Organocatalytic tandem reactions of polyfunctional compounds for the synthesis of enantioenriched heterocycles

TESI DI LAUREA SPERIMENTALE

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1. Introduction

1.1. Asymmetric organocatalysis

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 different types of chiral agents that can imprint chirality in reactions. The first method relies on chiral auxiliaries, i.e. on enantiopure compounds that are temporarily incorporated in a starting substrate to enable an asymmetric transformation. The second methodology is based on chiral substrates from a chiral pool source, used to afford enantiopure products. The last approach for the construction of enantiopure molecules is enantioselective catalysis using chiral catalysts. Until recently, the catalysts employed for enantioselective synthesis of organic compounds fell into two general categories – transition metal complexes and enzymes.

In enzymatic catalysis, a prochiral substrate is transformed by an enzyme into a chiral product. Enzymes usually achieve high values of enantioselction because they have a particular active site that it is created by a specific protein structure; other favourable aspects of their use are the very mild operating conditions and the absence of toxicity. Drawbacks are the elevated cost of isolated enzymes, and the generally narrow scope of enzymatic reactions.

Metallorganic catalysis employs instead a transition metal with enantiopure organic ligands, to carry out an asymmetric reaction. The advantage of this type of approach is a usually very low catalyst loading (substrate/catalyst ratio is up to 1,000,000/1) because of the very high TON or TOF parameters. The drawbacks are many; the first is that some metals have an elevated cost; moreover, metal complexes are often oxygen and moisture sensitive, and therefore the reaction solvent must be ultra-dry and oxygen-free. The most important drawback is however the elevate cost of the purification of the obtained products. Contamination with the sometimes highly toxic metal species must be avoided especially when the product is used for pharmaceutical applications.
Between the extremes of transition metal catalysis and enzymatic transformations, a third approach to the catalytic production of enantiomerically pure organic compounds has emerged – organocatalysis.¹

Organocatalysts are purely “organic” molecules, i.e. composed of (mainly) carbon, hydrogen, nitrogen, oxygen, sulphur and phosphorous atoms. Organocatalysts have several advantages. They are usually robust (organic molecules do not have the problem of getting oxidised by air, and they are resistant to water), inexpensive and readily available. They do not need to be used in special reaction vessels, so they feature easy working procedures. Organocatalysts are generally non-toxic for humans and environment and, because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, such as pharmaceutical products.

For all these reasons and for the possible green industrial applications, in the past decade organocatalysis has witnessed a very important development that can be noticed in the exponential increase in publications numbers. In Figure 1 it is shown the trend from 2000 to our days.

![Figure 1: Number of publications with keyword “organocatalysis” (SciFinder from 2000 to 2011).](image)

Unfortunately, there are also some drawbacks in organocatalytic methods, the major one being the high catalyst loading, with a typical substrate/catalyst ratio of 100/1 or less. This particular aspect prevents easy scale-up and the possible use in industrial settings.

Organocatalysts are classified in different classes depending on how they activate the substrates for the catalytic process. Nowadays, it is possible to distinguish three main areas of activation modes represented in Table 1:

- covalent catalysis
- non-covalent catalysis
- phase-transfer catalysis

In the covalent approach, the catalyst creates an activated complex characterised by the formation of a covalent interaction with the prochiral substrate.

In this area, three different mechanisms can be identified:

- enamine catalysis
- iminium-ion catalysis
- nucleophilic catalysis

Enamine catalysis is typical of primary or secondary amines and it is based on the formation of an enamine with aldehydes or ketones. α-Amino acids, such as for example L-proline and its derivatives, can be used as catalysts. The reversible formation of an enamine intermediate with the carbonyl compound activates the α-carbon of the starting substrate for reaction with electrophiles.

Iminium-ion catalysis is based instead on the capacity of chiral secondary or primary amines to function as enantioselective catalysts for several transformations that traditionally employ Lewis acid catalysts. The reversible formation of iminium ions from α,β-unsaturated ketones or aldehydes and the amine catalysts activates the double bond of the unsaturated carbonyl compound towards nucleophilic attack.

Nucleophilic catalysis involves a nucleophilic nitrogen, phosphorous, oxygen, sulphur or carbon atom for the formation of a covalent bond with a substrate. One of the most interesting branches is represented by carbene based catalysts. Deprotonation of e.g. a 1,2,4-triazole gives an active carbene species, which reacts with an aldehyde forming the so-called Breslow intermediate, that in turn adds to a second electrophile.
The second mode of activation is based on weak (non-covalent) interactions between catalysts and prochiral substrates. The main interactions are hydrogen-bonding and electrostatic.

To better describe this type of activation, it is useful to divide it according to three different mechanisms:

- hydrogen-bond catalysis
- Brønsted acid catalysis
- Brønsted base catalysis

Hydrogen-bonding is one of the most dominant forces in molecular interaction and recognition in biological systems. Hydrogen-bond catalysis uses H-bond donating chiral derivatives, e.g. thioureas, to imprint enantioselection. These catalysts form well-defined multiple hydrogen-bond interactions with the prochiral substrate. This powerful activation mode has become the foundation of a large and dynamic area of research.

Brønsted acid catalysis uses highly acidic catalysts to protonate a substrate, which results activated for nucleophilic addition. The most efficient catalysts recently developed are phosphoric acids derived from chiral binaphtyl scaffolds. They are strongly acidic, with $pK_a$ around 1 in water. Because of their capacity to activate carbonyl compounds e.g. imines through protonation, a wide range of nucleophiles have been demonstrated to participate in asymmetric nucleophilic addition processes. Notably, these chiral phosphoric acids can be considered to be bifunctional organocatalysts as, besides the acidic OH group, the P=O group can serve as a Lewis base. As demonstrated in some cases, both functionalities play a key role in the asymmetric transformation.

Chiral Brønsted bases are a very useful class of organocatalyst; the activation mode is opposite to that of Brønsted acid as they exert their activity mainly activating the nucleophilic component through deprotonation. The enantioselection is due to the strong ionic interactions between the catalyst and the substrate during the attack to the electrophilic partner. Cinchona alkaloids are certainly the most representative members of this class of organocatalysts. Also in this case the presence of a Lewis basic site (quinuclidine nitrogen) and of a Lewis acidic site (H-bonding) makes Cinchona alkaloids bifunctional catalysts.

Therefore, both Brønsted acid and bases species are able to mimic one of the fundamental enzymatic catalyst competencies: bifunctionality, that is, the ability of a
catalyst to employ Lewis/Brønsted acidic and Lewis/Brønsted basic functionalities synergistically to bring about the activation of both the nucleophilic and electrophilic components of a reaction simultaneously. A further example is given by Takemoto catalyst, represented in Table 1, which joins a basic tertiary amino group (Brønsted base catalysis) with a thiourea moiety (H-bond catalysis). Many other modified thiourea derivatives belong to this class of organocatalyst.

A conceptually different activation of organic substrates for asymmetric reactions is Phase-Transfer Catalysis (PTC). Phase-transfer catalysis mediated by chiral quaternary ammonium salts is based on a unique ion-pair-mediated reaction. The reaction pathway involves three main steps: 1) deprotonation of the active compound with a base, which generally occurs at the interface between two layers (either liquid/liquid or liquid/solid phases); 2) extraction of the anion into the bulk organic phase by ion exchange with the cation of the chiral quaternary ammonium salt, which forms a lipophilic ion pair; and 3) reaction of the ion pair with the electrophilic reagent followed by the concomitant regeneration of the catalyst.

Among the quaternary ammonium salt catalysts, Cinchona alkaloid derivatives have again been shown to be particularly efficient, but recently other types of quaternary salts not deriving from the chiral pool have been developed.
<table>
<thead>
<tr>
<th>Class of activation</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>Activation Mode</th>
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<tbody>
<tr>
<td>Covalent Catalysis</td>
<td>Enamine</td>
<td><img src="image" alt="Enamine Catalyst" /></td>
<td><img src="image" alt="Enamine Activation" /></td>
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<tr>
<td></td>
<td>Iminium-ion</td>
<td><img src="image" alt="Iminium-ion Catalyst" /></td>
<td><img src="image" alt="Iminium-ion Activation" /></td>
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<tr>
<td></td>
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<tr>
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<td><img src="image" alt="Hydrogen-bonding Catalyst" /></td>
<td><img src="image" alt="Hydrogen-bonding Activation" /></td>
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<tr>
<td>Brønsted base</td>
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<tr>
<td>Bifunctional acid-base</td>
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<td><img src="image" alt="Phase-transfer Catalyst" /></td>
<td><img src="image" alt="Phase-transfer Activation" /></td>
</tr>
</tbody>
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*Table 1: Activation mode in organocatalysis.*
1.2. *Cinchona* alkaloids

*Cinchona* alkaloids are a large class of compounds extracted from the bark of *Cinchona ledgeriana* (Figura 2).

![Image of Cinchona ledgeriana](image)

**Figure 2:** *Cinchona ledgeriana.*

This tree is cultivated above 1400 m in equatorial climatic zones, between Africa, Latin America and Indonesia (isle of Java). In Figure 3 are represented the most common structures: quinine (QN), quindine (QD), cinchonidine (CD), cinchonine (CN) with their Sigma-Aldrich prize and purity.

![Image of cinchona alkaloids](image)

**Figure 3:** The four main *Cinchona* alkaloids.

Approximately 700 tons of cinchona alkaloids are extracted annually and nearly half of it is used in the food and beverages industry as a bitter additive. The other major use of these alkaloids, especially quinine and quindine, deals with medicine since they are

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respectively an anti-malarial drug and a cardiac depressant. The *Cinchona* alkaloids have enjoyed a rich history in science, medicine, and chemistry.³

Since the development of the concept of organocatalysis in 2000, a great development of highly stereoselective reactions involving catalysts derived from *Cinchona* alkaloids occurred.⁴ For these remarkable results *Cinchona* alkaloids are nowadays recognised as useful chiral scaffolds for the preparation of “privileged catalyst”.⁵

The key for their successful use in organocatalysis derives from the easy derivatization of the main structure and the presence of different functional groups. The structure of the four main *Cinchona* alkaloids can be divided into three different parts: the quinoline ring, the 1,2-amino alcohol subunit and the quinuclidine moiety (Figure 4).

![Figure 4: Structure of Cinchona alkaloids.](image)

The structure contains five stereogenic centers, including a chiral nitrogen group; since it is the 1,2-amino alcohol subunit that is usually responsible for the catalytic activity, the enantioselection of the products depends on the configuration of these chiral centers. Quinine and quinidine as well cinchonidine and cinchonine present opposite absolute configurations at these centres (see Figure 3); for this reason these pairs of diastereoisomers often act as enantiomers and are named pseudoenantiomers (or quasienantiomers). Furthermore, the structure reported in Figure 4 presents two different active sites: the tertiary amino group, responsible for base/nucleophilic activation, and the secondary alcoholic group, capable of acid/hydrogen-bond activation.

Concerning functionalization, the structure presents different sites for simple selective transformations as represented in Figure 5. The secondary 9-hydroxy group can be easily

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derivatised or replaced by different groups, delivering at this position ethers, esters, ureas, amides, free amino group moieties and so on. Some of these transformations are concomitant with the inversion of configuration at the stereocenter. Also the 6'-methoxy group can be readily manipulated giving a free phenolic OH group, or even substituted with nitrogen functionalities such as (thio)urea moieties.

Even more important is the possibility to alkylate the tertiary nitrogen in order to obtain a quaternary chiral ammonium salt, valuable as a phase-transfer catalyst. Moreover, some sites such as the quinuclidinic double bond or the 9-hydroxy group are suitable for anchoring the structure to a solid support in order to obtain a heterogeneous catalyst.

Figure 5: Functionalisations on Cinchona Alkaloids.

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1.3. Domino (Cascade) catalysis

Natural compounds are very important for many applications, for example as pharmaceutical and agrochemical products. These compounds have often an elevated grade of structural sophistication which gives biological activities.

The demand for natural compounds is, for these reasons, very high. However, the natural sources are often insufficient. A typical example is Taxol, represented in Figure 6. Since its discovery, Taxol has been regarded as one of the most significant advances in cancer therapy. Although Taxol’s biological activity profile initially attracted the interest of the National Cancer Institute, further evaluation and even clinical trials were limited due to a major supply crisis.

![Figure 6: Taxol](image)

Isolation of Taxol from natural source was impractical since it gave low yields and led to ecological destruction of *Taxus Brevifolia* in old-grown forests. Each tree yielded only about 2 Kg of bark and approximately 10 Kg of dried bark were required to obtain 1 g of Taxol. As a result, extensive research efforts were initiated to find alternative sources of Taxol which included semisynthesis and chemical synthesis. Six independent total synthesis of Taxol have been achieved since 1994 as shown in Scheme 1. To date,
Wender’s synthesis of Taxol is the shortest and most efficient, with 37 steps and 0.4% overall yield starting from verbenone. It is thus clear how even the most efficient synthesis that has been accomplished to date cannot be employed to furnish quantities of Taxol on a scale suitable for therapy.

Scheme 1: Chemical synthesis of Taxol by stop-and-go approach.

Nature has evolved in a million of years and now has reached extraordinary levels of efficiency via enzymatic reactions for the construction of the targets. Nature biosynthesis in a short time converts simple raw materials in elaborate products with elevated selectivity, delivering various types of compounds. The rapidity of the synthesis is due to the fact that when an intermediate is produced by an enzymatic reaction, it is rapidly converted by another enzyme. The overall transformation is thus a multi-catalytic cascade reaction.

For example, the biosynthesis of Taxol uses a continuous series of 4 cascade sequences starting from the universal diterpene precursor geranylgeranyl diphosphate (GGPP) Scheme 2.

Scheme 2: Enzymatic cascade catalysis generating Taxol.

As described in the Taxol example, man-made procedures are instead stop-and-go or step-by-step syntheses, wherein synthesis is conducted as a stepwise process punctuated


by the isolation and purification of intermediates at each stage of the sequence. The synthesis of natural compounds generally involves an elevated number of steps, for example 20-30. As a consequence, the synthetic sequences start with large quantities (kg) of substrates, but give the desired products in little amounts, usually in the order of milligrams. This approach is obviously not compatible with the construction of natural compounds on industrial scale.

In contrast with the stop-and-go approach, one-pot reactions use a single reaction vessel, where a substrate is transformed to the product through multiple sequential reactions without the need of intermediate purifications. This approach undoubtedly reduces process time and waste production, and it has a clear link to industrial processes, for which economic and ecological profitability are the main issues of concern.

As one of the major hot topics in organic chemistry throughout the past decade, asymmetric organocatalysis has introduced new perspectives with regard to the design and application of one-pot processes in enantioselective transformations. Marked by its robust nature, organocatalysis is probably the most condition-tolerant method within the modern toolbox of asymmetric catalysis. Furthermore, organocatalysts are tolerant of numerous functional groups and can be employed under mild reaction conditions.

A domino reaction\(^\text{10}\) is defined as a reaction involving two or more bond forming transformations which take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step. All the transformation is effected by a single catalytic mechanism. Tandem (cascade) catalysis is reserved to describe sequential elaboration of the substrate transpiring via two (or more) mechanistically distinct catalytic processes. It allows the organic synthesis of complex multinuclear molecules from a single acyclic precursor.\(^\text{11}\)

Organocatalytic cascade\(^\text{12}\) reactions are emerging as a new tool in total synthesis of natural products; the number of publications from 2005 to 2011 has increased year by year and the target molecules have become more and more complex.\(^\text{13}\)

Organocatalytic cascade reactions have been able to exploit various types of activation, by combining for example enamine and iminium catalysis (tandem, triple-cascade even

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quadruple-cascade). An example of combining enamine and iminium catalytic modes is given in Scheme 3.\textsuperscript{14}

\textbf{Scheme 3:} Mannich-Michael cascade reaction used in the synthesis of \textit{ent}-Dihydrocorynantheol.

