Università degli Studi di Salerno

Dipartimento di Chimica e Biologica "Adolfo Zambelli"

Corso di Dottorato di ricerca in Chimica, XXXIV ciclo.

Tesi di dottorato in: ***Synthesis and cascade reactions of new heterocyclic compounds***

Tutor

Prof. *Antonio Massa*

Dottorando

Antonio Macchia

Coordinatore Dottorato

Prof. *Claudio Pellecchia*

A.A. 2021-2022 **VOLUME 1 DI 1**

Index

List of scientific publications

1. **Macchia, A.**, Summa, F., Monaco, G., Eitzinger, A., Ofial, A. R., Di Mola, A, Massa, A. Access to β-Alkylated γ-Functionalized Ketones via Conjugate Additions to Arylideneisoxazol-5-ones and $Mo(CO)_6$-Mediated Reductive Cascade Reactions" *ACS Omega* **2022**, *ACCEPTED.*

2. **Macchia, A.**, Summa, F.F., Di Mola, A., Tedesco, C., Pierri, G., Ofial A.R., Monaco, G., Massa, A. Base-Promoted Cascade Reactions for the Synthesis of 3,3- Dialkylated Isoindolin-1-ones and 3-Methyleneisoindolin-1-ones, *J. Org. Chem.* **2021**, 86, 21, 15128.

3. Eitzinger, A., Otevrel,J., Haider, V., **Macchia, A**., Massa, A., Faust, K., Spingler, B., Berkessel, A., Waser, M. Enantioselective Bifunctional Ammonium Salt-Catalyzed Syntheses of 3-CF_3S-, 3-RS-, and 3-F-Substituted Isoindolinones, *Adv. Synth. Catal.* **2021**, 363,1955.

4. **Macchia, A**., Eitzinger, A., Brière, J. F., Waser, M., Massa, A. Asymmetric Synthesis of Isoxazol-5-ones and Isoxazolidin-5-ones, *Synthesis* **2021**, 53, 107.

5. Di Mola, A., **Macchia, A**., Palombi, L, Massa, A. Methyl 2-(1-methyl-3-oxoisoindolin-1-yl)acetate, *Molbank* **2020**, 2020 (2), M1131.

6. **Macchia, A**., Cuomo, V.D., Di Mola, A., Tedesco, C., Pierri, G., Palombi, L., Filosa, R., Massa, A. On the necessity of one-pot tautomer trapping in asymmetric Michael reactions of arylideneisoxazol-5-ones, *Eur. J. Org. Chem.* **2020**, 2264.

7. Di Mola, A., **Macchia, A**., Tedesco, C., Pierri, G., Palombi, L., Filosa, R., Massa, A. Synthetic Strategies and Cascade Reactions of 2-Cyanobenzophenones for the Access to Diverse3,3-Disubstituted Isoindolinones and 3-Aryl-3-Hydroxyisoindolinones, *Chemistry Select* **2019**, 4, 4820.

List of abbreviations

Ac	acetyl
AIBN	2,2’-azobis (2-methylpropionitrile)
Alk	alkyl
Bn	benzyl
Boc	tert-buthoxycarbonyl
br	broad
Bu	butyl
C	concentration
c	cyclic
cat.	catalyst(s)
d	doublet
DCM	dichloromethane
dd	double doublet
ddd	doublet of double doublets
DFT	density functional theory
diast.	diastereomer
DMAP	4-(Dimethylamino) pyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	DeoxyriboNucleic Acid
dr	diastereoisomeric ratio
DTR	dynamic thermodynamic resolution
EDG	Electron Donating Group
EI	Electron Impact
er	enantiomeric ratio
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EWG	Electron Withdrawing Group
FDA	Food and Drug Administration
H	hydrogen
h	hour(s)

HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectrometry
Hz	Hertz
i	iso
IR	infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
LFER	Linear Free Energy Relationships
m	*meta*
m	multiplet
M	molar (concentration)
MALDI	Matrix-assisted laser desorption/ionization
Me	methyl
min	minutes
m.p.	melting point
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
m/z	atomic mass units per charge
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance spectroscopy
Nu	nucleophile
o	*ortho*
OC	organocatalysis
p	*para*
PG	protecting group
Ph	phenyl
PMB	(acetate) *p*-methoxy benzylacetate
Pr	propyl
PTC	Phase Transfer Catalyst/ or catalysis
q	quartet
rac	racemic
RNA	RiboNucleic Acid
r.t.	room temperature
s	singlet
s	*sec*

S_N	nucleophilic substitution
t	*tert*
t	triplet
T	Temperature
TFA	Trifluoroacetic acid
TS	transition state

Chapter 1. Introduction

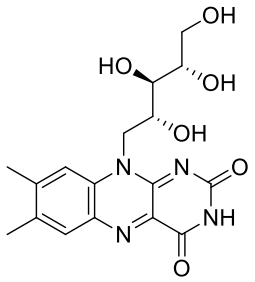
1.1 Importance of heterocyclic compounds

The core of this PhD thesis is the synthesis of new heterocyclic compounds of pharmacological interest, developing new multicomponent and cascade reactions. Heterocyclic compounds are cyclic compounds that contain at least one heteroatom in their carbon skeleton. The combination of different atoms, with different electronic properties, within a single cyclic structure, results in completely unique physical and chemical properties, which precisely distinguish them from the classic carbon-based cycles.

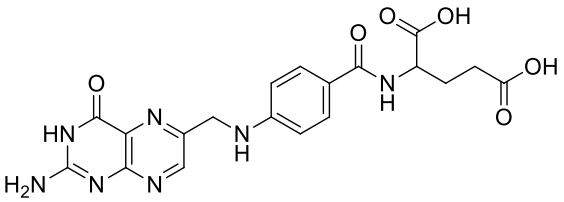
The importance of heterocycles is confirmed by the very ancient history behind them, begun in the 1800s, in step with the development of organic chemistry. In fact, the first isolated heterocycle dates to 1818, alloxan from uric acid by Brugnatelli.[1] Subsequently in 1821, Dobereiner,[2] isolated furfural thanks to the acidic treatment of starch. Pyrrole was obtained by Runge in 1834 for the first time as constituent of coal tar.[3] During the period 1885 to 1901 the chemist Albrecht Kossel,[4] awarded with Nobel Prize in Physiology or Medicine in 1910, was able to isolate the nitrogenous bases of DNA and RNA.

The great importance of heterocyclic compounds is related to their wide range of applications.[5] For example, in the last years, the biological and pharmacological activities of heterocyclic compounds have become uncountable, in fact, over 95% of drugs currently on the market have a heterocyclic core (**Figure 1.1.**).

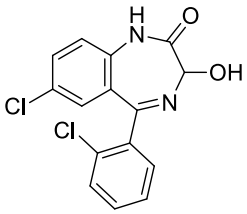
Herein are reported some examples: Riboflavin **1.1,** is a vitamin used to correct vitamin B2 deficiency,[6] folic acid **1.2** is a nutrient used to treat megaloblastic anemia, Lorazepam **1.3**, serves as short-acting benzodiazepine commonly used to treat panic disorders, severe anxiety, and seizures,[7] Anagrelide **1.4**, is a platelet-reducing agent used to treat thrombocythemia.[8] Codeine **1.5**, acts as opioid analgesic used to treat moderate to severe pain.[9]



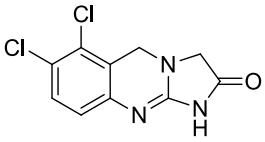
Riboflavin, **1.1.**



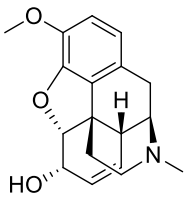
Folic Acid, **1.2.**



Lorazepam, **1.3.**



Anagrelide, **1.4.**

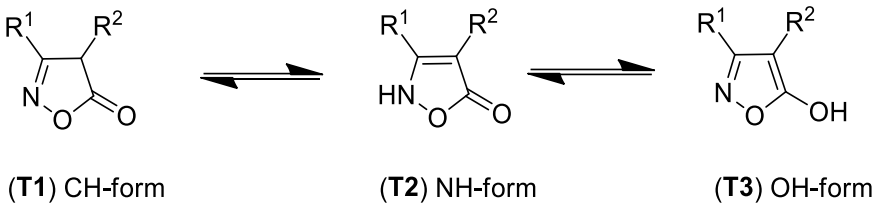


Codeine, **1.5.**

Figure 1.1. Examples of heterocyclic compounds based natural products and pharmaceutical applications.

The best-known heterocycles have 5 or 6-membered dimensions and the most common heteroatoms incorporated in the cycle are N, O and S. Among these we can recognize pyridines, furans, pyrroles and thiophenes. It has been estimated that about 70% of the scientific literature in the field of organic chemistry published in 2020 consists of synthesis, development and applications of heterocycles. In fact, even if predominantly heterocyclic compounds are used as pharmaceuticals, as agrochemicals, as antioxidants or as dyes, they are also finding an increasing use as intermediate in organic synthesis.[10,11]

An interesting phenomenon that occurs frequently in the heterocyclic compounds is the tautomeric equilibrium. Tautomers are structural isomers that undergo into rapid interconversion (**Scheme 1.1**). Both aromatic and non-aromatic heterocyclic compound can generate these equilibria. A worth mentioned class of heterocyclic that shows this equilibrium is that of isoxazol-5-one, that we will discuss in more detail in the **chapter 5**.



Scheme 1.1. Tautomerism in isoxazole-5-ones

In this class of compounds, three different tautomeric forms can exist, the **T1** CH-form (imine-like), the **T2** NH-form (enamine-like) and the **T3** OH-form (enol-like). Depending on the reaction conditions (e.g. polarity of the solvent) or the nature of substituent R^1 and R^2, one tautomeric form prevails over the others, affording totally different class of products.[12]

1.2 Multicomponent and cascade reactions for the synthesis of heterocyclic compounds

Heterocyclic chemistry is an inexhaustible resource of novel compounds and organic chemists have been engaged into extensive efforts to developing new and efficient synthetic routes. Currently, multicomponent and cascade reactions, which can be used to convert simple and widely accessible building blocks into highly complex compounds in one-pot fashion, are becoming a fundamental strategy for rapidly construction of complicated molecular scaffolds, especially heterocyclic natural products.[13,14,15,16]

A multicomponent reaction (MCR) is generally defined as any process that combines three or more reactants in a single pot to form products that incorporate structural features of each reagent (**Figure 1.2**).[17,18,19]

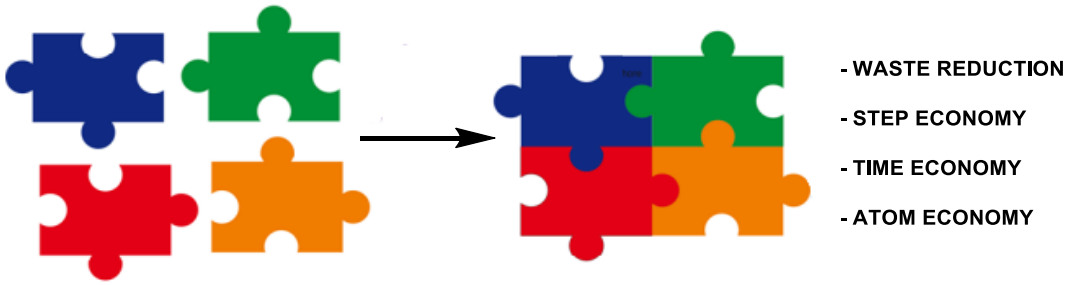
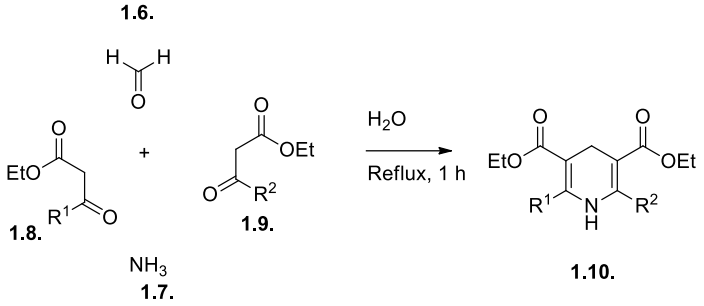


Figure 1.2. Schematic representation of a multicomponent reaction

One of the key aspects that pushes the modern chemistry towards MCR is the greener character of the whole process compared to step-by-step reaction. To notice that employing MCR, isolation and purification of intermediates are avoided, affording reduction in terms of reaction steps,[20] atom,[21] time and quantity of solvents and filtrating agents (silica gel, celite) and therefore wastes.[22]

One of the ancient examples of multicomponent reaction to give heterocyclic products is the Hantzsch dihydropyridine synthesis described in 1881 (**Scheme 1.2**), involving two β-chetoester molecules and formaldehyde.[23]



Scheme 1.2. Multicomponent reaction in the synthesis of dihydropyridine **1.10**

On the other side, a cascade, tandem or domino reaction is a consecutive series of intramolecular organic reactions which often proceed via highly reactive intermediates.[24] By cascade reaction it is meant a reaction with two or more steps in which no reaction intermediate is isolated (**Figure 1.3**). To be classified as cascade, a reaction must meet three basic requirements:

1. All reaction steps must take place in a single pot,
2. In this pot, at least one reaction condition must be the same throughout the whole process (e.g. solvent, temperatures),
3. each transformation must be independent from the previous step.

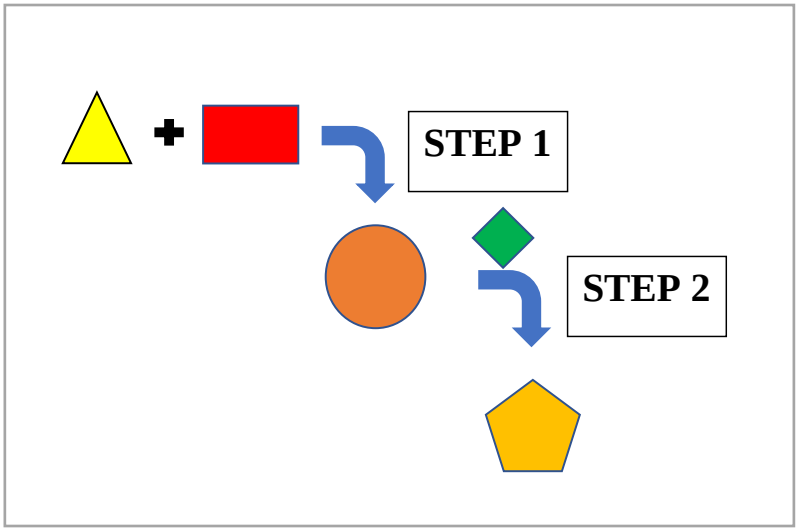
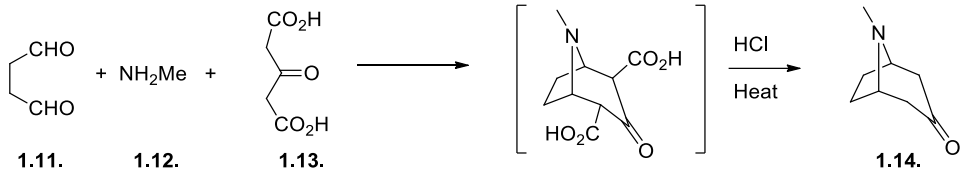


Figure 1.3. Schematic representation of a cascade reaction

The earliest example of a cascade reaction is arguably the synthesis of Tropinone reported in 1917 by Robinson.[25] Since then, the use of cascade reactions has proliferated in total synthesis (**Scheme 1.3**).[26]



Scheme 1.3. Cascade reaction in the synthesis of Tropinone **1.14**

Cascade reactions encompass a very wide range of reactions, ranging from anionic, cationic, radical, pericyclic and transition metal mediated reactions. The cascade reactions that I will mostly illustrate in this thesis concern anionic reactions.

As for multicomponent reaction, also cascade reactions are very favorable from the point of view of "green chemistry" as these reactions have the characteristics of a pot and atom economy. The time and waste economy aspects are also crucial because avoiding the purification of intermediates implies reduction of the waste produced and the time spent in carrying out the synthesis.

These reported examples show that a cascade reaction mechanism takes place when specific structural conditions of the substrates used occur. For examples, In the reported synthesis of Tropinone, the presence of a bifunctional substrate such as the carboxylic diacid allows both intermolecular and intramolecular Mannich reaction.

Therefore, the structural character of the substrates is fundamental to obtain cascade reaction mechanisms. However, other characteristics must also be observed to carry out a cascade reaction.

First, it is necessary to choose experimental conditions that avoid the formation of side products.[27] For example, malonic synthesis produces an equivalent quantity of CO_2 that could lead side reaction in presence of carbon and heteronucleophiles.[28]

Other important characteristics are the solvents used and the quantity of reagents used. It is advisable to use reagents with low boiling points as these are easily removed by concentration *in vacuo*, avoiding high evaporation temperatures which could warm the system and ruin the integrity. A final consideration is to be made on the amount of reagents employed, in fact, an excess of any reagents, or non-quantitive reactions, could lead to the formation of by-products in subsequent reaction steps. Therefore, it is necessary to consider all the possible reactivity of the various reagents present in the solution. This means that the optimization of the conditions of one-pot cascade reactions is extremely difficult compared to the traditional stop-and-go synthesis, where each intermediate is isolated and purified for the subsequent step.[29]

1.3 Multicomponent and one-pot cascade reactions in asymmetric synthesis of heterocycles

A further very important aspect of both multicomponent reactions (MCR) and cascade reactions is that they are widely used in asymmetric synthesis leading to enantio-enriched compounds using chiral catalysts starting from chiral or achiral compounds. The definition of chirality, from the Greek **χείρ (kheír)** meaning "hand", is due to Lord Kelvin who enunciated it during the "Baltimore Lectures", a series of lectures held at Johns Hopkins University in Baltimore starting from October 1st, 1884, and published twenty years later, in 1904, in which the English scientist, among other things, stated: "I call any geometrical figure, or groups of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself ".

Non-covalent organocatalysis plays an important role for the construction of heterocyclic compounds via asymmetric multicomponent and cascade reactions. Non-covalent organocatalysis means that the activation of substrates occurs through weak interactions between substrates and organocatalysts, mostly H bonds, Van der Waals forces, $\pi - \pi$ stacking, with a bond-enthalpy range from 0.4 kJ * mol^{-1} for the weakest Van der Waals force to 161.5 kJ * mol^{-1} in the ion HF^{-2}. Hydrogen-bond activation is certainly the best known and mostly used in asymmetric catalysis.

This type of activation occurs when acidic hydrogens are present in chiral organic catalyst that can interact with the functional group hydrogen bond of the substrate, to form hydrogen bridges. In particular, the interaction at H serves to stabilize anionic intermediates and transition states. A class of catalyst exhibiting activation properties by H-bonding is that of the organocatalysts of the cinchona alkaloids family, [30,31,32] in particular, in recent years the class of bifunctional organocatalysts has found widespread use (**Figure 1.4**).

These catalysts are called bifunctional as they have not only the H-bonding functionality due to the hydroxyl group, but also have a nucleophilic basic functionality (Brønsted base) given by the tertiary amino nitrogen.[33,34,35]

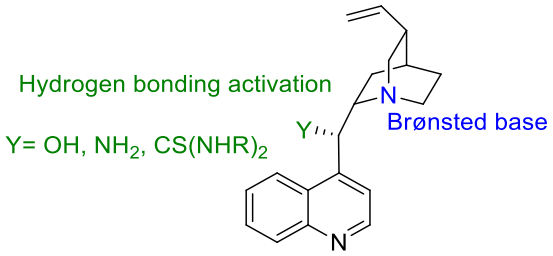


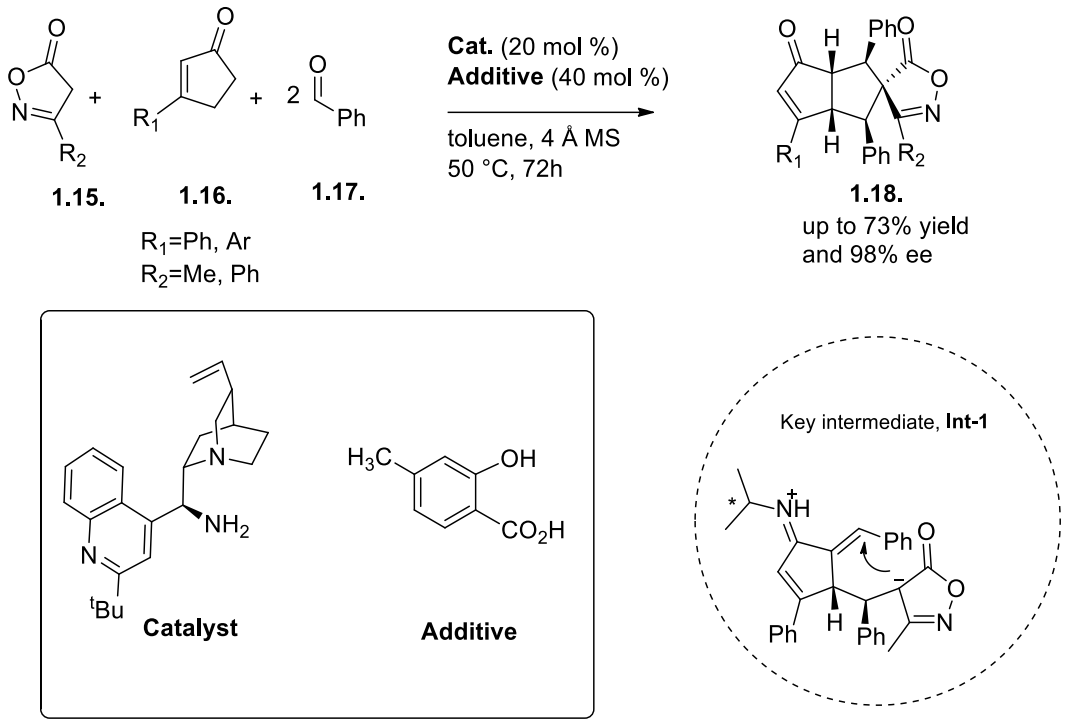
Figure 1.4. Examples of bifunctional organocatalysts

There are many examples of organocatalytic cascade and multicomponent enantioselective reactions for the construction of enantio-enriched heterocycle compounds.

Two important classes of heterocyclic compounds, obtained via multicomponent and cascade reactions, are the 3,3-disubstituted isoindolinones and isoxazol-5-ones, these scaffolds will be the matter of study of this PhD thesis.

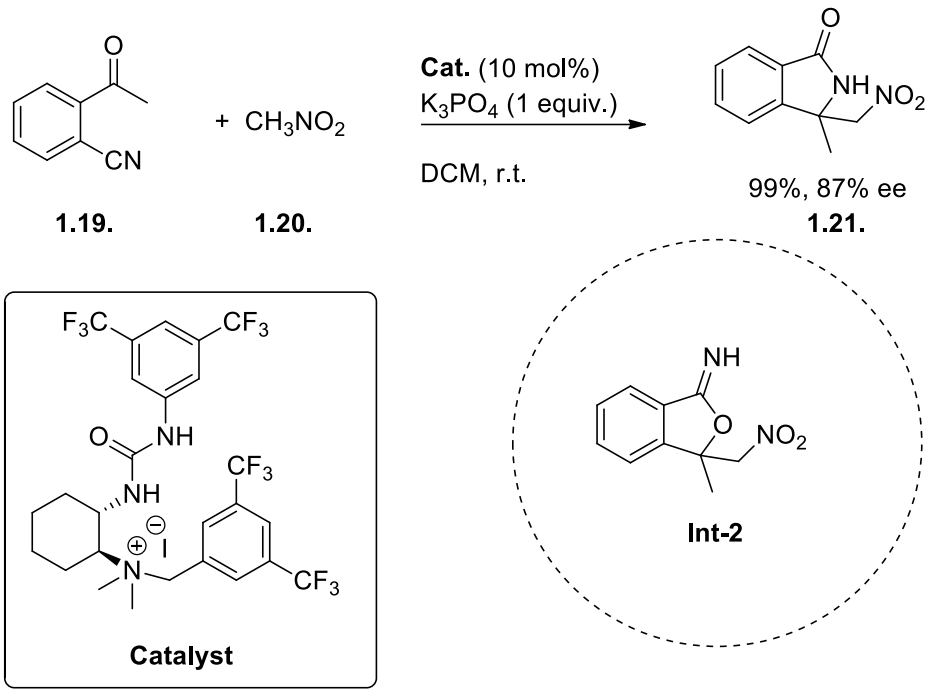
Chen *et al.*[36] reported the asymmetric aminocatalyzed synthesis of novel spiro-isoxazol-5-ones via four-component [5+1+1+1] formal cycloaddition reaction, involving 3-substituted cyclopent-2-enones with activated methylene nucleophiles and two molecules of aldehydes, in high yields and excellent enantiomeric excesses.

The reaction mechanism occurs via quintuple Knoevenagel condensation/Michael addition/retro-Michael addition/Michael addition/Michael addition sequence, where the key intermediate is the nucleophilic 4-H isoxazole-5-one (**Int-1**), leading the cyclization to get the spiro-based compound (**1.18**, **Scheme 1.4**).



Scheme 1.4. Cascade reactions in the synthesis of compound **1.18**

Massa *et al.*[37] reported the first asymmetric Henry-initiated synthesis of 3,3-disubstituted isoindolinones in quantitative yields and moderate enantiomeric excesses involving 2-cyanoacetophenone and nitromethane catalyzed by *trans*-1,2-cyclohexyldiamine based PTC. The reaction occurs via cascade mechanism where after Henry reaction of nucleophilic nitromethane to the carbonyl group, the cyclization onto cyano group leads the imidate-intermediate (**Int-2**). Further steps of Dimroth-type rearrangement and aza-Michael reaction gives the enantioenriched 3,3-disubstituted isoindolinone (**1.21**, **Scheme 1.5**).



Scheme 1.5. Cascade reactions in the synthesis of compound **1.21**

Chapter 2. Research Objectives

The main goal of this PhD thesis is the synthesis of new heterocyclic compounds of pharmaceutical interest through the development of new one-pot, cascade and multicomponent methodologies, starting from readily available multifunctional starting materials. In the first part of this thesis, the attention was focused on the study of the reactivity of the bifunctional electrophiles 2-carbonyl benzonitriles in one-pot cascade reactions, with carbon and hetero-nucleophiles affording new heterocyclic compounds through a cascade sequence of addition, cyclization and rearrangement reactions. In the **chapter 3.** the synthesis of 3-aryl-3-substituted isoindolinones starting from 2-cyanobenzophenones is reported.

In the **chapter 4.** the kinetic UV-Vis studies of 2-cyanoacetophenone and 2-cyanobenzophenone is described. This investigation was conducted during my period abroad under the supervision of Dr. Armin Ofial at LMU Munich in Germany, using the Mayr equation $\log k_{20^\circ C} = s_N(N+E)$. The aim of these studies is related to the possibility to predict the reactivity of these ketones in combination with different nucleophiles and therefore to enlarge the scope of the cascade reaction. Therefore, our attention focused on chloromethyl aryl sulfones as suitable nucleophiles in reactions with 2-cyanoacetophenones to obtain 3-alkyl-3-substituted isoindolinone. Also in this chapter, the use of 2-cyanobenzaldehyde in reactions with chloromethyl aryl sulfones will be deeply investigated, leading to 3-methyleneisoindolinones, further exploiting the reactivity of the α-leaving group.

Another purpose of this PhD thesis is the study of the reactivity of structurally complex 4-arylideneisoxazol-5-ones as Michael acceptors reported in **chapter 5**. This investigation led to development of multicomponent reactions, employing as nucleophiles dimethyl malonate and chloromethyl aryl sulfones, affording new complex heterocyclic compounds. An organocatalytic asymmetric version will be also presented when the reaction is carried out in the presence of dimethylmalonate. The secondary reactivity of the Michael adducts will be investigated, focusing the attention on the N-O bond cleavage promoted by molybdenum hexacarbonyl and water.

The **chapter 6** shows the preliminary results about asymmetric α-trifluoromethylthiolation of the 3-EWG phthalides, using bifunctional organocatalysts in collaboration with Prof. Giorgio Della Sala of Department of Chemistry and Biology of University of Salerno. This work is based on results of asymmetric α-trifluoromethylthiolation of 3-EWG obtained in collaboration with Prof. Mario Waser.

Chapter 3. Synthesis of 3,3-disubstituted isoindolinones and 3-methyleneisoindolinon-1-one via one-pot cascade reaction

3.1. Introduction

The 3,3-disubstituted isoindolinone core belongs to a class of heterocyclic compounds that possess considerable activity both for pharmaceutical and biological applications. They have been deeply studied in medicinal chemistry and many applications can be found in literature. [38,39,40] Herein some examples of bioactive molecules with 3,3-disubstituted isoindolinones moiety are reported (**Figure 3.1**).

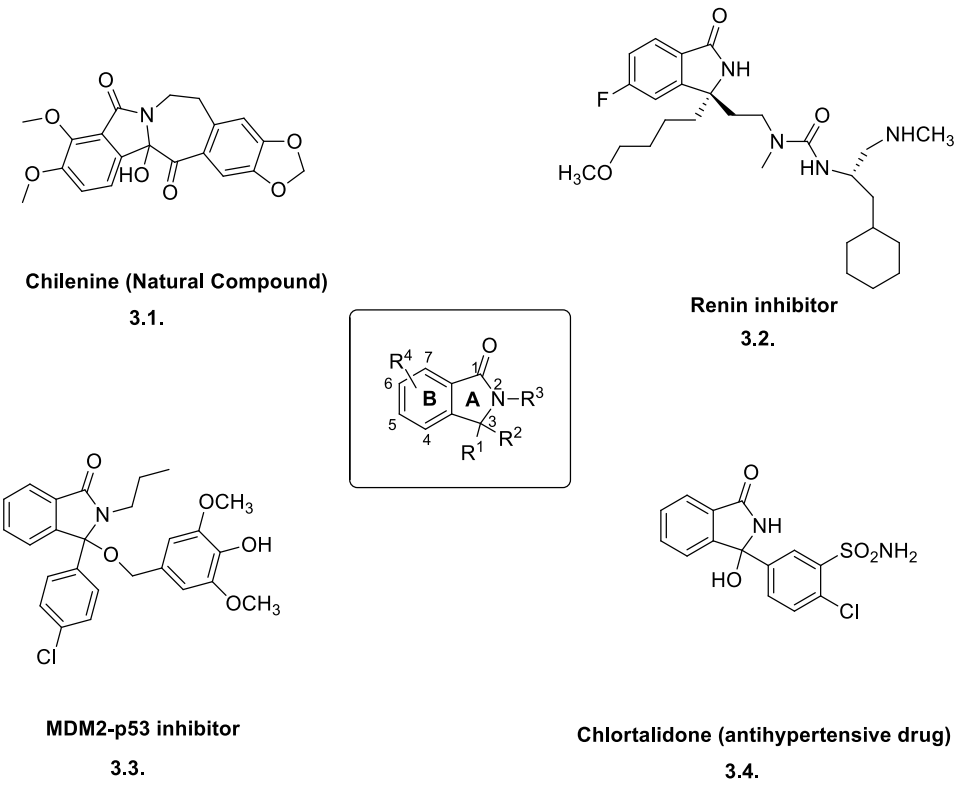
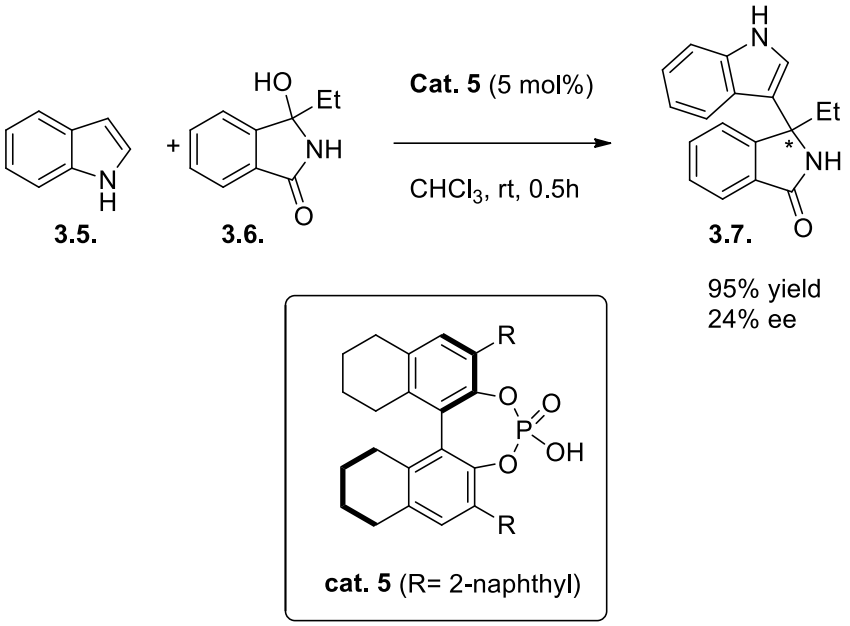


Figure 3.1. 3-3 disubstituted isoindolinone core motifs in bioactive molecules and pharmaceutical applications

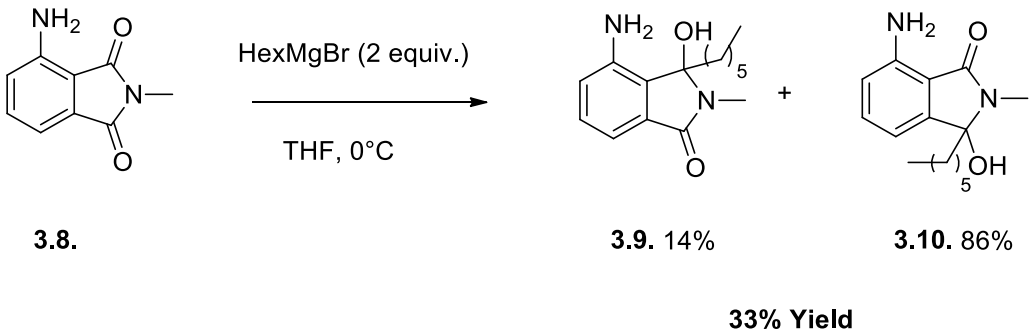
In literature few examples of synthesis of 3,3-disubstituted isoindolinones are reported and in many of them harsh conditions such as one or more metal complexes and high temperature, were employed.[41]

One of the most useful methodologies to get 3,3-disubstituted isoindolinones is the acid-catalyzed nucleophilic substitution of 3-hydroxy-3-substituted isoindolinones with a wide range of carbon and hetero-nucleophiles (**Scheme 3.1**).[42]



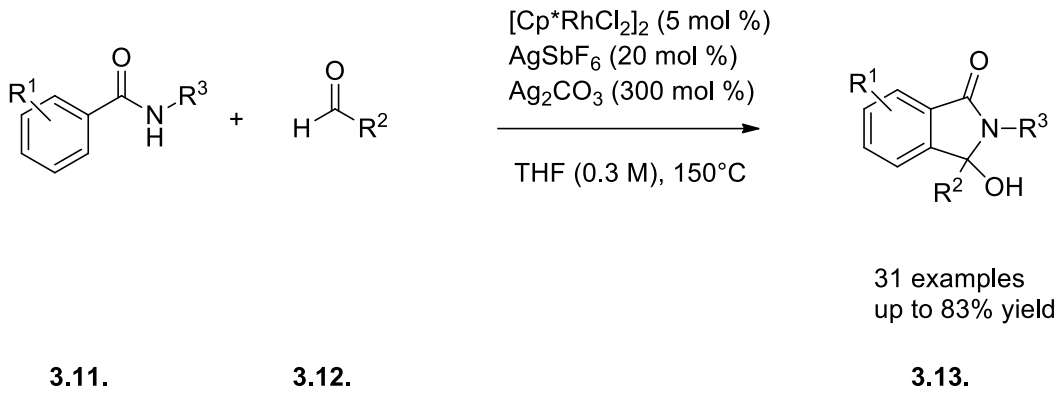
Scheme 3.1. Synthesis of 3,3-disubstituted isoindolone **3.7** via nucleophilic substitution of 3-OH-3-substituted isoindolinone **3.6**

However, the most widespread methodology to get the 3-hydroxy-3-substituted isoindolinones is the nucleophilic Grignard addition to substituted phthalimides (**3.8**, **Scheme 3.2.**). Thus, the challenge of this reaction is to get a selective nucleophilic addition, due to the presence of two carbonyl groups. Under this condition, a regioselective problem arises even in presence of hindered position or bulky nucleophile (as reported in **Scheme 3.2**), giving a mixture of products that need further purification.[43]



Scheme 3.2. Synthesis of 3-OH-3-substituted isoindolinones **3.9-3.10**

Other pathways were developed during the years, one of them is the benzamide cyclization.[44] This approach consists in a tandem Rh(III)-catalyzed oxidative acylation of secondary benzamides with aryl aldehydes and Ag_2CO_3 as oxidant (**Scheme 3.3**).



3.11. **3.12.** **3.13.**

Scheme 3.3. Synthesis of 3,3-disubstituted isoindolinones via Rh(III)-catalyzed oxidative acylation of secondary benzamides

In addition to the 3,3-disubstituted isoindolinones, one related important class of molecules, with an isoindolinonic core will be studied in this chapter, namely that of the 3-methyleneisoindolin-1-ones. This class of molecules has considerable pharmaceutical applications (**Figure 3.2**). In fact, thanks to their optical properties they are used in medicinal chemistry as photoluminescent biomarkers (**3.14-3.16**).[45,46] But not only that, they are important precursors in the synthesis of the Aristolactams (**3.17-3.19**).[47] These were found to be highly effective in the treatment of Parkinson's disease and Alzheimer's disease.

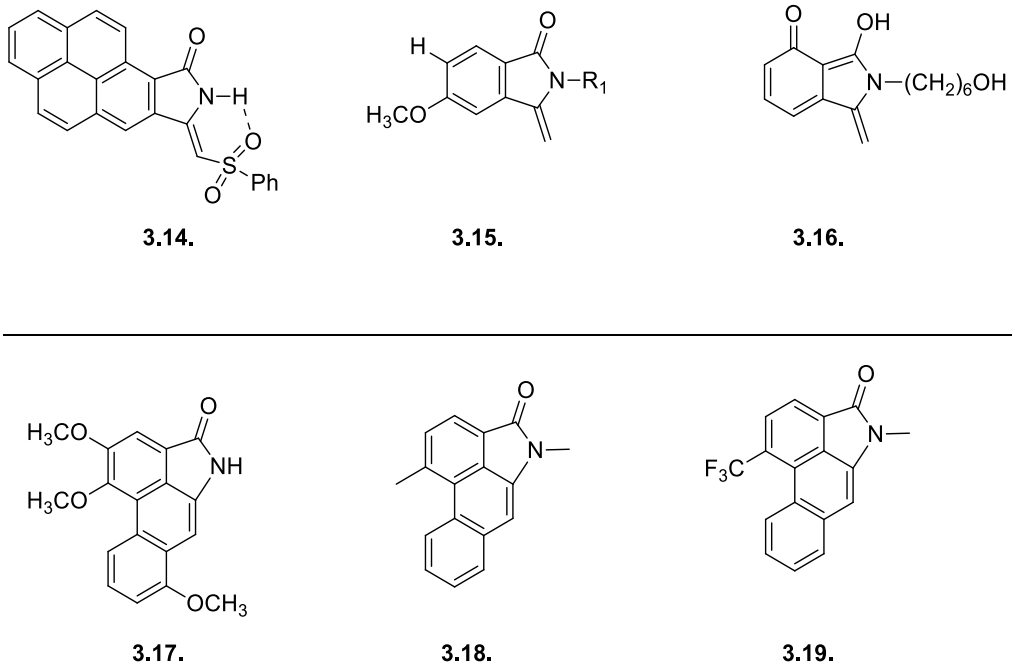
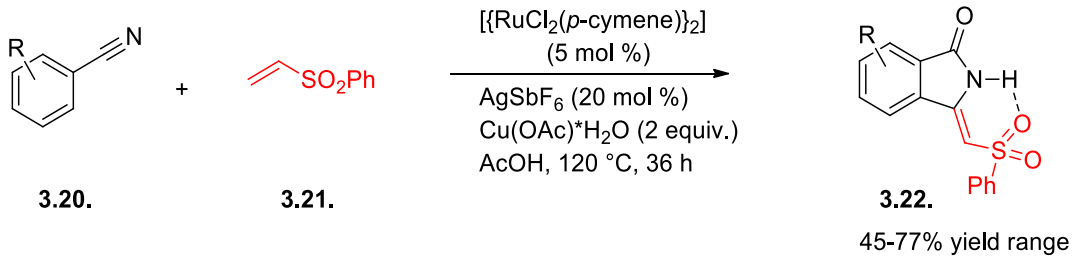


Figure 3.2. 3-methyleneisoindolin-1-one core motifs in bioactive and functional materials.

In the literature there are few examples of synthesis of these compounds and many using much more stringent conditions, such as Ru (II) / Ag (I) catalysis and excess of Cu (II) necessary for the oxidative cyclization at high temperature (**Scheme 3.4**).[48]



Scheme 3.4. Previous reported synthesis of 3-methyleneisoindolin-1-ones **3.22**

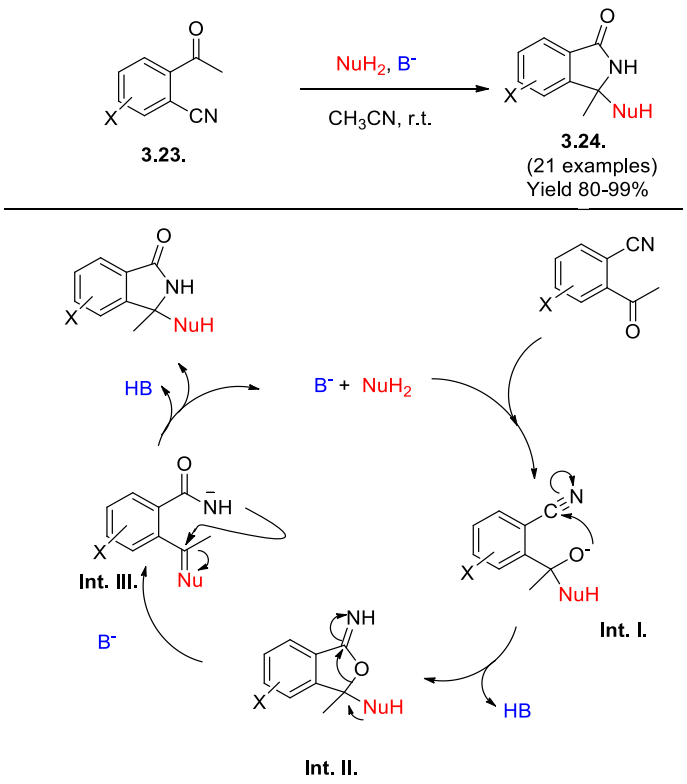
These published synthetic routes for 3,3-disubstituted isoindolinones and 3-methyleneisoindolin-1-ones, highlight a regioselectivity limitation (**Scheme 3.2**), harsh reaction conditions and expensive reagents (**Scheme 3.4**). At this point, it becomes necessary to develop a new synthetic methodology

to obtain 3,3-disubstituted isoindolinones and 3-Methyleneisoindolin-1-ones in a greener, milder and more regioselective way.

3.2. Previously reported synthesis of 3,3-disubstituted isoindolinones in cascade one-pot reaction.

A convenient, eco-sustainable and regioselective methodology to get the 3,3-disubstituted isoindolinones was developed by Prof. Massa's group.

Prof. Massa *et al*. [49] under very mild reaction conditions obtained in quantitative way 3,3-disubstituted isoindolinones starting from 2-cyanoacetophenones (**3.23.**) with different carbon- or hetero-nucleophiles (**Scheme 3.5.).** The mechanism is a cascade one-pot reaction in which the first step is the deprotonation of nucleophile addition to carbonyl group of 2-cyanoacetophenones. The ring closure leads to the first imidate intermediate (**Int II.**) Subsequently, due to the presence of an acid proton in alpha position of 3 position of ring A, a Dimroth-type rearrangement occurred (**Int III.**). The base catalyzes the ring opening of imidate and an aza-Michael reaction leads to 3,3-disubstituted isoindolinones in excellent yield (80-99%) with a wide variety of carbon and heteronucleophiles as dimethyl malonate, nitromethane, water and aliphatic amines. (**3.24.**)



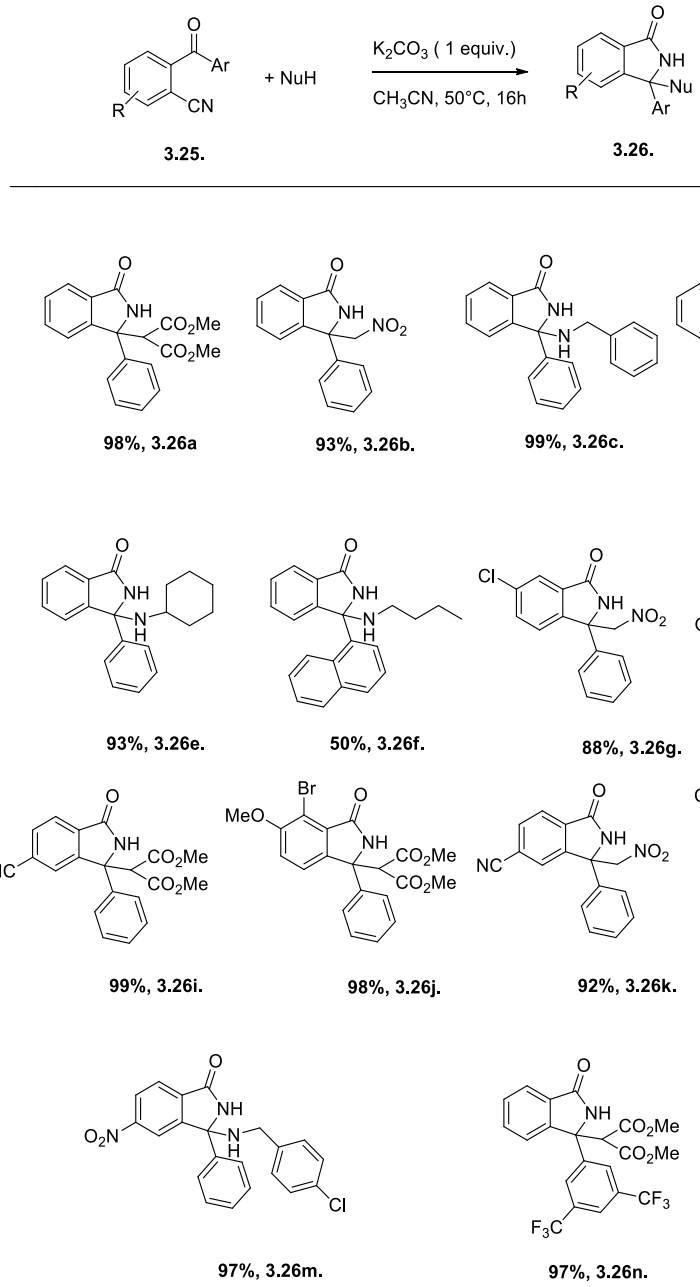
Scheme 3.5. Cascade reaction mechanism in the synthesis of 3,3-disubstituted isoindolinones **3.24**

3.3. Objectives

The objective of this chapter is to design a new synthetic pathway to get 2-cyanobenzophenones and exploit these substrates in one-pot cascade reaction, similar to one-pot cascade reaction reported for the 2-cyanoacetophenones.[49] This goal could allow the synthesis of new 3,3-disubstituted isoindolinones and improve eventually the synthesis of reported 3-aryl-3-hydroxy isoindolinones, overcoming for example the issue of the regioselectivity.

3.4. Result and discussion: 2-cyanobenzophenones in one-pot cascade reactions to get 3-aryl-3-substituted isoindolinones

The preliminary screening of conditions, performed by other component of the research group, of the reaction of 2-cyanobenzophenone and dimethyl malonate chosen as model nucleophile, revealed that in the presence of the cheap and environmentally friendly base K_2CO_3 in minimum amount of acetonitrile, led to the obtaining of a new 3,3-disubstituted isoindolinone in excellent yield and reasonable reaction time. This outcome indicates that 2-cyanobenzophenone shows a reactivity similar to 2-cyanoacetophenone, despite the increased steric hindrance. Then, as part of my work, the scope of the reaction was analyzed in the presence of carbon- and hetero-nucleophiles and with a wide range of 2-cyanobenzophenones, variously substituted both with electron withdrawing and donating groups (**Scheme 3.6**). Under the optimized conditions, a series of novel 3-aryl-3-disubstituted isoindolinones were easily obtained in very high yields, employing apart from dimethyl malonate, nucleophiles as nitromethane or primary aliphatic amines (**Scheme 3.6**).[50]



Scheme 3.6. Scope of Cascade Reactions of 2-Acylbenzonitriles **3.25** with carbon and hetero-nucleophiles

The results reported in **Scheme 3.6** show that the reaction proceeds in excellent yields with both carbon and nitrogen nucleophiles. About carbon nucleophiles, the use of dimethyl malonates (**3.26a-h-i-j-l-n**) result in very good yields (up to 93%), also the use of nitromethane in Henry-initiated cascade reaction has also been explored, affording yields higher than 88% (**3.26 b-g-k**). Nitrogen nucleophiles also bring very high yields except in for **3.26f** (50%), mainly due to steric hindrance both the 1-naphthyl group in position 3 and long-chain amine as nucleophile. The reaction tolerates

very well both EWG and EDG on the aromatic ring, moreover the nature of substituent doesn't affect the cascade process and the yield of the reaction.

The structure of dimethyl 2-(6-nitro-3-oxo-1-phenylisoindolin-1-yl)malonate **3.26h** was confirmed by X-ray analysis (**Figure 3.3.**), corroborating the cascade mechanism for this new reaction as proposed for the reactions of 2-cyanoacetophenones.

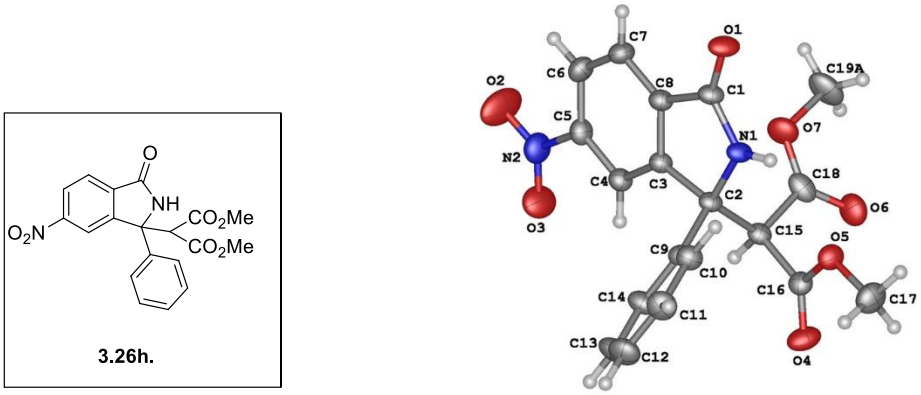
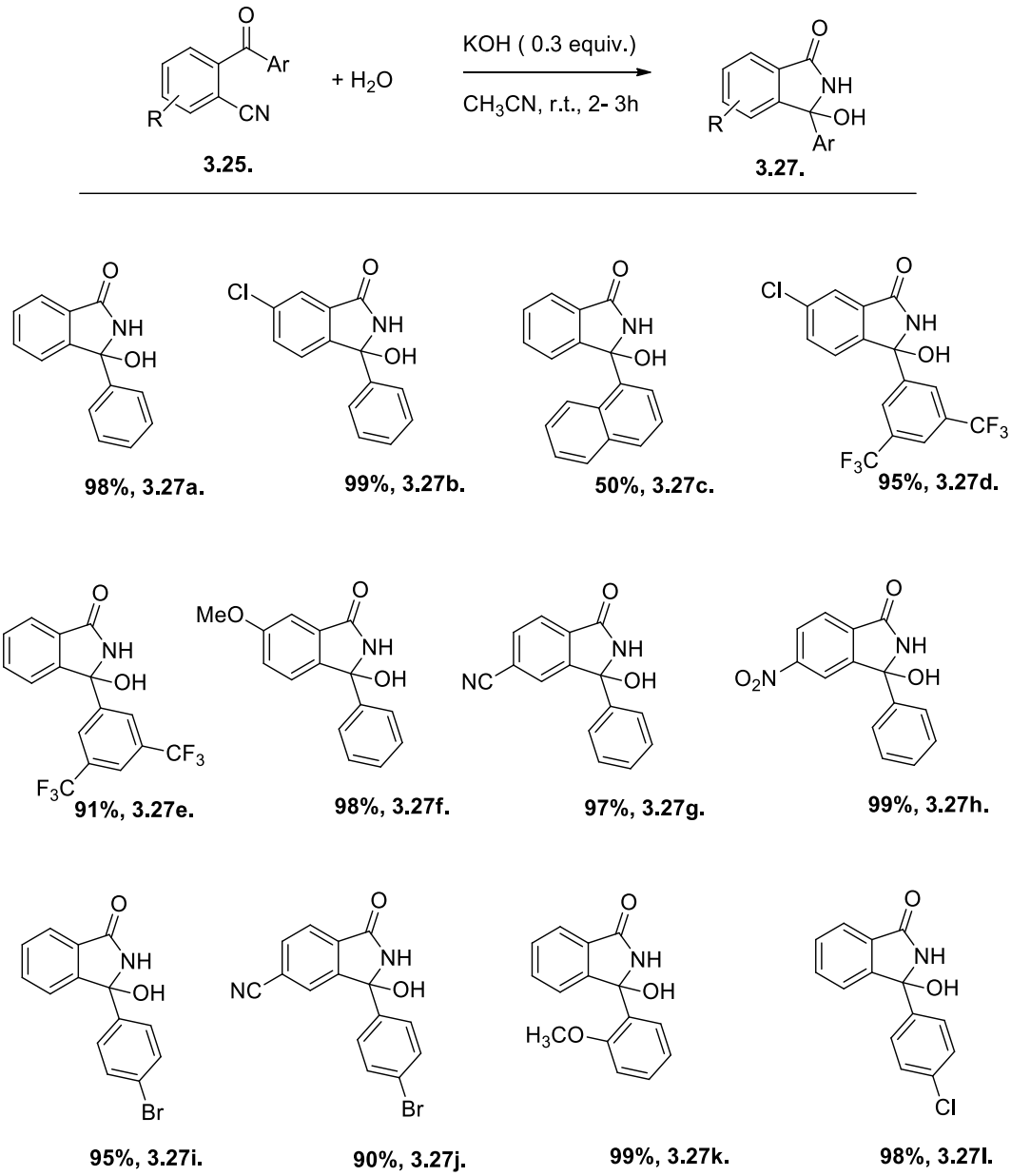


Figure 3.3. ORTEP diagrams for compound **3.26h**

We also focused on the possibility to obtain the precious 3-aryl-3-hydroxy isoindolinones, employing water as hetero-nucleophile. Once again, under the conditions used with 2-cyanoacetophenone,[49] it was also observed that the use of water as nucleophile led to the formation of novel 3-aryl-3-hydroxy isoindolinones (**3.27.**) in quantitative yields with potassium hydroxide in catalytic amount in acetonitrile (**Scheme 3.7.**) The use of this synthetic route has overcome the problem of regioselectivity due to the attack of alkyl Grignard reagents on substituted phthalimides as previously reported in literature.[43] As shown in the **Scheme 3.2** nucleophilic additions of n-hexyl magnesium bromide onto substituted phthalimides produce mixture of regioisomers. Thus, this new synthetic methodology allowed to obtain a new substituted 3-aryl-3-hydroxyisoindolinones in highly regiospecific manner and with greener and milder reaction conditions.

