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Sustainability and innovation of catalytic processes for the synthesis and transformation of heterocyclic systems of biological interest

PhD thesis of
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Abstract

Functionalized heterocycles represent one of the most widespread structural motifs found in both molecules of natural origin and in synthetic compounds exhibiting diverse activities across biological, pharmacological, agrochemical fields, and as materials endowed with different properties.

For these reasons, the demand for new, cleaner, and sustainable processes for the syntheses of heterocyclic compounds is continually increasing, as the known heterocyclic-forming reactions are often expensive, wasteful, and produce by-products. Among the modern synthetic methods, transition-metal catalysed reactions have emerged as a powerful and efficient tool for constructing a variety of heterocycle rings, resulting in shorter reaction times and higher yields when compared to other well-known methods reported in literature.

On these bases, the project proposed herein studies and develops synthetic strategies for heterocycles, based on different transition-metals *i.e.* copper, platinum, ruthenium, alongside organocatalysis and metal-free reactions. The involved reactions aim to be innovative, leading to sustainable, green, and cost-efficient preparation of this important class of compounds.

Contents

Abbreviation List

AE	Atom Economy
APIs	Active Pharmaceutical Ingredients
BPhen	Bathophenanthroline
BQ	Benzoquinone
COSY	Correlation Spectroscopy
CPA	Chiral Phosphoric Acids
CPME	Cyclopentyl methyl ether
DCE	Dichloroethane
DCM	Dichloromethane
DMAD	Dimethyl acetylenedicarboxylate
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DSI	Disulfonimide
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EW	Electron-withdrawing
e.r.	Enantiomeric ratio
FDA	Food and Drug Administration
Hex	Hexane
HSQC	Heteronuclear Single Quantum Coherence
IDP*i*	Imidodiphosphorimidates
IR	Infra-red
MeCN	Acetonitrile
Me-THF	2-Methyltetrahydrofuran
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy

Ph	Phenyl
PIDA	Phenyliodine(III) diacetate – $PhI(OAc)_2$
PIFA	Phenyliodine(III) bis-trifluoroacetate - $PhI(OCOCF_3)_2$
S.M.	Starting material
TBHP	tert-Butyl hydroperoxide
T.E.M.P.O.	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Ts	Tosyl
TS	Transition State

Introduction

The design and synthesis of poly-functionalized heterocycles have attracted significant attention due to their various applications in organic, bioorganic, and pharmacological fields.[1]

In particular, heterocycles bearing nitrogen atoms play a crucial role in life sciences, primarily because of their abundancy in nature, and since they serve as building blocks for a plethora of natural products *i.e.* alkaloids, hormones, antibiotics and vitamins.[2]

In 2014, an analysis of the database of *U.S.* FDA approved drugs, as reported by *Njardarson,* revealed that the 59% of the unique small-molecule drugs contain a nitrogen heterocycle. Furthermore, when considering the total number of the unique drugs, this percentage significantly increase to 84%.[3]

The distribution of aza-containing heterocycles revealed that six-membered rings are the most prevalent at 59%, followed by five-membered ones at 39%, highlighting the structural importance of nitrogen-based heterocycles in the field of drug design and drug discovery.

For these reasons, the increasing demand for novel aza-containing pharmaceutical compounds with enhanced efficiency and selectivity remains a necessity, prompting us to devise straightforward procedures to access to functionalized heterorings.

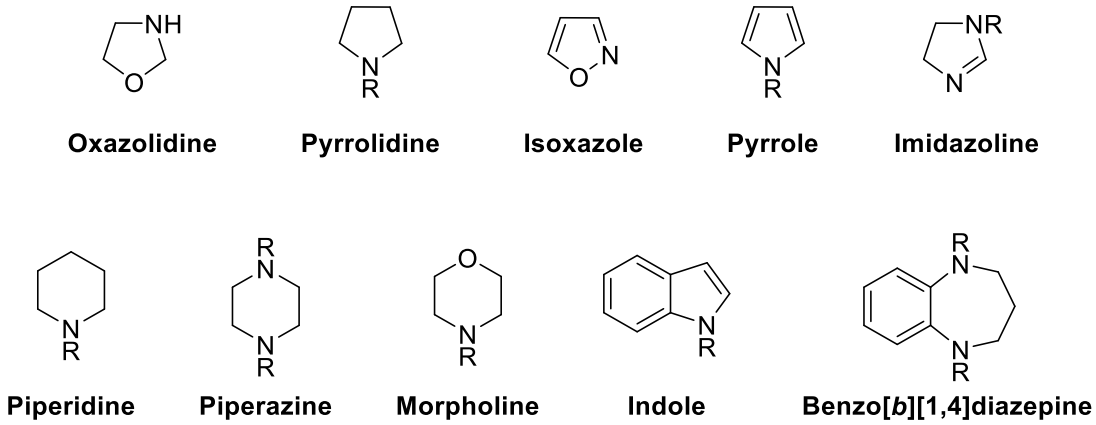


Fig.1.0 The most common *N*-containing heterocycles used in pharmaceuticals.

In general, heterocyclic chemistry provides useful tools to modulate polarity, solubility, and interactions in the reaction media, aiming to enhance physiochemical, pharmacological, and pharmacokinetic properties. As an example, in the field of drugs, we can mention the significant role of hydrogen bonds in aza-scaffolds as they increased physiological interactions, thereby carrying fundamental implications for bioactivity.[4]

These aspects underline the importance of alternative, cleaner and sustainable synthetic paths for heterocyclic compounds, representing a topic of considerable interest for the chemistry community and, in this domain, Green Chemistry plays an essential role.

Green Chemistry is defined as the "design of chemical products and processes to reduce or eliminate the use and the generation of hazardous substances". The principle of Green Chemistry demands for the development of new-chemical reactivities and conditions that could ideally enhance the efficiency of chemical synthesis with respect to resource and energy efficiency, selectivity, and simplicity of the reaction as well as environmental safety.[5]

In this direction, *Trost* introduced guidelines to assess the efficiency of chemical processes. In particular, the attention is focused on the importance of *atom-economy,* aiming to develop more sustainable synthetic pathways by reducing or eliminating the necessity to recycle undesirable by-products and maximizing the conversion of all the atoms involved in the process.[6]

These aspects have been incorporated into the "Twelve Principles of Green Chemistry" (**Fig 1.1**), which were developed by *Anastas* and *Warner* in the 1998, reflecting the efforts of chemists to achieve sustainability goals.

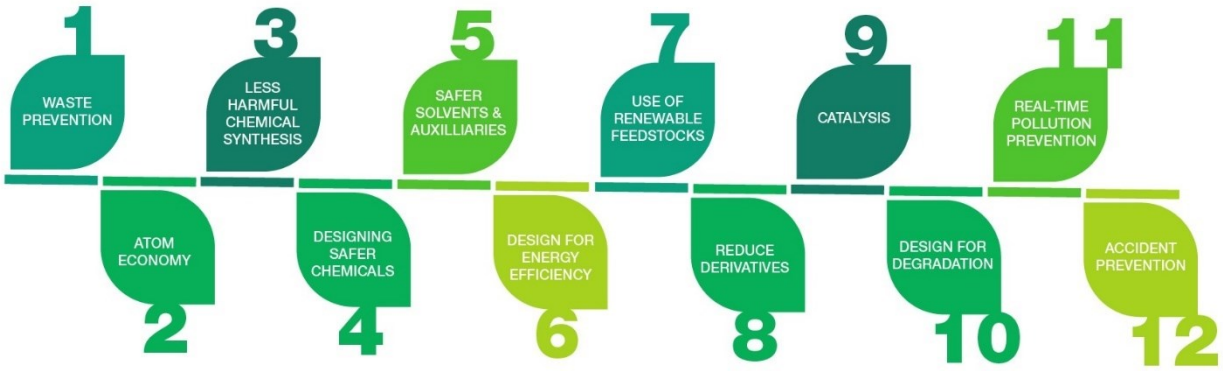


Fig 1.1 Twelve-Principles of Green Chemistry.[7]

"It is better to prevent waste that to treat or clean up waste after it has been created". As reported in the first principle of Green Chemistry, the most effective approach to address pollution is to prevent its generation.[8]

In the effort to effectively manage waste production, it becomes essential to establish metrics for its measurement. The 12 principles of Green Chemistry highlight two significant parameters for quantifying the waste: *E*-factor and the atom economy (AE).[9]

The *E(*nvironmental*)*-factor, as reported in the 1st principle, expresses the right amount of waste produced taking in account all the auxiliary component *i.e.* chemicals used for the work-up, the purification steps (silica, and solvent used) and solvents lost and its usually expressed in kgs/kg.

$$E\ factor = \frac{total\ mass\ of\ waste}{mass\ of\ product}$$

Eq. 1.1 Equation for the determination of the *E* factor.

In **Eq.1.1**, it is reported the equation for the determination of the *E*-factor; a higher value indicates a more significant environmental impact. As anticipated by the first principle of green chemistry, the ideal *E-factor* value is zero.

The atom economy (*AE*) is a theoretical way to measure what percentage of the atoms from the reactants end up in the desired product. Ideally, with an emphasis on waste prevention, the AE value should reach 100%.

$$AE(\%) = \frac{molecular\ weight\ of\ the\ product}{molecular\ weight\ of\ all\ reactants}\ x\ 100$$

Eq. 1.2 Equation for the determination of the atom economy.

However, the concept of Green Chemistry is not solved simply by satisfying mathematical formulas, there are numerous complexities involved. As example, replacing a toxic solvent with a benign one that decreases the efficiency of the process does not align with Green Chemistry because the primary objective is to ensure the maximum efficiency of the process. In particular, in the case of *Pharmaceutical Chemistry,* there is also a problem concerning the intellectual property that can preclude any innovation. The crucial aspect is to consider the environmental problems among the key points in the study of a synthetic process, implementing in that direction the synthetic paths compatible with the desired product.

In the field of sustainable synthetic processes, domino reactions have gained a significant position. As defined by *Tietze*, a domino reaction is a process in which two or more bond-forming transformations take place under the same reaction conditions without further addition of reagents or catalyst and where the nature of the product formed relies on the functionality generated in the previous steps.[10]

In an ideal scenario, the goals consist of achieving simplicity of the synthetic route, maximizing atom economy, utilizing readily available, low cost and environmentally friendly reagents, as well as obtaining high conversion and yields. From these perspectives, domino reactions fit perfectly;

furthermore, the increased synthetic efficiency of the procedure, especially through the reduction of the number of the laboratory operations required and the minimized amount of chemicals and solvents used, makes this methodology a "*green*" process.[11]

Among the various types of reactions that enable the achievement of domino processes, homogeneous catalysis promoted by transition metals play a prominent role.

It is widely recognized that in chemical synthesis, especially in the production of APIs (Active Pharmaceutical Ingredients) and fine chemicals, the use of stoichiometric quantities of both organic and inorganic reagents, particularly metals, constitute a significant source of waste. Consequently, driven by the necessity to minimize waste, there has been an increased focus over the past three decades on employing catalytic approaches.[8]

In the specific, as reported in the 9th principle of *Green Chemistry*, catalysis stands out as one of the most relevant and important tools to increase the sustainability of the processes since provides several advantages *i.e.* increased selectivity of the reaction.

In particular, the transition-metals catalysed reactions have proven to be a powerful and useful strategy for the construction of heterocyclic rings, resulting in several undoubted advantages compared to other methods, including the use of a great variety of starting materials, the mild reaction conditions, and low environmental impact.[12]

It follows that employing transition metals in domino reactions is a winning strategy. The literature has reported many examples of domino processes catalysed by metals. Other terms synonymous with "domino" are often used in the literature, such as cascade, tandem or also difunctionalization. In our work we opted to use the term difunctionalization because it appears more inclusive of all possible simultaneous or non-simultaneous processes involving more than one bond-forming reaction.

Aim of the thesis

During my PhD thesis, I was involved in several projects concerning the design and synthesis of diverse classes of heterocyclic compounds relevant to natural products, bioactive compounds, and drugs. The primary focus of my research was to develop optimal synthetic strategies for producing various-functionalized scaffolds, exploiting new reactivities while adhering to the *12 Principles of Green Chemistry* with particular attention on reducing environmental impact. This included efforts to decrease the number of synthetic steps, the reaction times and waste,[13] thus exploiting the reactivity of different catalytic systems.

For ease of reading, the thesis is divided in two main parts. The first part focuses on the study of transition-metal systems:

Chapter 1_ Copper catalysis

- 1.1 *One-pot* difunctionalization reactions
  - 1.1.1 Copper(II)-catalysed aminohalogenation of alkynyl carbamates
  - 1.1.2 Copper-catalysed cyclization in oxidative conditions
- 1.2 Methanol as C1 source for the synthesis of 1,3-polyheterocyclic systems

Chapter 2_Platinum catalysis

- 2.1 *One-pot* difunctionalization of terminal alkynes

Chapter 3_Ruthenium catalysis

- 3.1 Isoxazol-5-ones as a starting material for the synthesis of heterocyclic compounds
- 3.2 Rearrangement reactions of aromatic and heteroaromatic oximes

The second part refers to the organo-catalysis and the metal-free reactions:

Chapter 4_Organocatalysis

- 4.1 Catalytic enantioselective [3+2] cyclization reaction

Chapter 5_ Metal-free cyclization

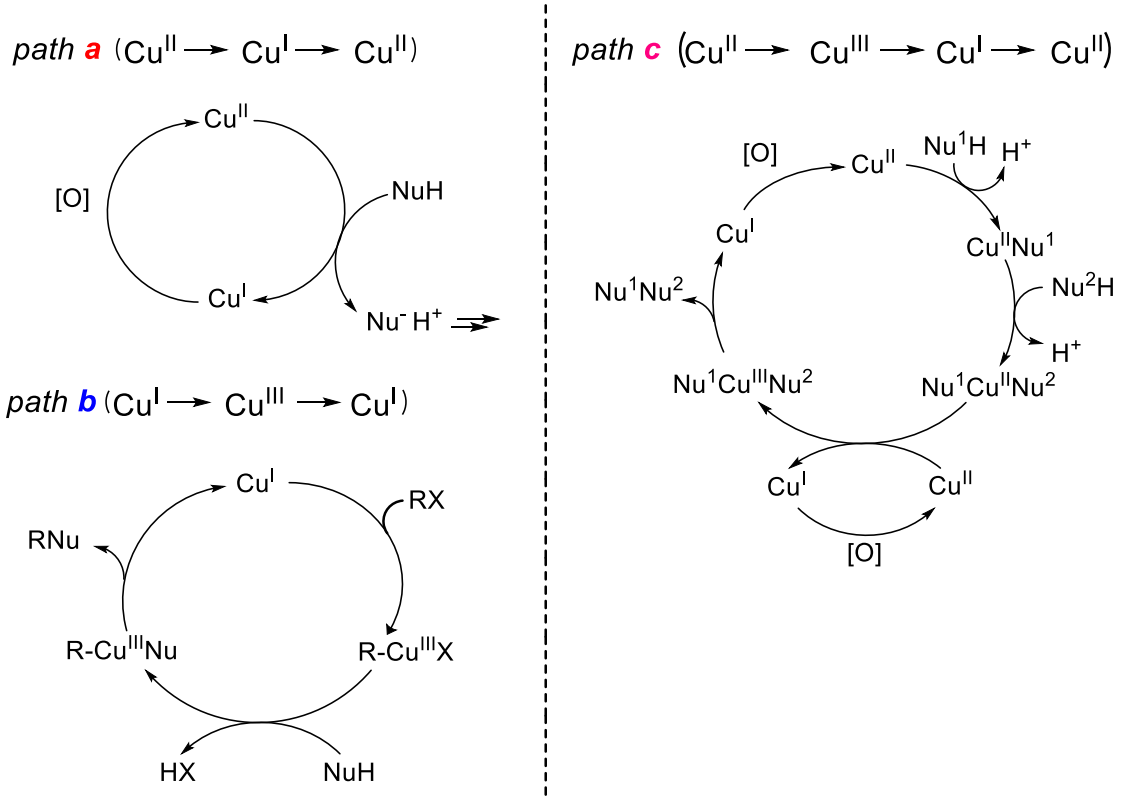
- 5.1 Synthesis of oxazolidine derivatives

Chapter 1_*Copper catalysis*

1.1 Introduction

In recent years, within the context of transition metal-catalysed reactions, there has been a renewed interest in copper catalysis. Compared to other precious transition-metal catalysts, copper is cost-effective, highly stable, and capable of tolerating numerous reactive functional groups. Additionally, it does not require strictly anaerobic and anhydrous conditions. For these reasons, its application in developing of new procedures for the synthesis of new C-C, C-O and C-N bonds has significantly increased.[14]

Copper is a multi-functional catalyst that can easily access the Cu(0), Cu(I), Cu(II), Cu(III) oxidative states. (**Scheme 1.1**) The pathway for copper-catalysed oxidations can involve single-electron transfer (**Scheme 1.1**, *path a*), two-electron process (**Scheme 1.1**, *path b*), or a cooperative combination of one- and two-electron processes (**Scheme 1.1**, *path c*). In addition, low valent copper species can be re-oxidized to oxidative states by O_2 or different oxidant agents.



Scheme 1.1 General reaction pathway of copper-catalysed oxidation reactions.

Overall, the majority of copper-catalysed couplings involves *Ullmann*-type reactions; consequently, the addition of heteroatoms *i.e.* N, O, S to C(sp^3)[15] or unsaturated carbon atoms *i.e.* alkene, alkynes and allenes[16] continue to be widely explored in synthetic procedures. As a result, copper catalysed oxidative processes represent a highly practical transformation methods and their use is also widespread in industrial synthesis.

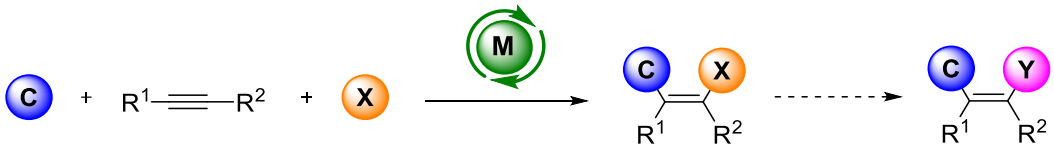
Copper (II)-catalysed aminohalogenation of alkynyl carbamates

1.2.1 Background

The development and study of direct difunctionalization reactions of C-C multiple bonds have significantly increased, emerging as a compelling approach to enhance reaction efficiency.[17]

This method offers advantages by enabling the synthesis of highly functionalized scaffolds through novel and efficient synthetic routes that are environmentally and economically favourable. The fascination regarding this type of reaction stems from the possibility of an intramolecular path, allowing the synthesis of cyclic compound from easily available substrates. Consequently, the synthesis of poly-functionalized heterocycles can be easily achieved, leading to a rapid increase in the structural complexity.[18]

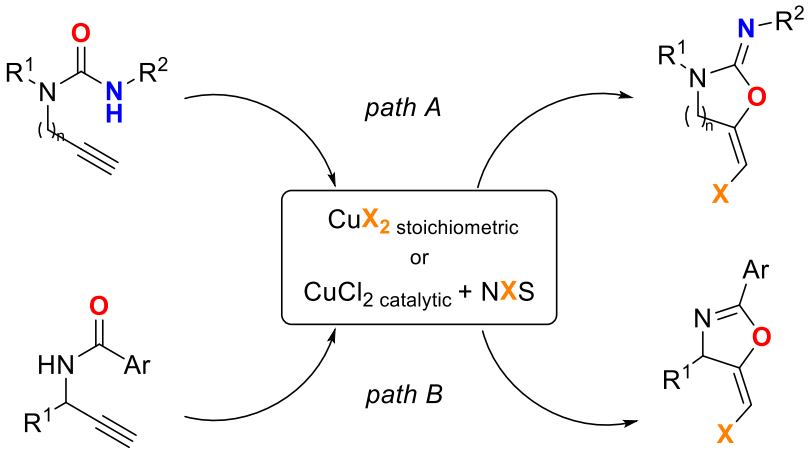
Beyond the potential for new functionalization, literature highlights the importance of halocyclization reactions.[19] The presence of an halogen allows further and easy functionalization, enabling the synthesis of more complex structures.



Scheme 1.2 Halocyclization reaction as tool to increase the functionalization.

In the presence of halogens, the copper catalyst is able to promote the synthesis of (poly)functionalized heterocyclic compounds from unsaturated substrate systems such as alkenes, alkynes, allenes. This leads to a rapid increase in the structural complexity through direct difunctionalization procedures.

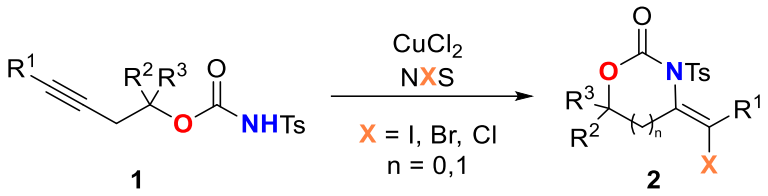
In this scenario, our research group published in 2015 the results regarding the studies of alkoxyhalogenation processes on alkynylureas (**Scheme 1.3**, *path A*) and alkynylamides (**Scheme 1.3**, *path B*), under copper catalysis. We exploited domino reactions for the synthesis of various halogen-substituted heterocycles through a completely selective *exo-dig* process.[20]



Scheme 1.3 Difunctionalization of alkynylureas (*path A*) and alkynylamides (*path B*).

1.2.2 Results and discussion

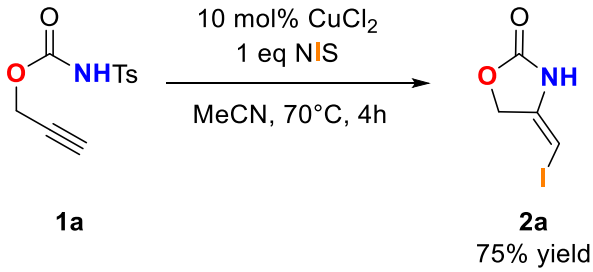
Continuing the focus on copper-catalysed reactions to produce functionalized heterocycles, we decided to investigate the reactivity of different substituted alkynylcarbamates **1** for the synthesis of five- and six-membered heterocyclic derivatives through an aminohalogenation process. (**Scheme 1.4**)



Scheme 1.4 Aminohalogenation processes on alkynylcarbamates.

The objective was to reproduce previously reported conditions, which had been already explored by our research group,[20] in an effort to obtain *N*-containing heterocycles of different sizes exploiting halocyclization for further functionalizations on the final products.

We began our investigation by evaluating the reactivity of simple *O*-alkynylcarbamates, testing our conditions on substrate **1a** (*N*-tosyl-*O*-propargylcarbamate), using $CuCl_2$ as catalyst and, in the presence of stoichiometric NIS as the halogen source. The reaction was performed in MeCN at 70 °C and allowed the isolation of the 4-iodomethylidene oxazolidinone **2a** in high yield (75% yield). The reaction led to the selective formation of the *E* isomer, determined by ^{1}H(NOESY) NMR experiment. (**Scheme 1.5**)



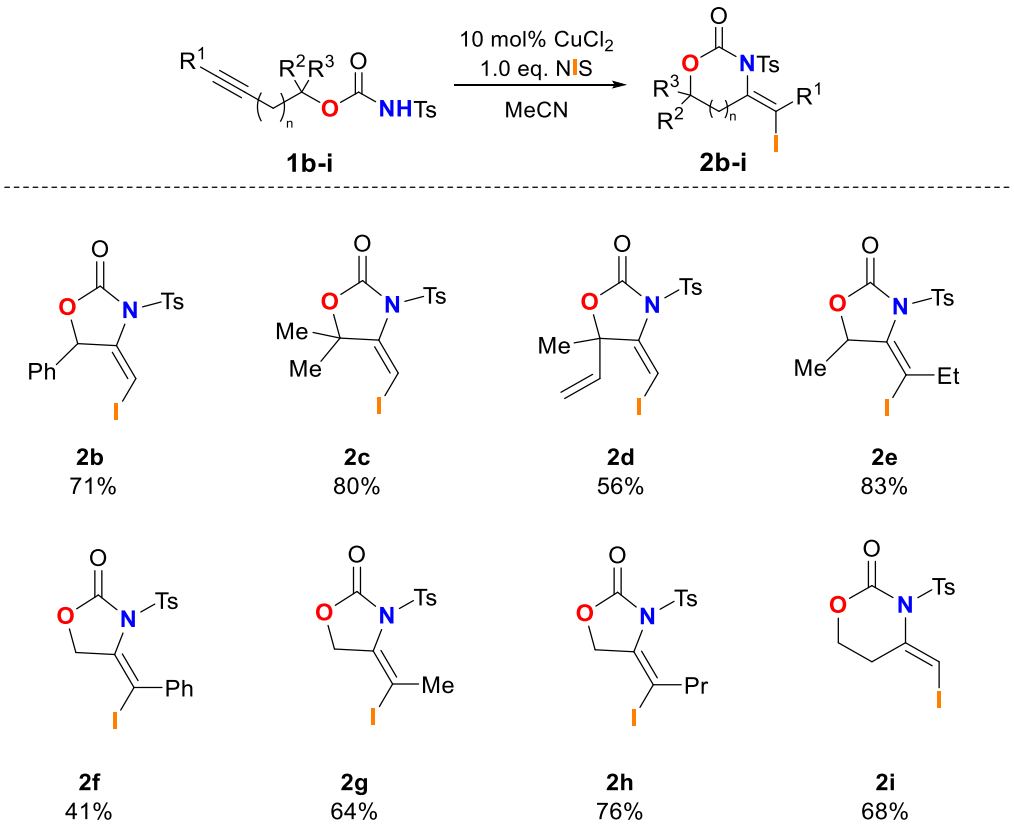
Scheme 1.5 Reaction performed of amino-iodination on substrate **1a**.

Having evaluate the applicability of our conditions on substrate **1a**, we continued by changing the substituent on the nitrogen atom of the alkynyl carbamates, as only the reactivity of the *N*-Ts derivative was tested.

We explored different *N*-arylcarbamates, to evaluate if different acidities of the *NH* group would lead to different outcome. Neither the presence *N*-phenyl, *N*-(4-nitro-phenyl) and *N*-(4-methoxy-phenyl)

derivatives resulted in the formation of the amino-halogenated product. Also performing the reaction with stoichiometric $CuCl_2$ did not allow the conversion of the starting material. We observed the formation of degradation products, beside unreacted substrate. Employing different solvent *i.e.* THF, DMF and DCE did not enhance the reaction outcomes.

Once the essential role of *N*-tosyl group was established, we exploited the extensibility of the amino-halogenation reaction by evaluating differently substituted *N*-tosyl-*O*-propynyl carbamates. (**Scheme 1.6**)



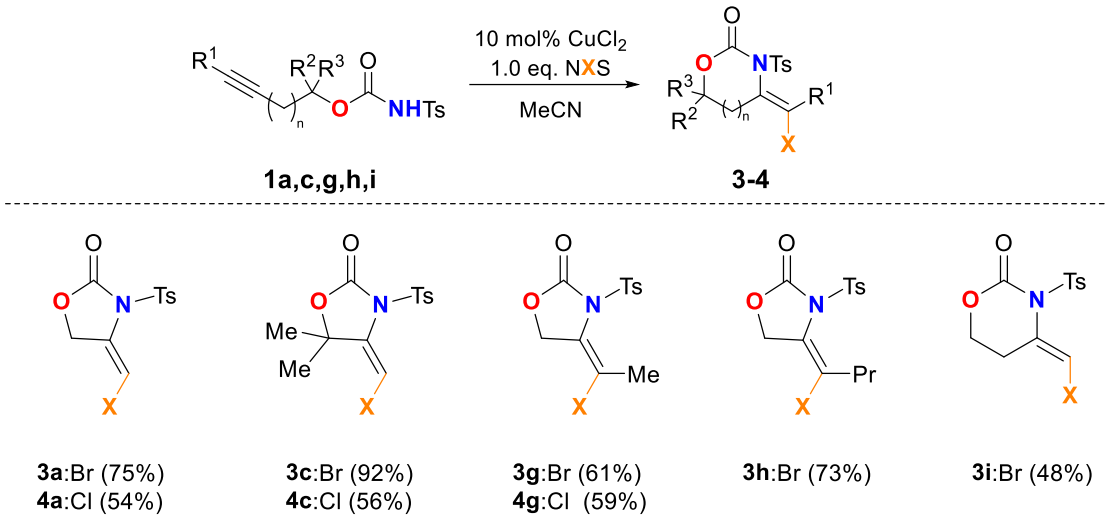
Scheme 1.6 Scope of the aminoiodination reactions.
Standard reaction conditions: **1b-i** (0.5 mmol), NIS (0.5 mmol), $CuCl_2$ (10mol%) in MeCN (10 ml).

The experiments showed the extendibility of this reaction strategy. As reported in **Scheme 1.6**, the presence of phenyl group in position α to the oxygen did not hinder the amino-iodination process, allowing the isolation of compound **2b** in high yield (71% yield). In a similar way, both α,α-disubstituted and terminal-substituted propargyl carbamates **1c-d**, **1e-h** underwent difunctionalization, through a *5-exo-dig* cyclization/iodination process; the efficiency of the reaction, in terms of isolated yield, depends on the nature of the substituent.

Having confirmed the effectiveness of these conditions for accessing five-membered rings, we also explored the possibility to obtain six-membered rings. For this purpose, butenyl carbamate **1i** was

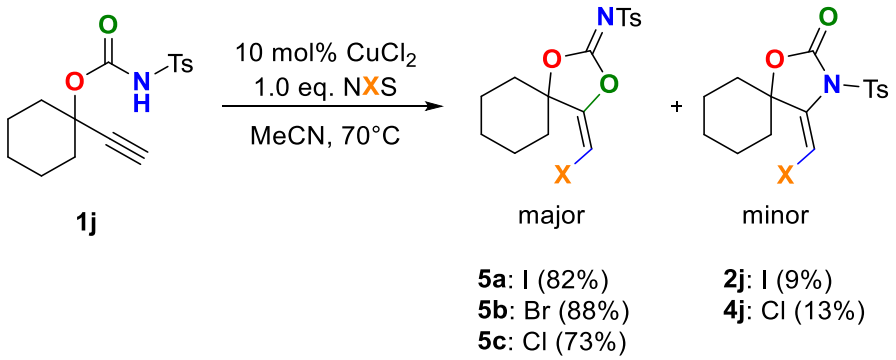
employed, resulting in the formation of a 1,3-oxazine derivative **2i** *via* a *6-exo-dig* amino-iodination process.

Following this positive outcome, we further explored other halosuccinimides as halogen source, resulting in the synthesis of the corresponding bromo- and chloro-derivatives (**Scheme 1.7**).



Scheme 1.7 Scope of bromo- and chloro-amination reactions.
Standard reaction conditions: **1a,c,g,h,i** (0.5 mmol), NXS (0.5 mmol), $CuCl_2$ (10mol%) in MeCN (10 ml).

In the attempt to expand the scope of the reaction, we tested bulkier substrates. In particular, we evaluated the reactivity of α,α-cyclohexyl-substituted propargyl carbamate **1j** under catalytic $CuCl_2$, in the presence of NXS in MeCN. Curiously, in this case we observed a different outcome in the cyclization step, in terms of the type of C-heteroatom bond formed. As reported in **Scheme 1.8**, we obtain as the major product the one arising from an alkoxyhalogenation process, with a final *E* configuration of the double bond.



Scheme 1.8. Cyclization/halogenation reaction on substrate **1j**.
Standard reaction conditions: **1j** (0.5 mmol), NXS (0.5 mmol), $CuCl_2$ (10mol%) in MeCN (10 ml).

Spectroscopic analytical data confirmed both the structures of major and minor products. In particular, NOESY experiments revealed a high NOE effect between the methylenic hydrogen atom and the *ortho*-H aromatic of the tosyl group of the structure **2j** (**Fig. 1.2**), confirming the oxazolidinic core and establishing the nature of compound **5**.

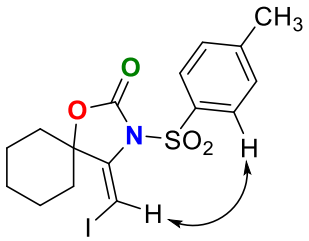


Fig 1.2 ^{1}H NOESY NMR experiment on **2j.**

Finally, X-ray analysis of compound **5a** confirmed the structure unequivocally. (**Fig 1.3**)

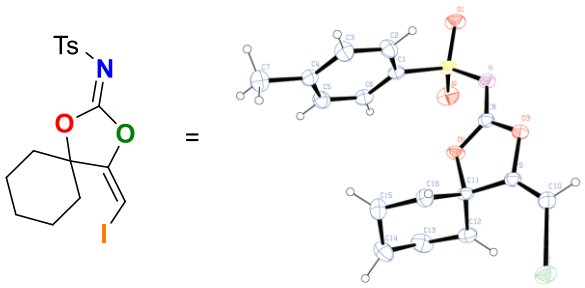


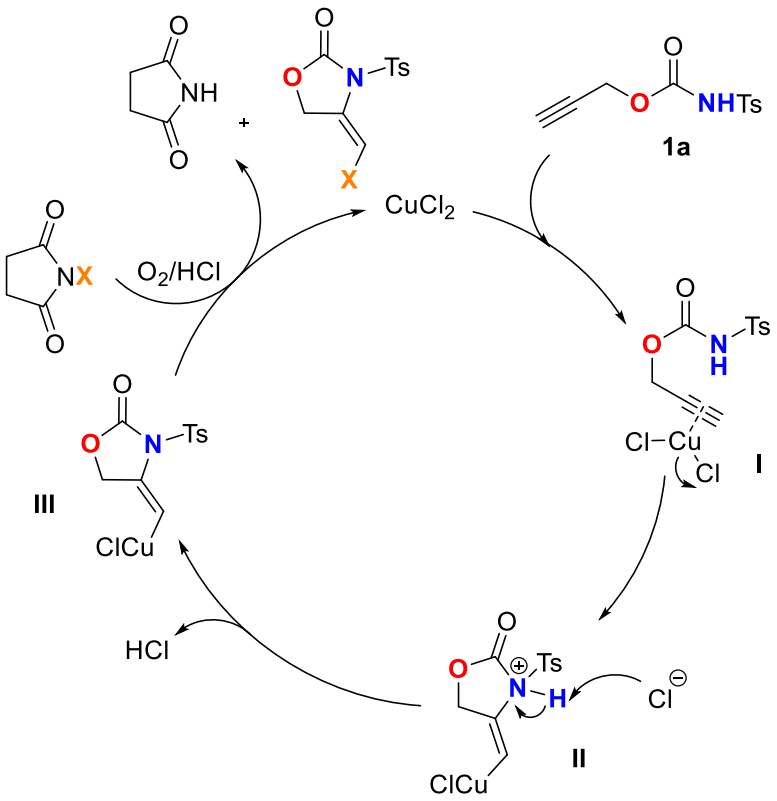
Fig 1.3 X-ray analysis of the compound **5a**.

To explain this behaviour, computational studies were performed in collaboration with Prof. *Contini* from Università degli Studi di Milano. In particular, the difference between the aminohalogenation and alkoxyhalogenation paths likely depended on the presence of the bulky substituent cyclohexyl on the carbon atom next to the oxygen. The bulky group hampered the nucleophilic approach on the internal triple bond. In this situation, the attack by the oxygen atom of the enolic form of the carbamate becomes more probable.

This anomalous behaviour appears to be an exception since experiment performed on *O*-(1-phenylpropinyl)-*N*-tosylcarbamate and *O*-(1-methyl-1-vinylpropinyl)-*N*-tosylcarbamate confirmed an exclusive amino-halogenation course.

To evaluate the mechanism of the reaction, we also performed few experiments in the presence of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxide). Using **1a** as reaction model substrate, we performed the reaction with stoichiometric amount of TEMPO, in the presence of both stoichiometric and catalytic amount of $CuCl_2$ and NIS as halogen source. In both cases the presence of this additive did not induce variations in the reaction path.

On the basis that no product was isolated performing the reaction in the absence of catalyst, a reaction mechanism is depicted in **Scheme 1.9**. We suggest an initial copper activation on the triple bond forming intermediate **I** followed by a nucleophilic attack from the nitrogen atom resulting in the copper substituted intermediate **II**. Next, the deprotonation step brings to the intermediate **III** which interacting with NXS providing the desired product with the regeneration of the catalyst through the action of oxygen.

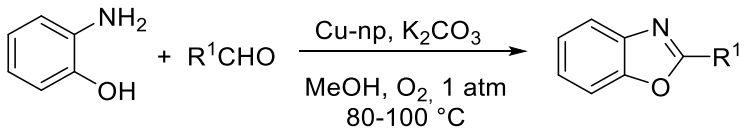


Scheme 1.9 Proposed mechanism on **1a** for the 5-*exo-dig* halo-cyclization.

Synthesis of benzoxazole derivatives and tetracyclic structures

1.3.1 Background

Several copper-catalysed reactions in combination with different oxidants[21] were reported in literature for the functionalization of unsaturated systems such as alkenes and alkynes. However, few studies exist regarding the use of hypervalent iodine(III) in the dual role of oxidant and as source of functional groups.[22] In this context, we have embarked on the study of electron-rich aromatic substrates, such as the *o*-aminophenols as suitable substrates to achieve benzoxazole nucleus. This heteroaromatic ring is of interest in natural and pharmaceutical compounds[23] as well as in organic materials for optical applications.[24] In the literature, one example of benzoxazoles synthesis is reported starting from 2-aminophenol in catalytic conditions.[25]



Scheme 1.10 Cu-Nanoparticles as efficient catalyst for the synthesis of 2-arylbenzoxazoles.

In this regard, we planned to investigate a copper-catalysed intramolecular alkoxylation reaction on *o*-aminophenols exploiting the reactivity of C(sp^3) carbon atom with the aim to easily obtain *N,O*-containing benzofused heterocycles. (**Fig 1.4**)

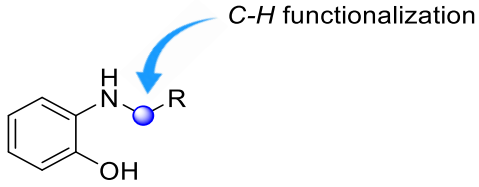
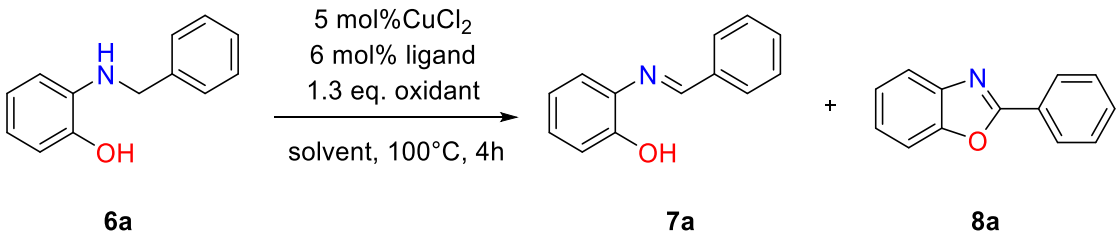


Fig. 1.4 C-H functionalization of C(sp^3) carbon atom.

1.3.2 Results and discussion

We used 2-(benzylamino)phenol **6a** as substrate to carry out preliminary experiments (**Scheme 1.11**) We first examined Cu(II) salts as catalyst, heating the reaction mixture at 100°C for 4h, screening different ligands, oxidants and solvents. (**Table 1.0**)



6a **7a** **8a**

Scheme 1.11 Reaction conditions: **6a** (1.0 mmol), $CuCl_2$ (5mol%), ligand (6mol%), oxidant (1.3 mmol), solvent (0.25M) heating at 100°C for 4h.

As shown in **Table 1.0** no remarkable outcome were obtained using Cu(II) catalysts; in most of the cases, beside the cyclization product obtained in low yield, we also observed the formation of the imine derivative.

Entry	Ligand	Oxidant	Solvent	Product (% yield)
1	---	---	Dioxane	**8a** (7)
2	---	BQ	Dioxane	**8a** (10)
3	---	BQ	Toluene	**7a** (15) + **8a** (15)
4	---	TBHP	Dioxane	**8a** (10)
5	1,10-phen	TBHP	Cl-benzene	**7a** (15) + **8a** (15)
6	8-OH-quin	TBHP	Toluene	**7a** (30) + **8a** (30)
7	---	TBHP	MeCN	**7a** (<5) + **8a** (17)
8	8-OH-quin	TBHP	MeCN	**7a** (<5) + **8a** (26)
9	---	H_2O_2	MeCN	---

Table 1.0 The yield values referred to the product **7a** are determined by ^{1}H-NMR spectrum, while for **8a** are reported the isolated yields.

Further screenings were conducted using CuCl and evaluating different reaction times. (**Table 1.1**) We observed that time is a crucial parameter for controlling the reaction. As expected, with short reaction times, we isolated, not only benzoxazole **8a**, but also the intermediate imine derivative **7a.**

However, when the reaction time was extended, we observed a decrease of yields, probably due to the degradation of the reagent.

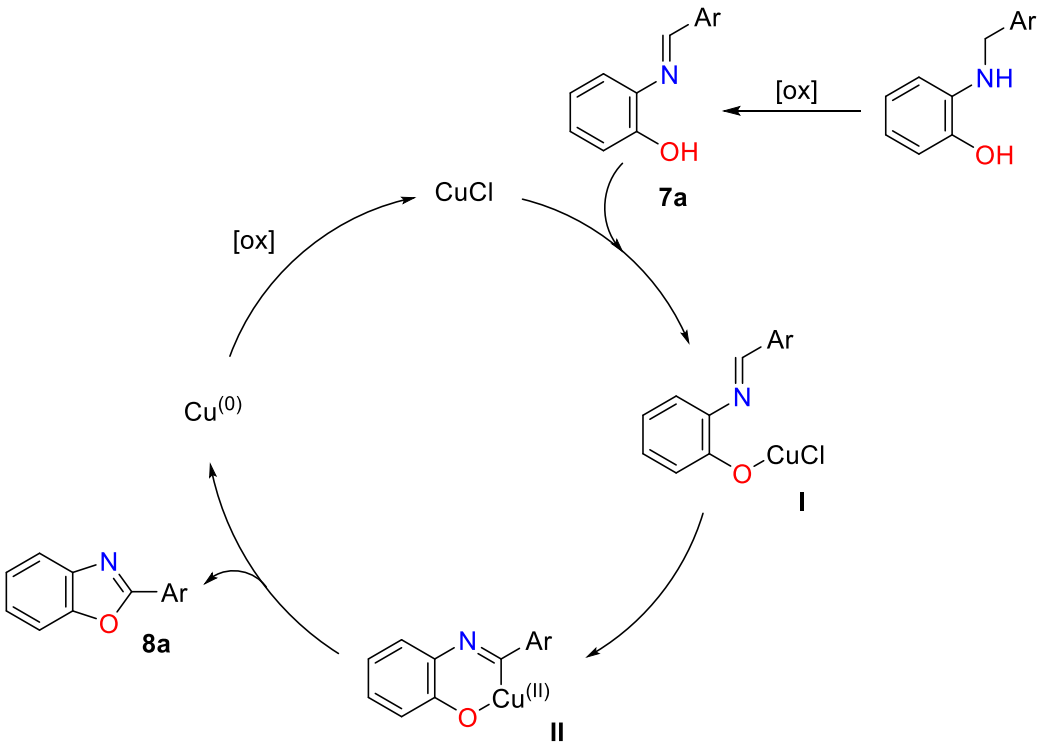
In this regard, the intramolecular coupling of substrate **6a** performed best in chlorobenzene at 100°C for 4 hours, using CuCl as catalyst, 8-hydroxy-quinoline as ligand and TBHP as oxidant. Under these conditions, only the cyclized product **8a** was obtained with a 66% yield. (**Table 1.10, entry 4**)

Entry	Ligand	Oxidant	Solvent	Time	Product (% yield)
1	8-OH-quin	TBHP	MeCN	4h	**8a** (25)
2	8-OH-quin	TBHP	MeCN	40 min	**8a** (45)
3	8-OH-quin	TBHP	DMF	40 min	**8a** (44)
4	---	TBHP	Cl-benzene	40 min	**8a** (66)
5	8-OH-quin	TBHP	Cl-benzene	40 min	**8a** (10)
6	1,10-phen	TBHP	Cl-benzene	40 min	**7a** (35) + **8a** (35)
7	8-OH-quin	O_2	Cl-benzene	40 min	**7a** (40) + **8a** (50)
8	8-OH-quin	TBHP	toluene	40 min	**7a** (20) + **8a** (55)
9	8-OH-quin	TBHP	DMC	2h	---
10	8-OH-quin	TBHP	Me-THF	2h	---
11	8-OH-quin	TBHP	EtOH/H_2O (1:1)	24h	

Table 1.1 Conditions tested with CuCl for the reaction of cyclization reported in **Scheme 1.11**.
The yield values referred to the product **7a** are determined by ^{1}H-NMR spectrum, while for **8a** are reported the isolated yields.

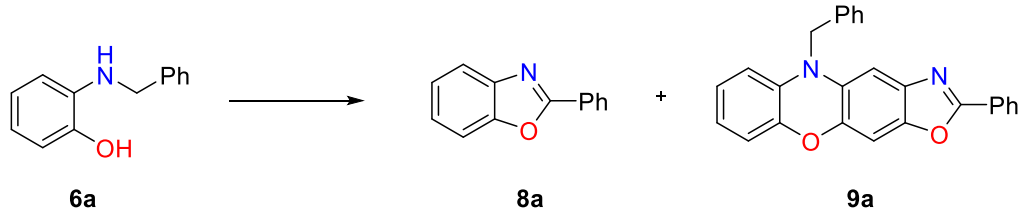
In an attempt to improve the reaction outcome, we also screened other Cu catalysts. However, CuBr and CuI resulted in lower reaction yields of 48% and 55% respectively.

Although some literature references reporting analogous reactivity suggest a radical mechanism,[26] the observed formation of the imine intermediate may suggest an initial oxidation of the benzylic carbon followed by and intramolecular alkoxylation step. Moreover, the reaction performed in the presence of a radical scavenger gave the same outcome. For these reasons, in **Scheme 1.12** depicts a possible reaction mechanism showing the Cu-oxygen complexation (intermediate **I**), which is capable of generating the cyclic intermediate **II.** From there, the demetallation step affords the product **8a**. The oxidant is necessary to convert the Cu(0) to the active form Cu(I).



Scheme 1.12 Proposed reaction mechanism.

When the reaction was performed in chlorobenzene, in the presence 1,10-phenantroline as ligand, side-product **9a** was observed in low yields. Product **9a** was isolated through flash column chromatography and spectroscopic analytical data as ^{1}H, ^{13}C NMR together with bi-dimensional correlations (COSY and HSQC) allow us to define its heteropolycyclic structure. (**Scheme 1.13**).



Scheme 1.13 Synthesis of the heteropolycyclic scaffold **9a**.

Having defined the structure of the tetracyclic product we decided to move our attention for the optimization of the reaction which led to the formation of this unusual polycyclic product.

Initially, we screened 2-benzylamino-phenol **6a** as model substrate for the optimization of the reaction. This involved testing the reactivity of CuCl as the catalyst with different ligands, oxidants, solvents, and varying reaction times. (**Table 1.2**)

Entry	Oxidant	Ligand	Solvent	Time (h)	Product (% yield)
1	TBHP	---	Dioxane	4	**8a** (10)
2	TBHP	---	Chlorobenzene	4	**8a** (44)
3	BQ	---	Toluene	4	**8a** (15)
4	H_2O_2	---	MeCN	4	S.M.
5	TBHP	8-OH-quinoline	Chlorobenzene	1	**8a** (66) + **9a** (traces)
6	TBHP	Phen	Chlorobenzene	4	**8a** (15) + **9a** (traces)
7	PIDA	---	Chlorobenzene	4	**9a** (24)
8	PIDA	Phen	Chlorobenzene	3	**9a** (58)
9	PIDA	BPhen[b]	Chlorobenzene	3	**9a** (53)
10	PIFA	BPhen	Chlorobenzene	3	S.M.
11	PIDA[c]	---	Toluene[d]	4	**9a** (18)
12	PIDA	BPhen	DMF	3	S.M.
13	PIDA	BPhen	MeCN	3	S.M.
14	PIDA	BPhen	Toluene	3	**9a** (67)
15	PIDA	BPhen	Toluene[c,e]	8	**9a** (72)
16	PIDA	BPhen	Toluene[f]	8	**9a** (42)

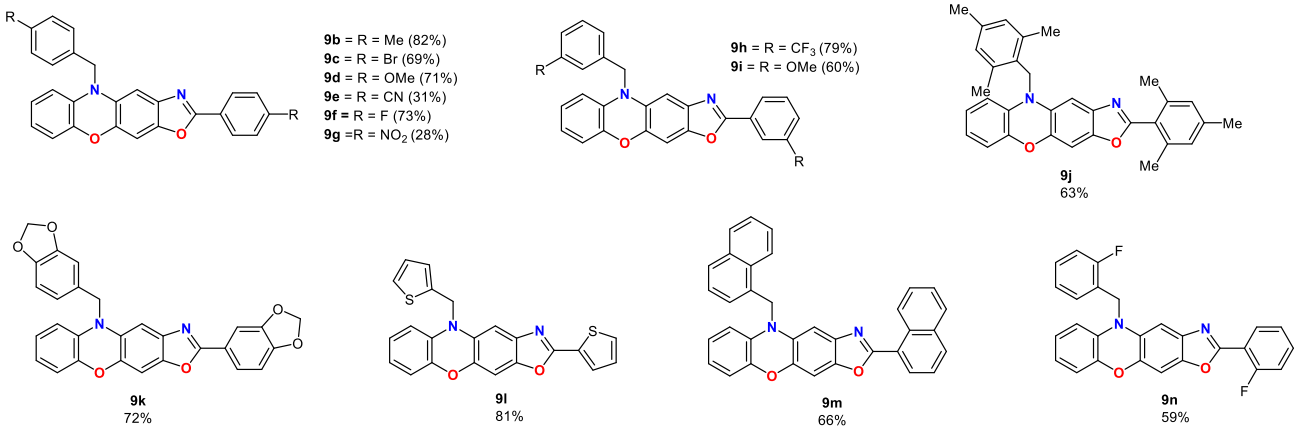
Table 1.2 Optimization of the reaction conditions for obtaining heteropolycyclic product **9a**.
Reaction conditions: in a sealed tube **6a** (1.0 mmol), CuCl (0.05 mmol), ligand (0.06 mmol), oxidant (1.3 mmol), solvent (0.07 M), at 100 °C for the indicated time. *b*) The use of 8-OH quinoline as a ligand provided only degradation products. *c*) No improvement of yields of **9a** was observed using 1.5 or 3.0 mmol of PIDA. *d*) Reaction performed without CuCl. *e*) In a 0.5 M solution. *f*) At 80 °C in a 0.1 M solution.

We observed that the use of TBHP or BQ allow only the formation of the benzoxazole derivatives, while the use of H_2O_2 does not yield any results. The addition of ligands such as 8-OH-quinoline and phenanthroline afforded different outcomes with the formation of the tetracyclic product, albeit in low yield. Switching to the use of hypervalent iodine species PIDA as oxidant agent, enhanced the formation of the tetracyclic product, conversely, the use of PIFA hampered the reaction.

More satisfactory results were obtained when a *N,N*-bidentate ligand was introduced. Further experiments were also performed to better evaluate the mechanism behind the formation of the tetracyclic product.

Experiments without the use of copper were conducted revealing that the dimerization/cyclization process occurred but with lower yield (18% of isolated product) besides the formation of a complex mixture of degradation products. After establishing the essential presence of PIDA as the oxidant agent and a diamino ligand, we screened different solvents. As reported in **Table 1.2**, entries **12** and **13**, no reactivity was observed when using DMF or MeCN, while switching to toluene resulted in better outcomes.

