SMALL MOLECULE ACTIVATION FOR THE FORMATION OF HETEROCYCLIC COMPOUNDS

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PhD Thesis

"Small Molecule Activation for the Formation of Heterocyclic Compounds"

Victor Laserna Ayora

Supervised by Prof. Arjan W. Kleij

Tarragona,

October 2017

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Prof. Dr. Arjan W. Kleij, Group Leader at the Institute of Chemical Research of Catalonia (ICIQ) and Research Professor of the Catalan Institution for Research and Advanced Studies (ICREA),

I STATE that the present study, entitled, "*Small Molecule Activation for the Formation of Heterocyclic Compounds*" presented by Victor Laserna Ayora for the award of the degree of Doctor, has been carried out under my supervision at the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, October 2017

Doctoral Thesis Supervisor
Prof. Dr. Arjan W. Kleij

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"*Who hasn't experienced the irresistible attraction of science, will never understand its tirany*"

Frankenstein. Mary Shelley

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General Introduction

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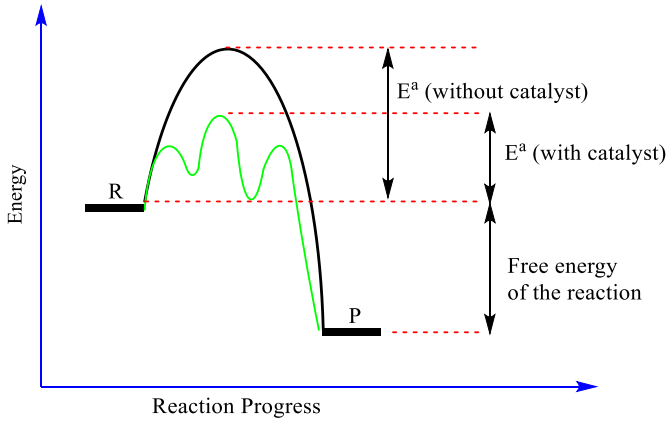
I.1. Catalysis Basics

Although we might not be fully aware, catalysis is an essential and vital technology that affects our everyday life. From the fibers of our clothes to the glucogen in our muscles, most everyday-life process involves in some way a catalytic process. The most biochemically significant processes and important industrial products implicate the use of catalysis at some point. According to the IUPAC, catalysis is the increase in the rate of a chemical reaction due to the participation of an additional substance called the catalyst,[1] which is not consumed in the catalytic process and can continue to act repeatedly. The catalyst role is to lower the activation energy (the minimum energy necessary to start a chemical reaction) of a certain process. Therefore, less energy is required to reach a certain transition state, defined as the state corresponding to the local maximum of potential energy along the reaction coordinate on the way to the final product(s).

Figure I.1 Energy profile for a model reaction with and without catalyst. R = reagent/substrate, P = product.



The presence of the catalyst does not affect the free energy of the starting materials or products. The principal description of this alternative, multistep pathway that the catalyst and the starting reactants undertake to lower the activation energy is called the catalytic cycle.

It is usually represented as a sequence of chemical reactions in the form of a loop, where the starting materials represent the starting point and ends with the final products while regenerating the catalyst. **Figure I.2** shows the catalytic cycle of an important reaction in industry: the Monsanto process, in which acetic acid is produced from methanol and CO.

Figure I.2 Catalytic cycle of the Monsanto process.

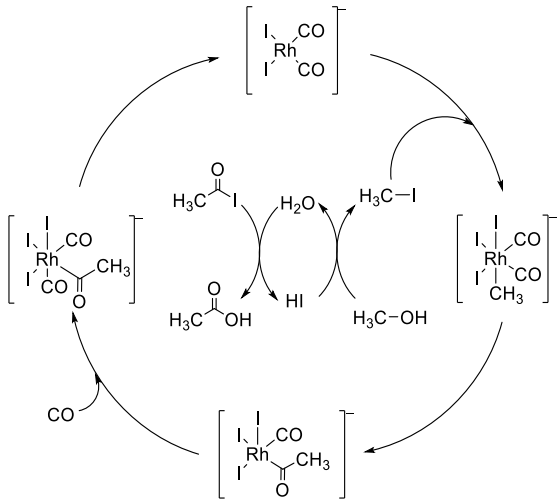


Figure I.2 shows a transition metal complex (M = Rh) as catalyst. Metal complexes consist of a metal ion (often called the coordination center) and a surrounding array of bound molecules and ions called the "ligands". Metal complexes are widely used as catalysts for organic transformations in industry and academia. Ligands usually bind to the metal center by coordinating motifs such as alcohols, amines, or phosphines, and their properties and structure generally have a huge impact on the catalyst activity and selectivity. By tuning the electronic and steric features of the ligand, manipulation of the metal environment can be achieved, which generally is key towards the development of optimal catalytic systems. Porphyrins, phosphines, phenantrolines, salens, salphens and amino triphenolate ligands are well-known examples of the wide variety of existing structures used in coordination chemistry and homogeneous catalysis.

Catalysis is a thriving research field in chemical science. The development of new active systems for known or new processes represents a huge challenge, and both the industrial and academic communities are dedicating a lot of effort and resources to achieve this goal. In catalyst development, the activity of the catalytic system in a given target reaction

is a key objective. The productivity of a certain system is measured by the Turn Over Number (TON), which is the number of chemical transformations of substrate molecules that a single catalytic site will execute under certain conditions. The TON per time unit is called the Turn Over Frequency (TOF) which gives an idea of the activity of a catalyst (i.e, the number of transformations of an active site per time unit). Other desired properties of a catalytic system include stability and robustness (to moisture and oxygen), availability, ease of synthesis in terms of cost and time, and low toxicity. The latter property become an important feature when the catalyst is used for drug manufacture. The next section will focus on examples of catalytic systems derived from amino triphenolate ligands.

I.2 Amino Triphenolate Ligands

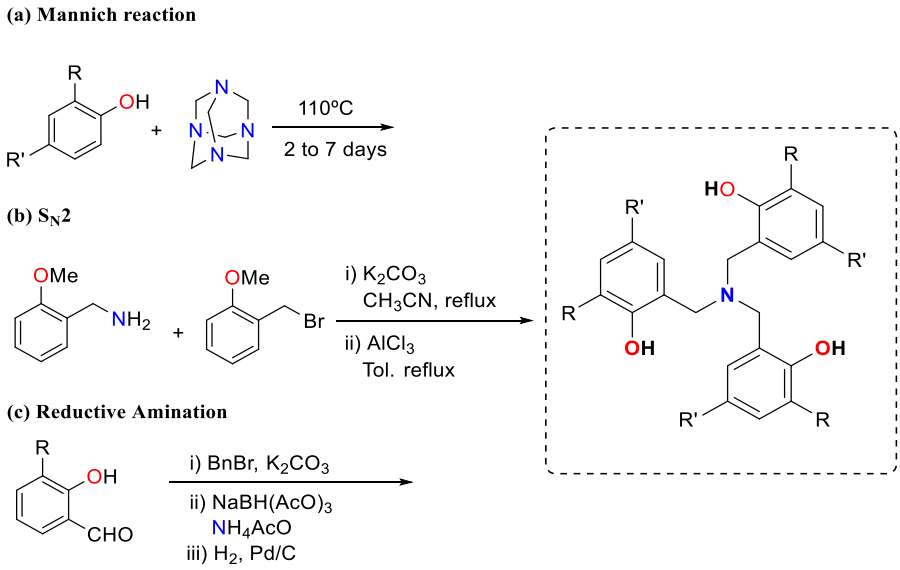
I.2.1 Amino Triphenolate Complexes

As mentioned in the previous section, controlling the electronic and steric features of the ligand in a metal complex is important, as these are used to tune the catalytic performance. Polydentate ligands are those that coordinate to the metal center through two or more atoms, and their use in catalysis science is widely spread as they typically afford robust and modular catalyst systems. In this context, triphenol amines have emerged as a significant example[2] of polydentate ligand which can form a wide array of metal complexes with high activity in various organic transformations. The modular nature of the phenol moieties, associated to the three-fold symmetry and tetradentate nature of the system, allows to obtain a large family of ligands and complexes. Steric and electronic factors play important roles in the stability and catalytic activity of these complexes; for instance, *ortho*-substitutions to the phenol oxygen donors (upon complexation with the metal ions) end up in close proximity to the metal coordination site and represent a tool towards steric control. Meanwhile, *para*-substitutions can modify the electronic properties of the ligand (and thus the electron density on the metal) without affecting the steric demand of the system, as these substituents are too far away from the active site.

Three main strategies exist to synthesize these amino triphenolate ligands. The first one is based on a Mannich reaction of *ortho*- and *para*-disubstituted phenols.[3] This approach

has some drawbacks as long reaction times and harsh conditions are typically necessary. Other methodologies have tried to improve on these issues. For example, the alkylation of 2-methoxybenzylamine with two equivalents of 2-methoxybenzylbromide provides an alternative route.[4] This method requires the protection (and subsequent deprotection) of the phenols, which adds a further two steps and therefore despite being milder in nature, the method does not significantly improve the overall yield. The third alternative consists of a threefold reductive amination starting from *ortho*-substituted salicylaldehydes using NH_4AcO as a nitrogen source and $NaBH(AcO)_3$ as reducing agent.[5] Again, extra steps are needed as the phenol moiety needs to be protected and deprotected, but the mild conditions and the availability of the reagents easily allows gram-scale synthesis and high yields.

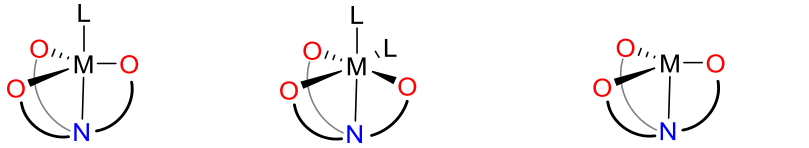
Figure I.3 Synthetic strategies for amino triphenol synthesis. (a) Mannich reaction. (b) S_N2 chemistry. (c) Reductive amination.



Amino triphenolate (ATP) complexes can be prepared from early transition metals (d^0-d^5) and main group elements (d^{10}); late transition metal complexes have been described but are still rare.[6] Most examples represent mononuclear complexes displaying a 1:1 metal/ligand stoichiometry. The trigonal bipyramidal (TBP) and octahedral (OCT) coordination geometries generally dominate whereas tetracoordinate complexes with a trigonal monopyramidal (TMP) geometry are more unusual. For TBP and OCT geometries,

usually the free coordination sites are occupied by solvent molecules or metal precursor ligand (e.g., an alkoxide, halide).

Figure I.4 Reported geometries for amino triphenolate complexes.



penta-coordinate trigonal bipyramidal (TBP) | hexa-coordinate octahedral (OCT) | tetra-coordinate trigonal monopyramidal (TMP)

Titanium complexes are the most extensively studied among the reported examples of ATP compounds. Kol and coworkers were the first to characterize Ti-ATP complexes[7] in 2001. Their synthesis involves a transesterification reaction from a metal alkoxide precursor. The final complex shows a slightly distorted trigonal bipyramidal geometry around the titanium, which lies 0.24 Å above the plane formed by the three oxygen atoms. The corresponding complexes with heavier elements from group IV have also been reported,[8–10] displaying mainly a penta-coordinate TBP geometry (**Figure I.4**). Complexes with octahedral configurations have also been described,[11] in these examples a bidentate ligand enforces a OCT configuration by occupying an axial and an equatorial position. The ability to coordinate bidentate ligands is valuable as it enables the activation of alkyl hydroperoxides and hydrogen peroxide to form peroxo complexes that are active in oxygen transfer reactions.

Previously it was described how substituents in the *ortho* position of the phenol units can affect the activity of the complex; steric hindrance around the metal affects the binding mode and the stability towards nucleophiles by creating a pocket around the binding site. Bulky substituents, such as *tert*-butyl, prevent the complex to aggregate into multinuclear structures whereas methyl groups show very little steric modulation potential.[12] The stability against moisture for Ti complexes is much higher when equipped with bulky *ortho*-substituents. Another example of this steric effect is the formation of Ti-hydroxo species. Terminal hydroxo complexes of titanium are rare, and only a few examples have been crystallographically characterized. The instability of terminal titanium hydroxides is due to the ease with which these complexes condense to form µ-oxo complexes. The Ti (*tert*-butoxide) derivative reacts with trifluoroacetic acid to form the trifluoroacetate (usually the

apical alkoxide ligand is labile),[13] which can be converted to the terminal hydroxide ATP-Ti(OH) complex in excellent yield by treatment of the complex with aqueous sodium hydroxide or by moisture. The hydroxo species is only stable in the presence of bulky *ortho* substituents such as *tert*-butyl; when the complex has sterically less congested Me or H groups, rapid condensation to the oxo bridged species occurs. The oxo-bridge forces the substituents present in the *ortho* position to be in close proximity such a situation is only feasible with small substituents.

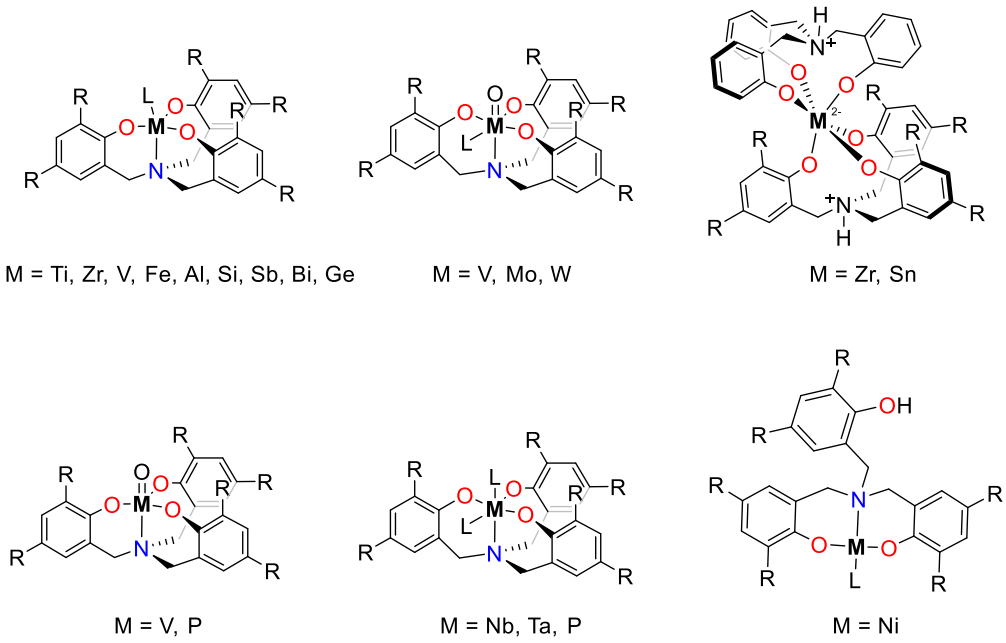
In group V ATP complexes, only vanadium is reported to give TBP structures, even though it can also adopt OCT geometries to accommodate an extra ligand. Vanadium amino triphenolates can be synthesized from V(III) chloride precursors or from vanadyl alkoxide species.[14] Both lead to the formation of C_3-symmetrical TBP species; the first category of reactions installs a THF molecule in the apical position, while the second category results in the formation of a complex with the axial position occupied by an oxo moiety. The latter case shows generally the V–N distances being significantly longer due to the *trans* influence of a strong π-donor ligand (cf., V=O unit). In V(V) complexes based on electron-poor amino triphenolate ligands the binding mode can change, and usually a molecule of solvent occupies an equatorial position resulting in an octahedral complex. Niobium ATP complexes have only been reported once[15] while Tantalum complexes are more common,[15–17] and all these cases report OCT coordination geometries.

The chemistry of ATP complexes has mainly focused on groups IV and V. Complexes with other transition metals have also been reported and some of these including aluminium-based complexes have only recently been recognized as versatile Lewis acid catalysts.[18–21] Regarding metals from groups VI and VII, only few examples of their ATP complexes have been reported, such as molybdenum (Mo) and tungsten (W) complexes.[22–24] Mo complexes incorporate an oxo group in the apical position, while the free equatorial site can be occupied by a variety of ligands such as a second oxo, alkoxide or halide ligand. These complexes formally bear a negative charge, so usually the protonated species of the ligand acts as counter cation.

Iron amino triphenolates were the first ATP complexes to be reported.[4] They are obtained by reaction of the alkaline triphenolate salt with $FeCl_3$. Pentacoordinate TBP structures are obtained where the apical position is occupied by a solvent molecule. Their

properties are very similar to the Ti(IV)-ATP complexes. A surprising example was reported by Itoh, who described a Ni(II) complex[25] obtained by reaction of the *ortho*-methyl substituted ligand with $NiCl_2$ in the presence of a base. The resulting Ni-complex has an unexpected coordination geometry, representing a four-coordinate, distorted square planar conformation. The triphenol amine acts as a tridentate ligand binding the metal with two phenolate oxygen atoms and the tertiary amine nitrogen donor. It is the only reported example of a transition metal ATP complex with a free phenol. Recently Co(II) complexes[6] were reported, and these are comprising of two different hemispheres, one containing an anionic $Co((ArO)_3N)^-$ while the other is a cationic $(ArO)_3NH^+$ unit and both are associated through hydrogen bonding and coulombic interactions. These Co(II) complexes can be easily converted into their Co(III) analogues in air in the presence of strong-field ligands such as dimethylaminopyridine or 2,2′-bipyridine.

Figure I. 5 Common configurations for ATP complexes.



ATP complexes of non-transition metals also exist, although the aluminium complexes only have gained importance over the years due to their potential to act as Lewis acid catalysts. Verkade and co-workers studied Al(III) ATP complexes bearing substituents with different steric requirements.[26,27] The reaction of $AlMe_3$ with the unsubtituted amino

triphenol led to formation of a dimeric complex where two ATP units are linked by two (strong) μ-oxo bridges. Upon substituting the *ortho* positions, a monomeric species with a TBP geometry is generally isolated, and the steric hindrance around the metal ion prevents dimerization or at least favors the dimer-to-monomer equilibrium. Solvent or water usually occupy the axial positions of the Al-ATP complexes. Some other metal ATP complexes have also been reported with phosphorus,[28–30] silicium,[31,32] antimony,[33,34] germanium,[35] tin[10] and bismuth,[34] but these are beyond the relevance of this thesis.

I.2.2 Catalytic Activity of Amino Triphenolate Complexes

Despite the number of characterized ATP complexes, the number of studies describing their catalytic activity is limited. These studies focus mainly on their properties as a Lewis acid (LA). ATP complexes, due to their high stability, are good candidates for application in LA catalysis, with the advantage that most LA´s used in organic chemistry are very often moisture-sensitive while ATP complexes tolerate to a certain extent the presence of water during catalytic events.

The ATP complexes have proven to be active catalysts in different oxidation and polymerization processes. Group IV and Ge ATP complexes are effective catalysts in the ring opening polymerization (ROP) of *rac*-lactide;[8,9,35,36] polylactic acid (PLA) is of interest due to its favorable (bio)degradability, bio-origin of the product, and use in high-value bio-medical applications. The polymerization process occurs typically via a coordination-insertion mechanism initiated by the alkoxo groups on the catalyst. The stereoselectivity of the polymerization strongly depends on the nature of the metal ion: Ge,[35] Zr and Hf complexes[8] afford the PLA displaying high reactivity and providing high heterotacticity under solvent-free conditions, while Ti ATP complexes selectively form atactic polymers.[36] ATP complexes can also be initiators of ethylene polymerization. Vanadium[37] and titanium[38] complexes using $AlMe_3$ as promotor have proven to be active systems in the ethylene polymerization, in copolymerizations of ethylene and propylene, and in the more challenging styrene polymerization.[15] The activation of peroxides is another reaction for which ATP complexes have shown to be efficient, and the mechanism first involves the coordination of the peroxide to the metal center followed by the oxygen transfer via an η_2 metalloperoxo intermediate.[39] These intermediates are capable of direct and selective oxidation of heteroatoms, which is important as those conversions are also involved in biochemical and

industrial oxidation processes.[40] Ti(IV) ATP complexes have proven to be active catalysts in the oxidation of sulfides[41] and amines[42] to afford the corresponding sulfoxides and nitrones selectively.

V-ATP complexes have gained momentum by virtue of the possibility of mimicking vanadium-dependent haloperoxidase enzymes (VHPO).[43] These enzymes are vanadium-dependent and able to oxidize halides to the corresponding 'X^+' species in the presence of hydrogen peroxide leading to halogenation of suitable substrates. VHPOs show a five-coordinate V(V) center with trigonal bipyramidal geometry reminiscent of vanadium ATP complexes, and therefore the latter are regarded as viable structural and functional models of VHPOs. The first report of vanadyl ATP complexes used as catalysts in oxidation reactions was in the epoxidation of styrene to styrene oxide using *tert*-butyl hydroperoxide as an oxidant.[14] Also, these vanadium complexes proved to be much more active than the analogous titanium complexes in the oxidation of sulfides.[44,45] Further to this, the bromination of aromatic rings was studied with these V-catalysts with encouraging results.[46]

Aluminum complexes are powerful LA catalysts used in organic synthesis.[47] After reporting on their synthesis and characterization, Verkade studied the potential of Al ATP compexes for binding substrates, even isolated a stable adduct with benzaldehyde coordinated in the apical position.[48] Another adduct between the Al complex and oxetane has been reported,[49] and the coordination of these molecules through the oxygen centers is associated with an increase in the electrophilic nature of the adjacent carbon atoms. The enhancement of the electrophilicity makes Al ATP complexes suitable catalysts for reactions such as the formation of cyanated species upon the addition of one equivalent of trimethyl silyl cyanide to aldehydes. More importantly, such a Lewis acid coordination potential was believed to be useful for the activation of epoxides in the coupling reaction with CO_2 to form cyclic and poly carbonates. Recently numerous reports have appeared describing metal ATP complexes as effective catalysts for these reactions, in particular those based on Fe(III),[50] Al(III)[19] and more recently V(V).[51] These complexes are among the most active catalysts reported to date for the the coupling of CO_2 and epoxides. The next section discusses in more detail the epoxide activation potential of these Lewis acids and the relevance of these Lewis acids for the chemistry described in this thesis.

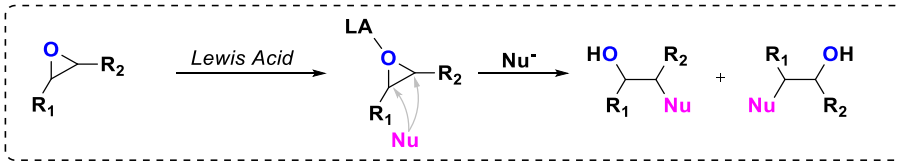
I.3 Epoxide Activation by Lewis Acids

I.3.1 Epoxide Ring Opening Reactions

Epoxides are three-membered cyclic ethers and their strained nature makes them more reactive than their homologous larger-size cyclic ethers. They are intermediates in many industrial processes and are produced on a large scale in industry. Epichlorohydrin, glycidol or epoxidized linolein are important intermediates in the synthesis of resins and plasticizers.

Ring opening reactions dominate epoxide chemistry as they behave as electrophiles which can be attacked by a wide range of nucleophiles such as halides, alcohols, amines, thiols and water. For weaker nucleophiles or hindered epoxides, the ring opening reaction can be sluggish and thus in those cases catalytic activation is required.[52,53] Lewis acid catalysts are often used for these type of reactions, with the oxygen atom binding to the metal center increasing the electrophilicity of the adjacent carbon atoms and facilitating the nucleophile-assisted ring opening process. The regioselectivity can be an issue for nonsymmetrically substituted epoxides as there are two electrophilic adjacent atoms present which may lead to two different regioisomers; generally the attack on the least-hindered carbon atom is favored but complete selectivity can typically not be achieved.

Figure I.6 Nucleophilic attack onto a nonsymmetrical oxirane substrate.



The most interesting product formed by direct ring opening of an epoxide are *β*-amino alcohols. Numerous natural, biologically active compounds and chiral auxiliaries are composed of *β*-amino alcohols.[54] Metoprolol, propranolol, atenolol and dopamine, for instance, are widely used drugs employed to control cardiovascular disorders. At an industrial level, this reaction is important to harden epoxy resins. Epoxy resins are high molecular weight polymers which normally contain at least two epoxide groups, while the hardeners are polyfunctional amines. The hardening (curing) process involves a nucleophilic attack by this

amine on the epoxide moiety forming a three-dimensional cross-linked thermoset structure. Uncured epoxy resins have only poor mechanical, chemical and heat resistance properties. In industry, this process does not require a catalyst as the reaction can be thermally driven. However, many catalyst systems exist which increase the electrophilicity of the oxirane through coordination or H-bonding. Hence, alumina, metal amides or triflamides, tetrafluoroborates and perchlorates of alkali metals, iron trifluoroacetate, silica gel, ionic liquids, triflates of metals, metal alkoxides or halides, microwave irradiation and zirconia compounds have been used to accelerate the curing process.

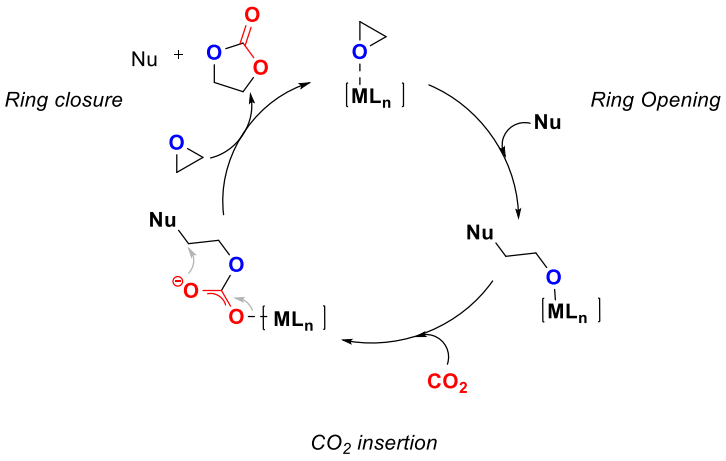
I.3.2 Epoxide Couplings with CO_2

An increasing part of the scientific community is focusing its attention on the coupling reaction between carbon dioxide (CO_2) and epoxides[55] to form cyclic or linear carbonates. The use of CO_2 as a renewable carbon feedstock in organic synthesis is an important goal as its massive emission as a waste material from combustion processes and industrial activities makes it readily accessible and cheap. Cyclic carbonates have been frequently associated with numerous applications involving them as nonprotic solvents,[56] electrolytes, and more recently as useful intermediates in organic synthesis. The mechanism for the formation of cyclic and polycarbonate involves the ring opening of epoxides, and therefore LA catalysts are typically used in these transformations. The catalyst systems are usually accompanied by a nucleophilic co-catalyst (nucleophilic species) mediating the ring opening of the epoxide. First, the epoxide occupies a coordination site in the metal complex, increasing its electrophilicity and facilitating the ring opening process by the nucleophilic attack of the cocatalyst. A metal alkoxide intermediate is then formed after the ring opening, followed by CO_2 insertion into the M–O bond yielding a linear carbonate intermediate that undergoes a ring closing process forming the cyclic carbonate (**Figure I.7**), and regenerating the nucleophilic cocatalyst. When alternating epoxide/CO_2 insertions take place, a polycarbonate chain is formed.

The selectivity towards cyclic or polycarbonate formation has been studied in detail[57,58] and depends on many variables such as reaction temperature, solvent, catalyst, cocatalyst, catalyst/cocatalyst ratio and the nature of the substrate. Among the different homogeneous catalytic systems active in CO_2/oxirane coupling chemistry, salen and salphen metal complexes, in combination with an ammonium halide as nucleophile are the most

extensively studied systems.[59,60] Salen and salphen complexes have relatively planar coordination geometries and are obtained from readily available chemicals.[61] Their structure-reactivity features can be easily fine-tuned from a reactivity point of view by incorporating electron-withdrawing or -donating groups into the ligand backbone. There is ample flexibility in the type of metal ions that can be incorporated, and the most active complexes reported to date for CO_2/epoxide coupling involve Zn,[62] Al[63] and Cr.[64] An example of such catalysts is North's dinuclear μ-oxo-bridged Al(salen) complex[63,65,66] which is catalytically active at room temperature and atmospheric pressure of CO_2. Its activity is due to the presence of two neighboring metal centers capable of simultaneously activating both the oxirane and CO_2.

Figure I.7: Generalized mechanism for the CO_2-epoxide coupling reaction to afford cyclic carbonates.



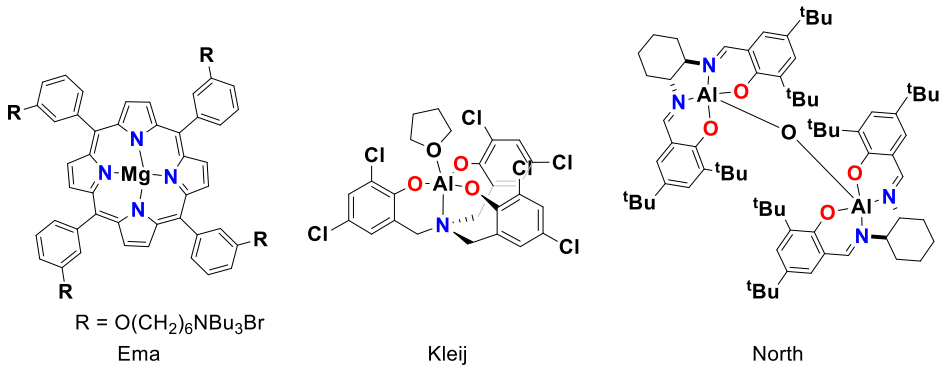
Bifunctional molecular catalysts may also be developed from these structures if a nucleophilic species is embedded into the structure. Usually an alkyl chain with an ammonium halide head group is used. As said, the nucleophile plays the role of cocatalyst in the ring opening of the epoxides, and thus the bifunctional catalytic system does not need the addition of an external nucleophile. Usually this type of systems are less active and need harsher conditions, and these aspects plus their recyclability features still need to be improved as only few examples are able to compete with the generally preferred binary systems.

Porphyrin-based catalysts are another class of powerful catalytic systems in CO_2/epoxide couplings. These catalysts have a planar geometry, which enables the coordination of oxiranes at one of the apical coordination sites. The most noticeable example

was reported by the group of Ema, who developed bifunctional magnesium metalloporphyrins.[67–69] To further enhance the catalytic activity of these bifunctional Mg(II) porphyrin systems, Mg(II) porphyrin complexes incorporating up to eight tetraalkyl ammonium bromide groups were prepared.[67] At a later stage, the same group also reported on an improved version of these catalysts focusing on dinuclear and trinuclear complexes of these bifunctional designs[70] with the aim of further increasing the observed TONs and TOFs. The kinetic data showed that the metal sites in the dinuclear and trinuclear complexes act virtually independently, with no observable cooperativity between the individual metal sites.

The use of ATP complexes is also eminent in the field of CO_2 catalysis as a result of their flexible coordination behavior (see section I.2.1). Several ATP complexes have been reported and employed as catalysts for CO_2/epoxide coupling reactions. Kleij recently reported on different ATP complexes being part of binary catalyst systems that are among the most active systems reported for this reaction, with a prominent role for Al-based complexes.[49,19,71] This earth-abundant, non-toxic Lewis acidic metal allowed the preparation of several robust and highly active ATP catalysts. The complex having both *ortho*- and *para*-chloro substitution on each phenolate unit turned out to be the most active species for cyclic carbonate formation. By installing electron-withdrawing groups in the ligand framework, the Lewis acidity of the metal center was thus increased, and concomitantly the activity of the system.

Figure I.8. Representative examples of active Lewis acid catalysts for epoxide-CO_2 coupling reactions.



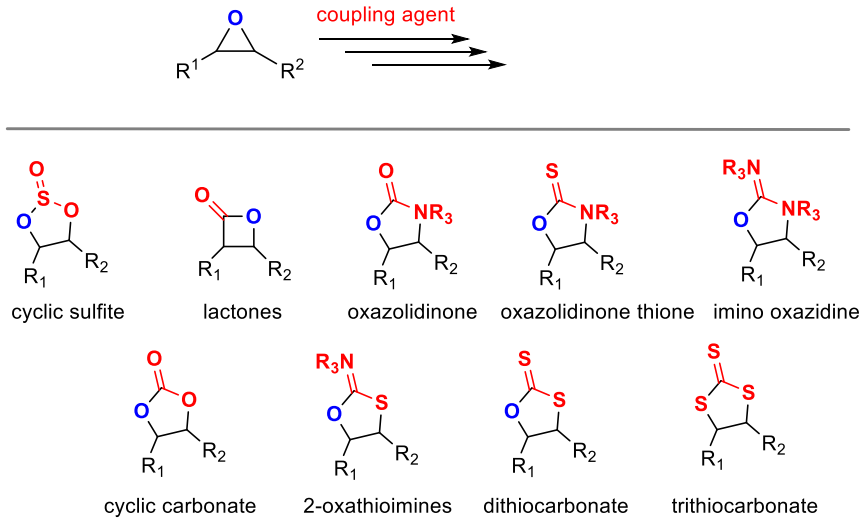
Ammonium halides are the usual nucleophiles used as cocatalysts in binary systems. Since Calo's[72] work, in which cyclic carbonates were formed by using molten ammonium

halides as medium, they have been widely used in catalytic amounts in the area of cyclic carbonate chemistry. Apart from chloride based salts such as tetrabutylammonium chloride (TBACl) and bis(triphenylphosphine)iminium chloride (PPNCl), azides, tertiary amines, phenoxide species and alkoxides have also been used, but since these possess lower nucleophilic character, all these additives are more frequently used as initiators in polycarbonate synthesis.

I.3.3 Epoxide Couplings towards Heterocycles

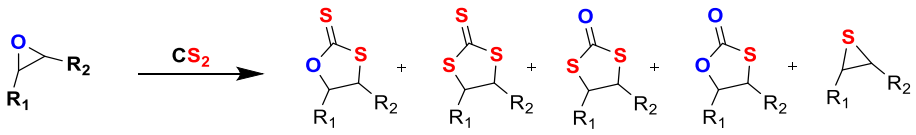
Small molecule catalysis and recycling has become a popular and rewarding theme in the field of organic synthesis.[73–75] In particular, the conversion of heterocumulenes such as carbon dioxide (CO_2),[76,77] as discussed in the previous section, seems to be a promising research topic to find environmentally benign alternatives for fossil fuel based chemistry. The reactive nature of ubiquitous and cheap epoxides makes them an ideal partner for rather unreactive coupling partners such as previously discussed CO_2 or other heterocumulenes such as SO_2, CS_2 or CO. Heterocyclic compounds are interesting target molecules for their wide range of applications in pharmaceuticals, agrochemicals, copolymers or as intermediates in fine chemistry. **Figure I.9** shows a few examples of heterocycles which can be formed through coupling reactions of heterocumulenes and epoxides. Some of these transformations are very similar to the CO_2/oxirane coupling reaction that has been intensively studied. In most cases, the mechanism involves a ring opening of the epoxide by a nucleophile, therefor LA systems developed for organic carbonate formation are also potentially useful towards these type of reactions.

Figure I.9: Representative examples of heterocycles derived from epoxide-heterocumulenes coupling reactions.



Sulphur-containing heterocycles have become interesting synthetic targets as some exhibit biological activity. The similarities between CS_2 and CO_2 suggest that their coupling with epoxides should be a straightforward process. However, the processes using CS_2 as reagent are rather underdeveloped compared to CO_2 based reactions. The main drawback is the high number of byproducts that are formed in the presence of CS_2 due to the higher reactivity of this reagent. Depending on the conditions and catalyst load, up to five different products have been characterized from the coupling of CS_2 and epoxides (see **Figure I.10**). Only the first left two have potential applications as substrates for polymerizations[78,79] and for their radioprotective[80] activity. Taguchi[81] and Endo[82] reported how triethyl amine or alkali metal salts could act as catalysts for the moderately selective production of dithiocarbonate, although high temperatures and pressures were necessary.

Figure I.10: Products formed in the epoxide/CS_2 coupling reaction.

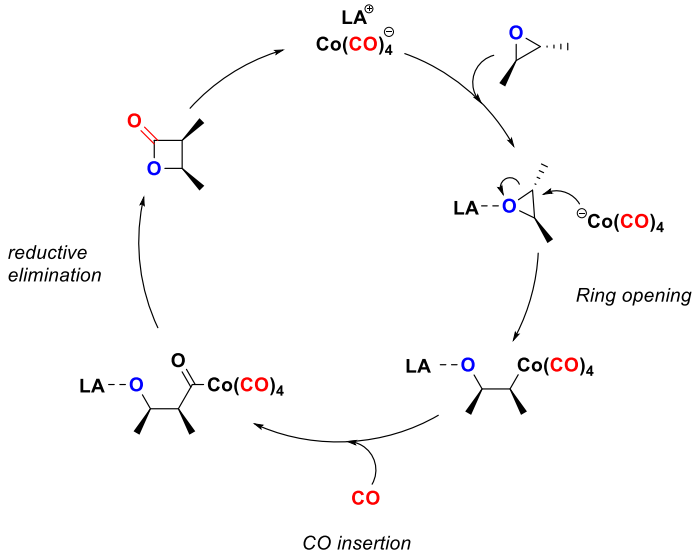


The latest significant contribution in this subfield is the work from North and coworkers who reported the activity of several salen systems (previously reported for CO_2/epoxide couplings) in this context,[83,84] Cyclic sulphites represent other sulphur-containing heterocycles derived from coupling reactions that involve SO_2 and epoxides, but their synthesis and applications will be described in chapter II.

Isocyanates are a popular coupling agent for epoxides as the resultant oxazolidinone products have multiple medicinal applications.[85–87] These types of couplings will be further discussed in chapter I. Epoxides also react to some extent with isothiocyanates[88,89] or carbodiimides,[90–92] to form 2-oxathioimines/oxazolidinone thione or imino-oxazolidines, respectively.

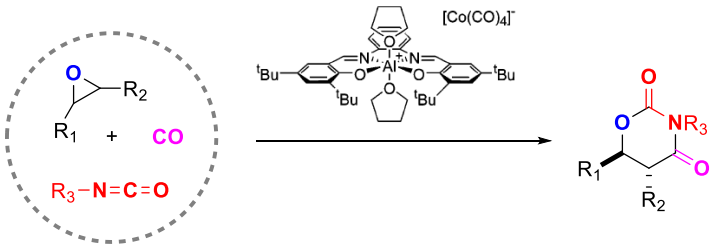
β-Lactones are heterocycles of great interest for their pharmaceutical properties, though despite this potential only scarce methods exist for the selective synthesis of *β*-lactones. Ring-expanding carbonylation of epoxides is an atom-economical and versatile method for the construction of *β*-lactones and higher homologues. A metal catalyst may facilitate the insertion of CO into one of the C–O bonds of the epoxide. Complexes containing a Lewis acid and a tetracarbonylcobaltate anion,[93–95] have emerged as useful catalysts for site-selective and stereospecific carbonylation of epoxides to form *β*-lactones. The catalytic system can be even tuned to mediate successive carbonylations yielding succinic anhydrides.[96] The LA in these catalysts are typically Al(III) or Cr(III) cations coordinated by a salen or porphyrin ligand, and the mechanism of these coupling is represented in **Figure I.11**. The Lewis acid activates the electrophilic position of the epoxide while the cobaltate acts as a nucleophile, and after ring opening insertion of a CO molecule into the C–Co bond occurs followed by a reductive elimination to yield the *β*-lactone product.

Figure I.11: Catalytic cycle of the carbonylation of epoxides.



Other metal complexes based on Fe[97] and Pd[98] are able to mediate or catalyze the ring-expanding carbonylation of epoxides with unsaturated substituents, including alkenyl and aryl epoxides. These reactions involve intermediate π-allyl complexes, which have been isolated by stoichiometric reactions with $Fe_2(CO)_9$.[97] Similar catalytic systems are able to catalyze the multicomponent reaction of CO, epoxides and isocyanates to yield 1,3-oxazinane-2,4-diones.[99]

Figure I.12: Multicomponent reaction to form 1,3-oxazinane-2,4 diones.



I.4 Thesis Aims

Heterocycles derived from coupling reactions between epoxides and heterocumulenes are interesting synthetic target for their wide range of applications. Therefore there exist huge impetus towards the development of efficient, new methods for these compounds. Additionally, the recycling of industrial waste by-products, such as CO_2 and SO_2, is of high importance as they represent raw materials associated to environmental concerns. Epoxides have been recognized as ideal coupling partners for their reactivity and availability. With previous studies reporting on the high activity of Al(III) ATP complexes in the coupling of epoxides and CO_2, we envisioned that such catalysts would provide a good starting point to explore the activity of these complexes in other coupling processes, that necessitate a Lewis acid activator. Apart from this, a wider application of the potential of Al(III) ATPs would expand the knowledge in the area of cyclic carbonate formation specifically aiming at challenging substrates that usually present lethargic reactivity. The creation of more complex, substituted cyclic carbonates and related heterocycles may revive their use as precursors in synthetic chemistry.

To summarize, the aims of the work described in these thesis are:

(i) To evaluate the potential of Al(III) amino triphenolate complexes for the activation of oxiranes and their coupling with different heterocumulenes targeting heterocyclic products such as oxazolidinones or cyclic sulphites.

(ii) To take advantage over the high activity of aluminium triphenolate complexes in epoxide/CO_2 coupling reactions with sterically hindered epoxides.

(iii) To explore and use more complex cyclic carbonate as reaction intermediates to access other value-added chemicals.

(iv) To obtain a higher degree of understanding of the mechanisms involved in heterocyclic synthesis from epoxides as to control the stereochemical features.

I.5 Summary

In Chapter I, we have studied the use of Al(III) amino triphenolates as catalysts in coupling reactions of epoxides and phenyl urethane. We have evaluated the potential of these catalysts to create a wide scope of oxazolidinones as to provide a new route towards the formation of nonsymmetrical ureas. These latter scaffolds are valuable organic molecules which recently have attracted attention for their catalytic activity in the area of organocatalysis. The results demonstrate that the prepared oxazolidinones can indeed be easily ring opened through aminolysis using various amines yielding nonsymmetrically substituted ureas. Thus a simple, selective and efficient method for the synthesis of these urea products has been enabled.

Chapter II describes the evaluation of the catalytic activity of amino triphenolate complexes in another coupling reaction involving epoxides and SO_2 as coupling partners. SO_2 is an exhaust gas in fossil fuel combustion processes and an industrial intermediate in sulfuric acid production. We have compared these coupling reactions with the known coupling reaction of CO_2 and epoxides, and differences and similarities were noted. This type of coupling reaction yields cyclic sulfites for which the most versatile methodology to date has been developed and further proved to be efficient, selective and having ample wide scope. The synthetic utility of the cyclic sulfites was demonstrated in the synthesis of (*N*)-substituted aziridines.

Chapter III reports how the Al(III) amino triphenolate system can be used to catalyze the coupling reaction of CO_2 and internal epoxides based on multicyclic scaffolds with different ring sizes. The reaction conditions and catalyst loadings were optimized to selectively form *cis*-carbonates. These *cis* carbonates can be converted via basic treatment into their corresponding *cis*-diols which are important building blocks in synthetic chemistry. The cyclic carbonates thus formed offer heterocyclic precursors with CO_2 acting as a protecting group in the synthesis of *cis*-diols, and presents a greener alternative to osmium-based methodologies.

In Chapter IV we present a one-pot method to prepare carbamates from cyclic epoxides, CO_2 and amines. The diastereoselectivity of the product could be controlled by

tuning the reaction conditions to selectively form either the *cis* or the *trans* configured carbamate. The key feature is to control the conditions to form either a cyclic or oligocarbonate intermediate, which subsequently delivers the corresponding carbamate by attack onto the carbonate-C center by an amine reagent. Thus, the intermediate configuration of the carbonate precursor determines the configuration of the final product, and importantly cyclic carbonates (mostly *cis*) and oligocarbonates (mostly *trans*) have opposite configurations. The ring size in the cycloalkene oxide substrate drastically affects the stereoselectivity, indicating that certain epoxides have a higher tendency to form oligomeric intermediates.

Finally, in Chapter V the stereoselective preparation of bicyclic, trisubstituted carbonates is reported enabled by coupling of CO_2 with cyclic *syn* epoxy alcohols. This work has unveiled a new depolymerization manifold opening up the possibility of producing these carbonates selectively and in high yield. The traditionally challenging coupling reactions between CO_2 and trisubstitued epoxides proved to be extremely sluggish and low yielding, and the work described in this chapter offers a useful alternative. Mechanistically, the cyclic carbonates are proposed to be formed through H-bond activation of the adjacent alcohol group in each repeating unit of an oligomeric/polymeric intermediate, and subsequent depolymerization delivers the products with an *anti/cis* configuration. *Syn* epoxy alcohols with fused rings of different sizes were studied to evaluate the favored manifold for each of these substrate classes.

Overall, the work described in this thesis supports the high efficiency/activity of the Al(III) amino triphenolate system in a series of Lewis acid catalyzed coupling reactions. The importance and potential of these coupling reactions is demonstrated by the preparation of various products with an increased synthetic value. The reactivity and limitations of cyclic epoxides in coupling reactions is described in detail, and new synthetic approaches that control the stereoselectivity outcome have become available. Efforts have thus focused on providing new reactivity going beyond the state of the art in epoxide/CO_2 couplings, and to provide new application potential for CO_2 and related heterocumulenes in synthetic chemistry.

I.6 References

(1) *IUPAC, Compendium of Chemical Terminology*; **1997**; Vol. 2nd Ed.

(2) Licini, G.; Mba, M.; Zonta, C. *Dalton Trans.* **2009**, 5265–5277.

(3) Hultzseh, K. *Chem. Ber.* **1949**, *82*, 16–25.

(4) Hwang, J.; Govindaswamy, K.; Koch, S. A. *Chem. Commun.* **1998**, 1667–1668.

(5) Prins, L. J.; Blázquez, M. M.; Kolarović, A.; Licini, G. *Tetrahedron Lett.* **2006**, *47*, 2735–2738.

(6) Martín, C.; Whiteoak, C. J.; Martin, E.; Escudero-Adán, E. C.; Galán-Mascarós, J. R.; Kleij, A. W. *Inorg. Chem.* **2014**, *53*, 11675–11681.

(7) Kol, M.; Shamis, M.; Kol, M. *Inorg. Chem. Commun.* **2001**, *4*, 177–179.

(8) Chmura, A. J.; Davidson, M. G.; Frankis, C. J.; Jones, M. D.; Lunn, M. D. *Chem. Commun.* **2008**, 1293–1295.

(9) Gendler, S.; Segal, S.; Goldberg, I.; Goldschmidt, Z.; Kol, M. *Inorg. Chem.* **2006**, *45*, 4783–4790.

(10) Davidson, M. G.; Doherty, C. L.; Johnson, A. L.; Mahon, M. F. *Chem. Commun.* **2003**, 1832–1833.

(11) Fortner, K. C.; Bigi, J. P.; Brown, S. N. *Inorg. Chem.* **2005**, *44*, 2803–2814.

(12) Nielson, A. J.; Shen, C.; Waters, J. M. *Polyhedron* **2006**, *25*, 2039–2054.

(13) Ugrinova, V.; Ellis, G.; Brown, S. N. *Chem. Commun.* **2004**, 468–469.

(14) Groysman, S.; Goldberg, I.; Goldschmidt, Z.; Kol, M. *Inorg. Chem.* **2005**, *44*, 5073–5080.

(15) Michalczyk, L.; De Gala, S.; Bruno, J. W. *Organometallics* **2001**, *20*, 5547–5556.

(16) Groysman, S.; Goldberg, I.; Kol, M.; Goldschmidt, Z. *Organometallics* **2003**, *22*, 3793–3795.

(17) Kim, Y.; Verkade, J. G. *Organometallics* **2002**, *21*, 2395–2399.

(18) Laserna, V.; Guo, W.; Kleij, A. W. *Adv. Synth. Catal.* **2015**, *357*, 2849–2854.

(19) Whiteoak, C. J.; Kielland, N.; Laserna, V.; Escudero-Adán, E. C.; Martin, E.; Kleij, A. W. *J. Am. Chem. Soc.* **2013**, *135* , 1228–1231.

(20) Laserna, V.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Adv. Synth. Catal.* **2016**, *358*, 3832–3839.

(21) Rintjema, J.; Epping, R.; Fiorani, G.; Martín, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 3972–3976.

(22) Lehtonen, A.; Kessler, V. G. *Inorg. Chem. Commun.* **2004**, *7*, 691–693.

(23) Lehtonen, A.; Sillanpää, R. *Polyhedron* **2007**, *26*, 5293–5300.

(24) Lehtonen, A.; Sillanpää, R. *Organometallics* **2005**, *24*, 2795–2800.

(25) Takayuki Nagataki, S. I. *Chem. Lett.* **2007**, *36*, 748–749.

(26) Kim, Y.; Verkade, J. G. *Inorg. Chem.* **2003**, *42*, 4804–4806.

(27) Su, W.; Kobayashi, J.; Ellern, A.; Kawashima, T.; Verkade, J. G. *Inorg. Chem.* **2007**, *46*, 7953–

7959.

(28) Chandrasekaran, A.; Day, R. O.; Holmes, R. R. *Inorg. Chem.* **2000**, *39*, 5683–5689.

(29) Timosheva, N. V.; Chandrasekaran, A.; Day, R. O.; Holmes, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 7035–7040.

(30) Timosheva, N. V.; Chandrasekaran, A.; Holmes, R. R. *Inorg. Chem.* **2004**, *43*, 7403–7411.

(31) Chandrasekaran, A. *J. Am. Chem. Soc.* **2000**, *122*, 1066–1072.

(32) Timosheva, N. V.; Chandrasekaran, A.; Day, R. O.; Holmes, R. R. *Organometallics* **2001**, *20*, 2331–2337.

(33) Kelly, B. V.; Weintrob, E. C.; Buccella, D.; Tanski, J. M.; Parkin, G. *Inorg. Chem. Commun.* **2007**, *10*, 699–704.

(34) Turner, L. E.; Davidson, M. G.; Jones, M. D.; Ott, H.; Schulz, V. S.; Wilson, P. J. *Inorg. Chem.* **2006**, *45*, 6123–6125.

(35) Chmura, A. J.; Chuck, C. J.; Davidson, M. G.; Jones, M. D.; Lunn, M. D.; Bull, S. D.; Mahon, M. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 2280–2283.

(36) Kim, Y.; Jnaneshwara, G. K.; Verkade, J. G. *Inorg. Chem.* **2003**, *42*, 1437–1447.

(37) Redshaw, C.; Rowan, M. A.; Homden, D. M.; Dale, S. H.; Elsegood, M. R. J.; Matsui, S.; Matsuura, S. *Chem. Commun.* **2006**, No. 31, 3329–3331.

(38) Wang, W.; Fujiki, M.; Nomura, K. *Macromol. Rapid Commun.* **2004**, *25*, 504–507.

(39) Schneider, C. J.; Penner-Hahn, J. E.; Pecoraro, V. L. *J. Am. Chem. Soc.* **2008**, *130*, 2712–2713.

(40) Sheldon, R.. *Metal Catalyzed Oxidations of Organic Compounds*; Academic press, **1981**.

(41) Mba, M.; Prins, L. J.; Licini, G. *Org. Lett.* **2007**, *9*, 21–24.

(42) Zonta, C.; Cazzola, E.; Mba, M.; Licini, G. *Adv. Synth. Catal.* **2008**, *350*, 2503–2506.

(43) Butler, A. *Coord. Chem. Rev.* **1999**, *187*, 17–35.

(44) Mba, M.; Pontini, M.; Lovat, S.; Zonta, C.; Bernardinelli, G.; Kündig, P. E.; Licini, G. *Inorg. Chem.* **2008**, *47*, 8616–8618.

(45) Smith, T. S.; Pecoraro, V. L. *Inorg. Chem.* **2002**, *41*, 6754–6760.

(46) Clague, M. J.; Keder, N. L.; Butler, A. *Inorg. Chem.* **1993**, *32*, 4754–4761.

(47) H. Yamamoto. *Lewis Acids in Organic Synthesis*; Wiley–VCH, Weinheim, **2001**.

(48) Su, W.; Kim, Y.; Ellern, A.; Guzei, I. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2006**, *128*, 13727–13735.

(49) Whiteoak, C. J.; Kielland, N.; Laserna, V.; Castro-Gomez, F.; Martin, E.; Escudero-Adán, E. C.; Bo, C.; Kleij, A. W. *Chem. Eur. J.* **2014**, *20*, 2264–2275.

(50) Whiteoak, C. J.; Martin, E.; Belmonte, M. M.; Benet-Buchholz, J.; Kleij, A. W. *Adv. Synth. Catal.* **2012**, *354*, 469–476.

(51) Miceli, C.; Rintjema, J.; Martin, E.; Escudero-Adán, E. C.; Zonta, C.; Licini, G.; Kleij, A. W. *ACS Catal.* **2017**, *7*, 2367–2373.

(52) Venkatasubbaiah, K.; Zhu, X.; Kays, E.; Hardcastle, K. I.; Jones, C. W. *ACS Catal.* **2011**, *1*,

489–492.

(53) Seth, K.; Roy, S. R.; Pipaliya, B. V; Chakraborti, A. K. *Chem. Commun.* **2013**, 5886–5888.

(54) Katerinopoulos, H. E.; Tagmatarchis, N.; Zaponakis, G.; Kefalakis, N.; Kordatos, K.; Spyrakis, M.; Thermoes, K. *Eur. J. Med. Chem.* **1995**, *30*, 949–954.

(55) Martín, C.; Fiorani, G.; Kleij, A. W. *ACS Catal.* **2015**, *5*, 1353–1370.

(56) Schaffner, B.; Schaffner, F.; Verevkin, S. P.; Borner, A. *Chem. Rev.* **2010**, *110*, 4554–4581.

(57) Taherimehr, M.; Al-Amsyar, S. M.; Whiteoak, C. J.; Kleij, A. W.; Pescarmona, P. P. *Green Chem.* **2013**, *15*, 3083–3090.

(58) Buchard, A.; Kember, M. R.; Sandeman, K. G.; Williams, C. K. *Chem. Commun.* **2011**, *47*, 212–214.

(59) Darensbourg, D. J. *Chem. Rev.* **2007**, *107*, 2388–2410.

(60) Decortes, A.; Castilla, A. M.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2010**, *49*, 9822–9837.

(61) Cozzi, P. G. *Chem. Soc. Rev.* **2004**, *33*, 410–421.

(62) Decortes, A.; Martínez Belmonte, M.; Benet-Buchholz, J.; Kleij, A. W. *Chem. Commun.* **2010**, 4580–4582.

(63) Melendez, J.; North, M.; Pasquale, R. *Eur. J. Inorg. Chem.* **2007**, 3323–3326.

(64) Castro-Osma, J. A.; North, M.; Wu, X. *Chem. Eur. J.* **2016**, *22*, 2100–2107.

(65) North, M.; Pasquale, R. *Angew. Chem. Int. Ed.*. **2009**, *48*, 2946–2948.

(66) Clegg, W.; Harrington, R. W.; North, M.; Pasquale, R. *Chem. Eur. J.* **2010**, *16*, 6828–6843.

(67) Ema, T.; Miyazaki, Y.; Shimonishi, J.; Maeda, C.; Hasegawa, J.-Y. *J. Am. Chem. Soc.* **2014**, *136*, 15270–15279.

(68) Maeda, C.; Shimonishi, J.; Miyazaki, R.; Hasegawa, J. Y.; Ema, T. *Chem. Eur. J.* **2016**, *22*, 6556–6563.

(69) Ema, T.; Miyazaki, Y.; Koyama, S.; Yano, Y.; Sakai, T. *Chem. Commun.* **2012**, *48*, 4489.

(70) Maeda, C.; Taniguchi, T.; Ogawa, K.; Ema, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 134–138.

(71) Laserna, V.; Fiorani, G.; Whiteoak, C. J.; Martin, E.; Escudero-Adan, E.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 10416–10419.

(72) Caló, V.; Nacci, A.; Monopoli, A.; Fanizzi, A. *Org. Lett.* **2002**, *4*, 2561–2563.

(73) Que, L.; Tolman, W. B. *Nature* **2008**, *455*, 333–340.

(74) Kennedy, C. R.; Lin, S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2016**, *55*, 12596–12624.

(75) Stephan, D. W.; Erker, G. *Angew. Chem. Int. Ed.* **2015**, *54*, 6400–6441.

(76) Aresta, M. *Carbon Dioxide as Chemical Feedstock*; Wiley-VCH, Weinheim, **2010**.

(77) Liu, Q.; Wu, L.; Jackstell, R.; Beller, M. *Nat. Commun.* **2015**, *6*, 5933.

(78) Motokucho, S.; Sudo, A.; Sanda, F.; Endo, T. *Chem. Commun.* **2002**, 1946–1947.

(79) Choi, W.; Sanda, F.; Kihara, N.; Endo, T. *J. Polym. Sci. Part A Polym. Chem.* **1997**, *35*, 3853–3856.

(80) Y. Robbe, J.P. Fernandez, R. Dubief, J.P. Chapat, H. Sentenac-Roumanou, M. Fatome, J.D.

Laval, G. S. *Eur. J. Med. Chem. Chem.Ther.* **1982**, *17*, 235–243.

(81) Taguchi, Y.; Yanagiya, K.; Shibuya, I.; Y. S. *Bull. Chem. Soc. Jpn* **1988**, *61*, 921–925.

(82) Kihara, N.; Nakawaki, Y.; Endo, T.; Utilization, R. *J. Org. Chem.* **1996**, *60*, 473–475.

(83) Beattie, C.; North, M. *ChemCatChem* **2014**, *6*, 1252–1259.

(84) Clegg, W.; Harrington, R. W.; North, M.; Villuendas, P. *J. Org. Chem.* **2010**, *75*, 6201–6207.

(85) Barbachyn, M. R.; Toops, D. S.; Grega, K. C.; Hendges, S. K.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H.; Buysse, J. M.; Demyan, W. F.; Kilburn, J. *Bioorg. Med. Chem.* **1996**, *6*, 1009–1014.

(86) Park, C. H.; Brittelli, D. R.; Wang, C. L. J.; Marsh, F. D.; Gregory, W. A.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1992**, *35*, 1156–1165.

(87) Brnardic, E. J.; Fraley, M. E.; Garbaccio, R. M.; Layton, M. E.; Sanders, J. M.; Culberson, C.; Jacobson, M. A.; Magliaro, B. C.; Hutson, P. H.; O'Brien, J. A.; Huszar, S. L.; Uslaner, J. M.; Fillgrove, K. L.; Tang, C.; Kuo, Y.; Sur, S. M.; Hartman, G. D. *Bioorganic Med. Chem. Lett.* **2010**, *20*, 3129–3133.

(88) Yavari, I.; Ghazanfarpour-Darjani, M. *J. Sulfur Chem.* **2014**, *35*, 477–483.

(89) Petrov, V. A.; Marshall, W. *J. Fluor. Chem.* **2011**, *132*, 41–51.

(90) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709–3715.

(91) Fujiwara, M.; Baba, A.; Matsuda, H. *J. of Heterocyclic Chem*. **1988**, 1351–1357.

(92) Saito, T.; Ote, T.; Kataoka, H.; Otani, T.; Kutsumura, N. *Heterocycles* **2010**, *82*, 305–310.

(93) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174–1175.

(94) John W. Kramer, Daniel S. Treitler, and G. W. C. *Org. Synth.* **2009**, *86*, 287–297.

(95) Kramer, J. W.; Joh, D. Y.; Coates, G. W. *Org. Lett.* **2007**, *9*, 5581–5583.

(96) Rowley, J. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 4948–4960.

(97) Bates, R. W.; Fernandez-Moro, R.; Ley, S. V. *Tetrahedron* **1991**, *47*, 9929–9938.

(98) Shimizu, I.; Maruyama, T.; Makuta, T.; Yamamoto, A. *Tetrahedron Lett.* **1993**, *34*, 2135–2138.

(99) Church, T. L.; Byrne, C. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 8156–8162.

Chapter I

Oxazolidinone Synthesis and their Conversion into Functional Non-Symmetrical Ureas

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UNIVERSITAT ROVIRA I VIRGILI
SMALL MOLECULE ACTIVATION FOR THE FORMATION OF HETEROCYCLIC COMPOUNDS
Victor Laserna Ayora

1.1 Introduction

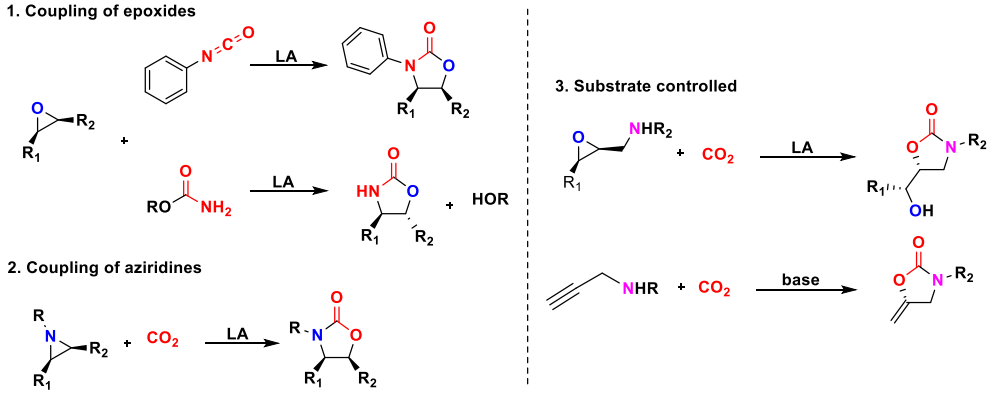
In the previous chapter, the importance of different heterocycles in organic and material chemistry was highlighted. Oxazolidinones are a prominent example of heterocycles which can be obtained by coupling reactions of heterocumulenes. Oxazolidinones are five-membered heterocycles bearing a carbamate moiety and the literature covers many different methodologies describing the synthesis of these molecules as they represent interesting scaffolds for various medicinal applications.[1–3] For instance, they are used as antimicrobial agents,[4] represent useful chiral auxiliaries,[5,6] synthetic intermediates,[7] and can be used as precursors of β-aminoalcohols.

1.1.1 Oxazolidinones

The first example of oxazolidinone synthesis based on heterocumulene couplings dates back to 1958.[8] Peppel reported how ammonium halides catalyze the coupling reaction between epoxides and isocyanates, and this was the first example where the coupling of these two molecules was favored over the polymerization of isocyanates to cyclic dimers or isocyanurates.[9] The activity was associated to the ability of ammonium halides to efficiently ring open the oxirane substrates. Through the following decades similar reports appeared demonstrating the usefulness of metal halide catalysts in these reactions,[10–13] recently a series of metallosalen systems have been studied showing significant catalytic activity in this type of coupling reaction.[14,15] The common mechanistic pathway involves a metal center coordinated by the oxygen atom of the epoxide which favors the ring opening of the epoxide by a halide nucleophile. Once the alkoxide is formed, it attacks the electrophilic carbon center of the isocyanate, followed by a ring-closure process mediated by the nitrogen atom which yields the oxazolidinone product. However, this process still poses some limitations: (1) regioselectivity of these reactions is often compromised, (2) the scope in both epoxides and isocyanates remains limited being restricted to mono-substituted epoxides and arylisocyanates, and (3) harsh reaction conditions (elevated temperatures) are necessary. Instead of using isocyanates as coupling partners for the epoxides, carbamates have also been studied in the same context.[16–18] The electrophilicity of the epoxide is enhanced with a Lewis

acid (LA) to favor the ring opening by the carbamate reagent. Regio- and stereoselectivity issues could this way be circumvented but the scope in epoxide partners remains so far underdeveloped.

Figure 1.1 Reported oxazolidinone synthesis through heterocumulene couplings.



An alternative to epoxide/isocyanate or epoxide/carbamate coupling reactions to access oxazolidinones is the reaction between aziridines and CO_2.[19] During the past decade, many different catalysts including DMAP,[20] alkali metal halides,[21] tetraalkyl ammonium halides,[22] and iodine[23] have been utilized to mediate the coupling of aziridines and CO_2 into either 4-substituted oxazolidinones or a mixture of 4- and 5-substituted oxazolidinones. A different approach towards oxazolidinone formation based on CO_2 coupling chemistry is through propargylic amines[24–26] or aminomethyl-substituted oxiranes.[27,28] The amine moiety is able to activate CO_2 forming an *in situ* carbamate species which can attack the electrophilic position of the adjacent epoxide or activated alkyne to form an oxazolidinone product.

The mechanistic manifolds that are involved in the above-mentioned coupling processes are slightly different. These pathways determine the regio- and stereo-outcome of the coupling process and thus the nature of the oxazolidinone product. Coupling reactions between epoxides and isocyanates involve a double inversion pathway, which means that the stereo-chemical configuration of the starting compound will be retained. For epoxide-carbamate and epoxy amine/CO_2 coupling reactions, however, there is only one S_N2 step involved in the mechanistic pathway which leads to formal inversion of configuration. The mechanistic manifold for aziridine-CO_2 couplings is not fully clear. Nguyen et al. recently studied this reaction using a Cr-salen catalyst both in the absence and presence of a

nucleophile,[29] and they concluded the occurrence of two alternative mechanisms. In the absence of a nucleophile, a transition state between the aziridine, CO_2 and Cr catalyst is formed with the ring opening happening by nucleophilic attack of one of the oxygen atoms. In the presence of DMAP, a double S_N2 sequence takes place in an analogous way to the formation of cyclic carbonates from epoxides and CO_2. Therefore, this latter reaction may have alternative mechanistic pathways involving one or two inversion steps depending on the presence/absence of an (external) nucleophile.

1.1.2 Ureas

Organic ureas are ubiquitous structures in organic chemistry and their re-emerging application potential in various areas of chemistry has been recently highlighted.[30] Prominent fields where ureas have gained importance include (asymmetric) organocatalysis[31] and supramolecular chemistry.[32] Organocatalytic activation of organic substrates by means of hydrogen-bonding patterns that comprise of the two urea NH groups has also been recognized as a powerful tool to orientate carbonyl-containing substrates. Chiral ureas have been developed successfully and applied as enantioselective mediators in, for instance, the asymmetric Strecker reaction.[33] Regarding supramolecular applications, *N,N´*-disubstituted urea derivatives have proven to be versatile building blocks for the preparation of hydrogen-bonded supramolecular polymers,[34,35] helical type foldamers[36] and anion transporting molecules.[37] Various synthetic methods exist towards the formation of nonsymmetrical ureas although in most cases reactive species such as carbonylimidazolide[38] or (*in situ* prepared) isocyanate reagents[39,40] are required.

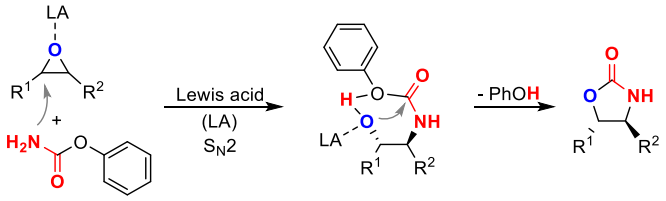
1.1.3 Project Aims and Strategy

Our primary interest in oxazolidinones involves their electrophilic carbonyl atom, which makes them suitable precursors for nonymmetrical ureas through nucleophilic attack of an amine (i.e., aminolysis). This ring opening reaction of oxazolidinones by amines could be a synthetic alternative for asymetrically substituted ureas which has not received a great deal of attention.