Nowadays, organocatalytic cascade reactions are not limited to amine catalysts. Significant contributions have also been made in the field of hydrogen-bonding and Brønsted–acid catalysis, as shown in the example reported in Scheme 4.\textsuperscript{15}


Scheme 4: Synthesis of natural tetrahydroquinolines via a double organocatalytic transfer hydrogenation.
2. Objective

Pentatonic heterocyclic scaffolds are very common in natural products. In particular, the tetrahydrofuran (THF)\(^{16}\) and the oxazine\(^{17}\) moieties are present in a variety of biologically active products. These facts have given great impetus to the research for new synthetic methodologies aimed at the preparation of these scaffold. As previously described, tandem and domino reactions have proved to be an effective tool in developing environmentally benign processes, since they generate several bonds in a “single pot” operation thereby minimizing the amount of waste that is generated.

Recently, our attention was captured by two synthetic procedures, reported in the literature, that allowed the preparation of pentatonic heterocyclic scaffolds via tandem reactions in a highly diastereoselective, but not enantioselective, manner.

Gharpure and Reddy\(^{18}\) reported an efficient synthesis of substituted tetrahydrofuran derivatives employing a tandem S\(_{N}\)2-Michael addition to vinylogous carbonates (Scheme 5). The authors proved that the reactivity of vinylogous carbonates is not limited to more classical radical reactions, but they are excellent Michael acceptors towards active methylene compounds such as malonates even under anionic conditions.

![Scheme 5: Tetrahydrofurans through a S\(_{N}\)2-Michael tandem sequence.](image-url)

Liu and Xu\(^{19}\) developed instead a new strategy for the atom-economic synthesis of fused oxazolines via a domino reaction, involving an aldol-cyclisation-Michael sequence of ethyl isocyanoacetate on the appropriate polyfunctional substrate (Scheme 6).

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Scheme 6: Fused tricyclic oxazolines through a domino aldol-cyclisation-Michael sequence.

The group where I worked during this thesis, has undertaken since some years several studies regarding the synthesis of new enantioenriched organic molecules through the use of enantioselective PTC.\(^\text{20}\) Besides, phase-transfer catalysis has proven to be very useful for carrying out asymmetric transformations with the types of nucleophiles that were employed by Gharpure and Reddy (active methylene compounds), and Liu and Xu (isocyanooacetates) in their studies.\(^\text{5}\) Consequently, it was decided to explore the possibility of synthesizing enantioenriched tetrahydrofuran and oxazoline derivatives, starting from the polyfunctionalised substrates described above, using asymmetric PTC methodologies (Scheme 7).

Scheme 7: Planned catalytic asymmetric domino reactions on polyfunctionalised substrates.

3. Results and Discussion

3.1. S\textsubscript{N}2-Michael tandem reactions

As mentioned, in 2010 Gharpure and Reddy\textsuperscript{18} reported that THF derivatives 3 can be assembled by the reaction of the iodine derivatives 1 with active methylene compounds 2, in the presence of catalytic amounts of the appropriate base under homogeneous conditions (NaOH in DMSO), \textit{via} a tandem S\textsubscript{N}2-Michael addition sequence (Scheme 8). To test the feasibility of the proposed THF derivatives synthesis in an enantioselective fashion via PTC catalysis, the preparation of two iodide derivatives 1 (bearing two different esters) was undertaken.

![Scheme 8: Gharpure and Reddy’s Synthesis of THF derivatives.](image)

3.1.1. Synthesis of substrates 1a and 1b

The synthesis of substrates 1a and 1b was achieved through a three steps methodology starting from ethylene glycol, optimizing literature procedures.

Ethylene glycol was mono-tosylated (Ts) in the presence of TsCl and catalytic amounts of N,N-dimethylaminopyridine (DMAP), in pyridine as the solvent (Scheme 9).\textsuperscript{21}

![Scheme 9: Synthesis of mono-protected ethylene glycol.](image)

The obtained tosyl derivative was reacted further with the commercially available ethyl propiolate using N-methyl morpholine (NMM) as the base in dichloromethane (DCM) as the solvent,\textsuperscript{18} providing the corresponding ethyl acrylate derivative in 62% yield after chromatographic purification (Scheme 10). Subsequently, the same reaction was repeated

using benzyl propiolate, which was first obtained in quantitative yield from propiolic acid as described in Scheme 11.\(^{22}\)

**Scheme 10:** Synthesis of acrylates precursors of 1a and 1b.

\[
\begin{align*}
\text{OTs} & \quad + \quad \text{NMM} \\
\text{OH} & \quad + \quad \text{DCM} \\
r_{t.}, & \quad 3 \text{ h} \\
\text{work up} & \quad \text{R= Et Y= 62\%} \\
\text{R= Bn Y= 60\%} & 
\end{align*}
\]

**Scheme 11:** Synthesis of benzyl propiolate.

The last step of the synthesis of substrates 1a and 1b was an \(\text{S}_2\) reaction between the OTs derivatives and sodium iodide, as shown in Scheme 12. Compound 1a was obtained as a yellow oil in 57\% yield, and compound 1b as a dark-yellow oil in 91\% yield.

**Scheme 12:** Synthesis of substrates 1a and 1b.

3.1.2. Reactivity of substrates 1a and 1b

We decided to first perform the \(\text{S}_2\)-Michael tandem reaction utilizing 1a as the model compound and a series of active methylene compounds 2, reported in Figure 8, in toluene as the solvent and using tetra-\(n\)-butylammonium bromide (TBAB, Figure 7) as the PTC catalyst, varying the inorganic base. We screened a few inorganic bases for each transformation, limiting our choice to bases which are typically used in PTC reactions with nucleophiles featuring a pK\(_a\) of 11-17 in DMSO, such as compounds 2.\(^{23}\) These bases are potassium carbonate, the stronger potassium phosphate, and cesium carbonate. It must be noted that even if cesium carbonate and potassium carbonate feature the same basicity, cesium carbonate is usually much more active under PTC conditions because its larger cation makes the base itself and the ion-pairs resulting from nucleophile deprotonation more reactive and more available in the organic layer. The crude mixtures

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\(^{22}\) Hoffman-La Roche Inc., Patent US5128448 A1, 1992

obtained from these reactions were analysed by $^1$H NMR spectroscopy to check if some product was formed, and eventually determine the conversion of the reaction. For each nucleophile employed, in Table 2 are reported the best results. The primary objective of this screening was the evaluation of the feasibility of this synthetic procedure under PTC conditions. The second was the synthesis and the isolation of the racemic products, which are necessary for the determination of the enantiomeric excess by chiral stationary phase HPLC. All the reactions were then repeated under homogeneous conditions ($K_2CO_3$ in DMSO as solvent), used in the original report, to compare the obtained results.

As shown in Table 2, product 3aa deriving from malononitrile 2a (Table 2, Entry 1) was obtained with 60% conversion. Unfortunately, it was not possible to analyse 3aa with the available HPLC instrument, which is equipped with a UV-detector, as 3aa does not absorb UV radiation either at 254 or at 215 nm. Using dimethylmalonate 2b as nucleophile, the adduct 3ab was obtained with 70% conversion (Table 2, Entry 2), when potassium phosphate was employed as the base. In this case, it was possible to detect and separate the two enantiomers by HPLC (Daicel Chiralpak AD-H column, 2-propanol/n-hexane 10/90, flow 0.75 mL/min, 215 nm, r.t.: 14.9 and 15.8 min). Product 3ac from dibenzylmalonate 2c (Table 2, Entry 3) was obtained with 55% conversion. Also in this case it was possible to detect and separate the two enantiomers by HPLC (Chiralpak AD-H column, 2-propanol/n-hexane 10/90, flow 0.75 mL/min, 215 nm, r.t.: 23.2 and 27.0
min). Surprisingly, the diketone 2d and the malonate derivative 2e did not furnish the desired products, even using different inorganic bases after prolonged reaction times (Table 2, Entries 4-7). The reaction with the sulfonylacetate 2f afforded instead the corresponding product 3af as a single diastereoisomer, although with moderate conversion (Table 2, Entry 8). Its enantiomers were detected and separated by HPLC (Chiralpak AD-H column, 2-propanol/n-hexane 10/90, flow 0.75 mL/min, 215 nm, r.t.: 31.3 and 33.5 min). Interestingly, by using the homogeneous conditions (DMSO/K₂CO₃) reported in the original paper, the opposite diastereoisomer was obtained, even if unfortunately, its relative configuration was not assigned. Also methyl cyanoacetate 2g furnished the product 3ag, and with very good conversion as a single diastereacetate (Table 2, Entry 9), but again it was not possible to detect it either at 254 or at 215 nm. Finally, the two nitro compounds 2h and 2i did not give the expected products (Table 2, Entries 10-11) using our set of inorganic bases.

**Table 2:** Synthesis of the racemic S₆2-Michael tandem products 3aa-3ai with 1a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2 (equiv.)</th>
<th>3</th>
<th>EWG</th>
<th>EWG1</th>
<th>Base</th>
<th>t (h)</th>
<th>χ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a (3)</td>
<td>3aa</td>
<td>CN</td>
<td>CN</td>
<td>K₂CO₃</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>2b (3)</td>
<td>3ab</td>
<td>CO₂Me</td>
<td>CO₂Me</td>
<td>K₂PO₄</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>2c (3)</td>
<td>3ac</td>
<td>CO₂Bn</td>
<td>CO₂Bn</td>
<td>K₂PO₄</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>4ᵇ</td>
<td>2d (2)</td>
<td>3ad</td>
<td>COPh</td>
<td>COPh</td>
<td>K₂CO₃</td>
<td>64</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5ᵇ</td>
<td>2d (2)</td>
<td>3ad</td>
<td>COPh</td>
<td>COPh</td>
<td>K₂CO₃</td>
<td>66</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6ᵇ</td>
<td>2e (2)</td>
<td>3ae</td>
<td>CO₂(4-OMeC₆H₄)</td>
<td>CO₂(4-OMeC₆H₄)</td>
<td>K₂CO₃</td>
<td>64</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7ᵇ</td>
<td>2e (2)</td>
<td>3ae</td>
<td>CO₂(4-OMeC₆H₄)</td>
<td>CO₂(4-OMeC₆H₄)</td>
<td>K₂CO₃</td>
<td>66</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>2f (3)</td>
<td>3af</td>
<td>CO₂Me</td>
<td>SO₃Ph</td>
<td>K₂PO₄</td>
<td>48</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>2g (3)</td>
<td>3ag</td>
<td>CO₂Me</td>
<td>CN</td>
<td>K₂CO₃</td>
<td>48</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>2h (3)</td>
<td>3ah</td>
<td>H</td>
<td>NO₂</td>
<td>K₂PO₄</td>
<td>48</td>
<td>&lt;5</td>
</tr>
<tr>
<td>11</td>
<td>2i (3)</td>
<td>3ai</td>
<td>Br</td>
<td>NO₂</td>
<td>K₂PO₄</td>
<td>48</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

a) Conditions: 1a (0.10 mmol), 2 (0.20-0.30 mmol), TBAB (0.020 mmol, 20 mol%), toluene (0.20 mL), inorganic base (0.50 mmol), stirring, r.t., 24-66 h, then plug filtration on silica gel. b) Determined by ¹H NMR spectroscopy on the crude mixture. A single diastereoisomer was observed for 3af,3ag. c) 1.0 mL of toluene was used. d) 50% w/v aqueous K₂PO₄ was used (3.3 equiv.).

Next, we analysed the reaction of 1b with the same methylene compounds 2 with the aim of (i) enlarging the scope of the reaction and (ii) introduce the benzyl group in the final THF derivative that could increase the capacity of absorbing the UV radiation. Also in this case, the reactions were performed both under PTC and homogeneous conditions and the best results with PTC are reported in Table 3.

20
Similarly to acceptor 1a, also 1b reacted well with 2a-c and 2f,g, furnishing the expected products 3ba-3bc and 3bf,3bg with moderate to good conversions (Table 3, Entries 1-3, 6,7). As expected, the higher UV absorbance given by the benzyl group in the molecule allowed the detection and separation of the enantiomers of 3ba, derived from malononitrile 2a (Daicel Chiralpak AD-H column, eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, 215 nm; r.t.: 25.5 and 33.6 min), and 3bg, derived from cyanoacetate 2g (Phenomenex Lux 5u Cellulose-1 column, eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, 215 nm; r.t.: 26.3 and 30.7 min). HPLC separation conditions were also found for the remaining compounds: 3bb (Daicel Chiralpak AS column, eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, 215 nm; r.t.: 16.1 and 17.7 min); 3bc (Daicel Chiralpak AD-H, eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, 215 nm; r.t.: 42.5 and 52.0 min). The similar reactivity displayed by 1b compared to 1a was further confirmed by the reactions with the sulfonyleacetate 2f, wherein the PTC procedure proved to be again diastereocomplementary compared to the homogeneous conditions, and by the lack of reactivity displayed by 2d, 2e, 2h and 2i (Table 3, Entries 4,5,6,8 and 9).

Table 3: Synthesis of the racemic S$_{N}$2-Michael tandem products with 1b.$^{a}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>2 (equiv.)</th>
<th>3</th>
<th>EWG</th>
<th>EWG1</th>
<th>Base</th>
<th>t (h)</th>
<th>$\chi$ (%)$^{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a (3)</td>
<td>3ba</td>
<td>CN</td>
<td>CN</td>
<td>K$_2$CO$_3$</td>
<td>48</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>2b (3)</td>
<td>3bb</td>
<td>CO$_3$Me</td>
<td>CO$_3$Me</td>
<td>K$_3$PO$_4$</td>
<td>48</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>2c (3)</td>
<td>3bc</td>
<td>CO$_3$Bn</td>
<td>CO$_3$Bn</td>
<td>K$_3$PO$_4$</td>
<td>48</td>
<td>61</td>
</tr>
<tr>
<td>4$^c$</td>
<td>2d (2)</td>
<td>3bd</td>
<td>COPh</td>
<td>COPh</td>
<td>K$_2$CO$_3$</td>
<td>64</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5$^e$</td>
<td>2e (2)</td>
<td>3be</td>
<td>CO$_3$(4-OMe-C$_6$H$_4$</td>
<td>CO$_3$(4-OMe-C$_6$H$_4$)</td>
<td>K$_2$CO$_3$</td>
<td>64</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>2f (3)</td>
<td>3bf</td>
<td>CO$_3$Me</td>
<td>SO$_2$Ph</td>
<td>K$_3$PO$_4$</td>
<td>48</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>2g (3)</td>
<td>3bg</td>
<td>CO$_3$Me</td>
<td>CN</td>
<td>K$_2$CO$_3$</td>
<td>48</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>2h (3)</td>
<td>3bh</td>
<td>H</td>
<td>NO$_2$</td>
<td>K$_2$CO$_3$</td>
<td>48</td>
<td>&lt;5</td>
</tr>
<tr>
<td>9</td>
<td>2i (3)</td>
<td>3bi</td>
<td>Br</td>
<td>NO$_2$</td>
<td>K$_3$PO$_4$</td>
<td>48</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

a) Conditions: 1b (0.10 mmol), 2 (0.20-0.30 mmol), TBAB (0.020 mmol, 20 mol%), toluene (0.20 mL), inorganic base (0.50 mmol), stirring, r.t., 48-64 h, then plug filtration on silica gel. b) Determined by $^1$H NMR spectroscopy on the crude mixture. A single diastereoisomer was observed for 3bf,3bg. c) 1.0 mL of toluene was used.

