+H]+ 277.1192, C14H17N2O4 requires 277.1188.
Procedure for the preparation of compound 5.67

![Chemical Structure](image)

To a solution of 5.73 (1.0 g, 3.62 mmol) in DCM (60 mL) was added dropwise TFA (4.7 mL, 61.52 mmol, 17.0 equiv.) and the mixture was stirred at room temperature for 18 hours. The solution was evaporated and the residue was purified by column chromatography eluting with EtOAc/Hexane (7:3) to obtain the product 5.67.

Brown solid, 555 mg, 87% yield, R$_f$ = 0.25 (EtOAc/Hexane 6:4).

$^1$H NMR (400 MHz, DMSO) $\delta$H = 12.62 (1H, br s), 8.04-8.02 (1H, m), 7.47-7.45 (1H, m), 7.32-7.26 (2H, m), 2.75 (3H, s)

$^{13}$C NMR (100.6 MHz, DMSO) $\delta$C = 143.8, 133.1, 125.5, 124.1, 123.6, 121.4, 119.6, 112.5, 14.8.

HRMS found: [M+H]$^+$ 177.0663, C$_9$H$_9$N$_2$O$_2$ requires 177.0664.

General procedure for the preparation of compounds 5.77 and 5.90-5.97

To a solution of tert-butyl 2-methyl-3-nitro-1H-indole-1-carboxylate 5.73 (138 mg, 0.50 mmol) in chloroform (1 mL), aldehyde (1.00 mmol, 2.0 equiv.) and piperidine (24.7 $\mu$L, 0.25 mmol, 0.5 equiv.) were added and the reaction mixture heated at 70 °C for 72 hours. The reaction mixture was allowed to cool to room temperature, then the precipitate was filtered under vacuum and washed with cold chloroform. The product did not require any further purification

**(E)-3-nitro-2-styryl-1H-indole 5.77**

![Chemical Structure](image)

Yellow solid, 123 mg, 93% yield, R$_f$ = 0.16 (EtOAc/Pet Ether 8:2).

$^1$H NMR (400 MHz, DMSO) $\delta$H = 12.87 (1H, br s), 8.12-8.10 (1H, m), 8.03 (1H, d, J = 16.4 Hz), 7.74-7.68 (3H, m), 7.54-7.33 (6H, m).
\(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta_c = 139.4, 137.1, 135.5, 134.5, 129.7, 129.2, 127.4, 125.1, 125.0, 123.6, 121.4, 120.0, 115.9, 112.5\).

HRMS found: [M+H]\(^+\) 265.0983, C\(_{16}\)H\(_{13}\)N\(_2\)O\(_2\) requires 265.0977.

\((E)-2-(4\text{-fluorostyryl})-3\text{-nitro-1H-indole 5.90}\)

Orange solid, 96 mg, 68% yield, \(R_f = 0.18\) (EtOAc/Pet Ether 8:2).

\(^1\)H NMR (400 MHz, DMSO) \(\delta_H = 12.80\) (1H, br s), 8.11-8.09 (1H, m), 7.95 (1H, d, \(J = 16.8\) Hz), 7.75-7.71 (2H, m), 7.68 (1H, d, \(J = 16.8\) Hz), 7.53-7.51 (1H, m), 7.36-7.28 (4H, m).

\(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta_c = 139.4, 136.2, 134.5, 132.2, 129.8, 125.5, 125.2, 124.0, 121.5, 120.3, 116.6, 116.4, 115.8, 112.6\).

HRMS found: [M+H]\(^+\) 283.0880, C\(_{16}\)H\(_{12}\)F\(_2\)N\(_2\)O\(_2\) requires 283.0883.

\((E)-2-(4\text{-chlorostyryl})-3\text{-nitro-1H-indole 5.91}\)

Yellow solid, 131 mg, 88% yield, \(R_f = 0.18\) (EtOAc/Pet Ether 8:2).

\(^1\)H NMR (400 MHz, DMSO) \(\delta_H = 12.77\) (1H, br s), 8.10-8.08 (1H, m), 7.98 (1H, d, \(J = 16.8\) Hz), 7.68-7.62 (3H, m), 7.52-7.49 (3H, m), 7.36-7.28 (2H, m).

\(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta_c = 139.1, 135.8, 134.5, 134.5, 134.3, 129.4, 129.2, 125.5, 124.0, 123.6, 121.5, 120.3, 116.6, 112.6\).