Having identified the optimal reaction conditions, we also investigated the behaviour of different substrates bearing both electron-withdrawing (EW) and electron-donating (ED) groups. All the substituents were tolerated by the catalytic system, the EW substituents led to lower yields. (**Scheme 1.14**)

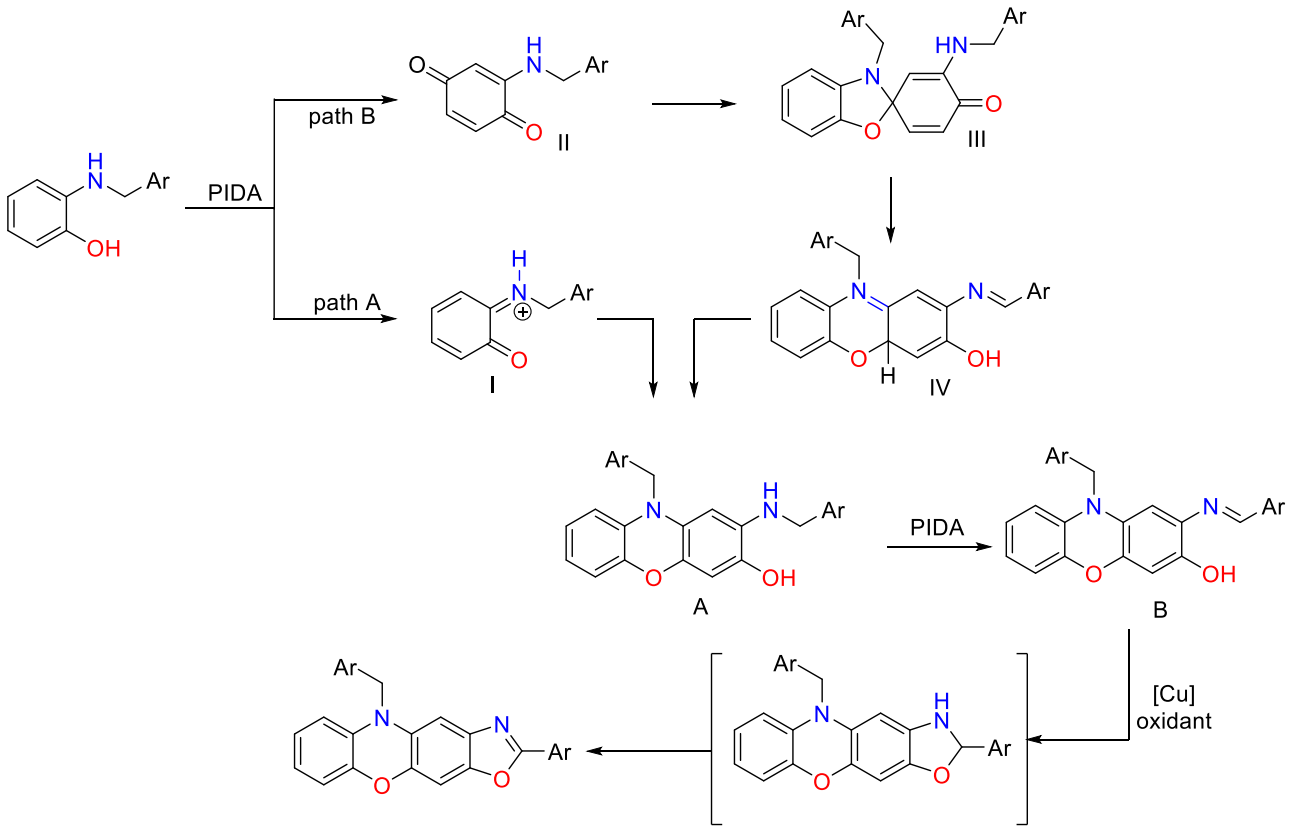


Scheme 1.14 Synthesis of oxazolo-phenoxazines **9b-n** in oxidative conditions.

Heterocyclic groups *i.e.* the thien-2-yl **9l**, proved effective in the dimerization/cyclization reaction with 81% yield. The inclusion of bulkier substituents, such as mesityl, piperonal and naphthyl groups, showcased the versatility and the extendibility of this methodology. On the other hand, the presence of methyl and nitro substituents in position 3- and 6- of the 2-aminophenols resulted only in a mixtures of degradation products.

Since the tetracyclic product is formed in traces when the reaction was performed without copper salt but with an excess of PIDA, a plausible mechanism of the reaction is depicted on in **Scheme 1.15.** We suggest as the key-intermediate phenoxazine A, even if never isolated, which may arise from two plausible way. The first proposed mechanism (**Scheme 1.15, *path A***) involves the oxidation/dearomatization of the substrate by the action of PIDA. The *o*-quinone type intermediate **I**, interacting with a second molecule of the starting material allow the formation of **A**. As an alternative pathway (**Scheme 1.15, *path B***), we suppose the formation of a spiro-intermediate **III**

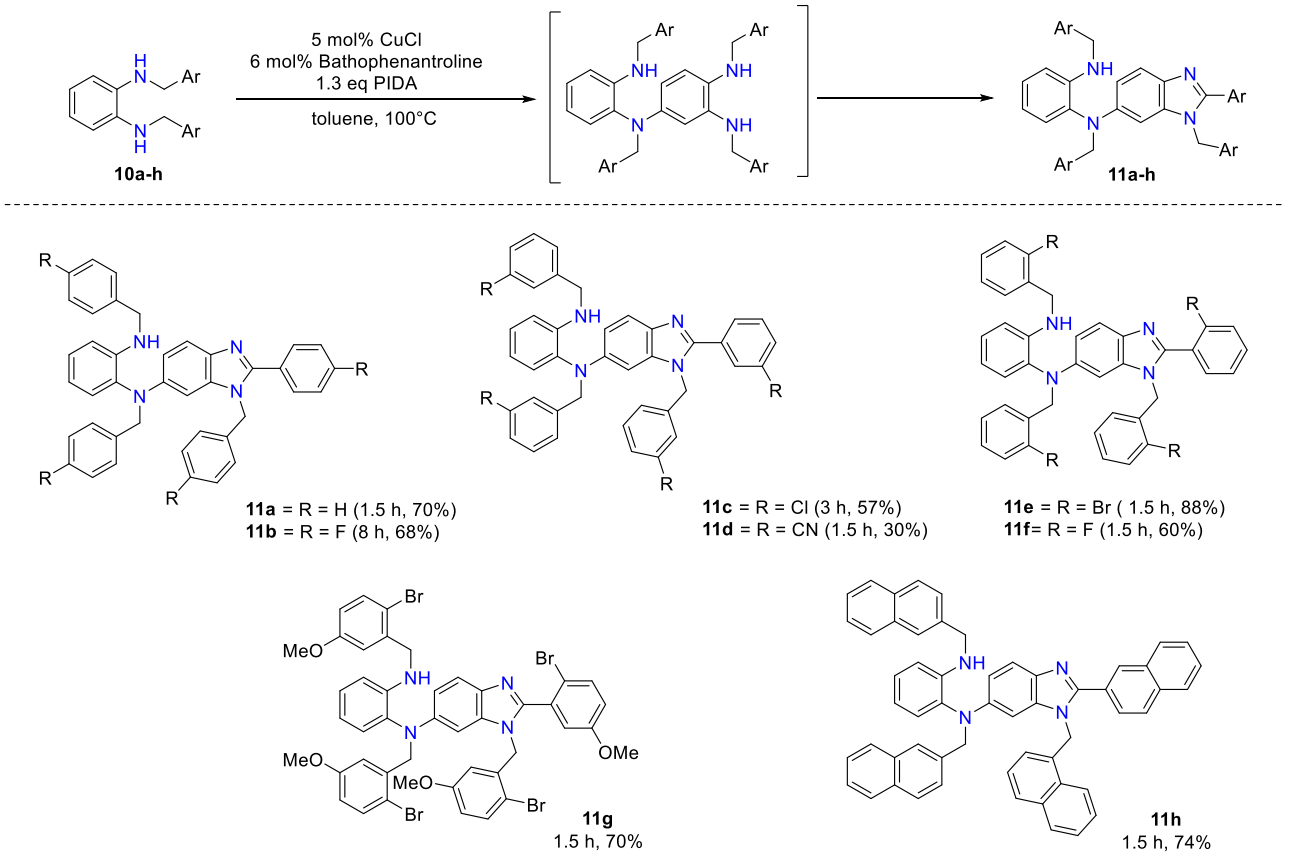
formed *in situ* due to the reaction between the 2-benzylamino-phenol and the formed *p*-quinone intermediate **II**, through a ring expansion process forming the phenoxazine **A**. The subsequent oxidation promoted by PIDA afforded the imine intermediate **B** which undergoes the Cu-catalysed oxidation to the final tetracyclic product.



Scheme 1.15 Proposed mechanism for the dimerization/cyclization.

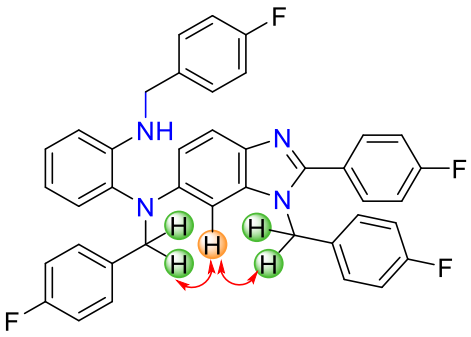
Having established the efficacy of this synthetic procedure and considering the analogy of the 2-aminophenols with 1,2-benzenediamines due to their structural and electronic similarities, we also explore the reactivity of *N,N'*-dibenzyl-1,2-benzenediamines.

In this case, we observed a different outcome, as reported in **Scheme 1.16** Compounds **10a-h**, treated in the previous reaction conditions allows the formation of the 5-membered ring through a dimerization step, but, in this case, no tetracyclic product was formed.



Scheme 1.16 The reactivity of *N,N'*-dibenzyl-1,2-benzenediamines **10a-h**.

^{1}H-NMR studies were performed with the aim to assess the correct position of the substituent on the benzimidazole nucleus. The ^{1}H-NOESY experiments were particularly useful to selectively assign the amino group at the 6-position, revealing the interaction between the aromatic proton at 6.35 ppm and the benzylic signal at 5.19, confirming the nature of the suggested structures. (**Fig 1.5**)



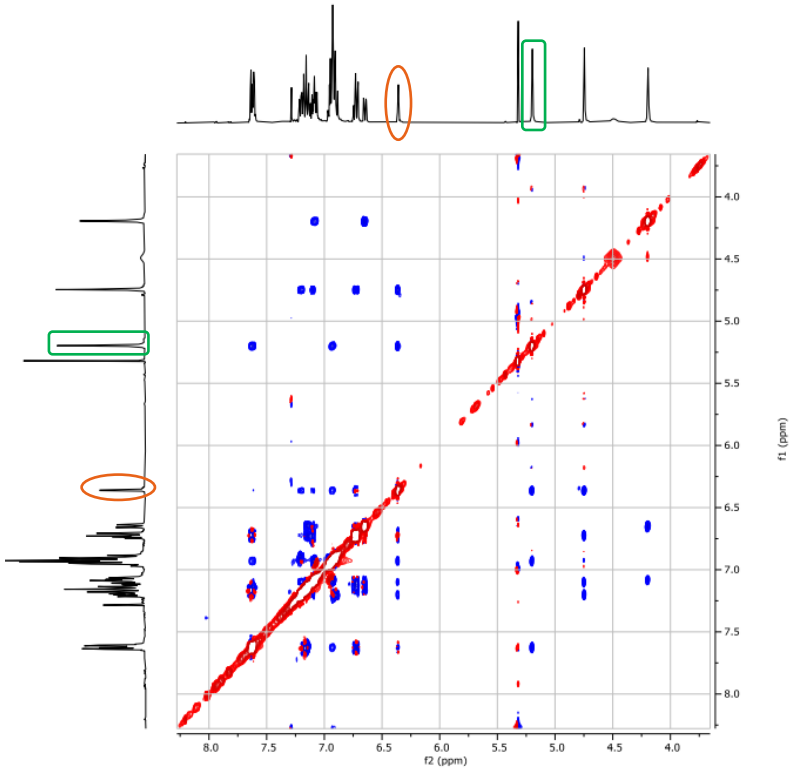
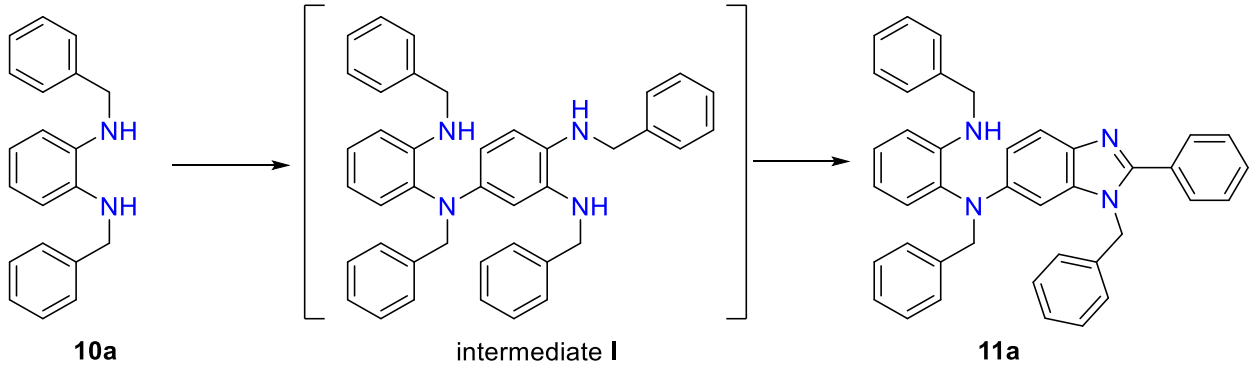


Fig 1.5 ^{1}H-NOESY experiment on compound **11b**.

We hypothesize that the presence of a second benzyl-amino substituent instead of the hydroxyl group, inhibits the formation of the second *C-N* bond, hampering the production of the phenazine scaffold. As observed previously, this reaction may involve an initial oxidation leading to the formation of the intermediate **I** which, through a second oxidation to the imino derivative, allows the formation of the 2,3-dihydrobenzimidazole **11a**. (**Scheme 1.17**)



Scheme 1.17 Possible mechanism on the *N,N'*-dibenzyl compound **10a**.

In accordance with literature data and the well-known fluorescent propertied of oxazolo-phenoxazine derivatives, an interesting aspect of this class of compound refers to an intense fluorescence in solution with the exception of the nitro derivative which showed a very feeble emission due to the quenching effect of the nitro group. In collaboration with the Università degli

Studi dell' Insubria, we observed that the emission maxima exhibits variations based on the substitution pattern on the oxazole ring. Generally, the λ_{em} shifts from blue to orange as the ED behaviour of the substituents decreased. (**Fig. 1.6**)

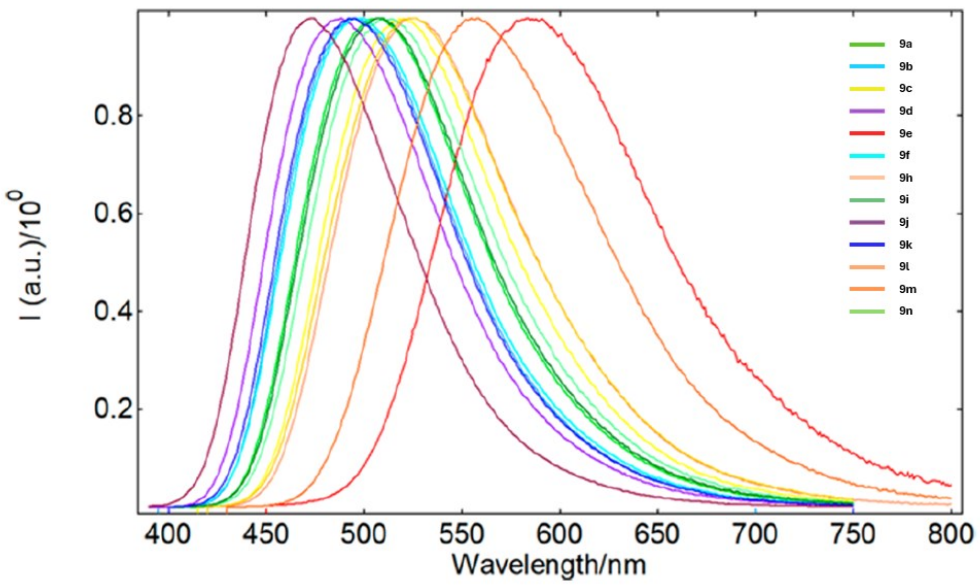


Fig 1.6 Normalized emission spectra of compound **9a-f, 9h-n** (DCM, $5 \cdot 10^{-5}$M).

Also, the evaluation of the emission behaviour on the Xa-g derivatives was evaluated. (**Fig 1.7**) In this case the fluorescence emission is centered in the UV zone to the blue region albeit with lower intensity compared to those previously examined for oxazolo-phenoxazine.

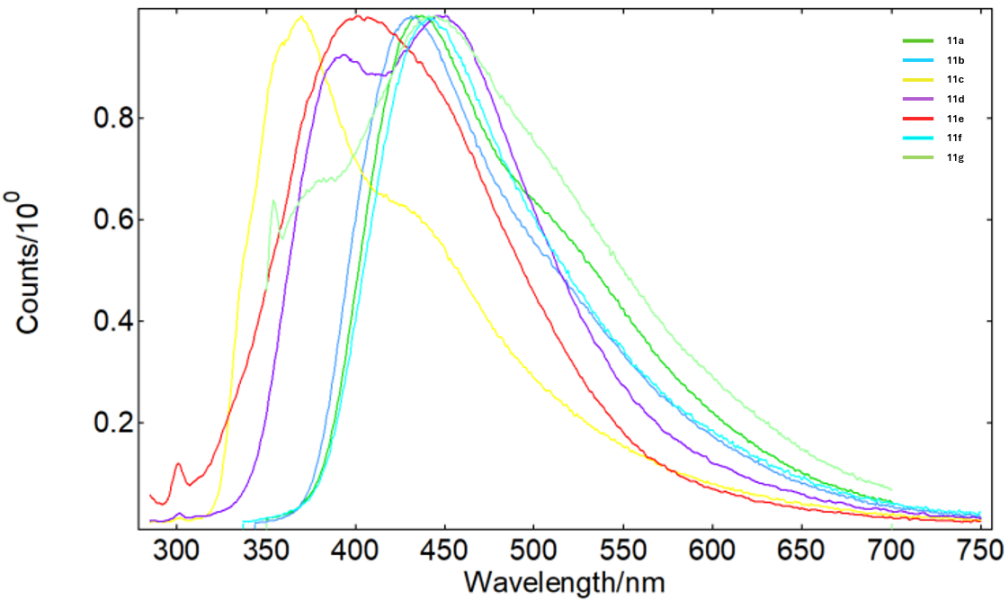


Fig 1.7 Normalized emission spectra of compounds **11a-g** (DCM, $5 \cdot 10^{-5}$ M).

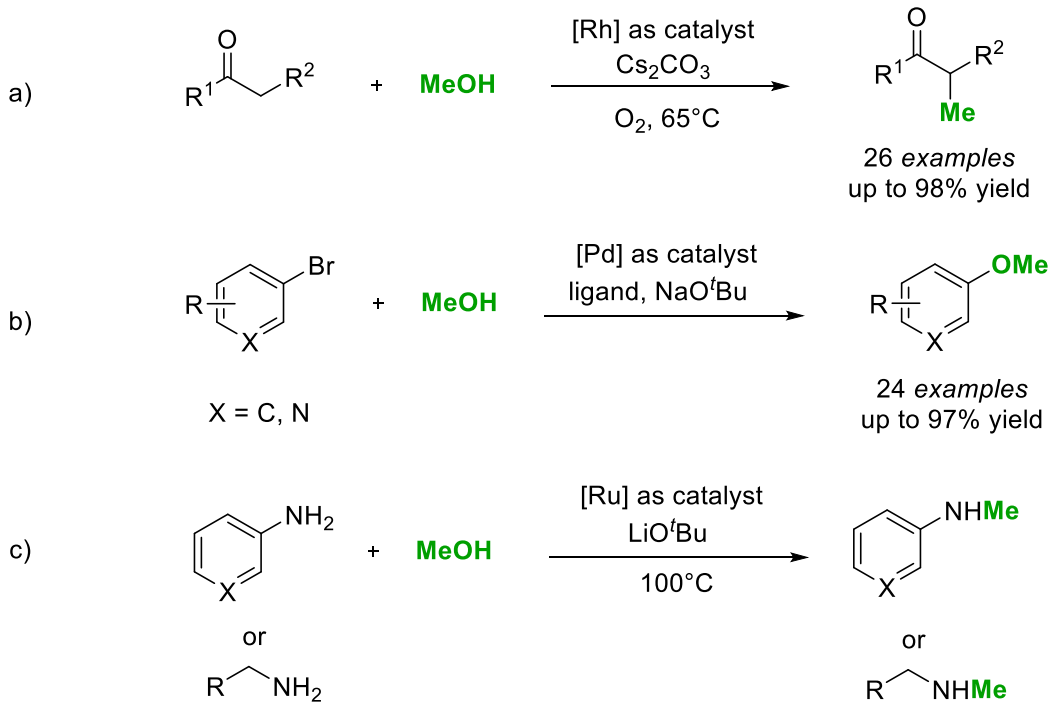
Methanol as a C1 source for the synthesis of 1,3-polyheterocyclic systems

1.4.1 Background

The development of sustainable processes that employ inexpensive, non-toxic, greener, and easily accessible raw material to enhance the efficiency of reactions remains a fundamental objective for both academic research and industrial production.[27] Within this scope, methanol presents itself as a fascinating chemical entity capable of various functions: as a raw material source for chemicals, an energy carrier, and a convenient material for energy storage. It is also known that solvents represent 80% of the waste generated during a synthetic process. From the perspective of sustainable chemistry, using a solvent as a reagent represent added value.

In recent times, beside the major role as solvent in synthetic applications, methanol has also garnered attention as a "green precursor" and renewable C1 source, gaining consideration as a feasible alternative to conventional reagents in various type of reactions of organic synthesis.[28]

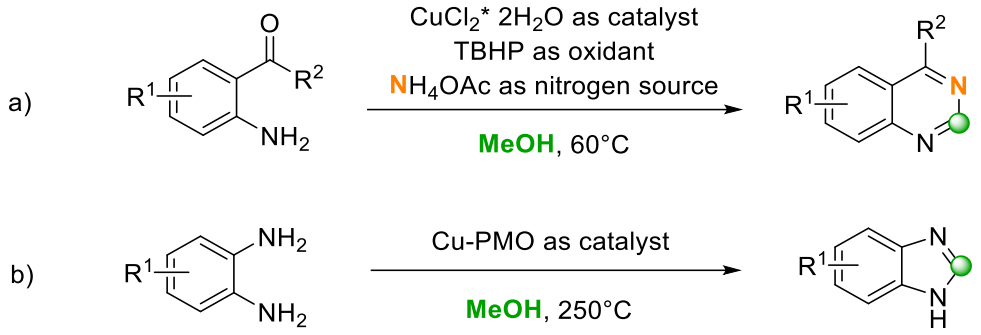
Specifically, it can also act as pro-electrophile in the presence of nucleophilic partners providing new C-C, C-N, C-O bond in processes involving C-methylation,[29] N-methylation,[30] C-methoxylation,[31] N-formylation[32]and aminomethylation[33].



Scheme 1.18 Methanol as sustainable C1 source in functionalization procedures.

Besides the above reported examples (**Scheme 1.18**) in which methanol can act as carbon source in functionalization procedures, we evaluated the possibility to use this small molecule as reagent also in functionalization and/or synthesis of various heterocycles.

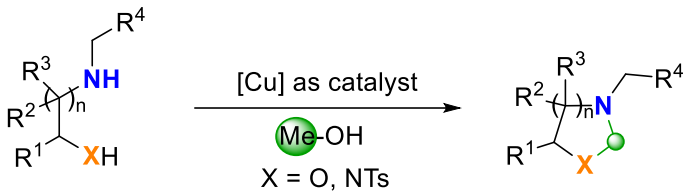
In the literature, some examples are reported in which methanol serves as C1 source, exploiting aromatic substrates for the construction of benzofused heterocycles, as quinazolines[34] and benzimidazole or benzoxazole derivatives.[35] (**Scheme 1.19**)



Scheme 1.19 Methanol as C1 source for the synthesis of quinazolines (**a**) and benzimidazole (**b**).

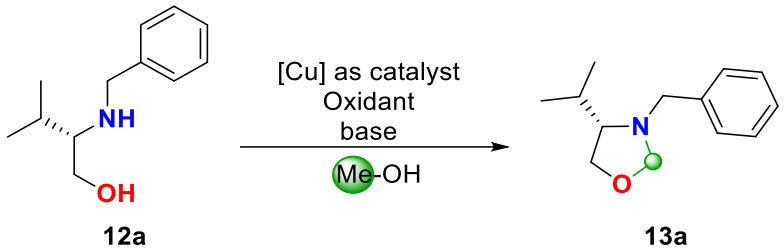
1.4.2 Results and discussion

We decided to evaluate copper-catalysed reactions for the preparation of 1,3-polyheterocyclic compounds, capitalizing on the double role of methanol as solvent and reagent though a "greener" procedure. We considered differently substituted aliphatic amino-alcohols and diamines. (**Scheme 1.20**)



Scheme 1.20 Synthesis of 1,3-polyheterocyclic scaffold.

As a starting point, we selected (*R*)-*N*-benzylvalinol (**12a**) as model substrate for the optimization of the reaction conditions. (**Scheme 1.21**)



Scheme 1.21 Optimization reactions on substrate **12a**.

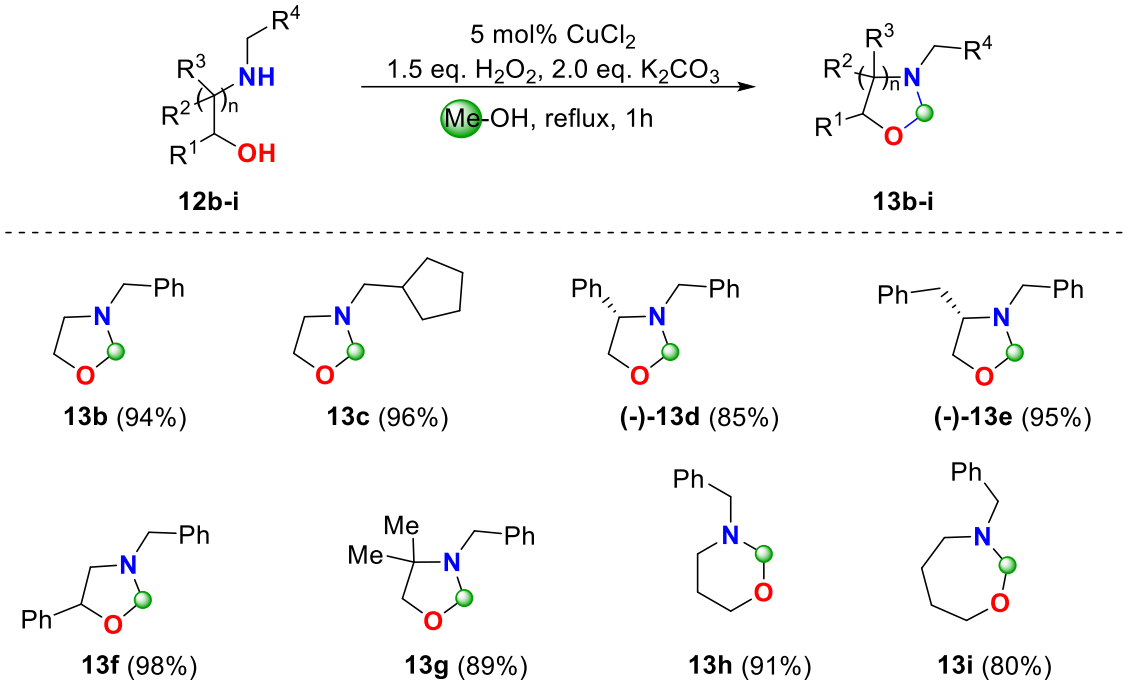
In this respect different Cu-catalysts, oxidant agents and solvents were tested. (**Table 1.3**) Preliminary studies were performed using $CuCl_2$ as copper catalyst, H_2O_2 as sustainable oxidant agent and methanol as solvent (**Table 1.3, entry 1**) obtaining the corresponding oxazolidine compound **13a** in 32% yield, beside unreactive substrate. We observed that the presence of K_2CO_3 as base enhance the reaction yield and two equivalents of base afforded completely conversion with higher yield (94%). (**Table 1.3**, **entry 2**)

Having established the mandatory role of the base for the complete conversion of the substrate we also proved that, in comparison with others oxidant agents, the H_2O_2 offers the best results in term of yields and to avoid degradation products.

Entry	Catalyst	Oxidant	Solvent	Product (yield %) [c]
1[a]	$CuCl_2$	H_2O_2[b]	MeOH	S.M. + **13a** (32)
2	$CuCl_2$	TBHP	MeOH	**13a** (72)
3	$CuCl_2$	$PhI(OAc)_2$	MeOH	**13a** (79)
4	$CuCl_2$	BQ	MeOH	Degradation products
5	$CuCl_2$	MnO_2	MeOH	Degradation products
6	$CuCl_2$	H_2O_2[b]	MeOH	**13a** (94)
7	$CuBr_2$	H_2O_2[b]	MeOH	Degradation products
8	$Cu(OTf)_2$	H_2O_2[b]	MeOH	**13a** (82)
9	---	H_2O_2[b]	MeOH	S.M.
10	$CuCl_2$	H_2O_2[b]	EtOH	S.M. + degradation products
11	$CuCl_2$	H_2O_2[b]	PrOH	S.M. + degradation products

Table 1.3 Reaction conditions: **12a** (1.0 mmol), [Cu] catalyst (5 mol%), oxidant agent (1.5 eq.), K_2CO_3 (2.0 mmol), solvent (0.1M), reflux 1h in oil bath. [a] reaction performed in the absence of base [b] H_2O_2 (30% in water), [c] Isolated yield.

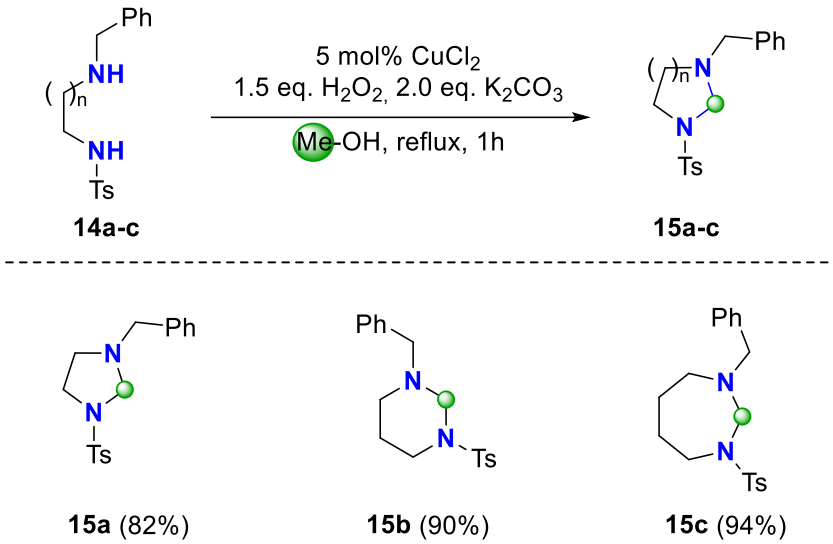
Once we found the optimal reaction conditions to promote the cyclization reaction on the model substrate, exploiting the reactivity of methanol in the double role of solvent and reagent, we proceeded to investigate the responses of different amino-alcohols. (**Scheme 1.22**) In specific, we demonstrated the extendibility to amino-alcohols with different chain length, enabling the synthesis of 1,3-oxazinane (**13h**) and 1,3-oxepane (**13i**) in very satisfactory yield.



Scheme 1.22 Cyclization reaction performed on different substrates.

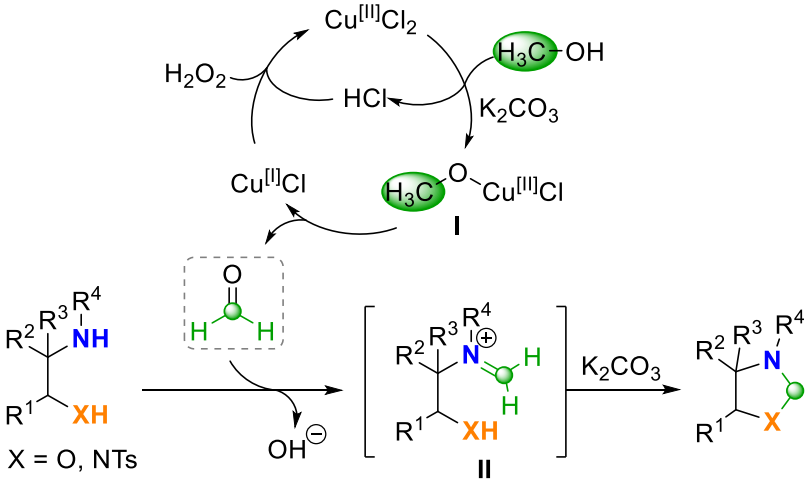
The investigation revealed that the outcome of the cyclization relies on the nature of the substituents on the substrates. It was observed that the presence of EW groups on the nitrogen atom *i.e.* tosyl or *t*-butoxycarbonyl groups or the presence of EW substituents on the benzyl groups hindered the reaction outcomes. Furthermore, the presence of amides or carboxylic acids did not yield any results.

Subsequently, due to the structural and electronical similarities of diamines to aminoalcohols, we explore the reactivity of *N*-benzyl-*N'*-tosyl diamine derivatives (**14**), under the previous reaction conditions. With diamine substrates of different lengths, we observed the almost quantitative conversion into imidazolidine (**15a**), hexahydropyrimidine (**15b**) and 1,3-diazepane(**15c**). (**Scheme 1.23**)



Scheme 1.23 Synthesis of imidazolidine (**15a**), hexahydropyrimidine (**15b**), 1,3-diazepane (**15c**).

The proposed mechanism involves the generation of a copper-methanolate complex **I** assisted by K_2CO_3, which is essential for the deprotonation of the alcohol. Subsequently, the *in situ* generation of formaldehyde and the concomitant formation of a Cu(I)-species, allows the generation of the iminium ion intermediate. This intermediate, undergoes an intramolecular nucleophilic attack, favoured by the base, resulting in the formation of the desire cyclic product. The presence of the oxidant agent also facilitates the regeneration of the catalyst.



Scheme 1.24 Proposed catalytic cycle.

As additional experiment to validate our hypothesis, we performed the reaction in deuterated methanol (CD_3OD). As reported in **Fig 1.8**, full deuteration at the 2-position was achieved, depicting the methylene signal unobservable in ^1H NMR spectra.

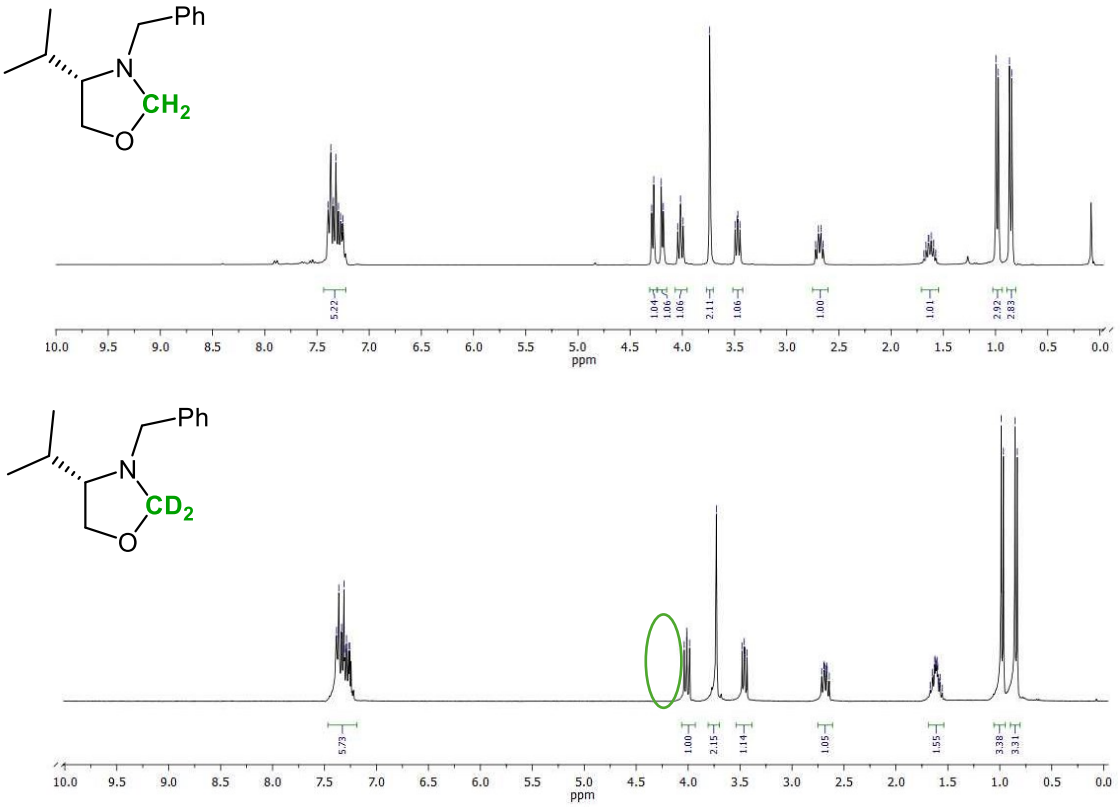


Fig. 1.8 [1]H-NMR crude of compound **13a** and **13j**.

To further validate the sustainability of the proposed methodology for achieving 1,3-polyheterocyclic compounds, an assessment of its *Environmental Factor* (E-factor) was also performed. Specifically, as described in principle n°1 of *Green Chemistry*, the *E*-factor quantified the amount of waste generated per kilogram of product and it is defined as "everything but the desire products", encompassing everything aside from the wanted compound, such as solvent lost and chemicals used in the work up.[9]

$$E\ factor = \frac{total\ mass\ of\ waste}{mass\ of\ product}$$

Eq. 1.1 Equation for the determination of the *E* factor.

To conduct this evaluation, we compared our synthesis to the one already reported in literature; [36] and, in the specific, we focused our attention on the calculation of the *E*-factor of compound **13e**. For the determination of the *E-factor*, we take in account all the amounts of reagents, solvents and auxiliaries used to perform the reaction. Compared to the reported synthesis, where the formation of the oxazolidine core was obtained using $(CH_2O)_n$ as carbon source and toluene as solvent with a *E* factor of ~ 32 calculated without considering the purification step (such as the quantity of silica

and solvent for the flash chromatography), our synthetic alternative yields the same *E*-factor value. Notably, the advantage of our synthesis is that it does not require purification steps thus confirming the improvement of the sustainability of this protocol.

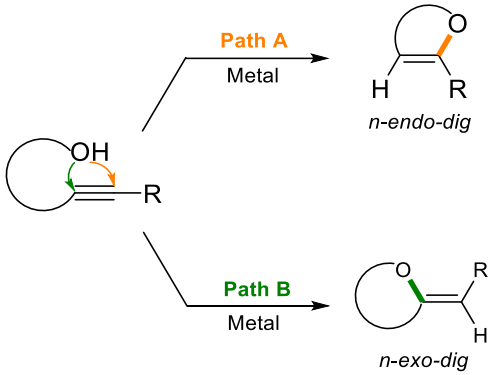
Chapter 2_*Platinum catalysis*

One-pot difunctionalization of terminal alkynes

2.1.1 Background

Among the several transition-metal catalysts explored to enable a direct and efficient approach for the *one-pot* difunctionalization of unsaturated systems, we have examined the activity of platinum-catalysts.[37]

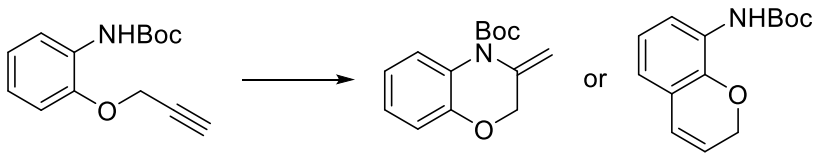
In literature, alkynes bearing an -OH group are reported to undergo intramolecular pathways leading to the synthesis of oxygen-functionalized heterocycles.[38] (**Scheme 2.1)**



Scheme 2.1 Synthesis of oxygen-functionalized heterocycles.

Besides the *N*-containing heterocycles, *O*-containing ones are widely employed in the construction of natural products and bioactive frameworks. In this context, the hydroalkoxylation of alkynes offered a prominent technique for the synthesis of various oxygen-containing rings.[39]

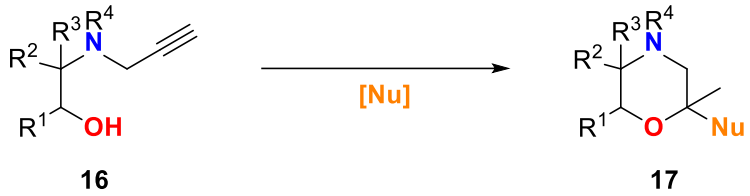
Our research group has previously employed the *O*-propargyl-2-aminophenols to study the divergent reactivity of the terminal triple bond, under palladium- and platinum-catalysis.[40]



Scheme 2.2 Reactivity of *O*-propargyl-2-aminophenols.

2.1.2 Results and discussion

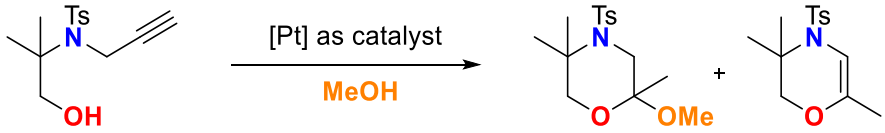
Continuing our efforts to explore the difunctionalization of unsaturated systems, we herein report a study on non-aromatic substrates such as *N*-propargyl-amino-alcohols. In these substrates, the two functional groups are sufficiently spaced to allow for an intramolecular hydroalkoxylation reaction and, in the presence of a second nucleophile, difunctionalization process occurs.



16 **17**

Scheme 2.3 Synthesis of different functionalize morpholine **17**.

Having extensively studied copper catalysis, we decided to investigate this type of cyclization by employing different copper salts, and MeOH as second nucleophile. (**Scheme 2.4**)



16a **17a** **18a**

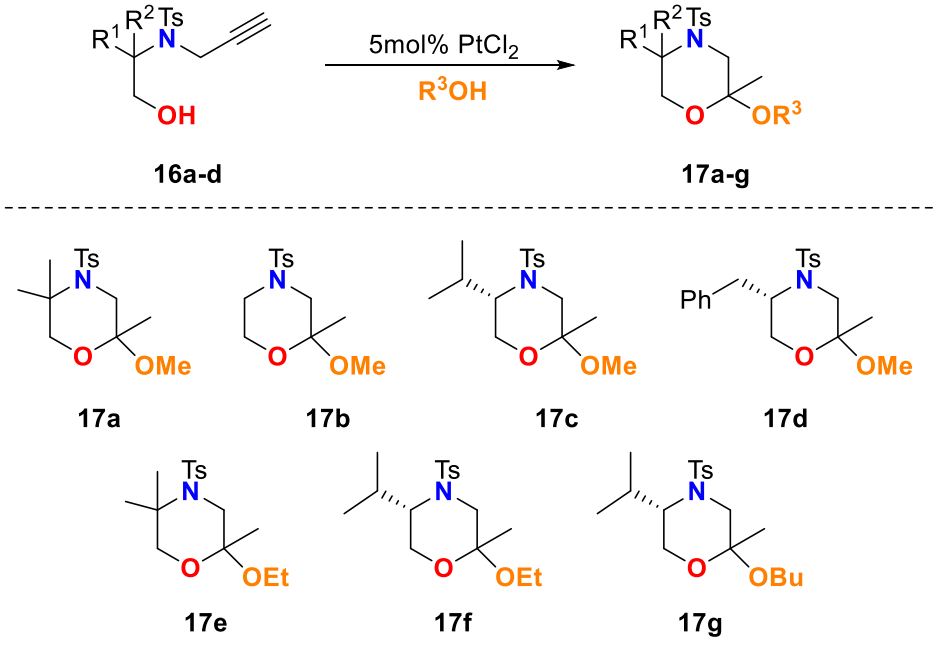
Scheme 2.4 Screening reaction on substrate **16a**.

As shown in **Table 2.1**, $CuCl_2$ did not yield any results. However, the use of $Cu(OTf)_2$ in the presence of MeOH allowed the isolation of a cascade product **17a**, albeit in low yield. Transitioning to platinum catalysts, we discovered that the use of $PtCl_2$ in the presence of MeOH, both as solvent and nucleophile, afforded the dialkoxylation product **17a** in quantitative yield. Additionally, the reactivity of $PtCl_4$ was examined, however, in this case, only the hydroalkoxylation product **18a** was obtained in quantitative yield.

Entry	Catalyst	Solvent	Temperature	Yield (%)
1	$CuCl_2$	THF/MeOH	r.t.	S.M. + degradation products
2	$CuCl_2$	MeOH	65°C	S.M. + degradation products
3	$Cu(OTf)_2$	THF/MeOH	r.t.	S.M. + degradation products
4	$Cu(OTf)_2$	MeOH	65°C	**17a** (25)
5	$PtCl_2$	THF/MeOH	r.t.	**17a** (25)
6	$PtCl_2$	MeOH	r.t.	**17a** (quantitative)
7	$PtCl_4$	MeOH	r.t.	**18a** (quantitative)

Table 2.1 Reaction performed on substrate **16a** in the presence of MeOH as nucleophilic species.

Following the positive results, we expanded the reaction to include other alcohols and to another nucleophile, as reported in **Scheme 2.4.**

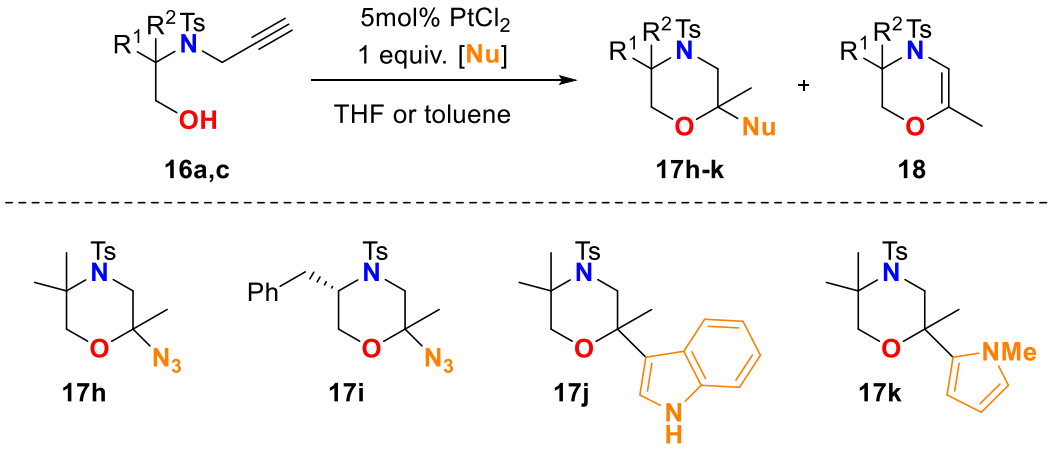


Scheme 2.4 Synthesis of different functionalized morpholine **17.**

The presence of other alcohols, *i.e.* EtOH, BuOH allowed the difunctionalization of the terminal alkyne, resulting in the formation of the corresponding 2-alkoxy substituted *N*-tosyl morpholine **17** in very satisfactory yield. This granted us to consider this procedure among the sustainable reactions in terms of atom economy and ease of work-up. However, the presence of bulky alcohols *i.e.* ^{i}PrOH,

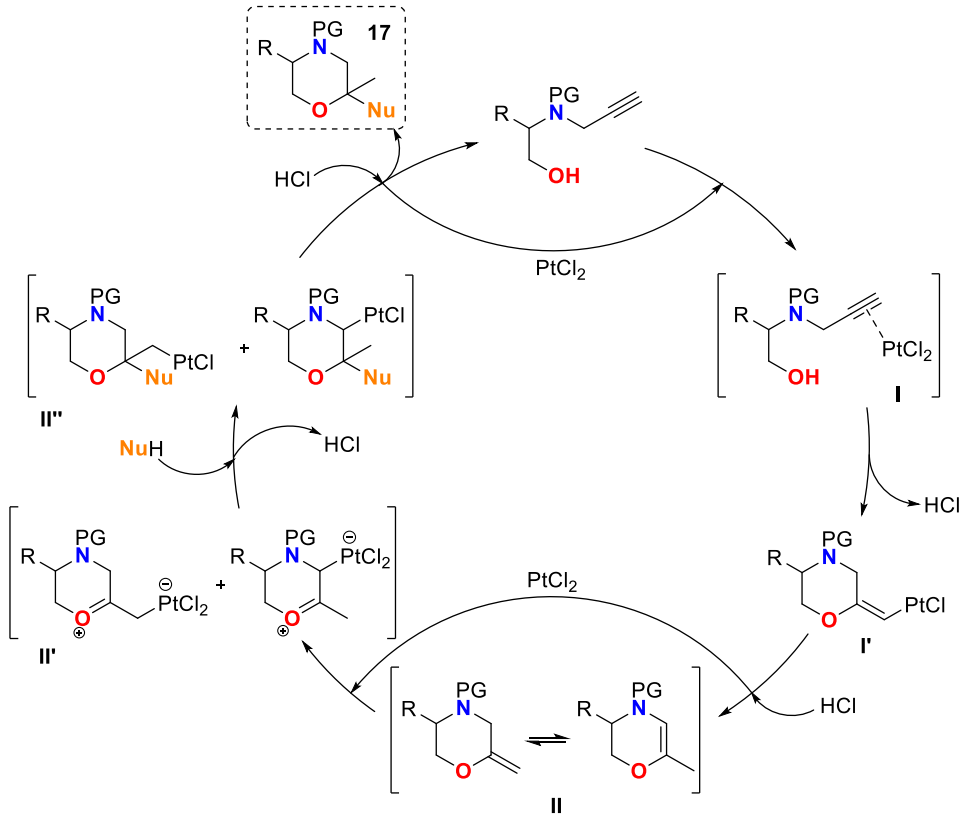
^{t}BuOH hampered the insertion of the nucleophile furnishing the hydroalkoxylation derivative **18**. This is likely due to the high steric hindrance of the nucleophilic species.

To evaluate the possibility obtaining different substituted morpholines, we conducted the reaction in THF or toluene as solvents, in the presence of various nucleophiles. (**Scheme 2.5**) This allowed for the formation, even if in lower yield, of 2-azido derivatives (**17h,i**), *N*-Me-indole-derivatives (**17j**) and *N*-methyl-pyrrol- derivatives (**17k**).



Scheme 2.5 Reaction performed with different nucleophiles.

In **Scheme 2.6** a possible mechanism is depicted. Based on literature knowledge and the studies performed, we suggest the initial addition of platinum to the alkyne moiety, forming the cyclized intermediate **I'**. Subsequently, upon obtaining of the 2-methylenemorpholine compound **II**, a second insertion of $PtCl_2$ allows for the insertion of the nucleophilic species. After the reductive elimination, the morpholine **17** is formed with the regeneration of the catalyst.



Scheme 2.6 Proposed reaction mechanism.

Since a new stereocenter is formed during the reaction, we describe herein an approach aimed to achieving stereoselectivity in the *gem*-difunctionalization reaction. Specifically, by exploiting the reactivity of platinum catalysts, we are currently evaluating the effectiveness of various amine type-chiral ligands. In collaboration with Prof. *Rimoldi*'s research group from Università degli Studi di Milano, we are exploring the reactivity of different chiral tetrahydroquinoline-type ligands, Campy (L1), MeCampy (L2) and *N*-Me MeCampy (L3). (**Fig. 2.0**)

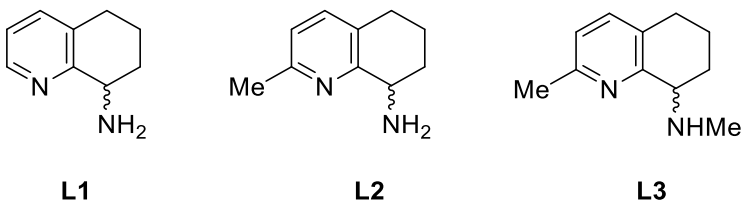
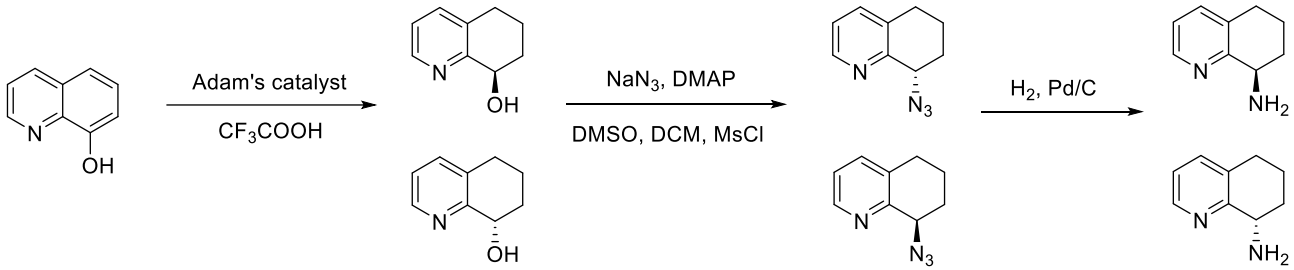


Fig. 2.0 Different chiral tetrahydroquinoline-type ligands.

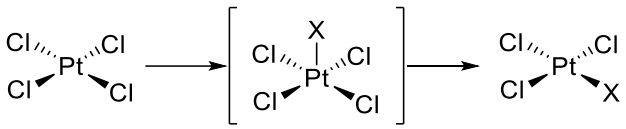
Although the above structures differ only for the presence of the methyl group at position 2 and on the amino group, this minimal structural difference has a substantial impact on both electronic properties and steric hindrance.

Starting from the appropriate isoquinoline, after the fine-tuned procedure from *Rimoldi*'s research group (**Scheme 2.7**) for obtaining of the corresponding ligands (**L1, L2, L3**),[41] the subsequent complexation reaction occurs due to the nitrogen atom's ability to act as a Lewis base and coordinate with a Lewis acid like platinum.



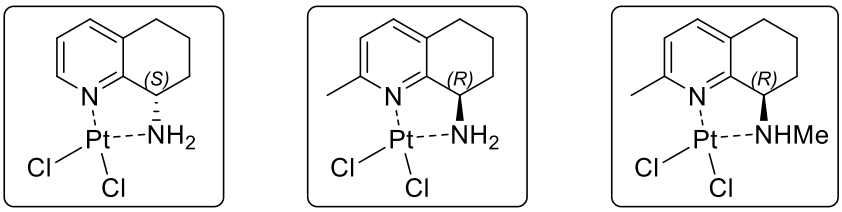
Scheme 2.7. General synthesis of the chiral ligands, CAMPY, **L1**.

