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# Isoxazolidines and oxazines: Preliminary studies for the synthesis of N,O-heterocyclic systems *via* an organocatalyzed 1,3-Dipolar Cycloaddiction and a tandem reaction mediated by TEMPO salts

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Never let defeat by the evidence that life puts in front of us.
Give and receive love, suffer, disappointment, know each other.
This is the life of those who choose to live, not only exist.
[the author]

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## 1. General introduction

Catalysis is the change in rate of a chemical reaction due to the participation of a substance called catalyst. Unlike other reagents that participate in the chemical reaction, a catalyst is not consumed by the reaction itself. Catalysts work by providing an (alternative) mechanism involving a different transition state and lower the activation energy.

The production of most industrially important chemicals involves catalysis. Similarly, most biochemically significant processes are catalyzed. Research into catalysis is a major field in applied science and involves many areas of chemistry, notably organometallic chemistry and materials science. Catalytic reactions are preferred in environmentally friendly green chemistry due to the reduced amount of waste generated, as opposed to stoichiometric reactions in which all reactants are consumed and more side products are formed.

If the target product is a single enantiomer of a chiral molecule it is crucial to obtain an enantiomerically pure product since the undesired enantiomer is considered a waste. This important consideration has led to the development of asymmetric synthesis. Asymmetric synthesis involves creation of one or more chiral centres from a prochiral raw material, using a chiral agent. Nowadays, the synthesis of enantiopure organic molecules featuring important biological activity is crucial for pharmaceutical/medicinal and agrochemical applications.

There are three main approaches to achieve a chiral target in enantioenriched form. The first used and the easiest one is the chiral pool synthesis. This method consists in manipulating a chiral starting material using a reagent that does not change the chirality of the substrate during the reaction. The problems of this approach are the need of having a relatively cheap starting material available, such as aminoacids and sugars, and the requirement (often) of long and difficult reaction routes. This gives costs for the industry and restriction to the number of the possible reactions. The second approach involves the use of a chiral auxiliary which is temporarily incorporated in a starting substrate to allow an asymmetric transformation. However, this strategy has the same problem of protecting groups, because auxiliaries need two more steps in the process (the insertion and the removal). The last strategy is enantioselective catalysis, which means that an enantiomerically pure catalyst

interacts with the substrate leading to the formation of one of the possible enantiomers as major product.

Traditionally, catalysts belong to two main categories: transition metal complexes and enzymes.

In the first case, the catalyst consists in a metal complexed with an enantiomerically pure organic ligand. The loading of the catalyst is usually relatively low but many transition metals are extremely sensitive to air. This means that the catalyst has to be treated carefully in an oxygen-free atmosphere, in extra-dry solvent and stored in glove box. They are also costly and toxic which means high cost of purification to avoid metal contamination in the product, important especially in the medicine field.

Enzymes catalyze reactions with high selectivity, having the proteins a weel-defined active site with a particular shape, that depends on the tertiary structure of the protein. Enzymes feature lots of advantages: first of all they are not toxic and not so problematic like transition metals; then, they are used under mild conditions; finally they can be fixed on a support for a better separation from the reaction mixture and for being easily recycled. The drawbacks are the often narrow scope of enzymatic reactions, the elevated cost of the isolation of the correct enzyme and the low number of catalytic cycles (compared with organometallic catalysis).

Recently, a third approach to asymmetric catalysis has emerged: organocatalysis,[1] that is the employment of a low molecular weight organic molecule as catalyst. This strategy combines the major advantages of these two categories: absence of transition metal and stability of the catalyst. There are some advantages in using an organocatalyst: first of all the catalyst is strictly “organic”; that means that it is composed by carbon, hydrogen and other non-metallic atoms and thus it does not contain toxic transition metals; organic catalysts are normally robust as they are not easily oxidized by air and show resistance to water, so that they can be stored for a relatively long time; they do not require troublesome work up procedures. For these reasons, they are becoming increasingly interesting for pharmaceutical processes, or in general for the preparation of compounds that do not tolerate metal contamination. As it is showed in Figure 1, the number of publications on the topic organocatalysis has increased considerably since 2000.[2] Unfortunately, there are also some drawbacks. Normally, the loading of the catalyst is higher than in organometallic catalysis,

with a typical substrate/catalyst ratio of 100/1. This particular aspect prevents the easy scale-up and the possible use in industrial settings.

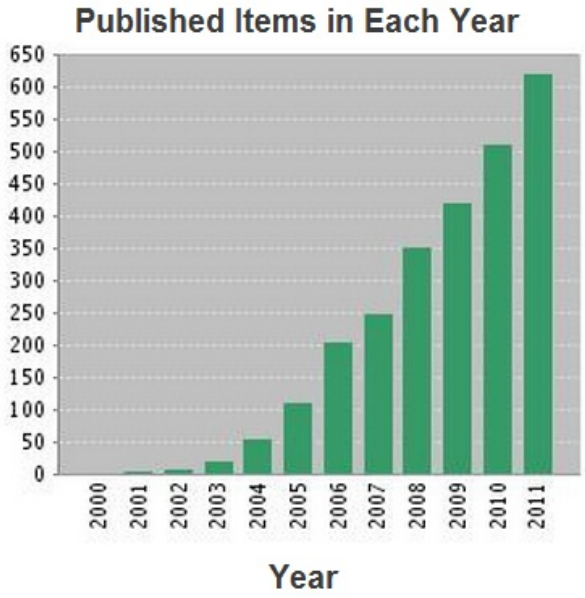



**Figure 1:** Data were obtained by a search on ISI Web of Knowledge in September 2012

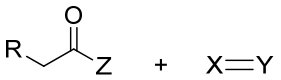
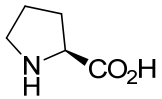
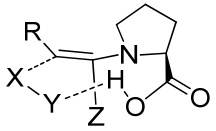
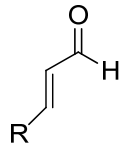
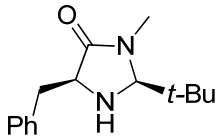
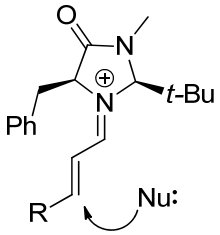
It is possible to classify organocatalysts into three categories: [3]

- Covalent catalysts
- Non-covalent catalysts
- Phase-transfer catalysts

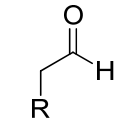
The main difference between the first two types is the strength of the interactions between the catalyst and the prochiral substrate: a covalent catalyst creates an activated intermediate involving a strong (covalent) interaction between catalyst and substrate. In the other case the interaction is weaker since is based on weak (non-covalent) interactions such as hydrogen bonds and electrostatics.

These three categories of catalysts encompass the most common modes in which organic catalysts activate the substrates, as summarized in Table 1.

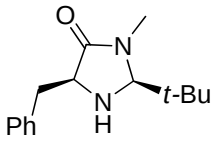
**Table 1**

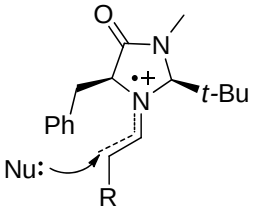
| Substrate | Catalyst | Activation mode | Examples of reaction variants |
|---|---|---|---|
| **Enamine catalysis** | | | |
|  R = any organic chain or ring sistem<br>Z = Alkyl, H<br>X = C, N, O, S<br>Y = generic atom |  |  | • Aldehyde-aldehyde cross aldol coupling<br>• Intramolecular α-alkylation<br>• Mannich reaction<br>• Michael reaction<br>• α-Amination<br>• α-Oxigenation<br>• α-Halogenation |
| **Iminium catalysis** | | | |
|  R = Alkyl, aryl |  |  | • Conjugate Friedel-Crafts reaction<br>• Diels-Alder reaction<br>• Dipolar cycloaddition<br>• Mukaiyama-Michael reaction |

**SOMO catalysis**




R = Alkyl, Aryl



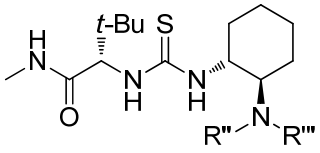



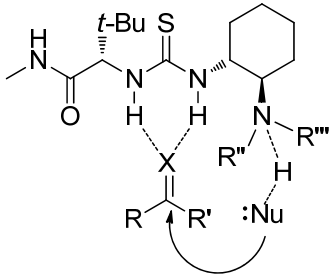

- α-Allylation
- α-Enolation
- α-Vinylation
- α-Heteroarylation

**Hydrogen-bonding catalysis**


R,R',R'',R''' = Alkyl, Aryl

X = O, NR



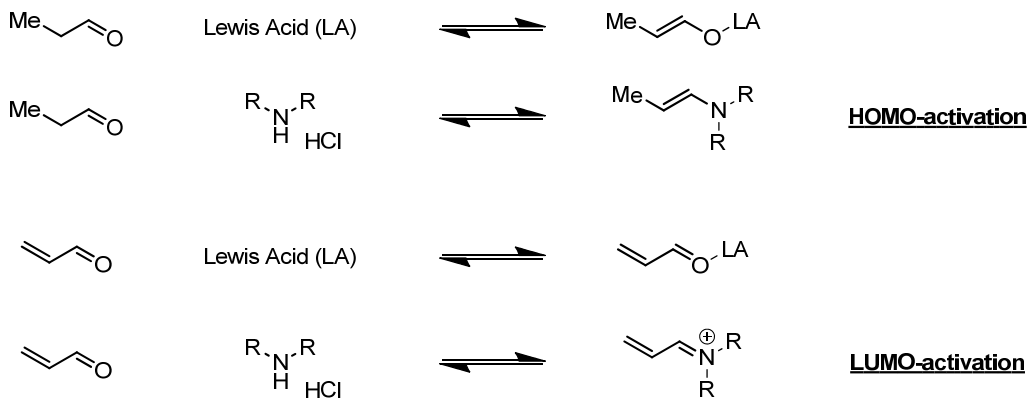

- Strecker reaction
- Mannich reaction
- Biginelli reaction
- Pictet-Spengler reaction

*Enamine Catalysis*

The first example of enamine catalysis appeared in 1971[4] and described the enantioselective intramolecular synthesis of the Wieland-Miescher ketone catalyzed by L-proline. At that time the mode of action of this catalyst was not clearly understood. Nowadays, it is known that primary and secondary amines typically form enamines with ketones or aldehydes. The formation of this reversible intermediate activates the *α*-carbon of the starting substrate for reaction with electrophiles (Scheme 1). L-proline, many of its derivatives and other α-amino acids can perform this kind of activation.

*Iminium Ion Catalysis*

Iminium catalysis was the first organocatalytic activation mode to be designed (rather than discovered) and introduced as a general strategy for asymmetric organic synthesis.[3] The idea was to emulate the dynamic equilibrium and the π orbital electronics that are involved in Lewis acid catalysis, with the reversible formation of iminium ions from α,β–unsaturated aldehydes and chiral amines. In this case the activation concerns the lowest unoccupied molecular orbital (LUMO) which is lowered, instead of the enamine catalysis where the activation consists in raising the higher occupied molecular orbital (HOMO)[5] as showed in the following Scheme.




**Scheme 1**: Enamine and iminium ion catalysis.

*SOMO catalysis*

The SOMO catalysis is a system that MacMillan's group introduced in 2006 based on the idea that using a "one-electron" oxidation on an electron-rich enamine complex, it is possible to generate a reactive radical cation with three π-electrons. This species has a singly occupied molecular orbital (SOMO) and its electrophilicity allowed it to react with a large group of weakly nucleophilic substrates, incompatible with the previous methods, leading to asymmetric α-functionalizations of carbonyl-containing compounds. SOMO activation offers a general mode of aldehyde activation. A prominent example is given by the α-alkylation of aldehydes which has traditionally being extremely challenging.

*Hydrogen Bond Catalysis*

Hydrogen bonding is the strongest interaction with which two or more molecules can interact each other. This kind of catalysis is based on well-defined hydrogen-bonding interactions able to stabilize the transition state of the reactions.[6]

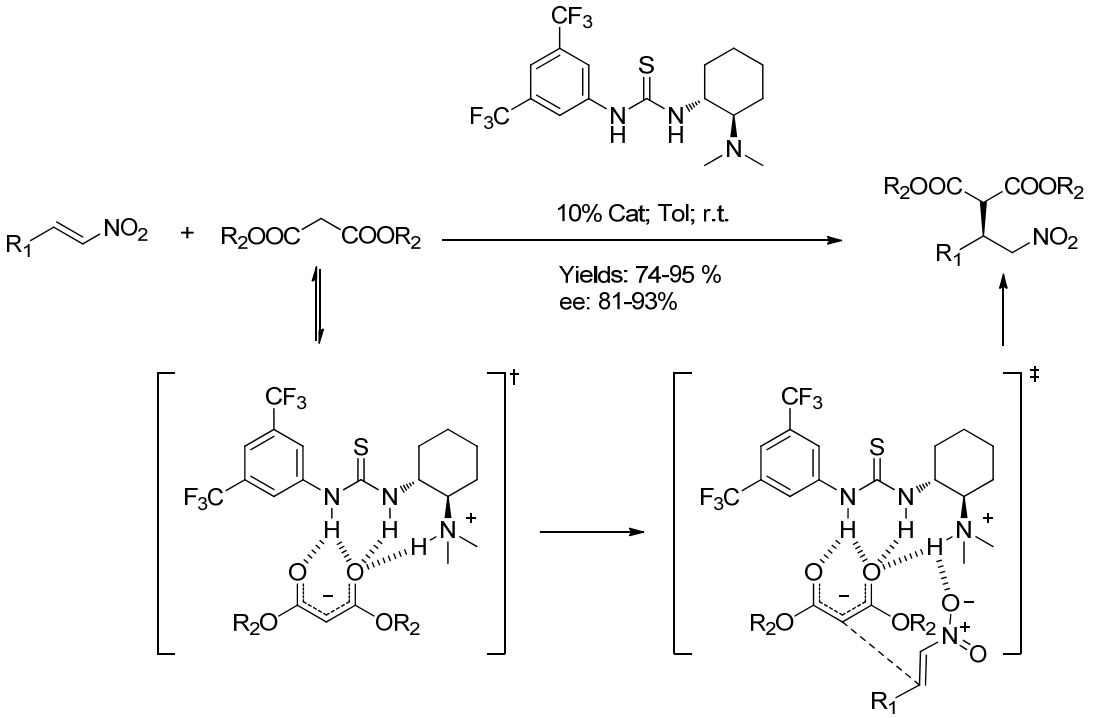
The use of this force in a catalytic processes started in the 1980's when it was discovered that the activated substrate and the relative transition state might be stabilized by a hydrogen bond system. The first researchers that unambiguously demonstrated the powerfulness of this approach were Jacobsen[7] and Corey[8] that proposed respectively in 1998 and in 1999 an asymmetric variant of a Strecker reaction activating an imine electrophile. The major examples of this category of catalyst are thioureas and many derivatives of *Cinchona*, natural substances that can be extracted from the bark of *cinchona ledgeriana*, a tropical plant.

The thiourea derivatives are able to enhance the electrophilicity of the substrate while the nucleophile can be activated through a different hydrogen bond. The enantioselection is given in the transition state by this highly ordered network of weak interactions that are essential for the generation of a geometrically defined transition state complex involving the catalyst coordinating both reagents.

During the development of the different areas previously illustrated, the important concept of *bifunctional catalysis* emerged.[9] This concept regards the capability of many

catalysts in using different kinds of activation in a cooperative way, in order to achieve a highly ordered transition state in the reaction.

Albeit many catalysts can be considered bifunctional, the thiourea moiety, associated with different groups, resulted one of the most common and versatile motif developed in this field. For example Takemoto[10] and co-workers developed the catalyst in the following scheme for the addition of malonates to nitroolefins (Scheme 2Errore. L'origine riferimento non è stata trovata.).




**Scheme 2:** Addition of malonates to nitroolefins catalyzed by bifunctional thioureas.

In this case the tertiary amine can deprotonate the malonate with the assistance of the thiourea moiety (soft-enolisation). The nitro group is then activated by the thiourea favouring the nucleophilic attack on the nitroolefin. It is also very important to underline how double hydrogen bond donors, such as thiourea derivatives, can "recognize" nitro compounds using non-covalent interactions.[11] Soft-enolisation of nitroalkanes promoted by bifunctional catalysts leads in fact to well-defined nitronate-catalyst assemblies, wherein electrostatics reinforce the coordination given by the network of hydrogen bonds (Figure 2).[12]

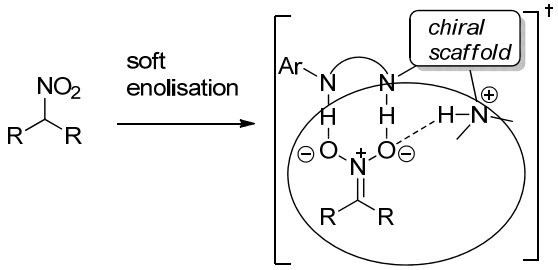



**Figure 2:** Example of soft enolisation

Another remarkable example of bifunctional catalysis was introduced by Ricci and co-workers when they developed the Friedel-Crafts alkylation of indoles with nitroalkenes with a *cis*-1,2-aminoindanol derived thiourea catalyst.[13] Figure 3 represent the proposed transition state of the reaction, in which the catalyst can direct the reaction path with the cooperative interaction of the two active sites of the catalyst with both substrates.

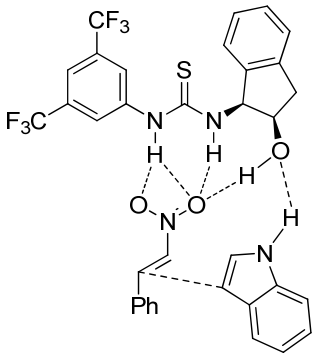


**Figure 3:** Proposed transition state

*Phase Transfer Catalysis*

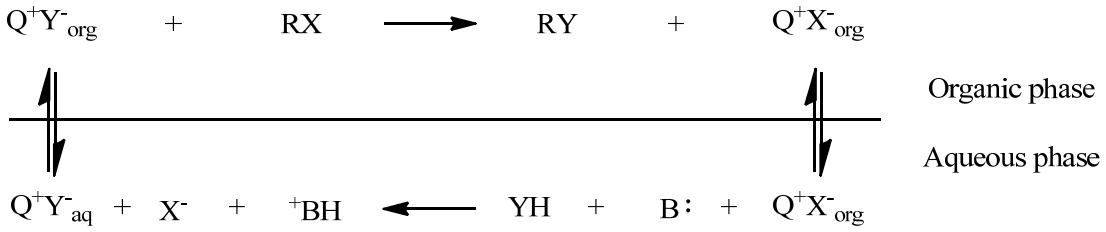
Phase-transfer catalysis is a completely different approach, developed to give a cheap solution to problems connected with the mutual unsolubility of the reagents and low reactivity of the anions. Before the PTC (phase-transfer catalysis) discovery, the solution to these problems was the employment of a solvent miscible with both the organic and the aqueous phases, such as ethanol, but the rate of acceleration was minimal. Alternatively, apolar aprotic solvent like *N,N*-dimethyl formamide (DMF) or dimethyl sulfoxide (DMSO) can be used but they are expensive and difficult to separate

from the final product due to their high boiling point. The discovery of PTC had a significant impact on the industrial development in the last quarter of the last century. It allows to achieve a group of reactions transporting one of the reagent in a phase where normally it is not soluble. The main steps of a typical phase-transfer catalysed reaction can be considered three (Scheme 3):

The deprotonation of the active compound, mediated by a base, is necessary if an anionic nucleophile (e.g. KCN) is not used, and it depends from the reaction condition (pH, pKa, etc…).

The quaternary salt (often represented with $Q^+$ or *quat*) using the equilibrium of solubility in the two phases, extracts the anion into the organic phase thanks to its lipophilicity.

Now the lipophilic ion-pair can react in the organic phase with the electrophilic reagent (RX), being both in the same layer; after the reaction has occurred there is another ion exchange, the quaternary ammonium salt is regenerated and, using again the equilibrium of solubility between the phases, returns in the aqueous phase, closing in this way the catalytic cycle.

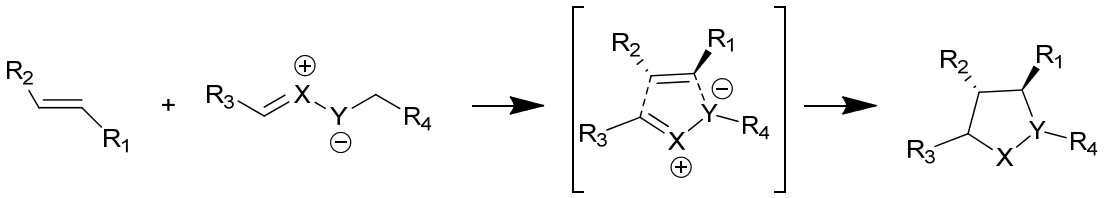



**Scheme 3**: General scheme of PTC

## 2. Organocatalyzed asymmetric [3 + 2]-dipolar cycloadditions with nitrones

### 2.1 Introduction

The 1,3-dipolar cycloaddition (1,3-DC),[14] also known as Huisgen cycloaddition[15], can be considered a classic transformation in organic chemistry[16] and consists of the reaction between a dipolarophile and a 1,3-dipolar compound that allows the synthesis of various five membered heterocycles (Scheme 4).



**Scheme 4:** general scheme of (1,3-DC)

An important feature of this type of reaction is its versatility, since dipolarophiles may be alkenes, alkynes and even other molecules with heteroatomic functional groups such as carbonyls and nitriles. Basically, the dipoles can be divided into two categories (Figure 4):

- Allyl anion type such as nitrones, azomethine ylides, nitro compound or carbonyl ylides and carbonyl imines bearing respectively a nitrogen or an oxygen atom at the central position of the dipole;
- Linear propargyl/allenyl anion type such as nitrile oxides, nitriles ylides or azides;

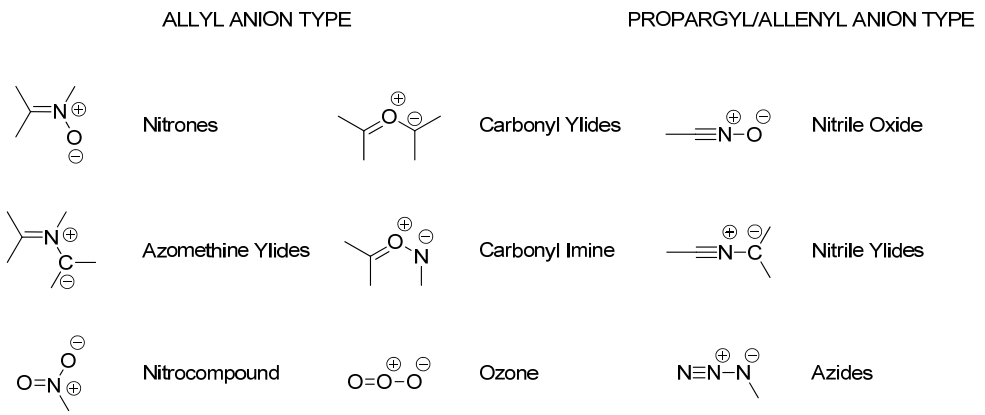



**Figure 4:** Principal classes of dipoles

In order to simplify the analysis, it is better to define the dipole as an **a-b-c** structure (Figure 5).

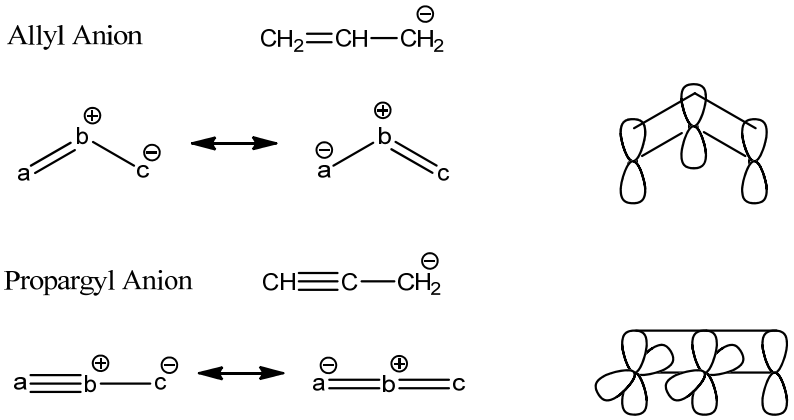



**Figure 5:** Dipoles as a-b-c structures

The allyl anion is characterized by four electrons in three parallel $p_z$ orbitals which are perpendicular to the dipole plane and to the plane that the dipole is bent. With this conformation, it is possible to draw two structures in which all the three atoms have an electron octet, and two resonances in which **a** or **c** has an electron sextet. The propargyl/allenyl anion type has another π orbital, which is orthogonal to the MO but it is not involved in the resonance and in the reaction. For these reasons the molecule is linear and the central atom is limited to the nitrogen. The 1,3-DC reaction involves 4π electrons from the dipole and 2π electrons from the alkene, so the 3 $p_z$ orbitals of the dipole and the 2 $p_z$ orbitals of the alkene are combined. About the mechanism there has been a long discussion because even if Huisgen collected a lot of data demonstrating the concerted mechanism, Firestone demonstrated with experimental facts that this reaction can proceed via a singlet diradical intermediate, thus stepwise. On the basis of the stereospecificity of the 1,3-DC reaction, the dispute was finally settled in favor of the concerted mechanism: for example the reaction between an aryl-nitrile oxide and a *trans*-dideuterated ethylene gave only the trans-isoxazoline, as predicted by a concerted mechanism. Considering the diradical mechanism that allowed the 180° rotation of the last bond, it would have been reasonable to expect a mixture of the two isomers. However, Huisgen demonstrated also that in some cases the 1,3-DC can take place in a

stepwise fashion, involving an intermediate which then cyclises to the final product. As a consequence, the stereospecificity of these reactions might be lost.