Melchiorre et al. and at a later stage Jacobsen and coworkers disclosed methods for the formation of chiral amino alcohols through a Co(salen) mediated enantio-selective

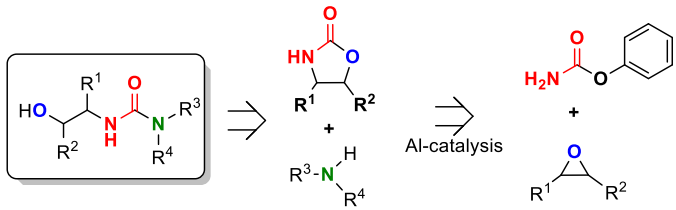
conversion of *meso*-cyclic epoxides in the presence of phenyl carbamate as nucleophile.[16–18] This approach demonstrated the use of a carbamate as a cheap and readily available reagent in the formal transfer of an "amide" unit to an epoxide giving enantio-enriched oxazolidinones being intermediates for chiral amino alcohols. The Co-catalyst acts here as a classical Lewis acid increasing the electrophilic character of the epoxide carbon atoms, and after nucleophilic attack by the carbamate reagent leading to ring opening of the epoxide, the formed alkoxide attacks the phenyl carbamate unit generating the oxazolidinone and phenol as byproduct (**Figure 1.2**).

Figure 1.2 Lewis acid phenyl carbamate addition to epoxides.



However, only a limited number of epoxide substrates was studied in these reports. In order to be able to develop a more general method towards oxazolidinone precursors *en route* to nonsymmetrical ureas, we envisioned that previously reported Lewis acidic Al(amino triphenolate) complexes would present an alternative catalyst for oxazolidinone formation (**Figure 1.2**), and decided to choose phenyl carbamate as a coupling partner for its availability and reactivity. Our aim is to show that these Al-catalysts provide easy access to a wider range of oxazolidinone precursors useful towards the preparation of highly functionalized ureas with excellent yields and regio-selectivities. This methodology would represent a practical synthesis of nonsymmetrical ureas from readily available and cheap starting materials combined with a highly modular nature of the reaction partners (see **Figure 1.3**).

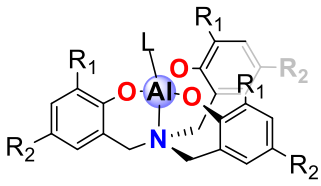
Figure 1.3. Modular approach towards non-symmetrical ureas through oxazolidinone intermediates.



1.2 Results and Discussion

1.2.1 Oxazolidinone Synthesis Optimization

Figure 1.4 Al-catalysts **1A–C** used in this work.

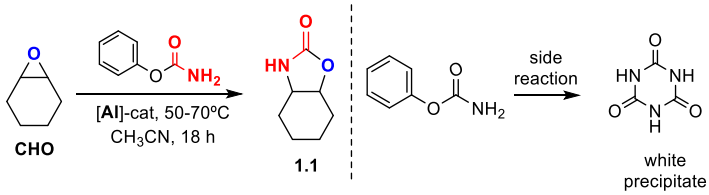


1A: $R^1 = R^2$ = Me; L = thf
1B: $R^1 = R^2$ = *t*Bu; L = thf
1C: $R^1 = R^2$ = Cl; L = thf

We first set out to test a small series of Al(amino triphenolate) complexes **1A-C** (**Figure 1.4**) in the synthesis of oxazolidinone **1.1** under various conditions (see **Table 1.1**) using the reaction of cyclohexene oxide (CHO) and phenyl carbamate as a benchmark reaction. The reaction without the catalyst does not proceed at 50ºC (*entry 1*), and at 70ºC some conversion of the phenyl carbamate reagent is noted, but no oxazolidinone could be observed in the reaction crude. In general we found that those reactions that were carried out at this latter temperature (*entries 2, 5–8*) caused (partial) decomposition of the carbamate reagent and a white precipitate was noted, which could be isolated and assigned to the formation of 1,3,5-triazine-2,4,6-(1H,3H,5H)-trione. This product is associated with the decomposition of the carbamate reagent that at high temperatures reacts with itself and forms this cyclic trimer (**Table 1.1,** side reaction). Therefore, we decided to further optimize the catalysis conditions at 50ºC using various catalysts, catalyst loadings and relative amount of the epoxide (CHO).

Al-catalyst **1A** performs much better than **1B** (*entries 5-8*, **Table 1.1**) although only moderate substrate conversion levels are observed at 50ºC (*entries 3* and *4*, **Table 1.1**). This is associated to the larger steric bulk present in catalyst **1B** near the active site which may hamper the epoxide coordination and the following nucleophilic attack.

Table 1.1 Screening of catalyst structures **1A-C** and reaction conditions in the synthesis of oxazolidinone **1.1** from CHO and phenyl carbamate.[a]

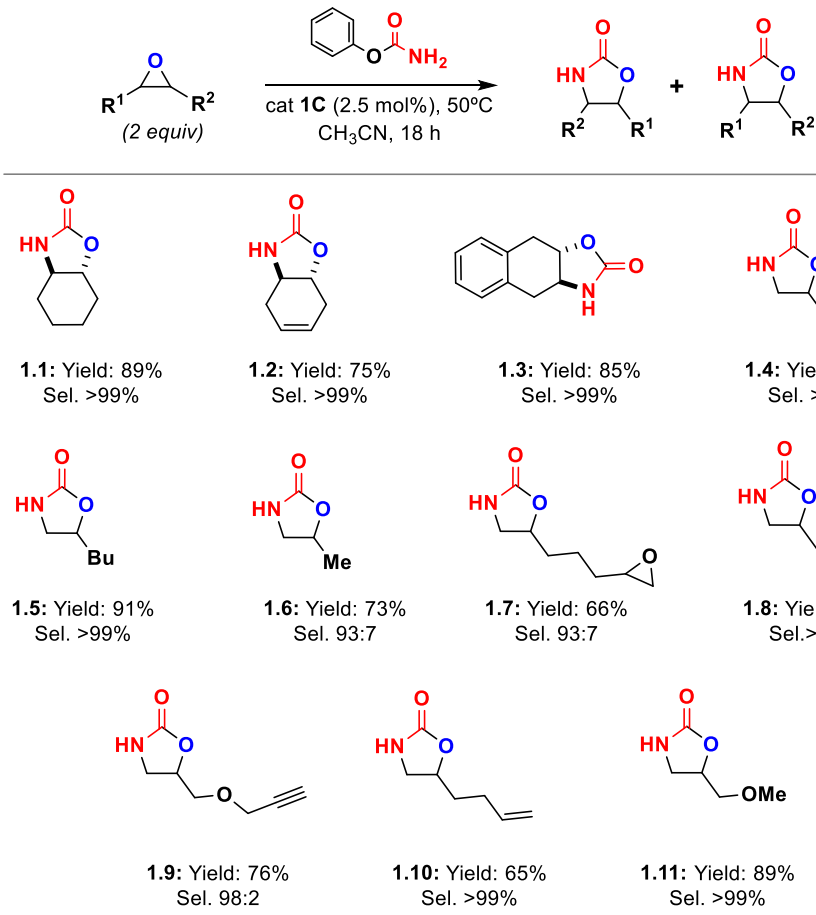


Entry	Cat.	Amount (mol%)	CHO (mmol)	T (ºC)	Conv.[b] (%)
1	–	–	1.0	50	0
2	–	–	1.0	70	17[c]
3	**1A**	2.5	1.0	50	41
4	**1A**	5.0	1.0	50	47
5	**1A**	2.5	1.0	70	94[c]
6	**1A**	5.0	1.0	70	99[c]
7	**1B**	2.5	1.0	70	10[c]
8	**1B**	5.0	1.0	70	15[c]
9	**1C**	2.5	1.0	50	95(89)[d]
10	**1C**	5.0	1.0	50	99
11	**1C**	2.5	0.5	50	81
12	**1C**	2.5	0.75	50	84
13	**1C**	2.5	2.0	50	99
14	**1C**	1.0	1.0	70	99[c]
15	**1C**	2.5	1.0	70	99(71)[c,d]

[a] General conditions: 0.5 mmol phenylcarbamate, catalyst **1A-C** (0–5 mol%), 18 h, CH_3CN. [b] Conversion of carbamate determined by ^1H NMR ($CDCl_3$) using mesitylene as internal standard. [c] White precipitate noted. [d] Isolated yield of oxazolidinone product in brackets.

Much higher activity was noted for the chloride-substituted Al-complex **1C** for which a loading of 2.5 mol% and an equimolar amount of epoxide (*entry 11*, **Table 1.1**) already provided 81% conversion. The electron-withdrawing groups in the ligand increase the Lewis acidity of the metal ion which enhances the reaction rate. Further increasing the epoxide/carbamate ratio to 2 led to nearly full conversion (95%) of the oxazolidinone product (*entry 9*, **Table 1.1**) and high isolated yield (89%). Therefore, these latter reaction conditions seem to be ideal for oxazolidinone synthesis.

Figure 1.5 Synthesis of oxazolidinones **1.1-1.11**. Reported are isolated yields after column purification; selectivities refer to regio-isomers formed in the case of terminal epoxide conversion (only the structure of the *major* isomer is shown).

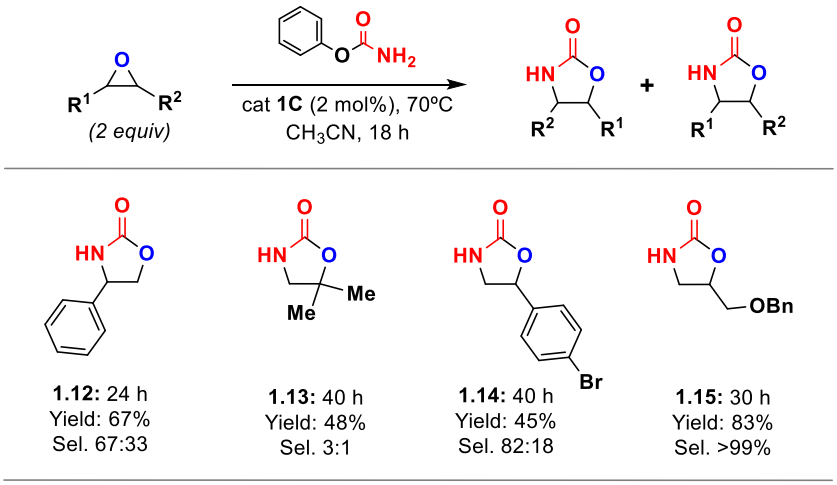


Having determined the most active Al catalyst (*i.e.*, **1C**) and suitable reaction conditions for oxazolidinone synthesis from various substituted epoxides and phenyl carbamate, we then started to investigate the scope of this process (**Figure 1.5**). In general, this Al-mediated synthesis allows for a wide range of (functional) groups to be present in the epoxide substrate including alkene (**1.2** and **1.10**), alkyl halide (**1.4**), epoxide (**1.7**), alkyne (**1.9**) and ether (**1.8**, **1.9** and **1.11**) groups. Compounds **1.1–1.3** comprise a cyclic dialkyl-substituted pattern. The alternative formation of acyclic and cyclic 4,5- and 5,5´-disubstituted oxazolidinones from either aziridines/CO_2,[19,41] epoxide/isocyanate[42] or propargylic amine/CO_2[43] substrate combinations typically require harsher reaction conditions, a higher

loading of catalyst and/or the use of stoichiometric/expensive additives, and more elaborative procedures. Various epoxide substrates gave slower reaction kinetics towards oxazolidinone formation compared to the products presented in **Figure 1.5**. In particular, the use of aromatic epoxides displayed significantly slower conversion kinetics. To overcome this limitation, we decided to increase the reaction time and temperature. Although at 70ºC some side reaction occurs (Figure to **Table 1.1**), by adding 2 equivalents of epoxide this could be minimized. The corresponding products **1.12-1.15** were obtained in reasonable yields (45-83%).

The majority of the oxazolidinone compounds could be isolated in good yields of up to 91% and high regio-selectivity for the 5–isomer with some exceptions (cf. the synthesis of **1.12-1.14).** Associated to the requirement to increase the reaction temperature, there is a loss of regioselectivity noted for these latter products. Although preferred nucleophilic attack occurs on the least hindered position of the epoxide, at higher temperature, the attack on the more substituted position becomes energetically feasible and the product of the reaction is thus a mixture of regioisomers.

Figure 1.6. Synthesis of oxazolidinones **1.12-1.15**. Reported are isolated yields after column purification; selectivities refer to regio-isomers formed with only the structure of the *major* isomer shown.



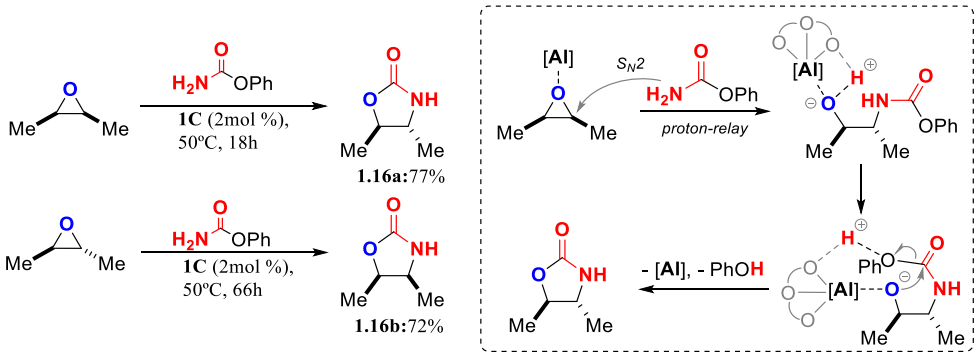
1.2.2 Mechanistic Considerations

Since these reactions occur with inversion of configuration at the carbon centre at the initial stage of the reaction (*i.e.* nucleophilic attack of the carbamate reagent onto the

epoxide-Al complex), those reactions that involve *cis*-configured carbon centres in the oxirane unit give rise to oxazolidinones with a *trans* disposition (*cf.*, syntheses of **1.1-1.3**). Thus these conversions proceed with formal inversion unlike the reactions between isocyanates and epoxides.[15] This inversion pathway was further substantiated by the synthesis of **1.16a** and **1.16b**. Both 2,3-dimethyl substituted epoxides with either a *cis*- or *trans*- configuration underwent the reaction to form the corresponding inversely configured oxazolidinone as depicted in **Figure 1.7**. The reaction based on the *cis*- configured epoxide was much faster, and steric hindrance could be the reason for this as in the conversion of the *cis*-configured epoxide the nucleophilic attack to ring-open the oxirane is less hindered.

A nucleophilic attack of the phenyl carbamate on the coordinated epoxide produces a reactive alkoxide which is stabilized by the Al complex (**Figures 1.7 and 1.8**) displaying dual character: the amino triphenolate ligand acts here as a basic site promoting proton relay increasing thereby the nucleophilic character of the alkoxide allowing for a more efficient ring-closing process to occur releasing the final (configurationally inverted) product and phenol as a leaving group.

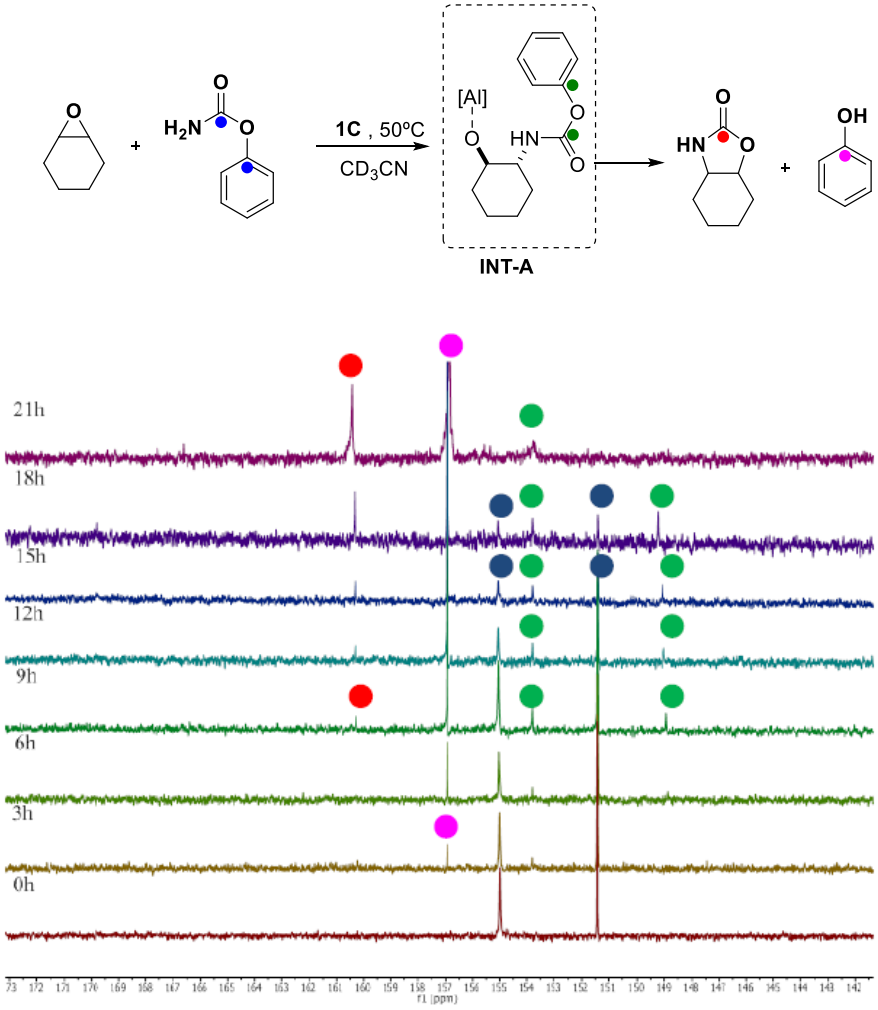
Figure 1.7 Proposed mechanism leading to formal inversion in *cis*- and *trans*-2,3-dimethyloxirane.



The presence of phenol is easily recognized in the reaction mixture, and ^{13}C NMR is a convenient technique to follow the course of the reaction. The ^{13}C NMR spectra recorded at different time intervals (**Figure 1.8**) show the presence of the oxazolidinone product (red), the phenyl carbamate reagent (blue), the released phenol (pink) and a species which was tentatively assigned to an "open" carbamate represented by **INT-A** (green), whose calculated chemical shift (δ = 154.4 ppm) value for the carbamate carbon agrees well with the experimentally observed one (δ = 154.1 ppm). The other species were assigned by making

use of reference data available in the literature. The formation and subsequent decay of the acyclic species **INT-A** can be followed in time, and after 21 h this species can still be observed as a minor component suggesting that the rate-limiting step is the cyclization of **INT-A** to form the oxazolidinone.

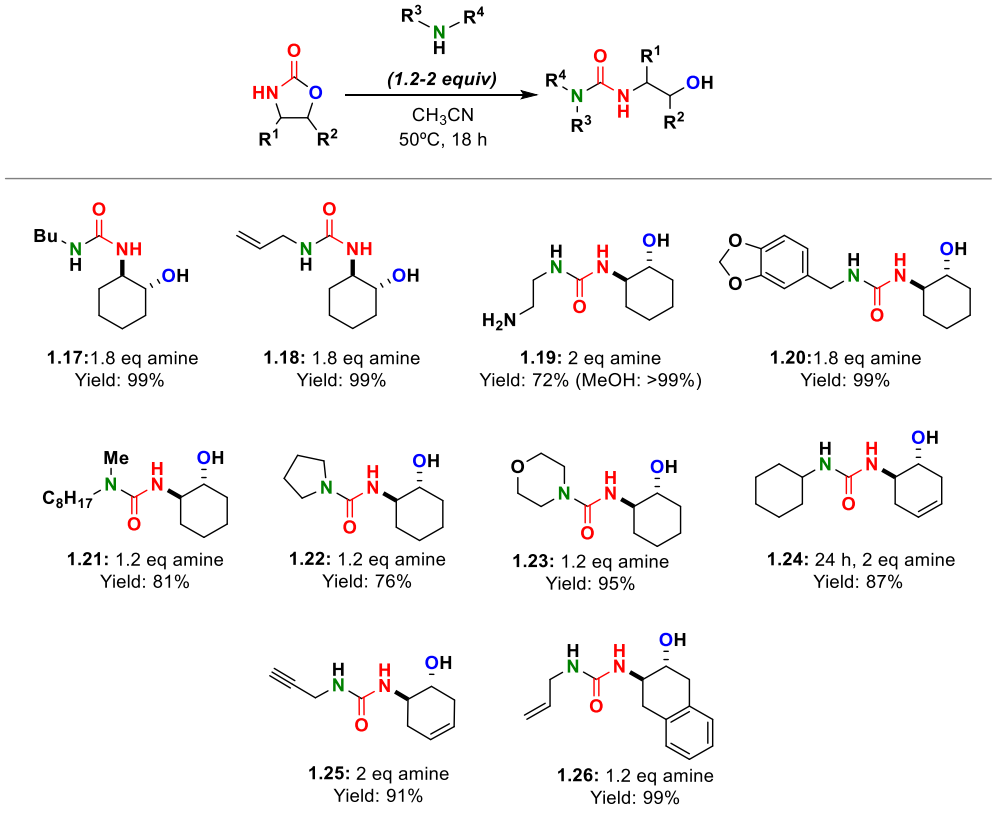
Figure 1.8 ^{13}C NMR monitoring of the reaction between CHO and phenyl carbamate and color coding for the (intermediate) products formed.



1.2.3 Nonsymmetrical Urea Synthesis

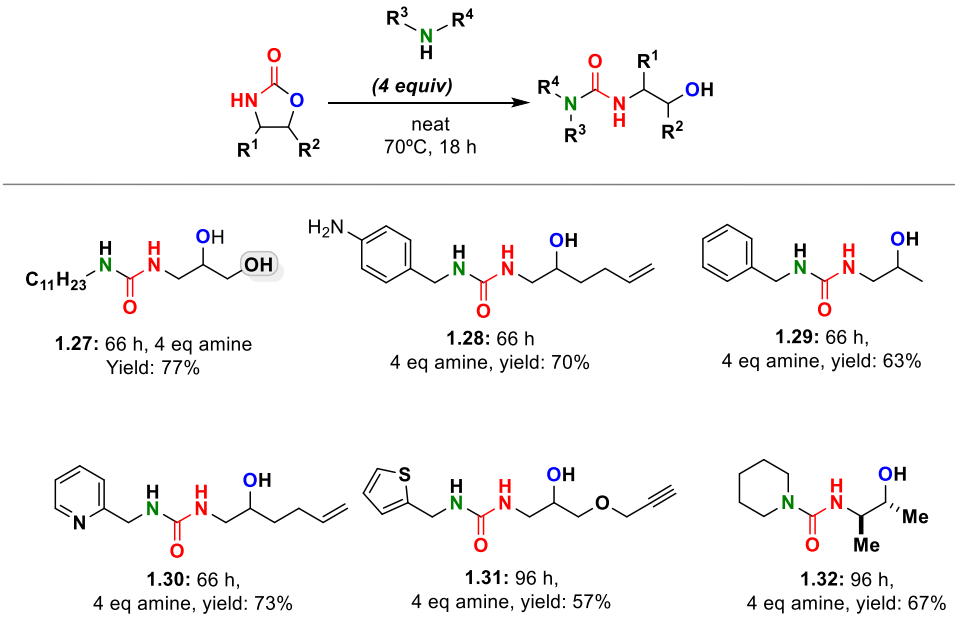
The oxazolidinones **1.1-1.16** serve as useful precursors towards the formation of highly functional, nonsymmetrical ureas as shown in **Figure 1.3**. Treatment of the respective oxazolidinone precursor with a suitable amine (1–4 equiv) allows for isolation of the urea product in high yield and chemo-selectivity. The formal aminolysis of the oxazolidinone occurs with exclusive preference for scission of the O–C(O) bond, and no amino alcohol derived from the hydrolysis of the oxazolidinone was observed. The formation of ureas **1.17–1.26** from bicyclic oxazolidinones proceeds generally under mild reaction conditions in the presence of a small excess of amine reagent in CH_3CN solvent.

Figure 1.9 Synthesis of nonsymmetrical ureas **1.17–1.26** from oxazolidinone precursors and primary/secondary amines. Reported yields are isolated ones after column purification/crystallization.



This procedure is attractive, practical and proceeds with full conversion of the starting materials. The *trans* configuration in these bicyclic structures is thermodynamically less stable compared to their *cis*-configured analogues and therefore the ring opening by amine nucleophiles should provide a driving force. The aminolysis reactions using either primary or secondary amines with diverse functionality worked conveniently yielding selectively the nonsymmetrical ureas. When using ethylene diamine (cf., synthesis of compound **1.19**), one of the amine groups remained unreacted even when using excess of the oxazolidinone, and no trace of the double urea was observed. If oxazolidinones derived from acyclic epoxides are used as starting materials (*i.e.*, **1.27-1.32**), the aminolysis reaction required generally higher temperature, longer reaction times and a larger excess of amine reagent (4 equiv) under solvent free conditions. In the latter cases, somewhat lower isolated yields are noted (up to 73%). Acyclic oxazolidinones lack the ring strain which is the driving force in bicyclic oxazolidinone aminolysis, therefore need more drastic conditions to overcome the kinetic activation barrier. Catalysts which have been reported to catalyze the aminolysis of cyclic carbonates such as TBD or DBU were added to the reaction but no rate acceleration was noted.

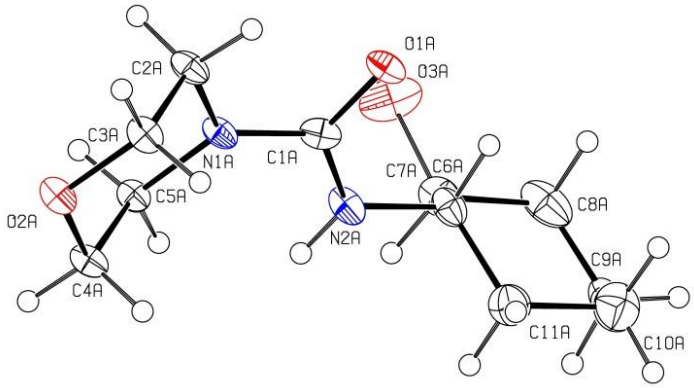
Figure 1.10 Synthesis of nonsymmetrical ureas **1.27–1.32** from oxazolidinone precursors and primary/secondary amines. Reported yields are isolated ones after column purification.



The scope shown in **Figure 1.9** and **1.10** illustrates that highly functionalized ureas can be prepared including those incorporating pyrrolidine (**1.22**), alkene (**1.18**, **1.26**, **1.28** and **1.30**), alkyne (**1.25** and **1.31**), heterocyclic (**1.23**, **1.24**, **1.31** and **1.32**), alkyl amine (**1.19**) and vicinal diol (**1.27**) groups. Note that urea **1.27** is derived from the oxazolidinone **1.4** which is based on the initial use of epichlorohydrin. The longer reaction time needed to convert **1.4** into **1.27** resulted in effective hydrolysis of the alkyl chloride bond which was in line with the NMR data and mass spectrometric analysis.

Both primary as well as secondary amines (*cf.*, syntheses of **1.21**, **1.22**, **1.23** and **1.32**) react smoothly with the oxazolidinone precursors further amplifying the potential scope of this urea formation reaction. The molecular structure of urea **1.23** (**Figure 1.11**) was determined by X-ray diffraction. Compound **1.23** was derived from oxazolidinone **1.1**. Thus, the relative configuration of the urea and the free alcohol groups (*trans*) is further testament of the proposed inversion mechanism as depicted in **Figure 1.2**.

Figure 1.11 X-ray molecular structure determined for urea **1.23.** Selected interatomic distances (Å) and angles (º): N(1A)-C(1A) = 1.366(5), N(2A)-C(1A)= 1.356(5),C(1A)-O(1A) = 1.248(5), N(2A)-C(6A)= 1.449(5); N(1A)-C(1A)-N(2A) = 117.8(4), N(1A)-C(1A)-O(1A) = 120.4(4), N(2A)-CC(1A)-CO(1A) = 121.8(4).

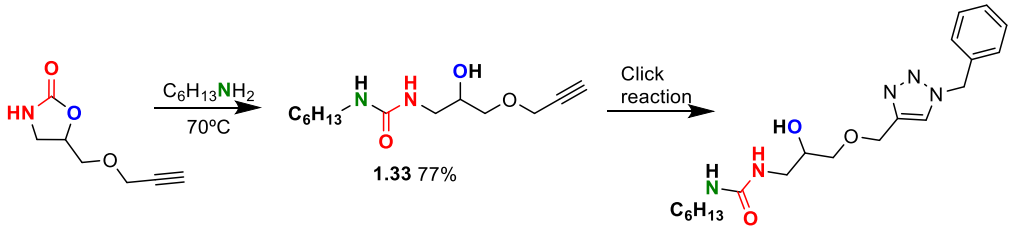


1.2.4 Post-Modification

The diversity of functional groups in the presented scope of urea products has potential in post-synthetic modifications as shown in **Figure 1.12**. To demonstrate further use of these scaffolds, urea **1.31** was subjected to “click” chemistry conditions using benzyl azide

as coupling partner: this afforded the triazole **1.33** smoothly in 91% yield. The use of click reactions to functionalize polymer supports with other macromolecular structures is interesting for catalytic and supramolecular applications and therefore this chemistry combined with suitable urea synthons opens up new opportunities in the aforementioned areas.

Figure 1.12 Post-modification of **1.33** using Click chemistry.



1.3 Conclusions

In this chapter we have described a simple but effective two-step method for the formation of highly functional, nonsymmetrical ureas. These ureas can be prepared from easy to prepare oxazolidinones using cheap and readily available epoxides and phenyl carbamate mediated by Al-catalysis. The methodology represents an alternative to the usual synthetic method involving carbonyl sources such as carbonyldiimidazole (CDI), phosgene or using azide derivatives (Curtius Rearrangement). The method is further characterized by its operational simplicity and wide scope in ureas that can be attained.

Furthermore we confirm the potential of aluminium amino triphenolate catalysts for Lewis acid activation of epoxides. We have also expanded the scope of oxazolidinone products formed by coupling of epoxides and carbamates, providing an alternative method which presents high regioselectivity for the 5-substituted oxazolidinone isomer.

1.4 Experimental Section

1.4.1 General Information and Instrumentation

^{1}H NMR and ^{13}C NMR spectra were recorded at r.t. on Bruker AV-300, AV-400 or AV-500 spectrometers and referenced to the residual deuterated solvent signals. Regio-isomeric ratios were calculated from the corresponding ^{1}H NMR spectra using signal integration. All reported NMR values are given in parts per million (ppm). FT-IR measurements were carried out on a Bruker Optics FTIR Alpha spectrometer equipped with a DTGS detector, KBr beam splitter at 4 cm^{-1} resolution. Mass spectrometric analyses and X-ray diffraction studies were performed by the Research Support Group at ICIQ. Commercially available epoxides, solvents, carbamate were purchased from various commercial sources (Acros, Aldrich and TCI) and used without further purification. When the epoxides were not commercially available, suitable alkene precursors were purchased and used as received. The alkenes were oxidized to the subsequent epoxide according to published literature. Carbon dioxide (purchased from PRAXAIR) was used without further purification or drying prior to its use.

Catalyst Synthesis

Synthesis of 1A: 2,4-dimethylphenol (10.1 g, 82.8 mmol), hexamethylene tetramine (HMTA; 2.56 g, 18.4 mmol) and *para*-toluene sulfonic acid (70 mg, 0.36 mmol) were heated at 110ºC for 24 h. Hereafter, 3 g (24.6 mmol) of 2,4 dimethylphenol were added to the mixture which was left at 110ºC for another 18 h. The reaction was then cooled down to rt and 20 mL of MeOH were added to the yellow slurry. The solution was sonicated until a pale yellow solid separated from the solution. The solid was filtered off, washed with cold MeOH and dried under vacuum. The compound was recrystallized from acetone. $AlMe_3$ (2 M in heptane, 1.19 mL, 2.38 mmol) was slowly added to a solution of the previously crystalized ligand (1.29 g, 2.38 mmol) in anhydrous THF (20 mL). The solution was stirred at rt for 2 h and then concentrated. Hexane was added to the residue resulting in precipitation of the complex, which was isolated by filtration and further dried under vacuum to yield a white powder.

Synthesis of 1B: 2,4-di-*tert*-butylphenol (8.25 g, 39 mmol), hexamethylene tetramine (HMTA; 1.2 g, 8.5 mmol) and *para*-toluene sulfonic acid (70 mg, 0.36 mmol) were heated at 110ºC for 24 h, and hereafter 2 g (9.45mmol) of 2,4-di-*tert*-butylphenol were added to the mixture which was left at 110ºC for another 18 h. The reaction mixture was cooled down to rt and 20 mL of MeOH were added to the yellow slurry. The solution was sonicated until a pale yellow solid separated from the solution. The solid was filtered off, washed with cold MeOH and dried under vacuum. The compound was recrystallized from acetone. $AlMe_3$ (2 M in heptane, 1.19 mL, 2.38 mmol) was slowly added to a solution of the previously crystalized ligand (1.6 g, 2.38 mmol) in anhydrous THF (20 mL). The solution was stirred at rt for 2 h and then concentrated. Hexane was added to the residue resulting in precipitation of the complex, which was isolated by filtration and further dried under vacuum to yield a white powder.

Synthesis of 1C: 2,4-dichlorophenol (4.0 g, 24.5 mmol) and hexamethylene tetramine (HMTA; 1.2 g, 8.5 mmol) were heated at 110ºC for 2.5 h. Herafter, the reaction was cooled down to rt and 20 mL of MeOH were added to the yellow slurry. The solution was sonicated until a pale yellow separated from the solution. The solid was filtered off and washed with cold MeOH. Then 100 mL of distilled water were added to the solid forming a suspension, which was slowly basified by adding dropwise 1M NaOH until all the solid had dissolved. Then the solution was neutralized with 1 M HCl. A white precipitate formed which was filtered off and dissolved in 10 mL of DCM, and addition of hexane caused precipitation of the product. The product was isolated as a white powder by filtration and dried under vacuum. $AlMe_3$ (2 M in heptane, 1.19 mL, 2.38 mmol) was slowly added to a solution of the previously isolated ligand (1.29 g, 2.38 mmol) in anhydrous THF (20 mL). The solution was stirred at rt for 2 h and then concentrated. Hexane was added to the residue resulting in precipitation of the complex, which was isolated by filtration and further dried under vacuum to yield a white powder.

Oxazolidinone Synthesis

Typically, phenyl carbamate (1 mmol), the epoxide (2 mmol), the aluminium catalyst (2 mol%) and acetonitrile (2 mL) were introduced into a glass vial (5 mL) equipped with a stirring bar. The vial was closed and introduced into a preheated silicon oil bath at the desired reaction temperature (50−70ºC) and stirred for 18 h. The reaction progress was monitored by

1H NMR. The reaction mixture was allowed to cool down and the product was purified by flash column chromatography using silica as the adsorbent.

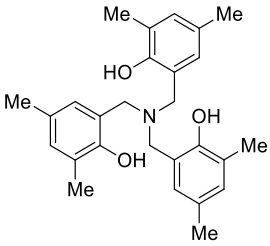
Urea Synthesis

Procedure A: Typically, the oxazolidinone (0.50 mmol) was introduced into an screw-cap vial equipped with a stirring bar. For the oxazolidinones based on bicyclic scaffolds, the amine reagents were introduced (typically 1.2 equiv but 1.8 equiv when dealing with volatile amines) with addition of acetonitrile (0.20 mL) and heated to the desired temperature (50ºC) for 18 h. Once the reaction mixture had cooled down to rt, the pure product was isolated by evaporation of the excess of amine and the crude ureas were recrystallized from dichloromethane or purified by flash column chromatography.

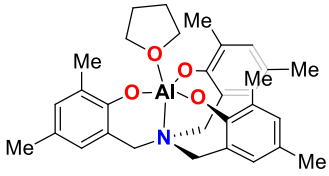
Procedure B: The monocyclic oxazolidinones (0.50mmol) were treated with the respective amine reagent (4 equiv) without adding any co-solvent and heated to 70ºC for 66 h. The products were then isolated by recrystallization from dichloromethane (urea **1.30**) or purified by flash column chromatography (**1.27-1.29**, **1.31** and **1.32**).

1.4.2 Spectroscopic Analysis for all Compounds

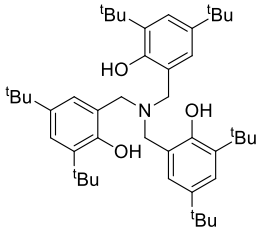
Ligands and Complexes



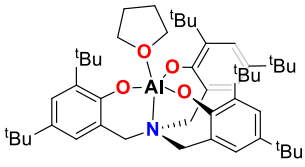
L1A:[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, J = 1.9 Hz, 3H), 6.74 (d, J = 1.9Hz, 3H), 3.63 (s, 6H), 2.22 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.10, 131.28, 129.12, 128.85, 124.56, 121.83, 56.53, 20.39, 15.90.



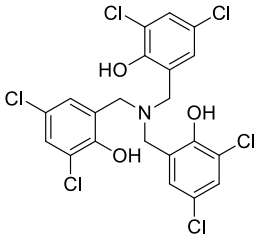
1A:[44] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, J = 2.3 Hz, 3H), 6.61 (d, J = 2.3 Hz, 3H), 4.26 (d, J = 13.8 Hz, 3H), 2.83 (d, J = 13.8 Hz, 3H), 2.20 (s, 9H), 2.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.25, 131.01, 126.95, 125.84, 120.63, 58.66, 25.60, 20.39.



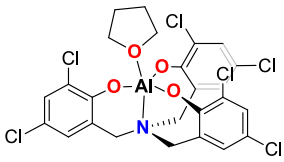
L1B:[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 2.4 Hz, 3H), 7.00 (d, J = 2.4 Hz, 3H), 3.66 (s, 6H), 1.42 (s, 27H), 1.30 (s, 27H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.40, 142.06, 136.40, 125.55, 123.95, 121.78, 56.51, 34.87, 34.18, 31.60, 29.66.



1B:[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 2.5 Hz, 3H), 6.88 (d, J = 2.4 Hz, 3H), 4.30 (d, J = 13.1 Hz, 3H), 4.01 (m, 4H), 2.95 (d, J = 13.0 Hz, 3H), 1.98 (m, 4H) 1.43 (s, 27H), 1.29 (s, 27H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.70, 139.20, 136.99, 123.77, 123.57, 121.26, 68.19, 59.03, 34.84, 34.05, 31.73, 29.58, 25.59.

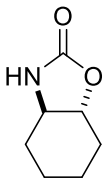


L1C:[45] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 2.5 Hz, 3H), 7.05 (d, J = 2.5 Hz, 3H), 3.75 (s, 6H). ^{13}C NMR (125 MHz, 298 K, $CDCl_3$) δ 149.83, 129.10, 128.54, 124.84, 124.72, 121.09 and 55.35.



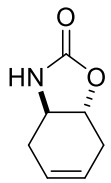
1C:[45] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 2.6 Hz, 3H), 6.90 (d, J = 2.6 Hz, 3H), 4.74 – 4.63 (m, 4H), 4.17 (d, J = 13.7 Hz, 3H), 2.94 (d, J = 14.1 Hz, 3H), 2.26–2.19 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.46, 129.75, 127.13, 124.68, 123.08, 122.16, 72.38, 58.26, 25.48.

Oxazolidinones 1.1-1.16



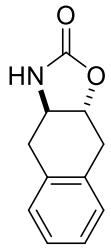
1.1

Oxazolidinone 1.1.[18] Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.1**: 125 mg (0.89 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (br s, 1H, NH), 3.91 (td, J = 11.4 and 3.7 Hz, 1H), 3.34 (m, 1H), 2.20 (m, 1H), 2.06 (m, 1H), 1.92 (m, 1H), 1.83 (m, 1H), 1.68 (m, 1H), 1.47 (m, 1H), 1.41 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.95, 83.83, 60.88, 29.13, 28.54, 23.75, 23.53. IR (neat, cm^{-1}): 3432, 1742, 1719, 1246, 1228, 1117, 1029, 949, 933, 778, 694, 518.



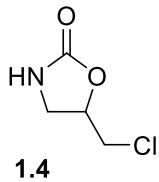
1.2

Oxazolidinone 1.2.[18] Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.2**: 104 mg (0.75 mmol, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (m, 2 H), 5.27 (br s., 1H, NH), 4.17 (m, 1 H), 3.58 (m, 1H), 2.61 (m, 1H), 2.47 (m, 2H), 2.25 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.34, 124.86, 124.64, 79.92, 56.79, 30.79, 29.84. IR (neat, cm^{-1}): 3441, 1713, 1261, 1193.



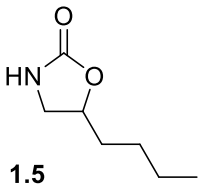
1.3

Oxazolidinone 1.3.[18] Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.3**: 157 mg (0.85 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 4H), 5.83 (br s, 1H), 4.33 (m, 1H), 3.75 (m, 1H), 3.31 (dd, J = 4.5 and 14.1 Hz, 1H), 3.19 (dd, J = 4.5 and 14.1 Hz , 1H), 3.14 (m, 1H), 2.95(m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.73, 132.63, 132.47, 130.47, 130.07, 127.04, 80.22, 57.31, 34.54, 33.45. IR (neat, cm^{-1}): 3412, 1747, 1445, 1217, 950, 677.



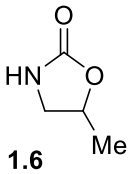
1.4

Oxazolidinone 1.4.[46] Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.4**: 110 mg (0.82 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (br s, 1H), 4.87 (m, 1H), 3.77 (t, 1H, J = 8.8 Hz), 3.73 (m, 2H), 3.57(m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.23, 74.73, 44.44, 43.60. IR (neat, cm^{-1}): 3421, 1736, 1388, 1251, 1123, 1079.



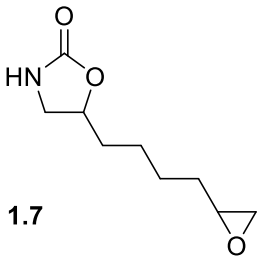
1.5

Oxazolidinone 1.5.[47] Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.5**: 130 mg (0.91 mmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (br s, 1H, NH), 4.65 (m, 1H), 3.68 (t, J = 7.8 Hz, 1H), 3.26 (t, J = 8.3, 1H), 1.82 (m, 1H), 1.67 (m, 2H), 1.48 (m, 1H), 1.39(m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.03, 77.17, 45.95, 34.59, 26.71, 22.37, 13.89. IR (neat, cm^{-1}): 3423, 1722, 1237, 1076, 962, 689.



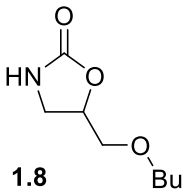
1.6

Oxazolidinone 1.6.[48] Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.6** 74 mg (0.73 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (br s, 1H), 4.74 (m, 1H), 3.68 (t, J = 8.5 Hz, 1H), 3.18 (t, J = 8.1 Hz, 1H), 1.43 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.52, 73.54, 47.45, 20.51. IR (neat, cm^{-1}): 3323, 1718, 1350, 1218, 1079 and 968.



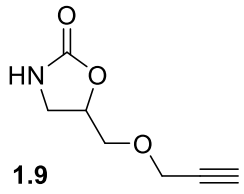
1.7

Oxazolidinone 1.7. Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.7**: 122 mg (0.66 mmol, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (br s, 1H), 4.65 (m, 1H), 3.70 (t, 1H, J = 8.5 Hz), 3.26 (t, J = 7.8 Hz, 1H), 2.94 (m, 1H), 2.79 (m, 1H), 2.50 (m, 1H), 1.83 (m, 1H), 1.77-1.42 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.93, 76.93, 52.11, 47.04, 45.93, 34.86, 32.27, 25.73, 24.49. IR (neat, cm^{-1}): 3254, 1736, 1291, 1174, 890, 784. HRMS (ESI+, MeOH): *m/z* calcd. 208.0944 $(M + Na)^+$, found: 208.0944.

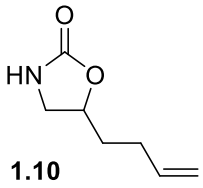


1.8

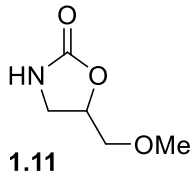
Oxazolidinone 1.8. Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.8**: 130 mg (0.75 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (br s, 1H, NH), 4.77 (m, 1H), 3.67 (m, 1H), 3.63 (m, 2H), 3.53 (m, 2H), 3.50 (m, 1H), 1.54 (m, 2H), 1.36 (m, 2H), 0.93(m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.71, 75.27, 71.78, 70.91, 42.65, 31.62, 19.20, 13.87. IR (neat, cm^{-1}): 3398, 1757, 1461, 1231, 1137, 968,737. HRMS (ESI+, MeOH): *m/z* calcd. 196.0944 $(M + Na)^+$, found: 196.0948.



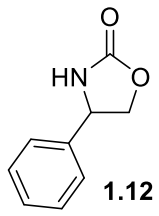
Oxazolidinone 1.9. Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.9**: 131 mg (0.76 mmol, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (br s, 1H, NH), 4.82 (m, 1H), 4.26 (m, 2H), 3.76 (d, J = 4.8 Hz, 2H), 3.69 (m, 1H), 3.54 (m, 1H), 2.49 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.44, 78.90, 75.27, 74.81, 69.76, 58.83, 42.54. IR (neat, cm^{-1}): 3431, 2141, 173, 1281, 1198, 1166. HRMS (ESI+, MeOH): *m/z* calcd. 178.0478 $(M + Na)^+$, found: 178.0475.



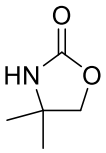
Oxazolidinone 1.10. Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.10**: 92 mg (0.65 mmol, 65%). ^{1}H NMR (400 MHz, MeOD) δ 5.93 (m, 1H), 5.13 (m, 2H), 4.73 (m, 1H), 4.65 (br s, 1H, NH), 3.75 (m, 1H), 3.32 (m, 1H), 2.27 (m, 2H), 1.86 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 161.00, 137.12, 114.58, 76.75, 45.47, 33.91, 28.69. IR (neat, cm^{-1}): 3441, 1713, 1217, 1177, 771. HRMS (ESI+, MeOH): *m/z* calcd. 164.0682 $(M + Na)^+$, found: 164.0688 $(M + Na)^+$.



Oxazolidinone 1.11. Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.11**: 116 mg (0.89 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (br s, 1H, NH), 4.76 (m, 1H), 3.67 (t, 1H, J = 8.7 Hz), 3.59 (d, J = 4.8 Hz, 2H), 3.47 (m, 1H), 3.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.69, 75.11, 72.78, 59.58, 42.51. IR (neat, cm^{-1}): 3451, 1736, 1258, 1179, 1091, 894. HRMS (ESI+, MeOH): *m/z* calcd. 154.0475 $(M + Na)^+$, found: 154.0481.

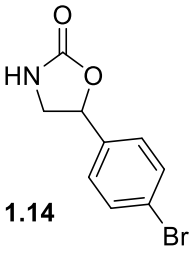


Oxazolidinone 1.12.[49] Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.12**: 109 mg (0.67 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 5H), 5.62 (t, J = 7.8 Hz, 1H), 3.97 (t, J = 8.1 Hz, 1H), 3.54 (t, J = 8.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.73, 138.51, 129.07, 125.79, 78.04, 48.41. IR (neat, cm^{-1}): 3294, 1735, 1454, 1226, 1027, 758, 698.



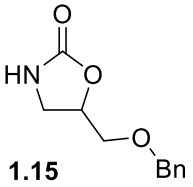
1.13

Oxazolidinone 1.13.[50] Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.13**: 56 mg (0.48 mmol, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (br s, 1H, NH), 4.09 (s, 2H), 3.37 (s, 2H), 1.50 (s, 6H), 1.37 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.73, 159.30, 81.05, 76.95, 55.24 52.72, 27.54, 27.20. IR (neat, cm^{-1}): 3384, 1725, 1374, 1300, 1216, 1080, 969, 770.



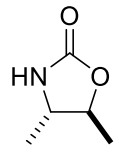
1.14

Oxazolidinone 1.14. Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.14**: 108 mg (0.45 mmol, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 8.44 Hz, 2H), 7.24 (d, J = 8.44 Hz, 2H), 5.82 (br s, 1H, NH), 5.56 (t, J = 8.1 Hz, 2H), 3.99 (t, J = 8.4 Hz, 2H), 3.49 (t, J = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.56, 137.55, 132.26, 127.44, 123.13, 77.28, 48.27. IR (neat, cm^{-1}): 3241, 1752, 1712, 1388, 1252, 1072, 982, 728, 504. HRMS (ESI+, MeOH): *m/z* calcd. 263.9625 $(M + Na)^+$, found: 263.9631.



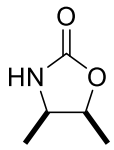
1.15

Oxazolidinone 1.15. Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.15**: 176 mg (0.83 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.63 (br s, 1H, NH), 4.77 (m, 1H), 4.60 (s, 2H), 3.65 (d, J = 4.9 Hz, 2H), 3.61 (t, J = 8.7 Hz, 1H), 3.47 (t, J = 7.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.80, 137.69, 128.74, 128.18, 128.00, 75.42, 73.92, 70.43, 42.83. IR (neat, cm^{-1}): 3261, 1736, 1452, 1237, 1081, 962, 737, 697. HRMS (ESI+, MeOH): *m/z* calcd. 230.0790 $(M + Na)^+$, found: 230.0788.



1.16A

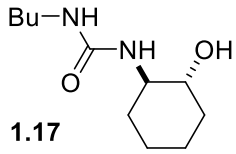
Oxazolidinone 1.16a.[51] Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.16a**: 88 mg (0.77 mmol, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (br s, 1H), 4.22 (m, 1H), 4.53 (m, 1H), 1.48 (d, J = 6.5 Hz, 3H), 1.28 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.30, 80.52, 55.33, 19.93, 19.34. IR (neat, cm^{-1}): 3281, 1731, 1251, 1189, 1025.



1.16B

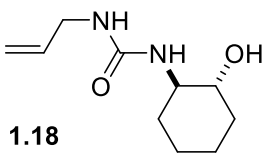
Oxazolidinone 1.16b.[51] Following the general procedure of oxazolidinone synthesis. Purification by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.16b**: 83 mg (0.72 mmol, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (br s, 1H), 4.74 (m, 2H), 3.91 (m, 2H), 1.33 (d, J = 6.5 Hz, 3H), 1.16 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.84, 76.19, 51.24, 15.69, 14.63. IR (neat, cm^{-1}): 3241, 1752, 1712, 1388, 1252, 1072, 982, 728, 504.

Nonsymmetrical Ureas 1.17-1.32



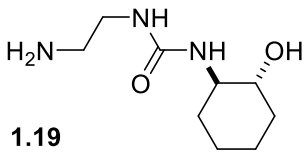
1.17

Urea 1.17. Following the procedure A of urea synthesis. Washed with dichloromethane and recrystallized from a mixture DCM: MeOH (10:1). Yield of **1.17**: 106 mg (0.49 mmol, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (br s, 1H, NH), 4.78 (br s, 1H, NH), 4.57 (br s, 1H, OH), 3.36 (m, 1H), 3.28 (m, 1H), 3.17 (m, 2H), 2.02 (m, 1H), 1.92 (m, 1H), 1.72 (m, 2H), 1.49 (m, 2H), 1.35 (m, 2H), 1.26 (m, 4H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.98, 76.26, 56.49, 40.37, 34.23, 32.24, 31.99, 24.85, 24.06, 20.06, 13.80. IR (neat, cm^{-1}): 3309, 2917, 2963, 1750, 1633, 1573, 1484, 1245, 1053, 934. HRMS (ESI+, MeOH): *m/z* calcd. 237.1573 $(M + Na)^+$, found: 237.1573.



1.18

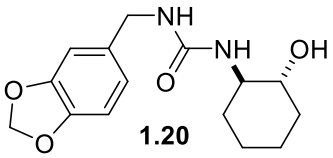
Urea 1.18. Following the procedure A of urea synthesis. Washed with dichloromethane and recrystallized from a mixture DCM: MeOH (10:1). Yield of **1.18**: 97 mg (0.49 mmol, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.25 (m, 1H), 5.14 (m, 1H), 5.00 (br s, 1H, NH), 4.63 (br s, 1H, NH), 4.13 (br s, 1H, OH), 3.82 (m, 2H), 3.39 (m, 1H), 3.31 (m, 1H), 2.03 (m, 1H), 1.94 (m, 1H) 1.73 (m, 2H), 1.27 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.60, 135.12, 115.98, 76.22, 56.59, 43.22, 34.26, 32.02, 24.83, 24.04. IR (neat, cm^{-1}): 3332, 2928, 2878, 1626, 1562, 1238, 1117, 983. HRMS (ESI+, MeOH): *m/z* calcd. 199.1444 $(M + Na)^+$, found: 199.1441.



1.19

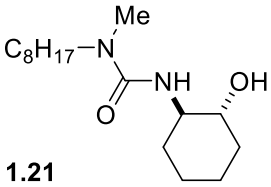
Urea 1.19. Following the procedure A of urea synthesis. Washed with dichloromethane and recrystallized from a mixture DCM: MeOH (10:1). Yield of **1.19**: 72 mg (0.36 mmol, 72%). ^{1}H NMR (500 MHz, MeOD) δ 3.41 (m, 1H), 3.34

(m, 1H), 3.26 (m, 2H), 2.78 (m, 2H), 2.04 (m, 2H), 1.78 (m, 2H), 1.38 (m, 3H), 1.24 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 160.23, 73.69, 55.43, 41.83, 41.36, 33.87, 31.78, 24.35, 23.83. IR (neat, cm^{-1}): 3312, 2912, 2891, 1620, 1584, 1321, 921 and 784. HRMS (ESI+, MeOH): *m/z* calcd. 202.1553 $(M + Na)^+$, found: 202.1550.



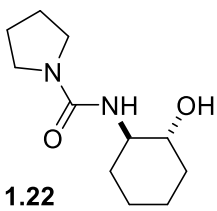
1.20

Urea 1.20. Following the procedure A of urea synthesis. Washed with dichloromethane and recrystallized from a mixture DCM: MeOH (10:1). Yield of **1.20**: 145 mg (0.50 mmol, 99%). ^{1}H NMR (400 MHz, MeOD) δ 6.87 (m, 1H), 6.82 (m, 2H), 5.98(s, 2H), 4.29 (s, 2H), 3.44 (m, 1H), 3.34 (m, 1H), 2.05 (m, 2H), 1.77 (m, 2H), 1.38 (m, 3H), 1.27 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 159.96, 147.81, 146.63, 133.82, 120.07, 107.41, 100.82, 73.62, 55.43, 43.17, 33.84, 31.74, 24.26, 23.79. IR (neat, cm^{-1}): 3306, 2925, 2855, 1609, 1524, 1451, 1070, 908, 729. HRMS (ESI+, MeOH): *m/z* calcd. 315.1320 $(M + Na)^+$, found: 315.1315.



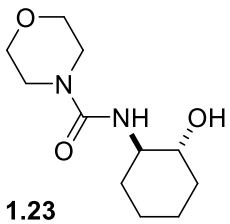
1.21

Urea 1.21. Following the procedure A of urea synthesis. Washed with dichloromethane and recrystallized from a mixture DCM: MeOH (10:1). Yield of **1.21**: 115 mg (0.40 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (br s, OH, 1H), 4.30 (br s, NH, 1H), 3.51(m, 1H), 3.25(m, 3H), 2.89 (s, 3H), 2.05 (m, 1H), 1.92 (m, 1H), 1.71 (m, 2H), 1.53(m, 2H), 1.30 (m, 14H), 0.91(t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.60, 76.82, 56.50, 49.18, 34.55, 34.49, 32.11, 31.79, 29.37, 29.22, 28.01, 26.85, 24.94, 24.02, 22.63, 14.08. IR (neat, cm^{-1}): 3306, 2925, 2855, 1609, 1524, 1451, 1070, 908, 729. HRMS (ESI+, MeOH): *m/z* calcd. 307.2356 $(M + Na)^+$, found: 307.2368.



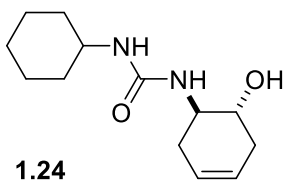
1.22

Urea 1.22. Following the procedure A of urea synthesis. Washed with dichloromethane and recrystallized from a mixture DCM: MeOH (10:1). Yield of **1.22**: 80 mg (0.38 mmol, 76%). ^{1}H NMR (500 MHz, MeOD) δ 3.52 (m, 1H), 3.43 (m, 5H), 2.08 (m, 1H), 2.00 (m, 5H), 1.79 (m, 2H), 1.38 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 158.32, 73.47, 56.20, 45.36, 34.27, 32.10, 25.10, 24.73, 24.15. IR (neat, cm^{-1}): 3403, 1603, 1470, 1451, 1091, 854. HRMS (ESI+, MeOH): *m/z* calcd. 235.1421 $(M + Na)^+$, found: 235.1417.



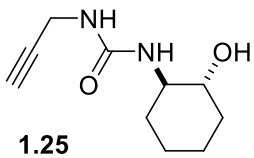
1.23

Urea 1.23. Following the procedure A of urea synthesis. Purified by column chromatography on silica gel (Hex: EtOAc 1:1). Yield of **1.23**: 108 mg (0.48 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (br s, 1H, NH), 4.28 (br s, 1H, OH), 3.72 (m, 4H), 3.54 (m, 1H), 3.39 (m, 4H), 3.30 (m, 1H), 2.07 (m, 1H), 1.96 (m, 1H), 1.75(m, 2H), 1.34 (m, 2H), 1.22 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.14, 76.47, 66.38, 56.61, 44.05, 34.61, 32.10, 24.88, 24.04. IR (neat, cm^{-1}): 3308, 2917, 2878, 1591, 1542, 1257, 1108, 991, 857. HRMS (ESI+, MeOH): *m/z* calcd. 251.1368 $(M + Na)^+$, found: 251.1366.



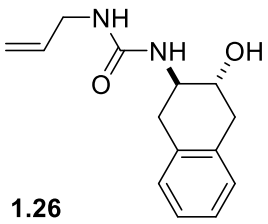
1.24

Urea 1.24. Following the procedure A of urea synthesis. Washed with dichloromethane and recrystallized from a mixture DCM: MeOH (10:1). Yield of **1.24**: 104 mg (0.43 mmol, 87%). ^{1}H NMR (500 MHz, MeOD) δ 5.60 (m, 2H), 3.71 (m, 2H), 3.68 (m, 1H), 3.49 (m, 1H), 2.54 (m, 1H), 2.43 (m, 1H), 2.09 (m, 1H), 1.94 (m, 1H), 1.87 (m, 2H), 1.72 (m, 2H), 1.60 (m, 1H), 1.37 (m, 2H), 1.16 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 159.31, 124.22, 124.03, 68.96, 50.62, 48.41, 33.29, 32.71, 30.75, 25.34, 24.61. IR (neat, cm^{-1}): 3295, 2948, 1625, 1571, 1105, 667. HRMS (ESI+, MeOH): *m/z* calcd. 239.1750 $(M + Na)^+$, found: 239.1754.



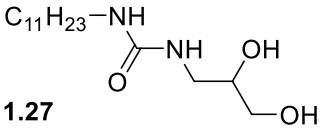
1.25

Urea 1.25 Following the procedure A of urea synthesis. Washed with dichloromethane and recrystallized from a mixture DCM: MeOH (10:1). Yield of **1.25**: 85 mg (0.44 mmol, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (m, 1H), 5.59 (m, 1H), 4.81 (br s, 1H, NH), 4.41 (br s, 1H, NH), 4.03 (m, 2H), 3.78 (m, 1H), 3.70 (m, 1H), 3.08 (br s, 1H, OH), 2.54 (m, 2H), 2.26 (t, J = 2.3 Hz, 1H), 2.17 (m, 1H), 1.98 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.49, 125.07, 124.09, 80.20, 71.78, 71.51, 52.87, 34.18, 32.07, 30.35. IR (neat, cm^{-1}): 3316, 2925, 2801, 1620, 1574, 1237, 1138, 751, 643. HRMS (ESI+, MeOH): *m/z* calcd. 217.0953 $(M + Na)^+$, found: 217.0947.



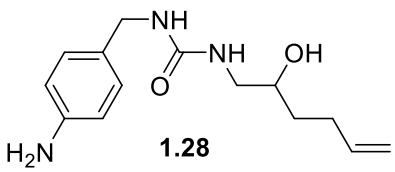
1.26

Urea 1.26. Following the procedure A of urea synthesis. Washed with dichloromethane and recrystallized from a mixture DCM: MeOH (10:1). Yield of **1.26**: 123 mg (0.50 mmol, 99%). ^{1}H NMR (400 MHz, MeOD) δ 7.17(m, 4H), 5.94 (m, 1H), 5.22 (m, 1H), 5.13 (m, 1H), 3.99 (m, 2H), 3.82 (m, 2H), 3.31 (dd, J = 16.3 and 4.3Hz, 1H), 3.19 (dd, J = 16.3 and 4.3 Hz, 1H), 2.92 (dd, J = 16.7 and 5.9 Hz, 1H), 2.71(dd, J = 17.2 and 5.1Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 159.71, 135.58, 133.67, 128.65, 128.47, 125.86, 125.76, 113.94, 68.91, 51.08, 41.95, 35.61, 33.43. IR (neat, cm^{-1}): 3317, 1677, 1561, 1127, 783. HRMS (ESI+, MeOH): *m/z* calcd. 269.1260 (M + Na)$^{+}$, found: 269.1263.



1.27

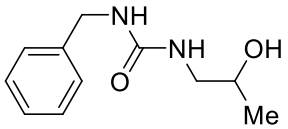
Urea 1.27. Following the procedure B of urea synthesis. Purified by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.27**: 111 mg (0.38 mmol, 77%). ^{1}H NMR (500 MHz, MeOD) δ 3.72 (m, 1H), 3.56 (d, J = 5.7 Hz, 2H), 3.36 (m, 1H), 3.24 (m, 1H), 3.17 (t, J = 7.1 Hz, 2H), 1.55 (m, 2H), 1.38 (m, 16H), 0.98 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.23, 75.30, 67.38, 46.34, 43.62, 35.60, 33.84, 33.27, 33.04, 33.00, 30.49, 26.27, 16.96. IR (neat, cm^{-1}): 3298, 2917, 2838, 2512, 1598, 1521, 1491. HRMS (ESI+, MeOH): *m/z* calcd. 311.2413 (M + Na)$^{+}$, found: 311.2323.



1.28

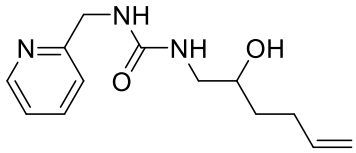
Urea 1.28. Following the procedure B of urea synthesis. Purified by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.28**: 92 mg (0.35 mmol, 70%). ^{1}H NMR (500 MHz, MeOD) δ 7.10 (d, J = 8.2 Hz, 2H), 6.75 (d, J = 8.2 Hz, 2H), 5.92 (m, 1H), 5.10 (m, 1H), 5.04 (m, 1H), 4.24 (s, 2H), 3.68 (m, 1H), 3.32 (dd, J = 13.9 and 4.5 Hz, 1H), 3.13 (dd, J = 13.9 and 6.9 Hz, 1H), 2.27 (m, 1H), 2.19 (m, 1H), 1.62 (m, 1H), 1.55 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.85, 150.22, 142.11, 132.90, 131.89, 119.20, 117.61, 74.10, 49.55, 47.12, 37.52, 33.42. IR (neat, cm^{-1}): 3309, 1708, 1618, 1573, 1517, 1381, 908, 826, 727, 491. HRMS (ESI+, MeOH): *m/z* calcd. 286.1530 (M + Na)$^{+}$, found: 286.1526.

1.29



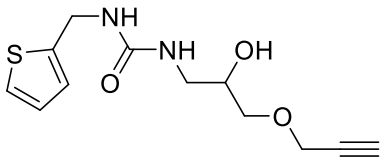
Urea 1.29. Following the procedure B of urea synthesis. Purified by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.29**: 66 mg (0.32 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.24 (br s, 1H, NH), 5.14 (br s, 1H, NH), 4.33 (d, J = 5.8 Hz, 2H), 3.84 (m, 1H), 3.28 (m, 1H), 3.04 (m, 1H), 1.13 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.30, 139.03, 128.65, 127.38, 127.34, 68.10, 48.05, 44.56, 20.63. IR (neat, cm^{-1}): 3316, 1680, 1630, 1561, 1253, 1120, 730, 697. HRMS (ESI+, MeOH): *m/z* calcd. 231.1104 $(M + Na)^+$, found: 231.1106.

1.30

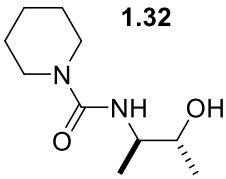


Urea 1.30. Following the procedure B of urea synthesis. Purified by column chromatography on silica gel (pure EtOAc). Yield of **1.30**: 87 mg (0.35 mmol, 70%). ^{1}H NMR (500 MHz, MeOD) δ 8.53 (d, J = 4.9 Hz, 1H), 7.88 (td, J = 7.7 and 3.0 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.38 (dd, J = 7.4 and 5.9 Hz, 1H), 5.91 (m, 1H), 5.10 (m, 1H), 5.02 (m, 1H), 4.51 (s, 2H), 3.69 (m, 1H), 3.34 (dd, J = 4.6 and 13.2 Hz, 1H), 3.14 (dd, J = 6.9 and 13.4, 1H), 2.29 (m, 1H), 2.19 (m, 1H), 1.64 (m, 1H), 1.55 (m, 1H). ^{13}C NMR (126 MHz, MeOD) δ 159.82, 159.20, 148.15, 138.16, 137.37, 122.16, 121.26, 113.67, 70.06, 45.68, 44.69, 33.57, 29.47. IR (neat, cm^{-1}): 3321, 2925, 2484, 1626, 1585, 1481, 1356, 1107, 981, 732, 615. HRMS (ESI+, MeOH)$^+$: *m/z* calcd. 250.1550 $(M + Na)^+$, found: 250.1562.

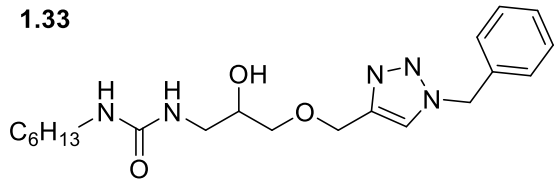
1.31



Urea 1.31 Following the procedure B of urea synthesis. Purified by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.31**: 76 mg (26 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, J = 4.9 and 1.8 Hz, 1H), 6.98 (m, 2H), 4.93 (br s, 1H, NH), 4.83 (br s, 1H, NH), 4.58 (d, J = 5.9 Hz, 2H), 4.18 (d, J = 2.3 Hz, 2H), 3.92 (m, 1H), 3.60 (m, 1H), 3.52 (m, 1H), 3.49 (m, 1H), 3.32 (br s, 1H, OH), 3.25 (m, 1H), 2.47 (t, J = 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.77, 142.19, 126.86, 125.46, 124.98, 79.36, 74.90, 71.54, 70.30, 58.61, 43.58, 39.54. IR (neat, cm^{-1}): 3301, 2855, 1637, 1561, 1207, 1095, 701. HRMS (ESI+, MeOH): *m/z* calcd. 291.0774 $(M + Na)^+$, found: 291.0786.



Urea 1.32. Following the procedure B of urea synthesis. Purified by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.32**: 67 mg (0.34 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (br s, 1H, NH), 3.78 (m, 1H), 3.69 (m, 1H), 3.34 (t, J = 5.7 Hz, 4H), 3.19 (br s, 1H, OH), 1.63 (m, 2H), 1.58 (m, 4H), 1.22 (d, J = 7.7 Hz, 3H), 1.20 (d, J = 8.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.32, 72.35, 52.31, 45.03, 25.58, 24.38, 20.85, 18.52. IR (neat, cm^{-1}): 3299, 2985, 1618, 1531, 1231. HRMS (ESI+, MeOH): *m/z* calcd. 201.1598 $(M + Na)^+$, found: 201.1599.