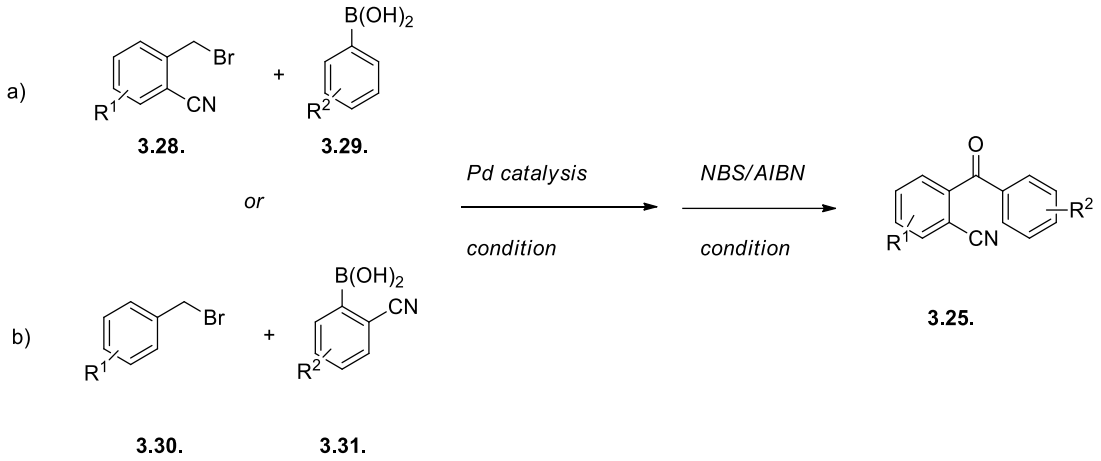


Scheme 3.7. Scope of Cascade Reactions of 2-Acylbenzonitriles **3.25** with water as nucleophile

The results reported in **Scheme 3.7** recall the results of **Scheme 3.6**, where the nature and position of substituents on both aromatic rings don't affect the yield of cascade process. A substrate with a much hindered 3-position, e.g. bearing a 1-naphthyl group, is the only examples where is observed a lower yield (**3.27c**, 50%) but in the other cases the yield exceeds 90%.

3.5. Synthesis of starting materials.

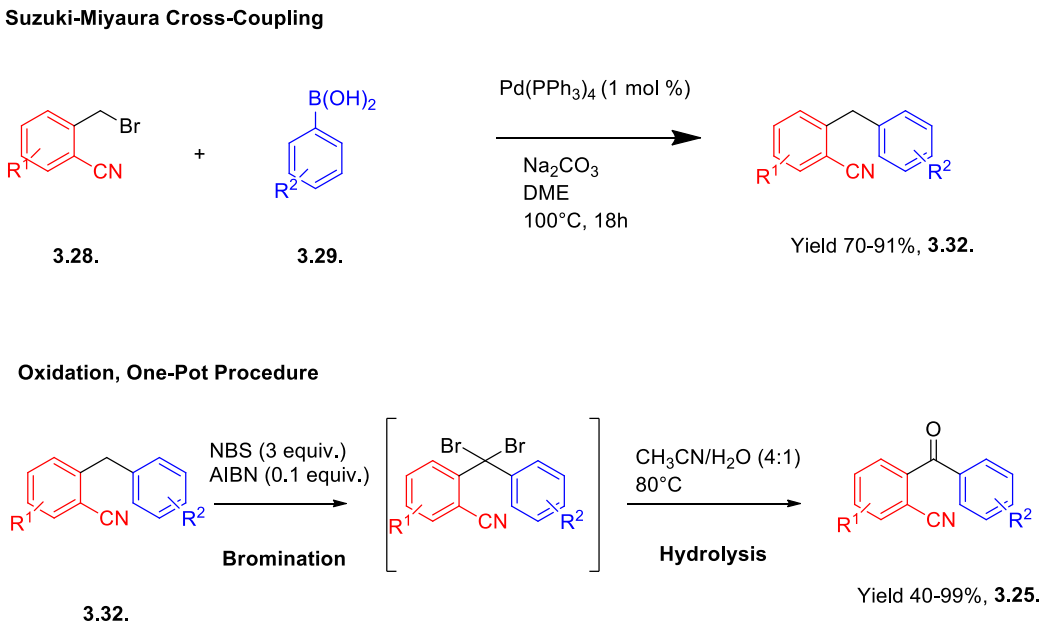
None of the 2-cyanobenzophenones employed in this work is commercially available. Despite several procedures are reported in literature,[51] our aim is to develop a novel and more efficient synthesis of 2-cyanobenzophenones consisting in a two-step reaction pathway. First step is a Suzuki-Miyaura palladium-catalyzed coupling [52] to obtain 2-benzylbenzonitrile **3.25** (**Scheme 3.8.**).



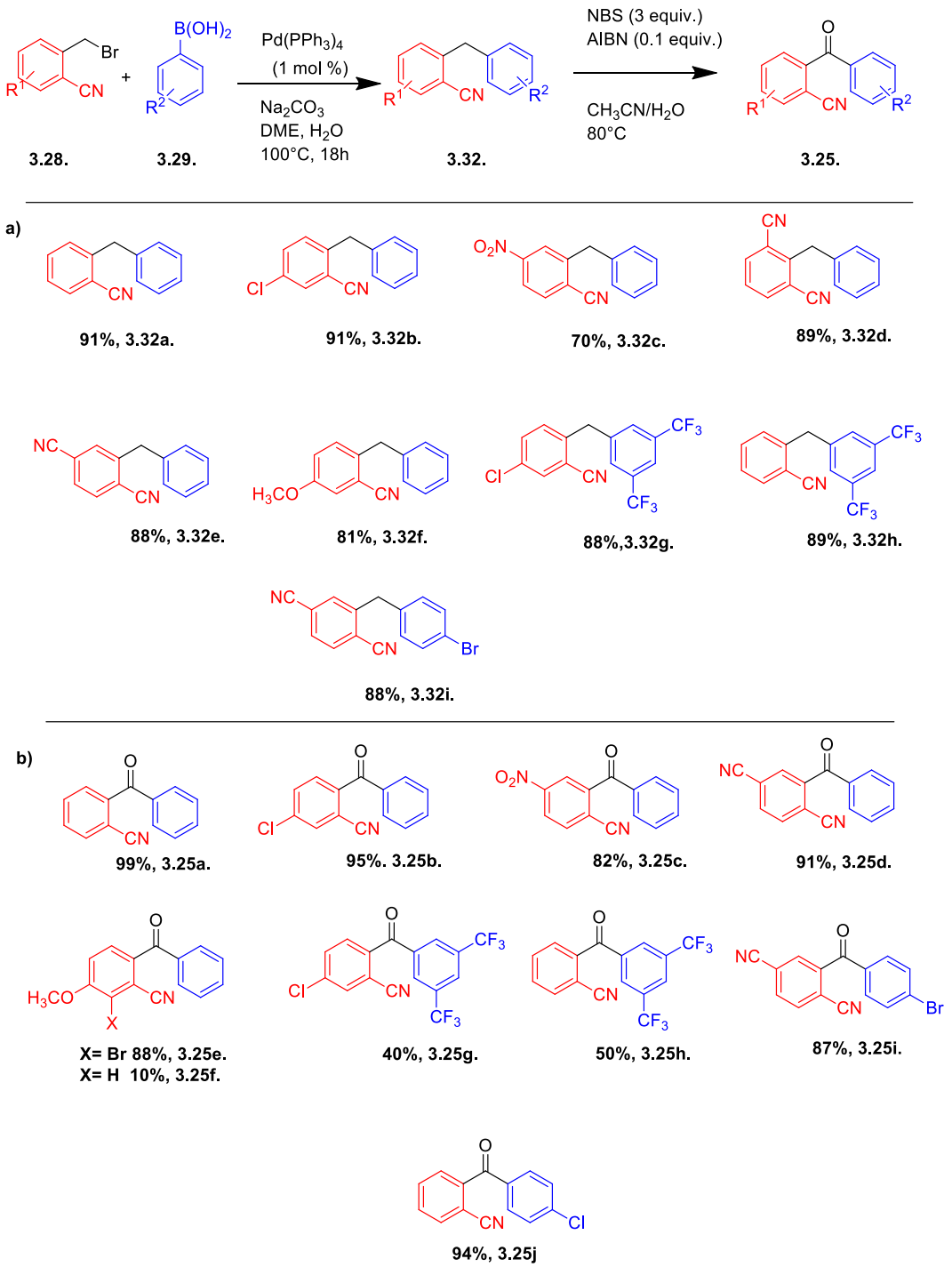
Scheme 3.8. Two-step reaction pathway for the synthesis of 2-cyanobenzophenones **3.25**

The reaction works both using substituted boronic acids with 2-(bromomethyl)benzonitrile (**a**) and 2-cyanoboronic acids with substituted benzylbromides giving comparable results (**b**).

Ketones were obtained through a modified Wohl-Ziegler reaction,[53] consisting of a sequence of bromination/oxidation/hydrolysis of the obtained 2-benzylbenzonitrile **3.25 (Scheme 3.9.),** using a mixture of CH_3CN / H_2O instead of the classic solvent CCl_4 (**Int I.**). The solvent plays a fundamental role, specifically, after radical halogenation through N-bromosuccinimide and radical activator AIBN, took place a S_N2 reaction, in which the intermediate dibromo is hydrolyzed with H_2O probably forming a gem-diol or α-bromohydrine. The last step of the reaction is the loss of either water molecule or HBr leading the formation of ketone. This synthetic methodology led to the synthesis of various substituted novel 2-cyanobenzophenones in very good yields (70 to 91%) (**Scheme 3.10)**.



Scheme 3.9. Two-step reaction pathway for the synthesis of 2-cyanobenzophenones **3.25**

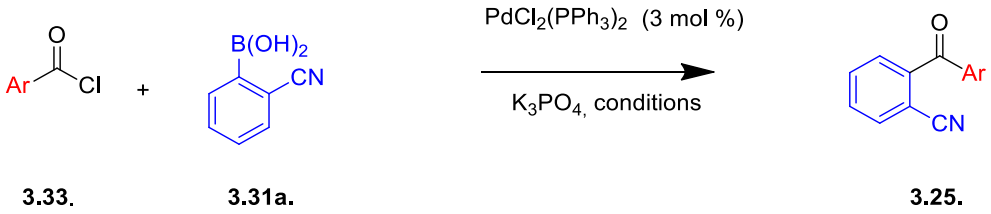


Scheme 3.10. Scope of Cascade Reactions in the synthesis of diaryl methanes (**3.32**) and 2-cyanobenzophenones (**3.25**)

The synthesis of diaryl methane via Suzuki coupling (**Scheme 3.10a)** tolerates both EWG and EDG, affording products in high yields (**3.32a-i**, 70-91%). The one-pot oxidation process produces ketones from moderate to high yields, except for strongly deactivated rings bearing two CF_3 groups (**3.25g** and **3.25h**). Moreover, the oxidation of **3.32f** produces **3.25f** in low yield (**10%**), because took place

a side reaction of electrophilic aromatic substitution catalyzed by the methoxy group in *ortho* position leading to **3.25e** in high yield (**88%**)

Direct coupling of 2-cyanoboronic acid **3.31a.** with acyl chlorides **3.33.** was also tested (**Scheme 3.11.)**. Even if this synthesis methodology is pot-convenient, only decomposition products at 100 °C in toluene are observed (**Table 3.1.**), which changes in THF at 60 ° C reaching a yield of 74%. These results gave the idea that the scope of this pathway is not convenient because limited to few substrates.



3.33. **3.31a.** **3.25.**

Scheme 3.11. Direct coupling reactions for the synthesis of 2-cyanobenzophenones **3.25**

Entry	Ar	Solvent	T° (C)	T (h)	Yield (%) [a]
1 [b,c]	Ph **(3.25a)**	Toluene	100	6	0
2 [b,d]	Ph **(3.25a)**	Toluene	100	6	0
3	Ph **(3.25a)**	Toluene	100	4	48
4	Ph **(3.25a)**	Toluene	100	24	40
5	Ph **(3.25a)**	THF	60	18	68
6	Ph **(3.25a)**	THF	60	24	74
7	1-Naphthyl **(3.25k.)**	THF	60	24	45
8	4-BrC_6H_4 **(3.25l.)**	THF	60	24	40
9	2-MeOC_6H_4 **(3.25m.)**	THF	60	24	35

[a] Yields refer to chromatographically pure compounds. [b] Catalyst-free conditions. [c] 4 eq of NaOH were used. [d] 4 eq of K_2CO_3 were used.

Table 3.1. Screening of reaction conditions for the synthesis of 2-cyanobenzophenones **3.25**

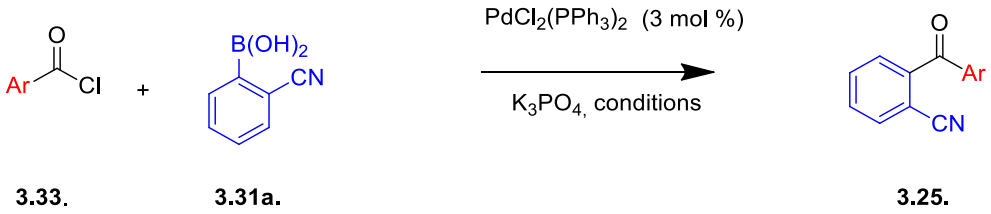
3.6. Conclusions

In conclusion a new synthetic methodology has been developed which leads to the synthesis of new 3,3-disubstituted isoindolinones. This class of molecules of pharmaceutical interest have been synthesized from moderate to high yields under mild reaction conditions. Unlike the examples reported in the literature which involve the use of metal complexes and Grignard reagents, mild reaction basic conditions were employed, such as cheap inorganic bases such as potassium carbonate and low temperature. This cascade reaction method has allowed to obtain compounds with a quaternary carbon, an important challenge in organic synthesis. The developed method is extremely versatile, leading to a huge variety of substituted aromatic ketones in combination with carbon and heteronucleophiles. Thanks to this cascade methodology, 3,3-disubstituted isoindolinones and 3-aryl-3-hydroxyisoindolinones were obtained in quantitative yields.

An important work has been carried out to optimize the synthesis of the starting materials, none of these are commercially available, to widen the library of 2-cyanobenzophenones.

3.7. Experimental part

General procedure for cross coupling palladium reaction between 2-cyanophenylboronic acid and aroyl chlorides. (**Scheme 3.S1.**)



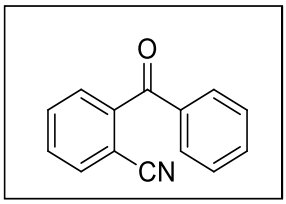
Scheme 3.S1. Direct coupling reactions for the synthesis of 2-cyanobenzophenones **3.25**

To a solution of 2-cyano phenylboronic acid **3.31a.** (0.34 mmol), dichlorobis-(triphenylphosphine) palladium (7.9 mg, 3 mol%) and K_3PO_4 x $2H_2O$ (108 mg, 1.5 mmol) in THF (2 mL) under nitrogen was added freshly prepared aroyl chloride **3.33.** (0.5 mmol). The reaction mixture was heated at 60°C for 24h. After evaporation of the solvent the crude was taken up with ethyl acetate and washed with a saturated solution of sodium bicarbonate, water, and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The resulting material was purified by column chromatography (silica gel, 1:9 ethyl acetate–hexanes) to give the ketones **3.25.**

Entry	**Conditions**	**Yield (3.25) (%)**
S1	K_3PO_4 x $2H_2O$	74
S2	Dry K_3PO_4	20
S3	K_3PO_4 x $2H_2O$ + 5 eq H_2O (introduced in the reaction system after the addition of the salt) 25	25

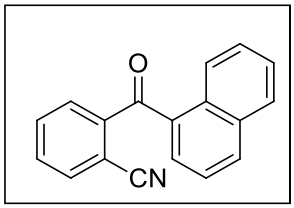
Table 3.S1. Influence of water in the synthesis of 2-cyanobenzophenones **3.25**

2-benzoylbenzonitrile (2-cyanobenzophenone) (3.25a)



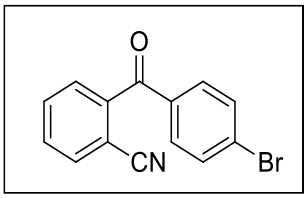
White solid (53 mg, 74%). Mp. 85-87°C. *Data in accordance with literature*.[54] **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2230, 1651. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88-7.82 (m, 3H), 7.73-7.65 (m, 4H), 7.53 (t, *J*= 8.1 Hz, 2H). **^{13}C NMR** (100 MHz, CDCl3): δ 193.8, 141.4, 135.9, 134.2, 133.9, 132.1, 131.4, 130.3, 130.1, 128.7, 117.1, 111.9. **ESI-HRMS**: Found: *m/z* 208.0768. Calcd for $C_{14}H_{10}NO$: $(M+H)^+$ 208.0757.

2-(1-naphthoyl)benzonitrile (3.25k)



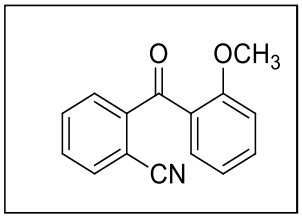
Pale solid (39 mg, 45%). Mp 94–95 °C. **IR** (KBr): $\tilde{\nu}$ (cm–1) 2232, 1654. Data in accordance with literature.[55] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.47 (dd, J= 7.2, 1.8 Hz, 1 H), 8.09 (d, J = 8.1 Hz, 1 H), 7.96 (dd, J= 7.8, 1.8 Hz, 1 H) 7.89 (dd, J= 7.9, 1.2 Hz, 1H), 7.69–7.58 (m, 6 H), 7.51 (t, J= 7.6 Hz, 1 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 196.4, 143.6, 136.1, 135.2, 134.98, 34.93, 133.6, 133.4, 132.7, 132.5, 132.1, 130.0, 129.6, 128.3, 127.0, 125.6, 118.7, 113.7. **ESI-HRMS**: Found: m/z 258.0919. Calcd for $C_{18}H_{12}NO$: $(M+H)^+$ 258.0913.

2-(4-bromobenzoyl)benzonitrile (3.25l)



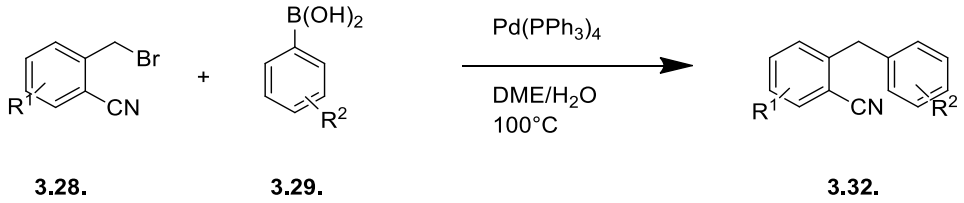
Pale yellow solid (39 mg, 40%). Mp 140–141°C.[56] **IR** (KBr): $\tilde{\nu}$ (cm–1) 2238, 1660. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.84-7.79 (m, 2H), 7.69-7.52 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 192.7, 140.9, 134.7, 134.3, 132.2, 132.1, 3131.7, 131.6, 129.9, 129.4, 116.9, 111.9. ESI-HRMS: Found: *m/z* 285.9858. Calcd for $C_{14}H_9BrNO$: $(M+H)^+$285.9862.

2-(2-methoxybenzoyl)benzonitrile (**3.25m)**



White solid (29 mg, 35%). Mp 89–90°C[57]. **IR** (KBr): $\tilde{\nu}$ (cm–1) 2227, 1602**.** **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.77 (dd, *J*= 6.2, 1.8 Hz, 1 H), 7.63-7.53 (m, 5H), 7.08 (t, *J*= 7.2 Hz, 1 H), 6.96 (d, *J*= 8.3 Hz, 1 H), 3.64 (s, 3H). **^{13}C NMR** (75 MHz, CDCl3): δ 193.6, 158.5, 142.4, 134.2, 134.1, 132.1, 131.4, 131.0, 130.2, 126.9, 120.9, 117.4, 111.6, 111.1, 55.5. **ESI-HRMS**: Found: *m/z* 238.0858. Calcd for $C_{15}H_{12}NO_2$: $(M+H)^+$ 238.0863.

General procedure for preparation of 2-cyanoacetophenones 3.25a-i. (Method A).

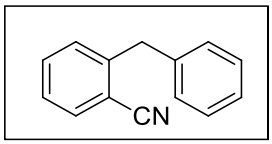


3.28. **3.29.** **3.32.**

Scheme 3.S2. Suzuki coupling for the synthesis of **3.32**, *method A*

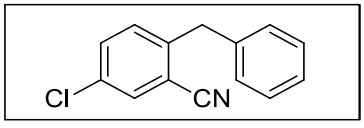
Diaryl methanes **3.32.** were synthesized from the corresponding 2-cyanobenzyl bromides **3.28.** and benzene boronic acids **3.29.** To a solution of commercial available 2-cyanobenzyl bromide **3.28.** (0.8 mmol, 1 equiv.) in 1,2- dimethoxyethane (1.6 mL) and water (800 μL) was added boronic acid **3.29.** (1.2 equiv.), sodium carbonate (2.1 equiv.) and Tetrakis(triphenylphosphine) palladium(0) (0.01 equiv.). The mixture was vacuum flushed with nitrogen and then heated to 100 °C overnight. [58] The solvent was removed and the residue was purified by column chromatography (silica gel, ethyl acetate-hexane from 1/100 to 5/100).

2-benzylbenzonitrile (3.32a)



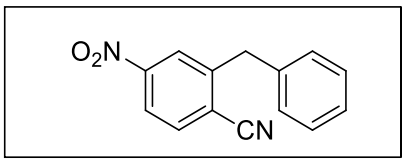
White solid (140 mg, 91%). Mp: 103-104°C. *Data in accordance with literature*.[59] **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2226, 1601. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63-7.66 (m, 1H), 7.47-7.52 (m, 1H), 7.21-7.34 (m, 7H), 4.21 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.0, 138.8, 133.0, 130.1, 129.0, 128.8, 126.9, 126.8, 118.3, 112.6, 40.2. **ESI HRMS**: Found: *m/z* 194.0981. Calcd for $C_{14}H_{12}N$: $(M+H)^+$ 194.0964.

2-benzyl-5-chlorobenzonitrile (3.32b)



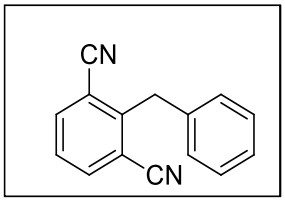
Pale yellow oil (162 mg, 91%). **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2222, 1493, 1483. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.59 (d, *J*= 2.2 Hz, 1H), 7.45 (dd, *J*= 2.2 Hz, 8.4Hz, 1H), 7.35-7.31 (m, 2H), 7.27-7.20 (m, 4H), 4.18 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 143.5, 138.3, 133.2, 132.6, 132.3, 131.4, 128.9, 128.8, 126.9, 116.9, 113.9, 39.6. **ESI-HRMS**: Found: *m/z* 228.0573. Calcd for $C_{14}H_{11}ClN$: $(M+H)^+$ 228.0575.

2-benzyl-4-nitrobenzonitrile (3.32c)



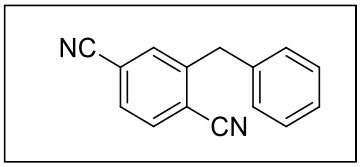
White solid (130 mg, 70%). Mp: 107-108°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2227, 1521, 1383. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15- (dd, *J*= 2.8 Hz, 8.4Hz, 1H), 8.13 (s, 1H), 7.84 (d, *J*= 8.4 Hz, 1H), 7.37-7.24 (m, 5H), 4.31 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 150.1, 147.5, 137.1, 134.1, 129.1, 128.9, 127.4, 124.7, 121.7, 118.2, 116.4, 40.1. **ESI HRMS**: Found: *m/z* 239.0823. Calcd for $C_{14}H_{11}N_2O_2$: $(M+H)^+$ 239.0815.

2-benzylisophthalonitrile (3.32d)



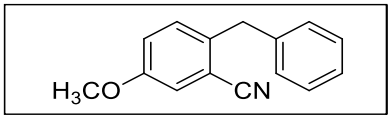
White solid (150 mg, 89%). Mp: 125-126°C. **IR** (KBr): $\tilde{\nu}$(cm^{-1}) 2234, 2227, 1421. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 (d, *J*= 7.8 Hz, 2H), 7.49 (t, *J*= 7.8 Hz, 1H), 7.40-7.27 (m, 5H), 4.47 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 148.3, 137.1, 136.8, 128.9, 128.8, 127.8, 127.3, 116.5, 114.8, 39.0. **ESI-HRMS**: Found: *m/z* 219.0923. Calcd for $C_{15}H_{11}N_2$: $(M+H)^+$ 219.0917.

2-benzylterephthalonitrile (3.32e)



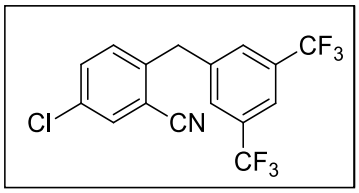
White solid (151 mg, 88%). Mp: 119-120°C. **IR** (KBr): $\tilde{\nu}$(cm^{-1}) 2237, 2222, 1461. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74 (d, *J*= 8.0 Hz, 1H), 7.59 (d, *J*= 8.0 Hz, 1H), 7.53 (s, 1H), 7.38-7.25 (m, 2H), 7.29 (d, *J*= 8.0 Hz, 1H), 7.22 (d, *J*= 7.2 Hz, 2H), 4.24 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 146.4, 137.1, 133.5, 133.4, 130.2, 129.1, 129.0, 127.4, 117.2, 116.8, 116.6, 116.5, 39.8. **ESI-HRMS**: Found: *m/z* 219.0921. Calcd for $C_{15}H_{11}N_2$: $(M+H)^+$ 219.0917.

2-benzyl-5-methoxybenzonitrile (3.32f)



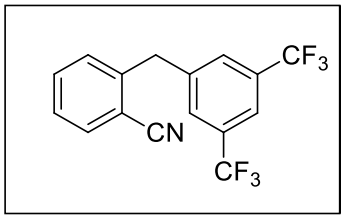
White solid (144 mg, 81%). Mp: 70-71°C. **IR** (KBr): $\tilde{\nu}$(cm^{-1}) 2218, 1608, 1568, 1248. **^{1}H NMR** (400 MHz, CDCl3): δ 7.35-31 (m, 2H), 7.27-7.19 (m, 4H), 7.14 (d, *J*= 2.5 Hz, 1H), 7.07 (dd, *J*= 8.6, 2.5 Hz, 1H), 4.17 (s, 2H), 3.83 (s, 3H). **^{13}C NMR** (100 MHz, CDCl3): δ 157.8, 139.3, 137.1, 131.2, 128.8, 128.6, 126.6, 119.7, 118.1, 116.9, 113.0, 55.6, 39.2. **ESI-HRMS**: Found: *m*/z 224.1083. Calcd for $C_{15}H_{14}NO$: $(M+H)^+$ 224.1070.

2-(3,5-bis(trifluoromethyl)benzyl)-5-chlorobenzonitrile (3.32g)



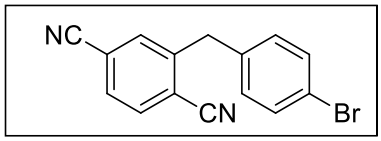
White solid (254 mg, 88%). Mp: 76-77°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2224, 1618, 1449. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.67 (s, 1H), 7.65 (s, 2H), 7.54 (dd, J= 8.4, 2.5 Hz, 1H), 7.21 (d, J= 8.4Hz, 1H), 4.30 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 140.9, 140.6, 133.8, 133.7, 132.8, 132.1 (q, 2JC-F= 30 Hz), 131.3, 128.9, 123.0 (q, 1JCF= 270 Hz), 121.1, 116.4, 114.2, 39.1. **ESI-HRMS**: Found: m/z 364.0318. Calcd for $C_{16}H_9ClF_6N$: $(M+H)^+$ 364.0322.

2-(3,5-bis(trifluoromethyl)benzyl)-benzonitrile (**3.32h)**



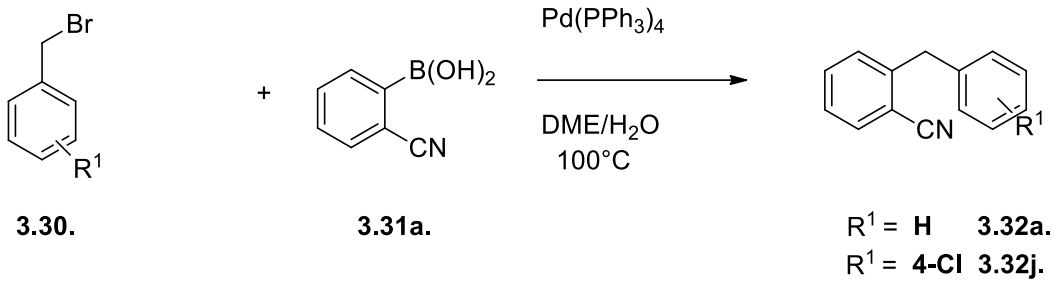
White solid (232 mg, 89%). Mp: 50-51°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2224, 1618, 1469. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.67-7.64 (m, 3H), 7.54 (dd, *J*= 8.4, 2.5 Hz, 1H), 7.39 (t, *J*= 7.6 Hz, 1H), 7.21 (d, *J*= 8.4Hz, 1H), 4.30 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 142.4, 141.1, 133.4, 133.3, 132.0 (q, 2*JC-F*= 30 Hz), 130.0, 129., 127.7, 123.1 (q, 1*J*C-F= 270 Hz), 120.9, 117.7, 112.7, 39.6. **ESI-HRMS**: Found: *m/z* 330.0732. Calcd for $C_{16}H_{10}F_6N$: $(M+H)^+$ 330.0712.

2-(4-bromobenzyl)benzene-1,4-dinitrile (3.32i)



Reaction was carried out using 0.8 mmol of 4-bromobenzeneboronic acid. White solid (208 mg, 88%). Mp: 88-89°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2234, 2227, 1421. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (d, *J*= 8.0 Hz, 1H), 7.64 (d, *J*= 8.0 Hz, 1H), 7.54 (s, 1H), 7.48 (d, *J*= 8.3 Hz, 2H), 7.11 (d, *J*= 8.3 Hz, 2H), 4.21 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): 145.6, 136.0, 133.6, 133.3, 132.2, 130.7, 130.5, 121.4, 117.0, 116.8, 116.3, 39.3. **ESI-HRMS**: Found: *m/z* 297.0044. Calcd for $C_{15}H_{10}BrN_2$: $(M+H)^+$ 297.0022.

General procedure for preparation of benzylbenzonitriles 3.32a. and 3.32j. (Method B).



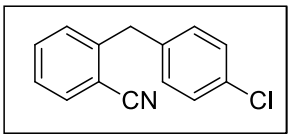
Scheme 3.S3. Suzuki coupling for the synthesis of **3.32**, *method B*

Diaryl methanes **3.32a** and **3.32j** were synthesized from the corresponding 2-cyanobenzene boronic **3.31a.** acid and benzyl bromides **3.30.**

To a solution of benzyl bromide **3.30.** (0.4 mmol, 1 equiv.) in 1,2-dimethoxyethane (800 mL) and water (400 mL) was added boronic acid **3.31a.** (1.2 equiv.), sodium carbonate (2.1 equiv.) and Tetrakis(triphenylphosphine) palladium (0) (0.01 equiv.). The mixture was vacuum flushed with nitrogen and then heated to 100 °C overnight.5 The solvent was removed and the residue was purified by column chromatography (silica gel, ethyl acetate-hexane from 1/100 to 5/100).

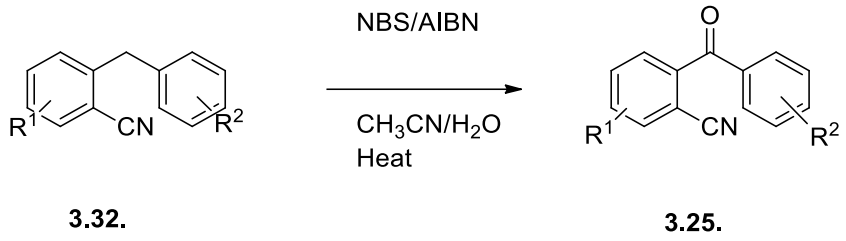
2-benzylbenzonitrile 3.32a. White solid (140 mg, 91%). *Data in accordance with those previously reported.* **ESI-HRMS**: Found: *m/z* 194.0981. Calcd for $C_{14}H_{12}N$: $(M+H)^+$ 194.0968.

2-(4-chlorobenzyl)benzonitrile (3.32j)



Colorless oil (80 mg, 89%). *Data in accordance with literature.*[60] **IR** (KBr): $\tilde{\nu}$(cm^{-1}) 2222, 1493, 1483. **^{1}H NMR** (400 MHz, CDCl3) δ 7.65 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.51 (ddd, *J* = 7.6, 1.2 Hz, 1H), 7.32 (1H, ddd, *J* = 7.6, 1.2 Hz,1H), 7.29-7.25 (3H, m), 7.16 (d, *J* = 8.4 Hz, 2H), 4.17 (s, 2H). **^{13}C NMR** (100 MHz, CDCl3) δ 144.2, 137.2,133.0, 132.9, 132.5, 130.2, 129.9, 128.8, 127.0, 118.0, 112.4, 39.4. **ESI-HRMS**: Found: *m/z* 228.0588. Calcd for $C_{14}H_{11}ClN$: $(M+H)^+$ 228.0580.

General procedure for the oxidation/hydrolysis of benzylbenzonitriles (Scheme 3.S4)

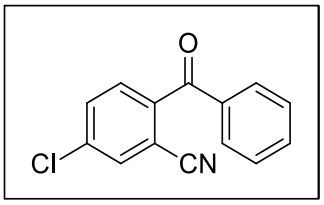


Scheme 3.S4. One-pot oxidation of diaryl methanes **3.32** for the synthesis of 2-cyanobenzophenones **3.25**

A mixture of 2-benzylbenzonitrile **3.32** (0.76 mmol), *N*-Bromosuccinimide (3.5 eq.) and AIBN (0.1 eq.) in CH_3CN/H_2O 4/1 (3.5 mL) was heated at 80°C under stirring till starting material disappeared.7 After cooling to room temperature, the solvent was removed under reduced pressure and the residue taken up with dichloromethane was washed with water. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product **3.25** was purified by flash chromatography (ethyl acetate-hexane 10/90).

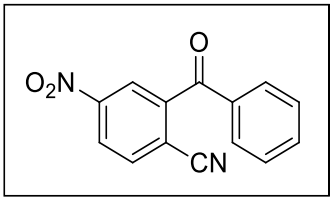
2-benzoylbenzonitrile 3.25a. White solid (154 mg, 99%). *Data in accordance with those reported in literature.*[61] **ESI-HRMS**: Found: *m/z* 208.0763. Calcd for $C_{14}H_{10}NO$: $(M+H)^+$ 208.0757.

2-benzoyl-5-chlorobenzonitrile (3.25b)



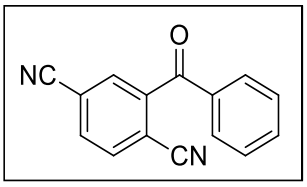
White solid (174 mg, 95%). Mp: 95-96°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2227, 1652. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (dd, *J* = 2.8 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.66-760 (m, 2H), 7.58 (s, 1H), 7.49 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.6, 139.6, 137.8, 135.6, 134.1, 133.9, 132.4, 131.4, 130.2, 128.8, 115.8, 113.6. **ESI-HRMS**: Found: *m/z* 242.0356. Calcd for $C_{14}H_9ClNO$: $(M+H)^+$ 242.0367.

2-benzoyl-4-nitrobenzonitrile (3.25c)



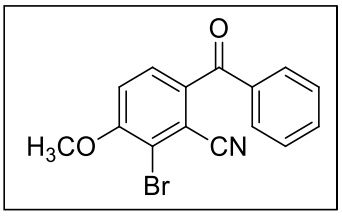
White solid (156 mg, 82%). Mp: 99-100°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2228, 1668, 1570, 1380. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.53 (d, *J*= 8.4 Hz, 1H), 8.49 (s, 1H), 8.10 (dd, *J*= 8.4, 1.3 Hz 1H), 7.83 (d, *J*= 7.5 Hz, 2H), 7.75 (t, *J*= 7.5 Hz, 1H), 7.56 (t, *J*= 8.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.6, 139.6, 137.8, 135.6, 134.1, 133.9, 132.4, 131.4, 130.2, 128.8, 115.8, 113.6. **ESI-HRMS**: Found: *m/z* 242.0356. Calcd for $C_{14}H_9ClNO_3$: $(M+H)^+$ 253.0608.

2-benzoyl-4-cyanobenzonitrile (3.25d)



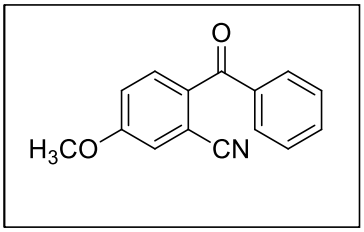
White solid (171 mg, 91%). Mp: 155-156°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2234, 2227, 1671. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96-7.92 (m, 3H), 7.78 (d, *J*= 7.2 Hz, 2H), 7.71 (d, *J*= 7.5 Hz, 1H), 7.55 (t, *J*= 7.5 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 191.5, 142.5, 134.8, 134.7, 134.4, 133.0, 130.3, 129.07, 116.4, 116.2, 115.9, 115.5. **ESI-HRMS**: Found: *m/z* 233.0714. Calcd for $C_{15}H_9N_2O$: $(M+H)^+$ 233.0709.

6-benzoyl-2-bromo-3-methoxybenzonitrile (3.25e)



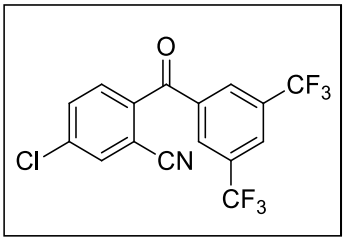
Yellow solid (210 mg, 88%). Mp: 138°C (dec.). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 2225, 1605. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (d, *J*= 7.3 Hz, 2H) 7.63 (t, *J*= 7.2 Hz, 1H), 7.57 (d, *J*= 8.6 Hz, 1H), 7.49 (t, *J*= 7.6 Hz, 2H), 7.10 (d, *J*= 8.6 Hz, 1H), 4.01 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): 192.3, 158.7, 136.2, 135.2, 133.7, 130.2, 128.6, 118.3, 116.5, 115.3, 113.6, 56.9. **ESI-HRMS**: Found: *m/z* 315.9952. Calcd for C15H11BrNO2: $(M+H)^+$ 315.9968.

2-benzoyl-5-methoxybenzonitrile (3.25f)



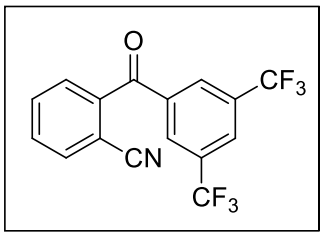
Pale oil (18 mg, 10%)[62]. **IR** (KBr): $\tilde{\nu}$(cm^{-1}) 2232, 1610.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (dd, *J*= 8.2, 1.2 Hz, 2H) 7.62 (d, *J*= 8.6 Hz, 2H), 7.49 (t, *J*= 8.2 Hz, 2H), 7.32 (d, *J*= 2.6 Hz, 1H), 7.13 (dd, *J*= 8.6, 2.6 Hz, 1H), 3.91 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 192.9, 161.66, 136.5, 133.1, 132.7, 130.0, 128.4, 119.7, 117.2, 116.9, 113.9, 55.8. **ESI-HRMS**: Found: *m/z* 238.0857. Calcd for $C_{15}H_{12}NO_2$: $(M+H)^+$ 238.0863.

2-(3,5-bis(trifluoromethyl)benzoyl)-5-chlorobenzonitrile (3.25g)



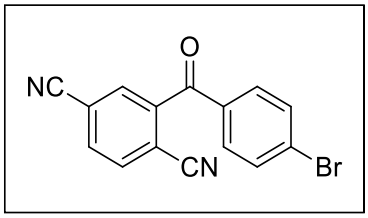
White solid (114 mg, 40%). Mp: 88-89°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 2227, 1652. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.21 (s, 2H), 8.15 (s, 1H), 7.78 (s, 1H), 7.74 (dd, *J*= 8.4 H, 1.6 Hz, 1H), 7.61 (d, *J*= 8.4 Hz, 1H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 189.8, 139.4, 137.4, 137.3, 134.7, 132.9, 132.6 (q, 2*J*C-F= 30 Hz), 131.4, 129.9, 127.1, 122.5 (q, 1*J*C-F=270 Hz), 115.3, 113.9. **ESI-HRMS**: Found: *m/z* 378.0108. Calcd for $C_{16}H_7ClF_6NO$: $(M+H)^+$ 378.0115.

2-(3,5-bis(trifluoromethyl)benzoyl)-benzonitrile (3.25h)



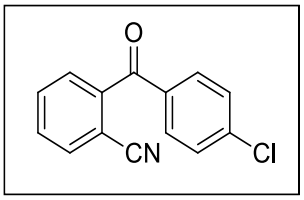
White solid (130 mg, 50%). Mp: 90-91°C. **IR** (KBr): $\tilde{\nu}$(cm^{-1}) 2227, 1672. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.24 (s, 2H), 8.14 (s, 1H), 7.93-7.91 (m, 1H), 7.78-7.76 (m, 2H), 7.66-7.4 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.9, 139.2, 137.6, 134.8, 132.6, 132.4 (q, $^{2}J_{C\text{-}F}$= 30 Hz), 130.0, 129.9, 126.9, 122.6 (q, $^{1}J_{C\text{-}F}$= 270 Hz), 116.5, 112.2. **ESI-HRMS**: Found: *m/z* 344.0510. Calcd for $C_{16}H_8F_6NO_2$: $(M+H)^+$ 344.0505.

2-(4-bromobenzoyl)benzene-1,4-dinitrile (3.25i)



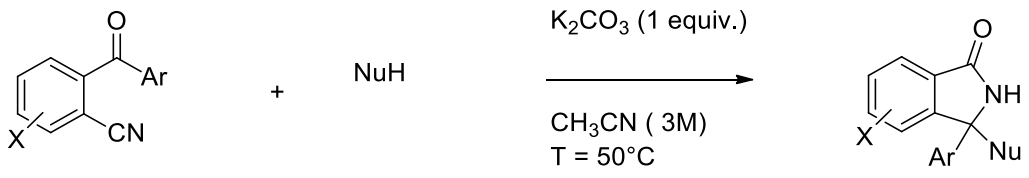
White solid (204 mg, 87%). Mp: 202-203°C. IR (KBr): $\tilde{\nu}$(cm^{-1}) 2232, 1655.**^{1}H NMR** (300 MHz, DMSO-d_6): δ 8.24 (s, 3H), 7.77-7.68 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.7, 141.5, 135.9, 135.7, 134.3, 133.7, 132.6, 132.5, 129.3, 117.4, 116.4, 115.9, 114.9. ESI-HRMS: Found: *m/z* 310.9825. Calcd for $C_{15}H_8BrN_2O$: $(M+H)^+$ 310.9815

2-(4-chlorobenzoyl)benzonitrile (3.25j)



Pale yellow solid (172 mg, 94%). Mp 119–120°C.[63] IR (KBr disk): $\tilde{\nu}$(cm^{-1}) 2238, 1660. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84-7.83 (m, 1H), 7.75-7.1 (m, 6H), 7.47 (d, *J*= 6.7 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.6, 140.9, 140.5, 134.3, 134.2, 132.3, 131.6, 129.9, 129.1, 127.4, 116.9, 111.8. **ESI-HRMS**: Found: *m/z* 242.0381. Calcd for $C_{14}H_9ClNO$: $(M+H)^+$ 242.0367.

General procedure for tandem reaction of 2-benzoylbenzonitriles with carbon- and hetero-nucleophiles, 3.26.

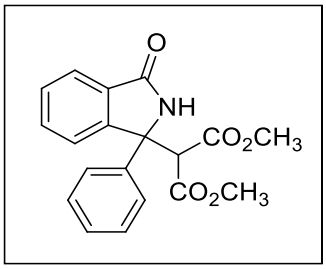


3.25. **3.26.**

Scheme 3.S5. Cascade reaction for the synthesis of 3,3-disubstituted isoindolinones **3.26**

2-benzoylbenzonitrile (**3.25.**) (0.2 mmol) was added to a solution of the nucleophile (3 eq.) and K_2CO_3 (1 eq.), in acetonitrile (130 μL) and the mixture was stirred at 50°C. After disappearing of the starting material, dichloromethane was added, and the mixture was filtered and the solvent evaporated in vacuo. The crude product was purified by flash chromatography (from Hexane 8: Ethyl acetate 2 to Hexane 6: Ethyl acetate 4).

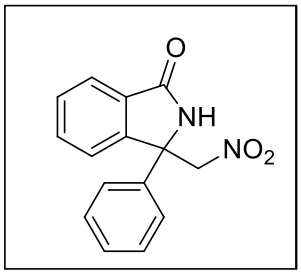
Dimethyl 2-(1-oxo-3-phenylisoindolin-3-yl)malonate (3.26a)



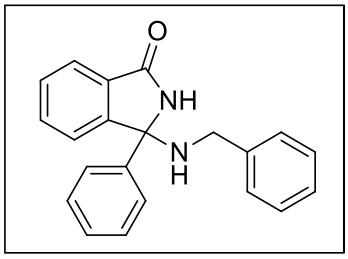
Reaction time 72h. White solid (46 mg, 97%). Mp. 198-199°C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3208, 1767, 1740, 1682. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J*= 8.0 Hz, 1H), 7.51 (s overlapped d, 1H), 7.48 (d, *J*= 8.0 Hz, 3H), 7.42-7.39 (m, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 4.81 (s, 1H), 3.62 (s, 3H), 3.38 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 167.7, 165.5, 148.3, 140.2, 132.4, 130.0, 129.2, 128.8, 128.2, 124.3, 123.9, 122.7, 66.2, 58.2, 52.9, 52.8. **ESI-HRMS**: Found: *m/z* 240.1168. Calcd for $C_{19}H_{18}NO_5$: $(M+H)^+$ 240.1179.

3-(nitromethyl)-3-phenylisoindolin-1-one (3.26b)

After disappearing of starting material, acetic acid (15 μL) diluted in dichloromethane (1 mL) was added. The filtered solution was purified on silica gel. White solid (47 mg, 89%). Mp. 218-219°C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3412, 1714, 1542. **^{1}H NMR** (400 MHz, Acetone-d_6) δ 7.80 (br s, 1H), 7.79-7.73 (m, 4H), 7.70 (d, *J*= 8.4 Hz, 1H), 7.61 (t, *J*= 8.4 Hz, 1H), 7.52 (t, *J*= 8.4 Hz, 1H), 7.40 (t, *J*= 8.4 Hz, 1H), 7.32 (t, *J*= 8.4 Hz, 1H), 5.78 (d, *J* = 13.5 Hz, 1H), 5.40 (d, *J*= 13.5 Hz, 1H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 168.8, 147.2, 139.2, 132.2, 130.8, 129.1, 129.0, 128.2, 125.0, 123.6, 123.3, 80.4, 65.1. **ESI-HRMS**: Found: *m/z* 269.0938. Calcd for $C_{15}H_{13}N_2O_3$: $(M+H)^+$ 269.0921.

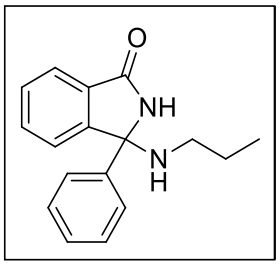


3-(benzylamino)-3-phenylisoindolin-1-one (3.26c)



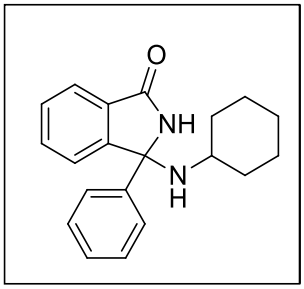
White solid (62 mg, 99%). Mp. 192-193°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3272, 1692, 1491. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J*= 7.2 Hz, 3H), 7.54 (s, 1H), 7.53-7.49 (m, 2H), 7.47-7.40 (m, 1H), 7.37-7.28 (m, 7H), 7.27 (d, *J*= 7.5 Hz, 1H), 3.86 (d, *J*= 12.7 Hz, 1H), 3.52 (d, *J*= 12.7 Hz, 1H), 2.32 (br s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.5, 149.4, 141.3, 139.8, 132.7, 130.5, 129.0, 128.9, 128.4, 128.1, 127.1, 125.8, 123.7, 123.1, 80.3, 46.7. **ESI-HRMS**: Found: *m/z* 315.1485. Calcd for $C_{21}H_{19}N_2O$: (M+H)+ 315.1492.

3-phenyl-3-(propylamino)isoindolin-1-one (3.26d)



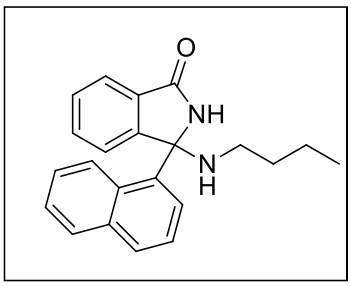
Reaction was carried out at 40°C. White solid (52 mg, 98%). Mp. 144-147°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3285, 1686. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J*= 7.8 Hz, 1H), 7.75 (d, *J*= 7.8 Hz, 1H), 7.49 (d, *J*= 7.8 Hz, 1H), 7.44 (t, *J*=6.2 Hz, 2H), 7.42-7.31 (m, 4H), 2.64-2.60 (m, 2H), 2.30-2.24 (m, 1H), 1.95 (br s, 1H), 1.50 (q, *J*= 7.3 Hz, 2H), 0.92 (t, *J*= 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.3, 149.8, 141.6, 132.5, 130.4, 128.8, 128.7, 128.3, 125.8, 123.6, 123.0, 80.3, 44.2, 23.6, 11.7. **ESI-HRMS**: Found: *m/z* 267.1498. Calcd for $C_{17}H_{19}N_2O$: $(M+H)^+$267.1492.

3-(cyclohexylamino)-3-phenylisoindolin-1-one (3.26e)



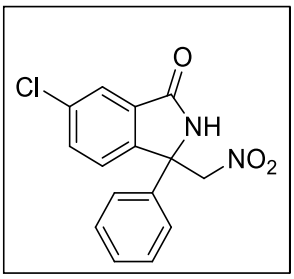
White solid (56 mg, 93%). Mp. 136-137°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3282, 1689. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J*= 7.2 Hz, 1H), 7.72 (d, *J*= 7.2 Hz, 2H), 7.46-7.39 (m, 3H), 7.33-7.25 (m, 3H), 7.05 (s, 1H), 2.38-2.33 (m, 1H), 1.95-1.83 (m, 2H), 1.62 (br s, 1H), 1.61-1.45 (m, 3H), 1.16-1.22 (m, 2H), 1.04 (t, *J*= 8.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.1, 150.1, 142.6, 132.4, 130.4, 128.7, 128.3, 125.6, 123.5, 123.4, 80.4, 50.9, 36.3, 36.0, 25.5, 25.3, 25.0. ESI-HRMS: Found: *m/z* 307.1821. Calcd for $C_{20}H_{23}N_2O$: $(M+H)^+$ 307.1805.

3-(butylamino)-3-(naphthalen-1-yl)isoindolin-1-one (3.26f)



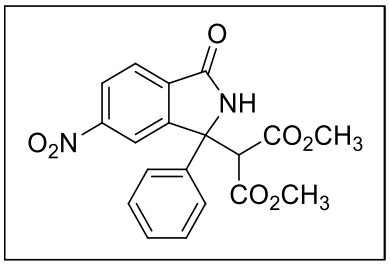
Yellow gum (34 mg, 50%). **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3282, 1681. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, *J*= 7.1 Hz, 1H), 7.97 (d, *J*= 7.3 Hz, 1H), 7.88 (d, *J*= 8.0 Hz, 1H), 7.80 (d, *J*= 8.0 Hz, 1H), 7.57 (t, *J*= 7.6 Hz, 1H), 7.47 (t, *J*= 7.3 Hz, 1H), 7.40 (t, *J*= 7.4 Hz, 1H), 7.33 (t, *J*= 7.1 Hz, 1H), 7.11-7.09 (m, 4H), 3.30-3.23 (m, 1H), 3.11-3.04 (m, 1H), 1.67 (br s, 1H), 1.27-0.85 (m, 4H), 0.64 (t, *J*= 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.0, 151.5, 134.3, 133.1, 132.6, 131.0, 130.7, 129.0, 128.9, 127.0, 126.4, 125.4, 124.8, 123.9, 121.9, 79.2, 39.5, 30.7, 20.5, 13.5. **ESI-HRMS**: Found: *m/z* 331.1817. Calcd for $C_{22}H_{23}N_2O$: $(M+H)^+$ 331.1805.

6-chloro-3-(nitromethyl)-3-phenylisoindolin-1-one (3.26g)



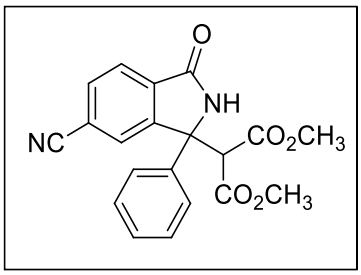
After disappearing of starting material, acetic acid (15 μL) diluted in dichloromethane (1 mL) was added, the solution was filtered and purified on silica gel. White solid (53 mg, 88%). Mp. 220-221 °C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3392, 1717, 1552. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.70 (s, 1H), 7.82 (d, *J*= 8.4Hz, 1H), 7.78-7.65 (m, 1H), 7.58 (d, *J*= 7.6 Hz, 2H), 7.39-7.29 (m, 4H), 5.67 (d, *J*= 13.2 Hz, 1H), 5.55 (d, *J*= 13.2 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 167.8, 146.2, 138.9, 133.2, 132.7, 129.4, 128.7, 125.9, 125.6, 123.4, 80.5, 65.5. **ESI-HRMS**: Found: *m/z* 303.0537. Calcd for $C_{15}H_{12}ClN_2O_3$: $(M+H)^+$ 303.0531.

Dimethyl 2-(6-nitro-1-oxo-3-phenylisoindolin-3-yl)malonate (3.26h)



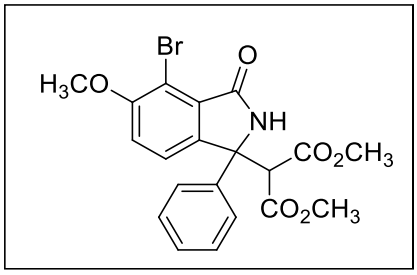
White solid (76 mg, 99%). Mp. 147-148°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3218, 1765, 1742, 1689, 1549. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (d, *J*= 8.3 Hz, 1H), 8.26 (s, 1H), 7.95 (d, *J*= 8.3 Hz, 1H), 7.79 (s, 1H), 7.50 (d, *J*= 7.3 Hz, 2H), 7.38 (t, *J*= 7.3 Hz, 2H), 7.35-7.33 (m, 1H), 4.89 (s, 1H), 3.65 (s, 3H), 3.45 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.6, 167.5, 165.2, 150.5, 149.7, 138.7, 135.4, 129.6, 128.8, 125.2, 124.5, 124.2, 118.3, 66.3, 57.6, 53.2, 53.1. **ESI-HRMS**: Found: *m/z* 385.1045. Calcd for $C_{19}H_{17}N_2O_7$: $(M+H)^+$ 385.1036.