Summarizing, several active methylene compounds, such as malononitrile 2a, malonates 2b,c, sulfonyleacetate 2f and cyanoacetate 2g, showed a good reactivity towards acceptors 1a and 1b under PTC conditions, and were thus identified as
promising candidates for the development of a catalytic asymmetric procedure based on PTC. Importantly, the use of a UV-active benzyl ester moiety in acceptor 1b allowed detection of the products 3ba and 3bg deriving from malononitrile 2a and cyanoacetate 2g, which could not be detected in the case of the ethyl ester acceptor 1a. Some nucleophiles (2d,e,h,i) did not react under PTC conditions. On the other hand, these latter substrates were not employed in the original publication.18 The low nucleophilicity of the highly delocalised enolate anion derived from 2d and the bulkiness of malonate 2e might be the reasons for the lack of reactivity of 2d and 2e. The notorious complication of nitroalkane alkylation reactions24 might have impeded the reaction between nitroalkanes 2h and 2i with the acceptors 1. Regarding the sequence of the reactions in this tandem process, we confirmed that the S_N2-alkylation precedes the Michael addition. Some reactions of Table 2 and 3, stopped before completion, showed indeed the presence of an intermediate compound deriving from the attack of the nucleophile 2 on the acceptor 1 still bearing the double bond functionality unreacted.

With these promising results regarding the reactivity of several nucleophiles 2 under PTC conditions, we started to evaluate the possibility of performing these reactions with chiral enantiopure PTC catalysts, derived from Cinchona alkaloids.

In these very preliminary experiments, we focalised our attention on the reaction of 1a with 2b and 2f, as reported in Table 4 and 5, in the presence of commercial PTC01 (Figure 9) derived from quinine, varying the inorganic base. Malonate 2b and sulfonylacetaete 2f were selected for this preliminary screening as these nucleophiles have been widely used in the past in asymmetric PTC reactions.20 All the reactions were carried out in toluene as the solvent (0.50 M), with five equivalents of the inorganic base and with 20 mol% catalyst loading, for 48 h at room temperature.

![Figure 9: N-Benzylquininium chloride, PTC01.](image)

As shown in Table 4, with dimethylmalonate 2b as nucleophile only cesium carbonate (Table 4, Entry 3) gave a good conversion in product 3ab, potassium carbonate and potassium phosphate not being able to promote the reaction to a sufficient extent (Table 4, Entries 1 and 2). Unfortunately, the reaction with cesium carbonate afforded the product 3ab with a disappointingly low ee.

Table 4: Screening of the base in the reaction with malonate 2b.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>(\chi(%))(^b)</th>
<th>ee (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K(_2)CO(_3)</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>K(_2)PO(_4)</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Cs(_2)CO(_3)</td>
<td>92</td>
<td>14</td>
</tr>
</tbody>
</table>

\(a\) Conditions: 1a (0.10 mmol), 2b (0.30 mmol), PTC01 (0.020 mmol, 20 mol\%), toluene (0.20 mL), inorganic base (0.50 mmol), stirring, r.t., 48 h, then plug filtration on silica gel. \(b\) Determined by \(^1\)H NMR spectroscopy on the crude mixture. \(c\) Determined by chiral stationary phase HPLC.

Also with sulfonylacetate 2f, between potassium carbonate, potassium phosphate and cesium carbonate, the latter base was found to be the most competent for the promotion of the reaction with 1a to give 3af (Table 5, Entries 1,2, and 5). However, it was possible in this case to isolate the product even in the reaction performed using potassium carbonate, which showed a slightly improved enantioselectivity compared to the other experiments. As many other chiral PTC reactions perform better, in terms of enantioselectivity, when aqueous bases are employed, we also tried the corresponding aqueous bases, which unfortunately did not lead to any improvement (Table 5, Entries 3,4,6). In this case, we extended this preliminary screening also to fluoride bases, such as potassium and cesium fluoride (Table 5, Entries 8,9). In line with the previous results, the cesium salt performed much better than its potassium counterpart, delivering the product 3af with enantiomeric excess comparable to potassium carbonate, but with slightly higher conversion. A weaker base such as potassium dihydrogen phosphate was found to be inactive in this reaction (Table 5, Entry 7).
Table 5: Screening of base for nucleophile 2f.<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>t (h)</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃</td>
<td>48</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>K₃PO₄</td>
<td>48</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>aq. K₃PO₄ (50% w/w)</td>
<td>48</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>aq. K₂CO₃ (50% w/w)</td>
<td>24</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Cs₂CO₃</td>
<td>24</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>aq. Cs₂CO₃ (50% w/w)</td>
<td>24</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>KH₂PO₄</td>
<td>48</td>
<td>&lt;5</td>
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<td>8</td>
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<td>18</td>
</tr>
<tr>
<td>9</td>
<td>KF</td>
<td>48</td>
<td>4</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 1a (0.10 mmol), 2f (0.30 mmol), PTC01 (0.020 mmol, 20 mol%), toluene (0.20 mL), inorganic base (0.50 mmol), stirring, r.t., 48 h, then plug filtration on silica gel. b) Determined by 1H NMR spectroscopy on the crude mixture. A single diastereoisomer was observed in all experiments. c) Determined by chiral stationary phase HPLC. d) 3.3 equiv. were used.

This very preliminary screening has indicated that the enantioselective S_N2-Michael tandem reaction leading to THF derivatives might be feasible, although at this stage the obtained results with the representative chiral catalyst PTC01 are certainly not satisfactory, in terms of both yield and enantioselectivity. Whereas it can be envisioned that a through screening of catalyst structures gives good chances in the development of this transformation in a highly enantioselective fashion, the low reactivity displayed by nucleophiles 2b and 2f in the presence of ordinary organic bases (Tables 4 and 5) represents a serious matter of concern. However, the broad spectrum of nucleophilic components which were identified during the preliminary screening with TBAB catalyst (Tables 2 and 3) increases the possibilities of finding a suitable nucleophile-electrophile couple for the disclosure of a highly efficient asymmetric synthesis of enantioenriched THF derivatives through the S_N2-Michael tandem reaction.
3.2. Aldol-cyclisation-Michael domino reactions

As previously mentioned, Liu and Xu\textsuperscript{19} developed a new strategy for the atom-economic synthesis of fused oxazolines 3 via a domino sequence, initiated by the aldol-cyclisation reaction of ethyl isocyanoacetate 2k with an appropriate aldehyde 1 bearing a Michael acceptor. Under the optimised conditions, fused tricyclic oxazolines were produced in good yields and in a highly diastereoselective manner.

![Scheme 13](image-url)

Scheme 13: Fused tricyclic oxazolines through a domino aldol-cyclisation sequence.

We decided to investigate the possibility of obtaining these oxazine derivatives in an enantioenriched form, by using asymmetric PTC catalysis. To this purpose, the synthesis of the aldehyde derivatives 1d and 1e, was undertaken. During the project development, in order to expand the substrate and catalyst structural variety, we have also decided to prepare the benzyl isocyanoacetate 2l and the new PTC catalysts PTC14 and PTC29, as outlined below. The remaining PTC catalysts were either commercially available, either previously prepared in the laboratory were this work was carried out.

3.2.1. Synthesis of substrates 1d and 1e

The synthesis of these substrates was carried out from commercial starting materials in a single step for substrate 1d, and in two steps for substrate 1e.

Substrate 1d (Scheme 14) was prepared by a Heck reaction, as described by Bryan and Lautens.\textsuperscript{25} 2-Bromobenzaldehyde (1 equiv.) was reacted with methyl acrylate (1.5 equiv.), in toluene as the solvent and in the presence of a palladium catalyst. The reaction mixture was refluxed with stirring for 40 h under N\textsubscript{2} atmosphere.

![Scheme 14](image-url)

Scheme 14: Synthesis of substrate 1d.

\textsuperscript{25} C. S. Bryan, M. Lautens, Org. Lett., 2010, 12, 2754.
Substrate 1e was obtained in two steps from a commercial phosphonium salt, which was dissolved in methanol and deprotonated by addition of an aqueous 2M sodium hydroxide solution, giving the corresponding ylide, as reported in Scheme 15.

Scheme 15: Synthesis of the ylide.

The second step of the sequence was a Wittig reaction between this ylide and o-phthalaldehyde, in DCM as solvent, as represented in Scheme 16. The reagents were added in equimolar amount.

Scheme 16: Synthesis of substrate 1e.

3.2.2. Synthesis of nucleophile 21

For the aldol-cyclisation-Michael reaction commercially available isocyanide nucleophiles were used, except for 21 which had to be prepared. For the synthesis of this compound it was used a procedure taken from a US patent,26 consisting in three steps.

The first step was the esterification of glycine with benzyl alcohol, that was used as a reagent and solvent. p-Toluenesulfonic acid was employed as dehydrating agent, in stoichiometric amount respect to the limiting reagent (glycine). This reaction was first carried out in a flask at 100 °C for 15 hours, but as the conversion was not complete, it was necessary to treat the crude further in a Dean-Stark apparatus (Scheme 17).

Scheme 17: Synthesis of glycine benzyl ester, tosylate salt.

The second step was the formylation of this benzyl ester with methyl formate, that was used as a regent and solvent. Triethylamine was employed as the base in excess respect

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to limiting reagent (glycine ester). The reaction is represented in Scheme 18 and proceeded in quantitative yield.

![Scheme 18: Formylation of the glycine ester.](image)

The last step in the synthesis of 21 was performed with the procedure depicted in Scheme 19. Benzyl 2-formamidoacetate was first dissolved in DCM, then excess triethylamine was added to this solution. The reaction mixture was cooled to 2 °C, followed by addition of POCl₃ in equimolar amounts. This dehydrating agent was added very slowly with stirring, maintaining the temperature below 4 °C. Finally, the reaction was quenched by neutralisation with an aqueous potassium carbonate solution, keeping the temperature below 30 °C during this quench.

![Scheme 19: Synthesis of nucleophile 21.](image)

### 3.2.3. Synthesis of catalysts PTC14 and PTC29

The synthesis of PTC14 was performed using a protocol developed in the laboratory where this work was carried out. Quinine was reacted with 1-(bromomethyl)-2-(trifluoromethyl)benzene in a mixture of toluene and THF (1:1) at 70 °C for 20 h, as represented in Scheme 20. The pure product PTC014 was collected by simple filtration.

![Scheme 20: Synthesis of the phase-transfer catalyst PTC14.](image)
Another catalyst that was prepared was PTC29, the simple N-benzylquininium salt with phenoxide as counter ion. The synthesis was carried out from N-benzylquininium chloride. The chloride anion was exchanged by stirring this salt with sodium phenoxide in methanol, as represented in Scheme 21.\textsuperscript{27}

![Scheme 21: Synthesis of PTC29.](image)

### 3.2.4. Reactivity of substrates 1c, 1d and 1e

The study of the aldol-cyclisation-Michael domino reaction, with the aim of obtaining an enantioenriched product with a PTC procedure, was carried out with electrophiles 1d and 1e (Figure 10) and isocyanoacetates. The prochiral substrates 1d and 1e have a similar Michael acceptor moiety compared to compounds 1a and 1b, but bears an aldehyde, instead of the iodine, which is able to undergo an aldol-cyclisation reaction.

![Figure 10: Electrophiles for aldol-cyclisation-Michael domino reaction.](image)

As previously mentioned, our work was based on the paper by Liu and Xu.\textsuperscript{19} They used sodium hydroxide as a base under homogeneous conditions (THF as solvent), which was delivering the products in good yields and diastereoselectivities but in racemic form. In order to verify the feasibility of those transformations under PTC conditions, which was the aim of this work, we used the same approach we had applied to the S$_{N}$2-Michael addition reaction on 1a and 1b. Thus, we first performed some experiments using a standard PTC procedure. To this end, we reacted 1d and 1e with methyl isocyanoacetate 2j in toluene as solvent, with TBAB as the phase-transfer catalyst and in the presence of

\[\text{PTC29} \rightarrow \text{PTC29} \]

\[\text{PTC29} + \text{MeOH} \rightarrow \text{PTC29} \]

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excess potassium carbonate (aqueous solution) as the base. As shown in Scheme 22, the reactions furnished the expected tandem products 3dj and 3ej with good results. Our PTC conditions afforded the diastereomeric products shown in Scheme 22, which is the same reported in the original publication, wherein the relative configuration of 3ej was unambiguously determined by X-ray crystallography. However, in our case small amounts of minor diastereomers of 3dj and 3ej (4% and 13%, respectively) were also detected by 1H NMR in the crude mixture. Besides confirming the viability of our approach, these experiments gave us the racemic materials necessary for the HPLC determination in the subsequent experiments with chiral enantiopure phase-transfer catalysts. HPLC conditions where the enantiomers of 3dj and 3ej could be detected and separated were in fact quickly identified (3dj: Daicel Chiralpak AD-H column, eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, wavelength 215 nm, r.t.: 29.3 and 43.0 min for the major diastereoisomer, 35.1 and 47.4 min for the minor diastereoisomer; 3ej: Daicel Chiralcel OJ-H column, eluent 2-propanol/n-hexane 30/70, flow 0.75 mL/min, wavelength 215 nm, r.t.: 42.2 and 61.0 min for the major diastereoisomer).

Scheme 22: Test reactions with acceptors 1d and 1e under PTC conditions.

Some control experiments at reduced reaction times with substrate 1d showed the presence of a reaction intermediate D (Scheme 23) featuring the oxazoline moiety next to the double bond. Based on this observation, a possible rationalization of the sequence of the steps in this domino process is shown in Scheme 23. A first aldol addition giving A is followed by ring closure and 1,3-H shift delivering the stabilised enolate C. This enolate C can undergo the intramolecular Michael addition to give the tricyclic product 3dj. However, apparently, after the 1,3-H shift C can be quenched by a proton source such as water or another acidic compound in the mixture, leading to the formation of the observed intermediate D. Given the disappearance of intermediate D with time, as well as the consistent increase in tricyclic product 3dj, it is clear that under PTC conditions the activated oxazoline ester in D can be deprotonated again, ultimately giving the intramolecular Michael addition step. A parallel sequence, wherein oxazoline B is
directly protonated after ring-closure, without undergoing the 1,3-H shift, might also be operative, and would lead to the same experimental observations.

**Scheme 23:** Hypothetical sequence of the events in the domino process.

Whatever the sequence of the events in this domino process (1,3-H shift or protonation of the oxazoline followed by deprotonation of the activated oxazoline-ester), in our planned asymmetric reaction the step determining the enantioselectivity of the whole reaction is the first aldol addition of the deprotonated cyanoacetate 2j to the aldehyde moiety of the acceptor 1d.

However, even after a careful literature search we could not find any examples of catalytic asymmetric aldol reactions (or aldol-cyclisation reactions giving oxazolines) with cyanoacetates under PTC conditions. Thus, we decided to tackle our planned domino sequence by first turning our efforts towards the catalytic asymmetric aldol addition of cyanoacetates to simple aldehydes, such as benzaldehyde 1c, in order to simplify the system. This latter transformation seemed to be already a formidable challenge by itself, considering that surprising lack of literature precedents. We assumed that, once a reliable protocol for the aldol-cyclisation reaction with simple aldehydes with chiral PTC would be established, the last intramolecular Michael addition step when
using the polyfunctional substrates 1d and 1e would proceed with very good diastereocontrol, as observed in the racemic version.

This change of plan required obviously to verify whether the aldol-cyclisation of cycanoacetate 2j to benzaldehyde 1c proceeded efficiently with PTC. As expected from the results already obtained with the more complex substrates 1d and 1e, a reaction of methylcyanoacetate 2j with benzaldehyde 1c afforded the corresponding product 3cj with very good results (Scheme 24). The oxazoline adduct was obtained with very good diastereoselectivity, favouring the trans isomer as determined by comparison of the \(^1\)H NMR spectrum of the obtained diastereomeric mixture of 3cj with literature data referring to the two isolated isomers.\(^{28}\) The obtainment of 3cj allowed the identification of suitable chiral stationary phase HPLC conditions for the detection and the separation of the two enantiomers of the major trans diastereoisomer (Daicel Chiralcel OJ-H column, eluent 2-propanol/n-hexane 20/80, flow 0.75 mL/min, wavelength 215 nm at r.t.: 20.8 and 38.9 min).

\[
\begin{align*}
\text{O} & \quad \text{CN} \quad \text{CO}_2R \\
1c & \quad \text{2j: } R = \text{Me} \\
2k: R = \text{Et} \\
2l: R = \text{Bn} \\
2m: R = \text{t-Bu} \\
\end{align*}
\]

Scheme 24: Synthesis of racemic product 3cj-3cm.