Urea 1.33. Synthesized following standard click chemistry procedures.[52] Purified by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **1.33**: 95 mg (0.45 mmol, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.38 (m, 2H), 7.28 (m, 2H), 5.52 (s, 3H), 5.07 (m, 1H, br s), 4.61 (s, 2H), 3.87 (m, 1H), 3.53 (d, J = 5.4 Hz), 3.43 (m, 1H), 3.22 (m, 1H), 3.14 (m, 2H), 1.47 (m, 2H), 1.28 (m, 6H), 0.89 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.89, 144.92, 134.33, 129.19, 128.89, 128.13, 122.58, 72.29, 70.36, 64.33, 54.26, 43.62, 40.61, 31.54, 30.16, 26.56, 22.59, 14.04. HRMS (ESI+, MeOH): *m/z* calcd. 412.2319 $(M + Na)^+$, found: 412.2308.

1.4.3 Crystallographic Data

All measured crystals reported in this thesis were stable under atmospheric conditions; nevertheless they were treated under inert conditions immersed in perfluoro-polyether as protecting oil for manipulation. Data Collection: measurements were made on a Bruker-Nonius diffractometer equipped with an APPEX II 4K CCD area detector, a FR591 rotating anode with Mo Kα radiation, Montel mirrors and a Kryoflex low temperature device (T = -173ºC). Full-sphere data collection was used with ω and ϕ scans. Programs used: data collection Apex2 V2011.3 (Bruker-Nonius 2008), data reduction Saint+Version 7.60A (Bruker AXS 2008) and absorption correction SADABS V. 2008–1 (2008). Structure

solution: SHELXTL Version 6.10 (Sheldrick, 2000) was used. Structure refinement: SHELXTL-97-UNIX VERSION.

Crystal data for urea ***1.23****:* $C_{11}H_{20}N_2O_3$, M_r = 228.29, monoclinic, P-1, a = 6.4520(13) Å, b = 9.1250(18) Å, c = 20.031(4) Å, α = 92.00º, β = 92.90º, γ = 90.06º, V = 1171.1(4) Å^3, Z = 4, ρ = 1.288 mg·M^{-3}, μ = 0.094 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 496, crystal size = 0.15 × 0.04 × 0.01 mm, θ(min) = 1.018º, θ(max) = 27.67º, 5421 reflections collected, 5421 reflections unique (R_{int} = 0.0365), GoF = 1.061, R_1 = 0.0812 and wR_2 = 0.2367 [$I > 2\sigma(I)$], R_1 = 0.0393 and wR_2 = 0.0887 (all indices), min/max residual density = -0.716/0.718 [e·Å^{-3}]. Completeness to θ(27.67º) = 98.9%.

1.5 References

(1) Vinh, D. C.; Rubinstein, E. *J. Infect.* **2009**, *59*, 59–74.

(2) Barbachyn, M. R.; Ford, C. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 2010–2023.

(3) Dotis, J.; Iosifidis, E.; Ioannidou, M.; Roilides, E. *Int. J. Infect. Dis.* **2010**, *14*, 638–648.

(4) Zappia G., Menendez P, Monache G.D., Misiti D., Nevola L., B. B. *Mini-Rev. Med. Chem.* **2007**, *4*, 389–409.

(5) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156.

(6) Heravi, M. M.; Zadsirjan, V. *Tetrahedron Asymmetr.* **2013**, *24*, 1149–1188.

(7) Procopiou, P. A.; Barrett, V. J.; Bevan, N. J.; Biggadike, K.; Box, P. C.; Butchers, P. R.; Coe, D. M.; Conroy, R.; Emmons, A.; Ford, A. J.; Holmes, D. S.; Horsley, H.; Kerr, F.; Li-Kwai-Cheung, A. M.; Looker, B. E.; Mann, I. S.; McLay, I. M.; Morrison, V. S.; Mutch, P. J.; Smith, C. E.; Tomlin, P. *J. Med. Chem.* **2010**, *53*, 4522–4530.

(8) Speranza, G. P.; Peppel, W. J. *J. Org. Chem.* **1958**, *23*, 1922–1924.

(9) Kogon, I. C. *J. Am. Chem. Soc.* **1956**, *78*, 4911–4914.

(10) Demaray, J. A.; Thuener, J. E.; Dawson, M. N.; Sucheck, S. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4868–4871.

(11) Herweh, J. E.; Kauffman, W. J.; Company, A. C. *Tetrahedron Lett.* **1971**, 809–812.

(12) Zhu, C. Qian, D. *Synlett* **1993**, 129–130.

(13) Shibata, I.; Baba, A.; Iwasaki, H.; Matsuda, H. *J. Org. Chem.* **1986**, *51*, 2177–2184.

(14) Beattie, C.; North, M. *RSC Adv.* **2014**, *4*, 31345–31352.

(15) Baronsky, T.; Beattie, C.; Harrington, R. W.; Irfan, R.; North, M.; Osende, J. G.; Young, C. *ACS Catal.* **2013**, *3*, 790–797.

(16) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**,

6, 3973–3975.

(17) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, *7*, 1983–1985.

(18) Birrell, J. A.; Jacobsen, E. N. *Org. Lett.* **2013**, *15*, 2895–2897.

(19) Pulla, S.; Felton, C. M.; Ramidi, P.; Gartia, Y.; Ali, N.; Nasini, U. B.; Ghosh, A. *J. CO_2 Util.* **2013**, *2*, 49–57.

(20) Shen, Y. M.; Duan, W. L.; Shi, M. *Eur. J. Org. Chem.* **2004**, 3080–3089.

(21) Hancock, M. T.; Pinhas, A. R. *Tetrahedron Lett.* **2003**, *44*, 5457–5460.

(22) Sudo, A.; Morioka, Y.; Koizumi, E.; Sanda, F.; Endo, T. *Tetrahedron Lett.* **2003**, *44*, 7889–7891.

(23) Kawanami, H.; Ikushima, Y. *Tetrahedron Lett.* **2002**, *43*, 3841–3844.

(24) Costa, M.; Chiusoli, G. P.; Rizzardi, M. *Chem. Commun.* **1996**, 1699–1700.

(25) Hase, S.; Kayaki, Y.; Ikariya, T. *Organometallics* **2013**, *32*, 5285–5288.

(26) García-Domínguez, P.; Fehr, L.; Rusconi, G.; Nevado, C. *Chem. Sci.* **2016**, *7*, 3914–3918.

(27) M. Karikomi; Yamazaki, T.; Toda, T. *Chem. Lett.* **1993**, 1965–1968.

(28) Rintjema, J.; Epping, R.; Fiorani, G.; Martín, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 3972–3976.

(29) Adhikari, D.; Miller, A. W.; Baik, M.-H.; Nguyen, S. T. *Chem. Sci.* **2015**, *6*, 1293–1300.

(30) Volz, N.; Clayden, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 12148–12155.

(31) Connon, S. J. *Chem. Commun.* **2008**, 2499–2510.

(32) Dawn, S.; Dewal, M. B.; Sobransingh, D.; Paderes, M. C.; Wibowo, A. C.; Smith, M. D.; Krause, J. A.; Pellechia, P. J.; Shimizu, L. S. *J. Am. Chem. Soc.* **2011**, *133*, 7025–7032.

(33) Su, J. T.; Vachal, P.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 197–200.

(34) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science.* **1997**, *278*, 1601–1604.

(35) Van Gorp, J. J.; Vekemans, J. A. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **2002**, *124*, 14759–14769.

(36) Rodriguez, J. M.; Hamilton, A. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 8614–8617.

(37) Hussain, S.; Brotherhood, P. R.; Judd, L. W.; Davis, A. P. *J. Am. Chem. Soc.* **2011**, *133*, 1614–1617.

(38) Padiya, K. J.; Gavade, S.; Kardile, B.; Tiwari, M.; Bajare, S. *Org. Lett.* **2012**, *14*, 2814–2817.

(39) Vinogradova, E. V; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 11132–11135.

(40) Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2531–2534.

(41) Fontana, F.; Chen, C. C.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3454–3457.

(42) Wang, P.; Qin, J.; Yuan, D.; Wang, Y.; Yao, Y. *ChemCatChem* **2015**, *7*, 1145–1151.

(43) Shi, M.; Shen, Y. M. *J. Org. Chem.* **2002**, *67*, 16–21.

(44) Whiteoak, C. J.; Kielland, N.; Laserna, V.; Castro-Gomez, F.; Martin, E.; Escudero-Adán, E.

C.; Bo, C.; Kleij, A. W. *Chem. Eur. J.* **2014**, *20*, 2264–2275.

(45) Whiteoak, C. J.; Kielland, N.; Laserna, V.; Escudero-Adán, E. C.; Martin, E.; Kleij, A. W. *J. Am. Chem. Soc.* **2013**, *135*, 1228–1231.

(46) Niemi, T.; Perea-buceta, J. E.; Fernµndez, I.; Alakurtti, S.; Rantala, E. *Chem. Eur. J.* **2014**, *20*, 8867–8871.

(47) Hu, N. X.; Otsubo, T.; Ogura, F. *J. Org. Chem.* **1989**, *54*, 4398–4404.

(48) Li, P.; Yuan, X.; Wang, S.; Lu, S. *Tetrahedron* **2007**, *63*, 12419–12423.

(49) Jiang, H.; Ye, J.; Qi, C.; Huang, L. *Tetrahedron Lett.* **2010**, *51*, 928–932.

(50) He, T.; Gao, W.; Wang, W.; Zhang, C. *Adv. Synth. Catal.* **2014**, *356*, 1113–1118.

(51) T. A. Foglia, D. S. *J. Org. Chem.* **1969**, *34*, 1680–1684.

(52) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210–216.

Chapter II

Aluminium Catalyzed Formation of Cyclic Sulfites from Sulfur Dioxide

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UNIVERSITAT ROVIRA I VIRGILI
SMALL MOLECULE ACTIVATION FOR THE FORMATION OF HETEROCYCLIC COMPOUNDS
Victor Laserna Ayora

2.1 Introduction

2.1.1 Sulfur Dioxide

Sulfur dioxide (SO_2) is a toxic gas (boiling point: −10ºC) produced by the combustion of sulfur or sulfur-containing ores. It is manufactured on a massive scale of millions of tons, and its primary use is as a feedstock in the industrial preparation of sulfuric acid, sulfuryl chloride, and metal sulfite salts.[1] The most direct and historical application is as food preserver (particularly in the wine industry) preventing oxidation and displaying antibacterial properties. There is, however, a concern regarding the anthropomorphic emissions of SO_2 into the atmosphere, and these emissions are caused by the presence of sulfur traces in fossil fuels which are burnt in power plants and other industrial facilities. Although the annual SO_2 emission is much lower than that of CO_2 and has attracted less attention, this hazardous gas is co-responsible for environmental issues such as acid rain. Being a problematic waste gas, it would thus be interesting to develop viable recycling strategies that exploit SO_2 as a chemical feedstock. Applications of SO_2 already exist in various fields such as in biological research,[2] synthesis of copolymers,[3–5] radical chemistry,[6–8] and food processing.

The use of SO_2 as a reagent in organic chemistry is comparatively underdeveloped,[9,10] as the compound is toxic and foul smelling: it has a series of associated safety considerations which have limited the synthetic use of SO_2. Despite these issues, SO_2 displays rich reactivity in organic chemistry as a result of its unique electronic structure.[11] The sulfur atom is amphoteric due to the presence of a lone pair in a high lying HOMO resulting in nucleophilic ability, while the molecule also has a low-lying LUMO with π-symmetry mostly concentrated on the sulfur atom giving it electrophilic properties. Moreover, it also possesses a sufficiently stable SOMO to participate in radical reactions. The development and wide application potential of other toxic, difficult to handle gaseous building blocks such as carbon monoxide (CO) contrasts with the underdeveloped chemistry of SO_2 especially when considering the ubiquity of the sulfonyl (SO_2) group in high-value compounds.[12,13] Recent progress in the chemistry of SO_2 is mainly a result of the use of more stable and easy to handle

surrogates such as DABSO, being a bis-SO_2 adduct of DABCO.[14] These surrogates provide SO_2-based compounds as bench-stable reagents, and this has greatly facilitated the use of SO_2 in synthetic chemistry. A better control over the SO_2 stoichiometry has allowed for the development of new reactions and has improved the efficiency of older and harsher methods, opening up new synthetic possibilities for the introduction of the sulfonyl moiety.

2.1.2 Cyclic Sulfites

An attractive target that can be prepared from SO_2 are cyclic sulfites (1,3,2-dioxathiolane-2-oxides) which can be prepared by coupling with epoxides providing structures of use in polymer science,[15–17] as electrolyte additives[18,19] or as synthetic intermediates.[20,21] The applications of cyclic sulfites have been somehow limited due to problems associated with their traditional synthesis. Cyclic *sulfates* are scaffolds with great potential as organic intermediates,[22] and recently they have been reported as useful compounds towards the total synthesis of macrosphelides,[23] as macrocyclic precursors for monodisperse poly(ethylene glycols)[24] and as substrates in Kumada-type couplings.[25] Although they have been known since 1932, the lack of an efficient method for preparing such cyclic sulfates has limited their application potential. The oxidation of cyclic sulfites by sodium periodate catalyzed by ruthenium tetraoxide represents an important development that has broadened the use of cyclic sulfate intermediates in synthesis. Cyclic sulfates have an electrophilic nature, which makes them very reactive towards nucleophilic ring opening, and typically these compounds are more reactive than epoxides. Nucleophilic attack generally occurs on one of the α-carbons generating a (linear) sulfate protecting group on a second position. Under more vigorous conditions, cyclic sulfates can serve as a starting point for two sequential substitution reactions, creating contiguous stereocenters. Furthermore, since the intermediate of this nucleophilic substitution reaction is generally a salt of a mono-sulfate ester, separation of the product from others is typically facile.

The SO_2 approach towards cyclic sulfites has been developed as a more sustainable methodology compared with the conventional preparation of these scaffolds through a base-assisted reaction of 1,2-diols with thionyl chloride. This latter process generates stoichiometric amounts of halide-containing by-products.[26–28] Despite the development of various effective homogeneous[29] and heterogeneous[30] catalyst systems for the coupling of epoxides and SO_2, there are still synthetic challenges to overcome pertinent to a more general

and sustainable route towards these cyclic sulfites. In particular, low-temperature conversions and further widening the scope in reaction partners may be required, to valorize these cyclic sulfites as chemical building blocks as only the more reactive terminal epoxides have been reported as substrates in this kind of coupling reaction. To this end, isolation of the pure sulfite targets is often hampered due to the presence of mixtures of poly- and cyclic sulfites. Moreover, as far as we know only limited potential towards the more challenging coupling of internal epoxides and SO_2 has been reported to date. Consequently, this restricts the synthesis of cyclic sulfites mostly to the use of terminal oxiranes with thus a more limited substitution diversity.

2.1.3 Project Aims

The present chapter focuses on the development of an efficient methodology towards the synthesis of cyclic sulfites using a binary aluminum amino triphenolate/tetrabutyl ammonium halide catalyst. The aim is to provide a much wider scope for these sulfur-containing heterocycles under attractively mild reaction conditions. Furthermore, the subsequent use of these cyclic sulfites as precursors for the formation of cyclic sulfates will offer new synthetic potential. The transformation of sulfites into sulfates and their application as molecular synthons is also demonstrated in this chapter with the aim to provide an easy entry towards the preparation of *N*-substituted aziridines, obtained through aminolysis and base-assisted cyclization.[31,32]

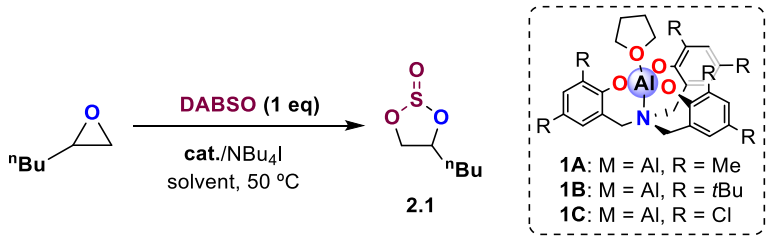
2.2 Results and Discussion

2.2.1 Optimization of Cyclic Sulfite Formation

Our first attempts to produce cyclic sulfites from epoxides and SO_2 were based on the use of DABSO (the bis-SO_2 adduct derived from DABCO: 1,4-diazabicyclo [2.2.2] octane) as an easy to handle SO_2 surrogate,[33] see **Table 2.1**. We tested the efficiency of Al(III) amino triphenolates, combined with an external nucleophile (NBu_4I) to mediate the epoxide ring opening, **1C** in acetonitrile gave the best results in terms of isolated yield (*entry 3*; 55% after 3 h, 63% after 6 h). Various polar solvents other than acetonitrile were also examined

but gave inferior results (entries *9–12*). Unfortunately the use of the nucleophilic additive only (*entry 13*), produced a yield slightly lower (45%) than noted for the best case scenario (*entry 3*). Various halide species by themselves have already been reported to mediate the formation of cyclic sulfites,[30,34] our goal was to increase the activity of this system by adding a Lewis acid, but the preliminary results showed little effect on the overall kinetics. To obtain more insight, we investigated the kinetic profile for the synthesis of compound **2.1** from 1,2-epoxyhexane and DABSO in more detail (**Figure 2.1**).

Table 2.1: Screening towards the formation of cyclic sulfite product **2.1**.[a]



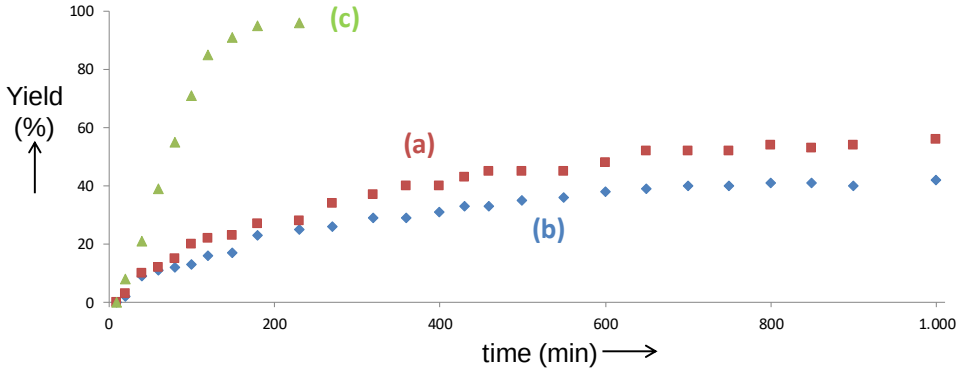
Entry	Cat.	Solvent	t (h)	Yield (%)[b]
1	**1A**	CH_3CN	3	41
2	**1B**	CH_3CN	3	51
3	**1C**	CH_3CN	3	55 (63)[c]
9	**1C**	EtOAc	6	59
10	**1C**	THF	6	23
11	**1C**	DMF	6	24
12	**1C**	MEK	6	19
13	–	CH_3CN	3	45

[a] General conditions: 3.0 mmol of 1,2-epoxyhexane, 2.5 mol% cat., 5.0 mol% NBu4I, solvent indicated (1.0 mL), 50 ºC, 1 equiv DABSO. [b] Isolated yield. [c] Isolated yield after a 6 h reaction time.

As can be judged from **Figure 2.1**, formation in the presence or absence of complex **1C** (*i.e.*, traces (a) and (b) in the graph) does not show much difference, and the yield of cyclic sulfite **2.1** reaches a plateau after around 600 min. This suggests either that the Lewis acid catalytic potential of Al-complex **1C** is significantly hampered or that the nucleophilic additive is consumed under these experimental conditions. The most likely reason for this

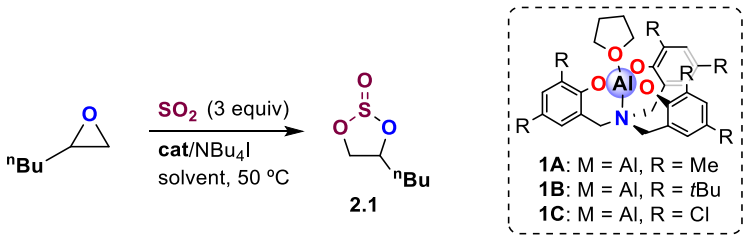
lethargic behavior is the release of the bicyclic amine DABCO during the course of the reaction when more SO_2 (DABSO) is consumed. Such diamines (and other *N*-donors) are good ligands for Al(III) and Fe(III) amino triphenolate complexes.[35–37] Therefore, the presence of DABCO almost certainly causes catalyst deactivation by amine coordination to its active site. DABCO is known to be able to react with different nucleophiles[38,39] so this could also be a potential parasitic reaction consuming the nucleophilic co-catalyst. In order to avoid *in situ* deactivation of the Al-complex and co-catalyst consumption, we designed a different protocol which does not involve the release of DABCO into the reaction mixture. This protocol takes advantage of easy *ex situ* SO_2 formation using copper powder and H_2SO_4 thereby generating SO_2. The SO_2 is then transported by a gentle nitrogen flow to a different reactor containing the epoxide and catalyst, and this should deliver a more productive protocol for cyclic sulfite formation.

Figure 2.1. Kinetic profiles determined by ^{1}H NMR (CD_3CN) for the synthesis of **2.1** using DABSO (1.2 eq.) and mesitylene as internal standard. (a) Using **1C**/NBu_4I as binary catalyst; (b) Using only NBu_4I; (c) With *ex-situ* generated SO_2 from H_2SO_4/Cu.



Indeed, when we tested such conditions (**Table 2.2**, **Figure 2.1** (c)) we noted that the reaction towards the formation of cyclic sulfite **2.1** proceeded smoothly and gave the product in nearly quantitative NMR yield after only 200 min. The conditions producing the *ex-situ* generated SO_2 and the addition of DABSO as an SO_2 surrogate are not exactly the same. In the latter method one equivalent of DABSO is added while in the *ex-situ* "method" 3 equiv of SO_2 may be generated to compensate for possible losses and taking into account the fact that the reduction of H_2SO_4 is not quantitative. However, the difference between the kinetic profiles led us to believe that the *ex situ* SO_2 generation method is more effective and we decided to focus on further optimizing the synthesis of cyclic sulfite **2.1** using this protocol.

Table 2.2: Screening towards the formation of cyclic sulfite product **2.1** with *ex-situ* formation of SO_2.[a]



Entry	Cat. (mol%)	Nu (mol%)	T (ºC)	Yield (%)[b]
1	–	NBu_4I (1.0)	50	11
2	–	NBu_4I (2.5)	50	29
3	–	NBu_4I (5.0)	50	61
4	–	NBu_4Br (2.5)	50	25
5	**1C** (0.5)	NBu_4I (2.5)	50	85
6	**1B** (0.5)	NBu_4I (2.5)	50	41
7	**1A** (0.5)	NBu_4I (2.5)	50	65
8	**1C** (1.0)	NBu_4I (2.5)	50	86
9	**1C** (1.0)	NBu_4I (1.0)	50	61
10	**1C** (0.5)	NBu_4I (2.5)	25	22
11	**1C** (0.5)	NBu_4I (2.5)	70	84

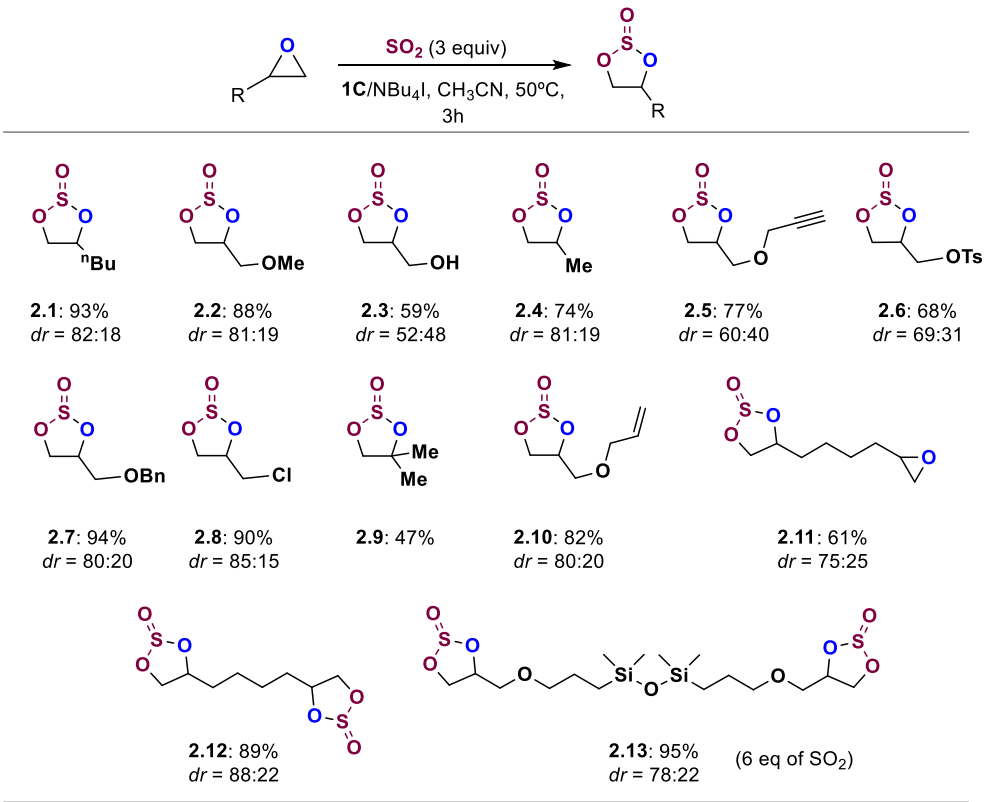
[a] General conditions: 3.0 mmol of 1,2-epoxyhexane, **C** (amount indicated), NBu_4X (amount indicated), CH_3CN (1.0 mL), Cu (3 equiv) in H_2SO_4 (10 mL) at 90 ºC (*ex situ*), 2 h. [b] NMR yields using mesitylene as an internal standard.

Table 2.2 summarizes the optimization experiments using the *ex situ* SO_2 methodology in the formation of **2.1**. Clearly, catalyst **1C** shows the best performance (entries *5–7*) with markedly better yields of compound **2.1** compared to the reaction in the absence of the complex (*cf.*, entries *2* versus *5*) or using lower amount of Al complex (0.5 mol%). Higher amounts of Al complex (*entry 8*) and an elevated temperature (70ºC, *entry 11*) barely affected the yield of **2.1**, suggesting that the conditions of *entry 5* and *8* are optimal.

2.2.2 Scope in Terminal Epoxides

Having determined a set of optimal reaction conditions, we then investigated the scope of terminal epoxide substrates in the formation of various cyclic sulfites (*cf.*, formation of compounds **2.1–2.13**, **Figure 2.2**) using 1.0 mol% of Al-complex **1C**, 2.5 mol% of NBu_4I in CH_3CN at 50ºC. Under these conditions, after 180 minutes cyclic sulfite **2.1** could be isolated in excellent yield (93%) as a mixture of two diastereoisomers in an 82:18 ratio.

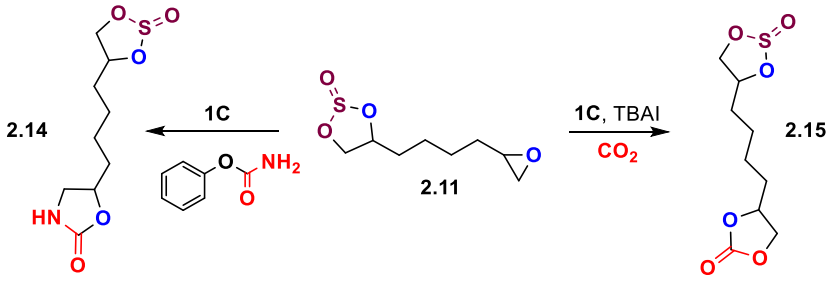
Figure 2.2. Synthesis of cyclic sulfites **2.1-2.13** from various terminal epoxides using *ex-situ* generated SO_2.



The presence of two diastereoisomers is the result of the non-planarity of the cyclic sulfite, with the sulfur lone pair either being on the same or opposite side of the ring substituent (see section 2.2.4). The two diastereoisomers can be readily assigned by NMR analysis. Many different and potentially useful substituents onto the cyclic sulfite ring can be introduced including alcohol (**2.3**), allyloxo (**2.10**), propargyloxo (**2.5**), and tosyl ester (**2.6**)

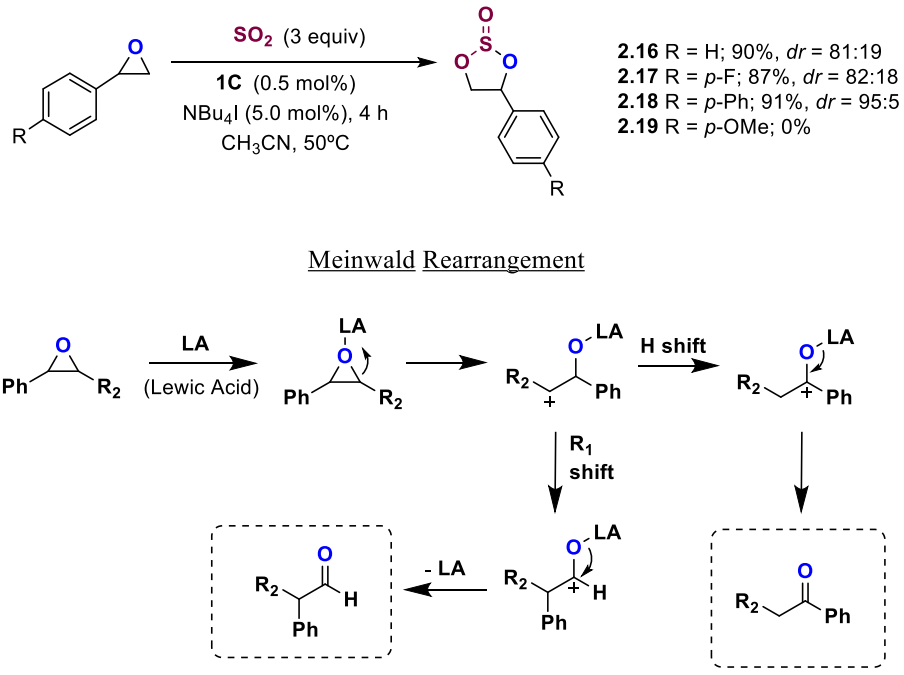
groups that do not hamper product formation. In the cases where the starting materials were volatile (**2.4** and **2.9**), the yields were slightly compromised by a loss of substrate through evaporation due to the nitrogen flow required to transport the *ex situ* generated SO_2 into the reaction vessel. Interestingly, mono-sulfite **2.11** derived from its bis-epoxide precursor could be isolated in 61% yield and incorporates a synthetically useful oxirane unit. By increasing the amount of SO_2 to 6 equiv, the bis-sulfite **2.12** was obtained as the major compound and isolated in good yield (89%). Compound **2.11** could be easily converted into the mixed sulfite/carbamate **2.14** (52%) and sulfite/carbonate **2.15** (81%) by treatment with phenyl carbamate and CO_2, respectively, under appropriate reaction conditions.[40,41] These latter conversions demonstrate the post-modification potential of functional sulfites.

Figure 2.3. Post-modification of **2.11** to the sulfite/carbamate **2.14** and the sulfite/carbonate product **2.15**.



In those cases where styrene oxides were used (*cf.*, the formation of **2.16**-**2.19**, **Figure 2.4**), a higher loading of the nucleophile was required as to prevent the preferred formation of ketone products through Meinwald rearrangement.[42] Epoxides are known to undergo a highly efficient and selective rearrangement in the presence of catalytic quantities of Lewis acids to give carbonyl compounds.[43,44] For the styrene based substrates we indeed were able to observe such side products as the intermediate of ring opening is able to stabilize benzylic carbocation favoring this side reaction. As expected, the substitution on the aromatic ring influenced greatly the reactivity. For cases with electron-withdrawing substituents on the aromatic ring we were able to inhibit this aforementioned rearrangement favoring almost exclusively the formation of cyclic sulfite, but with electron-donating substituents such as *para*-methoxy only the Meinwald rearrangement product was observed, and no trace of cyclic sulfite product was observed even at higher loadings of co-catalyst.

Figure 2.4 Scope in styrene derivatives and Meinwald rearrangement for styrene oxides.

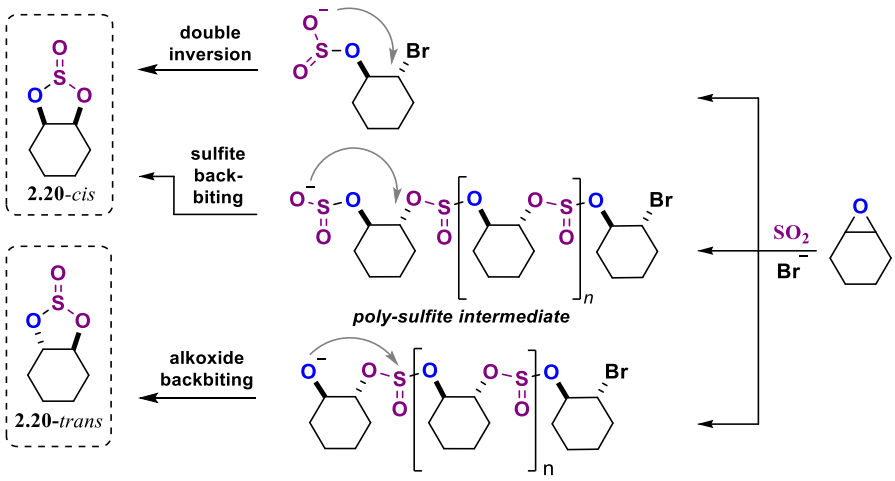


2.2.3 Scope in Internal Epoxides

Motivated by the successful preparation of functional mono-substituted sulfites, we next turned our focus on the more challenging conversion of internal epoxides. To the best of our knowledge, no efficient method has been reported for the coupling reaction of SO_2 and internal epoxides to yield multi-substituted cyclic sulfites. We considered cyclohexene oxide (CHO) as a representative epoxide and followed its conversion in time using the optimized conditions established for **2.1–2.13** (50 ºC, 3 equiv of SO_2, 1.0 mol% of **1C**). However, NBu_4Br was utilized instead, as bromide nucleophiles were previously shown to be more effective for internal epoxide conversion compared to iodide based ones.[41,45] The conversion at 50ºC proved to be a bit sluggish and, moreover, ^1H NMR analysis showed the presence of peaks reminiscent of poly-sulfites with only trace amounts of cyclic product (cf., **Figure 2.5**). Therefore, the reaction between CHO and SO_2 mediated by binary **1C**/NBu_4Br was then carried out at 70ºC for longer reaction times, and we found that the reaction mixture contained virtually only the cyclic sulfite product **2.20**. The latter was isolated in moderate yield (46%; **Figure 2.6**) by chromatographic purification. Notably, compound **2.20** was mostly isolated

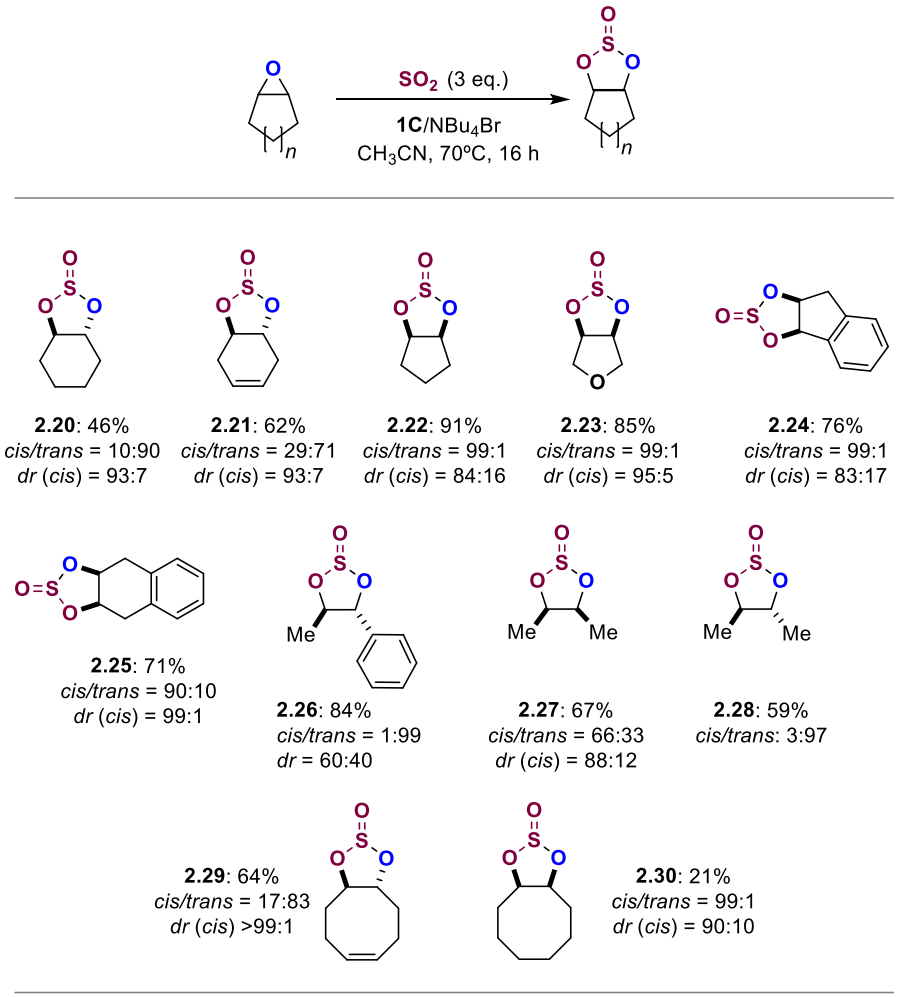
as the *trans* isomer which is the expected result if the cyclic sulfite would be formed by an alkoxide back-biting of an initially formed poly-sulfite polymer.[46] This suggests that CHO undergoes copolymerization faster than coupling with SO_2 in a classical double S_N2 pathway that is typically observed in the formation of mono-substituted *cyclic* sulfites. The polymer derived from CHO and SO_2 (when heated) over time undergoes depolymerization such as reported for poly-*carbonates*. This depolymerization reaction includes an attack of the metal-alkoxide onto the carbonate carbon center yielding a cyclic carbonate having a *trans* configuration. *Cis*-configured cyclic sulfite products can potentially form through two possible mechanistic scenarios: a traditional double inversion pathway, or *via* a depolymerization pathway initiated by a sulfite nucleophile (i.e., sulfite backbiting, **Figure 2.5**). As the cyclic sulfite synthesis was typically carried out under ambient pressure of SO_2, the double inversion pathway is the most likely mechanistic manifold towards the formation of the *cis* isomer.

Figure 2.5 Mechanistic pathways for the coupling of cyclohexene oxide and SO_2 to form cyclic sulfites.



We then tested other internal epoxides as reaction partners thereby producing, apart from **2.20**, cyclic sulfites **2.21–2.30** generally in appreciable yields (except for **2.30**; 21%).

Figure 2.6. Synthesis of cyclic sulfites **2.20-2.30** from various internal epoxides using *ex-situ* generated SO_2. Note that only the major stereoisomer is represented.



The more rigid nature of the eight-membered ring epoxide leading to cyclic sulfite **2.29** delivers the product in much better yield (64%) than noted for **2.30**. The likely reason for this is the unfavorable conformation upon activation by the Al(III) center in complex **1C** thereby complicating nucleophile-assisted ring opening. The introduction of a double bond in the eight-membered ring reduces the conformational complexity, and this should facilitate better its conversion into the cyclic sulfite. The fact that **2.29** is also predominantly *trans*-

configured gives the impression that the rigidity of the fused eight-membered ring somehow favors a polymerization process, meanwhile **2.30** probably forms *via* a double inversion pathway delivering a *cis* configured product.

The scope of products displayed in **Figure 2.6** shows that epoxides with different ring sizes are suitable coupling partners for SO_2, and as far as we are aware, our newly developed catalytic process is the first to exhibit such general potential towards the formation of cyclic sulfites from SO_2. For the conversion of *cis*-2, 3-dimethyloxirane (leading to **2.27**) and its *trans*-isomer (giving rise to **2.28**) different behavior was noted. Whereas the *trans* substrate retains the original stereochemistry (*cis*/*trans* = 97:3), the *cis*-substrate gives rise to *cis*/*trans*-**2.27** with significantly lower stereo-retention indicating, as already noted for bicyclic epoxides, the existence of competing pathways leading to the formation of this product.[47]

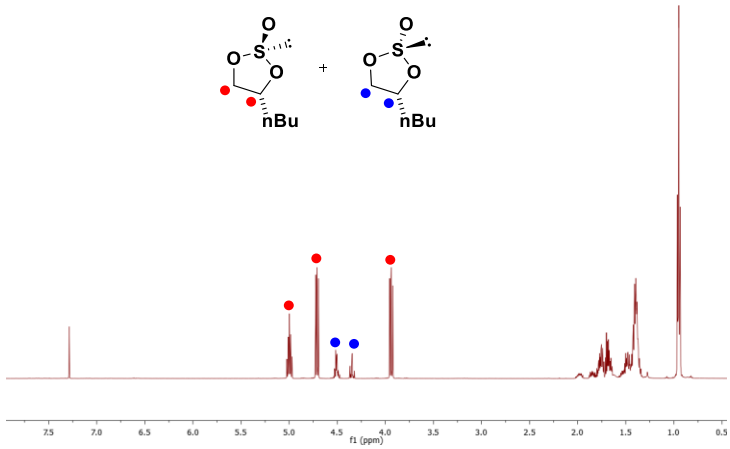
2.2.4 Stereochemistry of Cyclic Sulfites

SO_2 is a bent molecule with C_{2v} symmetry and the sulfur atom has a lone pair, which affects the final geometry of cyclic sulfites. Instead of being planar structures such as related cyclic carbonates or oxazolidinones, the sulfur atom in the cyclic sulfite has a tetrahedral geometry with three positions being occupied by oxygen atoms and the fourth by a lone pair. This creates two different possible configurations for the cyclic structure as both sides opposite to the heterocycle have different electronic environments. Mono-substituted epoxides therefore are isolated as mixtures of two different diastereoisomers which can be easily identified by NMR.

For instance, for cyclic sulfite **2.1** the major isomer is characterized by three distinct signals for the hydrogens attached to the sulfite ring (δ = 5.00, 4.71 and 3.94 ppm, respectively), whereas the minor isomer shows only two peaks located at 4.52 and 4.32 ppm (**Figure 2.7**). One species belongs to the configuration where the substituent is on the same side of the S=O unit while the other has the substituent on the side of the lone pair. The much larger difference in chemical shift for the H-atoms at the same side of the ring structure (δ = 1.06 vs 0.20 ppm) in the major isomer seems to suggest that this diastereo-isomer has the sulfur lone pair on the same face as the butyl substituent, as the lone pair is prone to cause a smaller anisotropic shift on nearby H atoms than an oxygen atom. There is a clear trend

observed upon analysis of all mono-substituted sulfites, and for most cases a preference for one diastereoisomer is noted with the *dr* typically being around 80:20. From the NMR spectra it is not possible to unambiguously determine which species is preferred, and therefore various cyclic sulfites were further examined by X-ray analysis.

Figure 2.7 ^{1}H NMR spectra showing the two diastereoisomers of *n*-butyl substituted cyclic sulfite **2.1**.

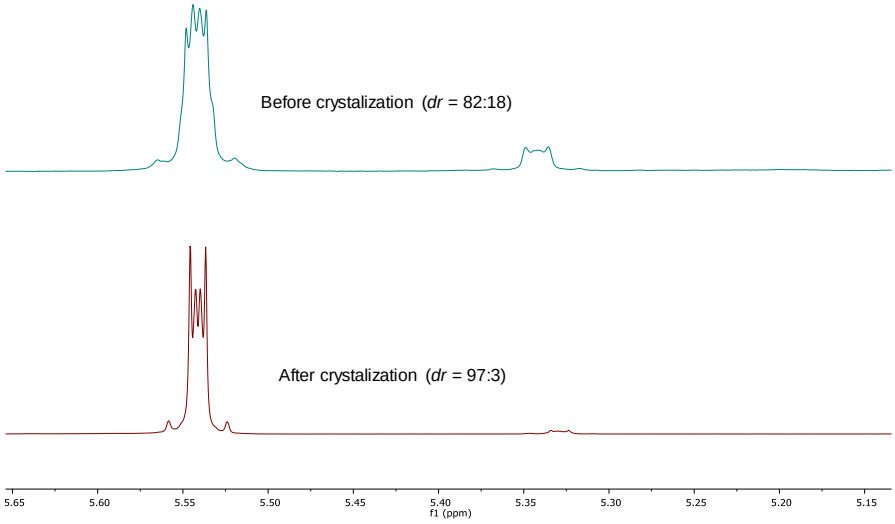


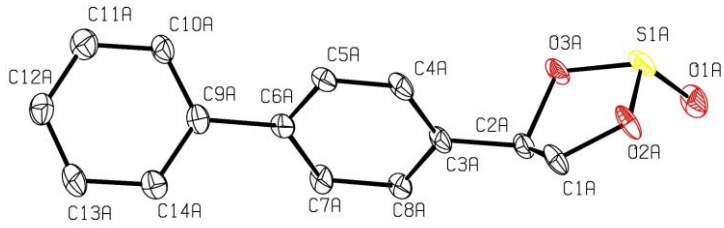
X-ray quality single crystals were obtained for cyclic sulfites **2.18**, **2.23** and **2.25**. Their molecular structures were determined and in all three cases the same stereochemical configuration was determined, i.e. with the ring substituents on the same side of the heterocyclic scaffold as the sulfur lone pair, and the S=O unit on the opposite side. In order to ascertain that indeed the major isomer had been crystallized, the crystals were analyzed by ^{1}H NMR and compared with the mixture obtained after isolation, and this was confirmed for both **2.18** as well as **2.23**.

When dealing with disubstituted epoxides, in particular with bicyclic starting materials, we observed in several cases that pure *cis*-configured epoxides were converted into mixtures of *cis*- and *trans*-configured product. This result is not fully unexpected as for coupling reactions of epoxides and CO_2 this has also been observed.[48,49] A mixture of diastereoisomers is an indication that polymeric intermediates may have been present during the formation of the cyclic sulfite structures and that the *trans*-isomers originate from a depolymerization pathway as explained in 2.2.3. *Cis*- and *trans*- cyclic sulfites can be easily

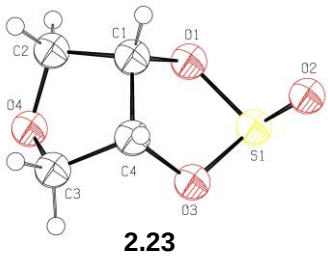
distinguished by ^{1}H NMR as single peaks appear for the *cis* isomer whereas two different ones are observed for the *trans* product.

Figure 2.8 ^{1}H NMR spectra showing the two diastereoisomers of cyclic sulfite **2.23,** and X-ray structures of **2.18**, **2.23** and **2.25**.

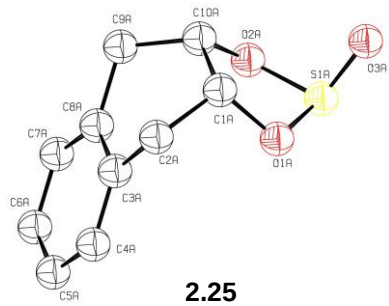




2.18



2.23



2.25

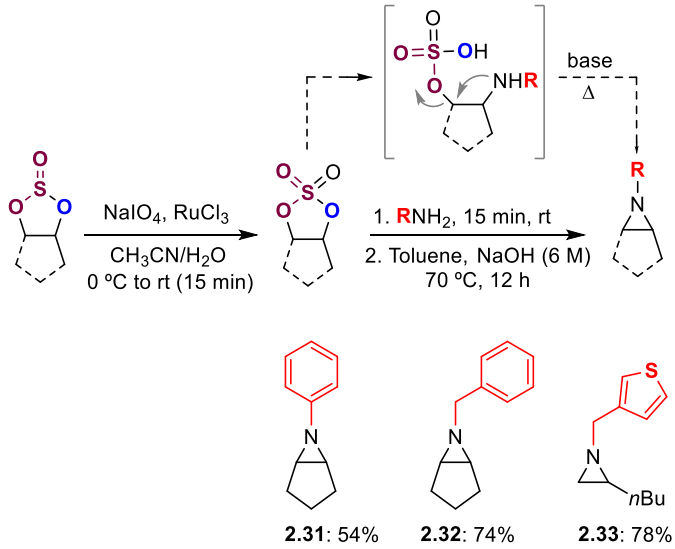
Various polysulfite formation reports for different types of epoxides and SO_2 further supports the idea that oligomeric intermediates are indeed possible. *Trans*-configured internal cyclic sulfites which have equal substituents have only one diastereoisomer, while the *cis*-configured ones should have two. In the ORTEP representations in Figure 2.8 it can be observed that the major diastereoisomer of two disubstituted cyclic sulfites **2.23** and **2.25** both have a *cis*-configuration.

2.2.5 Reactivity of Cyclic Sulfites

To confirm the potential of these cyclic sulfites in organic synthesis, we considered the formation of various derivatives by first oxidizing the respective sulfites to their sulfates.[21,22,50] A major drawback in the synthesis of these cyclic sulfates from acyclic diols and sulfuryl chloride (SO_2Cl_2) is that it often provides low yields of cyclic sulfates. Therefore, these cyclic sulfates are preferably prepared by other methods, such as oxidation of cyclic sulfites.[26] There are various oxidation methods which can achieve this transformation[51,52] but the use of $NaIO_4$ as oxidant in the presence of catalytic amounts of $RuCl_3$ was selected as it represents a simple and selective route.

We chose aziridines as a value-added target molecule. Aziridines are nitrogen analogs of epoxides, and they are important synthetic building blocks *en route* to structurally complex molecules because of their versatility in numerous regio- and stereoselective transformations such as nucleophilic ring opening, ring expansions and rearrangements reactions.[53–55] Cyclic sulfates are easily ring opened by amines allowing to form (*in situ*) their linear amino-sulfates which undergo base-assisted ring-closure to give the *N*-substituted aziridines as demonstrated for **2.31–2.33** which were isolated in appreciable yields.[31] The synthesis of known aziridines **2.31** and **2.32** (though prepared through different methodologies), and unreported aziridine **2.33** shows that the present modular protocol offers great potential towards a wide range of *N*-substituted aziridines including the use of poorly nucleophilic aromatic amines.

Figure 2.9. Synthesis of *N*-substituted aziridines **2.31–2.33** from cyclic sulfites through an oxidation, aminolysis and a ring-closure sequence.



2.3 Conclusions

In this chapter we have described a new catalytic procedure for the formation of functional cyclic sulfites from a wide range of terminal and internal epoxides and SO_2 under productive Al(III) catalysis. The process is characterized by its operational simplicity, unprecedented product scope and mild reaction conditions (ambient pressure, 50-70 ºC). Furthermore, the synthetic potential of these cyclic sulfites was further demonstrated by application in *N*-substituted aziridine synthesis. This work further widens the use of small molecules such as SO_2 in preparative chemistry, and offers new potential towards the construction of valuable chemicals.

2.4 Experimental Section

2.4.1 General Information and Instrumentation

Al(III) amino triphenolate complexes and the starting ligands were synthesized according to reported literature procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded at rt on Bruker AV-300, AV-400 or AV-500 spectrometers and referenced to the residual deuterated solvent signals. Diastereoisomeric ratios (*dr´*s) were calculated from the corresponding ^{1}H NMR spectra using signal integration where possible. All reported NMR values are given in parts per million (ppm). FT-IR measurements were carried out on a Bruker Optics FTIR Alpha spectrometer equipped with a DTGS detector, KBr beam splitter at 4 cm^{-1} resolution. Mass spectrometric analyses and X-ray diffraction studies were performed by the Research Support Area at ICIQ. Commercially available epoxides, solvents, co-catalysts, oxidants were purchased from various commercial sources (Acros, Aldrich and TCI) and used without further purification. When the epoxides were not commercially available, suitable precursors were purchased and used as received.

2.4.2 Synthetic Procedures

Cyclic Sulfite Synthesis

Copper powder (9.0 mmol) was added to sulfuric acid (10 mL) and then heated to 90ºC. This reaction vessel was connected to another one through a Teflon tube and an overpressure "trap" containing a solution of NaOH (2 M). The main reactor was charged with a solution of the epoxide (3.0 mmol), complex **1C** (0.5–1.0 mol %) and NBu_4I (2.5–5.0 mol %) in acetonitrile (1.0 mL), and a gentle flow of N_2 was adjusted such that the *ex situ* formed SO_2 was transported towards the reactor containing the substrate/catalyst. Once the SO_2 started to form (bubbles), the reaction flask was heated to 50 ºC and the mixture stirred for 3 h (for terminal epoxides) or 16 h (for internal epoxides). For those cases where the terminal epoxides were too volatile, the flow of SO_2 was passed through the solution for an hour and then the reaction vessel was sealed and heated for the corresponding reaction time. After each reaction, the solvent was removed and the product purified by column chromatography.

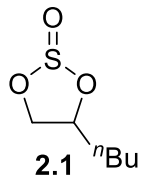
Cyclic Sulfate Synthesis

The respective cyclic sulfite (1.0 mmol) was dissolved into acetonitrile (1.0 mL) and cooled down to 0 ºC. Then $NaIO_4$ (1.2 equiv), $RuCl_3$ (1.0 mol %) and pre-cooled water (1.0 mL) were added to the reaction mixture. The mixture was stirred at rt for 15 min. Then the product was extracted with ethyl acetate and dried on anhydrous sodium sulfate. The crude product thus obtained was purified by column chromatography.

Aziridine Synthesis

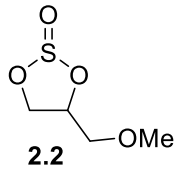
The respective cyclic sulfate (1.0 mmol) was combined with the corresponding amine (1.2 mmol) and this mixture was stirred for 15 min, where after toluene (2.0 mL) and NaOH (6 M, 2.0 mL) were added. This biphasic mixture was heated to 70 ºC and stirred for 12 h after which the product was extracted by ethyl acetate, concentrated and purified by column chromatography.

2.4.2 Spectroscopic Analysis for all Compounds



2.1

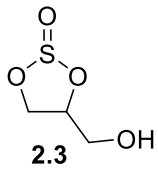
Cyclic Sulfite 2.1 (*dr* = 82:18): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.1**: 459 mg (2.79 mmol, 93%). *Major isomer*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (m, 1H), 4.71 (dd, J = 8.3 and 6.1 Hz, 1H), 3.94 (dd, J = 8.2 and 7.1 Hz, 1H), 1.76 (m, 1H), 1.68 (m, 1H), 1.41 (m, 4H), 0.95 (t, J = 6.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.21, 71.64, 31.88, 27.48, 22.34, 13.82. *Minor isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (m, 2H), 4.34 (m, 1H), 1.99 (m, 1H), 1.86 (m, 1H), 1.49 (m, 4H), 0.95 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 84.17, 70.20, 33.09, 27.99, 22.39, 13.82. IR (neat, cm^{-1}): 2964, 2873, 1522, 1202, 948, 677.



2.2

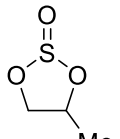
Cyclic Sulfite 2.2 (*dr* = 81:19): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.2**: 401 mg (2.64 mmol, 88%). *Major isomer*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (m, 1H), 4.72 (dd, J = 8.5 and 7.2 Hz, 1H), 4.30 (dd, J = 8.7 and 7.2 Hz, 1H), 3.53 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.33, 70.96, 68.69, 59.55. *Minor isomer*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (m, 1H), 4.56 (m, 1H),

4.53 (m, 1H), 3.75 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.00, 72.66, 69.15, 59.63. IR (neat, cm^{-1}): 1513, 1197, 1113, 1107, 963, 832, 746.



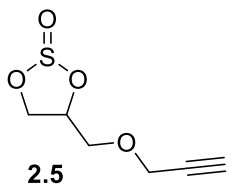
2.3

Cyclic Sulfite 2.3 (*dr* = 52:48): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.3**: 244 mg (1.77 mmol, 59%). *Major isomer*: ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 4.82 (m, 1H), 4.74 (m, 1H), 4.52 (dd, *J* = 8.6 and 7.4 Hz, 1H), 4.03 (dd, *J* = 3.8 and 13.2 Hz, 1H), 3.81 (dd, *J* = 4.2 and 14.7 Hz, 1H), 2.38 (br s, 1H, OH). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 83.78, 67.39, 60.78. *Minor isomer*: ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 5.08 (m, 1H), 4.76 (m, 1H), 4.37 (dd, *J* = 8.3 and 5.8 Hz, 1H), 3.87 (dd, *J* = 4.3 and 12.8 Hz, 1H), 3.76 (dd, *J* = 4.4 and 15.2 Hz, 1H), 2.38 (br s, 1H, OH). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 79.85, 68.22, 61.35. IR (neat, cm^{-1}): 3447, 1188, 1044, 943, 831, 677.



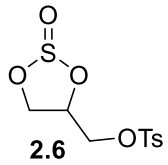
2.4

Cyclic Sulfite 2.4 (*dr* = 81:19): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.4**: 271 mg (2.22 mmol, 74%). *Major isomer*: ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 5.13 (m, 1H), 4.74 (dd, *J* = 8.4 and 6.0 Hz, 1H), 3.90 (dd, *J* = 8.2 and 7.0 Hz, 1H), 1.47 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 76.43, 72.82, 71.27, 17.63. *Minor isomer*: ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 4.64 (m, 1H), 4.53 (dd, *J* = 8.9 and 6.2 Hz, 1H), 4.32 (m, 1H), 1.64 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 80.22, 71.27, 17.63. IR (neat, cm^{-1}): 1198, 942, 824, 744, 668.



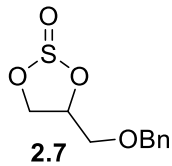
2.5

Cyclic Sulfite 2.5 (*dr* = 60:40): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.5**: 406 mg (2.31 mmol, 77%). *Major isomer*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (m, 1H), 4.76 (dd, *J* = 6.9 and 8.6 Hz, 1H), 4.37 (dd, *J* = 6.9 and 8.6 Hz, 1H), 4.27(m, 2H), 3.73 (m, 2H), 2.51 (t, *J* = 3.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.77, 78.23, 75.53, 68.53, 67.78, 58.48. *Minor isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (m, 1H), 4.60 (m, 1H), 4.59 (m, 1H), 4.24 (m, 2H), 3.95 (m, 2H), 2.51 (t, *J* = 3.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.73, 78.63, 75.47, 69.23, 68.81, 58.56. IR (neat, cm^{-1}): 3287, 1200, 1101, 961, 832, 749, 643. Elemental analysis: calcd. for $C_6H_8O_4S$: C 40.90, H 4.58, S 18.20; Found: C 40.75, H 4.72, S 17.43.



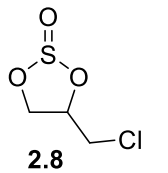
2.6

Cyclic Sulfite 2.6 (*dr* = 69:31) Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.6**: 594 mg (2.04 mmol, 68%). *Major isomer*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.39 (m, 2H), 5.08 (m, 1H), 4.73 (dd, J = 6.7 and 9.2 Hz, 1H), 4.35 (m, 1H), 4.15-4.07 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.68, 132.07, 130.14, 127.97, 76.88, 68.02, 67.12, 21.69. *Minor isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.39 (m, 2H), 4.58 (m, 1H), 4.52 (m, 1H), 4.32 (m, 1H), 4.15-4.07 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.65, 131.99, 129.98, 128.03, 78.70, 69.05, 68.56, 21.69. IR (neat, cm^{-1}): 1362, 1209, 1174, 947, 813, 729, 663, 552. HRMS (APCI+, MeOH): *m/z* calcd. 314.9965 $(M+H)^+$; found: 314.9966.



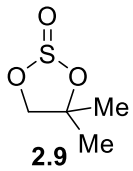
2.7

Cyclic Sulfite 2.7 (*dr* = 80:20): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.7**: 643 mg (2.82 mmol, 94%). *Major isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.30 (m, 5H), 5.10 (m, 1H), 4.72 (dd, J = 7.1 and 8.9 Hz, 1H), 4.35 (dd, J = 5.5 and 9.1 Hz, 1H), 3.69-3.54 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.19, 128.59, 128.11, 127.78, 78.51, 73.70, 68.84, 68.39. *Minor isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.30 (m, 5H), 4.64-4.54 (m, 3H), 3.94-3.77 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.28, 128.59, 128.11, 127.78, 81.07, 73.85, 70.21, 69.39. IR (neat, cm^{-1}): 2731, 1203, 1103, 964, 729, 696.



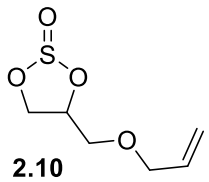
2.8

Cyclic Sulfite 2.8 (*dr* = 85:15): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.8**: 421 mg (2.70 mmol, 90%). *Major isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (m, 1H), 4.81 (dd, J = 8.4 and 7.1 Hz, 1H), 4.48 (dd, J = 8.4 and 4.2 Hz, 1H), 3.67 (dd, J = 5.2 and 11.6 Hz, 1H), 3.54 (dd, J = 7.71 and 11.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.85, 69.10, 42.34. *Minor isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76 (m, 1H), 4.68 (m, 1H), 4.66 (m, 1H), 4.48 (m, 1H), 3.96 (m, 1H), 3.80(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.76, 70.65, 43.5. IR (neat, cm^{-1}): 1200, 946, 836, 736, 683.



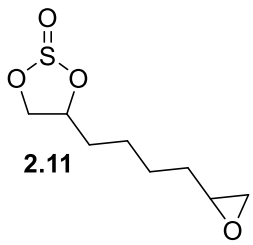
2.9

Cyclic Sulfite 2.9: Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.9**: 192 mg (1.41 mmol, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (d, J = 9.0 Hz, 1H), 4.17 (d, J = 9.4 Hz, 1H), 1.67 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 89.17, 75.46, 26.57, 26.40. IR (neat, cm^{-1}): 1203, 1143, 955, 864, 794, 673.



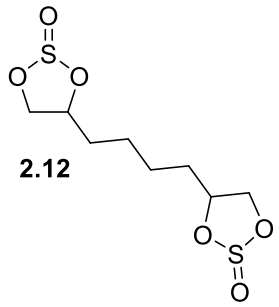
2.10

Cyclic Sulfite 2.10 (*dr* = 80:20): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.10**: 437 mg (2.46 mmol, 82%). *Major isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.27 (m, 2H), 5.07 (m, 1H), 4.72 (m, 1H), 4.32 (m, 1H), 4.05 (m, 2H), 3.59 (m, 1H), 3.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.76, 117.94, 78.49, 72.57, 68.81, 68.36. *Minor isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.27 (m, 2H), 4.65 (m, 1H), 4.57 (m, 1H), 4.55 (m, 1H), 4.08, 3.84 (m, 1H), 3.77 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.83, 117.94, 81.06, 72.67, 70.16, 69.35. IR (neat, cm^{-1}): 1202, 1101, 962, 832, 746, 682.

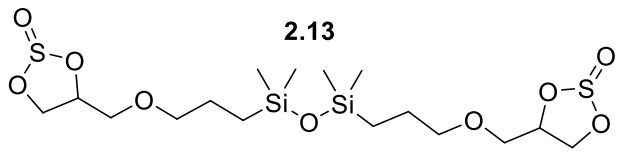


2.11

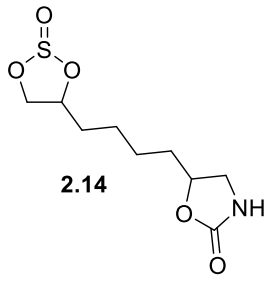
Cyclic Sulfite 2.11 (*dr* = 75:25): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.11**: 377 mg (1.83 mmol, 61%). *Major isomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (m, 1H), 4.73 (m, 1H), 3.95 (m, 1H), 2.92 (m, 1H), 2.77 (m, 1H), 2.49 (m, 1H), 2.03-1.37 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 80.00, 71.59, 52.02, 46.96, 32.18, 32.15, 32.11, 25.72. *Minor isomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (m, 2H), 4.35 (m, 1H), 2.92 (m, 1H), 2.77 (m, 1H), 2.49 (m, 1H), 2.03-1.37 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.86, 70.22, 52.02, 46.96, 33.34, 33.29, 32.21, 25.20. IR (neat, cm^{-1}): 2932, 1201, 948, 81, 676. HRMS (APCI+, MeOH): *m/z* calcd. $(M+Na)^{+}$: 229.0505, found: 229.0512.



Cyclic Sulfite 2.12 (*dr* = 78:22): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.12**: 720 mg (2.67 mmol, 89%). *Major isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (m, 2H), 4.73 (t, J = 6.3 and 8.2 Hz, 2H), 3.96 (t, J = 7.1 and 8.0 Hz, 2H), 1.90 (m, 4H), 1.57 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.88, 71.57, 32.03, 25.12. *Minor isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (m, 4H), 4.37 (m, 2H), 1.98 (m, 2H), 1.90 (m, 2H), 1.52 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.67, 70.19, 33.12, 25.54. IR (neat, cm^{-1}): 2945, 1194, 944, 830, 756, 672. HRMS (APCI+, MeOH): *m/z* calcd. $(M+Na)^+$: 293.0124, found: 293.0117.

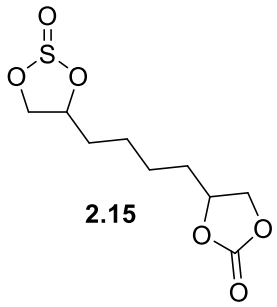


Cyclic Sulfite 2.13 (*dr* = 78:22): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.13**: 1395 mg (2.85 mmol, 95%). *Major isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (m, 1H), 4.72 (m, 1H), 4.55 (m, 1H), 3.74 (m, 1H), 3.61 (m, 1H), 3.53 (m, 1H), 3.46 (m, 4H), 1.59 (m, 4H), 0.51 (m, 4H), 0.08 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.52, 74.66, 69.14, 68.87, 23.36, 14.16, 0.29. *Minor isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (m, 1H), 4.57 (m, 1H), 4.55 (m, 1H), 3.84 (m, 1H), 3.74 (m, 1H), 3.46 (m, 4H), 1.59 (m, 4H), 0.51 (m, 4H), 0.08 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.11, 74.75, 71.07, 68.87, 23.36, 14.16, 0.29. IR (neat, cm^{-1}): 2954, 1253, 1206, 1116, 1046, 955, 835, 729.

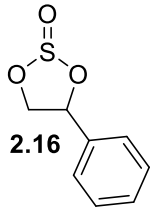


Cyclic Sulfite/Oxazolidinone 2.14 (*dr* = 80:20): Cyclic sulfite **2.11** (0.5mmol) was reacted with 5% of **1C** and 1.2 equiv of phenyl carbamate for 18h at 50ºC in ACN (1mL). Purified by column chromatography on silica gel (Hex: EtOAc, 1:1)*:* Yield of **2.14**: 129 mg (0.26 mmol, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (br s, 1H, NH), 4.99 (m, 1H), 4.72 (m, 1H), 4.65 (m, 1H), 4.51 (m, 2H), 4.35 (m, 1H), 3.95 (m, 1H), 3.70 (m, 1H), 3.25 (m, 1H), 1.95-1.35 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.51, 83.68, 79.89, 76.69, 71.56, 70.17, 45.85, 34.72, 34.62, 33.19, 32.10, 32.06, 29.69, 25.55, 25.13, 24.48, 24.43. IR (neat,

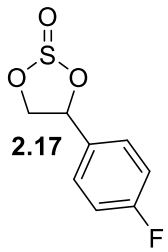
cm^{-1}): 3441, 2927, 1746, 1204, 938. HRMS (APCI+, MeOH): *m/z* calcd. 272.0587 $(M)^+$, found: 272.0561.