Dimethyl 2-(6-cyano-3-oxo-1-phenylisoindolin-1-yl)malonate (3.26i)



White solid (73 mg, 99%). Mp. 204-205°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3218, 2227, 1765, 1742, 1689. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, J= 7.7 Hz, 1H), 7.77 (s, 1H), 7.71-7.69 (m, 2H), 7.46-7.45 (m, 2H), 7.37 (t, J= 7.6 Hz, 2H), 7.31 (d, J= 7.0 Hz, 1H), 4.89 (s, 1H), 3.65 (s, 3H), 3.45 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.9, 167.4,165.2, 149.0, 138.8, 133.9, 132.7, 129.6, 128.8, 126.8, 124.9, 117.8, 115.8, 66.3, 57.7, 53.2, 53.0. **ESI-HRMS**: Found: m/z 365.1149. Calcd for $C_{20}H_{17}N_2O_5$: $(M+H)^+$ 365.1132.

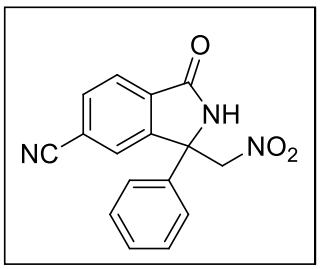
Dimethyl 2-(4-bromo-5-methoxy-3-oxo-1-phenylisoindolin-1-yl)malonate (3.26j)



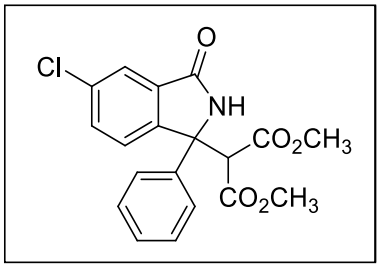
Reaction time 96h. White solid (88 mg, 98%). Mp. 205-206°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3214, 1766, 1740, 1686. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.48 (s, 1H), 7.47 (d, *J*= 7.5 Hz, 1H), 7.37 (t, *J*= 7.6 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 7.02 (d, *J*= 8.2 Hz, 1H), 4.78 (s, 1H), 3.91 (s, 3H), 3.66 (s, 3H), 3.51 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.9, 167.6, 165.4, 156.6, 142.2, 140.3, 129.3, 128.8, 128.2, 124.2, 122.3, 115.4, 108.7, 63.9,58.3, 56.7, 53.0, 52.9. **ESI-HRMS**: Found: *m/z* 448.0387. Calcd for $C_{20}H_{19}BrN_2O_6$: $(M+H)^+$ 448.0396.

3-(nitromethyl)-1-oxo-3-phenylisoindoline-5-carbonitrile (3.26k)

After disappearing of starting material, acetic acid (15 μL) diluted in dichloromethane (1 mL) was added, the solution was filtered and purified on silica gel. White solid (53 mg, 92%). Mp. > 250°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3392, 2231, 1717. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.34 (s, 1H), 7.91 (dd, *J*= 7.8, 1.2 Hz, 1H), 7.77 (d, *J*= 7.8 Hz, 1H), 7.55 (d, *J*= 7.6 Hz, 2H), 7.34 (t, *J*= 7.8 Hz, 2H), 7.27 (t, *J*= 7.6 Hz, 1H), 5.67 (d, *J*= 13.2 Hz, 1H), 5.49 (d, *J*= 13.2 Hz, 1H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 169.1, 149.5, 139.9, 136.6, 135.3, 131.0,130.4, 129.6, 127.1, 126.3, 120.0, 116.4, 81.8, 67.1. **ESI-HRMS**: Found: *m/z* 294.0867. Calcd for $C_{16}H_{12}N_3O_3$: $(M+H)^+$ 294.0873.

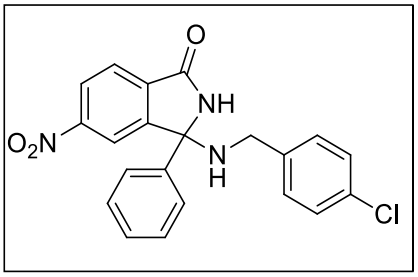


Dimethyl 2-(5-chloro-3-oxo-1-phenylisoindolin-1-yl)malonate (3.26l)



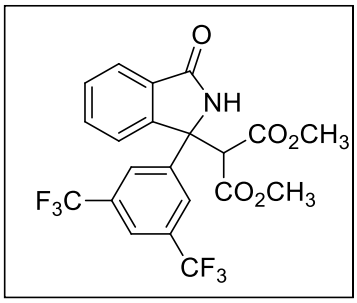
White solid (69 mg, 93%). Mp. 208°C (dec.). **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3216, 1764, 1742, 1685. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.60 (s, 1H), 7.45 (d, *J*= 7.5 Hz, 3H), 7.33 (t, *J*= 7.5 Hz, 3H), 7.27 (d, *J*= 7.2 Hz, 1H), 4.80 (s, 1H), 3.63 (s, 3H), 3.44 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.5, 167.6, 165.4, 146.5, 139.6, 135.1, 132.5, 131.8, 129.4, 128.4, 124.2, 124.1, 124.0, 66.0, 57.8, 53.0, 52.9. **ESI-HRMS**: Found: *m/z* 374.0787. Calcd for $C_{19}H_{17}ClNO_5$: $(M+H)^+$ 374.0795.

3-(4-chlorobenzylamino)-5-nitro-3-phenylisoindolin-1-one (3.26m)



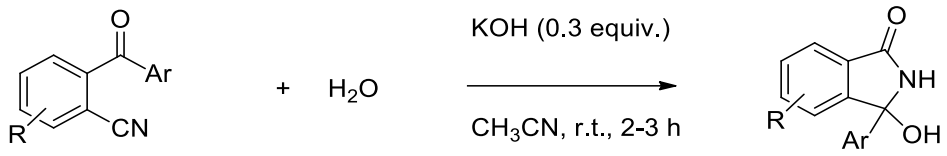
White solid (77 mg, 98%). Mp. 159-160°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3272, 1692, 1551. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.21 (dd, *J*= 8.2, 1.9 Hz, 1H), 8.12 (d, *J*= 1.9 Hz, 1H), 7.87 (d, *J*= 8.2 Hz, 1H), 7.71 (dd, *J*= 8.5, 1.2 Hz, 1H), 7.35-7.29 (m, 5H), 7.17 (q, *J*= 8.2 Hz, 4H), 3.76 (d, *J*= 13.1 Hz, 1H), 3.41 (d, *J*= 13.1 Hz, 1H), 2.33 (br s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.2, 152.4, 151.8, 141.1, 139.1, 136.9, 134.6, 130.8, 130.8, 130.7, 130.1, 126.9, 126.3, 126.2, 120.4, 81.7, 47.5. **ESI-HRMS**: Found: *m/z* 394.0959. Calcd for $C_{21}H_{17}ClN_3O_3$: $(M+H)^+$ 394.0953.

Dimethyl 2-(1-(3,4-bis(trifluoromethyl)phenyl)-3-oxoisoindolin-1-yl)malonate (3.26n)



White solid (92 mg, 97%). Mp. 194-195°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3214, 1768, 1740, 1685. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (s, 2H), 7.48 (s, 1H), 7.86 (d, *J*= 7.4 Hz, 1H), 7.82 (s, 1H), 7.60-7.56 (m, 2H), 7.50 (t, *J*= 7.4Hz, 1H), 7.39 (d, *J*= 7.3 Hz, 1H), 4.81 (s, 1H), 3.68 (s, 3H), 3.42 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.7, 167.4, 164.7, 146.6, 143.6, 133.0, 132.6 (q, $^{2}J_{C\text{-}F}$= 33 Hz), 130.0, 129.6, 124.9, 124.6, 122.8 (q, $^{1}J_{C\text{-}F}$= 270 Hz), 122.5, 122.4, 65.7, 58.0, 53.3, 53.1. **ESI-HRMS**: Found: *m/z* 476.0935. Calcd for $C_{21}H_{16}F_6NO_5$: $(M+H)^+$ 476.0927.

General procedure for tandem reaction of 2-benzoylbenzonitriles with the hydroxide anion, 3.27.

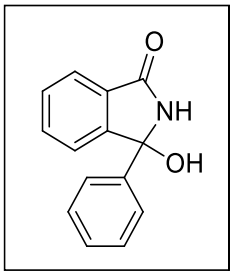


3.25. **3.27.**

Scheme 3.S6. Cascade reaction for the synthesis of 3,3-disubstituted isoindolinones **3.27**

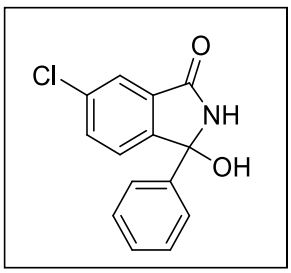
To a solution of 2-benzoylbenzonitrile **3.25.** (0.2 mmol) in acetonitrile (2 mL), KOH (0.3 eq) in water (200 μL) was added and the mixture was stirred at room temperature until disappearance of the starting material (TLC hexane-acetyl acetate 6:4). After the starting material disappeared (1-3h), the solution was diluted with dichloromethane, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography.

3-hydroxy-3-phenylisoindolin-1-one (3.27a)



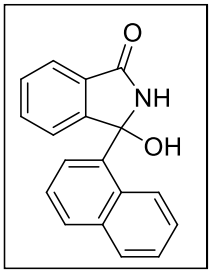
White solid (44 mg, 98%). Mp. 160–162 °C. *Data in accordance with literature*.[64,65] **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3242, 3180, 1695, 1403, 509. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 9.24 (s, 1H), 7.65 (dd, *J*= 6.5, 0.9 Hz, 1H), 7.58 -7.42 (m, 4H), 7.39 -7.25 (m, 4H), 6.90 (s, 1H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 169.9, 150.0, 139.9, 133.2, 129.5,
129.4, 128.6, 128.6, 125.5, 123.6, 122.9, 88.2. **ESI-HRMS**: Found: *m/z* 226.0881. Calcd for $C_{14}H_{12}NO_2$: $(M+H)^+$ 226.0873.

6-chloro-3-hydroxy-3-phenylisoindolin-1-one (3.27b)



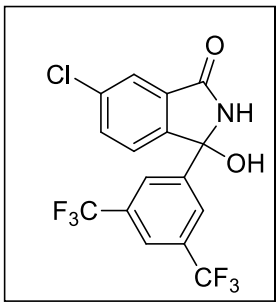
White solid (51 mg, 99%). Mp. 185-186°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3240, 3178, 1691, 1408, 512. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.61 (d, *J*= 1.9 Hz, 1H), 7.55 (dd, *J*= 8.1, 1.9 Hz, 1H), 7.46 (s, 1H), 7.44 (s, 1H), 7.35- 7.26 (m, 4H), 6.99 (s, 1H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 167.3, 149.8, 141.9, 134.2, 133.2, 132.8, 128.8, 128.4, 125.9, 125.2, 122.8, 87.5. **ESI-HRMS**: Found: *m/z* 260.0453. Calcd for $C_{14}H_{11}ClNO_2$: $(M+H)^+$ 260.0473.

3-hydroxy-3-(naphthalen-1-yl)isoindolin-1-one (3.27c)



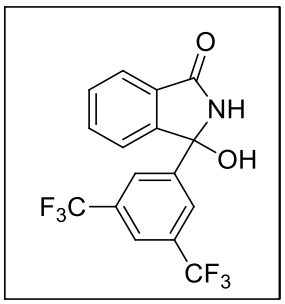
White solid (27 mg, 50%). Mp. 159–160 °C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3242, 3098, 1702, 1414, 525. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.15 (s, 1H), 7.98-7.93 (m, 1H), 7.91- 7.83 (m, 2H), 7.69 (dd, *J*= 6.2, 1.6 Hz, 1H), 7.57-7.48 (m, 4H), 7.45 (dd, *J*= 8.7, 1.7 Hz, 1H), 7.39-7.31 (m, 1H), 7.06 (s, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 168.9, 151.2, 139.9, 133.0, 132.9, 131.2, 129.4, 128.6, 128.37, 127.8, 126.7, 126.7, 124.45, 124.4, 123.3, 123.1, 87.8. **ESI-HRMS**: Found: *m/z* 276.1023. Calcd for $C_{18}H_{14}NO_2$: $(M+H)^+$ 276.1019.

3-(3,5-bis(trifluoromethyl)phenyl)-6-chloro-3-hydroxyisoindolin-1-one (3.27d)



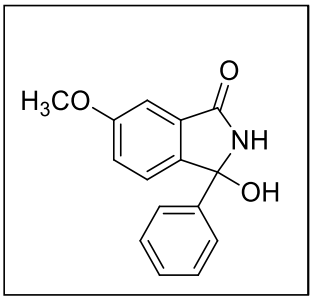
White solid (75 mg, 95%). Mp. 184 °C (dec.). **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3323, 3268, 1693, 627. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 8.01 (s, 1H), 8.05 (s, 2H), 7.67 (s, 1H), 7.60 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 7.53 (s, 1H), 7.42 (d, *J* = 8.1Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 167.3, 148.1, 145.5, 134.9, 133.2, 133.1, 131.4 (q, $^2J_{C\text{-}F}$= 30 Hz), 126.8, 125.3, 123.5 (q, $^1J_{C\text{-}F}$= 270 Hz), 122.0, 86.7. **ESI-HRMS**: Found: *m/z* 396.0231. Calcd for $C_{16}H_9ClF_6NO_2$: $(M+H)^+$ 396.0221.

3-(3,5-bis(trifluoromethyl)phenyl)-3-hydroxyisoindolin-1-one (3.27e)



White solid (65 mg, 91%). Mp. 184–185°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3343, 3270, 1703, 702, 680. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.14 (s, 1H), 8.04 (s, 2H), 7.71 (d, *J*= 7.3 Hz, 1H), 7.59 (t, *J*= 7.3 Hz, 1H), 7.55 (t, *J*= 7.3 Hz, 1H), 7.49 (s, 1H), 7.42 (d, *J*= 7.5 Hz, 1H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 168.3, 149.2, 145.7, 132.9, 130.3 (q, $^2J_{C\text{-}F}$= 30 Hz), 126.2, 124.9, 122.9 (q, $^1J_{C\text{-}F}$= 270 Hz), 122.8, 122.1, 121.3, 86.4. **ESI-HRMS**: Found: *m/z* 362.06140. Calcd for $C_{16}H_{10}F_6NO_2$: $(M+H)^+$ 362.06157.

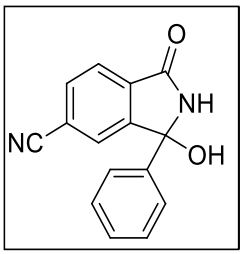
6-methoxy-3-hydroxy-3-phenylisoindolin-1-one (3.27f)



Reaction was carried out on 0.05 mmol. White solid (12 mg, 98%). Mp. 189–190 °C. IR (KBr): $\tilde{\nu}$ (cm–1) 3323,3250, 1669, 680. *Data in accordance with literature.* **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 7.44 (d, *J*= 7.5 Hz, 2H), 7.32 (t, *J*= 7.5 Hz, 2H), 7.28–7.25 (m, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 2.7 Hz, 1H), 7.06 (dd, *J* = 8.1, 2.7 Hz, 1H), 6.79 (s, 1H), 3.80 (s, 3H). **^{13}C NMR** (100 MHz DMSO-d_6) δ

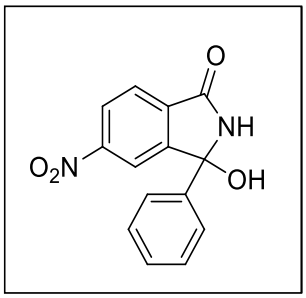
168.1, 160.1, 143.1, 142.4, 132.2, 128.1, 127.6, 125.4, 123.8, 119.2, 106.2, 87.0, 55.6. **ESI-HRMS**: Found: *m/z* 256.0964. Calcd for $C_{15}H_{14}NO_3$: (M+H)+ 256.0968.

3-hydroxy-1-oxo-3-phenylisoindoline-5-carbonitrile (3.27g)



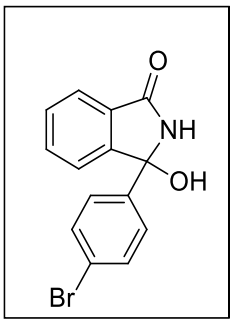
White solid (48 mg, 97%). Mp. 206-207°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3323, 3250, 2237, 1699, 689. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.65 (s, 1H), 7.93 (dd, *J*= 7.8, 1.1 Hz, 1H), 7.84 (s, 1H), 7.80 (d, *J*= 7.8 Hz, 1H), 7.49 (dd, *J*= 7.6, 1.6 Hz, 2H), 7.37-7.30 (m, 3H), 7.14 (s, 1H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 167.1,151.7, 141.3, 134.9, 133.9, 128.8, 127.6, 126.2, 124.2, 118.5, 115.1, 87.7. **ESI-HRMS**: Found: *m/z* 251.0825. Calcd for $C_{15}H_{11}N_2O_2$: $(M+H)^+$ 251.0815.

3-hydroxy-5-nitro-3-phenylisoindolin-1-one (3.27h)



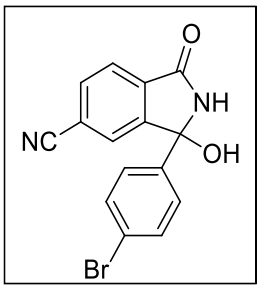
White solid (53 mg, 99%). Mp. 158-159°C. **IR** (KBr): $\tilde{\nu}$(cm^{-1}) 3328, 3259, 1678, 1580, 1015. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.30 (dd, *J*= 9.4, 1.5 Hz, 1H), 7.97 (s, 1H), 7.89 (d, *J*= 8.2 Hz, 1H), 7.52 (d, *J*= 8.2 Hz, 2H), 7.38-7.31 (m, 3H), 7.25 (s, 1H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 166.7, 152.3, 150.8, 141.1, 136.4, 128.9, 128.7, 125.9, 125.3, 124.8, 118.0, 87.6. **ESI-HRMS**: Found: *m/z* 271.0721. Calcd for $C_{14}H_{11}N_2O_4$: $(M+H)^+$ 271.0713.

3-(4-bromophenyl)-3-hydroxyisoindolin-1-one (3.27i)



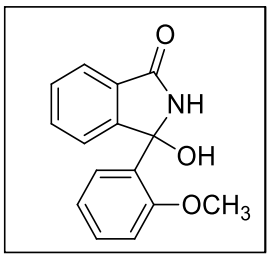
White solid (58 mg, 95%). Mp. 214–215°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3320, 3250, 1688, 978. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.28 (s, 1H). 7.65 (d, *J*= 7.4 Hz, 1H), 7.54 (d, *J*= 8.5 Hz, 3H), 7.48 (t, *J*= 7.3 Hz, 1H), 7.41 (d, *J*= 7.3 Hz, 2H), 7.30 (d, *J*= 7.3 Hz, 1H), 7.02 (s, 1H). **^{13}C NMR** (100 MHz, DMSO- d_6) δ 168.7, 150.8, 142.1, 132.9, 131.6, 130.9, 129.5, 128.3, 123.2, 123.1, 121.4, 87.4. **ESI-HRMS**: Found: *m/z* 303.9975. Calcd for $C_{14}H_{11}BrNO_2$: $(M+H)^+$ 303.9968.

3-(4-bromophenyl)-3-hydroxy-1-oxoisoindoline-5-carbonitrile (3.27j)



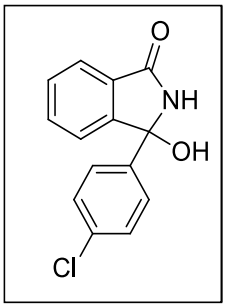
White solid (59 mg, 90%). Mp. 164-165.°C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3321, 3251, 2237, 1696, 998. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.70 (s, 1H). 7.96 (d, *J* = 7.7 Hz, 1H), 7.87 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 8.2Hz, 2H), 7.44 (d, *J* = 7.4 Hz, 2H), 7.25 (s, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 167.1, 151.2, 140.8, 134.9,
134.1, 131.7, 128.4, 127.3, 124.3, 121.9, 118.5, 115.2, 87.3. **ESI-HRMS**: Found: *m/z* 328.9945. Calcd for $C_{15}H_{10}BrN_2O_2$: $(M+H)^+$ 328.9920.

3-hydroxy-3-(2-methoxyphenyl)isoindolin-1-one (3.27k)



White solid (51 mg, 99%). Mp. 179-180 °C. **IR** (KBr): $\tilde{\nu}$ (cm^{-1}) 3351, 3271, 1656, 987.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 6.7 Hz, 1H), 7.47-7.40 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.1 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.64 (s, 1H), 3.34 (s, 3H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 172.6, 158.3, 152.0, 133., 133.0, 131.1, 129.9, 129.4, 128.8, 123.6, 123.4, 121.3, 113.0, 87.7, 55.9. **ESI-HRMS**: Found: *m/z* 256.0955. Calcd for $C_{15}H_{14}NO_3$: $(M+H)^+$ 256.0968.

3-(4-chlorophenyl)-3-hydroxyisoindolin-1-one (3.27l)

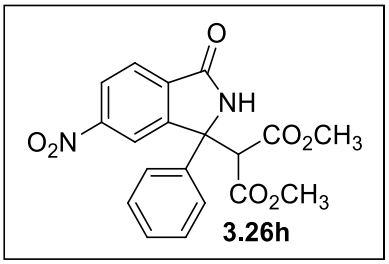


White solid (51 mg, 98%). Mp. 208–209°C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.28 (s, 1H). 7.65 (d, *J*= 7.4 Hz, 1H), 7.54(d, *J*= 8.5 Hz, 3H), 7.48 (t, *J*= 7.3 Hz, 1H), 7.41 (d, *J*= 7.3 Hz, 2H), 7.30 (d, *J*= 7.3 Hz, 1H), 7.02 (s, 1H). **^{13}C NMR** (100 MHz, DMSO- d_6) δ 168.2, 150.4, 141.2, 132.4, 132.4, 130.5, 129.1, 128.2, 127.4, 122.6, 122.5, 86.8. **ESI-HRMS**: Found: *m/z* 260.0468 Calcd for $C_{14}H_{11}ClNO_2$: $(M+H)^+$ 260.0473.

X-ray crystallography

Colorless prismatic single crystals of compound **3.26h** suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of methanol by dissolving 5 mg of the compound in 0.8 ml of hot methanol.

A crystal of 0.41 mm x 0.36 mm x 0.10 mm was selected, glued on a glass capillary and measured at room temperature using a Bruker D8 QUEST diffractometer equipped with a PHOTON II detector using Cu*K*α radiation (λ= 1.54178 Å). Data Indexing was performed using APEX3 software.1 Data integration and reduction were performed using SAINT[66]. Absorption correction was performed by multi-scan method in SADABS.1 The structures were solved using SHELXS-97 [67] and refined by means of full matrix least-squares based on *F*2 using the program SHELXL.[68] Non-hydrogen atoms were refined anisotropically. Hydrogen atom H1, attached to the nitrogen atom N1, has been localized from the difference density map and refined. The other hydrogen atoms were positioned geometrically and included in structure factors calculations but not refined. ORTEP diagrams were drawn using OLEX2 [69] (Fig. 1). The ester group C18>C19 is disordered over two
possible positions, in detail O6 and O7 atoms may be alternatively either carbonyl or alkoxy oxygen atoms. Occupancy factors for C19 A and C19 B have been refined with final values of 0.571(5) and 0.429(5).



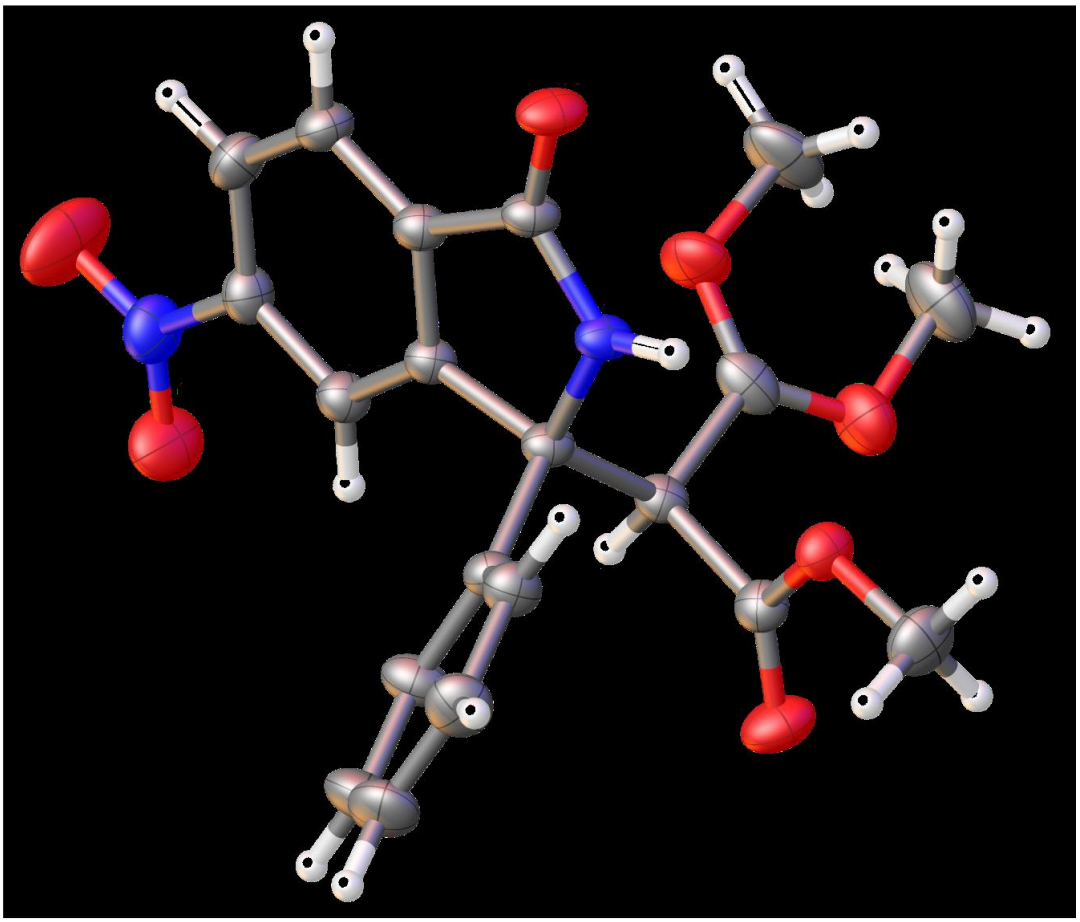


Figure 3.S1. ORTEP diagram for compound **3.26h**

Compound	**3.26h**
T (K)	296
Formula	$C_{19}H_{16}N_2O_7$
Formula weight	384.34
System	Triclinic
Space group	*P 1*
***a* (Å)**	8.8362(12)
***b* (Å)**	9.557(3)
***c* (Å)**	11.854(3)
***α* (°)**	107.334(18)
***β* (°)**	97.908(16)
***γ* (°)**	104.382(14)
***V* (Å^3)**	901.1(3)
Z	2
***Dx* (g cm^{-3})**	1.417
λ (Å)	1.54178
***μ* (mm^{-1})**	0.931
F_{000}	400
R1 (I > 2σI)	0.0437 (3192)
$_wR_2$	0.1155 (3383)
N. of param	271
GooF	1.044
***ρmin*, *ρ*max (eÅ^{-3})**	-0.192, 0.244

Table 3.S2. Crystallographic data for compounds **3.26h**

Chapter 4. Kinetic studies on 2-cyanoacetophenone and 2-cyanobenzophenone and use of chloromethyl aryl sulfones in one-pot cascade reactions

4.1. Introduction to Mayr Equation

The study of the reactivity of chemical species in each reaction environment has always been the challenge most faced by chemists.

Swain and Scott,[70] Edwards,[71] and Ritchie [72] were the firsts to investigate this topic. They analyzed the correlation among several experimentally measured rate constants using linear free energy relationships, LFER.

In the mid 90's Mayr and coworkers [73] managed to elaborate a unique form of LFER that can predict the chemical reactivity in both quantitative and qualitative way. They elaborated this equation from experimental studies, defined for a temperature of 20 °C.

$$\log k\ (20\ °C) = sN^*(N+E) \qquad \textit{Equation (1)}$$

This equation calculates the electrophilicity parameter (E) and nucleophilicity parameter (N) of a given pair of reagents, where sN is a constant defined for 20°C, calculated for each nucleophile. The reaction must carry out in thermostat environment set at 20°C. This equation over the years has found feedback in wide range of reactions and organic molecules. [74,75,76,77] This made possible to draw up a real database in which a wide range of Nucleophilicity and Electrophilicity parameters in different solvent are reported https://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/

An example to how calculate the **E** and **N** parameters exploiting Mayr equation, **$\log k$ (20 °C) = sN*(N+E)**, is reported in **Figure 4.1**. It was tested **209** different combinations of twenty-three diarylcarbenium ions and 38 π-systems (arenes, alkenes, allyl silanes and stannanes, silyl enol ethers, silyl ketene acetals, and enamines) and the measured rate constants were subjects of correlation studies, LFER. Employing this correlation method, the Electrophilicity parameter **E** of diarylcarbenium ions and Nucleophilicity parameter **N** and **sN** of π-nucleophiles were calculated.[78]

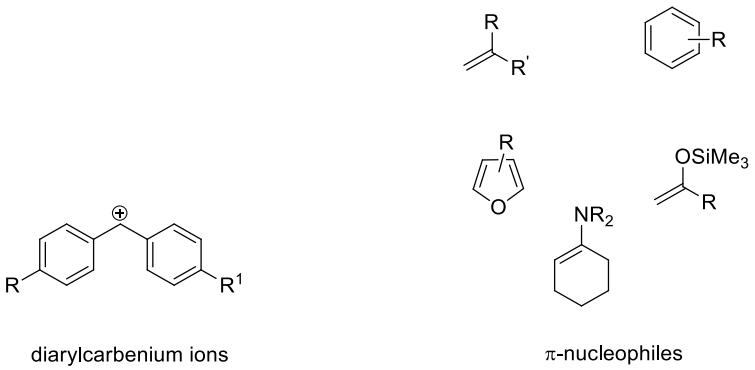


Figure 4.1. Basis sets of π-nucleophiles and diarylcarbenium ions

From the equation (1): **log *k* (20 °C) = sN*(N+E)** can be observed that the greater the difference in absolute value between N and E is, the greater the kinetic constant $k_{(20\,^{\circ}C)}$ measured. Therefore, this means that the reaction rate of a couple of electrophile and nucleophile rises, with increasing the difference in absolute value of **E** and **N** parameters.

4.2. Objectives

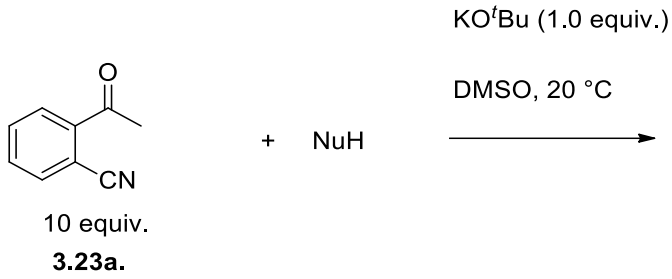
The goal of this chapter is to study the electrophilicity parameter of 2-cyanoacetophenones and 2-cyanobenzophenones through the Mayr equation, in collaboration with the group of Dr. Armin Ofial. These studies led us to identify chloromethyl aryl sulfones, a class of pronucleophiles bearing a leaving group in the alpha position, that made possible to extend the one-pot cascade reaction methodologies to the synthesis of new 3,3-disusbstitued isoindolinones and to 3-methyleneisoindolinones when 2-cyanobenzaldehydes were used.

4.3. Results and Discussion

4.3.1 Quantitative evaluation of E parameters of 2-cyanobenzophenone and 2-cyanoacetophenone

The aim of the work carried out at the LMU in Munich in the laboratories of Dr. PD Armin Ofial is the study of the reactivity of aromatic ketones involved in the synthesis of 3,3-disubstituted isoindolinones in a systematic and quantitative way.

The first electrophile to be tested is the 2-cyanoacetophenone (**3.23a**) with several tabulated carbon nucleophiles (**Scheme 4.1.**)



Scheme 4.1. Kinetical studies on 2-cyanoacetophenone **3.23a**

Several experimental conditions must be observed in order to perform UV-Vis measurements correctly. As said before, all these measurements are UV-Vis detected, so it is crucial that the absorption of the electrophile and the nucleophile must not overlap, this is because the progress of the reaction is monitored by decreasing the absorption maximum of the nucleophile (**Figure 4.2.**) Moreover, it is necessary to work in pseudo-first order conditions, in such a way the kinetics depend on a single reagent and in the specific, using the electrophile concentration ten times higher than nucleophile ones. The temperature and solvent conditions must be respected because each nucleophile-specific parameter is measured at 20 °C and in different solvents. Due to the use of air-sensitive bases, it is necessary to work in an inert atmosphere using three-way Schlenk flask, in one of these ways a transmission quartz probe inserted measuring the progress of the reaction. In the **Figure 4.2** are reported the UV-Vis absorbance spectrum of the electrophile and nucleophile. It's fundamental to choose a couple of nucleophile-electrophile that have different maximum of absorption, here the electrophile is 2-cyanoacetophenone **3.23a** (**283 nm**) and the nucleophile is 1-(trifluoromethyl) -4 - (((trifluoromethyl) sulfonyl) methyl) benzene **4.1** (**394 nm**). In this graph a slow decrease of absorbance of nucleophile was observed, meaning that the reaction is progressing.

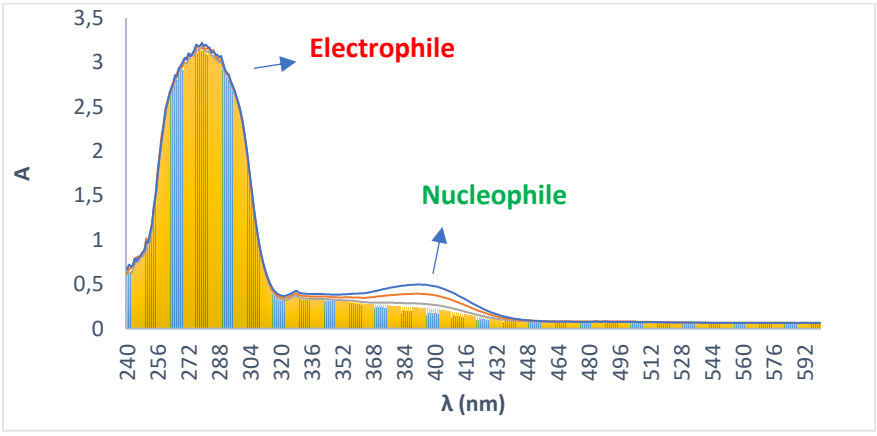


Figure 4.2. UV-Vis absorbance spectrum for the electrophile **3.23a** and nucleophile **4.1**

The experiment consists into a first activation of the pronucleophile with a strong base, usually KO^{t}Bu (pK_{aH} = 17) is used, then the electrophile is added to the reaction flask and a pseudo-first order decay

is recorded. From the slope of this exponential decay, the first kinetic constant k_{obs} was calculated. (**Figure 4.3.**)

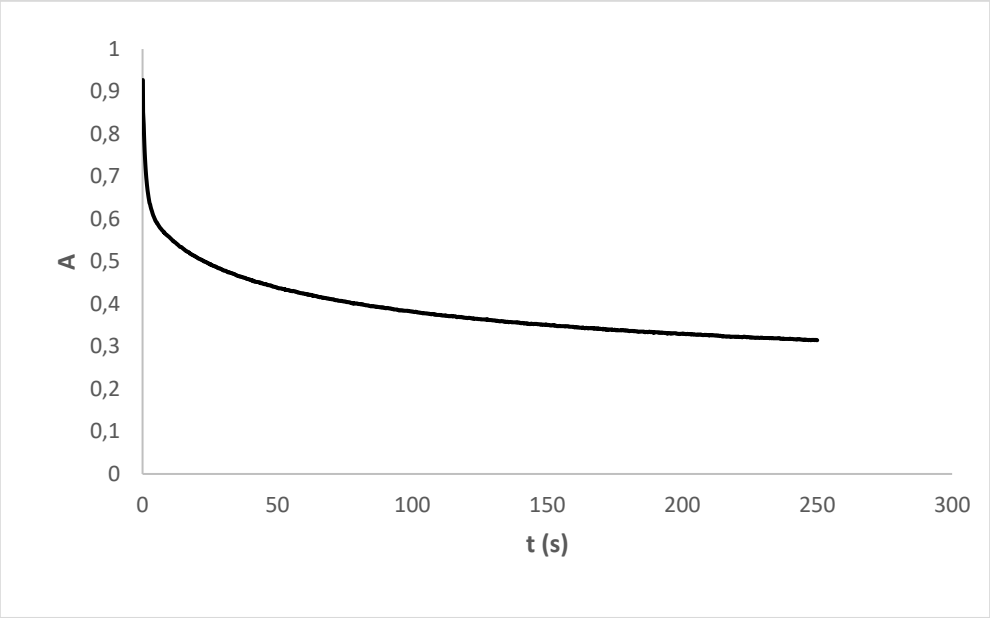


Figure 4.3. Profile of exponential decay of pseudo-first order for reaction depicted in **Scheme 4.1**

Subsequently the experiment is repeated at different concentrations of the electrophile, building a graph of k_{obs} for each concentration versus C (mol* l^{-1}), $k_{20\,°C}$ was calculated from the slope of the line. (**Figure 4.4.**).

Here the combination used is 2-cyanoacetophenone **3.23a** as electrophile and 1- (trifluoromethyl) -4 - (((trifluoromethyl) sulfonyl) methyl) benzene (**4.1**) as nucleophile with **N**= 17.33 and **sN** = 0.74.

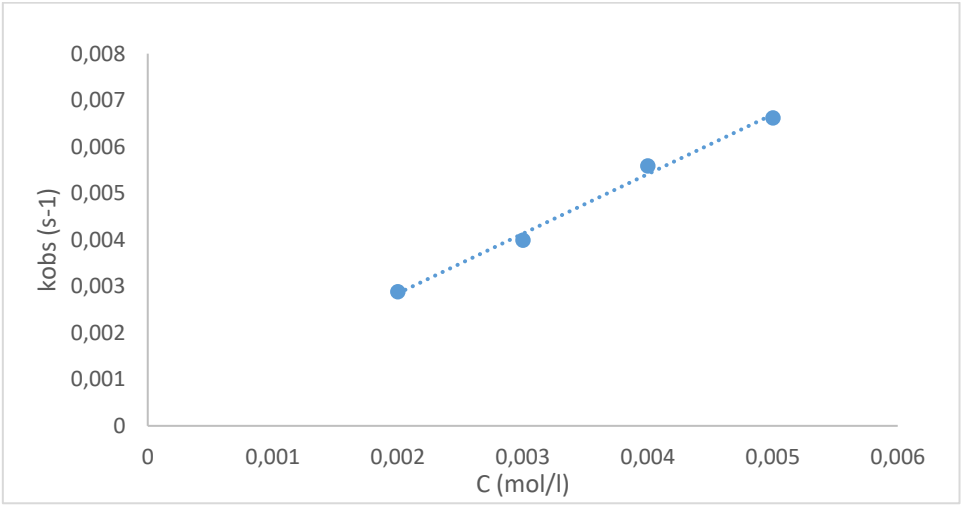


Figure 4.4. Linear correlation between k_{obs} and concentration of **3.23a** (mol/l)

The nucleophiles that gave the best decay profile for 2-cyanoacetophenone **3.23a.** are the following (**Figure 4.5.**):

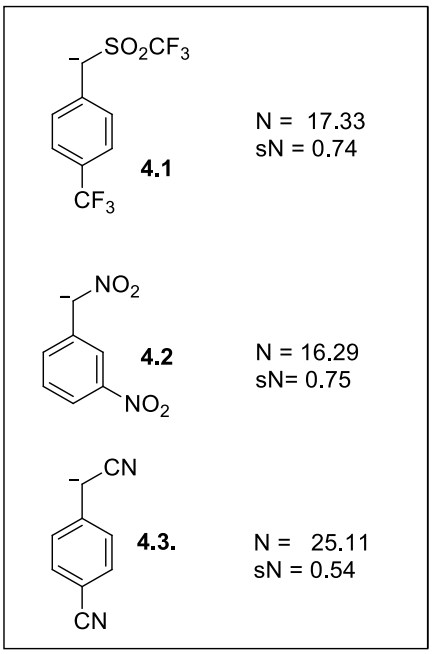


Figure 4.5. List of carbon pronucleophile employed to calculate **E** value for 2-cyanoacetophenone **3.23a**

Finally, to calculate the E parameter, log $k_{20°C}$ divided by the sN parameter was plotted versus the N nucleophilicity parameter and by setting the slope as a value of 1, the E parameter is obtained from the intercept value (**Figure 4.6.**):

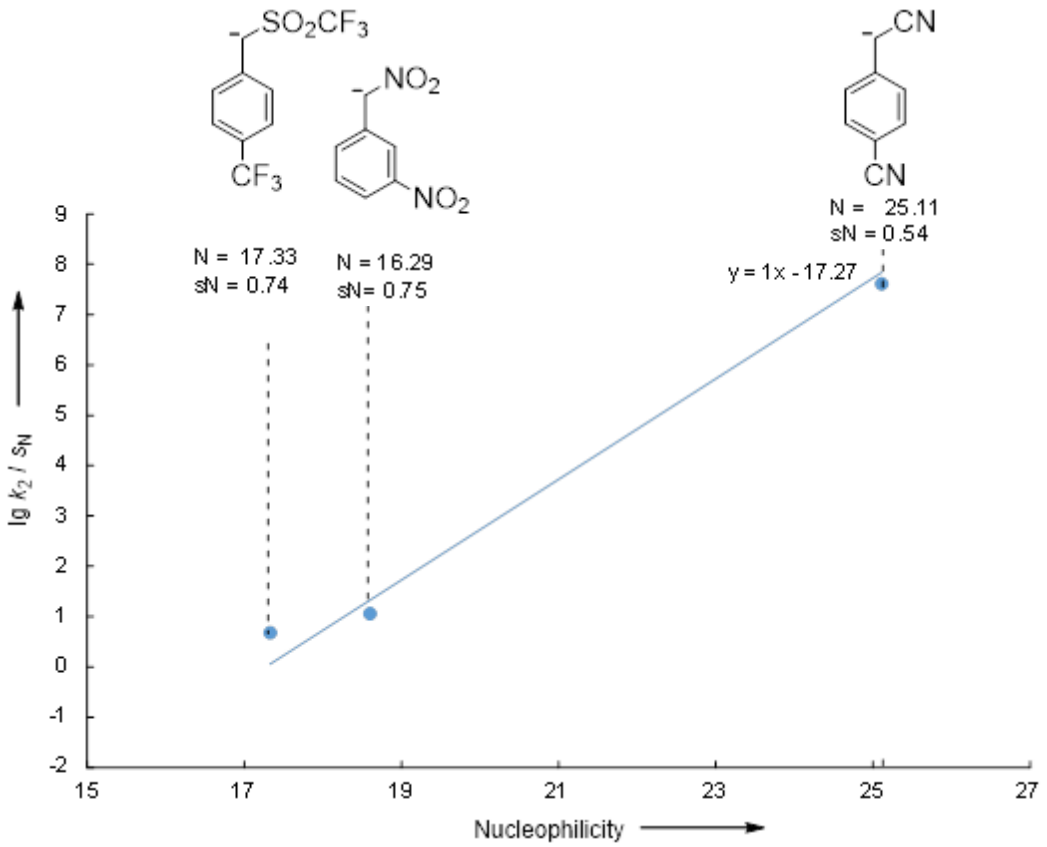
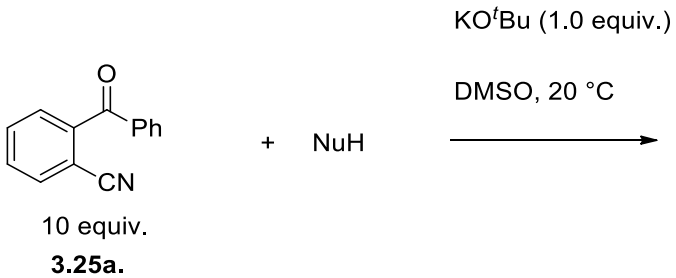


Figure 4.6. Determination of E parameter for compound **3.23a**

Parameter E calculated for 2-cyanoacetophenone (**3.23a.**) is **-17.27**. The experimental data confirm the initial hypothesis: the greater the difference of **E** and **N** measures, the greater the reaction rate is. 4- (cyanomethyl) benzonitrile (**4.3.**) measures a rate constant of $k_2 = 1.29 \times 10^4$ M^{-1} s^{-1}, much higher compared instead with 1-nitro-3- (nitromethyl) benzene (**4.2.**) $k_2 = 5.66$ M^{-1} s^{-1} and with 1- (trifluoromethyl) -4 - (((trifluoromethyl) sulfonyl) methyl) benzene (**4.1.**) which instead measures a constant of $k_2 = 3.17$ M^{-1} s^{-1}.

About 2-cyanobenzophenone, the nucleophiles that gave good exponential decays are the following (**Figure 4.7.**):



Scheme 4.2. Kinetical studies on 2-cyanbenzophenone **3.25a**

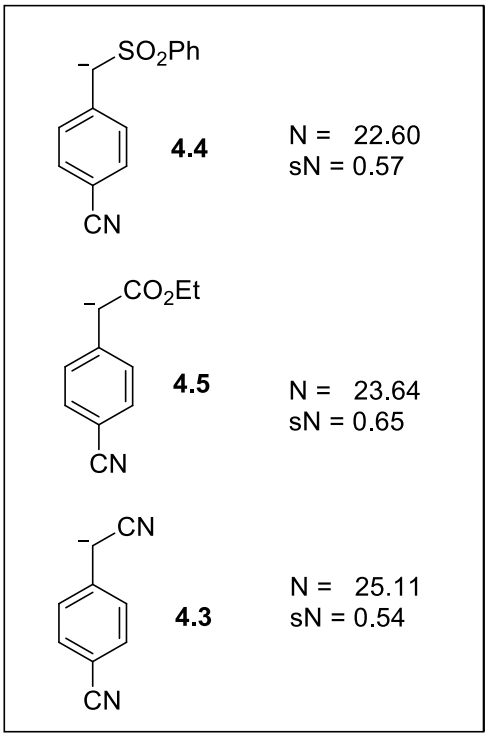


Figure 4.7. List of carbon pronucleophile employed to calculate the **E** value of 2-cyanobenzophenone **3.25a**

Repeating the same 3-step procedure done for 2-cyanoacetophenone (**3.25a.**), an E parameter equal to **-23.64** was calculated (**Figure 4.8.**).

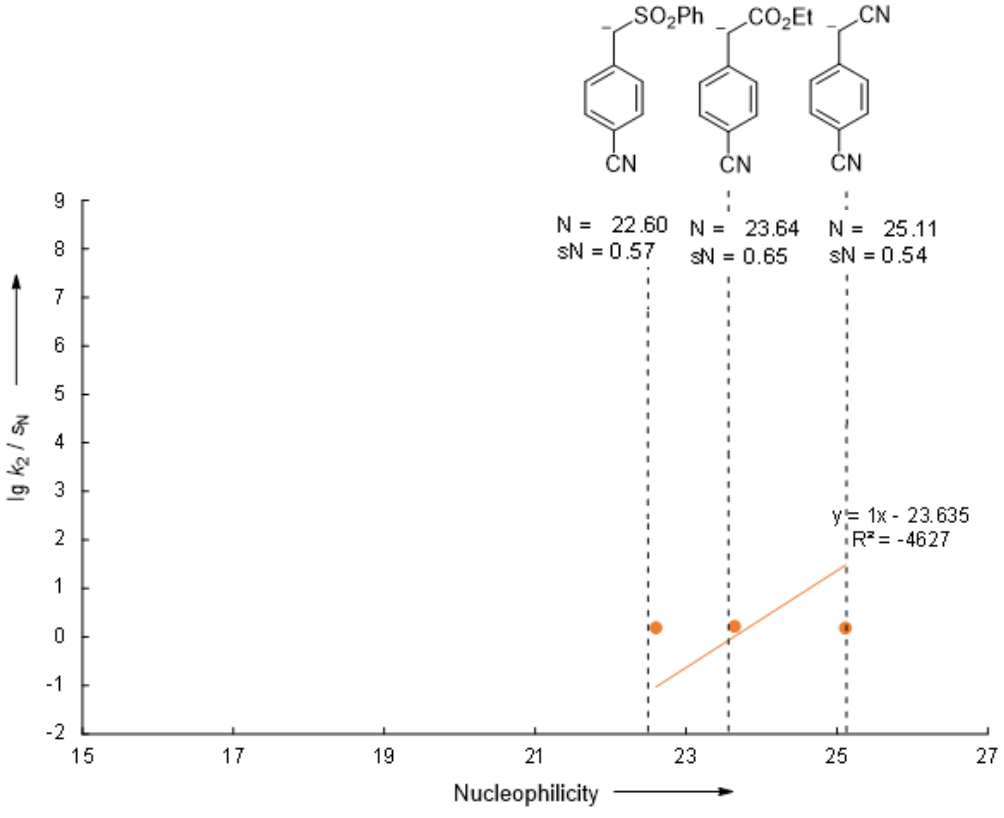
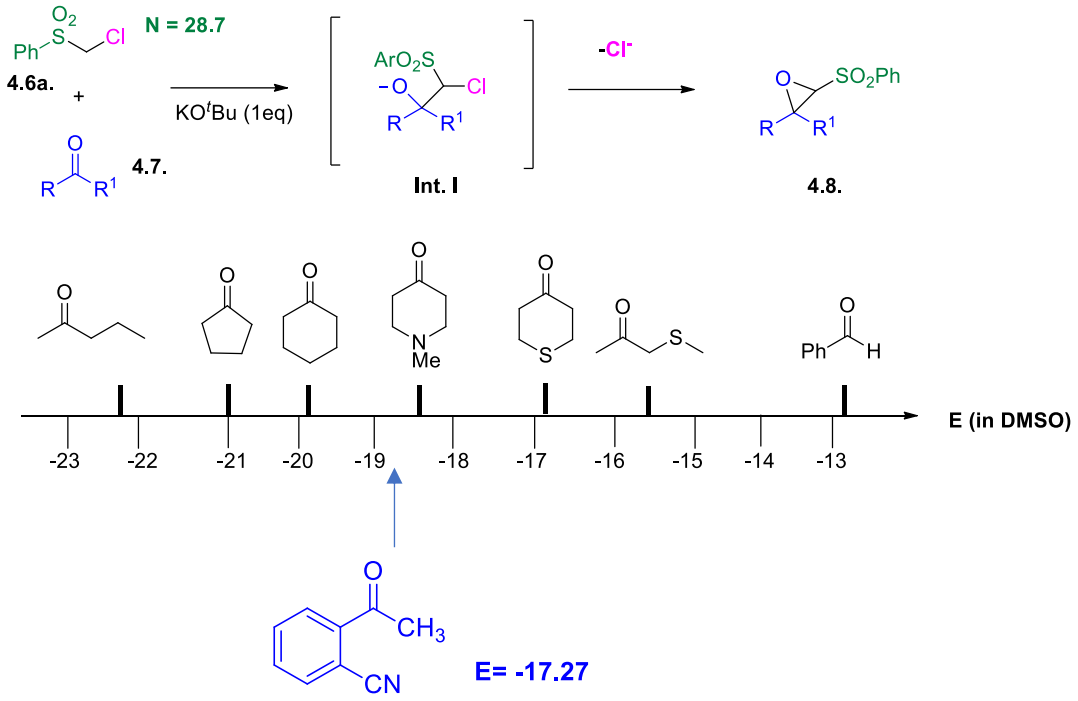


Figure 4.8. Determination of E parameter for **3.25a**

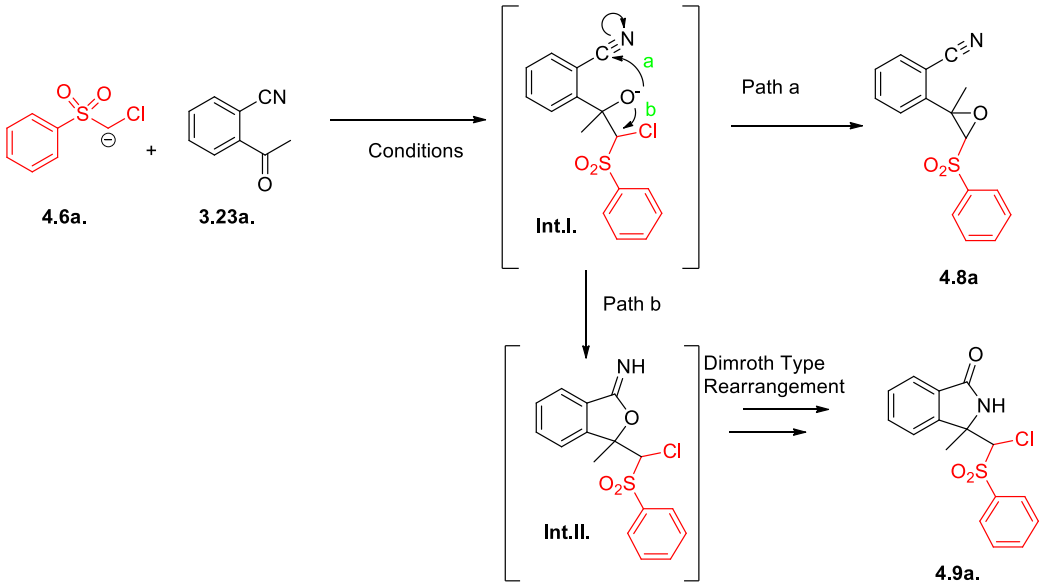
Unlike the value calculated for 2-cyanoacetophenone (**3.23a.**) in this case the value obtained is not to be considered valid. The reason lies in the graph shown in **figure 4.8.** Here, it is noted that as the nucleophilicity parameter increases, from 22.60 of **4.4.** to 25.11 of **4.3**., a slow decrease in the value of the kinetic constants is observed. This value disagrees with the Mayr equation, **log *k* (20 °C) = sN*(N+E)**, which states that as the difference between N and E increases, the value of k_{20} increases. These kinetical data, in conclusion, could refer to decomposition or side reactions of the reactants.

With these kinetic studies in hand, we noticed that 2-cyanoacetophenone (**3.23a**) has an E value that falls within the optimal range of electrophiles for the reaction with chloromethyl aryl sulfones, a pronucleophile with a leaving group in α-position. Moreover, in recent studies, Prof. Mayr, Dr. Ofial and coworkers have shown an interesting modified Darzens epoxidation between aliphatic ketones or aromatic aldehydes (**4.7.**) with chloromethyl aryl sulfones, (**4.6a.**) (**Scheme 4.3.**).[79,80] This is a modification of the classical Darzens epoxidation, usually carried out with α-halo ester. The reaction proceeds in high yields both with aliphatic ketones and aromatic aldehydes.



Scheme 4.3. Darzens reaction for the synthesis of epoxides **4.8**

Therefore, we thought to investigate the reactivity of chloromethyl aryl sulfones with 2-cyanoacetophenones that could give raise to two possible pathways, Darzens epoxidation (**path a**) or cyclization at cyano group (**path b**) (**Scheme 4.4)**.