The transition state of the concerted 1,3-DC reaction is controlled by the frontier molecular orbital (FMO), i.e. by the interactions HOMO-LUMO of the reagents. As it is showed in Figure 6, it is possible to identify three types of reaction: in the first type the dominant interaction is between the $HOMO_{dipole}$ and $LUMO_{alkene}$ (direct-electron-demand), in the second one the FMO of the dipole and the alkene are similar and in this case there is not any predominant interaction and both HOMO-LUMO are important; in the last type of 1,3-DC reaction the dominant interaction is between the $LUMO_{dipole}$ and $HOMO_{alkene}$ (inverse-electron-demand).

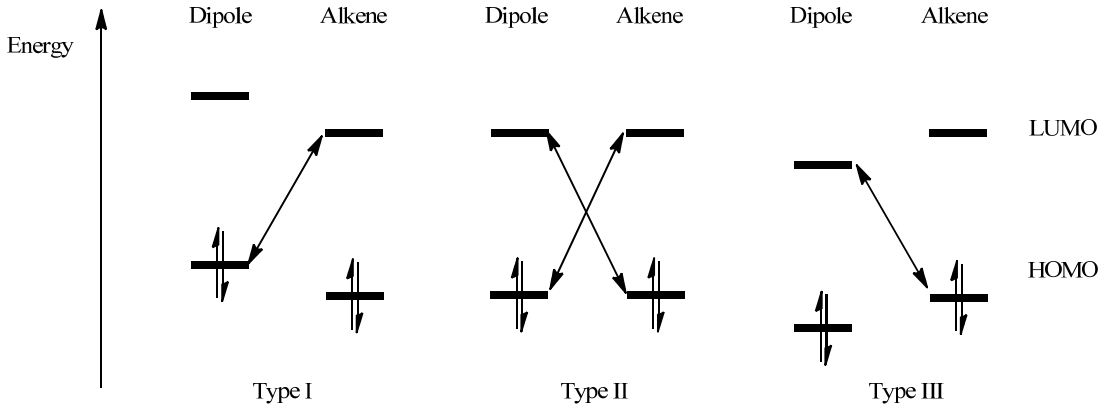



**Figure 6:** Different electron-demand in1,3-DC.

Metals, such as Lewis acids, can alter the energies of the orbitals. The coordination of a LA may influence in fact the energy of the reacting system lowering the energy of the LUMO. However, this coordination may give substantial effects also on the regioselectivity of the reaction, by changing the orbital coefficients of the reacting atoms in both the 1,3-dipole and the alkene. Ultimately, a ligand-metal complex can control the reaction in terms of regio-, diastereo- and enantioselectivity.

The 1,3-dipolar cycloaddition reaction of nitrones with dipolarophiles such as alkenes play an important role in the history of cycloaddition reactions and has received increasing attention in asymmetric synthesis over the past 20 years.[14] Regio- and stereoselective nitrone cycloaddition, followed by reduction of the N–O bond to

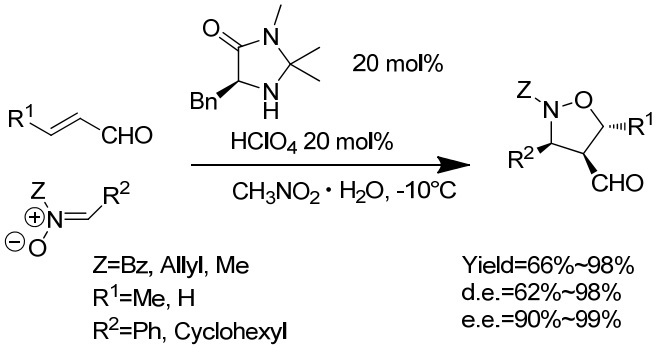
produce both an amino and a hydroxyl function, allows the synthesis of many products of potential interest.

One of the reasons for the success of the synthetic applications of nitrones is that, contrary to the majority of the other 1,3-dipoles, most nitrones are stable compounds that do not require an in situ formation.

Another synthetic utility of this reaction is the variety of attractive nitrogenated compounds, which are available from the thus-formed isoxazolidines. In particular, these products can be easily reduced under mild conditions to give the corresponding chiral 1,3-aminoalcohols. Moreover, isoxazolidines are an important target for industries because they can be readily converted in biologically important amino acids, γ-amino alcohols and other nitrogen containing compounds.[17]

The majority of the 1,3-dipolar cycloaddition reactions are diastereoselective and involve chiral alkenes[21] or chiral nitrones,[18] among which are also intramolecular versions. In addition, the catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones has gone through rapid developments during the last 12 years.[19]

The first example of organocatalyzed 1,3-DC was reported in 2000 by MacMillan[20] and co-workers; they showed that chiral imidazolidinone catalyst can activate the double bond of enals via iminium activation promoting in this way the reaction with nitrones (Scheme 5).




**Scheme 5:** the first organocatalytic 1,3-DC with nitrones.

In the following years several examples of organocatalyzed 1,3-DC have been published[21] using L-proline derivatives,[22] thiourea derivatives,[23] *N*-triflylphosphoramide[24] and a *Chincona*-alkaloid derived salt[25] (Figure 7) leading to the

corresponding cycloadducts in good or excellent enantioselectivity. Except the reaction involving the L-proline derivative, whuch proceeds through a mechanism similar to MacMillan's report (Scheme 5), all other examples deal with inverse-electron-demand 1,3-DC, i.e. the nitrone behaves as electrophilic reaction partner.

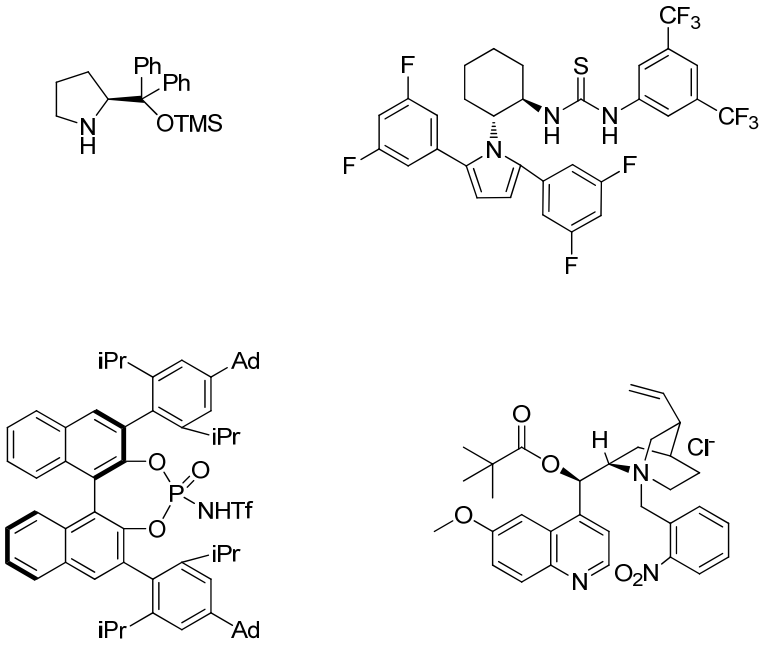


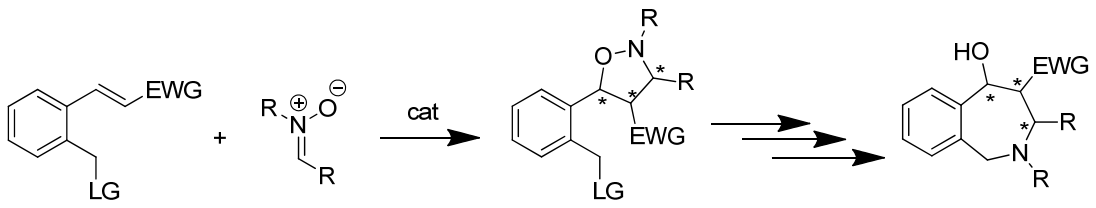

**Figure7:** organocatalysts used in 1,3-DC

## 2.2 Objective

Five-member ring heterocycles and their enantioselective synthesis is a hot research topic, since a large variety of molecules exhibiting biological activity has this motif in their structure.

This thesis is part of a wider research project, aiming at the achievement of an enantioselective synthesis of 2-benzoazepines with an hydroxyl group at the 5 position. This class of compounds is biologically interesting especially for their interactions with the central nervous system.[26] Some derivatives of this class show also a good bronchodilator activity, they can accelerate the wound healing of the skin and they can be used for curing some digestion disorders.[27]

As it is possible to see in the following scheme, the starting point of the planned synthetic sequence was an enantioselective direct-electron-demand [3+2]-DC between activated double bond derivatives and nitrones using an organocatalytic approach.

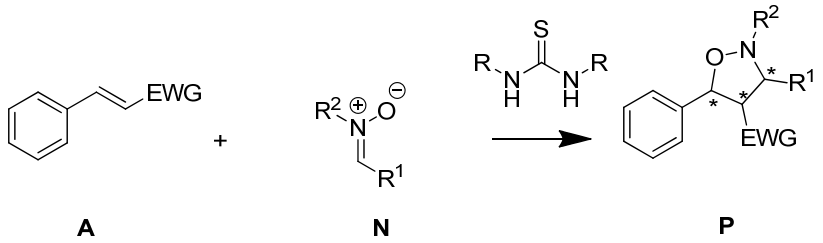



**Scheme 6**: planned sequence leading to 2-benzoazepines bearing a hydroxyl group at the 5-position.

Reported organocatalytic enantioselective direct-electron-demand (1,3)-DC with nitrones involve iminium-type activation of enals in all cases. However, all of these reactions are restricted to aliphatic enals, with cinnamoyl derivatives not showing any reactivity. Thus, as these protocols cannot be employed for the preparation of the target intermediate, we aimed in the first part of this thesis at developing an alternative organocatalytic strategy for the preparation of this intermediates.

In particular, we turned our attention towards a different type of substrate activation, that is the coordination of the carbonyl moiety of the cinnamoyl derivative with a hydrogen bond donor, able in principle to lower its LUMO energy and promoting the direct-electron-demand (1,3)-DC.

The objective of this part of the thesis was thus to evaluate the correctness of these assumptions, by studying the 1,3-dipolar cycloaddition reaction of various cinnamoyl derivatives with nitrones in the presence of achiral double hydrogen bond donors, such as thiourea derivatives, as catalysts (Scheme 7).




**Scheme 7**: objective of the first part

Once demonstrated the feasibility of this type of activation, a further objective of this part of the thesis was to test chiral enantiopure thioureas in this reaction, in order to obtain enantioenriched cycloadducts..

## 2.3 Results and discussion

### 2.3.1 Synthesis of the dipolarophiles

To study the feasibility of the planned dipolar cycloaddition, it was thought to use the series of a cinnamoyl derivative reported in Figure 8: some of them (**A1**, **A4**, **A6**, **A7**) are commercially available whereas derivatives **A2**, **A3** and **A5** had to be synthetized following literature procedures, as described below and reported in detail in the experimental part.

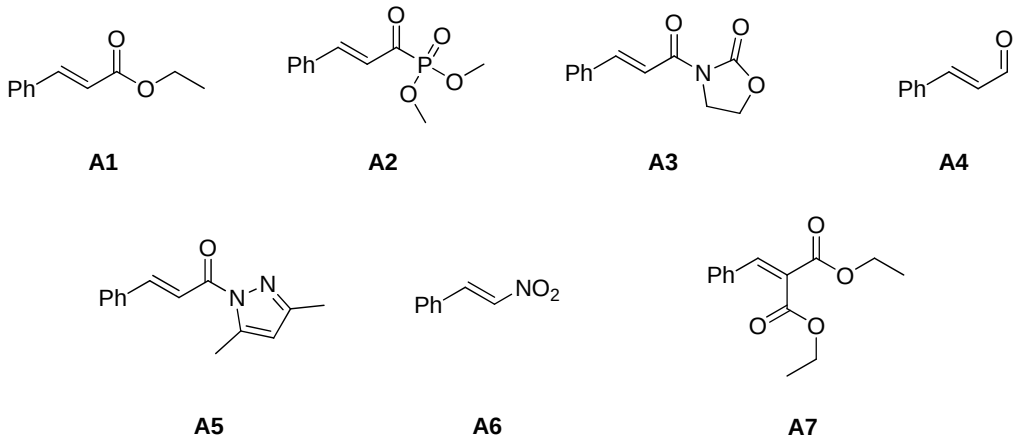
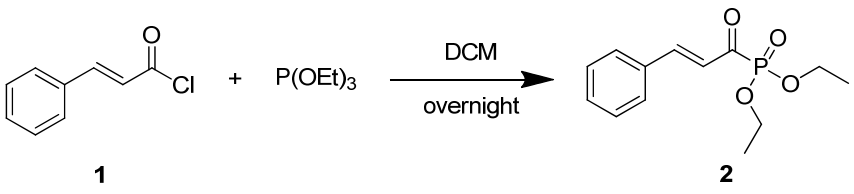


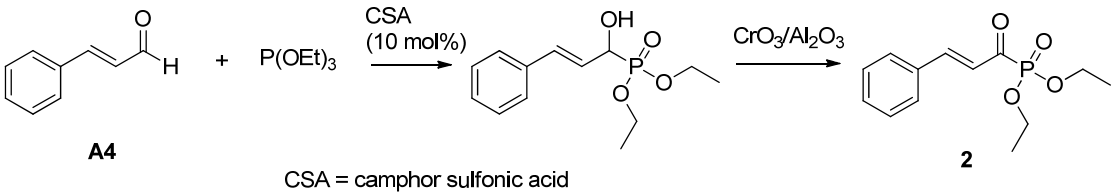

**Figure 8:** Cinnamoyl derivatives **A1-7** used as dipolarophiles.

The synthesis of **α-**ketophosphonates as dipolarophiles (**A2**) was particularly tricky. The first approach was to use an acceptor with two ethoxy group (**2**) that can be obtained by the Arbuzov reaction of cinnamoyl chloride **1** and triethyl phosphate (Scheme 8). Unfortunately, we were not able to repeat the reported synthetic procedure[28] and to obtain an adequately pure product.



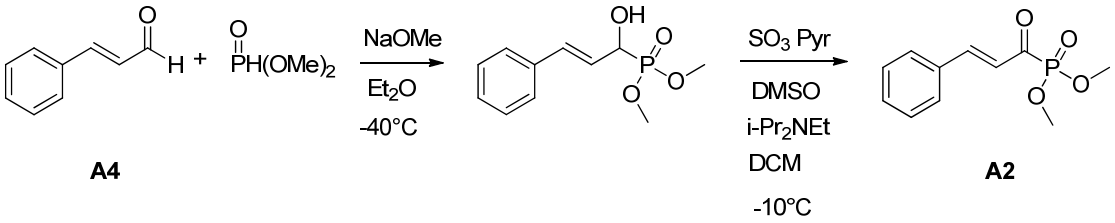

**Scheme 8:** Attempted synthesis of diethyl cinnamoylphosphonate **2**.

For this reason, we looked for an alternative procedure in the literature. We found another strategy to achieve the target substrate *via* the corresponding hydroxyphosphonate, using as starting compound the cinnamaldehyde **A4** instead of the cinnamoyl chloride (Scheme 9). The experimental yield was however not very high (15 %).[29]



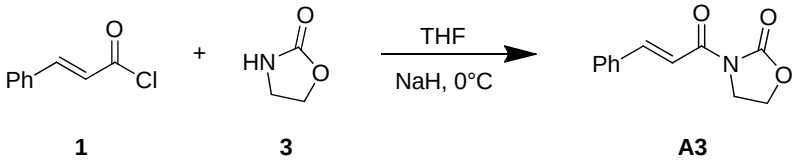

**Scheme 9:** Synthesis of diethyl cinnamoylphosphonate **2**.

So, we decided to vary the substrate structure, changing the ethyl esters to methyl, as this ester was reported to give a much better yield in a similar reaction sequence. It was assumed that this change would not affect too much the reactivity of the acceptor in the 1,3-DC. As sketched in Scheme 10, commercially available cinnamaldehyde **A4** was reacted with dimethyl phosphite. Oxidation of resultant allylic alcohol furnished the dienophile **A2** as a yellow oil in 78% overall yield (Scheme 10).[30]




**Scheme 10:** Synthesis of **A2**

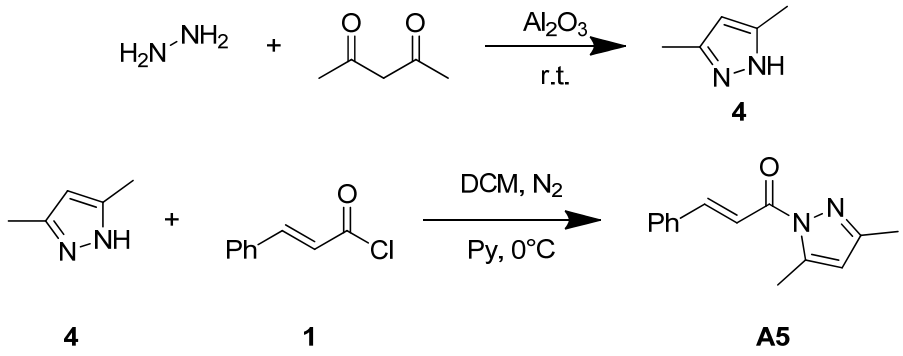
Next, we easily synthetized the oxazolidininone derivative **A3** from cinnamoyl chloride **1** and 2-oxazolidinone **3** using sodium hydride as the base (Scheme 11).[31] Chromatography of the crude reaction mixture (Hexane/EtOAc: 3/1), gave the pure product **A3** as a white solid in 92% yield.




**1** **3** **A3**

**Scheme 11:** Synthesis of **A3**

Dipholarophile **A5** was prepared in two steps (Scheme 12): first 2,4-dimethyl pirazole **4** was prepared by reaction of hydrazine with 2,4-pentanedione.[32] The obtained solid was used in the second step without further purification by reacting it with cinnamoyl chloride **1** and pyridine in DCM, to achieve **A5** after chromatography with Hexane/EtOAc: 25/1.[33]

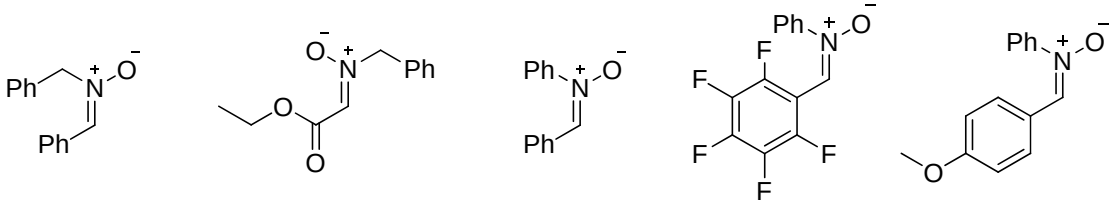



**4** **1** **A5**

**Scheme 12:** Synthesis of **A5**

### 2.3.2 Synthesis of nitrones

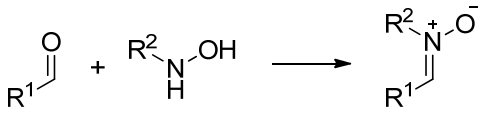
The nitrones chosen for this study are reported in Figure 9.



**N1** **N2** **N3** **N4** **N5**

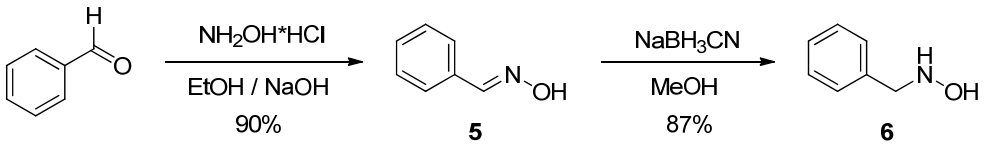
**Figure 9:** Dienophiles used (nitrones).

As far as the synthesis of the required nitrones is concerned, we followed the general procedures (Scheme 13) reported in the literature based on the condensation of an aldehyde with a hydroxylamine.[34]



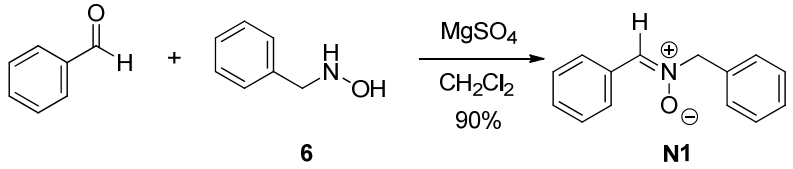
**Scheme 13:** General synthesis of nitrones.

*N*-Benzyl hydroxylamine **6**, necessary to prepare **N1** and **N2**, can be obtained by reaction of benzaldehyde and hydroxylamine hydrochloride, followed by reduction of the obtained benzaldehyde oxime **5** with sodium cyanoborohydride (Scheme 14).[34]



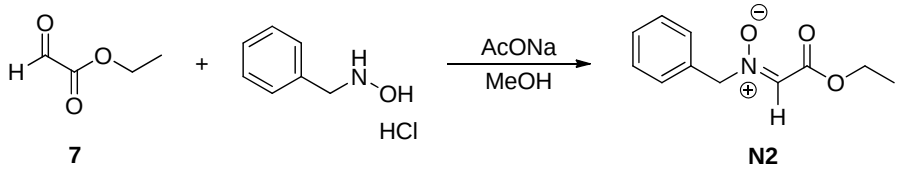

**Scheme 14:** Preparation of **6**

*N*-Benzyl nitrone **N1** was then obtained by condensation of benzaldehyde and *N*-benzyl hydroxylamine **6** in the presence of $MgSO_4$ (Scheme 15).[34]



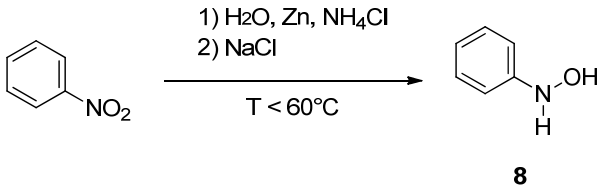

**Scheme 15:** Synthesis of **N1**

Nitrone **N2** was prepared by reaction of ethyl glyoxylate **7** with commercial *N*-benzyl hydroxylamine hydrochloride in acetate-buffered methanol solution in excellent yield (92%) (Scheme 16).[35]



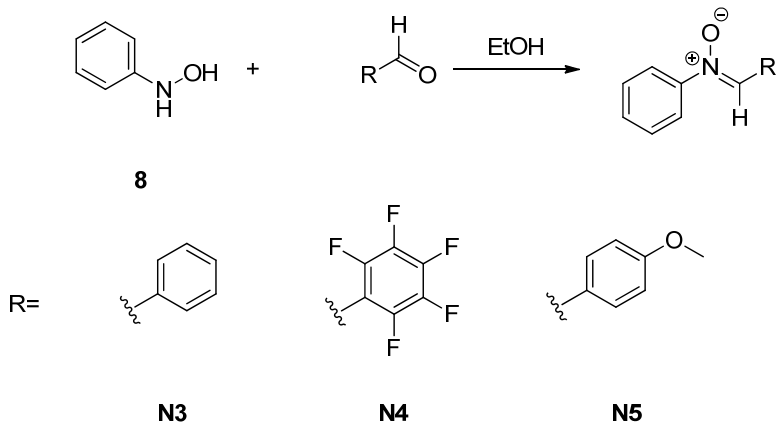

**Scheme 16:** Synthesis of **N2**

*N*-Phenyl hydroxylamine **8**, necessary to prepare **N3** was easily obtained by reduction of nitrobenzene with zinc dust (Scheme 17). This reaction was highly exothermic and for this reason the temperature was monitored during the slow addition of zinc dust and maintained below 60 °C by cooling the reaction flask with a water bath.[36]




**Scheme 17:** Synthesis of *N*-phenyl hydroxylamine **8**

*N*-Phenyl hydroxylamine **8** is very sensitive to light and for this reason was immediately reacted with 0.95 equivalent of benzaldehyde overnight to obtain **N3** in 85 % yield. The use of a small defect of the aldehyde is justified by the greater convenience in the purification of the final product. The same procedure was used for the preparation of nitrones **N4** and **N5** starting from pentafluorobenzaldehyde and 4-methoxybenzaldehyde (Scheme 18).




**Scheme 18:** Preparation of **N3-5**

### 2.3.3 Synthesis of the catalysts

As previously mentioned, we decided to test the possibility of activate the carbonyl moiety of the cinnamoyl derivative with a hydrogen bond donor, able to lower its LUMO energy and promoting the direct-electron-demand (1,3)-DC. Thus, we choose to evaluate thiourea derivatives since it is reported that this kind of organocatalyst are able to activate a large number of carbonyl compounds using this interaction.[11c]

All the catalyst that were tested in this screening are reported in Figure 10. Some of them are commercially available (**C2**, **C3**), some were already available in the laboratories where I did my research project. **C7** and **C8** were instead prepared.