Cyclic Sulfite/Carbonate 2.15 (*dr* = 77:23): Cyclic sulfite **2.11** (0.5mmol) was reacted with 0.5% of **1C** and 1% of TBAI for 18h at 70ºC in MEK (1mL) and 10 bar of CO_2. Purified by column chromatography on silica gel (Hex: EtOAc, 1:1)*:* Yield of **2.15**: 202 mg (2.43 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (m, 1H), 4.75 (m, 2H) , 4.56 (m, 1H), 4.52 (m, 2H), 4.36 (m, 1H), 4.09 (m, 1H), 3.96 (m, 1H), 1.98 (m, 1H), 1.83 (m, 2H), 1.74 (m, 3H), 1.60 (m, 2H), 1.50 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.91, 83.62, 79.88, 76.72, 76.70, 71.59, 70.20, 69.31, 69.29, 33.73, 33.61, 33.02, 32.01, 31.96, 25.44, 25.05, 24.26. IR (neat, cm^{-1}): 2932, 1787, 1200, 1167, 1061, 949. HRMS (APCI+, MeOH): *m/z* calcd. 273.0403 $(M)^+$, found: 273.0404.

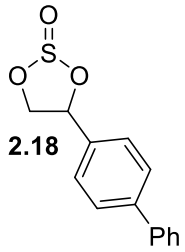


Cyclic Sulfite 2.16 (*dr* = 81:19): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.16**: 496 mg (2.70 mmol, 90%). *Major isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.34 (m, 5H), 5.98 (t, J = 6.9 Hz, 1H), 4.95 (dd, J = 6.5 and 8.4 Hz, 1H), 4.25 (dd, J = 7.4 and 8.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.53, 129.53, 129.07, 126.62, 80.91, 73.51. *Minor isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.34 (m, 5H), 5.43 (dd, J = 6.5 and 10.6 Hz, 1H), 4.77 (dd, J = 6.5 and 9.2 Hz, 1H), 4.50 (dd, J = 9.2 and 10.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.86, 129.44, 129.05, 127.50, 85.57, 71.44. IR (neat, cm^{-1}): 1457, 1202, 993, 960, 898, 769, 696, 669.

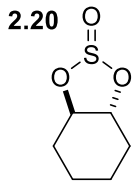


Cyclic Sulfite 2.17 (*dr* = 82:18): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.17**: 527 mg (2.61 mmol, 87%). *Major isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.14 (m, 2H), 5.94 (t, J = 7.1 Hz, 1H), 4.99 (dd, J = 6.5 and 8.5 Hz, 1H), 4.21 (dd, J = 7.3 and 8.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.32 (d, J = 254 Hz), 130.39 (d, J = 4 Hz), 128.61(d, J = 9.3 Hz), 116.16 (d, J = 22 Hz), 80.27, 73.39. *Minor isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.03 (m, 2H), 5.44 (dd, J = 6.8 and 10.6 Hz, 1H), 4.77 (dd, J = 6.6 and 9.2

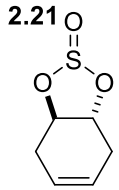
Hz, 1H), 4.49 (dd, *J* = 9.3 and 10.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.32 (d, *J* = 254 Hz), 129.54 (d, *J* = 8.5 Hz), 128.61(d, *J* = 9.3 Hz), 116.13 (d, *J* = 21.1 Hz), 84.82, 71.37. IR (neat, cm^{-1}): 1606, 1511, 1209, 1204, 1160, 998. 965, 903, 835, 762.



Cyclic Sulfite 2.18 (*dr* = 95:5): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.18**: 709 mg (2.73 mmol, 91%). *Major isomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.47 (m, 4H), 7.40 (m, 1H), 6.01 (t, *J* = 6.9 Hz, 1H), 5.01 (dd, J = 6.4 and 8.6 Hz, 1H), 4.28 (dd, *J* = 7.4 and 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.61, 140.14, 133.33, 128.91, 127.79, 127.14, 80.77, 73.44. IR (neat, cm^{-1}): 1621, 1488, 1202, 993, 795, 840, 760, 666. HRMS (APCI+, MeOH): *m/z* calcd. $(M+Na)^+$: 315.0664, found: 315.0660.

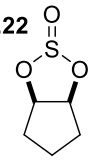


Cyclic Sulfite 2.20 (*cis/trans* = 10:90, *dr* (*cis*) = 93:7): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.19**: 224 mg (1.38 mmol, 46%). *Cis isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (m, 2H), 2.34, 1.99 (m, 2H), 1.85 (m, 2H). Note: other peaks cannot be observed, and traces of the other *cis* isomer can be observed at 4.53 ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.16, 27.61, 20.49. *Trans isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (m, 1H), 3.70 (m, 1H), 2.34 (m, 2H), 1.94 (m, 2H), 1.72 (m, 1H), 1.60 (m, 1H), 1.41 (m, 1H), 1.28 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 86.44, 80.28, 29.25, 28.28, 23.61, 23.34. IR (neat, cm^{-1}): 2958, 1521, 1202, 948, 677. HRMS (APCI+, MeOH): *m/z* calcd. $(M)^+$: 185.0233, found: 185.0236.

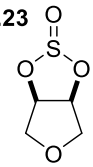


Cyclic Sulfite 2.21 (*cis/trans* = 29:71, *dr* (*cis*) = 93:7): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.20**: 297 mg (1.86 mmol, 62%). *Cis isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (m, 2H), 5.71 (m, 2H), 2.62-2.35 (m, 4H). Traces of other isomer can be observed at 4.74 ppm. ^{13}C NMR (126 MHz, CDCl3) δ 124.50, 76.95, 27.07. *Trans isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 2H), 4.56 (m, 1H), 4.01 (m, 1H), 2.56 (m, 1H), 2.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 124.42, 124.19,

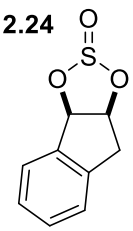
83.21, 77.79, 31.01, 29.97. IR (neat, cm^{-1}): 1641, 1498, 1205, 1011, 970, 885, 742, 649. HRMS (APCI+, MeOH): *m/z* calcd. $(M)^+$: 161.0261, found: 161.0267.

2.22 

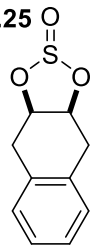
Cyclic Sulfite 2.22 (*cis/trans* = 99:1, *dr* (*cis*) = 84:16): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.21**: 404 mg (2.73 mmol, 91%). *Major isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (m, 2H), 2.06 (m, 2H), 1.82-1.66 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 85.44, 32.54, 21.92. *Minor isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (m, 2H), 2.24 (m, 2H), 2.06, 1.82-1.66 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 89.68, 33.34, 21.92. IR (neat, cm^{-1}): 2971, 1483, 1195, 943, 831, 698, 654. HRMS (APCI+, MeOH): *m/z* calcd. $(M+Na)^+$:171.0086, found: 171.0078.

2.23 

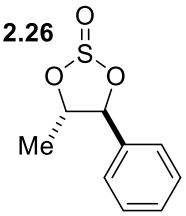
Cyclic Sulfite 2.23 (*cis/trans* = 99:1, *dr* (*cis*) = 95:5): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.22**: 383 mg (2.55 mmol, 85%). *Major isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53 (m, 2H), 4.18 (d, J = 11.2 Hz, 2H), 3.70 (d, J = 13.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.53, 72.62. *Minor isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (m, 2H), 4.33 (d, J = 11.2 Hz, 2H), 3.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 87.78, 72.62. IR (neat, cm^{-1}): 2875, 1459, 1185, 1078, 998, 912, 840, 686.

2.24 

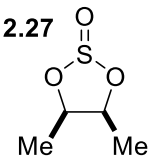
Cyclic Sulfite 2.24 (*cis/trans* = 99:1, *dr* (*cis*) = 83:17): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.24**: 447 mg (2.28 mmol, 76%). *Major isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 1H), 7.45-7.25 (m, 3H), 6.30 (d, J = 5.8 Hz, 1H), 5.76 (td, J = 1.7 and 5.9 Hz, 1H), 3.46 (m, 1H), 3.36 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.69, 136.81, 130.60, 128.04, 126.16, 125.39, 87.80, 83.16, 37.03. *Minor isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 1H), 7.45-7.25 (m, 3H), 6.11 (d, J = 6.5 Hz, 1H), 5.53 (d, J = 2.2 and 6.6 Hz, 1H), 3.61 (m, 1H), 3.54 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.11, 138.51, 130.61, 127.92, 125.84, 125.63, 90.03, 86.72, 39.50. IR (neat, cm^{-1}): 1701, 1587, 1569, 1499, 1198, 996, 940, 836, 754.

2.25 

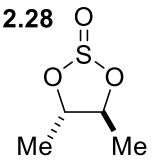
Cyclic Sulfite 2.25 (*cis/trans* = 90:10, *dr* (*cis*) > 99:1): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.25**: 447 mg (2.13 mmol, 71%). *Cis isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.23 (m, 2H), 5.43 (m, 2H), 3.07 (m, 2H), 3.03 (m, 2H). Traces of the other *cis* isomer can be observed at 4.68 ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.91, 128.41, 127.58, 78.08, 32.71. *Trans isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.04 (m, 4H), 4.34 (m, 1H), 4.13 (m, 1H), 3.55 (m, 1H), 3.39 (m, 1H), 3.12 (m, 1H), 2.91 (m, 1H). IR (neat, cm^{-1}): 3418, 2979, 1608, 1172, 969, 821, 716.

2.26 

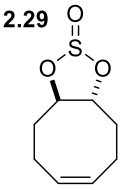
Cyclic Sulfite 2.26 (*cis/trans* = 1:99, *dr* (*trans*) = 60:40): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.26**: 498 mg (2.52 mmol, 84%). *Major isomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.39 (m, 5H), 5.48 (d, J = 9.4 Hz, 1H), 4.43 (m, 1H), 1.59 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.02, 129.74, 129.11, 127.14, 85.87, 85.49, 17.51 *Minor isomer:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.39 (m, 5H), 4.92-4.84 (m, 2H), 1.51 (d, J = 5.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.79, 129.42, 129.06, 127.53, 91.00, 80.94, 15.08. IR (neat, cm^{-1}): 1544, 1202, 1048, 955, 915, 855, 759, 685.

2.27 

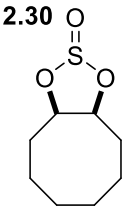
Cyclic Sulfite 2.27 (*cis/trans* = 66:33, *dr* (*cis*) = 88:12): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.27**: 273 mg (2.00 mmol, 67%). *Major cis isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (m, 2H), 1.32 (d, J = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.45, 14.33. *Minor cis isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (m, 2H), 1.55 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.12, 16.12. *Trans isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (m, 1H), 4.11 (m, 2H), 1.56 (d, J = 6.2 Hz, 3H), 1.47 (d, J = 6.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 85.25, 80.23, 17.87, 15.87. IR (neat, cm^{-1}): 1451, 1385, 1201, 1059, 1016, 899, 799, 690.

2.28 

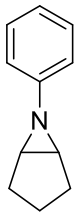
Cyclic Sulfite 2.28 (*cis/trans* = 3:97): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.28**: 240 mg (1.77 mmol, 59%). *Trans isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (m, 1H), 4.11 (m, 1H), 1.58 (d, J = 6.5 Hz, 3H), 1.47 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 85.24, 80.23, 17.88, 15.87. IR (neat, cm^{-1}): 2942, 1463, 1196, 941, 793, 700.

2.29 

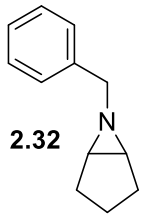
Cyclic Sulfite 2.29 (*cis/trans* = 17:83, *dr* (*cis*) >99:1): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.29**: 360 mg (1.92 mmol, 64%). *Cis isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (m, 2H), 5.06 (m, 2H), 2.60 (m, 4H), 2.45 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.57, 82.22, 27.19, 23.47. *Minor isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (m, 2H), 4.93 (m, 1H), 4.31 (m, 1H), 2.32 (m, 4H), 1.85 (m, 2H), 1.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.48, 129.09, 87.49, 82.96, 32.43, 29.37, 21.80, 21.71. IR (neat, cm^{-1}): 2941, 1471, 1197, 943, 794, 702. HRMS (APCI+, MeOH): *m/z* calcd. $(M+Na)^+$: 211.0383, found: 211.0391.

2.30 

Cyclic Sulfite 2.30 (*cis/trans* = 99:1, *dr* (*cis*) = 90:10): Following the procedure of cyclic sulfite synthesis. Purified by column chromatography on silica gel (pure DCM). Yield of **2.30**: 120 mg (0.63 mmol, 21%). *Cis isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (m, 2H), 2.02-1.86 (m, 5H), 1.79-1.70 (m, 3H), 1.56-1.93 (m, 5H), 1.42-1.30 (m, 3H). Traces of another isomer can be observed at 4.61 ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.72, 27.21, 26.37, 25.04. *Trans isomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (m, 1H), 4.30 (m, 1H), 2.43 (m, 1H), 2.36-2.23 (m, 3H), 2.19 (m, 2H), 1.82 (m, 4H), 1.51-1.44 (m, 4H). IR (neat, cm^{-1}): 2921, 2857, 1468, 1205, 935, 857, 779, 698.

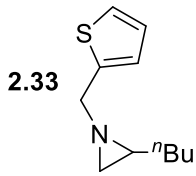
2.31 

Aziridine 2.31:[56] Following the procedure of aziridine synthesis. Purified by column chromatography on silica gel (Hex:EtOAc, 1:1). Yield of **2.31**: 86 mg (0.54 mmol, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 2H), 6.99 (m, 2H), 6.93 (m, 1H), 2.78 (s, 2H), 2.13 (m, 2H), 1.66 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.96, 128.83, 121.65, 120.87, 45.44, 27.54, 20.93.



2.32

Aziridine 2.32:[56] Following the procedure of aziridine synthesis. Purified by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **2.32**: 128 mg (0.74 mmol, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 3H), 7.26 (m, 1H), 3.46 (s, 2H), 2.10 (s, 2H), 1.98 (m, 2H), 1.61-1.45(m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.89, 128.18, 127.33, 126.58, 61.53, 45.26, 27.



2.33

Aziridine 2.33: Following the procedure of aziridine synthesis. Purified by column chromatography on silica gel (Hex: EtOAc, 1:1). Yield of **2.33**: 152 mg (0.78 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, J = 1.3 and 4.9 Hz, 1H), 6.97 (dd, J = 3.6 and 5.3 Hz, 1H), 6.95 (m, 1H), 3.70 (d, J = 13.6 Hz, 1H), 3.52 (d, J = 14.2 Hz, 1H), 1.65 (d, J = 3.8 Hz, 1H), 1.53-1.26 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.18, 126.49, 124.99, 124.41, 59.34, 40.08, 34.08, 32.60, 29.53, 22.45, 14.05. HRMS (APCI+, MeOH): *m/z* calcd. 196.1154 $(M)^+$, found: 196.1154

2.4.3 Crystallographic Data

Crystallografic data was obtained following the methodology described in chapter I.

*Crystal data for cyclic sulfite **2.18**:* $C_{14}H_{12}SO_3$, M_r = 260.30, monoclinic, P2(1), a = 5.7150(4) Å, b = 39.165 (4) Å, c = 5.8138 (4) Å, α = 90º, β = 114.065(9)º, γ = 90º, V = 1188.2(19) Å^3, Z = 4, ρ = 1.455mg·M^{-3}, μ = 0.269 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 544, crystal size = 0.20 × 0.08 × 0.01 mm, θ(min) = 3.12º, θ(max) = 26.69º, 12372 reflections collected, 4368 reflections unique (R_{int} = 0.0682), GoF = 1.039, R_1 = 0.0734 and wR_2 = 0.1811 [$I > 2\sigma(I)$], R_1 = 0.0876 and wR_2 = 0.1892 (all indices), min/max residual density = -0.605/1.116 [e·Å^{-3}]. Completeness to θ(26.69º) = 91.0%.

*Crystal data for cyclic sulfite **2.23**:* $C_4H_6SO_4$, M_r = 150.15, monoclinic, P21/c, a = 4.3700(3) Å, b = 11.7211(8) Å, c = 11.1311(7) Å, α = 90º, β = 100.0185(19)º, γ = 90º, V = 561.45(6) Å^3, Z = 4, ρ = 1.776 mg·M^{-3}, μ = 0.507 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 312, crystal size = 0.30 × 0.15 × 0.04 mm, θ(min) = 2.54º, θ(max) = 32.51º, 6736 reflections collected, 1865 reflections unique (R_{int} = 0.0365), GoF=1.046, R_1 = 0.0316 and wR_2 = 0.0830

[$I > 2\sigma(I)$], R_1 = 0.0393 and wR_2 = 0.0887 (all indices), min/max residual density = -0.312/0.544 [e·Å^{-3}]. Completeness to θ(32.51º) = 91.5%.

Crystal data for cyclic sulfite ***2.25****:* $C_{10}H_{10}SO_3$, M_r = 210.24, monoclinic, P21/c, a = 7.4377(13) Å, b = 11.56071(19) Å, c = 21.1227(4) Å, α = 90º, β = 90.0436(19)º, γ = 90º, V = 1816.24(5) Å^3, Z = 8, ρ = 1.538 mg·M^{-3}, μ = 0.331 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 880, crystal size = 0.20 × 0.10 × 0.10 mm, θ(min) = 2.01º, θ(max)=36.94º, 39202 reflections collected, 8857 reflections unique (R_{int}=0.0294), GoF = 1.081, R_1 = 0.0312 and wR_2 = 0.0900 [$I > 2\sigma(I)$], R_1 = 0.0358 and wR_2 = 0.0942 (all indices), min/max residual density = -0.387/0.694 [e·Å^{-3}]. Completeness to θ(32.51º) = 91.5%.

2.5 References

(1) Muller, H. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH, Weinheim, **2000**.
(2) Wang, X.; Jin, H.; Tang, C.; Du, J. *Eur. J. Pharmacol.* **2011**, *670*, 1–6.
(3) Schmidt-Winkel, P.; Wudl, F. *Macromolecules* **1998**, *31*, 2911–2917.
(4) Lobez, J. M.; Swager, T. M. *Macromolecules* **2010**, *43*, 10422–10426.
(5) Tanaka, N.; Sato, E.; Matsumoto, A. *Macromolecules* **2011**, *44*, 9125–9137.
(6) Titov, V. E.; Mishura, A. M.; Koshechko, V. G.; Pokhodenko, V. D.; Nauky, P. *Theor. Exp. Chem.* **2011**, *46*, 399–408.
(7) Andrieux, C.; Gelis, L.; Saveant, J. *J. Am. Chem. Soc.* **1990**, *112*, 786–791.
(8) Koshechko, V. G.; Kiprianova, L. A.; Kalinina, L. I. *J. Fluor. Chem.* **2009**, *130*, 317–320.
(9) Lugiņina, J. *Synlett* **2014**, *25*, 2962–2963.
(10) Deeming, A. S.; Emmett, E. J.; Richards-Taylor, C. S.; Willis, M. C. *Synthesis* **2014**, *46*, 2701–2710.
(11) Lloyd, D. R.; Roberts, P. J. *Mol. Phys.* **1973**, *26*, 225–230.
(12) Kleemann, A.; Engel, J. *Pharmaceutical Substances: Synthesis, Patents, and Application*, 4th ed.; Thieme: Germany, **2001**.
(13) Kramer, W.; Schirmer, U.; Jeschke, P.; *Modern Crop Protection Compounds*, 3rd ed.; Wiley-VCH, Weinheim, **2011**.
(14) Emmett, E. J.; Willis, M. C. *Asian J. Org. Chem.* **2015**, *4*, 602–611.
(15) Azuma, N.; Takata, T.; Sanda, F.; Endo, T. *Macromolecules* **1995**, *28*, 7331–7334.
(16) Azuma, N.; Sanda, F.; Takata, T.; Endo, T. *J. Polym. Sci.; A Polym. Chem.* **1997**, *35*, 1007–1012.

(17) Kricheldorf, H. R.; Petermann, O. *Macromolecules* **2001**, *34*, 8841–8846.

(18) Wrodnigg, G. H.; Besenhard, J. O.; Winter, M. *J. Power Sources* **2001**, *98*, 592–594.

(19) Yu, B. T.; Qiu, W. H.; Li, F. S.; Cheng, L. *J. Power Sources* **2006**, *158*, 1373–1378.

(20) Jeong, L. S.; Marquez, V. E. *Tetrahedron Lett.* **1996**, *37*, 2353–2356.

(21) Megia-Fernandez, A.; Morales-Sanfrutos, J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Curr. Org. Chem.* **2011**, *15*, 401–432.

(22) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051–7091.

(23) Häcker, C.; Plietker, B. *J. Org. Chem.* **2015**, *80*, 8055–8064.

(24) Zhang, H.; Li, X.; Shi, Q.; Li, Y.; Xia, G.; Chen, L.; Yang, Z.; Jiang, Z. X. *Angew. Chem. Int. Ed.* **2015**, *54*, 3763–3767.

(25) Ramírez-Contreras, R.; Morandi, B. *Org. Lett.* **2016**, *18*, 3718–3721.

(26) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc* **1988**, *110*, 7538–7539.

(27) Hardacre, C.; Messina, I.; Migaud, M. E.; Ness, K. A.; Norman, S. E. *Tetrahedron* **2009**, *65*, 6341–6347.

(28) García-Granados, A.; Parra, A.; Rivas, F.; Segovia, A. J. *J. Org. Chem.* **2007**, *72*, 643–646.

(29) Yang, Z.-Z.; He, L.-N.; Song, Q.-W.; Chen, K.-H.; Liu, A.-H.; Liu, X.-M. *Phys. Chem. Chem. Phys.* **2012**, *14*, 15832.

(30) Takenaka, Y.; Kiyosu, T.; Mori, G.; Choi, J. C.; Fukaya, N.; Sakakura, T.; Yasuda, H. *ChemSusChem* **2012**, *5*, 194–199.

(31) B.B. Lohray, Y. G. and K. B. S. *Tetrahedron Lett.* **1989**, *30*, 2623–2626.

(32) Buckley, B. R.; Patel, A. P.; Wijayantha, K. G. U. *J. Org. Chem.* **2013**, *78*, 1289–1292.

(33) Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. *Org. Lett.* **2011**, *13*, 4876–4878.

(34) Yang, Z.-Z.; He, L.-N.; Song, Q.-W.; Chen, K.-H.; Liu, A.-H.; Liu, X.-M. *Phys. Chem. Chem. Phys.* **2012**, *14*, 15832.

(35) Whiteoak, C. J.; Gjoka, B.; Martin, E.; Belmonte, M. M.; Escudero-Adán, E. C.; Zonta, C.; Licini, G.; Kleij, A. W. *Inorg. Chem.* **2012**, *51*, 10639–10649.

(36) Hwang, J.; Govindaswamy, K.; Koch, S. A. *Chem. Commun.* **1998**, 1667–1668.

(37) Su, W.; Kim, Y.; Ellern, A.; Guzei, I. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2006**, *128*, 13727–13735.

(38) Maraš, N.; Polanc, S.; Kočevar, M. *Org. Biomol. Chem.* **2012**, *10*, 1300.

(39) Sidney D. Ross, John J. Bruno, R. C. P. *J. Am. Chem. Soc.* **1963**, *85*, 3999–4003.

(40) Laserna, V.; Guo, W.; Kleij, A. W. *Adv. Synth. Catal.* **2015**, *357*, 2849–2854.

(41) Whiteoak, C. J.; Kielland, N.; Laserna, V.; Escudero-Adán, E. C.; Martin, E.; Kleij, A. W. *J. Am. Chem. Soc.* **2013**, *135*, 1228–1231.

(42) Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 582–585.

(43) Lamb, J. R.; Jung, Y.; Coates, G. W. *Org. Chem. Front.* **2015**, *2*, 346–349.

(44) Lamb, J. R.; Mulzer, M.; Lapointe, A. M.; Coates, G. W. *J. Am. Chem. Soc.* **2015**, *137*, 15049–15054.

(45) Laserna, V.; Fiorani, G.; Whiteoak, C. J.; Martin, E.; Escudero-Adan, E.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 10416–10419.

(46) Zhi, Y.; Wu, J.; Ma, A.; Tian, N.; Shan, S.; Jia, Q.; Su, H. *RSC Adv.* **2016**, *6*, 32881–32886.

(47) Darensbourg, D. J.; Chung, W. C. *Macromolecules* **2014**, *47*, 4943–4948.

(48) Darensbourg, D. J.; Yeung, A. D. *Polym. Chem.* **2015**, *6*, 1103–1117.

(49) Darensbourg, D. J.; Bottarelli, P.; Andreatta, J. R. *Macromolecules* **2007**, *40*, 7727–7729.

(50) Lohray, B. B. *Synthesis.* **1992**, 1035–1052.

(51) Berridge, M. S.; Franceschini, M. P.; Rosenfeld, E.; Tewsont, T. J. *J. Org. Chem.* **1990**, *55*, 1211–1217.

(52) Denmark, S. E. *J. Org. Chem.* **1981**, *46*, 3144–3147.

(53) McCoull, W.; Davis, F. A. *Synthesis* **2000**, *20*, 1347–1365.

(54) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258.

(55) Njardarson, J. T. *Synlett* **2013**, *24*, 787–803.

(56) Sternativo, S.; Marini, F.; Verme, F. Del; Calandriello, A.; Testaferri, L.; Tiecco, M. *Tetrahedron* **2010**, *66*, 6851–6857.

UNIVERSITAT ROVIRA I VIRGILI
SMALL MOLECULE ACTIVATION FOR THE FORMATION OF HETEROCYCLIC COMPOUNDS
Victor Laserna Ayora

Chapter III

Selective Access to Cyclic *cis*-Diol Scaffolds through Cyclic Carbonate Intermediates

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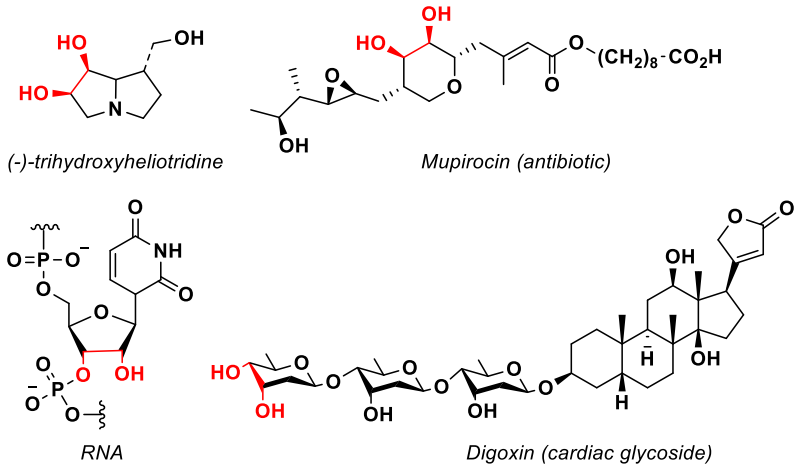
3.1 Introduction

3.1.1 *Cis*-Diol Synthesis

Cyclic *cis*-diol scaffolds are prevalent motifs in biologically relevant molecules such as (–)-trihydroxyheliotridine and Mupirocin (**Scheme 3.1**) and are thus interesting synthetic targets. Over the last decades, numerous synthetic approaches for the diastereoselective formation of *cis*-diols have been developed.[1,2] Most of these methods involve the dihydroxylation of alkenes, such as the Sharpless dihydroxylation[3] or the Woodward reaction[4]. Discovered in the 1930s, OsO_4 has been described as "the most reliable reagent available for the *cis* hydroxylation of alkenes to give the corresponding *cis*-diols"[5] and therefore it is not surprising that most dihydroxylation methods involve the use of this metal reagent or some derivative. In 1992, Sharpless[3] reported a catalytic system based on bis-cinchona alkaloid ligands, potassium osmate and stoichiometric amount of oxidant (e.g., *N*-methylmorpholine) which represented a big step forward in dihydroxylation methodologies. This protocol received a lot of attention due to the broad substrate scope and the high asymmetric induction that can be attained.

Scheme 3.1: Some examples of natural compounds with cyclic *cis*-diol substructures.



These methods that involve osmium reagents are powerful and reliable, but have as drawbacks the high price and toxicity of OsO_4 preventing its use in industry. OsO_4 is highly volatile, it easily sublimes and thus may cause acute poisoning to skin and eyes. To make the process more sustainable, several different research strategies have been developed towards the separation of the OsO_4 from the product by supporting it onto polymers,[6] propyltrimethoxysilane,[7] and ionic liquids[8]. All these approaches have in common that they require the presence of a terminal oxidant, limited to NMO (*N*-methylmorpholine)[6,8] or $K_3[Fe(CN)_6]$,[9] which have to be added in a large excess. To improve this latter issue, osmium based tris-(2-pyridylmethyl) amine complexes were developed as efficient catalysts[10,11] with H_2O_2 as oxidant in aqueous media. This method presented another step forward in the development of less toxic, environmentally more benign dihydroxylation methods, although the use of osmium was still a requisite.

Osmium-free dihydroxylation catalysts exist,[12] although most of them display substrate limitations and low conversions/product selectivity. Among these alternative catalysts ruthenium tetroxide, potassium permanganate and iron complexes have been the most widely studied. The potential of ruthenium oxide to mediate the dihydroxylation reaction was first reported by Sharpless albeit with low selectivities;[13] the high oxidative potential of Ru makes it difficult to terminate the reaction at the diol stage and typically the major products of these reactions are the hydroxy ketones or products arising from oxidative cleavage. The presence of bulky ligands in the ruthenium complex allows to modulate the oxidative potential of RuO_4,[14] and these complexes are therefore interesting alternatives for those substrates that easily give rise to over-oxidation or cleavage reactions. Catalytic versions of these reactions were published by Shing et al. who used $RuCl_3$ and $NaIO_4$ as a reoxidant.[15,16] This latter reaction is called the "flash" dihydroxylation due to its short reaction times and was particularly successful even for substrates that are difficult to oxidize with OsO_4. Some efforts to develop supported heterogeneous Ru-catalysts for dihydroxylation have focused on the use of Ru-nanoparticles.[17] One of the advantages of using Ru catalysis is that it offers potential for tandem metathesis/dihydroxylation cascades where first a substituted alkene is formed *in situ* by ring-closing or cross-metathesis, and then the alkene is *cis*-dihydroxylated utilizing the same ruthenium catalyst.[18,19] The drawback of the "Ru" approach is that there are only a few RuO_4-mediated asymmetric dihydroxylation reactions reported in the literature, and all are based on a chiral auxiliary approach.[20]

The permanganate ion (MnO_4^-) is a common oxidant in organic chemistry and has been used routinely in dihydroxylation reactions[21,22] since its discovery by Kekule in 1881. Many examples describe the application of permanganate, and the existing systems can be divided into three categories: (1) homogeneous oxidation protocols using potassium permanganate or tetralkylammonium permanganate,[23] (2) heterogeneous methods that involve a phase-transfer catalyst[24,25] and (3) catalytic homogeneous catalysts based on manganese complexes in the presence of a reoxidant.[26] As for Ru, the literature only reports a handful of Mn-catalysts for asymmetric dihydroxylation.[27,28]

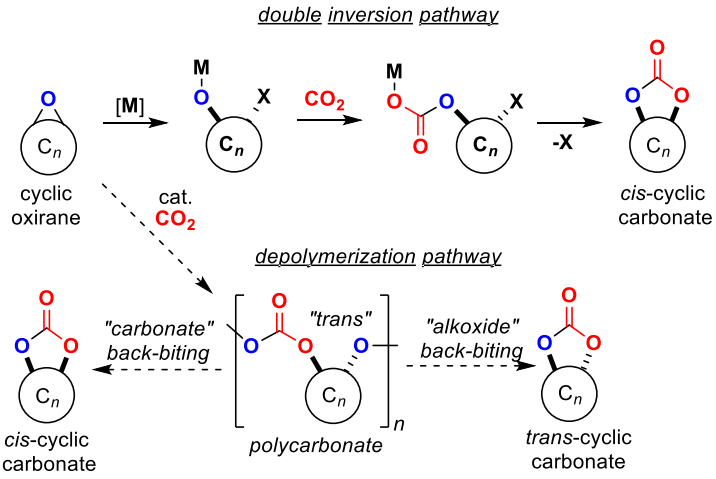
The interest in using iron complexes for dihydroxylation stems from nature. In nature, an important class of non-heme iron enzymes, the Rieske dioxygenases,[29] allow for the asymmetric *cis*-dihydroxylation of double bonds present in arenes. However, these dioxygenases are effective only for a small range of substrates, which reduces their synthetic utility. Similar biomimetic complexes, which are known to be active in alkene oxidation, were modulated in order to achieve a higher ratio of diol/epoxide,[30] although yields and turnovers were typically low. Recently developed catalysts have been able to dihydroxylate aromatic double bonds using H_2O_2 as oxidant, which is a promising result in this area of oxidation catalysis.[31–33] Further alternative dihydroxylation methods include the use of other metal-mediated processes based on molybdenum,[34] palladium,[35] cerium[36] or technetium[37] and even metal-free driven processes based on selenium[38] or oxone have been reported.[39]

3.1.2 Cyclic Carbonate Precursors

Carbon dioxide represents an interesting carbon feedstock for organic synthesis having a number of attractive features being renewable, cheap and readily available.[40] Recent progress in the area of CO_2 catalysis has witnessed a spectacular increase in the application of this C_1 synthon providing access to important and functional chemical intermediates, and precursors for (bio) renewable plastics. One of the areas of high activity is the preparation of cyclic organic carbonates from oxiranes/oxetanes precursors giving rise to five- and six ring-membered structures. As described in the introduction, this area has been developed to a sophisticated level, although important challenges remain to be solved. Many strategies and active catalyst systems have been developed for the transformation of mono-substituted epoxides and CO_2 to their corresponding cyclic carbonates,[41] and systems that work under mild conditions (rt and CO_2 pressures as low as 1 bar),[42,43] or have high TONs (>100.000)

and initial TOFs (>10.000 h^{-1}) have been reported.[44–46] However, efficient conversion of epoxides with more complicated substitution patterns (i.e., internal epoxides, bicyclic epoxides) remains a challenge and generally the required reaction conditions are much more demanding.[47] Thus, the preparation of organic carbonates from internal epoxides represents an ambitious target within the development of CO_2-based protocols. Such organic carbonates require the use of synthetically accessible epoxides that can be prepared from (renewable) olefins (such as unsaturated fatty acids and terpenes) using standard epoxidation methodologies. These sterically more hindered substrates are generally less reactive and there are no general methodologies available for their conversion into highly substituted cyclic carbonates. Apart from these renewable substrates, bicyclic epoxides such as cyclohexene oxide have a high tendency towards copolymerization in the presence of CO_2, which limits their selective conversion towards the *cyclic* carbonate derivative. In these cases, polycarbonates are the kinetically favored product, whilst cyclic carbonates are the thermodynamic ones.

Figure 3.2: Alternative pathways in cyclic carbonate formation.



This copolymerization tendency is particularly important to control the stereoselective outcome of the reaction as formation of the cyclic carbonate occurring through a double inversion pathway (**Figure 3.2**, top) leads to retention of the relative configuration at both carbon centers in the carbonate product, whereas *poly*-carbonate formation followed by an alkoxide-driven depolymerization pathway results in opposite stereochemistry (**Figure 3.2**, bottom). An alternative depolymerization pathway giving formal retention of the original

stereochemistry involves the backbiting of a carbonate intermediate, and this manifold is more relevant in cases where high pressures of CO_2 are involved. As the same *cis*-configured carbonate product can be generated through two distinct pathways, it is difficult to determine which pathway is prevalent; the high kinetic barriers reported for these depolymerization processes, however, suggest that the *cis*-configured carbonates are more likely formed through a double inversion pathway.

Studies to determine and compare the kinetic barriers in copolymerization/depolymerization processes versus double inversion pathways can give valuable information about the intermediates. Darensbourg et al. studied in depth the polymerization/depolymerization barriers of various terminal and internal epoxides.[48] This work demonstrated that for many acyclic epoxide substrates the polymeric intermediates are kinetically favored over the double inversion pathway, though fast subsequent depolymerization does not enable to isolate or observe easily the polymer intermediate. Some cyclic substrates and especially cyclohexene oxides have high barriers for depolymerization and therefore polycarbonate synthesis can be conveniently carried out. Whereas for mono-substituted epoxides the available manifolds towards cyclic carbonate formation result in the same product, for disubstituted epoxides it is important to exert control over the formation pathway in order to achieve diastereoselective synthesis of a single product.

3.1.3 Project Aim and Strategy

We set out to develop an approach towards functional cyclic *cis*-diol synthons using a versatile catalytic strategy that allows for an efficient and selective conversion of various (hetero)cyclic oxirane substrates, suppressing undesired polycarbonate formation and thus controlling the stereo-selectivity towards a *cis*-configured cyclic carbonate; the latter directly serves as a convenient precursor for *cis*-diols.

In order to achieve this objective, we chose to use amino triphenolate catalysts that have exhibited high activity and versatility in the formation of both cyclic[44,49,50] and polycarbonate[51] structures. Moreover, these systems also proved to be highly efficient for the conversion of acyclic internal epoxides with ample functionality. We envisaged that the catalytic formation of organic carbonates from internal oxiranes and CO_2 using earth-abundant and cheap metal catalysts followed by deprotection under basic conditions could

offer a useful and alternative sustainable approach toward diols. *Trans* 1,2-diols can be easily obtained by hydrolyzing an epoxide precursor under aqueous or basic conditions,[52] but methodologies to obtain the *cis*-diols (section 3.1.1) often require the use of osmium or ruthenium catalysis and thus greener and cheaper methodologies are of significant synthetic interest.

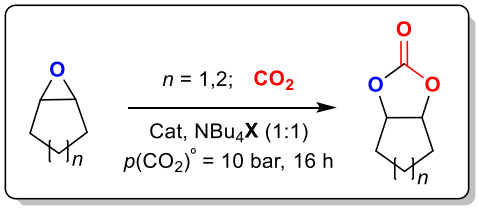
The synthesis of *cis*-diols through the intermediacy of cyclic carbonates implicates a dual role for CO_2 acting as a temporary protecting group to stir the stereo-selectivity of the process, and it represents also an oxygen source. Though some reports exist on *cis*-diol formation from organic carbonates,[53–56] the substrate scope to date remains highly limited and has been primarily based on terminal epoxides, which are relatively facile to convert. Further to this, our novel CO_2-based methodology would allow for a broader substrate scope and more ample functional group diversity, providing a wider range of accessible and functional *cis*-diol scaffolds.

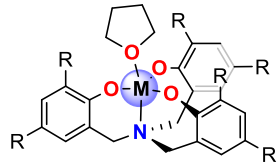
3.2 Results and Discussion

3.2.1 Optimization towards *Cis*-configured Cyclic Carbonates

Our first efforts focused on the chemo-selective conversion of some benchmark substrates including cyclopentene oxide (CPO) and cyclohexene oxide (CHO), see **Table 3.1**, that have previously been shown to easily form polycarbonates.[57–59] This screening stage afforded useful information about the required reaction conditions and type of (co)catalysts and their loadings to achieve high and selective conversions towards the *cyclic* carbonate.

Table 3.1: Product distribution from the coupling between cyclopentene (n = 1) and cyclohexene oxide (n = 2) and CO_2 using **1C** or **1D** as catalyst and NBu_4**X** as nucleophilic additive.[a] **CC** = cyclic carbonate, **PE** = polyether and **PC** = polycarbonate.





Entry	*n*	Co-cat. (X)	T (ºC)	CC (%)[b]	PE (%)[b]	PC (%)[b]
1	1	**I**	50	46	0	0
2	1	**Br**	50	54	0	0
3	1	**Cl**	50	21	0	0
4	1	**I**	70	76	0	0
5	1	**Br**	70	60	7	0
6	1	**Cl**	70	71	2	0
7	1	**I**	90	91	0	0
8	1	**Br**	90	>99	0	0
9	1	**Cl**	90	>99	0	0
10	2	**I**	50	0	0	61
11	2	**Br**	50	0	0	26
12	2	**Cl**	50	0	0	8
13	2	**I**	70	0	2	73
14	2	**Br**	70	0	22	76
15	2[c]	**Br**	70	46	5	0
16	2[d]	**Br**	70	56	3	0
17	2[e]	**Br**	70	68	6	0
18	2	**Cl**	70	0	45	55
19	2	**I**	90	0	3	78
20	2	**Br**	90	0	3	94
21	2	**Cl**	90	0	40	59

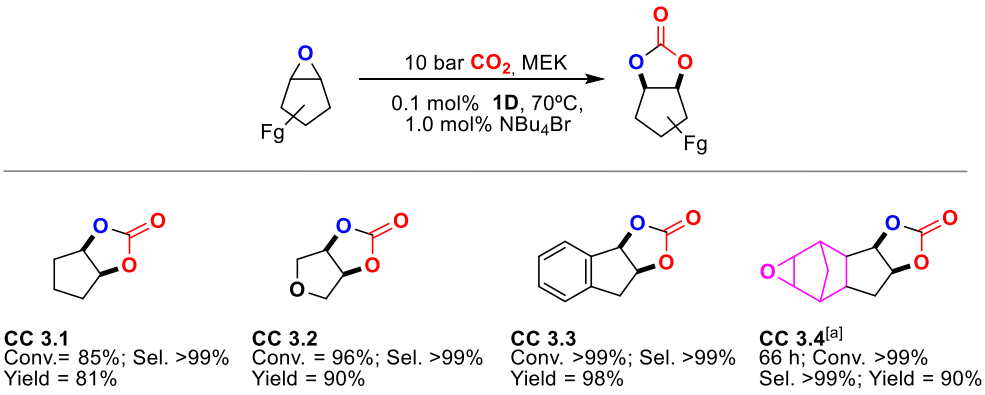
[a] Epoxide (1.00 g, 10 mmol), Fe complex **1D** (0.1 mol%), TBA**X** (co-cat: 0.1 mol%), 10 bar initial CO_2 pressure, 30 mL autoclave, 16 h. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Using 5 equiv of co-catalyst and MEK (2-butanone, 1.0 mL) as co-solvent. [d] Using 5 equiv of co-catalyst, MEK (1.0 mL) as co-solvent and using Al-catalyst **1C**. [e] Using 10 equiv of co-catalyst and MEK (1.0 mL) as co-solvent.

Two important requisites for selective conversion to the *cyclic* organic carbonate product were revealed upon variation of the reaction medium and the relative ratio between complex **1C** or **1D** and the nucleophile (NBu_4Br). For CPO (*entries 1-9*), the formation of the cyclic carbonate using various reaction conditions was selective and high yields of the cyclic carbonate product were achieved at 90 ºC using NBu_4**X** as additives (*entries 7-9*). However, under similar reaction conditions (i.e, solvent-free and a 1:1 ratio between catalyst and co-catalyst) polymer formation (either **PE**, **PC** or a combination of both) was clearly favored in the case of CHO (*entries 19-21*) with lower conversion levels at lower reaction temperatures (*entries 10-14*). The use of a co-solvent (2-butanone) and *excess* nucleophile (NBu_4**X**: with bromide generally giving the best results) suppressed the polymer formation from CHO (*entries 15-17*). Polyether (**PE**) formation was particularly observed when chloride was used as nucleophile. From **Table 3.1** it may be concluded that the ring size of the substrate will be key to the product (stereo)selectivity, and in general the use of solvent and excess of nucleophile favors the selectivity towards cyclic carbonate instead of polycarbonate. To ensure high substrate conversions, the catalyst loading was increased to 0.5 mol% and depending on the substrate either the Fe- (**1D**) or Al-catalyst (**1C**) was used in the substrate scope phase (*vide infra*). Although the Fe-complex was initially used, we found that Al complex **1C** consistently gave slightly higher yields and selectivities, and thus the latter was used for most of the substrates described in the next section.

3.2.2 Scope in Bicyclic Carbonate Products

Once the reaction conditions had been optimized, a series of cyclic oxiranes were screened as substrates to form their respective bi-, tri- and tetracyclic organic carbonates **3.1-3.18** (see **Figures 3.3-3.5**). We were pleased to find that the optimized reaction conditions (with some modifications when required and depending on the substrate), gave access to a wide range of organic carbonates in high yield and selectivity using catalysts **1C** or **1D**, and NBu_4Br as nucleophilic additive. In most cases, rather mild temperatures (70 ºC) could be used whereas in the synthesis of bis-carbonate **3.9** (66% yield) a somewhat elevated reaction temperature (85 ºC) was required to achieve high conversion of both oxirane fragments into their respective carbonates. Five-, six- and seven-membered ring oxiranes were all smoothly converted into their targeted products **3.1-3.18**.

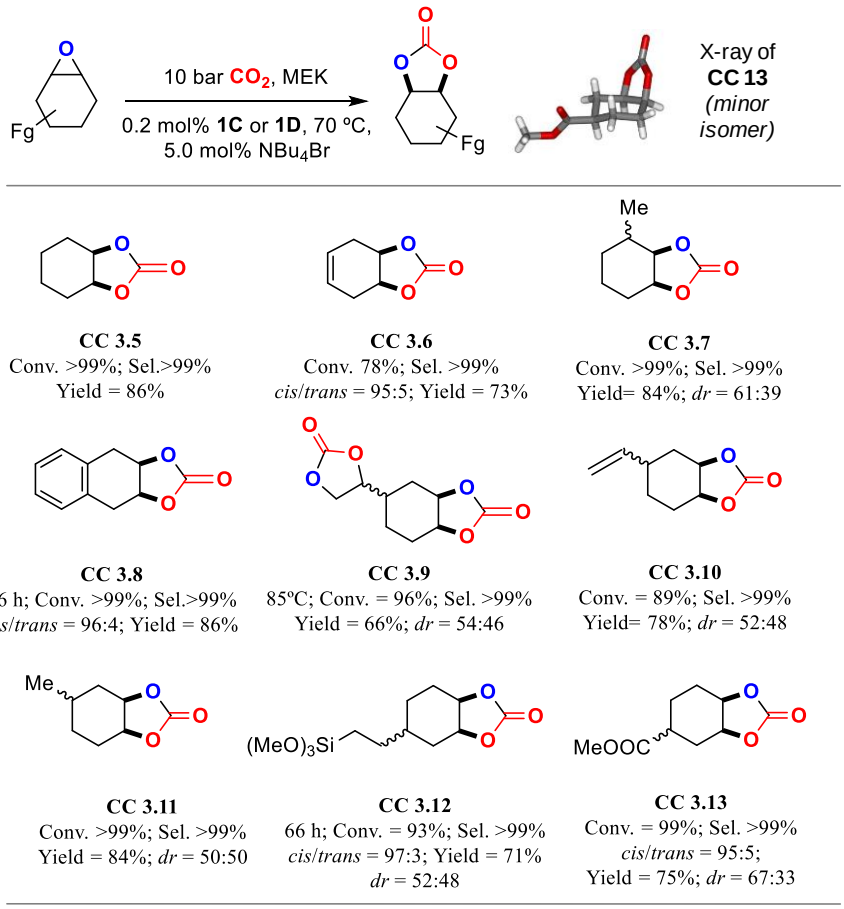
Figure 3.3. Formation of cyclic carbonates **3.1-3.4**.



*[a]Catalyst **1C** (0.2 mol% and 2% of NBu_4Br) was used in the synthesis of **CC 3.4***

In **Figure 3.3** the scope for cyclic epoxides with fused five-membered rings is presented. As already pointed out in **Table 3.1**, five-membered ring epoxides are selectively transformed into their corresponding carbonates with retention of the *cis*-configuration at 70 ºC and 10 bar of CO_2 with a catalyst loading of 0.1 mol% and 1 mol% of NBu_4Br in 18 h: the nucleophile loading was increased to ensure full conversion. For rather complex scaffolds such as the precursor of cyclic carbonate **3.4** slightly higher catalyst/nucleophile loadings (i.e., 0.5/2.0 mol%) and longer reaction times were used to obtain a high substrate conversion. To our surprise, the other epoxide moiety on this scaffold remained unreacted. The unreactive nature of this epoxide moiety was then further investigated by using an oxirane (norbornene oxide) resembling the part highlighted in purple. After prolonged reaction times (>3 days) and at elevated temperatures (100 ºC), the crude carbonate product was formed in only 6% yield. The unreactive nature of the second epoxy group in **3.4** is associated to the high steric impediment around the oxirane unit, which complicates the halide-assisted ring opening. For the fused five-membered ring bi/tricyclic carbonates **3.1-3.4**, no traces of the *trans* carbonate or polycarbonate were observed.

Figure 3.4. Formation of cyclic carbonates **3.5-3.13**.

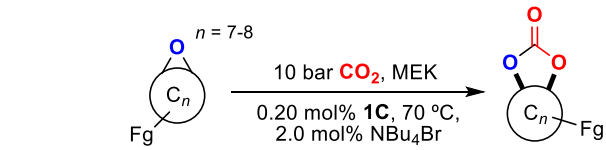


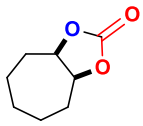
The presence of fused six-membered rings in epoxide substrates show much higher tendency towards the formation of a polymeric product, and therefore solvent (2-butanone) and a higher ratio between nucleophile/catalyst (5.0/0.2 mol%) were used in these cases (*cf*., results **Table 3.1**) in order to selectively form the *cis*-configured cyclic carbonate (**Figure 3.4**).

We then tried to expand the methodology towards larger fused-rings present in the bicyclic epoxides (seven and eight-membered ones) whose cyclic carbonates have seldom been reported. Seven-membered ring epoxides were readily and selectively transformed into their corresponding *cis*-configured cyclic carbonates by using 0.20 mol% of **1D** and 2.0 mol% of NBu_4Br in 66 h. In these cases (**Figure 3.5**, cyclic carbonates **3.14–3.18**) no polymer

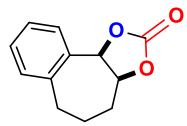
products were observed and only trace amount of the *trans* product was identified in the crude mixtures. Eight-membered ring carbonate **3.16** could only be isolated in 15% yield. This latter result suggests that activation of larger cycloalkenyl-based epoxides is more difficult through coordination to the Lewis acid as likely the nucleophilic ring-opening step is complicated by the relative non-reactive conformation of the oxirane substrate.

Figure 3.5. Formation of cyclic carbonates **3.14-3.18**.

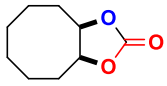




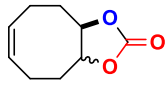
CC 3.14
66 h; Conv. = 99%
Sel. >99%; Yield = 85%



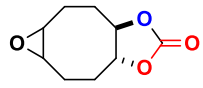
CC 3.15
66 h; Conv. = 99%
Sel. >99%; Yield = 85%



CC 3.16[a]
66 h; Conv. = 20%;
Sel. >99%; Yield = 15%



CC 3.17[a]
66 h; Conv. = 86%;
cis/*trans* = 87:13; Yield = 78%



CC 3.18[a]
66 h; Conv. >99%;
Yield = 52% (*trans*)

[a] catalyst/cocatalyst loadings was increased to 0.5 mol % and 5 mol%

This was further supported by using cyclooctadiene oxide as substrate furnishing carbonate **3.17** in good yield (78%): the presence of a double bond in the backbone is sufficient to result in significantly higher conversion and yield of the cyclic carbonate, and likely, the more rigid nature of the substrate backbone plays an important role. It however, biased the *cis*/*trans* ratio in the carbonate product **3.17** to 87:13 calculated by ^{1}H NMR spectroscopy. When the *bis*-oxirane derived from cyclooctadiene was used as substrate, the oxirane-derived *trans*-carbonate **3.18** was isolated in 52% yield having, as in **3.4**, a synthetically useful epoxide group incorporated. Unexpectedly, the presence of the epoxide ring in the precursor to **3.18** (sp^3- versus sp^2-hybridized C-centers in **3.17**) directs the stereoselectivity towards the *trans* carbonate. This indicates that the configuration of the

cyclic carbonate product may be a result of an initial copolymerization process following (fast) depolymerization.

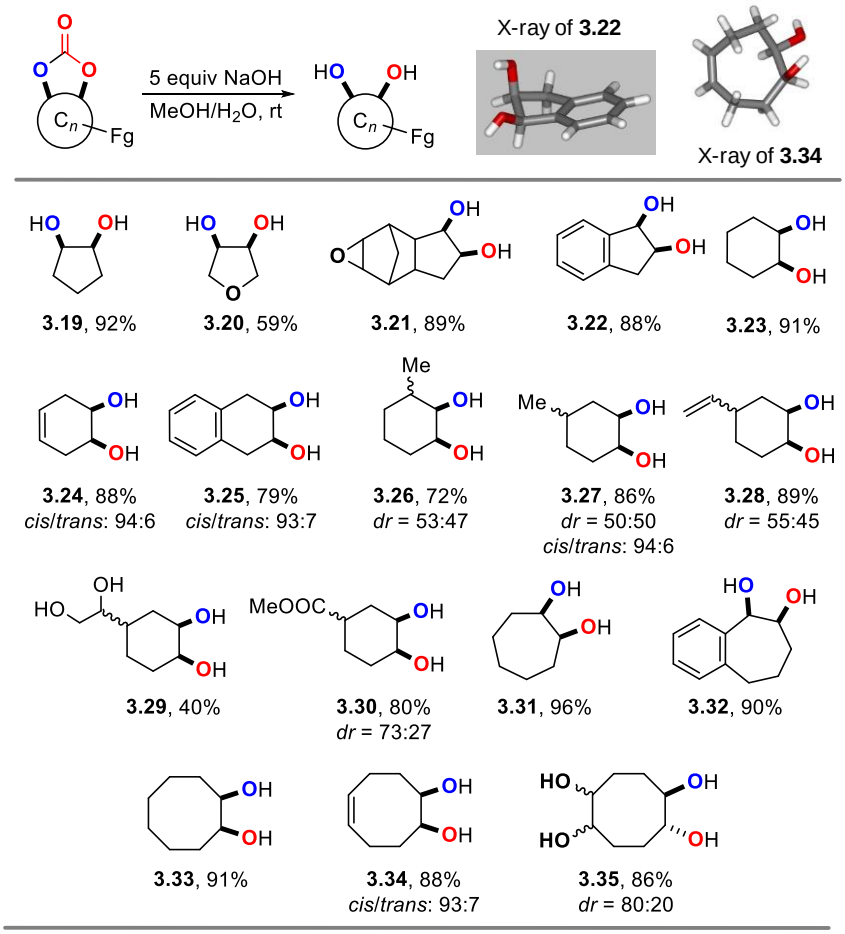
Interestingly, the binary catalyst system based on **1C** or **1D** tolerates a number of useful functionalities including ether (**3.2**), oxirane (**3.4**, **3.18**), *endo*- and *exo*-cyclic double bonds (**3.6**, **3.10** and **3.17**), trimethoxysilyl (**3.12**) and ester (**3.13**) groups. Of further note are the preparation of the substituted bicyclic carbonates **3.7-3.13** for which straightforward analysis by NMR spectroscopy was more challenging due to the presence of three stereocenters in these molecules. However, for a representative example we were able to separate the set of diastereoisomers (**3.13**) by column chromatography and the minor isomer was analyzed by X-ray analysis (see **Figure 3.4**, inset at the top). The major diastereoisomer having the ester group in an axial position was isolated as a viscous liquid. These combined data was used to assign both isomers present in the isolated product, and confirmed the *cis* nature of the carbonate unit.

Limitations exist for sterically too congested substrates such as norbornene oxide (cf., synthesis of **3.4,** second epoxide moiety) and cyclooctene oxide which only afforded low yields of the their corresponding cyclic carbonates. Also substrates that incorporate a carbonyl moiety next to the epoxide ring proved to be challenging. This is due to the electron-withdrawing properties of the ketone, which provokes a Meinwald type rearrangement leading to 1,3-dicarbonyl products.

3.2.3 Transformation of Cyclic Carbonates into *Cis*-Diols

The next step involved the formation of the *cis*-diol products by hydrolysis of the carbonate precursors **3.1–3.18** in the presence of a suitable base and this readily gave access to most diol targets in good to excellent yields (**Figure 3.6**).

Figure 3.6. Formation of *cis*-diol products **3.19–3.35** from carbonate precursors **3.1–3.18**. For the deprotection of carbonate **3.13** towards diol **3.30**, 3 equiv of K_2CO_3 (in MeOH) was used as base.



The deprotection of carbonate **3.12** was complicated as the resulting product was a difficult to interpret mixture of rather insoluble components. Likely, the silyloxy fragment gives rise to insoluble gels through cross-hydrolysis. The basic deprotection of **3.13** had to be carried out with a weaker base (K_2CO_3) in methanol giving *cis*-diol **3.30** selectively in high yield (80%). The yield of tetraol **3.29** (40%) was lower than generally observed for the other diol products as its isolation was more difficult. The oxirane group in **3.21** (89%) remained surprisingly unaffected under basic conditions showing again its unreactive nature. The relative *cis*-configuration in these diols was further supported by X-ray analysis of diol derivatives **3.22** and **3.34** (see inserts at the top in **Figure 3.6**). These results clearly show the generality of this approach toward useful cyclic *cis*-diol scaffolds using CO_2 as a temporary

and easily removable protecting group. The *cis* configuration of the carbonate was maintained in the *cis*-diols and was not affected by the basic conditions. Diastereoisomeric ratios (*dr´*s) also remained constant while converting the carbonate substrate into diol product, the hydrolysis thus only affected the carbonate moiety.

3.3 Conclusions

In summary, we here present an efficient and practical methodology towards cyclic *cis*-diols with ample scope and functional group diversity affording these synthons in high yield and diastereoselectivity with the preparation of their cyclic organic carbonate precursors being the key to success. Further to this, the current approach is also characterized by the use of accessible and powerful catalysts derived from amino triphenolate complexes incorporating cheap and earth-abundant metals, and the use of carbon dioxide as a temporary protecting group. These attractive features combined with the simple operational characteristics of this catalytic methodology may give a valuable starting point for the synthesis of tri- and even tetra-substituted *cis*-diol synthons, and may stimulate the advancement of alternative asymmetric preparations of this important class of organic compounds.

3.4 Experimental Section

3.4.1 General Information and Instrumentation

Typical procedure for organic carbonate formation:

The epoxide precursor (5 mmol) was charged into a 30 mL stainless steel autoclave along with the correct loading of catalyst and co-catalyst, and MEK (0.50 mL). The autoclave was subjected to three cycles of pressurization and depressurization with CO_2 (0.5 MPa, 5 bar), before final stabilization of pressure to 1.0 MPa (10 bar). The autoclave was sealed and heated to the required temperature for 18–66 h. After this time, an aliquot of the crude reaction mixture was collected and analyzed by ^{1}H NMR spectroscopy to determine the substrate conversion (solvent: $CDCl_3$) and selectivity of the catalytic reaction. Then, the product was

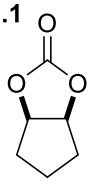
isolated/purified through a silica pad or column chromatography (see below for further details).

Typical deprotection procedure:

The respective carbonate (1.0 mmol) was dissolved into 1 M NaOH (5.0 mL). The mixture was left stirring for 2–3 h, until complete dissolution of the starting material and formation of a homogeneous, pale yellow solution was achieved. Hereafter, the diol was extracted with various portions of EtOAc, and isolated by removal of the solvent *in vacuo*.

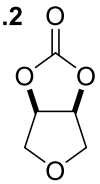
3.4.2 Spectroscopic Analysis for all Compounds

3.1

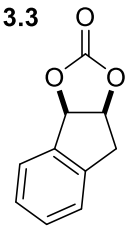


Cyclic Carbonate 3.1:[54] Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.1**: 518 mg (4.05 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (m, 2H), 2.14 (m, 2H), 1.79 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.46, 81.85, 33.17, 21.56. IR (neat, cm^{-1}): 2966, 1777, 1544, 1372, 12222, 1170, 1040 and 696.

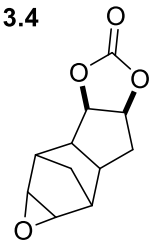
3.2



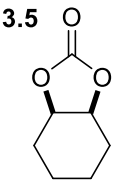
Cyclic Carbonate 3.2: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.2**: 585 mg (4.50 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (m, 2H), 4.24 (d, 2H, J = 12.4 Hz), 3.60 (d, 2H, J = 12.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.40, 80.06, 73.01. IR (neat, cm^{-1}): 1777, 1348, 1117, 1041, 784, 691. HRMS (APCI+, MeOH): *m/z* calcd. 131.0339 $(M+H)^+$, found: 131.0337.

3.3 

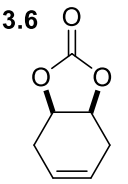
Cyclic Carbonate 3.3:[60] Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.3**: 862 mg (4.90 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.0 Hz, 1H), 7.44 (m, 1H), 7.35 (m, 2H), 6.01 (d, J = 7.0 Hz, 2H), 5.46 (m, 1H), 3.41 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.75, 140.10, 136.48, 131.08, 128.25, 126.50, 125.64, 83.62, 79.81, 38.04. IR (neat, cm^{-1}): 1775, 1396, 1312, 1082, 1012, 761, 698.

3.4 

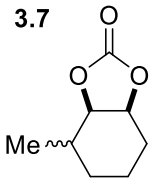
Cyclic Carbonate 3.4: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.4**: 936 mg (4.50 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (m, 1H), 4.97 (d, J = 6.3 Hz, 1H), 3.19 (d, J = 3.5 Hz, 1H), 3.14 (d, J = 3.5 Hz, 1H), 2.93 (m, 2H), 2.77 (m, 1H), 2.57 (m, 1H), 2.37 (m, 1H), 2.04 (m, 1H), 1.47 (dt, J = 1.95 and 10.1 Hz, 1H), 0.95 (d, J = 10.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.33, 84.45, 82.71, 50.48, 48.91, 48.38, 43.71, 39.88, 39.24, 32.38, 28.72. IR (neat, cm^{-1}): 2965, 1778, 1157, 1047, 843, 772. HRMS (ESI+, CH_3CN): *m/z* calcd. 231.0628 $(M+Na)^+$, found: 231.0627.

3.5 

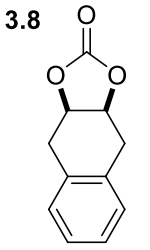
Cyclic Carbonate 3.5:[44] Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.5**: 610 mg (4.30 mmol, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (m, 2H), 1.89 (m, 4H), 1.62 (m, 2H), 1.44 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.34, 75.74, 26.77, 19.16. IR (neat, cm^{-1}): 2942, 1780, 1351, 1164, 1137, 1024, 994, 779, 729.

3.6 

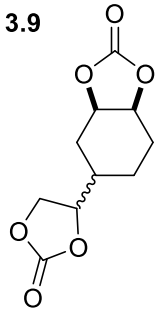
Cyclic Carbonate 3.6:[61] Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.6**: 515 mg (3.69 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (s, 2H), 5.7 (m, 2H), 5.01 (s, 2H), 4.31 (m, 2H), 2.60 (m, 2H), 2.58 (d, J = 16.1 Hz, 2H), 2.43 (m, 2H), 2.25 (d, J = 16.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.00, 125.62, 124.20, 79.87, 74.66, 29.74, 27.00. IR (neat, cm^{-1}): 1767, 1376, 1175, 1045, 892, 768, 705.

3.7 

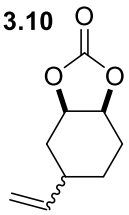
Cyclic Carbonate 3.7: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.7**: 661 mg (4.24 mmol, 84%). ^{1}H NMR (500 MHz, mixture of diastereoisomers, $CDCl_3$) δ 4.71 (m, 2H), 4.62 (m, 1H), 4.15 (m, 1H), 2.25 (m, 1H), 2.07 (m, 1H), 1.43-1.83 (m, 12H), 1.14 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, mixture of diastereoisomers, $CDCl_3$) δ 155.38, 155.35, 82.19, 80.05, 76.56, 76.02, 35.36, 34.49, 31.69, 29.30, 26.67, 26.37, 25.88, 19.09, 18.79, 17.49. IR (neat, cm^{-1}): 1786, 1459, 1310, 1135, 1025, 777. HRMS (APCI+, MeOH): *m/z* $(M+H)^+$ calcd. 157.0859, found: 157.0860.

3.8 

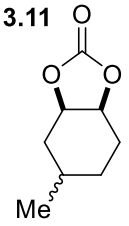
Cyclic Carbonate 3.8: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.8**: 817 mg (4.30 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 4H), 5.20 (s, 2H), 3.18 (d, J = 15.6 Hz, 2H), 2.93 (d, J =15.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.31, 132.08, 128.91, 127.94, 74.92, 32.81. IR (neat, cm^{-1}): 1773, 1376, 1167, 1049, 759, 614, 524. HRMS (ESI+, CH_3CN): *m/z* calcd. 191.0700 $(M+H)^+$, found: 191.0703.

3.9 

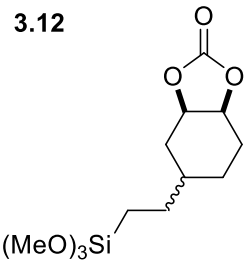
Cyclic Carbonate 3.9: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.9**: 752 mg (3.30 mmol, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.96–4.66 (m, 2H), 4.64–4.15 (m, 3H), 2.44–2.31 (m, 1H), 2.30–1.83 (m, 2H), 1.83–1.69 (m, 2H), 1.63–1.22 (m, 2H). ^{13}C NMR (126 MHz, mixture of diastereoisomers, $CDCl_3$) δ 154.71, 154.68, 154.65, 154.61, 154.54, 154.51, 79.33, 79.13, 79.01, 78.98, 75.34, 75.16, 75.09, 74.99, 74.67, 74.61, 74.57, 67.59, 67.54, 67.35, 36.62, 36.48, 33.28, 33.13, 28.85, 28.47, 27.78, 26.35, 25.77, 25.20, 25.04, 21.15, 20.56, 19.62, 19.12. IR (neat, cm^{-1}): 1775, 1384, 1198, 1028, 772. HRMS (APCI+, CH_3OH): *m/z* calcd. 251.0526 $(M+Na)^+$, found: 251.0527.

3.10 

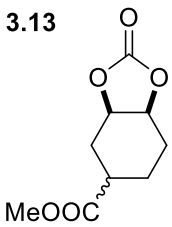
Cyclic Carbonate 3.10: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.10**: 655 mg (3.90 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (m, 2H), 4.99 (m, 4H), 4.72 (m, 4H), 2.25 (m, 5H), 2.00 (m, 1H), 1.66 (m, 5H), 1.37 (m, 2H), 1.17 (m, 1H). ^{13}C NMR (101 MHz, mixture of diastereoisomers, $CDCl_3$) δ 155.12, 155.09, 141.00, 140.91, 114.23, 113.94, 75.96, 75.60, 75.10, 36.33, 33.84, 33.52, 31.65, 26.64, 25.76, 25.68, 25.03. IR (neat, cm^{-1}): 1789, 1355, 1189, 1026, 914, 779. HRMS (ESI+, MeOH): *m/z* calcd: 191.0679 $(M+Na)^+$; found: 191.0682.

3.11 

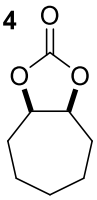
Cyclic Carbonate 3.11: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.11**: 655 mg (4.20 mmol, 84%). ^{1}H NMR (500 MHz, mixture of diastereoisomers, $CDCl_3$) δ 4.71 (m, 4H), 2.34 (m, 1H), 2.27 (m, 1H), 2.14 (m, 2H), 1.77 (m, 3H), 1.66 (m, 3H), 1.38 (m, 2H), 1.22 (m, 2H), 1.00 (m, 6H). ^{13}C NMR (126 MHz, mixture of diastereoisomers, $CDCl_3$) δ 155.24, 155.21, 76.49, 75.86, 75.60, 75.24, 36.32, 34.40, 28.36, 27.86, 27.42, 27.17, 26.04, 25.10, 21.87, 21.34. IR (neat, cm^{-1}): 1791, 1354, 1192, 1138, 1027, 780. HRMS (APCI+, MeOH): *m/z* calcd. 157.0859 $(M+H)^+$, found: 157.0857.