Scheme 4.4. Possible pathways for the synthesis of epoxide **4.8a** and 3,3-disubstitued isoindolinone **4.9a**

4.3.2 Chloromethyl aryl sulfones in one-pot cascade reactions with 2-cyanoacetophenone

In order to verify the possible synthetic pathways combining chloromethyl aryl sulfones and 2-cyanoacetophenone and the resulting products, two reaction conditions were explored **(Table 4.1)**. In the presence of weak base as potassium carbonate in acetonitrile at 50°C (**Entry 1**), a lower yield was obtained compared to much stronger basic condition, employing potassium *tert*-butoxide (**Entry 2**).

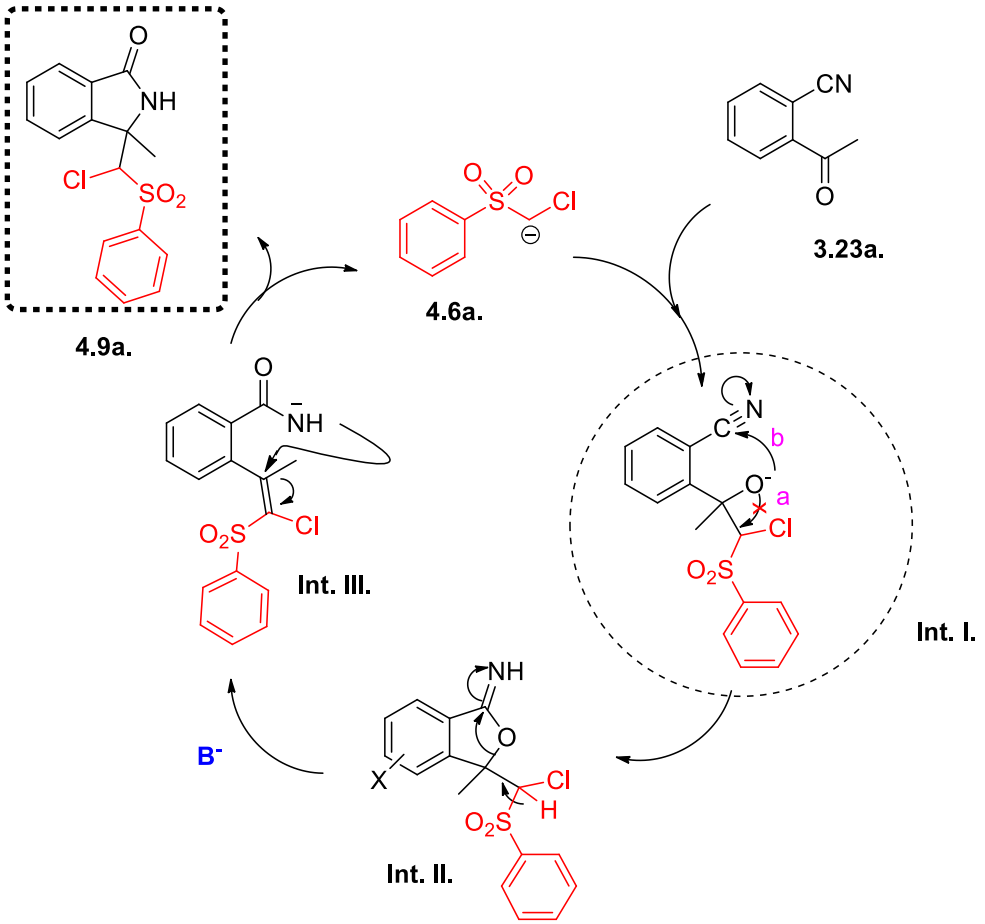
Entry	Conditions	Yield	dr
1	K_2CO_3, 50°C, 24h, CH_3CN	37	1,7:1
2	KO^{t}Bu, r.t., 24h, CH_3CN	85	1,5:1

Table 4.1. Preliminary screening of reaction conditions for the synthesis of epoxide **4.8a** and 3,3-disubstitued isoindolinone **4.9a**

In the presence of stoichiometric amount of the strong base potassium *tert*-butoxide in the same solvent (Entry 1), the starting materials disappeared after 24 reaction time and a new product was obtained. A 3,3-disubstituted isoindolinonic structure **4.9a.** bearing a tetrasubstituted carbon with an uncommon chloromethylsulphone side chain was attributed. This structure was confirmed by X-ray analysis (**Figure 4.9.**).

The mechanism supposed for the Darzens reaction is the first nucleophilic attack of chloromethyl aryl sulfone to the 2-cyanoacetophenone, subsequent intramolecular S_N2 reaction of the alkoxide with the displacement of chloride (**Int. I. a.**) and the formation of epoxide (**Scheme 4.5**). However, no epoxide was observed in the ^{1}H NMR spectrum of the crude product, but the formation of the isoindolinone core due to the alkoxide cyclization to the cyano group (**Int. I b.**) leading the formation of iminophthalan intermediate (**Int. II.**). Here Dimroth-type rearrangement base-catalyzed occurred, leading ring opening and intramolecular aza-Michael reaction to afford 3,3-disusbtituted isoindolinones (**4.9a**.).

Mechanism:



Scheme 4.5. Cascade reaction mechanism in the synthesis of 3,3-disubstitued isoindolinone **4.9a**

The formation of the 3,3-disubstituted isoindolinonic structure **4.9a.** was confirmed by X-ray analysis (**Figure 4.8.**). Moreover, to explain the observed selectivity, DFT calculations were carried out, thanks to Prof. Dr. Guglielmo Monaco of Department of Chemistry and Biology of University of Salerno.[81]

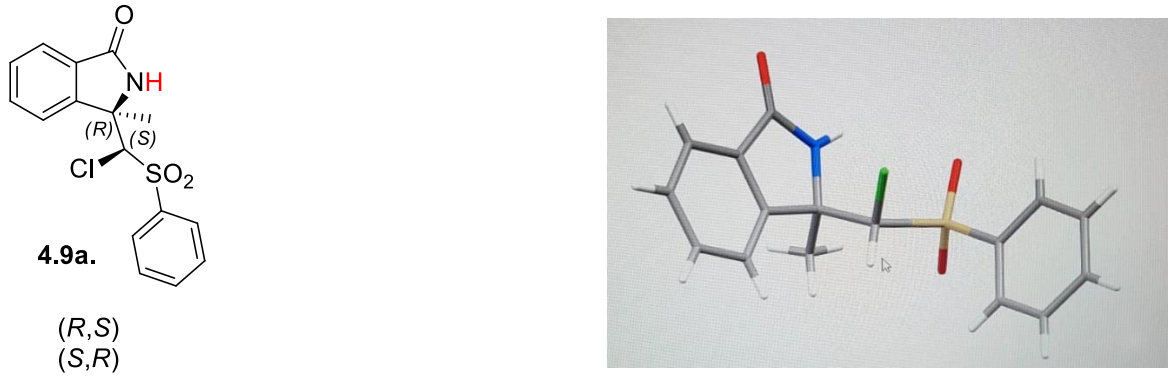
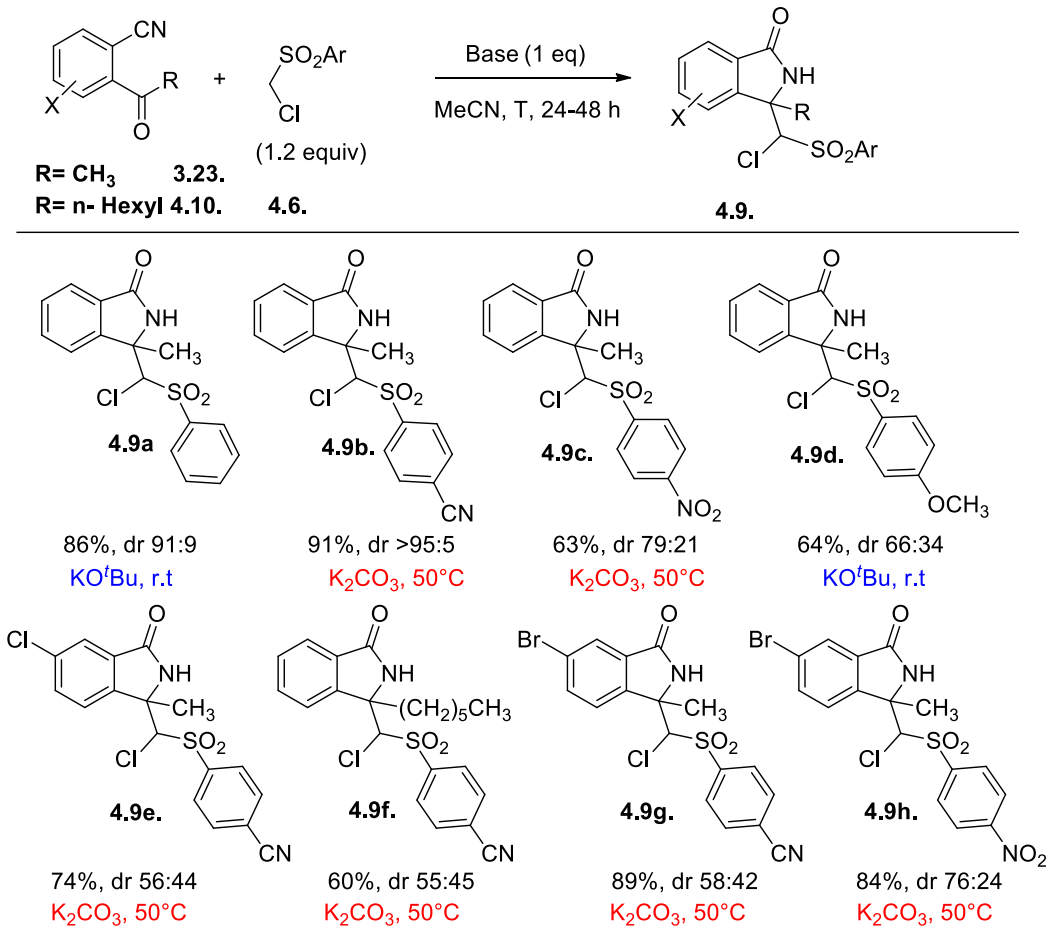


Figure 4.9. ORTEP diagram for compound **4.9a.**

Then, the scope of the reaction was analyzed. After a preliminary screening of conditions (**Table 4.1**) it was noticed that the reactivity of chloromethyl aryl sulfone depends on the substituent groups present on the aromatic ring. An electron-withdrawing (EWG) group in para position to the sulfone group tends to stabilize the negative charge better than an electron-donating group (EDG) in the same position, for this reason the acidity of the methylene groups is enhanced. Thus, with chloromethyl aryl (EWG) sulfones, a weak base such as potassium carbonate (**pK_{aH} = 10**) is strong enough for deprotonation of methylene moiety. Otherwise, with chloromethyl aryl (EDG) sulfone a stronger base such as potassium *tert*-butoxide (**pK_{aH} = 17**) is required (**Scheme 4.6.**).



Scheme 4.6. Scope of Cascade Reactions of 2-Acylbenzonitriles **3.23** and **4.10** with ((Chloromethyl)sulfonylbenzenes **4.6**

The reaction works well with a good variety of chloromethyl aryl sulfones and different substituted aromatic ketones, in yield range 60-91%, even with a much hindered 3-position (**4.9f**). In general, moderate diastereoseletivity was observed, even different electronic structure of substrates gave comparable results (e.g. **4.9d** (dr = 66:34) and **4.9g** (dr = 76:24)). Compounds **4.9a and 4.9b** were obtained almost as single diastereomers. The low diastereoselectivity of products reported in **Scheme 4.6** is mainly due to epimerization due to high acid proton in methylene group of ((Chloromethyl)sulfonyl)benzenes moiety.

Furthermore, it has been observed that the reaction is also effective with long-chain aromatic ketones (**4.9f.** 60% yield), widening the scope of the reaction.

An asymmetric organocatalyzed version of the latter was also preliminarily tested. Neither bifunctional organocatalysts belonging to cinchona alkaloids family nor cPTC (chiral phase transfer catalysts) produce an enantiomeric enrichment of the reaction mixture. In most of the cases there are just starting materials and degradation products in the ^{1}H NMR spectra of the crude products.

4.3.3 2-cyanobenzaldehydes in one-pot cascade reactions with chloromethyl aryl sulfones.

To broaden the scope of the reaction, another class of related bifunctional electrophiles, as 2-cyanobenzaldehydes (**4.13.**) was investigated. They are already thoroughly investigated by prof. Massa *et al.* in one-pot cascade reaction to afford 3-monosubstituted isoindolinones.[82]

As for 2-cyanoacetophenones, combining chloromethyl aryl sulfones (**4.6a)** and 2-cyanobenzaldehydes (**4.13**) we would have expected two possible products, either the epoxide through the Darzens mechanism (**4.11**) or the 3-monosubstituted isoindolinone (**4.12**, **Figure 4.10**).

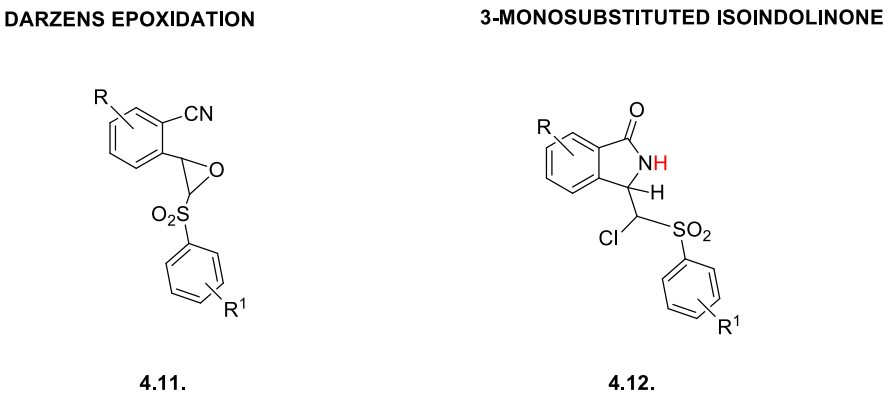
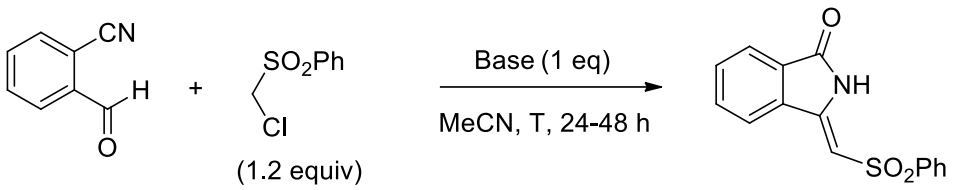


Figure 4.10. Expected products for cascade reaction involving **4.13a** and **4.6a**

According to the data shown in **Table 4.2.** none of these two was observed. Instead, the formation of a valuable phenyl sulfonyl-substituted 3- methyleneisoindolin-1-ones (**4.14a.**) was observed in quantitative yields employing basic mild conditions as potassium carbonate at 50°C (**Entry 3.**). The use of milder conditions is probably due to the higher reactivity of 2-cyanobenzaldehyde with respect to 2-cyanoacetophenone.

This compound is not new and has been characterized comparing ^{1}H NMR analysis with the reported one.[48] This class of compounds is particularly important since they show relevant optical properties and are intermediates in the synthesis of Aristolactams. However, they are obtained under very harsh reaction conditions in the presence of a combination of metal catalyst and reagents and the method affords only a limited number of products.[48]

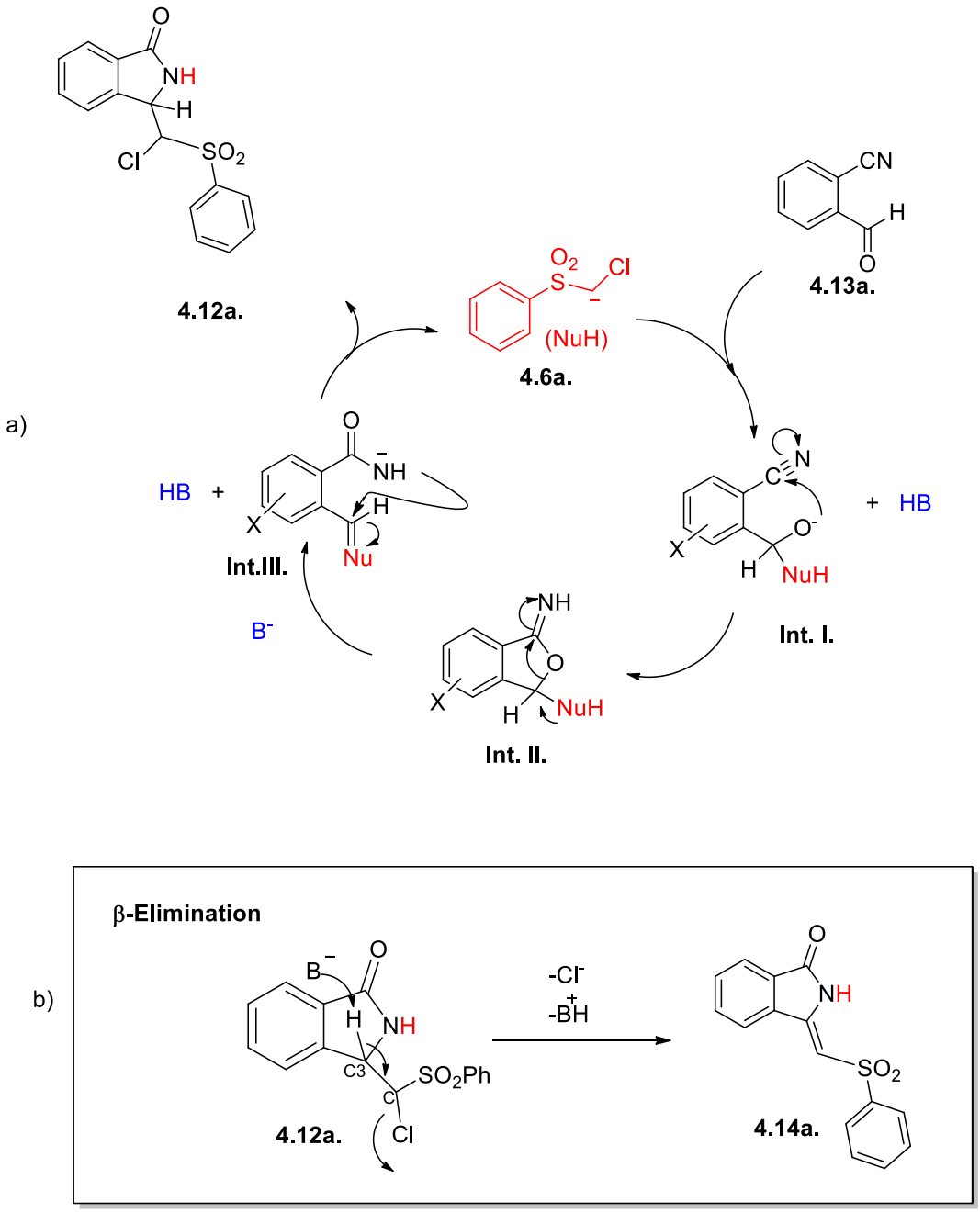


4.13a. **4.6a** **4.14a.**

Entry	Base (1 equiv.)	T (°C)	t (h)	Yield (%)
1	K_2CO_3	r.t.	48	41%
2	KO^tBu	r.t.	24	65%
3	K_2CO_3	50	48	99%
4	Et_3N	50	48	n.r.

Table 4.2. Screening of reaction conditions to get compound **4.14a**

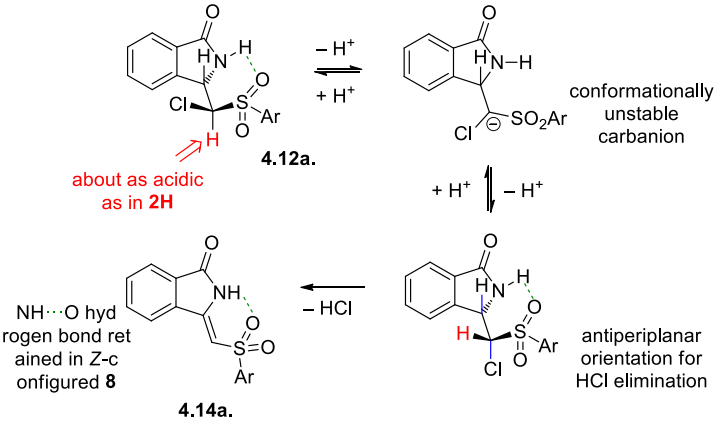
The explanation lies of the formation of observed product into a last-step of β-elimination of HCl molecule of 3-monosubstituted isoindolinones intermediate. The mechanism of this further step of the new cascade reaction is reported in **Scheme 4.7.a,** where the formation of the 3-monosubstituted isoindolinone through one-pot cascade occurs, leading to the synthesis of the 3-methyleneisoindolin-1-ones products **4.14a** (**Scheme 4.7.b**).



Scheme 4.7. Cascade reaction mechanism in the synthesis of (*Z*)-3-methyleneisoindolinon-1-one **4.14a**

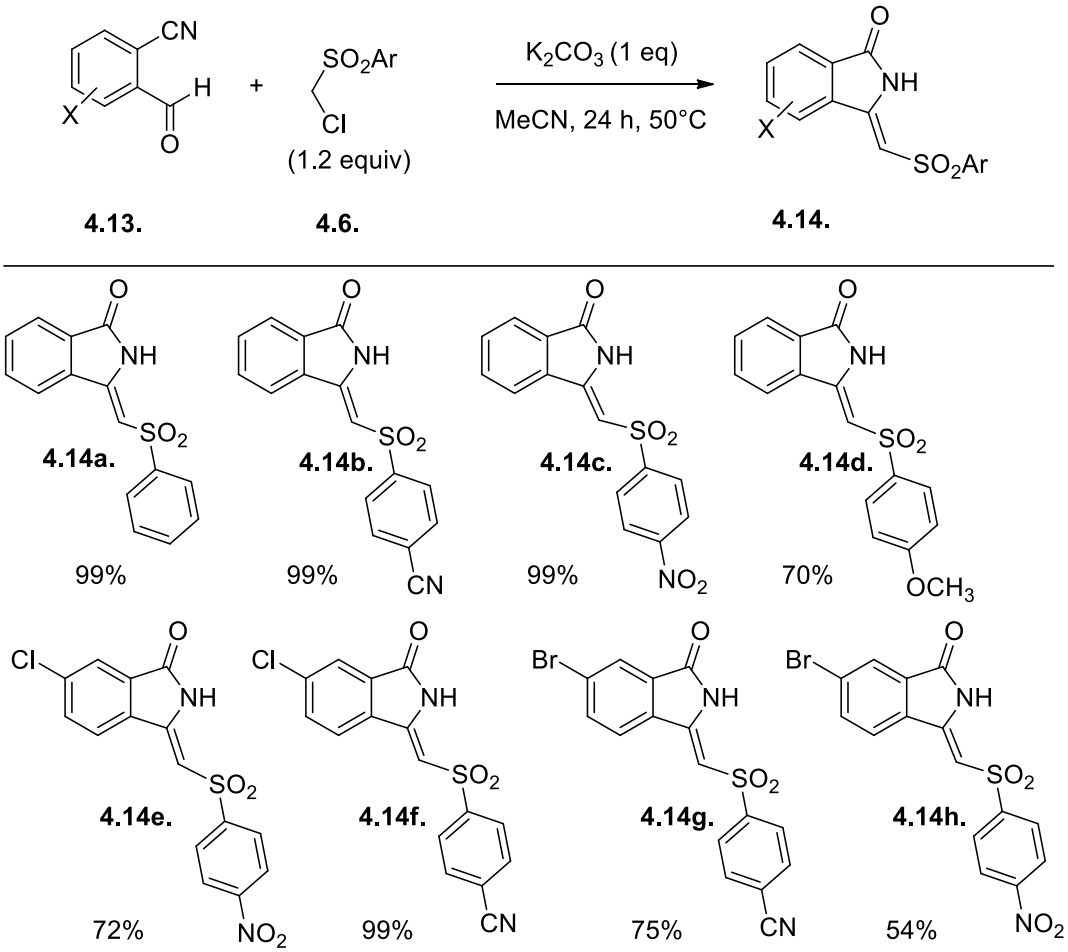
As suggested by mechanistic studies,[81] to explain the β-elimination, the dihedral angle of **4.12a**. product is -179° for H-C_3-C-Cl observed in the solid-state structure,[83] suggesting that the orientation is antiperiplanar at the end of the cascade mechanism. With this orientation of H-C_3-C-Cl, the elimination of HCl giving only the highly diastereoselective product **4.14a.** Z-configured. This

because the C-H bond of ((Chloromethyl)sulfonyl)benzenes moiety is very labile, leading epimerization and final β-eliminations under very mild basic conditions (**Scheme 4.8.**).



Scheme 4.8. (*Z*)-alkene formation favored by epimerization

Considering the convenience of the developed methodology with respect to that one reported in literature[48] an extensive screening of variously substituted aromatic aldehydes and chloromethyl aryl sulfones was carried out **(Scheme 4.9.)** The reaction gave quantitative yields and high *(Z)*-stereoselective yield under reaction conditions much milder than those reported in the literature.[48]



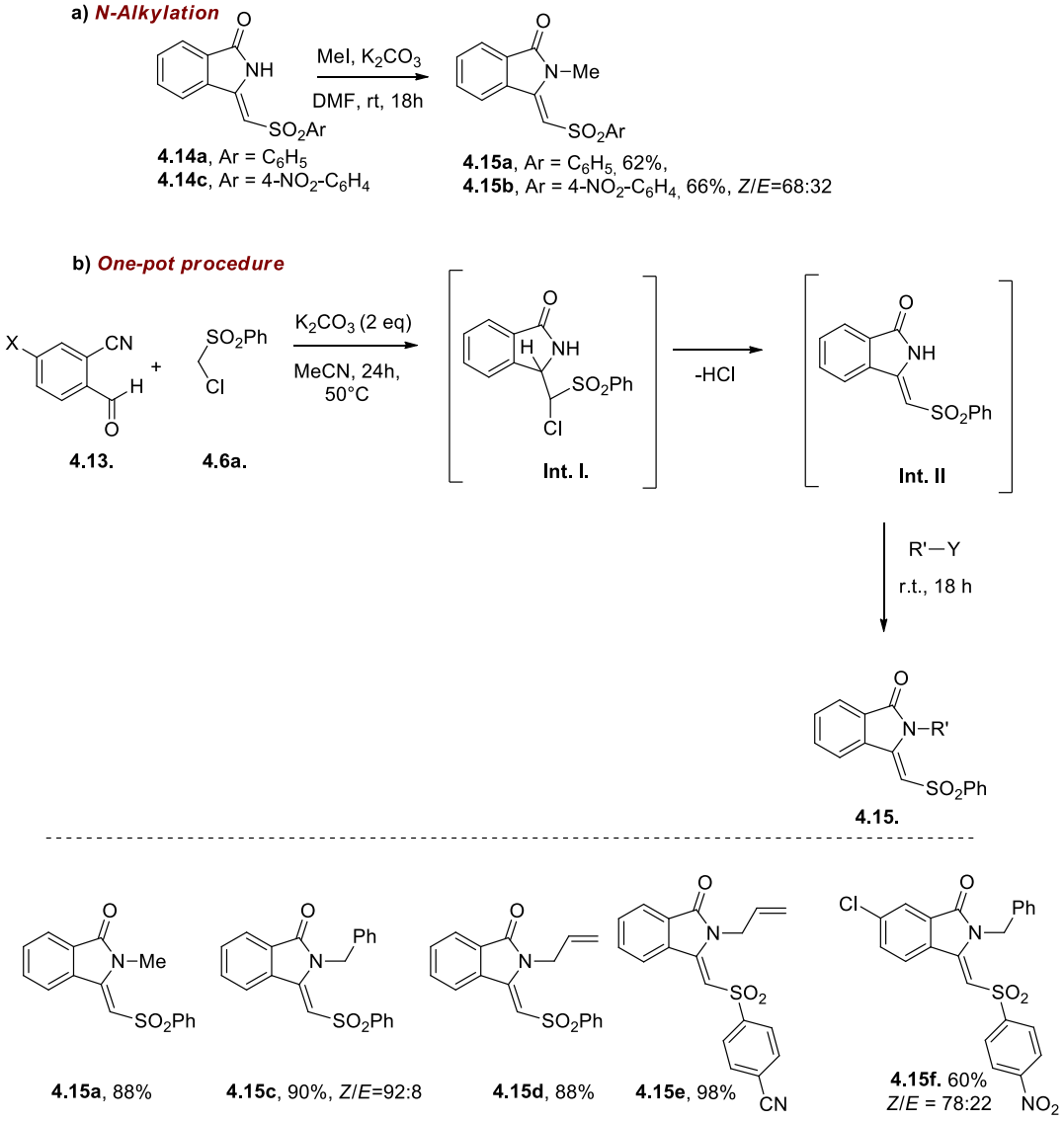
Scheme 4.9. Scope of Cascade Reactions of 2-Formylbenzonitrile **4.12** with ((Chloromethyl)sulfonylbenzenes **4.6**

This reaction is highly stereoselective, as only the formation of the Z isomer is observed (**Scheme 4.9.**). The *(Z)*-selectivity is given by the formation of the H bond between the NH group and the SO_2 group in the intermediate reaction preceding the HCl elimination. Corroboration of our hypothesis was also given by ^{1}H-NMR of the compound **4.14a.** reported in the literature.

As described by Hazra *et al.*[84] the (Z) configuration has a fundamental importance to exploit the optical and electronic properties of these molecules, due to π–π stacking required for mechanochromic properties. With this method developed by our group[81] a wide range of 3-methyleneisoindolin-1-ones products was obtained to improve further studies on electronic properties and fine tuning.

Furthermore, as reported by Jeganmohan *et al.*[47] the N-alkylated 3-methyleneisoindolin-1-ones are the precursors to the total synthesis of aristolactams, in this regard we have decided to develop new synthetic N-alkylation methodologies.

The NH product has been alkylated with a wide variety of electrophilic agents, from iodomethane to benzyl bromide (**Scheme 4.10.**). Two methods have been developed, the first (**Scheme 4.10.a**) is the direct alkylation of free NH-product in DMF at room temperature, obtaining good alkylation conversions (62-66 %). Subsequently, to improve the pot-efficiency of the reaction, a one-pot cascade reaction was devised. The process starts from the synthesis of 3-monosubstituted isoindolinone (**Int.I**) combining 2-cyanobenzaldehyde and chloromethyl aryl sulfones (**Int.II**) and finally, when the synthesis of the 3-methyleneisoindolinone was completed, the one-pot addition of the alkyl halide afforded the N-alkylation product in high yields (**Scheme 4.10.b**). Under these conditions, the NH product has been effectively alkylated with a wide variety of electrophilic agents, from iodomethane to benzyl bromide (**Scheme 4.10.**).



Scheme 4.10. a) Direct N-Alkylation of (*Z*)-3-methyleneisoindolinon-1-one **4.14a-c**. b) One-Pot Cascade Reaction/β-Elimination/N-Alkylation of **4.13** and **4.6a**

It has been observed that the N-alkylation product is not always obtained with perfect *(Z)* -selectivity. In some cases, an *(E)* / *(Z)* equilibrium is observed, especially when a nitro group is present on the chloromethyl aryl sulfone (**4.14c.**). This can be explained by the effect of the nitro group which tends to stabilize the intermediate with single bond character. Subsequent N-alkylation forms the amide in the *(E)/(Z)* mixture. The corresponding C-alkylation product was not observed. Even though an E/Z mixture was obtained in some cases, Reddy et al. reported that the geometry of the 3-methyleneindolin-1-ones does not affect the efficiency of the subsequent Diels-Alder reaction with benzynes, which yielded Aristolactams.[47]

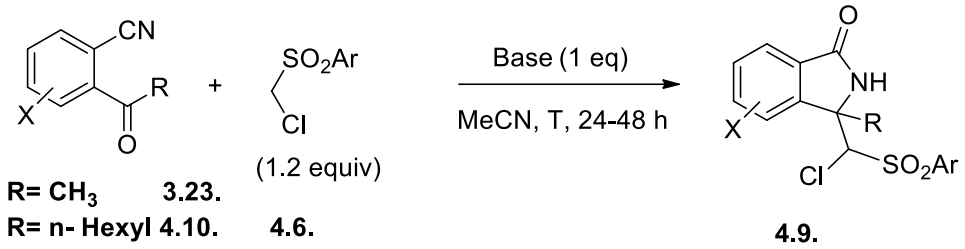
4.4. Conclusions.

In conclusion, in this chapter, thanks to the collaboration with Dr. Armin Ofial, we have carried out kinetic studies on 2-cyanoacetophenone and 2-cyanobenzophenone using the Mayr equation, employing a wide range of nucleophiles tabulated in Mayr database.[85] It was observed that bifunctional nucleophiles, bearing a leaving group in the alpha position, showed a good reactivity with 2-cyanoacetophenone (**3.23a**), determining in this way an E-value of **-17.27**. Based on these preliminary data three new synthetic methodologies have been developed for the construction of highly functionalized isoindolinones. The reaction of chloromethyl aryl sulfones with 2-cyanoacetophenones was investigated, affording 3,3-disubstituted isoindolinones in excellent yields and good diastereomeric ratios. Moreover, 2-cyanobenzaldehydes have also been investigated in one-pot cascade reaction affording 3-methyleneisoindolin-1-ones in quantitative yields and in a high (*Z*)-stereoselectivity under very basic mild conditions, involving a β-elimination reaction of HCl. Finally, two methodologies of N-alkylation of 3-methyleneisoindolinones were also designed, first with a direct N-alkylation of 3-methyleneisoindolin-1-ones in DMF, but a more challenging one-pot cascade multicomponent procedure was optimized, starting from the synthesis of 3-monosubstituted isoindolinones through β-elimination of HCl and finally N-alkylation affording N-alkylating-3-methyleneisoindolin-1-ones in very good yield and good (*Z*)-stereoselectivity.

4.5. Experimental part.

Starting material chloromethyl sulfonyl benzenes (**4.6.**) are synthetized according to literature, [86] syntheses of ketones (**3.23.)** and aldehydes [87] (**4.13.**) are reported by our group.

General procedure for the synthesis of 3,3-Disubstituted Isoindolinones with substituted ((Chloromethyl) sulfonyl)benzene (4.9.)



Scheme 4.S1. Synthesis of 3,3-disubstituted isoindolinones **4.9**

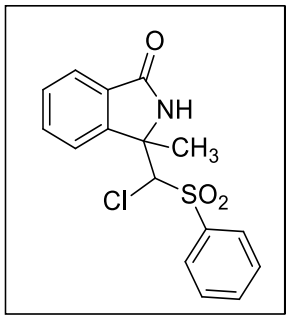
Procedure with Potassium Carbonate

2-Acetylbenzonitriles **3.23.** (0.137 mmol, 1.0 equiv) were added to a solution of substituted ((Chloromethyl)sulfonyl)benzenes **4.6.** (0.164 mmol, 1.2 equiv) and potassium carbonate (0.137 mmol, 19 mg, 1.0 equiv) in anhydrous CH_3CN (0.45 M, 0.30 mL) at 50 ºC in oil bath. The reaction mixture was stirred at the same temperature for 24 hours, then diluted with DCM and filtered off. The solution was evaporated affording the crude product as white solid, which was purified by column chromatography (Hexane: Ethyl acetate = 80:20) to provide **4.9b, 4.9c, 4.9e, 4.9f, 4.9g, 4.9h** (60-92%).

Procedure with Potassium *tert*-Butoxide

2-Acetylbenzonitriles **3.23.** (0.137 mmol, 1.0 equiv) were added to a solution of substituted ((Chloromethyl)sulfonyl)benzenes **4.6.** (0.164 mmol, 1.2 equiv) and potassium tert-butoxide (0.137 mmol, 15 mg, 1.0 equiv) in anhydrous CH_3CN (0.45 M, 0.30 mL) at r.t. The reaction mixture was directly purified by column chromatography (Hexane: Ethyl acetate = 80:20) to provide **4.9a** and **4.9d.** (64-86%).

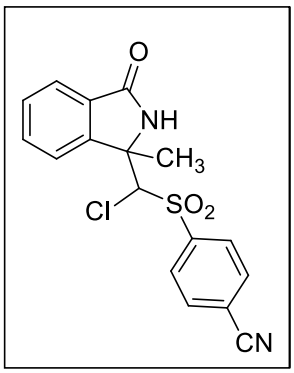
3-(Chloro(phenylsulfonyl)methyl)-3-methylisoindolin-1-one (**4.9a**)



White solid (86%, 40 mg). Mixture of diastereomers, dr.= 91:9. Recrystallization of **4.9a** (20 mg) from a hexane/EtOAc (2/1) mixture at -20°C yielded crystals, which were suitable for X-ray single crystal structure determination.[88]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.71 (t, *J* = 7.1 Hz, 1H), 7.59 (t, *J* = 7.3 Hz, 3H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.02 (brs, 1H), 5.10 (s, 1H, *major*), 4.49 (s, 1H, *minor*), 2.09 (s, 3H, *major*), 1.97 (s, 3H, *minor*). **^{13}C{^{1}H} NMR** (75.5 MHz, DMSO-d_6) δ 168.8, 149.4, 137.6, 134.8, 132.3, 131.1, 129.3, 129.1, 129.0, 123.0, 122.3, 75.9, 63.2, 24.8. **ESI-HRMS**: Found: *m/z* 358.0273 Calcd for $C_{16}H_{14}{}^{35}ClNO_3SNa^+$: $(M+nNa)^+$ 358.0275.

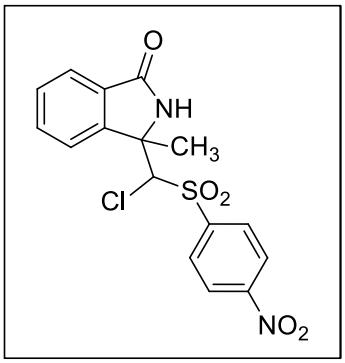
4-((Chloro(1-methyl-3-oxoisoindolin-1-yl)methyl)sulfonyl)benzonitrile (**4.9b**)



Yellow solid (91%, 45 mg). Single diastereoisomer. M.p. 196-197 °C (from hexane/ethyl acetate).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 2H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.73-7.60 (m, 3H), 7.51 (t, *J* = 7.2 Hz, 1H), 6.39 (s, 1H), 1.87 (s, 3H). **^{13}C{^{1}H} NMR** (75.5 MHz, DMSO-d_6) δ 168.8, 148.9, 141.6, 133.4, 132.3, 131.2, 129.6, 129.2, 123.0, 122.3, 117.4, 116.9, 76.0, 63.1, 24.8. **EI-HRMS**: Found: *m/z* 361.0397. Calcd for $C_{17}H_{14}{}^{35}ClN_2O_3S^+$: $(M+H)^+$ 361.0408.

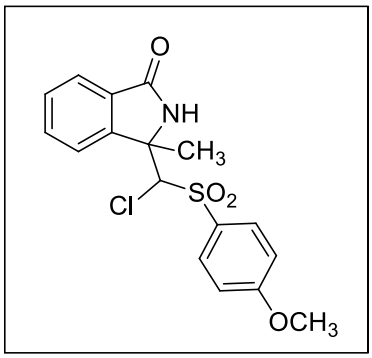
3-(Chloro((4-nitrophenyl)sulfonyl)methyl)-3-methylisoindolin-1-one (**4.9c**)



White solid (63%, 33 mg). Mixture of diastereoisomers, dr = 79:21.

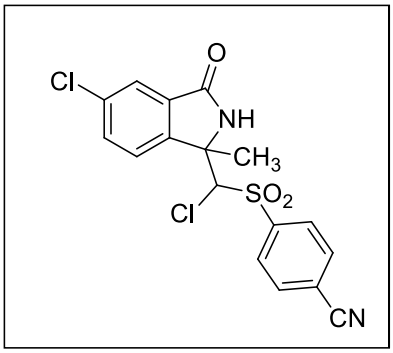
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.8 Hz, 2H, *major*), 8.15 (d, J = 8.8 Hz, 2H, *major* + *minor*), 7.87 (d, J = 7.5 Hz, 2H, *minor*), 7.73 (d, J = 7.5 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.55 – 7.52 (m, 1H), 7.40 (d, J = 7.6 Hz, 1H), 6.93 (s, 1H, *major* + *minor*), 5.15 (s, 1H, *major*), 4.56 (s, 1H, *minor*), 2.11 (s, 3H, *major*), 1.97 (s, 3H, *minor*). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6) δ 168.8, 150.9, 148.9, 142.9, 132.3, 131.2, 130.7, 129.2, 124.6, 123.1, 122.4, 76.0, 63.1, 24.8. **ESI-HRMS**: Found: *m/z* 381.0308. Calcd for $C_{16}H_{14}{}^{35}ClN_2O_5S^+$: $(M+H)^+$ 381.0306.

3-(Chloro((4-methoxyphenyl)sulfonyl)methyl)-3-methylisoindolin-1-one (4.9d)



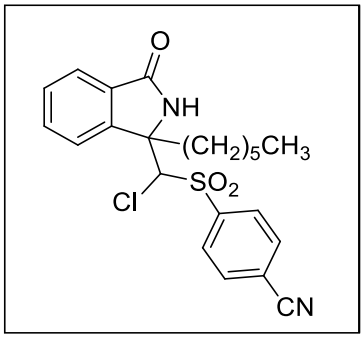
White solid (64%, 32 mg). Mixture of diastereoisomers, dr = 66:34. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 5H, *major* + *minor*), 7.74 (d, *J* = 7.1 Hz, 1H), 7.61 – 7.47 (m, 5H, *major* + *minor*), 7.38 (d, *J* = 7.6 Hz, 1H, *major*), 7.06 – 6.99 (m, 5H), 5.06 (s, 1H, *major*), 4.44 (s, 1H, *minor*), 3.89 (s, 3H, *major*), 3.88 (s, 3H, *minor*), 2.07 (s, 3H, *major*), 1.95 (s, 3H, *minor*). **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$) δ 169.6, 168.5, 164.9 (2C), 149.2, 148.3, 132.7, 132.2, 132.0, 131.3, 130.9, 129.6, 129.5, 128.3, 127.9, 124.9, 124.5, 124.3, 120.6, 114.7, 114.5, 79.0, 63.7, 55.9, 29.8, 29.5, 24.8, 20.7, 14.3. **ESI-HRMS**: Found: *m/z* 366.0563. Calcd for $C_{17}H_{17}{}^{35}ClNO_4S^+$: $(M+H)^+$ 366.0561

4-((Chloro(5-chloro-1-methyl-3-oxoisoindolin-1- l)methyl)sulfonyl)benzonitrile (4.9e)



White solid (74%, 40 mg). Mixture of diastereoisomers, dr = 56:44. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11-8.05 (m, 3H, *major* + *minor*), 7.91-7.88 (m, 3H, *major* + *minor*), 7.83 – 7.82 (m, 1H, *minor*),δ 7.66 (d, J = 7.8 Hz, 1H), 7.58 – 7.53 (m, 2H, *major* + *minor*), 7.39(s, 1H, *minor*), δ 7.34 (d, J = 7.7 Hz, 1H, *major*), 6.98 (s, 1H, *major*), 5.09 (s, 1H, *major*), 4.52 (s, 1H, *minor*), 2.09 (s, 3H, *major*), 1.96 (s, 3H, *minor*). **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.9, 166.9, 146.4, 145.8, 140.7, 136.6, 136.3, 133.2, 133.1, 133.1, 133.1, 132.7, 132.6, 130.4, 130.4, 126.1, 124.9, 124.6, 122.0, 119.0, 118.9, 116.9, 116.8, 115.0, 78.3, 63.7, 63.5, 24.6, 21.0. **ESI-HRMS**: Found: *m/z* 392.9874. Calcd for $C_{17}H_{11}{}^{35}Cl_2N_2O_3S^-$: $(M)^-$392.9873.

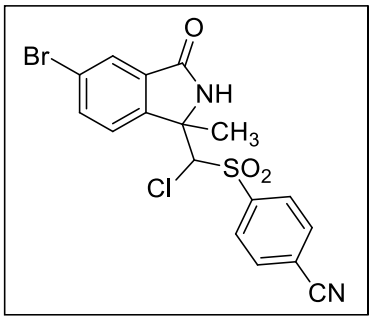
4-((Chloro(1-hexyl-3-oxoisoindolin-1-yl)methyl)sulfonyl)benzonitrile (4.9f)



Yellow solid (60%, 35.3 mg). Mixture of diastereoisomers, dr = 55:45. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06-8.03 (m, 3H, *major* + *minor*), 7.88-7.85 (m, 4H,*major* + *minor*), 7.67 (d, J = 7.5 Hz, 1H, *minor*), 7.59- 7.52 (m, 3H, *major* + *minor*), 7.35 (d, J = 7.5 Hz, 1H), 7.16 (s, 1H, *minor*), 6.81 (s, 1H, *major*), 5.15 (s, 1H, *major*), 4.57 (s, 1H, *minor*), 2.70– 2.63 (m, 1H), 2.49 – 2.43 (m, 1H), 2.38 – 2.31 (m, 1H), 1.19 – 1.14 (m, 9H, *major* + *minor*), 0.84-0.80 (m, 5H, *major* +

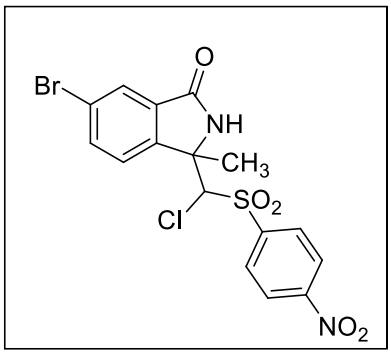
minor). **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$) δ 169.9, 169.0, 146.2, 145.3, 141.2, 133.1, 132.9, 132.8, 132.5, 132.3, 131.9, 130.4, 130.3, 129.9, 129.7, 124.9, 124.5, 120.9, 118.8, 118.6, 116.9, 117.0, 79.3, 67.5, 36.1, 32.1, 29.8, 29.2, 29.1, 24.0, 22.8, 22.6, 14.1. **ESI-HRMS**: Found: *m/z* 431.1196. Calcd for $C_{22}H_{24}{}^{35}ClN_2O_3S^+$: $(M+H)^+$ 431.1191.

4-(((5-Bromo-1-methyl-3-oxoisoindolin-1-l)chloromethyl)sulfonyl)benzonitrile (**4.9g**)



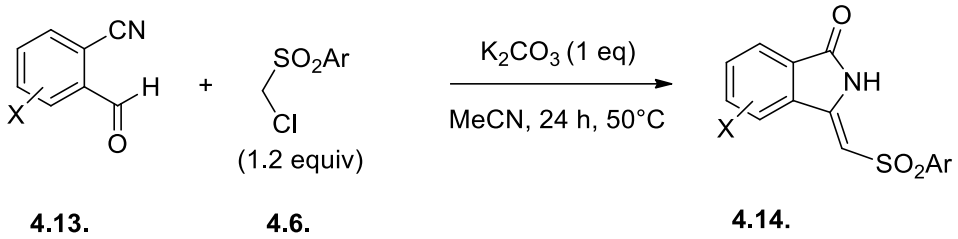
Yellow solid (89%, 53 mg). Mixture of diastereoisomers, dr = 58:42. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 – 8.05 (m, 2H, *major* + *minor*), 7.99 (s, 1H, *major*), 7.90-7.88 (m, 2H, *major* + *minor*), 7.73 – 7.69 (m, 1H), 7.60 (d, *J* = 8.1 Hz, 1H, *minor*),7.50-7.45 (m, 1H), 7.37 (s, 1H) , 7.29 (s, 1H), 6.96 (s, 1H, *major*), 5.08 (s, 1H, *major*), 4.52 (s, 1H, *minor*), 2.08 (s, 3H, *major*), 1.95 (s, 3H, *minor*). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6) δ 167.2 (*major*), 166.8 (*minor*), 147.8 (*major*), 146.4 (*minor)*, 141.5 (*major*), 141.1 (*minor*) 135.02 (*major*),134.6 (*minor*), 133.7, 133.5 (*major*), 133.3 (*minor*), 129.6, 125.7, 124.7, 122.5, 117.4, 117.0, 77.4, 75.6, 63.1 (*major*), 62.8 (*minor*), 26.4 (*minor)*, 24.5 (*major*). **ESI-HRMS**: Found: *m/z* 438.9517. Calcd for $C_{17}H_{13}{}^{79}Br^{35}ClN_2O_3S^+$: $(M+H)^+$ 438.9513.

6-Bromo-3-(chloro((4-nitrophenyl)sulfonyl)methyl)-3-methylisoindolin-1-one (**4.9h**)



White solid (84%, 53 mg). Mixture of diastereoisomers, dr = 76:24 **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.21 (s, 1H, *minor*), 8.89 (s, 1H, *major*), 8.49 (d, *J* = 9.0 Hz, 2H, *major*), 8.39 (d, *J* = 8.5 Hz, 2H, *minor*), 8.19 (d, *J* = 9.2 Hz, 2H, *major*), 7.89 – 7.84 (m, 2H), 7.80 – 7.76 (m, 1H), 7.71-7.69 (m, 1H, *major*), 7.61 (d, *J* = 8.6 Hz, 1H, *minor*), 6.62 (s, 1H, , *minor*), 6.46 (s, 1H,*major*), 1.87 (s, 3H, *major*), 1.61 (s, 3H, *minor*). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6) δ 167.2 (*major*), 166.8 (*minor*), 150.9 (*major*), 150.6 (*minor*), 147.8, 142.7 (*major)*, 142.4 (*minor*), 135.1, 133.7, 130.6, 125.8, 124.8, 124.6, 122.5, 77.4 (*minor*), 75.6 (*major*), 63.1 (*major*), 62.8 (*minor*), 26.4 (*minor*), 24.5 (*major*). **ESI-HRMS**: Found: *m/z* 492.9026. Calcd for $C_{16}H_{12}{}^{79}Br^{35}Cl_2N_2O_5SCl^-$: $(M+Cl)^-$ 492.9035

General procedure for the synthesis of 3-methyleneisoindolin-1-ones (4.14.)



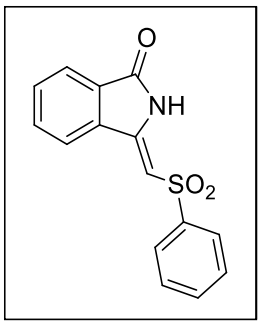
4.13. **4.6.** **4.14.**

Scheme 4.S2. Synthesis of 3-methyleneisoindolin-1-ones **4.14**

2-Formylbenzonitriles **4.13.** (0.137 mmol, 1.0 equiv) were added to a solution of ((Chloromethyl)sulfonyl)benzenes **4.6.** (0.164 mmol, 1.2 equiv) and potassium carbonate (0.137 mmol, 19 mg, 1.0 equiv) in anhydrous CH_3CN (0.45 M, 0.30 mL) at 50 ºC in oil bath. The reaction mixture was stirred at the same temperature for 24 hours, diluted with DCM and then filtered off. The filtrate was evaporated affording the crude product as white solid, which was purified by column chromatography (hexane/ethyl acetate = 80/20) to provide **4.14a-h** (54-99%).

The reaction was scaled up to 1.37 mmol (180 mg) of 2-formyl benzonitrile according to the above procedure **4.14a**. After 24h, the reaction mixture was diluted with DCM and filtered off. After evaporation of the solvent, the title compound was purified by crystallization (13 mL, $CHCl_3$: Hexane = 1:1 at -20°C) obtaining **4.14a** as pure solid in 99% yield (387 mg).

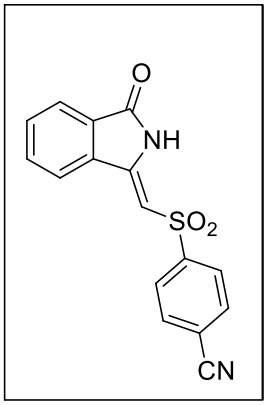
(Z)-3-((Phenylsulfonyl)methylene)isoindolin-1-one (4.14a)



White solid (99%, 39 mg). M.p. 181-182 °C (from hexane/ethyl acetate).

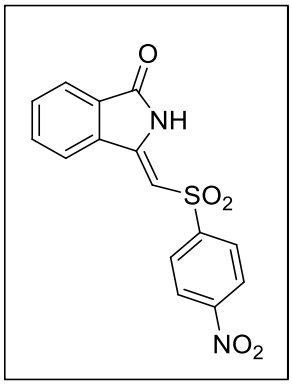
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.07 (d, J = 7.7 Hz, 3H), 7.83-7.64 (m, 6H), 6.95 (s, 1H). *Data were found in agreement with literature*.[48]

(Z)-4-(((3-Oxoisoindolin-1-ylidene)methyl)sulfonyl)benzonitrile (4.14b)



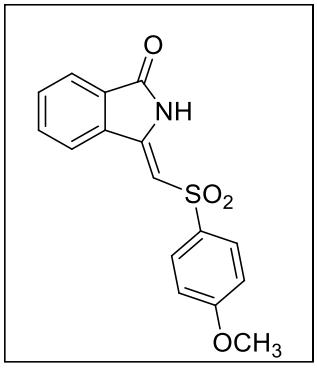
White solid (99%, 48.9 mg). M.p. 229–230 °C (from hexane/ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 2H), 7.92 – 7.90 (m, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.70 – 7.65 (m, 2H), 7.61 – 7.59 (m, 1H), 6.03 (s, 1H). **^{13}C{^{1}H} NMR** (75.5 MHz, DMSO-*d*$_6$) δ 167.9, 145.8, 145.1, 135.9, 133.8, 133.5, 132.6, 128.2, 127.7, 123.5, 122.6, 117.64, 115.9, 99.9. **EI-HRMS**: Found: *m/z* 361.0397. Calcd for $C_{16}H_{10}N_2O_3S^{\cdot+}$: $(M)^{\cdot+}$ 361.0408.

(Z)-3-(((4-Nitrophenyl)sulfonyl)methylene)isoindolin-1-one (4.14c)



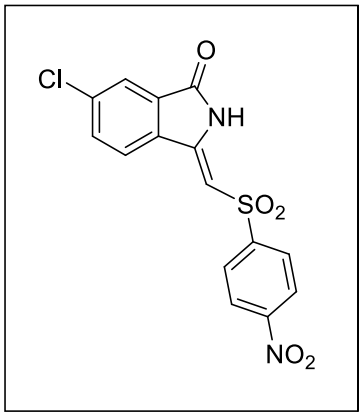
White solid (99%, 44 mg). M.p. 198-199 °C (from hexane/ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.41 (d, *J* = 8.6 Hz, 2H), 8.17 (d, *J* = 8.6 Hz, 2H), 7.93 – 7.91 (m, 1H), 7.70 – 7.67 (m, 2H), 7.62 – 7.59 (m, 1H), 6.05 (s, 1H). **^{13}C{^{1}H} NMR** (75.5 MHz, DMSO-*d*$_6$) δ 167.9, 150.3, 147.2, 145.3, 135.9, 133.5, 132.7, 128.5, 128.3, 124.9, 123.5, 122.6, 99.7. **EI-HRMS**: Found: *m/z* 330.0301. Calcd for $C_{15}H_{10}N_2O_5S^{\cdot+}$: $(M)^{\cdot+}$ 330.0305

(Z)-3-(((4-Methoxyphenyl)sulfonyl)methylene)isoindolin-1-one (4.14d)



White solid (70%, 30 mg). M.p. 200-201°C (from hexane/ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.88 (d, *J* = 8.8 Hz, 3H), 7.63 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.59-7.56 (m, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 6.08 (s, 1H), 3.87 (s, 3H). **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$) δ 167.5, 164.0, 143.0, 136.0, 133.2 132.3, 129.5, 129.1, 124.4, 121.4, 114.8, 101.2, 55.9. **EI-HRMS**: Found: *m/z* 315.0560. Calcd for $C_{16}H_{13}NO_4S^{\cdot+}$: $(M)^{\cdot+}$ 315.0560.