As in many asymmetric PTC reactions the enantioselectivity strongly depends on the steric features of the nucleophile,\(^6\) we decided to extend the reaction to other cyanoacetate esters 2k-m with different steric bulk at the ester group, such as the ethyl (2k), benzyl (2l) and the very bulky tert-butyl (2m). All reactions performed well, giving the corresponding products 3cj-3cm with good diastereoselectivities (Scheme 24), allowing us to find suitable conditions for the detection and the separation of the enantiomers of their major trans-diastereoisomers by chiral stationary phase HPLC (3ck: Daicel Chiralcel OJ-H column, eluent 2-propanol/n-hexane 20/80, flow 0.75 mL/min, wavelength 215 nm at r.t.: 16.5 and 28.4 min; 3cl: Daicel Chiralpak AD-H column, eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, wavelength 215 nm at r.t.: 21.0

and 27.0 min; 3cm: Daicel Chiralpak AD-H column, eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, wavelength 215 nm at r.t.: 9.2 and 10.7 min).

To develop an enantioselective aldol-cyclisation of cyanoacetates with aldehydes, we have initially tested a series of inorganic bases (5 equiv.) at different temperatures in the presence of the commercial PTC01 (10 mol%) derived from quinine as the catalyst, in toluene as the solvent (0.10 M). Methyl isocyanoacetate 2j was employed in this first screening as nucleophile. The obtained results are reported in Table 6.

**Table 6: Screening of base and temperature.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>η (%)</th>
<th>trans/cis&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
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<td>0</td>
<td>5.5</td>
<td>&gt;98</td>
<td>95:5</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
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<td>-20</td>
<td>24</td>
<td>&gt;98</td>
<td>92:8</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>aq. K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (50% y&lt;sub&gt;a&lt;/sub&gt;)</td>
<td>-20</td>
<td>24</td>
<td>&gt;98</td>
<td>92:8</td>
<td>7</td>
</tr>
<tr>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>&gt;98</td>
<td>88:12</td>
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</tr>
<tr>
<td>13</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-78</td>
<td>20</td>
<td>&gt;98</td>
<td>92:8</td>
<td>8</td>
</tr>
</tbody>
</table>

a) Conditions: 1c (0.10 mmol), 2j (0.20 mmol), PTC01 (0.020 mmol, 20 mol%), toluene (1.0 mL), inorganic base (0.50 mmol), stirring, 5.5-67 h, then plug filtration on silica gel. b) Determined by 1H NMR spectroscopy on the crude mixture. c) Determined by chiral stationary phase HPLC. d) 10 mol% catalyst was used.

All reaction performed well in terms of conversion, furnishing the corresponding oxazoline adduct 3cj with good diastereoselectivity but only low to moderate enantioselectivity. In all cases, the major stereoisomer of the product 3cj was the 4R,5S adduct, as depicted above Table 6. This stereochemical assignment was based on the comparison of the HPLC retention times and order of elution of the enantioenriched 3cj with literature data. As expected, lowering the reaction temperature increased reaction times and required a stronger base to maintain a good level of conversion. In particular, when solid potassium carbonate was used (Table 6, Entries 1, 3 and 6) the conversion
was complete at 0 and -20 °C, while decreased to 77% when working at -40 °C. The diastereomeric ratio was always very high at all temperatures, while the ee values increased as expected by lowering the temperature, till 24% ee at -40 °C. Contrary to many other chiral PTC reactions,6 the use of aqueous base did not lead to improvements, but furnished the product with comparable results (Table 6, Entries 2, 4, 5 and 7). Solid potassium phosphate (Table 6, Entries 8, 10 and 12) allowed to carry out the reaction at lower temperatures (-40, -60 and -78 °C) keeping a full conversion of the starting benzaldehyde 1c, but the obtained ee values were lower than in the case of solid potassium carbonate. A reaction with aqueous potassium phosphate (50% w/w) was performed at -40 °C (Table 6, Entry 9), but also in this case the adduct 3cj was obtained with a slightly lower ee value with respect to the corresponding solid base. It was not possible to perform the reaction with this aqueous base at lower temperatures because the solution freezes. Solid cesium carbonate (Table 6, Entries 11 and 13) was then tested, as this base is usually much more active than potassium carbonate under PTC conditions because its large cation makes it more available in the organic layer. Indeed, full conversion was achieved with this base even at -78 °C. However, enantioselectivity was not satisfactory even at this very low temperature.

From the results obtained in this screening of bases and temperatures it is was deduced that the best reaction conditions involved the use of solid or aqueous potassium carbonate at -40 °C. At this point, we decided to perform a thorough screening of PTC catalysts in this transformation (Table 7). Due to the relatively easier procedure when using an aqueous solution with respect to a solid we decided to operate with the latter in this screening. The catalysts that have been screened for the asymmetric aldol-cyclisation domino reaction are, for the most part, Cinchona alkaloid derivatives as depicted in Figure 11, but also a very different class of PTC catalysts, namely the biphenyl-based ammonium salts developed by Lygo29 (Figure 12), which were already available in the laboratory where this work was carried out.

Figure 11: PTC catalysts derived from *Cinchona* alkaloids.
As shown in Table 7, the PTC catalysts deriving from the four main *Chinchona* alkaloids (PTC01-PTC04, derived from quinine, quinidine, cinchonidine and cinchonine) were tested (Table 7, Entries 1-4) and it was demonstrated that the best result can be obtained with the N-benzylquininium chloride PTC01. Consequently, we decided to test mainly catalysts derived from quinine. It was clear that a free hydroxyl group at the 9-position is very important, since *O*-protected PTC catalysts PTC05 and PTC06 lowered drastically the ee values (Table 7, Entries 5 and 6). Catalysts bearing sterically demanding groups at the quinuclidinic nitrogen such as 9-methylanthracenyl or 1-methylnaphthyl (PTC10, PTC12 and PTC26, Entries 10, 12 and 26) and catalysts carrying *para*-substituted benzyl groups (PTC08 and PTC28, Entries 8 and 28), gave very bad results. Some *ortho*-substituted aromatics at the benzyl moiety of the quinuclidinic nitrogen such as in PTC09, PTC13 and PTC15 (Entries 9, 13 and 15) afforded instead consistently better results in term of enantioselectivity. On the contrary, PTC11, PTC14, PTC16 and PTC17 (Entries 11,14,16 and 17) bearing different *ortho*-substituents gave lower ee’s than PTC01. 2-Methylpyridine (PTC18) and 2-methylpyridine 1-oxide (PTC19) catalysts gave comparable results with respect to PTC01 (Entries 18 and 19). The last group of catalysts tested have more than one substitutent at the benzyl moiety of the quinuclidinic nitrogen, such as PTC07, PTC20, PTC21, PTC22, PTC23, PTC24, PTC25 and PTC27. Only catalysts PTC21 and PTC27 (Entries 21 and 27) afforded comparable results with respect to PTC01, whereas the remaining structures performed worse (Entries 7,20,21,22,23,24,25 and 27). With binaphthyl catalysts PTC30-PTC33, a complete conversion of the starting aldehyde **1c** was achieved, but **3c**j was obtained with low enantioselectivity, as reported in Entries 30-33. Finally, we have also tested a different approach to this reaction, by using the phenoxide catalyst PTC29. This ammonium salt, soluble in toluene, should be able to promote the reaction without the

**Figure 12:** List of LYGO catalyst.
Table 7: Screening of Phase Transfer Catalyst.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Cat</th>
<th>t (h)</th>
<th>(\chi) (%)</th>
<th>trans:cis</th>
<th>ee (%)</th>
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<td>97</td>
<td>84:16</td>
<td>3</td>
</tr>
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<td>aq. K₂CO₃ (50% (\gamma)_a)</td>
<td>PTC03</td>
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<td>87</td>
<td>88:12</td>
<td>4</td>
</tr>
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<td>4</td>
<td>aq. K₂CO₃ (50% (\gamma)_a)</td>
<td>PTC04</td>
<td>66</td>
<td>&gt;98</td>
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<td>12</td>
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<tr>
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<td>82</td>
<td>79:21</td>
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<td>&gt;98</td>
<td>86:14</td>
<td>2</td>
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<td>&gt;98</td>
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<td>10</td>
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<td>26</td>
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<td>12(^d)</td>
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\(\gamma\)_a: 0.10 mmol \(\gamma\)_a of PTC01-PTC33 0.010 mmol 10 mol% \(\gamma\)_a mL, inorganic base (0.50 mmol), stirring, -40 °C, 40-66 h, then plug filtration on silica gel. b) Determined by \(^1\)H NMR spectroscopy on the crude mixture. c) Determined by chiral stationary phase HPLC. d) Major isomer: 4\(\beta\),5\(\beta\). e) Catalyst loading 20 mol%. f) No conversion of the starting product also at -40 °C, 0 °C and r.t. in toluene or THF as solvents. g) Catalyst loading 5 mol%.

assistance of a stoichiometric amount of an inorganic base, as the phenoxide could in principle act as a strong homogeneous base. However, no conversion of the starting aldehyde 1c was observed either at -40 °C, 0 °C or r.t., or using THF as the solvent.
(Entry 29). Therefore, from this thorough screening it seems that catalyst PTC09, bearing an ortho-methoxy group at the benzyl moiety, is the most efficient in terms of asymmetric induction, leading to the formation of the product 3cj with a promising 34% ee under these reaction conditions (Entry 9).

A range of inorganic bases was next examined, as reported in Table 8, using the best PTC catalyst PTC09 in toluene (0.10 M) at -40 °C. Potassium carbonate, solid or as aqueous solution, gave the best outcome in terms of enantioselection, confirming the results derived from the preliminary screening reported in Table 6. It is important to note that lowering the amount of base to one equivalent (Entry 2) lowered the ee value to 28% whereas increasing it to 20 equivalents (Entry 4) increased the ee to 36%. In contrast with the results obtained with PTC01 (Table 6), solid potassium phosphate gave comparable results to potassium carbonate, when PTC09 was employed as catalyst (Entry 5). All the other bases tested afforded lower ee’s. Potassium hydrogen carbonate and dipotassium hydrogen phosphate did not promote the reaction (Entries 11 and 12). The most important observation is that the reaction is very robust as similar results are obtained with different bases in different amounts.

Table 8: Screening for the optimal base in the reaction with catalyst PTC09. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>( \chi (%) )</th>
<th>trans:cis</th>
<th>ee (%)</th>
</tr>
</thead>
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<td>&gt;98</td>
<td>95.5</td>
<td>34</td>
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<td>2</td>
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<td>97</td>
<td>91.9</td>
<td>28</td>
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<tr>
<td>3</td>
<td>aq. ( \text{K}_2\text{CO}_3 ) (50% ( \text{aq.} ))</td>
<td>&gt;98</td>
<td>91.9</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>aq. ( \text{K}_2\text{CO}_3 ) (50% ( \text{aq.} ))</td>
<td>&gt;98</td>
<td>91.9</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>( \text{K}_3\text{PO}_4 )</td>
<td>&gt;98</td>
<td>95.5</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>aq. ( \text{K}_3\text{PO}_4 ) (50% ( \text{aq.} ))</td>
<td>&gt;98</td>
<td>92.8</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>( \text{Cs}_2\text{CO}_3 )</td>
<td>&gt;98</td>
<td>94.6</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>( \text{Cs}_2\text{CO}_3 ) ( ^b )</td>
<td>&gt;98</td>
<td>94.6</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>CsF</td>
<td>&gt;98</td>
<td>95.5</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>( \text{Na}_2\text{CO}_3 )</td>
<td>85</td>
<td>92.8</td>
<td>28</td>
</tr>
<tr>
<td>11</td>
<td>KHCO(_3)</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>( \text{K}_2\text{HPO}_4 )</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>KF</td>
<td>80</td>
<td>88:12</td>
<td>5</td>
</tr>
</tbody>
</table>

a) Conditions: 1c (0.10 mmol), 2j (0.20 mmol), PTC09 (0.010 mmol, 10 mol%), toluene (1.0 mL), inorganic base (0.50 mmol), stirring, -40 °C, 68 h, then plug filtration on silica gel. b) Determined by \(^1\)H NMR spectroscopy on the crude mixture. c) Determined by chiral stationary phase HPLC. d) 1 equiv. of base. e) Conversion after 66 h. f) 20 equiv. of base.
A range of solvents and solvent mixtures was examined, and toluene emerged as the best reaction medium, in terms of ee (Table 9).

**Table 9:** Screening of solvents in the reaction catalysed by PTC09.4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>( \chi (%) ) (^{b})</th>
<th>trans:cis (^{b})</th>
<th>ee (%) (^{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>&gt;98</td>
<td>91:9</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>&gt;98</td>
<td>88:22</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>TBME</td>
<td>40</td>
<td>97:3</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>DCM:Tol 7:3</td>
<td>&gt;98</td>
<td>82:18</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>TBME:Tol 7:3</td>
<td>&gt;98</td>
<td>89:11</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>TBME:Tol 3:7</td>
<td>92</td>
<td>92:8</td>
<td>20</td>
</tr>
</tbody>
</table>

a) Conditions: 1c (0.10 mmol), 2j (0.20 mmol), PTC09 (0.010 mmol, 10 mol%), solvent (1.0 mL), inorganic base (0.50 mmol, 50\% \( \nu \)/w solution), stirring, -40 °C, 41 h, then plug filtration on silica gel. b) Determined by \(^1\)H NMR spectroscopy on the crude mixture. c) Determined by chiral stationary phase HPLC.

In order to improve the enantioselectivity of the reaction, we focused on possible variations at the ester moiety of the isocyanate partner 2, using PTC09 catalyst in toluene (0.10 M) and potassium carbonate (solid or 50\% \( \nu \)/w solution) as the base. Results are reported in Table 10. Using ethyl isocyanoacetate 2k (Entry 3) and benzy isocyanoacetate 2l (Entry 4) the corresponding oxazolines 3ck and 3cl were obtained with excellent conversions and with slightly higher ee’s compared to 3cj (Entry 1). Given this increase in stereoselectivity observed by using more sterically demanding ester groups, we turned our attention towards the very bulky tert-butyl ester derivative 2m.

However, the reaction performed with this substrate 2m (Entry 6) gave a rather unexpected result, as the corresponding product 3cm was obtained with opposite face selectivity (i.e. 4S,5R), as determined by comparing HPLC retention times and elution order of 3cm with literature values.28
Table 10: Generality of the aldol-cyclisation tandem reaction.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>2 (R)</th>
<th>Base</th>
<th>t (h)</th>
<th>(\chi) (%)(^b)</th>
<th>trans:cis(^b)</th>
<th>ee (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2j (Me)</td>
<td>aq. K(_2)CO(_3) (50% (v/v))</td>
<td>40</td>
<td>&gt;98</td>
<td>91:9</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>2k (Et)</td>
<td>aq. K(_2)CO(_3) (50% (v/v))</td>
<td>40</td>
<td>&gt;98</td>
<td>89:11</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>2k (Et)</td>
<td>K(_2)CO(_3)</td>
<td>68</td>
<td>&gt;98</td>
<td>95:5</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>2l (Bn)</td>
<td>aq. K(_2)CO(_3) (50% (v/v))</td>
<td>44</td>
<td>&gt;98</td>
<td>90:10</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>2l (Bn)</td>
<td>K(_2)CO(_3)</td>
<td>68</td>
<td>&gt;98</td>
<td>92:8</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>2m (t-Bu)</td>
<td>aq. K(_2)CO(_3) (50% (v/v))</td>
<td>46</td>
<td>&gt;98</td>
<td>86:14</td>
<td>23(^d)</td>
</tr>
</tbody>
</table>

a) Conditions: 1c (0.10 mmol), 2k-2m (0.20 mmol), PTC09 (0.010 mmol, 10 mol%), toluene (1.0 mL), inorganic base (0.50 mmol), stirring, -40 °C, 41 h, then plug filtration on silica gel. b) Determined by \(^1\)H NMR spectroscopy on the crude mixture. c) Determined by chiral stationary phase HPLC. d) Major isomer: 45:55.