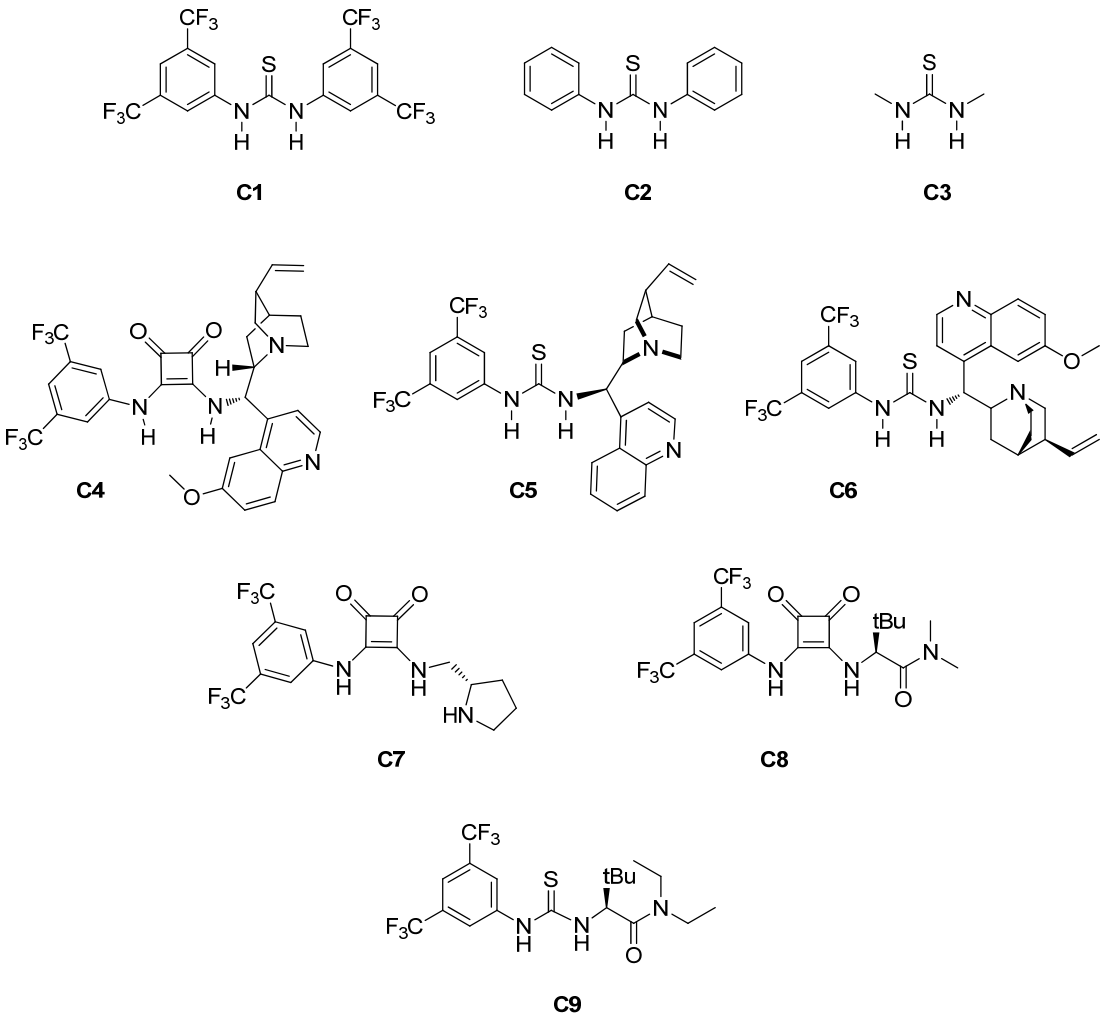
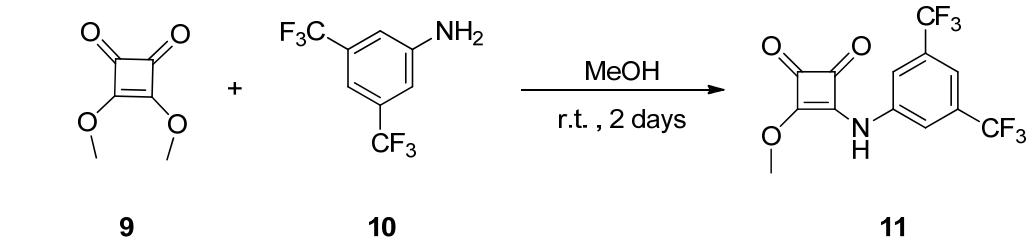



**Figure 10:** Catalysts employed in this study.

**C7** and **C8** have been prepared following the procedure reported in the experimental part. They are both squaramide derivatives and, as the thioures, have two H-bond donor (one more for **C7**) so they could interact with the substrate in the same way of thioureas. They are a little bit more twisted and we expected something different in terms of reactivity and enantiomeric excess.

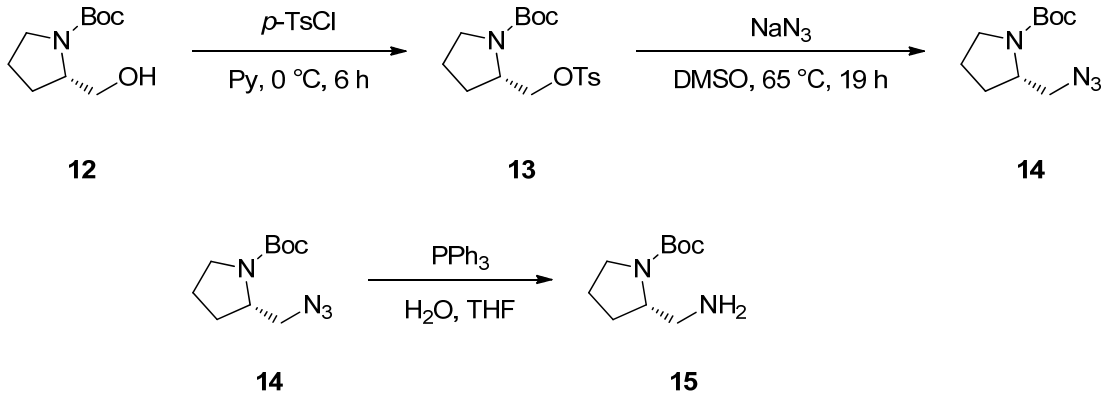
Both catalysts **C7** and **C8** have one synthetic intermediate in common (**11**), that has been prepared as shown in following scheme:




**9** **10** **11**

**Scheme 19:** Preparation of intermediate **11**.

The dimethoxycyclobutene-1,2-dione **9** (1 equivalent) was reacted with 3,5-bis(trifluoromethyl)aniline **10** (1.1 equivalent) in methanol and after two days of stirring, product **11** was recovered as a yellow solid after a simple vacuum filtration.[37]
To obtain catalyst **C7**, the *N*-Boc-protected (*S*)-prolinol **12** was tosylated, reacted with sodium azide giving the azide derivative **14**, that was reduced to the corresponding amine derivative **15** with triphenylphosphine (Scheme 20).

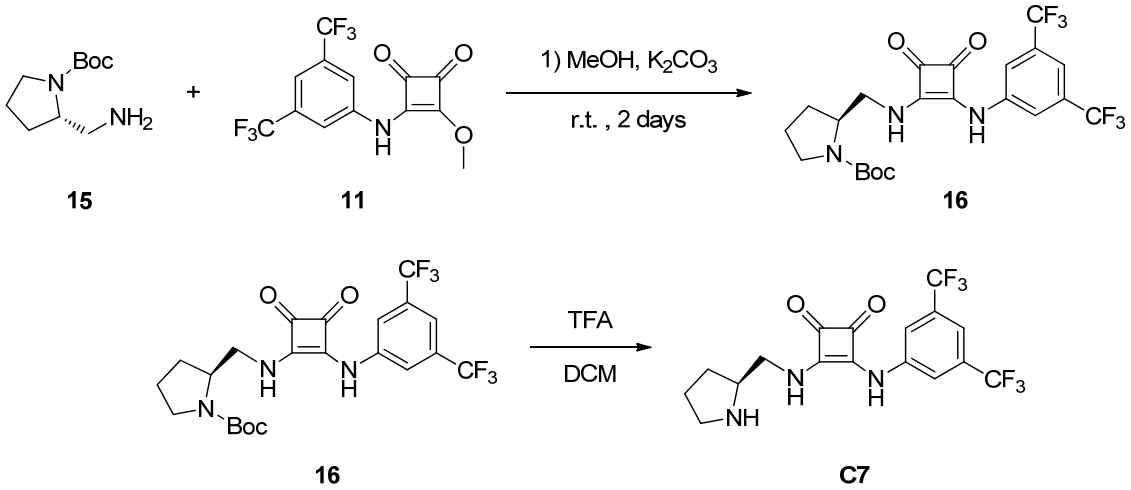



**12** **13** **14**

**14** **15**

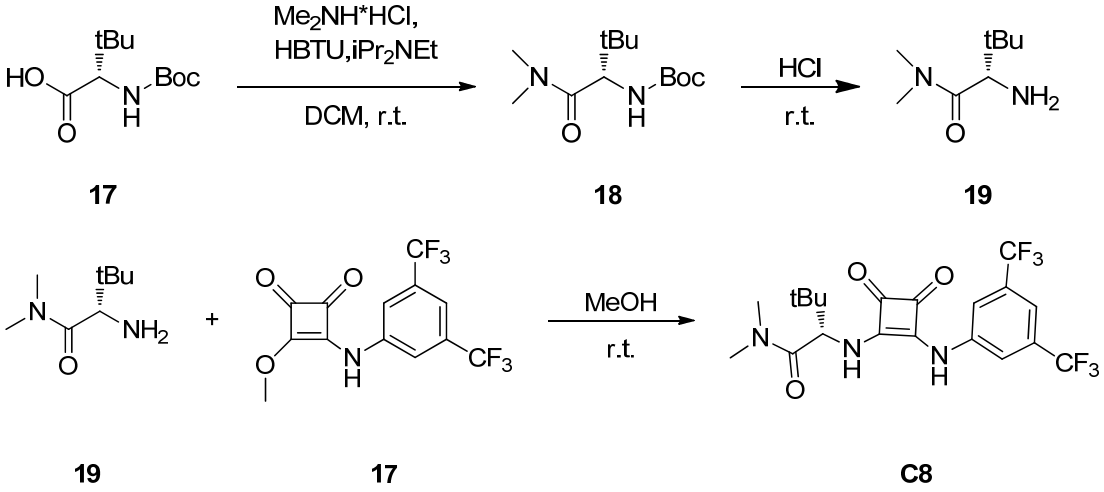
**Scheme 20:** Preparation of **15**.

Next (Scheme 21), the obtained amine **15** was reacted with **11** and the Boc-protecting group was removed under acidic conditions to achieve **C7**.[38]




**Scheme 21:** Preparation of **C7**.

In order to obtain **C8**, amide **19** was prepared starting from commercially available *N*-Boc-*L*-tert-leucine **17** (Scheme 22). The amino acid was transformed into the corresponding dimethylamide by reaction with dimethyl amine exploiting the *in situ* activation of HBTU (O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate) followed by deprotection of the Boc-group in acidic conditions. As in the previous case, amino derivative **19** was reacted with **17** to achieve **C8**.




**Scheme 22:** Synthesis of **C8**.

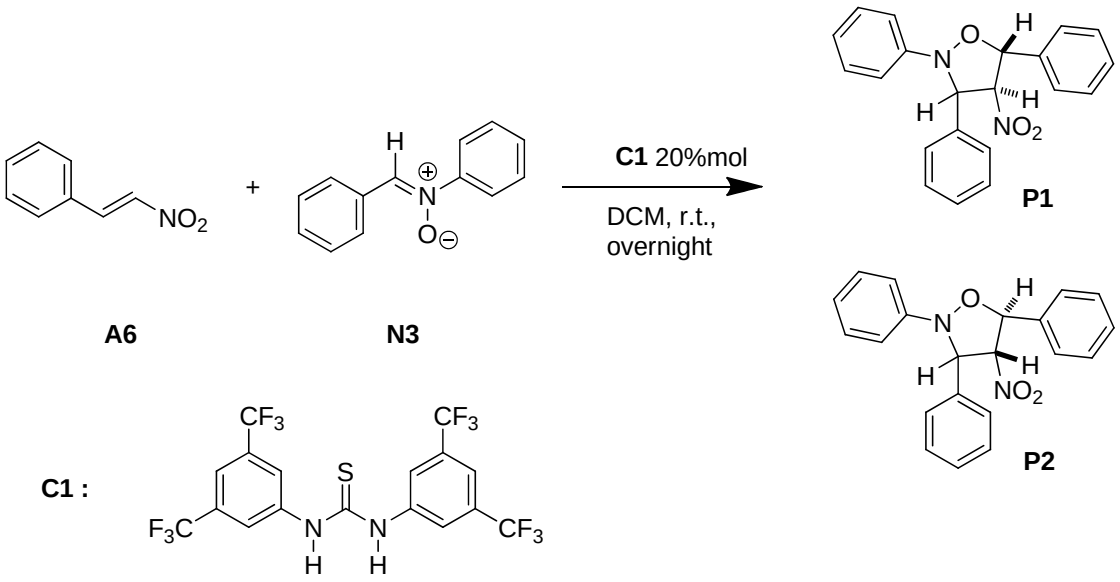
### 2.3.4 Screening in the organocatalyzed reactions

A preliminary screening with all the acceptors and all nitrones with the non-chiral catalyst **(C1)** was undertaken, in order to test the feasibility of the carbonyl activation by a hydrogen bond donor for 1,3-DC of nitrones.

All the combination of equimolecolar amount of the available dienophiles **A1-7** with the nitrones **N1-3**, at room temperature in DCM or toluene as the solvent in the presence of 20 mol% of **C1** did not afford the desired product and only the starting materials were detected in $^{1}$H-NMR of the crude reaction mixture.

The reactions were also repeated in toluene at reflux without the catalyst and also in this case no products were obtained.

The only combination that afforded the desired product was the reaction between nitrostyrene **A6** and nitrone **N3** as reported in Scheme 23.




**Scheme 23:** 1,3-DC between **A6** and **N3**.

This reaction was thus studied further. To be able to quickly determine the conversion of the reactions using $^{1}$H-NMR spectroscopy, we decided to add as internal standard 1,3,5-trimethoxybenzene (Figure 11) since it is cheap, it does not interact with the

investigated reaction and it gives intense peaks in a clean area of the spectrum of the crude reaction mixture.

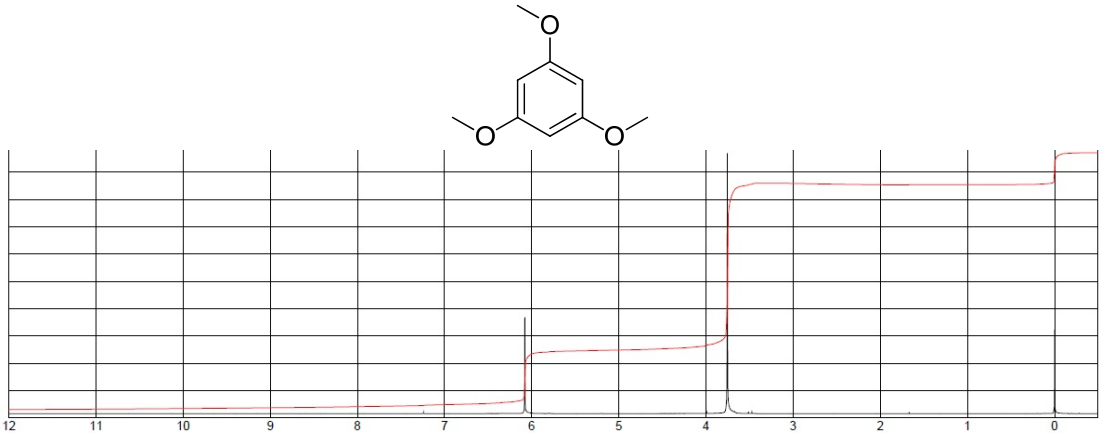
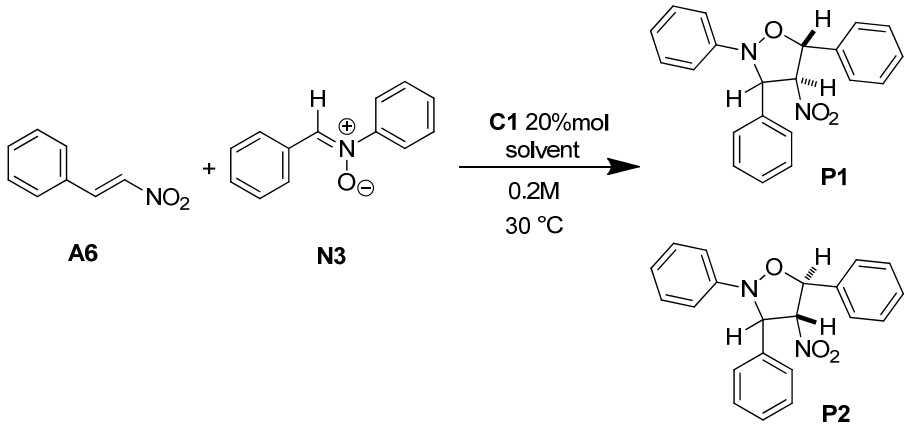



**Figure 11:** 1,3,5-trimethoxybenzene $^{1}$H-NMR spectrum.

The reaction between **A6** and **N3** was tested using different solvents (DCM, THF and toluene) and the conversions were checked at various reaction times. The results are reported in table 2. The reaction is very slow since it required 6/7 days to reach an acceptable conversion. Toluene was the best solvent as it allowed to obtain the target product in 39% yield with a 1:1 ratio between the two diastereoisomers **P1** and **P2** (entry 3) after 7 days.

**Table 2**: Screening of the solvents at various reaction time.

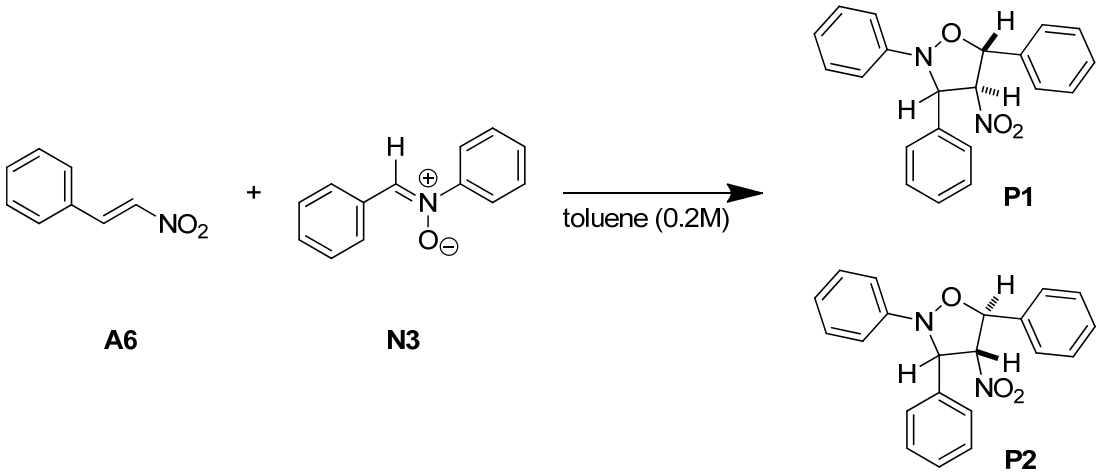



| Entry | Solvent | Reaction time (days) | Conversion (%)[1] | d.r.[1] |
|---|---|---|---|---|
| 1 | DCM | 1 | 4 | / |
| | | 2 | 18 | 1:1.3 |
| | | 6 | 28 | 1:1.3 |
| | | 7 | 32 | 1:1.3 |
| 2 | THF | 1 | 5 | / |
| | | 2 | 8 | / |
| | | 6 | 18 | 2:1 |
| | | 7 | 19 | 2.2:1 |
| **3** | **Toluene** | 1 | 14 | 1:1 |
| | | 2 | 22 | 1:1 |
| | | 6 | 38 | 1:1.1 |
| | | **7** | **39** | **1:1** |

[1] Determined by $^{1}$H-NMR spectroscopy.

Next, we evaluated the effect of the temperature performing the reaction between **A6** and **N3** in toluene at various temperatures and comparing the catalyzed reaction with the background reaction. The temperature screening is an important test because the reactivity and the activity of the catalyst may vary of a great deal in a restricted range of temperatures. The results of this screening, reported in table 3, are really interesting and lead to many deduction.

**Table 3:** Screening of temperatures




| Entry | Temp (°C) | **C1** (mol%) | Reaction time (days) | Conversion (%)[1] | d.r.[1] |
|---|---|---|---|---|---|
| 1 | 40 | 20 | 3 | 79 | 4.3:1 |
| | | | 5 | 52 | 1.2:1 |
| | | | 7 | 47 | 1.4:1 |
| 2 | 40 | / | 3 | 51 | 5.4:1 |
| | | | 5 | 79 | 4.3:1 |
| | | | 7 | 86 | 4.4:1 |
| 3 | 55 | 20 | 3 | 57 | 1.7:1 |
| | | | 5 | 54 | 1.8:1 |
| | | | 7 | 50 | 1.8:1 |
| 4 | 55 | / | 3 | 38 | 1.1:1 |
| | | | 5 | 84 | 4.3:1 |
| | | | 7 | 90 | 4.6:1 |

[1] Determined by $^{1}$H-NMR.

The catalyzed reaction had the best yield (79%) at 40 °C and after only three days (entry 1) whereas the corresponding non-catalyzed reaction needs two more days for achieving the same result (entry 2).

It is also interesting to observe that the conversion of the catalyzed reaction decreases by increasing the reaction time (entry 1) from 3 to 5 and then to 7 days. On the contrary the conversion of the non-catalyzed reaction grows in proportion to the reaction time as expected (entry 2).

Both the catalyzed and the non–catalyzed reaction were tested at 55 °C (entries 3 and 4). Also in this case the conversion of the catalyzed reaction started to decrease after 3

days whereas the conversion of the non-catalyzed reaction reach the best value after 7 days.

A possible explanation of for this behavior is that the catalyst catalyzes also the reverse reaction decomposing the product. In order to prove it, we tested the stability of the product in the presence of the catalyst at various temperature with a decomposition test (Table 4). This test consisted in stirring in a test tube 1 equivalent of the obtained product **P**, 1 equivalent of the internal standard and the catalyst **C1** in toluene, and in a second test tube a simple solution of the product and of the internal standard under the same conditions. Both samples were checked by $^{1}$H-NMR spectroscopy after the same reaction time.

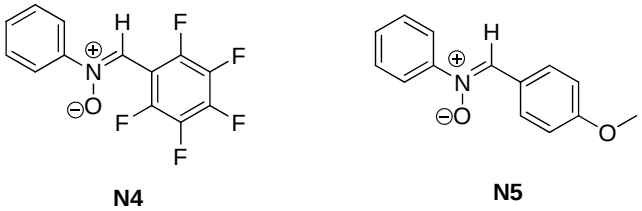
**Table 4:** decomposition tests (Toluene, concentration = 022mol/L)

| Entry | C1 (mol %) | Temp (°C) | Reaction time (hours) | $P_1$(%)[1] |
|---|---|---|---|---|
| 1 | 20 | 30 | 19 | 90 |
| | | 30 | 115 | 89 |
| 2 | / | 30 | 19 | 99 |
| | | 30 | 115 | 100 |
| 3 | 20 | 45 | 19 | 90 |
| | | 45 | 115 | 83 |
| 4 | / | 45 | 19 | 100 |
| | | 45 | 115 | 99 |
| 5 | 20 | 50 | 19 | 90 |
| | | 50 | 115 | 82 |
| 6 | / | 50 | 19 | 100 |
| | | 50 | 115 | 100 |

[1]Amount of $P_1$ determined by $^{1}$H-NMR.

The decomposition test performed at various temperature shows that the catalyst degrade the product strongly since 45 °C (Entry 3, 5). The decomposition of the product was observed also at 30 °C but not so effective (Entry 1). For these reasons it was chosen to operate at a temperature below 45 °C and with a reaction time not longer than 3 days.

Then, we tried to analyze the effect of the substrate substituents in this reaction. For this purpose two types of nitrones have been tested, one electron poor (**N4**) and the other one electron rich (**N5**) (Figure 12).




**N4** **N5**

**Figure 12:** Nitrones **N4** and **N5**

In Table 6 the results in terms of yield and diasteroselectivity obtained with nitrones **N4** and **N5** in the reaction with acceptor **A6** in the presence of catalyst **C1** (20 mol%), in toluene as the solvent are presented.

**Table 6:** Results of nitrones screening.

| Entry | Nitrone | Temp (°C) | Reaction time (hours) | Conversion (%)[1] | d.r. %[1] |
|---|---|---|---|---|---|
| 1 | **N4** | 30 | 68 | 7 | >99:1 |
| 2 | **N5** | 30 | 68 | 36 | 1.1:1 |
| 3 | **N4** | 45 | 140 | 32 | >99:1 |
| | | | 236 | 20 | >99:1 |
| 4 | **N5** | 45 | 140 | 55 | 1.1:1 |
| | | | 236 | 70 | 1.1:1 |

[1] Determined by $^{1}$H-NMR spectroscopy.