3.12 

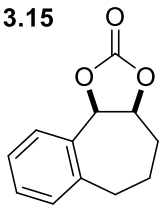
Cyclic Carbonate 3.12: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.12**: 1029 mg (3.55 mmol, 71%). ^{1}H NMR (500 MHz, mixture of diastereoisomers, $CDCl_3$) δ 4.79 (m, 1H), 4.72 (m, 1H), 4.66 (m, 2H), 3.61 (s, 9H), 3.56 (s, 9H), 2.32 (m, 2H), 2.23 (m, 1H), 2.12 (m, 1H), 1.84 (m, 1H), 1.67 (m, 4H), 1.14- 1.48 (m, 8H), 0.96 (m, 1H), 0.66 (m, 4H). ^{13}C NMR (101 MHz, mixture of diastereoisomers, $CDCl_3$) δ 155.20, 155.16, 77.22, 76.34, 75.97, 75.50, 50.59, 35.27, 33.91, 32.35, 32.07, 29.06, 28.79, 26.82, 26.00, 25.59, 24.99, 6.32, 6.21. IR (neat, cm^{-1}): 2939, 1795, 1452, 1353, 1188, 1075, 1028, 780. HRMS (ESI+, CH_3CN): *m/z* calcd. 291.1258 $(M+H)^+$, found: 291.1246.

3.13 

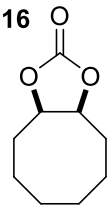
Cyclic Carbonate 3.13: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.13**: 7.50 mg (3.75 mmol, 75%). ^{1}H NMR (500 MHz, mixture of diastereoisomers, $CDCl_3$) δ 4.92 (m, 1H), 4.73 (m, 3H), 3.74(s, 3H), 3.73 (s, 3H), 2.74 (m, 1H), 2.36 (m, 3H), 2.26(m, 1H), 2.05 (m, 3H), 1.95-1.62 (m, 6H). ^{13}C NMR (126 MHz, mixture of diastereoisomers, $CDCl_3$) δ: 174.72, 173.78, 154.88, 154.77, 75.08, 74.91, 74.80, 52.33, 52.27, 37.90, 35.81, 29.80, 28.23, 25.51, 25.24, 21.93, 21.80. IR (neat, cm^{-1}): 2959, 1791, 1726, 1436, 1144, 1029, 772. HRMS (APCI+, MeOH): *m/z* calcd. 201.0757 $(M+H)^+$, found: 201.0756.

3.14 

Cyclic Carbonate 3.14:[47] Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.14**: 514 mg (3.30 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (m, 2H), 1.96 (m, 4H), 1.82 (m, 2H), 1.65 (m, 1H), 1.50 (m, 1H), 1.35 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.62, 79.82, 30.17, 29.94, 23.53. IR (neat, cm^{-1}): 2939, 1776, 1447, 1375, 1168, 1048, 771.

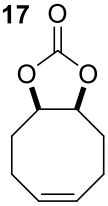
3.15 

Cyclic Carbonate 3.15: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.15**: 867 mg (4.25 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (m, 1H), 7.37 (m, 2H), 7.18 (m, 1H), 5.88 (d, 1H, J = 8.6 Hz), 4.95 (m, 1H), 2.83 (dq, J = 7.5 and 2.7 Hz, 1H), 2.50 (m, 1H), 1.97 (m, 1H), 1.84 (m, 1H), 1.76 (m, 1H), 1.44 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.08, 135.37, 133.03, 129.24, 128.84, 127.27, 124.58, 78.72, 77.44, 30.04, 26.29, 20.40. IR (neat, cm^{-1}): 2921, 1785, 1349, 1180, 1162, 1055, 766. HRMS (ESI+, MeOH): *m/z* calcd. 227.0679 $(M+Na)^+$, found: 227.0679.

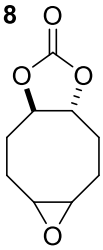
3.16 

Cyclic Carbonate 3.16: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.16**: 128 mg (0.75 mmol, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (m, 2H), 1.98 (m, 4H), 1.72 (m, 2H), 1.49 (m, 4H), 1.26 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.16, 81.18, 27.06, 25.97, 25.15. IR

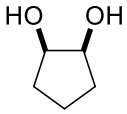
(neat, cm^{-1}): 2923, 1795, 1469, 1358, 1171, 1048, 751. HRMS (APCI+, MeOH): *m/z* calcd. 171.1016 $(M+Na)^+$, found: 171.1023.

3.17 

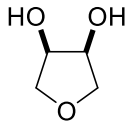
Cyclic Carbonate 3.17: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.17**: 655 mg (3.90 mmol, 78%). ^{1}H NMR (500 MHz, mixture of *cis* and *trans* species, $CDCl_3$) δ 5.70 (m, 4H), 4.80 (m, 2H; *cis*), 4.50 (m, 2H; *trans*), 2.56 (m, 2H), 2.30 (m, 4H), 2.21 (m, 4H), 1.71(m, 2H), 1.56 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.35, 154.19, 129.37, 129.29, 82.42, 80.14, 30.01, 27.73, 22.43, 20.57. IR (neat, cm^{-1}): 2944, 1779, 1175, 1041, 773, 711. HRMS (APCI+, MeOH): *m/z* calcd. 191.0679 $(M+Na)^+$, found: 191.0681.

3.18 

Cyclic Carbonate 3.18: Synthesized according to the typical procedure for organic carbonate formation. Purified by column chromatography (Hex: EtOAc, 2:1). Yield of **3.18**: 478 mg (2.60 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (m, 1H), 4.26 (m, 1H), 2.97 (m, 2H), 2.41 (m, 4H), 1.78 (m, 2H), 1.30 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.60, 81.95, 81.88, 53.48, 53.25, 29.08, 27.77, 23.33, 20.92. IR (neat, cm^{-1}): 2925, 1783, 1459, 1165, 1049, 855, 754, 480. HRMS (APCI+, MeOH): *m/z* calcd. 207.0629 $(M+Na)^+$, found: 207.0628.

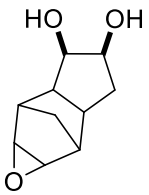
3.19 

***Cis*-Diol 3.19**:[54] Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.19**: 94 mg (0.92 mmol, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (m, 2H), 2.69 (s, 2H, OH), 1.86 (m, 3H), 1.66 (m, 2H), 1.51 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.90, 19.67, 30.83.

3.20 

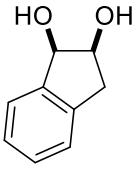
***Cis*-Diol 3.20**:[62] Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.20**: 61 mg (0.59 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (m, 2H), 3.94 (m, 2H), 3.77 (dd, J = 3.7 and 9.8 Hz, 2H), 3.01(s, 2H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.99, 71.35.

3.21



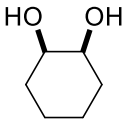
***Cis*-Diol 3.21**: Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.21**: 162 mg (0.89 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (m, 1H), 4.05 (m, 1H), 3.25 (m, 1H), 3.22 (m, 1H), 2.76 (m, 1H), 2.63 (m, 1H), 2.46 (m, 2H), 1.79 (m, 2H), 1.48(m, 1H), 0.89 (m, 1H), 0.87 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 77.45, 72.69, 51.89, 50.17, 42.33, 39.19, 37.99, 31.20, 29.97. HRMS (APCI+, MeOH): *m/z* calcd. 183.1016 $(M)^+$, found: 183.1021.

3.22



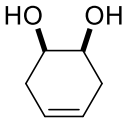
***Cis*-Diol 3.22**:[63] Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.22**: 132 mg (0.88 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 1H), 7.25 (m, 3H), 4.96 (d, J = 5.0 Hz, 1H), 4.44 (m, 1H), 3.07 (dd, J = 5.8 and 16.5 Hz, 1H), 3.04 (br s, 2H, OH), 2.95 (dd, J = 3.6 and 13.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.95, 140.15, 128.80, 127.16, 125.35, 125.06, 75.95, 73.45, 38.58.

3.23



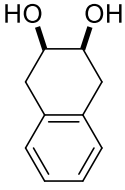
***Cis*-Diol 3.23**:[54] Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.23**: 106 mg (0.91 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (m, 2H), 2.11 (s, 2H, OH), 1.77 (m, 2H), 1.59 (m, 2H), 1.34 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.62, 29.92, 21.42.

3.24



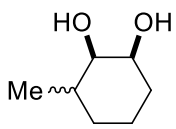
***Cis*-Diol 3.24**:[64] Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.24**: 100 mg (0.88 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (m, 2H), 5.56 (m, 2H), 3.97 (m, 2H), 3.72 (m, 2H), 2.53 (m, 2H), 2.37 (m, 2H), 2.29 (m, 2H), 2.15 (br s, 2H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 124.48, 123.68, 72.11, 68.90, 33.35, 30.99.

3.25



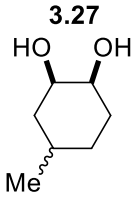
***Cis*-Diol 3.25**: Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.25**: 130 mg (0.79 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 4H), 4.18(m, 2H), 3.06 (m, 4H), 2.04 (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.87, 129.14, 126.29, 69.28, 34.41. HRMS (ESI+, CH_3CN): *m/z* calcd. 147.0804 $(M+H)^+$, found: 147.0801.

3.26



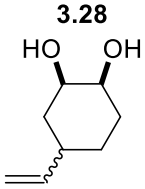
***Cis*-Diol 3.26**:[65] Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.26**: 94 mg (0.72 mmol, 72%). ^{1}H NMR (500 MHz, mixture of diastereoisomers, $CDCl_3$) δ 3.97 (m, 1H), 3.78 (br s, 1H, OH), 3.60 (m, 2H), 3.48 (br s, 1H, OH), 3.19 (m, 1H), 2.06 (br s, 1H, OH), 1.99 (br s, 1H, OH), 1.93 (m, 1H), 1.63(m, 1H), 1.42-1.81 (m, 6H), 1.04(d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, mixture of diastereoisomers, $CDCl_3$) δ 77.41, 73.89, 72.53, 69.64, 35.45, 33.31, 32.42, 31.22, 28.25, 26.65, 23.49, 21.87, 19.23, 18.29.

3.27



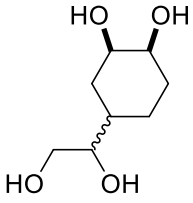
***Cis*-Diol 3.27**:[66] Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.27**: 112 mg (0.86 mmol, 86%). ^{1}H NMR (500 MHz, mixture of diastereoisomers, $CDCl_3$) *δ* 3.99 (m, 2H), 3.62 (m, 2H), 1.1-2.1 (m, 18H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, mixture of diastereoisomers, $CDCl_3$) δ 71.77, 71.73, 69.59, 68.70, 39.33, 37.40, 32.41, 30.95, 30.38, 28.58, 27.35, 25.13, 22.08, 21.50.

3.28



***Cis*-Diol 3.28**: Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.28**: 126 mg (0.89 mmol, 89%). ^{1}H NMR (300 MHz, mixture of diastereoisomers, $CDCl_3$) *δ* 5.74 (m, 2H), 5.03 (m, 1H), 4.97 (m, 1H), 4.95 (m, 1H), 4.92(m, 1H), 3.99 (m, 2H), 3.63(m, 2H), 2.70 (m, 3H), 2.37 (m, 1H), 1.99 (m, 3H), 1.72 (m, 4H), 1.44 (m, 6H). ^{13}C NMR (75 MHz, mixture of diastereoisomers, $CDCl_3$) *δ* 142.88, 142.76, 112.85, 112.59, 71.59, 71.54, 69.19, 68.68, 39.80, 36.59, 34.33, 34.08, 30.11, 29.58, 28.04, 24.79. HRMS (ESI+, MeOH): *m/z* calcd: 165.0886 $(M+Na)^+$; Found: 165.0883.

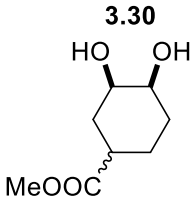
3.29



***Cis*-Diol 3.29**: Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.29**: 70 mg (0.40 mmol, 40%).^{1}H NMR (500 MHz, DMSO-d_6) *δ* 7.41 (s, 1H), 7.31 (s, 1H), 7.20 (s, 1H), 3.74 (m, 1H), 3.72–3.63 (m, 1H), 3.45–3.08 (m, 4H), 1.85–0.91 (m, 8H). ^{13}C NMR (101 MHz, mixture of diastereoisomers, DMSO-d_6) δ: 75.00, 74.86, 74.74, 74.58, 71.28, 71.22, 71.21, 68.67, 68.50, 68.17, 68.16, 63.98, 63.95, 63.77, 63.73, 38.75, 38.65, 34.61, 32.64, 32.46, 32.29, 31.63, 30.69,

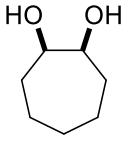
30.48, 29.93, 28.27, 28.05, 27.09, 24.55, 21.84, 20.22. HRMS (APCI+, MeOH): *m/z* calcd. 199.0941 $(M+Na)^+$, found 199.0940.

3.30



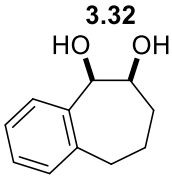
***Cis*-Diol 3.30**: Synthesized according to the typical deprotection method but instead of using 5 equiv of NaOH, 3 equiv of K_2CO_3 (in MeOH) was utilized. No further purification was necessary. Yield of **3.30**: 139 mg (0.80 mmol, 80%). ^{1}H NMR (500 MHz, mixture of diastereoisomers, DMSO-d_6) δ 4.47 (d, J = 5.7 Hz, 1H), 4.39 (d, J = 5.5 Hz, 1H), 4.35 (d, J = 3.2 Hz, 1H), 4.21 (d, J = 2.7 Hz, 1H), 3.73 (m, 1H), 3.67 (m, 1H), 3.59 (m, 1H), 3.57 (s, 3H), 3.57 (s, 3H), 3.37 (m, 2H), 2.56 (m, 1H), 2.32 (m, 1H), 1.92–1.73 (m, 2H), 1.71 (m, , 1H), 1.64 (m, 1H), 1.60–1.42 (m, 4H), 1.36 (m, 2H). ^{13}C NMR (126 MHz, mixture of diastereoisomers, DMSO-d_6) δ 175.74, 174.90, 69.92, 69.89, 67.68, 67.48, 51.31, 51.29, 40.53, 36.14, 33.69, 30.92, 29.72, 27.52, 26.07, 21.70. IR (neat, cm^{-1}): 3390, 2949, 1714, 1437, 1166, 1062 and 1012. HRMS (APCI+, MeOH): *m/z* calcd. 197.0784 $(M+Na)^+$, found: 197.0790.

3.31



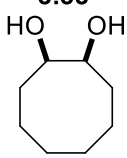
***Cis*-Diol 3.31**:[67] Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.31**: 124 mg (0.96 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (m, 2H), 3.20 (m, 2H, OH), 1.61-1.91 (m, 6H), 1.57 (m, 1H), 1.49 (m, 1H), 1.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 73.61, 30.87, 27.83, 22.6.

3.32



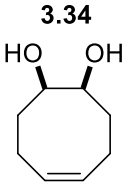
***Cis*-Diol 3.32**: Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.32**: 160 mg (0.90 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.24 (m, 2H), 7.13 (m, 1H), 4.98 (br s, 1H, OH), 4.01 (m, 1H), 3.05 (m, 1H), 2.69 (dq, J = 1.8 and 8.9 Hz, 1H), 2.26 (br s, 1H, OH), 2.17 (m, 1H), 2.00 (m, 1H), 1.79 (m, 1H), 1.66 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.86, 137.83, 129.83, 128.48, 128.44, 128.11, 126.33, 73.32, 34.84, 34.63, 30.92. HRMS (ESI+, MeOH): *m/z* calcd. 201.0886 $(M+Na)^+$, found: 201.0883.

3.33



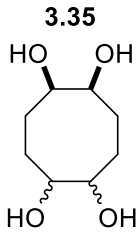
***Cis*-Diol 3.33**:[68] Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.33**: 131 mg (0.91 mmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93(d, J = 8.8 Hz, 2H), 2.07 (br s, 2H, OH), 1.92 (m, 2H), 1.72 (m, 4H), 1.55 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 73.15, 30.14, 26.23, 23.75.

3.34



***Cis*-Diol 3.34**: Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.34**:125 mg (0.88 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (m, 2H), 5.62 (m, 2H), 4.02 (m, 2H), 3.70 (m, 2H), 2.52 (m, 2H), 2.40 (m, 2H), 2.15 (m, 6H), 2.05 (m, 6H), 1.83 (m, 2H), 1.68 (br, OH). 13C NMR (126 MHz, $CDCl_3$) δ 129.94, 129.12, 99.99, 75.03, 33.42, 31.94, 29.70, 22.93. HRMS (APCI+, MeOH): *m/z* calcd. 125.0962 $(M+Na)^+$, found: 125.0961.

3.35



Diol 3.35: Synthesized according to the typical deprotection method. No further purification was necessary. Yield of **3.35**: 151 mg (0.86 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (m, 2H), 4.09 (m, 4H), 3.81 (m, 2H), 2.24 (m, 2H), 2.12 (m, 2H), 1.93 (m, 4H), 1.80 (m, 4H), 1.72 (m, 4H), 1.60 (br s, OH), 1.47 (br s, OH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.78, 71.93, 69.60, 68.79, 29.70, 28.68, 24.19, 21.95. HRMS (APCI+, MeOH): *m/z* calcd. 159.1016 $(M-H_2O)^+$, found: 159.1007.

3.4.3 Crystallographic Data

Crystallographic data was obtained following the methodology described on chapter I.

*Crystal data for cyclic carbonate **3.13**:* $C_9H_{12}O_5$, M_r = 200.19, triclinic, P-1, a = 6.0639(6) Å, b = 7.5678(8) Å, c = 10.1552(10) Å, α = 78.718(2)º, β = 83.302(3)º, γ = 83.929(2)º, V = 452.25(8) Å^3, Z = 2, ρ = 1.470mg·M^{-3}, μ = 0.121 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 212, crystal size = 0.45 × 0.40 × 0.15 mm, θ(min) = 2.055º, θ(max) = 35.195º, 9014 reflections collected, 3542 reflections unique (R_{int} = 0.0259), GoF = 1.090, R_1 = 0.0398 and wR_2 = 0.1069 [$I > 2\sigma(I)$], R_1 = 0.0456 and wR_2 = 0.1115 (all indices), min/max residual density = -0.469/0.326 [e·Å^{-3}]. Completeness to θ(35.195º) = 87.4%.

Crystal data for diol ***3.22****:* $C_9H_{10}O_2$, M_r = 150.17, monoclinic, C2/c, a = 22.5344(17) Å, b = 4.6367(4) Å, c = 28.687(3) Å, α = 90.0º, β = 100.466(3)º, γ = 90.0º, V = 2947.5(4) Å^3, Z = 16, ρ = 1.354mg·M^{-3}, μ = 0.095 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 1280, crystal size = 0.40 × 0.05 × 0.04 mm, θ(min) = 1.84º, θ(max) = 30.17º, 14954 reflections collected, 3925 reflections unique (R_{int} = 0.0708), GoF = 1.029, R_1 = 0.0509 and wR_2 = 0.1221 [$I > 2\sigma(I)$], R_1 = 0.0700 and wR_2 = 0.1333 (all indices), min/max residual density = -0.273/0.420 [e·Å^{-3}]. Completeness to θ(30.17º) = 89.6%.

Crystal data for diol ***3.34***: $C_8H_{14}O_2$, M_r = 142.19, monoclinic, P21/c, a = 10.5561(19) Å, b = 5.7184(8) Å, c = 12.873(2) Å, α = 90.0º, β = 98.248(5)º, γ = 90.0º, V = 769.0(2) Å^3, Z = 4, ρ = 1.228mg·M^{-3}, μ = 0.086 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 312, crystal size = 0.25 × 0.05 × 0.03 mm, θ(min) = 3.198º, θ(max) = 30.548º, 6159 reflections collected, 2237 reflections unique (R_{int} = 0.0222), GoF = 1.057, R_1 = 0.0385 and wR_2 = 0.1001 [$I > 2\sigma(I)$], R_1 = 0.0456 and wR_2 = 0.1055 (all indices), min/max residual density = -0.186/0.446 [e·Å^{-3}]. Completeness to θ(30.548º) = 95.0%.

3.5 References

(1) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
(2) Zaitsev, A. B.; Adolfsson, H. *Synthesis.* **2006**, 1725–1756.
(3) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *57*, 2768–2771.
(4) Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209–211.
(5) Schroeder, M. *Chem. Rev.* **1980**, *80*, 187–213.
(6) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229–11230.
(7) Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett.* **2001**, *3*, 2649–2651.
(8) Yao, Q. *Org. Lett.* **2002**, *4*, 2197–2199.
(9) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766–768.
(10) Sugimoto, H.; Kitayama, K.; Mori, S.; Itoh, S. *J. Am. Chem. Soc.* **2012**, *134*, 19270–19280.
(11) Fujieda, N.; Nakano, T.; Taniguchi, Y.; Ichihashi, H.; Sugimoto, H.; Morimoto, Y.; Nishikawa, Y.; Kurisu, G.; Itoh, S. *J. Am. Chem. Soc.* **2017**, 139, 5149–5155.
(12) Bataille, C. J. R.; Donohoe, T. J. *Chem. Soc. Rev.* **2011**, *40*, 114–128.
(13) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986–1987.
(14) Yip, W.-P.; Yu, W.-Y.; Zhu, N.; Che, C.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14239–14249.
(15) Shing, T. K. M.; Tai, V. W. F; Tam, E. K. W. *Angew. Chem. Int. Ed.* **1994**, *33*, 2312–2313.

(16) Shing, T. K. M.; Tam, E. K. W. *Tetrahedron Lett.* **1999**, *40*, 2179–2180.

(17) Ho, C. M.; Yu, W. Y.; Che, C. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 3303–3307.

(18) Scholte, A. A.; Mi, H. A.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 4759–4762.

(19) Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 1900–1903.

(20) Lee, A. W. M.; Chan, W. H.; Yuen, W. H.; Xia, P. F.; Wong, W. Y. *Tetrahedron Asymmetr.* **1999**, *10*, 1421–1424.

(21) Dash, S.; Patel, S.; Mishra, B. K. *Tetrahedron* **2009**, *65*, 707–739.

(22) Lee, D. G.; Chen, T. *J. Am. Chem. Soc.* **1989**, *111*, 7534–7538.

(23) Vijaykumar, D.; Mao, W.; Kirschbaum, K. S.; Katzenellenbogen, J. *J. Org. Chem.* **2002**, *67*, 4904–4910.

(24) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195–199.

(25) Cottrell, I. F.; Davis, P. J.; Moloney, M. G. *Tetrahedron Asymmetr.* **2004**, *15*, 1239–1242.

(26) De Vos, D. E.; De Wildeman, S.; Sels, B. F.; Grobet, P. J.; Jacobs, P. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 980–983.

(27) de Boer, J. W.; Browne, W. R.; Harutyunyan, S. R.; Bini, L.; Tiemersma-Wegman, T. D.; Alsters, P. L.; Hage, R.; Feringa, B. L. *Chem. Commun.* **2008**, 3747–3749.

(28) Bhunnoo, R. A.; Hu, Y.; Lain, D. I.; Brown, R. C. D. *Angew. Chem. Int. Ed.* **2002**, *41*, 3479–3480.

(29) Iwata, S.; Saynovits, M.; Link, T. a; Michel, H. *Structure* **1996**, *4*, 567–579.

(30) Chow, T. W. S.; Wong, E. L. M.; Guo, Z.; Liu, Y.; Huang, J. S.; Che, C. M. *J. Am. Chem. Soc.* **2010**, *132*, 13229–13239.

(31) Costas, M.; Que, Jr., L. *Angew. Chem. Int. Ed.* **2002**, *41*, 2179–2181.

(32) Chen, K.; Costas, M.; Kim, J.; Tipton, A. K.; Que, L. *J. Am. Chem. Soc.* **2002**, *124*, 3026–3035.

(33) Oldenburg, P. D.; Shteinman, A. A.; Que, L. *J. Am. Chem. Soc.* **2005**, 15672–15673.

(34) Biradar, A. V.; Sathe, B. R.; Umbarkar, S. B.; Dongare, M. K. *J. Mol. Catal. A.* **2008**, *285*, 111–119.

(35) Wang, W.; Wang, F.; Shi, M. *Organometallics* **2010**, *29*, 928–933.

(36) Horiuchi, C. A.; Dan, G.; Sakamoto, M.; Suda, K.; Usui, S.; Sakamoto, O.; Kitoh, S.; Watanabe, S.; Utsukihara, T.; Nozaki, S. *Synthesis* **2005**, *17*, 2861–2864.

(37) Pearlstein, R. M.; Davison, A. *Polyhedron* **1988**, *7*, 1981–1989.

(38) Santoro, S.; Santi, C.; Sabatini, M.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal.* **2008**, *350*, 2881–2884.

(39) Mudiganti, N. V. S.; Claessens, S.; Habonimana, P.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 3867–3874.

(40) Aresta, M. *Carbon Dioxide as Chemical Feedstock*; Wiley-VCH, Weinheim, **2010**.

(41) Martín, C.; Fiorani, G.; Kleij, A. W. *ACS Catal.* **2015**, *5*, 1353–1370.

(42) Castro-Osma, J. A.; North, M.; Wu, X. *Chem. Eur. J.* **2016**, *22*, 2100–2107.

(43) Martinez, J.; Castro-Osma, J. A.; Alonso-Moreno, C.; Rodriguez-Dieguez, A.; North, M.; Otero, A.; Lara-Sanchez, A. *ChemSusChem* **2017**, *10*, 1175–1185.

(44) Whiteoak, C. J.; Kielland, N.; Laserna, V.; Escudero-Adán, E. C.; Martin, E.; Kleij, A. W. *J. Am. Chem. Soc.* **2013**, *135*, 1228–1231.

(45) Qin, J.; Wang, P.; Li, Q.; Zhang, Y.; Yuan, D.; Yao, Y. *Chem. Commun.* **2014**, *50*, 10952–10955.

(46) Maeda, C.; Taniguchi, T.; Ogawa, K.; Ema, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 134–138.

(47) Kruper, W. J.; Dellar, D. V. *J. Org. Chem.* **1996**, *60*, 725–727.

(48) Darensbourg, D. J.; Wei, S. H. *Macromolecules* **2012**, *45*, 5916–5922.

(49) Whiteoak, C. J.; Kielland, N.; Laserna, V.; Castro-Gomez, F.; Martin, E.; Escudero-Adán, E. C.; Bo, C.; Kleij, A. W. *Chem. Eur. J.* **2014**, *20*, 2264–2275.

(50) Whiteoak, C. J.; Martin, E.; Belmonte, M. M.; Benet-Buchholz, J.; Kleij, A. W. *Adv. Synth. Catal.* **2012**, *354*, 469–476.

(51) Taherimehr, M.; Al-Amsyar, S. M.; Whiteoak, C. J.; Kleij, A. W.; Pescarmona, P. P. *Green Chem.* **2013**, *15*, 3083–3090.

(52) Wang, Z.; Cui, Y. T.; Xu, Z. B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270–2274.

(53) Gendre, P. Le; Braun, T.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1996**, *61*, 8453–8455.

(54) Beattie, C.; North, M.; Villuendas, P.; Young, C. *J. Org. Chem.* **2013**, *78*, 419–426.

(55) Sun, J.; Yao, X.; Cheng, W.; Zhang, S. *Green Chem.* **2014**, *16*, 3297–3304.

(56) Chang, L.; Ouyang, L.-M.; Xu, Y.; Pan, J.; Xu, J.-H. *J. Mol. Catal. B Enzym.* **2010**, *66*, 95–100.

(57) Darensbourg, D. J.; Chung, W. C.; Wilson, S. J. *ACS Catal.* **2013**, *3*, 3050–3057.

(58) Kember, M. R.; Knight, P. D.; Reung, P. T. R.; Williams, C. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 931–933.

(59) Wu, G. P.; Ren, W. M.; Luo, Y.; Li, B.; Zhang, W. Z.; Lu, X. B. *J. Am. Chem. Soc.* **2012**, *134*, 5682–5688.

(60) Darensbourg, D. J.; Wei, S. H.; Wilson, S. J. *Macromolecules* **2013**, *46*, 3228–3233.

(61) Darensbourg, D. J.; Chung, W.; Arp, C. J.; Tsai, F.; Kyran, S. J. *Macromolecules* **2014**, *47*, 7347–7353.

(62) Tomczyk, K. M.; Gu, P. A.; Parzuchowski, P. G.; Zachara, J.; Rokicki, G. *Green Chem.* **2012**, *14*, 1749–1758.

(63) Jones, K. M.; Tomkinson, N. C. O. *J. Org. Chem.* **2012**, *77*, 921–928.

(64) Maras, A.; Secen, H.; Sutbeyaz, Y.; Balci, M. *J. Org. Chem.* **1998**, *63*, 2039–2041.

(65) Boyd, D. R.; Sharma, N. D.; Berberian, M. V.; Dunne, K. S.; Hardacre, C.; Kaik, M.; Kelly, B.; Malone, J. F.; Mcgregor, S. T.; Stevenson, P. J. *Adv. Synth. Catal.* **2010**, *352*, 855–868.

(66) Article, E.; Bering, L.; Antonchick, A. P. *Chem. Sci.* **2016**, *8*, 452–457.

(67) Metin, O.; Alp, N. A.; Akbayrak, S.; Bicer, A.; Gultekin, M. S.; Ozkar, S.; Bozkaya, U. *Green Chem.* **2012**, *14*, 1488–1492.

(68) Emmanuvel, L.; Mahammad, T.; Shaikh, A.; Sudalai, A. *Org. Lett.* **2005**, *7*, 5071–5074.

Chapter IV

Stereodivergent Carbamate Synthesis by Selective Trapping of Oligo-Carbonate Intermediates

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‡ Equal contribution

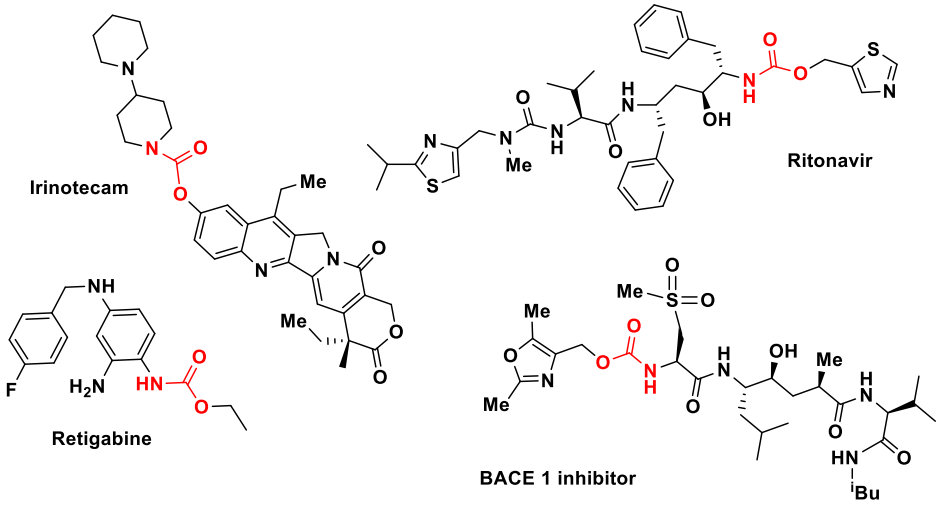
UNIVERSITAT ROVIRA I VIRGILI
SMALL MOLECULE ACTIVATION FOR THE FORMATION OF HETEROCYCLIC COMPOUNDS
Victor Laserna Ayora

4.1 Introduction

4.1.1 Carbamates

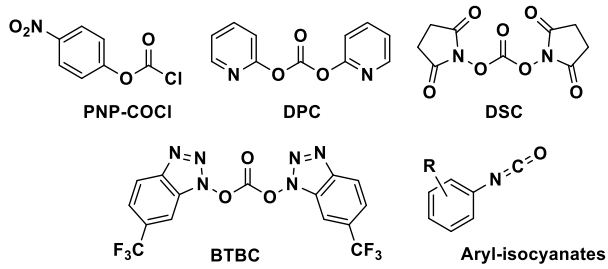
Carbamates are a class of compounds derived from carbamic acids. Without any substituents, carbamates are not stable at room temperature but substituted analogues are stable and can be found ubiquitously in a range of synthetic products of general use such as agrochemicals and pharmaceuticals.[1] They play an important role in the area of synthetic organic chemistry, particularly as synthetic intermediates for the protection of amino groups in peptide chemistry and as linkers in combinatorial chemistry. Despite this interesting potential, their most important role is in polymer science.[2] Polyurethanes (PUs) are polymers widely used in modern life due to their versatile properties. PUs represent a class of polymers that can display thermoplastic, elastomeric, and thermoset behavior, depending on their chemical and morphological macro- and microstructures. The global PU production currently accounts for around 5% of the entire polymer market, being the sixth most abundant polymer produced and utilized in our societies. They are structurally similar to oxazolidinones which are cyclic urethanes (chapter I).

Figure 4.1 Representative examples of pharmaceutical products with a carbamate moiety.



Their seemingly privileged incorporation into a wide range of chemical/pharmaceutical structures has been enabled by synthetic methodologies that are conventionally based on the use of toxic reagents such as phosgene, isocyanates and other carbonyl derivatives[3]. In **Figure 4.2** the most commonly employed precursors of carbamates are presented.

Figure 4.2 Reagents typically used in carbamate synthesis and their abbreviations.

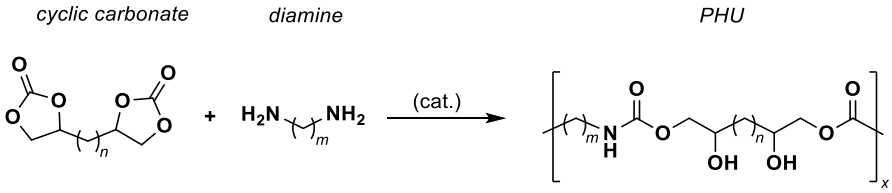


Notably, all of these methodologies using the reagents from **Figure 4.2** include either harsh reaction conditions, such as high temperature and pressure, and exhibit poor functional group tolerance. Therefore, development of new, effective, and chemoselective methodologies that can be carried out under mild conditions and are based on sustainable reagents is highly desirable.

4.1.2 Aminolysis of Cyclic Carbonates

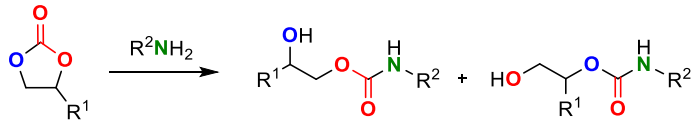
Driven by the need for more sustainable approaches towards carbamates, both linear[4,5] and cyclic organic carbonates[6–8] have become popular reaction partners of amines to afford these widely targeted molecules. This formal aminolysis process involves a nucleophilic attack of the amine reagent onto the carbonyl atom of the carbonate ring in a ring-opening process, yielding a hydroxy carbamate. This reaction is the basis of a promising alternative for the industrial preparation of PUs, by using dicarbonates and diamines to afford poly(hydroxy-urethanes) (PHUs), which are considered a greener alternative for phosgene-based PU synthesis. The carbonate structures can be easily obtained through epoxide/CO_2 coupling reactions (See: Introduction and chapter 3) providing a valorization process of a waste combustion product, which is relatively safe, cheap, and readily accessible.

Figure 4.3: Example of PHU formation between a diamine and a dicarbonate. Only one isomer of the PHU is shown here.



The aminolysis reaction of cyclic organic carbonates is well-documented and typically proceeds under mild reaction conditions when using simple primary or secondary alkyl amines and mono-substituted cyclic carbonate reagents. However, the reaction is highly sensitive towards the overall steric requirements thereby complicating the development of this reaction towards efficient methods for the conversion of highly substituted cyclic organic carbonates combined with primary and secondary amines. This aminolysis reaction is also chemoselective when using aliphatic, primary and secondary amines. If an aromatic amine is used, the reaction is much slower and the selectivity towards the hydroxy carbamate decreases, producing at high temperature various side products. Recently, a general method for the aminolysis of cyclic carbonates with aromatic amines was reported.[9] TBD was used (= 1,5,7-triazabicyclo[4.4.0]dec-5-ene) as organocatalyst which is able to induce a proton-relay mechanism which facilitates the nucleophilic attack on the carbonyl atom, yielding hydroxy carbamates. When dealing with mono-substituted carbonates, the aminolysis reaction can lead to two possible isomeric hydroxy carbamates depending on which C–O bond is broken during the carbamate formation (See **Figure 4.4**).

Figure 4.4: Example of hydroxy carbamate formation by aminolysis of a mono-substituted carbonate.



The regioselectivity towards either product is difficult to control, and only few reports show complete regiocontrol in the aminolysis and these usually involve substrates with highly substituted cyclic carbonates or those with strong electron-withdrawing groups.[8,10] An alternative approach to these hydroxyl carbamates was studied by Inoue in the 1980s.[11] This approach consists of a nucleophilic attack onto an epoxide by a carbamate

intermediate generated by an amine under high CO_2 pressures and stabilized by an Al(porphyrin) catalyst. This resulted in an effective approach to solve the regioselectivity issue as the nucleophilic attack was quite selective on the least hindered position of the epoxide substrate, although harsh conditions are necessary and the scope remained limited to only terminal epoxides.[12] The aminolysis of cyclic carbonates with more complex substitution patterns has seldom been studied. Our group has published how TBD can act as a catalyst in the regioselective aminolysis of a series of di- trisubstituted carbonates. As expected, the stereochemistry of the cyclic carbonate having *syn*-disubstitution was maintained during the aminolysis process, meaning that the hydroxy-carbamate product had a *cis* configuration.

Regarding cyclic scaffolds, *cis*-configured hydroxy carbamates are produced straightforwardly from their respective *cis*-cyclic carbonates whose synthetic methodology has advanced significantly over the years. However, the *trans*-hydroxy carbamates cannot be easily accessed synthetically through this approach as cyclic *trans* configured carbonates are not as accessible as their *cis*-configured analogues. Only Inoue[11] previously reported on the formation of a *trans*-hydroxy carbamate but the scope and yield remained highly limited. Few contributions have reported the formation of trace or very low amounts of *trans* cyclic carbonates from the depolymerization of poly-carbonate precursors, but these were neither isolated nor used in further synthesis.[13]

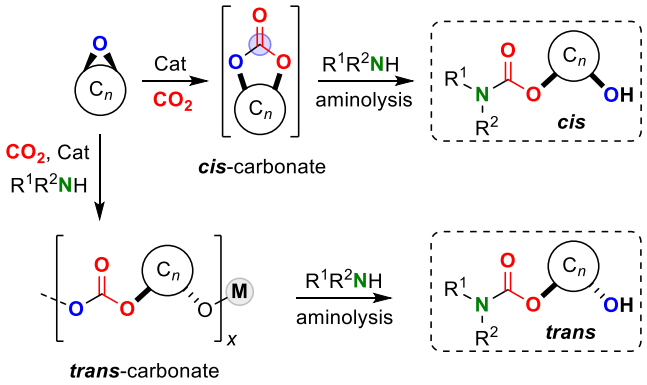
4.1.3 Project Aims and Strategy

We envisioned that the formation of a cyclic organic carbonate intermediate, using our previously described catalytic system based on a binary couple of an Al(amino triphenolate) complex and a suitable nucleophilic additive, and the aminolysis reaction could potentially be combined in a one-pot tandem, three-component approach. This would then afford the carbamate structures without the need for isolation of the cyclic carbonate product simplifying the synthetic protocol and thus using the carbonate as a reactive intermediate. We anticipated four main challenges to be solved with such an approach that aims at a general tandem three-component reaction having the amine partner added at the initial stage of the reaction. Firstly, the efficient formation of organic carbonates from the more challenging and much less reactive internal epoxides. Second, the competitive nature of the amine reagent that could block the Lewis acidic catalyst for effective turnover. In third place, the potential aminolysis of the epoxide substrate that could give substantial amino-alcohol side-product

formation in those cases where the formation of the organic carbonate is relatively slow. Finally, controlling the regio- and stereoselectivity of the process also represents a potential issue.

We were also interested to see whether the stereocontrol in the formation of the carbonate intermediate could be biased towards a stereodivergent methodology to achieve the formation of both *cis* and *trans*- hydroxy carbamates selectively from a single substrate. In order to tackle the stereoselectivity challenge, we considered that *in situ* and selective formation of a *trans*-carbonate (cyclic or polycarbonate) would trigger the formation of a *trans*-carbamate by aminolysis. The use of appropriate catalytic copolymerization conditions could selectively lead to a growing *trans*-configured oligo-carbonate chain with the amine actively participating in the aminolysis of the metal-bound oligomer in a one-pot approach, while using conditions which favor the formation of the *cis* cyclic carbonate would lead to the formation of the *cis* hydroxy-carbamate (see **Figure 4.5**).

Figure 4.5: Divergent approach towards carbamates using diastereo-isomeric carbonate intermediates. M stands for metal catalyst stabilizing an oligo-carbonate intermediate.



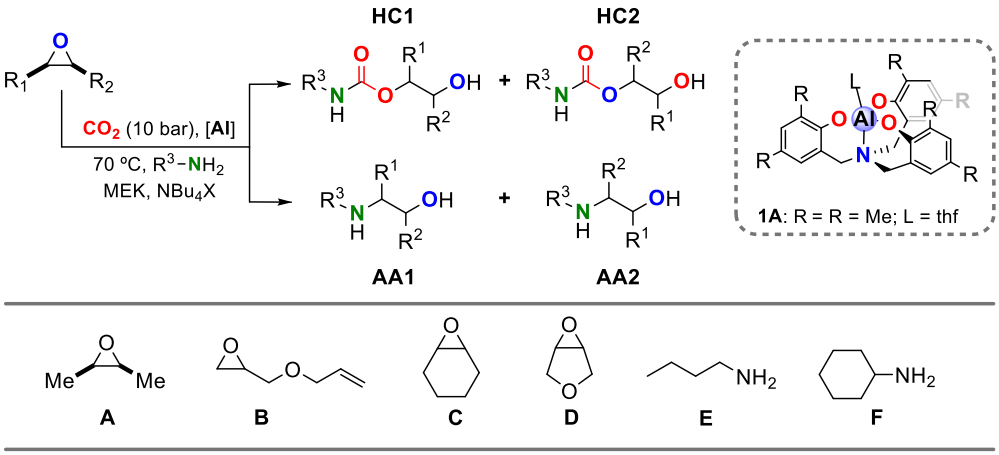
4.2 Results and Discussion

First we decided to investigate the influence of the presence of catalytic amounts of Al(amino triphenolate) complex **1A** and nucleophilic additive (NBu_4X; X = Br, I) on the selectivity and reactivity features of representative examples of various cyclic ethers and amines in the three-component based synthesis of carbamates derived from CO_2. From the

data reported for the conversion of epoxides **A-D** (**Table 4.1**), it is clear that in order to achieve both higher chemo-selectivity as well as high yields of the corresponding hydroxy carbamate products (**HC**) under mild conditions (10 bar, 70 ºC), the presence of both Al-catalyst and the nucleophilic additive (NBu_4X) is warranted. The conversion of terminal epoxides (**B**) into hydroxy carbamates (**HC**) is more favored and it can be observed that the presence of only the nucleophile is sufficient for an efficient reaction. For internal epoxides (**A**, **C** and **D**) the presence of both components of the binary catalyst **1C**/NBu_4Br is an important requisite for achieving high yields and selectivity for the carbamate product, in line with the more challenging nature of these substrates as a result of their ring-opening being energetically less favored.

The mild operating conditions (70 ºC, 10 bar) are not favorable for efficient carbamate formation in the absence of complex **1A** and nucleophile as evidenced in **Table 4.1**; the addition of the binary catalyst **1A**/NBu_4X significantly increases the yield of the desired products. The difference in yields towards **HC** (**Table 4.1**) in the presence/absence of nucleophile gives an idea about the contribution of the "CO_2-based carbamate-induced mechanism" versus the formation of the carbamate through a "carbonate intermediate". The contribution of each mechanism varies depending on the substrate but in general a significant increase in yield is noted in the presence of an external nucleophile (NBu_4X), indicating that the "carbonate pathway" is more dominant. When using terminal epoxides, the presence of 2.5 mol% of nucleophile is sufficient to achieve high conversions which are only slightly improved by adding Al-complex **1A**. The efficient formation of carbamates from terminal epoxides prompted us to examine the scope of these relatively easy to prepare targets (**Figure 4.6**) and evaluate the functional group tolerance/diversity. Using 0.5 mol% of **1A** and 2.5 mol% of NBu_4I we were able to isolate 10 structurally different carbamates through a one-pot three-component approach. Our catalytic system seems to overcome the predicted problems as the catalyst is not deactivated by the presence of the amine reagent, and it also increases the yield significantly in the conversion of the internal epoxides.

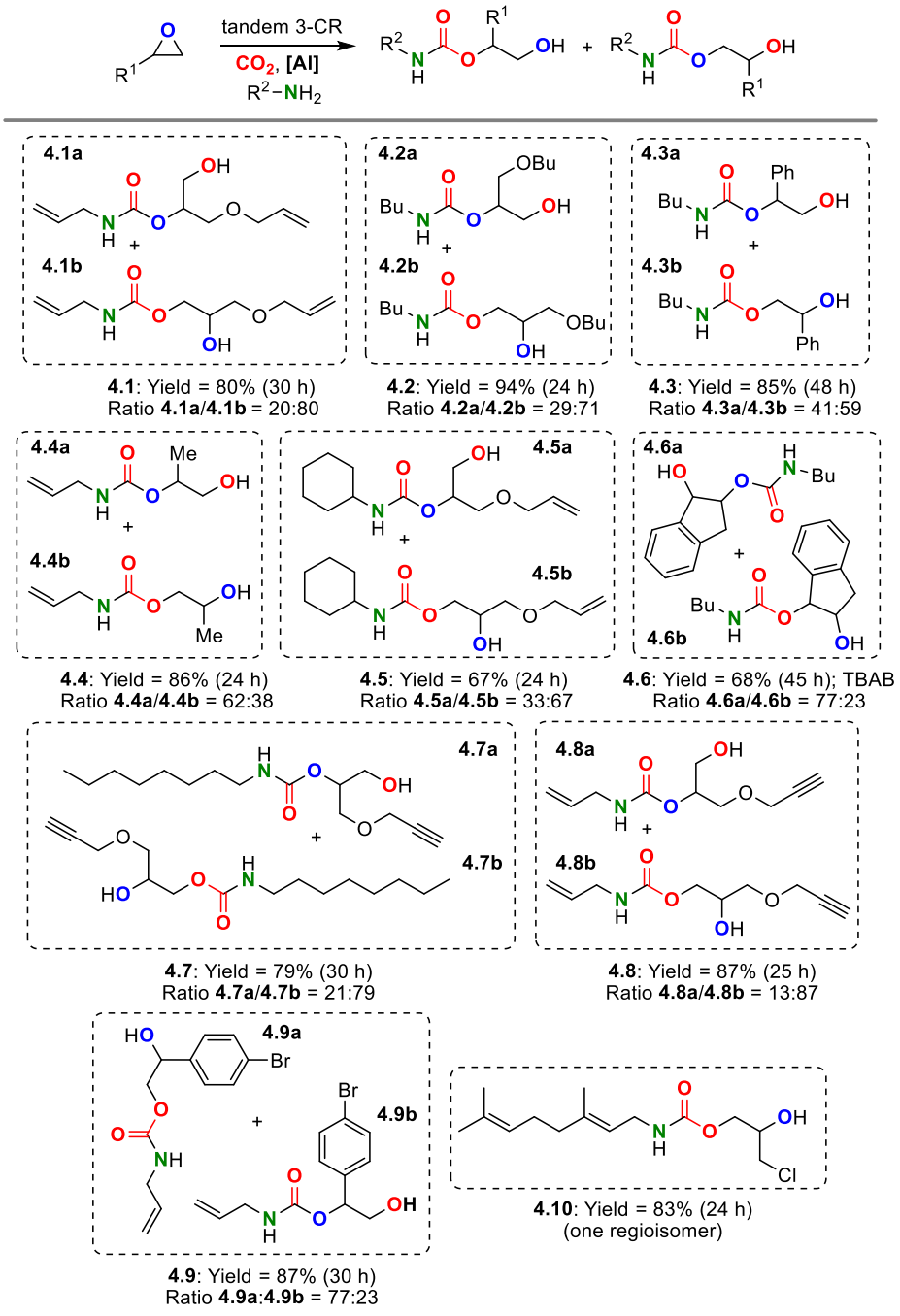
Table 4.1: One-pot approximation studies towards *in situ* carbamate formation. Subs stands for substrate combination.[a]



Entry	Subs.	Cat.	X	t (h)	% HC[b]	% AA[b]
1	**A+E**	–	–	30	14	<5
2	**A+E**	**1A**	–	30	19	<5
3	**A+E**	–	**Br**	30	13	<1
4	**A+E**	**1A**	**Br**	30	73 (61)[c]	<1
5	**B+F**	–	–	24	10	86
6	**B+F**	**1A**	–	24	<2	97
7	**B+F**	–	**I**	24	72[d]	8
8	**B+F**	**1A**	**I**	24	80(67)[c,e]	11
9	**C+E**	–	–	30	37	10
10	**C+E**	**1A**	–	30	34	25
11	**C+E**	–	**Br**	30	14[f]	8
12	**C+E**	**1A**	**Br**	30	76(60)[c]	16
13	**D+F**	–	–	70	<1	<1
14	**D+F**	**1A**	–	70	15	18
15	**D+F**	–	**Br**	70	9[g]	<5
16	**D+F**	**1A**	**Br**	70	79(76)[c]	17

Conditions: [a] 4 mmol of substrate, 70 ºC, 24–70 h, 0.5 mol% catalyst **1A**, 2.5 mol% NBu_4**X** (**X** = I or Br), 1.8 equiv of amine, $p(CO_2)$º = 10 bar. [b] Total yield of **HC** or **AA** product as determined by ^{1}H NMR using mesitylene as internal standard. [c] In parentheses the isolated yields. [d] 18% of cyclic carbonate observed. [e] 8% of cyclic carbonate observed. [f] 13% of cyclic carbonate observed. [g] 20% of cyclic carbonate observed.

Figure 4.6: Investigated scope of terminal epoxide/primary amine coupling reactions. General Conditions: 4 mmol of substrate, 70 ºC, 24–70 h, 0.5 mol% catalyst **1A**, 2.5 mol% NBu_4X (X = I or Br), 1.8 equiv of amine, $p(CO_2)^o$ = 10 bar.



Despite that amino alcohol (**AAs**) sub-products are formed originating from the nucleophilic attack of the amine onto the epoxide, their amount remains limited (<10%) in most of the reactions studied when a combination of **1A**/NBu_4X is present. In most of the reactions the major sub-product is the cyclic carbonate, which is the intermediate for the targeted carbamate product.

When *meso*-epoxide substrates such as **A**, **C** and **D** were used (Figure to **Table 4.1**), there are obviously no regioisomeric issues though the crude mixture of products displayed the presence of two stereoisomers, namely the *cis* and *trans* configured hydroxy carbamates. The success of the three-component synthesis of carbamates **4.1–4.10** (**Figure 4.6**) from cyclic ethers, amines and CO_2 under mild reaction conditions provided a starting point for the development of stereo-divergent and -selective formation of a series of functional carbamates (section 4.2.1).

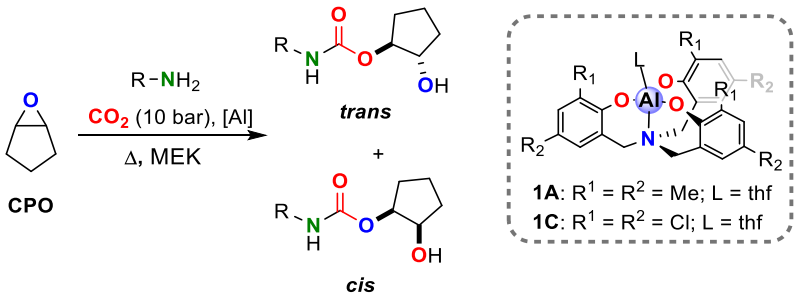
4.2.1 Parameter Screening towards Diastereoselective Synthesis

As part of this subsequent screening study, we initially considered the one-pot conversion of five-membered ring cyclic epoxides (cyclopentene oxide, CPO, and 3,4-epoxyfuran), three different primary amines $R^1–NH_2$ (R^1 = Cy, Bu, Octyl) and CO_2 by using Al(amino triphenolate) complexes **1A** and **1C** (**Table 4.2**). The use of this type of Al-complex has been reported for both polycarbonate[14] and cyclic carbonate formation[15] using slightly different reaction conditions and Al/nucleophile loadings. Suitable nucleophilic additives, which include NBu_4Br (Br) and PPNCl (Cl; PPN= bis(triphenylphosphine)iminium), were used as these were previously shown to have the best potential in the formation of polymeric carbonates in the presence of amino triphenolate complexes.

For Fe^{III} -based amino triphenolate complexes, a switch in chemoselectivity between cyclic and polycarbonate was observed in cyclohexene oxide/CO_2 couplings,[16] depending on the solvent, dilution, Fe/nucleophile ratio and the type of nucleophile used. Stronger nucleophiles generally favor double inversion pathways (cf., cyclic carbonate) while less nucleophilic species favor polycarbonate formation. To selectively form the *cis* carbamate product, we decided to use a two-step approach. To simplify the protocol, first the *cis* cyclic carbonate was formed by using the conditions reported in the previous chapter and once the reaction was complete, 1.2 equivalents of amine were added to the reaction crude that was

then stirred overnight. With this strategy, for CPO and 3,4-epoxyfuran the *cis* configured hydroxy carbamate was selectively formed using butyl amine (82% and 83% isolated yield respectively). In order to selectively form the *trans* diastereoisomer, other experimental conditions are required using a one pot strategy with the aim to form selectively an oligocarbonate intermediate *in situ* which may be intercepted by an amine to form a *trans*-carbamate product (**Table 4.2**).

Table 4.2 Screening of suitable catalytic conditions to form a *trans* carbamate from CPO.[a]



Entry	R^1	Cat. (mol%)	Nu (mol%)	T (ºC)	t (h)	Yield (%)[b]	*trans*:*cis* [c]
1	Oct	**1C**, 0.5	**Br**, 2.0	70	70	45	72:28
2	Oct	**1C**, 0.5	**Cl**, 1.0	60	24	7	85:15
3	Oct	**1A** 2.0	**Cl**, 2.0	60	60	45	96:4
4	Oct	**1A** 2.0	**Cl**, 2.0	70	60	49	83:17
5	Oct	**1A** 2.0	–	60	24	5	>99:1
6	Oct	**1A** 2.0	–	60	60	9	>99:1
7	Bu	**1C**, 0.5	**Br**, 2.0	70	70	73	57:43
8	Bu	**1A**, 2.0	**Cl**, 2.0	60	24	51	89:11
9	Bu	**1A**, 2.0	-	60	24	4	>99:1
10[d]	Bu	**1A**, 2.0	-	60	24	11	>99:1

[a] Using 4mmol of CPO, 0.5 mL MEK. [b] Carbamate NMR yield using mesitylene as internal standard. [c] Determined by ^{1}H NMR. [d] Reaction at 40 bar

Table 4.2 reports the use of typical copolymerization conditions (*i.e.*, using **Cl** as nucleophile, Al-complex **1A**, Al/Nu = 1, 60ºC) leading to the preferred formation of the targeted *trans*-carbamate product with high *dr´*s of up to 96:4 (*entry 3*) when *n*-octylamine is used and 89:11 in the case of *n*-butylamine (*entry 8*). In *entries 1* and *7* typical and known conditions are presented for the comparatively more preferred formation of *cyclic* carbonate

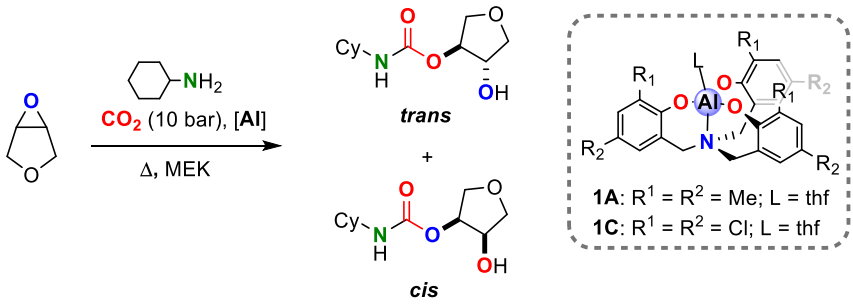
intermediate using complex **1C** (that has a higher Lewis acidity) and excess of a nucleophile. In both latter cases lower selectivity towards *trans* carbamate is noted, though >50% of the carbamate product is *trans*, suggesting that under these reaction conditions the formation of an oligomeric carbonate is still competitive. However, the carbamate yields remain rather low due to side reactions such as aminolysis. By lowering the temperature, the Al/Nu ratio and using a less nucleophilic co-catalyst (*entry 2*) the selectivity towards the *trans* product was improved, though a drastic decrease in carbamate yield was noticed and the main product under these conditions was the amino alcohol. There are generally two types of side-products observed, of which one is an amino alcohol produced by the aminolysis of the oxirane substrate. This side reaction is favored by more Lewis acidic catalysts such as **1C**, which is a strong activator for nucleophilic ring-opening by the amine reagent. The other observed side product, although generally formed in lower quantity compared to the amino alcohol, is a *cis* configured cyclic carbonate and its formation is favored again by the more Lewis acidic metal complex **1C**. This explains why in the presence of complex **1A,** usually higher selectivity towards the *trans* hydroxy carbamate is achieved, favoring the occurrence of a requisite oligocarbonate intermediate.

In the absence of nucleophile, much lower conversions are noted (*entries 5, 6, 9* and *10*) albeit under excellent diastereoselective control, and this is likely to be the result of a previously discussed background reaction.[11] Under the reaction conditions, the amine may react with CO_2 to form a carbamate species, which can affect ring-opening of the epoxide to form the *trans* carbamate, though in very low yield. This background reaction proceeded somewhat better under much harsher pressure conditions (i.e., 40 bar) with concomitant formation of substantial amino alcohol side-product. Apparently, under the mild conditions reported here, the formation of a carbamate nucleophile derived from the amine and CO_2 is either catalytically incompetent or only formed in very low amounts. The use of secondary amine reagents led only to amino alcohol product, that is, selective aminolysis of the oxirane substrate occurred.

To test the generality of the found trends with CPO, we decided to screen the conditions for a similar epoxide combined with a slightly more sterically hindered cyclohexyl amine (Cy; **Table 4.3**). In the absence of any catalyst the reaction does not take place (*entry 1*), and only slow aminolysis of the epoxide is observed. The presence of only Al complex **1C** favors formation of low amount of the *trans* product (*entry 2*), and if only nucleophile is used

very low conversion to a mixture of *cis* (major) and *trans* (minor) product is achieved. Yields and selectivities towards these diastereoisomers follow a similar trend as noted in **Table 4.2**. Comparing *entries 5* and *6* gives the impression that more diluted reaction mixtures show a higher tendency towards *cis* isomer formation. Higher loadings of Al-complex, higher reaction temperatures and/or the use of more nucleophilic co-catalyst also seem to reduce the ability of the binary catalyst to selectively form the *trans* carbamate (*entries 8-10*) probably by favoring the double inversion pathway and aminolysis of the epoxide.

Table 4.3: Screening of suitable catalytic conditions to form the *trans* carbamate from 3,4 epoxyfuran.[a]

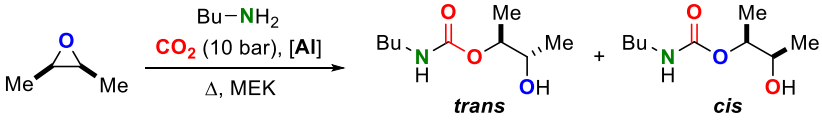


Entry	Cat. (mol%)	Nu (mol%)	MEK (mL)	T (ºC)	Yield %[b]	*trans*:*cis*[c]
1	–	–	1.0	70	<1	-
2	**1C**, 0.5	–	1.0	70	15	99:1
3	–	**Br**, 2.0	1.0	70	9[d]	36:64
4	**1C**, 0.5	**Br**, 2.0	1.0	70	81	76:24
5	**1C**, 0.5	**Cl**, 2.0	0.50	70	57	79:21
6	**1C**, 0.5	**Cl**, 2.0	2.0	70	55	63:37
7	**1A**, 1.0	**Cl**, 1.0	0	60	29	91:9
8	**1A**, 2.0	**Cl**, 2.0	1.0	70	35	57:43
9	**1A**, 0.5	**Br**, 2.0	2.0	90	46	70:30
10	**1A**, 2.0	**Br**, 2.0	2.0	70	26[e]	27:73

[a] Conditions: 4 mmol of epoxide, 1.2 equiv of amine, $p(CO_2)^0$ = 10 bar, 70 h reaction [b] Total yield of *cis* and *trans* carbamate products as determined by ^{1}H NMR using mesitylene as internal standard. [c] Determined by ^{1}H NMR. [d] 15% cyclic carbonate byproduct observed. [e] 59% amino alcohol byproduct observed.

Further combinations of internal epoxides (*cis*-2,3-epoxybutane and cyclohexene oxide) and butyl amine were then also probed under similar conditions (see **Tables 4.4** and **4.5**). In all these cases, good to excellent selectivity towards the *trans*-carbamates (*dr* >99:1) were obtained validating further the current one-pot approach. Therefore, the general perception is that in order to achieve high selectivities for the *trans* carbamate product, each combination of epoxide and amine reaction partners needs separate optimization of the reaction conditions, but generally *trans* carbamate formation is favored at lower temperatures, in the presence of weak(er) nucleophiles (**Cl**), and using Al-complex **1A** at loadings ≤ 1 mol%.

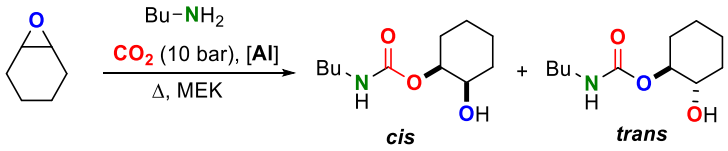
Table 4.4: Screening of suitable catalytic conditions to form the *trans* carbamate from *cis*-2,3-epoxybutane.[a]



Entry	Cat. (mol%)	Co-cat. (mol%)	T (ºC)	Time (h)	Yield[b] (%)	*trans*:*cis*[c]
1	-	-	70	30	14[d]	n.d
2	-	**Br**, 2.5	70	30	13[d]	n.d
3	**1C**, 0.5	-	70	30	18[d]	>99:1
4	**1C**, 0.5	**Br**, 2.5	70	30	61	67:33
5	**1A**, 0.5	**Br**, 2.5	70	30	50	67:33
6	**1A**, 0.5	**Cl**, 3.0	70	40	44	>99:1
7	**1C**, 1.5	**Cl**, 3.0	70	60	56	93:7

[a] Reaction conditions: 4 mmol of epoxide, 1.0 mL of MEK, 10 bar of CO_2 and 10 mmol of butylamine. [b] Isolated yield. [c] Determined by ^1H NMR. [d] NMR yield using mesitylene as an internal standard.

Table 4.5: Screening of suitable catalytic conditions to form the *trans* carbamate from CHO.[a]



Entry	Cat. (mol%)	Co-cat. (mol%)	T (ºC)	Time (h)	Yield %[b]	*trans*:*cis* [c]
1	**1C**, 0.5	-	70	30	34	99:1
2	-	**Br**, 2.0	70	30	14	87:13
3	-	-	70	30	37	99:1
4	**1C**, 0.5	**Br**, 2.0	70	30	76(60)	99:1

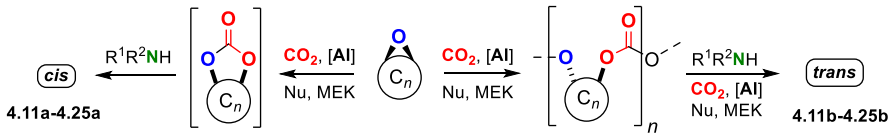
[a] Reaction conditions: 4 mmol of epoxide, 1.0 mL of MEK, 10 bar of CO_2 and 10 mmol of butylamine. [b] NMR yield using mesitylene as an internal standard. [c] Determined by ^{1}H NMR.

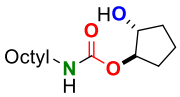
The use of CHO as substrate leads to selective formation of the *trans* carbamate product. This is due to the high tendency of CHO/CO_2 towards copolymerization. The *trans* carbamate product can only be derived from an oligomeric intermediate. Therefore, it seems reasonable to suggest that the formation of the *trans* cyclic carbonate from CHO in these conditions is through a polymeric intermediate followed by a carbonate-driven depolymerization or backbiting process (see previous chapter).

4.2.2 Scope of *cis*- and *trans*- Carbamate Products

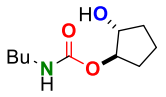
Having established a set of suitable reaction conditions leading selectively to *cis* and *trans*-configured carbamates, we then investigated the scope of carbamate products in more detail (**4.11–4.25**, **Figure 4.7**). The *cis*-carbamates **4.11a–4.25a** were prepared by prior formation of their *cis*-carbonates: the aminolysis reaction was then carried out by addition of the appropriate amine. Reported in **Figure 4.7** are the overall yields of **4.11a–4.25a** based on the starting epoxides, i.e. after two steps. In general, the stereo-control towards the *cis* and *trans*-carbamates **4.11b–4.25b** is excellent providing the compounds with *dr´*s of ≥ 93:7 (apart from **4.12b** and **4.23b**; *dr* = 89:11 and 77:23, respectively).