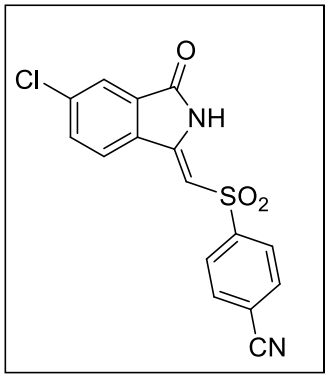
(Z)-6-Chloro-3-(((4-nitrophenyl)sulfonyl)methylene)isoindolin-1-one (4.14e)



White solid (72%, 36 mg). M.p. 234-235 °C (from hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.42 (d, *J* = 8.9 Hz, 2H), 8.16 (d, *J* = 8.9 Hz, 2H), 7.88 (s, 1H), 7.66 – 7.62 (m, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 6.03 (s, 1H). **^{13}C{^{1}H} NMR** (75.5 MHz, DMSO-d_6) δ 166.8, 150.3, 147.0, 144.4, 137.4, 134.6, 133.4, 130.3, 128.6, 124.9, 124.4, 123.4, 100.7. **EI-HRMS**: Found: *m/z* 363.9914. Calcd for $C_{15}H_9{}^{35}ClN_2O_5S^{\cdot+}$: $(M)^{\cdot+}$ 363.9915

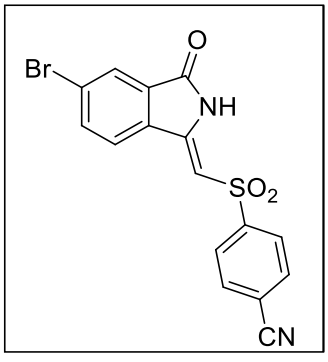
(Z)-4-(((5-Chloro-3-oxoisoindolin-1-ylidene)methyl)sulfonyl)benzonitrile (4.14f)



White solid (99%, 46 mg). M.p. 219-220 °C (Hexane/Ethyl acetate).

^{1}H NMR (400MHz, $CDCl_3$)δ9.43 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 6.01 (s, 1H). **^{13}C{^{1}H} NMR** (63 MHz, DMSO-d_6) δ 166.7, 145.6, 144.2, 137.4, 134.6, 133.8, 133.4, 130.3, 127.7, 124.4, 123.4, 117.6, 116.0, 100.8. **EI-HRMS**: Found: *m/z* 344.0021. Calcd for $C_{16}H_9{}^{35}ClN_2O_3S^{\cdot+}$: $(M)^{\cdot+}$ 344.0017

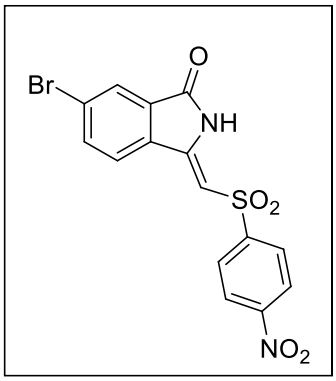
(Z)-4-(((5-Bromo-3-oxoisoindolin-1-ylidene)methyl)sulfonyl)benzonitrile (4.14g)



White solid (75%, 40 mg). M.p. 194-195 °C (from hexane/ethyl acetate).

^{1}H NMR (300 MHzDMSO-d_6) δ 10.75 (s, 1H), 8.25 (d, J = 8.2 Hz, 2H), 8.17 (d, J = 8.2 Hz, 2H), 8.00-7.95 (m, 3H), 7.05 (s, 1H). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6) δ 166.7, 145.7, 144.4, 136.2, 135.1, 133.8, 130.4, 127.7, 126.29, 125.9, 124.6, 117.7, 116.0, 100.8. **EI-HRMS**: Found: *m/z* 387.9515. Calcd for $C_{16}H_9{}^{79}BrN_2O_3S^{\cdot+}$: $(M)^{\cdot+}$ 387.9512.

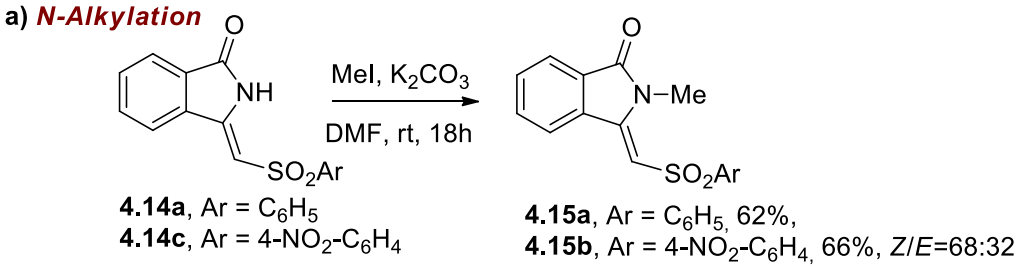
(Z)-6-Bromo-3-(((4-nitrophenyl)sulfonyl)methylene)isoindolin-1-one (4.14h)



Yellow solid (54%, 30 mg). M.p. 227-228 °C (from hexane/ethyl acetate).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 8.47 (d, J = 8.5 Hz, 2H), 8.33 (d, J = 8.5 Hz, 2H), 8.03 – 7.96 (m, 3H), 7.08 (s, 1H). **^{13}C{^{1}H} NMR** (75.5 MHz, DMSO-d_6) δ 166.7, 150.3, 147.0, 144.5, 136.3, 135.0, 130.4, 128.6, 126.3, 126.0, 125.0, 124.6, 100.7. **EI-HRMS**: Found: *m/z* 407.9402. Calcd for $C_{15}H_9{}^{79}BrN_2O_5S^{\cdot+}$: $(M)^{\cdot+}$ 407.9410

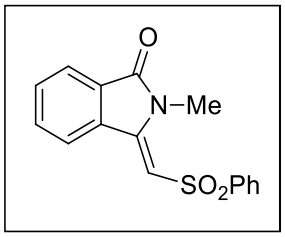
General procedure for the N-methylation of (Z)-3-((Phenylsulfonyl)methylene) isoindolin-1-ones (4.15)



Scheme 4.S3. Direct N-Alkylation of (*Z*)-3-methyleneisoindolinon-1-one **4.14a-c**.

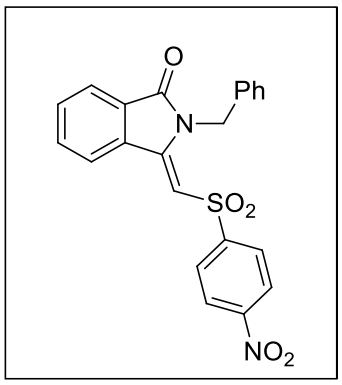
To a solution of **4.14a** or **4.14c** (0.14 mmol, 1.0 equiv) in anhydrous DMF (0.30M, 0.47 mL) was added potassium carbonate (0.21 mmol, 29.0 mg, 1.5 equiv) and CH_3I (0.21 mmol, 0.013 mL ,1.5 equiv). The reaction mixture was allowed to stir at room temperature for 18 hours and then diluted with ethyl acetate and washed with water (3 x 5 mL) obtaining crude product as white solid, which was purified by flash column chromatography (hexane/ethyl acetate = 80/20) to provide **4.15a.** (62%) and **4.15b.** (66%, *Z*/*E* = 68:32).

(Z)-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (4.15a)



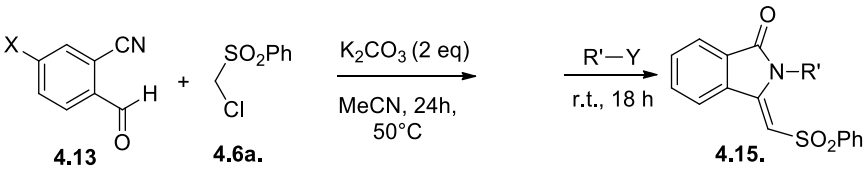
White solid (62%, 26 mg), M.p. 154-155 °C (from hexane/ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.6 Hz, 2H), 7.84-7.82 (m, 1H), 7.67-7.65 (m, 1H) 7.61-7.56 (m, 5H), 6.35 (s, 1H), 3.66 (s, 3H). **^{13}C{^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 168.2, 143.7, 143.0, 136.6, 133.6, 133.0, 131.6, 129.5, 127.9, 127.1, 124.0, 120.3, 103.9, 30.4. **ESI-HRMS**: Found: *m/z* 300.0690 Calcd for $C_{16}H_{14}N_3OS^+$: $(M+H)^+$ 300.0689.

(Z)-2-benzyl-3-(((4-nitrophenyl)sulfonyl)methylene)isoindolin-1-one (4.15b)



White solid (66%, 32 mg), mixture of isomers, *Z/E* = 68:32 **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.78 (d, *J* = 7.3 Hz, 1H, *E isomer*), 8.45-8.38 (m, 3H, *Z+E isomer*), 8.24-8.21 (m, 2H, *Z+E isomer*), 7.88-7.86 (m, 2H, *E isomer*), 7.70-7.58 (m, 4H, *Z+E isomer*), 6.27 (s, 1H,*Z isomer)*, 6.08 (s, 1H, *E isomer*), 3.64 (s, 3H, *Z isomer*), 3.22 (s, 3H, *E isomer*). **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$) δ 167.9 (*Z isomer*), 166.4 (*E isomer*), 150.4, 148.9(*E isomer*), 148.4 (*Z isomer*), 147.9, 145.3, 136.2, 133.5 (*E isomer*), 133.1 (*Z isomer*), 132.3 (*E isomer*), 132.0 (*Z isomer*), 131.7, 129.9, 128.4 (*Z isomer*), 128.0 (*E isomer*), 127.6, 124.6 (*Z isomer*), 124.6, 124.2 (*E isomer*), 123.9, 120.3, 105.6, 101.3, 30.4 (*Zisomer*), 26.4(*Eisomer*). **ESI-HRMS**: Found: *m/z* 345.0541 .Calcd for $C_{16}H_{13}N_2O_5S^+$: $(M+H)^+$ 345.0531.

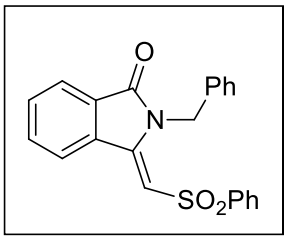
One-pot *N*-Alkylation of (Z)-3-((Phenylsulfonyl)methylene) isoindolin-1-one (4.15)



Scheme 4.S4. One-Pot Cascade Reaction/β-Elimination/N-Alkylation of **4.13** and **4.6a** for the synthesis of compound **4.15**

2-Formylbenzonitrile **4.13.** (0.14 mmol, 1.0 equiv) was added to a solution of **4.6a.** (0.14 mmol, 1.0 equiv) and potassium carbonate (0.28 mmol, 2.0 equiv) in anhydrous CH_3CN (0.45 M) at 50 °C in oil bath. The reaction mixture was allowed to stir at the same temperature for 24 hours, cooled at room temperature and treated with CH_3I or BnBr (0.21 mmol, 1.5 equiv). The reaction was monitored by TLC until the maximum conversion was reached. After 18 hours the crude reaction was diluted with DCM, filtered off and evaporated, affording the crude product as white solid. Purification by flash column chromatography (Hexane: Ethyl acetate = 70:30) provided **4.15a.** (88%) and **4.15c-4.15f**.

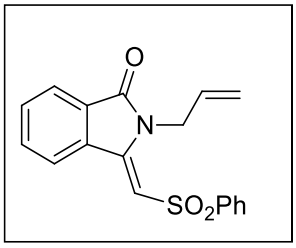
(Z)-2-benzyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (4.15c)



White solid (90%, 47 mg). Mixture of isomers, *Z/E* = 92:8

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 7.4 Hz, 1H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.67 (d, *J* = 7.1 Hz, 2H), 7.62 – 7.59 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.21 - 7.19 (m, 3H), 7.05 (s, 1H), 6.98 (dd, *J* = 7.4, 2.2 Hz, 1H), 5.57 (s, 1H, *E isomer*), 5.54 (s, 2H, *Z isomer*). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6) δ 168.6, 142.2, 142.1, 137.7, 137.4, 134.2, 133.9, 132.5, 129.7, 128.8, 127.2, 127.1, 126.9, 126.0, 124.0, 122.5, 105.1, 46.1. **ESI-HRMS**: Found: *m/z* 376.1024 Calcd for $C_{22}H_{18}NO_3S^+$: $(M+H)^+$ 376.1002.

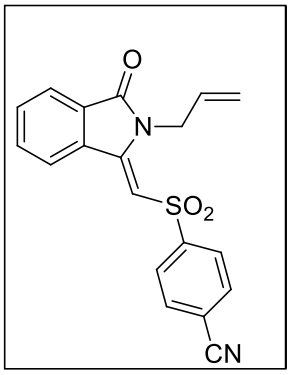
(Z)-2-allyl-3-((phenylsulfonyl)methylene)isoindolin-1-one(4.15d)



White solid (88%, 40 mg). M.p. 139-141 °C (Petroleum Ether /Ethyl acetate).

^{1}H NMR(300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.4 Hz, 2H), 7.85 - 7.83 (m, 1H), 7.60 - 7.54 (m, 6H), 6.30 (s, 1H), 5.90 - 5.78 (m, 1H), 5.04 - 4.93 (m, 4H). **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$) δ 168.3, 142.5, 142.3, 137.1, 133.6, 133.2, 132.4, 131.8, 129.5, 127.8, 127.3, 124.2, 120.5, 116.2, 103.7, 45.1. **ESI-HRMS**: Found: *m/z* 326.0845 Calcd for $C_{18}H_{16}NO_3S^+$: $(M+ H)^+$ 326.0846

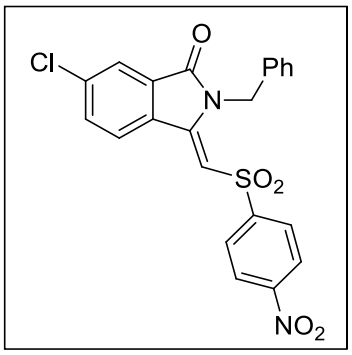
(Z)-4-(((2-allyl-3-oxoisoindolin-1-ylidene)methyl)sulfonyl)benzonitrile (4.15e)



White solid (98%, 48 mg). M.p. 156-158 °C (Petroleum Ether /Ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 3H), 7.66 – 7.59 (m, 3H), 6.22 (s, 1H), 5.86 – 5.76 (m, 1H), 5.01 – 4.88 (m, 4H). **^{13}C{^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ 168.2, 146.6, 143.9, 136.9, 133.4, 133.2 (x2), 132.4, 132.2, 128.0, 127.6, 124.5, 120.6, 117.2, 116.1, 101.5, 45.0. **MALDI-HRMS**: Found: *m/z* 351.0803Calcd for $C_{19}H_{15}N_2O_3S^+$: $(M+H)^+$ 351.0798

(Z)-2-benzyl-6-chloro-3-(((4-nitrophenyl)sulfonyl)methylene)isoindolin-1-one (4.15f)



White solid (60%, 38 mg). mixture of isomers, *Z/E* = 78:22

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.8 Hz, 1H, *minor*), 8.16 (d, *J* = 8.9 Hz, 1H, *minor*), 8.03 (d, *J* = 8.9 Hz, 2H, *major + minor*), 7.90 (s, 1H), 7.68 (d, *J* = 1.9 Hz, 1H, *minor*), 7.66 (d, *J* = 1.8 Hz, 1H, *major*), 7.61 (t, *J* = 8.8 Hz, 3H, *major + minor*), 7.53 (d, *J* = 8.3 Hz, 1H, *minor)*, 7.17 (d, *J* = 7.4 Hz, 2H), 6.90 (d, *J* = 6.6 Hz, 2H), 6.25 (s, 1H, *major*), 6.03 (s, 1H, *minor*), 5.65 (s, 2H,*major + minor*). **^{13}C{^{1}H} NMR** (100.5 MHz, DMSO-d_6) δ 167.3, 150.3, 147.2, 143.2, 137.7, 137.2, 136.0, 134.2, 129.0, 128.8, 128.5, 127.0, 125.7, 124.9, 124.7, 124.0, 104.2, 46.0. **MALDI-HRMS**: Found: *m/z* 477.0295 Calcd for $C_{22}H_{15}ClN_2O_5SNa^+$: $(M+nNa)^+$ 477.0282

X-ray analysis

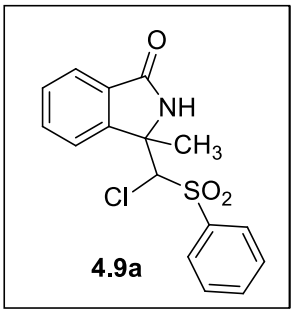
Colorless prismatic single crystals of compound **4.9a.** suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of **4.9a.** by dissolving 5 mg of the compound in 0.6 ml of hexane/AcOEt (2/1).

A crystal of 0.57 mm x 0.23 mm x 0.11 mm was selected and mounted on a nylon loop with paratone oil and measured at room temperature with a Bruker D8 QUEST diffractometer equipped with a PHOTON II detector using Cu$K\alpha$ radiation (λ= 1.54178 Å).

Data Indexing was performed using APEX3 software.[1] Data integration and reduction were performed using SAINT.[2] Absorption correction was performed by multi-scan method in SADABS.[2] The structure was solved using SHELXS-97[3] and refined by means of full matrix least-squares based on F^3 using the program SHELXL.[4] Non-hydrogen atoms were refined anisotropically, while hydrogen atoms were positioned geometrically and included in structure factors calculations but not refined. ORTEP diagram (**Figure 4.S1**) was drawn using OLEX2.[5]

Crystallographic data are reported in **Table 4.S1**.

CCDC- 2087404 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures



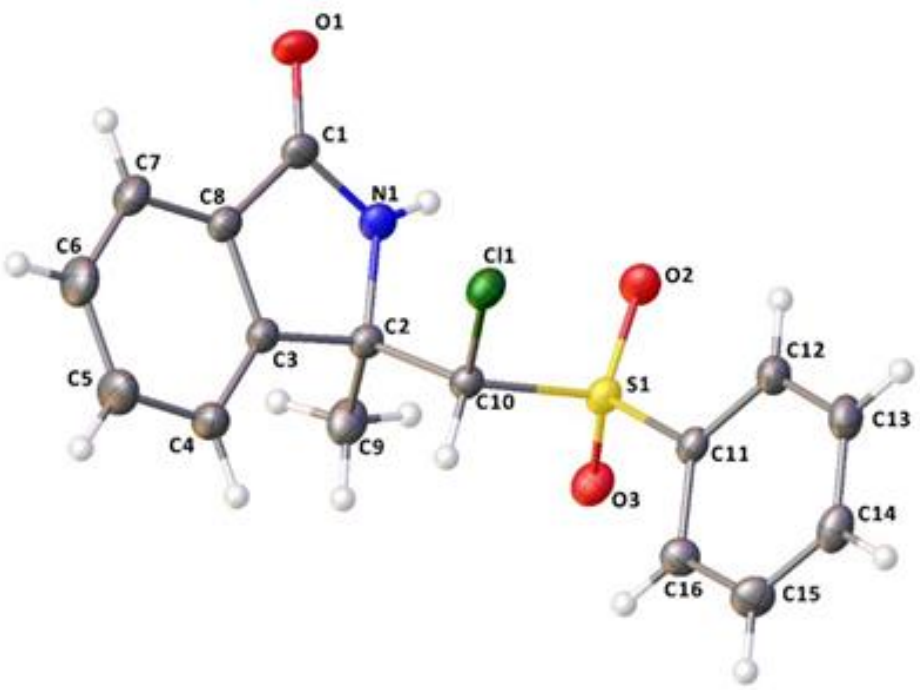


Figure 4.S1. ORTEP diagram for compound **4.9a.**

T(K)	296
Formula	$C_{16}H_{14}ClNO_3S$
Formula weight	335.79
System	Monoclinic
Space group	*C*2/c
***a* (Å)**	18.123(4)
***b* (Å)**	15.625(3)
***c* (Å)**	13.992(4)
***β* (°)**	128.262(12)
***V* (Å^3)**	3111.1(13)
Z	8
***Dx* (g cm^{-3})**	1.434
λ (Å)	1.54178
***μ* (mm^{-1})**	3.534
F_{000}	1392
R1 (I > 2σI)	0.0345(2922)
$_wR_2$	0.0978(3058)
N. of param.	205
GooF	1.054
ρ_{min}, ρ_{max} (eÅ^{-3})	-0.337, 0.271

Table 4.S1. Crystallographic data for compound **4.9a.**

Chapter 5. 4-arylideneisoxazol-5-ones as electrophiles in Michael Reactions

5.1. Introduction

The interest toward isoxazol-5-one based heterocyclic scaffolds has enhanced in the last years because they exhibit interesting pharmacological, biological [89] and optical properties.[90]
Herein are reported some examples of bioactive molecules with isoxazol-5-one core. (**Figure 5.1.**)

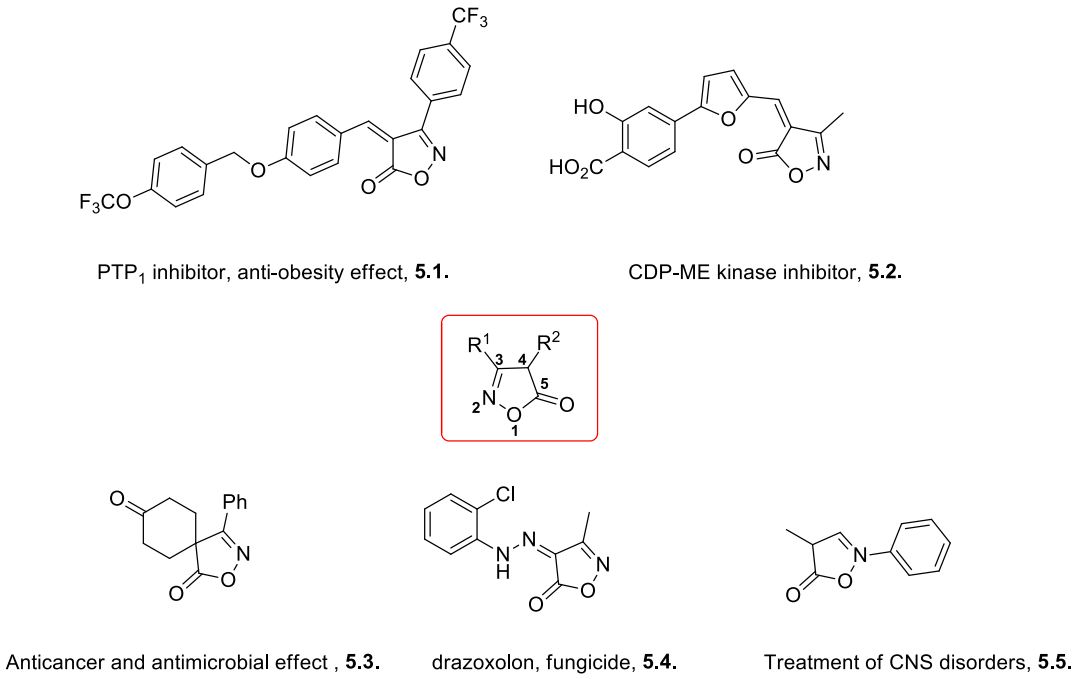
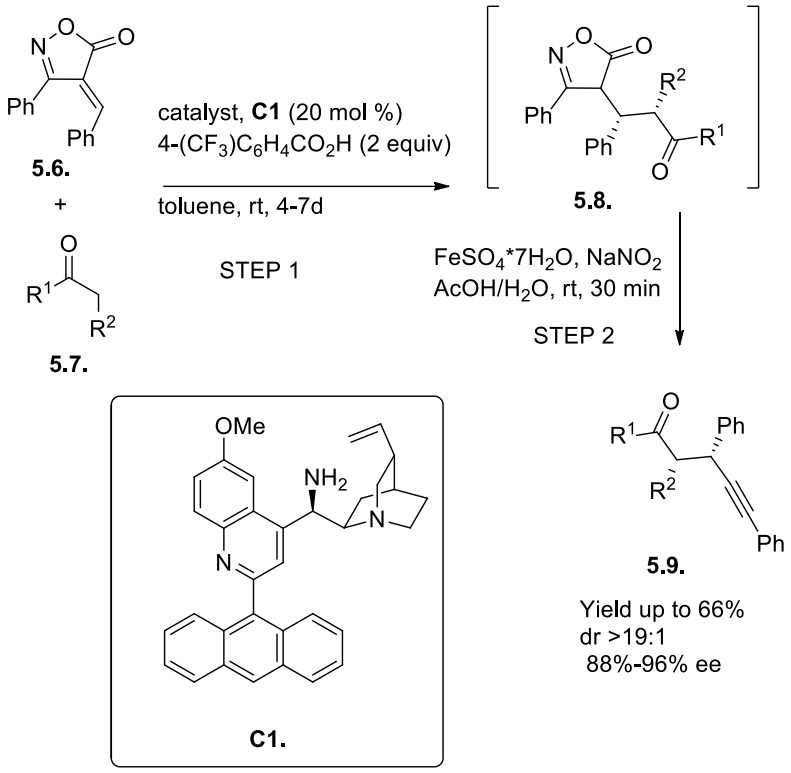


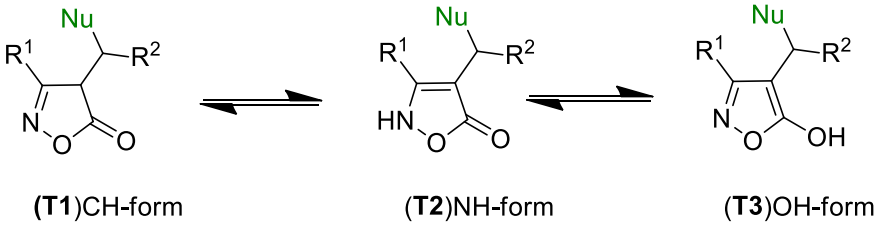
Figure 5.1. Isoxazol-5-one motifs in bioactive molecules and pharmaceutical applications.

In the literature there are few examples of 4-arylideneisoxazol-5-ones employed in conjugate additions, due to the low stability of the adducts. In these cases, usually the Michael adducts are never isolated but they are employed as substrate to study secondary reactivity for example in the N-O cleavage using $FeSO_4$ and $NaNO_2$ and generate new class of molecules (**Scheme 5.2.**).[91] Herein is reported the synthesis of alkyne derivatives through two-step cascade reaction. In the first step there is an aminocatalyzed conjugate addition of both acyclic and cyclic ketones (**5.7**) on 4-arylideneisoxazol-5-ones (**5.6**). The Michael adduct (**5.8**) is not isolated but used as substrate for the successive step of nitrosative degradation catalyzed by $FeSO_4$ and $NaNO_2$,[92] thus affording the alkyne motifs (**5.9**) bearing two contiguous stereocenters in good yields and excellent enantiomeric excesses.



Scheme 5.1. Michael adducts **5.8** as intermediate in nitrosative cleavage for the synthesis al alkynes motifs **5.9**

As noted in the Jurberg review,[93] ring of isoxazol-5-one can exist as tautomeric mixtures, even if there are conditions that favor some tautomeric forms over others (**Scheme 5.2**).

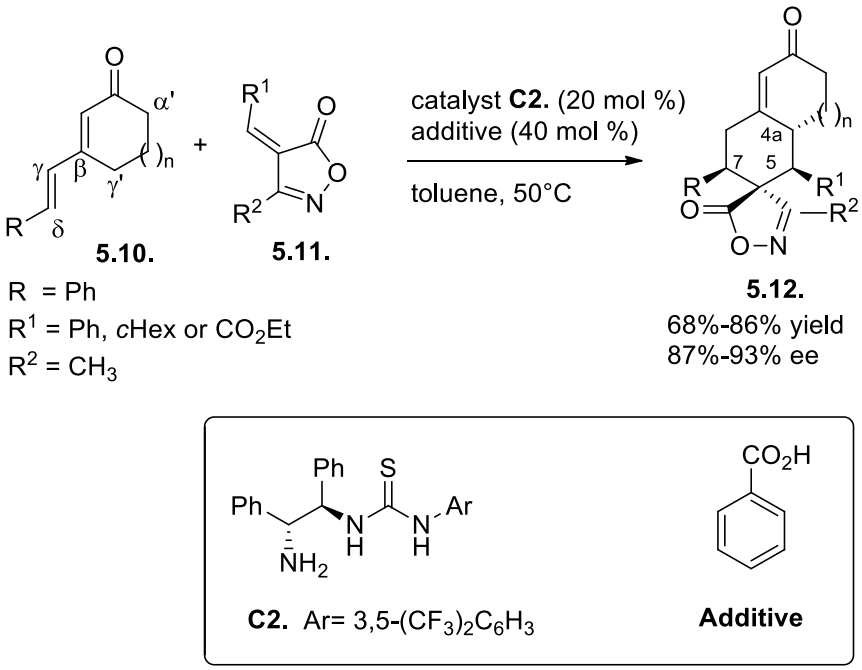


Scheme 5.2. Tautomerism in isoxazole-5-ones

The substituents R^1 and R^2 certainly play a crucial role in the predominance of a tautomeric species rather than another. When the substituents are R^1, $R^2 \neq H$ and solvents with low polarity ($CDCl_3$) the CH form (**T1, Scheme 5.2**) is predominant in the mixtures. High polarity solvents (DMSO, D_2O, DMF) which therefore favor H bonds, lead to the predominance of the enamine-like form (**T2,**

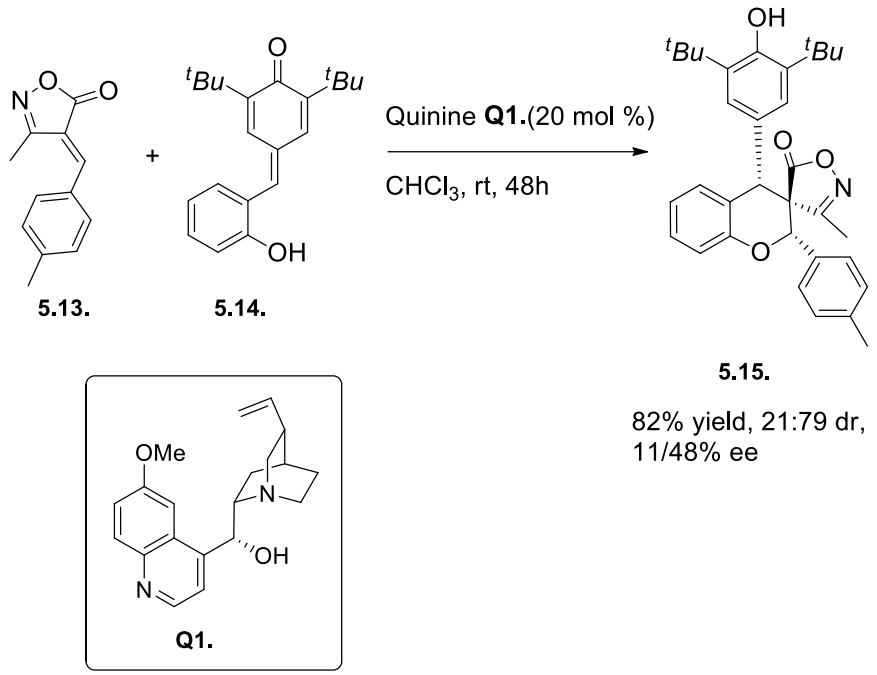
Scheme 5.2), while the enol-like form (**T3, Scheme 5.2**) is favored only when strongly basic reaction solutions are used.[12]

Chen and Ouyang [94] (**Scheme 5.3.**) reported an asymmetric thiourea catalyzed [4 + 2] cycloaddition with 4-arylideneisoxazol-5-ones and 2,4-dienone in good yield (68-86%) and very good enantiomeric excess (87-93%). Notably, the formation of quaternary spiro compounds (**5.12**) avoids tautomeric equilibria.



Scheme 5.3. Applications of 4-arylideneisoxazol-5-ones **5.11** as Michael acceptors, *example A*

Yu, Zhou *et al.*[95] described a cascade quinine catalyzed oxa-Michael/1,6-addition reaction of *o*-hydroxyphenyl-substituted p-QMs and 4-arylideneisoxazol-5-ones in very good yields (82%) but quite low ee (**Scheme 5.4**).



Scheme 5.4. Applications of 4-arylideneisoxazol-5-ones **5.11** as Michael acceptors, *example B*

5.2. Objectives

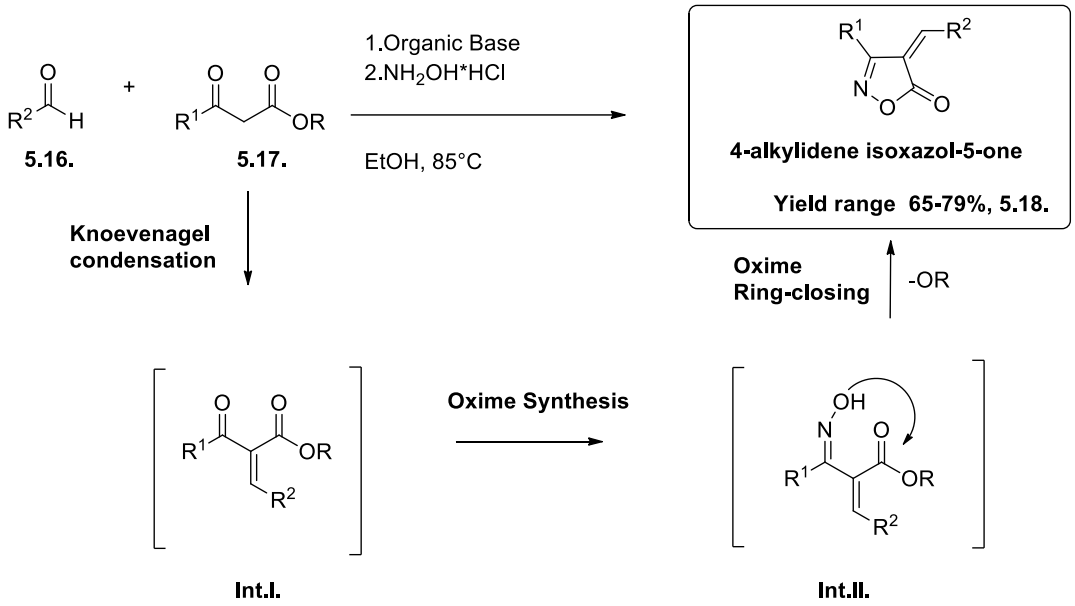
Considering the very few examples reported in literature, the aim of this part of the project is to investigate 1,4-conjugated additions of 4-arylideneisoxazol-5-ones in the presence of readily available nucleophiles and eventually to explore the reactivity of the obtained products. In particular, the possibility to develop new one-pot, cascade and multicomponent reactions will be considered. First dialkylmalonates and then chloromethyl aryl sulfones will be tested in Michael reactions with 4-arylideneisoxazol-5-ones. After that, asymmetric versions and the secondary reactivity of Micheal adducts using molybdenum hexacarbonyl will be investigated.

5.3. Results and discussion: Michael reaction on 4-arylideneisoxazol-5-ones

5.3.1. Preparation of 4-arylideneisoxazol-5-ones

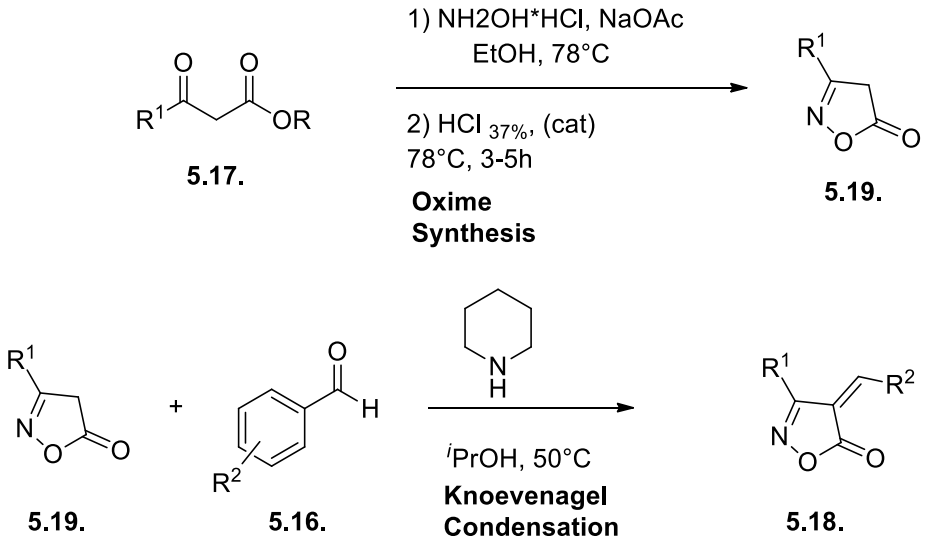
The preparation of starting materials 4-arylideneisoxazol-5-ones (**5.18.**) is also important since several methods are reported in literature but none of them shows a wide scope. Two possible synthetic routes were envisaged. The first is a one-pot three steps cascade reaction (**Scheme 5.5.**).[96] The first step consists in a Knoevenagel condensation between the alkyl/aryl-acetoacetate and the aldehyde catalyzed by an organic base (it changes for different substrates as reported in experimental

part) to afford alkene intermediate **(Int.I.)** then took place the oxime formation reaction using hydroxylamine hydrochloride, activated by sodium acetate. The last step is a cyclization through ring closure, elimination of the OR group and formation of 4-arylideneisoxazol-5-ones (**5.18.**) with yield range between 65 and 79%.



Scheme 5.5. One-pot cascade reaction for the synthesis of 4-arylideneisoxazol-5-ones **5.18**

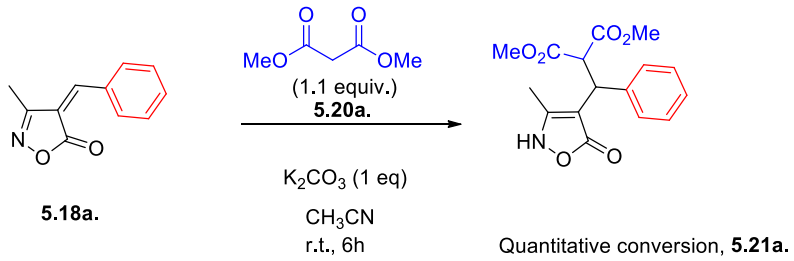
The second pathway is a two-step synthesis (**Scheme 5.6.**). First one is the cyclization through oxime intermediate to get isoxazol-5(4H)-one (**5.19.**), last step is the Knoevenagel condensation with aldehydes to get the 4-arylidineisoxazol-5-ones (**5.18.**).[97]



Scheme 5.6. Two-step reaction for the synthesis of 4-arylideneisoxazol-5-ones **5.18**

5.3.2. 1,4-conjugate additions on 4-arylideneisoxazol-5-ones

Preliminary experiments were carried out employing 4-benzylideneisoxazol-5-one as Michael acceptor (**5.18a.**) with dimethylmalonate (**5.20a**) as model nucleophile, under basic conditions, using readily available K_2CO_3 in acetonitrile as showed in **Table 5.1.** and **Scheme 5.7.** Dimethyl malonate as nucleophile produces poor conversion (evaluated to be about 25%) at room temperature in 2h (**entry 1 and 2**), while increasing reaction time to 6h, quantitative conversion in ^{1}H-NMR spectrum of the crude product was observed (**entry 2.**).



Scheme 5.7.

Entry	Base (equiv.)	Nucleophile (Equiv.)	T (°C)	t (h)	Solvent	Yield[a]
1	K_2CO_3(1)	Dimethyl malonate (1.5)	r.t.	2	CH_3CN	22%
2	K_2CO_3(1)	Dimethyl malonate (1.5)	r.t.	6	CH_3CN	99%

[a] Conversion in ^{1}H NMR spectrum of the crude product

Table 5.1. Screening of experimental conditions for Michael reaction to get compound **5.21a**

The ^{1}H NMR spectrum of the crude product (400 MHz, *Acetonitrile-d_3*) (**Figure 5.2.**) shows quantitative conversion in the Michael addition. It is possible to note the signals at **3.7** and **3.4 ppm** refers to the excess of dimethylmalonate. The ^{1}H NMR assignment of the Michael adduct in the enamine form is reported in **Figure 5.2**.

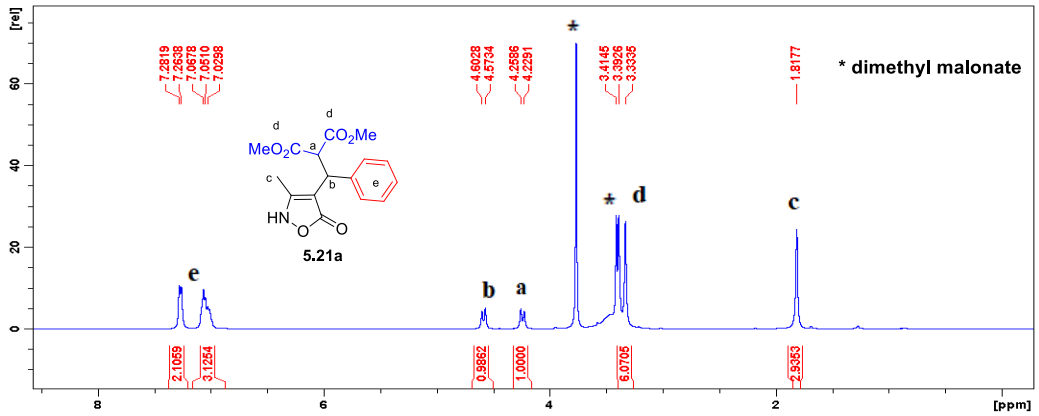


Figure 5.2. ^{1}H NMR spectrum of the crude compound **5.21a**

Nonetheless, after purification through silica gel, tautomeric equilibrium was observed, the two main tautomeric form possible under this reaction conditions, as explained before (**Scheme 5.1.**), should be the enamine-like **T2**, **5.21a** and enol-like form **T3**, **5.21b** (**Figure 5.3.** ^{1}H NMR spectrum of the pure compound, 400 MHz, *Acetonitrile-d*$_3$) as it can be noted for the presence of additional signals in the regions 4 - 5 and 2 -3 ppm.

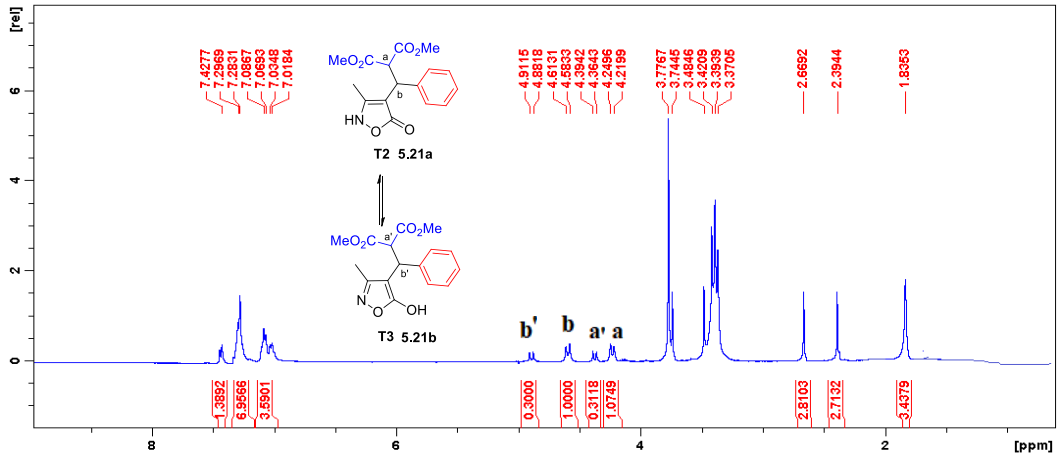


Figure 5.3. ^{1}H NMR spectrum of the pure compound **5.21a,** presence of tautomeric equilibrium with enol-like tautomer **T3**, compound **5.21b**

At this point, to improve the stability of the product and to force the reaction to give only one tautomer, we tried to entrap the major tautomer, supposed to be the enamine-like form **(T2)** with an electrophile, added at the end of the Michael reaction. Assuming that, at the end of the Michael reaction, many tautomers, as resonance hybrid of the anionic form, could be formed (**Scheme 5.8.**). The goal is to entrap the enamine-like (**T2**) using different electrophiles including iodomethane,

a

acetic anhydride and di *tert*-butyl dicarbonate, using K_2CO_3 as the base at room temperatures. Nicely, excellent yield has been obtained of one novel N-protected substituted isoxazole-5-one, which is stable in the chromatography. The ^{1}H-NMR spectrum of pure product (**Figure 5.4.**) corroborates the hypothesis of the formal entrapment of enamine-like tautomer (**T2**) (**5.22a.**).

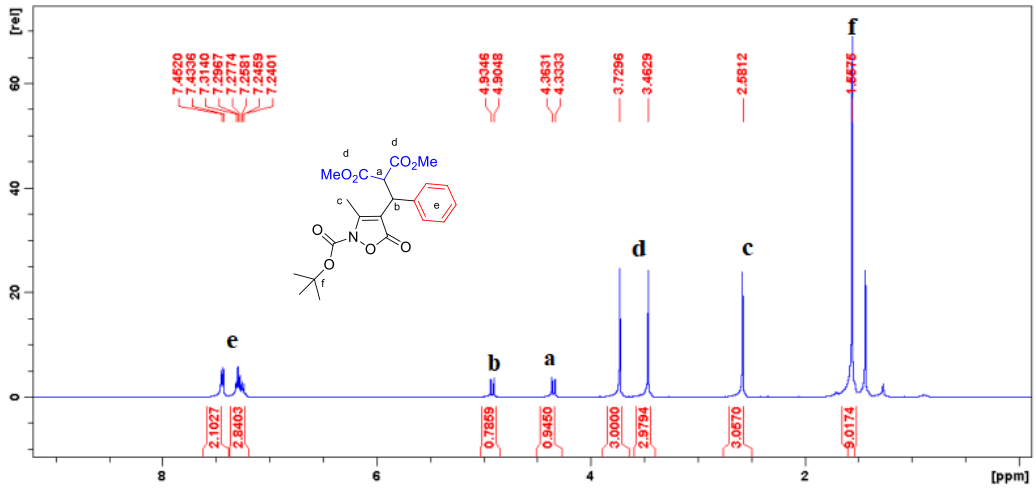
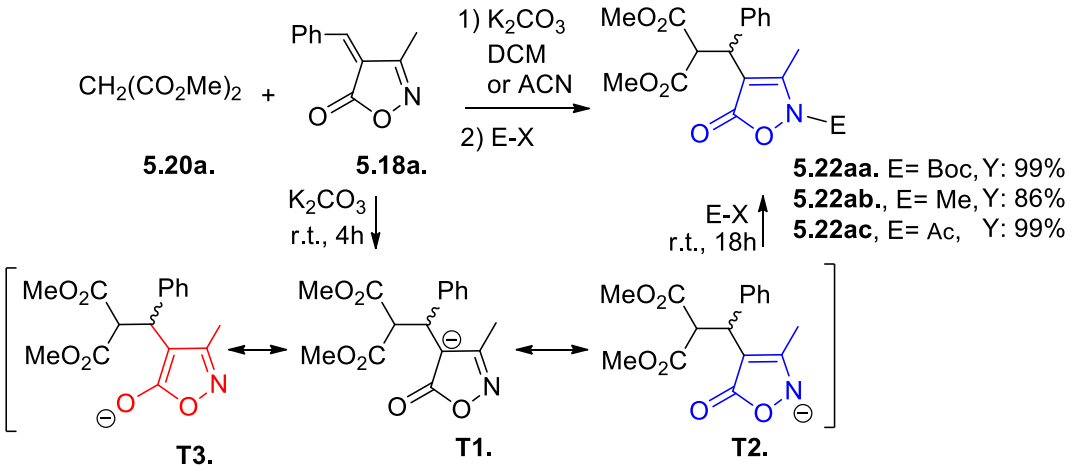


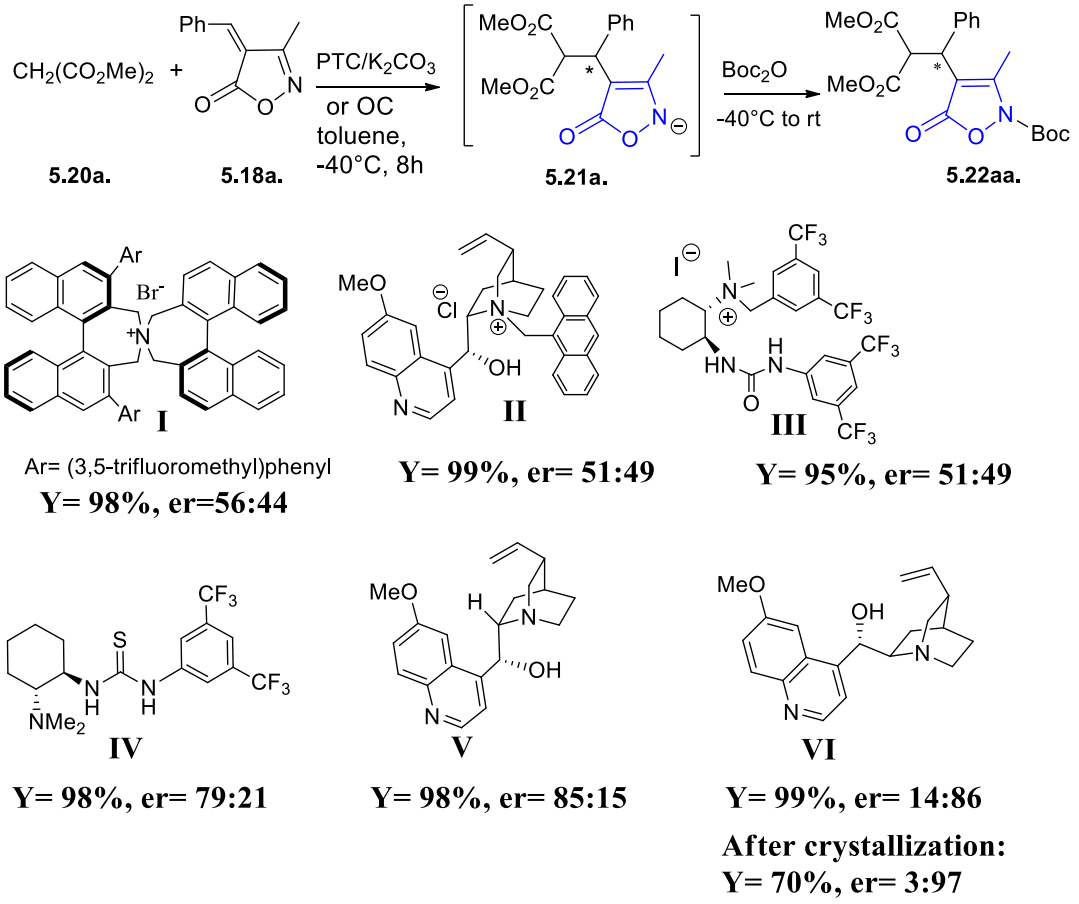
Figure 5.4. ^{1}H NMR spectrum of the pure compound **5.22aa**



Scheme 5.8. Formal entrapment of major tautomer, **T2**

5.3.3. Asymmetric organocatalyzed 1,4 conjugate additions on 4-arylideneisoxazol-5-ones

After this preliminary investigation, we envisaged to develop an asymmetric version of the reaction under organocatalytic conditions (**Scheme 5.9.**). A wide screening of chiral catalysts and reaction conditions was carried out. The best results were obtained performing the Michael reaction at low temperatures in the presence of quinidine (**VI**) and then a solution of electrophiles was added warming the system at room temperature.



Scheme 5.9. Cascade reaction for the synthesis of compound **5.22aa**

PTC conditions (**I-III**) gave excellent yields but only racemic mixture, instead cinchona alkaloids bifunctional catalysts (**IV-VII**) gave excellent yields and very good enantiomeric excess (**Table 5.2**). The OH in C^9 of the quinidine (**VI**) seems to play a key role in this catalytic system. The inversion in configuration of C^9 from (R) of the quinine (**V**) to (S) of epiquinine (**XIV**) led to a significant decrease in enantiomeric excess (almost racemic). There is a significant decrease in enantiomeric excess even by varying the substituents on the quinolinic moiety with H atom (catalysts **VII** and **X**) or with a

hydroxyl group (catalyst **VIII**) or with O^{i}Pr group (catalyst **XII**). The use of squaramides and thioureas was unsuccessful in terms of enantiomeric excess (**XV** and **XVI**).

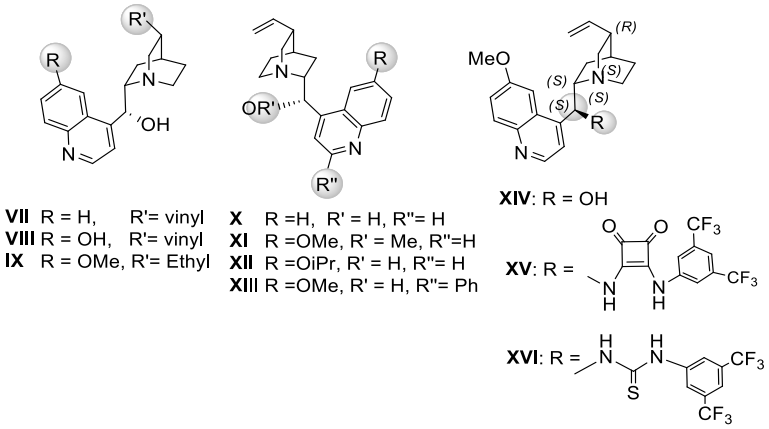


Figure 5.5. Bifunctional organocatalysts' screening

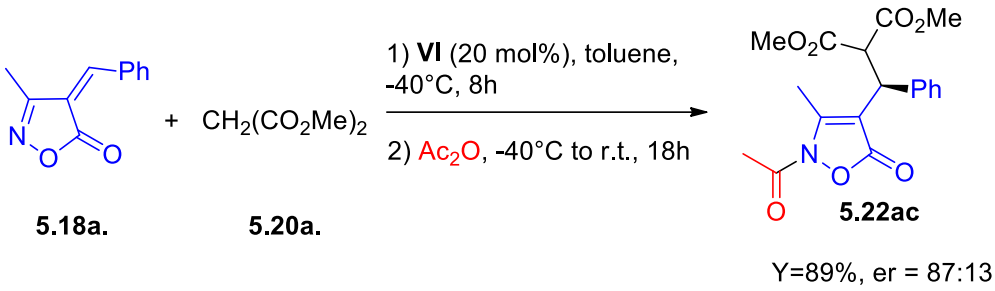
	5.22aa			**5.22aa**	
Cat	Y(%)	er	Cat	Y(%)	er
VII	98	52:48	**XII**	94	25:75
VIII	92	67:33	**XIII**[a]	40	20:80
IX	95	71:29	**XIV**	95	45:55
X	98	44:56	**XV**	99	50:50
XI	70	50:50	**XVI**	99	40:60

[a]Performed at rt for 24h

Table 5.2. Yield and enantiomeric ratios of **5.22aa** using organocatalysts depicted in **Figure 5.5**

In conclusion, the OH group of the quinidine (**VI**) and its configuration in C^{9} certainly plays a fundamental role in the activation of 4-arylideneisoxazol-5-ones (**5.18.**) via H-bonding interaction. Furthermore, any other different substituent on both quinuclidine and quinolinic rings leads to a decrease in the enantiomeric excess.