HRMS found: [M+H]\(^+\) 299.0588, C\(_{16}\)H\(_{12}\)Cl\(_2\)N\(_2\)O\(_2\) requires 299.0587.
(E)-2-(4-bromostyryl)-3-nitro-1H-indole 5.92

Orange solid, 156 mg, 91% yield, \( R_f = 0.17 \) (EtOAc/Pet Ether 8:2).

\(^1\)H NMR (400 MHz, DMSO) \( \delta_H = 12.78 \) (1H, br s), 8.12-8.10 (1H, m), 8.04 (d, \( J = 16.8 \) Hz), 7.69-7.63 (5H, m), 7.55-7.53 (1H, m), 7.38-7.34 (4H, m).

\(^{13}\)C NMR (100.6 MHz, DMSO) \( \delta_c = 138.9, 135.7, 134.7, 134.3, 132.2, 129.3, 125.2, 125.1, 123.7, 122.8, 121.3, 120.0, 116.6, 112.4. \)

HRMS found: \([M+H]^+\) 343.0092, C\(_{16}\)H\(_{12}\)BrN\(_2\)O\(_2\) requires 343.0082.

(E)-2-(4-methoxystyryl)-3-nitro-1H-indole 5.93

Yellow solid, 96 mg, 65% yield, \( R_f = 0.14 \) (EtOAc/Pet Ether 8:2).

\(^1\)H NMR (400 MHz, DMSO) \( \delta_H = 12.77 \) (1H, br s), 8.12-8.09 (1H, m), 7.90 (1H, d, \( J = 16.4 \) Hz), 7.71-7.64 (3H, m), 7.52-7.50 (1H, m), 7.38-7.30 (2H, m), 7.07-7.05 (2H, m), 3.83 (3H, s).

\(^{13}\)C NMR (100.6 MHz, DMSO) \( \delta_c = 160.9, 140.2, 137.4, 134.4, 129.4, 128.3, 125.3, 124.8, 123.8, 121.6, 120.2, 114.9, 113.4, 112.4, 55.6. \)

HRMS found: \([M+H]^+\) 295.1078, C\(_{17}\)H\(_{15}\)N\(_2\)O\(_3\) requires 295.1083.
(E)-3-nitro-2-(3-nitrostyryl)-1H-indole 5.94

![Chemical structure](image)

Orange solid, 122 mg, 79% yield, \( R_f = 0.15 \) (EtOAc/Pet Ether 8:2).

\(^1\)H NMR (400 MHz, DMSO) \( \delta \) = 12.78 (1H, br s), 8.31-8.03 (5H, m), 7.71-7.65 (2H, m), 7.51-7.48 (1H, m), 7.36-7.29 (2H, m).

\(^13\)C NMR (100.6 MHz, DMSO) \( \delta_c \) = 148.4, 138.0, 137.2, 134.4, 134.3, 133.2, 130.7, 125.5, 125.3, 123.8, 123.7, 121.5, 121.2, 120.0, 118.5, 112.4.

HRMS found: [M+H]^+ 310.0830, C\(_{16}\)H\(_{12}\)N\(_3\)O\(_4\) requires 310.0828.

(E)-2-(3-chlorostyryl)-3-nitro-1H-indole 5.95

![Chemical structure](image)

Dark yellow solid, 124 mg, 83% yield, \( R_f = 0.18 \) (EtOAc/Pet Ether 8:2).

\(^1\)H NMR (400 MHz, DMSO) \( \delta \) = 12.83 (1H, br s), 8.10-8.08 (1H, m), 8.00 (1H, d, \( J = 16.4 \) Hz), 7.68-7.59 (3H, m), 7.52-7.46 (3H, m), 7.38-7.30 (2H, m).

\(^13\)C NMR (100.6 MHz, DMSO) \( \delta_c \) = 138.8, 137.9, 135.6, 134.5, 134.1, 131.3, 129.5, 127.0, 126.2, 125.6, 125.5, 124.1, 121.4, 120.3, 117.6, 112.7.

HRMS found: [M+H]^+ 299.0584, C\(_{16}\)H\(_{12}\)ClN\(_2\)O\(_2\) requires 299.0587.

(E)-2-(2,6-dichlorostyryl)-3-nitro-1H-indole 5.96

![Chemical structure](image)

Yellow solid, 125 mg, 75% yield, \( R_f = 0.20 \) (EtOAc/Pet Ether 8:2).
1H NMR (400 MHz, DMSO) $\delta_H = 13.08$ (1H, br s), 8.15-8.10 (2H, m), 7.71 (1H, d, $J = 16.8$ Hz), 7.63-7.57 (3H, m), 7.44-7.35 (3H, m).