Figure 4.7: Formation of *cis* and *trans* carbamate products **4.11–4.25**

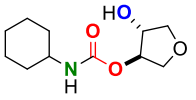




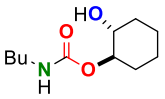
4.11a-*cis*: 66 h, 70ºC, 69%, *dr* = 99:1
4.11b-*trans*: 60 h, 45%, *dr* = 96:4
1A: 2 mol%, PPNCl 2 mol%, 60 ºC



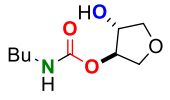
4.12a-*cis*: 50 h, 50ºC, 68%, *dr* > 99:1
4.12b-*trans*: 66 h, 51%, *dr* = 89:11
1A: 2 mol%, PPNCl 2 mol%, 60 ºC



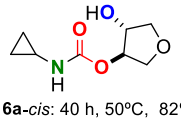
4.13a-*cis*: 40 h, 50ºC, 75%, *dr* > 99:1
4.13b-*trans*: 70 h, 57%, *dr* > 99:1
1C: 0.5 mol%, TBAB 2.5 mol%, 70 ºC



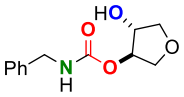
4.14a-*cis*: 30 h, 50ºC, 83%, *dr* > 99:1
4.14b-*trans*: 30 h, 60%, *dr* > 99:1
1C: 0.5 mol%, TBAB 2.5 mol%, 70 ºC



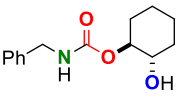
4.15a-*cis*: 40 h, 50ºC, 82%, *dr* > 99:1
4.15b-*trans*: 60 h, 67%, *dr* > 99:1
1C: 0.5 mol%, TBAB 2.5 mol%, 70 ºC



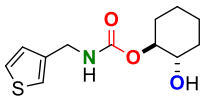
4.16a-*cis*: 40 h, 50ºC, 82%, *dr* > 99:1
4.16b-*trans*: 60 h, 50%, *dr* > 99:1
1C: 1.5 mol%, PPNCl 3 mol%, 60 ºC



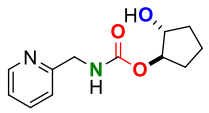
4.17a-*cis*: 40 h, 70ºC, 61%, *dr* = 99:1
4.17b-*trans*: 45 h, 60ºC, 65%, *dr* > 99:1
1A: 2 mol%, PPNCl 3 mol%



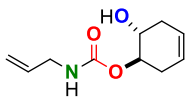
4.18a-*cis*: 45 h, 50ºC, 78%, *dr* > 99:1
4.18b-*trans*: 24 h, 72%, *dr* > 99:1
1C: 0.5 mol%, TBAB 2.5 mol%, 70 ºC



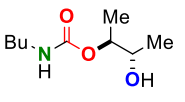
4.19a-*cis*: 40 h, 70ºC, 76%, *dr* > 99:1
4.19b-*trans*: 30 h, 52%, *dr* > 99%
1C: 0.5 mol%, TBAB 2.5 mol%, 70 ºC



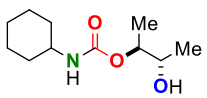
4.20a-*cis*: 30 h, 50ºC, 74%, *dr* = 99:1
4.20b-*trans*: 40 h, 43%, *dr* > 99:1
1A: 2 mol%, PPNCl 2 mol%, 60 ºC



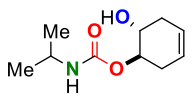
4.21a-*cis*: 30 h, 50ºC, 71%, *dr* > 99:1
4.21b-*trans*: 30 h, 54%, *dr* > 99:1
1C: 0.5 mol%, TBAB 2.5 mol%, 70 ºC



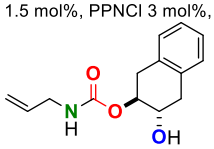
4.22a-*cis*: 30 h, 50ºC, 68%, *dr* = 99:1
4.22b-*trans*: 60 h, 56%, *dr* = 93:7
1C: 1.5 mol%, PPNCl 3 mol%, 70 ºC



4.23a-*cis*: 30 h, 50ºC, 66%, *dr* = 99:1
4.23b-*trans*: 30 h, 51%, *dr* = 77:23
1C: 1.5 mol%, PPNCl 3 mol%, 70 ºC



4.24a-*cis*: 30h, 50ºC, 71%, *dr* =99:1
4.24b-*trans*: 30 h, 47%, *dr* = 99:1
1C: 0.5 mol%, TBAB 2.5 mol%, 70 ºC



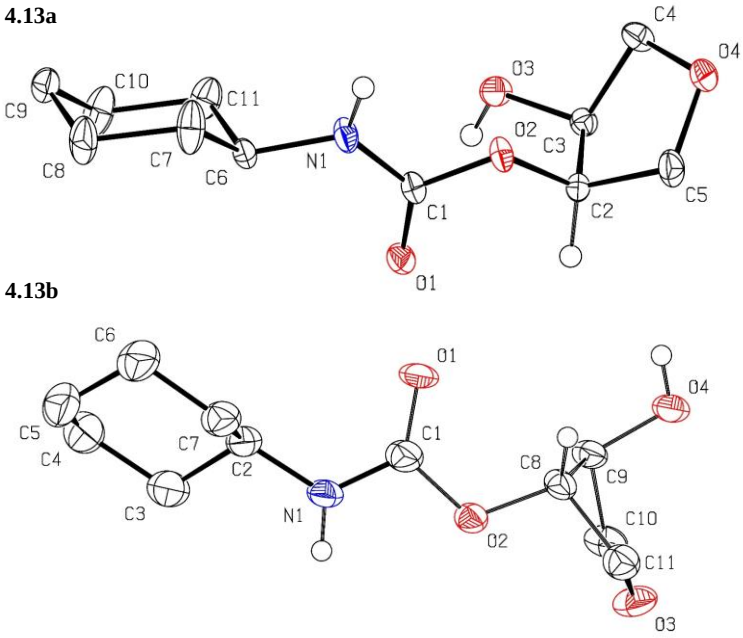
4.25a-*cis*: 66 h, 50ºC, 72%, *dr* = 99:1
4.25b-*trans*: 84 h, 60%, *dr* > 99:1
1C: 0.5 mol%, TBAB 2.5 mol%, 70 ºC

The approach is applicable towards various five- and six-membered cyclic and also acyclic epoxides (*cis*-2,3-epoxybutane, *cf.* formation of **4.22b** and **4.23b**) without compromising significantly the diastereo-selectivity of the reaction. Various functionalized amines are tolerated bearing allyl (**4.21b** and **4.25b**), cyclopropyl (**4.16b**), thiophenelyl (**4.19b**), and pyridyl (**4.20b**) groups whereas the use of use of more functional epoxides allows for the incorporation of potentially useful furan (**4.13b**, **4.15b** and **4.16b**) or cyclohexenyl (**4.21b** and **4.24b**) fragments. The molecular structures for carbamates **4.11–4.25** (both

diastereoisomers) were fully supported by 1D/2D NMR and IR spectroscopic techniques, and HRMS. For *cis*-**4.13a** and *trans*-**4.13b** the X-ray molecular structures (**Figure 4.8**) were determined and further supported their *cis* and *trans* assignment in line with the spectroscopic data.

The isolated yields for the *cis*-carbamates **4.11a–4.25a** were generally higher than those obtained for the *trans* diastereo-isomers **4.11b–4.25b**; this suggests that the one-pot approach with the amine present at the early stage of the reaction may, as expected, slow down overall kinetics as the amine may compete for coordination to the Al-center present in complexes **1A** or **1C**. Also, the formation of the amino alcohol may compete with the formation of the carbamate when a one-pot strategy is used.

Figure 4.8: X-ray molecular structures of compounds *cis*-**4.13a** and *trans*-**4.13b**.



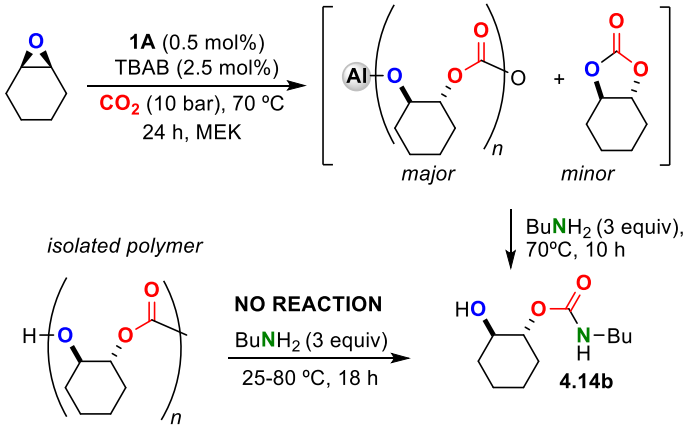
4.2.3 Mechanistic Insights

In order to gain some insight into the mechanism of *trans*-carbamate formation, several additional experiments were conducted to further support the idea of an oligomeric intermediate. Initially, an *isolated* sample of a copolymer based on CHO/CO_2 was subjected

to the general reaction conditions of the one-pot carbamate formation (*i.e.*, in the presence of CO_2, complex **1C**, NBu_4Br, MEK, 70ºC, 18 h) but the presence of the *n*-butyl amine did not provoke any observable aminolysis, not even at temperatures as high as 110 ºC as evidenced by ^{1}H NMR comparison: the polymer which was isolated by precipitation with acidic methanol from the reaction crude, remained unreacted (**Figure 4.9**). It is important to take into account that this isolation method protonates the terminal alkoxide of the polymer chain leaving an OH end-group which is much less nucleophilic than a metal-alkoxide upon oligomerization of CHO and CO_2.

We decided to freshly prepare the CHO/CO_2 copolymer in the absence of the amine using catalyst **1C** (0.5 mol%) and NBu_4Br (2 mol%) at 70 ºC for 24 h; at this stage ^{1}H NMR analysis showed virtually full conversion into a fully alternating poly(cyclohexene)carbonate (PCHC, 99% polymer selectivity) with trace amount (1%) of *trans*-cyclohexene carbonate (*trans*-CHC).

Figure 4.9: Support experiments for pathway 1 in **Figure 4.10**.

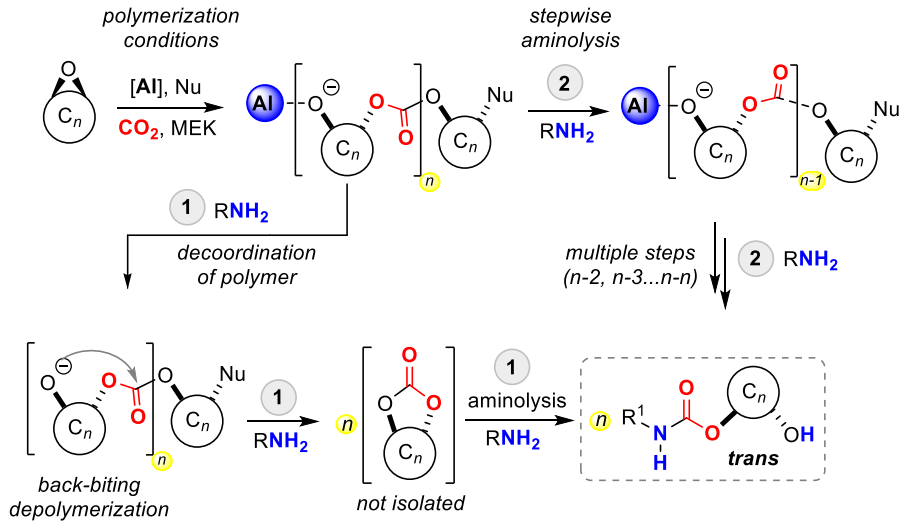


Without applying the usual work up and with the metal likely still bound to the polymer, it was treated with 3 equiv of *n*-butyl amine for 10 h at 70ºC and then an aliquot of the crude reaction mixture was analyzed by ^{1}H NMR. Fortunately, conversion (65%) to the carbamate **4.14b**-*trans* (*dr* > 99:1) was noted with the remaining 35% consisting of a mixture of 85% PCHC and 15% of *trans*-CHC (*i.e.*, a clear increase in the *trans* carbonate/polymer ratio), see **Figure 4.9**. The relative increase in *trans*-CHC can be explained by a depolymerization of the metal-free copolymer when adding the amine which may compete

for coordination to the Al-center (**Figure 4.10**, pathway 1). The decoordinated polymer then leads to *trans*-CHC by a relatively fast alkoxide back-biting process towards the *trans*-carbonate and *in situ* aminolysis to give *trans*-**4.14b** as product.

A similar polymer degradation/aminolysis sequence (**Figure 4.10**, pathway 1) seems plausible for the acyclic *cis*-2,3-epoxybutane case. In the absence of amine reagent and using the reaction conditions reported for *trans*-**4.22b** and *trans*-**4.23b** (**Figure 4.7**), ^{1}H NMR analysis showed the mixtures to contain only the cyclic carbonate product with a *trans* selectivity up to 83% in reasonable agreement with the reported *dr* values for the two carbamate products derived from *cis*-2-butene oxide. Copolymers derived from *cis*-2,3-epoxybutane have been reported recently by Darensbourg *et al*. showing that polymer-selective bifunctional M(salen) catalysts (M = Co, Cr) give virtually only *trans*-carbonate upon alkoxide backbiting.[17]

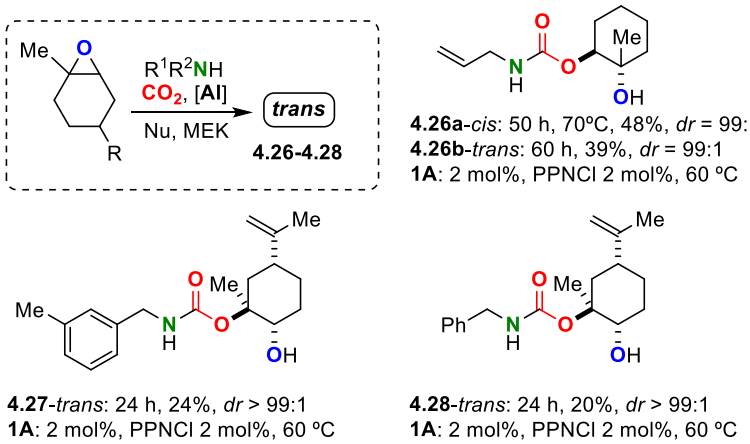
Figure 4.10: Mechanistic pathways through oligomeric carbonate intermediates.



The diastereoselective formation of *trans*-carbamates using substrates such as CPO or 3,4-epoxyfuran are slightly different to pathway 1 (**Figure 4.10**) and is more likely to undergo pathway 2. The group of Darensbourg has demonstrated that pathway 1 is thermodynamically not feasible due to a high ring strain present in the *trans*-carbonate and therefore preferably results in the re-formation of the starting epoxide and CO_2.

Under high pressure conditions, carbonate rather than alkoxide backbiting could be facilitated, which results in exclusive formation of the *cis*-carbonate.[18] We have shown through detailed computational studies that for the Al-mediated coupling between CO_2 and epoxides[19] and copolymerization of CO_2 and limonene oxide (LO)[14] the CO_2 insertion into an Al-alkoxide intermediate is rate-limiting due to a higher Lewis acidity of the Al complex compared to Co or Cr based salen catalysts making the Al-alkoxide less nucleophilic; therefore, we believe that possible polymer degradation in these cases should thus proceed through alkoxide back-biting considering the relatively low temperatures and pressures generally used (60–70ºC, 10 bar) for the carbamate formation reactions from CPO and the epoxy-furan (see **Figure 4.10**).

Figure 4.11: Mechanistic control experiments with trisubstituted epoxides.



Despite the effect of added amine on the metal-bound versus metal-free oligocarbonate equilibrium, the metal-free carbonate species based on CPO is unable to back-bite to give a *trans* cyclic carbonate as it is thermodynamically disfavored. Therefore, another degradation pathway leading to formal *trans*-carbamate formation needs to be considered when using the Al-based catalysts **1A** or **1C**. Since the LO/CO_2 coupling reaction was shown to give exclusive propagation towards a fully alternating copolymer with a concomitant high barrier for cyclic carbonate formation as is the case for CPO/CO_2 coupling, we envisioned that carbamate formations from tri-substituted cyclic oxiranes (**Figure 4.11**) would serve as useful control experiments to mimic the CPO case. Indeed, when we subjected both methyl-cyclohexene oxide and *cis*-limonene oxide to similar reaction conditions used for the

formation of carbamates **4.11b–4.25b**, we only observed the formation of *trans*-carbamates **4.26–4.28**. The origin of the *trans*-selectivity is hence ascribed to an attack of the amine on the oligocarbonate itself (**Figure 4.10**, pathway 2) through aminolysis at a carbonate linkage retaining the *trans* configuration in the final carbamate product.

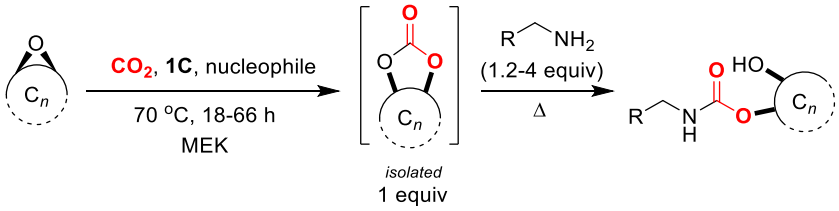
4.3 Conclusions

In summary, we here present an unprecedented catalytic approach towards *trans*-configured carbamates by selective trapping of *trans*-carbonate intermediates. Various control experiments have revealed that either *in situ* aminolysis of *trans* cyclic carbonates or aminolysis of *trans*-configured oligocarbonates is an efficient new approach to exert excellent diastereo-selective control in the synthesis of CO_2-derived functionalized carbamates with potential in synthetic chemistry. This methodology was recently extended to a chiral version by Lu *et al*. using Co-catalysis in a similar two step synthesis of *trans* hydroxy carbamates from *meso* epoxides.[20] This methodology is limited to aliphatic amines and moderate yields due to competing reactions such as the amino alcohol formation. However, it provides a new conceptual framework for the CO_2 catalysis community expanding on the synthetic utility of carbon dioxide as a carbon feed stock towards value-added chemicals.

4.4 Experimental Section

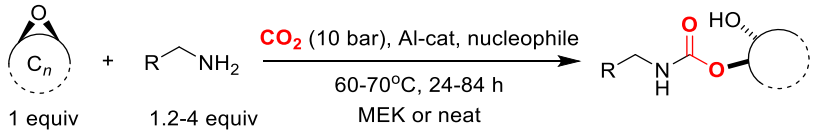
4.4.1 General Information and Instrumentation

Method A: General procedure for *cis* carbamate formation.



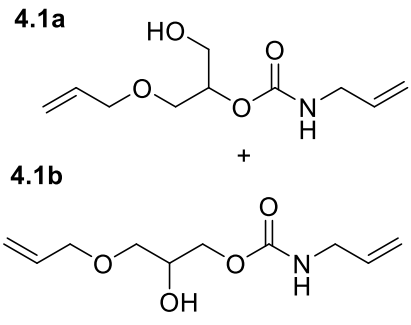
The cyclic carbonates were synthesized from carbon dioxide and the corresponding epoxide (4 mmol) according to reported literature procedures using Al(III) amino-triphenolate complex **1C** as catalyst (0.2 mol%) and NBu_4Br as cocatalyst (2.0 mol%) in MEK (1 mL). Hereafter, the respective carbonate (1 mmol, 1 equiv) and the corresponding amine (1.2 equiv for non-volatile amines; 4 equiv for volatile amines) were charged into a 5 mL round bottom flask and the reaction mixture was stirred at 50–70 ºC for the required time. After the reaction, analytically pure carbamate product was isolated by flash chromatography.

Method B: General one-pot procedure for *trans* carbamate formation.



The respective epoxide (4 mmol, 1 equiv), Al-complex (**1A** or **1C**, 0.5-2 mol%), amine (1.2 equiv for non-volatile amines; 3 equiv for volatile amines), NBu_4Br /PPNCl and MEK (l mL) were charged into a 30 mL stainless steel autoclave. The autoclave was then subjected to three cycles of pressurization and depressurization with carbon dioxide (5 bar), before final stabilization of the pressure to 10 bar. The autoclave was sealed and heated to 60–90 ºC and left stirring for the required time. Then the autoclave was cooled to rt and depressurized. After the reaction, the analytically pure carbamate product was then isolated by flash chromatography.

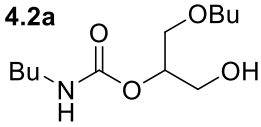
4.4.2 Spectroscopic analysis for all compounds



Carbamate mixture synthesized following method B, isolated as a mixture of **4.1a** + **4.1b**. Yield of **4.1a**+**4.1b** (*dr* = 20:80): 688 mg (3.20 mmol, 80%). **4.1a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94-5.79 (m, 2H), 5.30-5.12 (m, 4H), 4.87 (br s, 1H, NH), 4.92 (m, 1H), 3.80 (m, 2H), 3.65 (m, 2H), 3.81 (m, 2H), 4.03 (m, 2H), 2.44 (br, 1H). **4.1b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94-5.79 (m, 2H), 5.30-5.12 (m, 4H), 4.87 (br s, 1H, NH), 4.24-4.12 (m, 2H), 4.03 (m, 2H), 3.98 (m, 1H), 3.53-3.43 (m, 2H),

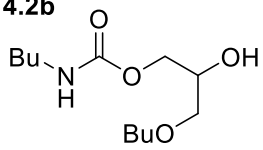
3.81 (m, 2H), 2.79 (br, 1H). **4.1a**+**4.1b**: ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.72, 156.35, 134.38, 134.29, 117.52, 117.47, 116.16, 74.14, 72.41, 70.94, 69.29, 66.43, 62.74, 43.53, 29.73. IR (neat, cm^{-1}): 3151, 1729, 1537, 1240, 1065, 961, 916. HRMS (ESI+, MeOH): *m/z* calcd. 238.1050 $(M+Na)^+$, found: 238.1047.

4.2a



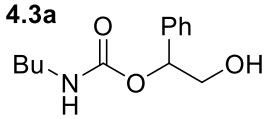
+

4.2b



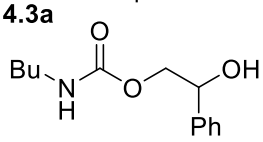
Carbamate mixture synthesized following method B, isolated as a mixture of **4.2a**+**4.2b**. Yield of **4.2a**+**4.2b** (*dr* = 29:71): 928 mg (3.76 mmol, 94%). **4.2a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (m, 1H), 4.77 (br s, 1H), 3.81 (m, 2H), 3.62 (m, 2H), 3.47 (m, 2H), 3.18 (m, 2H), 1.61-1.30 (m, 8H), 0.94-0.89 (m, 6H). **4.2b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (br s, 1H), 4.15 (m, 2H), 3.97 (m, 1H), 3.47 (m, 2H), 3.42 (m, 2H), 3.18 (m, 2H), 1.61-1.30 (m, 8H), 0.94-0.89 (m, 6H). **4.2a**+**4.2b**: ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.88, 156.52, 73.89, 71.62, 71.51, 71.51, 70.36, 69.43, 66.36, 63.33, 40.92, 32.05, 32.01, 31.74, 31.70, 19.97, 19.34, 19.31, 13.98, 13.96, 13.80. IR (neat, cm^{-1}): 3247, 1695, 1537, 1466, 1245, 1117, 1022. HRMS (ESI+, MeOH): *m/z* calcd. 270.1676 $(M+Na)^+$, found: 270.1672.

4.3a



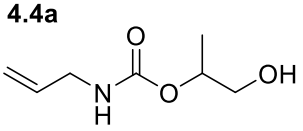
+

4.3a



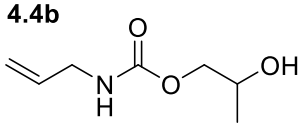
Carbamate mixture synthesized following method B, isolated as a mixture of **4.3a**+**4.3b**. Yield of **4.3a**+**4.3b** (*dr* = 41:59): 815 mg (3.44 mmol, 85%). **4.3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 5.77 (m, 1H), 4.87 (br s, 1H), 3.90-3.79 (m, 2H), 3.24-3.15 (m, 2H), 2.35 (br s, 1H), 1.53-1.43 (m, 2H), 1.39-1.26 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). **4.3b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.27 (m, 5H), 4.94 (m, 1H), 4.86 (br s, 1H), 4.27 (dd, *J* = 11.7, 3.0 Hz, 1H), 4.14 (dd, *J* = 11.8, 8.2 Hz, 1H), 3.21-3.15 (m, 2H), 1.53-1.43 (m, 2H), 1.40-1.28 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). Isomer **4.3a**: ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.00, 140.22, 128.62, 128.14, 126.29, 73.19, 70.15, 41.00, 32.06, 20.00, 13.83. Isomer **4.3b**: ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.46, 137.68, 128.71, 128.39, 126.61, 77.64, 66.73, 41.00, 32.04, 20.01, 13.83. IR (neat, cm^{-1}): 3308, 1695, 1452, 1246, 1139, 1050, 698. HRMS (ESI+, MeOH): *m/z* calcd. 260.1257 $(M+Na)^+$, found: 260.1266.

4.4a



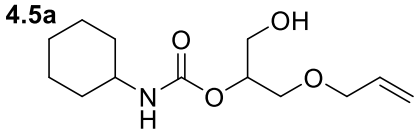
+

4.4b

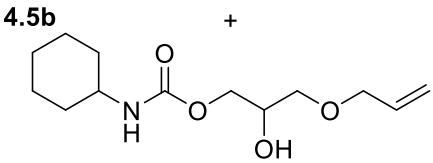


Carbamate mixture synthesized following method B, isolated as a mixture of **4.4a**+**4.4b**. Yield of **4.4a**+**4.4b** (*dr* = 20:80): 547 mg (3.44 mmol, 86%). **4.4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.80 (m, 1H), 5.23-5.12 (m, 2H), 4.91 (m, 1H), 4.82 (br s, 1H), 3.81 (m, 2H), 3.69 (m, 1H), 3.60 (m, 1H), 2.36 (br s, 1H), 1.24-1.19 (d, J = 6.5 Hz, 3H). **4.4b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.80 (m, 1H), 5.23-5.12 (m, 2H), 4.82 (br s, 1H), 4.12 (m, 1H), 4.03 (m, 1H), 3.95 (m, 1H), 3.81 (m, 2H), 2.36 (br s, 1H), 1.20 (d, J = 6.3 Hz, 3H). **4.4a**+**4.4b**: ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.79, 134.43, 116.35, 73.04, 70.45, 66.70, 66.63, 43.63, 43.61, 19.19, 16.70. IR (neat, cm^{-1}): 3331, 1695, 1521, 1277, 1148, 1078, 940, 917. HRMS (ESI+, MeOH): *m/z* calcd. 182.0788 $(M+Na)^+$, found: 182.0786.

4.5a

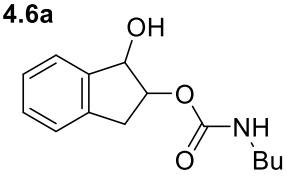


4.5b +

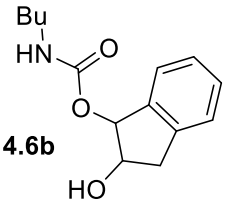


Carbamate mixture synthesized following method B, isolated as a mixture of **4.5a**+**4.5b**. Yield of **4.5a**+**4.5b** (*dr* = 33:67): 688 mg (2.68 mmol, 67%). **4.5a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94-5.83 (m, 1H), 5.29-5.17 (m, 2H), 4.86 (m, 1H), 4.77 (br s, 1H), 4.01 (m, 2H), 3.80 (m, 2H), 3.64 (m, 2H), 3.42 (m, 1H), 2.64 (br s, 1H), 1.94-1.08 (m, 10H). Isomer **4.5b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94-5.83 (m, 1H), 5.29-5.17 (m, 2H), 4.77 (br s, 1H), 4.19-4.09 (m, 2H), 4.01 (m, 2H), 3.97 (m, 1H), 3.52-3.42 (m, 3H), 2.91 (br s, 1H), 1.94-1.08 (m, 10H). **4.5a**+**4.5b**: ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.01, 155.63, 134.47, 134.34, 117.63, 117.51, 73.98, 72.53, 72.50, 70.99, 69.62, 69.56, 66.27, 63.41, 50.08, 33.44, 33.38, 25.58, 24.87. IR (neat, cm^{-1}): 3328, 1687, 1537, 1274, 1058, 925. HRMS (ESI+, MeOH): *m/z* calcd. 180.1519 $(M+Na)^+$, found: 180.1526.

4.6a



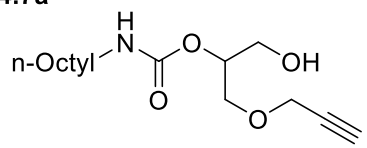
+



4.6b

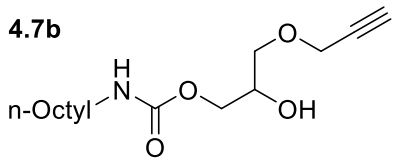
Carbamate mixture synthesized following method B, isolated as a mixture of **4.6a**+**4.6b**. Yield of **4.6a**+**4.6b** (*dr* = 77:23): 677 mg (2.72 mmol, 68%). **4.6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.42 (m, 1H), 7.30-7.22 (m, 3H), 5.41 (td, J = 5.3, 3.2 Hz, 1H), 5.21 (m, 1H), 4.75 (br s, 1H), 3.21-3.02 (m, 4H), 2.50 (br s, 1H), 1.52-1.43 (m, 2H), 1.38-1.27 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); **4.6b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.42 (m, 1H), 7.30-7.22 (m, 3H), 5.92 (d, J = 5.4 Hz, 1H), 4.82 (br s, 1H), 4.65 (m, 1H), 3.21-3.02 (m, 4H), 2.54 (br s, 1H), 1.52-1.43 (m, 2H), 1.38-1.27 (m, 2H), 0.91 (m, 3H). **4.6a**+**4.6b**: ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.45, 142.15, 141.23, 139.42, 129.62, 128.76, 127.37, 127.26, 126.21, 125.34, 125.08, 124.72, 77.95, 76.57, 75.73, 73.24, 41.04, 40.93, 38.52, 36.45, 32.02, 20.02, 13.83. IR (neat, cm^{-1}): 3331, 1686, 1538, 1257, 1162, 1032, 743. HRMS (ESI+, MeOH): *m/z* calcd. 272.1257 $(M+Na)^+$, found: 272.1261.

4.7a



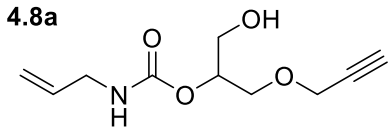
+

4.7b

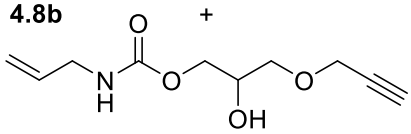


Carbamate mixture synthesized following method B, isolated as a mixture of **4.7a**+**4.7b**. Yield of **4.7a**+**4.7b** (*dr* = 21:79): 900 mg (3.16 mmol, 79%). **4.7a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (m, 1H), 4.80 (br, 1H), 4.18 (m, 2H), 3.80 (m, 2H), 3.74 (m, 2H), 3.17 (m, 2H), 2.87 (br s, 1H), 2.45 (m, 1H), 1.52-1.45 (m, 2H), 1.29-1.26 (m, 10H), 0.89-0.86 (m, 3H); **4.7b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (br, 1H), 4.22-4.10 (m, 4H), 4.01 (m, 1H), 3.63-3.52 (m, 2H), 3.17 (m, 2H), 2.87 (br s, 1H), 2.45 (m, 1H), 1.52-1.45 (m, 2H), 1.29-1.26 (m, 10H), 0.89-0.86 (m, 3H). **4.7a**+**4.7b**: ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.87, 79.40, 75.14, 75.04, 73.84, 70.83, 69.52, 69.08, 66.33, 63.09, 58.80, 58.77, 41.32, 31.92, 30.02, 29.97, 29.36, 29.33, 26.87, 22.77, 14.22. IR (neat, cm^{-1}): 3348, 1694, 1687, 1537, 1524, 1263, 1153 1097, 663. HRMS (ESI+, MeOH): *m/z* calcd. 308.1832 $(M+Na)^+$, found: 308.1846.

4.8a

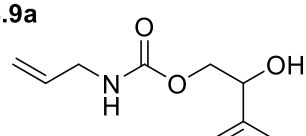


4.8b +

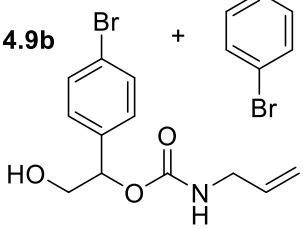


Carbamate mixture synthesized following method B, isolated as a mixture of **4.8a**+**4.8b**. Yield of **4.8a**+**4.8b** (*dr* = 13:87): 741 mg (3.48 mmol, 87%). **4.8a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82-5.72 (m, 1H), 5.33 (br s, 1H), 5.15-5.04 (m, 2H), 4.85 (m, 1H), 4.12 (m, 2H), 3.72 (m, 2H), 3.63 (m, 4H), 2.44-2.42 (m, 1H); **4.8b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82-5.72 (m, 1H), 5.33 (br s, 1H), 5.15 - 5.04 (m, 2H), 4.12 (m, 2H), 4.11-4.02 (m, 2H), 3.96 (m, 1H), 3.72 (m, 2H), 3.56-3.46 (m, 2H), 2.44-2.42 (m, 1H). **4.8a**+**4.8b**: ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.71, 134.37, 116.35, 79.36, 75.15, 75.06, 74.12, 70.79, 69.36, 68.95, 66.44, 58.77, 43.64. IR (neat, cm^{-1}): 3329, 1694, 1587, 1240, 1095, 923, 666. HRMS (ESI+, MeOH): *m/z* calcd. 236.0893 $(M+Na)^+$, found: 236.0898.

4.9a

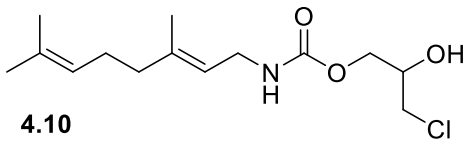


4.9b +



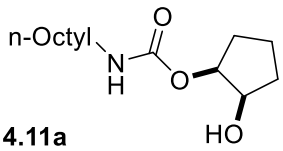
Carbamate mixture synthesized following method B, isolated as a mixture of **4.9a**+**4.9b**. Yield of **4.9a**+**4.9b** (*dr* = 77:23): 1044 mg (3.48 mmol, 87%). **4.9a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.28 (m, 2H), 5.85 (m, 1H), 5.17 (m, 2H), 4.93 (m, 1H), 4.88 (br s, 1H), 4.29 (m, 1H), 4.14 (m, 1H), 3.84 (m, 2H). Isomer **4.9b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.22 (m, 2H), 5.85 (m, 1H), 5.73 (m, 1H), 5.17 (m, 2H), 4.88 (br s, 1H), 3.84 (m, 2H), 3.79 (m, 2H). **4.9a**+**4.9b**: ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.79, 155.96, 139.19, 136.70, 134.18, 131.87, 131.73, 128.35, 128.01, 122.42, 122.01, 116.58, 116.49, 76.91, 72.50, 70.02, 66.23, 43.66, 29.82. IR (neat, cm^{-1}): 3368, 1696, 1519, 1252, 1070, 1009, 920, 819, 523. HRMS (ESI+, MeOH): *m/z* calcd. 322.0049 $(M+Na)^+$, found: 322.0040.

4.10



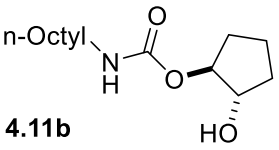
Carbamate synthesized following method B. Yield of **4.10**: 959 mg (3.32 mmol, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20-5.17 (m, 1H), 5.08-5.05 (m, 1H), 4.75 (br s, 1H), 4.30-4.19 (m, 2H), 4.03 (br s, 1H), 3.78 (t, *J* = 6.1 Hz, 2H), 3.62-3.55 (m, 2H), 3.19 (br s, 1H), 2.10-2.06 (m, 2H), 2.02-1.99 (m, 2H), 1.68 (s, 3H), 1.66 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.79, 140.26, 131.97, 123.89, 119.86, 70.53, 66.20, 45.64, 39.58, 39.17, 26.50,

25.82, 17.84, 16.40. IR (neat, cm^{-1}): 3357, 1696, 1537, 1453, 1250, 1141, 775. HRMS (ESI+, MeOH): *m/z* calcd. 312.1337 $(M+Na)^+$, found: 312.1325.



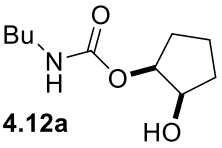
4.11a

Carbamate was synthesized following method A. Yield of **4.11a** (*dr* = 99:1): 190 mg (0.74 mmol, 74%). ^1H NMR (500 MHz, $CDCl_3$) δ 4.90-4.84 (m, 1H + 1H), 4.17-4.14 (m, 1H), 3.18-3.12 (m, 2H), 2.39 (br s, 1H), 1.98-1.69 (m, 4H), 1.68-1.62 (m, 1H), 1.57-1.45 (m, 3H), 1.31-1.22 (m, 10H), 0.88-0.85 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.61, 77.20, 73.51, 41.24, 31.90, 30.79, 30.02, 29.35, 29.31, 28.42, 26.89, 22.75, 19.52, 14.19. IR (neat, cm^{-1}): 3401, 2921, 1683, 1537, 1257, 1145, 592. HRMS (ESI): *m/z* calcd. 280.1883 $(M + Na)^+$, found: 280.1871.



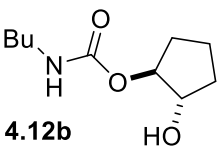
4.11b

Carbamate was synthesized following method B. Yield of **4.11b** (*dr* = 96:4): 442 mg (1.72 mmol, 43%). ^1H NMR (500 MHz, $CDCl_3$) δ 4.74 (br s, 1H), 4.69-4.65 (m, 1H), 4.09-4.05 (m, 1H), 3.52 (br s, 1H), 3.18-3.14 (m, 2H), 2.11-1.99 (m, 2H), 1.77-1.58 (m, 4H), 1.50-1.47 (m, 2H), 1.29-1.26 (m, 10H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.71, 84.55, 78.63, 77.41, 77.16, 76.91, 41.24, 32.51, 31.92, 30.23, 30.05, 29.36, 29.34, 26.89, 22.77, 21.44, 14.22. IR (neat, cm^{-1}): 3367, 2924, 1692, 1551, 1252, 1138 HRMS (ESI+, MeOH): *m/z* calcd. 280.1883 $(M + Na)^+$, found: 280.1883.



4.12a

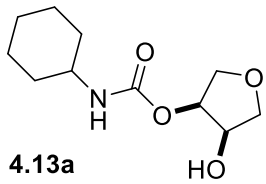
Carbamate was synthesized following method A. Yield of **4.12a** (*dr* = 99:1**)**: 167 mg (0.83 mmol, 83%). ^1H NMR (400 MHz,) δ 4.92-4.88 (m, 1H), 4.88 (br s, 1H), 4.19-4.15 (m, 1H), 3.12-3.16 (m, 2H), 2.22 (br s, 1H), 2.00-1.47 (m, 8H), 1.40-1.30 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$), δ 156.69, 77.10, 73.40, 40.85, 32.03, 30.73, 28.40, 19.98, 19.46, 13.79. IR (neat, cm^{-1}): 3348, 1695, 1537, 1245, 1159, 776. HRMS (ESI+, MeOH): *m/z* calcd. 224.1257 $(M + Na)^+$, found: 224.1254.



4.12b

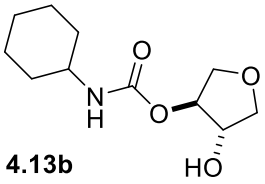
Carbamate was synthesized following method B. Yield of **4.12b** (*dr* = 89:11): 482 mg (2.40 mmol, 60%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.76 (br s, 1H), 4.69-4.68 (m, 1H), 4.09-4.05 (m, 1H), 3.57 (br s, 1H), 3.19-3.14 (m, 2H), 2.10-1.97 (m, 2H), 1.78-1.57 (m, 4H), 1.51-1.44 (m,

2H), 1.38-1.29 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.71, 84.47, 78.55, 40.91, 32.47, 32.10, 30.19, 21.43, 20.02, 13.84. IR (neat, cm^{-1}): 3341, 1694, 1467, 1159, 1063, 951. HRMS (ESI+, MeOH): *m/z* calcd. 224.1257 $(M + Na)^+$, found: 224.1251.



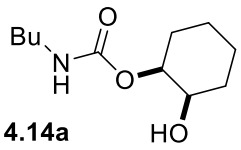
4.13a

Carbamate was synthesized following method A. Yield of **4.13a** (*dr* = 99:1): 187 mg (0.82 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06-4.80 (m, 2H), 4.43-4.40 (m, 1H), 4.04-4.00 (m, 1H), 3.97-3.93 (m, 1H), 3.84-3.80 (m, 1H), 3.69-3.66 (m, 1H), 3.49-3.40 (m, 1H), 2.84-2.83 (m, 1H), 1.95-1.89 (m, 2H), 1.72-1.67 (m, 2H), 1.61-1.56 (m, 1H), 1.38-1.28 (m, 2H), 1.20-1.09 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.27, 74.01, 72.32, 71.34, 70.93, 50.19, 33.35, 33.27, 25.51, 24.84. IR (neat, cm^{-1}): 3412, 3325, 3272, 1684, 1541, 1253, 1040, 890, 663. HRMS (ESI+, MeOH): *m/z* calcd. 230.1387 $(M + H)^+$, found: 230.1389.



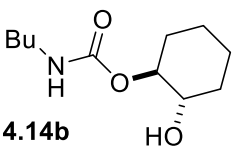
4.13b

Carbamate was synthesized following method B. Yield of **4.13b** (*dr* = 79:21): 613 mg (2.68 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90-4.89 (m, 1H), 4.69-4.67 (m, 1H), 4.32 (br s, 1H), 4.10 (dd, J = 10.4 and 5.4 Hz, 1H), 4.05 (dd, J = 9.8 and 5.4 Hz, 1H), 3.81-3.79 (m, 1H), 3.71-3.68 (m, 1H), 3.50-3.44 (m, 1H), 2.88 (s, 1H), 1.94-1.92 (m, 2H), 1.73-1.59 (m, 3H), 1.39-1.25 (m, 2H), 1.21-1.11 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.59, 81.55, 76.78, 73.49, 71.27, 50.18, 33.45, 33.41, 25.55, 24.86. IR (neat, cm^{-1}): 3438, 1687, 1452, 1276, 1107, 969. HRMS (ESI+, MeOH): *m/z* calcd. 252.1206 $(M + Na)^+$, found: 252.1214.



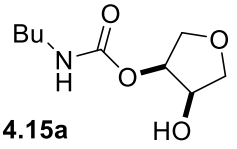
4.14a

Carbamate was synthesized following method A. Yield of **4.14a** (*dr* = 99:1): 148 mg (0.69 mmol, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (br s, 1H), 4.80- 4.79 (m, 1H), 3.86-3.85 (m, 1H), 3.18-3.14 (m, 2H), 1.84-1.79 (m, 1H), 1.74-1.68 (m, 5H), 1.50-1.44 (m, 2H), 1.37-1.30 (m, 4H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.62, 74.44, 69.68, 40.89, 32.09, 30.33, 27.54, 22.11, 21.31, 20.03, 13.83. IR (neat, cm^{-1}): 3364, 2943, 1692, 1532, 1258, 1141, 1077, 1012, 566. HRMS (ESI+, MeOH): *m/z* calcd. 238.1414 $(M + Na)^+$, found: 238.1407.



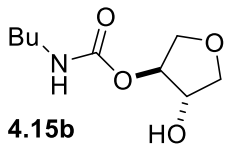
4.14b

Carbamate was synthesized following method B. Yield of **4.14b** (*dr* = 99:1): 387 mg (1.80 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (br s, 1H), 4.47-4.41 (m, 1H), 3.51-3.45 (m, 1H), 3.18 (q, J = 6.7 Hz, 2H), 2.79 (br s, 1H), 2.07-2.00 (m, 2H), 1.71-1.69 (m, 2H), 1.52-1.45 (m, 2H), 1.39-1.25 (m, 6H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.29, 78.82, 73.52, 40.91, 33.43, 32.07, 30.66, 24.11, 23.91, 20.02, 13.83. IR (neat, cm^{-1}): 3355, 2951, 1690, 1537, 1463, 1441, 1250, 1071, 556. HRMS (ESI+, MeOH): *m/z* calcd. 238.1414 (M + Na)+, found: 238.1406.



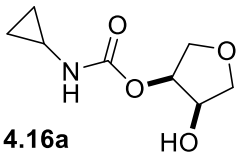
4.15a

Carbamate was synthesized following method A. Yield of **4.15a** (*dr* = 99:1): 152 mg (0.75 mmol, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (br s, 1H), 5.04-5.01 (m, 1H), 4.41-4.37 (m, 1H), 4.01-3.97 (m, 1H), 3.93-3.90 (m, 1H), 3.81-3.78 (m, 1H), 3.67-3.64 (m, 1H), 3.19-3.09 (m, 3H), 1.44 (m, 2H), 1.31 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.18, 73.98, 72.23, 71.18, 70.85, 40.90, 31.89, 19.92, 13.74. IR (neat, cm^{-1}): 3326, 1696, 1534, 1247, 1144, 1062, 1007, 620. HRMS (ESI+, MeOH): *m/z* calcd. 226.1050 $(M + Na)^{+}$, found: 226.1048.



4.15b

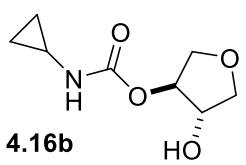
Carbamate was synthesized following method B. Yield of **4.15b** (*dr* = 99:1): 462 mg (2.28 mmol, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92-4.90 (m, 1H), 4.82 (br s, 1H), 4.31 (m, 1H), 4.09 (dd, J = 10.4, 5.1 Hz, 1H), 4.03 (dd, J = 9.8, 5.2 Hz, 1H), 3.80 (dd, J = 10.4, 2.4 Hz, 1H), 3.70 (dd, J = 9.8, 3.4 Hz, 1H), 3.17 (m, 2H), 1.48 (m, 2H), 1.34 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.34, 81.26, 76.30, 73.50, 71.22, 40.92, 31.99, 19.98, 13.80. IR (neat, cm^{-1}): 3355, 190, 1537, 1463, 1224, 1071, 556. HRMS (ESI+, MeOH): *m/z* calcd. 226.1050 $(M + Na)^{+}$, found: 226.1040.



4.16a

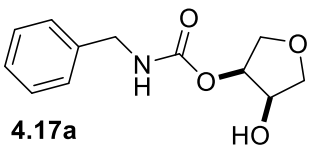
Carbamate was synthesized following method A. Yield of **4.18a** (*dr* = 99:1): 146 mg (0.78 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (br s, 1H), 5.07-5.06 (m, 1H), 4.45-4.42 (m, 1H), 4.02-3.94 (m, 2H), 3.88-3.81 (m, 1H), 3.72-3.65 (m, 1H), 2.72 (br s, 1H), 2.61-2.57 (m, 1H), 0.77-0.69 (m, 2H), 0.56-0.50 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.87,

74.24, 72.27, 71.34, 70.92, 23.26, 6.86, 6.82. IR (neat, cm^{-1}): 3326, 1687, 1529, 1266, 1075, 908, 756, 550. HRMS (ESI+, MeOH): *m/z* calcd. 210.0737 $(M + Na)^+$, found: 210.0736.



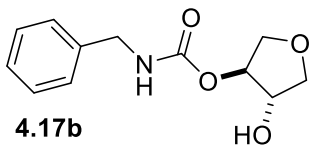
4.16b

Carbamate was synthesized following method A. Yield of **4.18b** (*dr* = 99:1): 538 mg (2.88 mmol, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (br s 1H), 4.94-4.92 (m, 1H), 4.31-4.29 (m, 1H), 4.10-3.99 (m, 2H), 3.79-3.69 (m, 2H), 3.48 (br s 1H), 2.58-2.55 (m, 1H), 0.74-0.71 (m, 2H), 0.53-0.50 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.07, 81.32, 76.22, 73.48, 71.18, 23.17, 6.85. IR (neat, cm^{-1}): 3305, 1694, 1525, 1263, 1216, 1079, 969, 775. HRMS (ESI+, MeOH): *m/z* calcd. 210.0737 $(M + Na)^+$, found: 210.0735.



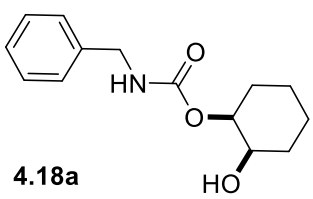
4.17a

Carbamate was synthesized following method A. Yield of **4.17a** (*dr* = 99:1): 144 mg (0.61 mmol, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.32 (m, 2H), 7.29-7.26 (m, 3H), 5.46 (br s, 1H), 5.10-5.07 (m, 1H), 4.43-4.40 (m, 1H), 4.35-4.34 (m, 2H), 4.03-4.00 (m, 1H), 3.95-3.92 (m, 1H), 3.85-3.82 (m, 1H), 3.68-3.65 (m, 1H), 2.53 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.21, 138.09, 128.85, 127.77, 127.60, 74.39, 72.28, 71.33, 70.93, 45.27. IR (neat, cm^{-1}): 3351, 1694, 1527, 1452, 1252, 1075, 1032, 698, 612. HRMS (ESI+, MeOH): *m/z* calcd. 260.0893 $(M + Na)^+$, found: 260.0893.



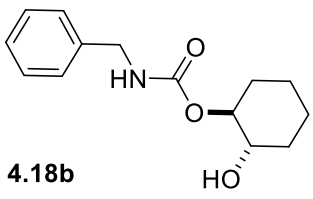
4.17b

Carbamate was synthesized following method B. Yield of **4.17b** (*dr* = 99:1): 616 mg (2.60 mmol, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.30-7.27 (m, 3H), 5.18 (br s, 1H), 4.96-4.94 (m, 1H), 4.37-4.33 (m, 3H), 4.12-4.09 (m, 1H), 4.05-4.02 (m, 1H), 3.83-3.81 (m, 1H), 3.72-3.69 (m, 1H), 3.08 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.37, 138.06, 128.90, 127.84, 127.63, 81.72, 76.52, 73.50, 71.24, 45.27. IR (neat, cm^{-1}): 3316, 1696, 1527, 1249, 1068, 973, 896, 698. HRMS (ESI+, MeOH): *m/z* calcd. 260.0893 $(M + Na)^+$, found: 260.0890.



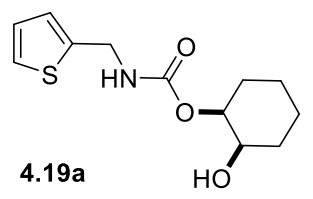
4.18a

Carbamate was synthesized following method A. Yield of **4.18a** (*dr* = 99:1): 204 mg (0.82 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 5.19 (br s, 1H), 4.87-4.85 (m, 1H), 4.37-4.35 (m, 2H), 3.89-3.87 (m, 1H), 2.34 (br s, 1H), 1.88-1.81 (m, 1H), 1.75-1.70 (m, 1H), 1.63-1.59 (m, 4H), 1.38-1.33 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.59, 138.46, 128.81, 127.70, 127.65, 74.85, 69.66, 45.25, 30.33, 27.52, 22.09, 21.29. IR (neat, cm^{-1}): 3344, 2937, 1679, 1538, 1264, 1078, 956, 701, 654, 592. HRMS (ESI+, MeOH): *m/z* calcd. 272.1257 $(M + Na)^+$, found: 272.1259.



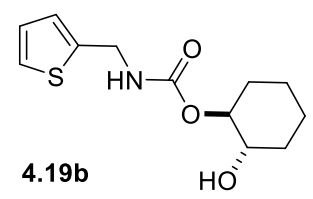
4.18b

Carbamate was synthesized following method B. Yield of **4.18b** (*dr* = 99:1): 498 mg (2.0 mmol, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 5.10 (br s, 1H), 4.51-4.47 (m, 1H), 4.38-4.36 (m, 2H), 3.52-3.45 (m, 1H), 2.75 (br s, 1H), 2.07-2.02 (m, 2H), 1.71-1.66 (m, 2H), 1.38-1.19 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.22, 138.43, 128.85, 127.72, 127.69, 79.21, 73.51, 45.29, 33.44, 30.63, 24.12, 23.91. IR (neat, cm^{-1}): 3397, 3275, 2975, 1676, 1537, 1450, 1259, 1044, 738, 697 HRMS (ESI+, MeOH): *m/z* calcd. 250.1438 $(M + Na)^+$, found: 250.1436.



4.19a

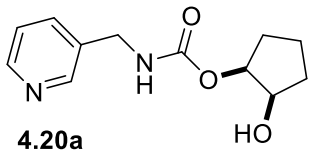
Carbamate was synthesized following method A. Yield of **4.19a** (*dr* = 99:1): 194 mg (0.76 mmol, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.22 (m, 1H), 6.99-6.94 (m, 2H), 5.17 (br s, 1H), 4.87-4.85 (m, 1H), 4.57-4.51 (m, 2H), 3.89-3.88 (m, 1H), 2.18 (br s, 1H), 1.91-1.83 (m, 1H), 1.73-1.59 (m, 5H), 1.38-1.33 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.20, 141.21, 127.06, 126.01, 125.34, 75.06, 69.64, 40.04, 30.37, 27.48, 22.11, 21.26. IR (neat, cm^{-1}): 3348, 1690, 1517, 1248, 963, 697. HRMS (ESI+, MeOH): *m/z* calcd. 278.0821 $(M + Na)^+$, found: 278.0821.



4.19b

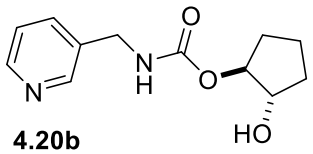
Carbamate was synthesized following method B. Yield of **4.19b** (*dr* = 99:1): 101 mg (2.08 mmol, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.22 (m, 1H), 6.98-6.94 (m, 2H), 5.12 (br s, 1H), 5.58-4.47 (m, 3H), 3.52-3.48 (m, 1H), 2.63 (br s, 1H), 2.05-2.03 (m, 2H), 1.72-1.69 (m, 2H), 1.38-1.22 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.81, 141.17, 127.06, 126.03, 125.35, 79.35, 73.45, 40.08, 33.40, 30.59, 24.13, 23.92. IR (neat, cm^{-1}): 3359, 1692, 1520, 1241, 1073, 1017, 658, 551. HRMS (ESI+, MeOH): *m/z* calcd. 278.0821 $(M + Na)^+$, found: 278.0814.



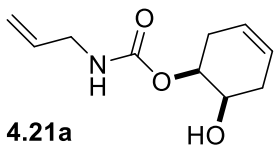
4.20a

Carbamate was synthesized following method A. Yield of **4.20a** (*dr* = 99:1): 167 mg (0.71 mmol, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53-8.52 (m, 1H), 7.67-7.64 (m, 1H), 7.27-7.17 (m, 2H), 5.99 (br s, 1H), 4.95-4.92 (m, 1H), 4.53-4.44 (m, 2H), 4.19-4.17 (m, 1H), 2.63 (br s, 1H), 1.99-1.76 (m, 4H), 1.72-1.62 (m, 1H), 1.58-1.51 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.87, 156.73, 149.23, 136.94, 122.54, 121.93, 77.63, 73.42, 46.07, 30.84, 28.37, 19.55. IR (neat, cm^{-1}): 3387, 1696, 1523, 1246, 1049, 7786. HRMS (ESI+, MeOH): *m/z* calcd. 259.1053 $(M + Na)^+$, found: 259.1055.



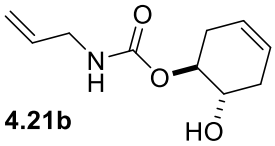
4.20b

Carbamate was synthesized following method B. Yield of **4.20b** (*dr* = 99:1): 509 mg (2.16 mmol, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49-8.48 (m, 1H), 7.65-7.61 (m, 1H), 7.25-7.25 (m, 1H), 7.17-7.15 (m, 1H), 6.13 (br s, 1H), 4.72-4.70 (m, 1H), 4.44-4.43 (m, 2H), 4.10-4.07 (m, 1H), 2.60 (br s, 1H), 2.06-2.03 (m, 1H), 1.97-1.94 (m, 1H), 1.71-1.56 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.54, 156.94, 149.10, 136.98, 122.52, 121.97, 84.15, 77.93, 45.98, 32.19, 29.98, 21.29. IR (neat, cm^{-1}): 3316, 2959, 1693, 1529, 1245, 1041, 971, 752, 615. HRMS (ESI+, MeOH): *m/z* calcd. 259.1053 $(M + Na)^+$, found: 259.1055.



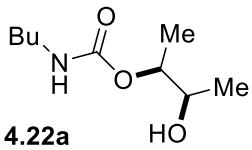
4.21a

Carbamate was synthesized following method A. Yield of **4.21a** (*dr* = 99:1): 134 mg (0.68 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.80 (m, 1H), 5.63-5.54 (m, 2H), 5.23-5.12 (m, 2H), 5.01-4.99 (m, 1H), 4.89 (brs, 1H), 4.05 (m, 1H), 3.83-3.80 (m, 2H), 2.45-2.20 (m, 4H), 1.63 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.62, 134.38, 124.03, 123.63, 116.45, 72.88, 67.85, 43.66, 31.54, 28.75. IR (neat, cm^{-1}): 3368, 1688, 1523, 1249, 1071, 1019, 665. HRMS (ESI+, MeOH): *m/z* calcd. 220.0944 $(M + Na)^+$, found: 220.0939.



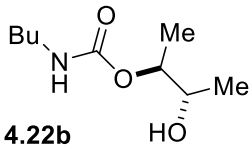
4.21b

Carbamate was synthesized following method B. Yield of 4.21b (*dr* = 99:1): 323 mg (1.64 mmol, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89-5.81 (m, 1H), 5.59-5.51 (m, 2H), 5.22-5.13 (m, 2H), 4.89 (br s, 1H), 4.81-4.76 (m, 1H), 3.85-3.82 (m, 3H), 2.60-2.51 (m, 3H), 2.17-2.11 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.75, 134.40, 124.51, 123.97, 116.44, 75.12, 69.68, 43.67, 33.52, 30.90. IR (neat, cm^{-1}): 3331, 1685, 1527, 1253, 1157, 1066, 1012, 972, 916, 598. HRMS (ESI+, MeOH): m/z calcd. 220.0944 $(M + Na)^+$, found: 220.0939.



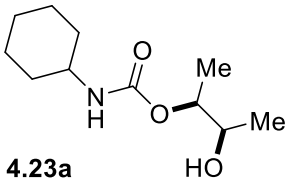
4.22a

Carbamate was synthesized following method A. Yield of **4.22a** (*dr* = 99:1): 129 mg (0.68 mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82-4.75 (m, 1H), 4.70 (br s, 1H), 3.93-3.85 (m, 1H), 3.21-3.14 (m, 2H), 2.32 (br s, 1H), 1.54-1.44 (m, 2H), 1.41-1.27 (m, 2H), 1.21-1.14 (m, 6H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.69, 74.79, 69.74, 40.78, 32.01, 19.93, 17.70, 14.64, 13.75. IR (neat, cm^{-1}): 3331, 1687, 1538, 1245, 1139, 1037, 978. HRMS (ESI+, MeOH): *m/z* calcd. 212.1257 $(M + Na)^+$, found: 212.1258.



4.22b

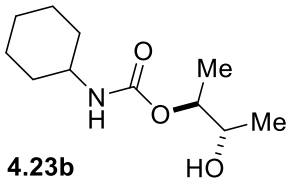
Carbamate was synthesized following method B. Yield of **4.22b** (*dr* = 93:7): 423 mg (2.24 mmol, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (br s, 1H), 4.67-4.62 (m, 1H), 3.73-3.68 (m, 1H), 3.20-3.15 (m, 2H), 1.51-1.45 (m, 2H), 1.38-1.31 (m, 2H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 156.73, 75.14, 70.20, 40.75, 31.99, 19.91, 19.02, 16.58, 13.73. IR (neat, cm^{-1}): 3328, 1687, 1537, 1244, 1140, 1057, 986. HRMS (ESI+, MeOH): *m/z* calcd. 212.1257 $(M + Na)^+$, found: 212.1256.



4.23a

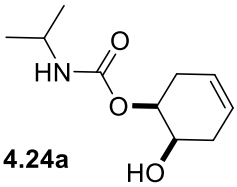
Carbamate was synthesized following method A. Yield of **4.23a** (*dr* = 99:1): 142 mg (0.66 mmol, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (br s, 1H), 4.74-4.69 (m, 1H), 3.85-3.80 (m, 1H), 3.45-3.41 (m, 1H), 2.87 (br s, 1H), 1.89-1.87 (m, 2H), 1.67-1.65 (m, 2H), 1.57-1.54 (m, 1H), 1.33-1.26 (m, 2H), 1.15-1.08 (m, 9H). ^{13}C NMR (126

MHz, $CDCl_3$) δ 155.82, 74.72, 69.81, 49.93, 33.39, 25.52, 24.84, 17.71, 14.65. IR (neat, cm^{-1}): 3320, 2931, 1681, 1530, 1232, 1041, 754. HRMS (ESI+, MeOH): *m/z* calcd. 259.1053 $(M + Na)^+$, found: 259.1055.



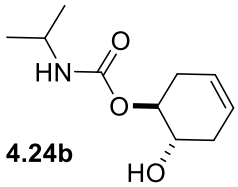
4.23b

Carbamate was synthesized following method B. Yield of **4.23b** (*dr* = 77:23): 438 mg (2.04 mmol, 51%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (br s, 1H), 4.59-4.56 (m, 1H), 3.67-3.64 (m, 1H), 3.44-3.37 (m, 1H), 2.86 (br s, 1H), 1.89-1.86 (m, 2H), 1.67-1.64 (m, 2H), 1.56-1.53 (m, 1H), 1.32-1.24 (m, 2H), 1.17-1.08 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.85, 75.08, 70.29, 49.90, 33.33, 25.50, 24.83, 19.07, 16.62. IR (neat, cm^{-1}): 3321, 2930, 1686, 1528, 1232, 1041, 776, 629. HRMS (ESI+, MeOH): *m/z* calcd. 259.1053 $(M + Na)^+$, found: 259.1055.



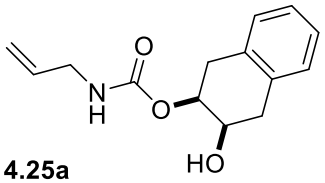
4.24a

Carbamate was synthesized following method A. Yield of **4.24a** (*dr* = 99:1): 141 mg (0.71 mmol, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.62-5.54 (m, 2H), 4.99-4.96 (m, 1H), 4.65 (br s, 1H), 4.06-4.04 (m, 1H), 3.83-3.78 (m, 1H), 2.55 (br s, 1H), 2.44-2.19 (m, 4H), 1.17 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.95, 124.07, 123.66, 72.51, 67.95, 43.34, 31.51, 28.89, 23.13. IR (neat, cm^{-1}): 3324, 1687, 1530, 1250, 1064, 1006, 696. HRMS (ESI+, MeOH): *m/z* calcd. 222.1101 $(M + Na)^+$, found: 222.1093.



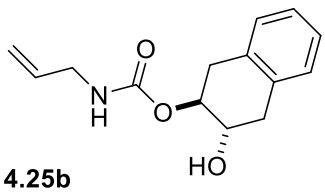
4.24b

Carbamate was synthesized following method B. Yield of **4.24b** (*dr* = 99:1): 374 mg (1.88 mmol, 47%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.58-5.50 (m, 2H), 4.78-4.72 (m, 1H), 4.66 (br s, 1H), 3.86-3.78 (m, 2H), 2.73 (br s, 1H), 2.60-2.49 (m, 2H), 2.17-2.10 (m, 2H), 1.17 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.10, 124.51, 124.00, 74.75, 69.74, 43.31, 33.57, 30.94, 23.12. IR (neat, cm^{-1}): 3323, 1682, 1530, 1256, 1067, 685. HRMS (ESI+, MeOH): *m/z* calcd. 222.1101 $(M + Na)^+$, found: 222.1093.



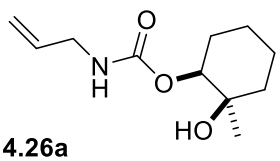
4.25a

Carbamate was synthesized following method A. Yield of **4.25a** (*dr* = 99:1): 177 mg (0.72 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.07 (m, 4H), 5.88-5.74 (m, 1H), 5.21-5.12 (m, 1H + 2H), 4.95 (br s, 1H), 4.25-4.21 (m, 1H), 3.82-3.79 (m, 1H), 3.12-3.06 (m, 3H), 3.01-2.95 (m, 1H), 2.83 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.73, 134.27, 133.29, 132.66, 129.32, 129.06, 126.45, 126.39, 116.46, 73.23, 68.28, 43.64, 34.65, 32.56. IR (neat, cm^{-1}): 3368, 1695, 1521, 1244, 1138, 1044, 915, 745, 563. HRMS (ESI+, MeOH): *m/z* calcd. 270.1101 $(M + Na)^+$, found: 270.1094.



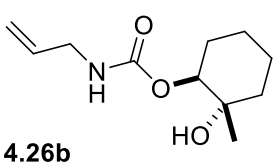
4.25b

Carbamate was synthesized following method B. Yield of **4.25b** (*dr* = 99:1): 592 mg (2.40 mmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17- 7.14 (m, 2H), 7.13-7.03 (m, 2H), 5.86 (ddd, *J* = 22.7, 10.7 and 5.5 Hz, 1H), 5.24-5.23 (m, 1H), 5.17-5.14 (m, 1H), 4.95 (td, *J* = 8.4 and 5.9 Hz, 1H), 4.89 (br s, 1H), 4.05 (q, *J* = 8.3 Hz, 1H), 3.83 (t, *J* = 5.1 Hz, 2H), 3.30 (dd, *J* = 16.3 and 5.8 Hz, 1H), 3.20 (dd, *J* = 16.3 and 5.6 Hz, 1H), 2.87 (dd, *J* = 16.3, 8.9 Hz, 2H), 2.79 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.71, 134.32, 133.72, 133.36, 128.89, 128.72, 126.59, 126.52, 116.52, 75.57, 70.16, 43.68, 36.48, 33.85. IR (neat, cm^{-1}): 3340, 1696, 1536, 1255, 1150, 1067, 986, 748. HRMS (ESI+, MeOH): *m/z* calcd. 270.1101 $(M + Na)^+$, found: 270.1098.



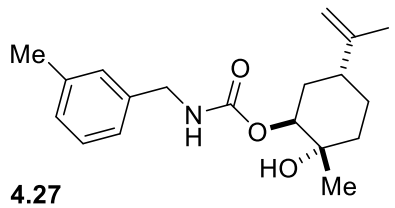
4.26a

Carbamate was synthesized following method A. Yield of **4.26a** (*dr* = 99:1): 102 mg (0.48 mmol, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89-5.81 (m, 1H), 5.21-5.12 (m, 2H), 4.89 (br s, 1H), 4.58-4.55 (m, 1H), 3.82-3.77 (m, 2H), 1.87-1.66 (m, 5H), 1.44-1.29 (m, 3H), 1.20 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.15, 134.57, 116.21, 78.23, 71.20, 43.62, 37.67, 27.62, 27.09, 23.77, 21.23. IR (neat, cm^{-1}): 3361, 2935, 1690, 1527, 1246, 1143, 925. HRMS (ESI+, MeOH): *m/z* calcd. 236.1257 $(M + Na)^+$, found: 236.1256.



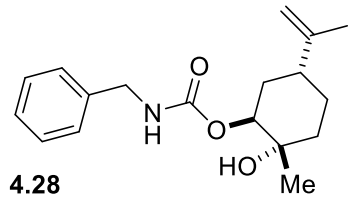
4.26b

Carbamate was synthesized following method B. Yield of **4.26b** (*dr* = 99:1): 332 mg (1.56 mmol, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.79 (m, 1H), 5.21-5.11 (m, 2H), 4.89 (br s, 1H), 4.59-4.56 (m, 1H), 3.80 (m, 2H), 2.63 (br s, 1H), 1.90-1.87 (m, 1H), 1.76-1.73 (m, 1H), 1.65-1.58 (m, 2H), 1.50-1.28 (m, 4H), 1.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.91, 134.51, 116.28, 79.63, 72.38, 43.62, 38.82, 28.99, 23.48, 22.75, 21.46. IR (neat, cm^{-1}): 3352, 1690, 1572, 1298, 1149, 1036, 936, 915. HRMS (ESI+, MeOH): *m/z* calcd. 236.1257 $(M + Na)^+$, found: 236.1251.



4.27

Carbamate was synthesized following method B. Yield of **4.27** (*dr* = 99:1): 304 mg (0.96 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.20 (m, 1H), 7.09-7.06 (m, 3H), 4.95 (br s, 1H), 4.75-4.73 (m, 2H), 4.30-4.28 (m, 2H), 4.12-4.10 (m, 1H), 2.34-2.37 (m, 5H), 2.15-2.21 (m, 1H), 1.88-1.84 (m, 1H), 1.76-1.65 (m, 5H), 1.56-1.49 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.71, 149.07, 138.62, 138.51, 128.72, 128.33, 124.62, 109.23, 82.65, 70.93, 44.93, 37.28, 33.90, 31.57, 25.99, 21.51, 21.46, 21.39. IR (neat, cm^{-1}): 3371, 1688, 1508, 1436, 1259, 1166, 1032, 885, 734, 698. HRMS (ESI+, MeOH): *m/z* calcd. 340.1883 $(M + Na)^+$, found: 340.1886.



4.28

Carbamate was synthesized following method B. Yield of **4.28** (*dr* = 99:1): 242 mg (0.80 mmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 2H), 7.31-7.29 (m, 3H), 4.96 (br s, 1H), 4.77-4.76 (m, 2H), 4.36-4.35 (m, 2H), 4.13 (m, 1H), 2.33 (m, 2H), 2.17-2.12 (m, 1H), 1.89-1.83 (m, 1H), 1.78-1.69 (m, 6H), 1.59 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.73, 149.04, 138.72, 128.84, 127.62, 109.29, 82.74, 70.99, 45.00, 37.31, 33.93, 31.61, 26.00, 21.42. IR (neat, cm^{-1}): 3368, 1690, 1497, 1453, 1259, 1167, 1029, 887, 731, 697. HRMS (ESI+, MeOH): *m/z* calcd. 326.1727 $(M + Na)^+$, found: 326.1731.