The complexation occurs as a result of the arrangement of atoms in a square-planar configuration within the complex. The trans effect, which is responsible for the coordination, is explained by the reaction mechanism through which these complexes are formed. The central platinum metal atom complexes the ligand *via* an associative mechanism forming a square-pyramidal configuration. As consequence of the formation of a penta-coordinated complex capable of simultaneously coordinating both the incoming and outgoing ligands, electrostatic repulsion causes the detachment of the chlorine in the trans position to the incoming ligand, restoring planar structure.[42]



Schem 2.8. Associative mechanism of platinum.

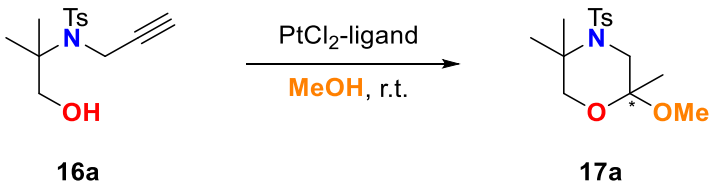
Once prepared, we proceeded with the screening of these chiral-catalyst systems. We evaluated the reactivity of the followed $PtCl_2$-ligands. (**Fig. 2.1**)



$PtCl_2$-L1 **$PtCl_2$-L2** **$PtCl_2$-L3**

Fig. 2.1 Chiral-catalytic systems synthetized.

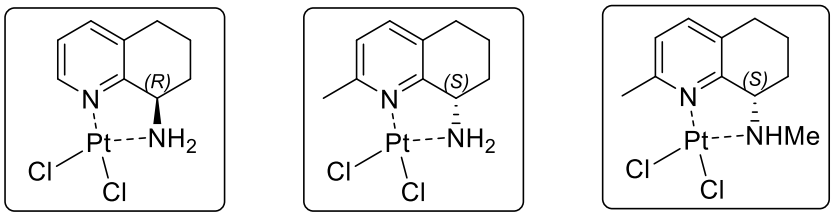
The reaction was carried out on **16a**, chosen as model substrate, in MeOH and in the presence of 5 mol% of chiral catalyst.



16a **17a**

Scheme 2.9 Evaluating the $PtCl_2$-ligands systems on substrate **16a**.

Only, L1- and L3-systems afforded the morpholine product in quantitative yield while using L2 systems resulted in the recovery of the starting material. Unfortunately, satisfactory results in terms of enantioselectivity have not been obtained thus far, as racemic mixtures were recovered in each case. We are currently working on optimizing the process. In particular, we are focusing on different screening reactions to evaluate the role of temperature, concentration and stoichiometry, as well as the reactivity of other chiral ligands. **Fig. 2.2.**



$PtCl_2$-L4 $PtCl_2$-L5 $PtCl_2$-L6

Fig. 2.2 Other catalytic systems.

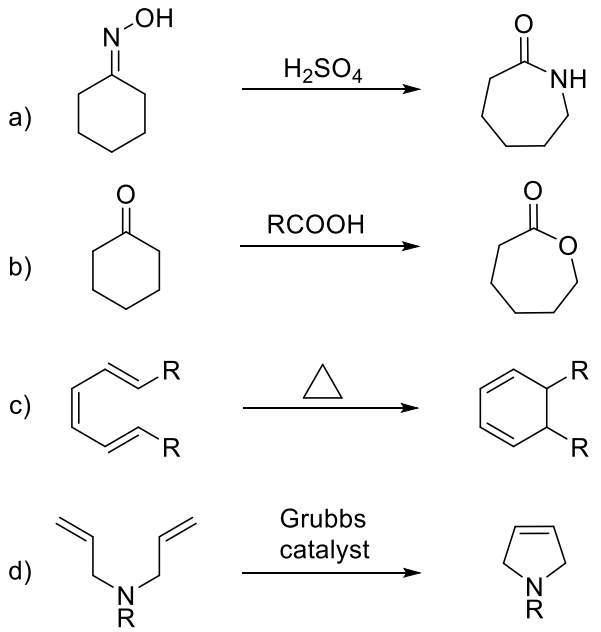
Due to the necessary presence of methanol as both solvent and reagent, we nevertheless observed low stereoselectivity, probably due to its interfering with the chiral catalytic systems. Consequently, we tested methanol in combination with various solvents such as MeCN, DMF, DCM, toluene, and different ethers including THF, Me-THF, CPME and cyrene. However, no improvement in the stereoselectivity was observed and next to compound **17a**, the hydroalkoxylation compound **18** was also reported.

Chapter 3_*Ruthenium catalysis*

3.1. Introduction

The literature reported an increase of a variety of chemical transformations, in particular, rearrangement type reactions play an important role for the development of new synthetic procedure to access to a plethora of organic compounds, to increase functionalities of preformed scaffolds and as alternative pathways to the synthesis of heterocyclic systems. [43]

The literature reports several rearrangements that are significant, from a synthetic perspective. Among these, we mention the Beckmann rearrangement, which is important on an industrial level for obtaining lactams starting from oximes, and the Baeyer-Villiger rearrangement, which yields lactones from cyclic ketones. Additionally, electrocyclic rearrangements can convert 1,3-dienes in cyclobutenes and 1,3,5-trienes in 1,3-cyclohexadienes upon treatment with UV light or heat. Within the realm of rearrangement, transition-metal-catalysed reactions have proven to be a powerful tool for promoting such transformations.[44] In this context, metathesis reactions are of particular importance for innovation and have vast applicability. Grubbs' discovery of the homogeneous ruthenium catalysts was awarded the Nobel Prize. Just as an example, we mention the synthesis of aza-heterocycles starting from diallyl amines. (**Scheme 3.1)** [45]



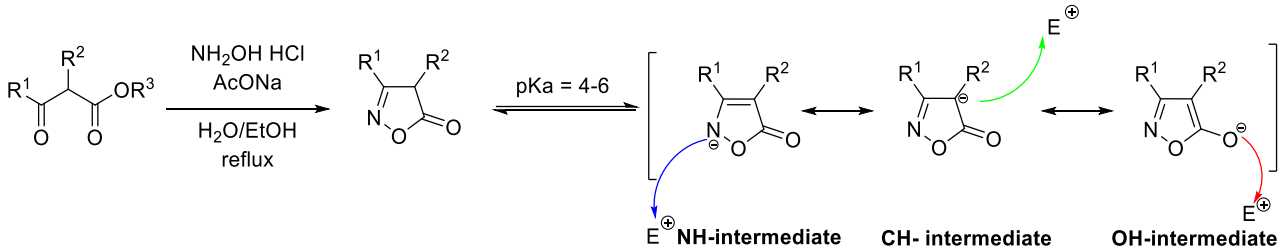
Scheme 3.1 Rearrangement reactions: a) Beckmann rearrangement; b) Bayer-Villiger rearrangement; c) electrocyclic rearrangement; d) metathesis reaction.

The interest in ruthenium catalysts is also attributed to the metal's strong affinity to heteroatoms for coordination.

Isoxazol-5-ones as a starting material for the synthesis of heterocyclic compounds

3.2.1 Background

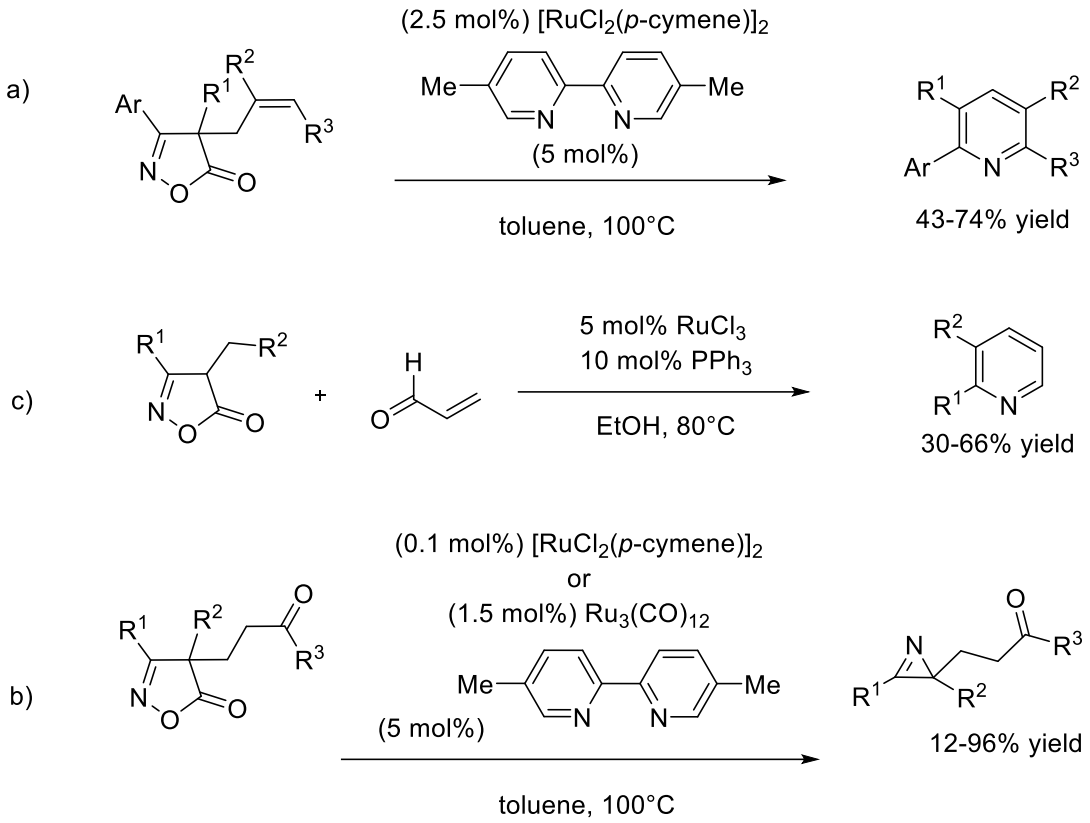
The isoxazole-5-ones are intriguing five-membered heterocycles, that participate in a rich panorama of chemical reactivity, being considered useful building blocks for chemical transformations. They possess three potential nucleophilic sites, in fact they exist as a mixture of three tautomeric forms, known as (‘*enamine-like’*) NH-form, (‘*imine-like’*) CH-form, and the (‘*enol-like’*) OH-form. The predominance of a particular tautomer over the others will depends on the nature of the substituents on the ring and the solvent employed.[46] (**Scheme 3.2**)



Scheme 3.2 Tautomeric forms of isoxazole-5-ones.

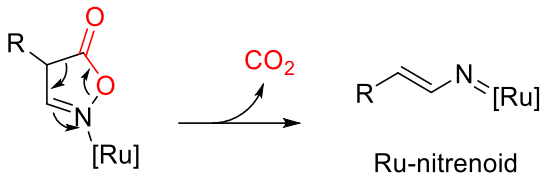
One of the most significant advantages in the utilizing of these compounds as building blocks, in the construction of more complex acyclic or cyclic molecules, lies in the ring opening capabilities, facilitated by the lability of the N-O bond. The nature of the final product obtained depends on the reaction conditions and the structural electronic properties of the substituents, particularly in position C4.[46]

The literature reports the Ru-catalyzed conversion of 4-allyl-isoxazol-5-ones into pyridines under various conditions, exploiting intra- or intermolecular rearrangement processes.[47a,b] (**Scheme 3.3a,b**) On the other hand, starting from substrates bearing different substituent in C4 and by using the same reaction conditions of the intramolecular process, aziridines could be obtained as exclusive product.[47c] (**Scheme 3.3c**)



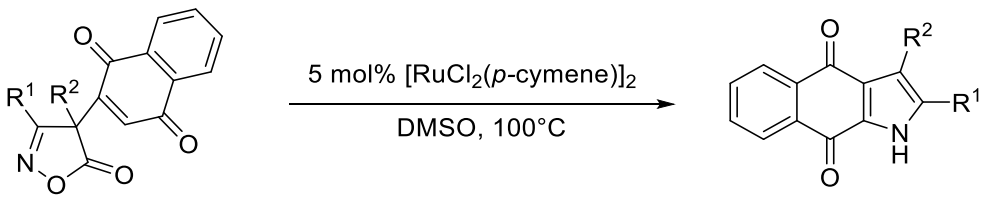
Scheme 3.3 Ru-catalysed cyclization processes.

It is important to highlight the common behaviour of all these reactions to occur with a decarboxylative rearrangement pathway coinciding with the generation of the Ruthenium-vinyl-nitrenoid species.[48] (**Scheme 3.4**)



Scheme 3.4 Ruthenium-catalysed decarboxylative path.

In this regard, in 2015 our research group, contributed by exploiting the reactivity of 4,4'-disubstituted isoxazole-5-ones, under ruthenium catalysis, for the synthesis of different benzo[*f*]indole-4,9-diones derivatives through a ring opening/ring closing pathway.[49] (**Scheme 3.5**)



Scheme 3.5 Conversion of isoxazole-5-ones to benzo-fused indole derivatives.

Our purpose was to study the reactivity of differently substituted isoxazole-5-ones under ruthenium catalysis, to investigate possible rearrangement processes resulting in the formation of different *N*-containing heterocycles.

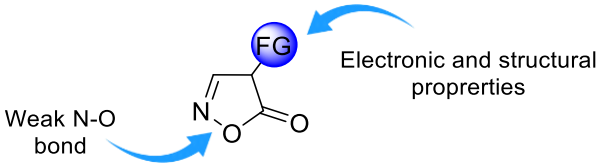
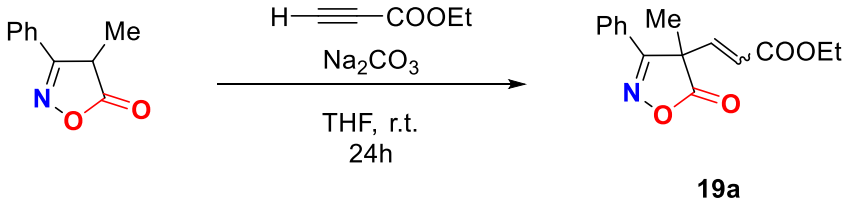


Fig. 3.1 Structures of Isoxazol-5-ones.

We will see how the nature of the obtained product will arise from the nature of the substituent in C4 position.

3.2.2 Results and discussion

As a starting point, we decided to initiate the studies by testing the reactivity of substituted 4-alkenyl-isoxazole-5-ones **19** under ruthenium catalysis**.** The synthesis of the intermediate 4-substituted isoxazole-5-ones **19a** is illustrated in **Scheme 3.6**.

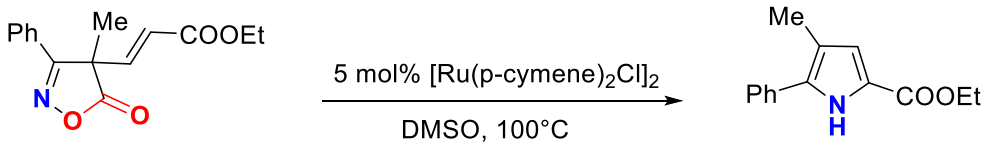


19a

Scheme 3.6 Preparation of 4-substituted isoxazol-5-ones **19a** by the reaction with alkynes.

The reaction was performed using ethyl propiolate, Na_2CO_3 as base, in THF under mild reaction conditions. We screened different conditions and observed that using TEA as base, in DCM, resulted in the formation of a mixture of 4- and 2-alkenyl isoxazole-5-ones, each existing as a mixture of *E/Z* isomers on the double bond. However, switching to Na_2CO_3 as base, led to improved regioselectivity of 4-alkenyl isoxazole-5-ones. In this case as well, a mixture of product was obtained, but with a higher ratio of 5:1 *E/Z* compared to the 3:1 ratio obtained previously.

At this point, the reaction on purified (*E*)-**19a** performed in the presence of 5 mol% of [Ru(*p*-cymene)Cl_2]$_2$ as catalyst, in DMSO at 100°C allowed the formation of 2,3,5-trisubstituted pyrrole in quite good yield. (**Scheme 3.7)**



19a **20a**

Scheme 3.7 Synthesis of the tri-substituted pyrrole **20a.**

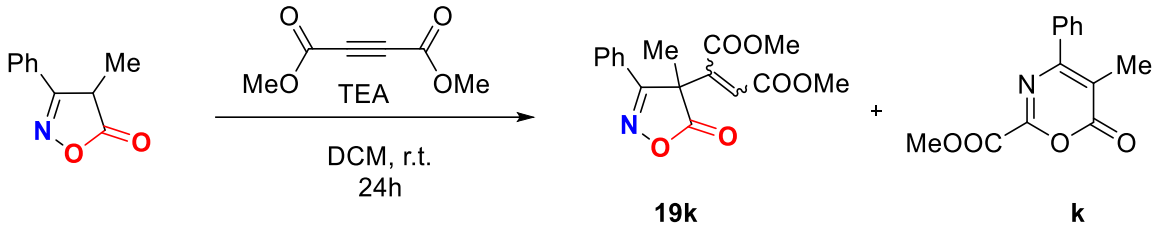
As well, we decided to test the reactivity of the (*Z*)-**19a** isomer. Fortunately, this isomer also undergoes the rearrangement, albeit with longer reaction time, due to the *in situ* conversion of the *Z* isomer into *E* isomer.

This allowed us to carry out the reaction on the *E/Z* mixture obtained from the previous reaction without purification, resulting in a simpler procedure and enhancing the reaction economy. This

approach reduced the need for purification steps and separation of the unreactive 2-alkenyl derivative.

Having established the efficacy of this synthetic procedure, we decided to expand the scope of the reaction to different substituted 4-alkenyl-isoxazole-5-ones prepared with different alkynes, bearing EW groups.

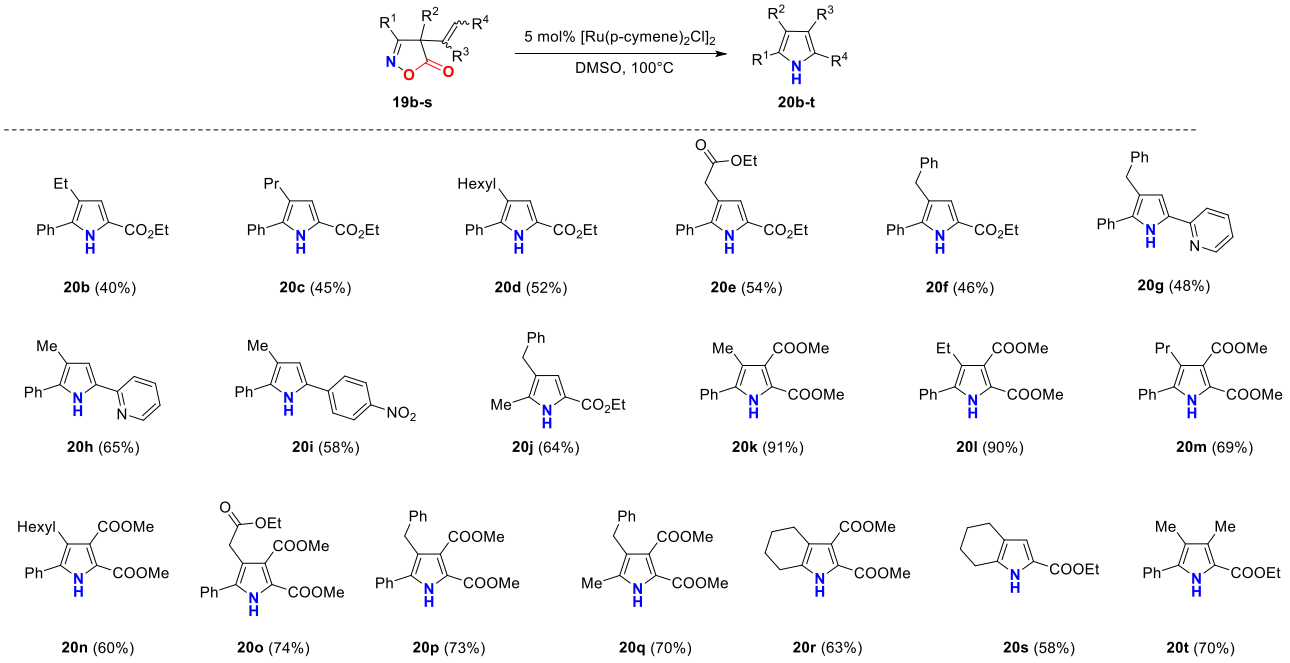
The C4 functionalization with ethyl propiolate occurred under the above conditions, while the reaction between isoxazolones and dimethyl acetylene dicarboxylate (DMAD) was performed in DCM at room temperature, with TEA as base. (**Scheme 3.8**)



Scheme 3.8 Preparation of 4-substituted isoxazol-5-ones **19k** by the reaction with DMAD.

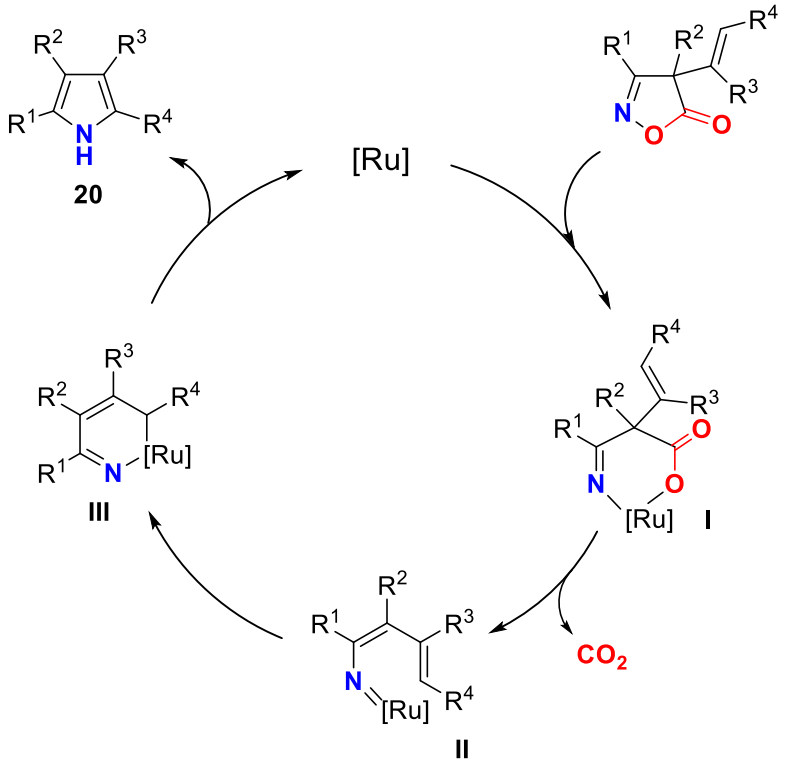
For the synthesis of this intermediate a large excess of alkyne was required to avoid the formation of a substituted 1,3-oxazin-6-one **k** as by-product.

As reported in **Scheme 3.9**, exploiting the Ru-catalysed reaction, three- and tetra-substituted pyrroles were obtained with satisfactory yields.



Scheme 3.9. Rearrangement of the isoxazol-5(4*H*)-ones into the tri- **19b-j,s** and tetra- substituted pyrroles **19k-r,t**.

A plausible reaction mechanism is depicted in **Scheme 3.10**.

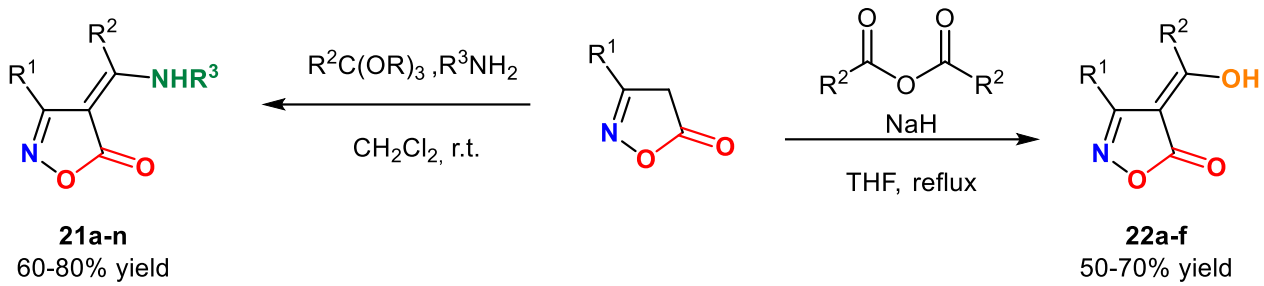


Scheme 3.10. Proposed reaction mechanism for the synthesis of tri- and tetra-substituted pyrroles through a decarboxylative path.

The mechanism involves the initial oxidative addition of Ruthenium catalyst, due to the cleavage of the N-O bond, forming the intermediate **I.** This intermediate then undergoes a decarboxylative step to generate a Ruthenium-nitrenoid species **II.** Following an electrocyclic reaction, intermediate **II** transforms into ruthenacyle **III.** Finally, reductive elimination of the metal allows the formation of the pyrrole with the consequent regeneration of the catalytic species.

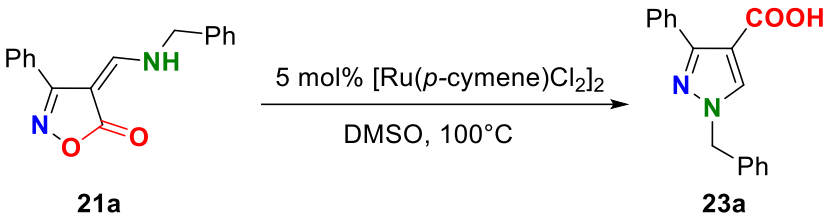
The proposed mechanism aligns with precedent literature data regarding the already known decarboxylative behaviour of the isoxazole-5-ones.[47]

Due to the fundamental role of the substituent in position C4, we decided to test the reactivity of isoxazole-5-ones bearing, a hetero-alkylidene moiety at this position. Specifically, we investigate the behaviour of 4-(2-hydroaminoalkylidenyl)- (**21**) and 4-(2-hydroxyalkylidenyl) isoxazole-5-ones (**22**) prepared from 3-substituted isoxazole-5-ones. (**Scheme 3.11**)



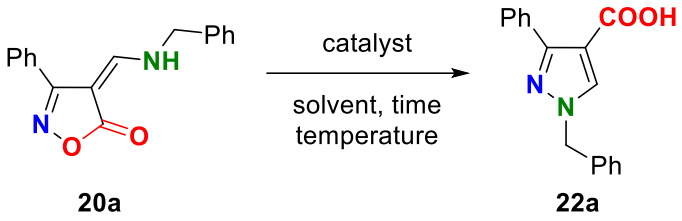
Scheme 3.11 Synthesis of 2-hydroamino- (**22**) and 2-hydroxyalkylidenyl (**22**) compounds.

In particular, compound **21a** was selected to study the reaction. We began by testing the reaction conditions previously used as reported in **Scheme 3.9**. In this case, we observed a different outcome and with the reaction furnishing a pyrazole derivative instead (**23a**). (**Scheme 3.12**)



Scheme 3.12 Synthesis of pyrazole derivative **23a**.

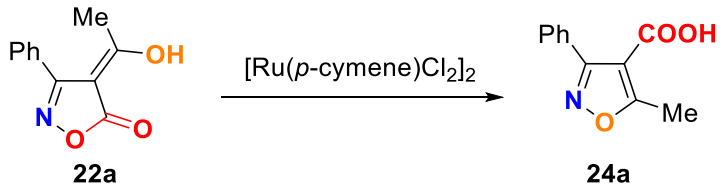
In the effort to improve the yields, we also explored different reaction conditions (**Table 3.1**).



Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Product (Yield%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$ (5)	DMSO	100	**22a** (49)
2	$[RuCl_2(p\text{-cymene})]_2$ (5)	MeCN	70	**22a** (68)
3	$Ru_3(CO)_{12}$ (5)	DMSO	100	S.M.
4[c]	$[RuCl_2(p\text{-cymene})]_2$ (5)	MeCN	70	S.M.
5[d]	$[RuCl_2(p\text{-cymene})]_2$ (5)	MeCN	70	S.M.
6	$Pd(OAc)_2$ (10)/PPh_3 (40)	toluene	80	degradation products
7	$Pd(PPh_3)_4$	toluene	80	degradation products
8	$[Ir(1,5\text{-cod})Cl]_2$ (10)	DMSO	80	S.M.
9	$[Ir(1,5\text{-cod})Cl]_2$ (10)	DMSO	100	S.M.
10	$[Ir(1,5\text{-cod})Cl]_2$ (10)	DMSO	120	S.M.
11	$FeCl_2$	MeCN	70	degradation products

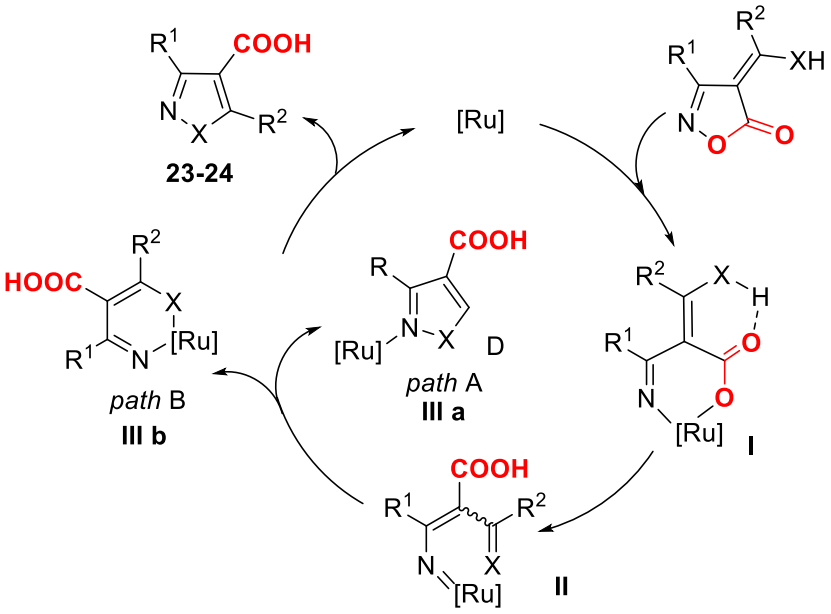
Table 3.13 a) Reaction conditions: **21a** (1.0 mmol), catalyst (5-10 mol%), solvent (3.0 mL), heating in oil bath, 24 hours. b) Isolated yields. c) With 1.1 eq. of TEA 1.1 eq.; d) With 1.1 eq. of Na_2CO_3.

Having identified the optimal reaction conditions, we proceeded to evaluate the reactivity of the 2-hydroxyalkydenyl derivatives. Remarkably, even on these substrates, a non-decarboxylative pathway was observed, resulting in the production of isoxazole derivatives (**24a**). (Scheme **3.14**)

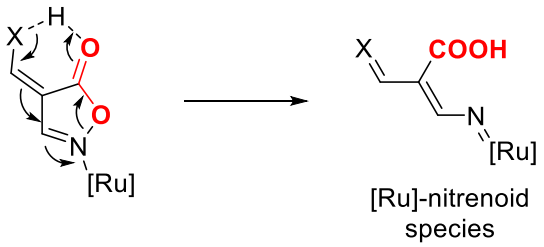


Scheme 3.14 Conversion of the 4*H*-isoxazol-5-ones (**22a**) into isoxazole-4-carboxilic-acids (**24a**)

To rationalize the presence of the carboxylic substituent in the final product, we propose a possible mechanism outlined in **Scheme 3.15**. Following the cleavage of the N-O bond, due to the insertion of the ruthenium catalyst, we hypothesize that the presence of the hydrogen on the heteroatom in position C4 stabilized, the intermediate **I** through an intramolecular hydrogen bond. This stabilization prevents the loss of carbon dioxide, leading to the generation of the nitrenoid species **II**. The subsequent formation of the intermediate **III** allows for the production of the pyrazole or isoxazole compounds, either through deligandation (**Scheme 3.15, path A**) or a reductive elimination step, (**Scheme 3.15, path B**) with the regeneration of the ruthenium catalyst.

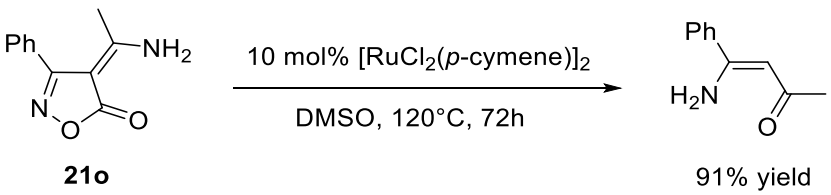


Scheme 3.15. Proposed mechanism for the synthesis of different substituted pyrazole and isoxazole through a NON-decarboxylative path.



Scheme 3.16 Mechanism for the formation of the ruthenium-nitrenoid intermediate without decarboxylation.

Further experiments were performed on substrate **20o**, to investigate the reactivity of the primary enamines in position C4. Treatment of the substrate under the same reaction conditions did not give the cyclized product. Instead, it quantitatively afforded (Z)-1-amino-1-phenyl-1-buten-3-one, thus confirming the inability of the primary aminoalkylidene derivatives to generate pyrazoles. (**Scheme 3.17**)

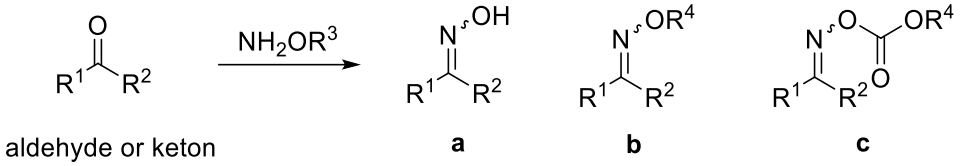


Scheme 3.17. Reaction performed on Isoxazole-5-ones bearing a primary enamine group in position C4.

Rearrangement reactions of aromatic and heteroaromatic oximes

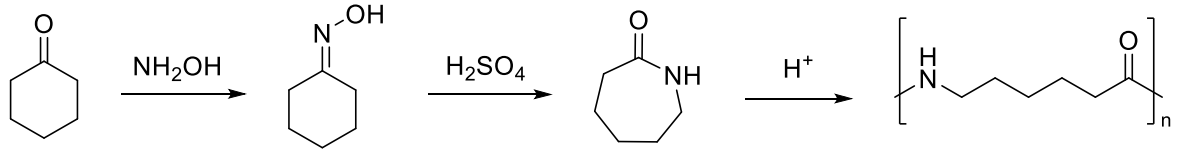
3.3.1 Background

Oximes constitute a versatile functional group that can be easily synthetized from aldehydes or ketones through nucleophilic addition of hydroxylamine derivatives, leading to the formation of different types of oximes: hydroxy oximes (**Scheme 3.18a**), oxime ethers (**Scheme 3.18b**) and oxime esters (**Scheme 3.18c**).[50]



Scheme 3.18. Synthesis of oxime (**a**) and oxime derivatives (**b, c**).

These compounds find extensive use in both laboratory and industrial applications. In particular, as mentioned previously, one of the most significant achievements in this field was the *Beckmann* rearrangement (**Scheme 3.19**).[51] This transformation enabled the synthesis of caprolactam, a key precursor for nylon-6, whit global production exceeding several million metric tons annually.



Scheme 3.19. Oxime as a precursor of Nylon-6.

Indeed, oximes play an important role in pharmaceutical applications as evidenced by their presence in commercial drugs like Pralidoxime and Obidoxime. (see **Fig. 3.2,** on the left)[52] Additionally, oxime ethers display various pharmaceutical properties, including antifungal, antibacterial, anti-inflammatory, anticonvulsant, and antitumor activities. (**Fig. 3.2,** on the right)[53]

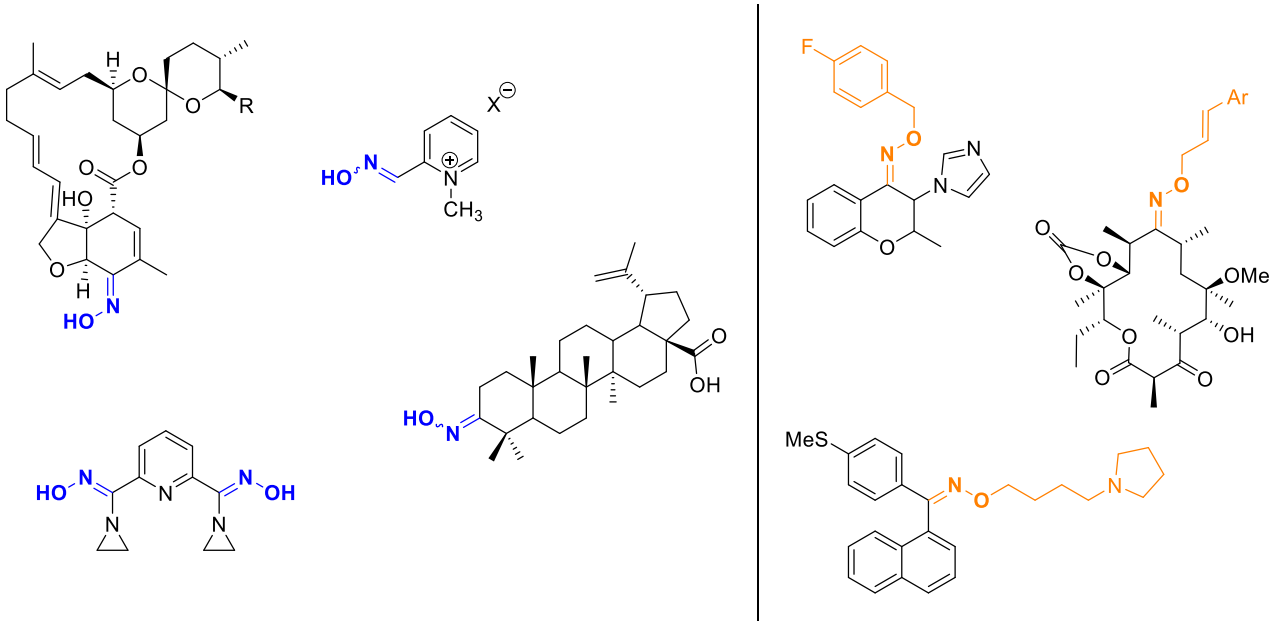


Fig. 3.2 Oximes and oxime-ethers with biological activity.

Among these important applications, oximes are employed as ligands for the complexing with transition metals (Pd, Cu, Ni, Re, Zn). This is owing to the presence of three active sites: C, N and O groups whose acidity can play a pivotal role in metals coordination (**Fig. 3.3**).[54]

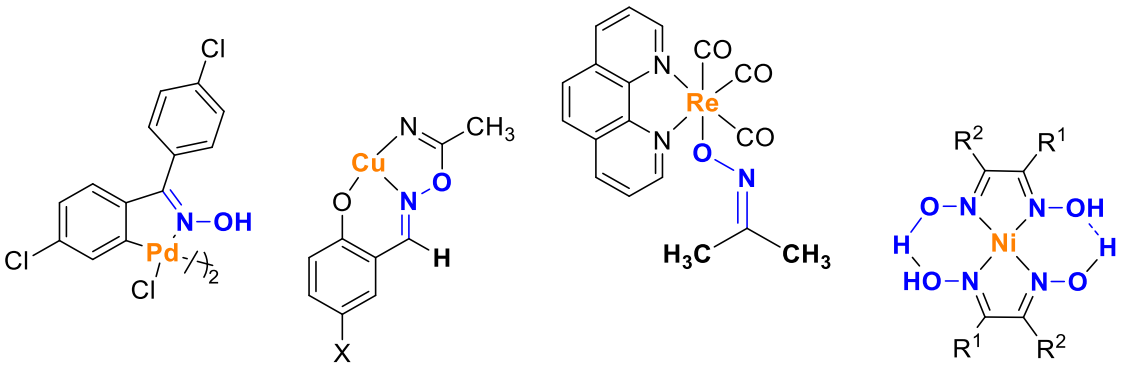
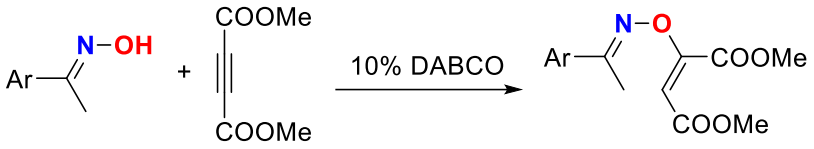


Fig. 3.3 Oxime complexation with transition-metals.

3.3.2 Results and discussion

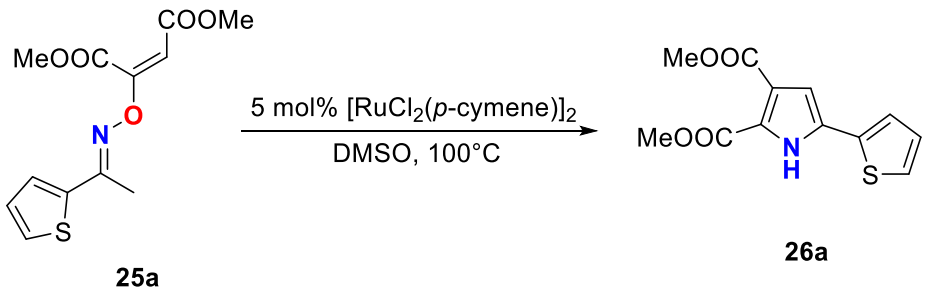
In recent years, there has been an increase or reports in the literature regarding the development of transition metal-catalysed transformation of oximes, particularly in the fields of direct C-H bond activation, Heck reactions and cross-coupling.[55] Conversely, to the best of our knowledge, only one oxime reaction under ruthenium catalysis is reported in literature.[56] Considering our ongoing studies on the rearrangement reactions of the isoxazole-5-ones under ruthenium catalysis, we considered the behaviour of different oxime derivatives, particularly the *O*-vinyl oximes, with Ru-catalysts.

The synthesis of the substrates follows methods described in the literature, starting from aryl- or heteroaryl-methyl ketones or aldehydes and NH_2OH, followed by the reaction with electron-poor alkynes, such as dimethyl acetylene dicarboxylate, under basic catalysis.[57] (**Scheme 3.20**)



Scheme 3.20 Synthesis of compound *O*-oxime ether (**25**).

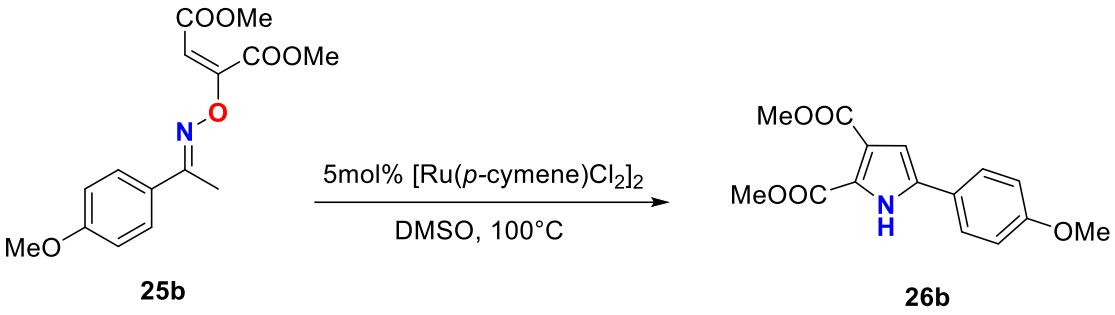
We employed the *O*-vinyl oxime **25a**, to investigate the reaction under $[Ru(p\text{-cymene})Cl_2]_2$ catalysis, using the same reaction conditions as those previously applied to the isoxazol-5-ones, operating at 100°C in DMSO as solvent. After 15 hours the reaction resulted in the formation of substituted pyrroles **23a**, evidently through a rearrangement process. (**Scheme 3.21**)



25a **26a**

Scheme 3.21 Synthesis of the tri-substituted pyrrole **26a**.

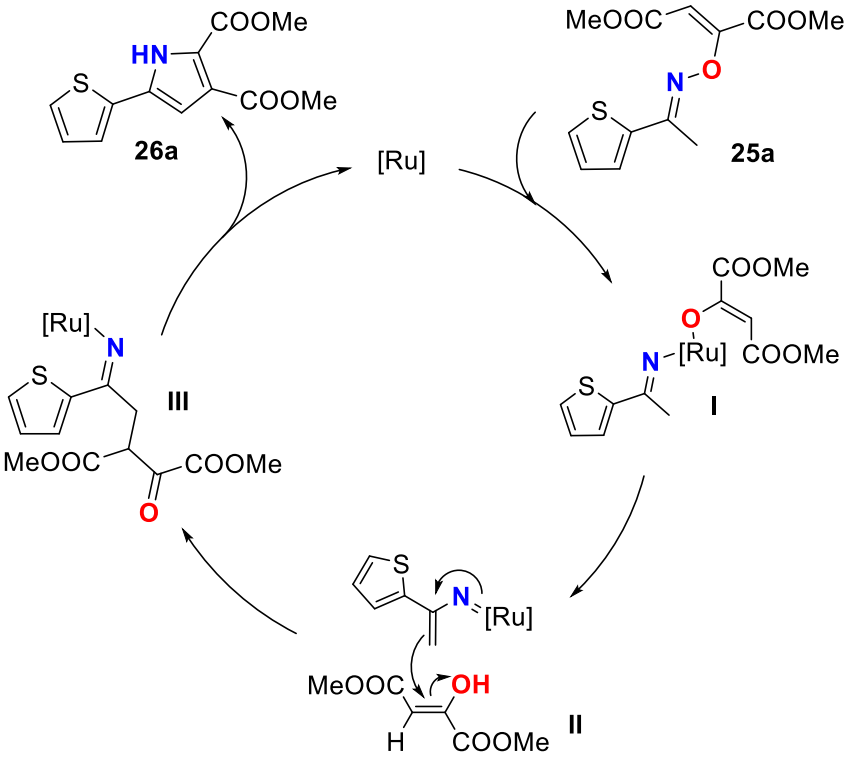
The result was confirmed by running the reaction on the substrate **25b**, obtaining the dimethyl 2-aryl- 1*H*-pyrrole-2,3-dicarboxylate **26b. (Scheme 3.22)**



25b 26b

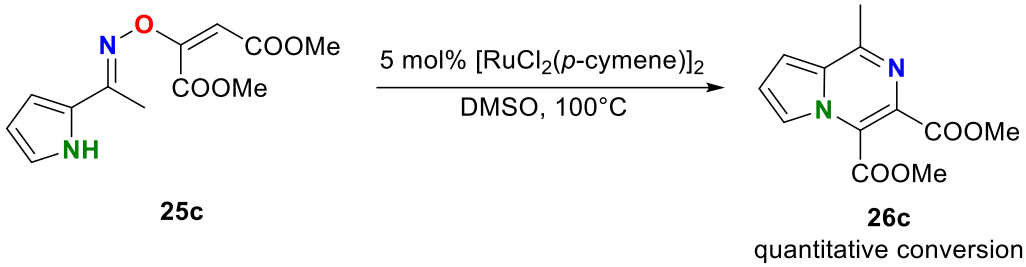
Scheme 3.22 Synthesis of pyrrole **26b.**

In analogy to previous studies involving ruthenium complexes on isoxazole rings, which have reported the insertion of the metal into the N-O bond, we propose an analogous mechanism. This mechanism is based on the oxidative addition of the Ru(II)-complex with the cleavage of the N-O bond and the formation of the intermediate **I** which can further evolve into the vinyl-nitrene-Ru intermediate **II**. A subsequent electrocyclic reaction produces the imino-carbonyl-Ru complex **III**. The ring closure of **III** then affords the product **26a** and the reductive elimination of the metal to restart the catalytic cycle. **(Scheme 3.22)**



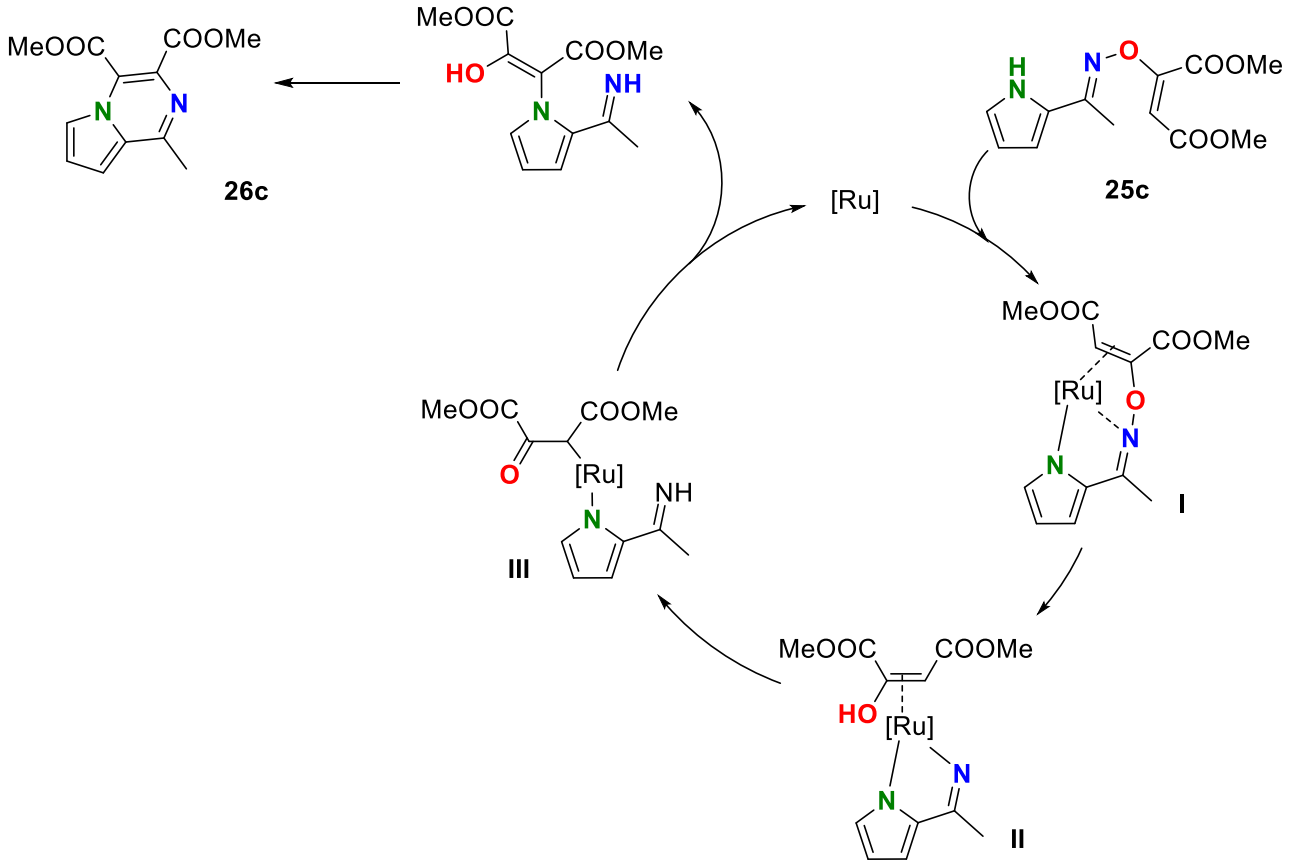
Scheme 3.22 Proposed reaction mechanism.

In the attempt to broaden the scope of the reaction, we also examined the reactivity of the *O*-vinyl-oxime **25c** derived from 2-acetyl pyrrole. (**Scheme 3.23**) Under the same reaction conditions, this substrate yielded a different outcome, resulting in the formation of the bicyclic systems pyrrolo[1,2-α] pyrazine **26c**, alongside a non-separable mixture of products.



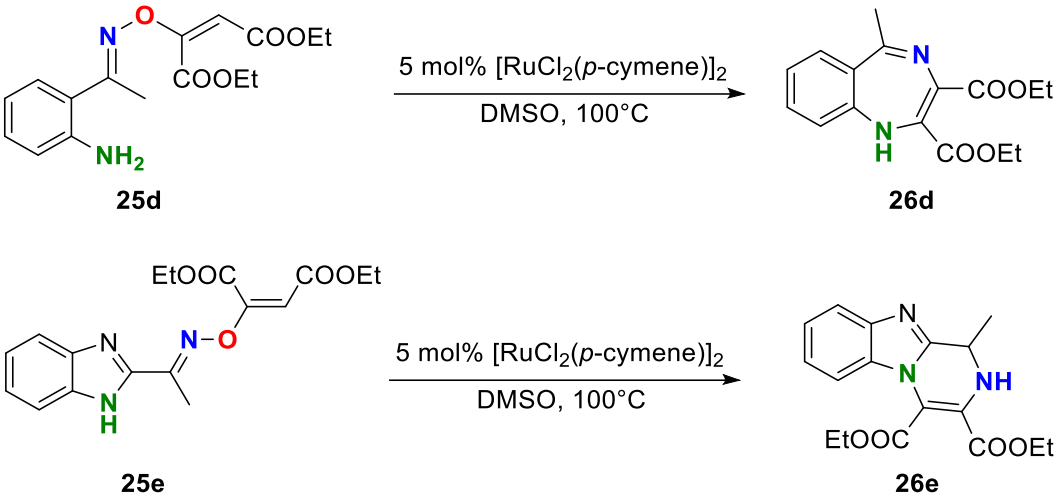
Scheme 3.23. Study of the reactivity of pyrrole-*O*-vinyl-oxime **25c**.