After this screening it was clear that the electron density of the ring influences the nitrone carbon and this had as effect a big difference on the diasteroselectivity of the reaction. The cycloaddition reaction with the electron deficient nitrone **N4** afforded the desired product with a lower conversion but in a more diasteroselective way (Entries 1 and 3). On the other hand the electron rich **N5** gave an higher yield but there was a very low diasteroselection (Entries 2 and 4).

Other non-chiral thioures (**C2** and **C3**) were also tested under similar reaction conditions in the reaction between **N4** and **A6** and the results obtained in terms of conversion and diasteroselectivity are reported in Table 7.

**Table7:** Results obtained with the other non-chiral thiourea catalysts **C2** and **C3**

| Entry | Temperature (°C) | Catalyst | Reaction time (hours) | Convertion %[1] | d.r. %[1] |
|---|---|---|---|---|---|
| 1 | r.t. | **C2** | 24 | 4 | >99:1 |
| 2 | r.t. | **C3** | 24 | 5 | >99:1 |
| 3 | 40 | **C2** | 66 | 46 | 3.2:1 |
| | | | 90 | 49 | 3.1:1 |
| | | | 138 | 54 | 3.5:1 |
| | | | 167 | 52 | 2.5:1 |
| 4 | 40 | **C3** | 66 | 54 | 3.9:1 |
| | | | 90 | 59 | 3.9:1 |
| | | | 138 | 70 | 4.4:1 |
| | | | 167 | 69 | 4.8:1 |

[1] Determined by $^1$H-NMR spectroscopy.

At room temperature both thioureas **C2** and **C3** were not able to activate the substrate and the yields were very low (Entries 1 and 2) whereas at 40 °C and with very long reaction times a moderate (Entry 3) or good yield (Entry 4) were obtained. The degradation effect noted with **C1** was not detected with **C2** and **C3** the (bis)trifluoromethyl.groups on the rings of the thiourea make it more electron deficient and so more reactive.

Having observed a small, yet detectable, influence of the catalyst **C1** on the reaction outcome, in order to obtain an enantiomerically enriched product, we run the reaction between **A6** and **N3** in the presence of the chiral enantiopure thioureas **C4-9**. The obtained results are reported in Table 8.

**Table 8:** Chiral catalyst screening

| Entry | Temperature (°C) | Catalyst | Reaction time (hours) | Conversion %[1] | d.r. %[1] |
|---|---|---|---|---|---|
| 1 | -20 | **C9** | 43 | 0 | / |
| | | | 140 | 10 | >99:1 |
| 2 | r.t. | **C4** | 24 | 0 | / |
| 3 | r.t. | **C5** | 24 | 0 | / |
| 4 | r.t. | **C6** | 24 | 0 | / |
| 5 | r.t. | **C9** | 43 | 14 | 2.5:1 |
| 6 | 40 | **C4** | 66 | 40 | 7.0:1 |
| | | | 90 | 47 | 10.8:1 |
| | | | 138 | 59 | 4.4:1 |
| | | | 167 | 62 | 4.6:1 |
| 7 | 40 | **C5** | 66 | 42 | 9.5:1 |
| | | | 90 | 54 | 3.2:1 |
| | | | 138 | 57 | 4.2:1 |
| | | | 167 | 66 | 5:1 |
| 8 | 40 | **C6** | 66 | 35 | 10.7:1 |
| | | | 90 | 45 | 10.3:1 |
| | | | 138 | 45 | 10.3:1 |
| | | | 167 | 54 | 12.5:1 |
| 9 | 40 | **C7** | 115 | n.d. | 4.5:1[2] |
| 10 | 40 | **C8** | 115 | n.d. | 1:1[2] |

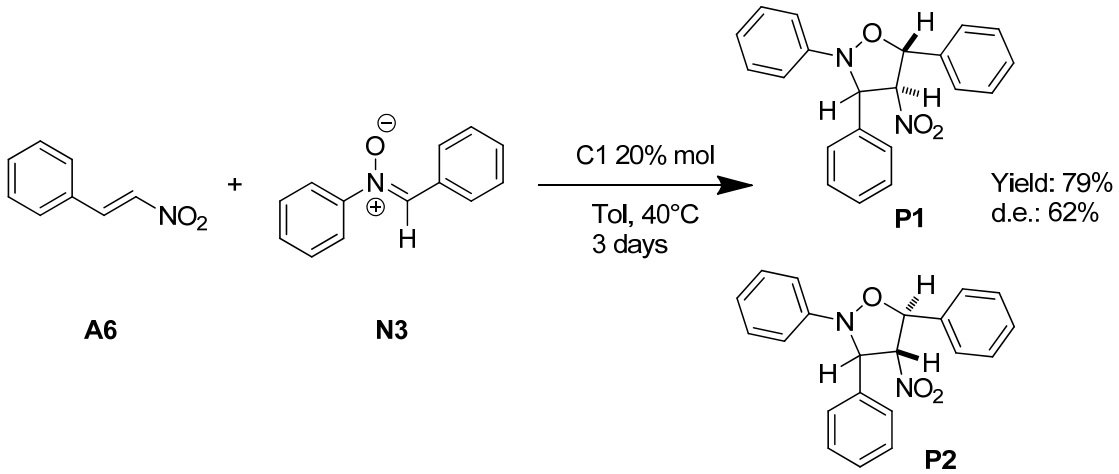
[1] Determined by $^{1}$H-NMR. [2]: Determined by HPLC

From these results is it possible to observe that the substrate is activated by all the catalysts at a temperature higher than 25 °C (Entries 8-12). In all cases, there was no decomposition of the product in the presence of the catalyst and **C6** gave the best diasteroselectivity (Entry 10).

As far as the enantioselectivity is concerned, the results are not presented in the table since all of them were between 0 and 4 %.

## 2.4 Conclusion and Outlook

In conclusion, the reaction between a range of acceptors **A1-6** and various nitrones **N1-3** was studied in the presence of the achiral thiourea **C1** under different reaction conditions. This study demonstrated a small activating effect by this double hydrogen bond donor in the reaction between nitrones **N3-5** and nitrostyrene **A6** .The best conditions which gave the highest yield and the best diasteroselection for this reaction are reported in Scheme 24.




**Scheme 24:** 1,3-DC between **N3** and **A6**, catalyzed by thiourea **C1**.

Unfortunately, by applying a series of chiral enantiopure catalysts **C4-C8** in this reaction did not result in any measurable asymmetric induction.

Thus, this reaction is still a challenge. Even if the obtained results are encouraging, large work needs to be done in order to develop this reaction with synthetically useful results.

To this end, it would be interesting to analyze deeper the role of the solvent in this reaction, using for example as starting point the reaction in THF because the yield in this solvent was remarkable (although lower than in toluene) and it was more diasteroselective than in toluene.

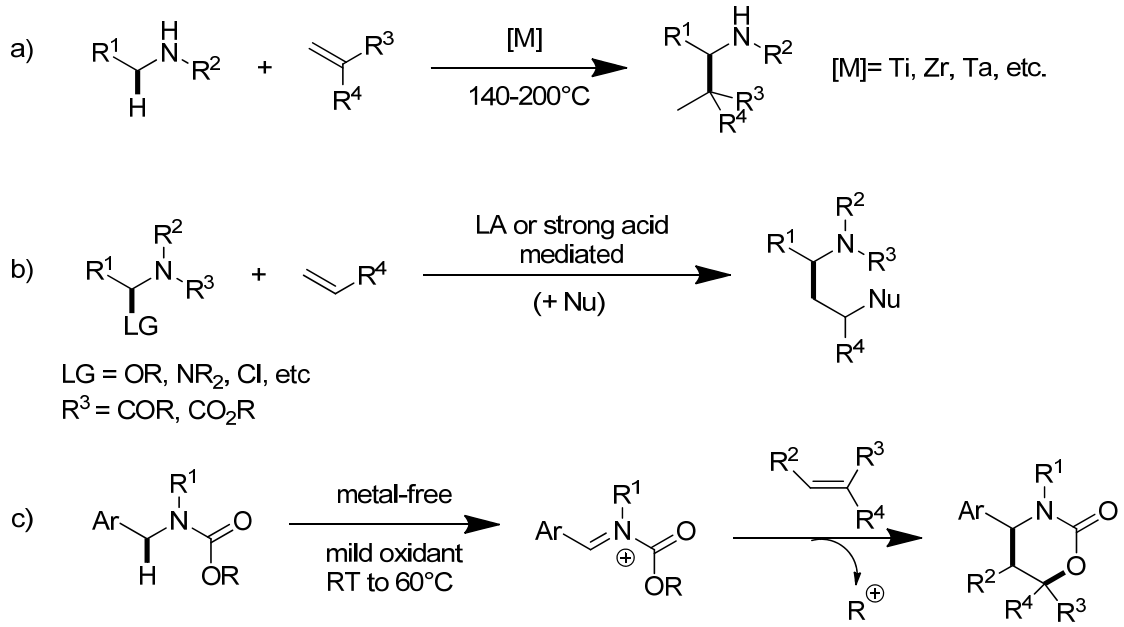
On the other side to improve the enantioselectivity it could be interesting to change the substrate (alkene) because from the results it is evident that the catalyst is not able to

imprint enantioselection in this reaction and this could come from the excessive distance between the activated group and the carbon that has to cyclize.

## 3. TEMPO-salt mediated tandem oxidative C-H functionalization/cyclization of benzyl amides with styrene: Synthesis of oxazines

The aminoalkyl group is one of the most frequently occurring functionalities present in natural products as well as in synthetic biological active compounds.[39] For this reason the direct functionalization of C($sp^3$)-H in the α-position to a nitrogen group is an emerging topic that have been developed in the last few years.[40]

Several methods for the metal-catalyzed activation of α-C($sp^3$)-H in amines and the subsequent addition to olefins have been reported. These procedures are usually catalyzed by Group 4 and 5 metals and required high temperature (140-200 °C), long reaction times and often the obtained regioselectivity is not satisfactory (Scheme 25, route a)[41] On the other hand, the α-amidoalkylations of simple olefins by forming the intermediate imines using amines bearing a leaving group at the α-position requires a Lewis acid or a strong acid preactivation (Scheme 25, route b).[42]

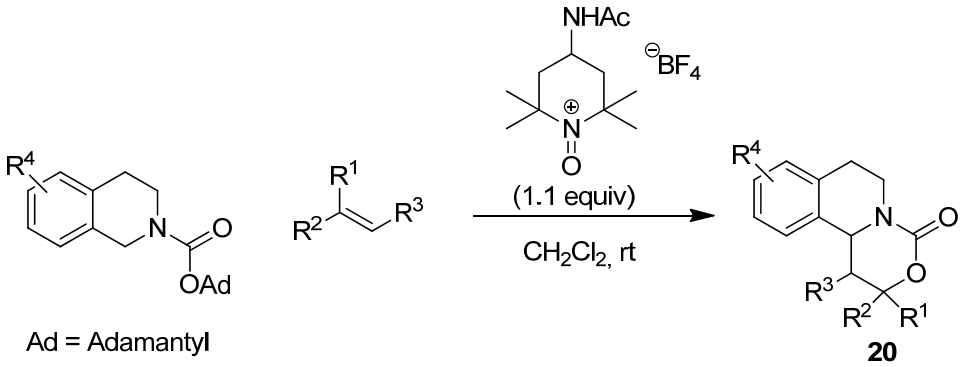



**Scheme 25:** α-alkylation of nitrogen compounds with olefins.

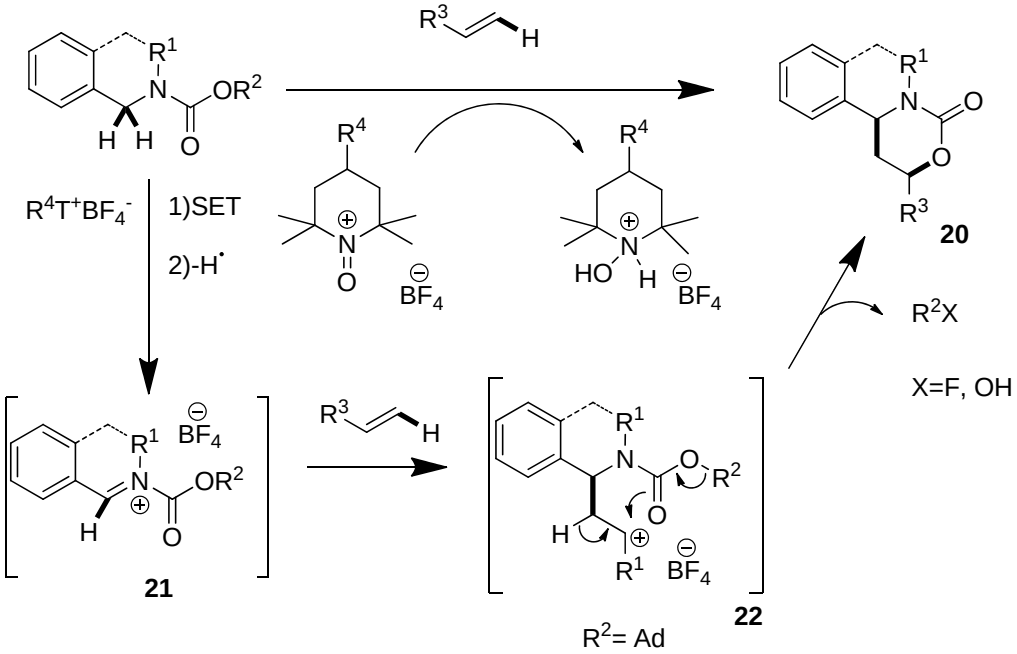
As an appealing alternative to these established methodologies, the group where I worked in Münster University have recently developed a new method for the highly

selective direct oxidative α-alkylation/cyclization tandem reaction of nitrogen compounds with olefins (Scheme 25, route c) for the synthesis of oxazinones. [43]

In particular, the reaction of tetrahydroisoquinoline derivatives (THIQs) with styrene derivatives and oxoammonium salt (4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate) as the oxidant afforded tricyclic derivative **20** in high yields and good diastereoselectivity (Scheme 26).



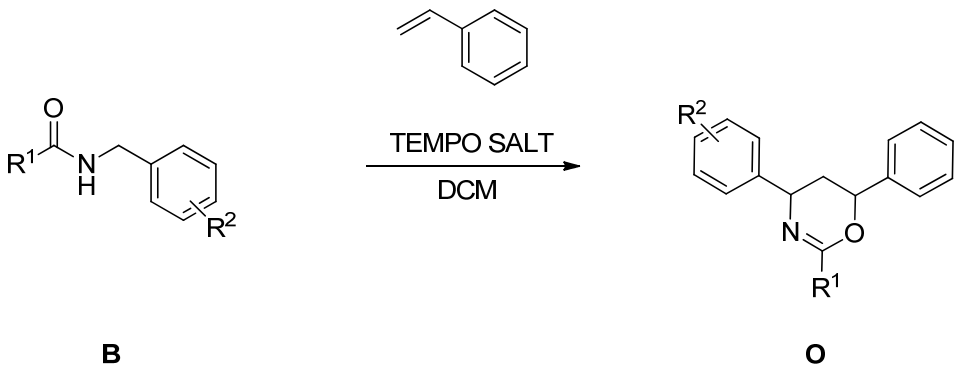

**Scheme 26.** Metal-Free tandem α-alkylation/cyclization of tetrahydroisoquinoline carbamates with olefins.



**Scheme 27.** Proposed mechanism for the tandem α-alkylation/cyclization.

As far as the accepted mechanism is concerned, an initial α-oxidation with the TEMPO salt generates the N-acyliminium ion **21** which undergoes nucleophilic addition of the olefin. Subsequently, the cleavage of the O-adamantyl bond and the concomitant attack of the carbamate oxygen atom at the carbocation center in **22** release oxazinone **20** and an adamantyl cation (Scheme 27).

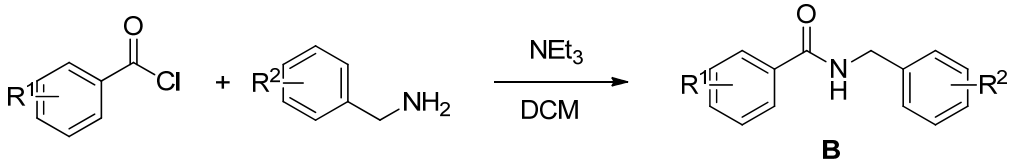
On these grounds, we decided to test the feasibility of a metal free TEMPO-salt (oxoammonium salt) mediated tandem oxidative C-H functionalization/cyclization of simple *N*-benzyl amides **B**, instead of tetrahydroisoquinoline derivatives, with the aim of achieving oxazine derivatives **O** as reported in Scheme 28.



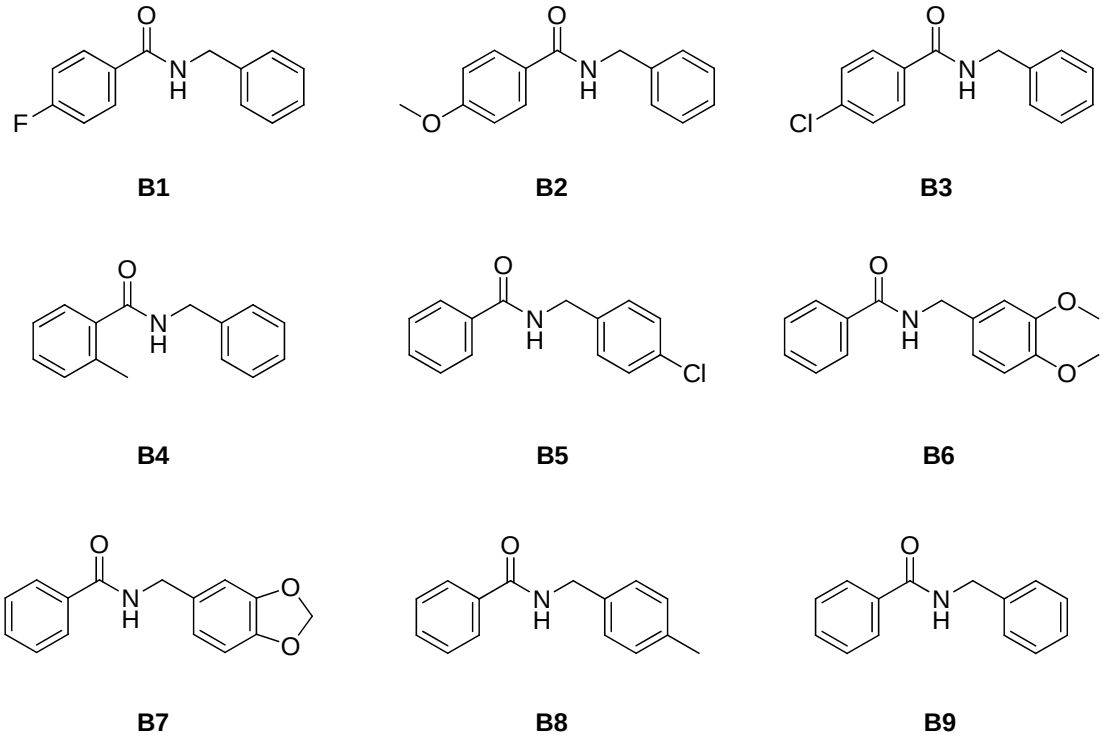

**B** **O**

**Scheme 28.** TEMPO-salt mediated tandem oxidative C-H functionalization/cyclization of *N*-benzyl amides.

For this purpose, we first undertook the preparation of a series of *N*-benzyl amides **B**. *N*-benzylbenzamides **B1-9** were readily prepared by reaction of benzoylchloride derivatives and benzylamines, in the presence of triethylamine in DCM as the solvent (Scheme 29). Chromatography of the crude reaction mixture led to the desired product in very good yields ranging between 92-98%.

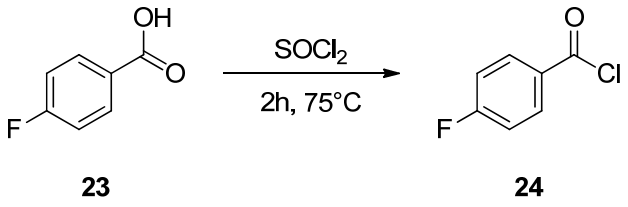



**B**



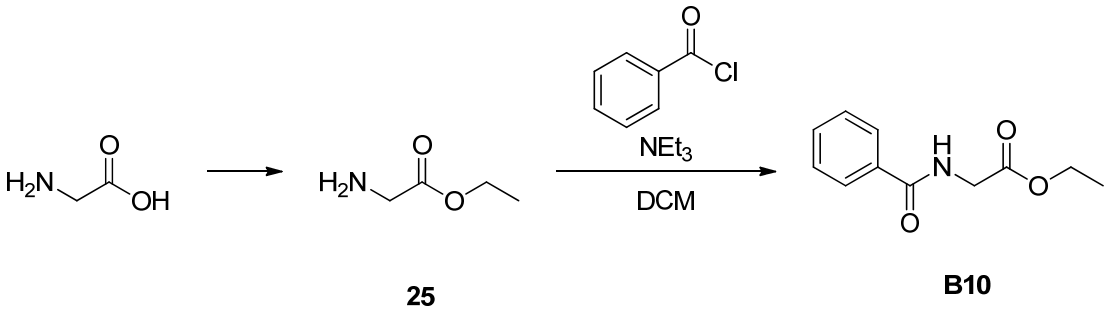

**Scheme 29:** Preparation of *N*-benzylbenzamides **B1-9**

4-Fluorobenzoyl chloride **24**, used in the preparation of **B1**, was not available in the laboratory and for this reason it was prepared from the corresponding carboxylic acid **23** by reaction with $SOCl_2$ in quantitative yield (Scheme 30).




**Scheme 30**. Preparation of 4-fluorobenzoyl chloride **24**

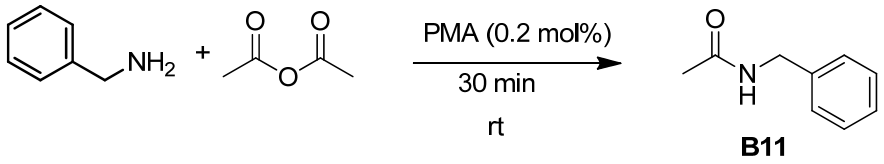
Besides the benzoyl dervatives **B1-B9**, **B10** was prepared in two steps: ethyl 2-benzoamidoacetate **25** was prepared by Fisher-esterification of glycine in EtOH followed by reaction with benzoyl chloride in 94 % of yield (Scheme 31).




**25** **B10**

**Scheme 31:** Synthesis of **B10.**

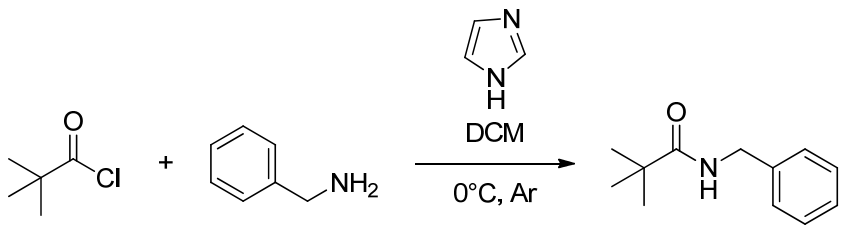
*N*-benzylacetamide **B11** was prepared by reaction of an equimolecular mixture of benzyl amine and acetic anhydride in the presence of 0.2 mol% di PMA ($H_3[P(MoO_{10})_4]\cdot nH_2O$), 99 % of yield (Scheme 32).




**B11**

**Scheme 32:** Synthesis of **B11**

*N*-benzylpivalamide **B12** was instead prepared by mixing in DCM pivaloyl chloride with 2 equivalents of N-methylimidazole, followed by the addition of benzylamine at 0 °C. After chromatographic purification, the product **B12** was obtained in 60% yield (Scheme 33).

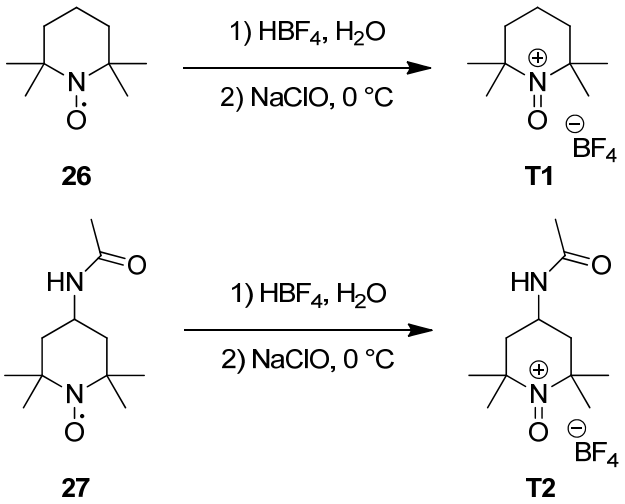



**B12**

**Scheme 33:** Preparation of **B12**.

TEMPO salts were prepared following literature procedures. 2,2,6,6-Tetramethylpiperidine-1-oxoammonium tetrafluoroborate **T1** was obtained by reaction

of 2,2,6,6-tetramethylpiperidine-1-oxyl with an aqueous solution of $HBF_4$ followed by the addition of an aqueous solution of NaOCl in 87 % yield,[44,] and 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate **T2** was prepared from 4-acetylamino-2,2,6,6-tetramethyl-1-piperidinyloxy (4-acetamido-TEMPO) using the same procedure in 49 % yield (Scheme 34).[45]

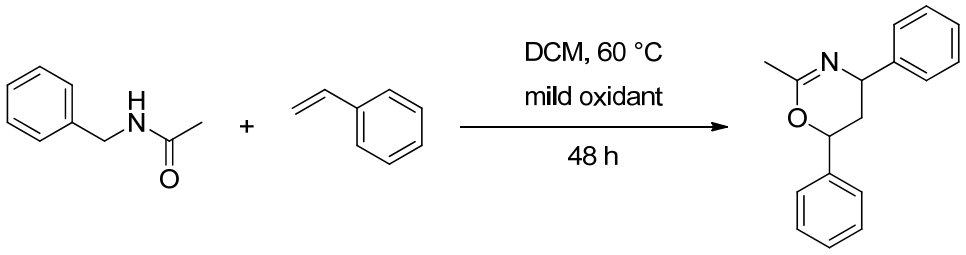



**Scheme 34:** Synthesis of TEMPO salts **T1** and **T2.**

Initially, we started to investigate the reaction of **B11** with styrene at 60 °C in DCM, in the presence of various oxidants (Table 9).