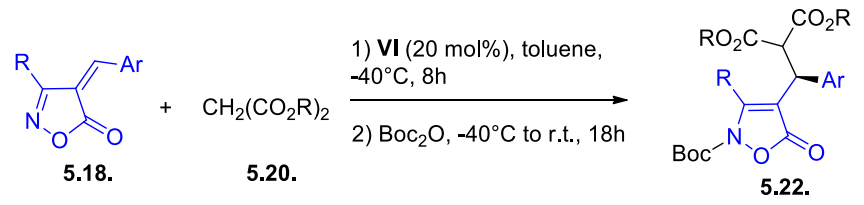
Moreover, it has been shown that the reaction in the asymmetric version can also be performed using different trapping agents, obtaining good yields and moderate enantiomeric excesses. In particular, employing acetic anhydride as the trapping agent, a yield of 89% and er 87:13 was obtained (**Scheme 5.10.**).[98]

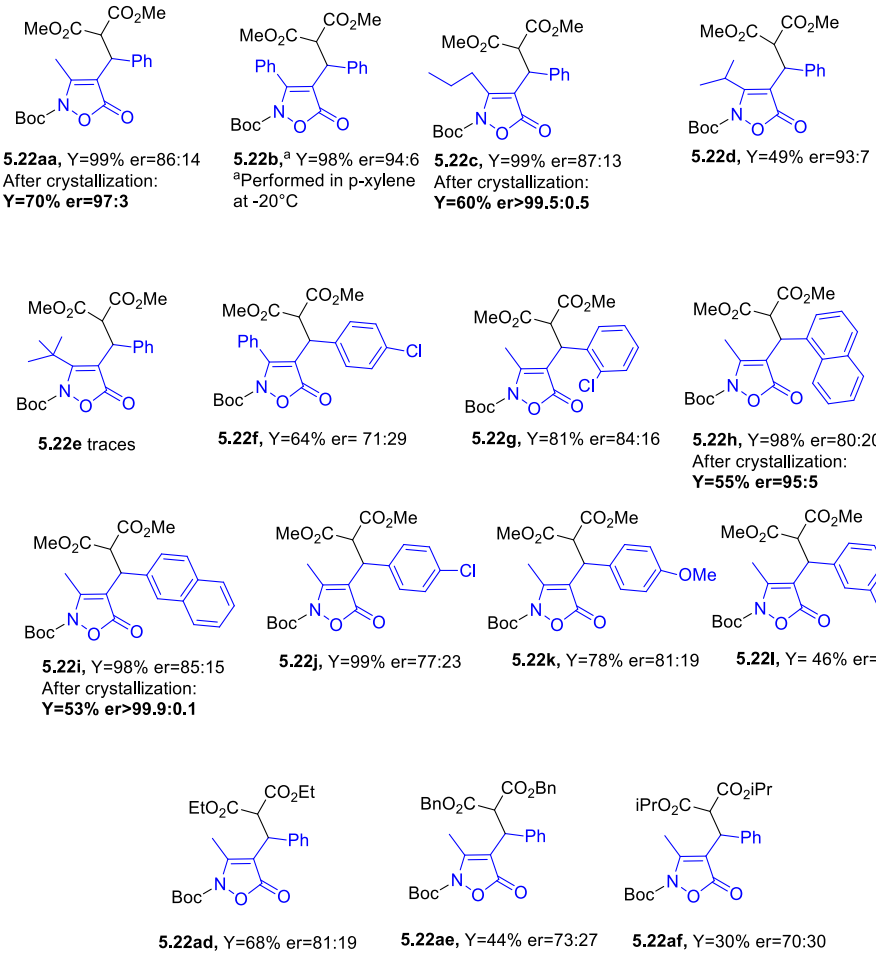


Scheme 5.10. Acetic anhydride as entrapping agent for the synthesis of compound **5.22ac**

The best reaction conditions were achieved using 20 mol% quinidine in toluene at –40°C for the Michael addition reaction and subsequent entrapping with di-*tert*-butyl-dicarbonate followed by warming up at room temperature (**Scheme 5.11.**).

Then the scope of the reaction was analyzed in the presence of di-alkyl malonates with variously substituted 4-arylideneisoxazol-5-ones. In this way a wide range of novel enantioenriched N-protected isoxazole-5-ones were obtained in excellent yields and from moderate to good enantioselectivity. In particular, it was observed that compared to **5.22aa,** the steric hindrance and substituents of the Ar group doesn't produce an improvement in enantioselective terms. Whereas it was observed a significant increase of the enantioselectivity at the increase of the steric hindrance of the R group in 3 position, reaching the very good 93:7 er with R=*i*-propyl and 94:6 with R=phenyl. Furthermore, a decrease of the reactivity has been observed for 4-benzylidene-3-(tertbutyl) isoxazol-5-one in the quinidine (**VI**) catalyzed pathway, while the respective racemic adduct **5.22e** was smoothly obtained under non-asymmetric conditions of **Scheme 5.8.** Also, the increase of the bulkiness of the di-alkyl malonates led to a progressive decrease of yields and er The reaction was also scaled up reacting 120 mg of **5.18a** in the presence of only 2 mol% of quinidine (**VI)**, giving similar yield and only slight decrease of er (95% and 83:17 er). After crystallization, a considerable enantiomeric enrichment in good yields was observed in some cases (**5.22aa**, **5.22c, 5.22h, 5.22i.**). The enantiomeric excesses were determined by HPLC performed in chiral column comparing the chromatograms with racemic samples. The racemate of the products were obtained according to the procedure described in **Scheme 5.8**.





Scheme 5.11. Scope of Cascade Reactions of 4-arylideneisoxazol-5-ones **5.18** and di-alkyl malonate **4.6**

With the enantio-enriched crystals of the compound **5.22aa** it was possible to obtain the absolute configuration by means of X-ray analysis (**Figure 5.6**), which confirms our hypothesis of the formal entrapment of the enaminic tautomer.

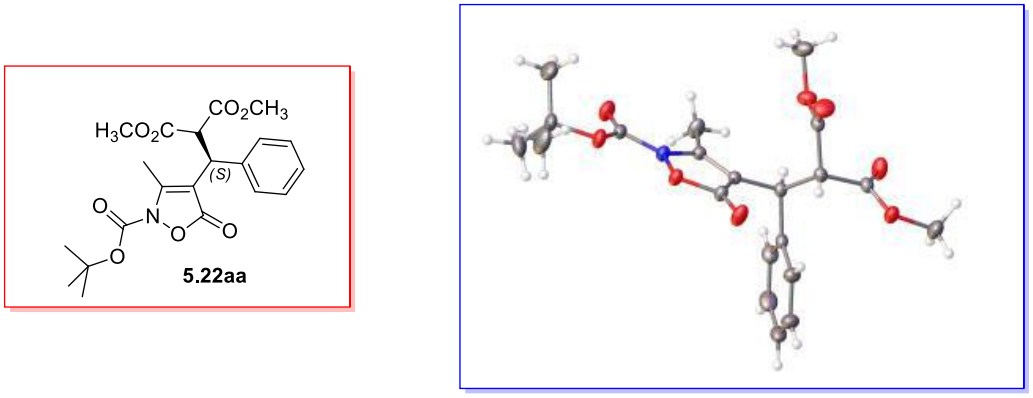
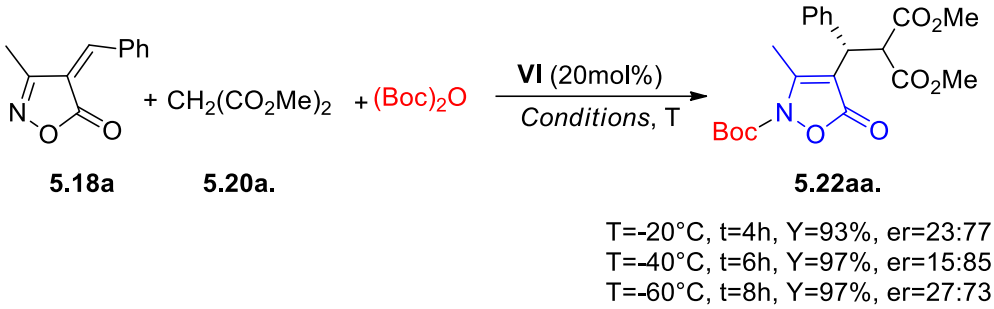


Figure 5.6. ORTEP diagram for compound **5.22aa**

A non-sequential one-pot three component reaction was carried out in order to compare these results obtained with those obtained with the sequential methodology **Scheme 5.11**.

Truly three-component one-pot reaction (**Scheme 5.12.**) means that since t = 0 there are both starting materials (**5.18a.** and **5.20a**) and the trapping agent, **Boc_2O**, in the reaction flask. Therefore, it differs from the three-component sequential, as in the latter the trapping agent was added only later. Various organocatalytic attempts have been carried out with different reaction conditions obtaining excellent yields and good enantiomeric excesses in the case in which Boc_2O is used as trapping agent (**Scheme 5.12**).

In the case of acetic anhydride, the yield lowers noticeably. We found the reason in the acetylation of OH in **C^9** of the catalyst leading a decrease of the overall yield of the reaction.

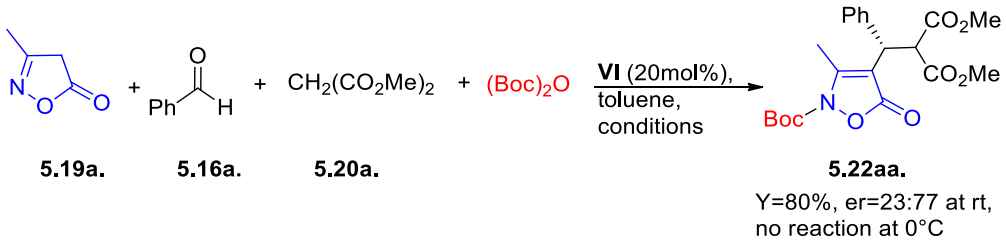


Scheme 5.12. Three-component one-pot reaction for the synthesis of **5.22aa**

5.3.4. Four-component Knoevenagel/Michael/protection reaction of isoxazole-5one

We decided to study a one-pot multicomponent cascade version, to further enhance the pot, atom and step-economy of the whole process. With this methodology the synthesis of the starting material 4-arylideneisoxazol-5-ones was avoided, because all the four reagents are in the reaction flask since t = 0, unlike the sequential multicomponent, in which the electrophilic agent was added subsequently to Michael addition.

This one-pot multicomponent cascade reaction consists in a three-steps synthesis (**Scheme 5.13**). The first step is the synthesis of 4-arylideneisoxazol-5-ones by Knoevenagel condensation (**5.19a** and **5.16a.**), the second step is the Michael addition of the condensation product with **5.20a**. to afford the enamine-like tautomer and finally entrapping with **Boc_2O**. It has been seen that the best reaction conditions in which this system works very well is at significantly higher temperatures, room temperatures, obtaining very good yield and moderate enantiomeric excess.



Scheme 5.13. Four-component one-pot reaction for the synthesis of **5.22aa**

5.4. Chloromethyl aryl sulfones as nucleophiles in Michael reaction on 4-arylideneisoxazol-5-ones

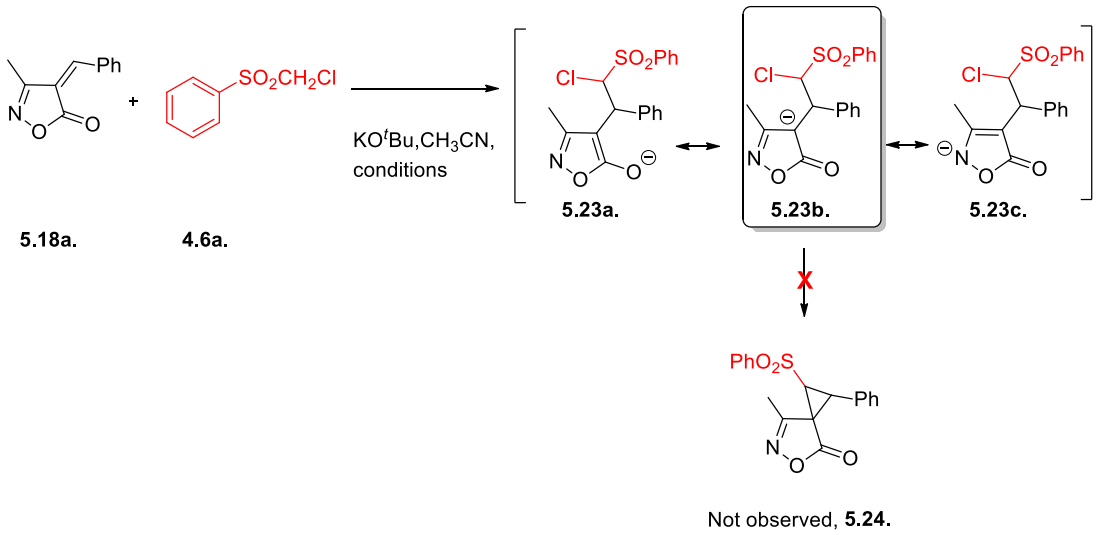
5.4.1. Objectives

The next objective of the thesis was the investigation the reactivity of chloromethyl aryl sulfones, already employed in the synthesis of 3,3-disubstituted isoindolinones and 3-methyleneisoindolinones (**Chapter 3**). as carbon nucleophiles in conjugated addition to 4-arylideneisoxazol-5-ones.

As reported in literature, the use of nucleophiles bearing a leaving group in the alpha position as chloromethyl aryl sulfones, in conjugated Michael additions, usually leads to the formation of cyclopropanes compounds.[99] Thus, the idea was to use this type of nucleophiles in conjugated addition to 4-arylideneisoxazol-5-ones to explore the possibility to obtain isoxazol-5-ones bearing cyclopropane moiety in the side chain, through a possible intramolecular displacement of the chloride in the Michael adducts (see **Scheme 5.14** of the next section).

5.4.2. Results and discussion: Michael reaction of chloromethyl aryl sulfones with 4-arylideneisoxazol-5-ones

The Michael addition of chloromethyl aryl sulfones on 4-arylideneisoxazol-5-ones under different conditions have been tested (**Table 5.3.**). In the presence of both weak organic (Et_3N) and inorganic bases (K_2CO_3) (**Entries 1 and 2**), only signals of starting materials are recorded in ^1H NMR spectrum of the crude product. On the contrary, using stoichiometric amount of a much stronger base as KO^{t}Bu (**Entry 3 and 4**), the starting materials disappeared, and the Michael adduct was observed in the ^1H NMR spectra of the crude products. However, the formation of the cyclopropane product was not observed (**Scheme 5.14**).

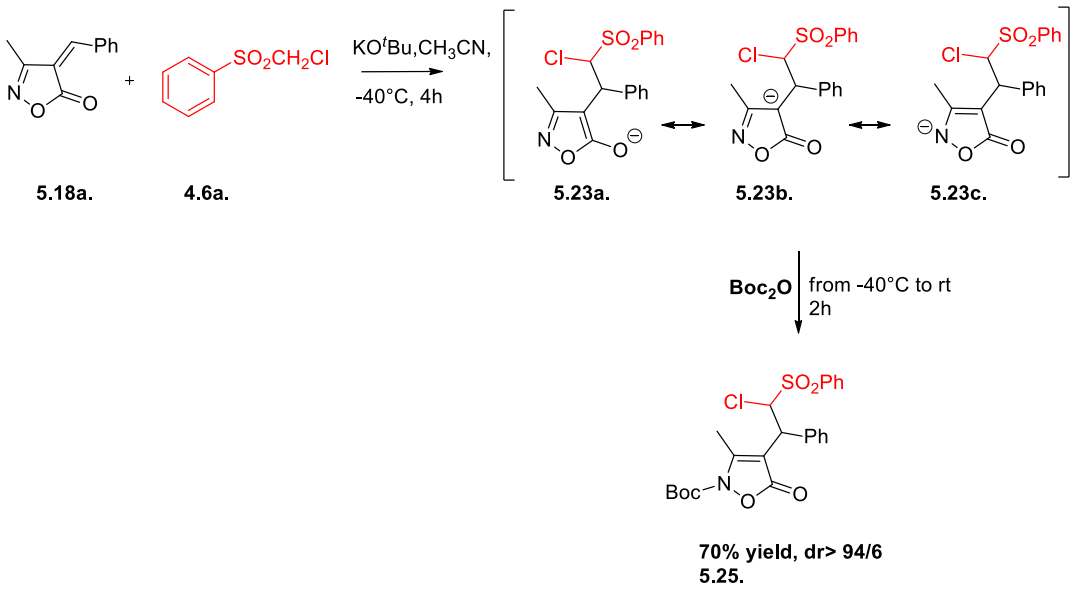


Scheme 5.14. Michael reaction of ((chloromethyl)sulfonyl)benzene **4.6a** with 3-methyl-4-benzylideneisoxazol-5-ones **5.18a**

Entry	Base (1 eq)	T (h)	Solvent	T (°C)	Yield
1	TEA	24	$CHCl_3$	r.t.	Starting materials
2	K_2CO_3	24	CH_3CN	50	Starting materials
3	KO^{t}Bu	2.5	CH_3CN	r.t.	Decomposition products
4	KO^{t}Bu	2.5	CH_3CN	-40	Decomposition products

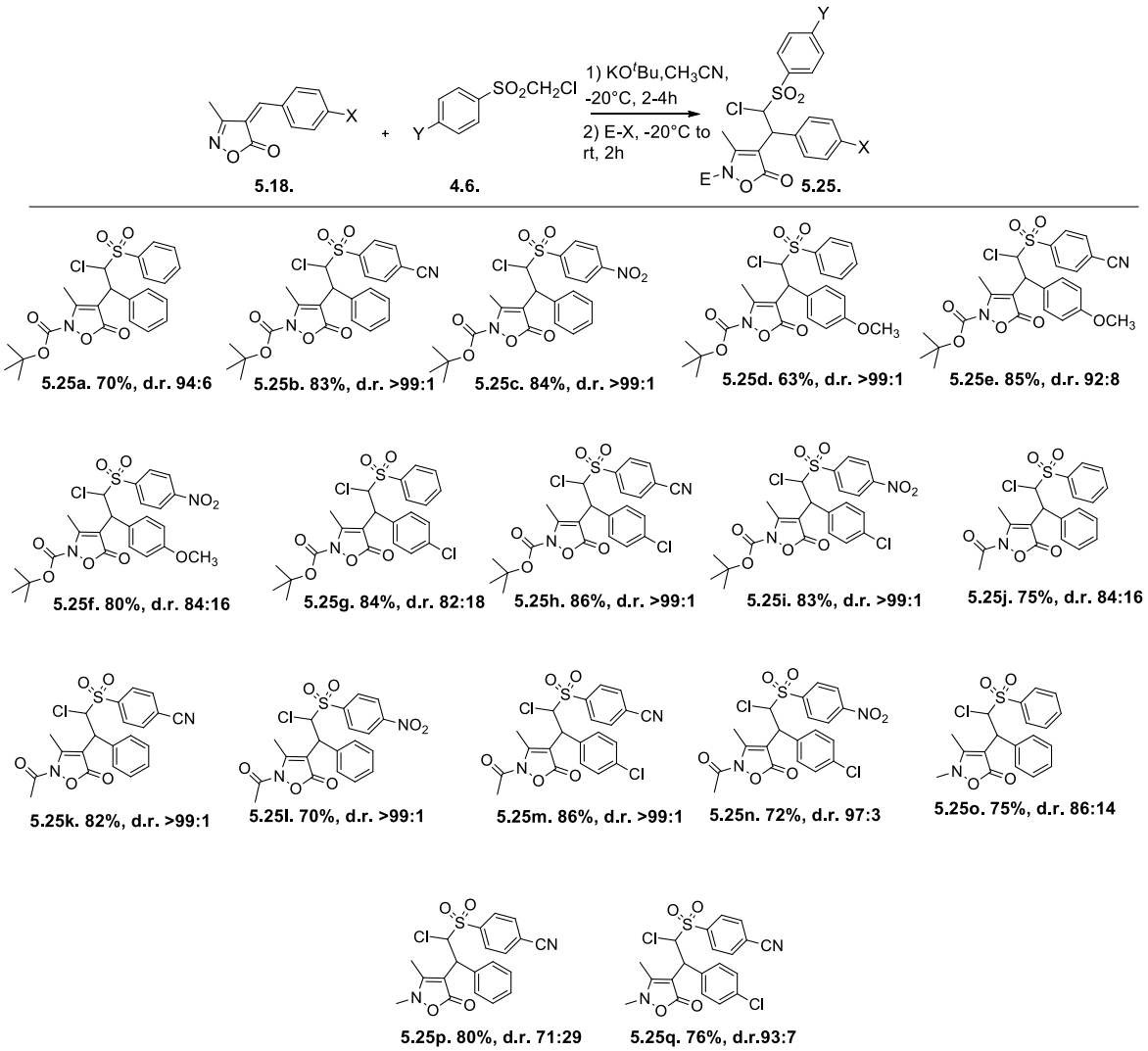
Table 5.3. Failed attempts to get compound **5.24**

At this point, it was observed that the Michael adduct is highly unstable under chromatographic purification, so we envisaged to use electrophilic agents to entrap the unstable Michael adduct (**Scheme 5.15**). As discussed in the previous **section 5.3**,[98] when an electrophile as 4-arylideneisoxazol-5-one (**5.18**) was used, at the end of the conjugated addition, a formal entrapment of enamine-like tautomer tautomer occurred. Therefore, we thought to add also in this reaction an electrophilic agent as di-*tert*-butyl-dicarbonate at the end of the Michael reaction. This led to a new stable N-Boc-protected isoxazole-5-one **5.25** with an uncommon chloromethyl phenylsulphonyl side chain in good yield and very high diastereomeric ratio (**Scheme 5.15**).



Scheme 5.15. Cascade reaction in the synthesis of compound **5.25**

Then, the scope of the reaction was analyzed in the presence of several substituted 4-arylideneisoxazol-5-ones (**5.18.**) and chloromethyl aryl sulfones and two other electrophilic trapping agents as acetic anhydride and iodomethane, apart from *di-tert*-butyl-dicarbonate. The one-pot cascade Michael addition and following enaminic-tautomer entrapment works very well both with 4-arylideneisoxazol-5-ones (**5.18.**) and chloromethyl aryl sulfones variously substituted on the aromatic ring, leading to a wide range of new N-protected isoxazole-5-ones in high yields and from moderate to very high diastereomeric ratios (**Scheme 5.16).** The formation of cyclopropyl ring was never observed. This outcome is very important since the strategy of the entrapping of Michael adducts of 4-arylideneisoxazol-5-ones is of general applicability to different type of nucleophiles.



Scheme 5.16. Scope of Cascade Reactions of 4-arylideneisoxazol-5-ones **5.18** and ((chloromethyl)sulfonyl)benzenes **4.6**

From **Scheme 5.16** it is possible to highlight that the reaction generally proceeds in high yields (63-86%), regardless of the EWG or EDG groups present on both aromatic rings and the trapping electrophilic agents employed. However, the reaction is highly diastereoselective in most of the reported products. The low diastereoselectivity of few products (**5.25f-g-j-o** and **p**) is mainly due to epimerization due to high acid proton of methylene group in ((Chloromethyl)sulfonyl)benzenes moiety.

Moreover, several attempts for asymmetric Michael reactions have also been performed. The reaction didn't work neither phase transfer catalytic systems nor bifunctional catalysis with cinchona alkaloids.

This is probably related to the weak basicity of the quinuclidine nitrogen (**pK_{aH} = 8-11**) of the organocatyst employed. As mentioned in the beginning of the chapter, weak bases as potassium carbonate (**pK_{aH} = 10**) are not enough basic to deprotonate the *CH_2* of the chloromethyl aryl sulfones (**4.6.**) but only stronger base as potassium *tert*-butoxide (**pK_{aH} = 17**) can do that, thus, this explains why no reaction is observed in organocatalyzed asymmetric reactions.

5.5. Secondary reactivity employing molybdenum hexacarbonyl

5.5.1. Objectives

This part of the project has been inspired by previous work reported by Massa *et al.* [100] regarding furans ring-opening in $Mo(CO)_6$-catalyzed reactions and by recent isoxazole N-O cleavage $Mo(CO)_6$-catalyzed reactions to get α-aminopyrrole [101] and nicotinates derivatives.[102] Therefore, we decided to investigate the use of $Mo(CO)_6$ on the Michael adducts to investigate the possibility to get new class of compounds, not easily obtainable with conventional methods.

5.5.2. Results and discussion: One-pot cascade reaction $Mo(CO)_6$-promoted

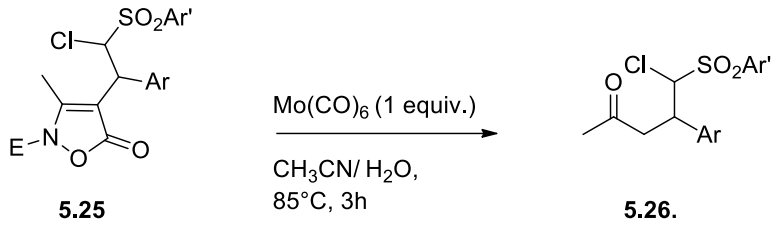
Various reactions are reported that involve the use of Molybdenum hexacarbonyl in the breaking of N-O bonds. However, this reactivity has only been studied on isoxazole [103,104,105] and N-Methylisoxazolidines scaffolds.[106]

The electronic structure of isoxazol-5-one is significantly different from those previously studied,[103-106] due to the presence of carbonyl group, making the system more electrophilic. Therefore, the interest was to investigate these reactions involving the cleavage of the N-O bond in the presence of $Mo(CO)_6$ and water.

After the reductive cleavage, because of the presence of the chloride leaving group in the side chain, intramolecular cyclizations could occur with carboxylate of enamine which could lead to different heterocyclic products.

However, after a screening of conditions and substrates we realized that, in the presence of $Mo(CO)_6$ and water in acetonitrile at 85°C, we observed the formation of a new class of branched ketones in high yield, bearing in the γ-position the chlorine group and the sulfone moieties when the N-Boc Michael adduct **5.25a** was used (**Table 5.4**), while in the presence of **5.25o** and **5.25j** we observed decomposition products and the recovery of the starting materials respectively. Nicely, this

uncommon class of ketones was obtained with retention of diastereoselectivity of the starting isoxazole-5-one **5.25a, scheme 5.17.**



5.25 **5.26.**

Scheme 5.17.

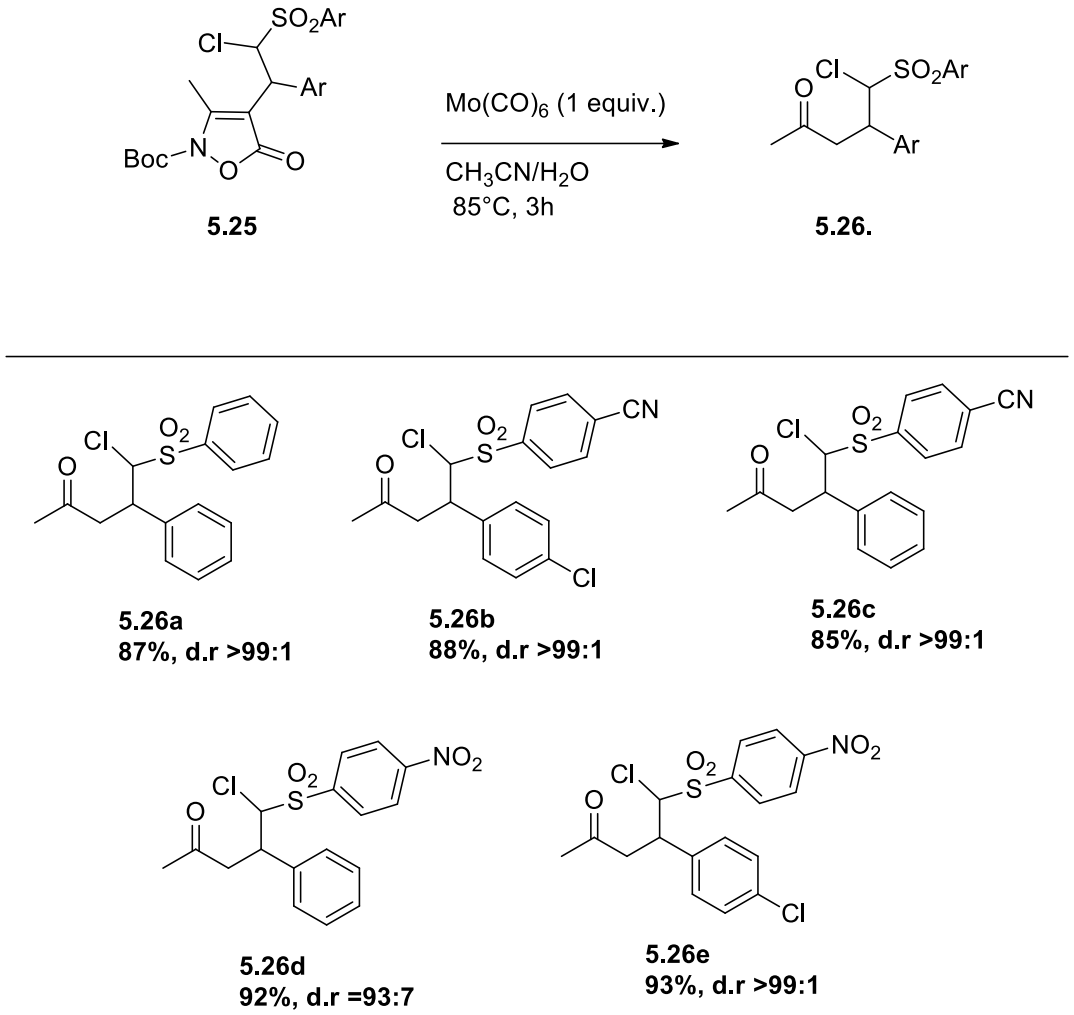
Entry	5.25	E	Yield[a]
1	5.25o	Me	Decomp.
2	5.25j	Ac	No react.
3	5.25a	Boc	87%

[a] Isolate Yield

Table 5.4. Influence of Boc-PG in $Mo(CO)_6$-promoted cascade process

Then, under the optimized conditions the scope was briefly analyzed employing different Boc-protected Michael adducts (**Scheme 5.18.**).

Scheme 5.18 reports synthesis of ketones in high yields and excellent diastereomeric ratio with both EWG and EDG on both aromatic rings, observing a retention of dr compared to starting material **5.25**.



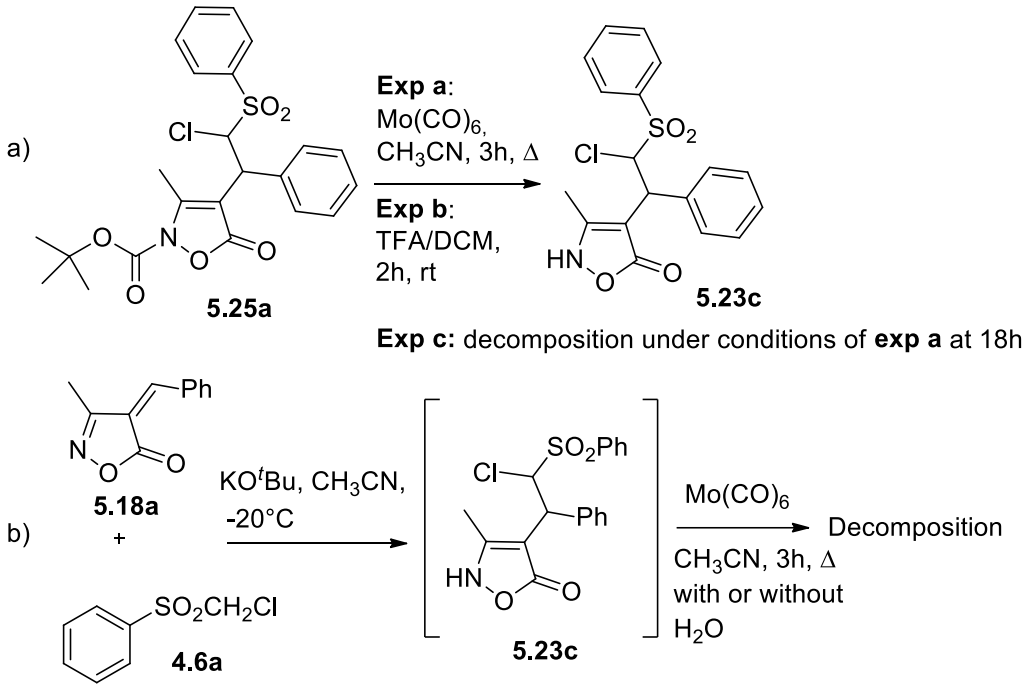
Scheme 5.18. Cascade reaction $Mo(CO)_6$-promoted

The mechanism, still under study, presumably involves elimination of Boc-deprotection, N-O bond cleavage, decarboxylation and finally the formation of the imine which is hydrolyzed by the water. Based on reactions reported in the cleavage of the isoxazole ring [107] the water has a double function, it breaks the Mo-N bond (in the coordination complex) and subsequently hydrolyzes the imine formed, affording **5.26.**

As mentioned before, the reaction works only in the presence of water. Several control experiments without water have shown only the formation of the deprotected Michael adducts in tautomeric mixture and degradation products (**Scheme 5.19a. Exp a.)**. Under the same conditions, extending the reaction time, decomposition products were observed in the ^{1}H NMR spectrum of the crude product (**Scheme 5.19a. Exp c.**)

Another crucial control experiment, however, was performed under acidic conditions of TFA in DCM **(Scheme 5.19a. Exp b.)**. In this way, the reaction produced a mixture of **5.23c.** and both starting materials **4.6a** and **5.25a**, after an aqueous work-up, as results of retro Michael-reaction, indicating

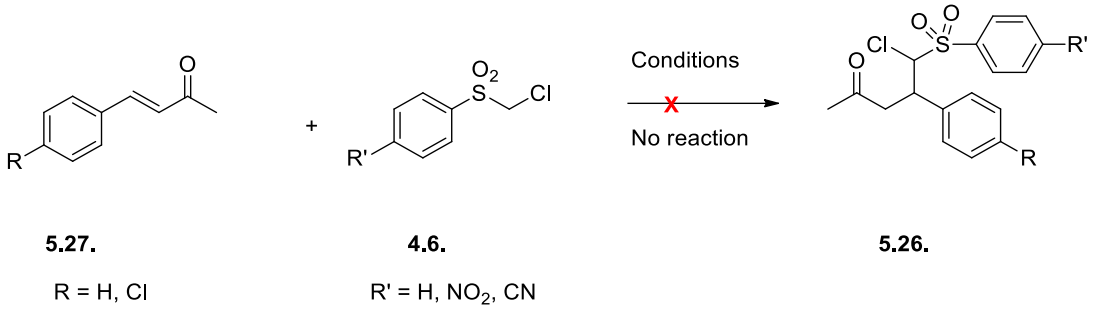
that acidic conditions are not sufficient to trigger the cleavage of the O-N bond. This experiment also supports our hypothesis that Boc deprotection is fundamental but insufficient because only the coordination nitrogen-$Mo(CO)_6$ pushes the reaction towards the ring opening and cascade reactions. Another very interesting aspect of this reaction is that the system leads to ketones only when the Michael product carries the Boc-protection. N-O cleavage reaction when conducted using N-acetylated (**5.25j.**) or N-methylated (**5.25o.**) products does not occur, giving only starting materials in the ^{1}H-NMR spectrum of the crude product (**Table 5.4**).



Scheme 5.19. a) Exp a) Importance of water in the cascade process; Exp b) Importance of $Mo(CO)_6$ in the cascade process. b) Failed one-pot cascade reactions for the synthesis of compound **5.26**

A one-pot version of this reaction was also tested starting from Michael reaction and subsequently adding $Mo(CO)_6$ with or without water (**Scheme 5.19b.**) However, the ketone was not observed, but only degradation products in ^{1}H NMR spectrum of the crude product.

This type of ketones synthesized have never been reported in the literature. However, a more direct synthetic route (**Scheme 5.20.**) of these could be a Michael reaction between chloromethyl aryl sulfones (**4.6.**) and variously substituted enones (**5.27.**) Various attempts have been made (**Table 5.5**) but none of these led the branched ketone series, observing in the ^{1}H NMR spectra of the crude products only decomposition products. Effectively making the $Mo(CO)_6$ catalyzed reaction the only possible way for the synthesis of these ketones.



5.27. **4.6.** **5.26.**

R = H, Cl R' = H, NO_2, CN

Scheme 5.20. Direct Michael reaction between enones **5.27** and ((chloromethyl)sulfonyl)benzenes **4.6** for the synthesis of branched ketones **5.26**

Entry	Base	Solvent	T (°C)	t (h)
1	K_2CO_3	Anhydrous CH_3CN	-20	3
2	KO^{t}Bu	Anhydrous CH_3CN	-20	3.5
3	KO^{t}Bu	Anhydrous CH_3CN	-40	3
4	KO^{t}Bu	Anhydrous THF	-78	1

Table 5.5. Failed attempts to get compound **5.26**

5.6. Overall conclusions

In this chapter it was seen how 4-arylideneisoxazol-5-ones (**5.18.**) can be excellent Michael acceptors in 1,4-conjugate addition with a great variety of nucleophiles. The reaction of these with malonates was first investigated, seeing how the tautomeric enamine-like form of Michael's adducts can be quantitatively trapped using a large variety of electrophilic trapping agents, leading to isolable and stable new derivatives.

An asymmetric organocatalyzed Michael reaction by cinchona alkaloids was also studied, obtaining quantitative yields and high enantiomeric excesses, subsequently increased by crystallization. Furthermore, it has been found that chloromethyl aryl sulfones (**4.6.**) are excellent carbon nucleophiles for Michael reactions on 4-arylideneisoxazol-5-ones, obtaining products in high yields and excellent diastereomeric ratio, it has also been observed that one-pot entrapment with electrophilic agents is the key step in this reaction, leading to N-protected Michael adducts, in the absence of these electrophiles, the just formed are unstable and cannot be isolated.

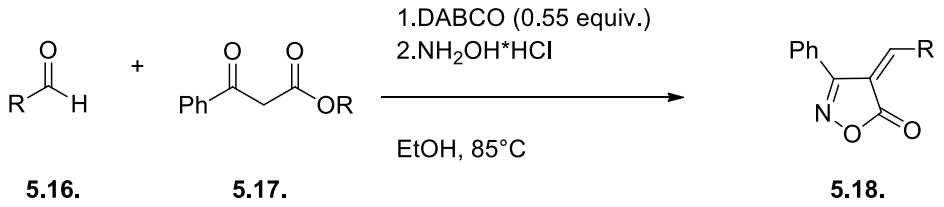
In the last part of this chapter, we dealt with the catalyzed N-O cleavage reaction of the N-protected Michael products with $Mo(CO)_6/H_2O$ system. A 4-step cascade one-pot reaction was observed that led to the synthesis of branched ketones never reported before in the literature in very good yields and excellent diastereomeric ratio.

5.7. Experimental part.

Preparation of starting materials.

Procedure with DABCO [108]

A mixture of 2 mmol ethyl benzoylacetate (**5.17.**), 2 mmol hydroxylamine hydrochloride and 1.1 mmol DABCO in 4 mL ethanol was refluxed for 3 min, after then 2 mmol aromatic aldehyde (**5.16.**) was added and the mixture was further refluxed for 1-15 min. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and the resulting crystal product (4) was collected by filtration and washed with water. The precipitate obtained is filtered, washed with water and recrystallized from an EtOH / H_2O mixture (95:5).



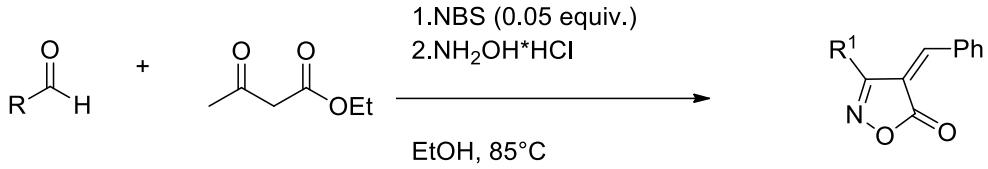
5.16. **5.17.** **5.18.**

R	Yield (%)
Ph	70
4-$MeOC_6H_4$	83
4-ClC_6H_4	37
4-MeC_6H_4	59

Scheme 5.S1. One-pot cascade reaction in the synthesis of 4-arylideneisoxazol-5-ones **5.18**, *DABCO-catalyzed*

Procedure with N-Bromosuccinimde[97]

A mixture of equimolar quantities of hydroxylamine hydrochloride (0.07 g, 1 mmol) and ethyl acetoacetate **5.17a**. (0.130 g, 1 mmol) in 5 mL water was stirred for 5 min. Aldehydes **5.16.** (0.112 g, 1 mmol) and NBS (5 mol%) were then added and the reaction mixture was stirred at room temperature for 95 min. The solid products were isolated by simple filtration, washed with water (5 mL), then recrystallized from ethanol.



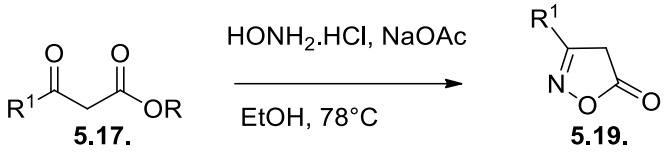
5.16. **5.17a.** **5.18.**

R^1	Yield (%)
CH_3	40
n-Propyl	30

Scheme 5.S2. One-pot cascade reaction in the synthesis of 4-arylideneisoxazol-5-ones **5.18**, *NBS-catalyzed*

Synthesis of 4-arylideneisoxazol-5-ones in two successive steps

FIRST STEP: Synthesis of isoxazol-5-ones from β-ketoesters



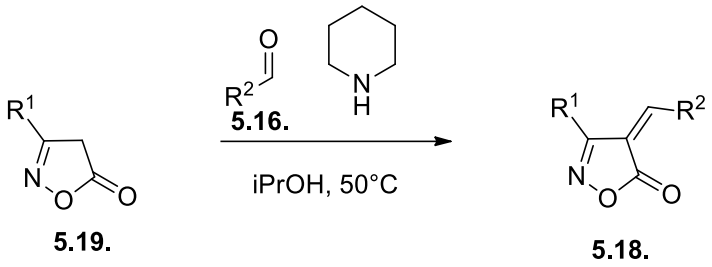
Scheme 5.S3. Synthesis of isoxazole-5(4H)-ones **5.19**

A round bottom flask is charged with $HONH_2.HCl$ (1.5 equiv.), EtOH (0.5M in respect to the β-ketoester), and NaOAc (1.5 equiv.). The mixture is allowed to stir at rt for 5 min. Then, the β -ketoester (1 equiv.) is added. The reaction is heated to reflux (bp-EtOH 78^{o}C) being followed by TLC (Reaction times observed of ca. 4-6h). Next, the solution is concentrated under reduced pressure, then diluted in H2O and AcOEt. The organic phase is separated, and the aqueous phase is extracted with AcOEt (2x). The combined organic phases are dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was then purified through silica-gel chromatography (Hexane: Ethyl acetate = 80:20).

Entry	R	Yield (%)
5.19a	Me	95
5.19b	*n*-propyl	76
5.19c	*i*-propyl	70
5.19d	*t*-butyl	92

Table 5.S1. List of synthetized compounds **5.19**

SECOND STEP: Knoevenagel condensation of aldehydes with isoxazol-5-ones



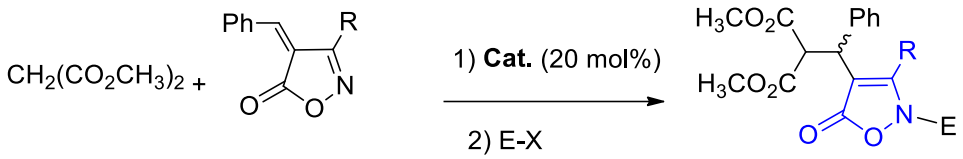
Scheme 5.S4. Knoevenagel condensation in the synthesis of 4-arylideneisoxazole-5-ones, **5.18**

A round bottom flask is charged with the isoxazol-5-one (1 equiv.), the aldehyde **5.16.** (1.2 equiv.) and *i*PrOH (0.5M in respect to the isoxazol-5-one). Then, piperidine (5 µL/ mmol isoxazol-5-one) is added. The solution is heated to 50 ºC and followed by TLC analysis. Upon complete consumption of the starting isoxazol-5-one (reaction times observed of *ca.* 3-5h), the solution is concentrated under reduced pressure. In some occasions, the condensed product precipitates and can be isolated by simple filtration. In other cases, one can purify by flash column chromatography.

Entry	R^1	R^2	Yield (%)
5.18a	Me	Ph	89
5.18b	Me	4-ClC_6H_4	50
5.18c	Me	2-ClC_6H_4	20
5.18d	Me	3-$NO_2C_6H_4$	41
5.18e	Me	4-$OMeC_6H_4$	70
5.18f	Me	1-Naphthyl	30
5.18g	Me	2-Naphthyl	63
5.18h	*n*-propyl	Ph	40
5.18i	*i*-propyl	Ph	66
5.18j	*t*-butyl	Ph	84

Table 5.S2. List of synthetized compounds **5.18**

General procedure for non-asymmetric one-pot Michael reaction sequential tautomer entrapping (5.22.).

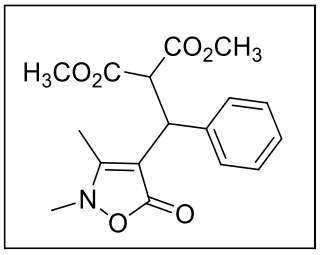


5.20a. **5.18.** **5.22.**

Scheme 5.S5. One-pot reaction in the synthesis of compound **5.22**

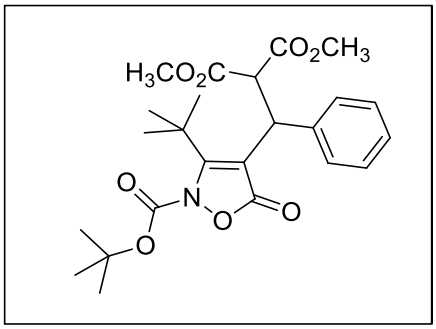
In a round bottom flask, K_2CO_3 (0.106 mmol, 1 eq) was added to a solution of dimethyl malonate (**5.20a.**) (0.140 mmol, 1.3 eq) in acetonitrile ([1] = 0.21M). The mixture was allowed to stir at r.t. for 5 min. Then, the starting material **5.18.** (0.106 mmol, 1 eq.) was added. Once no more starting material was detected on TLC (Reaction times observed of ca. 5h), the solution was quenched with the electrophile (0.127 mmol, 1.2 eq.) and at this point, the solution was allowed to stir overnight. The crude reaction mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 90/10 to 70/30) to afford products **5.22.** All the racemic compounds were synthesized according to the above procedure (Yields 60-98%). In the cases of the synthesis of compounds (**5.22ab**, **5.22f**), Et_3N (1 eq) in DCM was used.

Dimethyl-2-((2,3-dimethyl-5-oxo-2,5-dihydroisoxazol-4- yl)(phenyl)methyl)malonate (5.22ab)



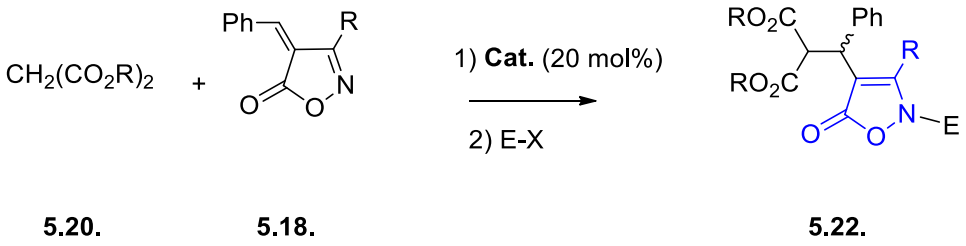
Brown solid (39 mg, 86%). Mp.74-76°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.36 Hz, 2H), 7.29 (t, *J* = 7.05 Hz, 2H), 7.23 (t, *J* = 7.13 Hz, 1H), 4.90 (d, *J* = 11.95 Hz, 1H), 4.27 (d, *J* = 11.95 Hz, 1H), 3.70 (s, 3H), 3.45 (s, 3H), 3.26 (s, 3H), 2.21 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.7, 168.6, 168.4, 161.6, 139.7, 128.6, 128.0, 127.4, 100.9, 53.3, 52.6, 52.4, 40.93, 37.4, 10.6. **ESI-HRMS**: Found: *m/z* 334.1270. Calcd for $C_{17}H_{20}NO_6$: $(M+H)^+$ 334.1285.

Dimethyl 2-((2-(tert-butoxycarbonyl)-3-(tert-butyl)-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)malonate (5.22e)



White solid (50 mg, 53%), M.p. 135 -136 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28-7.23 (m, 5H), 4.78 (d, *J* = 12.01 Hz,1H), 4.29 (d, *J* = 12.01 Hz, 1H), 3.65 (s, 3H), 3.51 (s, 3H),1.62 (s, 9H), 1.33 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ170.9, 167.8, 167.2, 162.2, 147.7, 138.9, 128.6, 128.3, 127.5,101.0, 86.6, 56.6, 52.5, 40.2, 33.9, 28.7, 27.4. **ESI-HRMS**: Found: *m/z* 462.2150. Calcd for $C_{23}H_{30}NO_8$: $(M+H)^+$ 462.2122.

General procedure for asymmetric one-pot Michael reaction sequential tautomer entrapping.

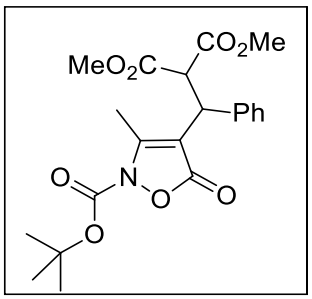


5.20. **5.18.** **5.22.**

Scheme 5.S6. Cascade reactions in the synthesis of compounds **5.22**

To a solution of dialkyl malonate **5.20.** (0.16 mmol, 1.5 eq) in toluene (xylene for R=Ph)) was added catalyst (0.0212 mmol, 0.2 eq). The mixture was allowed to stir at -40°C (-20°C for R=Ph) for 5 min. Then, 4-arylidenisoxazol-5-ones **5.18** (0.106 mmol, 1 eq.) was added and left to react at the above temperature. Once no more starting material was detected on TLC (Reaction times observed of *ca.* 8-10 h), the solution was quenched with di-*tert*-butyl dicarbonate (0.212 mmol, 2eq.) and the solution was allowed to warm-up to rt overnight. The crude reaction mixture was directly purified by flash chromatography (eluent: hexane/ethyl acetate 90/10 to 70/30) to afford the following products.

Dimethyl 2-((2-(tert-butoxycarbonyl)-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl) malonate (5.22aa)

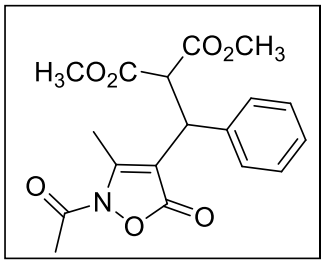


Yellow solid (42 mg, 99%). Mp. 140-142°C, $[\alpha]_D^{20}$ = +55.8 (c=0.51, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.93 Hz, 2H), 7.32-7.25 (m, 3H), 4.93 (d, *J* = 11.97 Hz, 1H), 4.35 (d, *J* = 11.97 Hz, 1H), 3.74 (s, 3H), 3.47 (s, 3H), 2.58 (s, 3H), 1.56 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.4, 168.1, 166.2, 155.3, 145.3, 138.9, 128.8, 127.9, 127.6, 104.9, 86.4, 53.0, 52.8, 52.5, 40.4, 27.9, 13.0. **ESI-HRMS**: Found:*m/z* 420.1642. Calcd for $C_{21}H_{26}NO_8$: (M+H)+ 420.1653.

Crystallization of 5.22aa (Y=70% er=97:3): 22 mg (0.052 mmol) of **3aa** (er=14:86) were dissolved at r.t. in 0.300 mL of Ethyl acetate and 0.600 mL of hexane. The solution was kept overnight at -15°C and the solution was carefully removed by a syringe.

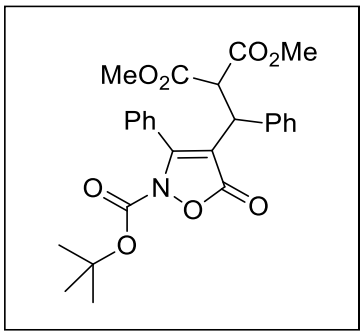
The solid was analyzed by **chiral HPLC**: ADH column,hexane-^{i}PrOH (8:2), flow 0.6 mL/min, t: 11.28 min and 12.82 min, er= 97:3.

Dimethyl-2-((2-acetyl-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)malonate (5.22ac)



Yellow oil (34mg,89%). $[\alpha]_D^{20}$ = +30.20 (c=1.1, $CHCl_3$)**.** **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.80 Hz, 2H), 7.31-7.25 (m, *3*H), 4.89 (d, *J* = 12.03 Hz, 1H), 4.38 (d, *J* = 12.03 Hz, 1H), 3.73 (s, 3H), 3.48 (s, 3H), 2.66 (s, 3H), 2,38 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.3, 168.3, 168.0, 165.7, 164.8, 154.6, 138.5, 128.9, 127.9, 106.3, 52.9, 52.8, 52.5, 40.0, 22.7, 13.3. **Chiral HPLC**: ADH column, hexane-^{i}PrOH (9:1), flow 1.0 mL/min, t: 17.04 min and 23.17 min, er= 87:13. **ESI-HRMS**: Found: *m/z* 362.1250 Calcd for $C_{18}H_{20}NO_7$: $(M+H)^+$ 362.1234.

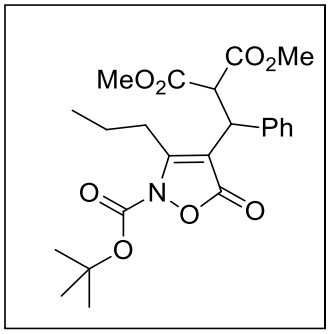
Dimethyl 2-((2-(tert-butoxycarbonyl)-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)malonate (5.22b)



Yellow oil (39 mg, 98%), $[\alpha]_D^{20}$ = +5.9 (c=1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.55-7.51 (m, 3H), 7.39 (d, *J* =5.93 Hz, 2H), 7.25 (m, 5H), 4.97 (d, *J* = 12.06 Hz, 1H), 4.14 (d, *J* = 12.06 Hz, 1H), 3.74 (s, 3H), 3.39 (s, 3H), 1.27 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 168.2, 166.7, 157.0, 145.3, 139.3, 130.7, 128.9, 128.7, 128.0, 127.7, 107.2, 86.3, 53.0, 52.9, 52.5, 40.5, 27.7. **Chiral HPLC**: IE-3 column, hexane-^{i}PrOH (9:1), flow 0.8 mL/min, t: 47.69 min and 50.56 min, er= 94:6**.** **ESI-HRMS**: Found: *m/z* 482.1805. Calcd for $C_{26}H_{28}NO_8$: $(M+H)^+$ 482.1809.