Regarding the mechanism, we propose the initial activation of the nitrogen atoms by ruthenium with the contemporary cleavage of the *N-O* bond and the coordination of the metal to the unsaturated system. Subsequently, the nucleophilic addition of the pyrrole nitrogen to the coordinated enol gave the intermediate **II**. Then, the reductive elimination of the metal produces the imino-enol **III** able to give the final product **26c** *via* the nucleophilic addition/dehydration thereby regenerating the ruthenium catalyst.



Scheme 3.24. Proposed mechanism for the synthesis of the bicyclic systems.

Having understood the potential of this rearrangement process, we applied the reaction on different *O*-vinyl oximes **25d**,**e** arising respectively from the 2-amino-acetophenone and the benzoimidazole-2-carbaldehyde. As supposed, from these substrates we reported the formation of the substituted benzodiazepine **26d** and benzo[4,5]imidazo[1,2-*a*]pyrazine **26e**. (**Scheme 3.25**)



Scheme 3.25. Synthesis of benzodiazepine **26d** and benzo[4,5]imidazo[1,2-*a*]pyrazine **26e.**

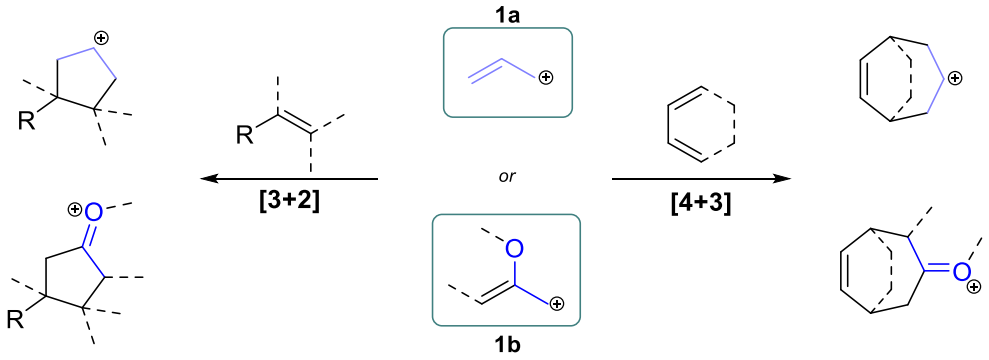
Chapter 4_*Organocatalysis*

Catalytic enantioselective [3+2] cycloaddition reaction: exploiting the reactivity of allyl-cation

4.1.1 Introduction

Cycloaddition reactions represent a fundamental class of chemical transformations wherein two or more unsaturated molecules combine to form cyclic compounds, often leading to an increase in molecular complexity. This represents a powerful and versatile tool extensively used for the synthesis of a plethora of molecular structures with different size and functionalities.[58]

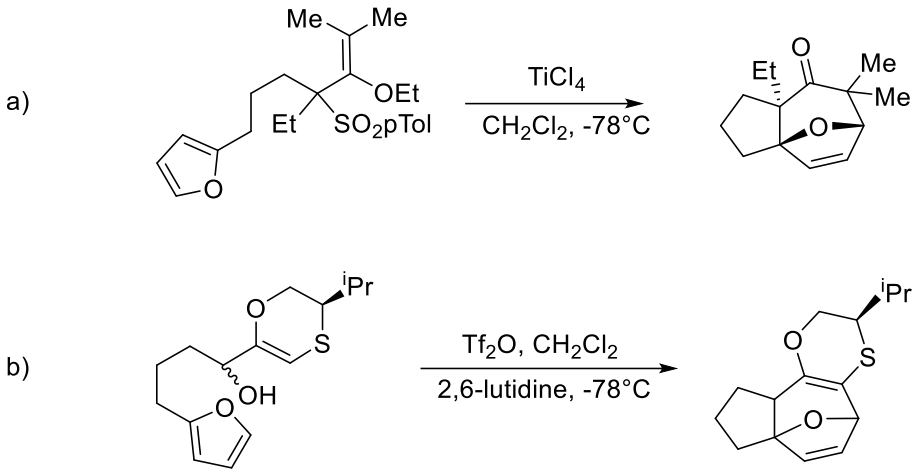
The use of allyl and oxyallyl cations as electrophiles in [3+2] and [4+3] cycloaddition pathways, play an important role, given their high reactivity as intermediates.[59a-d](**Scheme 4.2**) The advantages in the use of these skeletons come also from the ease of their *in situ* generation, starting from readily accessible precursors. Moreover, they are able to react with a wide range of substrates, potentially affording endless number of cycloaddition products.[58e-f]



Scheme 4.1 Cycloaddition of allyl (1a) and oxyallyl (1b) cations.

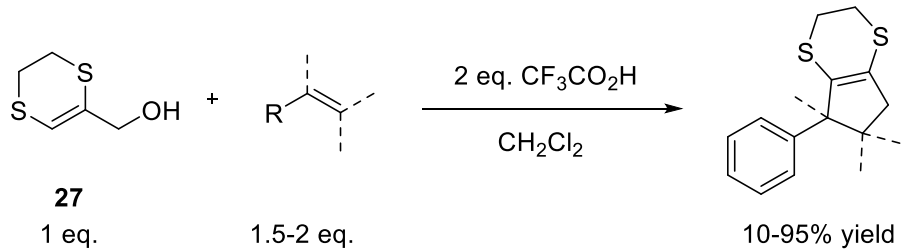
Nevertheless, this high reactivity implies that the initial carbocationic species formed is susceptible to subsequent reactions resulting in the generation of by-products or complex mixtures of products. This drawback makes the control of such reactions challenging, thereby limitating their synthetic applications. Despite this significant challenge, few examples in which both the allyl and the oxyallyl cation are used as synthetic precursors for more complex structures have been reported in literature.

Since 1991, *Harmata et al.* reported their pioneered studies on intramolecular [4+3] cycloaddition reactions, exploiting the reactivity of vinylthionium ions generated from allylic sulfones[60a] (**Scheme 4.2a**) and allylic sulphur stabilized alcohols[59b] as precursors of functionalized, fused, 5-7 carbocyclic systems. (**Scheme 4.2b**)



Scheme 4.3 *Harmata* studies on allylic sulfones (a) and allylic sulphur stabilized alcohols (b).

More recently, in 2016[61a] and later in 2022 [61b], *Winne et al.* explored sulphur containing heterocycles as possible precursor of reactive and stabilized allyl-type cations through simple treatment with protic acid. (**Scheme 4.4**) It has been proved that this method provides a successful access to a range of highly regio- and stereoselective cyclopentenoid scaffolds leading to complex natural products, such as ±Cuparene, also involving a hydrodesulphurization sequence.



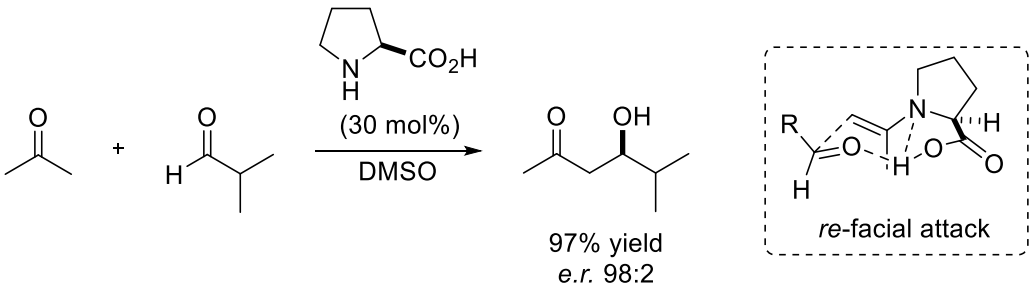
Scheme 4.4 [3+2] cycloaddition reaction between dtdh-2-methanol and different functionalized olefins, Prof *Winne.*

4.1.2 Background

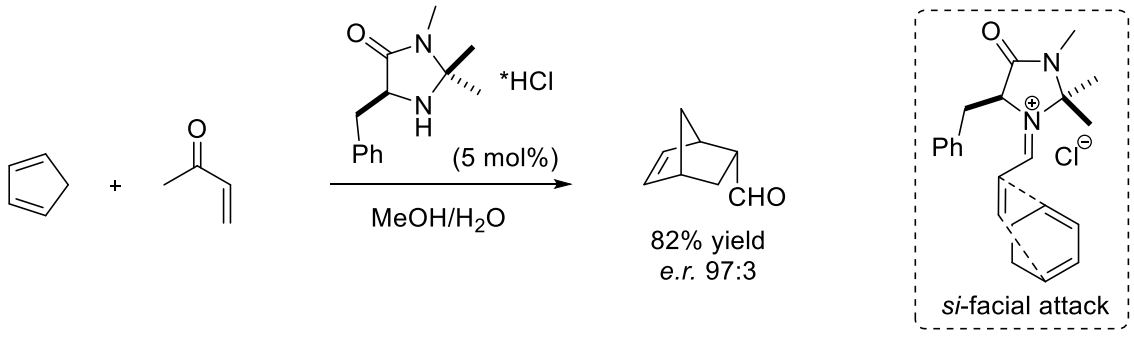
The term organocatalysis refers to the use of metal-free organic compounds that, even if in sub-stoichiometric amount, are capable of facilitating organic reactions.

Inspired by Nature and the ability of the enzyme of promoting enantioselective compounds, scientists have laid the groundwork for asymmetric organocatalysis, allowing a green and direct access to highly functionalized chiral products, including important key intermediates in the total syntheses of bioactive compounds.[62]

Even if nowadays organocatalysis is still a hot topic, it was only in the early 2000s that the avant-garde discovery of Prof *List* and Prof *MacMillan* marks the beginning of this area as a third strategy in asymmetric catalysis next to metal and enzymatic catalysis. They independently demonstrated that small organic molecules could act as catalyst for asymmetric transformation. In particular, *List*[63] reported how proline could promote the formation of new C-C bond in aldol-reactions *via* enamine catalysis (**Scheme 4.7**), and *MacMillan*[64] how imidazolidinone is able to catalyse Diels-Alder reactions *via* iminium ion catalysis. (**Scheme 4.8**)



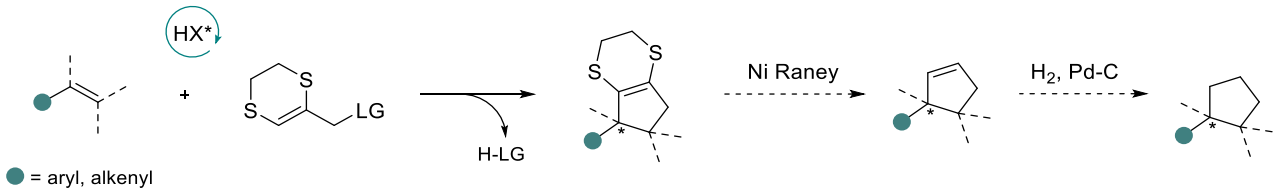
Scheme 4.7 Proline-catalysed direct asymmetric aldol reaction, Prof *List.*



Scheme 4.8 The fist highly enantioselective organocatalytic Diels-Alder reaction, Prof *MacMillan.*

Since then, the interest in this field has significantly increased due to the innovation and the novelty of the technique which represent a milestone in the synthesis of enantiopure compounds that would otherwise require numerous synthetic steps and the use of expensive chiral auxiliaries. Nowadays, organocatalysis stands as one of the most investigated fields in organic chemistry and it is widely recognized as a principal domain of enantioselective synthesis.[65]

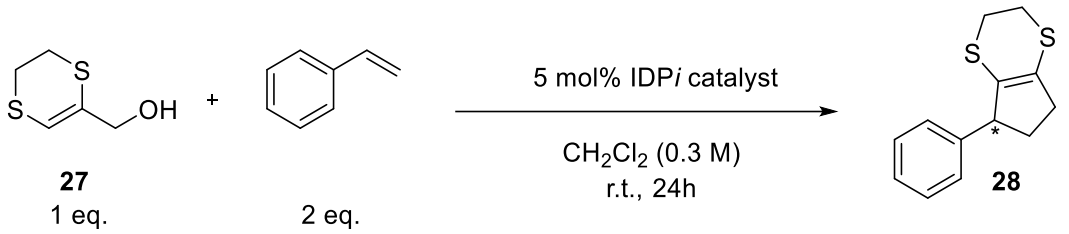
During my PhD I worked in Prof. *Benjamin List's* research group at MPI (Max-Planck-Institute für Kohlenforshung, Mülheim an der Ruhr, Germany) on the development and the optimization of catalytic enantioselective [3+2] cycloaddition reaction exploiting the reactivity of allyl-cation using IDP*i* (imidodiphosphorimidates) as organo-catalysts, already developed by *List* group in 2016.[66]
My goal was to use an organocatalytic approach to obtain enantiopure cyclopentenoid and cyclopentanoid scaffolds that are commonly used for pharmaceutical applications. (**Scheme 4.9**)



Scheme 4.9 Synthesis of enantiopure cyclopentenoid and ciclopentanoid scaffold.

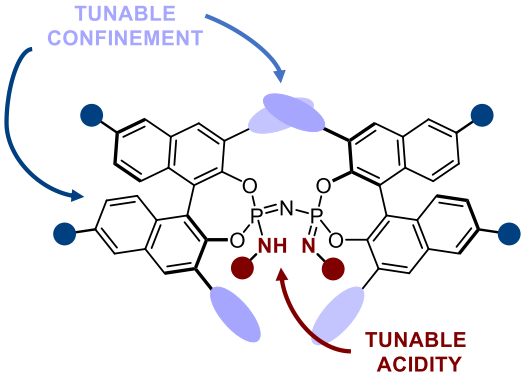
4.1.3 Results and discussion

As starting point, styrene was used as a model of olefin for the screening studies with (5,6-dihydro-1,4-dithiin-2-yl) methanol as allyl cation source. An initial attempt for the study of this [3+2] cycloaddition reaction was performed using 5 mol% of different substituted IDP*i* as Brønsted acid catalysts in CH_2Cl_2 (0.3 M) at room temperature for 24h. (**Scheme 4.10**)



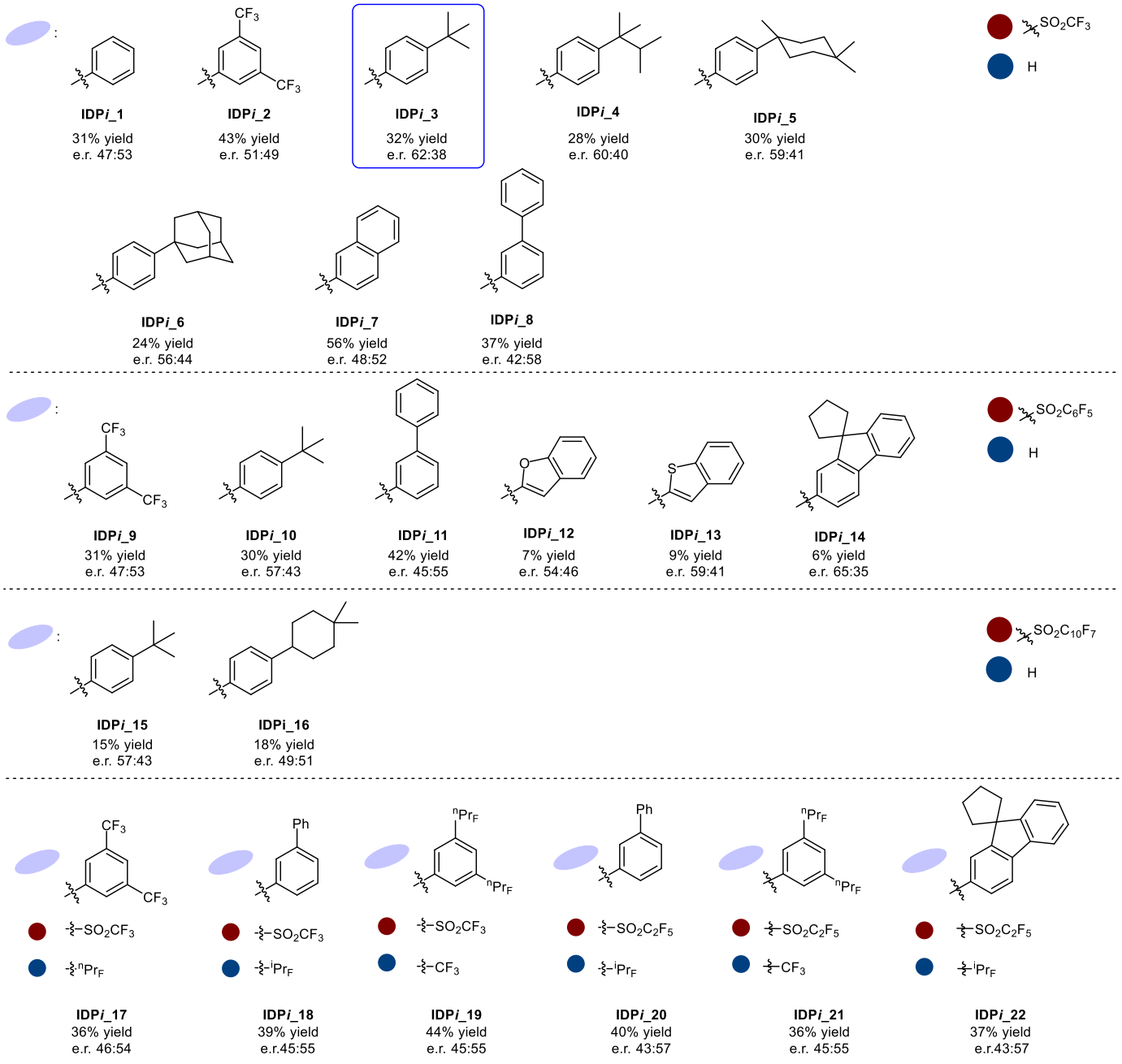
Scheme 4.10 Starting screening conditions.

The choice to initiate the catalyst screening with IDP*i* (pKa = 2.0 - 4.5 in MeCN) (**Imagine 4.1**) rather than other well-known Brønsted acid's catalysts is due to their higher acidity. For this purpose, different substituted IDP*i* catalysts were screened to evaluate their efficiency by varying both acidity and confinement of the catalytic system. (**Scheme 4.11**)



Imagine 4.1 IDPi catalysts with different modifications.

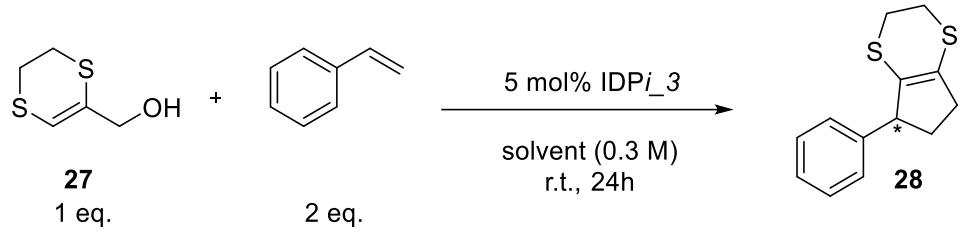
In **Scheme 4.11,** were depicted the differently substituted IDP*i* Brønsted acid catalysts used in the screening reaction, with the results of the yields and enantioselectivity.



Scheme 4.11 Multi-screening of different substituted IDP*i* catalysts.

All the catalysts demonstrated the capability to provide the desired product but, among them, only IDP*i*_3 emerged as the most promising candidate in this preliminary screening, exhibiting favourable results in both yield and enantiomeric ratio (30% yield, e.r. 62:38). Also, the IDP*i*_14 showed good results in terms of enantioselectivity (e.r. 65:35) but a low reaction yield was obtained (6%) probably due to the high sterical hindrance of the substituent in position 3,3' of the catalyst that probably hampered the reaction.

To further enhance these outcomes, additional investigations were conducted on solvent, concentration, temperature, and stoichiometry. Thus, starting from the above conditions different solvents were tested, at room temperature, for 24 hours. (**Scheme 4.12**)

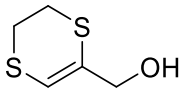
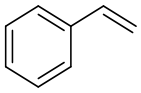


Entry	Solvent (0.3 M)	Yield (%)	e.r.
1	CH_2Cl_2	30	62:38
2	$CHCl_3$	37	58:42
3	THF	9	60:40
4	Et_2O	10	57:43
5	Toluene	45	56:44
6	Cyclohexyl	<10	61:39
7	MeOH	n.d.	n.d.

Scheme 4.12 Solvent screening at room temperature for 24h, 1eq. dtdh-2-methanol, 2eq styrene, 5mol% IDP*i*_3.

In addition to chloroform, both DCM and toluene showed good results in terms of reaction yields, although with a slight compromise in enantioselectivity. On the contrary, THF showed quite similar enantiomeric ratios to chloroform but with lower yield values. As a results, since no substantial improvement was observed, DCM was selected as solvent to continue the screening studies.

In the process of optimizing the reaction, the stoichiometry of the reagents was examined. Initially, we intended to employ the olefin as the limiting reagent for a better reaction's economy. Therefore, our initial attempts involved the use of an excess of dtdh-methanol **27**. (**Scheme 4.13, entry 1**) However, as reported in **Scheme 4.13, entry 3** showed the best results in term of yield and e.r.. It is worth noting that no product formation was detected when the olefin was employed as the limiting reagent (**Scheme 4.13**, **entry 1**) and no outstanding results were also observed, even working in a large excess of it. (**Scheme 4.13, entry 5**)

Entry			Yield (%)	e.r.
1	3	1	n.d.	n.d.
2	1	1	<10	45:55
3	1	2	32	62:38
4	1	5	40	46:54
5	1	10	25	57:43

Scheme 4.13 Reagent stoichiometry screening at room temperature for 24h with 5mol% IDP*i*_3.

Using the best conditions, found so far, the loading of the catalyst was also evaluated. (**Scheme 4.14**)

Entry	Reaction time (h)	IDP*i* (mol%)	Yield (%)	e.r.
1	24	1	n.d.	n.d.
2	72	1	<5	63.37
3	24	2.5	<10	62:38
4	72	2.5	<10	57:43

Scheme 4.14 Evaluation of the loading of the IDP*i*_3 catalysts for 24h and 72h using 1eq. dtdh-2-methanol, 2eq styrene in CH_2Cl_2 (0.3M).

In the attempt to enhance catalyst efficiency and fine-tune reaction conditions, we reduced the amount of catalyst used. The rationale behind this modification was to potentially decelerate the generation of the cationic intermediate aiming to enhance enantioselectivity.

However, the data indicated that reducing the catalyst amount not only led to a decrease in product yield but also did not confer any advantage in terms of enantioselectivity. In particular, using 1 mol% of IDP*i*_3 no product formation was observed (**Scheme 4.14, entry 1**) while working with 2.5 mol% lead to the same e.r. value obtained in the standard reaction condition (e.r. 62:38) but with a decrease in the yield (see difference between **Scheme 4.14, entry 3** and **Scheme 4.11**, IDP*i*_3).

Moreover, no improvement in term of yield was obtained leaving the reaction for 72 hours.

A further parameter explored for optimizing the reaction was the temperature. We envisage that decreasing the temperature, the rate of the formation of the cationic intermediate would slow sown, thus promoting enantioselectivity.

For this attempt, **IDP*i*_3** catalyst was tested at different temperature for 24h. (**Scheme 4.15**)

Entry	Temperature (°C)	Yield (%)	e.r.
1	r.t.	30	62:38
2	10	21	65:35
3	0	10	68:32
4	-10	<10	70:30
5	-20	<10	74:26
6	-30	<5	74:26
7	-40	<5	10:30
8	-50	<5	87:13

Scheme 4.15 Temperature screening for 24h using 1eq. dtdh-2-methanol, 2eq styrene, 5mol% IDP*i*_3 in CH_2Cl_2 (0.3M).

As expected, the enantioselectivity of this cyclization relies on the temperature. Low temperature gave higher enantioselectivity but sacrificing the yield of the reaction. (**Scheme 4.15**, **entry 8**)

In the attempt to increase the yield at lower temperature, the reaction was also performed for longer times but no improvement both in term of yield and e.r. was observed. Performing the reaction at low temperature for 5 days the catalyst reactivity seems to decrease. (**Scheme 4.16, entry 3**)

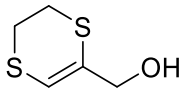
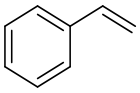
Entry	Temperature (°C)	Yield (%)	e.r.
1	-30	<5	77:23
2	-40	n.d.	n.d.
3	-50	n.d.	n.d.

Scheme 4.16 Temperature screening for 5 days using 1eq. dtdh-2-methanol, 2eq styrene, 5mol% IDP*i*_3 in CH_2Cl_2 (0.3M).

Even if the most favourable result in terms of enantiomeric ratio was achieved by working at -50°C for 24h (e.r. 87:13), the optimization process persisted at -20°C (e.r. 74:26).

This decision was motivated by the observation that, although working at -50°C led to higher enantioselectivity, it also resulted in a compromised yield. Therefore, it did not appear to be the optimal condition to pursue further optimization studies.

At this point, I chose to evaluate the impact of reagent stoichiometry by operating at -20°C. (**Scheme 4.17**)

Entry			Yield (%)	e.r.
1	3	1	n.d.	n.d.
2	1	1	<10	71.29
3	1	2	<10	74.26
4	1	5	<10	76:24

Scheme 4.17 Stoichiometry screening at -20°C using 5mol% IDP*i*_3 in CH_2Cl_2 (0.3M).

Compared with the results obtained by working at room temperature, as expected, working with styrene as limiting agent doesn't lead to the desired product; however, using excess of olefin leads to slightly better e.r. values. (**Scheme 17, entry 4**)

For the same reason, the concentration of the reaction was evaluated, and also in this case, the reaction performed at -20° (**Scheme 4.18**) does not lead any improvement.

Entry	Molarity (M)	Yield (%)	e.r.
1	0.15	<10	67:33
2	0.3	<10	74:26
3	0.6	<10	72:28
4	1	<10	71:29

Scheme 4.18 Concentration screening at -20°C using 1eq. dtdh-2-methanol, 5eq styrene, 5mol% IDP*i*_3 in CH_2Cl_2 (0.3M).

To complete this study also the other Brønsted acid catalysts were screened.
Specifically, CPA (Chiral Phosphoric Acid), IDP (ImidoDiPhosphate) and DSIs (DiSulfonImide) catalysts were examined despite their lower acidity in comparison with the IDP*i* ones to assess their efficacy in catalysing the cycloaddition reaction. (**Figure 4.19**)

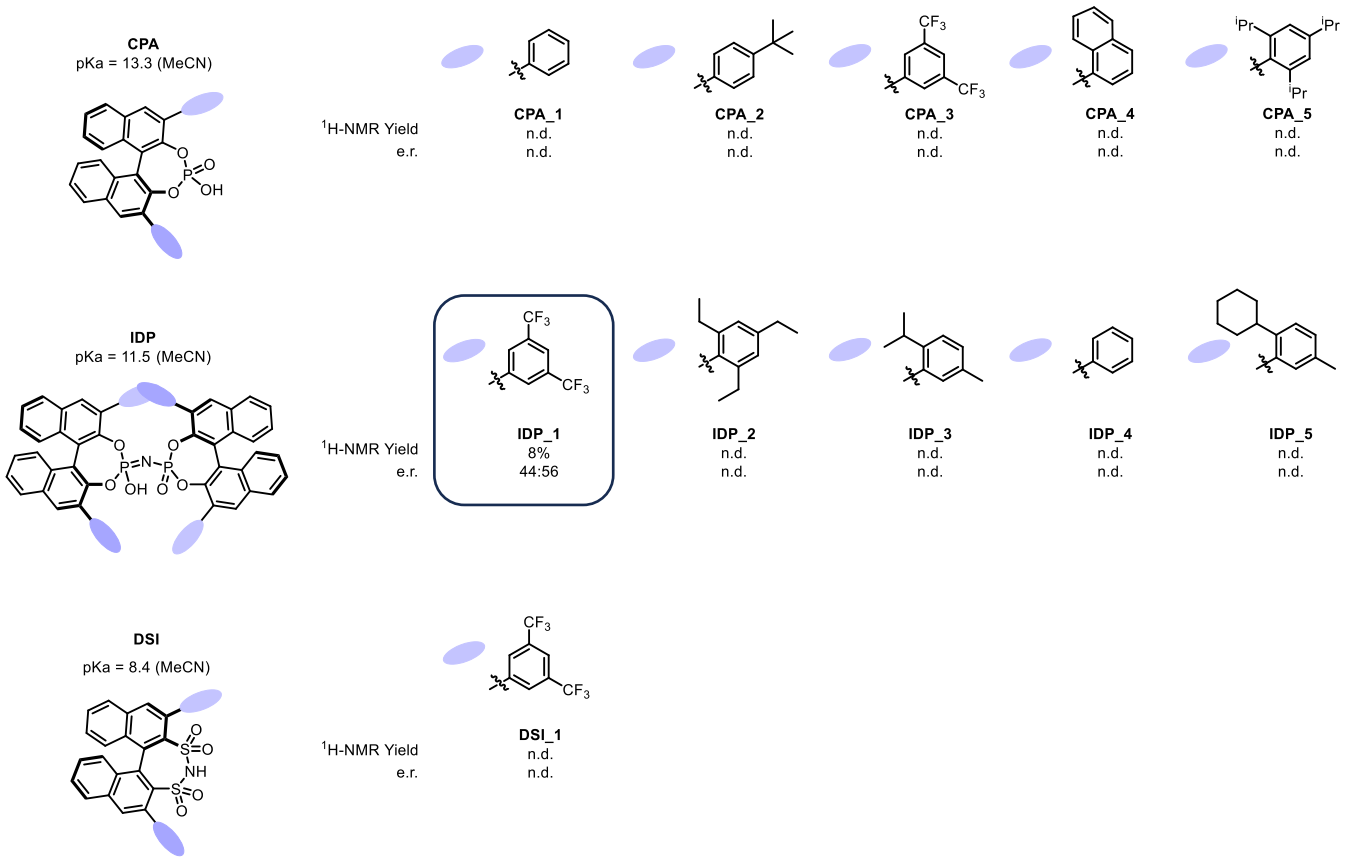


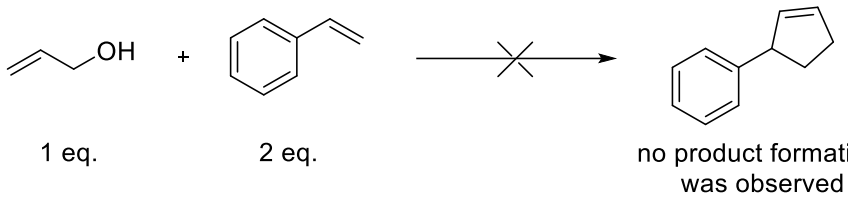
Figure 4.19 Brønsted acid catalysts screening at room temperature using 1eq. dtdh-2-methanol, 2eq styrene, 5mol% of catalyst in CH_2Cl_2 (0.3M).

However, as expected, most of the other tested Brønsted acids tested could not give any of the product. IDP_1, on the other hand, exhibited the "highest" reactivity, yielding 8% (e.r. 44:56) of the desired product when 5% of catalyst was used at room temperature. (**Scheme 4.19**)

Moreover, lower temperatures were investigated to assess if, similarly to the IDP*i* catalysts, reducing the temperature, an increase in the enantiomeric excess of the product could be achieved. Unfortunately, performing the reaction at temperature lower than 25°C for 2,3 and 5 days does not lead to any conversion of the starting material.

The experiments performed until now showed the importance of the stabilization of the allylic intermediate in order to promote the cyclization path.

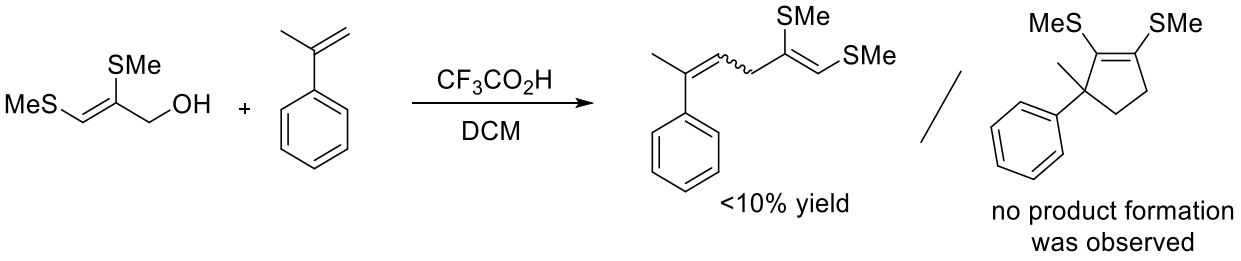
As negative control, the reaction was also performed in the presence of the simple allylic alcohol instead of the sulphur stabilized one (**Scheme 4.20**)



Scheme 4.20 Reaction between allyl alcohol and styrene performed at r.t. in the presence of 5 mol% of IDP*i*_3 in DCM (0.3M).

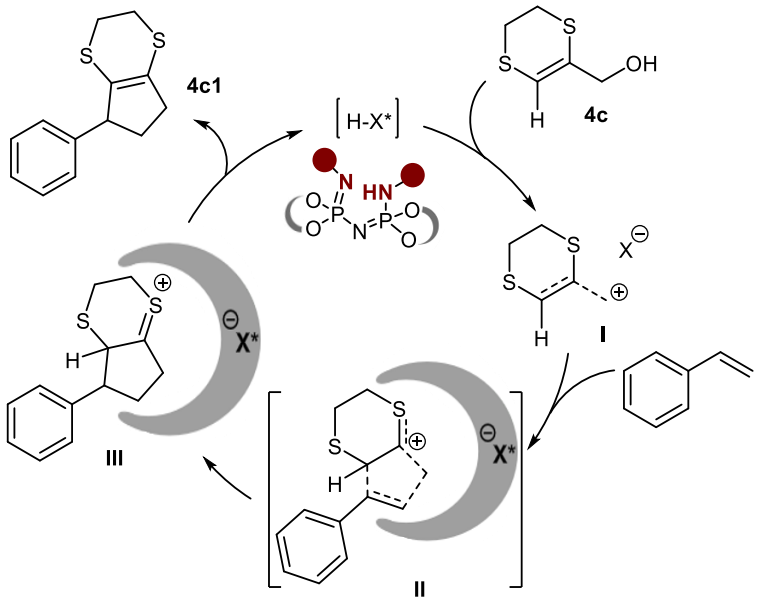
This condition highlights the importance of stabilizing the allylic moiety. As expected, only a complex mixture of products was detected without any indication regarding the desired product, highlighting the importance of the allylic intermediate with a view to enhance the reaction parameters.

As a further confirmation, *Winne* and co-workers also investigate the reactivity of noncyclic analogues of dtdh-2-methanol resulting in the uncyclized addition product. This highlights the importance of the cyclic nature of the allylic intermediate.[61a] (**Scheme 4.21**)



Scheme 4.21. Reactivity of noncyclic analogues, *Winne.*

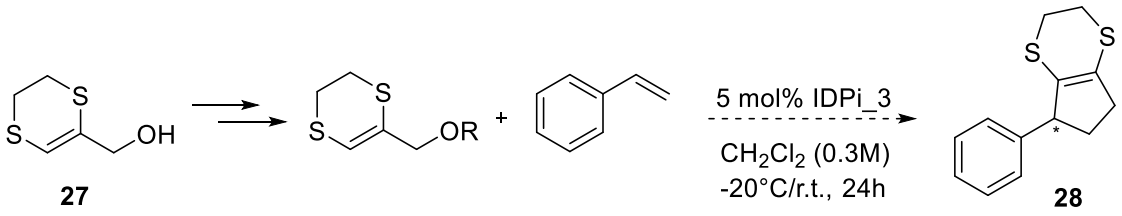
On the basis of the experiments reported in *Winne's* work and the screening explained above, having established the fundamental nature of the cyclic carbinol reagent, a plausible mechanism is depicted in **Scheme 4.22**.



Scheme 4.22. Proposed reaction mechanism for the IDP*i* catalysed [3+2] cycloaddition of styrene and (dtdh)-methanol.

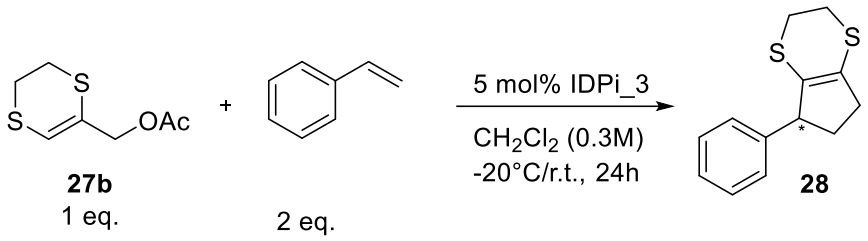
I suppose that the first activation of the dhdt-2-methanol occurs by the IDP*i* catalyst producing the stabilized allylic cation **I**. Subsequent nucleophilic attack by styrene results in the formation of intermediate **II** and the catalyst's confinement structure facilitates the cyclization step with the formation of the 5-membered cycle **III**. The following elimination step allows the formation of cyclopentenoid derivative with the regeneration the catalyst.

At this point, further experiments were performed to increase the stabilization of the sulphur reagent, thus evaluating the reactivity of the functionalized sulphur alcohol. (**Scheme 4.23**)



Scheme 4.23

So far, only the acetate substitution was tested, and it does not seem to lead an improvement for the reaction. (**Scheme 4.24**)



Entry	Temperature (°C)	Yield (%)	e.r.
1	r.t.	16	61:39
2	-20	<10	71:29

Scheme 4.24 Reaction performed on the -OAc derivative **27b**.

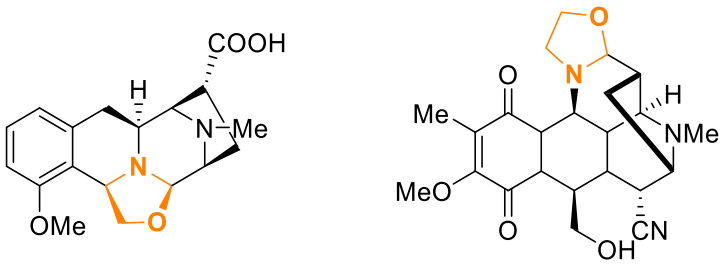
Further screening studies with different groups are currently underway to evaluate the effective influence of the leaving group in order to increase the reaction outcomes.

Chapter 5_*Metal free reactions*

Synthesis of oxazolidine derivatives

5.1.1 Background

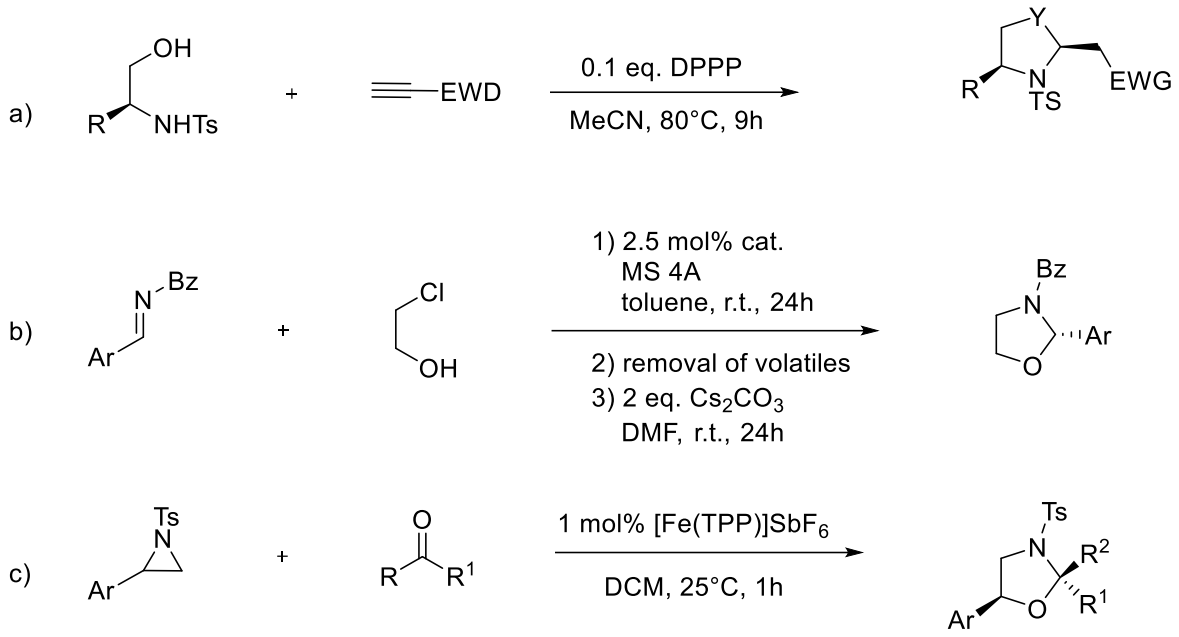
Despite the acknowledged potential of the oxazolidine derivatives, primarily known for their antibacterial properties and wide pharmacological spectrum suitable for use as anticonvulsants, anti-inflammatory agents, and antineoplastics, (**Fig 5.1**) the research and application of these compounds have been relatively limited compared to their derivatives *i.e.* oxazolidinones compounds.[67]



Quinocarcin **Cyanocycline A**

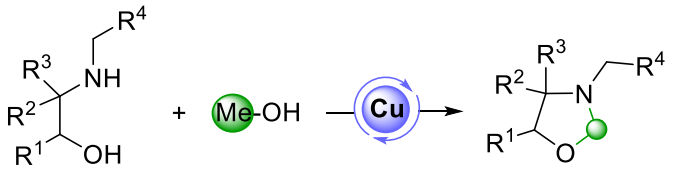
Fig 5.1 Oxazolidine presents in pharma.

Various methodologies for obtaining the oxazolidines stereoselectively are reported in the literature. In 2007, *Barcan* research group, reported a bisphosphine-catalyzed diastereoselective reaction of β-amino alcohols and monosubstituted alkynes bearing EW groups. (**Scheme 5.0, a**)[68]Later, in 2014, *J.C. Antilla*, reported the reactivity of imines and alcohols in the presence of a chiral magnesium phosphate catalysts, affording the product, through a hemiaminal intermediate. (**Scheme 5.0, b**)[69] Meanwhile, in 2019, *Matsubara* group, develop a high regio- and diastereoselective synthetic procedure exploiting the reactivity of aziridines with aldehydes, using the iron porphyrin Lewis's acid catalysts. (**Scheme 5.0, c**)[70]



Scheme 5.0 Stereoselective synthesis of oxazolidine derivatives.

In 2023, as previously discussed in Chapter 1.3, our research group had already explored synthetic strategies for producing oxazolidine derivatives by leveraging the reactivity of methanol in the dual role of solvent and reagent, employing a copper-based catalyst. (**Scheme 5.1**)

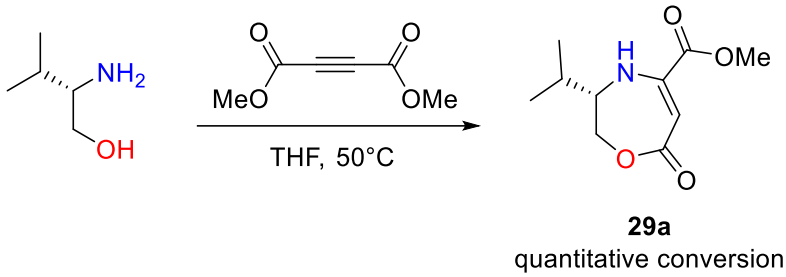


Scheme 5.1. Copper-catalyse synthesis of *N*-benzyl oxazolidine.

In this chapter we will discuss the synthesis of oxazolidine scaffolds through a different approach.

5.1.2 Results and discussion

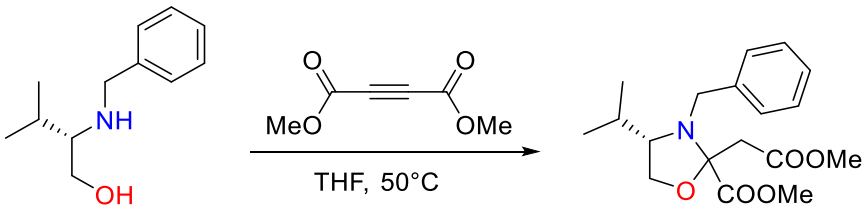
We initiated our investigation by examining the reactivity of the easily available (*L*)-valinol as model substrate, in the presence of dimethyl acetylene dicarboxylate, using THF and heating at 50°C for 48h. (**Scheme 5.3**). The reaction performed under these conditions allowed the isolation of the 7-membered cycle **29a**, without any purification steps, reporting quantitative conversion. A similar reaction pathway was reported in literature,[71] using a task-specific sulfonic ionic liquid as catalyst.



29a
quantitative conversion

Scheme 5.3 Synthesis of a 7-membered cycle.

In the effort to increase the scope, the reactivity of the *N*-benzyl derivative was evaluated but, in this case, a different outcome was observed. In fact, the reaction performed under the same reaction conditions afforded substituted oxazolidine **29b** (**Scheme 5.4**). The literature provides just one example of this cyclization using the scandium catalysis.[72]



29b
quantitative conversion

Scheme 5.4 Synthesis of oxazolidine **29a.**

To the best of our knowledge, no additional studies on the synthesis of these compounds have been documented. For this reason, we are persisting in our investigation on this reaction. Despite its simplicity, this method consistently produces oxazolidine derivatives with specific stereoselectivity, as evidenced by ^{1}H NMR studies.

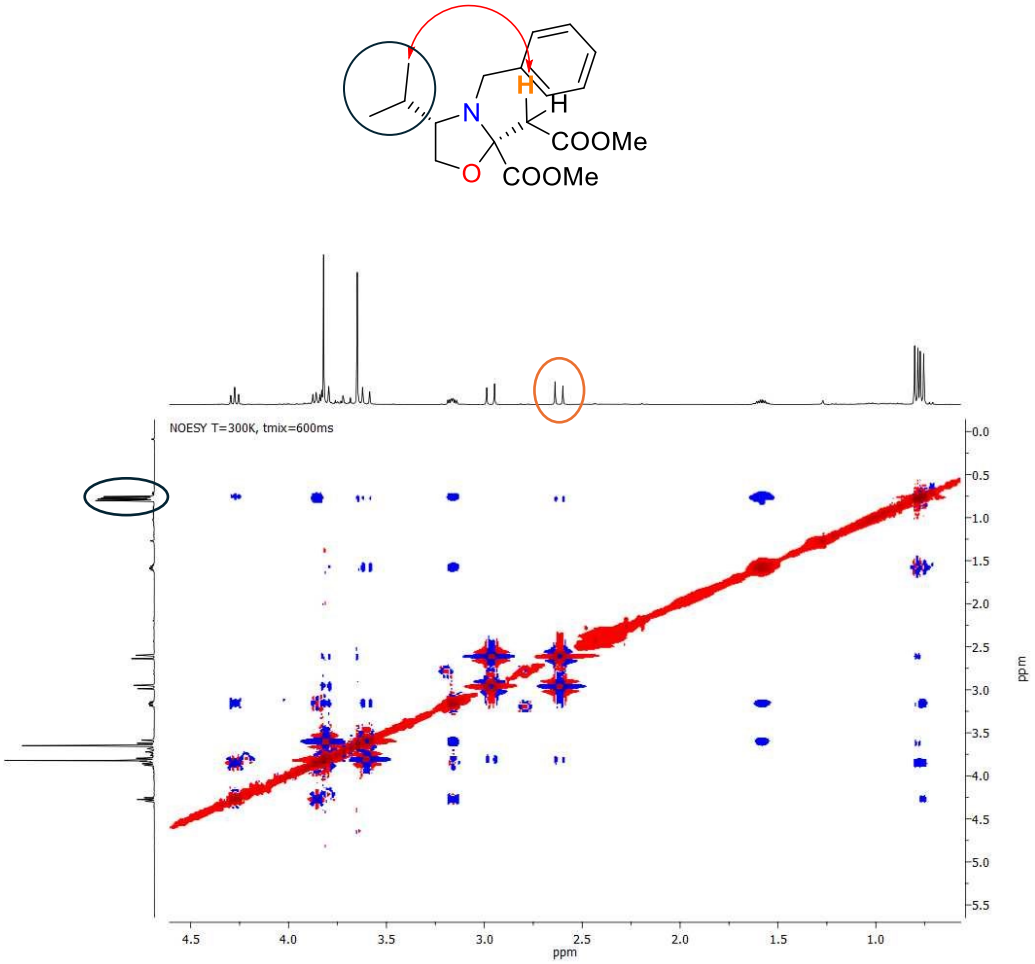
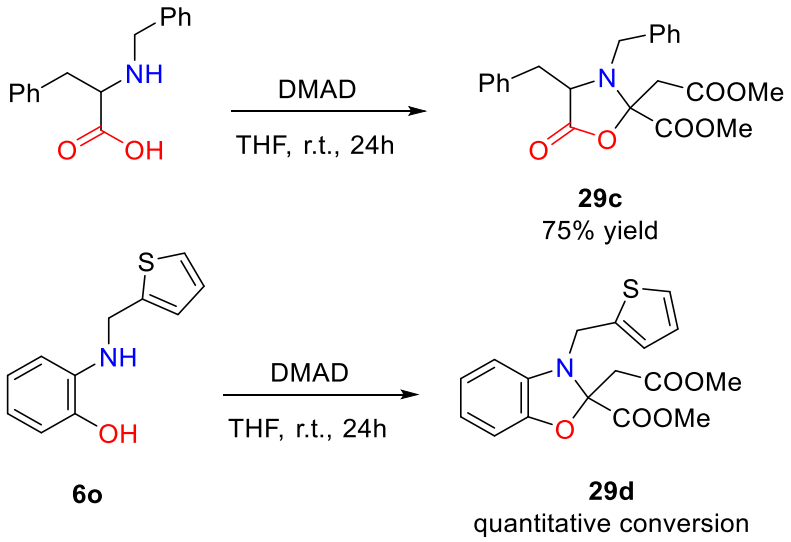


Fig. 5.2 NOESY experiment performed on substrate **29b**.

In the attempt to assess the potential of this reactivity, we also evaluated the transformations of aminoacids **29c** and aromatic aminoalcohols **29d**. (**Scheme 5.5**)



Scheme 5.5 Evaluation of the reactivity of *N*-benzyl(L)phenylalanine **29c** and on 2-((thiophen-2-ylmethyl)amino)phenol **29d.**

The results confirmed the potential of this procedure as it provides the synthesis of oxazolidines, while potentially tolerating a wide range of functional groups. The significance of this reaction lies for two aspects. The first one relies on the sustainability of the process. Considering the second principle of Green Chemistry, the atom economy of the reaction obtained is 100%. The second one is due the possibility to synthesize *N*-contained heterocycles that could potentially act as peptidomimetics (**Fig 5.3**), ligands, or chiral auxiliaries for transition metals.

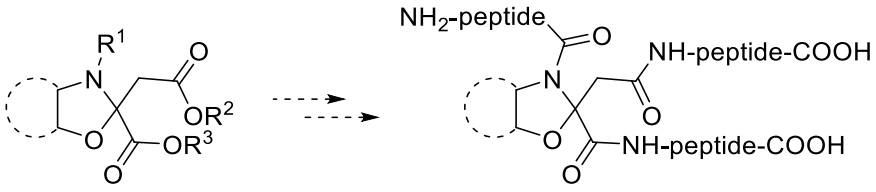
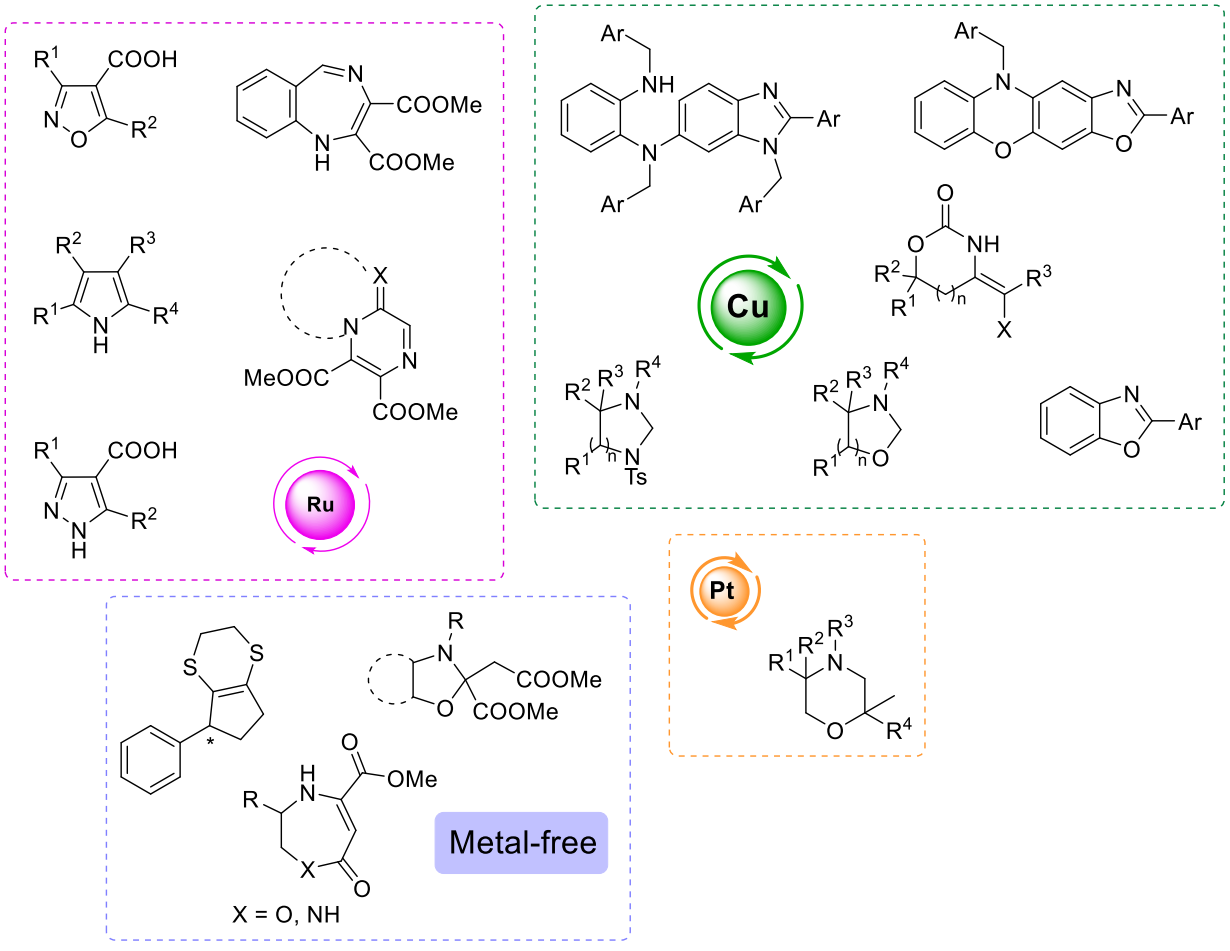


Fig. 5.3 Oxazolidine as peptidomimetics

Conclusion

In summary, a small library of *N*-containing heterocycles was synthetized exploiting the reactivity of various catalytic systems applied in different reaction typologies: difunctionalization of unactivated unsaturated systems as alkenes and alkynes, domino reactions, dimerization/cyclization of amino-phenols, rearrangements processes of isoxazole-5-ones and *O*-vinyl oximes, cycloaddition reactions. Our studies illustrated in particular, the efficacy of the transition-metals catalysis, in particular copper, platinum and ruthenium, as well as organocatalysis and metal-free synthetic paths to promote interesting and novel cyclization processes for the production of various five-, six- and seven-membered heterorings. Furthermore, it is important to highlight that our synthetic methodologies take note of some of the principles of Green Chemistry, thus highlighting the sustainability of our approaches. This aspect gains particularly significance in light of the growing importance placed on environmentally friendly practices in chemical synthesis. Additionally, the synthetized heterocycles constitute the essential core present in different compounds endowed with various application activities further highlighting the importance of our sustainable synthetic methods.