This unexpected result prompted us to investigate more thoroughly this reaction (Table 11). \(N\)-Benzyl quininium chloride PTC01 was tested again, affording a higher ee value compared with PTC09 (Entries 1 and 4), in sharp contrast with the methyl derivative 2j. For this reason we decided to repeat a second shorter PTC catalyst screening using tert-butyl isocyanatoacetate 2m and aqueous or solid potassium carbonate as the base (5 equiv.). It is possible to observe that the presence of a very bulky group at the quinuclidinic nitrogen as 9-methylantraceny (Entry 5) or the presence of an electron withdrawing groups at the ortho- or meta-position of the benzyl substituent at the quinuclidinic nitrogen gave better enantioselectivities (Entries 6-11). Lygo’s catalyst afforded again lower ee values (Entries 15-18).
Table 11: Screening of catalyst and base with tert-butyl isocyanooacetate 2m.*

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Cat</th>
<th>t (h)</th>
<th>$\chi$ (%)$^b$</th>
<th>trans: cis$^b$</th>
<th>ee (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC01</td>
<td>46</td>
<td>&gt;98</td>
<td>86:14</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC07</td>
<td>68</td>
<td>&gt;98</td>
<td>89:11</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC08</td>
<td>68</td>
<td>&gt;98</td>
<td>87:13</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC09</td>
<td>46</td>
<td>&gt;98</td>
<td>86:14</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC12</td>
<td>68</td>
<td>&gt;98</td>
<td>89:11</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC13</td>
<td>68</td>
<td>&gt;98</td>
<td>89:11</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC14</td>
<td>68</td>
<td>&gt;98</td>
<td>87:13</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC15</td>
<td>68</td>
<td>&gt;98</td>
<td>88:12</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC16</td>
<td>68</td>
<td>&gt;98</td>
<td>89:11</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC28</td>
<td>68</td>
<td>&gt;98</td>
<td>84:16</td>
<td>30</td>
</tr>
<tr>
<td>11</td>
<td>K$_2$CO$_3$</td>
<td>PTC07</td>
<td>68</td>
<td>&gt;98</td>
<td>93:7</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>K$_2$CO$_3$</td>
<td>PTC13</td>
<td>68</td>
<td>&gt;98</td>
<td>93:7</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>K$_2$CO$_3$</td>
<td>PTC14</td>
<td>68</td>
<td>&gt;98</td>
<td>91:9</td>
<td>36</td>
</tr>
<tr>
<td>14</td>
<td>K$_2$CO$_3$</td>
<td>PTC15</td>
<td>68</td>
<td>&gt;98</td>
<td>93:7</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC30$^a$</td>
<td>68</td>
<td>&gt;98</td>
<td>88:12</td>
<td>20</td>
</tr>
<tr>
<td>16</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC31$^a$</td>
<td>68</td>
<td>&gt;98</td>
<td>89:11</td>
<td>24</td>
</tr>
<tr>
<td>17</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC32$^a$</td>
<td>68</td>
<td>&gt;98</td>
<td>85:15</td>
<td>15</td>
</tr>
<tr>
<td>18</td>
<td>aq. K$_2$CO$_3$ (50% $^a$)</td>
<td>PTC33$^a$</td>
<td>68</td>
<td>92</td>
<td>89:11</td>
<td>20</td>
</tr>
</tbody>
</table>

*a) Conditions: 1c (0.10 mmol), 2m (0.20 mmol), PTC (0.010 mmol, 10 mol%), toluene (1.0 mL), inorganic base (0.50 mmol), stirring, -40 °C, 46-68 h, then plug filtration on silica gel. b) Determined by $^1$H NMR spectroscopy on the crude mixture. c) Determined by chiral stationary phase HPLC. d) 5 mol% of catalyst loading.

In summary, despite the many conditions tested, the enantioselections obtained are rather low and it seems thus very difficult at this stage to establish an efficient procedure. In order to have a chance of success for this reaction, it would probably be necessary to drastically change the type of substrates involved, using for example amides as activating groups instead of esters in the isocyanide donor 2, and/or switching to a different activation mode for the aldol-cyclisation reaction (e.g. homogeneous chiral Brønsted bases).

Although both approaches are well beyond the scope of this work, we decided to transfer anyway the best conditions found on benzaldehyde 1c (toluene (0.10 M)/aqueous potassium carbonate 5 equiv., catalyst PTC01 or PTC09, -40 °C) to substrates 1d and 1e. This would at least test the correctness of our assumption that the disclosure of an efficient aldol-cyclisation reaction on simple aldehydes such as benzaldehyde 1c could
be successfully translated to one-pot procedure and domino process with substrates 1d and 1e.

Firstly, we sought to determine if the Michael step of the domino reaction was active at -40 °C, leading to products 3dj,3ej. Unfortunately this was not the case, since at this temperature, even if the starting aldehydes were completely converted, a complicated mixtures of products mainly containing 3dj,3ej and intermediates D was obtained (Table 12, top results in each Entry). Therefore, we evaluated the possibility of developing a one-pot procedure with substrates 1d and 1e carrying out the aldol-cyclization step at -40 °C for a sufficient time, and the Michael reaction at room temperature (Table 12, bottom results in each Entry). The very preliminary results obtained applying this one-pot procedure were not satisfactory, because the enantiomeric excesses of the final products 3 slightly lowered compared to the reaction with the simpler benzaldehyde 1c (34% ee).

Table 12: One-pot procedure.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>T (°C) and t (h)</th>
<th>χ (%)</th>
<th>D:3dj</th>
<th>dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1d</td>
<td>PTC01 -40 °C-33 h</td>
<td>&gt;98c</td>
<td>68:32</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>r.t.-15h</td>
<td>&gt;98c</td>
<td>&lt;5:95</td>
<td>74:26</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>1d</td>
<td>PTC09 -40 °C-33 h</td>
<td>&gt;98c</td>
<td>50:50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>r.t.-15h</td>
<td>&gt;98c</td>
<td>&lt;5:95</td>
<td>79:21</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>1e</td>
<td>PTC09 -40 °C-21 h</td>
<td>&gt;98c</td>
<td>90d</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>r.t.-6h</td>
<td>&gt;98c</td>
<td>&lt;5:95</td>
<td>77:23</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>PTC09 -40 °C-40 h</td>
<td>&gt;98c</td>
<td>&gt;98c</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>r.t.-6h</td>
<td>&gt;98c</td>
<td>&lt;5:95</td>
<td>78:22</td>
<td>15</td>
</tr>
</tbody>
</table>

a) Conditions: 1d or 1e (0.10 mmol), 2j (0.20 mmol), PTC (0.010 mmol, 10 mol%), toluene (1.0 mL), inorganic base (0.50 mmol), stirring, -40 °C, 33 h, then r.t., 6-15 h, then plug filtration on silica gel. b) Determined by 1H NMR spectroscopy on the crude mixture. c) Determined by chiral stationary phase HPLC. d) Determined on the crude mixture after stirring at -40 °C. e) Determined by 1H NMR spectroscopy on the crude mixture after stirring at r.t. for further 6-15 h.
However, we eventually found that working at -20 °C for longer reaction time (70 h) and using a higher catalyst loading (20 mol%), not only the conversion of the starting aldehyde 1d was complete, as expected, but a considerably higher amount of the tricyclic product 3dj respect to the unyclised intermediate D was formed (Scheme 25), compared to the reactions performed at -40 °C (Table 12). More importantly, the enantioselectivity of the domino product 3dj raised to 39%, i.e. to the same value obtained with benzaldehyde 1c.

Scheme 25: Aldol-cyclisation-Michael domino reaction of 1d at -20 °C for prolonged reaction times.
4. Conclusion

This work focussed on the synthesis of enantioenriched tetrahydrofuran and tricyclic oxazoline derivatives through the use of asymmetric PTC procedures, starting from polyfunctionalised substrates (Scheme 26).

![Diagram](image)

**Scheme 26**: Planned catalytic asymmetric domino reactions on polyfunctionalised substrates.

In particular, the results achieved in this Thesis can be summarised as follows:

- A series of active methylene compounds (malonates, malononitrile, phenylsulfonylacetate) were found to cleanly undergo tandem S$_2$2-Michael reactions with substrates 1a and 1b under standard PTC conditions (TBAB catalyst, carbonate or phosphate inorganic bases, toluene as solvent), allowing the isolation of the corresponding racemic adducts 3. HPLC conditions assuring detection and separation of the two enantiomeric products were found in most cases.

- Similarly, the domino reactions between few isocyanoacetates 2 and substrates 1d and 1e were found to be feasible under standard PTC conditions, delivering the corresponding tricyclic oxazolines 3 in good yields and diastereoselectivities.

- Due to the surprising lack of precedents dealing with catalytic asymmetric aldol-cyclisation reactions of aldehydes under PTC conditions, a thorough screening of catalysts and reaction conditions with the simpler benzaldehyde 1c was undertaken. Unfortunately, this screening furnished only moderate enantioselectivities in the resulting products 3, despite the good yields and diastereoselectivities generally observed even at low temperatures.

- After a small adjustment, the best conditions found in the screening could be successfully translated to the preparation of the tricyclic target domino products 3.
Future work will focus on:
- A screening of catalysts and reaction conditions in the tandem S$_N$2-Michael reaction between active methylene compounds and substrate 1a and 1b, based on the information regarding the reactivity of the different methylene compounds obtained during the preparation of the racemic compounds.
- It is instead clear that to achieve good results in the domino aldol-cyclisation-Michael reaction with 1d and 1e it is necessary to drastically change the approach used. It can be envisioned that employing for example amides as activating groups instead of esters, and/or switching to a different activation mode for the aldol-cyclisation reaction, good results in terms of reactivity and enantioselectivity can be finally achieved even in this challenging transformation.
5. Experimental Section

5.1. General Methods

$^1$H, $^{13}$C NMR spectra were recorded on a Varian AS 300 or 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for $^1$H and $^{13}$C NMR ($^1$H NMR: 7.26 ppm for CDCl$_3$, 3.30 ppm for CD$_3$OD-d4; $^{13}$C NMR: 77.0 ppm for CDCl$_3$). $^{13}$C NMR spectra were acquired on a broad band decoupled mode. The coupling constant (J) was expressed in Hz.

Mass spectra were recorded on a micromass LCT spectrometer using electrospray ionization techniques (ESI).

The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H, Daicel Chiralpak AS, Daicel Chiralcel OJ-H or Phenomenex Lux 5u Cellulose-1 columns), using a UV detector operating at 254 or 215 nm.

5.2. Materials

Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated.

THF was distilled from Na before use. Pyridine was dried from molecular sieves. Chromatographic purifications were performed using 70-230 mesh silica.
5.3. Synthesis of substrate

5.3.1. 2-Hydroxyethyl 4-methylbenzenesulfonate

Ethylene glycol (6.75 mL, 120 mmol), TsCl (5.7 g, 30 mmol), pyridine (3.36 mL, 36 mmol) and DMAP (36 mg, 0.30 mmol) were stirred at room temperature for 1.5 h. The reaction mixture was then partitioned between DCM (20 mL) and HCl 2.0 M (20 mL). The layers were separated, and the organic phase was dried over MgSO₄, filtered and concentrated in vacuo to give a colourless oil. Yield 67% (4.4 g, 20.1 mmol).

1H NMR (CDCl₃, 400 MHz) δ (ppm): 7.81 (d, 2H, J=8.2), 7.36 (d, 2H, J=8.2), 4.15 (t, 2H, J=4.5), 3.82 (t, 2H, J=4.5), 2.45 (s, 3H), 2.00 (s, 1H).

5.3.2. (E)-Ethyl 3-(2-(tosyloxy)ethoxy)acrylate

2-Hydroxyethyl 4-methylbenzenesulfonate (20.1 mmol), ethyl propiolate (2.3 mL, 23 mmol), NMM (2.8 mL, 25 mmol) were stirred in DCM (20 mL) at room temperature for 3 h. HCl 2.0 M (10 mL x 2) was then added, the phases were separated, and the organic layer was dried over MgSO₄, filtered and concentrated in vacuo.

The reaction mixture was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate= 1/1) giving the title compound as a pale-yellow oil. Yield 62% (3.9 g, 12.4 mmol).

1H NMR (CDCl₃, 300 MHz) δ (ppm): 7.81 (d, 2H, J=8.2), 7.44 (d, 1H, J=12.6), 7.36 (d, 2H, J=8.2), 5.12 (d, 1H, J=12.6), 4.28 (m, 2H), 4.16 (q, 2H, J=7.1), 4.01 (m, 2H), 2.45 (s, 3H), 1.27 (t, 3H, J=7.1).
5.3.3. (E)-Ethyl 3-(2-iodoethoxy)acrylate 1a

(E)-Ethyl 3-(2-(tosyloxy)ethoxy)acrylate (12.4 mmol) and sodium iodide (2.25 g, 15 mmol) in acetone (15 mL) were refluxed for 12 h. The reaction mixture was then concentrated in vacuo and partitioned between DCM (20 mL) and water (20 mL). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo.

The reaction mixture was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate= 2/1) giving a yellow oil. Yield 57% (1.9 g, 7.0 mmol).

\[ ^1H \text{NMR (CDCl}_3, 300 MHz) \delta (ppm): 7.56 (d, 1H, J=12.6), 5.24 (d, 1H, J=12.6), 4.17 (q, 2H, J=7.1), 4.11 (t, 2H, J=4.7), 3.33 (t, 2H, J=4.7), 1.27 (t, 3H, J=7.1), \text{ESI-MS: 293 [M+ Na]}^+ \]

5.3.4. Benzyl propiolate²²

Propiolic acid (1.8 mL, 28.7 mmol), potassium carbonate (4.87 g, 35.2 mmol) in DMF (40 mL) were stirred at room temperature for 30 min. Benzyl bromide (3.8 mL, 31.4 mmol) was then added, and the mixture stirred at room temperature for 16 h.

The resulting heterogeneous mixture was poured into water (40 mL) and extracted with diethyl ether (3 x 40 mL).

The combined ether extracts were dried with MgSO₄, filtered and concentrated in vacuo. The title compound was used without further purifications.

\[ ^1H \text{NMR (CDCl}_3, 300 MHz) \delta (ppm): 7.36 (m, 5H), 5.21 (s, 2H), 2.89 (s, 1H). \]
5.3.5. (E)-Benzy1 3-(2-(tosyloxy)ethoxy)acrylate

2-Hydroxyethyl 4-methylbenzenesulfonate (approximately 22 mmol), benzyl propiolate (20.1 mmol), NMM (2.8 mL, 25 mmol) in DCM (20 mL), were stirred at room temperature for 3 h. HCl 2.0 M (10 mL x 2) was added to the reaction mixture, the phases were separated, the organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude mixture was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate= 2/1) giving the title compound as a brown-yellow oil. Yield 60% (4.7 g, 12.1 mmol).

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.79 (d, 2H, J=8.3), 7.47 (d, 1H, J=12.7), 7.35 (m, 7H), 5.17 (d, 1H, J=12.7), 5.15 (s, 2H), 4.27 (m, 2H), 4.00 (m, 2H), 2.44 (s, 3H).

5.3.6. (E)-Benzy1 3-(2-iodoethoxy)acrylate 1b

(E)-Benzy1 3-(2-(tosyloxy)ethoxy)acrylate (12.1 mmol) and sodium iodide (2.25 g, 15 mmol) in acetone (20 mL) were refluxed for 12h. The reaction mixture was then concentrated in vacuo and partitioned between DCM (20 mL) and water (20 mL). The organic layer was dried with MgSO₄, filtered and concentrated in vacuo.