$^{13}$C NMR (100.6 MHz, DMSO) $\delta_c = 137.5$, 134.6, 134.0, 132.6, 130.9, 130.2, 129.6, 125.9, 125.8, 124.5, 124.3, 121.3, 120.4, 112.9.

HRMS found: [M+H]$^+$ 333.0201, C$_{16}$H$_{11}$Cl$_2$N$_2$O$_2$ requires 333.0198.

**(E)-3-nitro-2-(2-(pyridin-2-yl)vinyl)-1H-indole 5.97**

![Chemical Structure](image)

Brown solid, 101 mg, 76% yield, $R_f = 0.12$ (EtOAc/Pet Ether 8:2).

1H NMR (400 MHz, DMSO) $\delta_H = 12.91$ (1H, br s), 8.70-8.68 (1H, m), 8.50 (1H, d, $J = 16.0$ Hz), 8.12-8.10 (1H, m), 7.87-7.85 (1H, m), 7.72 (1H, d, $J = 16.0$ Hz), 7.60-7.52 (2H, m), 7.39-7.31 (3H, m).

$^{13}$C NMR (100.6 MHz, DMSO) $\delta_c = 153.4$, 150.3, 138.5, 137.6, 136.1, 134.6, 125.9, 125.6, 124.3, 124.2, 124.0, 121.5, 120.3, 119.2, 112.7.

HRMS found: [M+H]$^+$ 266.0938, C$_{15}$H$_{12}$N$_3$O$_2$ requires 266.0930.

**Procedure for the preparation of compounds 5.107 and 5.108**

To a suspension of **5.77** (100 mg, 0.38 mmol) in toluene (1 mL) was added K$_2$CO$_3$ (261 mg, 1.89 mmol, 5.0 equiv.), N-benzylcinchonidinium bromide (35 mg, 0.076 mmol, 0.2 equiv.) and dimethylmalonate (216 $\mu$L, 1.89 mmol, 5.0 equiv.). The resulting mixture was stirred at 70 °C for 72 hours. The suspension was diluted with water (5 mL) and extracted with DCM (3 x 10 mL). The combined organic phases were anhydried of sodium sulphate, filtered and evaporated at reduced pressure. The crude was purified by column chromatography eluting with DCM/Pet Ether (6:4) to obtain the products **5.107** and **5.108**.
Methyl 4-(3-nitro-1H-indol-2-yl)-3-phenylbutanoate 5.107

Red oil, 35 mg, 27% yield, R_f = 0.19 (DCM/Pet Ether 7:3).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_H = 9.12\) (1H, br s), 8.20-8.18 (1H, m), 7.28-7.12 (8H, m), 3.71-3.62 (2H, m), 3.55-3.48 (4H, m), 2.75-2.62 (2H, m).

\(^13\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta_c = 173.2\), 142.3, 142.1, 132.7, 129.2, 127.7, 127.2, 124.6, 124.1, 121.6, 121.0, 111.47, 52.1, 41.4, 40.0, 33.7.

HRMS found: \([M+H]^+\) 339.1351, C\(_{19}\)H\(_{19}\)N\(_2\)O\(_4\) requires 339.1345.

10-Nitro-8-phenyl-8,9-dihydropyrido[1,2-a]indol-6(7H)-one 5.108

Yellow solid, 12 mg, 10% yield, R_f = 0.61 (DCM/Pet Ether 7:3).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_H = 8.56-8.54\) (1H, m), 8.29-8.27 (1H, m), 7.50-7.31 (7H, m), 4.23-4.17 (1H, m)3.64-3.58 (1H, m), 3.49-3.42 (1H, m)3.23-3.09 (2H, m).

\(^13\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta_c = 168.7\), 141.9, 140.5, 133.0, 129.9, 129.4, 128.1, 127.0, 126.7, 126.6, 122.0, 120.6, 116.5, 40.9, 38.0, 31.5..