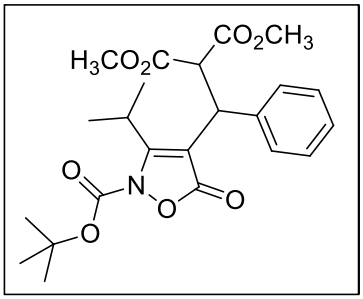
Dimethyl 2-((2-(tert-butoxycarbonyl)-5-oxo-3-propyl-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)malonate (5.22c)



Yellow oil (45 mg, 99%), $[\alpha]_D^{20}$ = +21.0 (c=0.52, CHCl3). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44(d, *J* = 6.96 Hz, 2H), 7.30- 7.23 (m, 3H), 4.95 (d, *J* = 11.87 Hz, 1H), 4.33 (d, *J* = 11.87 Hz, 1H), 3.72 (s, 3H), 3.45 (s, 3H), 2.91 (d, *J* = 6.81 Hz, 2H), 1.76-1.73 (m, 2H), 1.51-1.47 (m, 2H), 1.56 (s, 9H), 1.03 (t, *J* = 7.37 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.3, 168.2, 166.5, 159.2, 144.9, 139.4, 128.7, 128.0, 127.6, 104.5, 86.2, 53.2, 52.7, 52.4, 40.6, 28.3, 27.7, 21.3, 14.1. **ESI-HRMS**: Found: *m/z* 448.1996. Calcd for

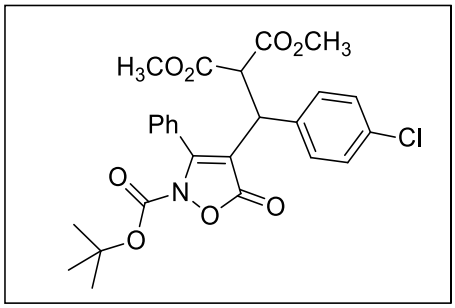
$C_{23}H_{30}NO_8$: $(M+H)^+$ 448.1966. **Crystallization of 5.22c (Y=60% er>99.5:0.5)**: 0.055 mmol (er=87:13) were dissolved at r.t. in 0.150 mL of Ethyl acetate and 0.300 mL of hexane. The solution was kept overnight at -15°C and the solution was carefully removed by a syringe. The solid was analyzed by **chiral HPLC**: ADH column, hexane-^{i}PrOH (95:5), flow 0.6 mL/min, t: 12.42 min and 13.90 min, er> 99.5:0.5

Dimethyl-2-((2-(tert-butoxycarbonyl)-3-isopropyl-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)malonate (5.22d)



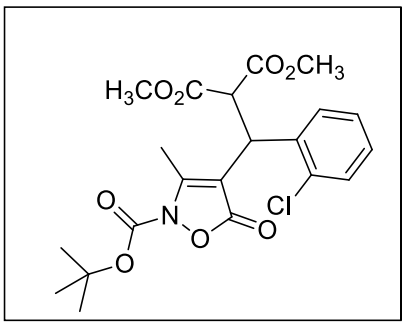
Yellow solid (29 mg, 49%), Mp.140°C, $[\alpha]_D^{20}$ = +17.0 (c=0.60, CHCl3). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46-7.44 (m, *J* = 7.31 Hz, 2H), 7.35-7.23 (m, 3H), 5.02 (d, *J* = 12.16 Hz, 1H), 4.55 (d, *J* = 12.16 Hz, 1H), 3.82-3.77 (m, 1H) ,3.72 (s, 3H), 3.48 (s, 3H), 1.56 (s, 9H), 1.37 (t, *J* = 8.12 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.3, 166.7, 163.1, 145.2, 139.4, 128.7, 128.1, 127.5, 104.9, 86.1, 53.3, 52.7, 52.4, 40.6, 27.9, 27.3, 19.1, 18.7. **Chiral HPLC**: ADH column, hexane-^{i}PrOH (9:1), flow 0.6 mL/min, t: 8.62 min and 9.61 min, er= 93:7**. ESI-HRMS**: Found: *m/z* 448.1942. Calcd for $C_{23}H_{30}NO_8$: $(M+H)^+$ 448.1966.

Dimethyl-2-((2-(tert-butoxycarbonyl)-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(4-chlorophenyl)methyl)malonate (5.22f)



Yellow oil (35 mg, 64%), $[\alpha]_D^{20}$ = +5.0 (c= 0.9, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58-7.52 (m, 3H), 7.40-7.39 (m, 2H), 7.20 (q, *J* = 8.40 Hz, 4H), 4.94 (d, *J* = 12.37 Hz, 1H), 4.14 (d, *J* = 12.37 Hz, 1H), 3.75 (s, 3H), 3.43 (s, 3H), 1.27 (s, 9H). **^{13}C NMR** (100 MHz, CDCl3): δ 167.9, 167.8, 166.3, 156.9, 144.9, 137.6, 133.4, 130.6, 129.2, 128.8, 128.5, 127.7, 106.5, 86.3, 52.8, 52.6, 52.4, 39.7, 27.5. **Chiral HPLC**: ODH column, hexane-^{i}PrOH (85:15), flow 0.6 mL/min, t: 14.17 min and 16.47 min, er= 71:29. **ESI-HRMS**: Found: *m/z* 516.1431.
Calcd for $C_{26}H_{27}ClNO_8$: $(M+H)^+$ 516.1420.

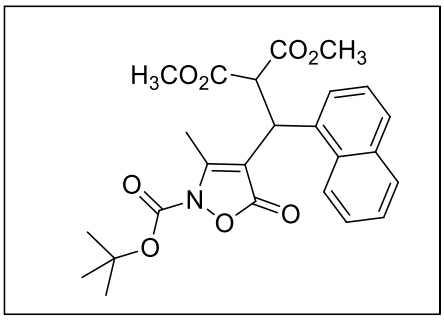
Dimethyl 2-((2-(tert-butoxycarbonyl)-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(2-chlorophenyl)methyl)malonate (5.22g)



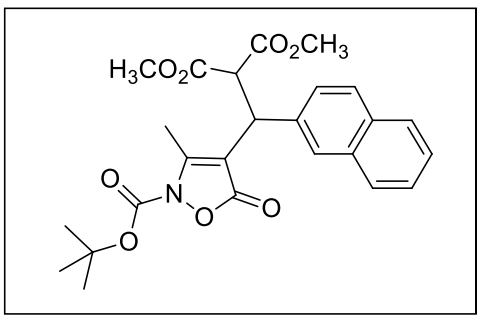
Yellow oil (67 mg, 81%), $[\alpha]_D^{20}$ = + 12.0 (c=0.54, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.31 Hz, 1H), 7.36-7.15 (m, 3H), 4.32 (d, *J* = 11.94 Hz, 1H), 4.04 (d, *J*= 11.94 Hz, 1H), 3.74 (s, 3H), 3.52 (s, 3H), 2.71 (s, 3H), 1.56 (s, 9H). **^{13}C NMR** (100 MHz, CDCl3): δ 168.1, 167.4, 165.9, 156.1, 145.2, 135.6, 133.1, 129.6, 128.6, 127.2, 103.2, 86.4,52.8, 52.6, 35.5, 27.9, 13.7. **Chiral HPLC**: ADH column, hexane-^{i}PrOH (9:1), flow 0.8 mL/min, t: 10.43 min and 11.22 min, er= 84:16. **ESI-HRMS**: Found: *m/z* 454.1201. Calcd for $C_{21}H_{25}ClNO_8$: $(M+H)^+$ 454.1263.

Dimethyl 2-((2-(tert-butoxycarbonyl)-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(naphthalen-1-yl)methyl)malonate (5.22h)

Yellow oil (49 mg, 98%), $[\alpha]_D^{20}$ = +123.2 (c=0.75, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.01 Hz, 2H), 7.77 (d, *J* = 8.01Hz, 2H), 7.61-7.64 (m, 3H), 5.37 (d, *J* =11.75 Hz, 1H), 5.05 (d, *J* = 11.75 Hz, 1H), 3.78 (s, 3H), 3.29 (s, 3H), 2.61 (s, 3H), 1.53 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.5, 167.8, 166.3, 155.4, 145.2, 134.4, 133.9, 130.7, 129.1, 128.1, 126.4, 126.1, 125.5, 122.4, 104.8, 86.3,53.5, 52.8, 52.4, 27.9, 13.5. **ESI-HRMS**: Found: *m/z* 470.1835. Calcd for $C_{25}H_{28}NO_8$: $(M+H)^+$ 470.1809. **Crystallization of 5.22h (Y=55% er=95:5)**: 0.059 mmol (er=81:19) were dissolved at r.t. in 0.150 mL of Ethyl acetate and 0.300 mL of hexane. The solution was kept overnight at -15°C and the solution was carefully removed by a syringe. The content of the solution was analyzed by **chiral HPLC** after the evaporation of the solvent: ADH column, hexane-^{i}PrOH (8:2), flow 0.6 mL/min, t: 20.00 min and 38.88 min, er= 95:5.



Dimethyl 2-((2-(tert-butoxycarbonyl)-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(naphthalen-2-yl)methyl)malonate (5.22i)

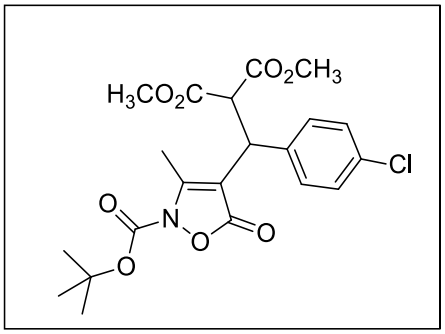


Yellow oil (49 mg, 98%), $[\alpha]_D^{20}$ = +69.9 (c=0.52, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.86-7.78 (m, 4H), 7.60 (d, *J* = 8.60 Hz, 1H), 7.48-7.45 (m, 2H), 5.04 (d, *J* = 11.91 Hz, 1H), 4.53 (d, *J* = 11.91 Hz, 1H), 3.75 (s, 3H), 3.40 (s, 3H), 2.60 (s, 3H), 1.55 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ

168.4, 168.2, 166.3, 155.4, 145.3, 136.4, 133.3, 132.6, 128.7, 127.9, 127.6, 126.6, 126.1, 125.9, 104.9, 86.4, 53.1, 52.8, 52.5, 40.5, 27.9, 13.0. **ESI-HRMS**: Found: *m/z* 470.1820. Calcd for $C_{25}H_{28}NO_8$: $(M+H)^+$ 470.1809.

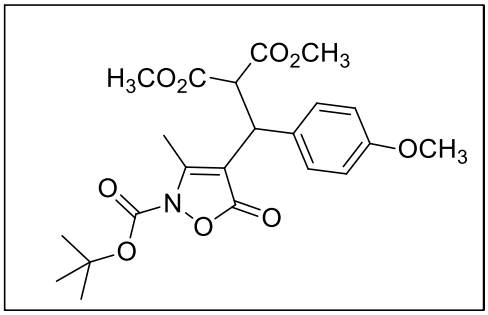
Crystallization of 5.22i (Y=53% er>99.9:0.1): 0.051 mmol (er=87:13) were dissolved at r.t. in 0.150 mL of Ethyl acetate and 0.300 mL of hexane. The solution was kept overnight at -15°C and the solution was carefully removed by a syringe. The content of the solution was analyzed by **chiral HPLC** after the evaporation of the solvent: IE-3 column, hexane-^{i}PrOH (8:2), flow 0.6 mL/min, t: 25.74 min and 33.12 min, **er > 99.9:0.1.**

Dimethyl 2-((2-(tert-butoxycarbonyl)-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(4-chlorophenyl)methyl)malonate(5.22j)



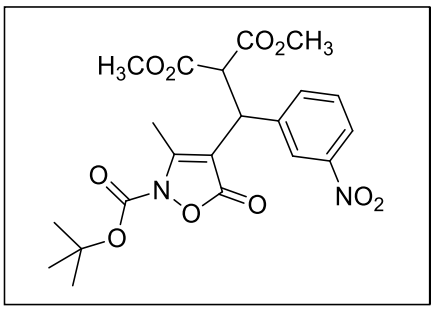
Yellow oil (39 mg, 99%), $[\alpha]_D^{20}$ = +22.1 (c=0.47, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.78 Hz,2H), 7.26 (d, *J* = 8.78Hz, 2H), 4.85 (d, *J* = 11.85 Hz, 1H),4.32 (d, *J* = 11.85 Hz, 1H), 3.71 (s, 3H), 3.49 (s, 3H), 2.57 (s,3H), 1.56 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.1,167.9, 166.0, 155.3, 145.1, 137.3, 133.5, 129.3, 128.9, 104.4,52.8, 52.5, 39.7, 27.9, 12.9. **Chiral HPLC**: IE-3 column, hexane-^{i}PrOH (8:2), flow 0.6 mL/min, t: 16.04 min and 20.89 min, er= 77:23. **ESI-HRMS**: Found: *m/z* 454.1210. Calcd for $C_{21}H_{25}ClNO_8$: $(M+H)^+$ 454.1263.

Dimethyl 2-((2-(tert-butoxycarbonyl)-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(4-methoxyphenyl)methyl)malonate(5.22k)



Brown oil (30 mg, 78%), $[\alpha]_D^{20}$ = +34.7 (c=0.57, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.70 Hz, 2H), 6.81 (d, *J* = 8.55Hz, 2H), 4.85 (d, *J* = 11.92 Hz, 1H), 4.30 (d, *J* = 11.84 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.48 (s, 3H), 2.57 (s, 3H), 1.55 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.8, 167.6, 165.9, 155.8, 148.3, 145.1, 140.8, 134.0, 129.8, 123.2, 122.7, 103.5, 86.8, 53.0, 52.8, 52.7, 39.9, 27.9, 13.1. **Chiral HPLC**: IE-3 column, hexane-^{i}PrOH (8:2), flow 0.6 mL/min, t: 25.58 min and 29.92 min, er= 81:19. **ESI-HRMS**: Found: *m/z* 450.1744. Calcd for $C_{22}H_{28}NO_9$: $(M+H)^+$ 450.1759.

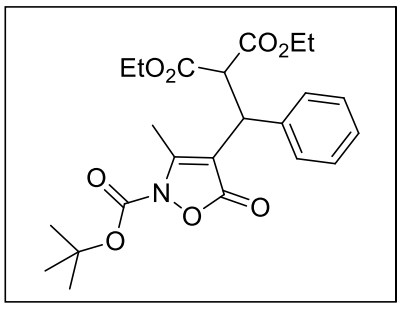
Dimethyl 2-((2-(tert-butoxycarbonyl)-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(3-nitrophenyl)methyl)malonate (5.22l)



Colorless oil (38 mg, 46%), $[\alpha]_D^{20}$ = + 7.0 (c=0.55, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.27-8.26 (m, 1H), 8.14-8.10 (m, 1H), 7.92 (d, *J* = 8.34 Hz, 1H), 7.51 (t, *J* = 7.99 Hz, 1H), 4.90 (d, *J* = 11.94 Hz, 1H), 4.60 (d, *J* = 11.94 Hz, 1H), 3.75 (s, 3H), 3.52 (s, 3H), 2.65 (s, 3H), 1.57 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.8, 167.6, 165. 9, 155.8, 148.3, 145.1, 140.8, 134.0, 129.8, 123.2, 122.7, 103.5, 86.8, 53.0, 52.8, 52.7, 39.9, 27.9, 13.1. **Chiral HPLC**: ADH column, hexane-^{i}PrOH (9:1), flow 1.0 mL/min, t: 19.81 min and 25.54 min, er= 74:26.
ESI-HRMS: Found: *m/z* 465.1494. Calcd for $C_{21}H_{25}N_2O_{10}$: $(M+H)^+$ 465.1504.

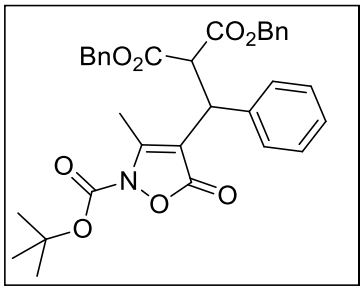
Diethyl 2-((2-(tert-butoxycarbonyl)-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)malonate (5.22ad)

Yellow solid (39 mg, 68%), Mp. 110-112°C, $[\alpha]_D^{20}$ = +12.9 (c= 0.5, $CHCl_3$)**. ^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.75 Hz, 2H), 7.31-7.24 (m, 5H), 7.25 (m, 5H), 4.89 (d, *J* = 12.21 Hz, 1H),



4.35 (d, *J* = 12.21 Hz, 1H), 4.19 (q, *J* = 6.99 Hz, 2H), 3.94 (q, *J* = 6.99 Hz, 2H), 2.59 (s, 3H). 1.56 (s, 9H), 1.25 (t, *J* = 7.12 Hz, 3H), 0.96 (t, *J* = 7.12 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.0, 167.8, 166.2, 155.2, 145.4, 139.0, 128.7, 121.1, 127.5, 105.2, 86.3, 61.6, 61.4, 53.2, 40.4, 27.9, 13.9, 13.6, 13.0. **Chiral HPLC**: ADH column, hexane-^{i}PrOH (8:2), flow 0.6 mL/min, t: 9.97 min and 10.94 min, er= 81:19. **ESI-HRMS**: Found: *m/z* 448.1942. Calcd for $C_{23}H_{29}NO_8$:$(M+H)^+$ 448.1966.

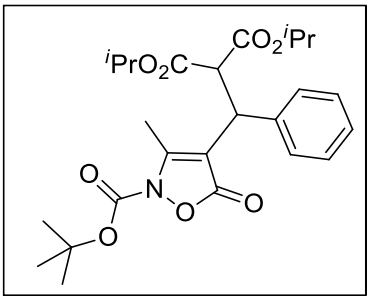
Dibenzyl 2-((2-(tert-butoxycarbonyl)-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)malonate (5.22ae)



Brown oil (20 mg, 44%), $[\alpha]_D^{20}$ = +12.2 (c=0.48, CHCl3). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43-7.40 (m, 2H), 7.35-7.23 (m, 11H), 7.02-6.99 (m, 2H), 5.14 (q, *J* = 12.32 Hz, 2H), 5.02 (d, *J* = 12.08 Hz, 1H), 4.93 (q, *J* = 12.32 Hz, 2H), 4.33 (d, *J* = 12.08 Hz, 1H), 2.42 (s, 3H), 1.56 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.5, 167.4, 166.3, 166.2, 156.4, 144.8, 139.1, 135.2, 135.1, 134.9, 130.3, 128.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 106.8, 85.9, 67.3, 66.9,53.1, 41.5, 40.4, 27.5. **Chiral**

HPLC: ADH column, hexane-^{i}PrOH (8:2), flow 0.6 mL/min, t: 20.42 min and 25.89 min, er= 73:27. **ESI-HRMS**: Found: *m/z* 572.2217. Calcd for $C_{33}H_{33}NO_8$: $(M+H)^+$ 572.2279.

Diisopropyl 2-((2-(tert-butoxycarbonyl)-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)malonate (5.22af)



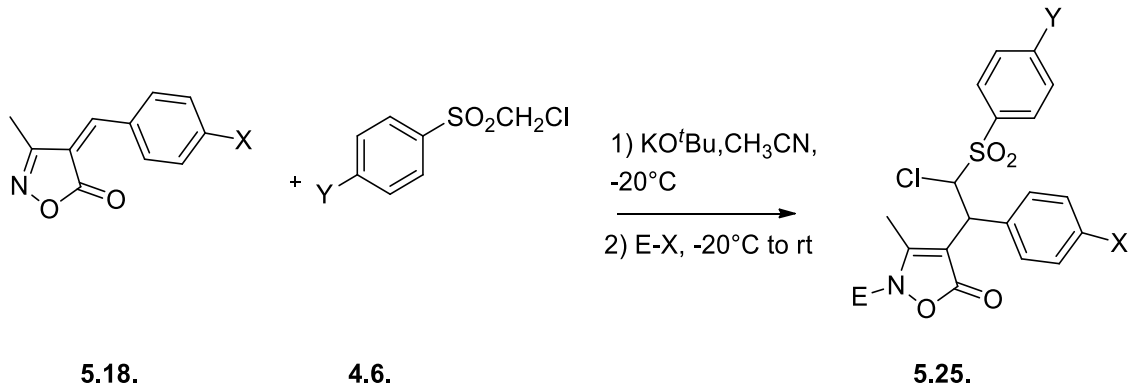
Yellow oil (21 mg, 30%), $[\alpha]_D^{20}$ = +13.4 (c=0.47, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.26 Hz, 2H), 7.28- 7.21 (m, 3H), 5.00 (t, *J* = 5.50 Hz, 1H), 4.81-4.74 (m, 2H), 4.30 (d, *J* = 12.08 Hz, 1H), 2.57 (s, 3H), 1.54 (s,9H), 1.20 (t, *J*= 5.91 Hz, 6H), 1.06 (d, *J* = 6.03 Hz, 3H), 0.85 (d, *J* = 6.24 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.6, 167.3, 166.2, 155,1, 145.5, 139.1, 128.6, 128.2, 127.5, 105.5, 86.2, 69.2, 68.8, 53.4, 40.3, 27.9, 21.5, 21.4, 21.3, 13.0. **Chiral HPLC**: ADH column, hexane-^{i}PrOH (8:2), flow 0.6 mL/min, t: 8.90 min and 9.49 min, er= 70:30. **ESI-HRMS**: Found: *m/z* 476.2245. Calcd for $C_{25}H_{33}NO_8$: $(M+H)^+$ 476.2279.

General procedure for asymmetric one-pot three component Michael reaction tautomer entrapping. To a solution of dimethyl malonate (0.16 mmol, 1.5 eq) in toluene (C=0.20M) was added quinidine (0.0212 mmol, 0.2 eq). The mixture was allowed to stir at -40°C for 5 min. Then, in this order 4-benzylidene-3-methylisoxazol-5(4H)-one **5.18a.** (0.106 mmol, 1 eq) and di-*tert*-butyl dicarbonate (0.212 mmol, 2eq.) were added and reacted for the time reported in **scheme 5.12.** The crude reaction mixture was directly purified by flash chromatography (eluent: hexane/ethyl acetate 90/10 to 80/20) to afford product **5.22aa** in 97% and 15:85 er

General procedure for asymmetric one-pot four component Knoevenagel/Michael/tautomer entrapping. To a solution of 3-alkylisoxazol-5(4H)-one **5.18.** (0.16 mmol, 1 eq) in toluene (C=0.20M) was added quinidine (0.032 mmol, 0.2 eq). The mixture was allowed to stir at r.t. for 5 min. Then, in this order, benzaldehyde (0.16 mmol, 1 eq.), dimethyl malonate (0.24 mmol, 1.5 eq) and di-*tert*-butyl decarbonate (0.32 mmol, 2eq.) were added. Once no more starting material was detected on TLC (reaction times observed of about 7h), the crude mixture was directly purified by flash chromatography (eluent: hexane/ethyl acetate 95/5 to 80/20) to afford **5.22aa** in 80% and er = 23:77

Chloromethyl aryl sulfone: Procedure with Potassium *tert*-butoxide.

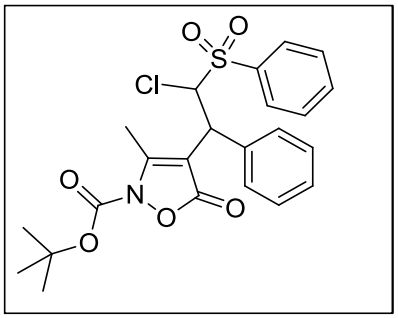
4-arylideneisoxazol-5-ones **5.18.** (0.107 mmol, 1.0 equiv.) were added to a solution of substituted Chloromethyl aryl sulfones **4.6.** (0.128 mmol, 1.2 equiv) and potassium *tert*-butoxide (0.107 mmol, 12 mg, 1.0 equiv) in anhydrous CH_3CN (0.21 M, 0.50 mL) at -20°C in refrigerator. The reaction mixture was monitored by TLC until complete disappearance of starting materials, after that the reaction mixture was quenched with trapping agents (0.214 mmol, 2 equiv.) and allowing to warm to room temperature. The reaction was allowed to stir until the complete disappearance of starting material. The solution was evaporated affording the crude product as white solid, which was purified by column chromatography (Hexane: Ethyl acetate = 80:20) to provide **5.25a-5.25q** (63-86 %).
Michael reaction is 5-fold scalable on **5.18a** substrate (0.535 mmol, 100 mg, 1 mmol) to afford product **5.25a** in 65 % yield (0.348 mmol, 166 mg).



5.18. **4.6.** **5.25.**

Scheme 5.S7. Cascade reactions in the synthesis of compounds **5.25**

Tert-butyl 4-(2-chloro-2-((4-cyanophenyl)sulfonyl)-1-phenylethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (5.25a)



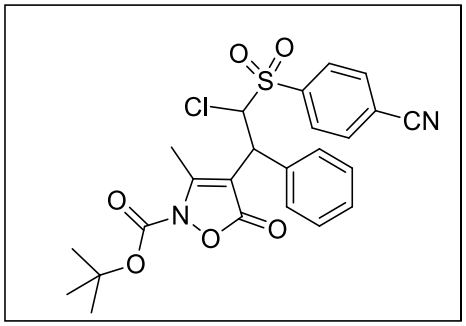
White solid (70%, 36 mg), Mixture of diastereoisomers, dr = 94:6.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ 7.96 (d, *J* = 7.8 Hz, 2H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 2H, *major + minor*), 7.46 (d, *J* = 6.6 Hz, 2H), 7.38 – 7.28 (m, 3H), 6.15 (d, *J* = 11.1 Hz, 1H, *major*), 6.09 (d, *J* = 10.7 Hz, 1H, *minor*), 4.33 (d, *J* = 11.1 Hz, 1H, *major + minor*), 2.60 (s, 1H, *major*), 2.54 (s, 1H, *minor*), 1.56 (s, 9H, *major + minor*).**^{13}C{^{1}H} NMR** (101 MHz, *$CDCl_3$*) δ 166.5, 154.2, 145.4, 138.8, 136.7, 134.7, 129.7 (x2), 129.2 (x2), 128.3, 105.0, 86.7, 72.3, 42.8, 28.1, 13.1.**MALDI-HRMS**: Found: *m/z* 516.0692 Calcd for $C_{23}H_{24}ClNO_6SK^+$: $(M+nK)^+$ 516.0644

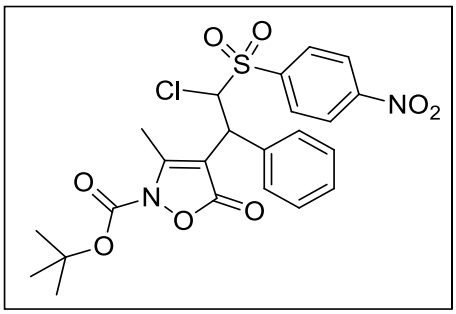
Tert-butyl 4-(2-chloro-2-((4-cyanophenyl)sulfonyl)-1-phenylethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (5.25b)

White solid (83%, 45 mg), Single diastereomer, M.p.205-207 °C (Hexane/ Chloroform)

^{1}H NMR (400 MHz, *$CDCl_3$*) δ 8.09 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 6.4 Hz, 2H), 7.32 (q, *J* = 8.5, 7.5 Hz, 3H), 6.20 (d, *J* = 11.1 Hz, 1H), 4.33 (d, *J* = 11.1 Hz, 1H), 2.60 (s, 3H), 1.56 (s, 9H). **^{13}C{^{1}H} NMR** (101 MHz, *$CDCl_3$*) δ 166.5, 154.4, 145.3, 141.0, 138.3, 132.9, 130.3, 129.3, 128.5, 128.2, 118.4, 117.1, 104.5, 87.0, 72.2, 42.7, 28.1, 13.1. **ESI-HRMS**: Found: *m/z* 501.0902 Calcd for $C_{24}H_{23}ClN_2O_6S^-$: $(M)^-$ 501.0893



Tert-butyl 4-(2-chloro-2-((4-nitrophenyl)sulfonyl)-1-phenylethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (5.25c)

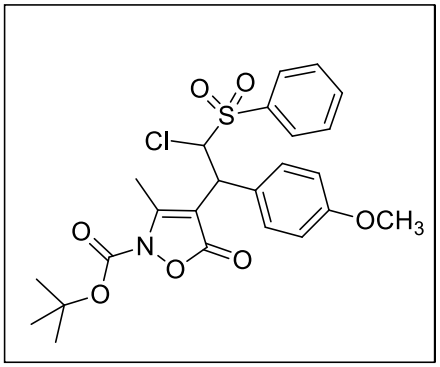


White solid (84%, 47 mg), Single diastereomer, M.p.186-188°C (Hexane/ Chloroform)

^{1}H NMR (400 MHz, *$CDCl_3$*) δ 8.42 (d, *J* = 8.9 Hz, 2H), 8.18 (d, *J* = 8.9 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.33 (q, *J* = 8.8, 7.8 Hz, 3H), 6.23 (d, *J* = 11.1 Hz, 1H), 4.34 (d, *J* = 11.1 Hz, 1H), 2.61 (s, 3H), 1.56 (s,9H). **^{13}C{^{1}H} NMR** (101 MHz,

CDCl₃) δ 166. 6, 154.5, 151.3, 145.3, 142.4, 138.2, 131.1, 129.4, 128.5, 128.2, 124.4, 104.4, 87.0, 72.2, 42.6, 28.1, 13.1.**ESI-HRMS**: found: 540.1201 Calcd for $C_{23}H_{27}ClN_3O_8S^+$: $(M+NH_4)^+$ 523.0864

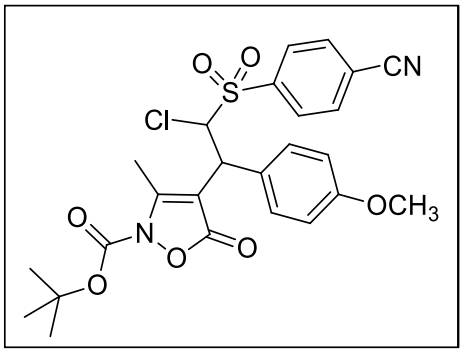
tert-butyl 4-(2-chloro-1-(4-methoxyphenyl)-2-(phenylsulfonyl)ethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (5.25d)



White solid (63%, 34 mg), M.p.235-237 °C (Hexane/ Chloroform)

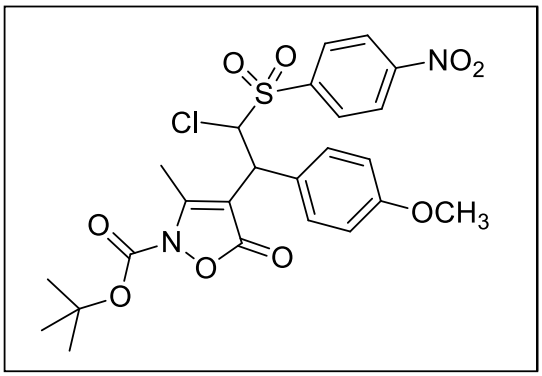
^{1}H NMR (400 MHz, *CDCl₃*) δ 7.95 (d, *J* = 7.1 Hz, 2H), 7.71 – 7.67 (m, 1H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.09 (d, *J* = 11.1 Hz, 1H), 4.28 (d, *J* = 11.1 Hz, 1H), 3.77 (s, 3H), 2.59 (s, 3H), 1.56 (s, 9H). **^{13}C{^{1}H} NMR** (101 MHz, *CDCl₃*) δ 166.6, 159.4, 154.0, 145.4, 136.7, 134.6, 130.9, 129.6, 129.4, 129.2, 114.5, 105.3, 86.7, 72.6, 55.4, 42.0, 28.1, 13.1. **ESI-HRMS**: Found: 530.1010 *m/z* Calcd for $C_{24}H_{26}ClNaNO_7^+$: 530.1016 $(M+nNa)^+$

Tert-butyl 4-(2-chloro-2-((4-cyanophenyl)sulfonyl)-1-(4-methoxyphenyl)ethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (5.25e)



White solid (85%, 49 mg), mixture of diastereomers, dr = 92:8 **^{1}H NMR** (300 MHz, *CDCl₃*) δ 8.14 (d, *J* = 7.4 Hz, 2H, *minor*), 8.08 (d, *J* = 8.0 Hz, 2H, *major*), 7.86 (d, *J* = 8.2 Hz, 2H, *major*), 7.77 (d, *J* = 7.9 Hz, 2H, *minor*), 7.38 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.14 (d, *J* = 11.0 Hz, 1H), 4.28 (d, *J* = 11.0 Hz, 1H), 3.78 (s, 3H), 2.67 (s, 3H,*minor*), 2.59 (s, 3H, *major*), 1.57 (s, 9H, *major* + *minor*). **^{13}C{^{1}H} NMR** (75 MHz, *CDCl₃*) δ 166.6, 159.6, 154.3, 145.4, 141.0, 132.9, 132.6, 130.3, 130.3, 129.7, 129.6, 129.4, 118.3, 117.1, 114.6, 104.8, 87.0, 77.2, 74.4 (*minor*), 72.5 (*major*), 55.4, 44.5 (*minor*), 41.8 (*major*), 28.1, 13.1. **ESI-HRMS**: Found: 531.1009 *m/z* Calcd for $C_{25}H_{24}ClN_2O_7S^-$: 531.0998 $(M)^-$

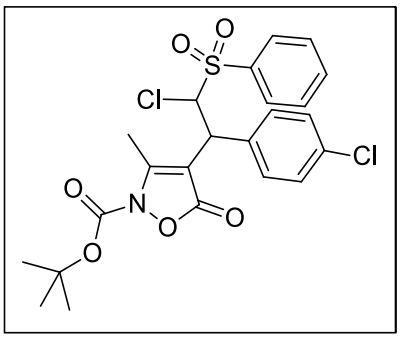
tert-butyl 4-(2-chloro-1-(4-methoxyphenyl)-2-((4-nitrophenyl)sulfonyl)ethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (5.25f)



White solid (80%, 47 mg), mixture of diastereomers, dr = 84:16

^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.40 (d, *J* = 8.8 Hz, 2H, *major*), 8.21 (d, *J* = 8.8 Hz, 2H, *minor*), 8.16 (d, *J* = 8.8 Hz, 2H, *major*), 7.81 (d, *J* = 8.8 Hz, 2H, *minor*), 7.38 (d, *J* = 8.7 Hz, 2H, *major*), 7.32 (d, *J* = 8.7 Hz, 2H, *minor*), 6.85 (d, *J* = 8.7 Hz, 2H, *major*), 6.67 (d, *J* = 8.7 Hz, 2H, *minor*), 6.17 (d, *J* = 11.0 Hz, 1H, *major + minor*), 4.29 (d, *J* = 11.1 Hz, 1H, *major + minor*), 3.77 (s, 3H, *major*), 3.72 (s, 3H, *minor*), 2.59 (s, 3H, *major*), 2.53 (s, 3H, *minor*), 1.56 (s, 9H, *major + minor*). **^{13}C{^{1}H} NMR** (75 MHz, *CDCl$_3$*) δ 166.7, 159.7, 154.3, 151.3, 145.4, 142.5, 131.1, 130.3, 129.4, 124.3, 124.0, 114.6, 104.7, 87.0, 74.5 (*minor*), 72.6 (*major*), 55.4, 44.6 (*minor*), 41.9 (*major*), 28.1, 13.1. **ESI-HRMS**: Found: 575.0854 *m/z* Calcd for $C_{24}H_{25}ClNaN_2O_9S^+$: 575.0854 $(M+nNa)^+$

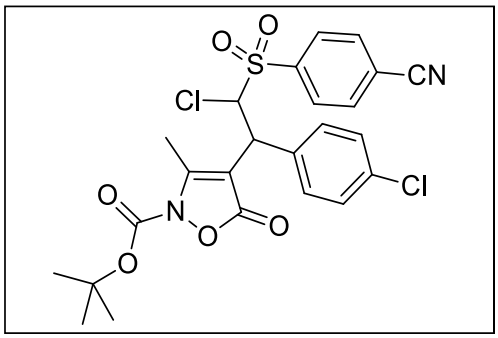
tert-butyl 4-(2-chloro-1-(4-chlorophenyl)-2-(phenylsulfonyl)ethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (5.25g).



White solid (84 %, 46 mg), Mixture of diastereomers, dr = 82:18

^{1}H NMR (300 MHz, *CDCl$_3$)* δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 7.1 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H, *major + minor*), 7.29 (d, *J* = 8.4 Hz, 2H, *major*), 6.07 (d, *J* = 11.1 Hz, 2H,), 4.32 (d, *J* = 11.1 Hz, 1H), 2.59 (s, 1H, *major*), 2.53 (s, 3H, *minor*), 1.56 (s, 9H). **^{13}C{^{1}H} NMR** (63 MHz, *CDCl$_3$*) δ 166.4, 154.4, 145.4, 137.2, 136.6, 134.7, 134.2, 129.7, 129.6, 129.5, 129.3, 129.2, 129.1, 104.5, 86.8, 73.9 (*minor*), 72.1 (*major*), 44.3 (*minor*), 42.3 (*major*), 28.1, 13.9(*minor*), 13.1 (*major*). **ESI-HRMS**: Found: 529.0960 *m/z* Calcd for $C_{23}H_{27}Cl_2N_2O_6S^+$: 529.0961 $(M+NH_4^+)^+$

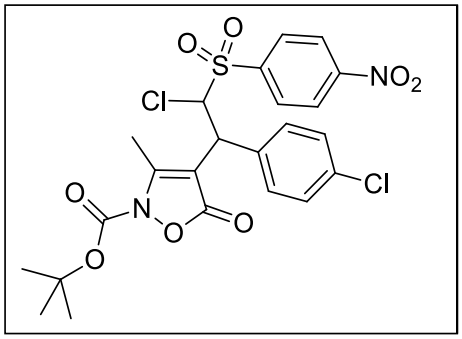
tert-butyl 4-(2-chloro-1-(4-chlorophenyl)-2-((4-cyanophenyl)sulfonyl)ethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (5.25h)



White solid (86%, 49 mg), Single diastereomers, M.p. 235-237 °C (Hexane/ Ethyl Acetate)

^{1}H NMR (300 MHz, *$CDCl_3$*) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.13 (d, *J* = 10.9 Hz, 1H), 4.32 (d, *J* = 11.1 Hz, 1H), 2.59 (s, 3H), 1.57 (s, 9H). **^{13}C{^{1}H} NMR** (101 MHz, *$CDCl_3$*) δ 166.5, 154.7, 145.3, 140.8, 136.7, 134.5, 133.0, 130.3, 129.6, 129.5, 118.5, 117.1, 104.0, 87.2, 72.0, 42.1, 28.1, 13.1. **ESI-HRMS**: Found: 535.0514 *m/z* Calcd for $C_{24}H_{21}Cl_2N_2O_6S^-$: 535.0503 $(M)^-$

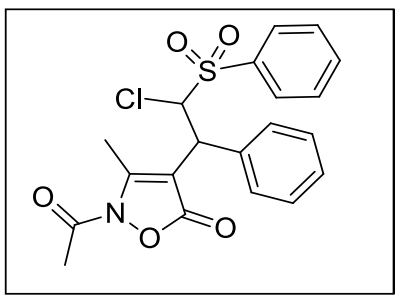
tert-butyl 4-(2-chloro-1-(4-chlorophenyl)-2-((4-nitrophenyl)sulfonyl)ethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (5.25i)



White solid (83%, 50 mg), Single diastereomer, M.p. 221-223 °C (Hexane/ Chloroform)

^{1}H NMR (400 MHz, *$CDCl_3$*) δ 8.43 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.18 (d, *J* = 11.1 Hz, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 2.62 (s, 3H), 1.54 (s, 9H). **^{13}C{^{1}H} NMR** (101 MHz, *$CDCl_3$*) δ 166.49, 154.70, 151.42, 145.25, 142.26, 136.63, 134.54, 131.08, 129.63, 129.51, 124.38, 103.92, 87.24, 77.16, 72.01, 42.13, 28.10, 13.09. **ESI-HRMS**: Found: 555.0413 *m/z* Calcd for $C_{23}H_{21}Cl_2N_2O_8S^-$: 555.0401 $(M)^-$

2-acetyl-4-(2-chloro-1-phenyl-2-(phenylsulfonyl)ethyl)-3-methylisoxazol-5(2H)-one (5.25j)

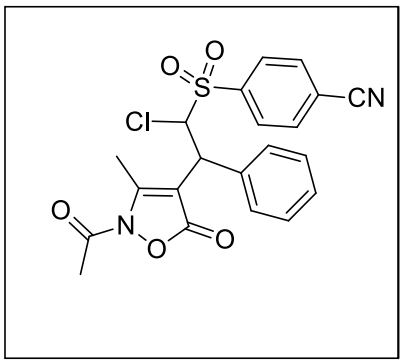


White solid (75%, 34 mg), mixture of diastereomers, dr = 84:16

^{1}H NMR (400 MHz, *$CDCl_3$*) δ 7.97 (d, *J* = 1.0 Hz, 1H), 7.95 (d, *J* = 1.0 Hz, 1H), 7.72 (t, *J* = 1.2 Hz, 1H, *minor*), 7.71 – 7.68 (m, 1H), 7.61– 7.56 (m, 3H), 7.47 – 7.42 (m, 3H), 7.36 – 7.29 (m, 3H), 7.24 – 7.23 (m, 1H, *minor*), 6.09 (d, *J* = 11.2 Hz, 1H, *major*), 6.04 (d, *J* = 10.7 Hz, 1H, *minor*), 4.40 (d, *J* = 10.7 Hz, 1H, *minor*), 4.34 (d, *J*

= 11.2 Hz, 1H, *major*), 2.68 (s, 3H, *major*), 2.62 (s, 3H, *minor*), 2.40 (s, 3H, *major*), 2.39 (s, 3H, *minor*). **^{13}C{^{1}H} NMR** (101 MHz, *CDCl$_3$*) 165.9, 165.1, 154.6 (*minor*), 153.5 (*major*), 138.4, 136.5, 134.7, 129.7 (*major*), 129.6 (*minor*), 129.3, 129.2 (*major*), 129.1 (*minor*), 128.4 (*minor*), 128.2 (*major*), 107.0 (*minor*), 106.3 (*major*), 74.0 (*minor*), 72. (major), 44.5 (*minor*), 42.6 (*major*), 22.9 (*minor*), 22.6 (*major*), 14.2 (*minor*), 13.4 *(major*). ESI-HRMS: Found: 442.0487 *m/z* Calcd for $C_{20}H_{18}ClNaNO_5S^+$: $(M+nNa)^+$ 442.0486

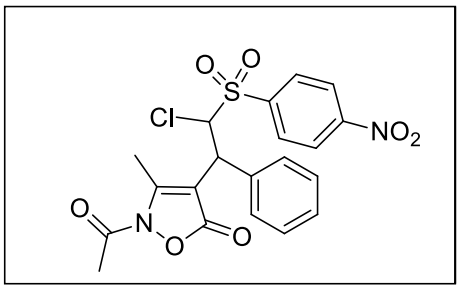
4-((2-(2-acetyl-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)-1-chloro-2-phenylethyl)sulfonyl)benzonitrile (5.25k)



White solid (82 %, 39 mg), Single diastereomer M.p. 220-222 °C (Hexane/ Ethyl Acetate)

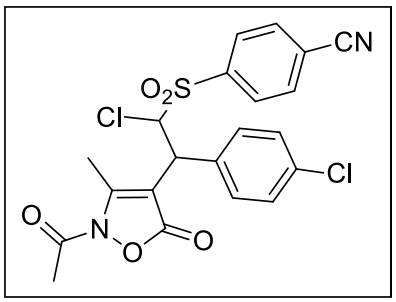
^{1}H NMR (250 MHz, *CDCl$_3$*) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 5.9 Hz, 2H), 7.40 – 7.30 (m, 3H), 6.14 (d, *J* = 11.1 Hz, 1H), 4.36 (d, *J* = 11.2 Hz, 1H), 2.68 (s, 3H), 2.41 (s, 9H). **^{13}C{^{1}H} NMR** (63 MHz, *CDCl$_3$*) δ 166.0, 165.1, 153.8, 140.8, 137.8, 132.9, 130.3, 129.4, 128.6, 128.2, 118.4, 117.1, 105.8, 77.7, 76.7, 72.0, 42.3, 22.8, 13.3. **EI-HRMS**: Found: 444.0537 *m/z* Calcd for $C_{21}H_{17}ClN_2O_5S^{\cdot+}$: 444.0547 $(M)^{\cdot+}$

2-acetyl-4-(2-chloro-2-((4-nitrophenyl)sulfonyl)-1-phenylethyl)-3-methylisoxazol-5(2H)-one (5.25l)



White solid (70%, 40 mg),sI M.p.226-228 °C (Hexane/ Chloroform) **^{1}H NMR** (400 MHz, *CDCl$_3$*) δ 8.42 (d, *J* = 8.7 Hz, 2H), 8.18 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.38 – 7.30 (m, 3H), 6.16 (d, *J* = 11.1 Hz, 1H), 4.37 (d, *J* = 11.1 Hz, 1H), 2.69 (s, 3H), 2.42 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, *CDCl$_3$*) δ 166.0, 165.1, 153.8, 151.5, 142.2, 137.8, 131.2, 129.5, 128.6, 128.2, 124.4, 105.8, 72.1, 42.3, 22.9, 13.4. **MALDI-HRMS**: Found: *m/z* 487.0359 Calcd for $C_{20}H_{17}ClNaN_2O_7S^+$: $(M+nNa)^+$ 487.0337

4-((2-(2-acetyl-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)-1-chloro-2-(4-chlorophenyl)ethyl)sulfonyl)benzonitrile (5.25m)

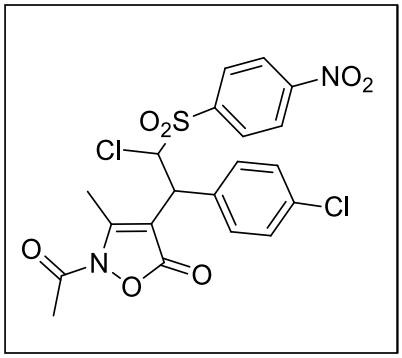


White solid (86 %, 44 mg), Single diastereomer M.p. 202-204°C (Hexane/ Ethyl Acetate)

^{1}H NMR (300 MHz, *CDCl$_3$*) δ 8.08 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 6.06 (d, *J* = 11.0 Hz, 1H), 4.34 (d, *J* = 11.1 Hz, 1H), 2.68 (s, 3H), 2.42 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, *CDCl$_3$*) δ 165.7, 164.9, 153.8, 140.4, 136.1, 134.4, 132.8, 130.1, 129.4, 118.3, 116.8, 105.1, 71.6, 41.6, 22.6, 13.2.

ESI-HRMS: Found: 501.0044 *m/z* Calcd for $C_{21}H_{16}Cl_2NaN_2O_5S^+$: 501.0055 $(M+nNa)^+$

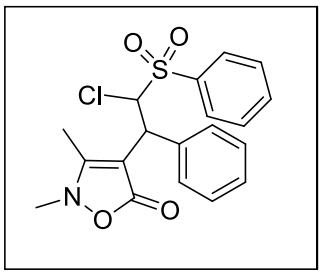
2-acetyl-4-(2-chloro-1-(4-chlorophenyl)-2-((4-nitrophenyl)sulfonyl)ethyl)-3-methylisoxazol-5(2H)-one (5.25n)



White solid (72%, 39 mg), Mixture of diastereomers, dr = 97:3

^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.42 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.09 (d, *J* = 11.1 Hz, 1H), 4.36 (d, *J* = 11.1 Hz, 1H), 2.69 (s, 3H), 2.43 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, *CDCl$_3$*) δ 166.0, 165.1, 154.0, 151.5, 142.1, 136.2, 134.7, 131.2, 129.6, 124.4, 105.2, 71.8, 41.8, 22.9, 13.4. **EI-HRMS**: Found: 498.0051 *m/z* Calcd for $C_{20}H_{16}Cl_2N_2O_7S^{\cdot+}$: 498.0055 $(M)^{\cdot+}$

4-(2-chloro-1-phenyl-2-(phenylsulfonyl)ethyl)-2,3-dimethylisoxazol-5(2H)-one (5.25o)

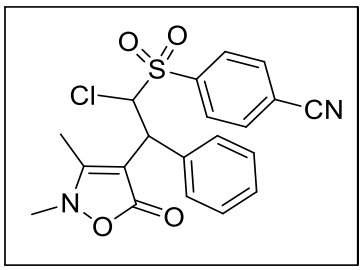


White solid (75% 32 mg), Mixture of diastereoisomers, dr = 86:14.

^{1}H NMR (300 MHz, *CDCl$_3$*) δ 7.96 – 7.92 (m, 2H, *major* + *minor*), 7.67 (t, *J* = 7.4 Hz, 1H, *major*), 7.58 – 7.49 (m, 5H), 7.42 – 7.37 (m, 1H, *minor*), 7.34 - 7.27 (m, 3H), 7.22 – 7.19 (m, 1H), 6.15 (d, J = 11.0 Hz, 1H, *major* + *minor*), 4.27 (d, J = 11.2 Hz, 1H, *major* + *minor*), 3.28 (s, 3H, *major* + *minor*), 2.24 (s, 3H, *major*), 2.17 (s, 3H, *minor*). **^{13}C{^{1}H} NMR** (75 MHz, *CDCl$_3$*) δ 169.8, 160.5, 139.6, 137.1, 134.4, 129.5, 129.1, 129.0, 128.4, 128.0, 100.9, 72.8, 43.4, 37.6, 10.7.

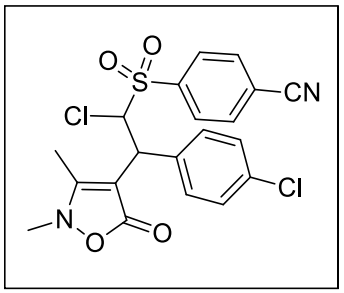
ESI-HRMS: Found: *m/z* 392.0718 Calcd for $C_{19}H_{18}ClNO_4S^+$: $(M+H)^+$ 392.0718

4-((1-chloro-2-(2,3-dimethyl-5-oxo-2,5-dihydroisoxazol-4-yl)-2-phenylethyl)sulfonyl)benzonitrile (5.25p)



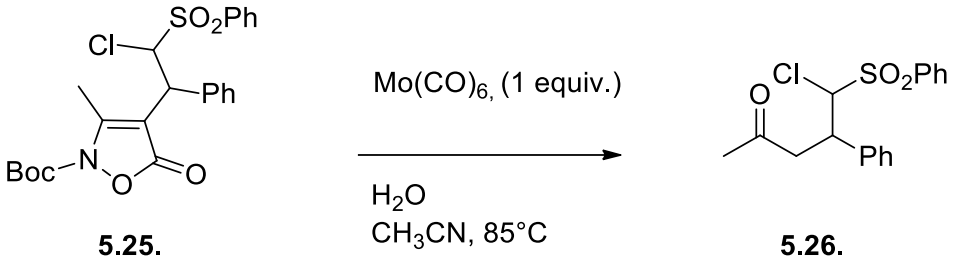
White solid (80%, 36 mg), mixture of diastereomers dr =71:29 **^{1}H NMR** (300 MHz, *CDCl$_3$*) δ 8.07 (d, *J* = 8.4 Hz, 2H, *major*), 7.85 (d, *J* = 8.4 Hz, 2H, *major*), 7.75 (d, *J* = 8.5 Hz, 2H, *minor*), 7.66 (d, *J* = 8.5 Hz, 2H, *minor*), 7.50 (d, *J* = 7.2 Hz, 2H, *major*), 7.45 (d, *J* = 7.7 Hz, 2H, *minor*), 7.35-7.28 (m, 4H, *major* + *minor*), 7.20 (d, *J* = 6.8 Hz, 1H), 6.21 (d, *J* = 11.0 Hz, 2H, *major* + *minor*), 4.26 (d, *J* = 10.9 Hz, 2H, *major* + *minor*), 3.32 (s, 3H, *major* + *minor*), 2.24 (s, 1H, *major*), 2.17 (s, 1H, *minor*). **^{13}C{^{1}H} NMR** (101 MHz, *CDCl$_3$*) δ 169.6, 160.2, 141.1, 139.0, 133.2, 132.7, 132.5, 130.0, 129.5, 129.0, 128.3, 128.2, 128.0, 118.0, 117.0, 100.0, 72.5, 43.0, 37.4, 10.6. **ESI-HRMS**: Found: *m/z* 417.0670 Calcd for $C_{20}H_{18}ClN_2O_4S^+$: $(M+H)^+$ 417.0670

4-((1-chloro-2-(4-chlorophenyl)-2-(2,3-dimethyl-5-oxo-2,5-dihydroisoxazol-4-yl)ethyl)sulfonyl)benzonitrile (5.25q)



White solid (76 %, 37 mg), Mixture of diastereomers 93:7 **^{1}H NMR** (300 MHz, *CDCl$_3$*) δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 2H), 7.23 (d, *J* = 4.4 Hz, 2H), 6.09 (d, *J* = 10.9 Hz, 1H), 4.20 (d, *J* = 11.1 Hz, 1H), 3.30 (s, 3H, *major*), 3.05 (s, 3H, *minor*), 2.20 (s, 9H, *major*), 2.13 (s, 9H, *minor*). **^{13}C{^{1}H} NMR** (75 MHz, *CDCl$_3$*) δ 169.7, 160.2, 141.1, 137.6, 134.2, 132.9, 130.2, 129.8, 129.3, 128.4, 118.3, 117.1, 99.5, 77.2, 72.4, 42.6, 37.5, 10.7. **ESI-HRMS**: Found: 451.0270 *m/z* Calcd for $C_{20}H_{17}Cl_2N_2O_4S^+$: 451.0286 $(M+H)^+$

2.2. Procedure for Molibdenum-catalyzed ring opening (5.26.)



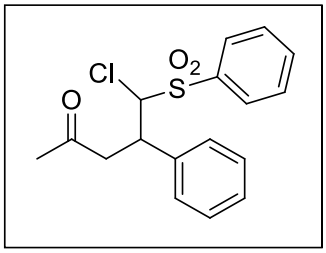
5.25. **5.26.**

Scheme 5.S8. Cascade reaction in the synthesis of branched ketones **5.26**

To a solution of **5.25.** (0.067 mmol, 1.0 equiv.) were added Molybdenum hexacarbonyl (0.067 mmol, 18 mg, 1.0 equiv.) and a catalytic amount of H_2O (200 μL) in CH_3CN (0.05 M) at 85°C in oil bath. The reaction mixture was monitored by TLC until complete disappearance of starting materials. The reaction mixture was allowed to cool down to room temperature, diluted with CH_3Cl filtered over celite. The solution was evaporated affording the crude product as yellow solid, which was purified by column chromatography (Hexane: Ethyl acetate = 95:5 to 80:20) to provide products **5.26a-5.26e** (84-93%).

N-O Cleavage reaction is 3-fold scalable on **5.25h** (0.201 mmol,108 mg, 1 equiv.) to afford **5.26b** in 80 % yield (0.161 mmol, 64 mg).