4.4.3 Crystallographic Data

Crystallographic data was obtained following the methodology described in chapter I.

Crystal data for carbamate ***4.13a****:* $C_{11}H_{19}NO_4$, M_r =229.13, triclinic, P-1, a = 6.7953(3) Å, b = 8.9016(4) Å, c = 10.1376(5) Å, α = 91.1523º, β = 90.8496(12)º, γ = 103.9588º, V = 594.86(5) Å^3, Z = 2, ρ = 1.280 mg·M^{-3}, μ = 0.097 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 248, crystal size = 0.30 × 0.20 × 0.10 mm, θ(min) = 2.01º, θ(max) = 31.671º, 7489 reflections collected, 3658 reflections unique (R_{int} = 0.0217), GoF = 1.059, R_1 =0.0405 and wR_2 = 0.1079 [$I > 2\sigma(I)$], R_1 = 0.0467 and wR_2 = 0.1125 (all indices), min/max residual density = -0.2540.383 [e·Å^{-3}]. Completeness to θ(31.671º) = 91.2%.

Crystal data for carbamate ***4.13b****:* $C_{11}H_{19}NO_4$, M_r =229.13, monoclinic, P21/c, a = 10.9738(13) Å, b = 5.6284(7) Å, c = 19.681(2) Å, α = 90.0º, β = 99.692 (19)º, γ = 90.0º, V = 1198.2(2) Å^3, Z = 4, ρ =1.271 mg·M^{-3}, μ = 0.096 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 496, crystal size = 0.15 × 0.10 × 0.03 mm, θ(min) = 1.883º, θ(max) = 27.916º, 11814 reflections collected, 2816 reflections unique (R_{int} = 0.0690), GoF = 1.030, R_1 =0.0636 and wR_2 = 0.1530 [$I > 2\sigma(I)$], R_1 = 0.0968 and wR_2 = 0.1710 (all indices), min/max residual density = -0.443/0.295 [e·Å^{-3}]. Completeness to θ(27.916º) = 99.4%.

4.5 References

(1) Ghosh, A. K.; Brindisi, M. *J. Med. Chem.* **2015**, *58*, 2895–2940.

(2) Engels, H. W.; Pirkl, H. G.; Albers, R.; Albach, R. W.; Krause, J.; Hoffmann, A.; Casselmann, H.; Dormish, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 9422–9441.

(3) Chaturvedi, D. *Tetrahedron* **2012**, *68*, 15–45.

(4) Han, C.; Porco, J. A. *Org. Lett.* **2007**, *9*, 1517–1520.

(5) Selva, M.; Tundo, P.; Perosa, A.; Dall'Acqua, F. *J. Org. Chem.* **2005**, *70*, 2771–2777.

(6) Annunziata, L.; Diallo, A. K.; Fouquay, S.; Michaud, G.; Simon, F.; Brusson, J.-M.; Carpentier, J.-F.; Guillaume, S. M. *Green Chem.* **2014**, *16*, 1947–1956.

(7) Blain, M.; Jean-Gérard, L.; Auvergne, R.; Benazet, D.; Caillol, S.; Andrioletti, B. *Green Chem.* **2014**, *16*, 4286–4291.

(8) Sopeña, S.; Laserna, V.; Guo, W.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Adv. Synth. Catal.* **2016**, *358*, 2172–2178.

(9) Guo, W.; Gonzalez-Fabra, J.; Bandeira, N. A. G.; Bo, C.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2015**, *54*, 11686–11690.

(10) Tomita, H.; Sanda, F.; Endo, T. *J. Polym. Sci. Part A Polym. Chem.* **2001**, *39*, 3678–3685.

(11) Kojima, F.; Takuzo, A.; Inoue, S. *J. Am. Chem. Soc.* **1986**, *108*, 391–395.

(12) Shang, J.; Guo, X.; Li, Z.; Deng, Y. *Green Chem.* **2016**, *18*, 3082–3088.

(13) Buchard, A.; Kember, M. R.; Sandeman, K. G.; Williams, C. K. *Chem. Commun.* **2011**, *47*, 212–214.

(14) Peña Carrodeguas, L.; Gonzalez-Fabra, J.; Castro-Gomez, F.; Bo, C.; Kleij, A. W. *Chem. Eur. J.* **2015**, *21*, 6115–6122.

(15) Whiteoak, C. J.; Kielland, N.; Laserna, V.; Escudero-Adán, E. C.; Martin, E.; Kleij, A. W. *J. Am. Chem. Soc.* **2013**, *135*, 1228–1231.

(16) Taherimehr, M.; Al-Amsyar, S. M.; Whiteoak, C. J.; Kleij, A. W.; Pescarmona, P. P. *Green Chem.* **2013**, *15*, 3083–3090.

(17) Darensbourg, D. J.; Chung, W. C. *Macromolecules* **2014**, *47*, 4943–4948.

(18) Darensbourg, D. J.; Yeung, A. D.; Wei, S.-H. *Green Chem.* **2013**, *15*, 1578–1583.

(19) Whiteoak, C. J.; Kielland, N.; Laserna, V.; Castro-Gomez, F.; Martin, E.; Escudero-Adán, E. C.; Bo, C.; Kleij, A. W. *Chem. Eur. J.* **2014**, *20*, 2264–2275.

(20) Liu, Y.; Ren, W.-M.; He, K.-K.; Zhang, W.-Z.; Li, W.-B.; Wang, M.; Lu, X.-B. *J. Org. Chem.* **2016**, *81*, 8959–8966.

UNIVERSITAT ROVIRA I VIRGILI
SMALL MOLECULE ACTIVATION FOR THE FORMATION OF HETEROCYCLIC COMPOUNDS
Victor Laserna Ayora

Chapter V

Stereoselective Preparation of Highly Substituted Organic Carbonates

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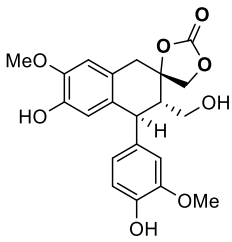
5.1 Introduction

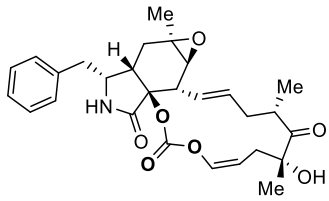
5.1.1 Multisubstituted Cyclic Carbonate Structures

Previous chapters have already discussed in detail how carbon dioxide offers a cheap and renewable carbon feedstock for fine-chemical synthesis[1,2] and the role of homogeneous catalysis to turn this waste into more complex molecules.[3–5] The potential of cyclic carbonates as intermediates has been widely demonstrated[6–8] but in order to increase their impact, the scope of functional carbonates that can be prepared via CO_2/epoxide coupling needs to be broadened. Whereas mono-substituted organic carbonates are fairly easily prepared and methodologies for di-substituted versions[9,10] have recently become available, it remains a huge challenge to prepare more densely substituted/functionalized organic carbonate scaffolds which ultimately may limit further exploration of the synthetic potential of these structures. The preparation of trisubstituted cyclic organic carbonates has been rarely reported[11–13] and with important limitations in scope and yield. Highly substituted epoxides that upon coupling with CO_2 would give cyclic carbonates remain challenging reaction partners. The importance of such highly substituted carbonates is a result of the presence of highly substituted patterns in many naturally occurring plant-based organic carbonates and naturally occurring terpene-based olefin precursors.

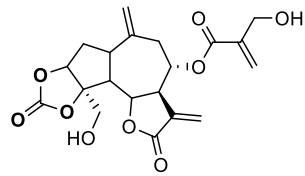
Figure 5.1 Selected examples of multisubstituted carbonates in natural products.



Cycloolivil Carbonate



Cytochalasin E



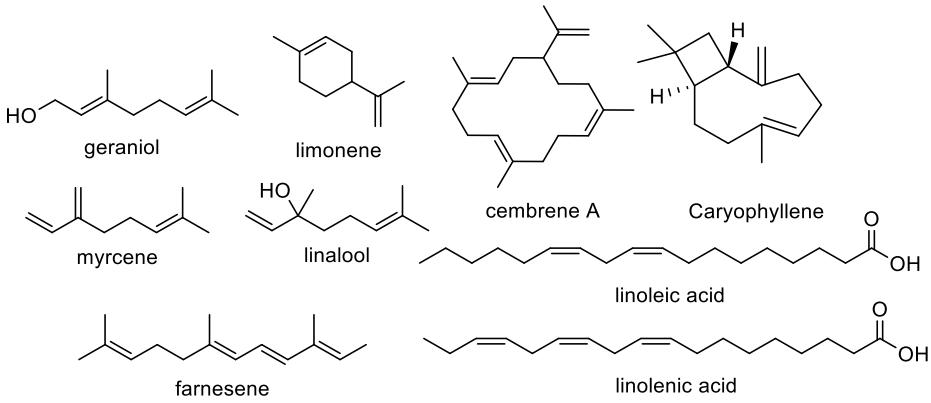
Hololeucin

The reported formation of densely substituted cyclic carbonates[12] has been achieved through a double inversion pathway, which involves the activation of the oxiranes by a Lewis acid catalyst and ring opening by an (external) nucleophile. However, as already mentioned

before, the limited methodologies known to date report low yields and low(er) selectivity. It is clear that in order to access multisubstitued cyclic scaffolds with potential in organic synthesis and having a bio-based origin, new strategies and catalytic processes must be devised.

These multisubstituted carbonates are not only interesting for their possible synthetic applications, they also represent scaffolds with potential in new electrolytes for lithium ion batteries, raw materials for thermally more resistive plastics, and environmentally friendly nonprotic solvents and degreasers.[14] To make these compounds completely bio-based, the epoxide in the coupling reaction with CO_2 should have a renewable origin instead of being derived from fossil fuels. Terpenes and fatty acids are classes of naturally occurring alkenes which can be easily oxidized to their corresponding epoxide derivatives. These bio-based alkenes incorporate generally more complex and substituted alkene fragments which are typically difficult to transform into carbonates using state-of-the-art catalysis. In **Figure 5.2** a selection of interesting bio-based structures is presented which may be transformed into biocarbonates but would require alternative and powerful catalytic methods for conversion into these targets.

Figure 5.2: Terpene and fatty acid structures which can be used to obtain bio-based cyclic carbonates.

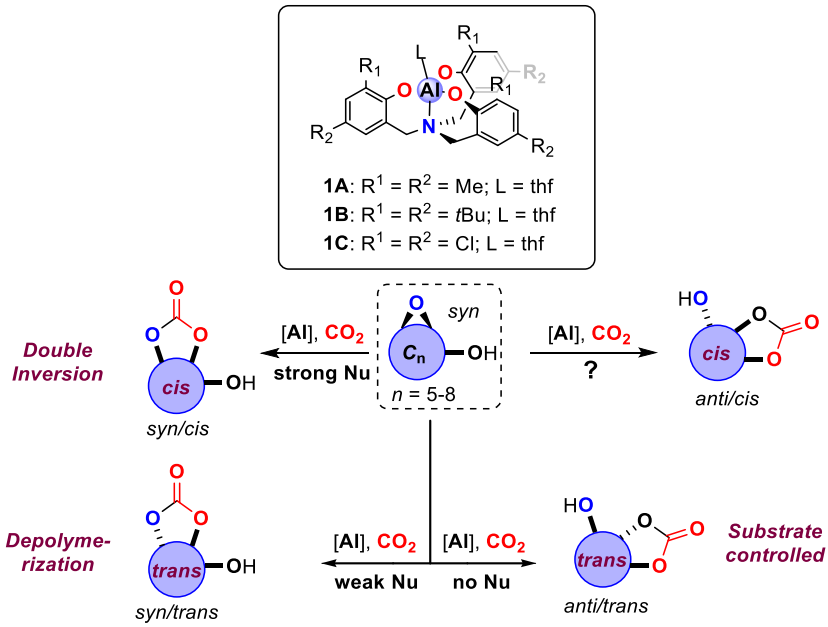


While searching for alternative approaches towards cyclic carbonate formation, our group reported on the use of acyclic epoxy alcohols that can be converted into organic carbonates through a substrate-controlled CO_2 activation process. In this new approach a pro-nucleophile in the molecule activates CO_2 forming a nucleophilic species which induces an intramolecular ring opening process following cyclic carbonate formation.[15]

5.1.2 Project Aims and Strategy

We set out to design a new conceptual approach towards cyclic *anti*/*cis* (note: *anti*/*cis* and *syn*/*cis* notations refer to the relative position of the OH group with respect to a *cis*-configured cyclic carbonate unit, see **Figure 5.3**) configured hydroxy carbonate scaffolds to investigate the synthetic stereodivergent potential of cyclic epoxy-alcohol substrates. We predicted that various cyclic hydroxy-carbonate scaffolds with different stereochemistry (**Figure 5.3**) could be produced from a common *syn*-configured cyclic epoxy alcohol precursor depending on different previously reported reaction manifolds. These structures represent stereodefined, protected triol scaffolds which are value-added intermediates in organic synthesis.

Figure 5.3. The conversion of different ring-size cyclic epoxy-alcohols into organic carbonate scaffolds with various stereochemical configurations.



A double inversion pathway (in the presence of excess, strong nucleophile) retains the original stereochemistry of the substrate and would afford a *syn*/*cis* configured product. An alkoxide driven depolymerization of a polycarbonate intermediate using a weak nucleophile would lead to a *syn*/*trans* isomer, whereas hydroxyl-mediated activation of carbon dioxide (*cf.*, no external nucleophile added) and intra-molecular ring-opening leads to an

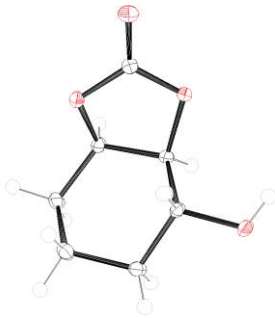
anti/*trans* configuration. These known manifolds lead to diastereoisomeric *syn*/*cis*, *syn*/*trans* and *anti*/*trans* configured organic carbonates but are not able to provide the corresponding *anti*/*cis* isomer for which thus a new approach needs to be developed (*vide infra*); such an approach would allow an entry towards the synthesis of multisubstituted carbonates.

5.2 Results and Discussion

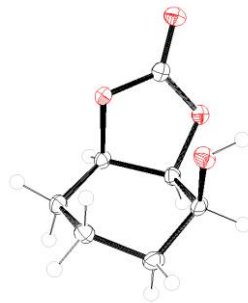
5.2.1 Optimization of Diastereocontrol

First, we examined the use of a simple and synthetically accessible epoxy-alcohol substrates based on a cyclohexyl skeleton (**Table 5.1**, compound **5.1a**) and its selectivity towards the formation of cyclic carbonates. We started by checking standard conditions typically used previously for cyclic epoxide coupling with CO_2. As for previous studies, neat conditions favored the formation of polymeric species (polyether mainly) so we decided to dilute the substrate using MEK as solvent.[16] Different reaction conditions varying the nucleophilic halide additive, Al-catalyst, temperature and pressure were probed. **Table 5.1** shows their influence on the composition of the product mixture. In general, we identified the three main products that were formed, *syn*/*cis*-**5.1c**, *anti*/*cis*-**5.1b** and triol **5.1d** which were unambiguously identified by 1D/2D NMR spectroscopy, and X-ray diffraction.

Figure 5.4 Molecular structures determined for **5.1b** and **5.1c**.

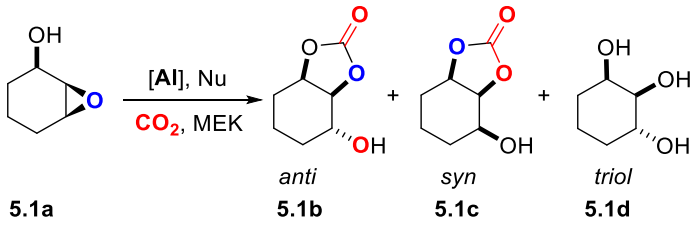


5.1b



5.1c

Table 5.1. Screening of Reaction Conditions for **5.1a**.[a]



Entry	Cat. (mol%)	Nu (mol%)	P (bar)	Conv (%)	Sel. to 5.1 b/c/d (%)[b]
1	-	**Br**, 2.5	10	51	60:40:0
2	-	**Br**, 5.0	10	73	41:50:9
3	-	**Br**, 10.0	10	99	23:68:9
4	-	**Br**, 20.0	10	99	15:72:12
5	-	**Br**, 25.0	10	99	13:82:5
6	-	**Cl**, 5.0	10	81	55:25:20
7	-	**I**, 10.0	10	99	22:62:16
8	**1C**, 0.5	**Br**, 0.5	10	99	83:0:17
9	**1C**, 0.5	**Br**, 1.0	10	99	83:0:17
10	**1C**, 0.5	**Br**, 1.0	40	99	93:0:7
11	**1C**, 0.5	**Br**, 1.0	10	99	83:0:17
12[b]	**1C**, 0.5	**Br**, 1.0	10	99	51:0:49
13[c]	**1C**, 0.5	**Br**, 1.0	10	99	44:0:56
14	**1C**, 0.5	**Br**, 2.5	10	99	59:0:41
15	**1C**, 2.5	**Br**, 2.5	10	99	71:0:49
16	**1C**, 5.0	**Br**, 5.0	10	99	59:0:41
17	**1C**, 2.5	**Br**, 1.0	10	99	4:0:33[d]
18	**1A**, 0.5	**Br**, 1.0	10	99	71:0:29
19	**1A**, 1.0	**Br**, 2.5	10	99	89:0:11
20	**1B**, 1.0	**Br**, 2.5	10	99	64:11:25
21	**1B**, 1.0	**Br**, 5.0	10	82	38:40:22

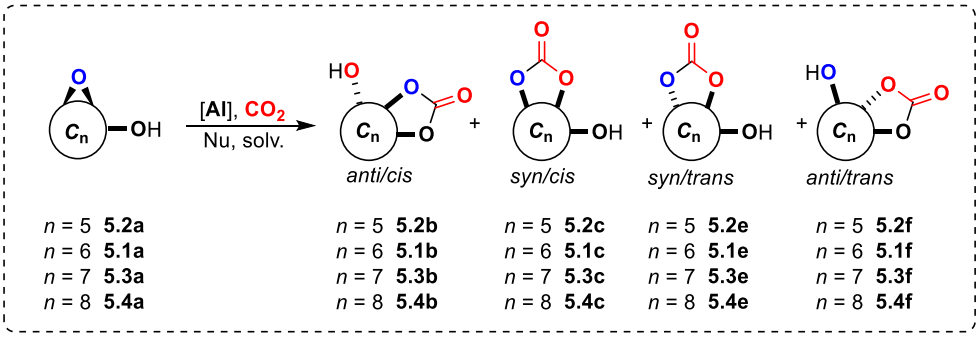
[a]General conditions: 0.50 mmol of **5.1a**, $p(CO_2)$º = 10 bar, 70 ºC, MEK (200 μL), amounts of [**Al**] and **Nu** indicated. **I/Br** is NBu_4I/Br and **Cl** stands for PPNCl. [b] Determined by ^1H NMR ($CDCl_3$). [c]At 50ºC. [d] Large amounts of polyether (>50%) were also formed.

The *syn/cis* isomer **5.1c** (82% yield) was formed as the major product by using only a nucleophilic additive (**Table 5.1**, *entries 1–6*; NBu_4Br), and its synthesis is likely the result of a double inversion mechanism. In order to get reasonable selectivity and conversion towards the *syn*/*cis* product **5.1c**, high loadings of nucleophile were necessary as otherwise mixtures of *syn/cis* and *anti/cis* were obtained. Similar behavior was observed by using different types of halide nucleophiles so we decided to focus on using bromide for this screening study. Using low catalyst loadings of bromide nucleophile or in the presence of both nucleophile and Al-complexes **1A–1C** (**Table 5.1**, *entries 8–21*), the diastereoselectivity progressively shifted towards the formation of *anti/cis* **5.1b** (*entry 8*; 83% yield).

The presence of the Al complex accelerated the reaction and shifted the stereoselectivity considerably though at higher [Al]/Nu ratios (*entry 17*) large amounts of polyether were observed. We then set out to optimize the reaction conditions to selectively form the *anti/cis* product **5.1b**. Using Al complexes and halide nucleophiles as binary catalysts we obtained mainly mixtures of **5.1b** and **5.1d**. The type of Al complex, the catalyst/nucleophile loadings and their ratios were varied to try to improve the selectivity towards **5.1b**. Low loadings and an Al/Nu ratio of 1:2 at high pressures of CO_2 yielded the best selectivity towards the target molecule (**Table 5.1**, *entry 10;* 93%). The use of complexes **1A** and **1C** afforded similar results, while the use of complex **1B** clearly proved to be less effective. The most favorable conditions towards the formation of **5.1b** suggest that the operating mechanism involves some kind of oligo- or polymeric intermediate being unstable in the presence of a (pro)nucleophile. Suitable nucleophiles may help to assist a depolymerization of the initially formed oligo/polycarbonate product. As previously shown in section **4.2.1**, the ring size in bi- or multicyclic epoxides can have a significant effect on the tendency towards polymerization (oligo/polycarbonate formation) and subsequent depolymerization to generate bi/multi-cyclic carbonates, and therefore we decided to study the products generated from various cyclic *syn* epoxy alcohols (section **5.2.2**).

5.2.2 Carbonate Synthesis from Different Hydroxy Epoxides

Figure 5.5 Hydroxyl-substituted cyclic epoxides studied and their conversion into carbonates.

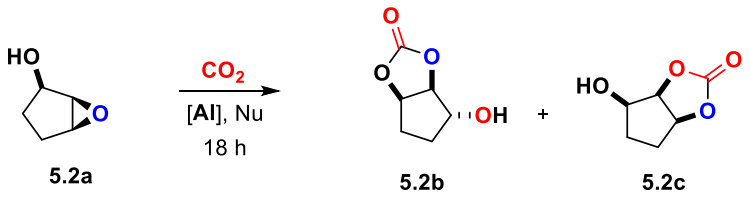


In order to gain more insight into the operating mechanism leading to these *anti*/*cis* configured bicyclic carbonates, we decided to consider various hydroxy-substituted cyclic epoxides (**Figure 5.5**, **5.2a–5.4a**). The conditions leading to the *anti/cis* bicyclic carbonates **5.1b–5.3b** (yield: 71–87%) had to be optimized individually (see below, **Tables 5.2–5.4**), whereas the synthesis towards *anti*/*cis* **5.4b** was not feasible.

5.2.2.1 Five-Membered Ring Structures

The first compound we studied was epoxy alcohol **5.2a**. The five-membered hydroxy-substituted epoxide when coupled with CO_2 in the presence of an amino triphenolate catalyst and a nucleophile yielded the carbonates **5.2b** and **5.2c** in an analogous way as observed for epoxy alcohol derivative **5.1a** containing a fused six-membered ring. The main difference was that the byproducts generated were a slightly more complex mixture of polyether, polycarbonate and triol structures which we were not able to fully characterize. The preparation of **5.2c** was achieved using only NBu_4Br in a 10 mol% loading. High selectivity towards the *syn/cis* isomer required lower Br loading than noted for **5.1a** (95% versus 68% with 10 mol% loading, respectively) confirming anticipated differences in reactivity controlled by the ring size in the epoxide substrate. This was further confirmed by comparing the results obtained when using the optimized Al/Nu loadings applied to substrate **5.1a** (**Table 5.2**, *entry 1*), the selectivity towards the *anti/cis* product decreased from 83% to 55%.

Table 5.2 Screening of reaction conditions towards formation of *anti/cis* **5.2b**.[a]



5.2a **5.2b** **5.2c**

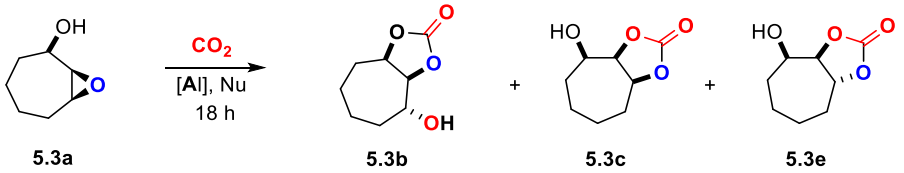
Entry	Cat. (mol%)	Nu (mol%)	Conv (%)	CC. Sel.	Sel. 5.2 b:c (%)
1	**1C**, 0.5	**Br**, 1.0	67	71	55:45
2	**1C**, 1.0	**Br**, 1.0	99	75	61:39
3	**1B**, 1.0	**Br**, 1.0	71	87	20:80
4	**1A**, 1.0	**Br**, 1.0	95	93	62:38
5	**1C**, 1.0	**Cl**, 1.0	99	77	97:3
6	**1A**, 1.0	**Cl**, 1.0	99	99	99:1
7	-	**Br**, 10.0	99	99	5:95

[a]General conditions: $p(CO_2)^o$ = 10 bar, 70 ºC, MEK was used as solvent, 0.5 mmol of substrate in 200 μL of solvent. In those cases where the selectivity towards cyclic carbonate was substantially lower than 100%, the byproducts represented a complex mixture assigned to polyether, oligo/polycarbonate intermediate and triols. **Br** is NBu_4Br and **Cl** stands for PPNCl, CC stands for cyclic carbonate.

By screening other conditions we observed that the presence of complex **1A** increased the selectivity towards carbonate products (*entry 4*). This can be associated to its lower Lewis acidity, while **1B** (probably less Lewis acidic) again proved to be the least selective/active one. To suppress the double inversion pathway and favor a polymeric pathway, the nucleophilicity of the nucleophile was changed from bromide (NBu_4Br) to chloride (PPNCl) which was reported to favor polycarbonate formation. By combining complex **1A** with chloride in a 1:1 ratio, the carbonate *anti/cis* **5.2b** could be selectively formed (99%, *entry 6*).

5.2.2.2 Seven-Membered Ring Structures

Table 5.3 Screening of reaction conditions towards the formation of *anti/cis* **5.3b**.[a]



5.3a **5.3b** **5.3c** **5.3e**

Entry	Cat. (mol%)	Nu (mol%)	Solv.	Conv (%)	CC. Sel.	Sel. 5.3 b:c:e (%)
1	**1C**, 1.0	**Cl**, 1.0	MEK	91	84	30:0:70
2	**1C**, 2.5	**Br**, 5.0	MEK	99	53	9:0:91
3	**1C**, 2.5	**Cl**, 1.0	MEK	99	76	38:0:62
4	**1C**, 5.0	**Cl**, 5.0	MEK	99	88	25:0:75
5	-	**Br**, 25.0	MEK	99	97	0:>99:0
6	**1A**, 5.0	DMAP, 5.0	Tol	99	95	>99:0:0
7	**1A**, 1.0	**Cl**, 5.0	Tol	99	90	23:0:77

[a]General conditions: $p(CO_2)^o$ = 40 bar, 70ºC, 0.5 mmol of substrate in 200 μL of solvent. In some cases, sub-products were formed that represented a complex mixture assigned to polyether, oligo/polycarbonate intermediate and diols. **Br** is NBu_4Br and **Cl** stands for PPNCl, CC stands for cyclic carbonate.

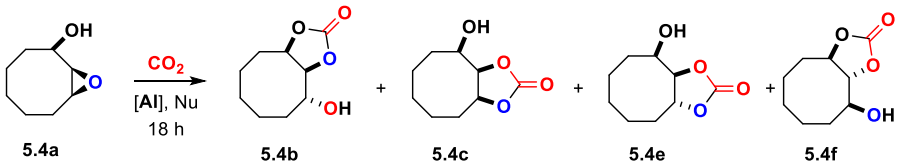
When the size of the fused cycloalkyl ring in the epoxide substrate was increased to seven, the optimized conditions determined for the synthesis of **5.2b** enabled us to isolate the product with a *syn/trans* configuration not observed for the previous substrates. The coupling reaction of seven-membered cycloalkene oxides with CO_2 was reported to yield a mixture of the *cis* and the *trans* configured cyclic carbonate[17] in line with our observations using **5.3a** as substrate. In smaller bicyclic carbonate structures having a *trans* configuration there exists higher ring strain which makes their synthesis thermodynamically unfavorable. The *syn/cis* configured isomer **5.3c** was obtained by using 25 mol% of nucleophilic additive. The same stereoselectivity was noted using lower loadings of nucleophile though with incomplete conversions after 18 h. The observed reactivity of substrate **5.3a** is slightly lower than for **5.1a** and **5.2a** and the [Al]/Nu loadings were therefore slightly increased to achieve complete

conversions. Upon variation of the Al complex, the nucleophile and [Al]/Nu ratios typically the formation of the *syn/trans* species (*entries 1-4* and *7*) was favored. We suspected that both **5.3b** and **5.3e** are the result of an *in situ* depolymerization process and decided to change the solvent to toluene with the intention to suppress side reactions and fortunately the selectivity towards carbonate products was indeed improved. Finally, inspired by the work from Kruper and Dellar who investigated the coupling reactions of CO_2 and cyclic epoxides using DMAP as nucleophile, we were able to selectively prepare **5.3b** in high yield.

5.2.2.3 Eight-Membered Ring Structures

Eight membered ring cycloalkene oxides were the last substrate class that was examined (**Table 5.4**) due to the unavailability of the starting materials for larger ring cycloalkene oxides. In these cases, we did not observe the formation of the *anti/syn* isomers. The *syn/cis* structure was obtained, as expected, using high loadings of nucleophile although full conversion was not achieved as the presence of 25 mol% of bromide only gave 26% conversion of substrate **5.4a**. Upon changing to a smaller nucleophile (Cl) the conversion into carbonate product could be slightly improved. The chloride nucleophile loading could not be increased above 10 mol% due to the poor solubility of PPNCl in the reaction medium. No side products were detected for this substrate and only mixtures of the different hydroxy-carbonates **5.4c**, **5.4e** and **5.4f** were identified. The most favored species in these mixtures was **5.4f** having an *anti/trans* configuration. The rationale towards formation of **5.4f** is the occurrence of activation of CO_2 by the alcohol moiety allowing to ring open the epoxide by the initially formed linear carbonate intermediate. This stereoisomer was only observed for substrate **5.4a**, and this *trans* configured stereoisomer seems to be thermodynamically favored as for most of the reaction conditions that were tried, compounds **5.4e** and **5.4f** turned out the main products formed. For both *trans* species **5.4e** and **5.4f** single crystal X-ray diffraction studies were performed to support their proposed stereochemical configurations (**Figure 5.6**).

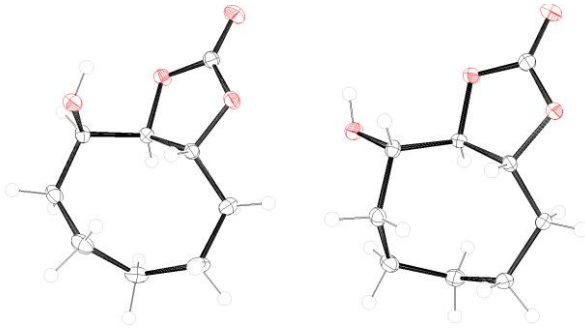
Table 5.4 Screening of reaction conditions towards formation of *anti/cis* **5.4b**.[a]



Entry	Cat. (mol%)	Nu (mol%)	Solv.	Conv (%)	Sel. to 5.4 b:c:e:f (%)
1	**1C**, 2.5	**Cl**, 2.5	MEK	99	0:0:41:59
2	**1C**, 2.5	**Cl**, 5.0	MEK	99	0:26:38:36
3	**1C**, 1.0	**Br**, 2.5	Tol	99	0:39:16:45
4	**1C**, 5.0	DIPEA, 10.0	MEK	99	0:0:0:99
5	**1A**, 1.0	**Cl**, 5.0	Tol	99	0:6:85:9
6	**1A**, 5.0	DMAP, 5.0	Tol	99	0:0:0:99
7	**1B**, 5.0	DIPEA, 10.0	MEK	0	0:0:0:0
8	-	**Br**, 25.0	MEK	26	0:99:0:0
9	-	**Cl**, 10.0	Tol	45	0.99:0:0

[a]General conditions: $p(CO_2)^o$ = 40 bar, 70 ºC, 0.5 mmol of substrate in 200 μL of solvent. **Br** is NBu_4Br and **Cl** stands for PPNCl.

Figure 5.6 Molecular structures determined for **5.4e** (left) and **5.4f** (right).



5.4e **5.4f**

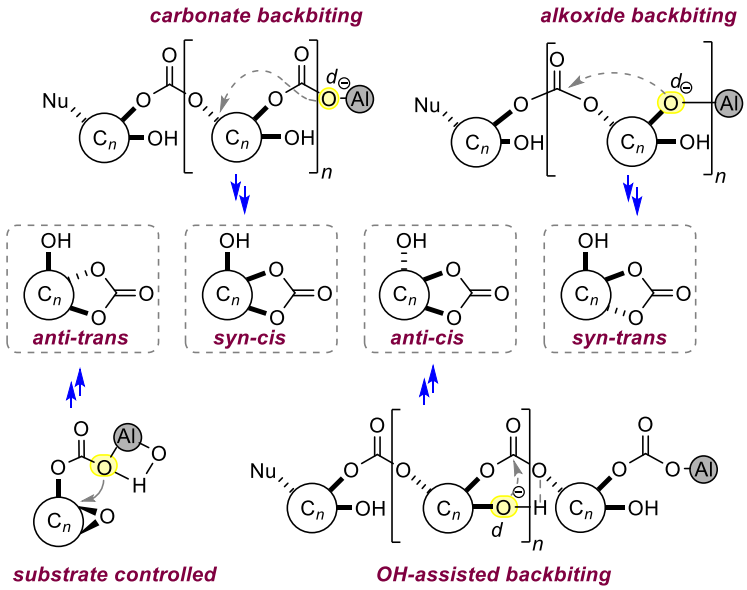
5.2.3 Mechanistic Insights

The synthesis of the isomeric *syn*/*cis* carbonates **5.1c–5.4c** was simply mediated by using high loadings of the nucleophilic additive NBu_4Br or PPNCl, and is pertinent to the aforementioned double inversion pathway.[2] In contrast, the manifold leading to **5.1b–5.4b** is different, and we propose that the applied experimental conditions favor a backbiting process of an oligomeric carbonate intermediate produced *in situ* from cyclic epoxides as previously reported.[18] Standard depolymerization[19] of oligo/polycarbonates would produce a *trans* configured cyclic carbonate product through a metal-alkoxide terminus (alkoxide backbiting, see **Figure 5.7**), and consequently a *syn*/*trans* configured product. Alternatively, carbonate backbiting (**Figure 5.7**) in a polymer with a metal-carbonate end-group would furnish a *syn*/*cis* carbonate product (i.e., the same configuration as the double inversion pathway). Therefore the mechanism accountable towards the formation of the *anti*/*cis* configured carbonates **5.1b–5.4b** is distinct from these previous reported depolymerization pathways. We propose that the hydroxy-unit is actively involved in the depolymerization process as outlined in **Figure 5.7** (OH–assisted backbiting). The OH group may be readily activated towards nucleophilic attack onto the adjacent carbonate unit through H–bonding and likely this process is favored over the standard depolymerization process for substrates of type **5.1a** and **5.2a** (with n = 5 or 6). An OH-assisted depolymerization nicely fits the experimentally observed formation of *anti*/*cis* configured carbonate products **5.1b–5.3b**.

The mechanistic hypothesis was further challenged by consideration of seven- and eight-membered ring cycloalkene oxide substrates as these are generally less prone towards copolymerization with CO_2. As mentioned before, Kruper and Dellar reported[17] the formation of a *trans*-configured carbonate product in high yield derived from cycloheptene oxide, which may be the result of an *in situ* depolymerization process. This latter example is one of the few reported cases where cyclic epoxides with fused rings larger than six are converted to their corresponding cyclic carbonates in reasonable yields but it also represents the only one where the product has the carbonate configuration inverted compared to the starting material, pointing to a co/depolymerization sequence. The experimental conditions were altered such that copolymerization would be favored[19–21] and this clearly increased the selectivity towards the *anti/syn* and the *syn/trans* configurations presumably originating from depolymerization pathways. The larger ring-size bicyclic carbonate products **5.3e** and **5.4e**, which we assume

to be generated *via* a standard alkoxide backbiting process (**Figure 5.7**) could be isolated, though their yields were modest/low due to competitive pathways leading to other stereoisomers. Such *trans* configured carbonates are typically not formed from smaller bicyclic epoxides (n = 5 or 6) as the intrinsic ring strain in the bicylic carbonate product would lead to decarboxylation and/or decomposition.[22–24]

Figure 5.7. Mechanistic pathways to the differently configured bicyclic carbonate products observed experimentally. Al stands for an Al-complex (**1A-1C**).



The *anti*/*trans* configured carbonate **5.4f** (86%) was obtained in high yield in the presence of **1A**/DMAP as binary catalyst and its configuration suggests the occurrence of substrate-assisted activation of CO_2 (**Figure 5.7**) facilitated by the Al-complex **1A** as previously described by us for *acyclic* epoxy-alcohols.[15] Thus, it seems that for larger ring-size hydroxy-substituted cycloalkanes the formation of an *anti*/*cis* configured bicyclic carbonate is less likely to occur due to competitive pathways that lead to other diastereoisomers. As far as we know, the formation of **5.4e** and **5.4f** represent rare examples of bicyclic carbonates with fused eight-membered rings, and their structures were unambiguously confirmed by X-ray analyses (**Figure 5.6**).

In various reactions that involved epoxy alcohol substrates **5.1a–5.4a** triol byproducts were observed, and the mechanism involved towards their formation remains

uncertain. The simplest explanation would be the involvement of a hydrolysis reaction by trace amounts of water present in the reaction mixture. However, a control reaction in the absence of CO_2, in which **5.1a** was heated to 70 ºC in MEK for 18h, did not show any conversion. When 0.5 mol% of Al-complex was combined with 1 mol% TBAB and substrate **5.1a** and left stirring overnight at this same temperature, a mixture of polyether (65%) and triol product (35%) had formed that leads to believe that triol formation may involve a similar initiation step as polyether formation.

5.2.4 Scope of Trisubstituted Carbonates

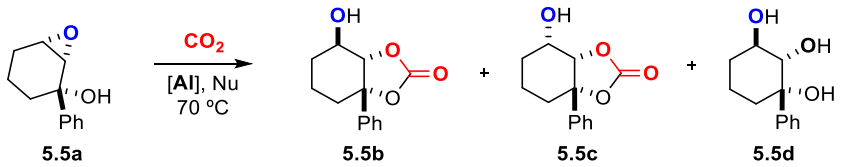
In order to examine whether the formation of the unusual *anti*/*cis* configured bicyclic carbonates could be extended to more functional derivatives, we then turned our focus on the conversion of more complex versions of hydroxy-substituted cyclohexene oxides. If generally applicable, this new mechanistic manifold could generate a wide series of challenging trisubstituted carbonates and involve a new approach to CO_2 valorization.

Substitutions on the epoxide carbons generated complex mixtures of products and only traces of the desired cyclic carbonates could be observed (**Table 5.5**). Further substitution on the hydroxylated carbon center, however, was tolerated and we were able to observe the formation of a trisubstituted cyclic carbonate product. The formation of the desired carbonate **5.5b** from phenyl substituted epoxy alcohol **5.5a** was then taken as a model case and optimized. **Table 5.5** shows all reaction conditions screened to optimize the formation of trisubstituted carbonate **5.5b**. Initially the optimized conditions for substrate **5.1a** were selected but the results were not as satisfactory as a significant higher amount of triol product was formed along with overall low conversions. We decided to use conditions that would favor *in situ* polycarbonate formation, and these led to full conversion of **5.5a** with 80% carbonate selectivity. The best conditions encompassed the use of chloride as nucleophile, toluene as solvent, **1A** as Al-complex and using [Al]/Cl ratio of 1:5 (**Table 5.5**, *entry 6*), and consequently the formation of the desired carbonate was favored over the triol. To obtain full substrate conversion it was necessary to increase the CO_2 pressure during the reaction.

Once we had optimized the reaction conditions for **5.5a,** we decided to expand the scope to other ring-substituents (**Figure 5.8**). Gratifyingly, the carbonate products **5.5b**-**5.18b**

could be generally prepared in good to excellent isolated yields of up to 85% and with wide functional group diversity allowing for the introduction of synthetically useful alkyne (**5.13b** and **5.16b**), vinyl/olefin (**5.15b** and **5.18b**) and *para*- and/or *meta*-halide substituted aromatic fragments (**5.7b** and **5.11b**).

Table 5.5: Screening of reaction conditions, solvents, Al complexes and nucleophiles for the conversion of epoxy-alcohol **5.5a**.[a]

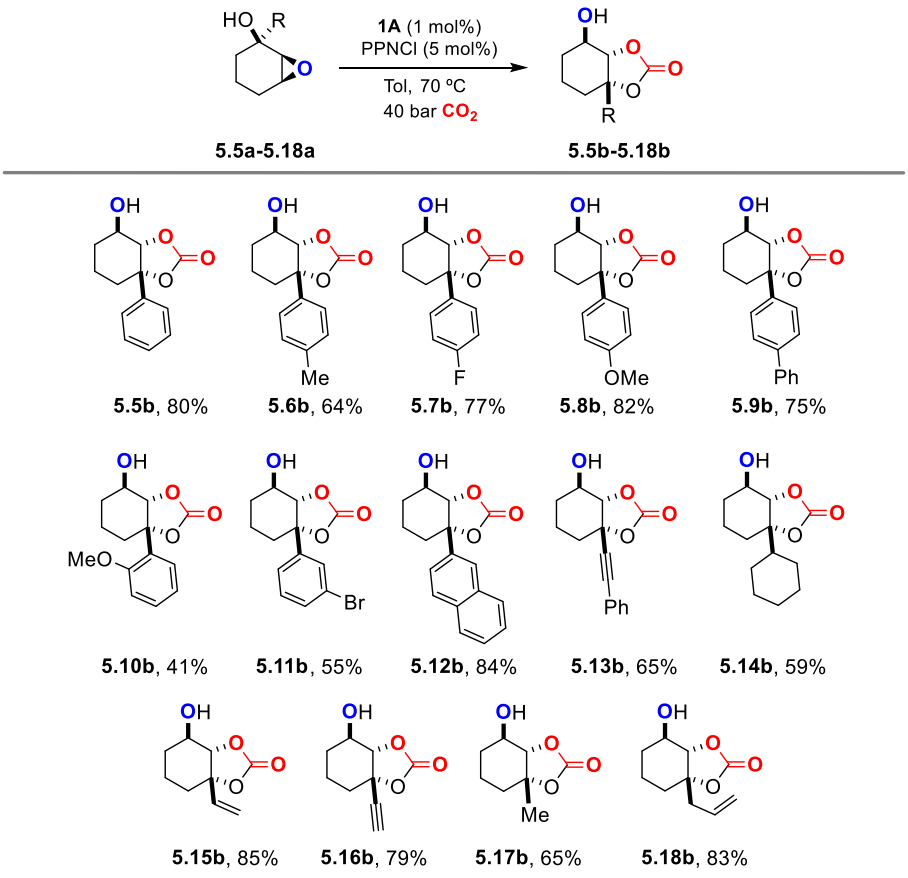


Entry	Cat.	Nu	Solv.	P	Conv (%)	Sel. for 5b/ 5.5c/5.5d (%)
1	**1C**, 0.5	**Br**, 1.0	MEK	10	21	53:3:44
2	**1C**, 0.5	**Br**, 2.5	MEK	10	34	52:12:36
3	**1C**, 1.0	**Br**, 2.5	MEK	40	64	22:19:59
4	**1C,** 1.0	**Cl**, 1.0	Tol	40	99	72:0:28
5	**1A**, 1.0	**Br**, 5.0	Tol	40	83	48:0:52
6	**1A**, 1.0	**Cl**, 5.0	Tol	40	99	80:6:14
7	**1A**, 1.0	DMAP, 10.0	Tol	40	73	63:0:27
8	-	**Br**, 5.0	MEK	10	27	21:59:20
9	-	**Cl**, 5.0	Tol	40	33	32:17:51

[a]General conditions: 70 ºC, 0.5 mmol of substrate in 200 μL of solvent. **Br** is NBu_4Br and **Cl** stands for PPNCl.

Hydroxy-cyclohexene oxide substrates with *ortho*-substituted aryl groups display more sluggish reactivity, and only a moderate yield for **5.10b** (41%) was obtained after 66 h indicating some degree of steric impediment in this transformation. Intriguingly, the straightforward and high yield synthesis of a series of *tri*-substituted, functional bicyclic carbonates could be easily achieved which is known to be extremely challenging in the area of CO_2/epoxide couplings. The presence of a vinyl group in the cyclic carbonate structure (such as in **5.15b**) conveniently allows for post-modification chemistry as recently demonstrated.[25,26]

Figure 5.8 Substrate scope for the conversion of various hydroxy-substituted cyclohexene oxides into *anti*/*cis* configured bicyclic carbonates.

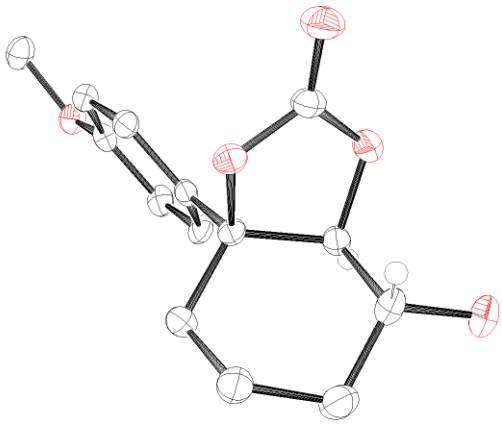


Conditions: 0.50 mmol epoxide substrate, toluene (200 mL), 18 h, 70 ºC, 40 bar CO_2. Reported yields are isolated ones after chromatographic purification.

The R–fragments (**Figure 5.8**) from the cyclohexene oxide substrates are not attached to the same carbon center as the (unprotected) alcohol group in the carbonate products *anti*/*cis* **5.1b** and **5.5b**-**5.18b**, and the X-ray structure determined for **5.8b** (**Figure 5.9**) was in line with the general spectroscopic assignments. These results further support that the original alcohol unit of the epoxide substrate is incorporated into the cyclic carbonate ring of the product and thus implies, as suggested, that this OH unit is actively involved towards the formation of the bicyclic carbonate product. In this context, we were surprised by the reaction outcome in the presence of only nucleophile. As expected, the conversion was much lower than noted for the non-substituted substrate **5.1a** at similar loadings of Al-complex and

nucleophile (the conversion dropped from 73 to 27%). However, the major product was still a trisubstituted cyclic carbonate which discards a standard double inversion pathway in this latter conversion as this would generate a different isomer.

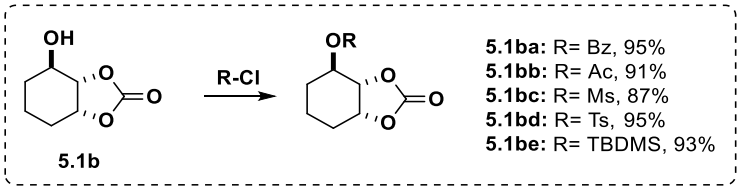
Figure 5.9 Molecular structure determined for **5.8b**.



5.2.5 Post-Modifications

Beside the formation of tri-substituted, functional carbonates **5.5b-5.18b**, *anti/cis* configured **5.1b** could be easily converted in high yield and selectivity into bicyclic carbonate scaffolds **5.1ba-5.1be**. These latter compounds incorporate rather common and synthetically useful protecting groups including benzoyl (Bz), mesyl (Ms) and a bulky silyl (TBDMS). Therefore, these conversions demonstrate that bicyclic carbonates can be attained that contain dissimilar protected OH moieties useful towards sequential transformations.

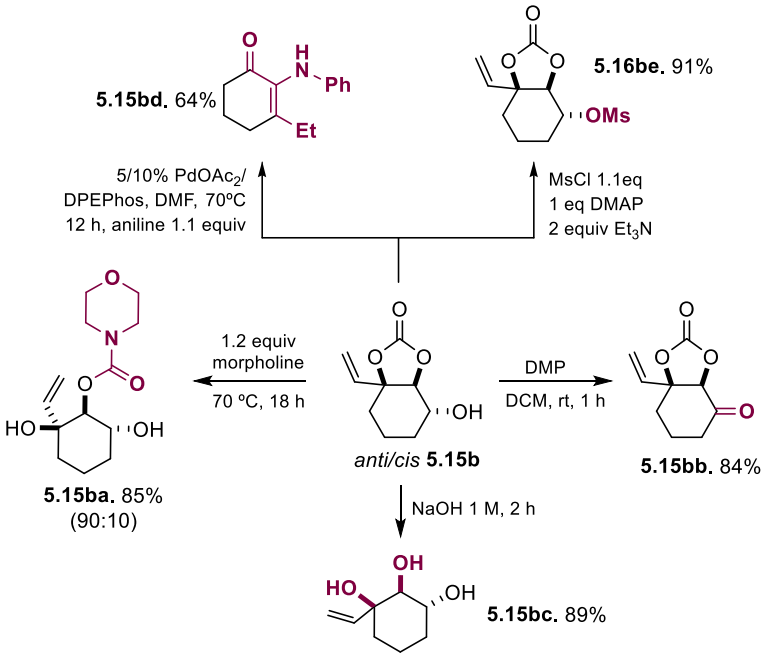
Figure 5.10. Hydroxy group protection: Ac = acetyl, Ts = tosyl.



Finally, we used vinyl-substituted bicyclic carbonate **5.15b** as a starting point to demonstrate the potential of these functionalized carbonates in organic synthesis and to access

other useful precursors (**Figure 5.11**). Treatment of **5.15b** with morpholine gave access to carbamate **5.15ba** in good yield (85%) and with high regioselectivity (90:10).[7] A Dess-Martin oxidation of **5.15b** furnished the ketone derivative **5.15bb** in 84% yield.

Figure 5.11 Synthetic potential of carbonate **5.15b** and conversion into its derivatives **5.15ba**–**5.15be**.



Simple hydrolysis under basic conditions converted **5.15b** into vinyl-substituted triol product **5.15bc** (89%) of potential use in natural product synthesis. A decarboxylative amination[25] gave access to selective formation of tetrasubstituted olefin **5.15bd** (64%). The formation of **5.15bd** was rather unexpected and the formation mechanism remains unclear, although it does confirm that decarboxylative conversion of this vinyl carbonate is feasible. As a final example, the alcohol fragment in **5.15b** could be protected by a mesyl group to afford **5.15be** in 91% yield. It should be noted that these transformations are rather general and should be applicable to the other bicyclic carbonates from **Figure 5.8**. The main objective of these reactions was to show the resistance of the carbonate scaffold during further chemical transformations in order to validate their potential as intermediates in (multi-step) synthetic processes.

5.3 Conclusions

In summary, we here present a unique manifold to access stereoselectively *anti*/*cis* configured bicyclic carbonates that are the result of a hydroxy-mediated depolymerization process of *in situ* prepared oligocarbonate precursors. This new manifold affords a wide range of challenging trisubstituted bicyclic carbonates that cannot be accessed through any previously reported methodology. Thus, this new depolymerization manifold provides a new valorization approach for carbon dioxide and its conversion into useful precursors for synthetic chemistry as demonstrated herein. This opens up the field to examine the use of other, related epoxy-alcohol scaffolds in various coupling reactions with a focus on synthetic applications.

Moreover it further confirms the hypothesis that not only *cyclic* carbonates can be used as synthetic intermediates, but also *oligo*-carbonates, as their electrophilic carbon center is susceptible towards nucleophilic attack both in an intra- and intermolecular way. The chemistry of epoxy alcohols thus generates value-added chemicals in a stereodivergent manner as the different available reaction manifolds give rise to the formation of different stereoisomeric products based on bicyclic scaffolds. The work presented in this chapter showcases a way to develop stereodivergent conversion of a single substrate by slightly changing the reaction conditions and/or metal/nucleophile combination or ratio to favor a specific target.

5.4 Experimental Section

5.4.1 General Information and Instrumentation

Commercially available alkenes, alkyl bromides, solvents, co-catalysts and oxidants were purchased from various commercial sources (Acros, Aldrich and TCI) and used without further purification. The non-commercial epoxides, cyclic carbonates and Al(III) amino triphenolate complexes **1A-C** were synthesized following methodologies explained in previous chapters. Carbon dioxide (purchased from PRAXAIR) was used without further

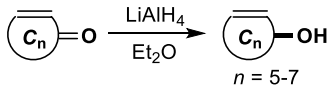
purification or drying prior to its use with the following specifications: CO_2-4X, analytical details: > 99.998% CO_2, < 10 ppm H_2O, < 5 ppm O_2, < 15 ppm N_2, < 5 ppm THC (such as methane). ^1H NMR, $^{13}C\{^1H\}$ NMR and related 2D NMR spectra were recorded at rt on a Bruker AV-300, AV-400 or AV-500 spectrometer and referenced to the residual deuterated solvent signals unless stated otherwise. All reported NMR values are given in parts per million (ppm). FT-IR measurements were carried out on a Bruker Optics FTIR Alpha spectrometer. Mass spectrometric analyses and X-ray diffraction studies were performed by the Research Support Group at ICIQ.

5.4.2 Synthetic Procedures

5.4.2.1 Epoxy Alcohol Synthesis

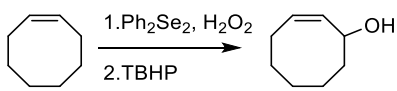
Synthesis of alkene precursors to 5.1a-5.18a

Figure 5.12: Reduction of cyclic enone precursors to allylic alcohols.



In a pre-dried 500 mL flask, the unsaturated cyclic ketone (25 mmol) was dissolved in diethyl ether (300 mL). The solution was cooled down to 0 ºC with an ice bath, after which $LiAlH_4$ (1.5 equiv) was slowly added to the solution, and the mixture was further stirred for 30 min. Then the reaction was carefully quenched by a combination of THF, acetone and water. The resultant colorless solution and grey precipitate were separated and the solution filtered through Na_2SO_4, and finally concentrated to yield a colorless oil.

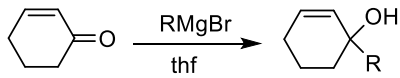
Figure 5.13: Oxidation of (*Z*)-cyclooct-2-en-1-ol to its allylic alcohol derivative.



(*Z*)-cyclooct-2-en-1-ol was prepared following a reported procedure.[27] In a 100 mL flask, diphenyl diselenide (2.00 g, 6.41 mmol) was dissolved into methylene chloride (21 mL). The yellow solution was cooled to 0 °C under argon and hydrogen peroxide solution (570 μL, 35 wt% in water, 221 mg, 6.51 mmol) was added dropwise. The reaction mixture was

vigorously stirred for 30 min (a colorless precipitate was observed) and magnesium sulfate (1.07 g, 8.89 mmol) was added. The reaction mixture was stirred for another 30 min and the ice bath was removed before adding cyclooctene (559 μL 469 mg, 4.26 mmol). The orange reaction mixture was rapidly stirred at rt under argon for 20 h. It was cooled down to 0 °C and *t*-butyl hydroperoxide solution (4.15 mL, 22.8 mmol: 5.5 M in decane) was slowly added. The ice bath was removed and the orange reaction mixture was stirred at rt for 20 h yielding a pale-orange solution with a colorless precipitate. The precipitate was filtered off and washed with ether. The orange filtrate was concentrated *in vacuo*, dissolved in ether (30 mL) and washed sequentially with sodium carbonate solution (5%, 26 mL), water (9 mL), ferrous sulfate solution (10%, 26 mL), water (20 mL), saturated sodium hydrogen carbonate solution (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate for 21 h and the solvent was removed *in vacuo*.

Figure 5.14: Nucleophilic attack on cyclohex-2-en-1-one to generate substituted allylic alcohols.

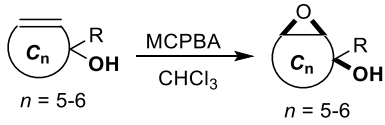


2 mmol of cyclohex-2-en-1-one (1.92 g) were introduced into a pre-dried 100 mL Schlenk flask under a N_2 atmosphere. Dry THF (20 mL) was introduced with a syringe into the Schlenk reactor and the mixture cooled to 0 ºC with an ice bath. In those cases where the Grignard reagent was commercially available (R = vinyl, methyl, propargyl, cyclohexyl, allyl, *p*-tolyl, phenyl, *p*-fluorophenyl) a solution in THF of the Grignard solution (22 mL at 1 M; 1.1 equiv, 22 mmol) was added dropwise to the reaction mixture. The mixture was then removed from the ice bath and stirred for 18 h. Hereafter, it was cooled to 0 ºC with an ice bath and quenched with an aqueous solution of NH_4Cl. The product was extracted with EtOAc (3 × 25 mL) and the solvent removed *in vacuo*.

In case the Grignard reagent was *not* commercially available, it was prepared by the following methodology: In a pre-dried Schlenk reactor, Mg turnings (20 mmol, 0.48 g) were introduced together with a small quantity of I_2 under N_2 and the mixture gently heated with a heat gun, and stirred for 20 min. Then THF (30 mL) was added to the solution which was further stirred for 4 h. Once the magnesium had fully dissolved, 2 mmol of cyclohex-2-en-1-one were added to the mixture and then stirred for 18 h.

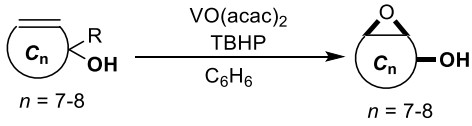
Synthesis of epoxy alcohols 5.1a-5.18a

Figure 5.15: Epoxidation of cyclic alkenes (*n* = 5 or 6).



Epoxidation procedure **A**: The corresponding alcohol precursor (2 mmol) was dissolved into $CHCl_3$ (50 mL) and cooled to 0 ºC with an ice bath. Then *meta*-chloro-perbenzoic acid (1.2 equiv, 2.4 mmol, 5.4 g) were slowly added. The reaction mixture was left stirring for 3 h at rt. Then the $CHCl_3$ was removed *in vacuo* and the precipitate was dissolved into EtOAc and washed two times with a saturated aqueous solution of $NaSO_3$, and two times with an aqueous solution of $NaHCO_3$ and brine. The resulting compound was further purified by column chromatography (SiO_2, EtOAc: Hex = 20:80).

Figure 5.16: Epoxidation of cyclic alkenes (*n* = 7 or 8).

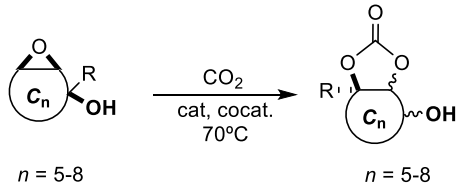


Epoxidation procedure **B**: The *syn*-epoxy alcohols with *n* = 7 or 8 were synthesized according to reported procedures.[28] To a solution of the alcohol precursor (2.67 mmol) in benzene (13 mL) was added $VO(acac)_2$ (70.7 mg, 0.267 mmol) and *t*-butyl hydroperoxide (TBHP, 2.82 M solution in CH_2Cl_2, 1.41 mL, 4 mmol) at 40 ºC. For *n* = 7 the reaction mixture was heated to 80 ºC and stirred for 15 min, for *n* = 8 the mixture was stirred for 12 h at 40 °C. Then the reaction mixture was quenched with water at 0 °C and the crude product was extracted with $CHCl_3$ (3 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography ($CHCl_3$) gave epoxides **5.3a** and **5.4a** as colorless oils.

5.4.2.2 General Procedures for the Cyclic Carbonate Synthesis

The requisite quantities and combinations of catalyst and co-catalyst (nucleophilic additive) were weighed into a 2 mL vial. The substrate (0.5 mmol) was added to this vial and the mixture was dissolved into an appropriate solvent (200 μL). The reaction mixture was transferred from the vial to a HEL multi-reactor system. The HEL system was closed and CO_2 was added to the desired pressure, and heated to the desired temperature after which the mixtures were stirred for 18 h. Then the HEL reactor was cooled down to rt, carefully depressurized and opened. For each of the reaction mixtures (**Figure 5.16**), the conversion to/yield of the product(s) were determined by ^{1}H NMR ($CDCl_3$) using mesitylene as internal standard.

Figure 5.17: Epoxide and CO_2 coupling reactions.



5.4.2.3 General Procedures for the Post-Modifications of Compound 5.15b

*Synthesis of **5.15ba:*** Compound **5.15b** (0.2 mmol, 37 mg) was weighed into a small vial and 1.2 equiv of morpholine were added. The reaction mixture was stirred overnight at 70 ºC. The product was purified by column chromatography (EtOAc). Isolated yield: 85%, product obtained as a mixture of regio-isomers (90:10) as determined by ^{1}H NMR.

*Synthesis of **5.15bb:*** compound **5.15b** (0.2 mmol, 37 mg) was weighed into a small vial and dissolved into DCM (0.3 mL). 1.1 Equiv of Dess–Martin periodinane were added to the solution which was then stirred for 3 h. The product was purified by column chromatography (EtOAc:Hex; 1:1). Isolated yield: 84%.

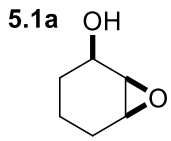
*Synthesis of **5.15bc:*** compound **5.15b** (0.2 mmol, 37 mg) was weighed into a small vial and NaOH solution (0.3 mL, 1 M in H_2O) was added and the mixture stirred for 2 h. The product was extracted by EtOAc and purified by column chromatography (EtOAc:Hex; 2:1). Isolated yield: 89%.

*Synthesis of **5.15bd:*** compound **5.15b** (0.2 mmol, 37 mg) was weighed into a small vial and DPEPhos (5 mol%), $Pd(OAc)_2$ (1 mol%), aniline (1.1 equiv) and DMF (0.2 mL) were added to the same vial. The reaction mixture was stirred for 18 h at 70 ºC. Then the product was purified by column chromatography (EtOAc:Hex; 1:5). Isolated yield: 64%.

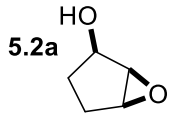
*Synthesis of **5.15be:*** compound **5.15b** (0.2 mmol, 37 mg) was weighed into a small vial and dissolved into DCM (0.2 mL) where after mesyl chloride (1.1 equiv), DMAP (1 equiv) and NEt_3 (2 equiv) were added. The reaction mixture was stirred for 2 h at rt and the product purified by column chromatography (EtOAc:Hex; 1:1). Isolated yield: 91%.

5.4.3 Spectroscopic Analysis for all Compounds

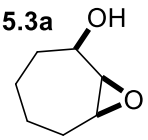
Epoxy Alcoholds 5.1a-5.18a



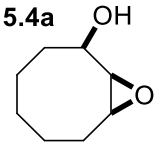
Compound **5.1a**:[29] Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.1a**: 166 mg (1.46 mmol, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04–3.98 (m, 1H), 3.43–3.27 (m, 2H), 2.24–2.16 (br s, 1H, OH), 1.87 (m, 1H), 1.85–1.74 (m, 1H), 1.57 (m, 2H), 1.53–1.39 (m, 1H), 1.26 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 67.07, 55.46, 55.37, 28.92, 23.09, 18.19.



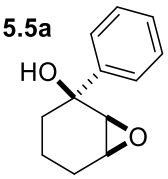
Compound **5.2a**:[28] Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.2a**: 172 mg (1.70 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (m, 1H), 3.48 (m, 1H), 3.46 (m, 1H), 2.39 (br s, 1H, OH), 2.09 (dd, J = 14.3 and 8.4 Hz, 1H), 1.93 (m, 1H), 1.64 (m, 1H), 1.26 (m, J = 12.9, 10.3 and 8.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 73.52, 58.89, 56.19, 26.91, 25.92.

5.3a 

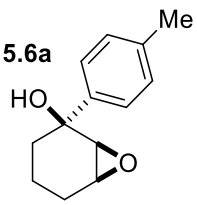
Compound **5.3a**:[28] Prepared following epoxidation procedure **B**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.3a**: 156 mg (1.22 mmol, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 (m, 1H), 3.28–3.23 (m, 1H), 3.17 (m, 1H), 2.24 (m, 1H), 2.03 (br s, 1H, OH), 1.80 (m, 2H), 1.77–1.63 (m, 2H), 1.66–1.53 (m, 1H), 1.57–1.36 (m, 1H), 1.04–0.92 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 71.64, 60.98, 54.55, 33.55, 28.30, 24.64, 24.06.

5.4a 

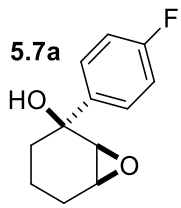
Compound **5.4a**:[28] Prepared following epoxidation procedure **B**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.4a**: 190 mg (1.34 mmol, 67%).^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (m, 1H), 3.05–2.99 (m, 1H), 2.96 (dt, J = 11.0 and 4.4 Hz, 1H) 2.21–1.79 (m, 4H), 1.73–1.19 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 66.25, 57.22, 57.12, 32.80, 26.05, 24.52, 24.22, 19.08.

5.5a 

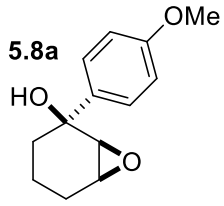
Compound **5.5a**:[30] Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.5a**: 330 mg (1.74 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.45 (m, 2H), 7.47–7.34 (m, 2H), 7.36–7.28 (m, 1H), 3.60 (m, 1H), 3.36 (d, J = 3.9 Hz, 1H), 2.78 (s, 1H, OH), 2.22–2.09 (m, 1H), 1.95–1.76 (m, 2H), 1.73–1.49 (m, 2H), 1.49–1.32 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.34, 128.30, 127.22, 125.10, 71.57, 58.95, 56.15, 37.82, 23.53, 15.80.

5.6a 

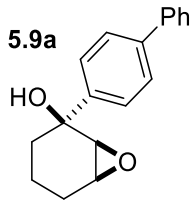
Compound **5.6a**: Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.6a**: 371 mg (1.82 mmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.39 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 3.58 (m, 1H), 3.34 (d, J = 3.8 Hz, 1H), 2.75 (d, J = 1.1 Hz, 1H), 2.38 (s, 3H), 2.18–2.09 (m, 1H), 1.94–1.76 (m, 2H), 1.64–1.46 (m, 2H), 1.37 (m, J = 11.8, 9.0, 6.2, 3.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.37, 136.85, 128.97, 125.04, 71.53, 59.04, 56.16, 37.67, 23.49, 21.05, 15.93. HRMS (ESI+, MeOH): *m/z* calcd. 227.1043 $(M + Na)^+$, found: 227.1043.



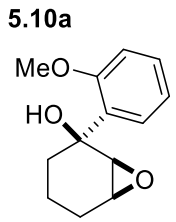
Compound **5.7a**:[30] Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.7a**: 370 mg (1.78 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.46 (m, 2H), 7.12–6.99 (m, 2H), 3.58 (m, 1H), 3.31 (d, J = 3.8 Hz, 1H), 2.95 (br s, 1H, OH), 2.14 (m , 1H), 1.93–1.83 (m, 1H), 1.81 (m, 1H), 1.61–1.47 (m, 2H), 1.40–1.26 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.92, 160.96, 141.09, 141.07, 126.91, 126.85, 115.14, 114.98, 71.35, 58.85, 56.16, 37.75, 23.40, 15.81.



Compound **5.8a**: Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.8a**: 330 mg (1.50 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.29 (m, 2H), 6.98–6.82 (m, 2H), 3.83 (s, 3H), 3.56 (m, 1H), 3.33 (d, J = 3.8 Hz, 1H), 2.87 (s, 1H), 2.16–2.02 (m, 1H), 1.94–1.72 (m, 2H), 1.64–1.42 (m, 2H), 1.41–1.18 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.70, 137.40, 126.37, 113.63, 71.47, 59.06, 56.17, 55.28, 37.43, 23.36, 16.12. HRMS (ESI+, MeOH): *m/z* calcd. 243.0992 $(M + Na)^+$, found: 243.0992.