As reported in the table both DDQ (2,3-dchloro-5,6-dicyano-1,4-benzoquinone) (entry 1) and *t*BuOOH (entry 2) did not promote the reaction and the starting materials were detected unchanged by $^1$H-NMR analysis of the crude reaction mixture.

**Table 9:** oxidant screening.

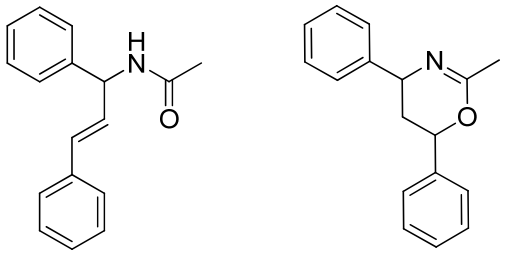



**B10** **O1**

| Entry | Oxidant | Conversion in **O1** (%)[1] |
|---|---|---|
| 1 | DDQ | 0 |
| 2 | *t*BuOOH | 0 |
| 3 | **T1** | 16[2] |
| 4 | **T2** | 36 |

[1] Determined by $^1$H-NMR spectroscopy.[2]beside the 32 % of the intermediate **I1**

In contrast, the $^1$H-NMR spectrum of the crude reaction mixture with **T1** (entry 3) showed a complete conversion of the starting amide **B11** and the presence of the desired product **O1**, beside an intermediate α-alkylated product whose structure was tentatively assigned as **I1**, in a 1:2 ratio (Scheme 35).




**I1** **O1**

**Scheme 35:** structure of the intermediate α-alkylated product **I1** and oxazine **O1**

Encouraged by this result we tried the reaction with **T2** (entry 4); also in this case the conversion of the starting amide was complete, and the desired α-alkylated/cyclized product was produced in 36 % yield. The intermediate **I1** in this case was not detected.

We then tried to isolate the obtained product **O1** by chromatography. Unfortunately, the purity of the isolated product was not very high and it was very difficult to eliminate the unreacted styrene and the TEMPO residues.

Another problem with this substrate was the reproducibility of the results. This could be explained with the partial instability of the product **O1** on the silica gel, leading to partial decomposition during purification.

In order to solve this problem we decided to try the reaction with the different amides synthesized. This screening put in evidence that the substrate **B9** furnished the most stable final product from the point of view of the chromatography. The purification is still not optimized and we did not achieve a good level of purity but the product seems more stable.

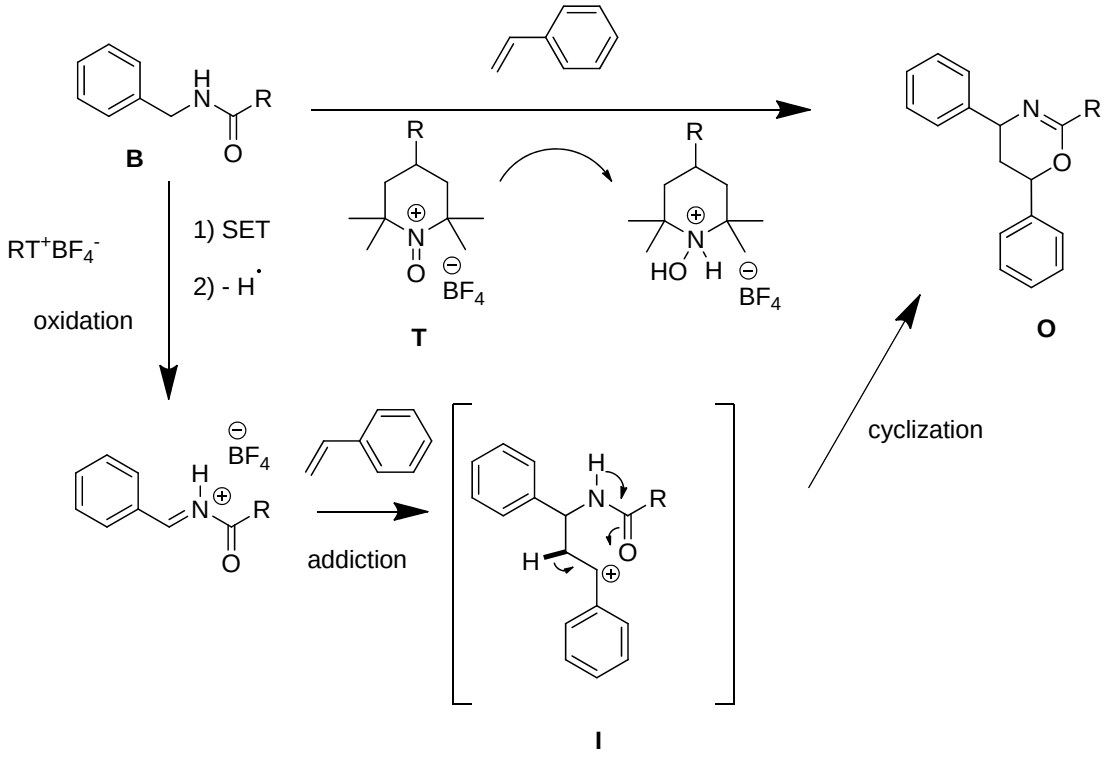



**Figure 50:** Scheme of the proposed mechanism.

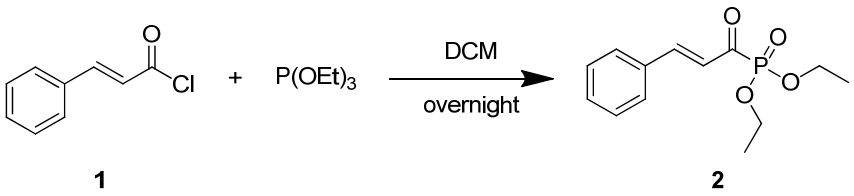
# 4. Experimental part

## 4.1. General Information and Materials

$^{1}$H- and $^{13}$C-NMR spectra were recorded in $CDCl_3$ (reference signal $^{1}$H = 7.26 ppm, $^{13}$C = 77.16 ppm) or DMSO-$d_6$ (reference signal $^{1}$H = 2.50 ppm, $^{13}$C = 39.5 ppm) or $D_2O$ (reference signal $^{1}$H = 4.75 ppm) on a Bruker ARX-300 and a Varian AV-300 or AV-400 MHz. Chemical shifts (δ) are given in ppm and spin-spin coupling constants (*J*) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F254 and a solution of $KMnO_4$ served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (HRMS) were recorded on a Bruker Daltonics MicroTof spectrometer (samples in $CH_3OH$ as solvent). Dichloromethane was distilled over $CaH_2$. Commercially available reagents were used without further purification.

## 4.2 Synthesis of acceptors

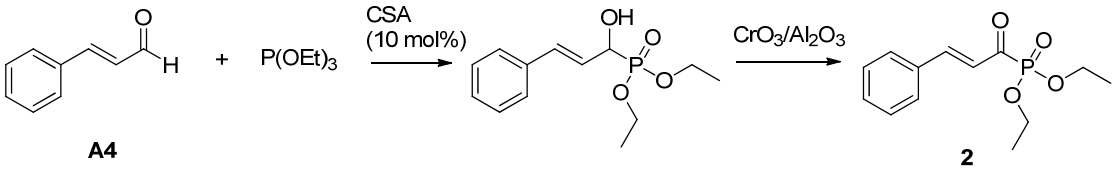
**Synthesis of diethyl cinnamoylphosphonate (2)**[28]




**1** **2**

A mixture of cinnamoyl choride (5 mmol), triethoxy phosphite (6 mmol) in DCM (50 ml) is stirred overnight at room temperature under Ar atmosphere. The reaction mixture is concentrated under vacuum and yielded without further purification. The yellow obtained oil was analyzed by $^{1}$H-NMR reveling the presence of the starting material and 5% of the desired product.

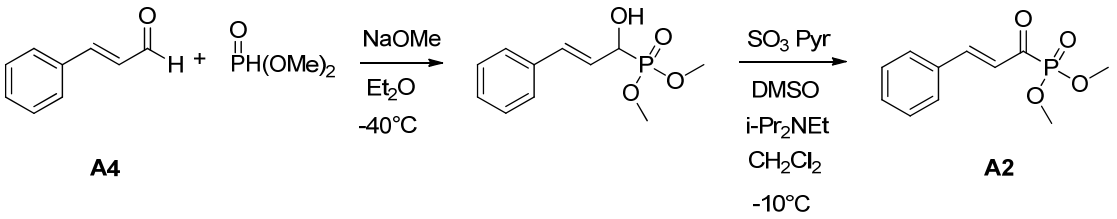
**Second synthesis of diethyl cinnamoylphosphonate (2)**[29]




CSA = camphol sulfonic acid

1) a mixture benzaldehyde (1 mmol), triethylphosphite (1 mmol) and CSA (0.1 mmol) was stirred vigorously at r.t. under solvent-free condition for 40 min. Reaction progress was monitored by TLC analysis (ethyl acetate/n-hexane: 1:9). After 40 min, 10 ml of water were added to the reaction mass and stirred again for other 4 min to obtain the solid product. Reaction mass containing product was poured on crushed ice and product was collected by simple filtration, washed with water and dried. The $^{1}$H-NMR of the crude showed the presence of the starting material and 15 % of the desired product. $^{1}$H-NMR was in agreement with the literature.

**Synthesis of dimethyl cinnamoylphosphonate (A2)**



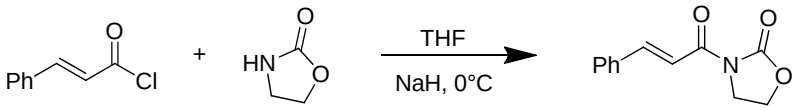

1) To a solution of 13,71g (104mmol) of cinnamaldehyde and 11,42 g (104 mmol) of dimethyl phosphyte in 105 ml of diethyl ether at -40 °C was added dropwise *via* syringe over 15 min 500 µL of saturated NaOMe/MeOH to afford a cloudy solution than gradually turns milky white. The reaction mixture was warmed to 25 °C and three 150 µL portions of saturated NaOMe/MeOH were added to the slurry until TLC analysis indicated the absence of starting materials. 50 mL of ether were added to the slurry; concentrated sulfuric acid (20 drops) was added and the reaction was concentrated in

vacuum. The resulting solid was dissolved in 250 mL of DCM and washed with one 100 mL portion of brine. The organic layer was dried with $MgSO_4$ filtered and concentrated in vacuum. The resulting solid was triturated with 200 mL of diethyl ether and filtered to afford a white solid (93.4 mmol, 90% of yield).

2) To a solution of 6 g (24.77 mmol) of (*E*)-1-hydroxy-3-phenyl-2-propenyl phosphonate in 250 mL of DMC at -10 °C was added 12.95 mL (74,32 mmol) of diisopropyl ethyl amine followed by a solution of 11.83g (74.32 mmol) of SO3∗Pyridine complex in 50 mL of DMSO. After 1 hour the reaction mixture was diluted with 500 mL of diethyl ether and washed with $H_2O$, 5% aqueous $NaHCO_3$, saturated aqueous $CuSO_4$ and brine. The ethereal solution was dried with $MgSO_4$, filtered and concentrated in vacuum to a yellow oil that was >95% pure by $^1$H-NMR analysis and could be used in subsequent reactions without further purification.

$^1$H-NMR was in agreement with the literature.[30]

**Synthesis of 1-(isoxazolidin-2-yl)-3-phenylprop-2-en-1-one (A3)**

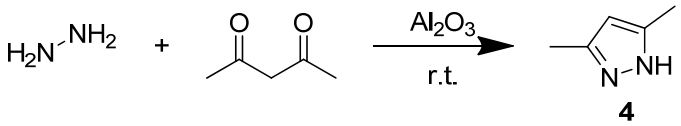



**1** **3** **A3**

Under $N_2$, to a flask containing 2-oxazolidinone (0.87 g, 1.0 mmol) and THF (20 mL), was added NaH (60% in mineral oil, 0.48 g, 12 mmol) in portions at 0 °C. After complete addition, the solution was stirred for 30 minutes at 0 °C. A solution of cinnamoyl chloride (1.83 g, 11 mmol) in 5 mL THF was then added dropwise at 0 °C over 10 minutes and the mixture was stirred at rt for 10 h. The reaction was quenched with 1 mL of saturated $NH_4Cl$ solution and extracted with EtOAc (3 x 30 mL). The extracts were combined, washed with brine (2 x 5 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography on silica gel using hexane/EtOAc (3:1) as eluent to yield 2.0 g of **A3** (92%) as colorless solid.

$^1$H-NMR was in agreement with the literature.[31]

**Synthesis of 3,5 Dimethyl-1*H*-pyrrole (4)**

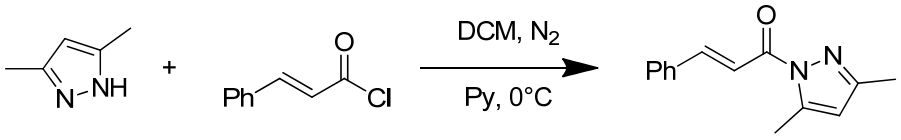



**4**

The 2,4 pentanedione (**8**) (3.00 g, 30 mmol ) was dispersed on alumina (Merck 60 neutral; 9.00g). To this, the hydrazine monohydrate (**7**) (1.50 g, 30 mmol) was added dropwise at 0 °C (ice bath) with an efficient stirring. The reagents must be completely absorbed on the solid support. The mixture was allowed to stir for 1 h at 20 °C and then the product was extracted with DCM (2x25ml) and concentrated under vacuum to give **4** as a colorless crystal (0.91 g, 32%).

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.26 (s,6H), 5.83 (s, 1H),6.68 (bs, 1H) .

**Synthesis of 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-phenylprop-2-en-1-one (A5)**




**4** **1** **A5**

The cinnamoyl chloride (**13**) (4.84 g, 29 mmol) was solved in 15ml of DCM. The **12** (2.78 g, 29 mmol) was solved in 15 ml of DCM and pyridine (2.99 g, 29 mmol). The solution of pyrrole was added drop wise at 0 °C under Argon atmosphere and then the mixture was stirred for 3 h at 0 °C. After stirring at 0 °C for 3 h, the reaction mixture was poured into $H_2O$ (20 mL) and extracted with DCM (20 mL x 3). The combined extracts were washed with brine, dried with $MgSO_4$, and evaporated in vacuum to give the product **A5** (6.32g, 96%).

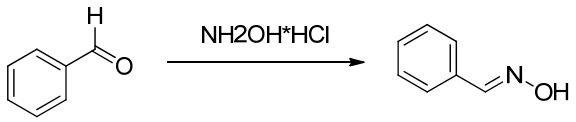
$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.30 (s,3H), 2.63 (s, 3H), 6.02 (s, 1H), 7.41-7.42 (m, 3H), 7.67-7.69 (m, 2H), 7.91 (d, $J$ = 16.0 Hz, 1H), 7.96 (d, $J$ = 16.0 Hz, 1H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 13.9, 14.8, 111.6, 118.0, 128.8, 128.9, 130.7, 134.9, 144.5, 146.3, 152.0, 165.6 .

HRMS (ESI): calculated for C14H14N2O·$Na^+$ $[M+Na]^+$: *m/z* = 249.1004, found: *m/z* = 249.1004

## 4.3 Synthesis of nitrones

### Synthesis of benzaldehyde oxime (5)



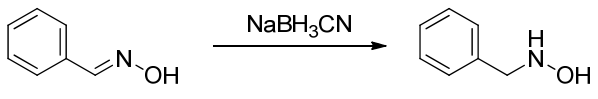

**5**

To a solution of benzaldehyde (3.18 g, 30 mmol) and hydroxylamine hydrochloride (6.45 g, 100 mmol) in 100 mL EtOH was added powdered NaOH (10.80 g, 270 mmol) in small portions. The mixture was allowed to stir at 25 °C for 30 min and then refluxed for another 30 min The reaction mixture was then cooled to 25°C, poured into a mixture of concentrated HCl (12 mL) and water (46 mL), carefully concentrated to one third of the original volume and finally extracted with DCM. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude yellow oil was used in the next reaction without further purification (2.78g, 78%).

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.43-7.46 (m, 3H), 7.64-7.67 (m, 2H), 8.27 (s, 1H), 9.8 (bs, 1H) .

HRMS (ESI): calculated for C7H7NO·$Na^+$ $[M+Na]^+$: *m/z* = 144.0425, found: *m/z* = 144.0420 .

### Synthesis of *N*-benzylhydroxyl amine (6)




**5** **6**

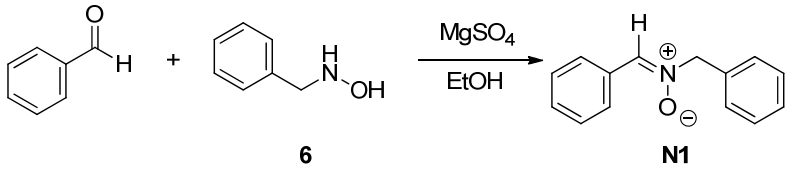
To a solution of benzaldehyde oxime (**5**) (4.19 g, 35 mmol) and $NaBH_3CN$ (3.70 g, 59 mmol) in 100 mL of MeOH at 0 °C, 12 N HCl (5.81 mL, 70 mmol) was added drop

wise. After addition the reaction mixture was allowed to stir at 25 °C for 4 h before adding 6N NaOH until pH ~ 9. The reaction mixture was concentrated under vacuum and the product was extracted with DCM, washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuum. The crude *N*-benzyl-hydroxylamine (**6**) was recrystallized from hexane/methanol = 4:1 to afford (2.14g, 50%) as colorless crystals.

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.95 (s, 2H), 5.95 (bs, 1H), 7.24-7.37 (m, 5H) .

HRMS (ESI): calculated for C7H9NO·$H^+$ $[M+H]^+$: *m/z* =124.0762, found: *m/z* = 124.0757 .

**Synthesis of *N*-benzylidene-benzylamine-*N*-oxid (N1)**

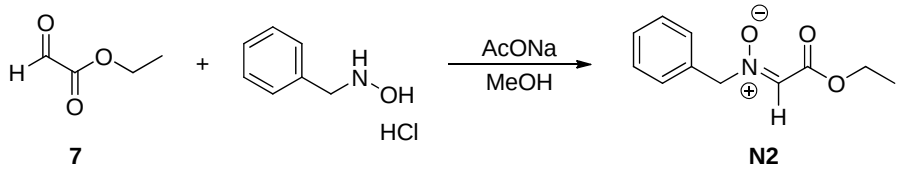



**6** **N1**

*N*-benzyl-hydroxylamine (**6**) (4.92 g, 40.0 mmol), benzaldehyde (4.25 g, 40.0 mmol) and $MgSO_4$ (4.82 g, 40.0 mmol) were stirred in 200 mL DCM for 15 h. Recrystallization from ether afforded 9.53 g (90%) *N*-benzylidene-benzylamine-*N*-oxid (**N1**).

$^1$H-NMR was in agreement with the literature.[32]

**Synthesis of *N*-(2-ethoxy-2-oxoethylidene)-1-phenylmethanamine oxide (N2)**

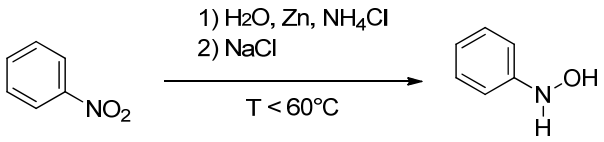



**7** **N2**

In a slurry, *N*-benzyl-hydroxylamine hydrochloride (3.20 g, 20 mmol) and anhydrous NaOAc (2.18 g, 26 mmol) in MeOH (20 mL) was stirred for 10 min at r.t. A solution of 50% ethyl glyoxylate (**7**) in toluene (4.08 g, 20 mmol) was then added. After stirring for

3 h at r.t., the reaction mixture was concentrated under vacuum. The white residue was partitioned between DCM (100 mL) and $H_2O$ (30 mL) and the separated aqueous phase was extracted with DCM (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and filtered through a short pad of silica gel. The filtrate was concentrated under vacuum to yield pure nitrone (**N2**) as white crystals (4.10 g, 92%).
$^1$H-NMR was in agreement with the literature.[33]

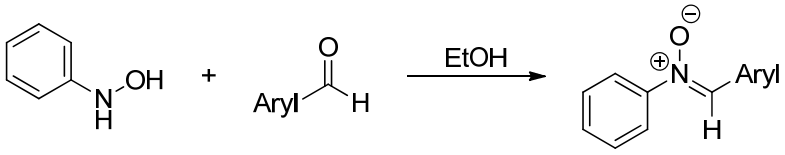
**Synthesis of *N*-phenylhydroxylamine (8)**.




**8**

To a stirred mixture of nitrobenzene (2.60 g, 21 mmol) and $NH_4Cl$ (1.30 g, 24 mmol) in $H_2O$ (40 mL) at 0°C was slowly added zinc dust (90%, 3.08 g, 42 mmol) while maintaining the temperature below 60 °C. After 15 min's stirring, the reaction mixture was filtered while still warm (≈ 40°C) and the solid was washed with hot water (2 x 10 mL). The filtrate was saturated with NaCl and cooled to 0 °C and the resulting yellow crystals were collected and dried. This crude *N*-phenylhydroxylamine (**8**) was used without further purification (1.78 g, 19 mmol, 78%).

**General procedure of synthesis of *N*-phenyl nitrones (N3-5)**

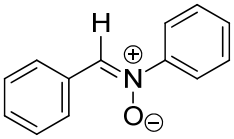



**8** **N3-5**

In a flame dried round-bottom flask, the corresponding benzaldehyde (0.95 equivalent) was added to a solution of the hydroxy amine (**8**) ( 1 equivalent) in EtOH (0.5 M). The

mixture was stirred overnight in the dark. A white precipitate was formed and after checking the full conversion by TLC analysis, a little amount of hexane(5 ml)was added to facilitate the precipitation and then the flask was stored in to the fridge (-10°C) for 5-10 hours. Then the precipitate was under vacuum filtrate using a glass frit. The mother-waters were concentrated to an half and then was added again hexane(5 ml) and putted in to the fridge. Several filtrations gave the crude product **N3-5** (95-98% pure by 1H-NMR) with traces of benzaldehyde. Recrystallization from EtOH afforded pure product.

***N*-benzylideneaniline oxide (N3):**



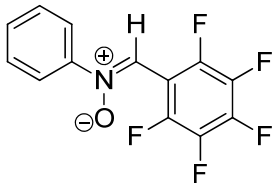

**N3**

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.42-7.52 (m, 6H), 7.71-7.80 (m, 2H), 7.92 (s, 1H), 8.38 (dd, $J$ = 6.9, 2.9, 2H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 122.0, 128.9, 129.4, 129.4, 130.2, 130.8, 131.3 .

HRMS (ESI): calculated for C13H11NO·$Na^+$ $[M+Na]^+$: $m/z$ = 220.0738, found: $m/z$ = 220.0734 .

***N*-((perfluorophenyl)methylene)aniline oxide (N4)**




**N4**

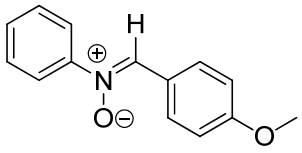
$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.46-7.56 (m, 3H), 7.75-7.83 (m, 2H), 7.93 (s, 1H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 106.4 (td, $J$ = 16.7, 4.1 Hz), 120.9, 122.0, 129.5, 131.4, 135.8-136.7 (m), 139.3-140.0 (m), 140.4-141.1 (m), 142.9-143.5 (m), 143.9-144.4 (m), 146.6 (td, $J$ = 7.9, 3.9 Hz), 147.9 .

$^{19}$F NMR $\delta$ -131.52 - -131.89 (m, 2F), -151.17 (tt, $J$ = 20.8, 3.7 Hz, 1F), -160.85 – -161.99(m, 2F) .

HRMS (ESI): calculated for C13H6F5NO·$Na^+$ $[M+Na]^+$: $m/z$ = 310.0267, found: $m/z$ = 310.0262 .