The reaction mixture was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate= 2/1) giving the title compound as a dark-yellow oil. Yield 91% (3.8 g, 11.1 mmol).

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.60 (d, 1H, J=12.6), 7.35 (m, 5H), 5.28 (d, 1H, J=12.6), 5.16 (s, 2H), 4.11 (t, 2H, J=4.8), 3.32 (t, 2H, J=4.8).
5.3.7. (E)-Methyl 3-(2-formylphenyl)acrylate 1d

2-Bromobenzaldehyde (1.2 mL, 10 mmol) was dissolved in toluene (20 mL). Pd(OAc)$_2$ (45 mg, 0.20 mmol), P(o-tolyl)$_3$ (122 mg, 0.20 mmol), methyl acrylate (1.3 mL, 15 mmol) and TEA (4 mL) were added under N$_2$ atmosphere. The reaction mixture was refluxed with stirring for 40 h, then cooled to r.t. and partitioned between DCM (20 mL) and water (20 mL). The organic layer was dried with MgSO$_4$, filtered and concentrated in vacuo.

The mixture was purified by silica-gel column chromatography (eluent: DCM) giving the title compound as a yellow solid. Yield 75% (1.43 g, 7.5 mmol).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm): 10.29 (s, 1H), 8.53 (d, 1H, J=15.9), 7.87 (m, 1H), 7.64-7.53 (various m, 3H), 6.37 (d, 1H, J=15.9), 3.83 (s, 3H).

5.3.8. 1-Phenyl-2-(triphenylphosphoranylidene)ethanone

(2-Oxo-2-phenylethyl)triphenylphosphonium bromide (10.23 g, 23 mmol), was dissolved in the minimal amount of MeOH. NaOH 2M (15 mL, 30 mmol) was then added, with vigorous stirring. After 30 min, DCM (40 mL) was added and the organic layer separated and washed with water (10 mL x 2). The organic layer was dried with MgSO$_4$, filtered and concentrated in vacuo. The solid was recrystallised from toluene giving the title compound as a white solid in a quantitative yield.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm): 8.00-7.33 (various m, 20H), 4.43 (d, 1H, $J_{HP}$ =24.6).
5.3.9. **(E)-2-(3-Oxo-3-phenylprop-1-en-1-yl)benzaldehyde 1e**

\[
\begin{align*}
\text{o-Phthalaldehyde (3.1 g, 23 mmol) was dissolved in DCM (46 mL). The previously prepared ylide (23 mmol) was dissolved in DCM (46 mL) and added dropwise to the o-phthalaldehyde solution in 30 min. The reaction mixture was stirred at room temperature for 16 h and then purified by filtration through a plug of silica-gel (eluent: } n \text{-hexane/ethyl acetate 7/3) giving the title compound as a dark-brown solid. Yield 90\% (4.9 g, 20.7 mmol).}
\end{align*}
\]

\[\text{H NMR (CDCl}_3, \text{ 300 MHz) } \delta (\text{ppm}): 10.33 (s, 1H), 8.56 (d, 1H, J=16.0), 8.04 (m, 2H), 7.90 (d, 1H, J=7.5), 7.75 (d, 1H, J=7.7), 7.70-7.40 (\text{various m, 5H}), 7.37 (d, 1H, J=16.0).\]

5.3.10. **2-(Benzyloxy)-2-oxoethanaminium p-toluenesulfonate**

\[
\begin{align*}
\text{Glycine (0.76 g, 10 mmol), benzyl alcohol (6.5 mL, 63 mmol), } p \text{-toluenesulfonic acid monohydrate (2.27 g, 11.9 mmol), were added to a flask under N}_2 \text{ atmosphere and the mixture was stirred at 100 °C for 15 h. After cooling to r.t., diethyl ether (38 mL) was added and the title compound precipitated as a white solid. The solid was filtered and washed with diethyl ether. The product was dried } in \text{ vacuo \text{ and the conversion of the starting product was checked by } H \text{ NMR (71\%). As the glycine was still present, the white solid was dissolved in a mixture of benzyl alcohol (2.80 mL, 27 mmol) and toluene (21.5 mL), } p \text{-Toluenesulfonic acid monohydrate (0.19 g, 0.98 mmol) was then added and the reaction mixture was refluxed for 5.5 h in a Dean-Stark apparatus. After cooling r.t., diethyl ether was added and the title compound precipitated as a white solid. The solid was filtered, washed with diethyl ether and dried } in \text{ vacuo \text{ giving the title compound in a quantitative yield.}}
\end{align*}
\]

\[\text{H NMR (CD}_3\text{OD, 300 MHz) } \delta (\text{ppm}): 7.72-7.68 (m, 2H), 7.73-7.32 (m, 5H), 7.25-7.20 (m, 2H), 5.28 (s, 2H), 3.87 (s, 2H), 2.36 (s, 3H).\]
5.3.11. Benzyl 2-formamidoacetate\textsuperscript{26}

2-(Benzyloxy)-2-oxoethanaminium \textit{p}-toluenesulfonate theoretical 10 mmol), methyl formate (7.8 mL, 126 mmol), TEA (1.5 mL, 11 mmol) were added in a flask under N\textsubscript{2} atmosphere, and the mixture was stirred at reflux for 22 h. The reaction was cooled to r.t., and concentrated \textit{in vacuo} giving an oil.

The oil was dissolved with DCM (20 mL), HCl 0.50 M (24 mL) was then added, the phases were separated, the organic layer was washed with a saturated solution of NaHCO\textsubscript{3}, dried with MgSO\textsubscript{4}, filtered and concentrated \textit{in vacuo} to give the title compound as a yellow oil in a quantitative yield.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) \(\delta\) (ppm): 8.25 (s, 1H), 7.40-7.34 (m, 5H), 6.15 (br s, 1H), 5.21 (s, 2H), 4.12 (d, 2H, J=5.4).

5.3.12. Benzyl 2-isocyanoacetate 2l\textsuperscript{26}

Under a N\textsubscript{2} atmosphere, benzyl 2-formamidoacetate (theoretical 10 mmol) was dissolved in DCM (15 mL) in a tree neck flask equipped with reflux condenser, thermometer. TEA (3.5 mL, 25 mmol) was added and the mixture was cooled to 2 \textdegree C under stirring. POCl\textsubscript{3} (1.0 mL, 10 mmol) was slowly added \textit{via} syringe in 50 min, while the temperature was maintained between 2-3.5 \textdegree C. The reaction mixture was stirred for 2 h while the temperature reached r.t.. A solution of K\textsubscript{2}CO\textsubscript{3} (2.00 g in 8.9 mL of water) was then slowly added while the temperature was maintained below 30 \textdegree C. The mixture was stirred for 1 h, and then water (15 mL) and DCM (7 mL) were added. The organic layer was separated, dried over MgSO\textsubscript{4}, filtered and concentrated \textit{in vacuo} to give the title compound as a dark-brown oil.

The oil was purified by silica-gel column chromatography (eluent: DCM) giving the title compound as a pale-yellow oil. Overall yield 55\% (0.96 g, 5.5 mmol).

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) \(\delta\) (ppm): 7.38 (m, 5H), 5.25 (s, 2H), 4.26 (s, 2H).
5.4. Synthesis of catalyst

5.4.1. \textit{N-(2-(trifluoromethyl)benzene) quininum bromide PTC14$^{209}$}

Quinine (0.6488 g, 2.0 mmol) and 1-(bromomethyl)-2-(trifluoromethyl)benzene (0.6215 g, 2.6 mmol) were dissolved in a mixture of toluene/THF 1/1 (6 mL). The resulting mixture was then heated up to 70 °C and stirred for 20 h at the same temperature. After cooling to r.t., the obtained precipitate was filtered. The solid was washed with a mixture of toluene/THF 2/1 (10 mL) and with diethyl ether (5 mL) giving the title compound as a white solid.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm): 8.84 (d, 1H, J=4.7), 8.53 (d, 1H, J=7.7), 8.11 (d, 1H, J=9.30), 7.90-7.80 (m, 3H), 7.71 (t, 1H, J=7.6), 7.43 (dd, 1H, J=9.2, J=2.5), 7.07 (d, 1H, J=2.6), 6.94 (d, 1H, J=12.5), 6.78 (d, 1H, J=7.1), 6.62 (d, 1H, J=7.1), 5.60 (ddd, 1H, J=17.2, J=10.5, J=6.9), 5.47 (d, 1H, J=12.2), 5.11 (d, 1H, J=10.5), 5.01 (d, 1H, J=17.2), 4.68 (d, 1H, J=13.0), 3.97 (s, 3H), 3.69-3.61 (m, 1H), 3.38-3.26 (m, 1H), 3.14 (dd, 1H, J=12.7, J=10.7), 2.96-2.86 (m, 1H), 2.63-2.52 (m, 2H), 2.39-2.29 (m, 1H), 2.09 (s, 1H), 1.94-1.81 (m, 1H), 1.55-1.45 (m, 1H).
5.4.2. N-Benzylquininium phenoxide PTC29

N-Benzylquininium chloride (45.1 g, 0.10 mmol) and sodium phenoxide (13.9 mg, 0.12 mmol) were dissolved in minimal quantities of methanol (approximately 6 mL) and stirred for 30 min at r.t.. The reaction mixture was concentrated in vacuo, and water (5 mL) and DCM (5 mL) were added. The organic layer was separated, dried over MgSO$_4$, filtered and concentrated in vacuo to give the title compound as a white solid.

$^1$H NMR (CD$_3$OD, 300 MHz) $\delta$(ppm): 8.78 (d, 1H, $J$=4.6), 8.04 (d, 1H, $J$=9.3), 7.89 (d, 1H, $J$=4.6), 7.68-7.52 (m, 6H), 7.40 (d, 1H, $J$=2.5), 7.17-7.11 (m, 2H), 6.81-6.72 (m, 3H), 6.62 (br s, 1H), 5.72 (ddd, 1H, $J$=17.4, $J$=10.6, $J$=7.1), 5.33 (d, 1H, $J$=12.6), 5.12 (d, 1H, $J$=17.1), 5.04 (d, 1H, $J$=10.4), 4.70 (d, 1H, $J$=12.5), 4.43-4.31 (m, 1H), 4.03 (s, 3H), 3.91-3.83 (m, 1H), 3.54-3.48 (m, 2H), 3.40-3.35 (m, 1H), 2.76-2.66 (m, 1H), 2.43-2.25 (m, 2H), 2.10-2.05 (m, 1H), 1.94-1.82 (m, 1H), 1.59-1.48 (m, 1H).
5.5. Synthesis of products

5.5.1. Dimethyl 2-(2-ethoxy-2-oxoethyl)dihydrofuran-3,3(2H)-dicarboxylate 3ab

(E)-Ethyl 3-(2-iodoethoxy)acrylate 1a (27.0 mg, 0.10 mmol) and the phase-transfer catalyst (PTC01, 20 mol%, 9.0 mg), were dissolved in toluene (0.20 mL). Dimethyl malonate 2b (28 µL, 0.30 mmol) and the base (Cs₂CO₃ 5 equiv., 0.163 g) were added and the resulting mixture was stirred at r.t. for 48 h.

The reaction mixture was filtered through a silica-gel plug, concentrated in vacuo, and analysed by ¹H NMR, to evaluate the conversion (92%).

The reaction mixture was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate 7/3) giving the title compound.

The ee (14%) of the title compound was determined by HPLC using a Daicel Chiralpak AD-H (eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, wavelength 215 nm, r.t.). The retention time of two enantiomers were 14.9 and 15.8 min (the retention times may change with the temperature).

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 4.75 (dd, 1H, J=10.0, J=3.05), 4.17 (q, 2H, J=7.10), 4.08 (m, 1H), 3.84 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.79-2.64 (m, 2H), 2.46-2.33 (m, 2H), 1.26 (t, 3H, J=7.10).
5.5.2. Methyl 2-(2-ethoxy-2-oxoethyl)-3-(phenylsulfonyl)tetrahydrofuran-3-carboxylate 3af

(E)-Ethyl 3-(2-iodoethoxy)acrylate 1a (27.0 mg, 0.10 mmol) and the phase-transfer catalyst (PTC01, 20 mol%, 9.0 mg), were dissolved in toluene (0.20 mL). Methyl 2-(phenylsulfonyl)acetate 2f (49.3 µL, 0.30 mmol) and the base (K₂CO₃ 5 equiv., 0.069 g, or CsF 5 equiv., 0.076 g) were added and the result mixture was stirred at r.t. for 48 h.

The reaction mixture was filtered through a silica-gel plug, concentrated in vacuo, and analysed by ¹H NMR, to evaluate the conversion (24% with K₂CO₃ and 45% with CsF) and the diastereoselection (≥ 98%).

The reaction mixture was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate 7/3) giving the title compound.

The ee (with K₂CO₃ 20%, with CsF 18%) of the title compound was determined by HPLC using a Daicel Chiralpak AD-H (eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, wavelength 215 nm, r.t.. The retention time of two enantiomers were 31.3 and 33.5 min (the retention times may change with temperature).

¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.95 (d, 2H, J=7.25), 7.70 (t, 1H, J=7.60), 7.57 (t, 2H, J=7.60), 4.88 (dd, 1H, J=9.75, J=2.5), 4.11 (q, 2H, J=7.1), 4.07 (m, 1H), 3.89 (q, 1H, J=8.10), 3.71 (s, 3H), 2.86 (t, 2H, J=7.10), 2.50 (dd, 1H, J=15.7, J=2.5), 2.32 (dd, 1H, J=15.7, J=9.75), 1.24 (t, 3H, J=7.10).
5.5.3. (4R,5S)-Methyl 5-phenyl-4,5-dihydrooxazole-4-carboxylate 3cj

Benzaldehyde 1c (10 µL, 0.10 mmol) and the phase-transfer catalyst (PTC09 10 mol%, 4.5 mg), were dissolved in toluene (1.0 mL) and the reaction mixture was cooled to -40 °C. Methyl-2-isocyanoacetate 2j (19 µL, 0.20 mmol) and the base (K$_2$CO$_3$ aq 50% w/w 0.1382 g or 89 µL) were added and the reaction mixture was stirred at -40 °C for 66 h.

The reaction mixture was filtered through a silica-gel plug, concentrated in vacuo, and it was analysed by $^1$HNMR, to evaluate the conversion (>98 %) and the diastereomeric ratio (91:9).

The ee (34%) of the major diastereoisomer was determined by HPLC using a Daicel Chiralcel OJ-H, (eluent 2-propanol/n-hexane 20/80, flow 0.75 mL/min, wavelength 215 nm, r.t.). The retention time of two enantiomers were 20.8 and 38.9 min (the retention times may change with the temperature).

$^1$H NMR (CDCl$_3$, 300 MHz) δ(ppm): 7.38-7.24 (m, 5H), 7.04 (d, 1H, J=2.10), 5.64 (d, 1H, J=7.80), 4.58 (dd, 1H, J=7.80, 2.15), 3.78 (s, 3H).

$^1$H NMR frequencies for the characterization of the minor diastereoisomer: 5.68 (d, 1H, J=11.0), 5.03 (dd, 1H, J=11.0, J=2.05).

The relative and absolute stereochemistry has been assigned by comparison with literature data.$^{28}$
5.5.4. (4R,5S)-Ethyl 5-phenyl-4,5-dihydrooxazole-4-carboxylate 3ck

Benzaldehyde 1c (10 µL, 0.10 mmol) and the phase transfer catalyst (PTC09 10 mol%, 4.5 mg), were dissolved in toluene (1.0 mL) and the reaction mixture was cooled to -40 °C. Ethyl-2-isocyanoacetate 2k (22 µL, 0.20 mmol) and the base (K₂CO₃ aq 50% w/w 0.1382 g or 89 µL) were added and the reaction mixture was stirred at -40 °C for 68 h.