Experimental part

General information

Chemicals were obtained from Sigma Aldrich and FluoroChem and used without further purification. At MPI solvents were purified by distillation by the technical department of Max-Planck-Institute für Kohlenforschung and stoked under argon. Absolute 1,4-dioxane, MTBE and DCE were purchased from commercial suppliers.

Chiral Brønsted acid catalysts (**Scheme 4.11**) were supplied by coworkers in *List*'s group or prepared according to the literature procedures.

High pressure liquid chromatography (HPLC): HPLC analysis on a chiral stationary phase were performed on a Shimadzu system equipped with a UV detector. Commercial HPLC-grade solvents were used, and measurements were conducted at 35 °C using 150 mm Chiralcel OJ-3R, 4.6 mm i.D.. The enantiomeric ratios were determined by comparing the samples with the appropriate racemic mixtures.

Thin-layer chromatographic separations were performed on Merck silica-gel 60-F_{254} precoated.

Melting points were determined by the capillary method with a Büchi B-540 apparatus and are uncorrected.

IR spectra were measured with a Jasco FT/IR 5300 spectrometer.

Optical rotations were measured on a Perkin–Elmer 343 polarimeter at 20 °C (concentration in g/100 mL).

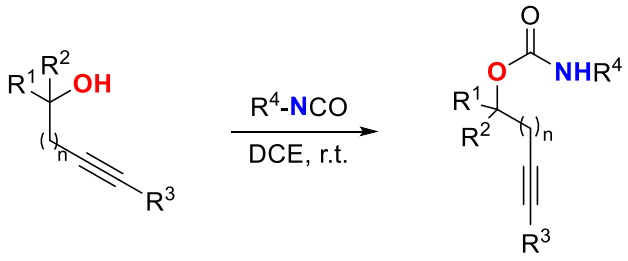
Nuclear Magnetic Resonance Spectroscopy (NMR): ^{1}H NMR and ^{13}C in open capillary tubes. NMR spectra were recorded with: AVANCE 400 Bruker spectrometer at 400 and 100 MHz, Varian Oxford 300 MHz spectrometer at 300 and 75 MHz and AVANCE 500 Bruker spectrometer at 500 and 125 MHz, respectively. Chemical shifts are given as δ values in ppm relative to residual solvent peaks ($CHCl_3$) as the internal reference, and the coupling constants *J* are reported in Hertz (Hz). ^{13}C NMR spectra are ^{1}H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence.

At Max-Planck-Institute für Kohlenforschung proton and carbon NMR spectra were recorded on Brucker AV-500 or AV-400 spectrometers in deuterated solvents at room temperature (298K).

Mass spectrometry: in the analytic department of the Institute of Pharmaceutical Department at the Università degli Studi di Milano mass spectra were determined with a LCQ Advantage Thermo Finningan.

Chapter 1.2_ *Copper (II)-catalysed aminohalogenation of alkynyl carbamates*

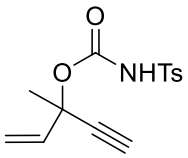
General procedure for the synthesis of O-alkynyl carbamates (**1a-j**)



a-j **1a-j**

To a stirred solution of the appropriate propargyl alcohol **a-j** (7.13 mmol) in DCE (10 ml) the appropriate isocyanate (7.13 mmol) was slowly added. After 24 hours the solvent was removed under reduced pressure. The characterization of products **1a, b, f, g, j**,[73] and **2c, i,**[74] are consistent with the ones reported in the literature.

N-Tosyl-*O*-(3-methylpenten-4-yn-3-yl)carbamate (**1d**)



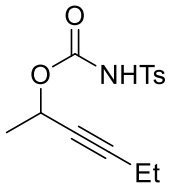
Compound **1d** was prepared according to general procedure starting from 3-methyl-1-penten-4-yn-3-ol (**d**) and isolated through flash chromatography (hex:EtOAc 7:3) as yellow oil (88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.88 (dd, *J* = 17.1, 10.3 Hz, 1H), 5.55 (d, *J* = 17.0 Hz, 1H), 5.24 (dd, *J* = 10.3, 0.5 Hz, 1H), 2.66 (s, 1H), 2.45 (s, 3H), 1.67 (s, 3H).

MS (ESI): m/z 294.10 $[M+H]^+$.

Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.78; found: C, 57.41; H, 5.18; N, 4.72.

N-Tosyl-*O*-(1-methyl-2-pentynyl)carbamate (**1e**)



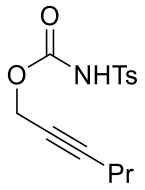
Compound **1e** was prepared according to the general procedure starting from 3-Hexyn-2-ol (**e**) and isolated through flash chromatography (hex:EtOAc 4:1) as a yellow oil (92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 5.20-5.17 (m, 1H), 2.27 (s, 3H), 1,99 (qd, *J* = 7.5, 1.8 Hz, 2H), 1.26 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H).

MS (ESI): m/z 318.25 $[M+ Na]^+$.

Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74; found: C, 56.96; H, 5.78; N, 4.78.

N-Tosyl-*O*-(2-hexynyl)carbamate (**1h**)



Compound **1h** was prepared according to general procedure starting from 2-hexyn-1-ol (**h**) and isolated through flash chromatography (hex:EtOAc 4:1) as white solid (92% yield); m.p. 84-85°C.

IR: 3221, 1763, 1458, 865 cm^{-1}.

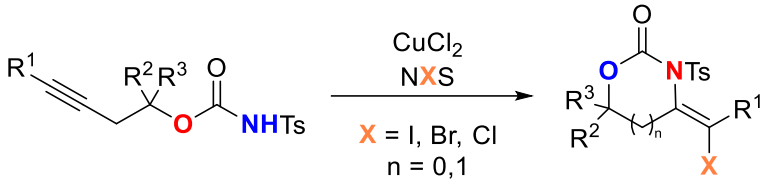
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93(d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.64 (t, *J* = 2,2 Hz, 2H), 2.41 (s, 3H), 2.12 (m, 2H), 1.44 (m, 2H), 0.90 (t, *J*=7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.08, 145.04, 135.40, 129.54, 128.44, 88.88, 72.94, 55.10, 21.65, 21.58, 20.60, 13.31.

MS (ESI): m/z 295.97 $[M+H]^+$.

Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74; found: C, 57.00; H, 5.84; N, 4.69.

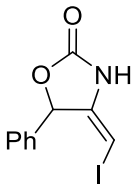
General procedure for the synthesis of 4-halomethylidene-3-tosyloxazolidin-2one (**2a-j, 3a, c, g, h, i, 4a, c, g, 5a, b, c**)



1 **2,3,4,5**

To a stirred solution of the appropriate *O*-alkynyl carbamate **1** (0.561 mmol) in MeCN (10 mL), halosuccinimide (0.561 mmol), and $CuCl_2$ (0.056 mmol) were added, and the reaction was heated for 2–21 hours. The resulting mixture was filtered through a silica pad and the solvent was removed under reduced pressure. The characterization of products **2a**[75] and **2g, 3a,g, 4a,g**[76] are consistent with the ones reported in the literature.

(4*E*)-4-(Iodomethylidene)-5-phenyl-3-tosyloxazolidin-2-one (**2b**)



Compound **2b** was prepared according to the general procedure starting from substrate **1b** and NIS, heating at 40°C for 18 hours and isolated through flash chromatography (hex:EtOAc 4:1) as a light-yellow solid (71% yield); m.p.: 127-129°C.

IR: 1794, 1385, 1136, 702, 696 cm^{-1}.

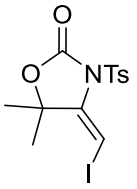
^1H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.39–7.22 (m, 5H), 6.94 (d, *J* = 2.1 Hz, 1H), 5.79 (d, *J* = 2.1 Hz, 1H), 2.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 146.8, 136.5, 134.0, 133.6, 130.1, 130.0, 129.0, 128.4, 128.2, 83.0, 59.1, 21.8.

MS (ESI): m/z 478.04 $[M+Na]^+$.

Anal. Calcd for $C_{17}H_{14}INO_4S$: C, 44.85; H, 3.10; N, 3.08; found: C, 44.90; H, 3.13; N, 3.04.

(4*E*)-4-(Iodomethylidene)-5,5-dimethy-3-tosyloxazolidin-2-one (**2c**)



Compound **2c** was prepared according to the general procedure starting from substrate **1c** and NIS, heating at reflux for 3 hours and isolated through flash chromatography (hex:EtOAc 9:1) as a light-yellow solid (80% yield); m.p.: 117-119°C.

IR: 1781, 1386, 1263, 1110, 865 cm^{-1}.

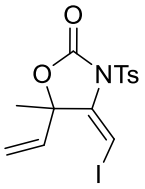
^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.85 (s, 1H), 2.46 (s, 3H), 1.69 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 146.4, 141.1, 134.2, 130.0, 128.2, 84.9, 52.3, 25.0, 21.8.

MS (ESI): m/z 429.93 $[M+ Na]^+$.

Anal. Calcd for $C_{13}H_{14}INO_4S$: C, 38.34; H, 3.47; N, 3.44; found: C, 38.38; H, 3.42; N, 3.47.

(4*E*)-4-(Iodomethylidene)-5-methyl-3-tosyl-5-vinyloxazolidin-2-one (**2d**)



Compound **2d** was prepared according to the general procedure starting from substrate **1d** and NIS, heating at 50°C for 20 hours and isolated through flash chromatography (hex:Et_2O 1:1) as a yellow solid (56% yield); m.p.:77-80°C.

IR: 1780, 1347, 1123, 815 cm^{-1}.

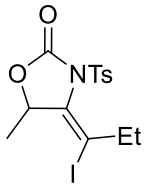
^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.91 (s, 1H), 6.05 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.33 (t, *J* = 13.5 Hz, 2H), 2.46 (s, 3H), 1.79 (s, 3H).

^{13}C NMR (100 MHz, CDCl3): δ = 149.3, 146.5, 139.3, 134.1, 133.5, 130.0, 128.2, 118.5, 85.2, 54.4, 23.0, 21.8.

MS (ESI): m/z 442.07 $[M+Na]^+$.

Anal. Calcd for $C_{14}H_{14}INO_4S$: C, 40.11; H, 3.37; N, 3.34; found: C, 40.15; H, 3.34; N, 3.39.

(4*E*)-4-(1-Iodopropylidene)-5-methyl-3-tosyloxazolidin-2-one (**2e**)



Compound **2e** was prepared according to the general procedure starting from substrate **1e** and NIS, heating at 40°C for 18 hours and isolated through flash chromatography (hex:EtOAc 4:1) as a pale brown wax (83% yield).

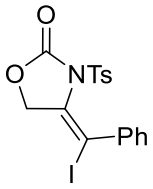
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.37 (q, *J* = 6.1 Hz, 1H), 2.60–2.50 (m, 2H), 2.43 (s, 3H), 1.68 (d, *J* = 6.5 Hz, 3H), 1.05 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=153.1, 146.1, 134.4, 132.0, 129.8, 128.9, 100.9, 82.6, 34.1, 21.7, 17.9, 14.8.

MS (ESI): m/z 443.97 $[M+Na]^+$.

Anal. Calcd for $C_{14}H_{16}INO_4S$: C,39.92; H, 3.83; N, 3.33; found: C, 39.90; H, 3.87; N, 3.29.

(4*E*)-4-(Iodo(phenyl)methylidene)-3-tosyloxazolidin-2-one (**2f**)



Compound **2f** was prepared according to the general procedure starting from substrate **1f** and NIS, heating at 45°C for 2 hours, under N_2, and isolated through flash chromatography (hex:EtOAc 7:3) as a yellow solid (41% yield); m.p.: 110-114°C.

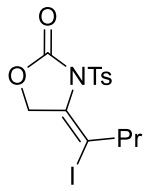
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.11 (m, 9H), 4.88 (s, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=145.6, 141.2, 133.9, 130.2, 129.6, 129.4, 129.2, 128.9, 128.6, 85.9, 74.7, 21.7.

MS (ESI): m/z 456.11 $[M+H]^+$.

Anal. Calcd for $C_{17}H_{14}INO_4S$: C, 44.85; H, 3.10; N, 3.08; found: C, 44.88; H, 3.14; N, 3.04.

(4*E*)-4-(1-Iodobutylidene)-3-tosyloxazolidin-2-one (**2h**)



Compound **2h** was prepared according to the general procedure starting from substrate **1h** and NIS, heating at 70°C for 8 hours and isolated through flash chromatography (hex:EtOAc 7:3) as a yellow solid (76% yield); m.p.:82-85°C.

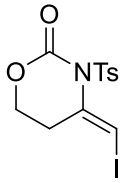
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 4.63 (t, *J* = 1.4 Hz, 2H), 2.67-2.57 (m, 2H), 2.46 (s, 3H), 1.69–1.56 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=154.0, 146.2, 134.7, 130.0, 128.4, 128.2, 99.3, 74.5, 41.8, 23.6, 21.8, 13.1.

MS (ESI): m/z 422.23 $[M+H]^+$.

Anal. Calcd for $C_{14}H_{16}INO_4S$: C, 39.92; H, 3.83; N, 3.33; found: C, 39.88; H, 3.87; N, 3.30.

(4*E*)-4-(Iodomethylidene)-3-tosyl-1,3-oxazin-2-one (**2i**)



Compound **2i** was prepared according to the general procedure starting from substrate **1i** and NIS, heating at 60°C for 8 hours and isolated through flash chromatography (hex:EtOAc 1:1) as a light-yellow solid (68% yield); m.p.: 112-115°C.

IR: 1712, 1370, 1163, 816 cm^{-1}.

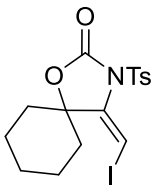
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.65 (s, 1H), 4.28 (t, *J* = 6.2 Hz, 2H), 2.88 (t, *J* = 6.2 Hz, 2H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 145.7, 135.3, 134.5, 129.7, 128.9, 73.5, 66.3, 32.6, 21.7.

MS (ESI): m/z 416.74 $[M+Na]^+$.

Anal. Calcd for $C_{12}H_{12}INO_4S$: C, 36.66; H, 3.08; N, 3.56; found: C, 36.61; H, 3.06; N, 3.59.

(4*E*)-4-(Iodomethylidene)-3-tosyl-1,3-oxo[4,5]spirodecan-2-one (**2j**)



Compound **2j** was prepared according to the general procedure starting from substrate **1j** and NIS, heating at 70°C for 3 hours and isolated through flash chromatography (hex:EtOAc 9:1) as a yellow wax (9% yield).

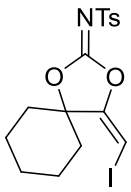
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.86 (s, 1H), 2.60–2.52 (m, 2H), 2.46 (s, 3H), 1.68–1.54 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 152.6, 137.0, 133.6, 130.0, 128.2, 75.9, 52.1, 32.2, 24.1, 21.8, 21.3.

MS (ESI): m/z 448.07 $[M+H]^+$.

Anal. Calcd for $C_{16}H_{18}INO_4S$: C, 42.96; H, 4.06; N, 3.13; found: C, 42.94; H, 4.04; N, 3.13.

(4*E*)-4-(Iodomethylidene)-2-tosylimine-1,3-dioxo[4,5]spirodecane (**5a**)



Compound **1j** was prepared according to the general procedure starting from substrate **5a** and NIS, heating at 70°C for 3 hours and isolated through flash chromatography (hex:EtOAc 7:3) as a yellow solid (82% yield); m.p.: 90-93°C.

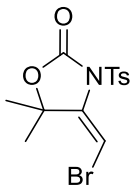
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.03 (s, 1H), 2.41 (s, 3H), 2.34–2.38 (m, 2H), 1.90–1.87 (m, 2H), 1.78–1.75 (m, 3H), 1.66–1.60 (m, 2H), 1.33–1.29 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 152.6, 143.6, 138.2, 129.3, 127.2, 50.3, 32.6, 24.0, 21.6, 21.2.

MS (ESI): m/z 448.03 $[M+H]^+$.

Anal. Calcd for $C_{16}H_{18}INO_4S$: C, 42.96; H, 4.06; N, 3.13; found: C, 42.92; H, 4.05; N, 3.16.

(4*E*)-4-(Bromomethylidene)-5,5-dimethyl-3-tosyloxazolidin-2-one (**3c**)



Compound **3c** was prepared according to the general procedure starting from substrate **1c** and NBS, heating at 40°C for 21 hours and isolated through flash chromatography (hex:DCM 1:1) as a white solid (92% yield); m.p.: 116-119°C.

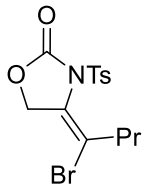
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.13 (s, 1H), 2.41 (s, 3H), 1.78 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 152.0, 143.8, 138.0, 129.4, 127.2, 84.8, 24.4, 21.6.

MS (ESI): m/z 381.46 [M+Na]+, 383.25 $[M+Na]^+$.

Anal. Calcd for $C_{13}H_{14}BrNO_4S$: C, 43.35; H, 3.92; N, 3.89; found: C, 43.39; H, 3.90; N, 3.86.

(4*E*)-4-(Bromobutylidene)-3-tosyloxazolidin-2-one (**3h**)



Compound **3h** was prepared according to the general procedure starting from substrate **1h** and NBS, heating at 70°C for 5 hours and isolated through flash chromatography (hex:EtOAc 4:1) as a yellow solid (73% yield); m.p.: 89-93°C.

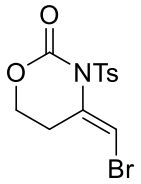
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 4.70 (s, 2H), 2.68 (m, 2H), 2.46 (s, 3H), 1.76 – 1.62 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=153.6, 146.2, 134.6, 130.0, 128.4, 125.8, 120.6, 70.5, 39.2, 21.7, 21.5, 13.3.

MS (ESI): m/z 373.67 $[M+ H]^+$, 375.38 $[M+H]^+$.

Anal. Calcd for $C_{14}H_{16}BrNO_4S$: C, 44.93; H, 4.31; N, 3.74; found: C, 44.90; H, 4.35; N, 3.77.

(4*E*)-4-(Bromomethylidene)-3-tosyl-1,3-oxazin-2-one (**3i**)



Compound **3i** was prepared according to the general procedure from substrate **1i** and NBS, heating at 40°C for 4 hours and isolated through flash chromatography (hex:EtOAc 1:1 and then 9.9:0.1 DCM:MeOH) as a light-yellow solid (48% yield); m.p.: 85-88°C.

IR: 1721, 1362, 1163, 816 cm^{-1}.

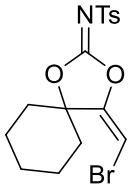
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.61 (s, 1H), 4.29 (t, *J* = 6.2 Hz, 2H), 2.88 (dd, *J* = 6.1, 5.5 Hz, 2H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 145.8, 135.2, 131.9, 129.8, 128.9, 102.2, 66.3, 28.7, 21.7.

MS (ESI): m/z 368.11 $[M+Na]^+$, 347.08 $[M+H]^+$.

Anal. Calcd for $C_{12}H_{12}BrNO_4S$: C, 41.63; H, 3.49; Br, 23.08; N, 4.05; found: C, 41.66; H, 3.45; N, 4.10.

(4*E*)-4-(Bromomethylidene)-2-tosylimine-1,3-dioxo[4,5] spirodecane (**5b**)



Compound **5b** was prepared according to the general procedure from substrate **1j** and NBS, heating at 70°C for 4 hours and isolated through flash chromatography (hex:EtOAc 6:4) as yellow wax (88% yield).

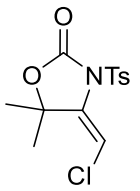
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.12 (s, 1H), 2.40 (s, 3H), 2.31-2.26 (m, 2H), 1.91–1.86 (m, 2H), 1.77-1.70 (m, 3H), 1.53-1.63 (m, 2H), 1.32–1.22 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 151.9, 143.7, 138.1, 129.4, 127.2, 84.9, 32.3, 24.0, 21.5, 21.2.

MS (ESI): m/z 400.05 $[M+H]^+$,401.98 $[M+H]^+$.

Anal. Calcd for $C_{16}H_{18}BrNO_4S$: C, 48.01; H, 4.53; N, 3.50; found: C, 48.06; H, 4.56; N, 3.45.

(4*E*)-4-(Chloromethylidene)-5,5-dimethy-3-tosyloxazolidin-2-one (**4c**)



Compound **4c** was prepared according to the general procedure from substrate **1c** and NCS, heating at 50°C for 8 hours and isolated through flash chromatography (hex:EtOAc 7:3) as white solid (56% yield); m.p.: 86-88°C.

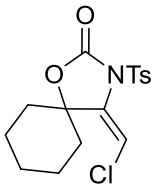
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.78 (s, 1H), 2.46 (s, 3H), 1.63 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 146.6, 138.8, 134.0, 130.0, 128.2, 96.0, 84.0, 24.7, 21.8.

MS (ESI): m/z 316.26 $[M+H]^+$.

Anal. Calcd for $C_{13}H_{14}ClNO_4S$: C, 49.45; H, 4.47; N, 4.44; found: C, 49.49; H, 4.44; N, 4.49.

(4*E*)-4-(Chloromethylidene)-3-tosyl-1,3-oxo[4,5]spirodecan-2-one (**4j**)



Compound **4j** was prepared according to the general procedure from substrate **1j** and NCS, heating at 70°C for 8 hours and isolated through flash chromatography (hex:EtOAc 7:3) as white solid (13% yield); m.p.: 115-118°C.

IR: 1796, 1372, 1110, 769 cm^{-1}.

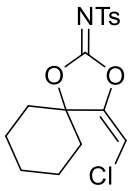
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.09 (s, 1H), 2.35 (s, 3H), 2.20-2.12 (m, 2H), 1.86-1.50 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 142.6, 137.1, 133.5, 128.4, 126.2, 98.1, 86.1, 31.2, 23.0, 20.5, 20.2.

MS (ESI): m/z 378.32 $[M+Na]^+$.

Anal. Calcd for $C_{16}H_{18}ClNO_4S$: C, 54.01; H, 5.10; N, 3.94; found: C, 54.06; H, 5.15; N, 3.90.

(4*E*)-4-(Chloromethylidene)-2-tosylimine-1,3-dioxo[4,5] spirodecane (**5c**)



Compound **5c** was prepared according to the general procedure from substrate **1j** and NCS, heating at 70°C for 8 hours and isolated through flash chromatography (hex:EtOAc 7:3) as yellow wax (73% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.74 (s, 1H), 2.39 (s, 3H), 2.34–2.26 (m, 2H), 1.65-1.48 (m, 8H).

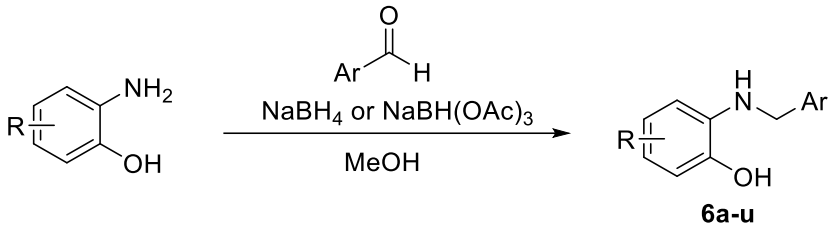
^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 146.4, 138.5, 134.1, 130.0, 128.2, 99.6, 86.0, 32.1, 24.2, 21.8, 21.2.

MS (ESI): m/z 378.15 $[M+Na]^+$.

Anal.Calcd for $C_{16}H_{18}ClNO_4S$: C, 54.01; H, 5.10; N, 3.94; found: C, 54.05; H, 5.15; N, 3.91.

Chapter 1.3_ *Synthesis of benzoxazole derivatives and tetracyclic structures*

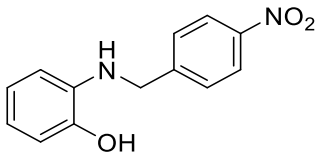
General procedure for the synthesis of 2-benzylamino-phenols (**6a-u**)



6a-u

To a solution of aminophenol (1 mmol) in MeOH (0.15 M), the appropriate aldehyde (1.0 mmol) was added at room temperature and stirred for 6 hours. The reaction was then cooled to 0°C and then $NaBH_4$ (0.5 mmol) was added portion wise and stirred 1 hour. After evaporation of the solvent, the solution was extracted with EtOAc (2 x 25ml), washed with brine (2 x 25ml), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the crude purified through silica column chromatography. The characterization of products **6a,**[77] **b,**[78] **c, d,**[79] **f, h**[80] **g,**[81] **i,**[82] **j,**[83] **p,**[84] **s,**[85] **t,**[86] **u**[87] are consistent with the ones reported in literature.

2-((4-nitrobenzyl)amino)phenol (**6e**)



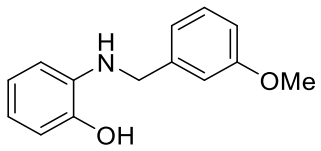
Compound **6e** was prepared according to general procedure from 4-nitrobenzaldehyde and isolated though flash chromatography (hex:EtOAc 7:3) as a beige solid (Yield 91%); m.p.: 86-88°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7Hz, 2H), 6.82−6.75 (m, 2H), 6.65 (t, *J* = 6.1 Hz, 1H), 6.50 (d, *J* = 9.4 Hz, 1H), 4.71 (bs, 1H), 4.50 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.5, 147.2, 143.2, 136.1, 127.9, 123.9, 121.8, 118.2, 114.5, 112.1, 47.7.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.15; H, 5.09; N, 11.30.

N-(3-Methylbenzyl)-2-aminophenol (**6k**)



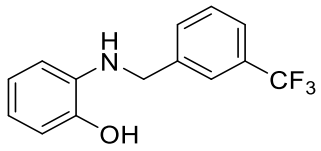
Compound **6k** was prepared according to general procedure from 3-methoxybenzaldehyde and isolated though flash chromatography (hex:EtOAc 4:1) as a beige oil (79% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 7.8 Hz, 1H), 7.01−6.98 (m, 2H), 6.86−6.84 (m, 2H), 6.75−6.63 (m, 3H), 4.65 (bs, 1H), 4.35 (s, 2H), 3.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9, 143.5, 141.1, 136.9, 129.6, 121.7, 119.9, 117.9, 114.5, 113.1, 112.7, 112.6, 55.3, 48.6.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.54; H, 6.72; N, 5.97.

N-(3-Trifluoromethylbenzyl)-2-aminophenol (**6l**)



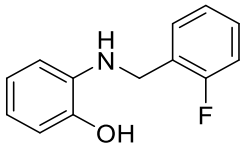
Compound **6l** was prepared according to general procedure from 3-(trifluoromethyl)benzaldehyde and isolated though flash chromatography (hex:EtOAc 4:1) as a brown solid (97% yield); m.p.: 80-83°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1H), 7.59 (t, *J* = 7.4 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.75−6.66 (m, 3H), 4.92 (bs, 1H), 4.44 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ =143.5, 140.5, 136.6, 131.3 (d, *J* = 32.2 Hz), 130.8 (q, *J* = 1.4 Hz), 129.1, 124.3 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.3 Hz), 124.1 (q, *J* = 3.8 Hz), 121.8, 118.4, 114.6, 112.6, 48.2.

Anal. Calcd for $C_{14}H_{12}F_3NO$: C, 62.92; H, 4.53; N, 5.24. Found: C, 62.81; H, 4.37; N, 5.37.

N-(2-Fluorobenzyl)-2-aminophenol (**6m**)



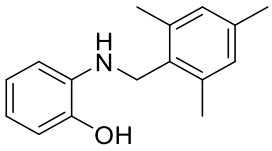
Compound **6m** was prepared according to general procedure from 2-fluorobenzaldhyde and isolated though flash chromatography (hex:EtOAc 9:1) as a yellow oil (83% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (t, *J* = 7.3 Hz, 1H), 7.29−7.22 (m, 1H), 7.12−7.06 (m, 2H), 6.85−6.81 (m, 1H), 6.78−6.74 (m, 1H), 6.71−6.64 (m, 2H), 4.42 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.0 (d, *J* = 245.7 Hz), 143.9, 136.5, 129.5 (d, *J* = 4.1 Hz), 128.8 (d, *J* = 8.1 Hz), 126.4 (d, *J* = 15.6 Hz), 124.2 (d, *J* = 3.5 Hz), 121.6, 118.3, 115.3 (d, *J* = 21.6 Hz), 114.5, 112.9, 42.3.

Anal. Calcd for $C_{13}H_{12}FNO$: C, 71.87; H, 5.57; N, 6.45. Found: C, 72.13; H, 5.86; N, 6.27.

N-(2,4,6-Trimethylbenzyl)-2-aminophenol (**6n**)



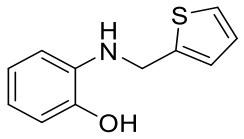
Compound **6n** was prepared according to general procedure from 2,4,6-trimethylbenzaldehyde and isolated though flash chromatography (hex:EtOAc 9:1) as a white solid (98% yield); m.p.: 117-118°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 3H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.70 (s, 2H), 4.25 (s, 2H), 2.40 (s, 6H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.7, 137.6, 137.4, 132.2, 129.2, 121.8, 117.8, 114.4, 112.3, 42.9, 21.0, 19.4.

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.51; H, 7.80; N,5.95.

2-((thiophen-2-ylmethyl)amino)phenol (**6o**)



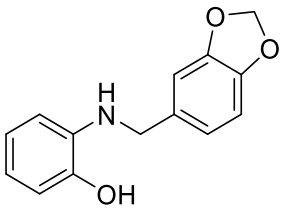
Compound **6o** was prepared according to general procedure from thiophene-2-carbaldehyde and isolated though flash chromatography (hex:EtOAc 4:1) as a brown solid (83% yield); m.p.: 81-84°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, 1H, J = 5.1 Hz), 6.89−6.88 (m, 1H), 6.83 (t, *J* = 5.1 Hz, 1H), 6.76−6.71 (m, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 6.56−6.54 (m, 2H), 4.79 (bs, 1H), 4.38 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.1, 142.8, 136.3, 126.9, 125.3, 124.7, 121.6, 118.9, 114.8, 113.3, 43.9.

Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82. Found: C, 64.27; H, 5.29; N, 6.90.

N-(Benzo[*d*][1,3]dioxol-5-yl-methyl)-2-aminophenol (**6q**)



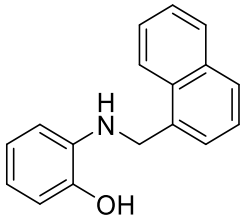
Compound **6r** was prepared according to general procedure from piperonal and isolated through flash chromatography (hex:EtOAc 3:2) as a yellow oil (88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 1H), 6.85−6.80 (m, 2H), 6.79−6.72 (m, 2H), 6.69−6.63 (m, 2H), 5.95 (s, 2H), 4.26 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.9, 146.8, 143.7, 136.4, 133.1, 121.7, 120.8, 118.3, 114.5, 112.9, 108.3, 108.2, 100.9, 48.6.

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.36; H, 5.56; N, 5.62.

N-(Naphtalen-1-yl-methyl)-2-aminophenol (**6r**)



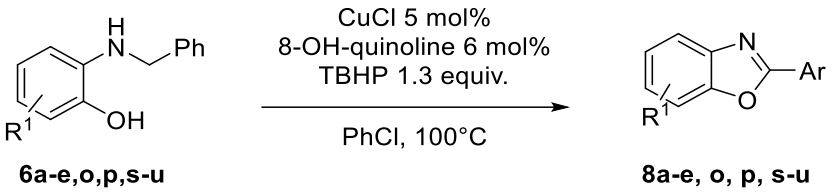
Compound **6r** was prepared according to general procedure from naphtaldehyde and isolated through flash chromatography (hex:EtOAc 9:1) as a beige solid (89% yield); m.p.: 117-120°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13−8.10 (m, 1H), 7.94−7.91 (m, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.57−7.53 (m, 3H), 7.45 (t, *J* = 8.2 Hz, 1H), 6.91 (t, *J* = 10.5 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.76−6.74 (m, 2H), 4.78 (s, 2H), 4.58 (bs, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.6, 137.0, 134.4, 133.9, 131.6, 128.8, 128.1, 126.3, 125.9, 125.8, 125.6, 123.5, 121.9, 118.0, 114.5, 112.6, 46.6.

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.77; H, 5.90; N,5.73.

General procedure for the synthesis of benzoxazole products (**8a-e, o, p, s-u**)

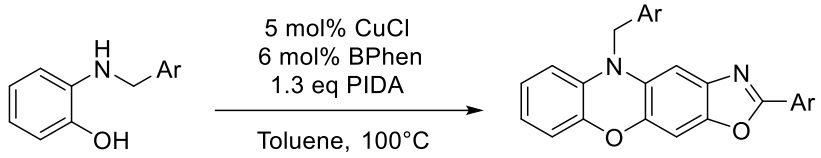


6a-e,o,p,s-u **8a-e, o, p, s-u**

Under nitrogen atmosphere, in a sealed tube, CuCl (0.005 mmol) and 8-OH-quinoline (0.006 mmol) are dissolved in 1 ml of PhCl. The mixture is stirred for 10 minutes at room temperature. Then a solution of substrate **6a-e, o, p, s-u** (1 mmol) in 2ml of PhCl and TBHP (1.3 mmol) are added. The mixture is stirred at 100°C for 40 minutes. The crude was then dissolved in brine (20 ml) and extracted with EtOAc (2 x 15ml), the organic phase is dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude was purified through flash chromatography.

The characterization of compounds **8a,**[88] **b,**[89] **c,** [90] **d,** [91] **e,** [92] **o,** [93] **p,** [94] **s,** [95] **t,** [96] **u** [97] are consistent with the ones reported in literature.

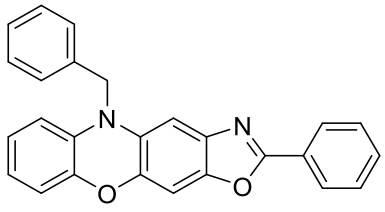
General procedure for the Dimerization/Cyclization of the N-benzylaminophenols (**9a-n**)



6a-b, e, g-o, q-r **9a-n**

In a sealed tube, to a stirred solution of bathophenantroline (0.06 mmol, 10.8 mg) in toluene (4.0 ml, 0.25M), CuCl (0.05 mmol, 4.9 mg) was added. After 10 minutes the appropriate 2-benzylaminophenol **9** (1.0 mmol) and PIDA (1.3 mmol, 418,7 mg) were added. The reaction was stirred at 100°C. The reaction mixture was then extracted with DCM (2 x 10 ml) and the solvent was evaporated under reduced pressure. The crude was purified through flash chromatography.

5-Benzyl-2-phenyl-*5H*-oxazolo[4,5-*b*]phenoxazine (**9a**)



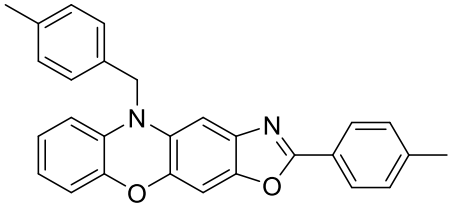
Compound **9a** was prepared according to general procedure starting from substrate **6a**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 15:1) as yellow solid (72% yield); m.p.: 237-239°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16−8.11 (m, 2H), 7.51−7.47 (m, 3H), 7.37−7.28 (m, 5H), 6.98 (s, 1H), 6.81−6.70 (m, 4H), 6.45 (d, *J* = 8.1 Hz, 1H), 4.89 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.6, 145.6, 144.6, 144.5, 137.4, 135.6, 133.5, 132.4, 131.2, 129.0, 128.9, 127.3, 127.1, 126.9, 126.0, 124.2, 121.4, 115.4, 112.4, 102.2, 98.3, 50.2.

Anal. Calcd for $C_{26}H_{18}N_2O_2$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.85; H, 4.49; N, 7.34.

5-(4-Methylbenzyl)-2-(p-tolyl)-*5H*-oxazolo[4,5-*b*]phenoxazine (**9b**)



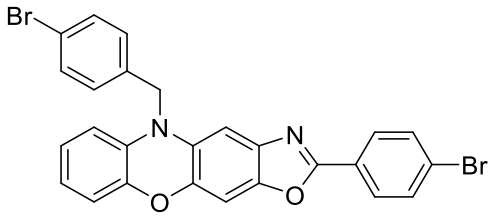
Compound **9b** was prepared according to general procedure starting from substrate **6b**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 11:1) as yellow solid (82% yield); m.p.: 213-214°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 6.85 (s, 1H), 6.71−6.62 (m, 3H), 6.58 (s, 1H), 6.36 (d, *J* = 7.9 Hz, 1H), 4.75 (s, 2H), 2.32 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.8, 145.5, 144.6, 144.4, 141.5, 137.7, 136.9, 133.7, 132.6, 132.2, 129.7, 129.6, 127.0, 125.9, 124.3, 124.1, 121.2, 115.3, 112.3, 102.2, 98.2, 49.9, 21.6, 21.0.

Anal. Calcd for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.47; H, 5.44; N, 6.51.

5-(4-Bromobenzyl)-2-(4-bromophenyl)-*5H*-oxazolo[4,5-*b*]-phenoxazine (**9c**)



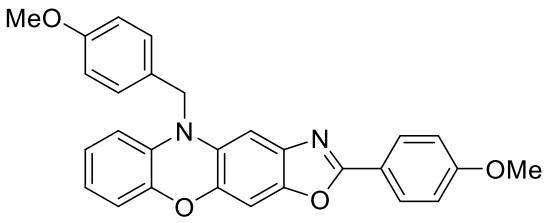
Compound **9c** was prepared according to general procedure starting from substrate **6g**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 11:1) as yellow solid (69% yield); m.p.: 253-254°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* =8.6 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.97 (s, 1H), 6.82−6.73 (m, 3H), 6.63 (s, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 4.83 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.1, 141.5, 140.4,140.2, 133.5, 130.4, 128.9, 127.9, 124.1, 123.6, 121.7, 121.4, 119.9,117.4, 116.9, 111.2, 110.3, 107.9, 102.3, 97.8, 94.2, 45.4.

Anal. Calcd for $C_{26}H_{16}Br_2N_2O_2$: C, 56.96; H, 2.94; N, 5.11. Found: C, 57.15; H, 3.17; N, 4.93.

5-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-*5H*-oxazolo[4,5-*b*]-phenoxazine (**9d**)



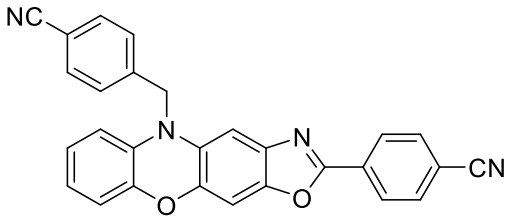
Compound **9d** was prepared according to general procedure starting from substrate **6i**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 3:1) as yellow solid (71% yield); m.p.: 242-243°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 9.0 Hz, 2H), 7.24 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 10.0 Hz, 2H), 6.94 (s, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.78−6.75 (m, 3H), 6.68 (s, 1H), 6.46 (s, 1H), 4.83 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.5, 158.4, 158.3, 144.9, 144.2, 143.6, 137.3, 133.3, 131.5, 128.3, 127.0, 126.7, 123.6, 120.7, 119.2, 114.8, 113.9, 113.8, 111.8, 101.6, 97.7, 54.9, 54.8, 49.0.

Anal. Calcd for $C_{28}H_{22}N_2O_4$: C,74.65; H, 4.92; N, 6.22. Found: C, 74.89; H, 5.19; N, 6.01.

4-(5-(4-Cyanobenzyl)-*5H*-oxazolo[4,5-*b*]phenoxazin-2-yl)-benzonitrile (**9e**)



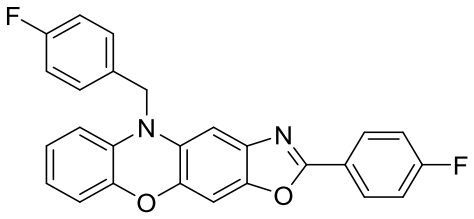
Compound **9e** was prepared according to general procedure starting from substrate **6j**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 3:1) as brown oil (31% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.01 (s, 1H), 6.82−6.78 (m, 3H), 6.58 (s, 1H), 6.36 (d, *J* = 7.6 Hz, 1H), 4.93 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.7, 146.3, 145.3, 144.3, 141.5, 137.9, 132.9, 132.7, 130.9, 127.3, 126.9, 124.4, 122.1, 118.5, 118.2, 115.8, 114.2, 112.1, 111.6, 102.1, 98.8, 50.0.

Anal. Calcd for $C_{28}H_{16}N_4O_2$: C, 76.35; H, 3.66; N, 12.72. Found: C, 76.58; H, 3.94; N, 12.49.

5-(4-Fluorobenzyl)-2-(4-fluorophenyl)-*5H*-oxazolo[4,5-*b*]-phenoxazine (**9f**)



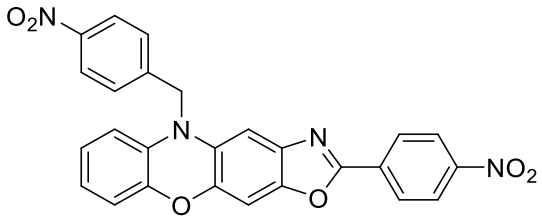
Compound **9f** was prepared according to general procedure starting from substrate **6h**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 4:1) as green solid (73% yield); m.p.: 205-206°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05−8.01 (m, 2H), 7.22−6.94 (m, 6H), 6.87 (s, 1H), 6.72−6.65 (m, 3H), 6.56 (s, 1H), 6.32 (d, *J* = 7.7 Hz, 1H), 4.76 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5 (d, *J* = 250.7 Hz), 162.1 (d, *J* = 245.2 Hz), 161.8 (d, *J* = 4.6 Hz), 145.7, 144.5 (d, *J* = 1.5 Hz), 137.6, 133.3, 132.2 (d, *J* = 3.1 Hz), 129.2 (d, *J* = 8.8 Hz), 127.7 (d, *J* = 8.1 Hz), 124.2, 123.4, 121.5, 116.3, 116.1, 116.0, 115.9, 112.2, 102.1, 98.4, 49.6.

Anal. Calcd for $C_{26}H_{16}F_2N_2O_2$: C, 73.23; H, 3.78; N, 6.57. Found: C, 73.44; H, 4.02; N, 6.37.

5-(4-Nitrobenzyl)-2-(4-nitrophenyl)-*5H*-oxazolo[4,5-*b*]-phenoxazine (**9g**)



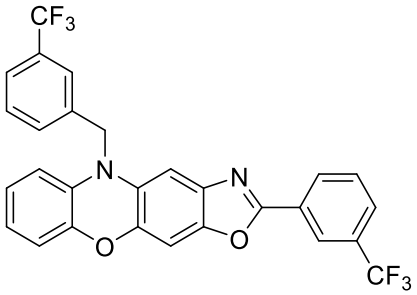
Compound **9g** was prepared according to general procedure starting from substrate **6e**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 4:1) as red solid (28% yield); m.p.: 229-231°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37−8.33 (m, 2H), 8.29−8.24 (m, 4H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.05 (s, 1H), 6.82 (s, 3H), 6.61 (s, 1H), 6.38 (d, *J* = 5.0 Hz, 1H), 4.99 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.8, 151.9, 150.7, 150.2, 147.1, 146.4, 143.3, 139.5, 136.9, 134.7, 131.6, 127.7, 127.1, 124.4, 124.3, 122.2, 115.9, 112.1, 102.1, 98.8, 49.8.

Anal. Calcd for $C_{26}H_{16}N_4O_6$: C, 65.00; H, 3.36; N, 11.66. Found: C, 65.13; H, 3.58; N, 11.49.

5-((3-Trifluoromethyl)benzyl)-2-(3-(trifluoromethyl)phenyl)-*5H*-oxazolo[4,5-*b*]phenoxazine (**9h**)



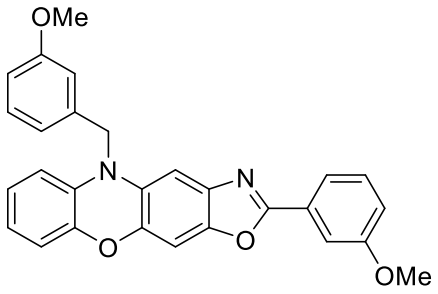
Compound **9h** was prepared according to general procedure starting from substrate **6l**, reaction time 7 h, and isolated through flash chromatography (DCM) as yellow solid (79% yield); m.p.: 209-210°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.62−7.56 (m, 3H), 7.52− 7.45 (m, 2H), 6.99 (s, 1H), 6.78 (s, 3H), 6.61 (s, 1H), 6.39 (d, *J* = 7.7 Hz, 1H), 4.92 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.2, 145.9, 145.0, 144.4, 137.7, 137.0, 132.9, 132.2, 131.8 (d, *J* = 6.9 Hz), 131.4 (d, *J* = 7.3 Hz), 129.9, 129.6, 129.5, 129.3, 127.9, 127.4 (q, *J* = 3.0 Hz), 125.2 (d, *J* = 26.2), 124.4 (q, *J* = 3.6 Hz), 124.3, 123.8 (q, *J* = 3.7 Hz), 122.9 (q, *J* = 3.7 Hz), 122.5 (d, *J* = 26.3 Hz), 121.8, 115.6, 112.2, 102.1, 98.6, 50.2.

Anal. Calcd for $C_{28}H_{16}F_6N_2O_2$: C, 63.88; H,3.06; N, 5.32. Found: C, 63.74; H, 2.88; N, 5.45.

5-(3-Methoxybenzyl)-2-(3-methoxyphenyl)-*5H*-oxazolo[4,5-*b*]-phenoxazine (**9i**)



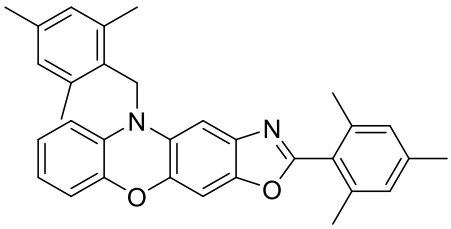
Compound **9i** was prepared according to general procedure starting from substrate **6k**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 4:1) as green solid (60% yield); m.p.: 220-222°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ=7.61 (d, *J* = 7.8 Hz, 1H), 7.54 (s, 1H), 7.28 (dd, *J* = 6.9, 7.3 Hz, 1H), 7.17 (dd, *J* = 6.9, 7.3 Hz, 1H), 6.93−6.59 (m, 9H), 6.35 (d, *J* = 7.8 Hz, 1H), 4.74 (s, 2H), 3.78 (s, 3H), 3.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.5, 160.2, 159.9, 145.7, 144.6, 137.8, 137.5, 133.5, 132.3, 130.1, 129.9, 128.3, 124.2, 121.3, 119.5, 118.3, 117.9, 115.3, 112.4, 112.3, 111.2, 102.4, 98.3, 55.5, 55.2, 50.3.

Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.91; H, 5.23; N, 6.02.

5-(2,4,6-Trimethylbenzyl)-2-(2,4,6-trimethylphenyl)-*5H*-oxazolo-[4,5-*b*]phenoxazine (**9j**)



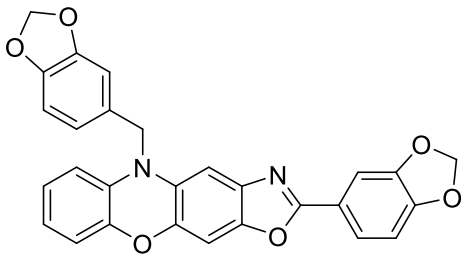
Compound **9j** was prepared according to general procedure starting from substrate **6n**, reaction time 7 h, and isolated through flash chromatography (DCM:PE 1:1) as yellow oil (63% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.01 (s, 1H), 6.95 (s, 2H), 6.85 (d, 3H, *J* = 6.9 Hz), 6.79 (d, 2H, *J* = 7.8 Hz), 6.75−6.71 (m, 1H), 6.51 (d, 1H, *J* = 8.0 Hz), 4.81 (s, 2H), 2.43 (s, 6H), 2.34 (s, 3H), 2.26 (s, 6H), 2.25 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 162.7, 146.2, 145.7, 145.5, 140.1, 138.5, 137.2, 136.7, 136.5, 134.3, 132.9, 130.1, 128.6, 124.9, 123.9, 121.3, 120.2, 115.6, 113.5, 103.3, 98.6, 46.9, 21.3, 20.8, 20.7, 20.3.

Anal. Calcd for $C_{32}H_{30}N_2O_2$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.21; H, 6.72; N, 5.71.

2-(Benzo[1,3]dioxol-5-yl)-5-(benzo[1,3]dioxol-5-ylmethyl)-*5H*oxazolo[4,5-*b*]phenoxazine (**9k**)



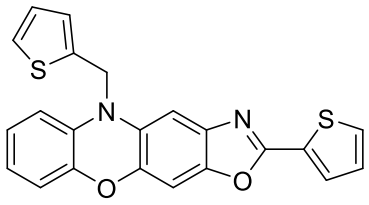
Compound **9k** was prepared according to general procedure starting from substrate **6q**, reaction time 7 h, and isolated through flash chromatography (DCM:PE 9:1) as yellow solid (72% yield); m.p.: 264-265°C.

^{1}H NMR (400 MHz, DMSO-d6): δ = 7.68 (d, *J* = 8.2 Hz, 1H), 7.55 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.96−6.93 (m, 2H), 6.91−6.82 (m, 6H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.19 (s, 2H), 6.05 (s, 2H), 4.96 (s, 2H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 161.7, 150.1, 148.0, 147.6, 144.9, 143.5, 143.1, 137.5, 132.9, 131.5, 129.,8, 124.4, 121.8, 121.2, 120.3, 119.2, 115.1, 112.5, 108.9, 108.5, 106.8, 106.3, 102.1, 101.9, 100.9, 98.5, 47.4.

Anal. Calcd for $C_{28}H_{18}N_2O_6$: C, 70.29; H, 3.79; N, 5.86. Found:C, 70.49; H, 4.06; N, 5.72.

2-(Thien-2-yl)-5-(thien-2-ylmethyl)-*5H*-oxazolo[4,5-*b*]-phenoxazine (**9l**)



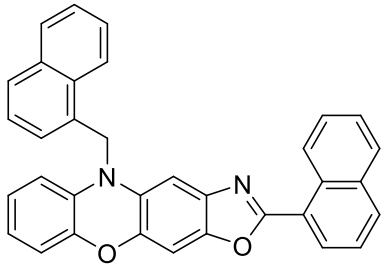
Compound **9l** was prepared according to general procedure starting from substrate **6o**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 4:1) as yellow solid (81% yield); m.p.: 226-227°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 3.9 Hz, 1H), 7.49 (d, *J* = 4.9 Hz, 1H), 7.23 (d, *J* = 4.9 Hz, 1H), 7.16 (dd, *J* = 3.9, 4.9 Hz, 1H), 6.99 (s, 1H), 6.96−6.94 (m, 2H), 6.86−6.82 (m, 2H), 6.78−6.76 (m, 2H), 6.62 (d, *J* = 7.7 Hz, 1H), 5.00 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.7, 145.4, 144.6, 144.5, 138.9, 137.6, 132.9, 131.9, 129.6, 129.5, 129.1, 128.2, 127.2, 125.2, 124.7, 124.1, 121.6, 102.3, 93.3, 46.4.