***N*-(4-methoxybenzylidene)aniline oxide (N5)**



**N5**

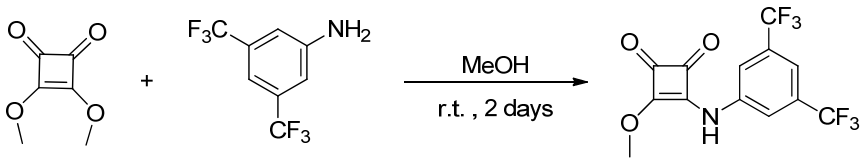
$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.87 (s, 3H), 6.98 (d, $J$ = 9Hz, 2H), 7.37-7.53 (m, 3H), 7.76 (dd, $J$ = 7.9, 1.8 Hz, 2H), 7.85 (s, 1H), 8.33-8.47 (m, 2H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 55.6, 114.2, 121.8, 123.9, 129.3, 129.8, 131.4, 134.4, 149.0, 161.7 .

HRMS (ESI): calculated for C14H13NO2·$Na^+$ $[M+Na]^+$: $m/z$ = 250.0844, found: $m/z$ = 250.0826 .

## 4.4. Synthesis of the catalysts

**Synthesis of 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (11)**



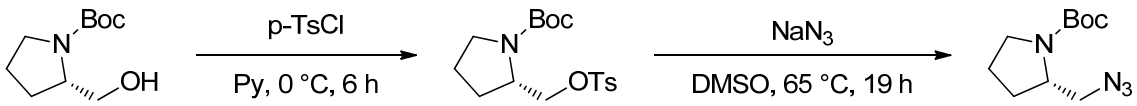

**9** **10** **11**

To a solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (**24**) (2.00 g, 14.1 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (**25**) (2.40 mL, 15.5 mmol, 1.1 equivalent). The mixture was stirred at r.t. for 2 days and a yellow precipitate was generated. The reaction mixture was filtered with the aid of MeOH and subsequently the yellow solid was dried in vacuum to give the desired product (2.37 g, 50% yield).

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.41 (s, 3H), 7.76 (s, 1H), 8.03 (s, 2H), 11.20 (s, 1H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 60.9, 116.3, 117.7, 119.3, 121.3, 124.9, 128.5, 131.2, 140.2, 169.1, 179.9, 184.5, 187.4 .

**Synthesis of (*S*)-*tert*-butyl 2(azidomethyl)pyrrolidine-1-carboxylate (14)**

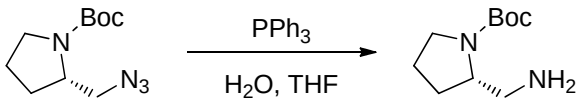



**12** **13** **14**

In a 25 mL round-bottom flask, **12** (2.01 g, 10 mmol) was dissolved in 10 mL of pyridine, and cooled down to 0 °C. Then, *p*-toluenesulfonyl chloride (2.29 g, 12 mmol) was added and the mixture was stirred at 0 °C for 6 h. After this time, the reaction mixture was diluted with 150 mL of diethyl ether and washed with 1M HCl, saturated $NaHCO_3$ and, finally, $H_2O$. The organic layer was dried with $Na_2SO_4$, filtered and concentrated under reduced pressure, to give **13** as a colorless oil (3.44 g, 97%).

**13** (3.44 g, 9.7 mmol) was dissolved in DMSO (75 mL) and sodium azide (3.43 g, 53.4 mmol) was added and the resulting mixture was heated to 65 °C for 19 h. Then, it was allowed to cool to room temperature, diluted with diethyl ether (50 mL), washed with $H_2O$ (3x30 mL) and brine (20 mL) and dried over $Na_2SO_4$. After removal of the solvent under reduced pressure, the title product (**14**) was obtained as a colorless oil. (1.74 g, 77%). It was not further purified and was stored in the refrigerator until used.

**Synthesis of (*S*)-*tert*-butyl-2-(aminomethyl)pyrrolidine-1-carboxylate (15)**

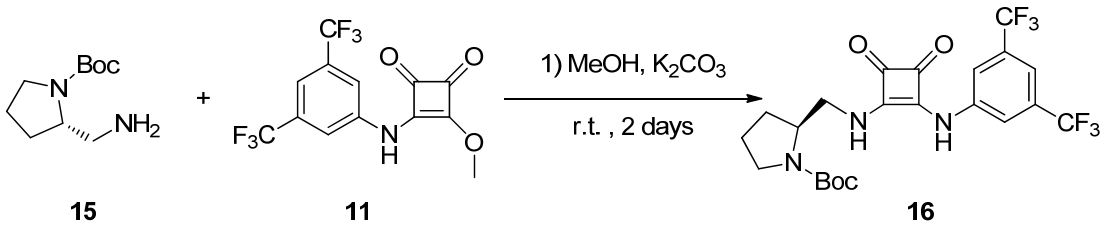



**14** **15**

The azide **14** (1.74 g, 7.66 mmol) in anhydrous THF (64 mL) was reduced with triphenylphosphane (4.02 g, 15.33 mmol) and $H_2O$ (0.28 ml, 15.33 mmol). The reaction mixture was heated to reflux until all the starting material had been consumed. The organic solvent was removed under reduced pressure. Diethyl ether (180 mL) was added to the remaining oil, and the pH of the aqueous phase was lowered to 1.75 with

2M HCl with vigorous stirring. The aqueous layer was separated and washed with diethyl ether (2 x 90 mL), and the pH was then adjusted to 13.0 (2 M NaOH). After extraction with DCM (5 x 80 mL), the combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. The amine **15** was obtained as a colorless liquid (1.11 g, 73% of yield) and used without additional purification.
$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.49 (s, 9 H), 1.70-2.01 (m, 6 H), 2.59-3.89 (bm, 5 H) .

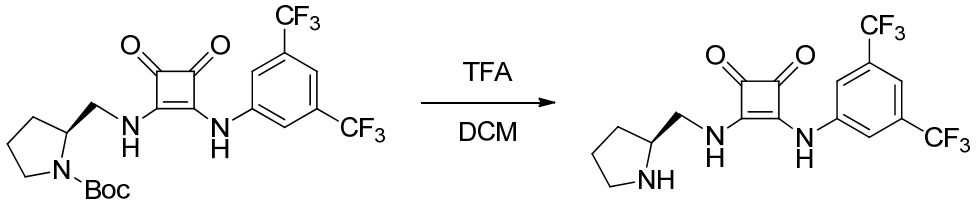
**Synthesis of (*S*)-*tert*-butyl-2-(((2-((3,5-bis(trifluoromethyl)phenyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)methyl)pyrrolidine-1-carboxylate (16)**




**15** **11** **16**

To a solution of **11** (1g, 2.95mmol) in MeOH (26 ml), **15** (0.562 g, 2.81 mmol) was added drop wise. Initially the reaction mixture became clear and the formation of white precipitate was observed over time. After 2 days of stirring at room temperature, the white precipitate was filtered, washed with a small amount of MeOH and dried.
$^1$H NMR (300 MHz, DMSO) $\delta$)1.51 (s, 9H), 2.07 (bm, 4H), 3.11 (bs, 1H), 3.31 (bm, 1H), 3.45 (bm, 2H), 3.90 (bm, 2H), 7.53 (s, 1H), 7.69 (bs, 1H), 8.21 (s, 2H) .

**Synthesis of (*S*)-3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(pyrrolidin-2-ylmethyl)amino)cyclobut-3ene-1,2-dione (C7)**




**16** **C7**

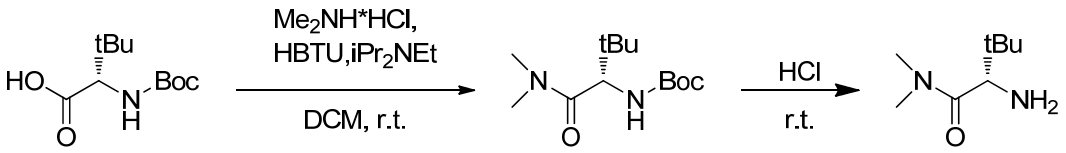
Subsequently, the collected white solid was suspended in DCM (17.6 ml) and TFA (4.4 ml) was added drop wise. After stirring overnight at r.t. , the reaction mixture was quenched with saturated aq. $NaHCO_3$ . the rapid formation of a white solid was observed as soon as basic pH was reached. Due to the low solubility of the product in common organic solvents, the solid was washed twice with $H_2O$ which was removed by decantation. The combined water phases were extracted with DCM/MeOH (10:1). The organic extracts were combined with the solid and concentrated under vacuum. After that, the residual water was azeotropically removed with toluene (20 mL) and the residue purified by FC on silica gel and then yielded (63%) .

$^1$H NMR (300 MHz, DMSO) $\delta$ 1.39-2.27 (m, 4H), 2.97 (bs, 1H), 3.05-3.32 (m, 1H), 3.67 8dt, $J$ = 13.7, 6.8 Hz, 1H), 3.84 (s, 1H), 4.50 (bs, 1H), 7.61 (s, 1H), 7.97 (s, 1H), 8.16 (s, 2H), 8.80 (bs, 1H) .

$^{13}$C NMR (75 MHz, DMSO) $\delta$ 22.9, 27.2, 44.5, 45.0, 59.3, 114.7, 115.0, 117.9, 118.9, 119.5, 119.6, 121.4, 125.0, 128.6, 128.8, 131.2, 131.6, 141.5, 158.9, 159.4, 163.3, 170.2, 180.7, 184.7 .

HRMS (ESI): calculated for C17H15F6N3O2·H$^+$ $[M+H]^+$: *m/z* = 408.1147, found: *m/z* = 408.1141 .

**Synthesis of (*S*)-2-amino-N,N,3,3-tetramethylbutanamide (25)**




**17** **18** **19**

**Step 1):** Diisopropylethylamine (1.52 mL, 8.75 mmol), then dimethylamine (0.224 g, 2.75 mmol) were added to a suspension of **17** (0.578 g, 2.5 mmol) and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) (1.04 g, 2.75 mmol) in DCM (25 mL) at 23°C. The reaction was stirred for 28 hours at 23 °C, then diluted with diethyl ether (50 mL), and washed twice with 1M hydrochloric acid (50 mL) then

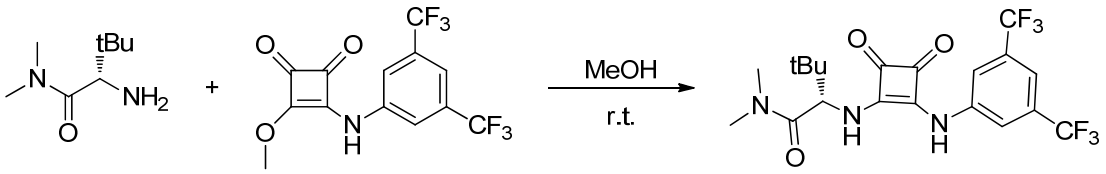
twice with saturated aqueous $NaHCO_3$ (50 mL), then once with brine. After drying over $Na_2SO_4$, the solution was concentrated, yielding the crude product (contaminated with tetramethylurea) as a foam which was used in the second step without further purification (0.605 g, 94% ).

$^1$H NMR (300 MHz, $CDCl_3$) 0.97 (s, 9H), 1.42 (s, 9H), 2.84 (s, 1H), 2.96 (s, 3H), 3.13 (s, 3H) .

**Step 2):** HCl (6 mL, 4M in dioxane) was added to crude Boc-2-amino-*N*,*N*-diisobutyl-3,3-dimethyl-butyramide (**18**) (2.5 mmol), and the resulting solution stirred at 23 °C for 2 hours. The mixture was concentrated to yield (S)-2-amino-N,N,3,3-tetramethylbutanamide hydrochloride (**19**) (contaminated with tetramethylurea) as a foam, which was used in next reaction without further purification (>99%).

$^1$H NMR (400 MHz, $CDCl_3$) 0.75-1.50 (bs, 9H), 2.80-3.40 (bm, 6H), 3.70 (s, 1H) .

**Synthesis of (*S*)-2-((2-((3,5-bis(trifluoromethyl)phenyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-*N*,*N*,3,3-tetramethylbutanamide (C8)**




**19** **11** **C8**

According to the synthesis of **C7**, to a solution of **11** (0.922 g, 2.50 mmol) in MeOH (25 ml), **19** (0.529 g, 2.50 mmol) was added drop wise. Initially the reaction mixture became clear and the formation of a precipitate was observed over time. After 2 days of stirring at room temperature, the white precipitate was filtered, washed with a small amount of MeOH and dried.

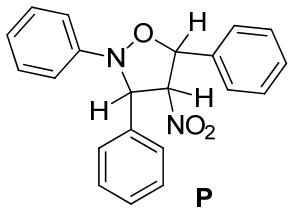
$^1$H NMR (300 MHz, DMSO) $\delta$ 0.97 (s, 9H), 2.90 (s, 3H), 3.10 (s, 3H), 5.17 (d, $J$ = 9.9 Hz, 1H), 7.65 (s, 1H), 8.06 (s, 2H), 8.28 (d, $J$ = 9.8 Hz, 1H), 10.46 (S, 1H).

$^{13}$C NMR (75 MHz, DMSO) $\delta$25.74, 35.03, 36.02, 37.80, 58.49, 114.75, 118.06, 121.35, 124.97, 131.15, 131.59, 141.11, 162.50, 168.83, 169.36, 180.29, 184.42.

HRMS (ESI): calculated for $C_{20}H_{21}F_6N_3O_3 \cdot Na^+$ $[M+Na]^+$: *m/z* = 488.1385, found: *m/z* = 488.1379 .

## 4.5. Organocatalyzed cicloaddition reaction with nitrones

**Data of the major diasteroisomer (P1)**




P

Chromatography: pentane/dichlomethane 5:3; Convertion: 79% in a yellow oil as a 4.3:1 mixture of two diastereomers.

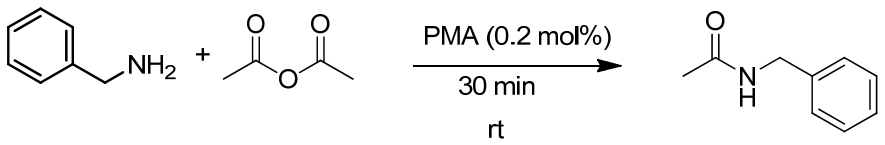
Major isomers (64% of yield) $^1$H NMR (300 MHz, $CDCl_3$) δ 5.46 (dd, *J* = 5.9, 4.2 Hz, 1H), 5.75 (d, *J* = 4.2Hz, 1H), 5.92(d, *J* = 5.9 Hz, 1H), 7.04-7.78 (m, 15H) .

$^{13}$C NMR δ 21.57, 74.19, 83.29, 101.79, 115.16, 123.18, 126.80, 128.34, 128.69, 129.11, 129.14, 129.35, 129.38, 135.38, 138.28, 149.31 .

HRMS (ESI): calculated for $C_{21}H_{18}N_2O_3 \cdot Na^+$ $[M+Na]^+$: *m/z* = 369.1215, found: *m/z* = 369.1210

## 4.7 Synthesis of benzyl amides

### Synthesis of *N*-benzylacetamide (B11)




**B11**

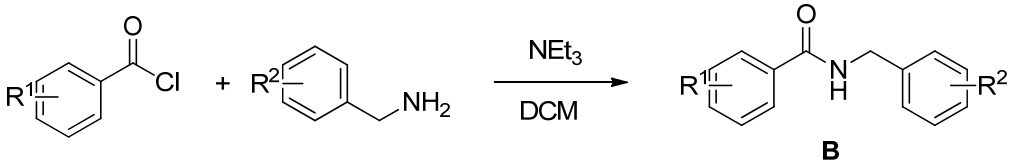
$H_3[P(MoO_{10})_4]\cdot nH_2O$ (PMA: 40 mg, 0.2 mol%) was added to a mixture of benzyl amine (10 mmol) and acetic anhydride (0.944 mL, 10 mmol). The reaction mixture was stirred at r.t. for 30 minutes. After completion of the reaction(by TLC), the mixture was diluted with a saturated aqueous $NaHCO_3$ (15 ml) and extracted with EtOAc (3x20 mL). Concentration of the combined organic layer under vacuum gave a crude mass, which was purified by FC; this gave the corresponding acetylated product (99%).

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.98 (s, 3H), 4.39 (d, $J$ = 5.7 Hz, 2H), 6.28 (s, 1H), 7.19-7.43 (m, 5H).

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 23.2, 43.7, 127.5, 127.9, 128.7, 138.3, 170.2 .

HRMS (ESI): calculated for $C9H11NO\cdot Na^+$ $[M+Na]^+$: *m/z* = 172.0738, found: *m/z* = 172.0735 .

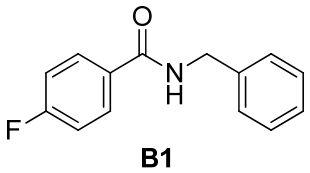
### General procedure for the synthesis of *N*-benzylbenzamide (B1-9)




**B**

The amine (4 mmol) in 10 ml of DCM was cooled with an ice bath. After 10 minutes the triethylamine (8 mmol) is added and the mixture is allowed to stir for other 10 minutes. After that time the phenyl chloride is added and then the mixture is slowly warm it up until r.t. and then stirred overnight. The product is purified by FC and then yielded (92-99%).

**N-benzyl-4-fluorobenzamide (B1)**



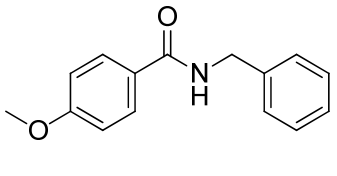

**B1**

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$4.62 (d, $J$ = 5.6 Hz, 2H), 6.45 (bs, 1H), 7.09 (t, $J$ = 8.6 Hz, 2H), 7.27-7.46 (m, 5H), 7.69-7.91 (m, 2H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 44.3, 115.6, 115.9, 127.8, 128.1, 128.9, 129.4, 129.5, 130.6, 160.7, 138.1, 163.2, 166.4, 166.5 .

HRMS (ESI): calculated for C14H12FNO·$Na^+$ $[M+Na]^+$: $m/z$ = 252.0801, found: $m/z$ = 252.0792 .

**N-benzyl-4-methoxybenzamide (B2)**



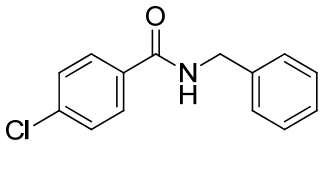

**B2**

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.84 (s, 3H), 4.62 (d, $J$ = 5.5 Hz, 2H), 6.45 (s, 1H), 6.85-6.97 (m, 2H), 7.21-7.46 (m, 5H), 7.71-7.84 (m, 2H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 44.2, 55.5, 113.9, 126.7, 127.7, 128.0, 128.9, 128.9, 138.5, 162.4, 167.0 .

HRMS (ESI): calculated for C15H15NO2·$Na^+$ $[M+Na]^+$: $m/z$ = 264.1000, found: $m/z$ = 264.0995 .

**N-benzyl-4-chlorobenzamide (B3)**



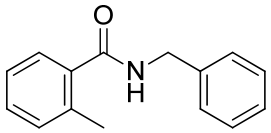

**B3**

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$4.63 (d, $J$ = 5.6 Hz, 2H), 6.45 (bs, 1H), 7.28-7.57 (m, 7H), 7.59-7.83 (m, 2H).

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 44.4, 127.9, 128.1, 128.5, 128.9, 132.8, 138.0, 166.4 .

HRMS (ESI): calculated for C14H12ClNO·$Na^+$ $[M+Na]^+$: $m/z$ = 268.0505, found: $m/z$ = 268.0496 .

**N-benzyl-2-methylbenzamide (B4)**



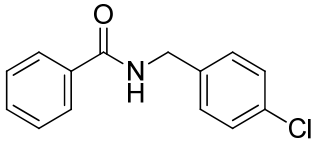
B4

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.46 (s, 3H), 4.61 (d, $J$ = 5.8 Hz, 2H), 6.13 (bs, 1H), 7.01-7.53 (m, 9H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 19.9, 44.0, 125.8, 126.8, 127.7, 127.9, 128.9, 130.1, 131.2, 136.3, 138.3, 170.0 .

HRMS (ESI): calculated for $C15H15NO{\cdot}Na^{+}$ $[M+Na]^{+}$: $m/z$ = 248.1051, found: $m/z$ = 248.1048 .

**N-(4-chlorobenzyl)benzamide (B5)**



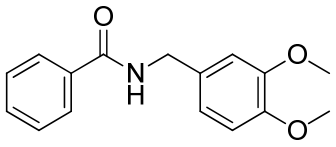
B5

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.60 (d, $J$ = 5.8Hz, 2H), 6.54 (s, 1H), 7.18-7.87 (m, 9H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 43.4, 127.1, 128.7, 128.9, 129.3, 131.8, 133.4, 134.2, 136.9, 167.6 .

HRMS (ESI): calculated for $C14H12ClNO{\cdot}Na^{+}$ $[M+Na]^{+}$: $m/z$ = 268.0505, found: $m/z$ = 268.0498 .

***N*-(3,4-dimethoxybenzyl)benzamide (B6)**



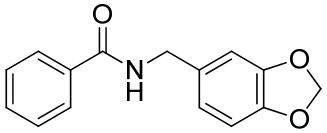
B6

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.85 (s, 3H), 3.86 (s, 3H), 4.57 (d, $J$ = 5.5 Hz, 2H), 6.45 (bs, 1H), 6.75-6.99 (m, 3H), 7.35-7.60 (m, 3H), 7.70-7.88 (m, 2H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 44.1, 56.0, 56.1, 111.3, 111.4, 120.4, 127.0, 128.7, 130.8, 131.7, 134.5, 148.7, 149.3, 167.4 .

HRMS (ESI): calculated for $C16H17NO3{\cdot}Na^{+}$ $[M+Na]^{+}$: $m/z$ = 294.1106, found: $m/z$ = 294.1096 .

***N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)benzamide (B7)**



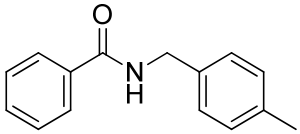
**B7**

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.50 (d, $J$ = 5.6 Hz, 2H), 5.92 (s, 2H), 6.63-6.70 (bs, 1H), 6.70-6.85 (m, 3H), 7.33-7.53 (m, 3H), 7.73-7.81 (m, 2H).

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 44.1, 108.5, 108.6, 121.3, 127.1, 128.7, 131.7, 132.2, 134.5, 147.1, 148.1, 167.5 .

HRMS (ESI): calculated for $C15H13NO3 \cdot Na^+$ $[M+Na]^+$: *m/z* = 278.0793, found: *m/z* = 278.0786 .

**N-(4-methylbenzyl)benzamide (B8)**



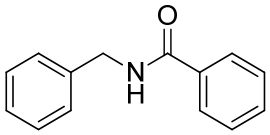
**B8**

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.35 (s, 3H), 4.61 (d, $J$ = 5.5Hz, 2H), 6.37 (bs, 1H), 6.88-7.94 (m, 9H).

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 21.3, 44.2, 127.1, 128.2, 128.8, 129.7, 131.7, 134.6, 135.3, 137.6, 167.5 .

HRMS (ESI): calculated for $C15H15NO \cdot Na^+$ $[M+Na]^+$: *m/z* = 248.1051, found: *m/z* = 248.1046 .

**N-benzylbenzamide (B9)**



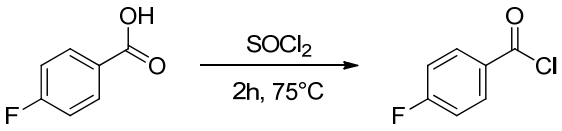
**B9**

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.65 (d, $J$ = 5.6 Hz, 2H), 6.46 (bs, 1H), 7.27-7.54 (m, 8H), 7.70-7.88 (m, 2H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 44.3, 76.7, 77.2, 77.4, 77.6, 127.1, 127.8, 128.1, 128.7, 128.9, 130.2, 131.7, 134.5, 138.3, 167.5 ..

HRMS (ESI): calculated for $C14H13NO \cdot Na^+$ $[M+Na]^+$: *m/z* = 234.0895, found: *m/z* = 234.0891 .

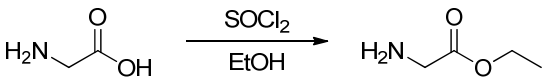
**Synthesis of 4-fluorobenzoyl chloride (22)**




**21** **22**

Thionyl chloride (1.96 ml, 25 mmol) and 4-fluorobenzoyl chloride (**21**) (0.70 g, 5 mmol) were heated for 2h at 75 °C. The usual work-up gave **22** that is used in the other reaction without further purification.

**Synthesis of ethyl-2-aminoacetate (23)**



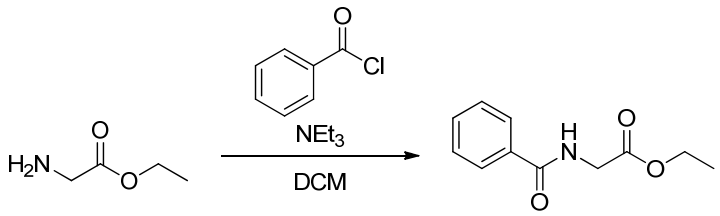

**23**

To a suspension of glycine (3.00 g, 40 mmol) in 40 ml of ethanol on an ice bath, thionyl chloride (11.62 ml, 160 mmol) was added drop wise for about 45 minutes and later refluxed for 1 h. Reaction was monitored through TLC by staining the plates with potassium permanganate reagent. The excess of ethanol was distilled off by adding 50 ml of toluene and the residue obtained was dried to get **23** as a white crystals (5.58 g, >99%).