The reaction mixture was filtered through a silica-gel plug, concentrated in vacuo, and it was analysed by ¹H NMR, to evaluate the conversion (>98 %) and the diastereomeric ratio (89:11).

The ee (37%) of the major diastereoisomer was determined by HPLC using a Daicel Chiralcel OJ-H, (eluent 2-propanol/n-hexane 20/80, flow 0.75 mL/min, wavelength 215 nm, r.t.). The retention time of two enantiomers were 16.5 and 28.4 min (the retention times may change with the temperature).

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.44-7.30 (m, 5H), 7.09 (d, 1H, J=2.16), 5.68 (d, 1H, J=7.80), 4.61 (dd, 1H, J=7.80, 2.17), 4.29 (q, 2H, J=14.2, J=7.2), 1.31 (t, 3H, J=7.2).

¹H NMR frequencies for the characterization of the minor diastereoisomer: 5.73 (d, 1H, J=11.2), 5.07 (dd, 1H, J=11.2, J=1.95).
5.5.5. (4R,5S)-Benzyl 5-phenyl-4,5-dihydrooxazole-4-carboxylate 3cl

Benzaldehyde 1c (10 µL, 0.10 mmol) and the phase-transfer catalyst (PTC09 10 mol%, 4.5 mg), were dissolved in toluene (1.0 mL) and the reaction mixture was cooled at -40 °C. Benzyl-2-isocyanoacetate 2l (35 µL, 0.20 mmol) and the base (K₂CO₃ aq 50% w/w, 0.1382 g or 89 µL) were added and the reaction mixture was stirred at -40 °C for 44 h.

The reaction mixture was filtered through a silica-gel plug, concentrated in vacuo, and it was analysed by ¹H NMR, to evaluate the conversion (>98 %) and the diastereomeric ratio (90:10%).

The ee (36%) of the major diastereoisomer was determined by HPLC using a Daicel Chiralpak AD-H, (eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, wavelength 215 nm, r.t.). The retention time of two enantiomers were 21.0 and 27.0 min (the retention times may change with the temperature).

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.42-7.27 (various m, 10H), 7.10 (d, 1H, J=2.10), 5.66 (d, 1H, J=7.80), 5.31 (d, 1H, J=12.2, Hₐ-CH₂), 5.23 (d, 1H, J=12.2, Hₐ-CH₂), 4.67 (dd, 1H, J=7.80, 2.15).

¹H NMR frequencies for the characterization of the minor diastereoisomer: 5.72 (d, 1H, J=11.0), 5.12 (dd, 1H, J=11.0, J=2.0).
5.5.6. (4S,5R)-tert-Butyl 5-phenyl-4,5-dihydrooxazole-4-carboxylate

Benzaldehyde 1c (10 µL, 0.10 mmol) and the phase-transfer catalyst (PTC09 10 mol%, 4.5 mg) were dissolved in toluene (1.0 mL) and the reaction mixture was cooled at -40 °C. tert-Butyl-2-isocyanoacetate 2m (29 µL, 0.20 mmol) and the base (K₂CO₃ 0.0691 g) were added and the reaction mixture was stirred at -40 °C for 44 h.

The reaction mixture was filtered through a silica-gel plug, concentrated in vacuo, and it was analysed by ¹H NMR, to evaluate the conversion (>98 %) and the diastereomeric ratio (93:7).

The ee (36%) of the major diastereoisomer was determined by HPLC using a Daicel Chiralpak AD-H, (eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, wavelength 215 nm, r.t.). The retention time of two enantiomers were 9.2 and 10.7 min (the retention times may change with the temperature).

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.43-7.28 (m, 5H), 7.08 (d, 1H, J=2.05), 5.61 (d, 1H, J=7.80), 4.51 (dd, 1H, J=7.80, 2.18), 1.52 (s, 9H).

¹H NMR frequencies for the characterization of the minor diastereoisomer: 5.69 (d, 1H, J=11.2), 4.94 (dd, 1H, J=11.2, J=2.00).

The relative and absolute stereochemistry has been assigned by comparison with literature data.
5.5.7. Methyl 4-(2-methoxy-2-oxoethyl)-4,8b-dihydro-3aH-indeno[2,1-d]oxazole-3a-carboxylate 3dj

(E)-Methyl 3-(2-formylphenyl)acrylate 1d (19 mg, 0.10 mmol) and the phase-transfer catalyst (PTC09 20 mol%, 9.0 mg) were dissolved in toluene (1.0 mL), the reaction mixture was cooled at -20 °C. Methyl-2-isocyanoacetate 2j (19 µL, 0.20 mmol) and the base (K₂CO₃ aq 50% w/w 0.138 g or 89 µL) were added and the reaction mixture was stirred at -20 °C for 70 h. The reaction mixture was filtered through a silica-gel plug, concentrated in vacuo, and it was analysed by ¹H NMR, to evaluate the conversion (>98%) and the diastereomeric ratio (96:4).

The ee (39%) of the major diastereoisomer was determined by HPLC using a Daicel Chiralpak AD-H, (eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, wavelength 215 nm, r.t.). The retention time of two enantiomers were 29.3 and 43.0 min (the retention times may change with the temperature).

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.49-7.13 (various m, 4H), 6.92 (s, 1H), 5.99 (s, 1H), 4.46-4.41 (m, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.96 (dd, 1H, J=17.1, J=9.10), 2.80 (dd, 1H, J=17.1, J=5.90).

¹H NMR frequencies for the characterization of minor diastereoisomer: 6.64 (s, 1H), 6.09 (s, 1H). Retention time of the two enantiomers of the minor diastereoisomer: 35.1 and 47.4 min

The relative and stereochemistry has been assigned by comparison with 3dk.

¹H NMR frequencies for the characterization of the intermediate D: 7.96 (d, 1H, J=16.0), 6.65 (d, 1H, J=7.4), 6.36 (d, 1H, J=16.0), 4.57 (dd, 1H, J=7.5, J=2.1), 3.85 (s, 3H), 3.82 (s, 3H).
5.5.8. Ethyl 4-(2-methoxy-2-oxoethyl)-4,8b-dihydro-3aH-indeno[2,1-d]oxazole-3a-carboxylate 3dk

(E)-Methyl 3-(2-formylphenyl)acrylate 1d (19 mg, 0.10 mmol) and the homogeneous catalyst (quinine 20 mol%, 6.5 g) were dissolved in THF (1.0 mL) Ethyl-2-isocyanooacetate 2k (22 µL, 0.20 mmol) and the base (K₂CO₃ aq 50% w/w 0.138 g or 89 µL) were added and the reaction was stirred at r.t. for 48 h. The reaction mixture was filtered through a silica-gel plug, concentrated in vacuo, and it was analysed by ¹H NMR, to evaluate the conversion (90%).

¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.31-7.03 (various m, 4H), 6.75 (s, 1H), 5.82 (s, 1H), 4.31-4.22 (m, 1H), 4.16 (q, 2H, J=7.20), 3.61 (s, 3H), 2.81 (dd, 1H, J=17.2, J=8.75), 2.63 (dd, 1H, J=17.1, J=5.90), 1.18 (t, 3H, J=7.25).

¹H NMR frequencies for the characterization of the minor diastereisomer: 6.67 (s, 1H), 6.13 (s, 1H).

The relative and stereochemistry has been assigned by comparison with literature data.¹⁹
5.5.9. Methyl 4-(2-oxo-2-phenylethyl)-4,8b-dihydro-3aH-indeno[2,1-d]oxazole-3a-carboxylate 3ej

(E)-Methyl 3-(2-formylphenyl)acrylate 1e (24 mg, 0.10 mmol) and phase-transfer catalyst (PTC09 10 mol%, 4.5 g) were dissolved in toluene (1.0 mL), the reaction mixture was cooled at -40 °C. Methyl-2-isocyanoacetate 2j (19 µL, 0.20 mmol) and the base (K$_2$CO$_3$ aq 50% w/w 0.138 g or 89 µL) were added and the reaction mixture were stirred at -20 °C for 21 h. Then, the temperature was left to rise to r.t. while the reaction mixture was stirred for 6 h. The reaction mixture was filtered through a silica-gel plug, concentrated in vacuo, and it was analysed by $^1$HNMR, to evaluate the conversion (100%) and the diastereoselection ratio (77:23).

The ee (20%) of the major diastereoisomer was determined by HPLC using a Daicel Chiralcel OJ-H, (eluent 2-propanol/n-hexane 10/90, flow 0.75 mL/min, wavelength 215 nm, r.t.). The retention time of two enantiomers was 42.2 and 61.0 min (the retention times may change with the temperature).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$(ppm): 7.60-7.14 (various m, 9H), 6.88 (s, 1H), 6.05 (s, 1H), 4.69-4.63 (m, 1H), 3.86 (s, 3H), 3.73 (dd, 1H, J=18.3, J=7.70), 3.39 (dd, 1H, J=18.3, J=5.90).

$^1$H NMR frequencies for the characterization of minor diastereisomers: 6.85 (s, 1H), 6.35 (s, 1H).
6. MSDS

6.1. Benzaldehyde

SIGMA-ALDRICH

SAFETY DATA SHEET
according to Regulation (EC) No. 1907/2006
Version 5.0 Revision Date 24.04.2012
Print Date 21.06.2012

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

1.1 Product identifiers
Product name : Benzaldehyde

Product Number : B1334
Brand : Sigma-Aldrich
Index-No. : 605-012-00-5
CAS-No. : 100-52-7

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@sigal.com

1.4 Emergency telephone number
Emergency Phone # : +39 02-6610-1029 (Centro Antiveloni Niguarda
Cal' 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)

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
Precautionary statement(s) : none
Supplemental Hazard Statements : none


Hazard symbol(s) : X
R-phrase(s) : R22
Harmful if swallowed.
2.3 Other hazards - none

3. COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substances
Synonyms: Artificial essential oil of almond

Formula: C7H14O
Molecular Weight: 106.12 g/mol

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<tr>
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<td>EC-No.</td>
<td>202-850-4</td>
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<tr>
<td>Index-No.</td>
<td>605-012-00-5</td>
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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
Central nervous system depression, Prolonged or repeated exposure to skin causes defatting and dermatitis.

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
No data available

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

5.4 Further information
Under fire conditions, material may decompose to form flammable and/or explosive mixtures in air. 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. Evacuate personnel to safe areas. 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). 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 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 under nitrogen. 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.

Air, light, and moisture sensitive.

7.3 Specific end uses
no data available

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1 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.

Immersion protection
Material: butyl-rubber
Minimum layer thickness: 0.3 mm
Break through time: > 480 min
Material tested: Butoject® (Aldrich Z677647, Size M)
Splash protection
Material: Chloroprene
Minimum layer thickness: 0.6 mm
Break through time: > 30 min
Material tested: Carnapren® (Aldrich Z677493, Size M)

data source: KCL GmbH, D-36124 Eichenzell, phone +49 (0)6659 873000, e-mail sales@kcl.de,
test method: EN374
If used in solution, or mixed with other substances, and under conditions which differ from EN 374,
contact the supplier of the CE approved gloves. This recommendation is advisory only and must
be evaluated by an Industrial Hygienist familiar with the specific situation of anticipated use by our
customers. It should not be construed as offering an approval for any specific use scenario.

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 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
                Colour: colourless
b) Odour        no data available
c) Odour Threshold no data available
d) pH           5,9 at 20 °C
e) Melting point/freezing point
                Melting point/range: -26 °C - lit.
f) Initial boiling point and boiling range
                178 - 179 °C - lit.
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
                Upper explosion limit: 8.5 % (V)
                Lower explosion limit: 1.4 % (V)
k) Vapour pressure 5 hPa at 45 °C
l) Vapour density 3.66 - (Air = 1.0)
m) Relative density 1.044 g/cm3 at 20 °C
n) Water solubility slightly soluble
o) Partition coefficient: n-octanol/water
                log Pow: 1.5
p) Autoignition temperature no data available
q) Decomposition temperature no data available
r) Viscosity no data available
s) Explosive 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
Air Exposure to moisture, Light, Heat, Heat, flames and sparks.
10.5 Incompatible materials
Strong oxidizing agents, Strong reducing agents, Strong bases, Alkali metals, Aluminium, Iron, phenols, Oxygen
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 - 1.300 mg/kg
Remarks: Behavioral: Somnolence (general depressed activity), Behavioral: Coma.
LD50 Dermal - rabbit - 1.250 mg/kg
Skin corrosion/irritation
Skin - rabbit - Skin irritation - 24 h
Serious eye damage/eye irritation
Eyes - rabbit - Mild eye irritation
Respiratory or skin sensitization
May cause allergic respiratory and skin reactions
Germ cell mutagenicity
Laboratory experiments have shown mutagenic effects.
Carcinogenicity
This product is or contains a component that is not classifiable as to its carcinogenicity based on its IARC, ACGIH, NTP, or EPA classification.

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. Causes respiratory tract irritation.
Ingestion   Harmful if swallowed.
Skin        Harmful if absorbed through skin. Causes skin irritation.
Eyes        Causes eye irritation.

Signs and Symptoms of Exposure
Central nervous system depression, Prolonged or repeated exposure to skin causes defatting and dermatitis.

Additional information
RTECS: CU4375000

12. ECOLOGICAL INFORMATION

12.1 Toxicity
Toxicity to fish  LC50 - Lepomis macrochirus - 1,07 mg/l - 96 h
mortality LOEC - Pimephales promelas (fathead minnow) - 0,45 mg/l - 7 d
mortality NOEC - Pimephales promelas (fathead minnow) - 0,22 mg/l - 7 d
LC50 - Leuciscus idus (Golden orfe) - 62 mg/l - 48 h
Toxicity to daphnia and other aquatic invertebrates  EC50 - Daphnia magna (Water flea) - 50 mg/l - 24 h

12.2 Persistence and degradability
Biodegradability  Biotic/Aerobic - Exposure time 28 d
Result: 95 % - 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
This combustible material may be burned in a chemical incinerator equipped with an afterburner and scrubber. 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

14.2 UN proper shipping name
ADR/RID: BENZALDEHYDE  IMDG: BENZALDEHYDE  IATA: Benzaldehyde
14.3 Transport hazard class(es)
ADR/RID: 9
IMDG: 9
IATA: 9

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
Copyright 2012 Sigma-Aldrich Co. LLC. License granted to make unlimited paper copies for internal use only.
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.
6.2. Methyl isocynoacetate

SIGMA-ALDRICH

SAFETY DATA SHEET
according to Regulation (EC) No. 1907/2006
Version 4.0 Revision Date 08.07.2010
Print Date 21.06.2012

GENER EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

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

Product name : Methyl isocynoacetate
Product Number : 238880
Brand : Aldrich
Company : Sigma-Aldrich S.r.l.
Via Gallarate 154
I-20151 MILANO
Telephone : +39 02-3341-7310
Fax : +39 02-3801-0737
Emergency Phone # : +39 02-6610-1029 (Centro Antivedeni Niguarda)
Ca’ Granda - Milano
E-mail address : eurtechserv@sial.com

2. HAZARDS IDENTIFICATION

Classification of the substance or mixture
According to Regulation (EC) No1272/2008
Acute toxicity, Inhalation (Category 4)
Acute toxicity, Dermal (Category 4)
Acute toxicity, Oral (Category 4)
Skin corrosion (Category 1B)

Causes burns. Harmful by inhalation, in contact with skin and if swallowed.

Label elements

Pictogram
Signal word
Hazard statement(s)
H302
H312
H314
H332
Precautionary statement(s)
P280
P305 + P351 + P338
P310
Hazard symbol(s)
C
R-phrase(s)
R34
R20/21/22
S-phrase(s)
S26

In case of contact with eyes, rinse immediately with plenty of water and
seek medical advice.

Wear suitable protective clothing, gloves and eye/face protection.

In case of accident or if you feel unwell, seek medical advice immediately
(show the label where possible).