Anal. Calcd for $C_{22}H_{14}N_2O_2S_2$: C, 65.65; H, 3.51; N, 6.96. Found: C, 65.90; H, 3.84; N, 6.75.

2-(Naphthalen-1-yl)-5-(naphthalen-1-ylmethyl)-*5H*-oxazolo[4,5-b]phenoxazine (**9m**)



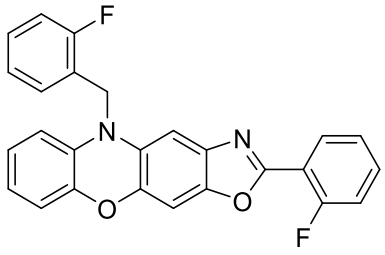
Compound **9m** was prepared according to general procedure starting from substrate **6r**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 8:2) as yellow solid (66% yield); m.p.: 240-242°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.24 (d, *J* = 8.5 Hz, 1H), 8.24 (d, *J* = 7.3 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.89 (t, *J* = 8.2Hz, 2H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.68−7.40 (m, 5H), 7.39−7.26 (m, 2H), 6.98 (s, 1H), 6.74 (dd, *J* = 5.7, 3.6Hz, 1H), 6.69−6.64 (m, 2H), 6.63 (s, 1H), 6.30 (dd, *J* = 5.7, 3.6 Hz, 1H), 5.27 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.3, 145.2, 144.8, 144.7, 138.2, 134.2, 133.9, 133.5, 132.2, 131.9, 130.8, 130.4, 129.2, 129.0, 128.7, 128.6, 127.9, 127.7, 126.4, 126.3, 126.2, 126.0, 125.6, 124.9, 124.2, 123.5, 123.1, 122.3, 121.3, 115.3, 112.6, 102.7, 98.2, 48.9.

Anal. Calcd for $C_{34}H_{22}N_2O_2$: C, 83.25; H, 4.52; N, 5.71. Found: C, 83.44; H, 4.82; N, 5.53.

5-(2-Fluorobenzyl)-2-(2-fluorophenyl)-*5H*-oxazolo[4,5-*b*]-phenoxazine (**9n**)



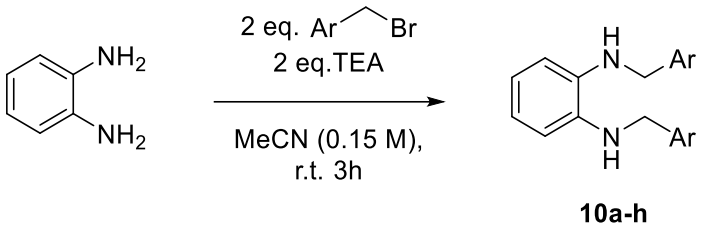
Compound **9n** was prepared according to general procedure starting from substrate **6m**, reaction time 7 h, and isolated through flash chromatography (hex:EtOAc 10:1) as yellow oil (59% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dd, *J* = 7.5, 7.4 Hz, 1H), 7.50−7.44 (m, 1H), 7.31−7.14 (m, 5H), 7.04 (d, *J* = 7.4 Hz, 1H), 7.01 (s, 1H), 6.80−6.72 (m, 3H), 6.71 (s, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 4.93 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.9 (d, *J* = 243.9 Hz), 160.4 (d, *J* = 257.0 Hz), 158.9 (d, *J* = 5.8 Hz), 145.5, 144.9, 144.6, 133.7, 133.2, 132.5 (d, *J* = 8.8 Hz), 132.0, 129.8 (d, *J* = 1.5 Hz), 128.9 (d, *J* = 8.1 Hz), 127.5 (d, *J* = 3.8 Hz), 124.5 (d, *J* = 3.8 Hz), 124.4 (d, *J* = 3.8 Hz), 124.3, 122.4, 122.2, 117.0 (d, *J* = 21.6 Hz), 115.8 (d, *J* = 20.4 Hz), 115.5, 112.2, 102.4, 98.4, 44.5.

Anal. Calcd for $C_{26}H_{16}F_2N_2O_2$: C, 73.23; H, 3.78; N, 6.57. Found: C, 73.12; H, 3.62; N, 6.72.

General procedure for the synthesis of N,N'-dibenzylbenzene-1,2-diamines (**10a-h**)

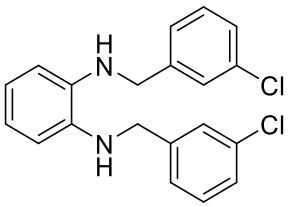


10a-h

In a solution of 1,2-phenylenediamine (1.0 mmol) in MeCN (0.15 M) the appropriate benzylbromide (2.0 mmol) and triethylamine (2.0 mmol) were added, the reaction was stirred for 3 hours at room temperature. The resulting mixture, after evaporation of the solvent, was extracted with DCM (2 x 10 ml), washed with H_2O (2 x 10 ml) and brine (10 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the residue was purified through flash chromatography.

The characterization of compounds **10a**, [98] **b** [99] are consistent with the one reported in literature.

N,N'-Di(3-chlorobenzyl)benzene-1,2-diamine (**10c**)



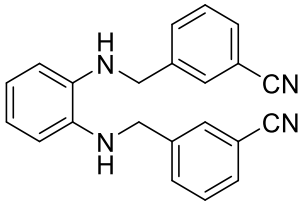
Compound **10c** was prepared according to general procedure from 3-chlorobenzyl bromide and isolated through flash chromatography (PE:DCM 7:3) as a yellow oil (56% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (s, 2H), 7.33−7.28 (m, 6H), 6.89−6.85 (m, 2H), 6.76−6.72 (m, 2H), 4.33 (s, 4H), 3.89 (br s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.7, 136.9, 134.6, 130.0, 127.9, 127.6, 125.9, 120.0, 112.6, 48.4.

Anal. Calcd. For $C_{20}H_{18}Cl_2N_2$: C 67.24, H 5.08, N 7.84; found: C 64.02, H 5.33, N 8.11.

N,N'-Di(3-cianobenzyl)benzene-1,2-diamine (**10d**)



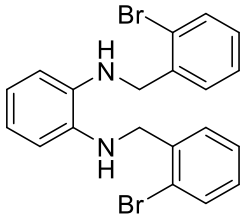
Compound **10d** was prepared according to general procedure from 3-(bromomethyl)benzonitrile and isolated through flash chromatography (EtOAc:toluene 1:4) as an orange wax (39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.48−7.44 (m, 2H), 6.82−6.79 (m, 2H), 6.66−6.62 (m, 2H), 4.43 (s, 4H), 4.02 (br s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.3, 136.5, 132.1, 131.0, 130.9, 129.4, 119.9, 119.0, 112.5, 112.4, 47.8.

Anal. Calcd for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; N, 16.56. Found: C, 77.91; H, 5.51; N, 16.83.

N,N'-Di(2-bromobenzyl)benzene-1,2-diamine (**10e**)



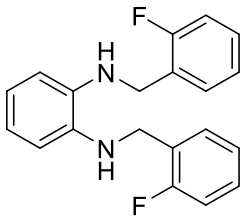
Compound **10e** was prepared according to general procedure from 2-bromobenzyl bromide and isolated through flash chromatography (hex:EtOAc 7:3) as a yellow oil (53% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J*=7.8 Hz, 2H), 7.29−7.25 (m, 2H), 7.16 (dd, *J* = 7.4 Hz, 2H), 7.05−7.02 (m, 2H), 6.69−6.64 (m, 2H), 6.56−6−51 (m, 2H), 4.29 (s, 4H), 3.78 (br s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.3, 136.9, 132.9, 129.6, 128.8, 127.6, 123.7, 119.9, 113.1, 49.0.

Anal. Calcd for $C_{20}H_{18}Br_2N_2$: C, 53.84; H, 4.07; N, 6.28. Found: C, 54.07; H, 4.36; N, 6.02.

N,N'-Di(2-fluorobenzyl)benzene-1,2-diamine (**10f**)



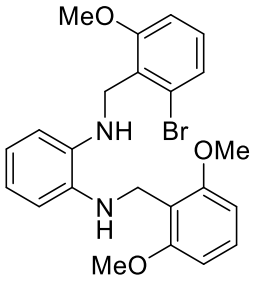
Compound **10f** was prepared according to general procedure from 2-fluorobenzyl bromide and isolated through flash chromatography (hex:EtOAc 9:1) as a yellow oil (32% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45−7.40 (m, 2H), 7.34−7.28 (m, 2H), 7.17−7.11 (m, 4H), 6.88−6.83 (m, 2H), 6.70−6.75 (m, 2H), 4.44 (s, 4H), 3.80 (br, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.1, 137.2, 129.8, 128.8, 126.4, 124.2, 119.8, 115.4, 112.7, 42.4.

Anal. Calcd for $C_{20}H_{18}F_2N_2$: C, 74.06; H, 5.59; N, 8.64. Found: C, 73.85; H, 5.92; N, 8.39.

N,N'-Di(2-bromo-5-methoxybenzyl)benzene-1,2-diamine (**10g**)



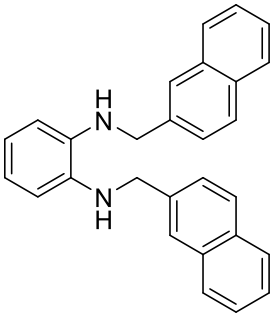
Compound **10g** was prepared according to general procedure from 2-bromo-5-methoxybenzyl bromide and isolated through flash chromatography (DCM:PE 9:1) as a yellow oil (30% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 3.0 Hz, 2H), 6.72−6.68 (m,2H), 6.62−6.53 (m, 5H), 4.25 (s, 4H), 3.79 (br, 2H), 3.62 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 139.4, 137.0, 133.4, 120.0, 115.4, 114.2, 113.8, 113.2, 55.5, 49.1.

Anal. Calcd for $C_{22}H_{22}Br_2N_2O_2$: C, 52.20; H, 4.38; N, 5.53. Found: C, 52.67; H, 4.56; N, 5.78.

N,N'-Di(naphthalen-2-yl-methyl)benzene-1,2-diamine (**10h**)



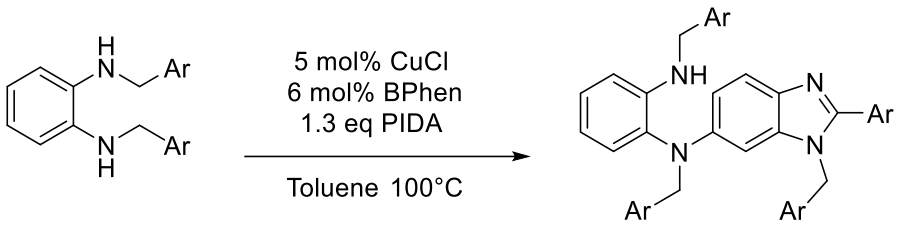
Compound **10h** was prepared according to general procedure from 2-(bromomethyl)naphthalene and isolated through flash chromatography (hex:EtOAc 9:1) as an orange oil (28% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92−7.75 (m, 8H), 7.56−7.54 (m, 2H), 7.49−7.44 (m, 4H), 6.82 (s, 4H), 4.52 (s, 4H), 3.82 (br, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.3, 136.9, 133.5, 132.8, 128.3, 127.8, 127.7, 126.3, 126.2, 126.1, 125.7, 119.6, 112.3, 49.1.

Anal. Calcd for $C_{28}H_{24}N_2$: C, 86.56; H, 6.23; N, 7.21. Found: C, 85.98; H, 6.78; N, 6.99.

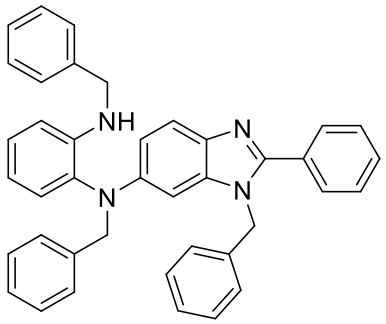
General procedure for the Dimerization/Cyclization of the N,N'-Dibenzyl-benzene-1,2-diamine **(11a-h)**



10a-h **11a-h**

In a sealed tube, to a stirred solution of bathophenantroline (0.06 mmol, 10.8 mg) in toluene (4.0 ml, 0.25M), CuCl (0.05 mmol, 4.9 mg) was added. After 10 minutes the appropriate *N,N'*-disubstituted benzene-1,2-diamine **10a-h** (1.0 mmol) and PIDA (1.3 mmol, 418,7 mg) were added. The reaction was stirred at 100°C. The reaction mixture was then extracted with DCM (2 x 10 ml) and the solvent was evaporated under reduced pressure. The crude was purified through flash chromatography.

N,N'-Dibenzyl-*N*-(1-benzyl-2-phenyl-*1H*-benzo[d]imidazol-6-yl)-benzene-1,2-diamine (**11a**)



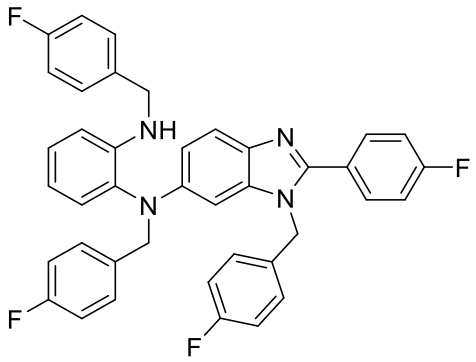
Compound **11a** was prepared according to general procedure starting from substrate **10a**, reaction time 1.5 h, and isolated through flash chromatography (hex:EtOAc 4:1) as yellow oil (70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56−7.50 (m, 3H), 7.33−7.28 (m, 3H), 7.14−7.08 (m, 11H), 7.05−7.93 (m, 4H), 6.89−6.84 (m, 2H), 6.61−6.52 (m, 3H), 6.37 (d, *J* = 2.1 Hz, 1H), 5.12 (s, 2H), 4.66 (s, 2H), 4.50 (br s, 1H), 4.09 (d, *J* = 3.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.6, 145.5, 144.9, 139.4, 138.9, 137.1, 136.4, 136.3, 133.8, 130.4, 129.5, 129.2, 129.0, 128.7, 128.6, 128.5, 128.4, 127.7, 127.6, 127.3, 127.1, 127.0, 126.9 126.3, 120.1, 117.6, 112.7, 111.6, 95.3, 56.7, 48.4, 47.7.

Anal. Calcd for $C_{40}H_{34}N_4$: C, 84.18; H, 6.00; N, 9.82. Found: C, 84.63; H, 5.91; N, 9.69.

N,N'-Di(4-fluorobenzyl)-*N*-(1-(4-fluorobenzyl)-2-(4-fluorophenyl)-*1H*-benzo[d]imidazol-6-yl)benzene-1,2-diamine (**11b**)



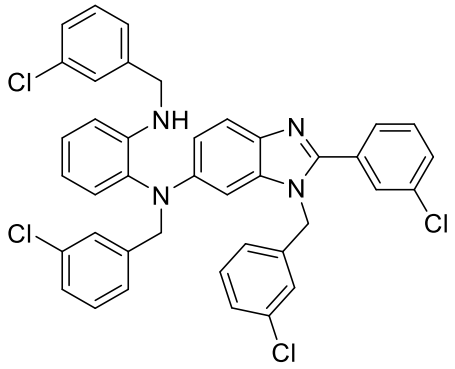
Compound **11b** was prepared according to general procedure starting from substrate **10b**, reaction time 8 h, and isolated through flash chromatography (hex:EtOAc 4:1) as yellow oil (68% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63−7.60 (m, 3H), 7.21−7.15 (m, 3H), 7.11−7.06 (m, 5H), 6.96−6.90 (m, 8H), 6.73−6.70 (m, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 1.9 Hz, 1H), 5.19 (s, 2H), 4.74 (s, 2H), 4.48 (br s, 1H), 4.18 (d, *J* = 2.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.6 (d, *J* = 251.5 Hz), 162.2 (d, *J* = 247.9 Hz), 161.9 (d, *J* = 246.1 Hz), 160.8 (d, *J* = 246.3 Hz), 151.6, 145.4, 144.7, 136.8, 134.8 (d, *J* = 3.1 Hz), 134.3 (d, *J* = 3.1 Hz), 133.5, 131.7 (d, *J* = 3.2 Hz), 130.9 (d, *J* = 8.5 Hz), 128.7 (d, *J* = 8.5 Hz), 128.6 (d, *J* = 8.4 Hz), 128.5, 127.8 (d, *J* = 8.4 Hz), 126.2 (d, *J* = 2.7 Hz), 120.2, 117.9, 116.0 (d, *J* = 21.9 Hz), 115.9 (d, *J* = 21.8 Hz), 115.3 (d, *J* = 21.5 Hz), 112.8, 111.7, 95.3, 55.8, 47.7, 47.0.

Anal. Calcd for $C_{40}H_{30}F_4N_4$: C, 74.75; H, 4.71; N, 8.72. Found: C, 75.06; H, 5.14; N, 9.21.

N,N'-Di(3-chlorobenzyl)-*N*-(1-(3-chlorobenzyl)-2-(3-chlorophenyl)-*1H*-benzo[d]imidazol-6-yl)benzene-1,2-diamine (**11c**)



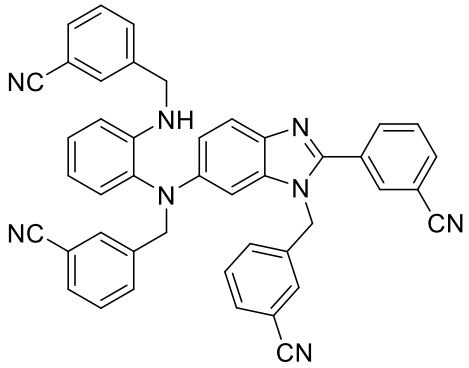
Compound **11c** was prepared according to general procedure starting from substrate **10c**, reaction time 3 h, and isolated through flash chromatography (hex:EtOAc 7:3) as yellow oil (57% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64−7.56 (m, 2H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.19 (s, 2H), 7.15−7.00 (m, 9H), 6.96 (s, 1H), 6.92 (s, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.69−6.62 (m, 2H), 6.53 (d, *J* = 7.9 Hz, 1H), 6.24 (d, *J* = 2.0 Hz, 1H), 5.14 (s, 2H), 4.69 (s, 2H), 4.42 (br s, 1H), 4.14 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.9, 145.6, 144.3, 141.4, 140.8, 137.7, 137.6, 136.7, 136.7, 135.1, 135.0, 134.5, 134.5, 133.1, 130.4, 130.2, 129.9, 129.9, 129.3, 128.9, 128.4, 128.3, 128.0, 127.4, 127.3, 127.1, 127.1, 127.0, 126.3, 125.1, 125.1, 124.2, 120.4, 118.2, 113.1, 111.8, 94.8, 56.4, 48.0, 47.2.

Anal.Calcd for $C_{40}H_{30}Cl_4N_4$: C, 67.81; H, 4.27; N, 7.91. Found: C, 66.89; H, 4.91; N, 7.69.

N,N'-Di(3-cianobenzyl)-*N*-(1-(3-cianobenzyl)-2-(3-cianophenyl)-*1H*-benzo[d]imidazol-6-yl)benzene-1,2-diamine (**11d**)



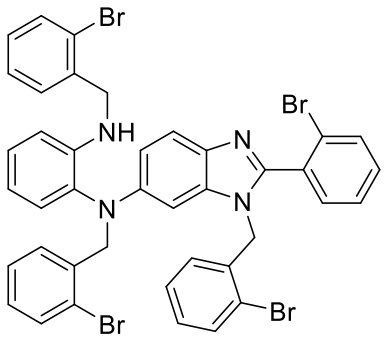
Compound **11d** was prepared according to general procedure starting from substrate **10d**, reaction time 1.5 h, and isolated through flash chromatography (hex:EtOAc 1:1) as yellow oil (30% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 1H), 7.85 (d, *J* = 6.7 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.63−7.51 (m, 2H), 7.48−7.40 (m, 4H), 7.38 (d, *J* = 6.4 Hz, 4H), 7.21 (d, *J* = 6.7 Hz, 1H), 7.18 (d, 2H, *J* = 3.4 Hz), 7.14 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.80 (d, 1H, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.22 (s, 1H), 5.31 (s, 2H), 4.87 (s, 2H), 4.56 (br s, 1H), 4.33 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.1, 145.6, 143.9, 140.9, 140.0, 137.2, 136.8, 136.4, 133.2, 133.0, 132.5, 131.9, 131.5, 131.3, 131.1, 131.0, 130.5, 130.4, 130.2, 130.1, 129.9, 129.5, 129.5, 129.5, 128.5, 128.4, 118.8, 118.6, 118.1, 117.8, 113.5, 113.4, 112.7, 112.7, 94.7, 55.9, 47.8, 46.9.

Anal. Calcd for $C_{44}H_{30}N_8$: C, 78.79; H, 4.51; N, 16.71. Found: C, 78.23; H, 4.91; N, 16.04

N,N'-Di(2-bromobenzyl)-*N*-(1-(2-bromobenzyl)-2-(2-bromophenyl)-*1H*-benzo[d]imidazol-6-yl)benzene-1,2-diamine (**11e**)



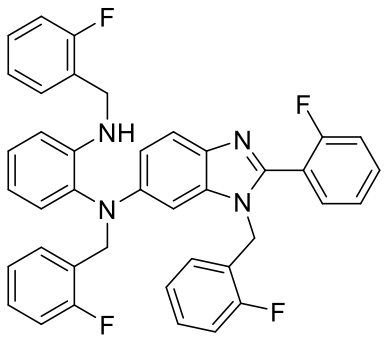
Compound **11e** was prepared according to general procedure starting from substrate **10e**, reaction time 1.5 h, and isolated through flash chromatography (hex:EtOAc 7:3) as yellow oil (88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55−7.51 (m, 2H), 7.45−7.32 (m, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.28−7.14 (m, 4H), 7.05 (d, *J* = 7.1 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.98−6.91 (m, 5H), 6.90−6.83 (m, 2H), 6.66−6.49 (m, 3H), 6.43 (d, *J* = 8.0 Hz, 1H), 6.35−6.20 (m, 1H), 5.05 (s, 2H), 4.70 (s, 2H), 4.62, (br s, 1H), 4.16 (d, J = 5.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.9, 145.3, 144.6, 138.0, 136.9, 136.4, 135.8, 134.7, 133.2, 133.0, 132.9, 132.8, 132.7, 132.5, 131.4, 129.2, 129.1, 128.7, 128.6, 128.5, 128.4, 127.9, 127.7, 127.6, 127.5, 127.4, 124.2, 123.2, 123.1, 122.7, 120.6, 117.9, 112.6, 111.8, 95.4, 56.9, 48.2, 47.8.

Anal. Calcd for $C_{40}H_{30}Br_4N_4$: C, 54.21; H, 3.41; N, 6.32. Found: C,54.63; H, 3.91; N, 6.59.

N,N'-Di(2-fluorobenzyl)-*N*-(1-(2-fluorobenzyl)-2-(2-fluorophenyl)-*1H*-benzo[d]imidazol-6-yl)benzene-1,2-diamine (**11f**)



Compound **11f** was prepared according to general procedure starting from substrate **10f**, reaction time 1.5 h, and isolated through flash chromatography (hex:EtOAc 3:2) as yellow wax (60% yield).

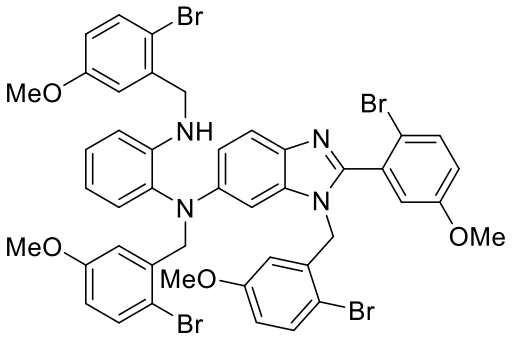
^{1}H NMR (400 MHz, $CDCl_3$): δ=7.68−7.60 (m, 2H), 7.53−7.44 (m, 1H), 7.36−7.26 (m, 2H), 7.25−

7.15 (m, 5H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.05−6.95 (m, 3H), 6.95−6.86 (m, 3H), 6.81−6.64 (m, 4H), 6.51 (d, *J* = 1.9 Hz, 1H), 5.21 (s, 2H), 4.86 (s, 2H), 4.65 (br s, 1H), 4.32 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.7 (d, *J* = 246.0 Hz), 160.6 (d, *J* = 246.3 Hz), 160.2 (d, *J* = 247.5 Hz), 160.1 (d, *J* = 247.3 Hz), 147.7, 145.4, 144.8, 136.7, 136.3, 133.2, 132.4 (d, *J* = 2.2 Hz), 131.9 (d, *J* = 8.2 Hz), 129.5 (d, *J* = 7.9 Hz), 129.4 (d, *J* = 3.9 Hz), 128.9, 128.8 (d, *J* = 4.3 Hz), 128.7, 128.6 (d, *J* = 8.6 Hz), 127.8, 126.2 (d, *J* = 14.0 Hz), 125.4 (d, *J* = 14.0 Hz), 124.7 (d, *J* = 3.5 Hz), 124.3 (d, *J* = 3.6 Hz), 124.1 (d, *J* = 3.6 Hz), 124.0 (d, *J* = 3.6 Hz), 122.8 (d, *J* = 14.1 Hz, d, *J* = 3.8 Hz), 120.3, 118.7 (d, *J* = 14.8 Hz, d, *J* = 3.8 Hz), 117.8, 116.0 (d, *J* = 21.5 Hz), 115.4 (d, *J* = 13.0 Hz), 115.3, 115.1 (d, *J* = 6.7 Hz), 112.5, 111.6, 95.1, 50.0 (d, *J* = 4.1 Hz), 42.06, 41.04 (d, *J* = 4.5 Hz).

Anal. Calcd for $C_{40}H_{30}F_4N_4$: C, 74.75; H, 4.71; N, 8.72. Found: C, 74.11; H, 5.03; N, 8.96.

N,N'-Di(2-bromo-5-methoxybenzyl)-*N*-(1-(2-bromo-5-methoxybenzyl)-2-(2-bromo-5-methoxyphenyl)-*1H*-benzo[d]imidazol-6-yl)-benzene-1,2-diamine (**11g**)



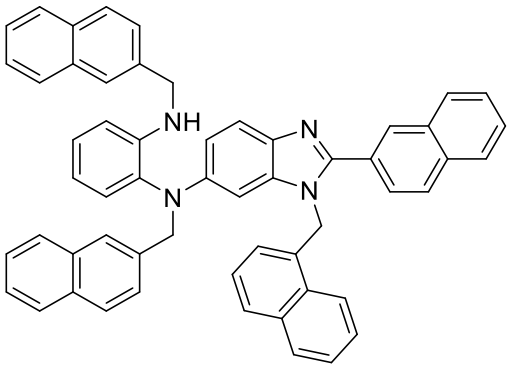
Compound **11g** was prepared according to general procedure starting from substrate **10g**, reaction time 1.5 h, and isolated through flash chromatography (hex:EtOAc 3:2) as yellow oil (70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.9 Hz, 1H), 7.45 (d, J = 8.9 Hz, 1H), 7.30−7.23 (m, 2H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 2.9 Hz, 1H), 6.84−6.75 (m, 2H), 6.69 (d, *J* = 2.8 Hz, 1H), 6.66−6.56 (m, 2H), 6.54 (dd, *J* = 3.0, 8.8 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 2H), 6.46 (dd, *J* = 2.9, 8.8 Hz, 1H), 6.33 (d, *J* = 1.7 Hz, 1H), 6.12 (d, *J* = 2.8 Hz, 1H), 5.05 (s, 2H), 4.70 (s, 2H), 4.58 (br s, 1H), 4.17 (d, *J* = 3.7 Hz, 2H), 3.62 (s, 3H), 3.54 (s, 3H), 3.43 (s, 3H), 3.41 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 159.0, 158.9, 158.8, 150.8, 145.0, 144.5, 139.0, 137.9, 136.3, 135.8, 135.7, 133.7, 133.4, 133.3, 133.2, 133.1, 132.7, 128.5, 127.9, 120.5, 118.0, 117.9, 117.4, 115.1, 114.4, 114.3, 114.3, 114.2, 114.1, 113.2, 113.1, 113.0, 112.9, 112.4, 111.9, 95.3, 57.1, 55.6, 55.4, 55.3, 55.2, 48.2, 48.0.

Anal. Calcd for $C_{44}H_{38}Br_4N_4O_4$: C, 52.51; H,3.81; N, 5.57. Found: C, 52.73; H, 4.22; N, 5.79.

N,N'-Di(Naphthalen-2-ylmethyl)-*N*-(1-(naphthalen-2-ylmethyl)-2-(naphthalen-2-yl)-*1H*-benzo[d]imidazol-6-yl)benzene-1,2-diamine (**11h**)



Compound **11h** was prepared according to general procedure starting from substrate **10h**, reaction time 1.5 h, and isolated through flash chromatography (hex:EtOAc 3:2) as yellow oil (74% yield).

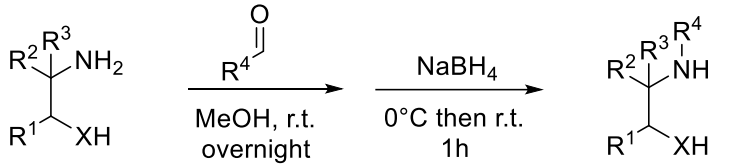
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 7.89−7.82 (m, 2H), 7.81−7.72 (m, 5H), 7.70 (d, *J* = 4.8 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.59−7.50 (m, 7H), 7.48 (d, *J* = 6.7 Hz, 1H), 7.46−7.40 (m, 6H), 7.39−7.31 (m, 2H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.12−7.05 (m, 2H), 6.86 (dd, *J* = 2.2, 8.9 Hz, 1H), 6.73−6.66 (m, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 2.0 Hz, 1H), 5.42(s, 2H), 4.96 (s, 2H), 4.67 (br s, 1H), 4.22 (d, *J* = 2.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.8, 145.5, 144.8, 137.5,136.8, 136.5, 134.0, 133.7, 133.6, 133.4, 133.3, 133.0, 132.8, 132.6,132.6, 128.8, 128.6, 128.5, 128.4, 128.2, 128.2, 127.9, 127.8, 127.7,127.6, 127.6, 127.6, 127.0, 126.6, 126.4, 126.3, 126.1, 126.0, 125.9,125.7, 125.6, 125.5, 125.4, 125.3, 125.1, 124.1, 120.3, 117.7, 112.8,111.7, 95.4, 57.0, 48.8, 47.7.

Anal. Calcd for $C_{56}H_{42}N_4$: C, 87.24; H,5.49; N, 7.27. Found: C, 87.63; H, 5.91; N, 6.69.

Chapter 1.4_ *Methanol as a C1 source for the synthesis of 1,3-polyheterocyclic systems*

General procedure for the synthesis of N-benzylaminoalcohol and N-benzyldiammine (**12a-i, 14a-c**)



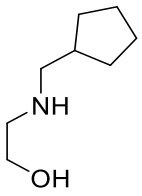
X: O, NTs

12a-j, 14a-c

To a 100 ml round bottom flask charged with the appropriate amino-alcohol or *N*-Ts diamine (1.0 mmol) in methanol (0.1 M) was added the corresponding aldehyde (1.0 mmol). The reaction was stirred overnight at room temperature. The solution was then cooled to 0°C and then $NaBH_4$ (0.5 mmol) was added portion wise. The resulting solution was stirred at room temperature for 1 hour. After the addition of water (30 ml), the solvent was removed under reduced pressure and the resulting phase was extracted with ethyl acetate (3 x 20 ml). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to give the desired product in quantitative yield.

The characterization of compounds **12a, b, d, e, g, h** [100], **12f** [101], **12i** [102], **14a** [103], **14b** [104] are consistent with the ones reported in literature.

2-((Cyclopentylmethyl)amino)ethanol (**12c**)



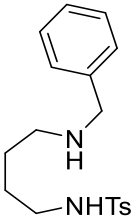
Compound **12c** was prepared according to the general procedure starting ethanolamine and isolated through flash chromatography (hex:EtOAc 3:1) as a yellow oil, (90% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.64-3.60 (m, 2H), 2.79 (br, 2H), 2.76-2.72 (m, 2H), 2.53 (d, *J* = 7.2 Hz, 2H), 2.04-1.94 (m, 1H), 1.76-1.69 (m, 2H), 1.63-1.46 (m, 4H), 1.18-1.09 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 60.6, 55.2, 51.3, 39.9, 30.8, 25.2.

Anal. Calcd for $C_8H_{17}NO$: C 67.10, H 11.90, N 9.78; found: C 67.14, H 11.95, N 9.76.

N-(4-Benzylamino)butyl)-4-methylbenzenesulfonamide (**14c**)



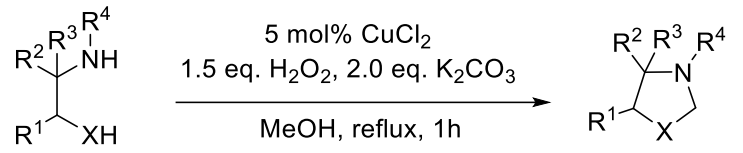
Compound **14c** was prepared according to general procedure from Putrescine and isolated through flash chromatography (hex:EtOAc 1:1) as pale-yellow liquid (86% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.73-7.68 (m, 2H), 7.43-7-39 (m, 2H), 7.34-7.23 (m, 5H), 5.83 (br, 2H) 3.88 (s, 2H), 2.86 (t, *J* = 6.1 Hz, 2H), 2.69 (t, *J* = 6.7 Hz, 2H), 2.38 (s, 3H), 1.71-1.62 (m, 2H), 1.57-1.48 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 142.9, 137.2, 135.3, 129.5, 129.3, 128.7, 128.2, 127.1, 52.5, 47.4, 42.6, 27.2, 25.5, 21.5.

Anal. Calcd for $C_{18}H_{24}N_2O_2S$: C 65.10, H 7.28, N 8.43; found: C 65.15, H 7.24, N 8.45.

General procedure for the synthesis of products (**13a-j, 15a-c**)

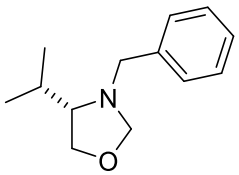


12a-i, 14a-c **13a-j, 15a-c**

To a stirred solution of the appropriate substrate (1 mmol) in MeOH (0.1 M) were added in the following order: H_2O_2 (30% aq, 1.5 eq), K_2CO_3 (2 eq) and $CuCl_2$ (5 mol%) and the mixture was heated to reflux for 1h. The solvent was then removed under reduced pressure, the crude was taken up with NH_4Cl saturated solution (20 ml) and extracted with AcOEt (2 x 20 ml), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified with FCC when necessary. (If the reaction is performed in large scale, no purification step is required)

The characterization of compounds **13b**,**f** [105] **13d**, [106] **13h** [107] are consistent with the ones reported in literature.

(-)-N-Benzyl-4-isopropyloxazolidine (**13a**)



Compound **13a** was prepared according to general procedure from substrate **12a** and isolated through flash chromatography (hex:EtOAc 7:3) as pale-yellow liquid (94% yield).

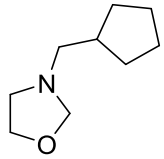
$[\alpha]_D$ = -23.8 (*c* = 1.04 g/mL in MeOH).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.27 (m, 5H), 4.28 (d, *J* = 5.9 Hz, 1H), 4.19 (d, *J* = 5.9 Hz, 1H), 4.02 (t, *J* = 7.7 Hz, 1H), 3.74 (s, 2H), 3.47 (dd, *J* = 8.1, 6.0 Hz, 1H), 2.69 (dd, *J* = 14.5, 7.3 Hz, 1H), 1.68-1.57 (m, 1H), 0.98 (d, *J* = 4.9 Hz, 3H), 0.88 (d, *J* = 5.0 Hz, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.7, 128.9, 128.3, 127.1, 85.9, 70.3, 67.7, 59.8, 31.2, 20.2, 18.7.

Anal. Calcd for $C_{13}H_{19}NO$: C 76.06, H 9.33, N 6.82; found: C 76.12, H 9.40, N 6.77.

N-(Cyclopentylmethyl)oxazolidine (**13c**)



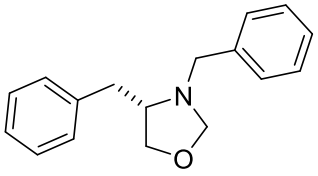
Compound **13c** was prepared according to general procedure from substrate **12c** and isolated through flash chromatography (hex:EtOAc 6:4) as colorless liquid (96% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.18 (s, 2H), 3.69 (t, *J* = 6.8 Hz, 2H), 2.85 (t, *J* = 6.7 Hz, 2H), 2.36 (d, *J* = 7.4 Hz, 2H), 1.97-1.92 (m, 1H), 1.81-1.73 (m, 2H) 1.62-1.51 (m, 4H), 1.24-1.17 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 86.9, 63.5, 59.8, 52.6, 39.5, 31.0, 25.1.

Anal. Calcd for $C_9H_{17}NO$ (155.1): C 69.63, H 11.04, N 9.02; found: C 69.70, H 11.08, N 8.98.

(-)-3,4-Dibenzyloxazolidine (**13e**)



Compound **13e** was prepared according to general procedure from substrate **12e** and isolated through flash chromatography (hex:EtOAc 4:1) as white solid (95% yield); m.p.: 51-53°C.

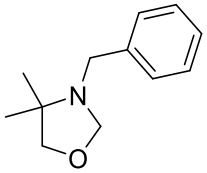
$[\alpha]_D$ = -46.3 (*c* = 0.96 g/mL in MeOH).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.31-7.15 (m, 10H), 4.45 (d, *J* = 5.6 Hz, 1H), 4.34 (d, *J* = 5.6 Hz, 1H), 3.98 (dd, *J* = 8.1, 6.9 Hz, 1H), 3.82-3.66 (m, 2H), 3.52 (dd, *J* = 8.1, 5.4 Hz, 1H), 3.38-3.15 (m, 1H), 2.91 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.64 (dd, *J* = 13.6, 7.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 139.4, 129.6, 129.1, 128.7, 128.6, 127.5, 126.6, 86.4, 69.7, 65.2, 59.2, 40.3.

Anal. Calcd for $C_{17}H_{19}NO$: C 80.60, H 7.56, N 5.53; found C 80.55, H 7.52, N 5.50.

N-Benzyl-4,4-dimethyl-oxazolidine (**13g**)



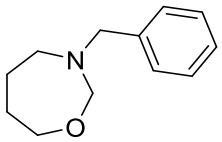
Compound **13g** was prepared according to general procedure from substrate **12g** and isolated through flash chromatography (hex:EtOAc 7:3) as yellow liquid (89% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.38-7.24 (m, 5H), 4.32 (s, 2H), 3.71 (s, 2H), 3.65 (s, 2H), 1.21 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.6, 128.3, 128.2, 126.9, 85.2, 78.7, 59.3, 49.9, 21.5.

Anal. Calcd for $C_{12}H_{17}NO$: C 75.35, H 8.96, N 7.32; found C 75.41, H 8.92, N 7.30.

N-Benzyl-1,3-oxazepane (**13i**)



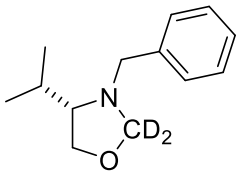
Compound **13i** was prepared according to general procedure from substrate **12i** and isolated through flash chromatography (hex:EtOAc 7:3) as pale-yellow liquid (80% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.36 – 7.21 (m, 5H), 4.41 (s, 2H), 3.89 (s, 2H), 3.78 (t, *J* = 5.2 Hz, 2H), 2.90 (t, *J* = 5.1 Hz, 2H), 1.86 – 1.75 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 139.3, 128.7, 128.2, 126.9, 85.2, 69.4, 55.7, 52.5, 29.9, 25.0.

Anal. Calcd for $C_{12}H_{17}NO$: C 75.35, H 8.96, N 7.32; found C 75.31, H 8.99, N 7.29.

(-)-*N*-Benzyl-4-isopropyloxazolidine-2,2-d_2 (**13j**)



Compound **13j** was prepared according to general procedure from substrate **12a** and isolated through flash chromatography (hex:EtOAc 7:3) as pale-yellow liquid (93% yield).

$[\alpha]_D$ = -24.9 (*c* = 1.05 g/mL in MeOH).

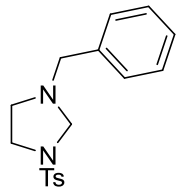
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.27 (m, 5H), 4.02 (t, *J* = 7.7 Hz, 1H), 3.74 (s, 2H), 3.47 (dd, *J* = 8.1, 6.0 Hz, 1H), 2.71-2.66 (m, 1H), 1.65-1.57 (m, 1H), 0.98 (d, *J* = 4.9 Hz, 3H), 0.88 (d, *J* = 4.9 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.7, 128.9, 128.3, 127.1, 70.4, 67.7, 59.8, 31.2, 20.2, 18.7.

^{2}H-NMR (400 MHz, $CDCl_3$): δ = 4.22 (d, *J* = 5.1 Hz, 2H, CD_2).

Anal. Calcd for $C_{13}H_{17}D_2NO$: C: 75.32, H: 10.21, N: 6.76; found C 10.26, H 6.77, N 10.22.

N-Benzyl-3-tosylimidazolidine (**15a**)



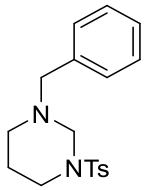
Compound **15a** was prepared according to general procedure from substrate **14a** and isolated through flash chromatography (hex:EtOAc 7:3) as colourless liquid (82% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.2 Hz, 2H;), 7.36 (d, *J* = 8.0 Hz, 2H), 7.34-7.25 (m, 3H), 7.20-7.14 (m, 2H), 4.01 (s, 2H), 3.51 (s, 2H) 3.38 (t, *J* = 6.5 Hz, 2H), 2.82 (t, *J* = 6.5 Hz, 2H), 2.48 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 143.6, 137.7, 134.3, 129.7, 128.5, 128.4, 127.7, 127.5, 70.0, 57.5, 52.5, 46.6, 21.6.

Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C 64.53, H 6.37, N 8.85; found C 64.57, H 6.32, N 8.89.

N-Benzyl-3-tosylhexahydropirimidine (**15b**)



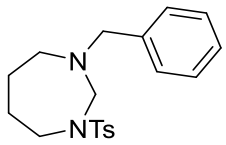
Compound **15b** was prepared according to general procedure from substrate **14b** and isolated through flash chromatography (hex:EtOAc 8:2) as yellow liquid (90% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.3 Hz, 2H), 7.35-7.28 (m, 7H), 4.00 (s, 2H), 3.74 (s, 2H), 3.26-3.22 (m, 2H), 2.68-2.64 (m, 2H), 2.43 (s, 3H), 1.66-1.59 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 143.3, 137.9, 135.2, 129.5, 129.0, 128.3, 127.4, 127.2, 67.5, 56.5, 50.1, 45.9, 21.5, 20.9.

Anal. Calcd for $C_{18}H_{22}N_2O_2S$: C 65.43, H 6.71, N 8.48; found C 65.49, H 6.74, N 8.51.

N-Benzyl-3-tosyl-1,3-diazepane (**15c**)



Compound **15c** was prepared according to general procedure from substrate **14c** and isolated through flash chromatography (hex:EtOAc 8:2) as pale-yellow liquid (94% yield).

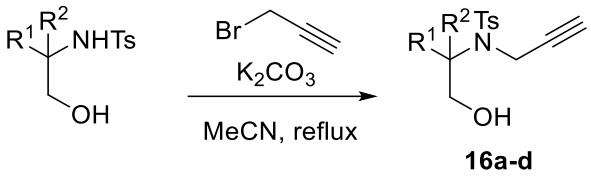
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.29 (m, 7H), 4.41 (s, 2H), 3.87 (s, 2H), 3.24 (t, *J* = 5.8 Hz, 2H), 2.72 (t, *J* = 5.3 Hz, 2H), 2.41 (s, 3H), 1.82 – 1.75 (m, 2H), 1.70–1.63 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 143.2, 139, 129.6, 128.8, 128.2, 126.9, 68.8, 56.4, 52.9, 48.2, 28.1, 24.8, 21.5.

Anal. Calcd for $C_{19}H_{24}N_2O_2S$: C 66.25, H 7.02, N 8.13; found C 66.27, H 7.05, N 8.09.

Chapter 2.1_ *One-pot difunctionalization of terminal alkynes*

General procedure for the synthesis of the N-tosyl-N-propargyl compounds **(16a-d)**

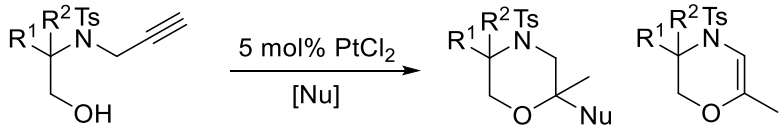


16a-d

To a solution of the appropriate *N*-tosylamino-alcohol (10 mmol) in MeCN (0.5 M), propargyl bromide (10 mmol) and K_2CO_3 (10 mmol) were added, and the solution was stirred at room temperature overnight. The crude was then filtered, and the solvent evaporated under reduced pressure.

The characterization of the products **16a,**[108] **b,**[109] **c, d** [110] are consistent with the ones reported in literature.

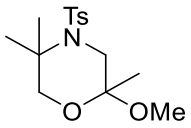
General procedure for the synthesis of the N-tosyl-morpholine derivatives **(17a-k)** *and the N-tosyl-3,4-dihydro-1,4-oxazine* (**18a-b**)



16a-d **17a-k** **18a-b**

To a solution of the appropriate *N*-Tosyl-*N*-propargylamino-alcohol (**16a-d**) (1 mmol) in the appropriate solvent (0.2 M), $PtCl_2$ (5mol%) was added and the reaction was stirred at room temperature for 24 hours. The solvent was then removed under reduced pressure, the crude diluted with NH_4Cl (15 mL) and extracted with EtOAc (3 x 15ml). The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The characterization of compound **18b**[111] is consistent with the one reported in literature.

2-Methoxy-2,5,5-trimethyl-4-tosylmorpholine (**17a**)

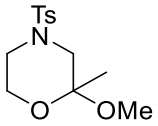


Compound **17a** was prepared according to general procedure from substrate **16a** and MeOH used both as solvent and nucleophile, and isolated through flash chromatography (hex:EtOAc 3:2) as brown liquid (93% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 3.72 (d, *J* = 13.3 Hz, 1H), 3.56 (d, *J* = 11.4 Hz, 1H), 3.25 (s, 3H), 3.21 (d, *J* = 13.3 Hz, 1H), 3.02 (d, *J* = 11.4 Hz, 1H), 2.40 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 140.2, 129.3, 127.0, 70.3, 56.1, 49.5, 48.2, 23.2, 21.8, 21.5, 20.9.

2-Methoxt-2-methyl-4-tosylmorpholine (**17b**)

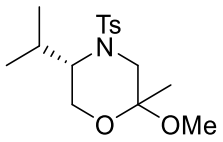


Compound **17b** was prepared according to general procedure from substrate **16b** and MeOH used both as solvent and nucleophile, and isolated through flash chromatography (hex:EtOAc 4:1) as yellow oil (95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.84 (td, *J* = 11.4, 2.8 Hz, 1H), 3.59-3.52 (m, 2H), 3.49-3.44 (m, 1H), 3.20 (s, 3H), 2.51 (td, *J* = 11.6, 3.4 Hz, 1H), 2.41 (s, 3H), 2.33 (d, *J* = 11.7 Hz, 1H), 1.24 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 132.9, 129.6, 127.8, 95.8, 59.4, 52.8, 48.3, 44.5, 21.5, 21.1.

(5*S*)-5-isopropyl-2-methoxy-2-methyl-4-tosylmorpholine (**17c**)

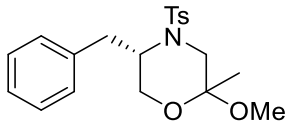


Compound **17c** was prepared according to general procedure from substrate **16c** and MeOH used both as solvent and nucleophile, and isolated through flash chromatography (hex:EtOAc 4:1) as yellow oil (90% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 3.74 (d, *J* = 14.6 Hz, 1H), 3.43 (d, *J* = 11.7 Hz, 1H), 3.24 (dd, *J* = 11.8, 2.4 Hz, 1H), 3.13 (d, *J* = 10.4, 1H), 3.03 (d, *J* = 14.6 Hz, 1H), 2.76 (s, 3H), 2.39 (s, 3H), 2.25-2.10 (m, 1H), 1.15 (s, 3H), 0.96 (dd, *J* = 6.5, 3.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.4, 138.4, 128.7, 127.8, 94.7, 58.5, 57.9, 48.5, 47.2, 24.7, 21.4, 20.4, 19.9, 19.6.

(5*S*)-5-benzyl-2-methoxy-2-methyl-4-tosylmorpholine (**17d**)

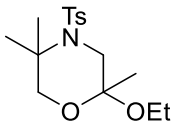


Compound **17d** was prepared according to general procedure from substrate **16d** and MeOH used both as solvent and nucleophile, and isolated through flash chromatography (hex:EtOAc 7:3) as yellow wax (85% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.1, 2H), 7.31-7.19 (m, 7H), 3.80-3.74 (m, 2H), 3.46-3.41(m, 1H), 3.31 (d, *J* = 13.0 Hz, 1H), 3.27-3.18 (m, 1H), 3.17-3.07 (m, 1H), 3.03 (s, 3H), 2.80 (dd, *J* = 13.1, 3.7 Hz, 1H), 2.41 (s, 3H), 1.32 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.9, 140.0, 137.8, 129.7, 129.2, 128.6, 127.5, 126.7, 95.1, 62.7, 48.0, 47.8, 36.6, 21.5, 21.5, 20.8,

2-Ethoxy-2,5,5-trimethyl-4-tosylmorpholine (**17e**)

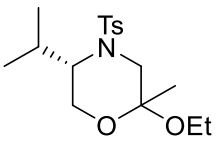


Compound **17e** was prepared according to general procedure from substrate **16a** and EtOH used both as solvent and nucleophile, and isolated through flash chromatography (hex:EtOAc 4:1) as pale yellow oil (90% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 3.81 (d, *J* =13.4 Hz, 1H), 3.59-3.42 (m, 3H), 3.23 (d, *J* = 13.4 Hz, 1H), 3.01 (d, *J* = 11.4 Hz, 1H), 2.40 (s, 3H),1.42 (s, 3H), 1.34 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.15 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 141.1, 129.2, 127.1, 96.8, 70.3, 58,4, 55.9, 49.7, 42.0, 22.9, 22.1, 21.6, 21.4, 15.4.

(5*S*)-2-ethoxy-5-isopropyl-2-methyl-4-tosylmorpholine (**17f**)

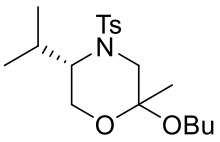


Compound **17f** was prepared according to general procedure from substrate **16c** and EtOH used both as solvent and nucleophile, and isolated through flash chromatography (hex:EtOAc 4:1) as yellow oil (90% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 3.71 (d, *J* = 14.5 Hz, 1H), 3.49-3.48 (m, 2H), 3.30-3.08 (m, 3H), 3.04 (d, *J* = 14.5 Hz, 1H), 2.38 (s, 3H), 2.29-2.13 (m, 1H), 1.19 (s, 3H), 1.00-0.95 (m, 6H), 0.75 (t, *J* = 7.0Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.2, 138.9, 129.1, 127.6, 94.6, 58.9, 58.1, 55.7, 48.7, 24.7, 21.4, 19.9, 19.7, 14.9.

(5*S*)-2-butoxy-5-isopropyl-2-methyl-4-tosylmorpholine (**17g**)

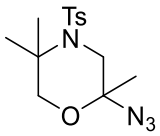


Compound **17g** was prepared according to general procedure from substrate **16c** using BuOH used both as solvent and nucleophile, and isolated through flash chromatography (hex:EtOAc 7:3) as orange oil (80% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 3.71 (d, *J* = 14.5 Hz, 1H), 3.50 (d, *J* = 1.9 Hz, 2H), 3.23-3.15 (m, 2H), 3.05 (d, *J* = 14.4 Hz, 1H), 2.39 (s, 3H), 2.32-2.15 (m, 1H), 1.39-1.28 (m, 1H), 1.19 (s, 3H), 1.13-1.05 (m, 3H), 0.98 (dd, *J* = 6.7 Hz, 3.9 Hz, 6H), 0.86-0.80 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.3, 139.0, 129.1, 127.5, 94.6, 60.3, 59.1, 58.0, 48.6, 31.7, 24.8, 21.5, 19.9, 19.7, 19.3, 13.8.

2-azido-2,5,5-trimethyl-4-tosylmorpholine (**17h**)

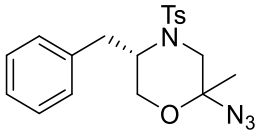


Compound **17h** was prepared according to general procedure from substrate **16a** using toluene as solvent and NaN_3 as nucleophile and isolated through flash chromatography (hex:EtOAc 7:3) as pale yellow oil (70% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.78 (d, *J* = 12.4 Hz, 1H), 3.71 (d, *J* = 13.0 Hz, 1H), 3.20 (d, *J* = 13.0 Hz, 1H), 3.09 (d, *J* = 11.8 Hz, 1H), 2.42 (s, 3H), 1.43 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 139.1, 129.6, 127.2, 127.0, 94.1, 70.7, 56.7, 49.9, 26.1, 23.9, 21.5, 20.4.