$^{1}$H NMR (300 MHz, $D_2O$) $\delta$ 1.26 (bt, $J$ = 6.8 Hz, 3H), 3.88 (s, 2H), 4.27 (bd, $J$ = 7.1 Hz, 2H) .

$^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 13.1, 40.1, 63.2, 168.1 .

**Synthesis of ethyl-2-benzamidoacetate (B11)**




**23** **B11**

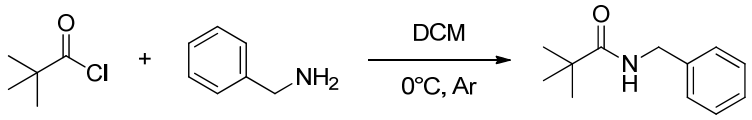
Glycine ethyl ester hydrochloride (**23**) (2.50 g, 18 mmol) in 50 ml of DCM was cooled with an ice bath. To the cold mixture was added with stirring $NEt_3$ (5.00 ml, 36 mmol). After 10 minutes of stirring benzoyl chloride (2.09 ml, 18 mmol) was introduced. Then, the mixture was allowed to slowly warm up to room temperature and stirring was continued overnight. DCM was removed under reduced pressure and the residue was taken up in saturated aqueous $NaHCO_3$ (*ca*. 50 ml) with stirring. After 30 minutes of stirring, **B11** precipitated and after filtration and drying, it was obtained as a crystalline white powder (3.52 g, 94%).

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.29 (t, $J$ = 7.2 Hz, 3H), 4.14-4.38 (m, 4H), 6.80 (bs, 1H), 7.34-7.58 (m, 3H), 7.71-7.88 (m, 2H).

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$14.3, 42.1, 61.8, 127.2, 128.8, 131.9, 133.9, 167.6, 170.3 .

HRMS (ESI): calculated for C11H13NO3·$Na^+$ $[M+Na]^+$: *m/z* =230.0793, found: *m/z* = 230.0788 .

**Synthesis of *N*-benzylpivalamide (B12)**




**25** **B12**

To a DCM solution ( 10 mL) of **25** (1.48 mL, 12 mmol) and *N*-methylimidazole (1.59 mL, 20 mmol), was added benzyl amine (0.980 ml, 10 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred overnight. Then, 3 M HCl was added to

the reaction mixture, and the organic layer was extracted with DCM three times. The combined organic layers were dried over anhydrous $MgSO_4$. After filtration and silica gel column, the desired amides were obtained in good yields ( 60%).

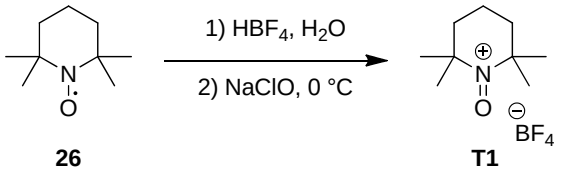
$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.23 (s, 9H), 4.44 (d, $J$ = 5.4Hz, 2H), 5.92 (bs, 1H), 7.18-7.43 (m, 5H) .

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 27.8, 38.9, 43.7, 127.6, 127.8, 128.9, 138.8, 178.5 .

HRMS (ESI): calculated for C12H17NO·$Na^+$ $[M+Na]^+$: *m/z* =214.1208, found: *m/z* = 214.1202 .

## 4.6. Synthesis of $T^+BF4^-$ and $NHAcT^+BF4^-$

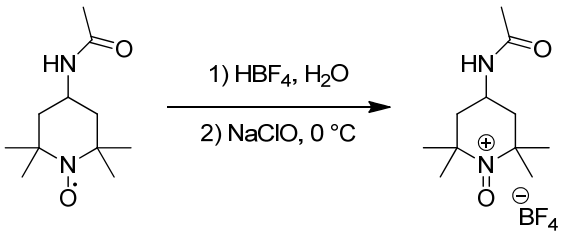
**Synthesis of 2,2,6,6-tetramethyl-1-oxopiperidin-1-ium tetrafluoroborate (T1):**




**26** **T1**

In a 50 mL round bottom flask, an aqueous solution of $HBF_4$ (48% aqueous solution, 2.95 mL, 22.08 mmol) was added to the heterogeneous solution of 2,2,6,6-tetramethylpiperidine-1-oxyl (3.00 g, 19.2 mmol) in distilled water (10 mL). The reaction mixture was stirred at room temperature for 30 min to give a yellow orange mixture. In ice bath, an aqueous solution of NaClO (13% aqueous solution, 5.06 mL, 9.6 mmol) was added to the solution for 1 h. The mixture is filtered with and the yellow solid was washed with cooled water (4 °C, 4 × 5 mL) and dichloromethane (3 × 5 mL). After dried under high vacuum at 50°C overnight, the product is obtained as a bright yellow solid (4.06 g, 87%).

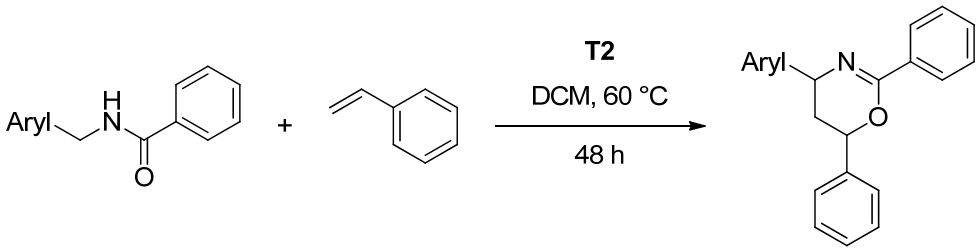
**Synthesis of 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidin-1-ium tetrafluoroborate (T2)**




27 T2

According to the procedure for the compound **T1,** the compound **T2** was obtained too as a yellow solid (48.5%).

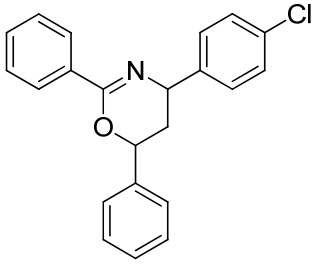
## 4.7. TEMPO-salt mediated tandem C-H functionalization/cyclization reaction




B O

**Data of the major diasteroisomers:**

**4-(4-chlorophenyl)-2,6-diphenyl-5,6-dihydro-4*H*-1,3-oxazine (O5)**



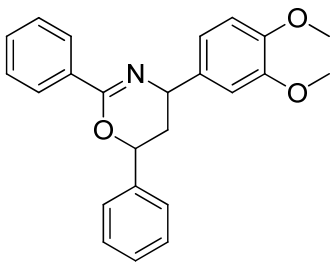

O5

Chromatography: pentane/dichlomethane/Ethylacetate 5.5:2:0.5 in gradient to obtain a 3:1 mixture of two diastereomers.

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.70 (dt, $J$ = 13.8, 11.6 Hz, 1H), 2.42 (ddd, $J$ = 13.6, 8.3, 5.2, 1H), 4.80 (dd, $J$ = 11.4,

4.7 Hz, 1H), 5.33 (dd, *J* = 11.7, 2.6 Hz, 1H), 7.17-7.62(m, 14H) .
HRMS (ESI): calculated for C14H13NO·$Na^+$ $[M+Na]^+$: *m/z* =348.1150, found: *m/z* = 348.1146 .

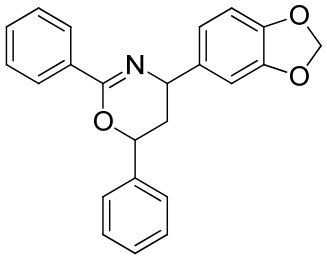
**4-(3,4-dimethylphenyl)-2,6-diphenyl-5,6-dihydro-4*H*-1,3-oxazine (O6)**



**O6**

Chromatography: pentane/dichlomethane/Ethylacetate 5.5:2:0.5 in gradient to obtain a 3:1 mixture of two diastereomers.
$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.87 (dt, *J* = 13.4, 11.6 Hz, 1H), 2.36 (ddd, *J* = 13.7, 8.4, 5.2 Hz, 1H), 3.88 (s, 6H), 4.90 (dd, *J* = 11.3, 4.6 Hz, 1H), 5.46 (dd, *J* = 11.8, 2.6 Hz, 1H), 7.30-7.67 (m, 13H) .
HRMS (ESI): calculated for C24H23NO3·$H^+$ $[M+H]^+$: *m/z* =374,1751, found: *m/z* = 374,1750 .

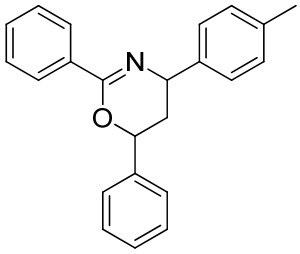
**4-(benzo[*d*][1,3]dioxol-5-yl)-2,6-diphenyl-5,6-dihydro-4*H*-1,3-oxazine (O7)**



**O7**

Chromatography: pentane/dichlomethane/Ethylacetate 5.5:2:0.5 in gradient to obtain a 2:1 mixture of two diastereomers.
$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.83 (dt, *J* = 13.5, 11.5 Hz, 1H), 2.51 (ddd, *J* = 13.6, 4.6, 2.5 Hz, 1H), 4.87 (dd, *J* = 11.4,4.6 Hz, 1H), 5.44 (dd, *J* = 11.8, 2.6 Hz, 1H), 5.95 (s, 2H), 6.74-8.22 (m, 13H) .
HRMS (ESI): calculated for C23H19NO3·$H^+$ $[M+H]^+$: *m/z* =358.1438, found: *m/z* = 358.1442 .

**2,6-diphenyl-4-(*p*-tolyl)-5,6-dihydro-4*H*-1,3-oxazine(O8)**



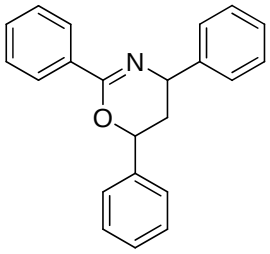
**O8**

Chromatography: pentane/dichlomethane/Ethylacetate 5.5:2:0.5 in gradient to obtain a 4:1 mixture of two diastereomers.

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.88 (dt, $J$ = 13.6, 11.6 Hz, 1H), 2.37 (s, 3H), 2.55 (ddd, $J$ = 13.7, 4.8, 2.6 Hz, 1H), 4.92 (dd, $J$ = 11.4, 4.7 Hz, 1H), 5.46 (dd, $J$ = 11.8, 2.6 Hz, 1H), 7.01-8.48 (m, 14H) .

HRMS (ESI): calculated for $C23H21NO \cdot H^+$ $[M+H]^+$: $m/z$ =328.1696, found: $m/z$ = 328.1692 .

**2,4,6-triphenyl-5,6-dihydro-4*H*-1,3-oxazine (O9)**



**O9**

Chromatography: pentane/dichlomethane/Ethylacetate 5.5:2:0.5 in gradient to obtain a 2.5:1 mixture of two diastereomers.

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.87 (dt, $J$ = 13.4, 11.5, Hz, 1H), 2.48-2.60 (ddd, 1H), 4.96 (dd, $J$ = 11.4, 4.6, Hz, 1H), 5.48 (dd, $J$ = 11.7, 2.6 Hz, 1H), 6.98-8.30 (m, 15H) .

HRMS (ESI): calculated for $C22H19NO \cdot H^+$ $[M+H]^+$: $m/z$ =314.1539, found: $m/z$ = 314.1543 .

## 5. Literature


[1] Berkessel, A; Groegel, H. *Asymmetric organocatalysis: from Biomimetic Concept to Applications in Asymmetric Synthesis* (Wiley-VCH, 2005).

[2] Number of publications with keyword "organocatalysis" (ISI web of knowledge in 2012)

[3] David W. C. MacMillan, *Nature* **2008**, *455*, 304 – 308.

[4] Hajos, Z. G.; Parrish, D.R. *Asimmetric synthesis of optically active polycyclic organic compounds*. German patent DE 2102623 (1971)

[5] Lelais, G.; MacMillan D. W. C. *Aldrichimica Acta* **2006**, *39*, 79 – 87.

[6] Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci.,* **2010**, *107*, 20678; Zhang, Z. Schreiner, P. *Chem. Soc. Rev.,* **2009**, *38*, 1187; Taylor, M. S. Jacobsen, E. N. *Angew. Chem. Int. Ed.,* **2006**, *45*, 1520

[7] Sigman, M. Jacobsen, E. N.. *J. Am. Chem. Soc.* **1998***, 120*, 4901 – 4902.

[8] Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157–160 .

[9] Bernardi, L.; Fini, F.; Fochi, M.; Ricci, A. *Chimia,* **2007**, *61*, 224.

[10] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.,* **2003**, *125*, 12672.

[11] Reviews: a) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7496; b) Connon, S. J.; *Chem. Commun.* **2008**, 2499; c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; d) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632; e) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785; f) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229; g) Zhang, Z.; Schreiner, P. *Chem. Soc. Rev.* **2009**, *38*, 1187.

[12] For related computational studies: a) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151; b) Tan, B.; Lu, Y.; Zeng, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682; c) Cucinotta, C. S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. L. *Chem. Eur. J.* **2009**, *15*, 7931; d) Hammar, P. ; Marcelli, T.; Hiemstra, H.; Himo, F. *Adv. Synth. Catal.* **2007**, *349*, 2537; e) Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16016.

[13] Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci A. *Angew. Chem. Int. Ed.,* **2005**, *44*, 6576.

[14] (a) Pessisier, H. *Tetrahedron* **1997**, *63*, 3235 – 3285; (b) Gothelf, K.V.; Jørgensen, J. A. *Chem. Rev*. **1998**, *98*, 863 – 909;

[15] (a) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *75*, 604. (b) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *75*, 742.

[16] Padwa, A. *1,3-Dipolar cycloaddition chemistry*, Wiley, New York, 1984. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; John Wiley and Sons: Hoboken NJ, **2003**.

[17] Lv, Y.; Zhong, G. *Chem. Commun*. **2010**, *46*, 2504 – 2506.

[18] Frederickson, M. *Tetrahedron* **1997**, *53*, 403.

[19] Gothelf, K. V.; Jorgensen, K. A. *Chem. Commun.* **2000**, 1449 – 1458.

[20] Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874 – 9875.

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

[22] (a) Rios, R.; Ibrahem, I.; Vesely, J.; Zhao, G.-L.; C_ordova, A. *Tetrahedron Lett*. **2007**, *48*, 5701 – 5705; (b) Chow, S. S.; Nevalainen, M.; Evans, C. A.; Johannes, C. W. *Tetrahedron Lett*. **2007**, *48*, 277 – 280.

[23] Du, W.; Liu, Y.-K.; Yue, L.; Chen, Y.-C. *Synlett* **2008**, 2997 – 3000.

[24] Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed*. **2008**, *47*, 2411 – 2413.

[25] Gioia, C.; Fini, F.; Mazzanti, A.; Bernardi, L.; Ricci, A. *J. Am. Chem. Soc.* **2009**, *131*, 9614 – 9615.

[26] Wirt, U.; Fröhlich, R.; Wünsch, B. *Tetrahedron: Asymmetry*, **2005**, *16*, 2199 – 2202

[27] Yang, M. G.; Shi, J.; Modi, D. P.; Wells, J. *Bioorg. Med. Chem. Lett.*, **2007,** *17, 14,* 3910 – 3915

[28] Opaleva, E. N.; Dogatina, A. V. Ionin, B. I. *Russ. J. Gen. Chem,* **1977**, *67*, 347 – 348.

[29] Kaboudin, B. *Tetrahedron Lett*. **2000**, *41*, 3169 – 3171.

[30] Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635 – 1649.

[31] Sibi, M. P.; Manyem, S. *Org. Lett*. **2002**, *4*, 2929 – 2932.

[32] Texier-Boullet, F.; Klein, B.; Hamelin, J. *Synthesis*, **1986**, 409 – 411.

[33] Sibi, M. P.; *J. Am. Chem. Soc.* **2007**, 8064 – 8065.

[34] Aschwanden, P.; Kværnø, L.; Geisser, R.; Kleinbeck, F;. Carreira E. M. *Org. Lett.* **2005,** *7*, 5741 – 5742.

[35] Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *Synthesis* **2009**, 3174 – 3176.

[36] Evans, D. A.; Song, H.-J.; Fandrick K. R. *Org. Lett.* **2006**, *8*, 3351 – 3354.

[37] H., Konishi, T., Y., Lam, J., P., Malerich and V., H., Rawal, *Org. Lett.* **2010**, *12*, 2028 – 2031.

[38] Albrecht, Ł.; Dickmeiss, G.; Cruz Acosta, F.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543.

[39] Lednicer, D.; Mitsche, L. A. *The Organic Chemistry of Drug Synthesis*, *Vol 7*, Wiley, New York, **1997.**

[40] Review on C(sp3)-H bond functionalization adjacent to nitrogen in heterocycles: K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069 – 1084. For selected recent reviews on cross-dehydrogenative couplings, including amino α-C(sp3)-H bond functionalizations: a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335 – 344; b) Scheuermann, C. J. *Chem. Asian J.* **2009**, *4*, 436; c) Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, 353 – 369; d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780 – 1824; e) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215 – 1292.

[41] For a recent overview on catalytic hydroaminoalkylations, see: Roesky, P.W. *Angew. Chem. Int. Ed.* **2009**, *48*, 4892 – 4894. For the initial studies, involving activation of α-C-H bond in apposition to an amino group, see: a) Clerici, M. G.; Maspero, F. *Synthesis* **1980**, 305 – 306; b) Nugent, W. A.; Ovenall, D. W.; Holmes, S. J. *Organometallics* **1983**, *2*, 161 – 162. For the formation of linear products using a metal-catalyzed reaction, see for example: a) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935 – 10941; b) Pan, S.; Endo, K.; Shibata, T.*Org. Lett.* **2011**, *13*, 4692 – 4695.

[42] a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817 – 3856; b) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431 – 1628, and references cited therein. See also: c) Zaugg, H. E. *Synthesis* **1970**, 49 – 73; d) "Addition to N-Acyliminiumions": Hiemstra, H.; Speckamp, W. N. *Comprehensive Organic Syntheses*, Vol. 2 (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**. For an example of an electrochemical approach

using α-$SiMe_3$ as a leaving group, see: Suga, S.; Tsutsui, Y.; Nagaki, A.; Yoshida, J. *Org. Lett.* **2003**, *5*, 945 – 947, and references cited therein.

[43] Richter, H.; Fröhlich, R.; Daniliuc, C. G.; Mancheño, O. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 8656 – 8660.

[44] For the synthesis of $T^+BF_4^-$: a) Yonekuta, Y.; Oyaizu, K.; Nishide, H. *Chem. Lett.* **2007**, *36*, 866 – 867. b) Richter, H.; Mancheño O. G. *Eur. J. Org. Chem.* **2010**, 4460–4467.

[45] Bobbitt, J. M.; Merbouh N. *Org. Synth.***2005**, *82*, 80 – 86.

**Acronym:**

| | |
|---|---|
| Ad | Adamantane |
| $Ac_2O$ | Acetic anhydride |
| B: | Base |
| Bn | Benzyl |
| Boc | t-Butyloxycarbonyl ($COtC_4H_9$) |
| CSA | Camphorsulfonic Acid |
| d, t, dd | Doublet, triplet, double doublet, |
| dt, ddd, m | Double triplet, double double doublet, multiplet. |
| DCM | Dichloromethane |
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| DMF | N,N-DiMethylFormamide |
| DMSO | DiMethyl SulfOxide |
| d.r. | Diastereoisomeric Ratio |
| *E* | Entgegen (opposite, trans) |
| ee | Enantiomeric Excess |
| equiv. | Equivalent |
| EtOAc | Ethyl acetate |
| EWG | Electron Withdrawing Group |
| FC | Flash column |
| h | Hour(s) |
| LG | Leaving Group |
| NMM | 4-MethylMorpholine |
| Nu: | Nucleophilic |
| Ph | Phenylic group |
| PTC | Phase Transfer Catalysis |
| Py | Pyridine |
| r.t. | Room temperature |
| s, bs | Singlet, broadened singlet |
| t | Time |
| T | Temperature |
| tBu | tert-Butyl |
| TFA | Trifluoroacetic acid |

| | |
|---|---|
| THF | TetraHydroFuran |
| TLC | Thin layer chromatography (for analysis) |
| Ts | Tosyl (p-$CH_3C_6H_4SO_2$) |
| *p*-TsCl | 4-Methylbenzenesulfonyl chloride |
| TsOH | 4-Methylbenzenesulfonic acid |
| *Z* | Zusammen (together, cis) |

# SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006
Version 5.0 Revision Date 11.09.2012
Print Date 03.10.2012
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

## 1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

### 1.1 Product identifiers

Product name : N-Benzylideneaniline N-oxide

Product Number : S861243
Brand : Aldrich
CAS-No. : 1137-96-8

### 1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Laboratory chemicals, Manufacture of substances

### 1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich S.r.l.
Via Gallarate 154
I-20151 MILANO

Telephone : +39 02-3341-7310
Fax : +39 02-3801-0737
E-mail address : eurtechserv@sial.com

### 1.4 Emergency telephone number

Emergency Phone # : +39 02-6610-1029 (Centro Antiveleni Niguarda Ca' Granda - Milano)

## 2. HAZARDS IDENTIFICATION

### 2.1 Classification of the substance or mixture

**Classification according to Regulation (EC) No 1272/2008 [EU-GHS/CLP]**
Acute toxicity, Oral (Category 4)
Eye irritation (Category 2)

**Classification according to EU Directives 67/548/EEC or 1999/45/EC**
Harmful if swallowed.

### 2.2 Label elements

**Labelling according Regulation (EC) No 1272/2008 [CLP]**
Pictogram

Signal word Warning

Hazard statement(s)
H302 Harmful if swallowed.
H319 Causes serious eye irritation.

Precautionary statement(s)
P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

Supplemental Hazard Statements none

**According to European Directive 67/548/EEC as amended.**
Hazard symbol(s)

R-phrase(s)
R22 Harmful if swallowed.

S-phrase(s) none

**2.3 Other hazards** - none

## 3. COMPOSITION/INFORMATION ON INGREDIENTS

**3.1 Substances**

Formula : C13H11NO
Molecular Weight : 197,24 g/mol

| Component | Concentration |
|---|---|
| **N-Benzylideneaniline N-oxide** | |
| CAS-No. 1137-96-8<br>EC-No. 214-509-2 | - |

## 4. FIRST AID MEASURES

**4.1 Description of first aid measures**

**General advice**
Consult a physician. Show this safety data sheet to the doctor in attendance.

**If inhaled**
If breathed in, move person into fresh air. If not breathing, give artificial respiration. Consult a physician.

**In case of skin contact**
Wash off with soap and plenty of water. Consult a physician.

**In case of eye contact**
Rinse thoroughly with plenty of water for at least 15 minutes and consult a physician.

**If swallowed**
Never give anything by mouth to an unconscious person. Rinse mouth with water. Consult a physician.

**4.2 Most important symptoms and effects, both acute and delayed**
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

**4.3 Indication of any immediate medical attention and special treatment needed**
no data available

## 5. FIREFIGHTING MEASURES

**5.1 Extinguishing media**

**Suitable extinguishing media**
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

**5.2 Special hazards arising from the substance or mixture**
Carbon oxides, nitrogen oxides (NOx)

**5.3 Advice for firefighters**
Wear self contained breathing apparatus for fire fighting if necessary.

**5.4 Further information**
no data available

## 6. ACCIDENTAL RELEASE MEASURES

**6.1 Personal precautions, protective equipment and emergency procedures**
Use personal protective equipment. Avoid dust formation. Avoid breathing vapors, mist or gas. Ensure adequate ventilation. Avoid breathing dust.

### 6.2 Environmental precautions
Do not let product enter drains.

### 6.3 Methods and materials for containment and cleaning up
Pick up and arrange disposal without creating dust. Sweep up and shovel. Keep in suitable, closed containers for disposal.

### 6.4 Reference to other sections
For disposal see section 13.

## 7. HANDLING AND STORAGE

### 7.1 Precautions for safe handling
Avoid contact with skin and eyes. Avoid formation of dust and aerosols.
Provide appropriate exhaust ventilation at places where dust is formed.Normal measures for preventive fire protection.

### 7.2 Conditions for safe storage, including any incompatibilities
Store in cool place. Keep container tightly closed in a dry and well-ventilated place.

### 7.3 Specific end uses
no data available

## 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

### 8.1 Control parameters

**Components with workplace control parameters**

### 8.2 Exposure controls

**Appropriate engineering controls**
Handle in accordance with good industrial hygiene and safety practice. Wash hands before breaks and at the end of workday.

**Personal protective equipment**

**Eye/face protection**
Safety glasses with side-shields conforming to EN166 Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

**Skin protection**
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

The selected protective gloves have to satisfy the specifications of EU Directive 89/686/EEC and the standard EN 374 derived from it.