Other hazards
Lachrymator.

3. COMPOSITION/INFORMATION ON INGREDIENTS

<table>
<thead>
<tr>
<th>CAS-No.</th>
<th>EC-No.</th>
<th>Index-No.</th>
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<td>-</td>
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</table>

For the full text of the H-Statements mentioned in this Section, see Section 16.

4. 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.

5. FIRE-FIGHTING MEASURES

Suitable extinguishing media
For small (incipient) fires, use media such as "alcohol" foam, dry chemical, or carbon dioxide. For large fires, apply water from as far as possible. Use very large quantities (flooding) of water applied as a mist or spray; solid streams of water may be ineffective. Cool all affected containers with flooding quantities of water.

Special protective equipment for fire-fighters
Wear self contained breathing apparatus for fire fighting if necessary.

Further information
Use water spray to cool unopened containers.

6. ACCIDENTAL RELEASE MEASURES

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

Environmental precautions
Prevent further leakage or spillage if safe to do so. Do not let product enter drains.
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). Keep in suitable, closed containers for disposal.

7. HANDLING AND STORAGE

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.

Conditions for safe storage
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. Moisture sensitive.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Personal protective equipment
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).

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

Eye protection
Tightly fitting safety goggles. Faceshield (8-inch minimum). Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

Skin and 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.

Hygiene measures
Handle in accordance with good industrial hygiene and safety practice. Wash hands before breaks and at the end of workday.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance
Form clear, liquid
Colour dark yellow

Safety data
pH no data available
Melting point no data available
Boiling point 75 - 76 °C at 13 hPa - llt.
Flash point 84 °C - closed cup
Ignition temperature  no data available
Lower explosion limit  no data available
Upper explosion limit  no data available
Density  1.09 g/cm³ at 25 °C
Water solubility  no data available

10. STABILITY AND REACTIVITY

Chemical stability
Stable under recommended storage conditions.

Conditions to avoid
Exposure to light may affect product quality.
Heat, flames and sparks.

Materials to avoid
Strong oxidizing agents, Strong bases, Strong acids, Aluminum

Hazardous decomposition products
Hazardous decomposition products formed under fire conditions. - Carbon oxides, nitrogen oxides (NOx)

11. TOXICOLOGICAL INFORMATION

Acute toxicity
no data available

Skin corrosion/irritation
no data available

Serious eye damage/eye irritation
no data available

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  Harmful if inhaled. Material is extremely destructive to the tissue of the mucous membranes and upper respiratory tract.
Ingestion  Harmful if swallowed. Causes burns.
Skin  Harmful if absorbed through skin. Causes skin burns.
Eyes  Causes eye burns.

Signs and Symptoms of Exposure
Material is extremely destructive to tissue of the mucous membranes and upper respiratory tract, eyes, and skin, Cough, Shortness of breath, Headache, Nausea
12. ECOLOGICAL INFORMATION

Toxicity
no data available

Persistence and degradability
no data available

Bioaccumulative potential
no data available

Mobility in soil
no data available

PBT and vPvB assessment
no data available

Other adverse effects
no data available

13. DISPOSAL CONSIDERATIONS

Product
This combustible material may be burned in a chemical incinerator equipped with an afterburner and scrubber. Offer surplus and non-recyclable solutions to a licensed disposal company. Contact a licensed professional waste disposal service to dispose of this material.

Contaminated packaging
Dispose of as unused product.

14. TRANSPORT INFORMATION

ADR/RID
UN-Number: 2922  Class: 8 (6.1)  Packing group: II
Proper shipping name: CORROSIVE LIQUID, TOXIC, N.O.S. (Methyl isocyanoacetate)

IMDG
UN-Number: 2922  Class: 8 (6.1)  Packing group: II
EMS-No: F-A, S-B
Proper shipping name: CORROSIVE LIQUID, TOXIC, N.O.S. (Methyl isocyanoacetate)
Marine pollutant: No

IATA
UN-Number: 2922  Class: 8 (6.1)  Packing group: II
Proper shipping name: Corrosive liquid, toxic, n.o.s. (Methyl isocyanoacetate)

15. REGULATORY INFORMATION

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

16. OTHER INFORMATION

Text of H-code(s) and R-phrase(s) mentioned in Section 3

Acute Tox.  Acute toxicity
H302  Harmful if swallowed.
H312  Harmful in contact with skin.
H314  Causes severe skin burns and eye damage.
H332  Harmful if inhaled.
Skin Corr.  Skin corrosion
C  Corrosive
R20/21/22  Harmful by inhalation, in contact with skin and if swallowed.
R34  Causes burns.
Further information
Copyright 2010 Sigma-Aldrich Co. License granted to make unlimited paper copies for internal use only. 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 Co., shall not be held liable for any damage resulting from handling or from contact with the above product. See reverse side of invoice or packing slip for additional terms and conditions of sale.
6.3. N-Benzylquininium chloride

SIGMA-ALDRICH

SAFETY DATA SHEET
according to Regulation (EC) No. 1907/2006
Version 4.0 Revision Date 25.07.2010
Print Date 21.06.2012
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

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

Product name : N-Benzylquininium chloride
Product Number : 374482
Brand : Aldrich
Company : Sigma-Aldrich S.r.l.
Via Gallarate 154
I-20151 MILANO
Telephone : +39 02-3341-7310
Fax : +39 02-3801-0737
Emergency Phone # : +39 02-6610-1029 (Centro Antiveneni Niguarda
Ca’ Granda - Milano)
E-mail address : eurtechserv@silal.com

2. HAZARDS IDENTIFICATION

Classification of the substance or mixture
Not a dangerous substance according to GHS.
This substance is not classified as dangerous according to Directive 67/548/EEC.

Label elements
This substance is not classified as dangerous according to Directive 67/548/EEC.

Other hazards - none

3. COMPOSITION/INFORMATION ON INGREDIENTS

Synonyms : QUIBEC
Formula : C_{27}H_{31}ClN_{2}O_{2}
Molecular Weight : 451,00 g/mol

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<th>Index-No.</th>
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4. FIRST AID MEASURES

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

In case of skin contact
Wash off with soap and plenty of water.

In case of eye contact
Flush eyes with water as a precaution.

If swallowed
Never give anything by mouth to an unconscious person. Rinse mouth with water.
5. FIRE-FIGHTING MEASURES

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

Special protective equipment for fire-fighters
Wear self contained breathing apparatus for fire fighting if necessary.

6. ACCIDENTAL RELEASE MEASURES

Personal precautions
Avoid dust formation. Avoid breathing vapors, mist or gas.

Environmental precautions
Do not let product enter drains.

Methods and materials for containment and cleaning up
Sweep up and shovel. Keep in suitable, closed containers for disposal.

7. HANDLING AND STORAGE

Precautions for safe handling
Provide appropriate exhaust ventilation at places where dust is formed. Normal measures for preventive fire protection.

Conditions for safe storage
Keep container tightly closed in a dry and well-ventilated place. Store in cool place.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Personal protective equipment

Respiratory protection
Respiratory protection is not required. Where protection from nuisance levels of dusts are desired, use type N95 (US) or type P1 (EN 143) dust masks. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Hand 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.

Eye protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

Skin and body protection
Choose body protection in relation to its type, to the concentration and amount of dangerous substances, and to the specific workplace. The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Hygiene measures
General industrial hygiene practice.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance
Form powder
Colour beige
Safety data

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<th>Property</th>
<th>Value</th>
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<tr>
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<td>Melting point</td>
<td>200 - 205 °C - dec.</td>
</tr>
<tr>
<td>Boiling point</td>
<td>no data available</td>
</tr>
<tr>
<td>Flash point</td>
<td>no data available</td>
</tr>
<tr>
<td>Ignition temperature</td>
<td>no data available</td>
</tr>
<tr>
<td>Lower explosion limit</td>
<td>no data available</td>
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<tr>
<td>Upper explosion limit</td>
<td>no data available</td>
</tr>
<tr>
<td>Water solubility</td>
<td>no data available</td>
</tr>
</tbody>
</table>

10. STABILITY AND REACTIVITY

Chemical stability
Stable under recommended storage conditions.

Conditions to avoid
no data available

Materials to avoid
Strong oxidizing agents

Hazardous decomposition products
Hazardous decomposition products formed under fire conditions. - Carbon oxides, nitrogen oxides (NOx), Hydrogen chloride gas

11. TOXICOLOGICAL INFORMATION

Acute toxicity
no data available

Skin corrosion/irritation
no data available

Serious eye damage/eye irritation
no data available

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. May cause respiratory tract irritation.

Ingestion: May be harmful if swallowed.
Skin
May be harmful if absorbed through skin. May cause skin irritation.

Eyes
May cause 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
Toxicity
no data available

Persistence and degradability
no data available

Bioaccumulative potential
no data available

Mobility in soil
no data available

PBT and vPvB assessment
no data available

Other adverse effects
no data available

13. DISPOSAL CONSIDERATIONS
Product
Offer surplus and non-recyclable solutions to a licensed disposal company.

Contaminated packaging
Dispose of as unused product.

14. TRANSPORT INFORMATION
ADR/RID
Not dangerous goods

IMDG
Not dangerous goods

IATA
Not dangerous goods

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

16. OTHER INFORMATION
Further information
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6.4. Toluene

SIGMA-ALDRICH

SAFETY DATA SHEET
according to Regulation (EC) No. 1907/2006
Version 5.1 Revision Date 09.01.2012
Print Date 21.06.2012

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: Toluene

Product Number: 244511
Brand: Sigma-Aldrich
Index-No.: 601-021-00-3
CAS-No.: 108-88-3

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]
- Flammable liquids (Category 2)
- Reproductive toxicity (Category 2)
- Aspiration hazard (Category 1)
- Specific target organ toxicity - repeated exposure (Category 2)
- Skin irritation (Category 2)
- Specific target organ toxicity - single exposure (Category 3)

Classification according to EU Directives 67/548/EEC or 1999/45/EC
- Highly flammable. Possible risk of harm to the unborn child. Harmful: danger of serious damage to health by prolonged exposure through inhalation. Harmful: may cause lung damage if swallowed. Irritating to skin. Vapours may cause drowsiness and dizziness.

2.2 Label elements

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

Signal word: Danger

Hazard statement(s)
- H225: Highly flammable liquid and vapour.
- H304: May be fatal if swallowed and enters airways.
- H315: Causes skin irritation.
- H336: May cause drowsiness or dizziness.
- H381d: Suspected of damaging the unborn child.
H373  May cause damage to organs through prolonged or repeated exposure.
Precautionary statement(s)
P210  Keep away from heat/sparks/open flames/hot surfaces. - No smoking.
P261  Avoid breathing dust/ fume/ gas/ mist/ vapours/ spray.
P281  Use personal protective equipment as required.
P301 + P310 IF SWALLOWED: Immediately call a POISON CENTER or doctor/ physician.
P331  Do NOT induce vomiting.
Supplemental Hazard Statements

Hazard symbol(s)

R-phrase(s)
R11   Highly flammable.
R38   Irritating to skin.
R48/20 Harmful: danger of serious damage to health by prolonged exposure through inhalation.
R63   Possible risk of harm to the unborn child.
R65   Harmful: may cause lung damage if swallowed.
R67   Vapours may cause drowsiness and dizziness.
S-phrase(s)
S36/37 Wear suitable protective clothing and gloves.
S46   If swallowed, seek medical advice immediately and show this container or label.
S62   If swallowed, do not induce vomiting: seek medical advice immediately and show this container or label.

2.3 Other hazards - none

3. COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substances
Formula : C_7H_8
Molecular Weight : 92.14 g/mol

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
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<td>CAS-No.</td>
<td>108-86-3</td>
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<td>EC-No.</td>
<td>203-625-9</td>
</tr>
<tr>
<td>Index-No.</td>
<td>601-021-00-3</td>
</tr>
</tbody>
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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
Lung irritation, chest pain, pulmonary edema. Inhalation studies on toluene have demonstrated the development of inflammatory and ulcerous lesions of the penis, prepuce, and scrotum in animals.

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. Evacuate personnel to safe areas. 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.
Handle and store under inert gas.

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
   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: -93 ºC
f) Initial boiling point and boiling range 110 - 111 ºC
g) Flash point 4,0 ºC - 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: 7 %(V)
   Lower explosion limit: 1,2 %(V)
k) Vapour pressure 29,1 hPa at 20,0 ºC
l) Vapour density no data available
m) Relative density 0,865 g/mL at 25 °C
n) Water solubility no data available
o) Partition coefficient: n-octanol/water no data available
p) Autoignition temperature 535,0 °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. Extremes of temperature and direct sunlight.

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
LD50 Oral - rat - > 5.580 mg/kg
LC50 Inhalation - rat - 4 h - 12.500 - 28.800 mg/m3
LD50 Dermal - rabbit - 12.196 mg/kg

Skin corrosion/irritation
Skin - rabbit - Skin irritation - 24 h

Serious eye damage/eye irritation
no data available

Respiratory or skin sensitization
no data available

Germ cell mutagenicity
Genotoxicity in vitro - rat - Liver
DNA damage

Carcinogenicity
IARC: 3 - Group 3: Not classifiable as to its carcinogenicity to humans (Toluene)

Reproductive toxicity
Damage to fetus possible
Suspected human reproductive toxicant
Reproductive toxicity - rat - inhalation
Paternal Effects: Spermatogenesis (including genetic material, sperm morphology, motility, and count).
Experiments have shown reproductive toxicity effects in male and female laboratory animals.

Developmental Toxicity - rat - Oral
Effects on Embryo or Fetus: Fetotoxicity (except death, e.g., stunted fetus).

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. Vapours may cause drowsiness and dizziness.
Ingestion | Harmful if swallowed. Aspiration hazard if swallowed - can enter lungs and cause damage.
Skin | Harmful if absorbed through skin. Causes skin irritation.
Eyes | Causes serious eye irritation.

Signs and Symptoms of Exposure
Lung irritation, chest pain, pulmonary edema. Inhalation studies on toluene have demonstrated the development of inflammatory and ulcerous lesions of the penis, prepuce, and scrotum in animals.

Additional Information
RTECS: XS5250000

12. ECOLOGICAL INFORMATION

12.1 Toxicity
Toxicity to fish
LC50 - Lepomis macrochirus (Bluegill) - 74.00 - 340.00 mg/l - 96 h
LC50 - Oncorhynchus mykiss (rainbow trout) - 7.63 mg/l - 96 h
NOEC - Pimephales promelas (fathead minnow) - 5.44 mg/l - 7 d
LOEC - Pimephales promelas (fathead minnow) - 8.04 mg/l - 7 d

Toxicity to daphnia and other aquatic invertebrates
EC50 - Daphnia magna (Water flea) - 8.00 mg/l - 24 h

Toxicity to algae
Immobilization EC50 - Daphnia magna (Water flea) - 6 mg/l - 48 h
EC50 - Chlorella vulgaris (Fresh water algae) - 245.00 mg/l - 24 h
EC50 - Pseudokirchneriella subcapitata (green algae) - 10.00 mg/l - 24 h

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
Toxic to aquatic life.
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: 1294  
IMDG: 1294  
IATA: 1294

14.2 **UN proper shipping name**
ADR/RID: TOLUENE  
IMDG: TOLUENE  
IATA: Toluene

14.3 **Transport hazard class(es)**
ADR/RID: 3  
IMDG: 3  
IATA: 3

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**
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Ringraziamenti

Eccoci!!! Sono alla fine di un percorso durato cinque anni, che sono stati davvero belli e piacevoli. Ho conosciuto tante persone e tanta nuova chimica, ho fatto tante belle esperienze che in queste tre pagine non si possono riassumere tutte.

Ringrazierò sempre tantissimo i miei genitori Gianna e Roberto per avermi permesso di studiare a Bologna e assieme a mia sorella Alessandra, avermi sempre dato il loro supporto in tutte le cose che ho fatto in questi cinque anni di studio.

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