(5*S*)-2-azido-5-benzyl-2-methyl-4-tosylmorpholine (**17i**)

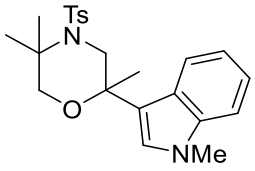


Compound **17i** was prepared according to general procedure from substrate **16c** using toluene as solvent and NaN_3 as nucleophile and isolated through flash chromatography (hex:EtOAc 7:3) as yellow oil (75% yield).

^{1}H NMR (300 MHz, CD_3OD): δ = 7.73 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.28-7.10 (m, 5H), 3.93 (dd, *J* = 11.6, 1.9 Hz, 1H), 3.75 (d, *J* = 9.9 Hz, 1H), 3.64 (d, *J* = 13.1 Hz, 1H), 3.26 (d, *J* = 11.6, 1H), 3.19 (d, *J* =13.2 Hz, 1H), 3.03 (dd, *J* = 13.0, 10.4 Hz, 1H), 2.61 (dd, *J* = 13.0, 4.5 Hz, 1H), 2.40 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (100 MHz, CD_3OD): δ = 143.4, 137.9, 137.5, 129.2, 128.9, 128.2, 127.1, 126.1, 92.0, 62.6, 58.8, 53.7, 33.1, 25.5, 20.00.

2,5,5-trimethyl-2-(1-methyl-1*H*-indol-2-yl)-4-tosylmorpholine (**17j**)

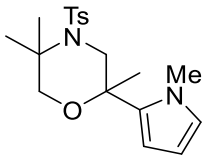


Compound **17i** was prepared according to general procedure from substrate **16a** using toluene and *N*-Me-indole and isolated through flash chromatography (hex:EtOAc 4:1) as brownish wax (82% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.33 (dd, *J* = 8.1, 3.0 Hz, 3H), 7.28 (d, *J* = 3.4 Hz, 1H), 7.27-7.22 (m, 1H), 7.14-7.09 (m, 1H), 7.03 (s, 1H), 4.18 (s, *J* = 12.9 Hz, 1H), 3.77 (s, 3H), 3.39 (d, *J* = 11.7 Hz, 1H), 3.32 (d, *J* = 12.9 Hz, 1H), 3.13 (d, *J* = 11.7 Hz, 1H), 2.47 (s, 3H), 1.64 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H).

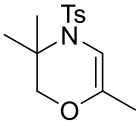
^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 138.5, 137.5, 129.6, 127.7, 127.5, 126.0, 121.6, 120.9, 119.1, 115.1, 109.3, 74.3, 72.9, 56.9, 50.2, 32.8, 27.7, 24.5, 21.5, 19.7.

2,5,5-trimethyl-2-(1-methyl-1*H*-pyrrol-2-yl)-4-tosylmorpholine (**17k**)



Compound **17j** was prepared according to general procedure from substrate **16a** using toluene and *N*-Me-pyrrole and isolated through flash chromatography (hex:EtOAc 7:3) as white solid (70% yield).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.58 (t, *J* = 2.1 Hz, 1H), 6.11 (dd, *J* = 2.6, 1.9 Hz, 1H), 3.85 (d, *J* =12.8 Hz, 1H), 3.72 (s, 2H), 3.63 (s, 3H), 3.32 (d, *J* = 12.8 Hz, 1H), 2.45 (s, 3H), 1.50 (s, 3H), 1.28-1.23 (m, 6H).
The full characterization is *on-going.*

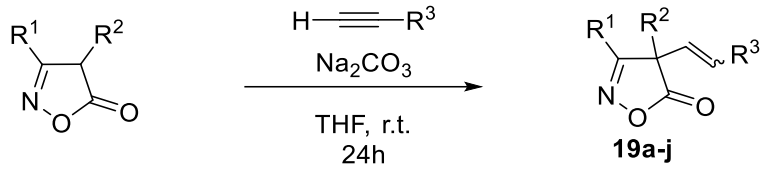
3,3,6-trimethyl-4-tosyl-3,4-dihydro-2*H*-1,4-oxazine (**18a**)



Compound **18a** was prepared according to general procedure from substrate **16a** and isolated through flash chromatography (hex:EtOAc 8:2) as pale yellow oil (90% yield).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.09 (s, 1H), 3.46 (s, 2H), 2.43 (s, 3H), 1.82 (d, *J* = 1.0 Hz, 3H), 1.29 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 139.1, 136.5, 129.6, 126.8, 101.2, 74.7, 55.5, 22.8, 21.5, 17.4.

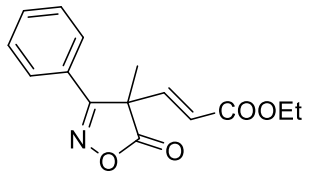
Chapter 3.2_ *Isoxazol-5-ones as a starting material for the synthesis of heterocyclic compounds*

General procedure for the synthesis of 4-alkenyl-isoxazol-5-ones (**19a-j**)



To a stirred solution of the appropriate isoxazol-5-one (1.0 mmol), Na_2CO_3 (1.0 mmol) in THF (10 ml) the appropriate alkyne (1.0 mmol) was added. After 24 hours the solvent was removed under reduced pressure. The crude was diluted with water (20 ml) and extracted with EtOAc (3 x 20 ml), the organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The final products were purified through flash chromatography.

Ethyl (*E*)-3-(4-methyl-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)acrylate **(19a)**



Compound **19a** was prepared according to general procedure using ethyl propiolate (98 mg) and isolated through flash chromatography (hex:EtOAc 3:2) as light-yellow oil (50% yield).

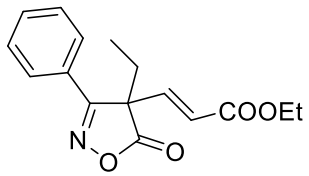
IR: 1793.8, 1710.6 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.69 (m, 2H), 7.56–7.43 (m, 3H), 6.97 (d, *J* = 16.0 Hz, 1H), 6.10 (d, *J* = 16.0 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.77 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 167.0, 164.8, 140.7, 132.1, 129.2, 127.2, 126.6, 125.8, 61.1, 51.1, 20.9, 14.1.

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13; found: C, 66.08; H, 5.40; N, 5.22.

Ethyl (*E*)-3-(4-Ethyl-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)acrylate **(19b)**



Compound **19b** was prepared according to general procedure using ethyl propiolate (98 mg) and isolated through flash chromatography (hex:EtOAc 3:1) as light-yellow oil (40% yield).

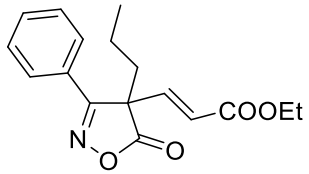
IR: 1771, 1696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74-7.71 (m, 2H), 7.56-7.44 (m, 3H), 6.98 (d, *J* = 15.9 Hz, 1H), 6.07 (d, *J* = 15.9 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.36-2.15 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.41 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 165.7, 164.9, 140.5, 132.1, 129.3, 126.9, 126.8, 125.6, 61.1, 57.1,28.8, 14.1, 8.8.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88; found: C, 66.97; H, 5.81; N, 4.99.

Ethyl (*E*)-3-(5-oxo-3-phenyl-4-propyl-4,5-dihydroisoxazol-4-yl)acrylate **(19c)**



Compound **19c** was prepared according to general procedure using ethyl propiolate (98 mg) and isolated through flash chromatography (hex:EtOAc 3:1) as light-yellow oil (37% yield).

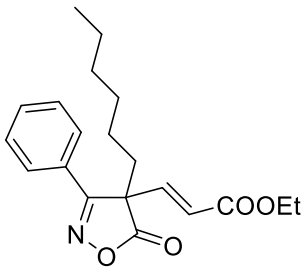
IR: 1786, 1702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74-7.71 (m, 2H), 7.54-7.44 (m, 3H), 6.96 (dd, *J* = 15.9 Hz, 1H), 6.05 (dd, *J* = 15.9 Hz, 1H), 4.23-4.15 (m, 2H), 2.26-2.05 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 165.9, 164.9, 140.7, 132.1, 129.3, 127.0, 126.9, 125.5, 61.1, 56.3, 37.4, 17.9, 14.1,13.6.

Anal. Calcd for $C_{17}H_{19}NO_4$: C 67.76; H, 6.36; N, 4.65; found: C, 67.90; H, 6.30; N, 4.73.

Ethyl (*E*)-3-(4-hexyl-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)acrylate (**19d**)



Compound **19d** was prepared according to general procedure using ethyl propiolate (98 mg) and isolated through flash chromatography (hex:EtOAc 3:1 and then hex:Et_2O 5:1) as colourless oil (38% yield).

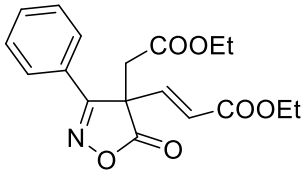
IR: 1789, 1712 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.74-7.71 (m, 2H), 7.54-7.44 (m, 3H), 6.96 (d, *J* = 15.9 Hz, 1H), 6.06 (d, *J* = 15.9 Hz, 1H), 4.23-4.15 (m, 2H), 2.22-2.16 (m, 2H), 1.27 (t, *J* = 7.2, 3H), 1.19-1.16 (m, 8H), 0.79 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 165.9, 164.9, 140.7, 132.2, 129.4, 126.9, 126.9, 125.5, 61.2, 56.4, 35.3, 31.0, 28.7, 24.3, 22.3, 14.1, 13.9.

Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08; found: C, 69.77; H, 7.50; N, 4.12.

Ethyl (*E*)-3-(4-(2-ethoxy-2-oxoethyl)-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)acrylate (**19e**)



Compound **19e** was prepared according to general procedure using ethyl propiolate (98 mg) and isolated through flash chromatography (hex:EtOAc 2:1) as light-yellow oil (43% yield).

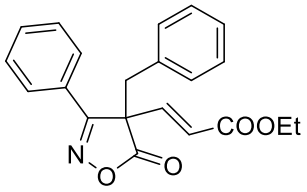
IR: 1793, 1717, 1695 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.66-7.63 (m, 2H), 7.56-7.43 (m, 3H), 6.90 (d, *J* = 15.9 Hz, 1H), 6.08 (d, *J* = 15.9 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.06-4.01 (m, 2H), 3.34 (d, *J* = 17.3 Hz, 1H), 3.15 (d, *J* = 17.3 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 167.6, 165.2, 164.5, 139.1, 132.2, 129.4, 127.1, 126.6, 126.2, 61.9, 61.4, 53.3, 38.1, 14.1, 13.7.

Anal. Calcd for $C_{18}H_{19}NO_6$: C,62.60; H, 5.55; N, 4.06; found: C, 62.50; H, 5.50; N, 4.18.

Ethyl (*E*)-3-(4-benzyl-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)acrylate (**19f**)



Compound **19f** was prepared according to general procedure using ethyl propiolate (98 mg) and isolated through flash chromatography (hex:EtOAc 3:1) as white wax (35% yield).

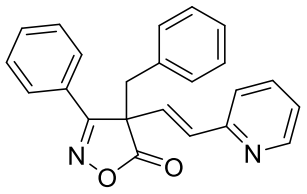
IR: 1779, 1699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74-7.71 (m, 2H), 7.60-7.47 (m, 3H), 7.22-7.10 (m, 5H), 6.83-6.80 (m, 2H), 6.20 (d, *J* = 16.2 Hz, 1H), 4.28-4.18 (m, 2H), 3.51 (q, *J* = 13.5 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 165.2, 164.8, 140.4, 132.4, 132.1, 129.4, 129.3, 128.6, 128.1, 127.4, 127.2, 126.1, 61.2, 58.1, 40.9, 14.1.

Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01; found: C, 72.23; H, 5.58; N, 3.90.

(*E*)-4-benzyl-3-phenyl-4-(2-(pyridin-2-yl)vinyl)isoxazol-5(4*H*)-one (**19g**)



Compound **19g** was prepared according to general procedure using 2-ethynylpyridine (103 mg) and isolated through flash chromatography (hex:EtOAc 3:1) as brown wax (35% yield).

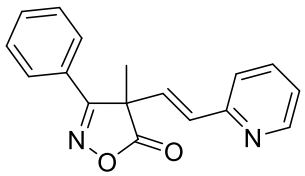
IR: 1768, 1584 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 4.3 Hz, 1H), 7.77-7.73 (m, 2H), 7.54 (dt, *J* = 7.7, 1.7 Hz, 1H), 7.43-7.35 (m, 3H), 7.27-7.18 (m, 3H), 7.12-7.05 (m, 2H), 7.01 (m, 2H), 6.76 (d, *J* = 15.8 Hz, 1H), 6.06 (d, *J* = 15.8 Hz, 1H), 3.44 (q, *J* = 13.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3, 164.8, 152.6, 146.9, 136.3, 133.1, 132.9, 130.8, 130.0, 128.7, 128.6, 128.3, 128.1, 127.8, 127.1, 124.1, 122.6, 57.5, 46.9.

Anal. Calcd for C23H18N2O2: C,77.95; H, 5.12; N, 7.90; found: C, 77.82; H, 5.23; N, 7.99.

(*E*)-4-methyl-3-phenyl-4-(2-(pyridine-2-yl)vinyl)isoxazole-5(4*H*)-one (**19h**)



Compound **19h** was prepared according to general procedure using 2-ethynylpyridine (103 mg) and isolated through flash chromatography (hex:EtOAc 3:2 and then DCM 100%) as light-yellow oil (60% yield).

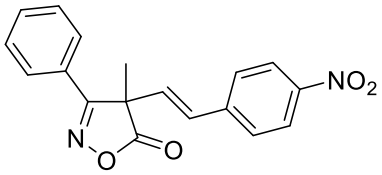
IR: 1765, 1581 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 4.3 Hz, 1H), 7.83-7.67 (m, 2H), 7.64 (td, *J* = 7.7, 1.8 Hz, 1H), 7.52 – 7.40 (m, 3H), 7.24 – 7.16 (m, 2H), 6.92 (d, *J* = 15.8 Hz, 1H), 6.72 (d, *J* = 15.8 Hz, 1H), 1.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7, 167.9, 153.4, 149.7, 136.7, 133.7, 131.8, 129.1, 128.5, 127.3, 127.1, 123.2, 122.8, 51.4, 21.1.

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07; found: C, 73.51; H, 4.98; N, 10.18.

(*E*)-4-methyl-4-(4-nitrostyryl)-3-phenylisoxazol-5(4*H*)-one (**19i**)



Compound **19i** was prepared according to general procedure starting using 1-ethynyl-4-nitrobenzene (147 mg) and isolated through flash chromatography (hex:EtOAc 3:2) as red solid (50% yield); m.p.: 123-125°C.

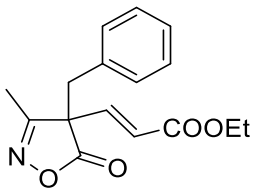
IR: 1770, 1591, 1497 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.03-7.99 (m, 2H), 7.64-7.60 (m, 2H), 7.52-7.46 (m, 1H), 7.43-7.37 (m, 2H), 7.02-6.97 (m, 2H), 6.87 (d, *J* = 11.7 Hz, 1H), 6.04 (d, *J* = 11.7 Hz, 1H), 1.76 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =179.2, 168.0, 147.4, 141.1, 134.6, 131.9, 129.7, 129.0, 129.0, 127.7, 126.6, 123.2, 49.4, 25.5.

Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69; found: C, 67.20; H, 4.50; N, 8.58.

Ethyl (*E*)-3-(4-benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)acrylate (**19j**)



Compound **19j** was prepared according to general procedure using ethyl propiolate (98 mg) and isolated through flash chromatography (hex:EtOAc 7:3) as yellow oil (55% yield).

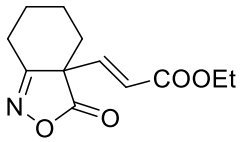
IR: 1787, 1715 cm^{-1}.

^1H NMR (300 MHz,$CDCl_3$): δ = 7.29-7.25 (m, 3H), 7.11-7.08 (m, 2H), 6.83 (d, *J* = 15.9 Hz, 1H), 6.12 (d, *J* = 15.9 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.30 (d, *J* = 13.8 Hz, 1H), 3.11 (d, *J* = 13.8 Hz, 1H), 2.10 (s, 3H), 1.29 (t, J = 7.14, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 165.8, 164.8, 138.5, 132.5, 129.1, 128.9, 128.2, 125.6, 61.2, 58.2, 40.5, 14.0, 12.8.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88; found: C, 66.76; H, 6.09; N, 4.98.

Ethyl (*E*)-3-(3-oxo-4,5,6,7-tetrahydrobenzo[*c*]isoxazol-(3*H*)-yl)acrylate (**19s**)



Compound **19s** was prepared according to general procedure using ethyl propiolate (98 mg) and isolated through flash chromatography (hex:EtOAc 3:2) as yellow oil (45% yield).

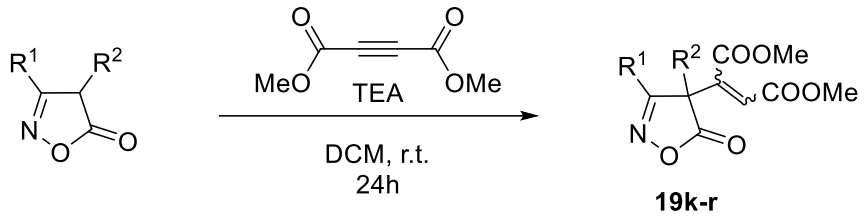
IR: 1787, 1710 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.80 (d, *J* = 16.0 Hz, 1H), 5.97 (d, *J* = 16.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.77-2.71 (m, 1H), 2.42-2.31 (m, 2H), 2.17-2.11 (m, 1H), 1.84-1.71 (m, 2H), 1.64-1.44 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 169.9, 164.7, 139.3, 126.4, 61.1, 51.9, 35.4, 27.1, 25.5, 20.7, 14.1.

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90; found: C, 60.68; H, 6.40; N, 5.99.

General procedure for the synthesis of 4-alkenyl-isoxazol-5-ones (**19k-r**)

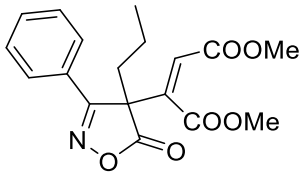


19k-r

To a stirred solution of the appropriate isoxazol-5-one (1.0 mmol) in DCM (10 ml), DMAD (4.0 mmol, 568 mg) and triethylamine (100 µL) were added. After 24 hours the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

The characterization of compound **19k,l**[112] are in agreement with data reported in literature.

Dimethyl 2-(5-oxo-3-phenyl-4-propyl-4,5-dihydroisoxazol-4-yl)maleate (**19m**)



Compound **19m** was prepared according to general procedure and isolated through flash chromatography (hex:EtOAc 3:1) as red wax (45% yield).

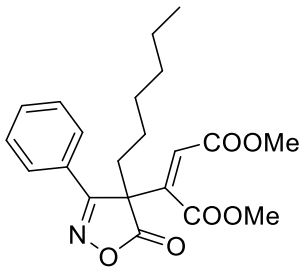
IR: 1760, 1696 cm^{-1}.

^{1}H NMR (300 MHz, CDCl3): δ = 7.74-7.72 (m, 2H), 7.54-7.26 (m, 3H), 6.34 (s, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 2.12-2.07 (m, 2H), 1.25-1.22 (m, 2H), 0.87 (t, *J* = 5.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl3): δ = 176.8, 165.0, 164.9, 164.4, 141.9, 132.2, 129.3, 126.9, 126.8, 125.9, 57.1, 52.9, 52.5, 35.1, 17.4, 13.7.

Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N,4.06; found: C, 62.74; H, 5.50; N, 4.17.

Dimethyl 2-(4-hexyl-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)maleate (**19n**)



Compound **19n** was prepared according to general procedure and isolated through flash chromatography (hex:EtOAc 4:1) as red oil (51% yield).

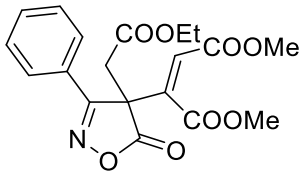
IR: 1772, 1705 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74-7.71 (m, 2H), 7.55-7.42 (m, 3H), 6.34 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.14-2.09 (m, 2H), 1.21-1.06 (m, 6H), 0.79 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.7, 164.9, 164.3, 141.9, 132.1, 129.2, 126.8, 125.8, 57.1, 52.8, 52.4, 33.0, 31.0, 28.7, 23.7, 22.2, 13.7.

Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62; found: C 65.01; H, 6.58; N, 3.58.

Dimethyl 2-(4-(2-ethoxy-2-oxoethyl)-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)maleate (**19o**)



Compound **19o** was prepared according to general procedure and isolated through flash chromatography (hex:EtOAc 7:3) as light-yellow oil (48% yield).

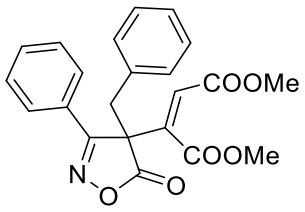
IR: 1793, 1730, 1699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 2H), 7.55-7.43 (m, 3H), 6.15 (s, 1H), 4.09-3.97 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.24 (q, *J* = 16.8 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl3): δ = 175.1, 167.3, 165.1, 164.5, 163.7, 142.2, 132.2, 129.3, 127.3, 126.3, 123.8, 62.0, 53.7, 53.3, 52.6, 36.8, 13.7.

Anal. Calcd for $C_{19}H_{19}NO_8$: C, 58.61; H, 4.92; N, 3.60; found: C, 58.75; H, 4.85; N, 3.72.

Dimethyl 2-(4-benzyl-5-oxo-3-phenyl-4,5-dihidroisoxazol-4-yl)maleate (**19p**)



Compound **19p** was prepared according to general procedure and isolated through flash chromatography (hex:EtOAc 3:1) as red oil (62% yield).

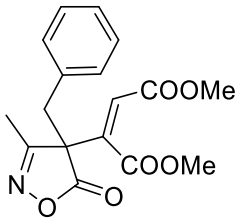
IR: 1790, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73-7.69 (m, 2H), 7.59-7.46 (m, 3H), 7.24-7.11 (m, 3H), 6.78-6.75 (m, 2H), 6.48 (s, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.44 (dd, *J* = 28.3, 12.9 Hz, 2H).

^{13}C NMR (100 MHz, CDCl3): δ = 176.1, 164.9, 164.3, 164.2, 141.7, 132.1, 131.4, 129.6, 129.2, 128.6, 128.3, 127.3, 127.0, 126.1, 58.6, 53.1, 52.5, 38.9.

Anal. Calcd for C22H19NO6: C, 67.17; H, 4.87; N, 3.56; found: C, 67.30; H, 4.80; N, 3.68.

Dimethyl 2-(4-benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)maleate (**19q**)



Compound **19q** was prepared according to general procedure and isolated through flash chromatography (hex:EtOAc 3:2) as light-yellow oil (50% yield).

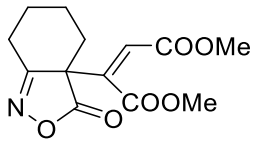
IR: 1789, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29-7.26 (m, 3H), 7.11-7.09 (m, 2H), 7.02 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3. 58 (d, *J* = 7.7 Hz, 1H), 3.13 (d, *J* = 7.7 Hz, 1H), 2.24 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 165.8, 165.1, 164.6, 136.6, 132.3, 131.9, 130.0, 128.6, 128.3, 53.3, 52.5, 38.7, 29.7, 13.5.

Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23; C, 61.47; H, 5.28; N, 4.33.

Dimethyl 2-(3-oxo-4,5,6,7-tetrahydrobenzo[*c*]isoxazol-3a(3*H*)-yl)maleate (**19r**)



Compound **19r** was prepared according to general procedure and isolated through flash chromatography (DCM:EtOAc 12:1) as yellow oil (46% yield).

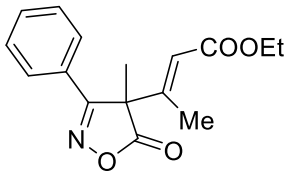
IR: 1795, 1700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.18 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.72-2.71 (m, 1H), 2.58-2.54 (m, 1H), 2.42-2.31 (m, 1H), 2.19-2.10 (m, 1H), 1.80-1.58 (m, 4H).

13C NMR (100 MHz, $CDCl_3$): δ = 169.5, 165.5, 163.9, 141.2, 124.7, 53.4, 53.0, 52.4, 33.8, 27.5, 26.0, 20.8.

Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98; found: C, 55.70; H, 5.29; N, 4.89.

Ethyl (*E*)-3-(4-methyl-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)but-2-enoate (**19t**)



Compound **19t** was prepared according to general procedure and ethyl 2-butynoate (448 mg) and isolated through flash chromatography (hex:EtOAc 3:1) as light-yellow oil (20% yield).

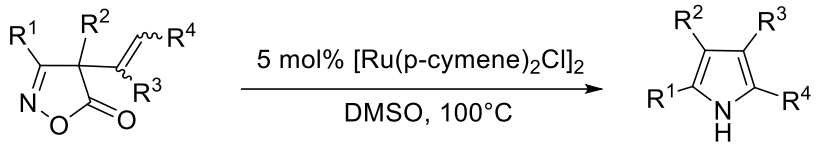
IR: 1792, 1710 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (m, 2H), 7.49 (m, 3H), 6.12 (d, *J* = 1.2 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.13 (d, *J* = 1.2 Hz, 3H), 1.70 (s, 3H), 1.29 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 167.3, 165.4, 149.6, 132.1, 129.3, 126.8, 126.7, 120.2, 60.5, 56.8, 19.6, 16.1, 14.1.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88; C, 66;99 H, 6.04; N, 4.77.

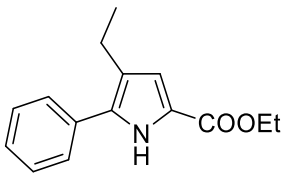
General procedure for the synthesis of tri- and tetra-substituted pyrrole (**20a-t**)



19a-t **20a-t**

In a sealed tube, to a solution of **19a-t** (1.0 mmol) in DMSO (6 ml), [Ru(*p*-cymene)Cl_2]$_2$ (0.05 mmol) was added. The reaction was stirred for 24h at 100°C. The reaction mixture was washed with brine (3 x 10 ml) and aqueous solution was extracted with EtOAc (3 x 10 ml). The organic phase is dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude is than purified through flash chromatography. The characterization of the products **20a, h, i,**[113] **k, l,**[114] **n,** [115]**, r**[116]**, s**[117] are consistent with data reported in literature.

Ethyl 4-ethyl-5-phenyl-1*H*-pyrrole-2-carboxylate (**20b**)



Compound **20b** was prepared according to general procedure starting from substrate **19b** (287 mg) and isolated through flash chromatography (hex:EtOAc 7:3) as light-yellow oil (40% yield).

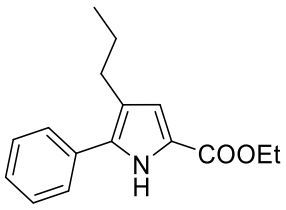
IR: 3310, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.42 (s, 1H), 7.50-7.40 (m, 4H), 7.36-7.26 (m, 1H), 6.89 (d, *J* = 2.7 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.65 (q, *J* = 7.5 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 133.3, 132.4, 128.7, 127.4, 127.3, 125.2, 121.7, 115.9, 60.3, 19.5, 15.2, 14.5.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76; found: C, 74.16; H, 7.15; N, 5.68.

Ethyl 5-phenyl-4-propyl-1*H*-pyrrole-2-carboxylate (**20c**)



Compound **20c** was prepared according to general procedure starting from substrate **19c** (301 mg) and isolated through flash chromatography (hex:EtOAc 3:1) as light-yellow solid (45% yield); m.p.: 87-89°C.

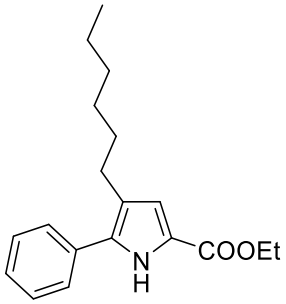
IR: 3290, 1674 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.13 (s, 1H), 7.49 –7.40 (m, 4H), 7.36–7.33 (m, 1H), 6.86 (d, *J* = 2.7 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 1.68-1.60 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 133.4, 132.4, 128.7, 127.5, 127.3, 123.6, 121.7, 116.5, 60.2, 28.4, 23.9, 14.5, 13.9.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; found: C, 74.56; H, 7.55; N, 5.49.

Ethyl 4-hexyl-5-phenyl-1*H*-pyrrole-2-carboxylate (**20d**)



Compound **20d** was prepared according to general procedure starting from substrate **19d** (343 mg) and isolated through flash chromatography (hex:EtOAc 4:1) as white solid (52% yield); m.p.: 59-61°C.

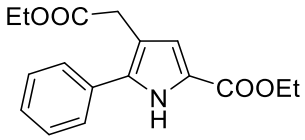
IR: 3450, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.14 (s, 1H), 7.49-7.40 (m, 4H), 7.36-7.30 (m, 1H), 6.86 (d, *J* = 2.6 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 1.65-1.58 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.32-1.26 (m, 4H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 133.4, 132.5, 128.7, 127.5, 127.4, 123.9, 121.7, 116.4, 60.2, 31.6, 30.8, 29.1, 26.3, 14.5, 13.9.

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68; found: C, 76.10; H, 8.49; N, 4.77.

Ethyl 4-(2-ethoxy-2-oxoethyl)-5-phenyl-1*H*-pyrrole-2-carboxylate (**20e**)



Compound **20e** was prepared according to general procedure starting from substrate **19e** (345 mg) and isolated through flash chromatography (hex:EtOAc 7:3) as orange oil (54% yield).

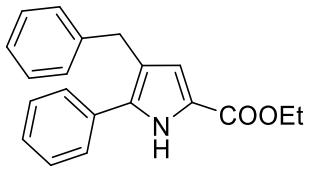
IR: 3260, 1730, 1680 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.38 (s, 1H), 7.51-7.35 (m, 5H), 6.96 (d, *J* = 2.4 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.57 (s, 2H), 1.33 (t, *J* = 7.1, 3H), 1.25 (t, *J* = 7.1, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 161.2, 134.9, 131.5, 128.9, 127.9, 127.7, 122.2, 117.3, 114.9, 60.8, 60.3, 32.4, 14.4, 14.1.

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65; found: C, 67.89; H, 6.30; N, 4.60.

Ethyl 4-benzyl-5-phenyl-1*H*-pyrrole-2-carboxylate(**20f**)



Compound **20f** was prepared according to general procedure starting from substrate **19f** (349 mg) and isolated through flash chromatography (hex:EtOAc 3:1) as brown wax (48% yield).

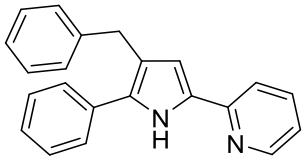
IR: 3305, 1671 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.07 (s, 1H), 7.45-7.36 (m, 5H), 7.32-7.27 (m, 2H), 7.25-7.19 (m, 3H), 6.76 (d, *J* = 2.7 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 2H), 1.34 (t, *J* = 7.1, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 141.3, 133.9, 131.9, 128.9, 128.5, 128.4, 127.7, 127.3, 125.9, 122.0, 121.6, 117.4, 60.3, 32.4, 14.4.

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59; found: C, 78.80; H, 6.19; N, 4.70.

2-(4-Benzyl-5-phenyl-1*H*-pyrrole-2-yl)pyridine (**20g**)



Compound **20g** was prepared according to general procedure starting from substrate **19g** (354 mg) and isolated through flash chromatography (hex:EtOAc 3:1) as brown wax (48% yield).

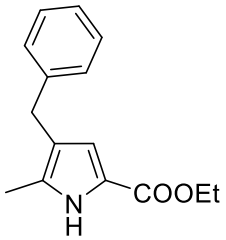
IR: 3430, 1593 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.59 (bs, 1H), 8.45 (d, *J* = 4.8 Hz, 1H), 7.59-7.27 (m, 13H), 7.02 (m, 1H), 6.55 (d, *J* = 2.6 Hz, 1H), 4.06 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 148.8, 141.8, 136.2, 132.8, 131.0, 128.7, 128.5, 128.3, 126.8, 126.7, 125.7, 121.5, 120.3, 118.0, 110.2, 32.7.

Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03; found: C, 85.21; H, 5.80; N, 9.11.

Ethyl 4-benzyl-5-methyl-1*H*-pyrrole-2-carboxylate (**20j**)



Compound **20j** was prepared according to general procedure starting from substrate **19j** (287 mg) and isolated through flash chromatography (hex:EtOAc 7:3) as pale-brown solid (64% yield); m.p.: 98-100°C.

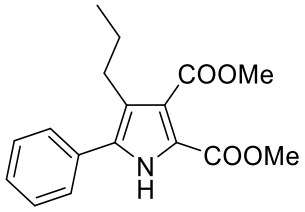
IR: 3280, 1661 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.39 (s, 1H), 7.33-7.28 (m, 2H), 7.23-7.19 (m, 3H), 6.71 (d, *J* = 2.5 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 2.25 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 141.5, 130.9, 128.4, 128.3, 125.8, 121.1, 119.9, 116.5, 60.0, 32.2, 14.5, 11.5.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76; found: C,74.11; H, 7.00; N, 5.68.

Dimethyl 5-phenyl-4-propyl-1*H*-pyrrole-2,3-dicarboxylate (**20m**)



Compound **20m** was prepared according to general procedure starting from substrate **19m** (345 mg) and isolated through flash chromatography (hex:EtOAc 4:1) as brown oil (60% yield).

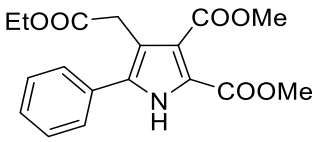
IR: 3290, 1723, 1689 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.19 (s, 1H), 7.47-7.35 (m, 5H), 3.91 (s, 3H), 3.84 (s, 3H), 2.61 (t, *J* = 3.9 Hz, 2H), 1.58-1.46 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 160.5, 133.1, 131.5, 128.9, 128.2, 127.8, 123.8, 121.9, 120.3, 51.9, 51.8, 26.8, 24.5, 13.9.

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65; found: C, 67.83; H, 6.40; N, 4.61.

Dimethyl 4-(2-ehtoxy-2-oxoethyl)-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**20o**)



Compound **20o** was prepared according to general procedure starting from substrate **19o** (389 mg) and isolated through flash chromatography (hex:EtOAc 3:2) as white solid (73% yield); m.p.: 98-100°C.

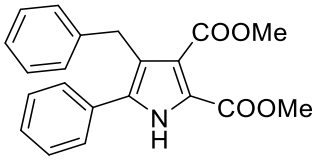
IR: 3280, 1727, 1692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.27 (brs, 1H), 7.47–7.40 (m, 5H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 6H), 3.68 (s, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 164.9, 160.4, 134.3, 130.5, 129.0, 128.6, 128.0, 121.7, 121.2, 116.3, 60.8, 52.0, 51.7, 31.3, 14.1.

Anal. Calcd for $C_{18}H_{19}NO_6$: C,62.60; H, 5.55; N, 4.06; found: C 62.51; H, 5.66; N, 4.11.

Dimethyl 4-benzyl-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**20p**)



Compound **20p** was prepared according to general procedure starting from substrate **19p** (393 mg) and isolated through flash chromatography (DCM:EtOAc 19:1) as brown oil (69% yield).

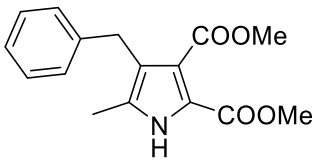
IR: 3280, 1725, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.19 (s, 1H), 7.41-7.37 (m, 5H), 7.23-7.08 (m, 5H), 4.07 (s, 2H), 3.87 (s, 3H), 3.69 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 160.4, 140.7, 134.0, 130.9, 128.9, 128.4, 128.2, 128.1, 127.7, 125.8, 121.3, 51.9, 51.7, 30.6.

Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01; found: C, 72.23; H, 5.40; N, 3.97.

Dimethyl 4-benzyl-5-methyl-1*H*-pyrrole-2,3-dicarboxylate (**20q**)



Compound **20q** was prepared according to general procedure starting from substrate **19q** (331 mg) and isolated through flash chromatography (hex:EtOAc 7:3) as yellow oil (73% yield).

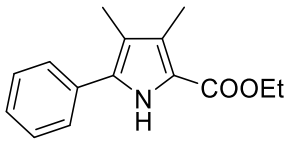
IR: 3280, 1720, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.25 (brs, 1H), 7.26-7.21 (m, 2H), 7.16-7.10 (m, 3H), 3.88 (s, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 2.17 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 160.7, 140.7, 130.5, 128.3, 128.2, 125.8, 121.5, 121.3, 118.9, 51.8, 30.5, 11.4.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88; found: C, 66.94; H, 5.90; N, 4.82.

Ethyl 3,4-dimethyl-5-phenyl-1*H*-pyrrole-2-carboxylate (**20t**)



Compound **20t** was prepared according to general procedure starting from substrate **19t** (287 mg) and isolated through flash chromatography (hex:EtOAc 7:3) as yellow oil (70% yield).

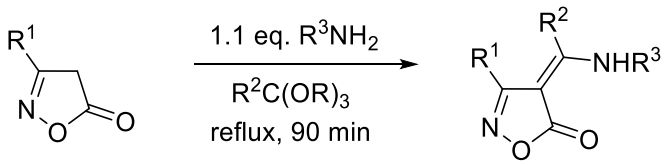
IR: 3280, 1720, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (brs, 1H), 7.48-7.40 (m, 4H), 7.35-7.30 (m, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 2.15 (s, 3H), 6 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl3): δ = 162.1, 132.9, 129.1, 127.8, 127.6, 119.0, 118.2, 60.3, 30.0, 14.9, 10.9, 10.3.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76; found: C, 74.15; H, 7.11; N, 5.70.

General procedure for the synthesis of 4-aminoalkylidene-isoxazol-5-(4H)-ones (**21a-q**)

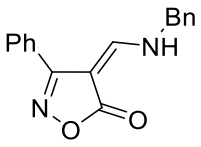


21a-q

To a solution of the appropriate isoxazole-5-(4*H*)-one (1 mmol) and orthoester (2 ml), after gentle heating, the appropriate primary amine (1.1 mmol) was added, and the reaction is stirred at reflux for 90 minutes. The solvent was then evaporated under reduced pressure and the crude was purified through flash chromatography.

The characterization of the product **21b**[118] is consistent with the one reported in literature.

(Z)-4-((Benzylamino)methylene)-3-phenylisoxazol-5(4*H*)-one (**21a**)



Compound **21a** was prepared according to general procedure using benzylamine (120 μL), trimethyl orthoformiate and isolated through flash chromatography (DCM:EtOAc 4:1) as yellow solid (72% yield); m.p.: 131-133°C.

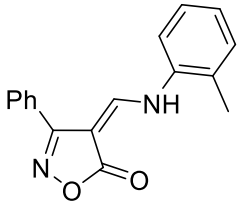
IR: 3091, 1678 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.50 (br s, 1H), 7.67 (s, 1H), 7.57-7.54 (m, 2H), 7.49-7.40 (m, 3H), 7.38-7.35 (m, 3H), 7.31-7.26 (m, 2H), 4.63 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.9, 161.4, 153.5, 135.0, 130.4, 129.3, 129.2, 128.7, 128.6, 127.8, 127.6, 90.1, 53.7.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.21; H, 5.31; N, 9.89.

(Z)-3-Phenyl-4-((2-tolylamino)methylene)isoxazol-5(4*H*)-one (**21c**)



Compound **21c** was prepared according to general procedure using *o*-toluidine (117 μL), trimethyl orthoformiate and isolated through flash chromatography (hex:EtOAc 9:1) as orange wax (68% yield).

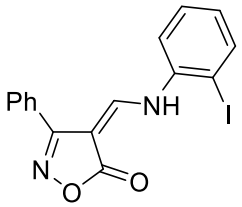
IR: 3087, 1675 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.04 (d, *J* = 12.7 Hz, 1H), 8.09 (d, *J* = 12.7 Hz, 1H), 7.66-7.63 (m, 2H), 7.57-7.53 (m, 3H), 7.32-7.26 (m, 2H), 7.22-7.18 (m, 2H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.8, 161.1, 146.1, 136.4, 131.6, 130.6, 129.2, 128.4, 128.3, 127.7, 127.6, 126.7, 116.0, 92.9, 17.2.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.19; H, 4.98; N, 10.21.

(Z)-4-(((2-Iodophenyl)amino)methylene)-3-phenylisoxazol-5(4*H*)-one (**21d**)



Compound **21d** was prepared according to general procedure using 2-iodoaniline (240.9 mg), trimethyl orthoformiate and isolated through flash chromatography (hex:MeOH 18:1) as orange wax (58% yield).

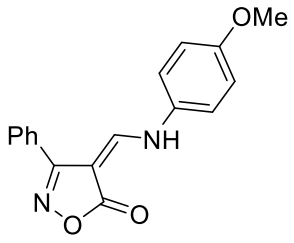
IR: 3113, 1684 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.00 (d, *J* = 12.3 Hz, 1H), 7.98 (d, *J* = 12.3 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.67-7.60 (m, 2H), 7.57-7.50 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.9, 161.2, 145.4, 140.4, 139.2, 130.7, 129.8, 129.3, 128.2, 127.8, 127.7, 116.9, 94.2, 89.7.

Anal. Calcd. for $C_{16}H_{11}IN_2O_2$: C, 49.25; H, 2.84; N, 7.18. Found: C, 49.38; H, 2.61; N, 7.42.

(Z)-4-(((4-Methoxyphenyl)amino)methylene)-3-phenylisoxazol-5(4*H*)-one (**21e**)



Compound **21e** was prepared according to general procedure using *p*-anisidine (128 μL), trimethyl orthoformiate and isolated through flash chromatography (DCM, EtOAc 4:1) as orange wax (59% yield).

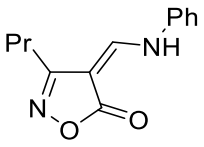
IR: 3099, 1680 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (br s, 1H), 7.56-7.48 (m, 2H), 7.42-7.38 (m, 3H), 7.28-7.23 (m, 1H), 7.04 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.7, 161.3, 158.5, 146.2, 131.1, 130.6, 129.4, 129.3, 128.5, 128.4, 127.8, 126.3, 119.6, 115.3, 91.7, 55.6.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.64; H, 4.60; N, 9.73.

(Z)-4-((Phenylamino)methylene)-3-propylisoxazol-5(4*H*)-one (**21f**)



Compound **21f** was prepared according to general procedure using aniline (100 μL), triethyl orthoformiate and isolated through flash chromatography (DCM:EtOAc 4:1) as pale brown solid (82% yield); m.p.: 122-123°C.

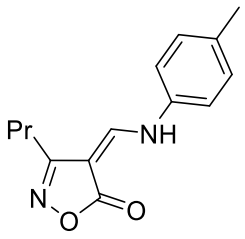
IR: 3085, 1679 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1H), 7.3 (t, *J* = 7.8 Hz, 2H), 7.19-7.12 (m, 3H), 2.49 (t, J = 7.4 Hz, 2H), 1.69- 1.59 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.0, 162.1, 144.4, 137.6, 129.8, 126.2, 117.4, 93.0, 27.4, 20.3, 13.6.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.08; H, 5.93; N, 12.34.

(Z)-3-Propyl-4-((4-tolylamino)methylene)isoxazol-5(4*H*)-one (**21g**)



Compound **21g** was prepared according to general procedure using *p*-toluidine (121 μL), trimethyl orthoformiate and isolated through flash chromatography (hex:MeOH 18:1) as orange solid (77% yield); m.p.: 122-125°C.

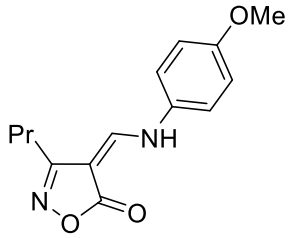
IR: 3105, 1687 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.37 (s, 3H), 1.80-1.71 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.3, 162.0, 144.1, 136.5, 135.4, 130.5, 117.5, 93.0, 27.7, 20.8, 20.6, 13.8.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.11; H, 6.38; N, 11.62.

(Z)-4-(((4-Methoxyphenyl)amino)methylene)-3-propylisoxazol-5(4*H*)-one (**21h**)



Compound **21h** was prepared according to general procedure using *p*-anisidine (128 μL), triethyl orthoformiate and isolated through flash chromatography (hex:EtOAc 3:2) as red wax (75% yield).

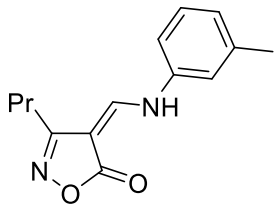
IR: 3086, 1673 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.73 (s, 3H), 2.48 (t, *J* = 7.4 Hz, 2H), 1.70-1.60 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.3, 162.0, 158.2, 144.6, 131.1, 119.3, 115.1, 92.4, 55.5, 27.6, 20.5, 13.8.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.86; H, 5.94; N, 10.60.

(Z)-3-Propyl-4-((3-tolylamino)methylene)isoxazol-5(4*H*)-one (**21i**)



Compound **21i** was prepared according to general procedure using m-toluidine (118 μL), trimethyl orthoformiate and isolated through flash chromatography (hex:EtOAc 1:1) as orange wax (80% yield).

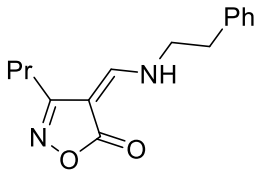
IR (neat) v: 3097, 1682 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.45 (br s, 1H), 7.85 (s, 1H), 7.24-7.20 (m, 1H), 6.98-6.92 (m, 3H), 2.50 (t, *J* = 7.5 Hz, 2H), 2.30 (s, 3H), 1.71-1.62 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.3, 162.2, 144.2, 140.4, 137.8, 129.9, 127.3, 118.3, 114.7, 93.3, 27.8, 21.4, 20.7, 13.9.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.57; H, 6.83; N, 11.14.

(Z)-4-((Phenethylamino)methylene)-3-propylisoxazol-5(4*H*)-one (**21j**)



Compound **21j** was prepared according to general procedure using phenethylamine (139 μL), triethyl orthoformiate and isolated through flash chromatography (hex:EtOAc 1:1) as brown wax (63% yield).

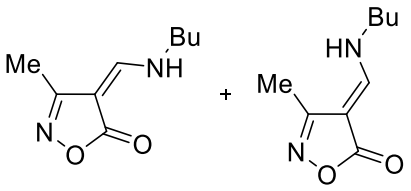
IR: 3105, 1686 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.97 (br s, 1H), 7.24-7.01 (m, 5H), 3.60 (q, *J* = 6.4 Hz, 2H), 2.87 (t, *J* = 6.7 Hz, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 1.48-1.37 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.7, 161.3, 151.5, 136.0, 128.1, 127.9, 126.0, 88.7, 50.5, 35.9, 26.6, 19.8, 12.8.

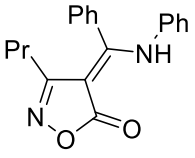
Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.52; H, 7.23; N, 10.60.

4-((Butylamino)methylene)-3-methylisoxazol-5(4*H*)-one (**21k**)



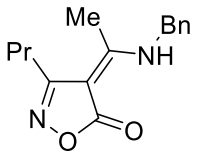
Compound **21k** was prepared according to general procedure using butylamine (109 μL), trimethyl orthoformiate and isolated through flash chromatography (hex:EtOAc 3:2) as brown wax (79% yield).
IR: 3270, 1694 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (br s, 1H), 7.41-7.35 (m, 1H), 3.43 (q, 2H, J = 6.7 Hz), 2.13 (s, 3H), 1.69-1.60 (m, 2H), 1.44-1.33 (m, 2H), 0.97-0.89 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.7, 158.7, 158.6, 152.2, 49.9, 32.3, 19.6, 13.5, 10.8.
Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.51; H, 7.96; N, 15.59.

(Z)-4-(Phenyl(phenylamino)methylene)-3-propylisoxazol-5(4*H*)-one (**21l**)



Compound **21l** was prepared according to general procedure using aniline (100 μL), and triethyl orthobenzoate isolated through flash chromatography (hex:EtOAc 3:2) as yellow wax (71% yield).
IR: 2994, 1632 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.9 (br s, 1H), 7.53- 7.48 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.32-7.28 (m, 2H), 7.19-7.09 (m, 3H), 6.81 (d, *J* = 7.7 Hz, 2H), 1.84 (t, *J* = 7.6 Hz, 2H), 1.25-1.15 (m, 2H), 0.60 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.0, 162.0, 136.8, 131.0, 130.6, 129.1, 128.9, 128.5, 126.7, 124.4, 91.9, 29.8, 20.3, 13.7.
Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.67; H, 5.69; N, 9.37.

(Z)-4-(1-(Benzylamino)ethylidene)-3-propylisoxazol-5(4*H*)-one (**21m**)



Compound **21m** was prepared according to general procedure using benzylamine (120 μL), triethyl orthoacetate and isolated through flash chromatography (hex:EtOAc 3:2) as yellow wax (74% yield).

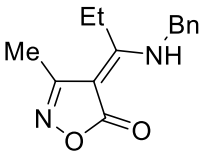
IR: 3090, 1675 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.73 (br s, 1H), 7.33-7.24 (m, 3H), 7.19 (d, *J* = 8.8 Hz, 2H), 4.56 (d, *J* = 6.2 Hz, 2H), 2.53 (t, *J* = 7.4 Hz, 2H), 2.26 (s, 3H), 1.69-1.59 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.7, 165.3, 161.2, 135.4, 129.3, 128.3, 126.9, 89.6, 47.3, 30.9, 20.5, 15.8, 13.9.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.90; H, 6.86; N, 10.62.

(Z)-4-(1-(Benzylamino)propylidene)-3-methylisoxazol-5(4*H*)-one (**21n**)



Compound **21n** was prepared according to general procedure using benzylamine (120 μL), triethyl orthopropionate and isolated through flash chromatography (hex:EtOAc 3:2) as yellow wax (80% yield).

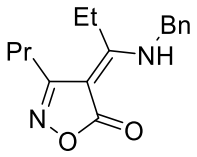
IR: 3291, 1679 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.6 (br s, 1H), 7.33-7.25 (m, 3H), 7.21 (d, *J* = 7.1 Hz, 2H), 4.58 (d, 2H), 2.62 (q, *J* = 7.7 Hz, 2H), 2.23 (s, 3H), 1.19 (t, *J* = 7.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.9, 170.5, 157.5, 135.5, 129.2, 128.4, 127.0, 89.1, 46.9, 22.1, 14.6, 12.6.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.05; H, 6.42; N, 11.19.

(Z)-4-(1-(Benzylamino)propylidene)-3-propylisoxazol-5(4*H*)-one (**21o**)



Compound **21o** was prepared according to general procedure using benzylamine (120 μL), triethyl orthopropionate and isolated through flash chromatography (hex:EtOAc 3:2) as orange oil (63% yield).

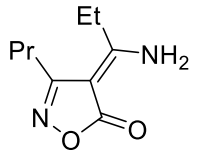
IR: 3091, 1673 $cm^{-1.}$

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.7 (br s, 1H), 7.30-7.17 (m, 5H), 4.56 (d, *J* = 6.1 Hz, 2H), 2.59 (q, *J* = 7.7 Hz, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 1.71-1.61 (m, 2H), 1.17 (t, *J* = 7.7 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.1, 170.5, 160.9, 135.6, 129.2, 128.3, 127.0, 88.2, 46.9, 30.6, 22.2, 20.3, 14.0, 12.6.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.37; H, 7.41; N, 10.58.

(Z)-4-(1-Aminopropylidene)-3-propylisoxazol-5(4*H*)-one (**21p**)



Compound **21p** was prepared according to general procedure using ammonia (26 μL), triethyl orthopropionate and isolated through flash chromatography (hex:EtOAc 1:1) as orange oil (71% yield).

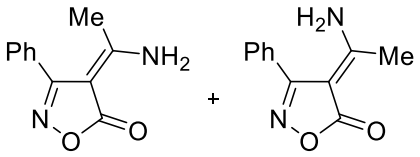
IR: 3098, 1664 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (br s, 1H), 6.51 (br s, 1H), 2.70 (q, *J* = 7.6 Hz, 2H), 2.60 (t, *J* = 7.4 Hz, 2H), 1.80-1.70 (m, 2H), 1.35 (t, *J* = 7.5 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ=175.6, 170.4, 161.2, 89.0, 30.8, 26.3, 20.3, 14.0, 11.6.

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.55; H, 7.58; N, 15.11.

4-(1-Aminoethylidene)-3-phenylisoxazol-5(4*H*)-one (**21q**)



Compound **21q** was prepared according to general procedure using ammonia (26 μL), triethyl orthoacetate and isolated through flash chromatography (hex:EtOAc 1:1) as orange solid (63% yield); m.p.: 201-203 °C.

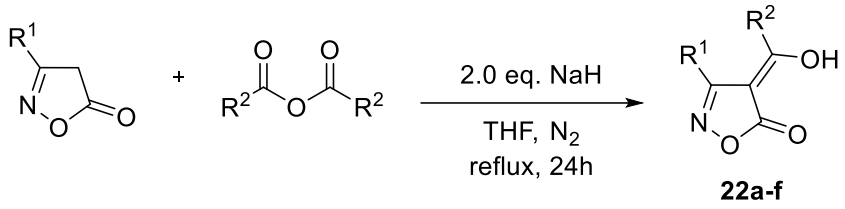
IR: 3102, 1671 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.45 (br s, 2H), 7.55-7.46 (m, 7H), 7.34-7.28 (m, 3H), 7.12 (br s, 2H), 2.18 (s, 3H), 1.86 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 188.4, 176.4, 173.8, 167.9, 162.6, 162.4, 133.4, 131.0, 129.6, 128.9, 128.7, 128.5, 127.8, 127.0, 90.2, 87.8, 27.4, 20.0.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.52; H, 4.68; N, 13.60.