**Body Protection**
Complete suit protecting against chemicals, The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

**Respiratory protection**
For nuisance exposures use type P95 (US) or type P1 (EU EN 143) particle respirator.For higher level protection use type OV/AG/P99 (US) or type ABEK-P2 (EU EN 143) respirator cartridges. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

## 9. PHYSICAL AND CHEMICAL PROPERTIES

### 9.1 Information on basic physical and chemical properties

| | | |
|---|---|---|
| a) | Appearance | Form: solid |
| b) | Odour | no data available |
| c) | Odour Threshold | no data available |

| | | |
|---|---|---|
| d) | pH | no data available |
| e) | Melting point/freezing point | Melting point/range: 113 - 114 °C |
| f) | Initial boiling point and boiling range | no data available |
| g) | Flash point | no data available |
| h) | Evaporation rate | no data available |
| i) | Flammability (solid, gas) | no data available |
| j) | Upper/lower flammability or explosive limits | no data available |
| k) | Vapour pressure | no data available |
| l) | Vapour density | no data available |
| m) | Relative density | no data available |
| n) | Water solubility | no data available |
| o) | Partition coefficient: n-octanol/water | log Pow: 1,88 |
| p) | Autoignition temperature | no data available |
| q) | Decomposition temperature | no data available |
| r) | Viscosity | no data available |
| s) | Explosive properties | no data available |
| t) | Oxidizing properties | no data available |

**9.2 Other safety information**
no data available

## 10. STABILITY AND REACTIVITY

**10.1 Reactivity**
no data available

**10.2 Chemical stability**
no data available

**10.3 Possibility of hazardous reactions**
no data available

**10.4 Conditions to avoid**
no data available

**10.5 Incompatible materials**
Strong oxidizing agents

**10.6 Hazardous decomposition products**
Other decomposition products - no data available

## 11. TOXICOLOGICAL INFORMATION

**11.1 Information on toxicological effects**

**Acute toxicity**
no data available

**Skin corrosion/irritation**
no data available

**Serious eye damage/eye irritation**
no data available

**Respiratory or skin sensitization**
Prolonged or repeated exposure may cause allergic reactions in certain sensitive individuals.

**Germ cell mutagenicity**
no data available

**Carcinogenicity**

IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

**Reproductive toxicity**
no data available

**Specific target organ toxicity - single exposure**
no data available

**Specific target organ toxicity - repeated exposure**
no data available

**Aspiration hazard**
no data available

**Potential health effects**

| | |
|---|---|
| **Inhalation** | May be harmful if inhaled. May cause respiratory tract irritation. |
| **Ingestion** | Harmful if swallowed. |
| **Skin** | May be harmful if absorbed through skin. May cause skin irritation. |
| **Eyes** | Causes eye irritation. |

**Signs and Symptoms of Exposure**
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

**Additional Information**
RTECS: Not available

## 12. ECOLOGICAL INFORMATION

**12.1 Toxicity**
no data available

**12.2 Persistence and degradability**
no data available

**12.3 Bioaccumulative potential**
no data available

**12.4 Mobility in soil**
no data available

**12.5 Results of PBT and vPvB assessment**
no data available

**12.6 Other adverse effects**
no data available

## 13. DISPOSAL CONSIDERATIONS

**13.1 Waste treatment methods**

**Product**
Offer surplus and non-recyclable solutions to a licensed disposal company. Contact a licensed professional waste disposal service to dispose of this material. Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber.

**Contaminated packaging**
Dispose of as unused product.

## 14. TRANSPORT INFORMATION

**14.1 UN number**

ADR/RID: - IMDG: - IATA: -

**14.2 UN proper shipping name**

ADR/RID: Not dangerous goods
IMDG: Not dangerous goods
IATA: Not dangerous goods

**14.3 Transport hazard class(es)**

ADR/RID: - IMDG: - IATA: -

**14.4 Packaging group**

ADR/RID: - IMDG: - IATA: -

**14.5 Environmental hazards**

ADR/RID: no IMDG Marine pollutant: no IATA: no

**14.6 Special precautions for user**

no data available

## 15. REGULATORY INFORMATION

This safety datasheet complies with the requirements of Regulation (EC) No. 1907/2006.

**15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture**

no data available

**15.2 Chemical Safety Assessment**

no data available

## 16. OTHER INFORMATION

**Further information**



The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

# SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006
Version 4.3 Revision Date 15.01.2012
Print Date 03.10.2012
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

## 1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

### 1.1 Product identifiers

Product name : Styrene

Product Number : W323306
Brand : Aldrich
Index-No. : 601-026-00-0
CAS-No. : 100-42-5

### 1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Laboratory chemicals, Manufacture of substances

### 1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich S.r.l.
Via Gallarate 154
I-20151 MILANO

Telephone : +39 02-3341-7310
Fax : +39 02-3801-0737
E-mail address : eurtechserv@sial.com

### 1.4 Emergency telephone number

Emergency Phone # : +39 02-6610-1029 (Centro Antiveleni Niguarda Ca' Granda - Milano)

## 2. HAZARDS IDENTIFICATION

### 2.1 Classification of the substance or mixture

**Classification according to Regulation (EC) No 1272/2008 [EU-GHS/CLP]**
Eye irritation (Category 2)
Flammable liquids (Category 3)
Acute toxicity, Inhalation (Category 4)
Skin irritation (Category 2)

**Classification according to EU Directives 67/548/EEC or 1999/45/EC**
Flammable. Harmful by inhalation. Irritating to eyes and skin.

### 2.2 Label elements

**Labelling according Regulation (EC) No 1272/2008 [CLP]**
Pictogram

Signal word Warning

Hazard statement(s)
H226 Flammable liquid and vapour.
H315 Causes skin irritation.
H319 Causes serious eye irritation.
H332 Harmful if inhaled.

Precautionary statement(s)
P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

Supplemental Hazard none

Statements

**According to European Directive 67/548/EEC as amended.**

Hazard symbol(s)

R-phrase(s)

| | |
|---|---|
| R10 | Flammable. |
| R20 | Harmful by inhalation. |
| R36/38 | Irritating to eyes and skin. |

S-phrase(s)

| | |
|---|---|
| S23 | Do not breathe gas/fumes/vapour/spray. |

**2.3 Other hazards**

Lachrymator.

## 3. COMPOSITION/INFORMATION ON INGREDIENTS

**3.1 Substances**

Synonyms : Phenylethylene
Vinylbenzene

Formula : $C_8H_8$ $C_8H_8$

Molecular Weight : 104,15 g/mol

| Component | Concentration |
|---|---|
| **Styrene** | |
| CAS-No. 100-42-5<br>EC-No. 202-851-5<br>Index-No. 601-026-00-0 | - |

## 4. FIRST AID MEASURES

**4.1 Description of first aid measures**

**General advice**
Consult a physician. Show this safety data sheet to the doctor in attendance.

**If inhaled**
If breathed in, move person into fresh air. If not breathing, give artificial respiration. Consult a physician.

**In case of skin contact**
Wash off with soap and plenty of water. Consult a physician.

**In case of eye contact**
Rinse thoroughly with plenty of water for at least 15 minutes and consult a physician.

**If swallowed**
Do NOT induce vomiting. Never give anything by mouth to an unconscious person. Rinse mouth with water. Consult a physician.

**4.2 Most important symptoms and effects, both acute and delayed**
Dermatitis, Central nervous system depression, Nausea, Dizziness, Headache

**4.3 Indication of any immediate medical attention and special treatment needed**
no data available

## 5. FIREFIGHTING MEASURES

**5.1 Extinguishing media**

**Suitable extinguishing media**
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

**5.2 Special hazards arising from the substance or mixture**
Carbon oxides

**5.3 Advice for firefighters**
Wear self contained breathing apparatus for fire fighting if necessary.

**5.4 Further information**
Use water spray to cool unopened containers.

## 6. ACCIDENTAL RELEASE MEASURES

**6.1 Personal precautions, protective equipment and emergency procedures**
Use personal protective equipment. Avoid breathing vapors, mist or gas. Ensure adequate ventilation. Remove all sources of ignition. Beware of vapours accumulating to form explosive concentrations. Vapours can accumulate in low areas.

**6.2 Environmental precautions**
Prevent further leakage or spillage if safe to do so. Do not let product enter drains. Discharge into the environment must be avoided.

**6.3 Methods and materials for containment and cleaning up**
Contain spillage, and then collect with an electrically protected vacuum cleaner or by wet-brushing and place in container for disposal according to local regulations (see section 13).

**6.4 Reference to other sections**
For disposal see section 13.

## 7. HANDLING AND STORAGE

**7.1 Precautions for safe handling**
Avoid contact with skin and eyes. Avoid inhalation of vapour or mist.
Keep away from sources of ignition - No smoking.Take measures to prevent the build up of electrostatic charge.

**7.2 Conditions for safe storage, including any incompatibilities**
Store in cool place. Keep container tightly closed in a dry and well-ventilated place. Containers which are opened must be carefully resealed and kept upright to prevent leakage.

Recommended storage temperature: 2 - 8 °C

Light sensitive.

**7.3 Specific end uses**
no data available

## 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

**8.1 Control parameters**

**Components with workplace control parameters**

**8.2 Exposure controls**

**Appropriate engineering controls**
Handle in accordance with good industrial hygiene and safety practice. Wash hands before breaks and at the end of workday.

**Personal protective equipment**

**Eye/face protection**
Face shield and safety glasses Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

**Skin protection**
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

The selected protective gloves have to satisfy the specifications of EU Directive 89/686/EEC and the standard EN 374 derived from it.

**Body Protection**
Complete suit protecting against chemicals, Flame retardant antistatic protective clothing, The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

**Respiratory protection**
Where risk assessment shows air-purifying respirators are appropriate use a full-face respirator with multi-purpose combination (US) or type ABEK (EN 14387) respirator cartridges as a backup to engineering controls. If the respirator is the sole means of protection, use a full-face supplied air respirator. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

## 9. PHYSICAL AND CHEMICAL PROPERTIES

### 9.1 Information on basic physical and chemical properties

| | | |
|---|---|---|
| a) | Appearance | Form: liquid, clear<br>Colour: colourless |
| b) | Odour | no data available |
| c) | Odour Threshold | no data available |
| d) | pH | no data available |
| e) | Melting point/freezing point | Melting point/range: -31 °C - lit. |
| f) | Initial boiling point and boiling range | 145 - 146 °C - lit. |
| g) | Flash point | 32,0 °C - closed cup |
| h) | Evaporation rate | no data available |
| i) | Flammability (solid, gas) | no data available |
| j) | Upper/lower flammability or explosive limits | Upper explosion limit: 8,9 %(V)<br>Lower explosion limit: 1,1 %(V) |
| k) | Vapour pressure | 16,5 hPa at 37,7 °C<br>5,7 hPa at 15,0 °C |
| l) | Vapour density | no data available |
| m) | Relative density | 0,906 g/cm3 at 25 °C |
| n) | Water solubility | insoluble |
| o) | Partition coefficient: n-octanol/water | no data available |
| p) | Autoignition temperature | 490,0 °C480,0 °C |
| q) | Decomposition temperature | no data available |
| r) | Viscosity | no data available |
| s) | Explosive properties | no data available |
| t) | Oxidizing properties | no data available |

### 9.2 Other safety information
no data available

## 10. STABILITY AND REACTIVITY

**10.1 Reactivity**
no data available

**10.2 Chemical stability**
no data available

**10.3 Possibility of hazardous reactions**
no data available

**10.4 Conditions to avoid**
Heat, flames and sparks.

**10.5 Incompatible materials**
Oxidizing agents, Copper

**10.6 Hazardous decomposition products**
Other decomposition products - no data available

## 11. TOXICOLOGICAL INFORMATION

**11.1 Information on toxicological effects**

**Acute toxicity**
LD50 Oral - rat - 2.650 mg/kg
Remarks: Behavioral:Somnolence (general depressed activity). Liver:Other changes.

LC50 Inhalation - rat - 4 h - 12.000 mg/m3

**Skin corrosion/irritation**
Skin - rabbit - Skin irritation

**Serious eye damage/eye irritation**
Eyes - rabbit - Eye irritation - 24 h

**Respiratory or skin sensitization**
no data available

**Germ cell mutagenicity**
Laboratory experiments have shown mutagenic effects.

**Carcinogenicity**

This product is or contains a component that has been reported to be possibly carcinogenic based on its IARC, ACGIH, NTP, or EPA classification.

IARC: 2B - Group 2B: Possibly carcinogenic to humans (Styrene)

**Reproductive toxicity**
no data available

**Specific target organ toxicity - single exposure**
no data available

**Specific target organ toxicity - repeated exposure**
no data available

**Aspiration hazard**
no data available

**Potential health effects**

| | |
|---|---|
| **Inhalation** | Harmful if inhaled. Causes respiratory tract irritation. |
| **Ingestion** | May be harmful if swallowed. |
| **Skin** | May be harmful if absorbed through skin. Causes skin irritation. |
| **Eyes** | Causes serious eye irritation. |

**Signs and Symptoms of Exposure**
Dermatitis, Central nervous system depression, Nausea, Dizziness, Headache

**Additional Information**
RTECS: WL3675000

## 12. ECOLOGICAL INFORMATION

### 12.1 Toxicity

| | |
|---|---|
| Toxicity to fish | LC50 - Leuciscus idus (Golden orfe) - 17,00 - 66,00 mg/l - 48 h |
| | NOEC - Pimephales promelas (fathead minnow) - 4 mg/l - 96 h |
| | LC50 - Pimephales promelas (fathead minnow) - 4,08 mg/l - 96 h |
| | LOEC - Pimephales promelas (fathead minnow) - 7,6 mg/l - 96 h |
| Toxicity to daphnia and other aquatic invertebrates | EC50 - Daphnia magna (Water flea) - 182,00 mg/l - 24 h |
| | NOEC - Daphnia magna (Water flea) - 1,9 mg/l - 48 h |
| | LOEC - Daphnia magna (Water flea) - 3,3 mg/l - 48 h |
| | EC50 - Daphnia magna (Water flea) - 4,7 mg/l - 48 h |

### 12.2 Persistence and degradability

| | |
|---|---|
| Biodegradability | aerobic - Exposure time 28 d<br>Result: > 60 % - Readily biodegradable. |

### 12.3 Bioaccumulative potential
no data available

### 12.4 Mobility in soil
no data available

### 12.5 Results of PBT and vPvB assessment
no data available

### 12.6 Other adverse effects
Toxic to aquatic life.
no data available

## 13. DISPOSAL CONSIDERATIONS

### 13.1 Waste treatment methods

**Product**
Burn in a chemical incinerator equipped with an afterburner and scrubber but exert extra care in igniting as this material is highly flammable. Offer surplus and non-recyclable solutions to a licensed disposal company.

**Contaminated packaging**
Dispose of as unused product.

## 14. TRANSPORT INFORMATION

### 14.1 UN number

| | | |
|---|---|---|
| ADR/RID: 2055 | IMDG: 2055 | IATA: 2055 |

### 14.2 UN proper shipping name

| | |
|---|---|
| ADR/RID: | STYRENE MONOMER, STABILIZED |
| IMDG: | STYRENE MONOMER, STABILIZED |
| IATA: | Styrene monomer, stabilized |

### 14.3 Transport hazard class(es)

| | | |
|---|---|---|
| ADR/RID: 3 | IMDG: 3 | IATA: 3 |

**14.4 Packaging group**

| | | |
|---|---|---|
| ADR/RID: III | IMDG: III | IATA: III |

**14.5 Environmental hazards**

| | | |
|---|---|---|
| ADR/RID: no | IMDG Marine pollutant: no | IATA: no |

**14.6 Special precautions for user**
no data available

## 15. REGULATORY INFORMATION

This safety datasheet complies with the requirements of Regulation (EC) No. 1907/2006.

**15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture**
no data available

**15.2 Chemical Safety Assessment**
no data available

## 16. OTHER INFORMATION

**Further information**



The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

# SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006
Version 5.0 Revision Date 08.09.2012
Print Date 03.10.2012
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

## 1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

### 1.1 Product identifiers

Product name : TEMPO

Product Number : 214000
Brand : Aldrich
CAS-No. : 2564-83-2

### 1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Laboratory chemicals, Manufacture of substances

### 1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich S.r.l.
Via Gallarate 154
I-20151 MILANO

Telephone : +39 02-3341-7310
Fax : +39 02-3801-0737
E-mail address : eurtechserv@sial.com

### 1.4 Emergency telephone number

Emergency Phone # : +39 02-6610-1029 (Centro Antiveleni Niguarda Ca' Granda - Milano)

## 2. HAZARDS IDENTIFICATION

### 2.1 Classification of the substance or mixture

**Classification according to Regulation (EC) No 1272/2008 [EU-GHS/CLP]**
Skin corrosion (Category 1B)

**Classification according to EU Directives 67/548/EEC or 1999/45/EC**
Causes burns.

### 2.2 Label elements

**Labelling according Regulation (EC) No 1272/2008 [CLP]**
Pictogram

Signal word Danger

Hazard statement(s)
H314 Causes severe skin burns and eye damage.

Precautionary statement(s)
P280 Wear protective gloves/ protective clothing/ eye protection/ face protection.
P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P310 Immediately call a POISON CENTER or doctor/ physician.

Supplemental Hazard Statements none

**According to European Directive 67/548/EEC as amended.**

Hazard symbol(s)

R-phrase(s)

| | |
|---|---|
| R34 | Causes burns. |

S-phrase(s)

| | |
|---|---|
| S26 | In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. |
| S36/37/39 | Wear suitable protective clothing, gloves and eye/face protection. |
| S45 | In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). |

**2.3 Other hazards** - none

## 3. COMPOSITION/INFORMATION ON INGREDIENTS

**3.1 Substances**

Formula : $C_9H_{18}NO$

Molecular Weight : 156,25 g/mol

| Component | | Concentration |
|---|---|---|
| **2,2,6,6-Tetramethylpiperidinooxy** | | |
| CAS-No. | 2564-83-2 | - |
| EC-No. | 219-888-8 | |

## 4. FIRST AID MEASURES

**4.1 Description of first aid measures**

**General advice**
Consult a physician. Show this safety data sheet to the doctor in attendance.

**If inhaled**
If breathed in, move person into fresh air. If not breathing, give artificial respiration. Consult a physician.

**In case of skin contact**
Take off contaminated clothing and shoes immediately. Wash off with soap and plenty of water. Consult a physician.

**In case of eye contact**
Rinse thoroughly with plenty of water for at least 15 minutes and consult a physician.

**If swallowed**
Do NOT induce vomiting. Never give anything by mouth to an unconscious person. Rinse mouth with water. Consult a physician.

**4.2 Most important symptoms and effects, both acute and delayed**
Cough, Shortness of breath, Headache, Nausea, Vomiting

**4.3 Indication of any immediate medical attention and special treatment needed**
no data available

## 5. FIREFIGHTING MEASURES

**5.1 Extinguishing media**

**Suitable extinguishing media**
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

**5.2 Special hazards arising from the substance or mixture**
Carbon oxides, nitrogen oxides (NOx)

**5.3 Advice for firefighters**
Wear self contained breathing apparatus for fire fighting if necessary.

### 5.4 Further information
no data available

## 6. ACCIDENTAL RELEASE MEASURES

### 6.1 Personal precautions, protective equipment and emergency procedures
Use personal protective equipment. Avoid dust formation. Avoid breathing vapors, mist or gas. Ensure adequate ventilation. Evacuate personnel to safe areas. Avoid breathing dust.

### 6.2 Environmental precautions
Do not let product enter drains.

### 6.3 Methods and materials for containment and cleaning up
Pick up and arrange disposal without creating dust. Sweep up and shovel. Keep in suitable, closed containers for disposal.

### 6.4 Reference to other sections
For disposal see section 13.

## 7. HANDLING AND STORAGE

### 7.1 Precautions for safe handling
Avoid formation of dust and aerosols.
Provide appropriate exhaust ventilation at places where dust is formed.Normal measures for preventive fire protection.

### 7.2 Conditions for safe storage, including any incompatibilities
Store in cool place. Keep container tightly closed in a dry and well-ventilated place.

Recommended storage temperature: 2 - 8 °C

### 7.3 Specific end uses
no data available

## 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

### 8.1 Control parameters

**Components with workplace control parameters**

### 8.2 Exposure controls

**Appropriate engineering controls**
Handle in accordance with good industrial hygiene and safety practice. Wash hands before breaks and at the end of workday.

**Personal protective equipment**

**Eye/face protection**
Face shield and safety glasses Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

**Skin protection**
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

The selected protective gloves have to satisfy the specifications of EU Directive 89/686/EEC and the standard EN 374 derived from it.

**Body Protection**
Complete suit protecting against chemicals, The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

**Respiratory protection**
Where risk assessment shows air-purifying respirators are appropriate use a full-face particle respirator type N100 (US) or type P3 (EN 143) respirator cartridges as a backup to engineering controls. If the respirator is the sole means of protection, use a full-face supplied air respirator. Use

respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

## 9. PHYSICAL AND CHEMICAL PROPERTIES

### 9.1 Information on basic physical and chemical properties

| | | |
|---|---|---|
| a) | Appearance | Form: crystalline<br>Colour: red |
| b) | Odour | no data available |
| c) | Odour Threshold | no data available |
| d) | pH | no data available |
| e) | Melting point/freezing point | Melting point/range: 36 - 38 °C - lit. |
| f) | Initial boiling point and boiling range | no data available |
| g) | Flash point | 67 °C - closed cup |
| h) | Evaporation rate | no data available |
| i) | Flammability (solid, gas) | no data available |
| j) | Upper/lower flammability or explosive limits | no data available |
| k) | Vapour pressure | no data available |
| l) | Vapour density | no data available |
| m) | Relative density | no data available |
| n) | Water solubility | no data available |
| o) | Partition coefficient: n-octanol/water | no data available |
| p) | Autoignition temperature | no data available |
| q) | Decomposition temperature | no data available |
| r) | Viscosity | no data available |
| s) | Explosive properties | no data available |
| t) | Oxidizing properties | no data available |

### 9.2 Other safety information

no data available

## 10. STABILITY AND REACTIVITY

### 10.1 Reactivity

no data available

### 10.2 Chemical stability

no data available

### 10.3 Possibility of hazardous reactions

no data available

### 10.4 Conditions to avoid

no data available

### 10.5 Incompatible materials

Strong oxidizing agents, Strong acids

### 10.6 Hazardous decomposition products

Other decomposition products - no data available

## 11. TOXICOLOGICAL INFORMATION

### 11.1 Information on toxicological effects

**Acute toxicity**
no data available

**Skin corrosion/irritation**
Skin - rabbit - Severe skin irritation - 4 h

**Serious eye damage/eye irritation**
Eyes - rabbit - Severe eye irritation - 24 h

**Respiratory or skin sensitization**
no data available

**Germ cell mutagenicity**
no data available

**Carcinogenicity**

IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

**Reproductive toxicity**
no data available

**Specific target organ toxicity - single exposure**
no data available

**Specific target organ toxicity - repeated exposure**
no data available

**Aspiration hazard**
no data available

**Potential health effects**

| | |
|---|---|
| **Inhalation** | May be harmful if inhaled. Material is extremely destructive to the tissue of the mucous membranes and upper respiratory tract. |
| **Ingestion** | May be harmful if swallowed. Causes burns. |
| **Skin** | May be harmful if absorbed through skin. Causes skin burns. |
| **Eyes** | Causes eye burns. |

**Signs and Symptoms of Exposure**
Cough, Shortness of breath, Headache, Nausea, Vomiting

**Additional Information**
RTECS: TN8991900

## 12. ECOLOGICAL INFORMATION

### 12.1 Toxicity
no data available

### 12.2 Persistence and degradability
no data available

### 12.3 Bioaccumulative potential
no data available

### 12.4 Mobility in soil
no data available

### 12.5 Results of PBT and vPvB assessment
no data available

**12.6 Other adverse effects**
no data available

## 13. DISPOSAL CONSIDERATIONS

**13.1 Waste treatment methods**

**Product**
Offer surplus and non-recyclable solutions to a licensed disposal company. Contact a licensed professional waste disposal service to dispose of this material. Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber.

**Contaminated packaging**
Dispose of as unused product.

## 14. TRANSPORT INFORMATION

**14.1 UN number**

| | | |
|---|---|---|
| ADR/RID: 3263 | IMDG: 3263 | IATA: 3263 |

**14.2 UN proper shipping name**

| | |
|---|---|
| ADR/RID: | CORROSIVE SOLID, BASIC, ORGANIC, N.O.S. (2,2,6,6-Tetramethylpiperidinooxy) |
| IMDG: | CORROSIVE SOLID, BASIC, ORGANIC, N.O.S. (2,2,6,6-Tetramethylpiperidinooxy) |
| IATA: | Corrosive solid, basic, organic, n.o.s. (2,2,6,6-Tetramethylpiperidinooxy) |

**14.3 Transport hazard class(es)**

| | | |
|---|---|---|
| ADR/RID: 8 | IMDG: 8 | IATA: 8 |

**14.4 Packaging group**

| | | |
|---|---|---|
| ADR/RID: II | IMDG: II | IATA: II |

**14.5 Environmental hazards**

| | | |
|---|---|---|
| ADR/RID: no | IMDG Marine pollutant: no | IATA: no |

**14.6 Special precautions for user**
no data available

## 15. REGULATORY INFORMATION

This safety datasheet complies with the requirements of Regulation (EC) No. 1907/2006.

**15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture**
no data available

**15.2 Chemical Safety Assessment**
no data available

## 16. OTHER INFORMATION

**Further information**

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.