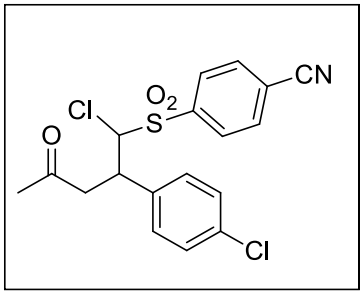
5-chloro-4-phenyl-5-(phenylsulfonyl)pentan-2-one (5.26a)



Colourless oil (87%, 20 mg). Single diastereomer.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ 7.85 (d, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.39 – 7.28 (m, 5H), 5.29 (d, *J* = 5.3 Hz, 1H), 4.58 – 4.26 (m, 0H), 3.28 (dd, *J* = 18.2, 7.6 Hz, 1H), 3.06 (dd, *J* = 18.2, 6.0 Hz, 1H), 2.13 (s, 2H). **^{13}C{^{1}H} NMR** (101 MHz, *CD_2Cl_2*) δ 206.0, 138.2, 137.5, 134.9, 130.2, 130.1, 129.6, 128.7, 128.4, 77.5, 47.2, 41.1, 30.7. **ESI-HRMS**: Found: 375.0223, Calcd for $C_{17}H_{17}ClKO_3S^+$: $(M+nK)^+$ 375.0219.

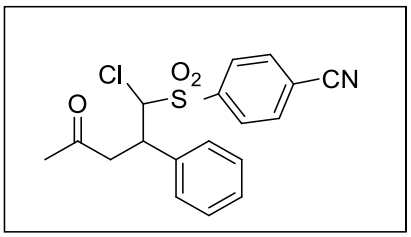
4-((1-chloro-2-(4-chlorophenyl)-4-oxopentyl)sulfonyl)benzonitrile (5.26b).



Colourless oil (88%, 24 mg). Mixture of diastereomers: 94:6

^{1}H NMR (300 MHz, *$CDCl_3$*) δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.28 (m, 4H), 5.34 (d, *J* = 4.7 Hz, 1H), 4.37 – 4.33 (m, 1H), 3.20 (dd, *J* = 18.5, 8.1 Hz, 1H), 2.99 (dd, *J* = 18.5, 5.4 Hz, 1H), 2.15 (s, 3H). **^{13}C{^{1}H} NMR** (151 MHz, *CD_2Cl_2*) δ 205.8, 141.2, 136.1, 134.5, 133.3, 131.6, 130.8, 129.0, 118.6, 117.6, 77.3, 46.8, 40.1, 30.7. **ESI-HRMS**: Found: m/z 418.0053 Calcd for $C_{18}H_{15}C_{l2}NNaO_3S^+$: $(M+nNa)^+$ 418.0047

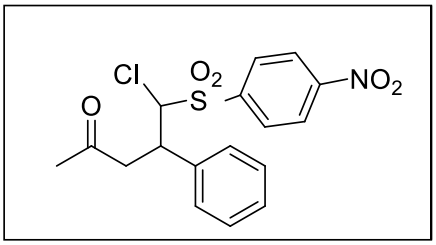
4-((1-chloro-4-oxo-2-phenylpentyl)sulfonyl)benzonitrile (5.26c)



Colourless oil (85 %, 21 mg), Single diastereomer.

^{1}H NMR (300 MHz, *CDCl$_3$*) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.50 – 7.00 (m, 5H), 5.37 (d, *J* = 4.9 Hz, 1H), 4.33-4.27(m, 1H), 3.20 (dd, *J* = 18.4, 8.2 Hz, 1H), δ 2.97 (dd, *J* = 18.4, 5.4 Hz, 1H), 2.11 (s, 3H). **^{13}C{^{1}H} NMR** (75 MHz, *CD$_2$Cl$_2$*) δ 205.7, 140.8, 137.2, 132.8, 130.4, 129.8, 128.4, 128.3, 118.0, 117.3, 77.2, 46.6, 40.5, 30.3. **ESI-HRMS**: Found: 360.0474, Calcd for $C_{18}H_{15}ClNO_3S^-$: $(M)^-$: 360.0467

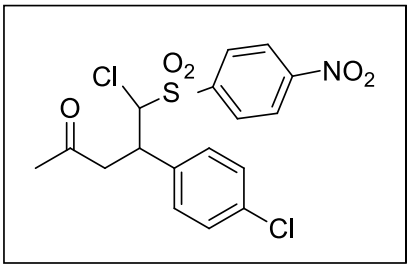
5-chloro-5-((4-nitrophenyl)sulfonyl)-4-phenylpentan-2-one (5.26d)



Colourless oil (92 %, 24 mg), Single diastereomer.

^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.28 (d, *J* = 8.9 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.53 – 7.18 (m, 5H), 5.44 (d, *J* = 4.8 Hz, 1H), 4.49 – 4.25 (m, 1H), 3.24 (dd, *J* = 18.4, 8.2 Hz, 1H), 3.01 (dd, *J* = 18.4, 5.4 Hz, 1H), 2.15 (s, 3H). **^{13}C{^{1}H} NMR** (75 MHz, *CD$_2$Cl$_2$*) δ 206.0, 151.5, 142.7, 137.5, 131.7, 130.2, 128.9, 128.7, 124.5, 77.7, 47.0, 40.9, 30.7. **ESI-HRMS**: Found: 380.0372, Calcd for $C_{17}H_{15}ClNO_5S^-$: $(M)^-$: 380.0365

5-chloro-4-(4-chlorophenyl)-5-((4-nitrophenyl)sulfonyl)pentan-2-one (5.26e)



Colourless oil (93 %, 26 mg), Single diastereomer.

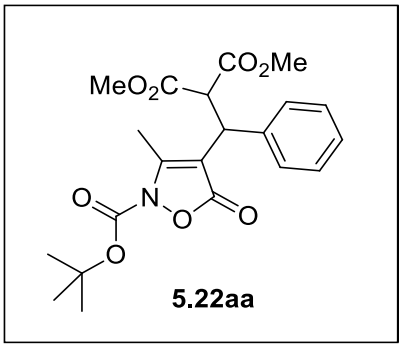
^{1}H NMR (300 MHz, *CDCl$_3$)* δ 8.35 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.66 – 7.26 (m, 4H), 5.37 (d, *J* = 4.7 Hz, 1H), 4.40-4.34 (m, 1H), 3.21 (dd, *J* = 18.5, 8.2 Hz, 1H), 3.00 (dd, *J* = 18.5, 5.3 Hz, 1H), 2.16 (s, 2H). **^{13}C{^{1}H} NMR** (101 MHz, *CD$_2$Cl$_2$*) δ 205.8, 151.7, 142.7, 136.1, 134.6, 131.7, 131.6, 129.0, 124.6, 77.3, 46.8, 40.2, 30.7. **ESI-HRMS**: Found: 413.9980, Calcd for $C_{17}H_{14}Cl_2NO_5S^-$: $(M)^-$: 413.9975

Single crystal X-ray diffraction

Colourless needle-like single crystals of compound **rac-5.22aa** suitable for X-ray diffraction analysis were obtained by slow evaporation, dissolving 4 mg of the compound in hexane/AcOEt = 0.400/0.200 mL. A crystal of 0.47 mm x 0.35 mm x 0.08 mm was selected for the measurement. Colourless needle-like single crystals of enantiopure compound **(+)-5.22aa** suitable for X-ray diffraction analysis were obtained by slow evaporation, dissolving 5 mg of the compound in hexane/AcOEt = 0.600/0.300 mL. A crystal of 0.37 mm x 0.21 mm x 0.09 mm was selected for the measurement. Both crystals were mounted on a cryoloop with paratone oil and measured at room temperature with a Bruker D8 QUEST diffractometer equipped with a PHOTON II detector using Cu*Kα* radiation (λ= 1.54178 Å). Data indexing was performed using APEX3.[109] Data integration and reduction were performed using SAINT. Absorption correction was performed by multi-scan method in SADABS. [109] The structures were solved using SHELXS-97[110] and refined by means of full matrix least-squares based on F [110] using the program SHELXL.[111] Hydrogen atoms were positioned geometrically and included in structure factors calculations but not refined. Compound **5.22aa** crystallizes as a conglomerate in space group P212121. For the enantiopure compound (CCDC-1971494) the absolute configuration of C10 atom was determined as (S).

ORTEP diagram in **Figure 5.S1** were drawn using OLEX.

Crystallographic data are reported in **Table 5.S3.**



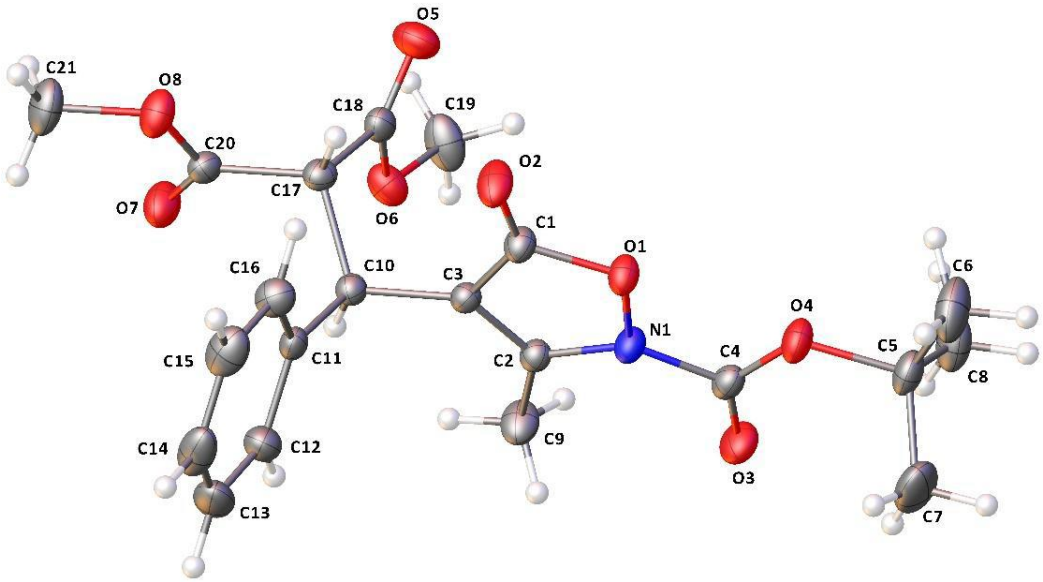


Figure 5.S1 ORTEP diagram for compound ***rac*-5.22aa**.

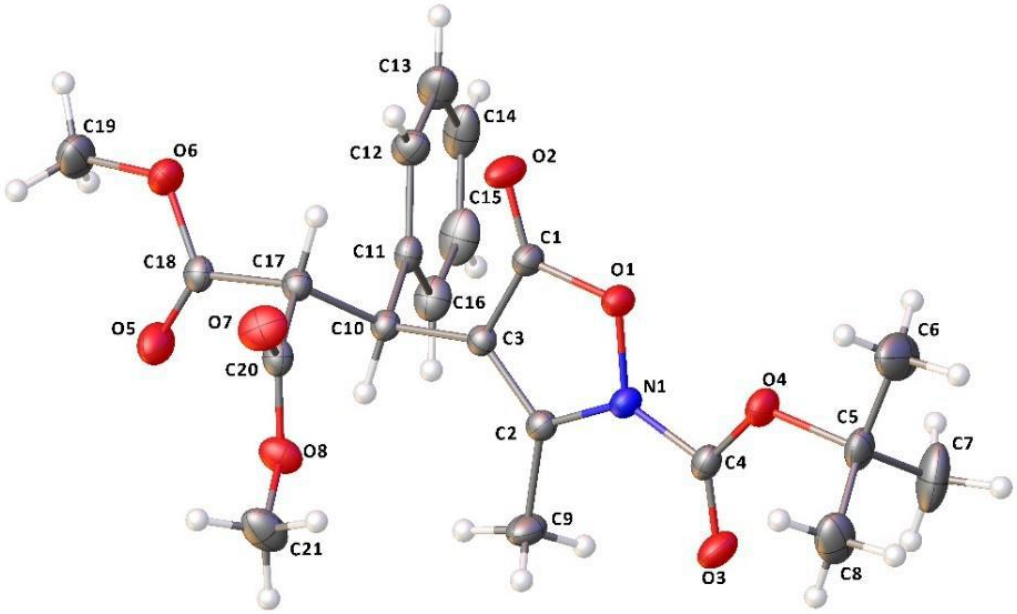


Figure 5.S2 ORTEP diagram for compound **(+)-5.22aa**.

	***rac*-5.22aa**	**(+)-5.22aa**
T (K)	296	296
Formula	$C_{21}H_{25}NO_8$	$C_{21}H_{25}NO_8$
Formula weight	419.42	419.42
System	Orthorhombic	Orthorhombic
Space group	*P* 212121	*P* 212121
***a* (Å)**	9.088(3)	9.088(3)
***b* (Å)**	10.197(4)	10.189(8)
***c* (Å)**	23.329(7)	23.235(17)
***α* (°)**	90	90
***β* (°)**	90	90
***γ* (°)**	90	90
***V* (Å^3)**	2161.9(13)	2150(2)
Z	4	4
***Dx* (g cm^{-3})**	1.289	1.296
λ (Å)	1.54178	1.54178
***μ* (mm^{-1})**	0.832	0.839
F_{000}	888.0	888.0
R1 (I > 2σI)	0.0367(3524)	0.0354(3606)
$_wR_2$	0.0978(3743)	0.1059(3988)
N. of param.	278	278
GooF	1.064	1.056
***ρmin*, *ρ*max (eÅ^{-3})**	-0.107, 0.178	-0.182, 0.241

Table 5.S3 Crystallographic data for compounds ***rac*-5.22aa, (+)-5.22aa.**

Chapter 6. Asymmetric α-trifluoromethylthiolation of 3-EWG phthalides.

6.1. Introduction: SCF_3 and medicinal chemistry.

Over the past 15 years, the role of fluorinated molecules, bearing the moiety SCF_3 has grown exponentially in pharmaceutical, agrochemical and material chemistry (**Figure 6.1.**).[112]

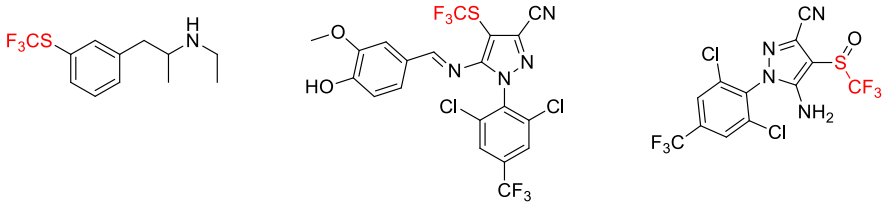


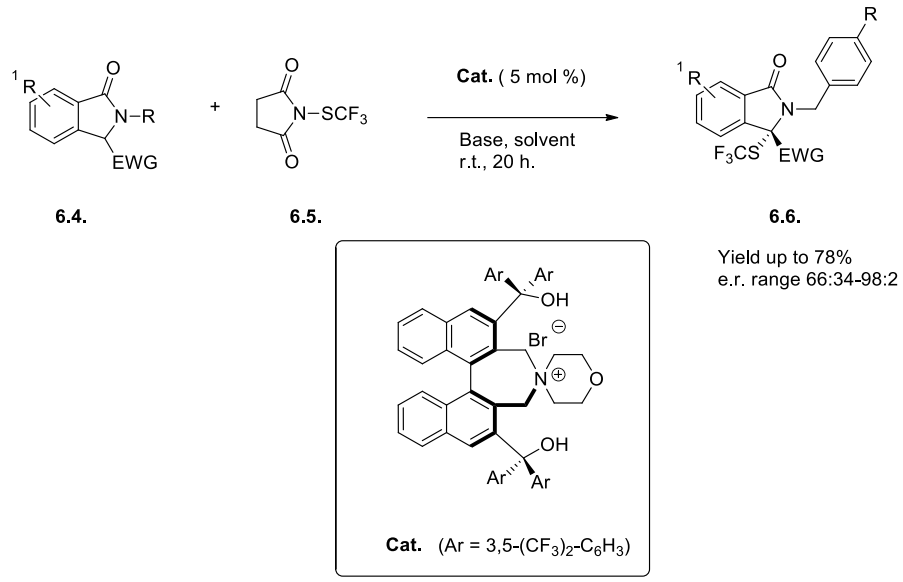
Figure 6.1. Applications of organic molecules bearing an SCF_3 group

Fluorine is a small atom with a van der Waals radius of 1.47 Å, close to the 1.20 Å value for hydrogen.[113,114] Furthermore, the high electronegativity (3.98 on the Pauling electronegativity scale compared to 2.20 for H, 3.44 for O, and 2.55 for C) means that the bond is highly polarized.

One of the most important features of fluorine is the increasing of lipophilicity of the molecules. This property is very important as the plasmatic membranes of all cells are highly lipophilic and therefore, they allow the transition of similar species. The degree of lipophilicity of a molecule is measured with the logP, octanol / water partition coefficient. This coefficient measures the percentage of a research molecule dissolved in an organic phase such as octanol and in the aqueous phase. Obviously, the higher this ratio, the greater the lipophilicity of the molecule. For examples, in the amines [115] by replacing an atom of H with one of fluorine, a notable decrease in basicity is observed in the various fluorinated ethylamines (pK_{aH} from **10.7** $CH_3CH_2NH_2$ to **5.7** $CF_3CH_2NH_2$) due to the strongly inductive effect of fluorine which therefore tends to absorb the electron density of the N making the doublets less available to accept protons. Therefore, the percentage of molecules that will be protonated is lower, increasing the concentration in the organic phase, or in octanol. By increasing the average residence time in the organic phase, the molecule results more bioavailable, for example.

6.2. Objectives and results: α-trifluoromethylthiolation of 3-EWG phthalides.

Based on the excellent results obtained in collaboration with Prof. Waser [116] **Scheme 6.1,**[1] another fruitful collaboration with Prof. Della Sala on α-trifluoromethylthiolation of 3-EWG phthalides was established.



Scheme 6.1. α-trifluoromethylthiolation reaction of 3-EWG isoindolinones **6.4**

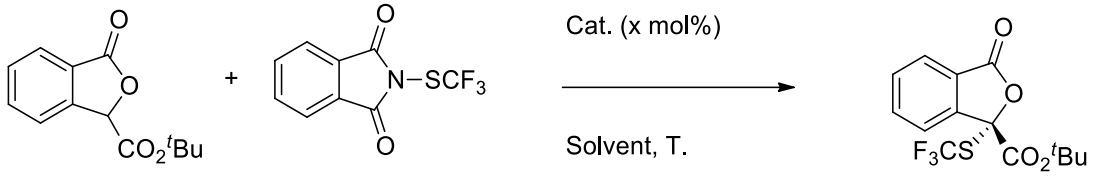
Various examples of trifluoromethylthiolation have been developed during the years using liquid / solid phase transfer catalytic systems by Della Sala *et al.*[117,118]

Preliminary screening employing Maruoka catalysts under the conditions used by Waser *et al.*[116] leads only racemic mixture 52:48.

Then, it was thought to carry out an asymmetric α-trifluoromethylthiolation of 3-EWG-phthalides using cinchona alkaloids bifunctional organocatalysts. Recent works dealt very well the heterofunctionalization of 3-EWG phthalides using this type of catalytic system.[119,120,121,122]

Preliminary screening (**Scheme 6.2.**) was performed using *tert-butyl 3-oxo-1,3-dihydroisobenzofuran-1-carboxylate* [123] (**6.7.**) with phthalimide-SCF_3 (**6.8.**) as a donor of SCF_3^+.

[1] **Scheme 6.1** reported the enantioselective studies carried out by Prof. Dr. Mario Waser's research group.[116] My contribution is limited to the synthesis of some starting materials **6.4.**



6.7. **6.8.** **6.9.**

Scheme 6.2. α-trifluoromethylthiolation reaction of 3-EWG phthalides, **6.7**

Entry	Cat. (mol %)	Solvent	Temperature (°C)	Time (h)	Yield	er
1	T1 (10)	Toluene	r.t.	24	40%	51:49
2	Q2 (10)	DCM	-20	24	92%	76:24
3	T2 (10)	Toluene	r.t.	48	66%	61:39
4	Q1 (10)	DCM	-20	24	No reaction	--
5	Q2 (20)	Toluene	0	24	20%	76:24

Table 6.1. Screening of reaction condition to get compound **6.9**

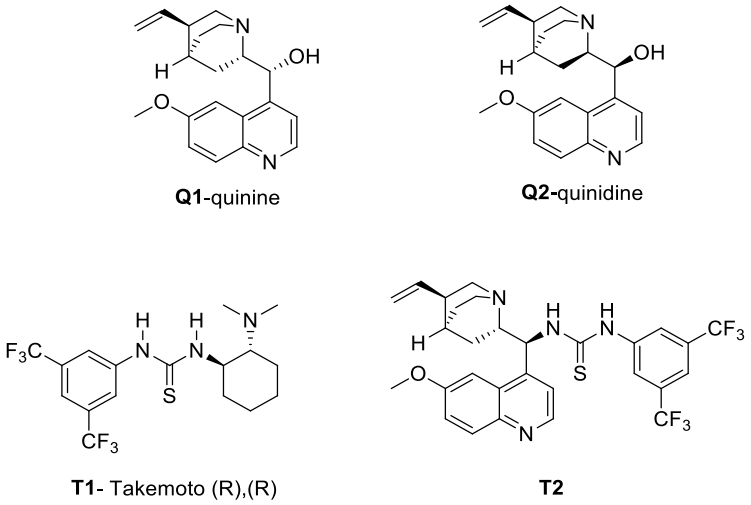
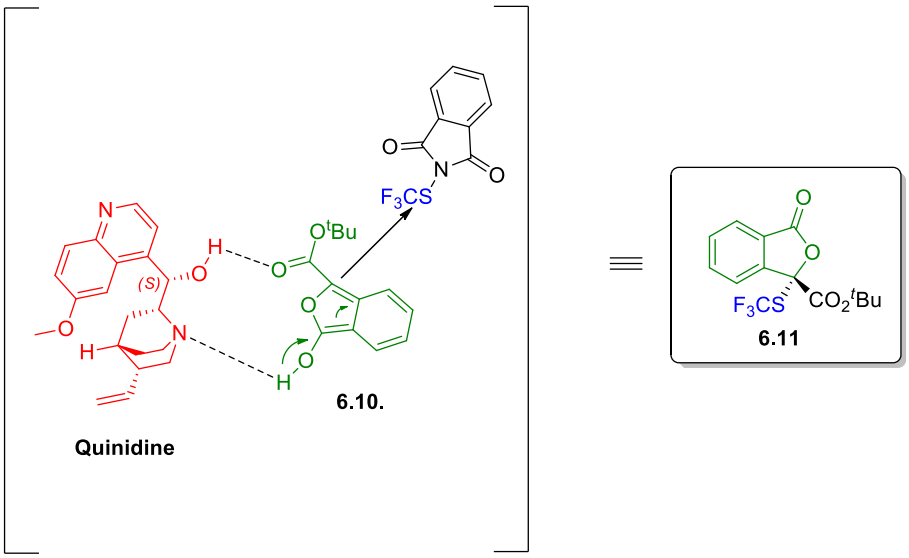


Figure 6.2. Structure of organocatalysts reported in **Table 6.1**

The catalyst that gave the best result is quinidine-**Q2**, both in **Entry 2** and in **Entry 5** an er = 76:24 but in **Entry 2**. the reaction involves a higher yield and a lower quantity of catalyst (10 mol%). The use of thiourea-based catalysts produces very low er (**Entry 3**). Unfortunately, using quinine-**Q1** with the same conditions of **Entry 2** no reaction was observed. Other studies are ongoing to improve the enantioselectivity of the process.

The proposed mechanism for this reaction recalls the *Li and Cheng mechanism* for the functionalization of phthalides with quinine-thiourea based maleimides (**Scheme 6.5.**).[124]

In this mechanism, where quinidine is used as a catalyst as it has given the best results, it is possible to see how the hydrogen of the OH group forms H bonds with the substrate, while the quinuclidinic nitrogen exhibits Brønsted base behavior going to tear a proton from the enol, restoring the aromaticity of the system. This coordination makes the carbon in 3 position highly nucleophilic, easily taking the trifluoromethyltio group from the donor. The most interesting result was obtained with quinidine in 20 mol%, reaching an enantiomeric ratio of 76:24.



Scheme 6.3. Proposed mechanism for the α-trifluoromethylthiolation reaction of compound **6.10**.

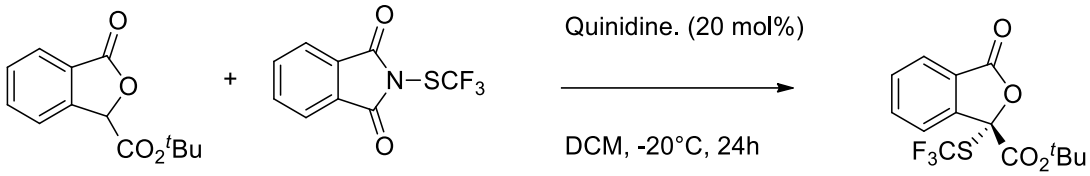
6.3. Considerations on the α-trifluoromethylthiolation of 3-EWG phthalides

Thanks to the results obtained by Prof. Dr. Waser on the α-trifluoromethylthiolation of 3-EWG isoindolinones,[116] were tested the same conditions for the α-trifluoromethylthiolation of 3-EWG phthalides. However, these conditions led only to the formation of racemic mixtures. Employing a different catalytic system, e.g. the bifunctional organocatalysts belonging to the cinchona alkaloid family, very interesting preliminary results were obtained in terms of yield and enantiomeric excesses. Future studies will address the widen of substrates, as well as class of catalysts (Epiquinidine and so on) and decreasing the amount of the latter (less than 10 mol%).

6.4. Experimental Part

tert-butyl 3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**num**) was prepared according to literature.[123]

Procedure of α-Trifluoromethylthiolation of 3-EWG phthalides



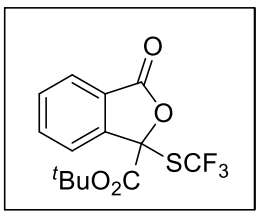
6.7. **6.8.** **6.9.**

Scheme 6.S1. α-trifluoromethylthiolation reaction of 3-EWG phthalides, **6.9**

Tert-butyl 3-oxo-1,3-dihydroisobenzofuran-1-carboxylate **6.10.** (0.10 mmol), SuccN-SCF_3 reagent **6.8.** (0.12 mmol) and quinidine (20 mol%) were dissolved in the respective solvent and stirred at -20°C in refrigerator for 24h. After the solvent was concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (heptanes/EtOAc = 5/1) through a short column to yield pure **6.11**.

tert-butyl 3-oxo-1-((trifluoromethyl)thio)-1,3-dihydroisobenzofuran-1-carboxylate (6.9.)

White solid (92%,), M.p. 174-176 °C (from hexane/ethyl acetate). $[\alpha]_D^{24}$ (c = 1.00, $CHCl_3$) = -28.4°,



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.7 Hz, 1H), 7.88 – 7.66 (m, 3H), 1.49 (s, 9H). **HPLC:** (YMC-SB, n-hexane/IPA = 99/1, 0.5 mL/min, 10 °C) Retention times: t_{minor} = 16.5 min, t_{major} = 17.9 min.

Chapter 7. Conclusions

This doctoral thesis work has addressed different topics, with the common motif of the search and the development of new one-pot, cascade and multicomponent reactions that allow the easy access to heterocyclic compounds with potential pharmaceutical interest.

In **chapter 3**, the synthesis of 3,3-disubstituted isoindolinones through one-pot cascade reaction involving variously substituted 2-cyanobenzophenones and carbon and hetero-nucleophiles was investigated. It has been seen that this reaction shows a wide applicability for different substrates, tolerating a great variety of functional groups and a great diversity of nucleophiles, both carbon and heteronucleophiles.

Subsequently, during a period of study at the LMU in Munich under the supervision of PD. Dr. Armin OFIAL, the electrophilicity parameter of 2-cyanoacetophenone was quantitatively studied through the Mayr equation, **log $k_{20°C}$ = sN*(N+E)**, through UV-Vis kinetical studies. The calculated electrophilicity parameters allowed us to establish which combinations between electrophiles and nucleophiles could give the best reactivity.

Subsequently, thanks to these studies, it was seen that chloromethyl aryl sulfones are excellent carbon nucleophiles in combination with 2-cyanoacetophenones, giving one-pot cascade reactions to obtain 3,3-disubstituted isoindolinones in quantitative yields. In addition, the use of 2-cyanobenzaldehydes as electrophiles, led to get 3-methyleneisoindolin-1-ones because of a further β-elimination reaction following the cascade process. It should be emphasized that this type of molecule had never been obtained under mild basic reaction conditions such as these reported. These compounds possess excellent optical properties which make them widely used as fluorescent biomarkers in medicinal chemistry as well as being fundamental intermediates for the synthesis of Aristolactams.

In **chapter 5**, we focused on the use of 4-arylideneisoxazol-5-ones as Michael acceptors in 1,4-conjugated addition reactions. The problem of the rapid tautomeric equilibrium between the various forms of the Michael adduct was immediately highlighted, solved thanks to the idea of trapping the majority tautomer with an electrophilic agent. Firstly, we investigated an asymmetric organocatalyzed version of Michael reaction using di-alkyl malonates as carbon nucleophiles, bifunctional organocatalysts and carbon electrophiles as trapping agents. This catalytic system has allowed us to get excellent yields and good enantiomeric excesses, subsequently increased by crystallization. Furthermore, the multicomponent reactions (MCR) asymmetric organocatalyzed 1,4-conjugate additions at both three and four components were studied, affording moderate enantiomeric ratio.

Further Michael reactions between chloromethyl aryl sulfones and 4-arylidenisoxazol-5-one, followed by formal tautomer entrapping were developed, obtaining products of Michael addition/entrapping in high yields and high diastereomeric ratios. The second reactivity of Michael products was investigated in the presence of molybdenum hexacarbonyl. A one-pot four steps cascade reaction comprising deprotection, ring-opening of isoxazole-5-ones and decarboxylation was observed, leading to branched aliphatic ketones, never reported in the literature. Several control experiments, using enones as Michael acceptors, have shown that this type of synthesis proposed by us is the only possible synthetic way for the synthesis of the latter.

In the **chapter 6**, based on results obtained by Prof. Dr. Mario Waser on the α-heterofunctionalization of 3-EWG isoindolinones, preliminary promising results concerning the α-trifluoromethylthiolation of 3-EWG phthalides were obtained. After a preliminary screening under Waser's conditions, that give only purely racemic results, more encouraging results, changing the conditions of the system, in terms of yield and enantiomeric excess were reached.

References

[1] G. Brugnatelli (**1818**) "Sopra i cangiamenti che avvengono nell' ossiurico (ac. urico) trattato coll' ossisettonoso (ac. nitroso)" (On the changes that occur in uric acid (uric acid) treated with nitric acid (nitric acid)), *Giornale di Fisica, Chimica, Storia Naturale, Medicina, ed Arti, 2nd series*, 1 : 117-129. Brugnatelli called it ossieritrico (erythric acid) [p. 117].

[2] J.W. Döbereiner. Ueber die medicinische und chemische Anwendung und die vortheilhafte Darstellung der Ameisensäure. *Annalen der Pharmacie* **1832**, 3 (2), 141.

[3] F. F Runge. "Ueber einige Produkte der Steinkohlendestillation" [On some products of coal distillation]. *Annalen der Physik und Chemie*, **1834**,31 (5): 65.

[4] A. Kossel: Zur Chemie des Zellkerns. In: *Zeitschrift für physiologische Chemie* Band 7, **1882–1883**, S. 7.

[5] a) C. Lamberth. *Pest Manag Sci* **2013**, 69: 1106, b) M.D Delost, D.T. Smith, B.J. Anderson, J.T. Njardarson. *J. Med. Chem.* **2018**, 61, 10996.

[6] Northrop-Clewes CA, Thurnham DI. The discovery and characterization of riboflavin. *Ann Nutr Metab.* **2012**,61(3):224.

[7] Systematic review of the benzodiazepines. Guidelines for data sheets on diazepam, chlordiazepoxide, medazepam, clorazepate, lorazepam, oxazepam, temazepam, triazolam, nitrazepam, and flurazepam. Committee on the Review of Medicines. Br Med J. **1980** Mar 29,280(6218):910.

[8] M.G. Mazzucconi, R. Redi, S. Bernasconi, L. Bizzoni, F. Dragoni, R. Latagliata, C. Santoro, F. Mandelli. *Haematologica.* **2004** Nov,89(11):1306.

[9] M. Bhandari, A. Bhandari. *Pharm Methods*. **2011** Jan,2(1):3.

[10] F.R. Petronijevic, P. Wipf. *J. Am. Chem. Soc.* **2011**, 133, 7704.

[11] K. C. Nicolaou, H. Zhang, J. S. Chen, J. J. Crawford, L. Pasunoori. *Angew. Chem., Int. Ed.* **2007**, 46, 4704.

[12] F. da Silva, A. G. Fernandes, S. Thurow, M. L. Stivanin, I. D. Jurberg. *Synthesis* **2018**, 50, 2473.

[13] A. Znabet, M.M. Polak, E. Janssen, F.J.J. deKanter, n.j. Turner, R.V.A. Orru, E. Ruijter. *Chem. Commun*., **2010**, 46, 7918.

[14] A. Znabet, E. Ruijter, F.J.J. De. Kanter, V. Kohler, M. Helliwell, N.J. Turner, R.V.A Orru. *Angew. Chem., Int. Ed.*, **2010**, 49, 5289.

[15] C.G. Saluste, R.J.Whitby, M. Furber. *Angew. Chem., Int. Ed*., **2000**, 39, 4156.

[16] a) A. T. Balaban, D. C. Oniciu, A. R. Katritzky, *Chem. Rev.* **2004**, 104, 2777, b) M. A. P. Martins, W. Cunico, C. M. P. Pereira, A. F. C. Flores, H. G. Bonacorso, N. Zanatta. *Curr. Org. Synth.* **2004**, 1, 391, c) S. V. Druzhinin, E. S. Balenkova, V. G. Nenajdenko. *Tetrahedron* **2007**, 63, 7753.

[17] R.W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating. *Acc. Chem. Res*, **1996**, 29, 3, 123.

[18] J.-P. Wan, J. Zhou, H. Mao, Y.-J. Pan, A.-X. Wu. *Tetrahedron* **2008**, 64, 11115.

[19] J S. B. Nosachev, E. A. Tyrkova, A. G. Tyrkov. *Russ. J. Org. Chem.* **2009**, 45, 24.

[20] (a) P. A. Wender, M. P. Croatt, B. Witulski. *Tetrahedron* **2006**, 62, 7505, (b) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow. *Acc. Chem. Res.* **2008**, 41, 40, (c) P. A. Wender. *Nat. Prod. Rep.* **2014**, 31, 433.

[21] (a) B. M. Trost. *Science*, **1991**, 254, 1471, (b) B. M. Trost, *Angew. Chem., Int. Ed.,* **1995**, 34, 259.

[22] P. T. Anastas, J. C. Warner. *Green Chemistry*: Theory and Practice, Oxford University Press, New York, **1998**.

[23] A. Hantzsch. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1637.

[24] L. F. Tietze, U. Beifuss *Angew. Chem. Int. Ed*. **1993**, 32, 131.

[25] R. Robinson. *J. Chem. Soc., Trans.,* **1917**, 762.

[26] a) W. S. Johnson, M. B. Gravestock, B. E. McCarry. *J. Am. Chem. Soc*., **1971**, 93, 4332. b) K. C. Nicolaou, N. A. Petasis, R. E. Zipkin, J. Uenishi. *J. Am. Chem. Soc*., **1982**, *104*, 5555. c) S. Piettre, C. H. Heathcock. *Science*, **1990**, *248*, 1532.

[27] W. Watson. *Org. Process Res. Dev*., **2012**, 16, 1877.

[28] P. S. Mahajan, J. P. Mahajan, S. B. Mhaske. *Synth. Commun*. **2013**, 43, 2508.

[29] Y. Hayashi.*Chem. Sci*., **2016**, 7, 866.

[30] (a) P. M. Pihko. *Hydrogen Bonding in Organic Synthesis*, Wiley-VCH: Weinheim **2009**, (b)M. S. Taylor, E. N. Jacobsen. *Angew. Chem. Int. Ed.* **2006**, 45, 1520, (c) X. You,W. Wang. *Chem. Asian. J.* **2008**, 3, 516.

[31] (a) M. C. Etter, Z. Urbañczyk-Lipkowska, M. Zia-Ebrahimi, T. W. Panunto. *J. Am. Chem. Soc.* **1990**, 112, 8415, (b) M. C. Etter. *Acc. Chem. Res.* **1990**, 23, 120, (c) M. C. Etter. *J. Phys. Chem.* **1991**, 95, 4601.

[32] (a) J. F. Blake, W. L. Jorgensen. *J. Am. Chem. Soc.* **1991**, 113, 7430, (b) J. F. Blake, D. Lim, W. L. Jorgensen. *J. Org. Chem.*, **1994**, 59, 803.

[33] H. Hiemstra, H. Wynberg *J. Am. Chem. Soc.* **1981**, 103, 417.

[34] E. S. Choong, *Cinchona Alkaloids in Synthesis and Catalysis*, **2009** WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

[35] M. G. Núñez, A. J. M. Farley, D. J. Dixon. *J. Am. Chem. Soc.* **2013**, 135, 16348.

[36] W. Xiao, Z. Zhou, Q.-Q. Yang, W. Du, Y.-C. Chen. *Adv. Synth.Catal.* **2018**, 360, 3526.

[37] F. Romano, A. Di Mola, L. Palombi, M. Tiffner, M. Waser, A. Massa. *Catalysts* **2019**, 9, 327.

[38] T. D. Heightman. *J. Med. Chem.***2021**, 64(16), 12286.

[39] R. K.Dempster, L. B. Hutcherson, F. A. Luzzio. *From Abstracts, 42nd Central Regional Meeting of the American Chemical Society*, Indianapolis, IN, United States, June 8-10, **2011**, CERM-243.

[40] S. Ito, Y. Hirata, Y.Nagatomi, A. Satoh, G. Suzuki, T. Kimura, A. Satow, S. Maehara, H. Hikich, M. Hata. *Bioorg. Med. Chem. Lett.* **2009**, 19(18), 5310.

[41] L. Chen, Z. Yun-Xiang. *Adv. Synth. Catal.* **2021**, *363*, 1.

[42] X. Yu, A. Lu, Y. Wang, G. Wu, H. Song, Z. Zhou, C. Tang. *Eur. J. Org. Chem*. **2011**, 892.

[43] H. Neumann, D. Strubing, M. Lalk, S. Klaus, S.Hubner, A. Spannenberg, U. Lindequist, M. Beller. *Org. Biomol. Chem.,* **2006**, 4, 1365.

[44] S. Sharma, E. Park, J. Park, I.S. Kim. *Org. Lett.* **2012**, 14, 906.

[45] (a)Y. Kato, H. Ebiike, K. Achiwa, N. Ashizawa, T. Kurihara, F. Kobayashi. *Chem. Pharm. Bull*. **1990**, 38, 2060. (b) Y.Kato, M. Takemoto, K. Achiwa. *Chem. Pharm. Bull.* **1999**, 47, 529. (c) H. M. Botero, C. Tränkle, K. Baumann, R. Pick, E. Mies-Klomfass, E. Kostenis, K. Mohr, U. Holzgrabe, *J. Med. Chem.* **2000**, 43, 2155. (d) S. Omura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya,, H. Tsuchiya, Y. Takahashi,, R. J Masuma,. *Antibiot.* **1977**, 30, 275.

[46] J.Tang, P.Sivaguru, Y. Ning, G.Zanoni, X. Bi *Org. Lett.* **2017**, 19, 4026.

[47] M. C. Reddy, M. Jeganmohan. *Chem. Sci.* **2017**, 8, 4130.

[48] M. C. Reddy, M. Jeganmohan. *Org. Lett.* **2014**, 16, 4866.

[49] A. Di Mola, M. Di Martino, V. Capaccio, G.Pierri, L. Palombi, C. Tedesco, A. Massa *Eur. J. Org. Chem.* **2018**, 1699.

[50] A. Di Mola, A. Macchia, C. Tedesco, G. Pierri, L. Palombi, R. Filosa, Massa, A. *ChemistrySelect*, **2019**, 4(17), 4820.

[51] a)D-L. Zhu, Q. Wu, D. J. Young, H. Wang, Z.-G. Ren, H.-X. Li *Org. Lett.* **2020,** 22(17), 6832; b) A. Nagaki,K. Sasatsuki, S. Ishiuchi, N. Miuchi, M. Takumi, J. Yoshida. *Chem. Eur. J.* **2019**, 25, (19), 4946.

[52] N. Miyaura, K.Yamada, A. Suzuki. *Tetrahedron Letters.* **1979** 20 (36), 3437.

[53] a)A. Wohl. *Berichte der deutschen chemischen Gesellschaft*. **1919**, 52: 51. b) K. Ziegler, G. Schenck, E. W. Krockow, A. Siebert, A. Wenz, H. Weber. *Justus Liebig's Annalen der Chemie*, **1942,** 551: 1, c) Djerassi. *Chem. Rev*. **1948**, 43, 2, 271.

[54] a) K. Kobayashi, T. Shiokawa, H. Omote, K. Hashimoto, O. Morikawa, H. Konishi. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1126. b) G. W. Ebert, R.D Rieke. *J. Org. Chem.* **1988**, *53*, 4482.

[55] K.Kobayashi, K. Hashimoto,T. Ukon, S. Fukamachi, O. Morikawa, H. Konishi *Synthesis* **2008**, 4, 584.

[56] S. S. Mochalov, A.N. Fedotov, E. V. Trofimova, N.S. Zefirov. *Russ. J. Org. Chem.,* **2018**, 54, 403.

[57] H. Neumann, A. Brennfuhrer, M. Beller *Chem. Eur. J*. **2008**, 14, 3645.

[58] S. Guo, Q. Zhang, H. Li, H. Guo, W. He. *Nano Research*, **2017**, 10, 3261.

[59] a) X. Yu, Y. Wang, G. Wu, G. H. Song, H. Z. Zhou, C. Tang. *Eur. J. Org.Chem.* **2011**, 3060. b) M. U. Chen, Q. A. Chen, Y. Duan,, Z. S. Ye, Y. G. Zhou. *Chem. Commun.* **2012**, *48*, 1698, c) T. Nishimura, A.Noishiki, Y. Ebe, T. Hayashi. *Angew. Chem. Int. Ed.* **2013**, *52*, 1777, d) J. Q. Zhou, W. J. Sheng, J. H. Jia, Q. Ye, J. R. Gao, Y. X. Jia. *Tetrahedron Lett.* **2013**, *54*, 3082, e) J. Suć, I. Dokli, M. Gredicak. *Chem. Commun.* **2016**, *52*, 2071, f) A. Suneja, R. A. Unhale, V. K. Singh. *Org.Lett.* **2017**, *19*, 476, g) X. H. Chen, Q. Wei, S. W. Luo, H. Xiao, L. Z.Gong. *J. Am. Chem. Soc.* **2009**, *131*, 13819, h) Y. C. Wang, J. L.Wang, K. S. Burgess, J. W. Zhang, Q. M. Zheng, Y. D. Pu, L. Y. Yan, X. B. Chen. *RSC Adv.* **2018**, *8*, 5702.

[60] L. Zhang, G. Yean, S. Chiba *Org. Lett.* **2011**, 13, 1622. b) T. Tou, Y. Yoshimi, T. Morita, Y. Tokunaga, M. Hatanaka. *Tetrahedron* **2009**, 65, 263.

[61] C. Y. Hao, D. Wang, Y. W. Li, L. L. Dong, Y. Jin, X. R. Zhang, H. Y. Zhu, S.Chang *RSC Adv.* **2016**, 6, 86502.

[62] R. Isaacs, C.J. Dinsmore, C.J. McIntyre, L.S. Payne, D.A. Claremon, *PCT Int. Appl.* (**2005**), WO 2005030727 A1 20050407

[63] K. Kobayashi, T. Shiokawa,H. Omote,K. Hashimoto,O. Morikawa, H. Konishi. *Bull. Chem. Soc. Jpn.* **2006**, 79, 1126.

[64] D. Glavac, I. Dokli, M. Gredicak. *Curr. Org. Chem*, **2017**, 21**,** 1335.

[65] T. Nishimura, A. Noishiki, Y. Ebe and T. Hayashi, *Angew. Chem., Int. Ed*. **2013**, *52*, 1777.

[66] 1. Bruker. APEX3, SAINT and SADABS. Bruker AXS Inc, Madison, Wisconsin, USA, **2015**.

[67] G. M. Sheldrick. *Acta Cryst*. **2008**, A64, 112.

[68] G. M. Sheldrick. *Acta Cryst*. **2015**, C71, 3.

[69] O. V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A. Howard, H. J. Puschmann. *Appl. Cryst.* **2009**, 339.

[70] G. Swain, C. B. Scott. *J. Am. Chem. Soc.* **1953**, 75, 141.

[71] a) J. O. Edwards. *J. Am. Chem. Soc*. **1954**, 76, 1540, b) J. O. Edwards, *J. Am. Chem. Soc.* **1956**, 78, 1819, c) J. O. Edwards, R. G. Pearson, *J. Am. Chem. Soc.* **1962**, 84, 16.

[72] C. D. Ritchie. *Acc. Chem. Res.* **1972**, 5, 348.

[73] H. Mayr, M. Patz. *Angew. Chem. Int. Ed.* **1994**, 33, 938.

[74] Z. Li, R.J. Mayer, A. R. Ofial, H. Mayr. *J. Am. Chem. Soc.* **2020**, 142, 8383.
[75] R. J. Mayer, P. W. A. Allihn, N. Hampel, P. Mayer, S. A. Sieber, A. R. Ofial. *Chem. Sci.* **2021**, *12*, 4850.
[76] A. Eitzinger, R. J. Mayer, N. Hampel, P. Mayer, M. Waser, A. R. Ofial,. *Org. Lett.* **2020**, *22*, 2182.
[77] R. J. Mayer, N. Hampel, P. Mayer, A. R. Ofial, H. Mayr. *Eur. J. Org. Chem.* **2019**, 412.
[78] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A.R. Ofial, G. Remennikov, H. Schimmel. *J. Am. Chem. Soc.* **2001**, 123, 39, 9500.
[79] Z. Li, H. Jangra, Q. Chen, P. Mayer, A.R. Ofial, H. Zipse, H. Mayr. *J. Am. Chem. Soc.* **2018**, 140, 5500.
[80] H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, 36, 66.
[81] A.Macchia, F.F. Summa, A. Di Mola, C. Tedesco, G. Pierri, A.R. Ofial, G. Monaco, A. Massa. *J. Org. Chem.* **2021**, 86, 21, 15128.
[82] a) A. Massa, P. Roscigno, P. De Caprariis, R. Filosa, A. Di Mola. *Adv. Synth. Catal*., **2010**, 352, 3348, b) V.More, A. Di Mola, M. Perillo, P. De Caprariis, R. Filosa, A. Peduto, A. Massa. *Synthesis*, **2011**,18, 3027, c) V. More, R. Rohlmann, O. García Mancheño, C. Petronzi, L. Palombi, A. De Rosa, A. Di Mola, A. Massa. *RSC Advances* **2012**, 2, 3592.
[83] The conformation of 4a can be identified by the following threedihedral angles: θ1 ≡ Car−SO_2−CHCl−(C = O), θ2 ≡ Cl−C−C−O,and θ3 ≡O−C−Car−Car(C≡N), which can be described by the IUPACone-letter notation16 C, G±, A±, T (which is shorter than thecorresponding Klyne−Prelog notation17sp, sc±, ac±, ap). Dihedralangle θ2 must be antiperiplanar (T) for epoxide formation, while θ3must by synperiplanar (C) for the closure of the five-membered ring.
Starting from a set of conformers obtained by Confab,18 we have generated new conformers by changing the values of angles θ1 and θ2.The exclusion of duplicates and high energy candidates led to 9 conformers for (R,R)-4a and 11 conformers for (R,S)-4a. Geometries were optimized in the gas phase, and energies of species in solution were obtained by a single-point PCM calculation on the gas-phase-optimized energies. Minimum energy conformers for both configurations were then reoptimized by PCM.
[84] B. Roy, M.C. Reddy, P. Hazra. *Chem. Sci.* **2018**, 9, 3592.
[85] https://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/
[86] Z. Li, Q. Chen, P. Mayer, H. Mayr. *J. Org. Chem*. **2017**, 82, 2011.
[87] A. Di Mola, T. Caruso, P. De Caprariis, A. Massa. *ARKIVOC* (Gainesville, FL, United States), **2016** (4), 10.
[88] CCDC-2087404 contains the supplementary crystallographic data for this paper available free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures
[89] A. A. G. Fernandes, A. F. da Silva, S. Thurow, C. Y. Okada Jr, I. D. Jurberg, Targets in Heterocyclic Systems -Chemistry and Properties, Attanasi, O. A., Spinelli, D., Eds., *Italian Society of Chemistry*, Rome, **2018**, 22, 409.
[90] S. A. Laufer, S. Margutti. *J. Med. Chem*., **2008**, 51, 2580.
[91] Jurberg, I. D. *Chem. Eur. J.* **2017**, 23, 9716, J. Boivin, S. Huppé, S. Zard *Tetrahedron Lett*., **1996**, 37, 8735.
[92] a) Review: S. Z. Zard.*Chem. Commun.* **2002**, 1555, (b) S. L. Abidi. *J. Chem. Soc., Chem. Commun.* **1985**, 1222, (c) S. L. Abidi. *Tetrahedron Lett.* **1986**, 27, 267. (d) S. L. Abidi. *J. Org. Chem.* **1986**, 51, 2687. (e) E. J. Corey, W.L. Seibel, J.C. Kappos, *Tetrahedron Lett.* **1987**, 28, 4921. (f) J. Boivin, L. Elkaim, P.G. Ferro, S. Z. Zard. *Tetrahedron Lett.* **1991**, 32,5321.

[93] A. F. da Silva, A. A. G. Fernandes, S. Thurow, M. L. Stivanin, I. D. Jurberg. *Synthesis*, **2018**, 50, 2473.

[94] W. Xiao, Q.Yang, Z. Chen,Q. Ouyang, W. Du, Y. Chen *Org. Lett.* **2018**, 20, 236.

[95] Z. Ye, L. Bai, Y. Bai, Z. Gan, H. Zhou, T. Pan, Y. Yu, J. Zhou. *Tetrahedron* **2019**,75, 682.

[96] a) A. R. Katritzky, P. Barczynski, D.L. Ostercamp, T.I. Yousaf. *J. Org. Chem.* **1986**, 51, 4037, b) N. Jacobsen, H. Kolind-Andersen, J. Christensen. *Can. J. Chem.* **1984**, 62, 1940, c) E. Abignente, P. de Caprariis. *J. Heterocycl. Chem.* **1983**, 20, 1597.

[97] H. Kiyani, A. Kanaani, D. Ajloo, F. Ghorbani, M. Vakili. *Res. Chem. Intermed.*, **2014**, 41(10), 7739.

[98] A. Macchia, V.D. Cuomo, A. Di Mola, C. Tedesco, G. Pierri, L. Palombi, R. Filosa, A. Massa. *Eur. J. Org. Chem.* **2020**, 2264.

[99] S. E. Gibson, R. Gil, F. Prechtl, A. J. P. White, D. J. J Williams. *Chem. Soc., Perkin Trans* 1,**1996**, 1007-1013.

[100] A. Massa, R. Acocella, M. De Rosa, A. Soriente, R. Villano, A. Scettri. *Tetrahedron Lett.* **2003**, 44, 835.

[101] E.E. Galenko, S.A. Linnik, O.V. Khoroshilova, M.S. Novikov, A.F. Khlebnikov. *J. Org. Chem.* **2019**, 84, 11275.

[102] E.E. Galenko, M.A. Kryukova, M.S. Novikov, A.D. Khlebnikov. *J. Org. Chem.* **2021** *86* (9), 6888.

[103] R. C. F. Jones, S.H. Dunn, K. A. M. Duller. *J. Chem. Soc., Perkin Trans. 1*,**1996**, 1319-1321.

[104] a) M.Nitta, T. Kobayashi. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1401. b M.Nitta, T. Kobayashi. *J. chem. soc, chem. commun.* **1982,** 877. c) R.C.F. Jones, G. Bhalay, P. A. Carter. *J. Chem.* SOC., *Perkin Trans. I* **1993,** 1715.

[105] C.S. Li, E. Lacasse. *Tetrahedron Lett.*, **2002**, 43, 3565.

[106] S. Cicchi, A. Goti, A. Brandi, A. Guarna, F. De Sarlo. *Tetrahedron Lett.*, **1990**, 31,3351.

[107] G. K. Tranmer, W. Tam. *Org. Lett.* **2002**, 4, 4101.

[108] M. Mirzazadeh, G. H. Mahdavinia. *E-Journal of Chemistry*, **2012**, 9(1), 425.

[109] Bruker (**2015**). APEX3, SAINT and SADABS. Bruker AXS Inc, Madison, Wisconsin, USA

[110] G. M. Sheldrick *Acta Cryst.* A64, **2008**, 112.

[111] G. M. Sheldrick *Acta Cryst. C71*, **2015**, 3.

[112] a) P. Shah, A. D. Westwell. *J. Enzyme Inhib. Med. Chem*. **2007**, 22, 527, b) J. P. Bégué, D. Bonnet-Delpon. *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley: Hoboken, NJ, **2007**, pp 1−365, c) S.Purser, P. R. Moore, S. Swallow, V.Gouverneur. *Chem. Soc. Rev*. **2008**, 37, 320, d) W. K. Hagmann. *J. Med. Chem.* **2008**, 51, 4359.
(g) T. Yamazaki, T. Taguchi, I. Ojima. *In Fluorine in Medicinal Chemistry and Chemical Biology*, Ojima, I., Ed., Wiley-Blackwell, Chichester, U.K., **2009** pp 1−46.

[113] H. J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl. Fluorine in medicinal chemistry. *ChemBioChem* **2004**, 5, 637.

[114] (a) D. O'Hagan, *Chem. Soc. Rev.* **2008**, 37, 308. (b) L. Hunter. *Beilstein J. Org. Chem.* **2010**, 6, 38.

[115] K. Müller, C. Faeh, S. Diederich. *Science* **2007**, 317, 1881.

[116] A. Eitzinger, J. Otevrel, V. Haider, A. Macchia, A. Massa, K. Faust, B. Spingler, A. Berkessel, M. Waser. *Adv. Synth. Catal.* **2021**, 363,1955.

[117] M. Sicignano, R. I. Rodríguez, V. Capaccio, F. Borello, R. Cano, F. De Riccardis, L. Bernardi, S. Díaz-Tendero, G. Della Sala, J. Alemán. *Org. Biomol. Chem.* **2020**, 18(15), 2914.

[118] V. Capaccio, M. Sicignano, R.I. Rodríguez, G. Della Sala, J. Alemán. *Org. Lett.* **2020**, 22(1), 219.
[119] T. Xiao, L. Li, G. Lin, Z. Mao, L. Zhou. *Org. Lett*. **2014**, 16, 3380.
[120] W. Liu, Z.P. Hu, Y,Yan, W. Liao. *Tetrahedron Lett.* **2018**, 59, 3132.
[121] J. Luo, H. Wang, F. Zhong, J. Kwiatkowski, L. Xu, Y. Lu. *Chem. Commun.*, **2012**, 48, 4707.
[122] J. Luo, H. Wang, F. Zhong, J. Kwiatkowski, L. Xu, Y. Lu. *Chem. Commun.*, **2013**, 49, 5775.
[123] M. Sicignano, R. Schettini, G. Pierri, M. L. Marino, I. Izzo, F. De Riccardis, L. Bernardi, G. Della Sala. *J. Org. Chem.* **2020**, 85, 11, 7476.
[124] J. Wang, X. Li, J.P. Cheng. *Sci China Chem.*, **2019**, 62, 649.