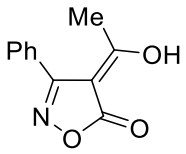
General procedure for the synthesis of 4-hydroxyalkylidene-isoxazol-5-ones (**22a-f**)



22a-f

To a stirred solution of the appropriate isoxazole-5-ones (1.0 mmol) in THF dry (10 ml) at 0°C, NaH (2.0 mmol) and the appropriate anhydride (2.0 mmol) were added under N_2 atmosphere. The resulting reaction mixture was stirred for 30 minutes at 0°C and then allowed to reach room temperature. After this time the reaction was heated at reflux for 24h. The solvent was then evaporated under reduced pressure, the crude was diluted with aqueous HCl (2M, 5 ml) and extracted with DCM (3 x 5 ml). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The final products were purified by flash chromatography. The characterization of the product **22b**[119] is consistent with the one reported in literature.

(Z)-4-(1-Hydroxyethylidene)-3-phenylisoxazol-5(4*H*)-one (**22a**)



Compound **22a** was prepared according to general procedure using acetic anhydride (189 μL) and isolated through flash chromatography (hex:EtOAc 3:2) as red solid (78% yield); m.p.: 98-101°C.

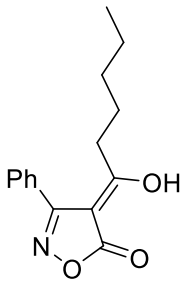
IR: 3198, 1721 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (br s, 1H), 7.68-7.63 (m, 1H), 7.55-7.48 (m, 4H), 2.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ=174.8, 163.2, 161.5, 132.2, 130.7, 129.2, 128.9, 128.7, 128.6, 126.6, 98.0, 34.0.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.27; H, 4.29; N, 7.11.

(*Z*)-4-(1-Hydroxyhexylidene)-3-phenylisoxazol-5(4*H*)-one (**21c**)



Compound **21c** was prepared according to the general procedure using hexanoic anhydride (462 μL), and isolated through flash chromatography (hex:EtOAc 3:2) as yellow wax (71% yield).

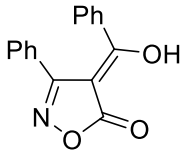
IR: 3214, 1661 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.50-7.38 (m, 2H), 7.33-7.15 (m, 3H), 2.57-2.53 (m, 2H), 1.45-1.31 (m, 2H), 1.25-1.11 (m, 4H), 0.78 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD): δ = 197.5, 179.0, 165.9, 133.9, 130.8, 130.0, 129.8, 128.7, 127.7, 93.2, 40.6, 32.9, 26.4, 23.6, 14.4.

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.36; H, 6.80; N, 5.57.

(*Z*)-4-(Hydroxy(phenyl)methylene)-3-phenylisoxazol-5(4*H*)-one (**22d**)



Compound **22d** was prepared according to the general procedure using benzoic anhydride (377 μL), and isolated through flash chromatography (hex:EtOAc 3:2) as orange solid (69% yield); m.p.: 145-147°C.

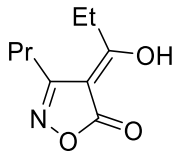
IR: 3062, 1633 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.33 (br s, 1H), 7.48-7.38 (m, 1H), 7.35-7.28 (m, 3H), 7.20-7.11 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.3, 177.9, 161.2, 133.1, 130.8, 130.1, 129.6, 128.5, 128.4, 128.3, 128.0, 95.9.

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.66; H, 3.92; N, 4.96.

(*Z*)-4-(1-Hydroxypropylidene)-3-propylisoxazol-5(4*H*)-one (**22e**)



Compound **22e** was prepared according to the general procedure using propionic anhydride (256 μL), and isolated through flash chromatography (hex:EtOAc 3:2) as orange solid (92% yield); m.p.: 99-103°C.

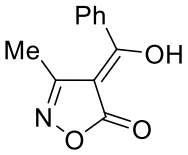
IR: 3107, 1666 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.3 (br s, 1H), 2.85-2.79 (m, 4H), 1.75-1.65 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3): δ =173.0, 172.8, 164.1, 95.8, 31.2, 29.3, 19.9, 13.6, 8.8.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.16; H, 7.03; N, 7.92.

(*Z*)-4-(Hydroxy(phenyl)methylene)-3-methylisoxazol-5(4*H*)-one (**22f**)



Compound **22f** was prepared according to the general procedure using benzoic anhydride (377 μL), and isolated through flash chromatography (hex:EtOAc 7:3) as orange oil (82% yield).

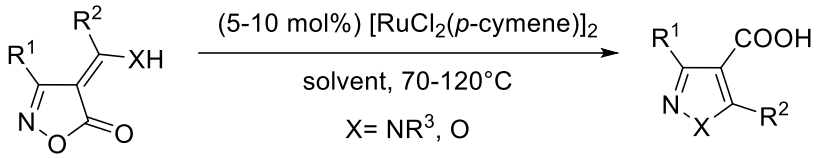
IR: 3068, 1654 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.0 (br s, 1H), 7.69-7.60 (m, 3H), 7.58-7.54 (m, 2H), 2.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.8, 177.5, 157.7, 133.3, 131.5, 128.8, 128.7, 97.9, 14.4.

Anal. Calcd. for $C_{11}H_9NO3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.20; H, 4.25; N, 7.12.

General procedure for the synthesis of pyrazole- (**23a-o**) *and isoxazole-* (**24a-f**) *4-carboxylic acids*

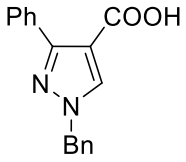


21a-o, 22a-f **23a-o, 24a-f**

In a sealed tube, to a solution of the appropriate 4-alylidenisoxazol-5-one (1.0 mmol) in the solvent (3 ml), $[RuCl_2(p\text{-cymene})]_2$ (5-10mol%) was added and the reaction is stirred at reflux until complete conversion of the substrate. The reaction mixture is then washed with brine (3 x 10 ml), extracted with EtOAc (3 x 10 ml), the organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The final products were purified by flash chromatography to afford pyrazole-4-carboxylic acids or isoxazole-4-carboxylic acid.

The characterization of compounds **24a**,[120] **24d**[121] are consistent with the ones reported in literature.

1-Benzyl-3-phenyl-1*H*-pyrazole-4-carboxylic acid (**23a**)



Compound **23a** was prepared according to the general procedure starting from substrate **21a** (278 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in MeCN at 70°C for 18h and isolated through flash chromatography (hex:EtOAc 1:1) as brown solid (68% yield); m.p.: 150-153°C.

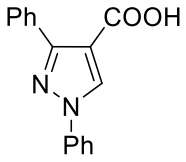
IR (neat) = 3125, 1724 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1H), 7.79 (d, 2H, *J* = 9.3 Hz), 7.47-7.32 (m, 8H), 5.35 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.0, 153.7, 135.9, 134.9, 132.0, 129.3, 129.1, 128.6, 128.5, 128.2, 127.9, 111.0, 56.6.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.69; H, 4.86; N, 10.41.

1,3-Diphenyl-1*H*-pyrazole-4-carboxylic acid (**23b**)



Compound **23b** was prepared according to the general procedure starting from substrate **21b** (264 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in MeCN at 70°C for 24h and isolated through flash chromatography (hex:EtOAc 1:1) as orange solid (91% yield); m.p.: 204-206°C.

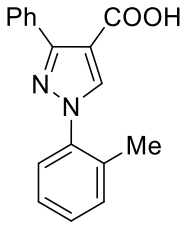
IR: 3156, 1664 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 7.90-7.83 (m, 2H), 7.80-7.74 (m, 2H), 7.54-7.40 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.6, 154.5, 139.1, 133.4, 131.8, 129.6, 129.4, 128.8, 128.0, 127.7, 119.7, 119.6, 112.7.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.66; H, 4.79; N, 10.38.

3-Phenyl-1-(2-tolyl)-1*H*-pyrazole-4-carboxylic acid (**23c**)



Compound **23c** was prepared according to the general procedure starting from substrate **21c** (278 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in MeCN at 70°C for 24h and isolated through flash chromatography (hex:EtOAc 1:1) as brown solid (76% yield); m.p.: 128-132°C.

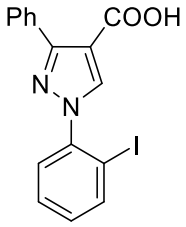
IR: 3181, 1674 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (s, 1H), 7.90 (d, *J* = 9.3 Hz, 2H), 7.48-7.31 (m, 7H), 2.36 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.3, 153.9, 138.8, 137.4, 133.6, 131.8, 131.5, 129.4, 129.2, 128.7, 127.9, 126.8, 126.0, 111.6, 18.1.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.52; H, 4.78; N, 10.32.

1-(2-Iodophenyl)-3-phenyl-1*H*-pyrazole-4-carboxylic acid (**23d**)



Compound **23d** was prepared according to the general procedure starting from substrate **21d** (390 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in MeCN at 70°C for 24h and isolated through flash chromatography (hex:EtOAc 3:2) as grey solid (74% yield); m.p.: 169-172°C.

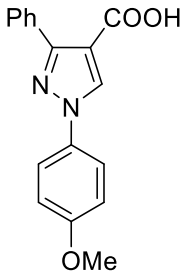
IR: 3190, 1677 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.54-7.43 (m, 5H), 7.23-7.19 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.8, 154.3, 142.3, 140.3, 138.0, 131.6, 130.9, 129.5, 129.2, 128.9, 127.9, 127.8, 111.8, 93.9.

Anal. Calcd. for $C_{16}H_{11}IN_2O_2$: C, 49.25; H, 2.84; N, 7.18. Found: C, 49.28; H, 2.58; N, 7.32.

1-(4-Methoxyphenyl)-3-phenyl-1*H*-pyrazole-4-carboxylic acid (**23e**)



Compound **23e** was prepared according to the general procedure starting from substrate **21e** (294 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in MeCN at 70°C for 18h and isolated through flash chromatography (hex:EtOAc 2:3) as yellow solid (82% yield); m.p.: 165-167°C.

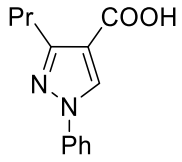
IR: 3204, 1700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1H), 7.87 (d, *J* = 9.4 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 2H), 7.46-7.40 (m, 3H), 7.01 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.1, 159.1, 154.2, 133.3, 132.8, 131.9, 129.4, 128.8, 128.0, 121.3, 114.7, 112.1, 55.6.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.12; H, 4.91; N, 9.76.

1-Phenyl-3-propyl-1*H*-pyrazole-4-carboxylic acid (**23f**)



Compound **23f** was prepared according to the general procedure starting from substrate **21f** (230 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in MeCN at 70°C for 24h and isolated through flash chromatography (hex:EtOAc 1:1) as brown solid (82% yield); m.p.: 137-138°C.

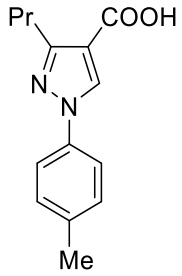
IR: 3162, 1682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H), 1.86-1.76 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.9, 157.0, 139.2, 132.3, 129.5, 127.3, 119.5, 112.9, 29.6, 22.3, 14.0.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.53; H, 6.25; N, 12.36.

3-Propyl-1-(4-tolyl)-1*H*-pyrazole-4-carboxylic acid (**23g**)



Compound **23g** was prepared according to the general procedure starting from substrate **21g** (244 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in MeCN at 70°C for 24h and isolated through flash chromatography (hex:EtOAc 9:1) as grey solid (76% yield); m.p.: 141-143°C.

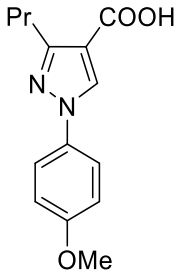
IR: 3158, 1634 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.30 (s, 3H), 1.76-1.67 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.8, 156.8, 137.2, 137.0, 132.1, 130.0, 119.4, 112.8, 29.6, 22.3, 20.9, 14.0.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.60; H, 6.81; N, 11.19.

1-(4-Methoxyphenyl)-3-propyl-1*H*-pyrazole-4-carboxylic acid (**23h**)



Compound **23h** was prepared according to the general procedure starting from substrate **21h** (260 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in MeCN at 70°C for 24h and isolated through flash chromatography (hex:EtOAc 1:1) as brown solid (91% yield); m.p.: 126-128°C.

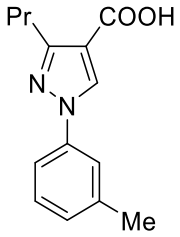
IR: 3016, 1682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.96 (t, *J* = 7.5 Hz, 2H), 1.85-1.76 (m, 2H), 1.03 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.7, 158.9, 156.8, 132.9, 132.2, 121.2, 114.6, 112.4, 55.6, 29.6, 22.3, 14.0.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.78; H, 5.94; N, 10.51.

3-Propyl-1-(3-tolyl)-1*H*-pyrazole-4-carboxylic acid (**23i**)



Compound **23i** was prepared according to the general procedure starting from substrate **21i** (244 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in MeCN at 70°C for 24h and isolated through flash chromatography (hex:EtOAc 9:1) as yellow wax (73% yield).

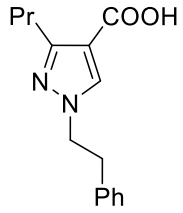
IR: 3175, 1682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.42 (s, 1H), 7.55 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 2.98 (t, *J* = 7.6 Hz, 2H), 2.44 (s, 3H), 1.86-1.77 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.7, 157.0, 139.8, 139.2, 132.3, 129.3, 128.2, 120.3, 116.6, 112.7, 29.6, 22.4, 21.5, 14.0.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.96; H, 6.48; N, 11.59.

1-Phenethyl-3-propyl-1*H*-pyrazole-4-carboxylic acid (**23j**)



Compound **23j** was prepared according to the general procedure starting from substrate **21j** (258 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in MeCN at 70°C for 24h and isolated through flash chromatography (hex:EtOAc 1:1) as white solid (69% yield); m.p.: 147-148°C.

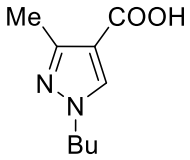
IR: 3182, 1694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 7.33-7.23 (m, 3H), 7.08 (d, *J* = 8.1 Hz, 2H), 4.30 (t, *J* = 7.0 Hz, 2H), 3.18 (t, *J* = 7.1 Hz, 2H), 2.90 (t, *J* = 6.8 Hz, 2H), 1.80-1.69 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.2, 156.2, 137.5, 135.1, 128.7, 128.6, 126.9, 110.4, 53.9, 36.5, 29.5, 22.5, 13.9.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.96; H, 6.86; N, 10.51.

1-Butyl-3-methyl-1*H*-pyrazole-4-carboxylic acid (**23k**)



Compound **23k** was prepared according to the general procedure starting from substrate **21k**(182 mg), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%) in DMSO at 120°C for 48h and isolated through flash chromatography (hex:EtOAc 1:1) as yellow oil (51% yield).

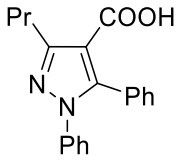
IR: 3295, 1717 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 4.05 (t, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 1.90-1.81 (m, 2H), 1.40-1.29 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ=176.2, 160.6, 133.8, 106.3, 52.2, 32.0, 29.7, 15.5, 14.1.

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.47; H, 7.56; N, 15.18.

1,5-Diphenyl-3-propyl-1*H*-pyrazole-4-carboxylic acid (**23l**)



Compound **23l** was prepared according to the general procedure starting from substrate **21l** (306 mg), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%) in DMSO at 120°C for 18h and isolated through flash chromatography (hex:EtOAc 3:2) as green solid (87% yield); m.p.: 177-180°C.

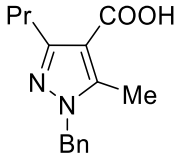
IR: 3167, 1671 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38-7.29 (m, 3H), 7.27-7.24 (m, 5H), 7.17-7.15 (m, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 1.87-1.78 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ=168.0, 156.5, 147.0, 139.2, 130.5, 129.6, 129.0, 128.7, 128.0, 127.7, 125.4, 120.3, 110.2, 30.2, 22.4, 14.2.

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.71; H, 5.79; N, 9.31.

1-Benzyl-5-methyl-3-propyl-1*H*-pyrazole-4-carboxylic acid (**23m**)



Compound **23m** was prepared according to the general procedure starting from substrate **21m** (258 mg), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%) in DMSO at 120°C for 72h and isolated through flash chromatography (hex:EtOAc 3:2) as yellow wax (62% yield).

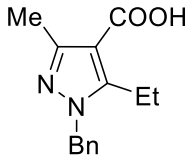
IR: 3186, 1671 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.27-7.19 (m, 3H), 7.02 (d, *J* = 8.6 Hz, 2H), 5.22 (s, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 1.70-1.61 (m, 3H), 0.91 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.5, 154.6, 144.4, 135.0, 127.8, 126.8, 125.6, 107.7, 51.9, 29.0, 21.4, 12.9, 10.5.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.96; H, 6.87; N, 10.63.

1-Benzyl-5-ethyl-3-methyl-1*H*-pyrazole-4-carboxylic acid (**23n**)



Compound **23n** was prepared according to the general procedure starting from substrate **21n** (244 mg), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%) in DMSO at 120°C for 72h and isolated through flash chromatography (hex:EtOAc 3:2) as orange was (58% yield).

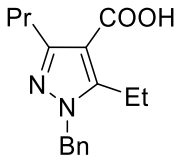
IR: 3063, 1690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.27-7.17 (m, 3H), 7.04 (d, *J* = 7.7 Hz, 2H), 5.21 (s, 2H), 2.84 (q, *J* = 7.5 Hz, 2H), 2.41 (s, 3H), 0.99 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.5, 151.8, 150.9, 136.4, 128.8, 127.9, 126.7, 108.5, 52.7, 18.9, 14.3, 13.2.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.95; H, 6.42; N, 11.61.

1-Benzyl-5-ethyl-3-propyl-1*H*-pyrazole-4-carboxylic acid (**23o**)



Compound **23o** was prepared according to the general procedure starting from substrate **21o** (272 mg), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%) in DMSO at 120°C for 72h and isolated through flash chromatography (hex:EtOAc 3:2) as yellow wax (51% yield).

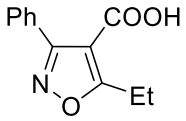
IR: 3173, 1679 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.27 (m, 3H), 7.10 (d, *J* = 8.6 Hz, 2H), 5.29 (s, 2H), 2.93-2.85 (m, 4H), 1.78-1.69 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 155.7, 150.9, 136.6, 128.8, 127.8, 126.6, 107.7, 52.8, 30.1, 22.4, 18.9, 14.0, 13.2.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.82; H, 7.15; N, 10.44.

5-Ethyl-3-phenylisoxazole-4-carboxylic acid (**24b**)



Compound **24b** was prepared according to the general procedure starting from substrate **22b** (217 mg), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%) in MeCN at 70°C for 2h and isolated through flash chromatography (hex:EtOAc 7:3) as grey solid (87% yield); m.p.: 149-151°C.

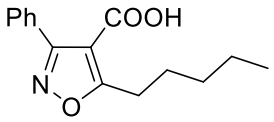
IR: 2984, 1680 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.60 (m, 2H), 7.52-7.43 (m, 3H), 3.20 (q, *J* = 7.6 Hz, 2H), 1.40 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.1, 167.4, 162.8, 129.9, 129.4, 128.2, 128.1, 106.6, 21.5, 11.4.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.57; H, 4.97; N, 6.67.

5-Pentyl-3-phenylisoxazole-4-carboxylic acid (**24c**)



Compound **24c** was prepared according to the general procedure starting from substrate **22c** (259 mg), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%) in DMSO at 120°C for 6h and isolated through flash chromatography (hex:EtOAc 7:3) as yellow wax (86% yield).

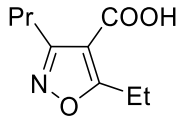
IR: 2960, 1682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.62 (m, 2H), 7.48-7.43 (m, 3H), 3.15 (t, *J* = 7.6 Hz, 2H), 1.85-1.78 (m, 2H), 1.42-1.35 (m, 4H), 0.92 (t, *J* = 9.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ=180.2, 165.0, 161.7, 128.9, 128.4, 127.1, 127.0, 105.8, 30.3, 26.6, 25.9, 21.2, 12.8.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.27; H, 6.76; N, 5.65.

5-Ethyl-3-propylisoxazole-4-carboxylic acid (**24e**)



Compound **24e** was prepared according to the general procedure starting from substrate **22e** (183 mg), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%) in DMSO at 120°C for 6h and isolated through flash chromatography (hex:EtOAc 7:3) as yellow oil (93% yield).

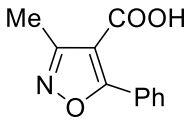
IR: 2929, 1666 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.13 (q, *J* = 7.6, Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 1.83-1.71 (m, 2H), 1.34 (t, *J* = 7.6 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.3, 166.5, 163.7, 106.4, 27.9, 21.2, 20.9, 13.9, 11.3.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.73; H, 7.33; N, 7.83.

3-Methyl-5-phenylisoxazole-4-carboxylic acid (**24f**)



Compound **24f** was prepared according to general procedure starting from substrate **22f** (203 mg), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%) in MeCN at 70°C for 5h and isolated through flash chromatography (hex:EtOAc 7:3) as white solid (93% yield); m.p.: 151-153°C.

IR: 3136, 1714 cm^{-1}.

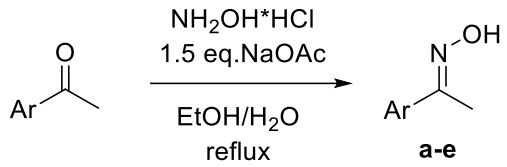
^1H NMR (400 MHz, $CDCl_3$): δ = 7.93-7.90 (m, 2H), 7.57-7.48 (m, 3H), 2.55 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.4, 166.9, 161.3, 131.5, 129.4, 128.4, 126.7, 107.3, 12.3.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.29; H, 4.28; N, 6.51.

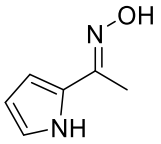
Chapter 3.3_ *Rearrangement reactions of aromatic and heteroaromatic oximes*

General procedure for the synthesis of aryl ketoximes and heteroaryl oximes (**a-e**)



To a solution of ketone (1.0 mmol) in EtOH (12 mL) a solution of sodium acetate (1.5 eq), hydroxylamine hydrochloride (1.5 eq) in H_20 (3 mL) was added. The reaction is then stirred at reflux overnight. After full conversion the mixture was cooled to r.t., the solvent was removed under reduced pressure. The crude is then washed with a solution of NaOH 1M and extracted wit EtOAC (10ml x 3), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The characterization of oximes **a**,[122] **b**,[123] **d**,[124] **e**[125] is consistent with the one reported in literature.

1-(1*H*-pyrrol-2-yl)ethan-1-one oxime (**c**)



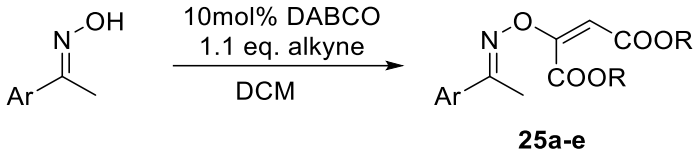
Compound **c** was prepared according to the general procedure starting from ketone (124 mg) and isolated through flash chromatography (hex:EtOAc 3:2) as orange solid (78% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.71 (s, 1H), 8.81 (s, 1H), 7.01 (td, *J* = 2.8, 1.4 Hz, 1H), 6.64 – 6.57 (m, 1H), 6.30 (dt, *J* = 3.9, 2.6 Hz, 1H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.06, 125.77, 121.26, 113.80, 108.72, 18.08.

ITMS + c HESI m/z 125.17 $[M+H]^+$.

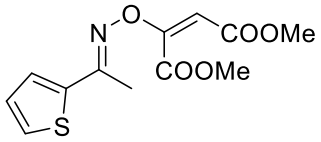
General procedure for the synthesis of O-vinylketoxime derivatives (**25a-e**)



25a-e

To a stirred solution of oxime (1 mmol) and DABCO (10%mol) in DCM-dry (20mL) at 0°C was added dropwise a solution of dimethyl or diethyl acetylenedicarboxylate (1.1 eq) in DCM-dry (6ml) over 15 min. The reaction mixture was allowed to warm to room temperature and stirred for 20min. DCM was removed under reduce pressure and the reaction mixture was suspended NH_4Cl water and extracted with EtOAc (10 ml x 3), dried over Na_2SO_4, filtered, and evaporated under reduced pressure.

Dimethyl 2-(((1-(thiophen-2-yl)ethylidene)amino)oxy)maleate (**25a**)



Compound **25a** was prepared according to the general procedure and isolated as a mixture of isomers (E/Z=78/22) through flash chromatography (hex:EtOAc 3:1) as an orange oil (72% yield).

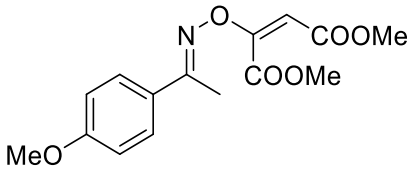
Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.32 (m, 2H), 7.03 (dd, *J* = 5.0, 3.9 Hz, 1H), 6.03 (s, 1H), 3.86 (s, 4H), 3.73 (s, 3H), 2.46 (s, 3H).

Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 3.9, 1.2 Hz, 1H), 7.62 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.13 (dd, *J* = 5.2, 3.9 Hz, 1H), 6.13 (s, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 2.37 (s, 3H).

E/Z mixture: ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.97, 162.88, 155.79, 153.17, 150.56, 137.65, 132.29, 132.22, 129.41, 129.20, 128.65, 128.53, 127.35, 127.21, 126.37, 126.27, 106.83, 105.69, 96.61, 96.29, 77.37, 77.05, 76.73, 60.39, 53.01, 52.87, 52.85, 51.84, 51.82, 51.77, 51.65, 29.69, 19.76, 14.20, 13.87.

ITMS + c HESI m/z 284.93 $[M + H]^+$, 589.26 (dimer).

Dimethyl 2-(((1-(4-methoxyphenyl)ethylidene)amino)oxy)maleate (**25b**)



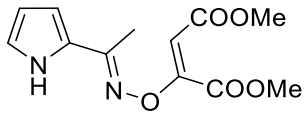
Compound **25b** was prepared according to the general procedure and isolated as single isomer through flash chromatography (hex:EtOAc 3:1) as a yellow solid (97% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.00 (s, 1H), 3.87 – 3.77 (m, 6H), 3.68 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.17, 163.02, 161.31, 159.63, 153.51, 128.27, 126.89, 113.87, 104.93, 55.28, 52.72, 51.65, 13.42.

ITMS + c HESI m/z 308.46 $[M+H]^+$.

Dimethyl 2-(((1-1*H*-pyrrol-2-yl)ethylidene)amino)oxy)maleate (**25c**)



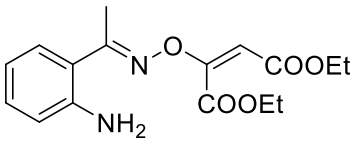
Compound **25c** was prepared according to the general procedure using and isolated as a single isomer through flash chromatography (hex:EtOAc 4:1) as a brown oil (74% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.98 (s, 1H), 7.20 – 7.11 (m, 1H), 6.70 – 6.61 (m, 1H), 6.32 – 6.22 (m, 1H), 5.50 (s, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 2.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.92, 162.90, 158.58, 149.28, 123.97, 123.38, 116.03, 108.87, 97.90, 52.79, 51.80, 17.88.

ITMS + c HESI m/z 267.20 $[M + H]^+$.

Diethyl 2-(((1-2-aminophenyl)ethylidene)amino)oxy)maleate (**25d**)

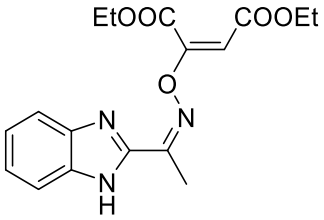


Compound **25d** was prepared according to the general procedure.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 5.97 Hz, 1H), 7.17-7.13 (m, 1H), 7.74-6.68 (m, 2H), 5.96 (s, 1H), 4.35-4.29 (m, 2H), 4.22-4.17 (m, 2H), 2.51 (s, 3H), 1.34 (t, *J* = 5.34 Hz, 3H), 1.27 (t, *J* = 5.34 Hz, 3H).

The full characterization is *on-going.*

Diethyl 2-(((1-(1*H*-benzo[*d*]imidazol-2-yl)ethylidene)amino)oxy)maleate (**25e**)



Compound **25e** was prepared according to the general procedure and isolated through flash chromatography (hex:EtOAc 3:1) as yellow oil (64% yield).

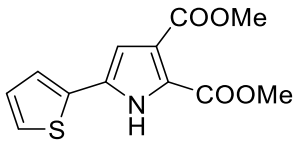
^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.14 (brs, 1H), 7.88 (d, *J* = 5.9 Hz, 1H), 7.67 (d, *J* = 5.9 Hz, 1H), 7.34 (dd, *J* = 25.0, 17.4 Hz, 2H), 5.69 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 3H), 1.40-1.34 (m, 6H)

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.6, 161.7, 157.9, 150.8, 142.1, 125.2, 123.1, 120.6, 112.5, 100.4, 62.5, 61.2, 18.1, 14.5, 14.0.

General procedure for the Ru-catalyzed rearrangement process (**26a-e**)

To a solution of vinyl-oxime **25** (1 mmol) in DMSO-dry (1.5 mL), [Ru(*p*-cymene)Cl_2]$_2$ (5mol%) was added and the reaction was stirred at 100°C for 15h. The solution was then diluted with brine (30 ml) extracted with EtOAc (10 mL x 3), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The final products were purified though flash chromatography.

Dimethyl 5-(thiophen-2-yl)-1*H*-pyrrole-2,3-dicarboxylate (**26a**)



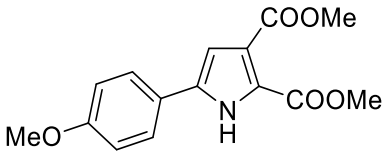
Compound **26a** was prepared according to the general procedure and isolated through flash chromatography (hex:EtOAc 2:1) as yellow solid (64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.25 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.09 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.84 (d, *J* = 3.1 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.00, 160.45, 133.10, 129.43, 128.03, 125.36, 123.84, 122.33, 121.47, 111.06, 52.32, 51.95, 29.71.

ITMS + c HESI m/z 266.28 $[M+H]^+$

Dimethyl 5-(4-methoxyphenyl)-1*H*-pyrrole-2,3-dicarboxylate (**26b**)



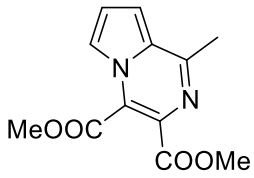
Compound **26b** was prepared according to the general procedure and isolated through flash chromatography (hex:EtOAc 2:1) as pale brown solid (56% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ=7.48 (d, J = 3.1 Hz, 2H), 6.95 (d, J = 9.3 Hz, 2H), 6.82 (d, J = 3.1 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.41, 160.79, 159.79, 135.07, 126.34, 123.08, 122.08, 121.55, 114.51, 109.79, 52.18, 51.88, 29.70.

ITMS + c HESI m/z 290.88 $[M+H]^+$.

Dimethyl 1-methylpyrrol[1,2-α]pyrazine-3,4-dicarboxylate (**26c**)



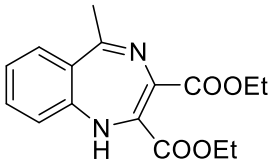
Compound **25c** was prepared according to the general procedure starting from vinyloxime **24c** (266 mg) ad isolated through flash chromatography (hex:EtOAc 2:1) as orange oil (92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 2.7, 1.3 Hz, 1H), 7.02 (dd, *J* = 3.7, 2.2 Hz, 1H), 6.99 (dd, *J* = 4.2, 1.3 Hz, 1H), 4.06 (s, 3H), 4.00 (s, 3H), 2.78 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.16, 163.27, 154.68, 129.72, 128.09, 122.61, 117.33, 117.00, 105.94, 29.70, 21.84.

ITMS + c HESI m/z 249.87 $[M+H]^+$.

Diethyl 5-methyl-1*H*-benzo[e][1,4]diazepine-2,3-dicarboxylate (**26d**)

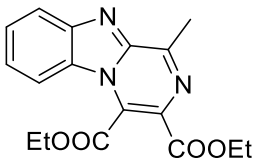


Compound **26d** was prepared according to the general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28-8.26 (m, 1H), 8.11-8.09 (m, 1H), 7.84-7.80 (m, 1H), 7.73-7.69 (m 1H), 4.55-4.45 (m, 4H), 2.77 (s, 3H), 1.47-1.41 (m, 6H).

The characterization is *on-going.*

Diethyl 1-methylbenzo[4,5]imidazo[1,2-α]pyrazine-3,4-dicarbozylate (**26e**)



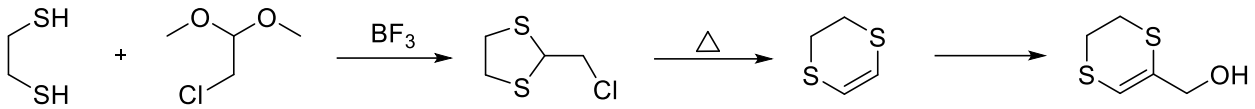
Compound **25e** was prepared according to the general procedure starting from vinyloxime **24e** (317 mg) and isolated through flash chromatography (hex:EtOAc 7:3) as brown oil (89% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 4.16 Hz, 1H), 7.76 (8.56 1H), 7.69 (7.56 1H), (1H), 4.75-4.70 (m, 2H), 4.56-4.51 (m, 2H), 3.10 (s,3H), 1.53-1.46(m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 161.9, 154.5, 144.7, 141.3, 128.2, 128.1, 127.6, 124.7, 124.6, 121.9, 113.2, 63.6, 62.6, 21.7, 14.3, 13.8.

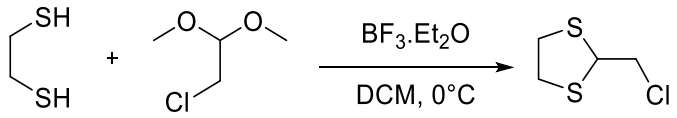
Chapter 4.1_ *Organocatalysis*

General procedure for the synthesis of (5,6-dihydro-1,4-dithiin-2-yl)methanol reagent (**27**)



27

*General procedure for the synthesis of 2-(chloromethyl)-1,3-dithiolane (**a**)*



a

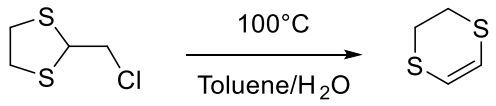
In a round-bottom flask, a solution of 1,2-ethanedithiol (11.2 mmol) and 2-chloro-1,1-dimethoxyethane (9.3 mmol) in DCM (25 ml, 0.35 M) was cooled down to 0°C with an ice bath and then, after the addition of $BF_3.Et_2O$ (5 mmol, 3.8 M), the reaction mixture is slowly warmed to room temperature. After 24 hours the reaction is quenched with a saturated solution of Na_2CO_3 (40 ml) and extracted with DCM (30 ml x 3). The combined organic phases are washed with NaOH (1M) and NaCl (15 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure.

The resulting product **4a** was used without further purification.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 4.67 (t, *J* = 7.3 Hz, 1 H), 3.64 (d, *J* = 7.3 Hz, 2 H), 3.26 (s, 4 H).

The analytical data are in agreement with the ones reported in literature.[61]

*General procedure for the synthesis of 2,3-dihydro-1,4-dithiine (**b**)*



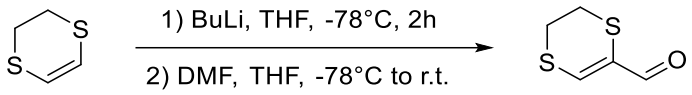
a **b**

In a pressure tube containing a solution of (**a**) (900 mg) in Toluene (10 ml) and H_2O (10 ml) is heated up to 100°C under heavy stirring. After a couple of hours, the reaction was cooled to room temperature. The organic phase is separated, and the aqueous one is extracted with EtOAc (10 ml x 2). The combined organic phases were washed with a saturated solution of NaCl (5 ml), dried over Na_2SO_4 and the solvent is removed under reduced pressure. The obtained product was then purified by flash chromatography (EtOAc to petroleum ether, 0% to 0.5%) obtaining a yellow oil (75% yield).

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.10 (s, 2H), 3.20 (s, 4H).

The analytical data are in agreement with the ones reported in literature.[61]

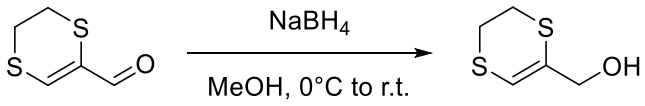
*General procedure for the synthesis of 5,6-dihydro-1,4-dithiine-2-carbaldeyde (**c**)*



b **c**

A solution of 2,3-dihydro-1,4-dithiine (**b**) (42.3 mmol) in THF dry (85 ml) is cooled to -78°C and BuLi (22 mL, 2.5 M in hexane) is slowly added. After 2h DMF (63.4 mmol) is added dropwise and 2h later the solution is allowed to reach room temperature. After the complete conversion of starting material, the reaction is quenched with $NaHCO_3$ (50 ml) and extracted with Et_2O (80 ml x 3). The combined organic phases were washed with a saturated solution of NaCl (50 ml), dried over Na_2SO_4 and the solvent is removed under reduced pressure. The obtained product is directly used in the next step without further purification. The analytical data are in agreement with the ones reported in literature.[61]

General procedure for the synthesis of (5,6-dihydro-1,4-dithiin-2-yl)methanol (**27**)



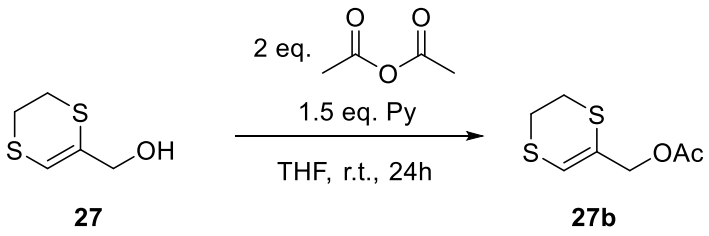
c **27**

To a solution of 5,6-dihydro-1,4-dithiine-2-carbaldehyde (**c**) (42.3 mmol) in MeOH dry (110 ml) at -10°C, $NaBH_4$ (63.4 mmol) is added portion wise. After 1h the reaction is quenched with a saturated solution of $NaHCO_3$ (50 ml) and extracted with Et_2O (200 ml x 3). The combined organic phases were washed with a saturated solution of NaCl (50 ml), dried with anhydrous Na_2SO_4 and the solvent is removed under reduced pressure. The crude material is purified via flash chromatography (20% AcOEt in petroleum ether) obtaining a yellow oil (50% yield over two steps).

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.24 (s, 1 H), 4.11 (d, J=5.3 Hz, 2 H), 3.13 - 3.24 (m, 4 H), 1.83 (t, J=5.3 Hz, 1 H).

The analytical data are in agreement with the ones reported in literature.[61]

General procedure for the synthesis of (5,6-dihydro-1,4-dithiin-2-yl)methyl acetate (**27b**)



27 **27b**

To a 5 ml reaction flask were added (dhdt)-2-methanol (**26**) (100 mg, 1.0 eq), Ac_2O (0.127 mL, 2 eq.) and 5 ml of THF. The reaction was cooled to 0° C and then pyridine (82 uL, 1.5 eq.) was slowly added. The reaction was then allowed to warm at room temperature.

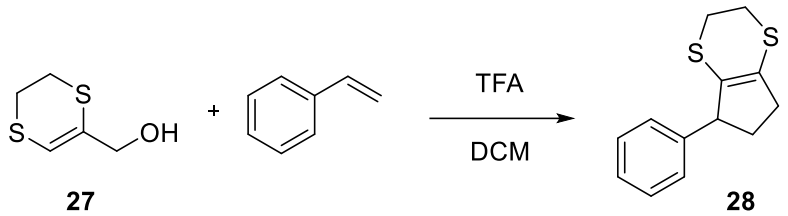
After 24 hours, a saturated aqueous solution of NH_4Cl (10 ml) was added all at once. After addition of ethyl acetate (10 ml), the layers were separated, and the aqueous phase was extracted with ethyl acetate (10 ml x 2). The combined organic layers were washed with brine (5 ml x 2), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude was used without purification.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.30 (s, 1H), 4.56 (s, 2H), 3.21-3.15 (m, 4H), 2.08 (s, 3H).

^{13}C-NMR (126MHz, $CDCl_3$): δ = 170, 123, 116, 68, 27, 26, 21.

The analytical data are in agreement with the ones reported in literature. [61]

General procedure for the synthesis of the racemate (**28**)

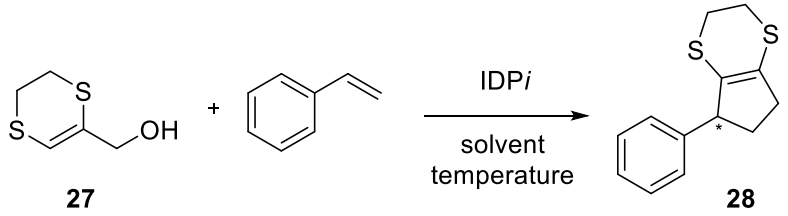


27 **28**

A solution of (5,6-dihydro-1,4-dithiin-2-yl)methanol (**27**) (0.5 mmol) in DCM dry (5 ml) premixed with the olefin (1.5 eq.) was cooled to -78°C under an argon atmosphere. At this temperature, a freshly prepared solution of trifluoroacetic acid (2 eq.) in DCM (0.5 ml) was added. The resulting mixture was stirred and allowed to warm gradually to room temperature. The reaction was monitored by TLC (2% of EtOAc in hexane). Then, a saturated aqueous solution of $NaHCO_3$ (5 ml) was added all at once. After addition of DCM (5 ml), the layers were separated, and the aqueous phase was extracted with DCM (5 ml x 2). The combined organic layers were washed with brine (2.5 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting product was purified by flash chromatography over silica (2% of AcOEt in hexane) as a white solid.

The analytical data are in agreement with the ones reported in literature. [61]

General procedure for the screening

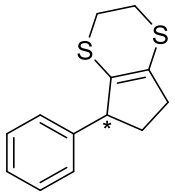


27 **28**

In a GC vial, a solution of (5,6-dihydro-1,4-dithiin-2-yl)methanol **26** (0.025 mmol) and olefin (0.05 mmol), in the appropriate solvent (0.3M), was cooled to the set reaction temperature. Subsequently, the IDP*i* catalyst was added. After 24 hours the crude reaction is quenched with 0.30 mg of internal standard (1,3,5-trimethoxybenzene) and 20 µL of triethylamine. The product is then purified by preparative TLC (2% of AcOEt in hexane); r.f. = 0.4.

The enantiomeric ratio was determined by HPLC analysis using 150 mm Chiralcel OJ-3R, 4.6 mm i.D. (run time = 15 min, solvent: MeCN/H_2O = 85:15, oven temperature: 35°C, 1.0 ml/min, 11.7 MPa, 298 K) = 87:13 (achieved performing the reaction at -50°C).

5-phenyl-2,3,6,7-tetrahydro-5H-cyclopenta[*b*][1,4]dithiine (**28**)

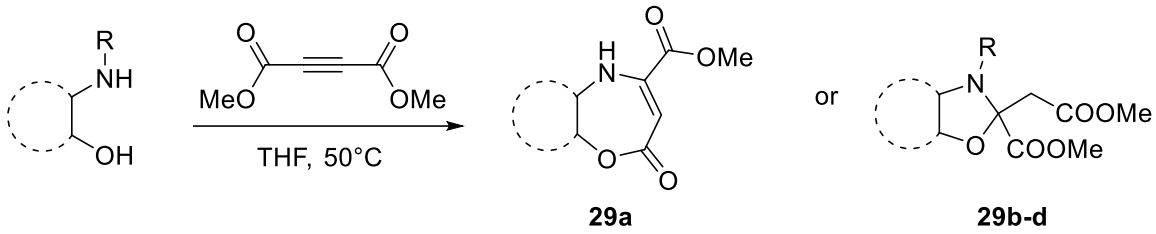


^{1}H-NMR (500MHz, $CDCl_3$): 7.35-7.31 (m, 2H), 7.26-7.21 (m, 3H), 3.88 (ddt, *J* = 8.39, 6.16, 1.91 Hz, 1H), 3.25-3.19 (m, 2H), 3.17-3.13 (m, 2H), 2.67 (dddd, *J* = 15.7, 8.8, 4.9, 2.1 Hz, 1H), 2.56 (dddd, *J* = 15, 8.8, 6.1, 1.8 Hz, 1H), 2.48-2.41 (m, 1H), 1.87 (ddt, *J* = 12.4, 8.9, 6.0 Hz, 1H).

The analytical data are in agreement with the ones reported in literature. [61]

Chapter 5.1_ *Synthesis of oxazolidine derivatives*

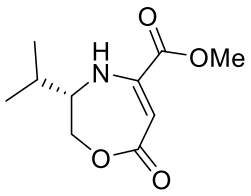
General procedure for the cyclization reaction to afford compound (**29a-d**)



29a **29b-d**

To a solution of the appropriate substrate (1.0 mmol) in THF (4 ml), acetylene dicarboxylate (1.0 mmol) was added, and the reaction was stirred at 50°C for 48h. The solvent was then removed under reduced pressure, the crude reaction was diluted with H_2O (30 ml) and extracted with EtOAc (3 x 20 ml). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

Methyl (*S*)-3-isopropyl-7-oxo-2,3,4,7-tetrahydro-1,4-oxazepine-5-carboxylate (**29a**)

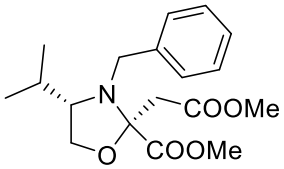


Compound **29a** was prepared according to general procedure starting from substrate *L*-valinol (103 mg) and isolated without further purification as orange oil (quantitative conversion).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (s, 1H), 5.60 (s, 1H), 4.45 (ddd, *J* = 11.2, 3.4, 1.3 Hz, 1H), 4.31 (dd, *J* = 11.2, 7.7 Hz, 1H), 3.69 (s, 3H), 3.27 (ddd, *J* = 7.5, 6.7, 2.9 Hz, 1H), 1.91 – 1.78 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 160.4, 144.2, 89.4, 69.6, 53.9, 50.9, 29.8, 18.7, 18.5.

Methyl (2*R*,4*S*)-3-benzyl-4-isopropyl-2-(2-methoxy-2-oxoethyl)oxazolidine-2-carboxylate (**29b**)

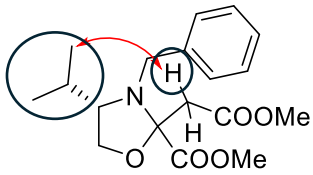


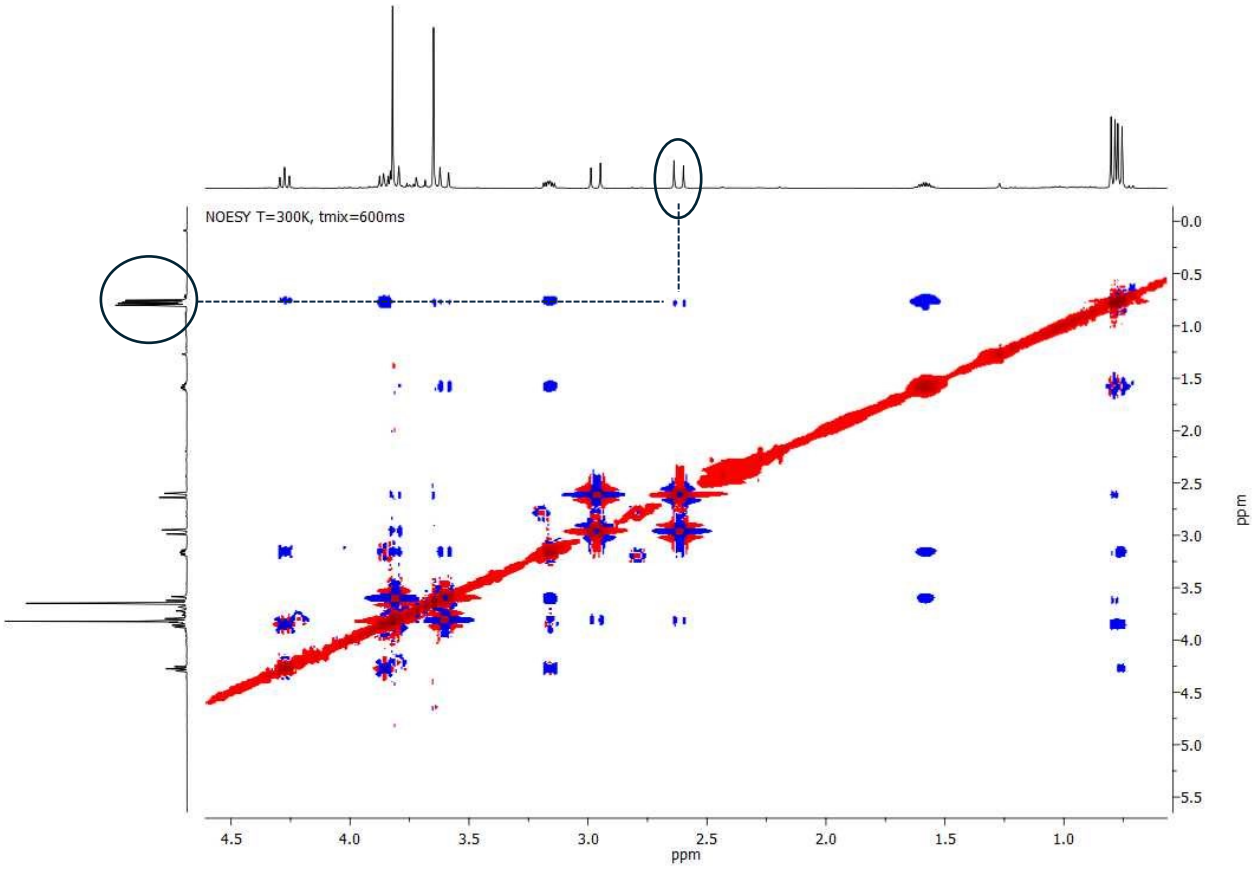
Compound **29b** was prepared according to general procedure starting from substrate **11a** (193 mg) and isolated without purification as pale-yellow oil (quantitative conversion).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.24 (m, 5H), 4.28 (t, *J* = 8.0 Hz, 1H), 3.88-3.86 (m, 1H), 3.84-3.80 (m, 4H), 3.66 (s, 3H), 3.61 (d, *J* = 14.4 Hz, 1H), 3.20-3.13 (m, 1H), 2.98 (d, *J* = 16.0 Hz, 1H), 2.63 (d, *J* = 16.0 Hz, 1H), 1.62-1.53 (m, 1H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H).

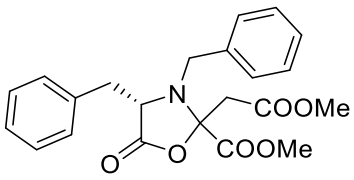
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.7, 170.0, 138.9, 128.6, 128.2, 127.2, 96.4, 67.3, 67.1, 52.8, 51.7, 51.6, 51.9, 28.2, 18.8, 14.4.

^{1}H NOESY experiment:





Methyl (4S)-3,4-dibenzyl-2-(methoxy-2-oxoethy)-5-oxooxazolidine-2-carboxylate (**29c**)

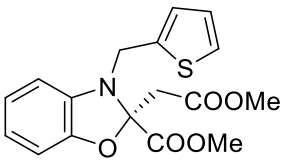


Compound **29c** was prepared according to general procedure starting from *N*-benzyl-*L*-phenylalanine (255 mg) and isolated through flash chromatography (hex:EtOAc 8:2) as white solid (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.32 (m, 3H), 7.28-7.22 (m, 5H), 7.18-7.11 (m, 2H), 3.90-3.82 (m, 4H), 3.76-3.71 (m, 1H), 3.66 (d, *J* = 14.1 Hz, 1H), 3.62 (s, 3H), 3.01-2.86 (m, 3H), 2.46 (d, *J* = 16.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 168.3, 167.5, 136.6, 136.2, 129.7, 129.0, 128.6, 128.3, 128.1, 126.8, 94.2, 62.3, 52.9, 52.7, 51.9, 40.6, 37.2.

Methyl (*R*)-2-(2-methoxy-2-oxoethyl)-3-(thiophen-2-ylmethyl)-2,3-dihydrobenzo[*d*]oxazole-2-carboxylate (**29d**)



Compound **29d** was prepared according to general procedure starting from substrate **6o** (205 mg) and isolated without purification as black oil (quantitative conversion).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.28 (m, 1H), 7.14-7.13 (m, 1H), 7.00 (d, *J* = 4.9 Hz, 1H), 6.80-6.60 (m, 3H), 6.25 (d, *J* = 7.3 Hz, 1H), 4.44 (s, 2H), 3.75 (s, 3H), 3.66 (s, 3H), 3.35 (d, *J* = 16.2 Hz, 1H), 3.06 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): 168.9, 167.7, 148.6, 138.3, 137.4, 126.7, 126.4, 121.8, 121.7, 119.0, 107.8, 106.8, 98.7, 52.8, 51.9, 43.9, 40.4.

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