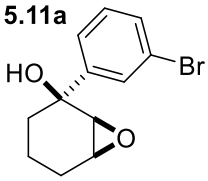
Compound **5.9a**: Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.9a**: 495 mg (1.86 mmol, 93%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.55 (m, 5H), 7.54–7.44 (m, 3H), 7.40 (m, 1H), 3.63 (m, 1H), 3.42 (d, J = 3.8 Hz, 1H), 2.98 (br s, 1H, OH), 2.24–2.12 (m, 1H), 2.02–1.83 (m, 2H), 1.73–1.53 (m, 2H), 1.51–1.33 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.42, 140.79, 140.16, 131.89, 128.82, 127.13, 127.05, 125.66, 71.59, 58.97, 56.19, 37.73, 23.54, 15.94. HRMS (ESI+, MeOH): *m/z* calcd. 289.1199 $(M + Na)^+$, found: 289.1197.



Compound **5.10a**: Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.10a**: 356 mg (1.62 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.6, 1.8 Hz, 1H), 7.35–7.23 (m, 1H), 7.04 (td, J = 7.5, 1.1 Hz, 1H), 6.94 (dd, J = 8.2, 1.1 Hz, 1H), 3.87 (s, 3H), 3.59–3.54 (m,

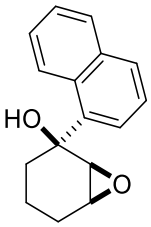
1H), 3.52 (s, 1H), 3.36 (d, *J* = 4.0 Hz, 1H), 2.24–2.13 (m, 1H), 1.93–1.76 (m, 2H), 1.69–1.53 (m, 2H), 1.43–1.25 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.65, 133.73, 128.36, 126.38, 120.76, 110.96, 70.45, 59.61, 56.05, 55.21, 35.25, 23.87, 15.34. HRMS (ESI+, MeOH): *m/z* calcd. 243.0992 $(M + Na)^+$, found: 243.0992.

5.11a



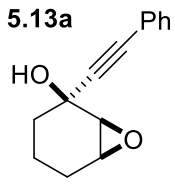
Compound **5.11a**: Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.11a**: 279 mg (1.04 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (t, *J* = 1.8 Hz, 1H), 7.47–7.41 (m, 2H), 7.38–7.22 (m, 1H), 3.59 (m, 1H), 3.30 (d, *J* = 3.8 Hz, 1H), 2.94 (s, 1H), 2.22–2.10 (m, 1H), 1.96–1.83 (br s, 1H, OH), 1.84–1.77 (m, 1H), 1.66–1.48 (m, 2H), 1.44–1.25 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.79, 130.32, 129.87, 128.43, 123.80, 122.60, 71.19, 58.59, 56.08, 37.89, 23.50, 15.51. Peaks observed at 145.31, 128.27, 127.19, 125.13, 71.55, 58.94, 56.12, 37.70 and 15.83 ppm correspond to the *anti* isomer. HRMS (ESI+, MeOH): *m/z* calcd. 290.9991 $(M + Na)^+$, found: 290.9987.

5.12a



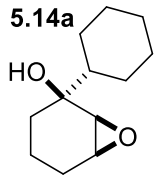
Compound **5.12a**: Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.12a**: 365 mg (1.52 mmol, 76%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 1.8 Hz, 1H), 7.93–7.82 (m, 3H), 7.63 (dd, *J* = 8.6 and 1.8 Hz, 1H), 7.55–7.45 (m, 2H), 3.67 (m, 1H), 3.46 (d, *J* = 3.8 Hz, 1H), 2.93 (br s, 1H, OH), 2.26–2.10 (m, 1H), 2.06–1.90 (m, 1H), 1.94–1.84 (m, 1H), 1.78–1.52 (m, 2H), 1.49–1.35 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.66, 133.08, 132.57, 128.18, 128.15, 127.57, 126.20, 125.96, 123.76, 123.45, 71.68, 58.95, 56.23, 37.79, 23.64, 15.76. HRMS (ESI+, MeOH): *m/z* calcd. 263.1043 $(M + Na)^+$, found: 263.1041.

5.13a



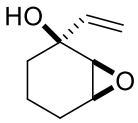
Compound **5.13a**:[31] Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.13a**: 295 mg (1.38 mmol, 69%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.45 (m, 3H), 7.34 (m, 2H), 3.53–3.40 (m, 2H), 2.51 (s, 1H, OH), 1.99–1.88 (m, 2H), 1.84 (m, 2H), 1.63 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.85, 128.68, 128.30, 122.17, 89.28, 85.67, 67.95, 58.35, 55.78, 34.48, 22.44, 18.34.

5.14a



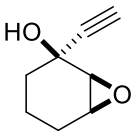
Compound **5.14a**: Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.14a**: 274 mg (1.40 mmol, 70%).^{1}H NMR (500 MHz, $CDCl_3$) δ 3.39 (dd, J = 4.0 and 2.0 Hz, 1H), 3.10 (dd, J = 3.9 and 1.2 Hz, 1H), 2.61 (s, 1H, OH), 2.13 (dq, J = 14.9 and 1.8 Hz, 1H), 2.00–1.90 (m, 1H), 1.86–1.69 (m, 4H), 1.67–1.42 (m, 4H), 1.39–1.03 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 69.78, 58.41, 55.75, 47.67, 30.80, 26.99, 26.74, 26.61, 26.54, 26.30, 24.55, 13.85. HRMS (ESI+, MeOH): *m/z* calcd. 219.1356 $(M + Na)^+$, found: 219.1353.

5.15a



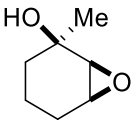
Compound **5.15a**:[32] Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.15a**: 260 mg (1.86 mmol, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (dd, J = 17.5 and 10.9 Hz, 1H), 5.43 (dd, J = 17.5 and 1.2 Hz, 1H), 5.26 (dd, J = 10.9 and 1.2 Hz, 1H), 3.42 (m, 1H), 3.13 (d, J = 3.8 Hz, 1H), 2.04–1.94 (m, 1H), 1.80 (m, , 1H), 1.67–1.58 (m, 1H), 1.52 (m, 1H), 1.49–1.35 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.79, 114.82, 70.61, 58.02, 55.83, 34.18, 23.12, 16.39.

5.16a



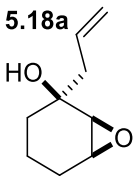
Compound **5.16a**:[32] Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.16a**: 201 mg (1.46 mmol, 73%).^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37 (m, 2H), 2.67 (s, 1H, OH), 2.57 (s, 1H), 1.99–1.79 (m, 2H), 1.85–1.63 (m, 2H), 1.55 (m, J = 11.2, 6.4 and 3.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.29, 73.74, 67.34, 58.17, 55.68, 34.12, 22.26, 18.10.

5.17a



Compound **5.17a**:[33] Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.17a**: 225 mg (1.76 mmol, 88%).^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (m, J = 4.2, 3.0 and 1.5 Hz, 1H), 3.03 (d, J = 3.9 Hz, 1H), 2.42 (s, 1H, OH), 2.06–1.96 (m, 1H), 1.79–1.70 (m, 1H), 1.64–1.56 (m, 1H), 1.54–1.45 (m, 1H), 1.36 (s, 3H), 1.42–1.24 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 67.72, 59.16, 55.92, 35.99, 26.05, 23.60, 16.42.

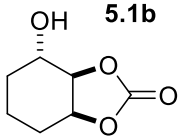
5.18a



Compound **5.18a**:[34] Prepared following epoxidation procedure **A**. The product was purified by column chromatography on silica gel (Hex:EtOAc, 4:1). Yield of **5.18a**: 286 mg (1.86 mmol, 93%).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (m, 1H), 5.20–5.09 (m, 2H), 3.36 (dt, J = 4.1 and 2.0 Hz, 1H), 3.08 (d, J = 3.9 Hz, 1H), 2.57 (s, 1H), 2.39 (dt, J = 7.3 and 1.3 Hz, 2H), 2.09–1.99 (m, 1H), 1.69 (m, 1H), 1.57–1.41 (m, 2H), 1.40–1.23 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.83, 118.56, 68.60, 58.00, 55.71, 44.10, 34.09, 23.82, 15.28.

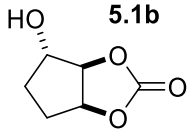
Cyclic Carbonates

5.1b



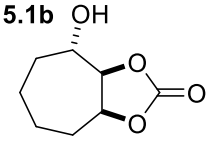
Compound **5.1b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 70 mg (0.44 mmol, 88%).^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92–4.84 (m, 1H), 4.45 (t, J = 6.7 Hz, 1H), 3.85 (m, 1H), 3.32 (br s, 1H, OH), 2.23–2.11 (m, 1H), 1.95 (m, Hz, 1H), 1.81–1.65 (m, 2H), 1.56 (m, 1H), 1.37 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.28, 81.95, 77.68, 70.88, 29.24, 25.91, 17.33. IR (neat, cm^{-1}): 3436, 2928, 1778, 1360, 1192, 1158, 1038, 991 and 779. HRMS (ESI+, MeOH): *m/z* calcd. 181.0471 $(M + Na)^+$, found: 181.0473.

5.1b



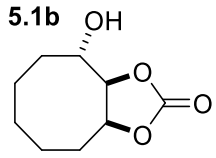
Compound **5.2b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 62 mg (0.43 mmol, 87%).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26–5.18 (m, 1H), 4.85 (dd, J = 6.5 Hz, 1.4 Hz, 1H), 4.44 (d, J = 3.8 Hz, 1H), 2.29–2.09 (m, 2H), 2.00 (br s, 1H. OH), 2.01–1.82 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.88, 85.39, 81.59, 75.06, 30.21, 30.20. IR (neat, cm^{-1}): 3462, 2921, 1796, 1372, 1167, 1068. HRMS (ESI+, MeOH): *m/z* calcd. 167.0315 $(M + Na)^+$, found: 167.0309.

5.1b

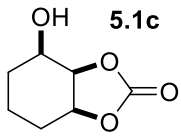


Compound **5.3b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 62 mg (0.36 mmol, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (m, 1H), 4.61 (t, J = 8.8 Hz, 1H), 4.06–3.96 (m, 1H), 2.91 (br s, 1H, OH), 2.15 (m, 1H), 2.02–1.94 (m, 1H),

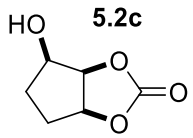
1.97–1.80 (m, 2H), 1.69 (q, *J* = 12.0 Hz, 1H), 1.49 (m, 2H), 1.28–1.17 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.05, 83.91, 78.43, 71.46, 33.45, 30.01, 26.39, 23.98. IR (neat, cm^{-1}): 3428, 2921, 1766, 1454, 1378, 1185, 1049, 773. HRMS (ESI+, MeOH): *m/z* calcd. 195.0628 $(M + Na)^+$, found: 195.0630.



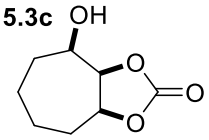
Compound **5.4b**: Prepared from the corresponding *anti* epoxy alcohol.[28] The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 74 mg (0.40 mmol, 79%).^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85–4.72 (m, 1H), 4.53 (dd, *J* = 9.9 Hz, 7.4 Hz, 1H), 4.15 (td, *J* = 10.3 and 4.4 Hz, 1H), 2.70 (br s, 1H), 2.00 (m, 3H), 1.84–1.69 (m, 2H), 1.54 (m, 2H), 1.47–1.35 (m, 2H), 1.23–1.08 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.39, 83.49, 80.31, 68.12, 33.98, 28.14, 26.43, 25.53, 22.09. IR (neat, cm^{-1}): 3486, 2921, 1775, 1365, 1186, 1064, 1023, 780. HRMS (ESI+, MeOH): *m/z* calcd. 209.0784 $(M + Na)^+$, found: 209.0790.



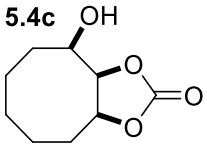
Compound **5.1c:** Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 65 mg (0.41 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (dt, *J* = 6.8 and 4.8 Hz, 1H), 4.69 (dd, *J* = 6.7 and 4.1 Hz, 1H), 4.04 (m, 1H), 2.46 (d, *J* = 6.8 Hz, 1H), 1.96 (m, 2H), 1.94–1.87 (m, 1H), 1.91–1.80 (m, 1H), 1.83–1.67 (m, 1H), 1.49–1.36 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.60, 77.16, 76.40, 66.01, 26.99, 25.65, 14.54. IR (neat, cm^{-1}): 3428, 2921, 1779, 1179, 1044, 980, 772. HRMS (ESI+, MeOH): *m/z* calcd. 181.0471 $(M + Na)^+$, found: 181.0468.



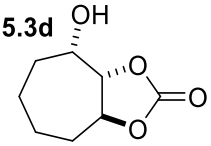
Compound **5.2c**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 66 mg (0.46 mmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (m, 1H), 4.90 (dd, *J* = 6.6 Hz, 4.9 Hz, 1H), 4.20–4.12 (m, 1H), 2.52 (br s, 1H, OH), 2.21–2.10 (m, 1H), 2.11–1.91 (m, 1H), 1.91–1.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.06, 79.93, 79.88, 73.42, 28.80, 28.77. IR (neat, cm^{-1}): 3412, 2921, 1765, 1375, 1167, 1083, 1034. HRMS (ESI+, MeOH): *m/z* calcd. 167.0315 $(M + Na)^+$, found: 167.0308.

5.3c 

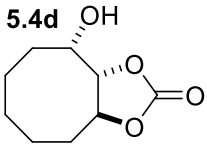
Compound **5.3c**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 81 mg (0.47 mmol, 95%).^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (td, J = 8.9 and 4.2 Hz, 1H), 4.78 (dd, J = 9.1 and 2.2 Hz, 1H), 4.16 (dt, J = 9.2 and 1.7 Hz, 1H), 2.48 (br s, 1H, OH), 2.24 (m, 1H), 2.08 (m, 1H), 1.95 (m, 1H), 1.92–1.77 (m, 1H), 1.82–1.69 (m, 1H), 1.71–1.46 (m, 2H), 1.40–1.25 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.01, 82.39, 78.37, 70.22, 31.28, 30.23, 24.26, 22.42. IR (neat, cm^{-1}): 3447, 2921, 1769, 1379, 1182, 1036, 773. HRMS (ESI+, MeOH): *m/z* calcd. 195.0628 $(M + Na)^+$, found: 195.0636.

5.4c 

Compound **5.4c**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 89 mg (0.48 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75–4.65 (m, 2H), 4.40 (m, 1H), 2.98–2.80 (m, 1H), 2.18 (d, J = 5.2 Hz, 1H), 2.09–1.98 (m, 3H), 1.72–1.64 (m, 1H), 1.62–1.52 (m, 4H), 0.80 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.46, 82.54, 80.74, 72.64, 35.21, 25.87, 24.98, 24.10, 19.04. IR (neat, cm^{-1}): 3359, 2921, 1784, 1368, 1173, 1050, 811, 672. HRMS (ESI+, MeOH): *m/z* calcd. 209.0784 $(M + Na)^+$, found: 209.0779.

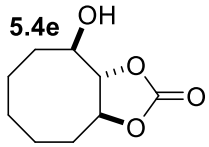
5.3d 

Compound **5.3d**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 50 mg (0.29 mmol, 59%).^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96–4.86 (m, 1H), 4.42 (m, 1H), 4.38 (dd, J = 10.7 and 2.8 Hz, 1H), 2.34 (m, 1H), 1.98 (m, 1H), 1.72 (m, 5H), 1.45 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.71, 84.61, 76.11, 64.38, 33.38, 28.44, 24.05, 20.13. IR (neat, cm^{-1}): 3447, 2921, 1784, 1381, 1184, 1058, 778. HRMS (ESI+, MeOH): *m/z* calcd. 195.0628 $(M + Na)^+$, found: 195.0634.

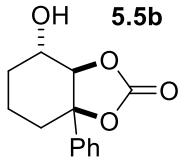
5.4d 

Compound **5.4d:** Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 33 mg (0.18 mmol, 36%).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09–5.00 (m, 1H), 4.54 (dd, J = 9.2 and 2.3 Hz, 1H), 4.28 (dt, J = 6.3 and 2.8 Hz, 1H), 2.58 (br s, 1H, OH), 2.28

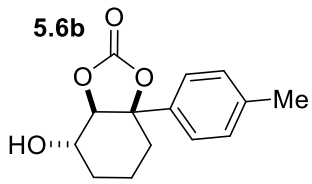
(m, 1H), 1.96 (m, 1H), 1.90–1.52 (m, 7H), 1.37–1.24 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.25, 84.10, 76.13, 66.65, 33.04, 29.02, 26.56, 21.64, 19.18. IR (neat, cm^{-1}): 3449, 2921, 1790, 1455, 1386, 1193, 1056, 774. HRMS (ESI+, MeOH): *m/z* calcd. 209.0784 $(M + Na)^+$, found: 209.0788.



Compound **5.4e**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 80 mg (0.43 mmol, 86%).^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (m, 1H), 4.50 (t, J = 9.1 Hz, 1H), 3.93 (td, J = 8.6 and 3.0 Hz, 1H), 2.74 (br s, 1H, OH), 2.27 (m, 1H), 2.08–1.91 (m, 2H), 1.90–1.73 (m, 3H), 1.66 (dt, J = 13.3 and 8.2 Hz, 1H), 1.57 (qd, J = 9.1 and 4.2 Hz, 1H), 1.47–1.36 (m, 1H), 1.34–1.22 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.77, 86.13, 78.64, 73.53, 33.01, 28.46, 26.30, 20.75, 20.67. IR (neat, cm^{-1}): 3446, 2921, 1797, 1455, 1383, 1192, 1063, 774. HRMS (ESI+, MeOH): *m/z* calcd. 209.0784 $(M + Na)^+$, found: 209.0789.

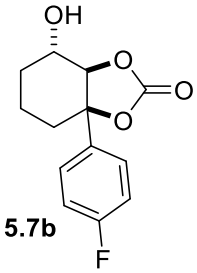


Compound **5.5b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 94 mg (0.40 mmol, 80%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.39 (m, 4H), 7.42–7.31 (m, 1H), 4.64 (d, J = 5.8 Hz, 1H), 4.07 (m, 1H), 2.29 (dt, J = 15.3 and 3.8 Hz, 2H), 2.14–1.57 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.09, 141.68, 128.89, 128.52, 124.25, 87.02, 85.79, 71.11, 34.76, 28.07, 17.56. IR (neat, cm^{-1}): 3463, 2852, 1801, 1739, 1449, 1365, 1217, 1034. HRMS (ESI+, MeOH): *m/z* calcd. 257.0784 $(M + Na)^+$, found: 257.0783.



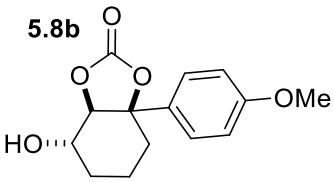
Compound **5.6b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 79 mg (0.32 mmol, 64%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.3 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 4.62 (d, J = 5.9 Hz, 1H), 4.04 (m, 1H), 2.38 (s, 2H), 2.31–2.24 (m, 1H), 2.09–2.03 (m, 1H), 1.97 (m, 1H), 1.86–1.77 (m, 1H), 1.76–1.56 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.25, 138.69, 138.41, 129.52, 124.18, 87.13, 85.96, 71.21, 34.82, 28.20, 21.02, 17.68. IR (neat, cm^{-}

[1]): 3442, 2921, 1794, 1514, 1453, 1362, 1226, 1064, 1034, 814, 776. HRMS (ESI+, MeOH): *m/z* calcd. 271.0941 $(M + Na)^+$, found: 271.0953.



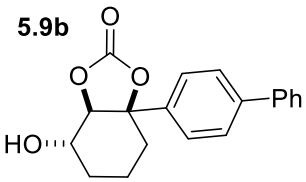
5.7b

Compound **5.7b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 96 mg (0.38 mmol, 77%).[1]H NMR (500 MHz, $CDCl_3$) δ 7.51–7.41 (m, 2H), 7.16–6.99 (m, 2H), 4.62 (d, J = 5.6 Hz, 1H), 4.08 (m, 1H), 2.63 (br s, 1H, OH), 2.29–2.20 (m, 1H), 2.06 (m, 1H), 1.97 (m, 1H), 1.83 (m, 1H), 1.81–1.66 (m, 1H), 1.69–1.58 (m, 1H). [13]C NMR (126 MHz, $CDCl_3$) δ 162.57(d, J = 251 Hz) , 154.03, 137.49 (d, J = 3.2 Hz), 126.27 (d, J = 10.2 Hz), 115.85 (d, J = 20.9 Hz), 86.71, 85.49, 70.60, 34.82, 27.88, 17.28. IR (neat, cm^{-1}): 3433, 2921, 1796, 1605 1510, 1227, 1031, 834, 776. HRMS (ESI+, MeOH): *m/z* calcd. 275.0690 $(M + Na)^+$, found: 275.0695.



5.8b

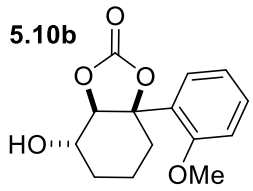
Compound **5.8b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 108 mg (0.41 mmol, 82%).[1]H NMR (500 MHz, $CDCl_3$) δ 7.46–7.33 (m, 2H), 6.98–6.88 (m, 2H), 4.61 (d, J = 5.8 Hz, 1H), 4.05 (dq, J = 9.2 and 4.4 Hz, 1H), 3.84 (s, 4H), 2.44 (d, J = 3.6 Hz, 1H), 2.31–2.20 (m, 1H), 2.10–2.02 (m, 1H), 1.97 (ddd, J = 15.5, 11.7 and 5.2 Hz, 1H), 1.86–1.67 (m, 1H), 1.67–1.58 (m, 2H). [13]C NMR (126 MHz, $CDCl_3$) δ 159.62, 154.24, 133.53, 125.62, 114.20, 86.98, 85.80, 71.07, 55.37, 34.85, 28.17, 17.61. IR (neat, cm^{-1}): 3159, 2921, 1794, 1616, 1516, 1142, 1026, 829. HRMS (ESI+, MeOH): *m/z* calcd. 287.0890 $(M + Na)^+$, found: 287.0880.



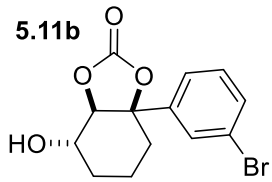
5.9b

Compound **5.9b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 118 mg (0.38 mmol, 75%).[1]H NMR (300 MHz, $CDCl_3$) δ 7.68–7.60 (m, 3H), 7.59–7.51 (m, 3H), 7.50–7.43 (m, 2H), 7.42–7.36 (m, 1H), 4.68 (d, J = 5.8 Hz, 1H), 4.12–4.03 (m, 1H), 2.47 (br s, 1H, OH),

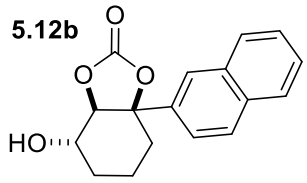
2.31 (dd, *J* = 15.7 and 4.1 Hz, 1H), 2.12–1.96 (m, 2H), 1.92–1.51 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.15, 141.54, 140.54, 140.12, 128.89, 127.71, 127.59, 127.13, 124.77, 87.03, 85.76, 71.06, 34.74, 28.09, 17.57. IR (neat, cm^{-1}): 3516, 2921, 1778, 1487, 1404, 1220, 1032, 832, 763, 697. HRMS (ESI+, MeOH): *m/z* calcd. 333.1097 $(M + Na)^+$, found: 333.1109.



Compound **5.10b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 53 mg (0.20 mmol, 41%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (td, *J* = 7.9, 1.7 Hz, 1H), 7.37 (m, 1H), 7.04 (td, *J* = 7.6 and 1.1 Hz, 1H), 6.97 (dd, *J* = 8.2 and 1.2 Hz, 1H), 4.92 (d, *J* = 6.8 Hz, 1H), 3.92 (s, 3H), 3.95-3.85 (m, 1H), 2.46 (br s, 1H, OH), 2.39–2.24 (m, 1H), 2.13 (m, 1H), 2.06–1.93 (m, 1H), 1.89–1.75 (m, 1H), 1.69–1.57 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.74, 130.05, 125.25, 121.23, 111.44, 86.92, 85.99, 73.58, 55.31, 31.77, 29.07, 19.25. IR (neat, cm^{-1}): 3427, 2929, 1799, 1585, 1490, 1241, 1034, 756. HRMS (ESI+, MeOH): *m/z* calcd. 287.0890 $(M + Na)^+$, found: 287.0887.

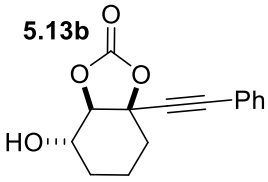


Compound **5.11b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 85 mg (0.27 mmol, 55%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (t, *J* = 1.9 Hz, 1H), 7.50 (m, 1H), 7.41 (m, 1H), 7.35–7.24 (m, 1H), 4.61 (d, *J* = 5.6 Hz, 1H), 4.08 (dt, *J* = 8.5 and 5.0 Hz, 1H), 2.44 (br s, 1H, OH), 2.28–2.16 (m, 1H), 2.01 (m, 2H), 1.88–1.53 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.78, 144.02, 131.73, 130.49, 127.65, 123.10, 123.00, 86.31, 85.21, 70.51, 34.56, 27.67, 17.15. IR (neat, cm^{-1}): 3440, 2926, 1799, 1568, 1229, 1034, 777. HRMS (ESI+, MeOH): *m/z* calcd. 334.9889 $(M + Na)^+$, found:334.9883.

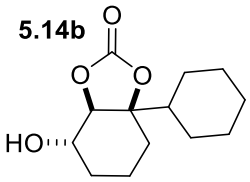


Compound **5.12b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 119 mg (0.42 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.9 Hz, 1H), 7.97–7.82 (m, 3H), 7.61–7.49 (m, 2H), 7.48 (dd, *J* = 8.6 and 2.0 Hz, 1H), 4.77 (d, *J* = 5.8 Hz, 1H), 4.08 (dt, *J* = 9.8 and

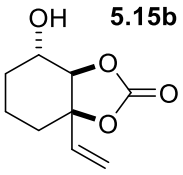
5.1 Hz, 1H), 2.82–2.77 (m, 1H), 2.39–2.26 (m, 1H), 2.16–2.04 (m, 2H), 1.91–1.81 (m, 1H), 1.85–1.61 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.35, 138.68, 132.95, 132.85, 129.05, 128.36, 127.61, 126.87, 126.82, 123.39, 121.97, 87.28, 85.74, 71.08, 34.58, 28.11, 17.63. IR (neat, cm^{-1}): 3437, 3057 2926, 1793, 1357, 1793, 1357, 1206, 1065, 1031, 736. HRMS (ESI+, MeOH): *m/z* calcd. 307.0941 $(M + Na)^+$, found: 307.0940.



Compound **5.13b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 85 mg (0.33 mmol, 65%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.43 (m, 2H), 7.41–7.30 (m, 3H), 4.59 (d, J = 6.0 Hz, 1H), 4.03–3.88 (m, 1H), 2.38 (dd, J = 15.3 and 5.0 Hz, 1H), 2.15 (m, 1H), 1.96 (m, 1H), 1.87–1.78 (m, 1H), 1.77–1.49 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.79, 131.96, 129.46, 128.44, 120.89, 87.40, 85.50, 79.41, 70.31, 33.10, 28.07, 17.02. IR (neat, cm^{-1}): 3449, 2952, 2253,1798, 1444, 906, 725. HRMS (ESI+, MeOH): *m/z* calcd. 257.0808 $(M + Na)^+$, found: 257.0795.

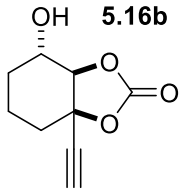


Compound **5.14b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 72 mg (0.30 mmol, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (d, J = 5.4 Hz, 1H), 3.99–3.89 (m, 1H), 2.39 (br s, 1H, OH), 2.04–1.95 (m, 1H), 1.94–1.83 (m, 3H), 1.8–1.69 (m, 4H), 1.65–1.52 (m, 2H), 1.44 (m, 1H), 1.30–1.19 (m, 3H), 1.19–1.04 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.68, 88.50, 81.71, 70.69, 45.84, 26.85, 26.83, 26.19, 26.12, 25.96, 16.23. HRMS (ESI+, MeOH): *m/z* calcd. 263.1254 $(M + Na)^+$, found: 263.1255.

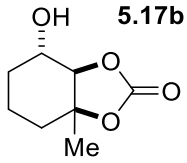


Compound **5.15b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 77 mg (0.42 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (dd, J = 17.2 and 10.9 Hz, 1H), 5.51 (d, J = 17.2 Hz, 1H), 5.33 (d, J = 10.9 Hz, 1H), 4.27 (d, J = 5.9 Hz, 1H), 3.97 (m, 1H), 2.50 (br s, 4H), 2.13–2.01 (m, 1H), 2.01–1.91 (m, 1H), 1.91–1.71 (m, 2H), 1.66–1.56 (m, 1H), 1.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.62, 137.13, 116.02, 85.44, 84.28, 70.51, 31.37,

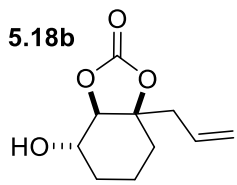
28.48, 17.30. IR (neat, cm^{-1}): 3442, 2921, 1789, 1366, 1230, 1030, 776. HRMS (ESI+, MeOH): *m/z* calcd. 207.0628 $(M + Na)^+$, found: 207.0628.



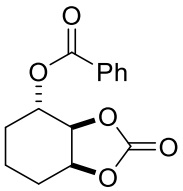
Compound **5.16b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 73 mg (0.40 mmol, 79%).^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (d, J = 6.0 Hz, 1H), 3.90 (m, 1H), 2.77 (s, 1H), 2.35–2.25 (m, 1H), 2.06 (m, 1H), 1.99–1.86 (m, 1H), 1.85–1.73 (m, 1H), 1.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.43, 85.04, 80.60, 78.34, 75.92, 70.01, 32.82, 27.96, 16.77. IR (neat, cm^{-1}): 3444, 3282, 2121, 1797, 1364, 1228, 1029. HRMS (ESI+, MeOH): *m/z* calcd. 207.0628 $(M + Na)^+$, found: 207.0625.



Compound **5.17b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 55 mg (0.32 mmol, 65%).^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (d, J = 5.5 Hz, 1H), 3.98 (m, 1H), 2.46 (br s, 1H, OH), 2.11–1.96 (m, 1H), 1.99–1.82 (m, 1H), 1.83–1.67 (m, 1H), 1.73–1.56 (m, 1H), 1.52 (s, 3H), 1.61–1.37 (m, 1H), 1.33–1.20 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.49, 85.05, 84.20, 69.92, 32.71, 28.26, 25.66, 17.05. IR (neat, cm^{-1}): 3450, 2921, 1798, 1365, 1229, 1039, 777. HRMS (ESI+, MeOH): *m/z* calcd. 195.0628 $(M + Na)^+$, found: 195.0635.



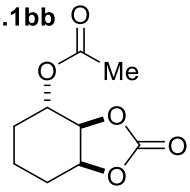
Compound **5.18b**: Prepared following the general procedure for cyclic carbonate synthesis. The product was purified by column chromatography on silica gel (Hex:EtOAc, 2:1). Yield of **5.1a**: 81 mg (0.41 mmol, 83%).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.33–5.20 (m, 2H), 4.26 (d, J = 5.6 Hz, 1H), 3.99 (m, 1H), 2.59–2.45 (m, 2H), 2.42 (br s, 1H, OH), 2.10–1.95 (m, 1H), 1.99–1.86 (m, 1H), 1.78 (td, J = 10.0 and 5.1 Hz, 1H), 1.71 (m, 1H), 1.64–1.54 (m, 1H), 1.53–1.43 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.37, 130.15, 121.24, 85.40, 82.99, 70.13, 43.00, 30.30, 27.83, 16.65. IR (neat, cm^{-1}): 3440, 2921, 1783, 1345, 1044, 1201, 1034, 988, 766, 732. HRMS (ESI+, MeOH): *m/z* calcd. 221.0792 $(M + Na)^+$, found: 221.0784.



5.1ba

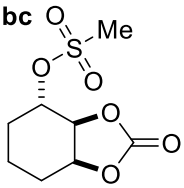
Compound **5.1ba**: Yield 126 mg (0.48 mmol, 95%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–7.97 (m, 2H), 7.66–7.51 (m, 1H), 7.53–7.37 (m, 2H), 5.28 (m, 1H), 4.96 (m, 1H), 4.76 (t, J = 6.5 Hz, 1H), 2.28–2.13 (m, 2H), 1.97–1.83 (m, 1H), 1.86–1.68 (m, 2H), 1.66–1.52 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.29, 154.23, 133.44, 129.69, 128.49, 77.30, 76.56, 72.33, 26.15, 25.82, 16.51. IR (neat, cm^{-1}): 2926, 1824, 1712, 1265, 1154, 1113, 1029, 711. HRMS (ESI+, MeOH): *m/z* calcd. 285.0733 $(M + Na)^+$, found: 285.0726.

5.1bb



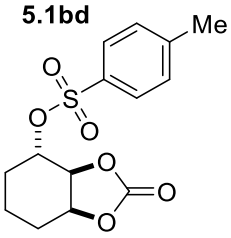
Compound **5.1bb**: Yield 92 mg (0.46 mmol, 91%).^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (m, 1H), 4.88 (dt, J = 6.7 and 4.0 Hz, 1H), 4.56 (t, J = 6.6 Hz, 1H), 2.09 (s, 3H), 2.24–1.96 (m, 2H), 1.95–1.51 (m, 3H), 1.39 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.79, 154.29, 77.55, 76.73, 72.14, 26.29, 25.76, 21.00, 16.65. IR (neat, cm^{-1}): 2947, 1795, 1733, 1373, 1231, 1146, 1033. HRMS (ESI+, MeOH): *m/z* calcd. 223.0577 $(M + Na)^+$, found: 223.0584.

5.1bc



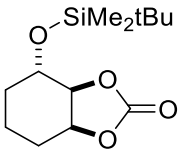
Compound **5.1bc**: Yield 104 mg (0.44 mmol, 87%).^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (dt, J = 7.2 and 3.7 Hz, 1H), 4.72–4.59 (m, 2H), 3.14 (s, 3H), 2.31–2.20 (m, 2H), 1.85–1.73 (m, 2H), 1.71–1.58 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.70, 80.67, 77.77, 38.52, 28.40, 25.41, 16.96. IR (neat, cm^{-1}): 3473, 3036, 2941, 1793, 1339, 1149, 1047, 967, 826, 516. HRMS (ESI+, MeOH): *m/z* calcd. 259.0247 $(M + Na)^+$, found:259.0249.

5.1bd



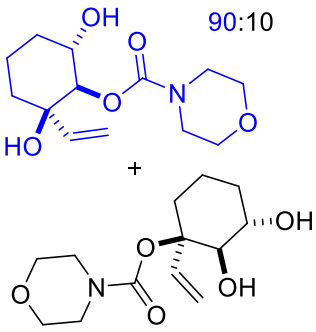
Compound **5.1bd**: Yield 150 mg (0.48 mmol, 95%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.77 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 4.82 (dt, J = 6.2 and 4.0 Hz, 1H), 4.60–4.47 (m, 2H), 2.47 (s, 3H), 2.07 (m, 2H), 1.86–1.47 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.59, 145.48, 132.95, 130.06, 127.88, 79.01, 76.79, 76.40, 27.03, 25.25, 21.71, 16.13. IR (neat, cm^{-1}): 2951, 1799, 1598, 1357, 1174, 1040, 994, 921, 789, 663. HRMS (ESI+, MeOH): *m/z* calcd. 335.0560 $(M + Na)^+$, found: 335.0564.

5.1be

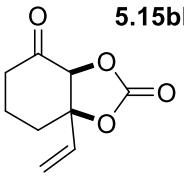


Compound **5.1be**: Yield 125mg (0.46 mmol, 93%).^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (dt, J = 6.6 and 4.2 Hz, 1H), 4.39 (t, J = 6.2 Hz, 1H), 3.87 (m, 1H), 2.13–2.03 (m, 1H), 1.87–1.75 (m, 2H), 1.75–1.65 (m, 1H), 1.62–1.50 (m, 1H), 1.49–1.38 (m, 1H), 0.92 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.91, 81.09, 76.98, 70.65, 29.63, 25.92, 25.66, 17.96, 16.49, 4.88. IR (neat, cm^{-1}): 2951, 2857, 1804, 1723, 1462, 1252, 1103, 1033, 833, 775. HRMS (ESI+, MeOH): *m/z* calcd. 273.1517 $(M + Na)^+$, found: 273.1511.

5.15ba

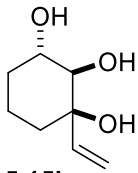


Compound **5.15ba**: Yield 46 mg (0.17 mmol, 85%).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (dd, J = 17.2 and 10.7 Hz, 1H), 5.31 (dd, J = 17.2 and 1.1 Hz, 1H), 5.14 (dd, J = 10.7 and 1.2 Hz, 1H), 4.61 (d, J = 9.5 Hz, 1H), 3.93 (m, 1H), 3.66 (m, 4H), 3.48 (m, 4H), 2.77 (br s, 1H), 2.16–2.07 (m, 1H), 1.80–1.64 (m, 2H), 1.61–1.47 (m, 2H), 1.39 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.91, 142.82, 113.38, 82.44, 75.84, 70.00, 66.45, 44.33, 36.54, 33.77, 18.93. IR (neat, cm^{-1}): 3427, 2941, 1678, 1429, 1243, 1111, 732. HRMS (ESI+, MeOH): *m/z* calcd. 294.1312 $(M + Na)^+$, found: 294.1310.



5.15bb

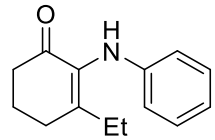
Compound **5.15bb**: Yield 31 mg (0.17 mmol, 84%).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (dd, J = 17.2 and 10.9 Hz, 1H), 5.54 (d, J = 17.2 Hz, 1H), 5.44 (d, J = 10.9 Hz, 1H), 4.56 (s, 1H), 2.81–2.64 (m, 1H), 2.55–2.40 (m, 1H), 2.08–1.89 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.05, 152.99, 135.64, 117.39, 87.37, 81.12, 37.64, 32.07, 18.73. IR (neat, cm^{-1}): 3464, 2931, 1800, 1730, 1619, 1340, 1051, 939. HRMS (ESI+, MeOH): *m/z* calcd. 205.0471 $(M + Na)^+$, found: 205.0464.



5.15bc

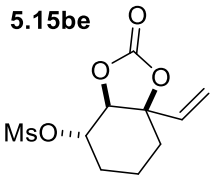
Compound **5.15bc**: Yield 28 mg (0.18 mmol, 89%).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (dd, J = 17.3 and 10.7 Hz, 1H), 5.40 (dd, J = 17.3 and 1.2 Hz, 1H), 5.23 (dd, J = 10.7 and 1.2 Hz, 1H), 3.80 (m, 1H), 3.31 (d, J = 8.9 Hz, 1H), 2.40 (br s, 1H), 2.30 (br s, 2H), 2.08–2.00 (m, 1H), 1.81–1.68 (m, 2H), 1.68–1.55 (m, 1H), 1.50–1.43 (m, 1H), 1.41–1.22 (m, 1H). ^{13}C NMR (126

MHz, $CDCl_3$) δ 143.00, 114.13, 78.88, 75.32, 71.40, 35.76, 32.33, 19.12. IR (neat, cm^{-1}): 3361, 2938, 2867, 1642, 1370, 1062, 921, 803. HRMS (ESI+, MeOH): *m/z* calcd. 281.0835 $(M + Na)^+$, found: 281.0835.



5.15bd

Compound **5.15bd**: Yield 28 mg (0.13 mmol, 64%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (dd, J = 8.6 and 7.3 Hz, 2H), 6.86–6.76 (m, 1H), 6.65 (dt, J = 7.8 and 1.1 Hz, 2H), 5.76 (s, 1H), 2.69–2.43 (m, 4H), 2.34–2.18 (m, 2H), 2.10–1.96 (m, 2H), 1.06 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.54, 152.59, 145.39, 132.65, 128.90, 119.27, 115.33, 37.35, 29.08, 27.38, 21.96, 11.19. IR (neat, cm^{-1}): 3354, 2963, 1717, 1663, 1598, 1495, 1435, 1258, 1025, 799. HRMS (ESI+, MeOH): *m/z* calcd. 216.1380 $(M + Na)^+$, found: 216.1383.

5.15be


Compound **5.15be**: Yield 47 mg (0.18 mmol, 91%).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dd, J = 17.2 and 10.9 Hz, 1H), 5.54 (d, J = 17.2 Hz, 1H), 5.40 (d, J = 10.9 Hz, 1H), 4.75 (m, 1H), 4.45 (d, J = 6.2 Hz, 1H), 3.13 (s, 3H), 2.23–2.09 (m, 2H), 1.85–1.61 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.14, 136.26, 117.09, 85.06, 80.49, 80.20, 38.54, 30.90, 27.59, 17.07. IR (neat, cm^{-1}): 2940, 1802, 1352, 1174, 1039, 936, 816, 525. HRMS (ESI+, MeOH): *m/z* calcd. 285.0410 $(M + Na)^+$, found: 285.0403.

5.4.4 Crystallographic Data

Crystallographic data was obtained following the methodology described in chapter I.

*Crystal data for cyclic carbonate **5.1b**:* $C_7H_{10}O_4$, M_r = 158.15, monoclinic, P2(1)/n, a = 8.3814(4) Å, b = 7.0296(3) Å, c = 12.3499(5) Å, α = 90.0º, β=96.2862(12)º, γ = 90.0º, V = 723.26(5) Å^3, Z = 4, ρ = 1.452 mg·M^{-3}, μ = 0.120 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 544, crystal size = 0.20 × 0.08 × 0.01 mm, θ(min) = 2.8º, θ(max) = 32.538º, 11223 reflections collected, 2462 reflections unique (R_{int} = 0.0286), GoF = 1.103, R_1 = 0.0381 and wR_2 = 0.0999 [$I > 2\sigma(I)$], R_1 = 0.0425 and wR_2 = 0.1034 (all indices), min/max residual density = -0.371/0.330 [e·Å^{-3}]. Completeness to θ(32.538º) = 93.6%.

*Crystal data for cyclic sulfite **5.1c**:* $C_7H_{10}O_4$, M_r = 158.15, monoclinic, P2(1)/n, a = 6.5169(10) Å, b = 11.8049(18) Å, c = 9.5214(15) Å, α = 90.0º, β = 105.261(19)º, γ = 90.0º, V =

706.67(19) Å^3, Z = 4, ρ = 1.486 mg·M^{-3}, μ = 0.123 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 336, crystal size = 0.40 × 0.15 × 0.10 mm, θ(min) = 2.81º, θ(max) = 29.842º, 7627 reflections collected, 1781 reflections unique (R_{int}=0.0365), GoF = 1.113, R_1 = 0.0386 and wR_2 = 0.0965 [$I > 2\sigma(I)$], R_1 = 0.0479 and wR_2 = 0.1005 (all indices), min/max residual density = -0.312/0.544 [e·Å^{-3}]. Completeness to θ(29.842º) = 87.8%.

Crystal data for cyclic sulfite ***5.4e****:* $C_9H_{14}O_4$, M_r = 186.09, tetragonal, P-42(1)c, a = 12.8527(8) Å, b = 12.8527(8) Å, c = 10.7921(7) Å, α = 90.0º, β = 90.0º, γ = 90.0º, V = 1782.8(3) Å^3, Z = 8, ρ = 1.387 mg·M^{-3}, μ = 0.109 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 800, crystal size = 0.16 × 0.09 × 0.06 mm, θ(min) = 2.241º, θ(max) = 35.072º, 30162 reflections collected, 3812 reflections unique (R_{int} = 0.0237), GoF = 1.115, R_1 = 0.0315 and wR_2 = 0.0862 [$I > 2\sigma(I)$], R_1 = 0.0337 and wR_2 = 0.0876 (all indices), min/max residual density = -0.202/0.389 [e·Å^{-3}]. Completeness to θ(35.07º) = 97.9%.

Crystal data for cyclic sulfite ***5.4f****:* $C_9H_{14}O_4$, M_r = 186.09, monoclinic, P21/c, a = 12.0341(7) Å, b = 5.5237(3) Å, c = 13.2673(8) Å, α = 90.0º, β = 90.9950(19)º, γ = 90.0º, V = 881.79(9) Å^3, Z = 4, ρ = 1.403 mg·M^{-3}, μ = 0.110 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 400, crystal size = 0.50 × 0.25 × 0.08 mm, θ(min) = 3.071º, θ(max)=30.034º, 6331 reflections collected, 2228 reflections unique (R_{int}=0.0335), GoF=1.074, R_1 = 0.0386 and wR_2 = 0.0954 [$I > 2\sigma(I)$], R_1 = 0.0458 and wR_2 = 0.1001 (all indices), min/max residual density = -0.281/0.311 [e·Å^{-3}]. Completeness to θ(30.03º) = 86.4%.

Crystal data for cyclic sulfite ***5.8b****:* $C_{14}H_{16}O_5$, M_r = 264.27, orthorhombic, Pbcn, a = 34.027(12) Å, b = 9.443(3) Å, c = 7.924(3) Å, α = 90.0º, β = 90.0º, γ = 90.0º, V = 2545.9(15) Å^3, Z = 8, ρ = 1.379 mg·M^{-3}, μ = 0.105 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 1120, crystal size = 0.15 × 0.10 × 0.02 mm, θ(min) = 2.238º, θ(max) = 27.000º, 20682 reflections collected, 2755 reflections unique (R_{int} = 0.0480), GoF = 1.114, R_1 = 0.0459 and wR_2 = 0.1047 [$I > 2\sigma(I)$], R_1 = 0.0705 and wR_2 = 0.1259 (all indices), min/max residual density = -0.321/0.385 [e·Å^{-3}]. Completeness to θ(27.00º) = 99.2%.

5.5 References

(1) Liu, Q.; Wu, L.; Jackstell, R.; Beller, M. *Nat. Commun.* **2015**, *6*, 5933.

(2) Kielland, N.; Whiteoak, C. J.; Kleij, A. W. *Adv. Synth. Catal.* **2013**, *355*, 2115–2138.

(3) Zhang, Z.; Liao, L. L.; Yan, S. S.; Wang, L.; He, Y. Q.; Ye, J. H.; Li, J.; Zhi, Y. G.; Yu, D. G. *Angew. Chem. Int. Ed.* **2016**, *55*, 7068–7072.

(4) Carry, B.; Zhang, L.; Nishiura, M.; Hou, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 6257–6260.

(5) Thenert, K.; Beydoun, K.; Wiesenthal, J.; Leitner, W.; Klankermayer, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 12266–12269.

(6) Guo, W.; Martínez-Rodríguez, L.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 11037–11040.

(7) Sopeña, S.; Laserna, V.; Guo, W.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Adv. Synth. Catal.* **2016**, *358*, 2172–2178.

(8) Khan, A.; Yang, L.; Xu, J.; Jin, L. Y.; Zhang, Y. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11257–11260.

(9) Sopeña, S.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *ACS Catal.* **2017**, 7, 3532–3539.

(10) Castro-Osma, J. A.; Lamb, K. J.; North, M. *ACS Catal.* **2016**, *6*, 5012–5025.

(11) Maeda, C.; Shimonishi, J.; Miyazaki, R.; Hasegawa, J. Y.; Ema, T. *Chem. Eur. J.* **2016**, *22*, 6556–6563.

(12) Fiorani, G.; Stuck, M.; Martín, C.; Belmonte, M. M.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *ChemSusChem* **2016**, 1304–1311.

(13) Bähr, M.; Bitto, A.; Mülhaupt, R. *Green Chem.* **2012**, *14*, 1447–1454.

(14) Webster, D. C.; Crain, A. L. *Prog. Org. Coatings* **2000**, *40*, 275–282.

(15) Rintjema, J.; Epping, R.; Fiorani, G.; Martín, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 3972–3976.

(16) Laserna, V.; Fiorani, G.; Whiteoak, C. J.; Martin, E.; Escudero-Adan, E.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 10416–10419.

(17) Kruper, W. J.; Dellar, D. V. *J. Org. Chem.* **1996**, *60*, 725–727.

(18) Liu, Y.; Ren, W.-M.; He, K.-K.; Zhang, W.-Z.; Li, W.-B.; Wang, M.; Lu, X.-B. *J. Org. Chem.* **2016**, *81*, 8959–8966.

(19) Darensbourg, D. J.; Wei, S. H. *Macromolecules* **2012**, *45*, 5916–5922.

(20) Wu, G. P.; Wei, S. H.; Ren, W. M.; Lu, X. B.; Xu, T. Q.; Darensbourg, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 15191–15199.

(21) Darensbourg, D. J.; Yeung, A. D. *Macromolecules* **2013**, *46*, 83–95.

(22) Darensbourg, D. J.; Bottarelli, P.; Andreatta, J. R. *Macromolecules* **2007**, *40*, 7727–7729.

(23) Darensbourg, D. J.; Wei, S. H.; Wilson, S. J. *Macromolecules* **2013**, *46*, 3228–3233.

(24) Darensbourg, D. J.; Wei, S.; Yeung, A. D.; Ellis, W. C. *Macromol. Rapid Commun.* **2013**, *46*, 5850–5855.

(25) Guo, W.; Martinez-Rodriguez, L.; Kuniyil, R.; Martin, E.; Escudero-Adan, E. C.; Maseras, F.; Kleij, A. W. *J. Am. Chem. Soc.* **2016**, *138*, 11970–11078.

(26) Cai, A.; Guo, W.; Martinez-Rodriguez, L.; Kleij, A. W. *J. Am. Chem. Soc.* **2016**, *138*, 14194–14197.

(27) Becker, N.; Carreira, E. M. *Org. Lett.* **2007**, *9*, 3857–3858.

(28) Uesugi, S.; Watanabe, T.; Imaizumi, T.; Masatoshi, S.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2014**, *16*, 4408–4411.

(29) Elhalem, E.; Comin, M. J.; Rodriguez, J. B. *Eur. J. Org. Chem.* **2006**, 4473–4482.

(30) Siewert, J.; Sandmann, R.; Von Zezschwitz, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7122–7124.

(31) Dai, L. Z.; Shi, M. *Tetrahedron Lett.* **2008**, *49*, 6437–6439.

(32) Sepulveda, J.; Soriano, C.; Mestres, R.; Sendra, J. *Bull. Soc. Chim. Fr.* **1983**, *7*, 240–244.

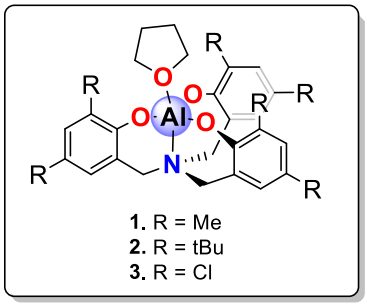
(33) Magnusson, G.; Thoren, S. *J. Org. Chem.* **1973**, *38*, 1380–1384.

(34) Shibata, I.; Fukuoka, S.; Yoshimura, N.; Matsuda, H.; Baba, A. *J. Org. Chem.* **1997**, *62*, 3790–3791.

General Conclusions

Lewis acid catalyzed coupling reactions between epoxides and different heterocumulenes can lead to a wide variety of interesting heterocycles. Aluminium amino triphenolates (ATP) have proven to be very active catalyst in the activation of epoxides towards the formation of cyclic carbonates via CO_2 couplings, and we set out to explore further catalytic potential in the synthesis of other heterocyclic targets. Amino triphenolate systems are highly modular, with coordination geometries controlled by the ligand, and in particular by the nature of the substituents in *ortho*-position of the phenol units which are able to influence the reactivity and stability of the metal ion. The ATP complexes (**Figure C1**) are tunable and readily synthesized catalysts with great potential in Lewis acid catalysis. Using this type of Lewis acid (in most cases combined with halides), we have developed a series of straightforward and simple methodologies for the synthesis of oxazolidinones, cyclic sulfites, and cyclic carbonates with challenging substitution patterns. In particular, we have devised methodologies for more complex heterocyclic compounds which have been reported scarcely.

Figure C1: Aluminium amino triphenolate catalysts.



In order to prepare a series of oxazolidinones, we used phenyl carbamate as a key coupling partner. The drawback in these preparations is the formation of an equivalent of phenol byproduct, but this is off-set by the high regioselectivity attained towards the formation of the 5-substituted oxazolidinone for nearly all examples studied. Furthermore, the addition of an external nucleophile was not necessary as the intermediate amide species was

nucleophilic enough to ring open the activated oxiranes. Although this type of coupling reaction had been described for similar catalytic systems, we have significantly expanded the scope of these transformations. These oxazolidinone compounds proved to be useful intermediates in the synthesis of nonsymmetrically substituted ureas. *Trans* configured oxazolidinones with a cyclic backbone readily reacted with amines to produce α-hydroxy ureas. When the backbone was acyclic, the reaction was more sluggish and required harsher reaction conditions to take place. Simple and new synthetic approaches towards the synthesis of nonsymmetrical ureas are of great use, as during the last decade ureas have become increasingly important as reagents, catalysts, and building blocks for supramolecular materials.

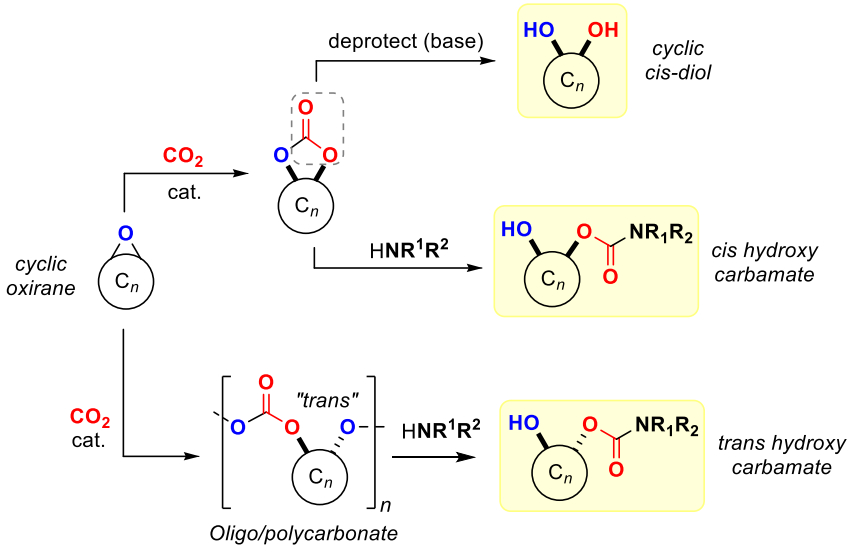
Cyclic sulfites are also interesting targets as their oxidized forms (sulfates) play significant roles in organic chemistry. Typically cyclic sulfites are synthesized by combining thionyl chloride and diols; though alternative coupling of epoxides with the SO_2 gas has been reported, this chemistry remained underdeveloped. With a binary catalyst system consisting of an Al(III) amino triphenolate complex and a halide cocatalyst we were able to develop further this alternative approach. We reported the formation of both mono- and more challenging disubstituted cyclic sulfites which could be easily oxidated to their sulfate analogues. To prove the potential of these sulfate scaffolds, various examples were used to prepare their respective aziridines by treatment of the sulfates with different amines under basic conditions.

We also focused on investigating appealing though more elusive CO_2/epoxide coupling reactions. In particular, we focused our interest on epoxides with cyclic scaffolds. We have been interested in understanding how to control the mechanistic manifolds leading to stereodivergent coupling reactions based on the use of CO_2 as feedstock. First of all we developed an efficient “double inversion pathway” for cyclic carbonate formation from five-, six-, seven- and eight-membered ring epoxides. The carbonate products retained the original *cis* configuration from the starting epoxide despite the fact that generally cyclic epoxides have high endency towards the formation of oligomeric/polymeric carbonate with opposite *trans* stereochemistry. Therefore, the formation of the latter species had to be suppressed to favor the cis configures cyclic carbonates and a method was developed based on optimal use of the catalyst to nucleophile ratio. The synthetic significance of this approach is reflected in the easy preparation of valuable *cis*-diols from their cyclic carbonate precursors. *Cis*-diols in

cyclic structures are a common feature in many bio-based molecules and the most common synthetic methodologies to synthesize them involve the use of toxic osmium reagents. Our methodology thus offers an alternative method using earth abundant metal catalysis, and highlights the idea of using CO_2 as a temporary protecting group towards the formation of *cis*-diol structures.

Cyclic carbonates undergo an aminolysis reaction in the presence of amines to generate hydroxycarbamates. The use of a binary catalyst based on Al(III) ATP complex and a suitable nucleophile a three-component one pot methodology has been developed to produce the hydroxycarbamates from epoxides, amines and CO_2 in a stereoselective fashion. First, by using monosubstituted cyclic carbonatess and converting them into hydroxycarbamates in the presence of various amines, mixtures of the two possible regioisomeric products were obtained in high yield. Upon using *meso* cyclic epoxides this problem of regioselectivity could be avoided but created a new stereoselectivity challenge as the ring substituents can be in a *cis* or *trans* disposition.

Figure C2: Cyclic or oligo/polycarbonates as intermediates.



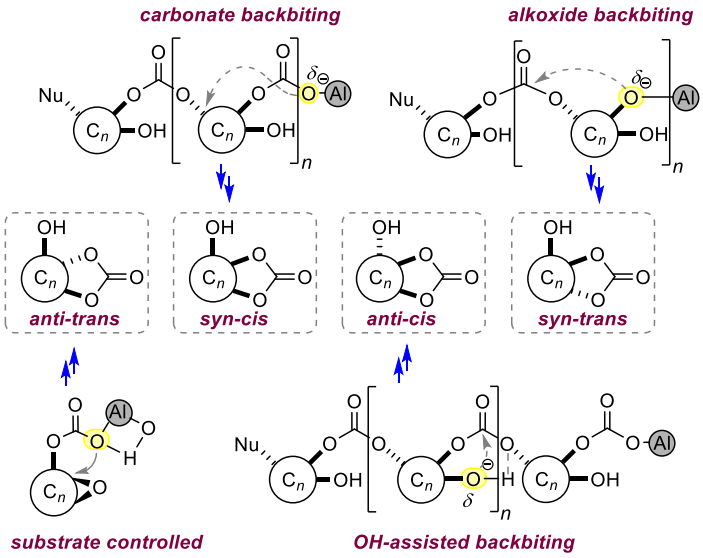
By tuning the reaction conditions that would favor copolymerization of the epoxide and CO_2 (**Figure C2**) we were able to selectively form the *trans* hydroxycarbamate products, while their *cis* isomers could be obtained in a two step process first preparing the cyclic

carbonate precursors followed by aminolysis. Intrigued by the possibility of using oligomeric intermediates to design stereodivergent processes, we decided to examine a series of cyclic *syn* configured hydroxy epoxides incorporating a pro-nucleophile in the molecule. **Figure C3** summarized the different mechanistic manifolds leading to different stereoconfigurations of the cyclic hydroxy-substituted cyclic carbonates. A detailed study was performed to elucidate the influence if different ring size, nucleophile, catalyst and catalyst/nucleophile ratio to stir the stereoselectivity of the epoxide/CO_2 coupling process.

The tendency of six-membered ring epoxides to favor copolymerization enables to stir the reaction towards the formation of an *anti/cis* configuration through a depolymerization process assisted by the OH functionality. Every other imaginable depolymerization process would either lead to *trans* configurations in the cyclic carbonate product but this was not observed in those cases where five- or six-membered ring epoxides were investigated as substrates. By increasing the fused ring size to seven or eight, synthesis of *trans* configured cyclic carbonates was feasible possible and we were able to produce both *syn/trans* and *anti/trans* hydroxy-carbonate bicyclic carbonates that were derived from known depolymerization pathways or a substrate controlled manifold (**Figure C3**).

The six membered ring epoxides were then used to prepare a wider scope of challenging trisubstituted cyclic carbonates, which have seldom been reported in the literature as conventional epoxide/CO_2 coupling approaches suffer from low reactivity of the involved trisubstituted epoxides. Therefore, an alternative mechanism towards the formation of trisubstituted cyclic carbonates may revive the interest in these scaffolds and amplify their potential in synthetic chemistry. Cyclic epoxides from eight-membered rings are generally difficult to prepare by conventional methods, and our approach offers a viable and potentially useful methodology to construct these types of compounds in a stereoselective fashion.

Figure C3: Different mechanistic manifolds of hydroxy-appended cyclic epoxides.



Throughout this research program we have achieved the synthesis of different products with high control over the stereo-, chemo- and regioselectivity features by studying the mechanistic pathways and trying to use conditions which favor the selective formation of only one product. The CO_2/epoxide coupling reactions represent a vibrant field of chemistry which has extensively expanded in the last decade and multiple catalytic systems have been described able to catalyze this process. In this thesis we have specifically focused on alternative approaches toward the synthesis of more challenging cyclic carbonates and related heterocycles, as to provide potential to use these scaffolds as intermediates in synthetic chemistry.

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Acknowledgements

This thesis is a summary of the academic part of the last four years, but a lot happens while we try to make the chemistry work. These results do not belong to me alone but to a great group of people who have helped me, supported me and made this time very enjoyable, both personally and professionally. Therefore, I cannot finish this thesis without some special goodbye's and thank you's. I hope I do not forget anyone.

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The years 2013 and 2014 were rather busy for the Kleij group, with five new PhD students starting. Leticia, Luis, Jeroen, Sergio and I, with all of us finishing, it is finally safe to say that the lab has survived us all. Jeroen, We spent so many hours sitting side by side but I still have not managed to find a Dutch word I can pronounce, thanks for adopting me in all the running, climbing and hiking activities, it has been great. Luis, we all know that behind that curtain of indifference you try to show us, you love us to bits, this last year has not been

the same without you. Sergio, thanks for the hangover half marathons, 91 km walks, the Perpignan-Girona visits…god knows where we will end up next. And of course Leti, you have played the role of sister, mother and best friend during the PhD, and for that I will forever be grateful. Nunca olvidaré tus enseñanzas, ni como con telebasura y chocolate, todos los dramas son siempre más llevaderos. Ya nos veremos por ahí, porque ya sabes, sobrevivimos a tu tesis, somos inmortales.

Outside the lab I also owe some thank you's. Pablo and Funes, you have been here since the first day I stepped into Tarragona, and here we are, five years older, not much wiser. Special mention too for Sergi, Marcos, Adiran, Marta and Elena; thanks for being part of it too. As promised, Ruth, thank you for taking me out that lonely Berkelyan 27th birthday and proving you should get to know people by yourself. Thank you Cristina for your unfiltered honesty, believe it or not, it taught me a lot. A los Malagueños, gracias por esos audios grupales que me mantienen un poquito más cerca de casa. Por supuesto agradecimiento especial para Ary, gracias por la ayuda gráfica, lo que hay dentro es un tostón, pero la portada quedo macanuda.

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Y gracias Mar por aparecer aquel fin de año. Tu solita eres capaz de calmar cualquier neurosis con una llamada desde el otro lado del mundo.

Curriculum Vitae

Victor Laserna Ayora was born on August 23 (**1989**) in Málaga. He decided to study Chemistry at the University of Malaga, where he obtained his BSc degree in **2012**, obtaining first class honours. During his undergraduate studies, he collaborated with the heterogeneous catalysis group under the supervision of Pedro J. Meireles. After he obtained his BSc, he spent an internship at ICIQ as a summer fellow under the supervision of Arjan W. Kleij working on coupling reactions between oxiranes and CO_2. Hereafter, he moved to Madrid to obtain his MSc degree in "Energy and Future Fuels" in the Autonoma University of Madrid. During his MSc studies, his research focused on the valorization of biomass, in particular the transformation of furfural into value-added chemicals such as succinic acid. This research was developed at the CSIC institute of petrol chemistry in the group of Manuel Lopez Granados. He obtained his MSc degree in September **2013** and decided to move back to Tarragona to start his PhD under the supervision of Arjan W. Kleij where he performed the research described in this thesis. His research was first funded by an ICIQ predoctoral fellowship, then by an FI grant from the Cataluña government, and later followed by an FPU grant from the Ministerio de Educación y Ciencia of Spain (MINECO). During his PhD studies, he spent four months at U.C. Berkeley in the group of John F. Hartwig working on catalytic Rh–O migratory insertions. The results of this thesis have been communicated as an oral contribution at the CARISMA-COST meeting on small molecule activation (Tarragona, **2015**) and as a poster at the Zing conference "Carbon Dioxide Conversion Catalysis" (Albufeira, **2016**).

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List of Publications

- "*Substrate Triggered Stereoselective Preparation of Highly Substituted Organic Carbonates*" Laserna, Victor; Martin, Eddy, Escudero-Adan, Eduardo C.; Kleij, Arjan W. *ACS Catal.*, **2017**, *7*, 5478–5482.

- "*Aluminium-Catalyzed Formation of Functional 1,2,3-Dioxathiolane 2-Oxides from Sulphur Dioxide: An Easy entry towards N-Substituted Aziridines*" Laserna, Victor; Martin, Eddy; Escudero-Adan, Eduardo C.; Kleij, Arjan W. *Adv. Synth. Catal*., **2016**, *358*, 3832-3839.

- "*Regioselective, Organocatalytic formation of Carbamates from Cyclic Carbonates*" Sopena, Sergio; Laserna, Victor; Guo, Wusheng; Martin, Eddy; Escudero-Adan, Eduardo C.; Kleij, Arjan W. *Adv. Synth. Catal*., **2016**, *358*, 2172-2178.

- "*Catalytic One-Pot Oxetane to Carbamate Conversions: Formal Synthesis of Drug Relevant Molecules*" Guo, Wusheng; Laserna, Victor; Rintjema, Jeroen; Kleij, Arjan W. *Adv. Synth. Catal*., **2016**, *358*, 1602-1607.

- "*Stereodivergent Carbamate Synthesis by Selective in Situ Trapping of Organic Cabonate Intermediates*" Guo, Wusheng; Laserna, Victor; Martin, Eddy; Escudero-Adan, Eduardo C.; Kleij, Arjan W. *Chem. Eur. J.*, **2016**, *22*,1722-1727.

- "*Metal Complexes Catalyzed Cyclizations with CO_2.* BOOK CHAPTER In: *Topics in Organometallic Chemistry",* J. Rintjema, L. Peña Carrodeguas, V. Laserna, S. Sopeña, A. W. Kleij , Ed. Xiao-Bing Lu, Springer, **2016**, *53*, 39-71 (ISBN: 1436-6002)

- "*Aluminium–Catalyzed Oxazolidinone Synthesis and Conversion into Functional Non-Symmetrical Ureas*" Laserna, Victor; Guo, Wusheng; Kleij, Arjan W. *Adv. Synth. Catal.*, **2015**, *357*, 2849-2854.

- "*Carbon Dioxide as a Protecting Group. Highly Efficient and Selective Catalytic Access to Cyclic Diol Scaffolds*" Laserna, Victor; Fiorani, Giulia; Whiteoak, Christopher J.; Martin, Eddy; Escudero-Adan, Eduardo; Kleij, Arjan W. *Angew. Chem. Int. Ed.*, **2014**, *53*, 10416-10419.

- "*Highly Active Aluminium Catalysts for the Formation of Organic Carbonates from CO_2 and Oxiranes*" Whiteoak, Christopher J.; Kielland, Nicola; Laserna, Victor; Castro-Gomez, Fernando; Martin, Eddy; Escudero-Adan, Eduardo C.; Bo, Carles; Kleij, Arjan W. *Chem. Eur. J.*, **2014**, *20*, 2264-2275.

- "*A Powerful Aluminum Catalyst for the Synthesis of Highly Functional Organic Carbonates*" Whiteoak, Christopher J.; Kielland, Nicola; Laserna, Victor; Escudero-Adan, Eduardo C.; Martin, Eddy; Kleij, Arjan W. *J. Am. Chem. Soc.*, **2013**, *135*, 1228-1231.

- "*Poly(styrene sulfonic acid): An Acid Catalyst from Polystyrene Waste for Reactions of Interest in Biomass Valorization*" Alonso-Fagundez, N.; Laserna, V.; Alba-Rubio, A. C.; Mengibar, M.; Heras, A.; Mariscal, R.; Granados, M. Lopez. *Catal. Today*, **2014**, *234*, 285-294.

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