HRMS found: \([M+H]^+\) 307.1089, C\(_{18}\)H\(_{15}\)N\(_2\)O\(_3\) requires 307.1083.
Procedure for the preparation of 5.113 via electrophilic chlorination

\[
\begin{align*}
\text{To a solution of 5.73 (100 mg, 0.36 mmol) in DCM (1 mL) was added triethylamine (65.6} \\
\text{μL, 0.47 mmol, 1.3 equiv.) followed by DCDMH (93 mg, 0.47 mmol, 1.3 equiv.). The} \\
\text{resulting mixture was stirred for 1 hour at room temperature. The mixture was diluted with} \\
\text{water (7 mL) and extracted with DCM (3 x 10 mL). The combined organic phases were} \\
anhydrified on Na$_2$SO$_4$, filtered and evaporated at reduced pressure. The crude product} \\
\text{was purified by column chromatography eluting with DCM/ Pet Ether (2:8) to obtain} \\
5.113. \\
\end{align*}
\]

Yellow solid, 85 mg, 76% yield, R$_f$ = 0.42 (DCM/ Pet Ether 1:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 8.29-8.27$ (1H, m), 8.18-8.16 (1H, m), 7.50-7.43 (2H, m), 5.36 (2H, s), 1.76 (9H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_C = 148.6, 137.1, 134.5, 131.5, 127.5, 125.8, 121.3, 121.0, \\
115.6, 87.9, 35.0, 28.0.$

HRMS found: [M]$^+$ 310.0726, C$_{14}$H$_{15}$ClN$_2$O$_4$ requires 310.0720.

Spectroscopic details of compounds 5.114, 5.119, 5.120, 5.122 and 5.123/5.124

Compound 5.114 was prepared and isolated following the general procedure for the electrophilic chlorination of 5.73 and using the appropriate base, electrophilic chlorinating reagent and reaction time, as described in Chapter 5, Table 10, entry 2.

\[
\begin{align*}
\text{**tert-butyl 2-(dichloromethyl)-3-nitro-1H-indole-1-carboxylate 5.114**} \\
\end{align*}
\]

Yellow solid, 40 mg, 33% yield, R$_f$ = 0.47 (DCM/ Pet Ether 1:1).
$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 8.28-8.26$ (1H, m), 8.12 (1H, s), 8.02-8.00 (1H, m), 7.54-7.45 (2H, m), 1.78 (9H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 148.1, 134.5, 128.1, 126.1, 121.6, 119.9, 118.7, 114.6, 112.4, 88.9, 59.2, 28.1$.

HRMS found: [M]$^+$ 344.0325, C$_{14}$H$_{14}$Cl$_2$N$_2$O$_4$ requires 344.0331.

Compounds 5.119, 5.120, 5.122 and 5.123/5.124 were prepared according to the general procedure for the electrophilic chlorination, using 5.67 (70 mg, 0.40 mmol) as substrate with the appropriate base, electrophilic chlorinating reagent and reaction time, as described in Chapter 5, Table 12, entry 2.

2-(chloromethyl)-3-nitro-1$^H$-indole 5.119

![Image of 2-(chloromethyl)-3-nitro-1$^H$-indole 5.119]

Brown solid, 26 mg, 31% yield, $R_f = 0.27$ (EtOAc/ Pet Ether 3:7).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 9.23$ (1H, br s), 8.30-8.28 (1H, m), 7.49-7.47 (1H, m), 7.44-7.37 (2H, m), 5.32 (2H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 137.8, 132.7, 126.5, 125.4, 124.7, 121.7, 121.0, 112.0, 39.1$.

HRMS found: [M]$^+$ 210.0189, C$_9$H$_7$ClN$_2$O$_2$ requires 210.0196.

2-(dichloromethyl)-3-nitro-1$^H$-indole 5.120

![Image of 2-(dichloromethyl)-3-nitro-1$^H$-indole 5.120]

Brown solid, 43 mg, 44% yield, $R_f = 0.45$ (EtOAc/ Pet Ether 3:7).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H = 9.29$ (1H, br s), 8.34-8.31 (1H, m), 7.85 (1H, s) 7.53-7.51 (1H, m), 7.47-7.44 (2H, m).
$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c = 132.5, 126.9, 125.0, 123.2, 122.2, 119.3, 113.6, 111.7, 55.6$.

HRMS found: [M]$^+$ 243.9807, C$_9$H$_6$Cl$_2$N$_2$O$_2$ requires 243.9806.

3-nitro-$1H$-indole-$2$-carbaldehyde 5.122

![3-nitro-1H-indole-2-carbaldehyde](image)

Brown solid, 17 mg, 23% yield, $R_f = 0.53$ (EtOAc/ Pet Ether 3:7).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H =$ 10.1 (1H, s), 9.32 (1H, br s), 7.77-7.75 (1H, m), 7.45-7.44 (2H, m) 7.27-7.23 (1H, m).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c =$ 180.3, 136.5, 130.4, 128.7, 125.7, 122.0, 120.7, 118.0, 112.9.

HRMS found: [M$+$H]$^+$ 191.0449, C$_9$H$_7$N$_2$O$_3$ requires 191.0457.

1-chloro-$2$-methyl-$3$-nitro-$1$H-indole 5.123 or 3-chloro-$2$-methyl-$3$-nitro-$3$H-indole 5.124.

Brown oil, 77 mg, 92% yield, $R_f = 0.64$ (EtOAc/ Pet Ether 3:7).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta_H =$ 7.55-7.48 (3H, m), 7.31-7.26 (1H, m).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta_c =$ 172.3, 153.7, 133.4, 133.3, 127.8, 123.5, 121.6, 100.7, 14.7.
Chapter 2: $^1$H-NMR and $^{13}$C-NMR

Compound 2.117
Compound 2.120
Compound 2.127
Compound **2.128**
Compound 2.129
Compound 2.130

---

272
Compound 2.131

\[
\begin{align*}
\text{NO}_2 & \\
\text{N} - \text{O} & \\
\text{NH} & \\
\text{I} & \\
\end{align*}
\]
Compound 2.138
Compound 2.139
Compound 2.140
Compound 2.141
Compound 2.142
Appendix Chapter 2

Compound 2.143

![Chemical Structure Image]

**Chemical Structure Formula:**

\[
\text{Compound } 2.143
\]

**NMR Spectrogram:**

- **δ (ppm):** Various peaks indicating the chemical shifts of different functional groups.
- **Integration:** Peaks indicated with integration values.
- **Resonance Frequencies:** Peaks corresponding to different chemical shifts.

---

279
Compound 2.150
Compound 2.151
Compound 2.152
Compound 2.154
Compound 2.155
Compound 2.114
Compound 2.172
Compound 2.174
Chapter 3: $^1$H-NMR and $^{13}$C-NMR

Compound 3.75

![NMR Spectra]

The NMR spectra show the chemical shifts and coupling constants for the compound, indicating the presence of various functional groups and the configuration of the molecule. Further analysis is required to interpret the specific chemical environment and bonding.
Compound 3.91

[Chemical structure diagram]

[Graph showing NMR spectra with ppm values]
Compound 3.92
Appendix Chapter 3

Compound 3.94
Appendix Chapter 3

Compound 3.95

N-O
\[\text{NO}_2\]

8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5 ppm

169.11  159.82  128.90  53.72  51.00  57.75  39.39  18.78

155  140  125  110  95  80  65  50  35  20  0 ppm
Compound \((E/Z)-3.98\)
Compound (E/Z)-3.100
Compound (E/Z)-3.101
Compound (E/Z)-3.102
Compound \((E)-3.103\)
Compound (E)-3.104
Compound (E)-3.105
Compound 3.110
Compound 3.114
Appendix Chapter 4

Compound 4.168
Compound 4.180
Compound 4.168 rac.

<Sample Information>

Sample Name: Racemate without MeOH
Sample ID: CM 512
Data Filename: CM 512.AS-C01%-0'5mL-25C001.lcd
Method Filename: AS-C01%-0'5 mL-25 C-80 min.lcm
Batch Filename: Vial # Sample Type: 1-79 Unknown
Injection Volume: 10 µL
Date Acquired: 22/09/2015 14:31:13 Acquired by: System Administrator
Date Processed: 22/09/2015 15:13:32 Processed by: System Administrator

Detector A Channel 1 254nm

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Compound 4.168

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- Method Filename: AS-C01H-05 mL-25 C-25 min.icm
- Batch Filename: 
- Vial #: 1-82
- Injection Volume: 5uL
- Date Acquired: 26/04/2016 16:41:25
- Acquired by: System Administrator
- Date Processed: 26/04/2016 16:20:46
- Processed by: System Administrator

Chromatogram:

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Chapter 5: $^1$H-NMR and $^{13}$C-NMR

Compound 5.73
Appendix Chapter 5

Compound 5.67

\[
\begin{align*}
\text{NO}_2
\end{align*}
\]
Compound 5.77
Appendix Chapter 5

Compound 5.90
Compound 5.93

[Chemical structure and spectrum images]
Compound 5.94
Compound 5.95
Appendix Chapter 5

Compound 5.96

[Chemical structure image]

[Graphs and spectra images]
Compound 5.97
Compound 5.108
Compound 5.113
Compound 5.114
Compound 5.119
Compound 5.120
Compound 5.122
Compound 5.123/5.124